Cardiovascular Complications Following COVID-19

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4.1 Introduction

The ongoing COVID-19 pandemic has affected a huge population of the world, and most of them have made a successful recovery from the acute phase. Survivors of acute illness may experience a wide range of signs and symptoms after recovery which impact their quality of life and add to their disability. These residual sequelae/symptoms are increasingly being reported by recovering patients irrespective of the severity of acute COVID-19 infection. This chapter focusses on cardiovascular complications following COVID-19 infection, common clinical presentations, natural course, evaluation and management in addition to prevention strategies.

4.2 Terminologies Used to Describe Post-acute COVID-19 Phase

In the absence of universally accepted definition, post-COVID-19 syndrome by consensus is defined as signs and symptoms that develop during or after an infection consistent with COVID-19 which continue for more than 12 weeks and are not explained by alternative diagnosis. Common terminologies used are post-COVID-19 syndrome, long-term COVID-19, post-acute sequelae of SARS-CoV-2 (PASC) or long haulers. Also popular in medical fraternity is the term 'long COVID' which is

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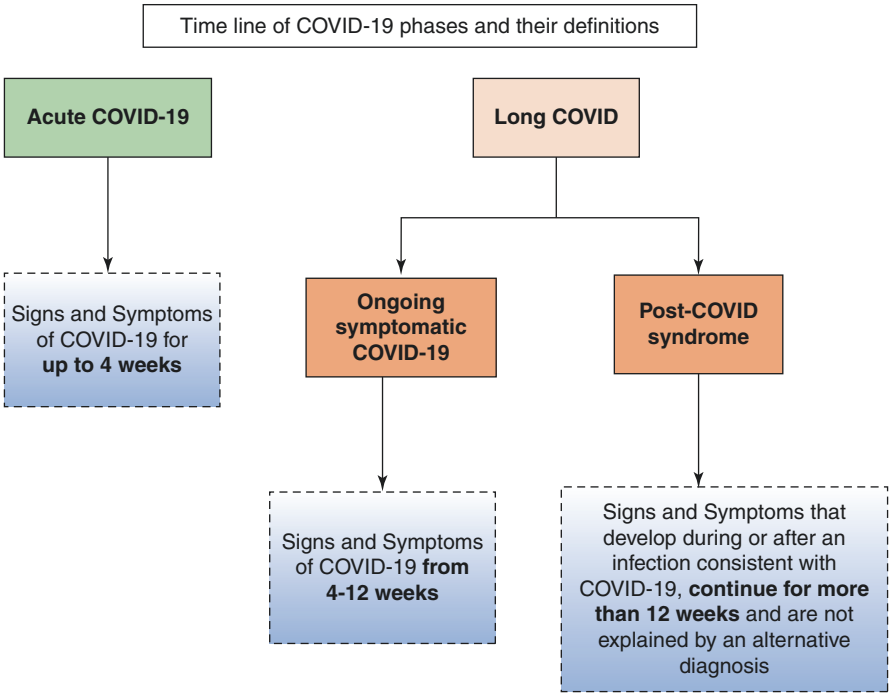

Fig. 4.1 Terminology and definition of acute COVID-19 and long COVID

defined by the National Institute for Health and Care Excellence as symptoms that continue or develop after acute COVID-19. Definitions of various phases of COVID-19 are shown in Figure 4.1 [1–3].

4.3 Cardiovascular Sequelae Post-acute COVID-19 and Pathophysiology

Admitted COVID-19 patients who have survived the acute phase of illness (asymptomatic or symptomatic) seem to have three times greater risk of major adverse cardiovascular events, while mild COVID-19 patients do not seem to have a higher cardiovascular sequelae when matched to controls [4]. However, the focus on cardiovascular sequelae is ever increasing as survivors of acute COVID-19 infection are experiencing persistent symptoms and a decline in quality of life. The risk of cardiovascular sequelae is higher in those requiring hospitalization. This association of increased cardiovascular events post-viral illnesses and post-pandemic has been reported earlier too [5]. Although majority of literature currently is observational with risk of inherent bias, there is considerable evidence pertaining to the symptoms as well as cardiac abnormalities detected on diagnostic testing [6]. While patients with mild or moderate-severe COVID-19 infection are expected to have symptoms of cardiovascular disease lingering on in the post-COVID-19 phase, asymptomatic

patients also seem to be variably affected [7]. The spectrum of cardiac manifestations (fatigue, dyspnoea, angina and palpitations) in these long haulers depends not only on the severity of acute COVID-19 infections but also on duration after apparent recovery (Fig. 4.1).

