Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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REVIEW

Myocarditis and Cardiac Complications Associated With COVID-19 and mRNA Vaccination: A Pragmatic Narrative Review to Guide Clinical Practice

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Coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus is likely to remain endemic globally despite widespread vaccination. There is increasing concern for myocardial involvement and ensuing cardiac complications due to COVID-19, however, the available evidence suggests these risks are low. Pandemic publishing has resulted in rapid manuscript availability though pre-print servers. Subsequent article retractions, a lack of standardised definitions, over-reliance on isolated troponin elevation and the heterogeneity of studied patient groups (i.e. severe vs. symptomatic vs all infections) resulted in early concern for high rates of myocarditis in patients with and recovering from COVID-19. The estimated incidence of myocarditis in COVID-19 infection is 11 cases per 100,000 infections compared with an estimated 2.7 cases per 100,000 persons following mRNA vaccination. For substantiated cases, the clinical course of myocarditis related to COVID-19 or mRNA vaccination appears mild and self-limiting, with reports of severe/fulminant myocarditis being rare. There is limited data available on the management of myocarditis in these settings.

Clinical guidance for appropriate use of cardiac investigations and monitoring in COVID-19 is needed for effective risk stratification and efficient use of cardiac resources in Australia. An amalgamation of national and international position statements and guidelines is helpful for guiding clinical practice. This paper reviews the current available evidence and guidelines and provides a summary of the risks and potential use of cardiac investigations and monitoring for patients with COVID-19.

Keywords COVID-19 • SARS-CoV-2 • Coronavirus • mRNA • Vaccination • Myocarditis • Pericarditis • Troponin • Biomarker • Echocardiography • Cardiac magnetic resonance imaging

Introduction

The severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) is approaching worldwide endemic status. The clinical manifestations of Coronavirus disease (COVID-19), particularly the potential cardiac complications such as myocarditis, heart failure and cardiovascular death, are feared, particularly in the context of media reports of sudden

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death. However, the true incidence of these outcomes has been difficult to quantify, as estimates of global case numbers are limited by testing protocols and reporting activity [1]. Although potentially serious, clinically significant cardiac complications are relatively infrequent. While cardiac complications appear more common following COVID-19 infection rather than following vaccination [2], the incidence of vaccine-induced complications such as myocarditis can be expected to rise as messenger ribonucleic acid (mRNA) based inoculation becomes omnipresent.

Studies in patients with COVID-19 initially raised concern for high rates of *clinically suspected* myocarditis based on elevated biomarkers, particularly high-sensitivity cardiac troponin [3]. Similarly, early imaging studies reported alarming rates of myocarditis in patients with past COVID-19 infection [4]. The availability of non-peer-reviewed manuscripts on pre-print servers and the rapid rate of publication acceptance during the pandemic, the prevalence of troponin elevation of questionable clinical significance, and non-specific cardiac magnetic resonance (CMR) findings, have contributed to an initially overinflated estimation of the incidence and risk of myocarditis. Current data suggests that myocarditis is an uncommon complication of COVID-19 [5].

Less than 2 years after identification of the virus, global COVID-19 experience remains relatively immature. At the onset of the COVID-19 pandemic, several national and international guidelines and position statements were developed to guide the investigation, monitoring and management of patients with suspected cardiac complications. However, established guidelines have been principally based on expert opinion and observational or case series data. The accumulation of prospective global data and increasing local experience affords the opportunity to re-evaluate the true incidence of cardiac complications of COVID-19 and mRNA vaccination to guide clinical practice. This review was conducted to evaluate the incidence of substantiated cardiac complications of COVID-19 infection and mRNA vaccination in adult patients to provide evidence to inform and risk stratify allocations of community and hospital-based cardiology resources and services. Evidence on the epidemiology, investigations and management of myocarditis are summarised and recommendations for cardiac investigations are provided and have been drawn from robust original studies, available meta-analyses and position statements from international cardiology societies [5–12].

We conducted a pragmatic narrative review of the literature using PubMed with the generic terms "coronavirus", "SARS-CoV-2", "COVID-19" and "cardiology". Specific search terms included "troponin", "biomarker", "electrocardiography", "telemetry", "imaging", "echocardiography", "cardiac magnetic resonance", "arrhythmia", "myocarditis", "heart failure", "hospitalisation" and "mortality". Reference lists of papers of interest and position statements were also reviewed. The Cardiac Society of Australia and New Zealand (CSANZ) position statements, guidance from The Australian Technical Advisory Group on Immunisation (ATAGI), European Society of Cardiology (ESC) guidelines, and statements and recommendations endorsed by the American College of Cardiology (ACC) and American Heart Association (AHA) were reviewed.

Spectrum of Cardiac Complications of COVID-19

The angiotensin converting enzyme 2 receptor, thought to be the viral entry point of SARS-CoV-2, is highly distributed in pulmonary epithelium in addition to systemic organs including the myocardium [13]. Following infection, it is theorised that myocardial injury characterised by elevated biomarkers (i.e., troponin) may result from direct viral damage. However, it is more likely that systemic inflammation or stress related to COVID-19 infection drives myocardial injury [14], where the presence of pre-existing cardiac disease often predicts worse prognosis [15].

Cardiac troponin is elevated in a high proportion of patients with COVID-19 [16], however, interpretation within clinical context is required. Though strongly associated with outcome, particularly in patients with cardiovascular disease and risk factors [15], elevated troponin is more likely a marker of disease severity and the end-organ effects of systemic illness in the majority of cases. Myocardial involvement may range from minor asymptomatic troponin elevation to fulminant myocarditis and heart failure, as described in case reports [17,18]. There appears to be a marginal increase in the risk of arrhythmia, stress cardiomyopathy and myocardial infarction due to plaque instability or supply-demand mismatch (i.e. type 2 myocardial infarction) [19]. Biomarker elevation due to right-heart strain is also expected in cases of COVID-19 pneumonia or pulmonary embolism [17].

