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Paper Title: A Narrative Review on Increased Prevalence of CV Complications following a COVID-19 Infection: The Risks and Considerations for Effective Management and Practice.

Running title: Increased Prevalence of CV Complications following a COVID-19 Infection

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Abstract:

The COVID-19 pandemic was one of the largest risks to global population health in recent years and acute infection and the persistent symptoms of Long COVID will likely continue to affect global health for years to come. Long COVID is very complex and impacts multiple systems and organs resulting in an extensive and undulating presentation of symptoms. COVID-19 has been shown to cause various cardiovascular (CV) injuries following acute infection with many patients suffering long-lasting impairment. This review article discusses the prevalence of CV complications following an acute COVID-19 infection and considers effective prevention and disease management strategies to help restore functional status and quality of life in patients.

Introduction:

The coronavirus disease 2019 (COVID-19) is arguably the greatest threat to population health and well-being since the 1918 Great Influenza epidemic or Spanish Flu. Whilst the pandemic status of COVID-19 has been removed, the threat to population health remains due to sustained and widespread transmission and viral mutations. There can be no doubt that despite the widespread removal of free testing, mandatory isolation, and social distancing guidelines that COVID-19, through sustained and free transmission, will continue to affect population health and wellbeing for years to come. Whilst the severity of acute infection has been significantly impacted by the development and widespread rollout of vaccinations, the persistent, episodic and debilitating condition, known as post-COVID condition or Long COVID, remains a very real threat to population health [1]. The incidence rate for Long COVID is estimated to be around one in every ten cases, affecting 10–30% of non-hospitalized patients, 50–70% of hospitalized patients[2,3] and 10–12% of vaccinated cases [4]. Recent estimates report that Long COVID affects around 65 million people worldwide [5] with contrasting figures provided by data modelling groups who suggest the number could be as high as 155 million [6]. To date, there has been no distinct phenotype or risk associated with Long COVID cases and it has been linked with all ages and acute phase disease severities. Accordingly, the data suggests an increased prevalence of Long COVID between the ages of 36 and 50 years, and most Long COVID cases are in non-hospitalized patients with a mild acute illness [7] which is to be expected as these populations represent the majority of overall COVID-19 cases. What is most problematic about Long COVID is a complex multisystemic pathophysiology which results in a broad and undulating patient presentation that consists of around 200 symptoms [5]. In the absence of effective treatments and the development and implementation of fragmented, ineffective and under-resourced Long COVID management services [8], Long COVID will likely pose sustained pressure on healthcare services for years to come.

Increased Prevalence of CV Complications, following a COVID-19 Infection

Whilst initially characterised as a respiratory illness, wider systemic issues are now acknowledged and well-documented. A prospective cohort study of low-risk individuals looked specifically at organ damage in the heart, lungs, liver, kidneys, pancreas and spleen and demonstrated that 70% of its 201 patients had sustained damage to at least one organ and 29% had multi-organ damage [9] which largely remained unchanged 12 months later (59% and 27% respectively)[10]. Within the context of acute cardiac injury, SARS-CoV-2 can cause acute

myocarditis and pericarditis, with myocardial injury occurring in five of the first 41 patients diagnosed with COVID-19 in Wuhan, China [11]. This mainly manifested as an increase in levels of high-sensitivity cardiac troponin I and creatine kinase indicating acute myocardial injury and mostly resulting in admissions to an intensive care unit [12].

