ORIGINAL ARTICLE

Cardiovascular Risk Assessment after COVID-19 Infection before Resuming Sports Activities - Practical Flowchart and Meta-Analysis

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Abstract

Background: The risk of sports-related sudden cardiac arrest after COVID-19 infection can be a serious problem. There is an urgent need for evidence-based criteria to ensure patient safety before resuming exercise.

Objective: To estimate the pooled prevalence of acute myocardial injury caused by COVID-19 and to provide an easy-to-use cardiovascular risk assessment toolkit prior to resuming sports activities after COVID-19 infection.

Methods: We searched the Medline and Cochrane databases for articles on the prevalence of acute myocardial injury associated with COVID-19 infection. The pooled prevalence of acute myocardial injury was calculated for hospitalized patients treated in different settings (non-intensive care unit [ICU], ICU, overall hospitalization, and non-survivors). Statistical significance was accepted for p values <0.05. We propose a practical flowchart to assess the cardiovascular risk of individuals who recovered from COVID-19 before resuming sports activities.

Results: A total of 20 studies (6,573 patients) were included. The overall pooled prevalence of acute myocardial injury in hospitalized patients was 21.7% (95% CI 17.3-26.5%). The non-ICU setting had the lowest prevalence (9.5%, 95% CI 1.5-23.4%), followed by the ICU setting (44.9%, 95% CI 27.7-62.8%), and the cohort of non-survivors (57.7% with 95% CI 38.5-75.7%). We provide an approach to assess cardiovascular risk based on the prevalence of acute myocardial injury in each setting.

Conclusions: Acute myocardial injury is frequent and associated with more severe disease and hospital admissions. Cardiac involvement could be a potential trigger for exercise-induced clinical complications after COVID-19 infection. We created a toolkit to assist with clinical decision-making prior to resuming sports activities after COVID-19 infection.

Keywords: Risk Factors; COVID-19; Betacoronavirus; Myocarditis; Inflammation; Sudden Cardiac Death; Sports Medicine; Sports.

Introduction

The recent severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) outbreak has created an unprecedented global challenge and triggered the implementation of interventions to promote social distancing, including cancellation of sports events. Importantly, coronavirus disease (COVID-19) affects relatively young people, with 77.8% of diagnoses in the age range of 30-69 years.[1] Around 80% of patients have mild disease, 15% moderate disease and 5% severe disease, requiring admission to intensive care units (ICU).[1]

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Most of the competitive and recreational athletes infected with COVID-19 fall into the low-risk group and have mild disease. However, many cases of young, healthy subjects who develop severe systemic illness have been reported. Cardiovascular (CV) complications are strongly associated with mortality among infected patients, but the pathophysiological pathway of cardiac involvement is still unclear.[2] Several mechanisms of myocardial injury have been proposed, including systemic inflammation (cytokine storm), microvascular dysfunction, immunological factors, direct cellular damage by viral invasion, stress cardiomyopathy and hypoxia.[3] Cases of acute myocarditis due to COVID-19, confirmed by cardiac magnetic resonance, endomyocardial biopsies and post-mortem analyses, have been reported.[4-6] Myocardial injury is defined as a troponin level above the 99th percentile, with prevalence rates in published data ranging from 7.2 to 27.8% in hospitalized patients. However, a definitive diagnosis and the prevalence of myocarditis is difficult to establish in most settings.[7,8] Furthermore, the pathophysiology of COVID-19-related acute cardiac injury remains unknown and limited data about the long-term sequelae are available.

Exercise is a known trigger for sudden cardiac arrest after myocarditis. Usually, a 3 to 6 months of exercise restriction is recommended.[9] As society returns to "normal" after COVID-19, a considerable number of recovered individuals will face the challenge to resume regular exercise, which is associated with health benefits. Although some experts have issued statements, no evidence-based recommendations are yet available. Therefore, we identified an urgent need to collate existing evidence of recommendations on resuming physical activity after COVID-19, which could be used as basis for policy-making to sports authorities.

The aim of the current review and meta-analysis was to estimate the pooled prevalence of acute myocardial injury caused by COVID-19 infection and to provide a CV risk assessment toolkit for patients recovered from COVID-19 to resume sports activities.