Persistent immune activation post-acute phase, persistent low-grade viremia and residual and ongoing structural/functional changes in myocardium have all been implicated in the pathophysiology of long-term cardiovascular sequelae [8]. A schema of pathophysiology of acute COVID-19 and its subsequent evolution into long-term sequelae is shown in Fig. 4.2. There is considerable heterogeneity in the expression of symptoms and structural/functional abnormalities pertaining to cardiovascular system. Most of the patients having persistent symptoms are usually survivors of mild-moderate acute COVID-19 infection. Few have evidence of cardiac injury evident on cardiac magnetic resonance imaging following mild COVID-19 infection, while those with moderate to severe COVID-19 infection may

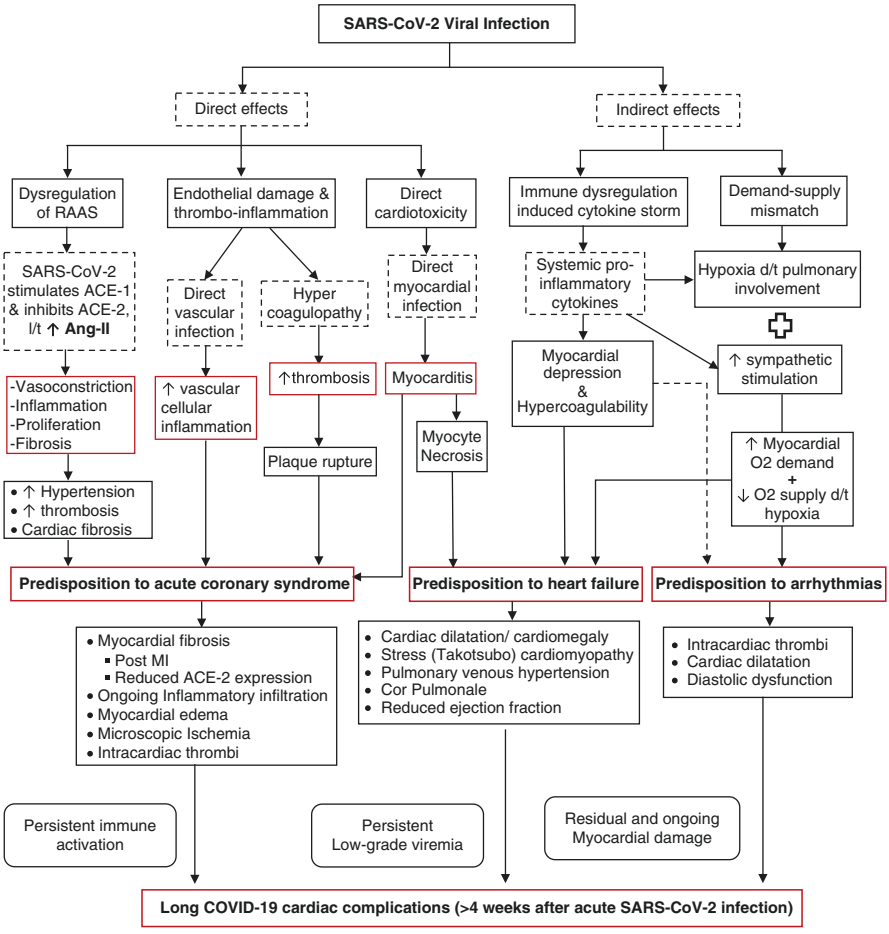

Fig. 4.2 Pathophysiology of long-term cardiovascular sequelae after acute COVID-19 infection

present with biomarker evidence of myocardial injury with or without left ventricular systolic dysfunction. Collateral damage can also be seen in patients presenting late to healthcare facilities with acute cardiac emergencies and culminate into long-lasting/irreversible myocardial injury [9].

4.4 Population at Risk of Post-COVID-19 Sequelae

Patients with severe COVID-19 manifestations, elderly, female sex, poor socioeconomic status, pre-existing comorbidities (diabetes, obesity, coronary artery disease, prior heart failure) and population living in rural areas with poor healthcare services are predisposed to development of long-term cardiac and extracardiac sequelae after apparent recovery [10].