Myocarditis Due to COVID-19

Most reports of myocarditis due to COVID-19 are *clinically suspected*, based principally on elevated biomarkers, and are not well validated. Where elevated troponin alone is used as a definition, myocardial injury in the context of COVID-19 is common, with an estimated prevalence up to 40% [16,20]. Although troponin elevation is strongly associated with outcome [16,21], the mechanisms for its release are highly varied [22]. Biomarkers are central to the diagnosis of myocarditis and myocardial injury, however, elevated troponin detected by high-sensitivity assays does not substantiate the diagnosis of myocarditis without supporting clinical or imaging evidence. In most published studies on COVID-19 there is little corroborating data using multimodality imaging, biomarkers and endomyocardial biopsy results. Available data suggests that the pattern of myocardial inflammation is often highly variable [23] with some studies suggesting a macrophage-dominant pattern associated with subclinical left ventricular (LV) dysfunction [24]. Large epidemiological studies estimate the rate of clinically suspected myocarditis related to COVID-19 at 11 cases per

100,000 infections [2], though the criteria for the diagnosis of myocarditis have not been consistently stated. Similarly, there is little data on the rates of myocarditis specifically associated with newer viral variants, such as the Delta and Omicron strains.

Early imaging reports raised concern over the high prevalence of radiological myocarditis on CMR imaging in recovered COVID-19 survivors, present weeks after initial infection [25]. Subsequent CMR studies in health care workers recovered after mild infection have been more reassuring, with similar rates of cardiovascular abnormalities in seropositive compared with seronegative cases [26]. A major limitation to the validity of CMR-based studies has been the lack of concordance with accepted revised Lake Louise CMR criteria for myocarditis, where the presence of late gadolinium enhancement, T1 and T2 criteria on CMR imaging confirms the diagnosis of myocarditis in the appropriate clinical setting [27]. Radiological findings may not specifically represent myocardial involvement of COVID-19 given the lack of baseline imaging prior to infection, limited imaging during the acute infectious period and limited correlation to positive biopsies. Also, co-infection with other viruses (e.g. Influenza A and Respiratory Syncytial Virus) may occur in one fifth of COVID-19 cases [28], and may not have been excluded as the underlying cause of myocardial inflammation. While CMR proven myocardial oedema may be common during the acute phase of illness [29], irreversible myocardial injury as a result of COVID-19 appears to be rare and of limited functional consequence [30]. Furthermore, the short-term clinical significance and long-term outcomes related to these CMR findings has not been established. Endomyocardial biopsies are often unrevealing with non-specific inflammatory changes, whilst autopsy studies suggest that the true prevalence of myocarditis, particularly that of clinical significance [23], is far lower than what is suspected from imaging studies.

The 2013 European Society of Cardiology (ESC) position statement on myocarditis presents diagnostic criteria for clinically suspected myocarditis where endomyocardial biopsy has not been performed [31]. In the absence of angiographically detectable coronary disease, known pre-existing cardiovascular disease or significant extra-cardiac causes, the diagnostic criteria use both clinical features and objective evidence such as raised cardiac biomarkers, changes on ECG or abnormal cardiac imaging [31]. In the setting of COVID-19 infection without a significant history of cardiac disease, there should be a high index of suspicion for myocarditis in patients presenting with acute severe cardiac failure or cardiogenic shock. Recommended investigations in suspected cases of COVID-19 myocarditis are discussed below and presented in Table 1.

Evidence for the management of COVID-19 related myocarditis is limited. General management strategies for myocarditis are established [31] and there are no specific recommendations for the treatment of myocarditis associated with COVID-19 [12,22]. Guideline-directed heart failure therapy is recommended in cases of ventricular dysfunction. Advanced heart failure and mechanical therapies (i.e., extracorporeal membrane oxygenation) are reasonable strategies for unstable patients as a bridge to recovery or cardiac transplant [11]. There is insufficient evidence to recommend antiviral or immunomodulatory therapy (steroids and intravenous immunoglobulin), except when accompanied by significant respiratory involvement where corticosteroids may be of benefit [12]. Following a diagnosis of myocarditis, restriction of physical activity is recommended, and is based on expert opinion. For myocarditis associated with COVID-19 and other aetiologies, the ESC recommend at least 6 months exercise restriction and pre-participation screening prior to return to competitive sport, and make similar suggestions for non-athletes [12,31]. The ACC/AHA guidelines consider return to sport following 3–6 months exercise restriction and normal pre-participation testing, but do not make recommendations specific to myocarditis associated with COVID-19 [32]. Clinical follow-up is at the treating clinician's discretion, but may be guided by severity of myocarditis and other organ involvement, the presence of pre-existing cardiovascular disease, ongoing active issues (i.e. LV dysfunction, arrhythmia) or high-risk features (i.e. high burden of scar/late gadolinium enhancement on CMR).

Myocarditis Due to mRNA Vaccination

The risk of mRNA vaccine induced myocarditis is approximately 2.7 excess cases per 100,000 persons [2]. However, there is a strong bias to young males aged under 30 years, with incidence rates of 10.7 cases per 100,000 [33] and up to 15.9 cases per 100,000 persons aged 16–19 [34]. Most cases of myocarditis occur within 2–3 days [33,35], with the majority occurring within 7, days, most frequently after the second vaccine dose [33,34], but may occur after a second exposure in those receiving a first vaccine dose after previous viral infection. There are differences in the rate of reported myocarditis with variations of mRNA-based vaccines [36], however, the precise mechanism for mRNA vaccination related myocarditis is unclear and is under investigation [35]. Non-mRNA vaccines have not been associated with an increased risk of myocarditis/pericarditis.

The diagnosis of vaccine induced myocarditis should be established clinically with an appropriate temporal relationship to vaccination and supportive investigations. A 12-lead ECG, chest X-ray and high-sensitivity troponin should be obtained. Whilst ECG and chest X-ray findings may be non-specific, a modest elevation of troponin is expected in myocarditis [37]. Pericarditis has also been reported, and without the overlap syndrome of myopericarditis, may present with normal troponin and exhibit classic ECG findings of PR segment depression and diffuse ST segment elevation. Non-invasive imaging with transthoracic echocardiography is reasonable to evaluate cardiac function and exclude complications such as pericardial effusion, where supported by

Table 1 **Summary of clinical investigations recommended in suspected/positive COVID-19 cases.**