Methods

Study identification and selection

We performed a literature search of Medline and Cochrane Library (Cochrane Central Register of Controlled Trials) databases using the search terms "COVID-19" and "myocardial injury" on 11 June 2020. We also searched the references of the articles using the same keywords. Articles that reported the prevalence of acute myocardial injury due to confirmed COVID-19 infection were included. Acute myocardial injury was defined as elevation of cardiac troponin above the 99th percentile upper reference limit with or without new abnormalities in electrocardiography (ECG) or transthoracic echocardiography (TTE). Exclusion criteria were non-English language, duplicate publications, and publications only available as abstract or oral presentation.

A total of 107 studies were retrieved from the Medline database, six studies were identified in the Cochrane database, and seven studies were identified by reference cross-checking. From all these studies, 67 were excluded based on title and abstract evaluation, as they did not meet the inclusion criteria. A full-text analysis of 52 studies was conducted by two independent reviewers (LP and PD). Of these studies, 32 did not meet the inclusion criteria and were excluded. Finally, a total of 20 studies were included in the meta-analysis. Figure 1 shows the details of the study identification and selection process.

Study endpoints and data collection

The primary endpoint of the study was prevalence of acute myocardial injury. The following data were also collected: date of publication, study setting (ICU or non-ICU, survivors vs non-survivors), study location, and participants' gender, age and history of previous CV disease.

Data analysis and statistical methods

The prevalence of acute myocardial injury was calculated as a proportion (number of affected subjects per total number of participants). Statistical analyses were performed using the R Statistical Software (R Core Team 2020) with the package for meta-analysis.[10] Since the heterogeneity between the cohorts of the studies analyzed did not allow a single metanalysis, a four-group analysis was performed according to the setting – "non-ICU": cohort of hospitalized patients out of ICU; "ICU": cohort of hospitalized patients in ICU; "non-survivors": cohort of hospitalized patients with an outcome of death; and "overall hospitalized patients": cohort that included studies with hospitalized patients regardless of the setting in which they were treated.