4.5 Cardiovascular Complications Following COVID-19

The long-term sequelae include increased myocardial oxygen demands, irreversible remodelling, myocardial fibrosis/myocardial scar, persistent left ventricular systolic and diastolic dysfunction, heart failure, autonomic dysfunction and arrhythmias. Many of the lingering signs and symptoms seen in patients after they have apparently recovered from acute illness—especially fatigue, dyspnoea, angina and palpitations—appear to have an underlying cardiovascular component. This can occur de novo in an asymptomatic COVID-19 patient or in symptomatic COVID-19 patients with no clinically apparent cardiac involvement during the acute phase. Those who develop viral myocarditis, acute coronary syndrome (ACS), pulmonary embolism (PE), stress-induced cardiomyopathy and arrhythmias during the acute phase are at heightened risk of developing long-term COVID-19 cardiovascular complications and adverse outcomes. These subsets of patients typically have comorbid conditions such as diabetes mellitus, hypertension, obesity, dyslipidaemia and chronic kidney disease which would complicate their recovery after the acute phase.

Up to 20% of patients hospitalized with COVID-19 have clinically significant cardiovascular involvement, while subclinical involvement may be much more common [11, 12]. Epidemiological burden of cardiovascular sequelae post-COVID-19 is variably reported due to inherent bias of observational studies and considerable heterogeneity of studies published. Disproportionate fatigue is the most common symptom in survivors of acute COVID-19. Dyspnoea is by far the second most frequent symptom that persists despite apparent recovery from acute COVID-19 and is multifactorial in aetiology (cardiac, pulmonary or deconditioning to list a few). Prevalence of dyspnoea is reported to be between 22 and 43% in various studies [13].

High index of suspicion of dyspnoea of cardiac origin especially in the setting of ACS, PE, myocarditis and tachyarrhythmias is the key for early diagnosis of worsening cardiac status and initiating appropriate treatment accordingly. Chest pain is reported in survivors of moderate-severe COVID-19 in 18%, 13% [14] and 5% [15] at day 30, day 60 and day 180 of follow-up, respectively. Chest pain consistent with

typical angina should be differentiated from atypical or non-anginal chest pain on the basis of quality of pain, aggravating and relieving factors. Palpitations have been noted in 9%, 14% [14] and 9% [16] at day 30, day 60 and day 180 of follow-up, respectively. Differentials for palpitations in post-COVID-19 syndrome include inappropriate sinus tachycardia, postural orthostatic tachycardia syndrome consequent to hyperadrenergic state, or premature ventricular ectopics or ventricular arrhythmias consequent to adverse remodelling, myocardial fibrosis and scarring. Although various tachyarrhythmias and bradyarrhythmias have been reported in acute phase of illness, the prevalence of clinically significant arrhythmias post-recovery from acute illness remains uncertain. Reports of postural orthostatic tachycardia syndrome and autonomic dysfunction have also been reported with COVID-19 as was with other viral illnesses [17]. Although symptoms may be self-limiting for few, most still remain symptomatic beyond 6 months after contracting COVID-19 [16].

A large systematic review of 35 studies published by Ramadan et al [6]. has reported the prevalence of cardiac symptoms and abnormalities (detected on various investigation modalities according to the timeline of evaluation of follow-up) on both short-term and medium-term follow-up. Short-term follow-up (<3 months) has shown prevalence of chest pain, dyspnoea and palpitation to the tune of 25%, 36% and 6%, respectively, while medium-term (3–6 months) follow-up revealed a prevalence of 6%, 3% and 9% for chest pain, dyspnoea and palpitation, respectively (Figs. 4.3 and 4.4). Survivors of acute COVID-19 with cardiovascular