	CSANZ	ESC [5,11,12]	AHA/ACC/ASE/SCAI	Suggested Approach
Bedside Tests				
High-sensitivity troponin	On admission and daily if elevated [8] as screening for suspected myocarditis and acute HF.	Not routine. Suspected type 1 MI or LV dysfunction.	Routine if suspected cardiac involvement [61]. Only if MI clinically suspected [43].	Measure for suspected acute coronary syndrome, new HF or LV dysfunction, and in suspected cases of myocarditis.
B-type natriuretic peptide	Consider adjunctive [8].	Only when HF is suspected on clinical grounds.	If HF suspected suspected [43].	Measure for cases of suspected HF.
Electrocardiogram	On admission and repeat second daily if troponin elevated [8,10].	Critically ill patients or in clinically indicated cases. On QT-prolonging drugs.	Routine if suspected cardiac involvement [61].	Perform in symptomatic patients requiring hospital admission, those with cardiovascular disease and those in whom QT-prolonging drugs are to be used.
Continuous cardiac monitoring (telemetry)	Elevated troponin [8] or at risk of QT prolongation [10].	If QTc prolonged ≥500 ms or increased by ≥60 ms on QT prolonging medication. Febrile Brugada Syndrome patients.	In those at risk of clinical deterioration, cardiovascular risk factors or on essential QTc prolonging medications [47]. Consider use of mobile telemetry units.	Monitor those at risk of arrhythmia, including LV dysfunction, HF, myocarditis, MI.
Non-Invasive Imaging				
Chest X-ray	On admission [8].	Heart failure cases.	Routine if suspected cardiac involvement [61].	Hospitalised symptomatic patients.
Echocardiography	Suspicion of heart failure/ myocarditis, significant arrhythmias, significant ECG changes, haemodynamic instability, previous heart disease with shock, prior to extracorporeal membrane oxygenation, rising troponin over 3 days, significant pericardial effusion [8,9]. Targeted study using POCUS where appropriate.	Significantly elevated troponin (>5 x ULN) and not consistent with MI, acute HF/shock, significantly elevated BNP, malignant ventricular arrhythmia. Targeted study using POCUS where appropriate.	Restrict unless expected to affect outcome [53]. Targeted study (consider POCUS) as first line. Follow up study recommended at 2-6 months for those with LV dysfunction during the acute phase [61].	Indicated in suspected HF or myocarditis, significant arrhythmias or ECG changes, more than mild pericardial effusion on chest CT, haemodynamic instability or previous heart disease with shock. Consider POCUS as first-line imaging modality.
Cardiac magnetic resonance imaging	Not recommended in COVID-19 [8]. Consider in myocarditis post mRNA vaccine as guided by cardiologist [38].	Suspected acute myocarditis with clinical signs or symptoms not explained by other diagnostic tools.	Consider in myocarditis or stress cardiomyopathy in new LV dysfunction with non-dilated LV and a non-coronary distribution of wall motion abnormalities, with no known cardiomyopathy. Useful for MINOCA [61].	Avoid in COVID-19. Reasonable to confirm myocarditis associated with mRNA vaccination in those with significantly elevated troponin elevation or ECG changes. LGE may inform risk of arrhythmia.

Table 1. (continued).

	CSANZ	ESC [5,11,12]	AHA/ACC/ASE/SCAI	Suggested Approach
Interventional Procedures				
Angiography (including CT coronary angiography)	STEMI when angiography determines outcome. Consider fibrinolysis where appropriate. Delay in stable NSTEACS, consider angiography for very high-risk or unstable cases. CT coronary angiography can be considered for select patients [6].	STEMI indication. Consider in cardiogenic shock. Angiography <24 hrs in very high-risk NSTEACS. Await two negative swab results within 48 hrs and no clinical suspicion of COVID-19 for other cases. Consider as may expedite risk stratification and facilitate early discharge. Use COVID-19 dedicated laboratory.	Primary PCI should remain standard of care for STEMI or very high-risk NSTEACS in PCI-capable centres [62]. Fibrinolysis may be preferable for STEMI in stable patients [63] non-PCI capable centres [62]. Delay angiography in stable NSTEACS [62,63] Consider CT coronary angiography [61].	Perform in STEMI where angiography will significantly alter outcome. Consider fibrinolysis in appropriately selected patients. Defer in NSTEACS if no high-risk features.
Pericardiocentesis	No formal recommendation.	No formal indications. Consider bedside procedure where possible.	No formal recommendation.	Indicated for treatment of tamponade where appropriate, where expectant management is likely to result in preventable poor outcome.
Myocardial biopsy	Not recommended [8].	Not routinely recommended. Consider in refractory or severe heart failure if determines management.	No formal recommendation.	Not recommended to confirm myocarditis.
Elective echocardiography, angiography and electrophysiology studies	Delay or postpone in stable patients based on clinical urgency and triage system [6,7,9,10].	Avoid elective procedures.	Defer in/outpatient investigations and procedures for stable patients [62,63].	Deferral of elective procedures as per local policy.

Abbreviations: CSANZ, Cardiac Society of Australia and New Zealand; ESC, European Society of Cardiology; AHA, American Heart Association; ACC, American College of Cardiology; ASE, American Society of Echocardiography; SCAI, Society for Cardiovascular Angiography and Interventions; MI, myocardial infarction; LV, left ventricular; HF, heart failure; ECG, electrocardiogram; POCUS, point-of-care ultrasound; BNP, brain natriuretic peptide; CT, computed tomography; MINOCA, myocardial infarction with non-obstructive coronary arteries; LGE, late gadolinium enhancement; STEMI, ST-elevation myocardial infarction; NSTEACs, non-ST elevation acute coronary syndromes; PCI, percutaneous coronary intervention.

bedside investigations. Left ventricular function is often preserved or only mildly impaired [35]. Vaccine associated myocarditis is reportable to the Therapeutic Goods Administration (TGA), and unlike cases of myocarditis suspected to be due to COVID-19, there is no infection risk and advanced imaging with CMR may be helpful to establish the diagnosis. Hospitalisation for confirmed cases is recommended until symptom resolution and identification of peak biomarkers [38], although the clinical presentation is usually mild and self-limiting [34]. Importantly, the risk of myocarditis, pericarditis and arrhythmia appears higher after COVID-19 infection than vaccination [39]. Figure 1 demonstrates typical findings in a case of acute mRNA vaccine induced myopericarditis.