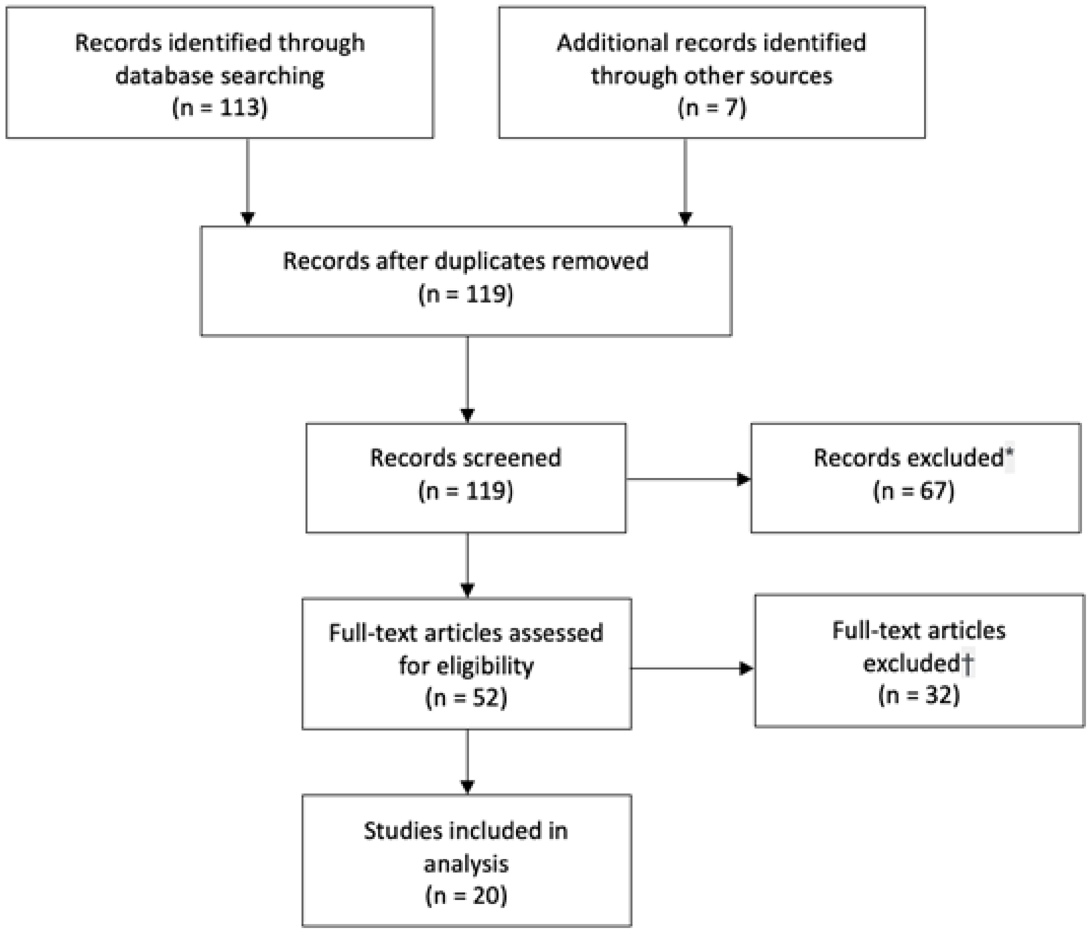

Figure 1 – Flow diagram of the study selection process
**Reasons for exclusion: 40 review studies not relevant to this meta-analysis, 11 studies were written in non-English language, 8 studies were case reports, 7 studies were on children and 1 study was an editorial comment.*
†24 were study reviews that did not provide any new data, 6 studies were drug trials, one study was a trial protocol, and one study was on oncological patients and could not be included in the analysis.

Some studies were included in more than one group analysis if they provided information that matched more than one setting. A random effects model was used for each setting to calculate the pooled prevalence. Pooled prevalence and 95% confidence intervals (CI) were expressed as percentages. The I^2 statistic was used to assess heterogeneity across studies; moderate heterogeneity was defined as values between 30-60%. Statistical significance was accepted for p values <0.05.

A clinical management flowchart for individuals recovered from COVID-19 was built as a cardiovascular risk assessment tool. The flowchart was based on the different treatment settings, which were surrogate markers for disease severity according to the metanalysis.

Results

Prevalence of acute myocardial injury

A total of twenty studies were included. The total number of participants included in the non-ICU, ICU, non-survivors and overall hospitalized settings were 518, 1042, 368 and 6573, respectively. Table 1 shows the key characteristics of the included studies and the numbers of participants in each setting. Forest plots of pooled data are depicted in Figure 2. The overall pooled prevalence of acute myocardial injury considering all hospitalized patients was 21.7%, (95% CI 17.3-26.5%, $p < 0.01$, $I^2 = 93\%$), and increased with increasing disease severity. The pooled

Table 1 – Summary of studies included in the meta-analysis

						Number of participants included (n)			
Author	Cohort (setting)	Location	Age	Males	Previous CVD	Non-ICU	ICU	Non-Survivors	Overall Hospitalized
Huang, C[17]	Hospitalized (ICU vs Non-ICU)	Wuhan, China Jinyintan Hospital	49 (41–58)	73	15	28	13		41
Zhou, F[18]	Hospitalized (Survivors vs Non-survivors)	Wuhan, China Jinyintan Hospital and Pulmonary Hospital	56 (46–67)	62	30 HTN 19 DM 8 CAD			54	191
Wang, D[7]	Hospitalized (ICU vs Non-ICU)	Wuhan, China Zhongnan Hospital	56 (42-68)	75	20	102	36		138
Shi, S[19]	Hospitalized (Cardiac injury vs without cardiac injury)	Wuhan, China Renmin Hospital	64 (range 21-95)	49.3	30.5 HTN 14.4 DM 10.6 CAD				416
Guo, T[8]	Hospitalized (Cardiac injury vs without cardiac injury)	Wuhan, China Seventh Hospital	58.5 (14.7)	48.7	32.6 HTN 15.0 DM 11.2 CAD				187
Yang, X[20]	ICU (survivors vs non-survivors)	Wuhan, China Jinyintan Hospital	59.7 (13.3)	67	10		52	32	
Ruan, Q[21]	Hospitalized (survivors vs non-survivors)	Wuhan, China Jinyintan Hospital	50 (44-81) 67 (15-81)	68	8.7			68	
Zhou, B[22]	Hospitalized (Severe vs Very Severe)	Wuhan, China Tongji Medical College	63 (58-69) 67 (66-75)	50	0†	26 SEVERE*	8 VERY SEVERE*		
Yang, F[23]	Non-survivors	Wuhan, China Renmin Hospital	69.8 (15)	53.3	17.4			92	
Deng, Q[24]	Hospitalized (Severe vs Very Severe)	Wuhan, China Renmin Hospital	65 (49-71)	50.9	32.1 HTN 17.0 DM 13.4 CAD	45 NON-SEVERE‡	67 SEVERE‡		112
Aggarwal, S[25]	Hospitalized (Severe vs non-severe)	Iowa, USA UnityPoint, Des Moines Hospital	67 (range 38-95)	75	57 HTN 19 DM 19 CAD				16
Wei, J[26]	Hospitalized (Cardiac injury vs without cardiac injury)	Sichuan, China Chengdu and West China Hospital	49 (34-62)	54	21 HTN 14 DM 5 CAD				101
Li, D[27]	Hospitalized (Cardiac injury vs without cardiac injury)	China ERS-COVID-19 study (2 hospitals)[28]	CI 71 (66-83), No CI 60 (48-68)	CI 24 (61.5), No CI 75 (52.4)	0†				182
Shi, S[29]	Severe and critical hospitalized patients (survivors vs non-survivors)	Wuhan, China Renmin Hospital	63 (50– 72)	48	29.7 HTN 14.5 DM 8.9 CAD		671	62	
Ni, W[30]	Hospitalized (survivors vs non-survivors)	Wuhan, China Central Hospital	67 (57–73)	57.4	49.3 HTN 26.7 DM 14.2 CAD			60	176

