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Usefulness of echocardiography to detect cardiac involvement in COVID-19 patients

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Abstract

Coronavirus disease 2019 (COVID-19) outbreak is a current global healthcare burden, leading to the life-threatening severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, evidence showed that, even if the prevalence of COVID-19 damage consists in pulmonary lesions and symptoms, it could also affect other organs, such as heart, liver, and spleen. Particularly, some infected patients refer to the emergency department for cardiovascular symptoms, and around 10% of COVID-19 victims had finally developed heart injury. Therefore, the use of echocardiography, according to the safety local protocols and ensuring the use of personal protective equipment, could be useful firstly to discriminate between primary cardiac disease or COVID-19–related myocardial damage, and then for assessing and monitoring COVID-19 cardiovascular complications: acute myocarditis and arrhythmias, acute heart failure, sepsis-induced myocardial impairment, and right ventricular failure derived from treatment with high-pressure mechanical ventilation. The present review aims to enlighten the applications of transthoracic echocardiography for the diagnostic and therapeutic management of myocardial damage in COVID-19 patients.

KEYWORDS

heart failure, COVID-19, echocardiography, myocardial injury, myocarditis, SARS-CoV2

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) pandemic is currently affecting 212 countries throughout the world, with high morbidity and mortality rates.[1] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection could be easily transmitted through human-to-human contact or respiratory droplets, and individuals with underlying cardiovascular disease are at highest risk for severe disease and death, reaching 10.5% fatality rate.[2] Even though the clinical manifestations of COVID-19 are dominated by respiratory symptoms,[3] some infected patient initially presents typical cardiovascular symptoms (ie, chest discomfort, palpitations, dyspnea).[4] In these cases, it could be challenging for the clinician to establish whether symptoms represent the first expression of SARS-CoV-2 cardiac involvement, or they derive from a primary cardiac pathologic condition. Moreover, several cases of COVID-19–induced myocardial damage has been observed, particularly in critical subjects (in China, 11.8% of dead subjects without underlying cardiovascular disease had myocardial injury[5]), consisting in acute myocardial injury and myocarditis, cardiac arrest, heart failure (HF) due to pulmonary hypertension (PH), or shock states.[6] This is probably due to coronavirus-related damage which also involves heart and other organs, provoking degeneration and necrosis of parenchymal cells and formation of hyaline thrombus in small vessels, as shown in a

postmortem examination of 3 COVID-19 victims.[7] In two studies by Shi et al[8] and Guo et al,[9] among 460 and 187 patients hospitalized for COVID-19, respectively, 20% and 28% had acute myocardial injury, which was associated with higher mortality and incidence of complications, such as acute respiratory distress syndrome (ARDS), malignant arrhythmias, acute renal injury, and coagulopathy. Echocardiography is considered the first-choice diagnostic technique for the evaluation of myocardial structure and function, due to its high availability and cost-effectiveness.[10] For this reason, a conscious inhospital application of transthoracic echocardiography (TTE), using a focused and safe approach, according to the latest European Association of Cardiovascular Imaging (EACVI) and American Society of Echocardiography (ASE) recommendations,[11,12] could reduce the potential risks of COVID-19 heart injury, providing early detection and treatment. These documents do not provide strict indications on whether to perform or reject an echocardiographic examination in this period of social distancing, since it should be tailored on the single patient, trying to avoid unnecessary examinations. However, American College of Cardiology (ACC) Clinical Guidance for COVID-19 suggests that patients demonstrating HF, arrhythmia, electrocardiographic (ECG) changes, or cardiomegaly should undergo echocardiography.[13] Moreover, the evaluation of the right ventricle (RV) could be important in ventilated patients for the early assessment of high positive end-expiratory pressures (PEEP)-induced cardiopulmonary overload and in patients with suspected acute cor pulmonale.