The guidance statement published by the Australian Technical Advisory Group on Immunisation (ATAGI) is endorsed by the CSANZ and several other governing medical bodies, and recommends that the mRNA vaccine can be received with precautions for most patients regardless of the history of pre-existing cardiovascular disease [38]. In cases of myocarditis following mRNA vaccination, further doses of the mRNA vaccine are not recommended, with alternate non-mRNA formulations being preferred. Myocarditis due to other causes is not a contraindication to mRNA vaccination following recovery. Post-vaccination pericarditis is not a preclusion to further doses, depending on normal investigation results and a recovery period of at least 6 weeks. Management of patients with confirmed myocarditis in the setting of a preceding mRNA vaccination is largely supportive. Cases should be treated as for myocarditis from other causes, with guideline directed heart failure therapies if indicated, exercise restriction (as aforementioned) and cardiology follow-up.

Cardiac Biomarker Testing in COVID-19

Cardiac biomarkers are elevated in up to half of patients admitted with COVID-19 [40] and although are associated with increasing illness severity [15,41], the interpretation of troponin and B-type natriuretic peptide (BNP) should be made in clinical context.

Troponin: Depending on the cohort studied, high-sensitivity troponin is elevated in as many as 40% of hospitalised patients with COVID-19 [16,20], however, most cases of infection do not require inpatient admission. Any magnitude of troponin elevation is associated with increased risk of adverse outcome [15,16,21], with higher levels seen in patients with pre-existing cardiovascular disease or risk factors. There are several mechanisms of troponin elevation, which most commonly reflects overall disease severity and secondary myocardial injury. The rise in troponin often mirrors other acute phase reactants and markers of end organ dysfunction such as lactate dehydrogenase, ferritin, interleukin-6 and D-dimer [42].

Troponin elevation may reflect direct myocardial injury or represent sequelae of systemic inflammation and critical illness. Although it is a specific marker of myocyte injury, it is not specific for myocarditis or myocardial infarction in the absence of a supporting clinical syndrome. Small elevations in troponin are expected, particularly in older patients or those with pre-existing cardiovascular disease. Routine troponin measurement is not supported by either the ESC [11] or ACC [43], where it is reserved for those patients where acute type 1 myocardial infarction is suspected, or in cases of likely myocarditis or acute heart failure. The CSANZ do recommend a routine screening troponin on admission for all patients with COVID-19 to screen for cardiomyopathy or myocarditis [8], despite there being little evidence that unselected testing changes management [11].

BNP: Serum BNP is elevated in a high proportion of patients hospitalised with COVID-19 and predicts mortality [40]. Exclusion of acutely decompensated heart failure and prognostication in pulmonary embolism are the strongest indications for measurement. However, an elevated BNP represents the acute haemodynamic stress of COVID-19 and right heart strain in the setting of pneumonia or pulmonary embolism. Although BNP does risk stratify patients with COVID-19 [41], routine measurement is not recommended as there is limited evidence it alters clinical outcomes [11].

Cardiac Monitoring and Electrocardiography in COVID-19

Arrhythmias are common in COVID-19, being reported in up to 20% of hospitalised patients [15]. The vast majority (82%) are benign, consisting of transient atrial fibrillation, atrial flutter, and supraventricular tachycardia [44]. Life-threatening arrhythmias, such as ventricular tachycardia and ventricular fibrillation, are uncommon (4-6%) [15] but are predictably associated with the severity of illness and with elevated cardiac biomarkers and LV dysfunction [15,44–46]. Most life-threatening arrhythmias occur in critically unwell patients on mechanical ventilation, or with haemodynamic or biochemical derangement [44]. Continuous cardiac monitoring is reasonable in patients with COVID-19 who are critically unwell or those at risk of deterioration, such as those with significant pre-existing cardiovascular disease [47].

An admission 12-lead ECG is recommended for patients hospitalised with symptomatic infection. Any abnormality on 12-lead ECG is predictive of outcome in symptomatic patients admitted with COVID-19 [48]. Although the QTc interval should be monitored for those exposed to QT prolonging medications such as antimicrobial therapy and antiarrhythmics [10,44], a prolonged QRS duration or the presence of a left bundle branch block appear to be the most predictive independent risk factors for mortality [48].