As highlighted in the Central Illustration, there is a developing narrative that has been substantiated with detailed analysis of large data sets, it provides a concerning outlook regarding the substantial increase in long-term, risk of cardiovascular disease, which includes heart attack and stroke, following a SARS-CoV-2 infection [13]. Further risk factors include cerebrovascular disorders, dysrhythmias, ischemic and non–ischemic heart disease, pericarditis, myocarditis, heart failure, and thromboembolic disease [14] (Figure 1). Wan *et al* [15] completed a prospective cohort analysis of patients following a COVID-19 infection between March 2020 and November 2020 and completed an 18-month follow-up on 7,584 patients. During the acute phase, patients with COVID-19 were associated with a significantly higher short-term risk of cardiovascular disease (CVD) (hazard ratio [HR]: 4.3, 95% confidential interval [CI]: 2.6– 6.9)) and all-cause mortality (HR: 81.1, 95% CI: 58.5–112.4) when compared with a control sample (n=75,774). In the post-acute phase, 7,139 patients persisted with a higher risk of CVD in the long-term (HR: 1.4, 95% CI: 1.2–1.8) and all-cause mortality (HR: 5.0, 95% CI: 4.3–5.8) compared to a control sample (n= 71,296). Further data from Yeo *et al* [16] used the Centre for Disease Control National Vital Statistics System to assess the extent and disparity in excess acute myocardial infarction (AMI) and associated mortality during the pandemic, specifically targeting the Omicron (B.1.1.529) variant. The Vital Statistics System identified 1,522,669 reported AMIs between January 2012 and March 2022. Prior to the pandemic, AMI-associated mortality demonstrated a reduction in temporal trends over time relative to demographic groups and regions. These trends reverted during the pandemic and demonstrated a significant rise in AMI and mortality amongst the youngest-aged females and males. Upon further inspection, the semi-annual percentage change in the youngest and middle-aged groups in AMI-associated mortality increased by 5.3% (95% CI:1.6%–9.1%) and 3.4% (95% CI: 0.1%–6.8%), respectively. The excess death rate was also increased for the 25–44 years age groups, demonstrating a range from 23% to 34% for the youngest compared to 13%–18% for the oldest age groups. A recent systematic review [17] and meta-analysis that yielded 1,244,604 confirmed COVID-19 infections, concluded over a mean follow-up period of 8.5 months that the risk of AMI is 4 cases per 1,000 (2 cases per 1,000 in a control cohort). This was associated with an increased incident risk of 1.93 (95% CI: 1.65–2.26). Data produced

from the meta-regression also highlighted that the increased risk was also associated with age and sex (male). Whilst the exact pathophysiological mechanisms, risks, and long-term impacts upon cardiovascular health for COVID-19 and Long COVID patients remain largely unknown, the data summarised here and elsewhere is compelling and demonstrates a clear association between COVID-19 and Long-COVID and an increase in CVD risks and mortality. The increased risk to population health must be addressed as part of bespoke Long COVID and clinical investigations screening patients to detect cardiac damage/abnormalities and inform the development of appropriate and safe methods to manage the condition and, where possible, increase functional status and quality of life.

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Considerations for effective prevention, management, and practice

Preventative Approaches

The established cause-effect relationship between modifiable lifestyle behaviours and the risk for the premature onset of chronic diseases predisposes physical inactivity and poor diets as two of the most pertinent unhealthy living risk factors for CVD[18]. Whilst the notion of prevention in the context of an unexpected global pandemic that globally, we were unprepared for seems somewhat quizzical. It has long been understood the role of exercise, healthy eating and the benefits of engaging and practising healthy lifestyle behaviours and the protective effects this has on developing chronic disease[19]. There is conflicting data on the protective benefits of cardiorespiratory fitness [20] in the prevention of severe acute infection and more chronic issues, however, it is entirely plausible that lifestyle choices surrounding exercise, diet, smoking and alcohol consumption could offer improved patient outcomes [21,22]. The caveat to that this is not a uniform response which is demonstrated by the increasing incidence of Long COVID amongst previously fit, healthy, and even athletic populations [23,24].

The complexity and interactive nature of chronic disease is an important consideration in the design, development and implementation of prevention and optimal management strategies to ensure broad efficacy and effectiveness[25]. This remains true in the global response to COVID-19 which is equally, if not more, complex in its pathophysiology and epidemiology[26]. Since the start of the COVID-19 pandemic, various lifestyle factors (i.e., physical activity, alcohol consumption, obesity, smoking and sleep quality) have been associated with disease severity, patient outcomes and even mortality[27]. But as is the case with many other chronic diseases, there are multi-dimensional factors that affect patient outcomes. Despite a move towards

endemic status, COVID-19 is still very much present in society. Whilst the impacts of acute infection have largely been attenuated by effective vaccination programmes and increased treatment plans, the longer-term effects and risks to population health are ever-present. Therefore, to protect population health and well-being, preventative and proactive approaches will play a significant role if we are to prevent the incidence of Long COVID in community settings. The rollout and scaling up of preventive roles, like with many chronic disease areas are hindered by a lack of a united showing from leading healthcare organisations and political leaders [28]. Arguably, the most important medical breakthrough in recent times is the COVID-19 vaccination, which undoubtedly saved millions of lives and has also demonstrated a partial (not complete) reduction in the development of Long COVID [29]. However, waning immunity of all current approved COVID-19 vaccinations demonstrates a notable reduction in the protection offered [30], therefore requiring repeat vaccinations. However, access to COVID-19 vaccinations in most countries is not universal and has been limited to those deemed to be at greater risk (e.g., the elderly and those with co-morbidities). There is also potential to address health outcomes with other important agendas such as climate emergency and a need for clean air. It is well established that COVID-19 is airborne [31], yet access to adequate ventilation within schools, colleges, hospitals and places of employment where individuals co-exist creates an opportunity for heightened and sustained viral transmission.