The present review discusses the different clinical inhospital applications of echocardiography, from emergency department to COVID wards and ICU, to highlight its usefulness for assisting clinicians in the daily diagnostic and therapeutic management of COVID-19–affected patients.

2 | SUSPECTED ACUTE CORONARY SYNDROMES

As reported by the National Health Commission of China (NHC), some of the confirmed cases of SARS-CoV-2 patients first showed cardiovascular rather than respiratory symptoms.[9] After the nasal or pharyngeal swab has done to test COVID-19 patients' status before the admission[14], the first step of triaging usually comprises ECG and blood cardiac enzymes dosage; however, evidence has shown that troponin and brain natriuretic peptide (BNP) levels could increase due to COVID-19 itself, proportionally to the severity of the disease.[9] In fact, a meta-analysis showed that troponin I values were significantly higher in patients with severe compared to those with mild illness due to SARS-CoV-2 infection.[15]

He et al conducted a study in critical COVID-19 patients dividing them into two groups according to the presence (24 patients, 44.4%) or absence (30 patients, 55.6%) of myocardial injury, revealing that the injury group presented significantly higher inhospital mortality (75.0% [18/24] vs. 26.7% [8/30], $P = .001$), C-reactive protein (CRP), and N-terminal pro-BNP (NT-pro-BNP, $P < .01$).[6] Chen Chen et al also analyzed 150 COVID-19 subjects and found 22 of them (14.7%) having troponin elevation, which was independently correlated with COVID-19 critical severity with multivariate regression analysis (odds ratio, OR = 26.909, 95% CI 4.086-177.226, $P = .001$).[16]

Accordingly, ACC COVID-19 clinical guidance pointed out that that classic symptoms and presentation of acute myocardial infarction may be unclear in the context of COVID-19, resulting in underdiagnosis.[13] Moreover, in a small Italian report of 28 COVID-19 patients with ST-elevation myocardial infarction (STEMI), 78.6% of them presented with acute chest pain, while 82.1% had regional wall-motion abnormalities at TTE.[17]

In fact, echocardiography could support diagnosis in this setting, revealing suggestive signs of acute myocardial infarction, new-onset or worsening congestive HF, pericardial effusion or tamponade, and RV overload due to pulmonary embolism or cor pulmonale (Table 1). This would lead to an accurate triaging, ensuring each patient the appropriate treatment.

3 | ACUTE MYOCARDITIS AND ARRHYTHMIAS

Various degrees of myocardial injury (defined as raised troponin levels over the 99th percentile of reference range) have been recently shown in patients with COVID-19.[18,19] In a clinical study involving 138 patients with COVID-19, 10 patients (7.2%) had acute myocardial injury[20] and 23 (16.7%) had arrhythmia, the majority of them during hospitalization in intensive care unit (ICU). There are many possible causes of acute myocardial injury in critically ill patients, including acute coronary syndrome, HF, myocarditis, hypotension or shock, sepsis, and infection. To date, the mechanism responsible of myocardial injury in COVID-19 is uncertain; however, hypothesis has focused on local or systemic immune response, possibly causing cardiomyocytes degeneration and/or microvascular thrombosis.[21] Accordingly, current reports suggest that the majority of COVID-19 patients with myocardial injury without evidence of epicardial coronary artery thrombosis, show imaging data supporting the diagnosis of acute myocarditis[21,22]; also, cases of fulminant myocarditis and fatal arrhythmias have been described.[23,24] Even if a direct cardiotropic localization SARS-CoV-2 into myocytes has never been demonstrated, some authors showed autoptic findings (eg, lymphocyte infiltrates and macrophagic response) compatible with viral myocarditis.[25-27]