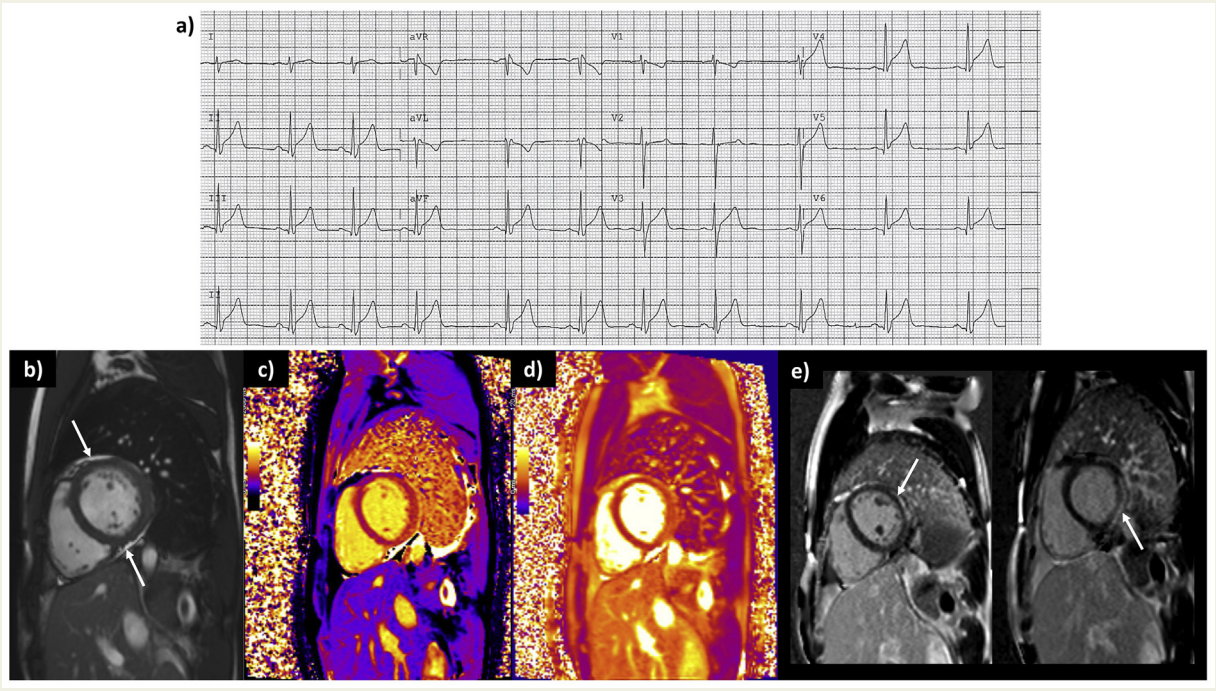

Figure 1 Electrocardiogram and cardiac resonance imaging in an example case of myocarditis following mRNA vaccine. A 16-year-old male presented with typical central chest pain with onset 2 days post second dose of mRNA vaccination. The ECG was consistent with myopericarditis with supporting peak troponin I of 19,322 ng/L. Non-sustained ventricular tachycardia was recorded on telemetry. Echocardiography demonstrated normal LV size with mildly reduced systolic function (ejection fraction 51%) with mid-septal regional wall motion abnormalities. Global longitudinal strain was 18.2%. Inpatient CMR identified a small pericardial effusion and myocardial oedema with mid-wall LGE confirming acute myocarditis. Though there were no preceding viral symptoms, a viral screen for other causes was performed and was negative.

a) 12-lead ECG demonstrating myopericarditis with diffuse ST segment elevation and PR depression.
b) Short axis CMR imaging at the mid left ventricular level demonstrating pericardial effusion (arrows).
c) Native T1 mapping showing elevated values in the lateral segments consistent with myocardial inflammation. Normal T1 values were identified in the remote myocardium.
d) T2 mapping showing elevated T2 values in the lateral segments consistent with myocardial oedema. Normal T2 values were identified in the remote myocardium.
e) Late gadolinium enhancement images at basal and mid ventricular levels showing a sub-epicardial to mid-wall pattern of regional fibrosis, as typically seen in myocarditis (arrows).

Abbreviations: ECG, electrocardiograph; CMR, cardiac magnetic resonance; LV, left ventricular; LGE, late gadolinium enhancement.

Non-Invasive Cardiac Imaging in COVID-19

Echocardiography: Non-invasive cardiac imaging is useful in evaluating patients with COVID-19 who have clinical or biochemical suggestion of cardiac involvement and may assist in establishing the diagnosis of myocardial complications such as ventricular dysfunction and myocarditis. In a global prospective survey of echocardiography in patients with presumed or confirmed COVID-19, an abnormal study was common in those with a clinical indication for echocardiography, despite lacking pre-existing cardiovascular disease (46%) [49]. However, these were cases for which imaging was clinically indicated and likely overestimates the true community prevalence. The strongest predictors of LV dysfunction are abnormal biomarkers (troponin and BNP), whereas right ventricular function is more closely related to illness severity. In unselected patients, the detection of clinically relevant findings on echocardiography appears to be around 24%, and is less frequent in those without known cardiovascular disease (14%) and elevated biomarkers [50]. In hospitalised patients, the absence of biomarker elevation is reassuring, with no urgent echocardiogram findings in 95.1% of ward-based patients and 91.3% of those admitted to intensive care [50]. Abnormal global longitudinal strain (GLS) and indices of right heart function were predictive of COVID-19 morbidity [51].

Whilst echocardiography provides incremental prognostic information, exposure risks (staff and equipment) must be weighed against the utility of the test, as routine echocardiography in unselected patients may have limited clinical utility. Despite the prevalence of abnormal findings, the

echocardiogram may only change management (disease-specific therapy, level of care and haemodynamic support) in a select number of cases [49]. The absence of positive biomarkers is reassuring and may serve as an appropriate gatekeeper, supporting the deferral of non-urgent imaging until infection transmission risk subsides [52].

Where imaging is required urgently, point-of-care ultrasound may be useful to identify gross abnormalities [53]. However, formal transthoracic echocardiography remains preferable in patients with clinical heart failure, haemodynamic instability, concerning ECG changes (including frequent ectopy or non-sustained ventricular tachycardia), and with cardiac biomarkers suggestive of myocarditis [9,11]. Transoesophageal echocardiography is a potential aerosol-generating procedure and should be performed only when the benefits strongly outweigh the risks [9,11,53].

Computed Tomography

Whilst principally utilised for pulmonary pathology, computed tomography (CT) may provide incremental information on COVID-19 cardiac complications such as intracardiac thrombus, right heart strain, pericardial and pleural effusions. Although chest CT or pulmonary angiography studies are rarely gated for coronary assessment, prognostically significant coronary artery pathology may be detectable [54] and may help defer formal coronary assessment where clinically appropriate.

Cardiac Magnetic Resonance Imaging

Although not routinely recommended in COVID-19, CMR provides the highest resolution assessment of myocardial structure and function and is the optimal modality in the assessment of acute and chronic myocarditis. Abnormalities in tissue characterisation are common in cases of COVID-19 [30], however, these findings are not specific for acute myocarditis in COVID-19. Studies of CMR are also limited by adherence to defined criteria for myocardial inflammation and parametric mapping protocols [4] Myocardial oedema is common [29], is central to the diagnosis of acute myocarditis, and is particularly useful in suspected acute cases following mRNA vaccination. Reporting of late gadolinium enhancement (LGE) patterns has been heterogenous with highly variable degrees of scar and fibrosis [17,30,55,56]. Despite the high variability in reported tissue characteristic findings, left ventricular function appears to be normal in most patients [30] and many cases of suspected myocarditis may be presumed based on biomarker elevation, rather than diagnostic criteria or histological results. The ESC suggest that CMR has limited utility in this context but may be necessary in selected cases [11]. CSANZ recommends that inpatient CMR be avoided, given the substantial exposure risks associated with lengthy scan times and equipment contamination [8]. In patients with mRNA vaccination induced myocarditis, CMR may prove a valuable imaging modality to temporally confirm the diagnosis in the absence of endomyocardial biopsy. In practice, CMR should probably be reserved for those with significant biomarker elevation, myocardial dysfunction on echocardiography, or for diagnostic clarity.