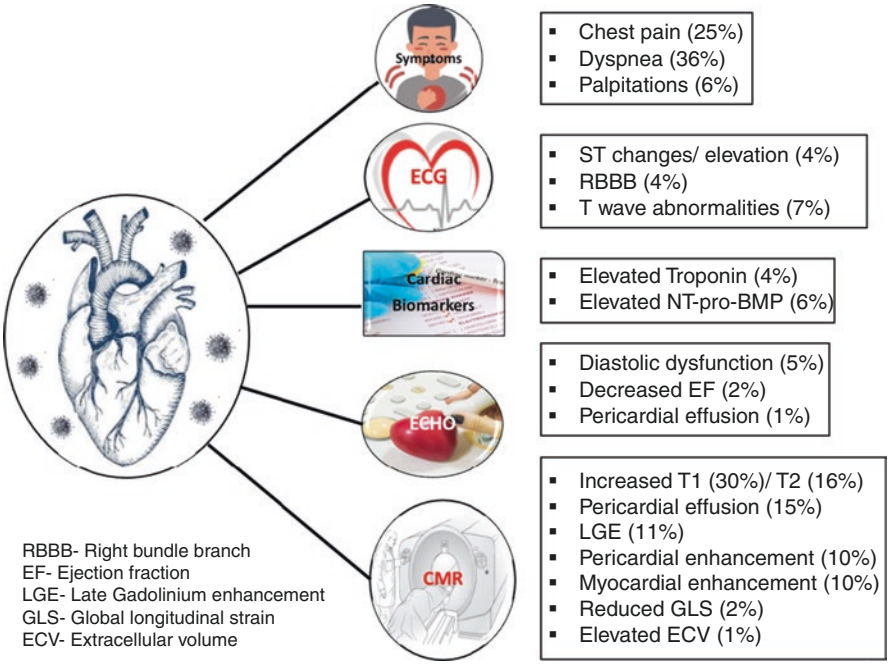

Fig. 4.3 Short-term cardiac sequelae post-COVID-19 (1–3 months) [6]

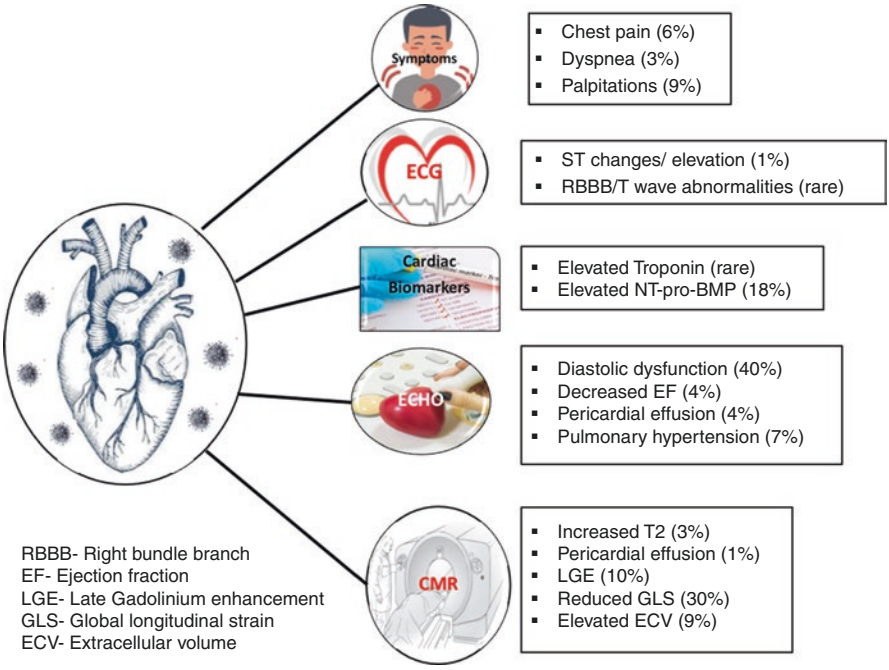

Fig. 4.4 Medium-term cardiac sequelae post-COVID-19 (3–6 months) [6]

events such as myocardial infarction, stroke, venous thromboembolism and arrhythmias would result in symptoms which would persist beyond 6 months (long-term follow-up). However, data is scarce on long-term prevalence of these symptoms.

Two large recently published studies have thrown some light over the long-term sequelae of COVID-19 in the academic year 2022. The first study was 'The Hamburg City Health Study' which followed up patients with mild to moderate SARS-CoV-2 infection for a median period of 9.2 months and looked for cardiac involvement and patient outcomes in comparison to matched cohort. While both echocardiography and cardiac magnetic resonance (CMR)-derived left ventricular systolic function (left ventricular ejection fraction) or right ventricular systolic function (tricuspid annular plane systolic excursion) were numerically reduced in patients with mild to moderate SARS-CoV-2 infection when compared to controls, only the reduction in echocardiography-derived LVEF and TAPSE (tricuspid annular plane systolic excursion) was found to be statistically significant when compared to controls [LVEF, 57.9 vs. 59.1%; regression coefficient −0.93 (95% CI: −1.54,−0.32); adjusted $P = 0.015$; TAPSE, 23.0 vs. 23.9 mm; regression coefficient − 0.72 (95% CI: −1.24, −0.21); adjusted $P = 0.031$, respectively]. Assessment of LVEF and TAPSE by CMR showed no significant differences when compared to controls. Further there were no intergroup differences in other cardiac parameters such as left

ventricular diastolic function, peak tricuspid regurgitation velocity and myocardial fibrosis when assessed by CMR [18].