Yang, Q[31]	Hospitalized (moderate vs severe or critical)	Wuhan, China Third Hospital	56 (44-64)	48.5	27.1 HTN 14.7 DM	103 MODERATE§	33 SEVERE/ CRITICAL§		136
Zhao, M[32]	Hospitalized	Wuhan, China Renmin Hospital	61 (46-70)	46.6	28.2 HTN 11.8 DM 6 CAD				1000
Arentz, M[33]	Hospitalized in ICU	Washington state, USA Evergreen Hospital	70 (range, 43-92)	52	33.3 DM		21		
Richardson, S[34]	Hospitalized	12 hospitals in New York, USA	63 (52-75)	60.3	56.6 HTN 33.8 DM 11.1 CAD				3522
Suleyman, G[16]	Admitted to Emergency department	Hospitals in Henry Ford Health System in Detroit, Michigan, USA	57.5 (16.8)	44.1	63.7 HTN 38.4 DM 12.7 CAD	214	141		355
		Total number of participants				518	1042	368	6573

CAD: coronary artery disease; CI: Cardiac injury; DM: diabetes mellitus; ECG: electrocardiography; HTN: hypertension; ICU: intensive care unit; IQR: interquartile range; SD: standard deviation
Age data is presented as median (IQR) or Mean (SD); Male gender and Previous CVD expressed as %
Ruan, Q[35]; Zhou, B[36]; Ni, W[30] did not provided level of accepted significance. Arentz, M[33] and Richardson, S[34] did not performed analysis of significance. All other studies accepted p values < 0.05 for statistically significant differences.
**Severe disease considered as one of the following: 1) Respiratory distress with respiratory rate more than 30 times/min; 2) Oxygen saturation ≤93% in resting state; 3) PaO2/FiO2≤300mmHg; Very severe disease considered as one of the following: 1) Respiratory failure in need of mechanical ventilation; 2) Shock; 3) Other organ dysfunction.*
†Excluded patients with previous cardiovascular disease
‡Severe defined as having one of the following: respiratory distress and respiratory rate higher than 30 times per minute; fingertip blood oxygen saturation less than 93% at rest; partial arterial oxygen pressure (PaO2) / fraction of inspiration oxygen (FiO2) less than 300mmHg, respiratory failure requiring mechanical ventilation; shock; multiple organ failure, requiring intensive care management
§Moderate considered as having one of the following: fever and respiratory symptoms, pneumonia manifestations in the imaging; Severe and critical defined as having one of the following: shortness of breath with respiratory rate (RR) ≥30 bpm or finger SpO2 ≤93% at rest, respiratory failure (requiring mechanical ventilation), shock or other organ failure (requiring ICU monitoring and treatment)

prevalence of acute myocardial injury was the lowest for the non-ICU setting, 9.5% (95% CI 1.5–23.4%, $p < 0.01$, $I^2 = 94$). Patients admitted to ICU had a pooled prevalence of acute myocardial injury of 44.9% (95% CI 27.7-62.8%, $p < 0.01$, $I^2 = 95\%$), whereas non-survivors had the highest pooled prevalence of acute myocardial injury, 57.7% (95% CI 38.5-75.7%, $p < 0.01$, $I^2 = 93\%$). The pooled prevalences showed high heterogeneity among the settings, with $I^2 > 90\%$.