Interventional Cardiology Procedures in COVID-19

Detailed recommendations for the utilisation of interventional cardiology facilities for acute coronary syndrome are available [6,7]. In brief, high-risk patients with ST-elevation myocardial infarction (STEMI) should not proceed to angiography unless urgent catheterisation is deemed likely to significantly alter outcome. To limit exposure, fibrinolysis may be the preferred reperfusion option, even in centres with cardiac catheterisation facilities. Primary intervention using appropriate personal protective equipment (PPE) is appropriate in patients with STEMI and low risk of exposure. For non-ST elevation acute coronary syndromes (NSTEACs), invasive intervention can be reasonably deferred in most cases as there is no strong evidence for reduced mortality or non-fatal myocardial infarction with early invasive angiography [57]. Similarly, invasive angiography should be deferred in all but the highest-risk cases of type 2 myocardial infarction. Management strategies for unstable patients (haemodynamic instability, ongoing ischaemia or arrhythmias) require individual appraisal. Patients with stable coronary artery disease can be appropriately managed with medical therapy [58].

Electrophysiology procedures, including implantation of permanent pacemakers, should be based on clinical assessment as established in national guidelines, and remote device monitoring employed where appropriate [10].

Endomyocardial biopsy is the gold standard for the diagnosis of myocarditis, however, there is limited data regarding the role of biopsy in COVID-19 related disease. Autopsy data suggests the true incidence of clinically significant myocarditis due to COVID-19 is low [23], and biopsy is therefore not routinely recommended. Similarly, pericardiocentesis should only be considered as an urgent therapeutic option in high-risk patients where patient prognosis will be significantly improved.

Discussion

The COVID-19 knowledge base is rapidly expanding. With the increasing emergence of prospective data, the true incidence of myocarditis and serious cardiac complications are more clearly delineated. Early research raised concern for the potentially serious complications associated with myocardial involvement in COVID-19, based principally on elevated troponin levels and non-specific or potentially temporally

unrelated findings on CMR tissue characterisation. With more robust evidence emerging, the initial concern over biomarker elevation and the potential relationship with myocarditis and significant myocardial injury has been tempered, with acceptance that myocardial injury or low-level inflammation is common but of minimal clinical significance. The incidence rate of myocarditis in those with COVID-19 is approximately 11 per 100,000 cases, compared with approximately 2.7 per 100,000 cases in those who have received the mRNA vaccination [2]. Given the significant overall benefit in reduction of hospitalisation and serious illness [35], vaccination is uniformly recommended. Cases in whom significant myocardial involvement occurs are likely to present with more severe illness, and cardiac biomarkers are likely to be more substantially elevated. As such, the presence of normal biomarkers is very reassuring, and in such patients, few major abnormalities are found on echocardiography. Cardiac biomarkers, therefore, serve as an appropriate gatekeeper for cardiac imaging. Where abnormalities are found on highly sensitive imaging techniques such as CMR, there appears to be little long-term consequence.

Overall recommendations considering the evidence and available clinical guidelines are presented in Table 1 and are clinically based, utilising a staged approach to the evaluation of patients with COVID-19. Bedside and advanced imaging techniques appear to be unnecessary for most cases, where clinical reasoning should guide the use of these tests based on the likelihood the results will change management. This approach aims to minimise exposure risk to staff and patients, whilst continually balancing the equation of benefits and risks. Finally, although Australian data exists [59], the national experience has been limited and the intention to share data within Australian research groups appears low (i.e. 20%) [60]. Australia is well-suited to "Big Data" initiatives, and given the demand on public resources, equipment, PPE and hospital beds, the allocation of research funding should arguably be determined by the likelihood that studies will be additive to the established worldwide experience. Finally, a mature and cognisant approach to managing patients with COVID-19 is required, whereby appropriate testing procedures should be based on robust evidence and the likelihood of altering the overall management strategy.

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References

[1] Whittaker C, Walker PGT, Alhaffar M, Hamlet A, Djaafara BA, Ghani A, et al. Under-reporting of deaths limits our understanding of true burden of covid-19. BMJ. 2021;375:n2239.
[2] Barda N, Dagan N, Ben-Shlomo Y, Kepten E, Waxman J, Ohana R, et al. Safety of the BNT162b2 mRNA Covid-19 vaccine in a nationwide setting. N Engl J Med. 2021;385(12):1078–90.
[3] Imazio M, Klingel K, Kindermann I, Brucato A, De Rosa FG, Adler Y, et al. COVID-19 pandemic and troponin: indirect myocardial injury, myocardial inflammation or myocarditis? Heart. 2020;106(15):1127–31.
[4] Friedrich MG, Cooper LT. What we (don't) know about myocardial injury after COVID-19. Eur Heart J. 2021;42(19):1879–82.
[5] The Task Force for the management of COVID-19 of the European Society of Cardiology. European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 1—epidemiology, pathophysiology, and diagnosis. Eur Heart J. 2021.
[6] Lo STH, Yong AS, Sinhal A, Shetty S, McCann A, Clark D, et al. Consensus guidelines for interventional cardiology services delivery during covid-19 pandemic in Australia and new Zealand. Heart Lung Circ. 2020;29(6):e69–77.
[7] Parsonage WA, Cullen L, Brieger D, Hillis GS, Nasis A, Dwyer N, et al. CSANZ Position Statement on the Evaluation of Patients Presenting With Suspected Acute Coronary Syndromes During the COVID-19 Pandemic. Heart Lung Circ. 2020;29(7):e105–10.
[8] Lal S, Hayward CS, De Pasquale C, Kaye D, Javorsky G, Bergin P, et al. COVID-19 and Acute Heart Failure: Screening the Critically Ill - A Position Statement of the Cardiac Society of Australia and New Zealand (CSANZ). Heart Lung Circ. 2020;29(7):e94–8.
[9] Wahi S, Thomas L, Stanton T, Taylor A, Mahadevan D, Evans G, et al. CSANZ Imaging Council Position Statement on Echocardiography Services During the COVID-19 Pandemic. Heart Lung Circ. 2020;29(6):e78–83.
[10] Kumar S, Haqqani H, Wynn G, Pathak RK, Lipton J, Mahajan R, et al. Position Statement on the Management of Cardiac Electrophysiology and Cardiac Implantable Electronic Devices in Australia During the COVID-19 Pandemic: A Living Document. Heart Lung Circ. 2020;29(6):e57–68.
[11] Task Force for the management of COVID-19 of the European Society of Cardiology. European Society of Cardiology guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 1-epidemiology, pathophysiology, and diagnosis. Eur Heart J. 2022;43(11):1033–58.
[12] The Task Force for the management of COVID-19 of the European Society of Cardiology. ESC guidance for the diagnosis and management of cardiovascular disease during the COVID-19 pandemic: part 2—care pathways, treatment, and follow-up. Eur Heart J. 2022;43(11):1059–103.
[13] Nicin L, Abplanalp WT, Mellentin H, Kattih B, Tombor L, John D, et al. Cell type-specific expression of the putative SARS-CoV-2 receptor ACE2 in human hearts. Eur Heart J. 2020;41(19):1804–6.
[14] Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC. COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. Nat Rev Cardiol. 2020;17(9):543–58.
[15] Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with Coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5(7):811–8.
[16] Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, et al. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. J Am Coll Cardiol. 2020;76(5):533–46.
[17] Guglin M, Ballut K, Ilonze O, Jones M, Rao R. Clinical variants of myocardial involvement in COVID-19-positive patients: a cumulative experience of 2020. Heart Fail Rev; 2021.
[18] Pellicori P, Doolub G, Wong CM, Lee KS, Mangion K, Ahmad M, et al. COVID-19 and its cardiovascular effects: a systematic review of prevalence studies. Cochrane Database Syst Rev. 2021;3:CD013879.
[19] Kang Y, Chen T, Mui D, Ferrari V, Jagasia D, Scherrer-Crosbie M, et al. Cardiovascular manifestations and treatment considerations in COVID-19. Heart. 2020;106(15):1132–41.
[20] Aikawa T, Takagi H, Ishikawa K, Kuno T. Myocardial injury characterized by elevated cardiac troponin and in-hospital mortality of COVID-19: an insight from a meta-analysis. J Med Virol. 2021;93(1):51–5.
[21] Figliozzi S, Masci PG, Ahmadi N, Tondi L, Koutli E, Aimo A, et al. Predictors of adverse prognosis in COVID-19: a systematic review and meta-analysis. Eur J Clin Invest. 2020;50(10):e13362.