The second study was from the US Department of Veterans Affairs national healthcare database which enrolled a massive cohort of ~1.5 lakh US veterans who survived first 30 days of SARS-CoV-2 infection and were followed up longitudinally for 12 months, and comparison was made with a contemporary cohort and a historical cohort. Estimates of risks and 12-month burden of prespecified incident cardiovascular outcomes in the overall cohort according to nature of care received in the setting of acute infection were calculated. Risks and burdens of individual cardiovascular outcomes are shown in Table 4.1. In this study, the risks and burdens of cardiovascular disease were evident not only in patients who were hospitalized or

Table 4.1 Risks and 12-month burdens of incident post-acute COVID-19 cardiovascular outcomes per 1000 persons compared with the control cohort [19]

Cardiovascular outcome	Risk of outcome (HR (95% CI))	Burden of outcome[a] (HR (95% CI))
Cerebrovascular disorders	1.53 (1.45, 1.61)	5.48 (4.65, 6.35)
• Stroke	1.52 (1.43, 1.62)	4.03 (3.32, 4.79)
• Transient ischemic attacks	1.49 (1.37, 1.62)	1.84 (1.38, 2.34)
Dysrhythmia	1.69 (1.64, 1.75)	19.86 (18.31, 21.46)
• Atrial fibrillation	1.71 (1.64, 1.79)	10.74 (9.61, 11.91)
• Sinus tachycardia	1.84 (1.74, 1.95)	5.78 (5.07, 6.53)
• Sinus bradycardia	1.53 (1.45, 1.62)	4.62 (3.90, 5.38)
• Ventricular arrhythmias	1.84 (1.72, 1.98)	4.18 (3.56, 4.85)
• Atrial flutter	1.80 (1.66, 1.96)	3.10 (2.55, 3.69)
Inflammatory heart disease	2.02 (1.77, 2.30)	1.23 (0.93, 1.57)
• Pericarditis	1.85 (1.61, 2.13)	0.98 (0.70, 1.30)
• Myocarditis	5.38 (3.80, 7.59)	0.31 (0.20, 0.46)
Ischemic heart disease	1.66 (1.52, 1.80)	7.28 (5.80, 8.88)
• Acute coronary disease	1.72 (1.56, 1.90)	5.35 (4.13, 6.70)
• Myocardial infarction	1.63 (1.51, 1.75)	2.91 (2.38, 3.49)
• Ischemic cardiomyopathy	1.75 (1.44, 2.13)	2.34 (1.37, 3.51)
• Angina	1.52 (1.42, 1.64)	2.50 (2.00, 3.03)
Other cardiac disorders	1.72 (1.65, 1.79)	12.72 (11.54, 13.96)
• Heart failure	1.72 (1.65, 1.80)	11.61 (10.47, 12.78)
• Non-ischemic cardiomyopathy	1.62 (1.52, 1.73)	3.56 (2.97, 4.20)
• Cardiac arrest	2.45 (2.08, 2.89)	0.71 (0.53, 0.93)
• Cardiogenic shock	2.43 (1.86, 3.16)	0.51 (0.31, 0.77)
Thrombotic disorders	2.39 (2.27, 2.51)	9.88 (9.05, 10.74)
• Pulmonary embolism	2.93 (2.73, 3.15)	5.47 (4.90, 6.08)
• Deep vein thrombosis	2.09 (1.94, 2.24)	4.18 (3.62, 4.79)
• Superficial vein thrombosis	1.95 (1.80, 2.12)	2.61 (2.20, 3.07)
Major adverse cardiovascular outcome (Composite of myocardial infarction, stroke and all-cause mortality)	1.55 (1.50, 1.60)	23.48 (21.54, 25.48)
Any cardiovascular outcome	1.63 (1.59, 1.68)	45.29 (42.22, 48.45)

[a]Number of excess cases per 1000 individuals

required intensive care but also in those who were not hospitalized. This study highlights the importance of developing an algorithm for early detection of cardiovascular sequelae and institution of timely intervention to mitigate the deleterious effects of this virus on the heart [19].