Moreover, in a retrospective study by Ruan et al evaluating factors associated with mortality in 150 COVID-19 subjects, patients who died showed higher levels of troponin, myoglobin, C-reactive protein, serum ferritin, and interleukin-6, suggesting a high inflammatory burden in COVID-19 with a possible rise in myocarditis-related cardiac events.[28] For acute myocarditis, a combination of cardiac magnetic resonance (CMR) and myocardial biopsy is the reference diagnostic method,[29] preceded by coronary angiography to rule out acute coronary syndromes. This is also valid for COVID-19 patients. Accordingly, *Inciardi et al* presented a case of a 53-year COVID-19

TABLE 1 Useful echocardiographic findings to aid early diagnosis of acute myocardial involvement in COVID-19 patients

Suggested diagnosis	Echocardiographic findings
Acute coronary syndromes	• New regional LV or RV wall-motion abnormalities • New functional mitral regurgitation
Acute heart failure	• Unknown LV dilation and dysfunction • High LV filling pressures (transmitral PWD or TDI) • IVC dilation and/or elevated systolic PAP
Cardiac tamponade	• Considerable pericardial effusion • Respiratory variation of transmitral PWD pattern • RV dilation with interventricular septum shift • Diastolic RV and/or right atrial collapse • Dilated and noncollapsible IVC
Pulmonary embolism or acute cor pulmonale	• RV dilation and dysfunction ("McConnell's sign"[a]) • Elevation of mean and systolic PAP • Meso-systolic notch with transpulmonary PWD • RV failure secondary to high PEEP

Abbreviations: IVC = inferior vena cava; LV = left ventricle; PAP = pulmonary artery pressure; PEEP = positive end-expiratory pressures; PWD = pulsed wave Doppler; TDI = tissue Doppler imaging.

[a]McConnell's sign: depressed contractility of RV free wall compared to RV apex. Common finding in case of pulmonary embolism.

TABLE 2 Possible echocardiographic characteristics of acute myocarditis

Echocardiographic parameters	Typical findings
LV dimensions	Either normal or increased
LV septal thickness	Either normal or increased (transient LV pseudohypertrophy)
LV systolic function	• LV diffuse hypokinesis • Patchy LV dysfunction (not corresponding coronary flow distribution or ECG anomalies) • Normal LV EF • Reduced LV strain by STE (segmental localization with bull's eye)
LV diastolic function	Common LV diastolic dysfunction (↓ E/A, ↑ E/E′)
Right ventricle	Sometimes RV global systolic dysfunction with or without RV dilation
Pericardium	Pericardial effusion Brightness of myo-pericardium

Abbreviations: EF = ejection fraction; LV = left ventricle; STE = speckle tracking echocardiography.

woman who developed acute myocarditis diagnosed, after exclusion of coronary disease and TTE findings consistent with acute myocarditis (increased wall thickness, diffuse echo-bright myocardial appearance and diffuse LV hypokinesis, with LVEF 40%), by CMR as increased wall thickness with diffuse biventricular hypokinesis and signs of marked biventricular myocardial interstitial edema by T2-mapping sequences and late gadolinium enhancement.[22]

However, in critical patients and in this reduced healthcare services emergency status, CMR and myocardial biopsy could not be promptly available and coronary angiography would put unstable patients at higher risks. Therefore, an echocardiographic study could be used as the first investigation tool to orient diagnosis with high-sensitive but less specific findings, that are listed in Table 2.[30] Additionally, LV longitudinal strain proved to correlate with myocardial edema detected by CMR in patients with acute myocarditis [31] and its bull's eye representation shows the localization of myocardial damage, with GLS typically reducing from endocardial to epicardial layer (Figure 1).