[22] Hendren NS, Drazner MH, Bozkurt B, Cooper LT Jr. Description and proposed management of the acute COVID-19 cardiovascular syndrome. Circulation. 2020;141(23):1903–14.
[23] Halushka M, Vander Heide RS. Myocarditis is rare in COVID-19 autopsies: cardiovascular findings across 277 postmorten examinations. Cardiovasc Pathol. 2021;50:107300.
[24] Weckbach LT, Curta A, Bieber S, Kraechan A, Brado J, Hellmuth JC, et al. Myocardial inflammation and dysfunction in COVID-19-associated myocardial injury. Circ Cardiovasc Imaging. 2021;14(1):e012220.
[25] Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from Coronavirus disease 2019 (COVID-19). JAMA Cardiol. 2020;5(11):1265–73.
[26] Joy G, Artico J, Kurdi H, Seraphim A, Lau C, Thornton GD, et al. Prospective case-control study of cardiovascular abnormalities 6 months following mild COVID-19 in healthcare workers. JACC Cardiovasc Imaging. 2021;14(11):2155–66.
[27] Ferreira VM, Schulz-Menger J, Holmvang G, Kramer CM, Carbone I, Sechtem U, et al. Cardiovascular magnetic resonance in nonischemic myocardial inflammation: expert recommendations. J Am Coll Cardiol. 2018;72(24):3158–76.
[28] Kim D, Quinn J, Pinsky B, Shah NH, Brown I. Rates of co-infection between SARS-CoV-2 and other respiratory pathogens. JAMA. 2020;323(20):2085–6.
[29] Chen BH, Shi NN, Wu CW, An DA, Shi YX, Wesemann LD, et al. Early cardiac involvement in patients with acute COVID-19 infection identified by multiparametric cardiovascular magnetic resonance imaging. Eur Heart J Cardiovasc Imaging. 2021;22(8):844–51.
[30] Kotecha T, Knight DS, Razvi Y, Kumar K, Vimalesvaran K, Thornton G, et al. Patterns of myocardial injury in recovered troponin-positive COVID-19 patients assessed by cardiovascular magnetic resonance. Eur Heart J. 2021;42(19):1866–78.
[31] Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, et al. Current State of Knowledge on Aetiology, Diagnosis, Management, and Therapy of Myocarditis: A Position Statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2013;34(33):2636–48, 48a-48d.
[32] Maron BJ, Udelson JE, Bonow RO, Nishimura RA, Ackerman MJ, Estes NAM, et al. Eligibility and disqualification recommendations for competitive athletes with cardiovascular abnormalities: Task Force 3: hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy and other cardiomyopathies, and myocarditis. Circulation. 2015;132(22):e273–80.
[33] Witberg G, Barda N, Hoss S, Richter I, Wiessman M, Aviv Y, et al. Myocarditis after Covid-19 vaccination in a large health care organization. N Engl J Med. 2021:NEJMoa2110737.
[34] Mevorach D, Anis E, Cedar N, Bromberg M, Haas EJ, Nadir E, et al. Myocarditis after BNT162b2 mRNA vaccine against Covid-19 in Israel. N Engl J Med. 2021:NEJMoa2109730.
[35] Bozkurt B, Kamat I, Hotez PJ. Myocarditis with COVID-19 mRNA vaccines. Circulation. 2021;144(6):471–84.
[36] Husby A, Hansen JV, Fosbøl E, Thiesson EM, Madsen M, Thomsen RW, et al. SARS-CoV-2 vaccination and myocarditis or myopericarditis: population based cohort study. BMJ. 2021;375:e068665.
[37] Nassar M, Nso N, Gonzalez C, Lakhdar S, Alshamam M, Elshafey M, et al. COVID-19 vaccine-induced myocarditis: case report with literature review. Diabetes Metab Syndr. 2021;15(5):102205.
[38] Australian Government. Guidance on Myocarditis and Pericarditis after mRNA COVID-19 Vaccines. Updated 8 November 2021. https://www.health.gov.au/resources/publications/covid-19-vaccination-guidance-on-myocarditis-and-pericarditis-after-mrna-covid-19-vaccines. Accessed November 30, 2021.
[39] Patone M, Mei XW, Handunnetthi L, Dixon S, Zaccardi F, Shankar-Hari M, et al. Risks of myocarditis, pericarditis, and cardiac arrhythmias associated with COVID-19 vaccination or SARS-CoV-2 infection. Nature Medicine. 2021.
[40] Stefanini GG, Chiarito M, Ferrante G, Cannata F, Azzolini E, Viggiani G, et al. Early detection of elevated cardiac biomarkers to optimise risk stratification in patients with COVID-19. Heart. 2020;106(19):1512–8.
[41] Zinellu A, Sotgia S, Carru C, Mangoni AA. B-type natriuretic peptide concentrations, COVID-19 severity, and mortality: a systematic review and meta-analysis with meta-regression. Front Cardiovasc Med. 2021;8:690790.
[42] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054–62.