4.6 Investigations for Evaluation of Cardiovascular Sequelae Post-acute COVID-19

Patients with cardiovascular issues during acute infection or those having signs and symptoms pertaining to cardiac involvement after apparent recovery should be monitored with serial clinical examinations, electrocardiogram, laboratory tests, including cardiac biomarkers (troponin/NT-pro-BNP), and echocardiogram on follow-up visits. Additional diagnostic tests such as cardiac MRI, cardiac pulmonary exercise testing, rhythm monitoring by Holter, chest CT and lower extremity duplex testing are offered according to individual symptoms and examination or test findings, keeping in with clinical standards. Electrocardiogram (ECG), chest radiographs, biomarkers (troponin I, B-type natriuretic peptide), echocardiogram (ECHO) and cardiac magnetic resonance (CMR) imaging have all been used for assessment of cardiac sequelae. Various abnormalities that would suggest cardiovascular involvement on these investigations and their prevalence on short-term and medium-term follow-up have been summarized in Figs. 4.3 and 4.4 [6]. Whether these cardiovascular sequelae detected on various investigations resolve over time or persist forever is yet to be determined and would require long-term follow-up studies. Also, whether patients who have normal troponin levels, ejection fraction and CMR are at increased risk of development of heart failure in future will also require prospective studies to address the same.

4.7 Management

The management of patients with post-COVID-19 cardiac sequelae depends on the status of pre-existing cardiac comorbidities and the cardiac condition developed during the acute phase (ACS, PE, tachy- or bradyarrhythmias, etc.) or during recovery. There is no recommendation currently available for evaluation and management of these patients with varied symptomatology. Hence a careful evaluation with meticulous clinical judgement should guide the modality of investigations in this population. A careful history pertaining to symptoms relevant to cardiovascular sequelae such as dyspnoea, chest pain, palpitation and fatigue should be taken. It should be determined whether symptoms are of new onset, persistent or worsening of pre-existing symptoms. Clinical examination in these patients should focus on vital signs (heart rate, blood pressure and saturation), and patient should also be

checked for postural hypotension in patients presenting with presyncope or syncope. A systematic cardiovascular system examination for murmurs, pericardial rub, abnormal diastolic heart sounds, jugular venous pressure and signs of pulmonary oedema should be looked for.

Patients with new-onset or persistent dyspnoea or worsening of pre-existing dyspnoea should undergo chest radiograph to differentiate cardiac versus pulmonary causes of dyspnoea. Cardiopulmonary exercise testing (CPX) can further help in differentiating the aetiology of dyspnoea (cardiac versus pulmonary versus deconditioning). Patients with fatigue and palpitations should have a baseline 12-lead ECG with Holter reserved only for patients having an unremarkable baseline ECG. Echocardiogram should not be routinely performed and is reserved for those patients with history or biomarker evidence of myocardial injury, orthopnea, abnormal jugular venous or auscultatory findings or abnormal chest X-ray or ECG. Although CMR can be used to detect myocarditis that was not evident in acute phase, its clinical utility is questionable, and routine use of CMR for detecting myocardial injury should be strongly discouraged.

Symptom-guided investigations and appropriate guideline directed medical therapy (GDMT) in patients with predisposing or perpetuating factors such as diabetes mellitus, hypertension, obesity, atrial fibrillation and prior ACS and heart failure are key for optimal outcomes in these patients. Patients (nonathletes) with symptoms but no abnormalities on imaging should be advised on dos and don'ts during the post-COVID-19 phase. The dos include restructuring of daily routines, emphasis on maintaining healthy weight, moderate-intensity exercise (30 min per day, five times a week), meditation/yoga, vaccination 3 months post-recovery (if not previously vaccinated) and avoidance of alcohol/smoking/self-medications. Patients with persistent symptoms (such as fatigue, cough, breathlessness, fever) should limit activity to 60% of maximum heart rate until 2–3 weeks after symptoms resolve, while they should refrain from intense cardiovascular exercise for up to 3 months after myocarditis or pericarditis [20].