4 | ACUTE HEART FAILURE

In patients with COVID-19, cardiovascular involvement leading to cardiac dysfunction and failure is not uncommon, probably due to systemic inflammatory response, innate immune-related myocardial damage, or respiratory-induced hypoxemia during COVID-19 progression.[16,32] This also affects patients without history of chronic HF, which could rapidly develop severe HF and die for sudden cardiac death after COVID-19 infection. In fact, the most likely mechanism of HF in these patients is consequent to lung

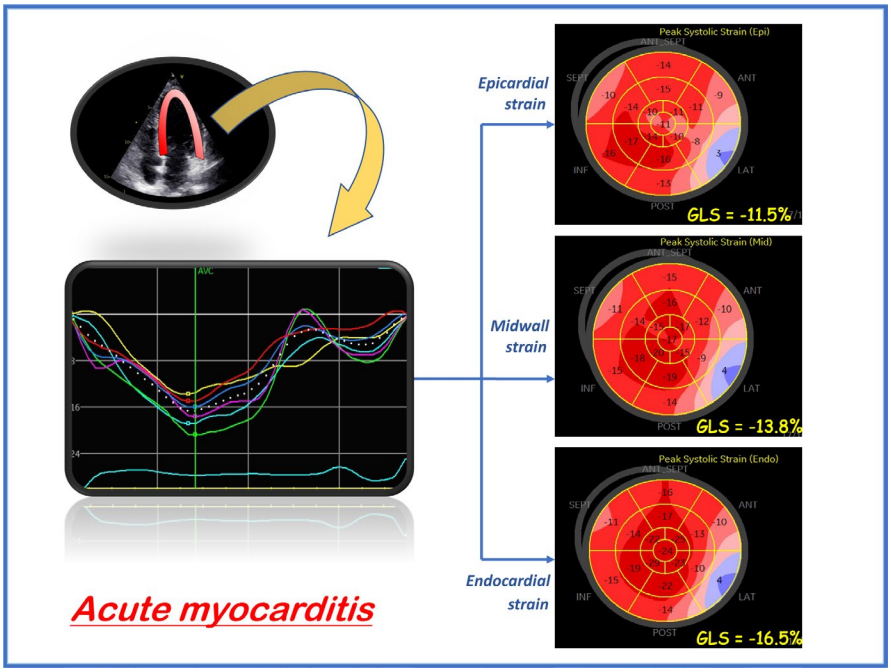

FIGURE 1 Example of speckle tracking analysis in acute myocarditis, showing a regional area of severe reduction of global longitudinal strain (GLS), and a typical three-layer variation (GLS worsening from endocardial to epicardial layer)