Cardiovascular risk assessment before resuming sports activities

We propose a CV risk assessment tool, constructed based on the estimated disease severity, for patients who recovered from COVID-19 infection and wish to resume sports activities. A flowchart summarising our approach is presented in Figure 3. The treatment settings were used as surrogate markers for disease severity (outpatient, mild disease; 'inpatient non-ICU setting', moderate disease and 'inpatient ICU setting', severe disease). For the purpose of our study, a simplified approach to disease classification was defined as follows: 1) Mild disease – patients treated at home, who responded well to symptomatic medication and did not show signs of respiratory insufficiency; 2) Moderate disease – patients with some degree of respiratory insufficiency or need for hospitalization for supplemental oxygen or symptomatic control; 3) Severe disease – patients with respiratory or other end-organ failure requiring mechanical ventilation, ICU admission, or any other vital organ support.

Discussion

Our study results showed that the overall prevalence of COVID-19-related acute myocardial injury is high, and increases with disease severity, as observed by the increased prevalence in the inpatient non-ICU setting, inpatient ICU setting and non-survivors.

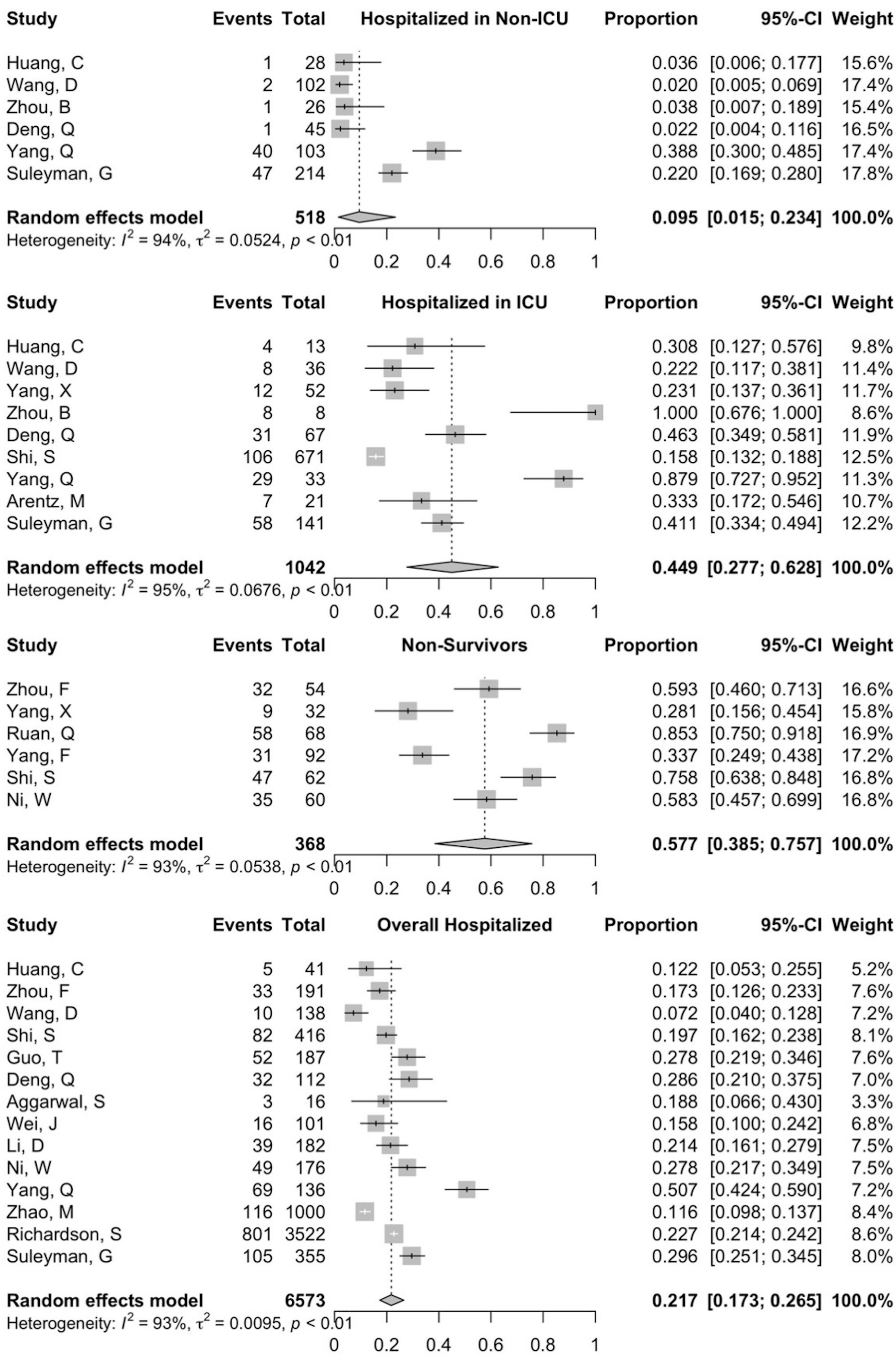

Figure 2 – Forest plot of the pooled prevalence of acute myocardial injury

CI: confidence interval; ICU: intensive care unit; IV: individual value

Prevalence and 95% confidence intervals expressed as proportions

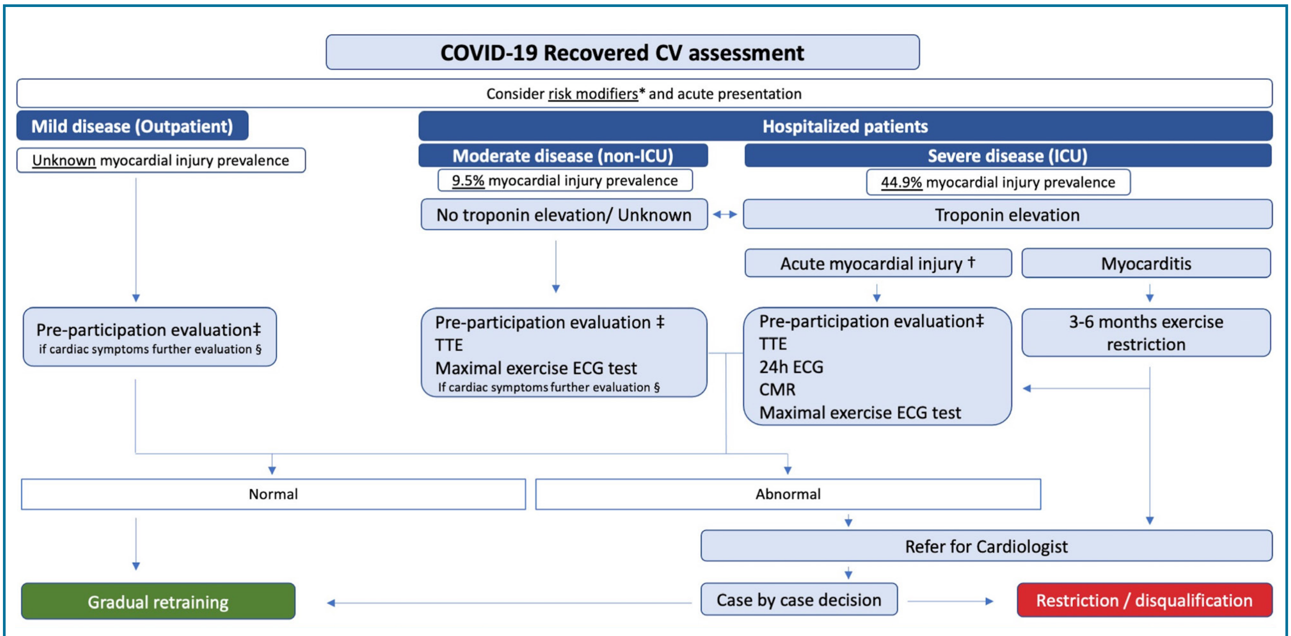

Figure 3 – Cardiovascular assessment flowchart for patients recovered from COVID-19 to resume sports activities