[43] Januzzi J Jr. Troponin and BNP use in COVID-19. American College of Cardiology. 18 March 2020. Available at: www.acc.org/latest-in-cardiology/articles/2020/03/18/15/25/troponin-and-bnp-use-in-covid19. [accessed 30.10.21].
[44] Coromilas EJ, Kochav S, Goldenthal I, Biviano A, Garan H, Goldbarg S, et al. Worldwide survey of COVID-19-associated arrhythmias. Circ Arrhythm Electrophysiol. 2021;14(3):e009458.
[45] Bhatla A, Mayer MM, Adusumalli S, Hyman MC, Oh E, Tierney A, et al. COVID-19 and cardiac arrhythmias. Heart Rhythm. 2020;17(9):1439–44.
[46] Parwani AS, Haug M, Keller T, Guthof T, Blaschke F, Tscholl V, et al. Cardiac arrhythmias in patients with COVID-19: lessons from 2300 telemetric monitoring days on the intensive care unit. J Electrocardiol. 2021;66:102–7.
[47] Varma N, Marrouche NF, Aguinaga L, Albert CM, Arbelo E, Choi JI, et al. HRS/EHRA/APHRS/LAHRS/ACC/AHA worldwide practice update for telehealth and arrhythmia monitoring during and after a pandemic. Circ Arrhythm Electrophysiol. 2020;13(7):e009007.
[48] Lanza GA, De Vita A, Ravenna SE, D'Aiello A, Covino M, Franceschi F, et al. Electrocardiographic findings at presentation and clinical outcome in patients with SARS-CoV-2 infection. Europace. 2021;23(1):123–9.
[49] Dweck MR, Bularga A, Hahn RT, Bing R, Lee KK, Chapman AR, et al. Global evaluation of echocardiography in patients with COVID-19. Eur Heart J Cardiovasc Imaging. 2020;21(9):949–58.
[50] Szekely Y, Lichter Y, Taieb P, Banai A, Hochstadt A, Merdler I, et al. Spectrum of cardiac manifestations in COVID-19: a systematic echocardiographic study. Circulation. 2020;142(4):342–53.
[51] Lassen MCH, Skaarup KG, Lind JN, Alhakak AS, Sengelov M, Nielsen AB, et al. Echocardiographic abnormalities and predictors of mortality in hospitalized COVID-19 patients: the ECHOVID-19 study. ESC Heart Fail; 2020.
[52] Yuan N, Wu S, Rader F, Siegel RJ. Determining which hospitalized coronavirus disease 2019 patients require urgent echocardiography. J Am Soc Echocardiogr. 2021;34(8):831–8.
[53] Kirkpatrick JN, Mitchell C, Taub C, Kort S, Hung J, Swaminathan M. ASE Statement on Protection of Patients and Echocardiography Service Providers During the 2019 Novel Coronavirus Outbreak: Endorsed by the American College of Cardiology. J Am Soc Echocardiogr. 2020;33(6):648–53.
[54] Agricola E, Beneduce A, Esposito A, Ingallina G, Palumbo D, Palmisano A, et al. Heart and lung multimodality imaging in COVID-19. JACC Cardiovasc Imaging. 2020;13(8):1792–808.
[55] Ojha V, Verma M, Pandey NN, Mani A, Malhi AS, Kumar S, et al. Cardiac magnetic resonance imaging in Coronavirus disease 2019 (COVID-19): a systematic review of cardiac magnetic resonance imaging findings in 199 patients. J Thorac Imaging. 2021;36(2):73–83.
[56] Kariyanna PT, Sutarjono B, Grewal E, Singh KP, Aurora L, Smith L, et al. A systematic review of COVID-19 and myocarditis. Am J Med Case Rep. 2020;8(9):299–305.
[57] Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J. 2021;42(14):1289–367.
[58] Maron DJ, Hochman JS, Reynolds HR, Bangalore S, O'Brien SM, Boden WE, et al. Initial invasive or conservative strategy for stable coronary disease. N Engl J Med. 2020;382(15):1395–407.
[59] Bhatia KS, van Gaal W, Kritharides L, Chow CK, Bhindi R, Investigators A-C. The incidence of cardiac complications in patients hospitalised with COVID-19 in Australia: the AUS-COVID study. Med J Aust. 2021;215(6):279.
[60] Seidler AL, Aberoumand M, Williams JG, Tan A, Hunter KE, Webster A. The landscape of COVID-19 trials in Australia. Med J Aust. 2021;215(2):58–61.e1.
[61] Rudski L, Januzzi JL, Rigolin VH, Bohula EA, Blankstein R, Patel AR, et al. Multimodality imaging in evaluation of cardiovascular complications in patients with COVID-19: JACC Scientific Expert Panel. J Am Coll Cardiol. 2020;76(11):1345–57.
[62] Mahmud E, Dauerman HL, Welt FGP, Messenger JC, Rao SV, Grines C, et al. Management of Acute Myocardial Infarction During the COVID-19 Pandemic: A Position Statement from the Society for Cardiovascular Angiography and Interventions (SCAI), the American College of Cardiology (ACC), and the American College of Emergency Physicians (ACEP). J Am Coll Cardiol. 2020;76(11):1375–84.
[63] Welt FGP, Shah PB, Aronow HD, Bortnick AE, Henry TD, Sherwood MW, et al. Catheterization laboratory considerations during the coronavirus (covid-19) pandemic: from the ACC's Interventional Council and SCAI. J Am Coll Cardiol. 2020;75(18):2372–5.