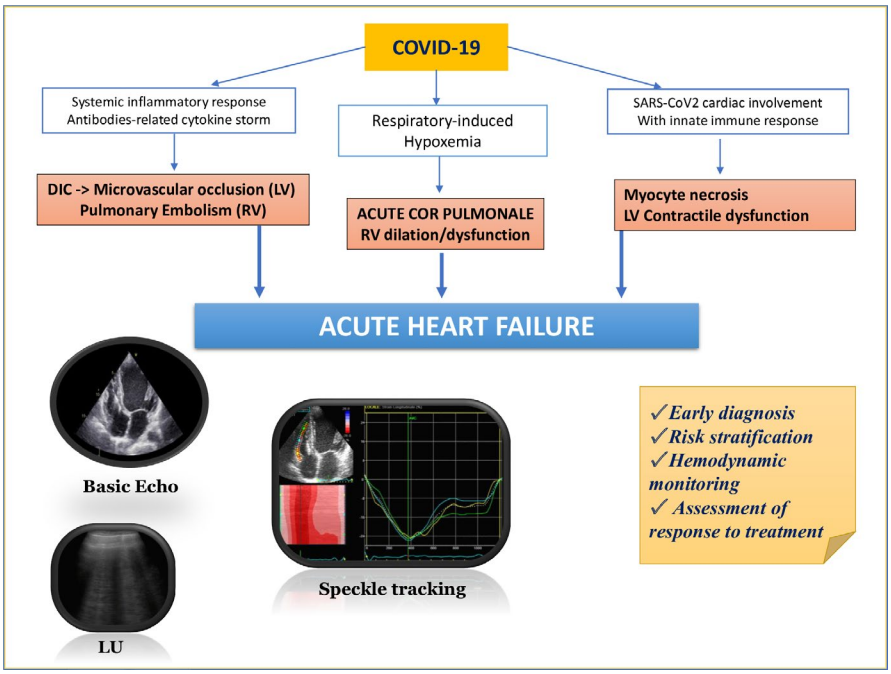

FIGURE 2 Pathophysiologic hypotheses and usefulness of a comprehensive diagnostic and prognostic approach [basic and advanced echocardiography + lung ultrasound] for acute heart failure in COVID-19 patients. DIC = disseminated intravascular coagulation; LU = lung ultrasound; LV = left ventricle; RV = right ventricle

disease, leading to oxygen supply/demand imbalance, high pulmonary vascular resistance, and PH, eventually causing acute RV overload and failure.[33]

Therefore, in patients hospitalized for COVID-19, LV and RV structure and function changes and cardiac filling pressures should be assessed. For this purpose, beyond basic echocardiographic parameters, additive tools could represent a strong support for clinicians: Firstly, lung ultrasound (LU) offers important information on acute hemodynamic changes in HF, through dynamic signs (ie, homogenous and diffuse B-lines and bilateral pleural effusion), allowing a quick diagnosis and monitoring of acute pulmonary edema.[34] In this setting, it is important to differentiate between the typical LU signs of pulmonary edema and of COVID-19 leading to ARDS (ie, congestion, coalescent B-lines, the so-called "white lung," air bronchogram)[35]: Even if clinical presentation are crucial for differential diagnosis, there are some notable differences between cardiogenic and COVID-19 B-lines: unlike the first, B-lines have a patchy and nongravity-related distribution, are commonly separated and coalescent, and present well-defined spared areas in COVID-19 pneumonia[36]. However, sometimes these patients could show overlap patterns; thus, LU results should be taken cautiously.[37]

In addition, offline speckle tracking analysis provides noninvasive early detection of myocardial damage in patients with HF, studying the deformation of all cardiac chambers, which revealed to have a correlation with LV filling pressures.[38-41]

A comprehensive evaluation of these patients, including clinical, basic, and advanced ultrasonographic parameters, could be useful for an accurate prognostic assessment: In fact, it has been demonstrated that, in patients with acute HF, underlying pathologies, changes in renal function and TTE findings are associated with mortality.[42] Moreover, a recent study by Li et al investigating inhospital mortality in 120 patients with COVID-19 has shown RV dilation and dysfunction in nonsurvivors and found global right ventricular longitudinal strain (RVLS) < 23% to be an independent predictor of mortality with multivariate analysis (AUC = 0.87, $P < .001$).[43]

As regards treatment, ACC guidance for COVID19 advises the clinicians to be careful in using intravenous fluid therapy in patients with HF or volume overload conditions, since fluid administration for viral infection should be used cautiously and attentively monitored.[13,44] Furthermore, the response to HF treatment should be continuously assessed since, in case of failing pharmacological therapy for HF, a timely transition to more aggressive treatment with extracorporeal membrane oxygenation (ECMO) or circulatory assistance devices, such as intra-aortic balloon pump, could be necessary to assist hemodynamics and improve outcome.[9] Therefore, focused but thorough and, if necessary, repeat ultrasound examination is important in COVID-19 patients with possible or overt HF not only for diagnosis and prognosis, but also to assess patients' clinical status and response to therapy (Figure 2).