CV: Cardiovascular; ECG: Electrocardiography; ICU: intensive care unit; CMR: cardiac magnetic resonance; TTE: transthoracic echocardiography
** Risk modifiers (Pre-existing CV disease; Exercise type (intensity and competitive level)*
† Acute myocardial injury: evidence of myocardial injury at hospital admission - Elevated serum biomarkers of myocardial injury (troponin)
‡ 12-lead ECG included
§ Systematically search for symptoms of myocardial injury (chest pain, syncope, palpitations, dyspnea, fatigue); consider additional testing accordingly

Risk stratification and flowchart implementation

The pooled prevalence of acute myocardial injury showed that patient care setting reflected disease severity. Estimation of disease severity is the first step to determine the treatment approach and ensure patient safety. Although it is not known if COVID-19-related myocarditis is associated with sudden cardiac death, the prevalence of myocardial injury may be the best approximation for risk stratification based on available data. We present a proposed flowchart (Figure 3) that aids clinical decision-making for cardiovascular workup. We acknowledge that the decision to admit patients to the ICU varies widely based on local policies and other non-clinical factors such as availability of resources (e.g., beds, ventilators, healthcare insurance, etc.). However, we believe that this was the simplest and most practical way to standardise data from different cohorts. In addition, this approach based on patient care setting is fast and easy-to-use for physicians evaluating individuals wishing to engage in exercise training after COVID-19 infection.