Anecdotal reports of sudden cardiac deaths after resumption of their active lifestyle post-recovery have stirred an active debate regarding whether routine echocardiograms/CMR/coronary angiograms should be performed prior to resumption of active lifestyle. Routine investigation of these apparently healthy adults is neither recommended nor warranted. Athletes post-COVID-19 who have evidence of exercise-induced cardiac remodelling (physiological) with no ongoing clinical concerns and normal ECG and biomarkers should be permitted for graded return to play. In those with ongoing clinical concerns, CMR and other secondary imaging modalities as directed by clinical suspicion should be performed and pathologies appropriately treated before resumption of athletic activities [21]. An algorithm for evaluating patients with cardiac sequelae and their management is shown in Fig. 4.5.

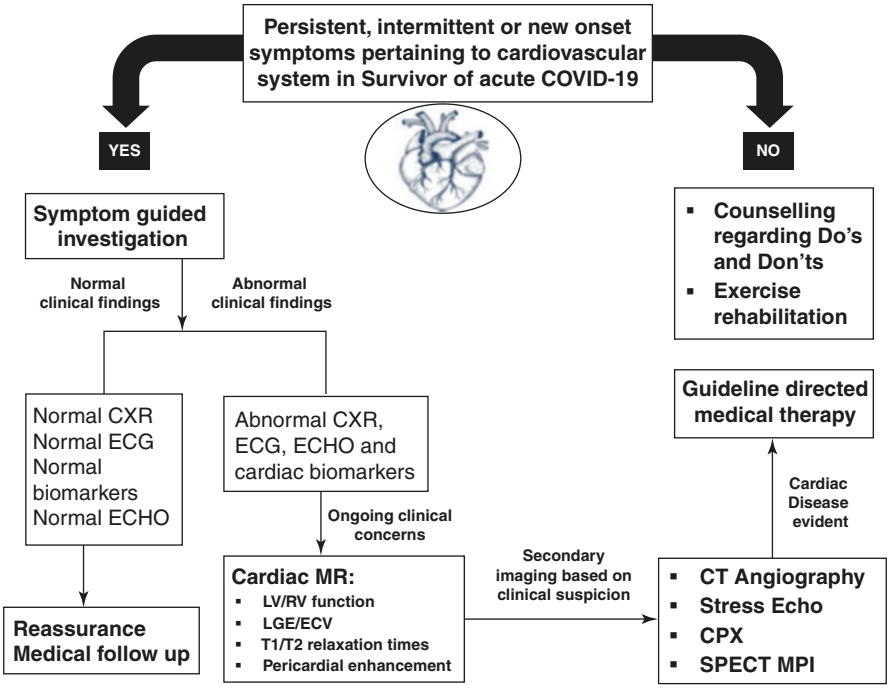

Fig. 4.5 Algorithm for evaluation and management of post-COVID-19 sequelae

4.8 Prevention Strategies

The most cost-effective strategy would be vaccination to prevent from acute COVID-19 in the first place in addition to hand hygiene and social distancing. Also, in survivors of acute infection with persistent or ongoing symptoms, vaccination (after COVID-19) has been reported with resolution of these symptoms [22]. Telephonic follow-up in patients with persistent symptoms and outpatient follow-up visits for those with underlying predisposing factors will help in early diagnosis and treatment of these long haulers. All patients post-discharge should be monitored for cardiovascular risk factors like tobacco use, high blood pressure, raised blood sugars and dyslipidaemia. Diligent management of these risk factors is mandatory to reduce the heightened risk of major adverse cardiovascular events in them. All patients with pre-existing atherosclerotic cardiovascular disease should also be on aspirin and statins as per standard guidelines.

4.9 Conclusion

On completion of 2 years of the pandemic, we are now experiencing an ever-increasing population who have survived the pandemic but have persistent, intermittent or new-onset symptoms pertaining to cardiovascular system. Pathophysiology of these cardiac sequelae is complex and multifactorial. Careful identification of predisposing factors, meticulous history, examination and clinically directed investigations help us in early diagnosis and treatment of these patients.

4.10 Take-Home Message

- Cardiovascular sequelae are seen in patients with previous cardiac comorbidities and also seen in healthy survivors of acute illness including those with mild COVID-19.
- Admitted patients of COVID-19 have three times higher probability of major adverse cardiovascular events including heart failure, acute coronary syndrome and cardiovascular mortality.
- Diligent management of cardiovascular risks like blood pressure, diabetes, dyslipidaemia and lifestyle is needed in survivors of COVID-19 to reduce major adverse cardiovascular events.
- Cardiac investigations in these predisposed populations should be clinically driven.
- Exercise prescription post-acute COVID-19 should be individualized to prevent worsening of cardiac symptoms and sudden cardiac deaths.

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