5 | SEPSIS

In a recent study by Zhou et al involving 191 COVID-19 subjects, a half of their patients finally developed sepsis at a median of 9 days. In particular, sepsis was the most frequently observed complication, followed by respiratory failure, ARDS, HF, and septic shock.[45]

Sepsis is caused by exaggerate host response to infection leading to life-threatening multiorgan failure (MOF), recognized with altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities, or low blood pressure. This could lead to septic shock, that is persisting hypotension despite volume resuscitation and hemodynamic instability requiring vasopressor treatment.[46] The first diagnostic approach could be done with sequential organ failure assessment (SOFA) score, which is a good diagnostic marker for sepsis and septic shock, reflecting the degree of MOF.[47]

However, several authors investigated the role of echocardiography for the study of septic shock, which could offer important information on cardiac loss of function due to sepsis. It has been shown that in these patients a certain grade of diastolic dysfunction could be detected by power and tissue Doppler imaging (TDI): The most used parameter is transmitral E/E′ ratio, with a lack of defined cutoff value; however, a higher proportion of diastolic dysfunction with values of E′ < 8-10 cm/s was found to be independently associated with higher risk of death[48] (odds ratio, OR 7.7 of ICU mortality in a study by Mourad et al[49]). Moreover, advanced echocardiography has shown good results for the evaluation of patients with septic shock: Orde et al demonstrated the superior value of STE over basic echocardiography in 60 patients with septic shock, detecting LV strain and RV strain impairment in 69% and 72% of patients, respectively, with only 33% patients having reduced LV ejection fraction (EF) and 32% having RV dysfunction based on conventional echocardiography (tricuspid annular plane systolic excursion, TDI s′ wave, RV fractional area change); moreover, they found RV-free wall strain to be moderately associated with 6-month mortality (OR 1.1, AUC 0.68).[50] Afterward, Chang et al proposed a cutoff of GLS absolute value <13% as the best marker of ICU mortality in septic shock.[51]

The use of echocardiography in this clinical setting could help clinicians in early recognizing myocardial damage due to COVID-derived sepsis.

6 | CRITICAL PATIENTS: FOCUS ON THE RIGHT VENTRICLE

According to common ARDS management,[52] WHO indications emphasize treatment with mechanical ventilation with high PEEP and prone positioning for COVID-19 patients who finally develop ARDS.[53] Nevertheless, the potential harmful effect of high PEEP,[54] in means of end-inspiratory overdistension leading to lung injury and higher pulmonary vascular resistance, should not be overlooked[55]; in fact, WHO recommends limiting this therapeutic strategy to moderate or severe ARDS and to responders.[53] Owing to the close lung-heart interaction, this effect could also lead to acute cor pulmonale, causing RV systolic and diastolic overload.[56] This is clearly shown by TTE as new RV dilation, end-systole paradoxical septal movement, and reduced RV overall function[57,58] and is characterized by poor prognosis due to circulatory failure.[59,60] In the retrospective study by Zhou et al investigating the clinical course of 191 SARS-CoV-2 patients, 17% of patients required mechanical ventilation, 97% of whom died.[45] Whether it was due to the end-stage disease or to ventilation-induced heart and/or lung complications is not known.

However, further evidence on this topic is timely needed in order improve the therapeutic management of COVID-19 patients.

Transesophageal echocardiography (TOE) has been widely used for monitoring ventilated patients in the last years. In fact, in these patients TTE is often challenging, due to the position of patients with lower mobility, and the poor acoustic window due to hyperinflated lungs. However, the development of new indices for the assessment of LV systolic/diastolic function and filling pressures by TDI, and of RV dimension and function, have led to reconsider the use of serial TTE for noninvasive monitoring of ventilated patients.[61]

Thanks to the widespread use of echocardiography in ICU, RV dimension and function could be closely monitored in these patients.[62,63] As Repessé et al suggested, a RV-driven adjustment of PEEP levels could help intensivists to find a balance between risks

and benefits of this therapeutic approach (ie, lung recruitment and overdistension),[56] thus preventing early mortality for ventilation-induced RV failure. LU could be an important ally also in this context.[64] In addition, RV myocardial performance index (RV MPI), also known as "Tei index" determined on trans-tricuspid velocities by pulsed wave or tissue Doppler imaging, is a high-sensitive index for the diagnosis of RV dysfunction.[65] It could be used for monitoring high-PEEP response in intubated patients, since it has shown to predict RV damage caused by mechanical ventilation[66] and high PEEPs.[67]