The objective of the flowchart is to serve as an aid to clinical decision-making. This flowchart should only be applied to individuals who had completely recovered. Although the management of infected individuals falls out of the scope of our work, it has been proposed an interval of at least seven days free from symptoms before resuming exercise.[11-13] Full recovery must be confirmed (as recommended by local authorities) before conducting additional diagnostic tests. In particular, a treadmill test or other exercise tests, and pulmonary function tests (PFT) have an associated risk of aerosolization and should preferably be avoided in SARS-Cov-2 positive patients. However, if these tests are essential, adequate personal protective equipment must be used. For sports activities, local authorities' recommendations for the use of personal protective equipment and social distancing should be followed.

We also recommend that this cardiovascular risk assessment tool be used regarding potential risk factor modifiers. Age, male gender and previous CV disease have been associated with adverse outcomes.[14] The impact of exercise type, exercise intensity, and a state of deconditioning on immune system, oxidative stress and inflammation has been extensively debated in the literature. For competitive athletes, team physicians, exercise physiologists and coaches should all be involved to prescribe an appropriate training plan with progressive increases in exercise intensity. In clinical practice, we suggest that patients with pre-existing CV diseases, such as coronary artery disease (CAD), heart failure, cardiomyopathies, and arrhythmias warrant further CV investigations before resuming sports activities, preferably with a cardiology specialist. The type of sport, intensity and competitive level should also be taken into account. High-intensity sports athletes, elite and professional athletes often undergo routine cardiovascular screening that may include TTE and maximal exercise test as a pre-participation evaluation. We recommend that the physician repeat the screening after recovery from COVID-19.

Based on our findings, we recommend that a full pre-participation clinical evaluation (including a resting 12-lead ECG) be performed in all recovered individuals willing to return to sports activities. The ECG is a key component of the pre-participation screening as recommended by most European societies.[15] Special attention should be placed on QT interval measurements in patients treated with chloroquine or hydroxychloroquine.

Outpatient setting

Suleyman et al.[16] reported a prevalence of myocardial injury of 1,9% (2 of 108) in symptomatic patients treated in an outpatient setting, however, cardiovascular outcomes of these patients were not evaluated. To the best of our knowledge, there is no other work addressing the prevalence or the outcomes of myocardial injury in outpatients with COVID-19 infection. Moreover, management of asymptomatic patients wishing to engage in sports is also an important issue, with no data supporting safety. Clinical experience suggests that the majority of athletes will probably experience mild or asymptomatic disease, and be treated in an outpatient setting. Therefore, the prevalence of myocardial injury is expected to be even lower in athletes compared with the non-ICU hospitalized setting. In addition, it is reasonable to assume that young, healthy individuals will most likely be able to recover from a more severe form of the disease without seeking medical attention. In our opinion, a pre-participation clinical evaluation (including resting ECG) is mandatory and we strongly recommend a systematic approach to identify signs and symptoms of cardiac disease (e.g. chest pain, syncope, palpitations, dyspnoea or abnormal fatigue). The presence of these signs and symptoms should warrant further investigations with TTE, maximal exercise ECG test or 24-hour ambulatory ECG monitoring test based on the symptoms exhibited. Referral to a cardiologist is recommended if any of these tests are abnormal.

Inpatient setting

Although non-CV assessments are outside the scope of our review, it is important to note that most of hospital admission criteria are based on pulmonary disease. For that reason, PFTs, lung CT scans (if not performed during admission) and routine laboratory tests may provide further information to assess exercise fitness.