Moreover, it seems that severe COVID-19 infection could precipitate predisposition to acute venous thromboembolism, as shown in recent case reports,[68,69] and highlighted by *Dolhnikoff* et al on autoptic evidence,[70] which could lead to further deterioration of patients' clinical status. Beyond clinical suspicion, echocardiographic signs of RV overload (ie, pulmonary ejection acceleration time < 60 ms with a peak systolic tricuspid valve gradient < 60 mm Hg, or with depressed contractility of RV free wall compared to RV apex, the so-called *McConnell's sign*) could suggest the diagnosis of acute PE with high positive predictive value.[71] This should aid in providing early full anticoagulation therapy to these patients, avoiding long waiting times due to computed tomography (CT) scarce availability, and repeat CT scan with further radiation exposure.

Therefore, serially performing TTE in critical patients could represent a useful tool to guide airway management and to early recognize possible COVID-19 thromboembolic complications.

7 | THE CHOICE OF THE RIGHT DEVICE AND TECHNIQUE

Due to the need of balancing between risks of contagion for and benefits for patients, the common indications and modalities to perform echocardiography should be reconsidered in COVID-19 patients; therefore, the choices for the use of portable devices and transesophageal echocardiography should be tailored on the single patients depending on his clinical status and cardiovascular conditions.

Portable machines have the advantage to be easier to clean and to cover than common echocardiographic machines and could be preferred for a basic assessment of biventricular function, valvular disease, and pericardial effusion.[13] However, in patients with suspected or known cardiac impairment or in uncertain clinical cases, the quality of the TTE evaluation could be sacrificed using portable echocardiographers. As an alternative, we propose the use of a dedicated echocardiographic machine in COVID units which should also be sanitized after use, thus combining safety and effectiveness. In addition, for difficult cases or severe cardiac dysfunction, we suggest performing a comprehensive image acquisition with offline measurement of complex and advanced parameters in a safe environment and at clinician time discretion, in order to obtain a complete echocardiographic examination reducing the time of exposure to SARS-CoV-2.

As regards TOE, there are several clinical settings in which this would provide more accurate information than TTE, such as a better anatomic insight into valvular heart disease, exclusion of vegetations on valvular structures or central venous catheters, or intracardiac shunts, assessment of RV function in ventilated patients, poor quality of bedside TTE images.

However, TOE might be stressful to COVID-19 patients and, as suggested by EACVI consensus document, it should be avoided in most patients with ongoing COVID-19. Moreover, the risk of contamination of healthcare workers and surfaces is very high during the procedure due to droplets and aerosols containing virus, therefore, in each case of performing TOE to suspected or known COVID-19 patients, wearing advanced personal protective equipment (filtering face piece particulate class-3 (FFP3) respirator, gown, gloves, and eye protection) is compulsory, and a dedicated transoesophageal probe in COVID units would be required. All this given, we suggest to carefully consider each indication for TOE and procrastinate them if inappropriate.

Usefulness of echocardiography for ECMO monitoring is a widely discussed topic in the recent times. In fact, TTE or TOE have a pivotal role not only for the evaluation of biventricular function pre-, during, and post-ECMO and a serial assessment of patient's loading conditions, which could help therapeutic management and decision-making, but also for anatomic assessment of the correct positioning of the device, and the presence of complications such as intracardiac thrombotic formations. The latter application could be of great importance in COVID-19 patients for their known pro-thrombotic state, as shown by Schmiady et al in a case-report describing a young patient with severe COVID-19 respiratory consequences requiring veno-venous ECMO assistance, who developed multiple thrombi, including in inferior vena cava (IVC) and right atrium, and underwent TOE-guided percutaneous thrombectomy. TOE would possibly offer most reliable information for this purpose, but the previous discussed concerns should be considered and the use of TTE should be preferred when applicable.[72]

8 | CONCLUSIONS

Echocardiography is a precious tool in the hands of an expert operator to improve diagnostic procedures and therapeutic management of patients with COVID-19, aiding clinicians in early recognizing subtle cardiac damage and providing adequate treatment for SARS-CoV-2–infected subjects. The use of TTE could change the diagnostic workup of acute coronary syndromes, myocarditis, acute left or right ventricular failure, and secondary myocardial damage due to sepsis or mechanical ventilation, allowing noninvasive assessment and monitoring.

However, the prevention of COVID-19 spread should not be forgotten; therefore, it is crucial to bear in mind the mandatory use of personal protective equipment (with the use of FFP3 respirator, gown, gloves, and eye protection to face COVID-19 ill),[12] and the safety recommendations to perform echocardiography at the time

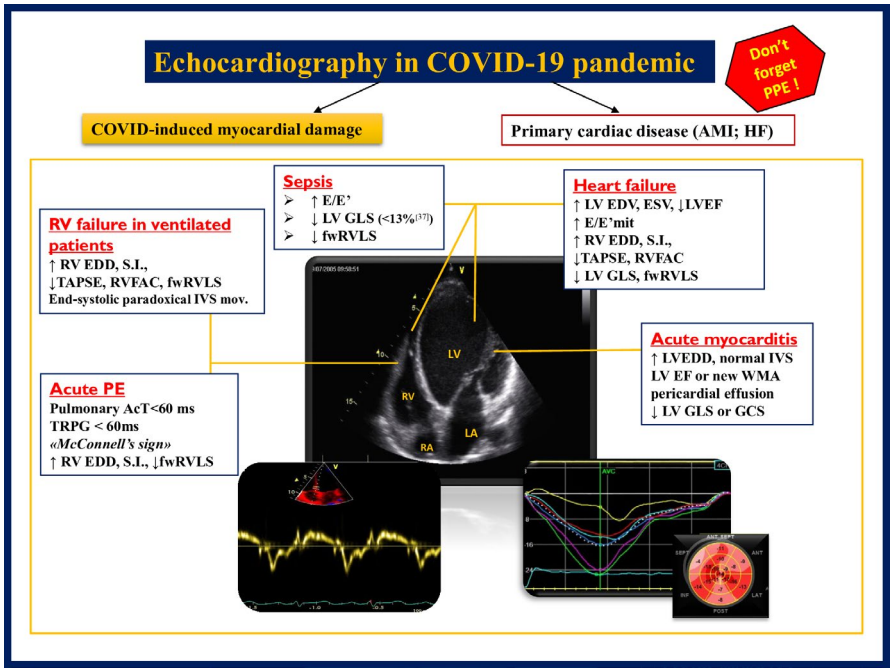

FIGURE 3 Reference indices for the use of echocardiography in COVID-19 patients in different possible clinical scenarios. McConnell's sign = echocardiographic evidence of depressed contractility of RV free wall compared to RV apex. AcT = right ventricular outflow Doppler acceleration time; AMI = acute myocardial infarction; EDV = end-diastolic volume; EF = ejection fraction; ESV = end-systolic volume; GCS = global circumferential strain; GLS = global longitudinal strain; fwRVLS = free wall right ventricular longitudinal strain; HF = heart failure; IVS = interventricular septum; LA = left atrium; LV = left ventricle; PPE = personal protective equipment; RA = right atrium; RV = right ventricle; RVFAC = right ventricular fractional area change; SI = sphericity index; TAPSE = tricuspid annular plane systolic excursion; TRPG = tricuspid regurgitant pulmonary gradient; WMA = wall-motion abnormalities

of COVID outbreak. Figure 3 resumes the parameters to assess for different suitable applications of echocardiography in COVID-19 patients.

CONFLICT OF INTEREST

No disclosures.

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