Elevation of serum biomarkers of cardiac injury has shown to be an important prognostic factor among hospitalized patients for COVID-19.[8] For recovered individuals treated in an inpatient setting who wish to resume exercise, the physician should carefully assess patients for evidence of myocardial injury (i.e. serum troponin above the 99th percentile of upper reference limit during hospitalisation). If a patient is discharged from hospital with a definitive diagnosis of myocarditis, specific treatment recommendations must be followed,[9] with exercise restrictions for 3 to 6 months and regular follow-up with a cardiologist. As recommended by the European Association of Preventive Cardiology, these patients may resume training and competition if left ventricle systolic function has returned to the normal range, serum biomarkers of myocardial injury have normalized and clinically relevant arrhythmias, such as frequent or complex repetitive forms of ventricular or supraventricular arrhythmias are absent on 24-h ECG monitoring and exercise test. Regular surveillance should be kept for two years and annually if late gadolinium enhancement persists on cardiac magnetic resonance (CMR)[9]

Patients without a definitive diagnosis of myocarditis, but with evidence of acute myocardial injury, fall into a "grey area". It is reasonable to consider that this group of patients may have recovered but with cardiac sequelae. Whether or not this will impact on clinical events is still unknown. However, we suggest that these patients undergo an assessment of cardiac anatomy and function, with specific focus on arrhythmias in a resting state and during exercise. Moreover, CMR imaging may play a fundamental role in the assessment of the risk for adverse outcomes during follow-up and should be performed when available.

With respect to hospitalized patients in a non-ICU setting without elevation of troponin, or in cases where cardiac biomarkers were not assessed, the authors recommend performing a TTE and maximal exercise ECG test as part of the clinical evaluation, including a 12-lead ECG. Signs and symptoms of cardiac disease must also be assessed.

Based on published data, young, healthy individuals who require ICU admission are rare. A minority group will most likely have a severe form of disease that will impact on physiological functions, including respiratory, cardiovascular, renal, and musculoskeletal. A multidisciplinary approach and a complete cardiac assessment (12-lead ECG, TTE, 24h ECG ambulatory monitoring and maximal exercise ECG test) is therefore recommended. If cardiac abnormalities are detected in these patients a CMR to assess myocardial sequelae should also be completed.

Limitations

Most data on the prevalence of myocardial injury derived from one country (China), especially from the city of Wuhan. Additionally, there isn't any information regarding the level of physical activity from participants of the studies. Also, the possibility that duplicate patients were included in the meta-analysis cannot be excluded. Therefore, it is difficult to extrapolate these results to a worldwide scenario and particularly to competitive athletes. Still, the authors point out that exercise-associated sudden cardiac death after a viral myocarditis is a significant issue in the context of SARS-COV-2 pandemic and for any individual wishing to engage in physical activity after SARS-COV-2 infection.

Our meta-analysis included different cohorts that may have different policies for COVID-19 testing. Also, the criteria for hospital and ICU admission may vary significantly from one place to another, as may the availability of resources. This may influence such decisions, and hence the prevalence and severity of COVID-19-associated cardiac injury. These limitations may affect the proportion of patients with COVID-19-related myocardial injury. Therefore, our approach may be unpredictable in different contexts and must never replace a thorough clinical judgement.

Statistical analysis suggests significant heterogeneity in the prevalence of acute myocardial injury among the patient care settings. However, the clinical meaning of such heterogeneity for the purpose of a prevalence study may be irrelevant given that the prevalence of myocardial injury is used as a parameter of disease severity rather than for clinical decision-making.

The absence of clinical trials including individuals who resumed sports activities after COVID-19 infection makes it difficult to establish the link between myocardial injury and sports-related adverse outcomes.

It is also likely that this meta-analysis overestimates the prevalence of myocardial injury due to selection bias, since some of the studies excluded patients without clinical records of cardiac biomarkers.

Our approach is focused on the clinical safety of patients, however, no cost-effectiveness data are available. Furthermore, the sports community involves different financial capacities that may make this strategy difficult to implement in some settings and may carry a heavy burden of costs.

Conclusions

Our data showed that the prevalence of myocardial injury in patients with COVID-19 is high and may be associated with disease severity. As myocardial involvement can be a trigger for severe clinical complications induced by exercise, we provide a practical flowchart to assist clinical decisions that may be the basis for evidence-based recommendations.

Our study proposes a CV risk stratification strategy for patients recovered from COVID-19 infection to resume any type of physical activity. Further studies are required to test the sensitivity and specificity of this approach in a real clinical scenario and its economic impact on a global scale.

Author contributions

Conception and design of the research: Puga L, Dinis P, Teixeira R, Dores H, Goncalves L. Acquisition of data: Puga L, Dinis P. Analysis and interpretation of the data: Puga L, Dinis P, Ribeiro J, Teixeira R. Statistical analysis: Puga L, Ribeiro J, Teixeira R. Writing of the manuscript: Puga L, Dinis P Critical revision of the manuscript for intellectual content: Goncalves L, Dores H, Teixeira R, Dinis P.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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