Whilst these suggestions seem entirely plausible, implementation of these effective preventative measures would require a monumental step change in political agenda and thinking. It makes sense that prevention efforts are prioritized over the need for ongoing management of chronic disease to mitigate the projected near-and-long-term health consequences and the directly related physical, social, and economic environmental impacts. But at present, a lack of priority for developing and instilling prevention methods is an additional factor which poses a risk to population health and heaps pressure on developing effective management strategies.

Management Strategies

Whilst prevention of chronic disease is preferred, in many cases including in recent times where healthcare provision and lifestyle factors have been impeded by COVID-19, there must be total alignment of political agendas in relation to health and well-being, societal and economic factors. Whilst prevention is desirable, the stark reality is that this is unlikely as evidenced by decades of global prevalence data demonstrating continued acceleration [32]. Therefore, there is

an urgent need to implement effective management of CVD that can distinguish between the modifiable and non-modifiable risk factors, the latter of which now includes COVID-19 infection. Currently, it is not known whether resulting CV damage following a COVID-19 infection is reversible. With a significant increase in CV-related events and associated mortality, an important part of the management process is to obtain a comprehensive and interdisciplinary approach that focuses on the total risk for each patient [33]. An important component here is the need to make diagnostic screening widely accessible to fully characterise the extent of cardiac injury. Detailed insight from screening methods is imperative to inform the design and implementation of personalised management strategies that seek to consider risk factors collectively rather than individually in a whole risk profile and may be better equipped to reduce long-term risk, and symptoms, and improve/restore quality of life. Such an approach should be incorporated into the entire decision-making process that is truly interdisciplinary [8] and adopts the intricacies of a systems science approach[25]. Adopting more coordinated approaches could lead to the design and implementation of efficient and effective management services that improve patient outcomes and more broadly address a significant and growing burden on healthcare services worldwide.

Within the development of management services, it is important to consider both pharmacological and lifestyle approaches. Previous literature has demonstrated the efficacy of pharmacological [34] and lifestyle [35] approaches to managing CVD but the additional dynamic and interrelating nature of COVID-19 could pose additional complexity. Research has demonstrated via in vivo and in vitro studies that tanshinone IIA (TsIIA) and salvianolate (STS) have numerous cardioprotective effects which include antioxidative, anti-inflammatory, endothelial protection, myocardial protection, anticoagulation, vasodilation, and anti-atherosclerotic, as well as reducing proliferation and migration of vascular smooth muscle cells, the full detail of which has been expertly summarised by Ren *et al* [36]. The role of positive lifestyle factors in the management of chronic conditions is of equal importance [37] but to date these approaches demonstrate little/no success at a population level.

Considerations for Practise

The magnitude of increased CV events and mortality following a COVID-19 infection tells a compelling story that, if not addressed, will plague population health and wellbeing for generations to come. With COVID-19 being normalised within society, our attention must shift from preventive (proactive) approaches to developing detailed and effective management

(reactive) services. Arguably the most important component here is to increase screening and diagnostic processes following a COVID-19 infection to detect CV abnormalities and injury that could pose a risk to health and mortality. Making access to screening and diagnostic tools for a virus that transmits freely within community settings, might appear ambitious and in some sense, not practical or economically viable. However, the long-term risk to global health could have a devasting impact for generations to come. The data is compelling, and the risk to population health must be addressed as part of bespoke Long COVID and interdisciplinary clinical investigations to detect cardiac damage/abnormalities and inform the development of appropriate and safe methods to manage the condition and where possible increase functional status and quality of life. To do this effectively it might be prudent to look beyond and establish collaborative links that sit outside of 'usual' clinical practice [38,39]. This could facilitate the development of 1) avoiding increasing pressure on already stretched healthcare services and 2) delivering these approaches at the scale that is and will be required.

Conclusion:

Despite being in the endemic phase of the pandemic, there is no doubt that COVID-19 will continue to affect the global population for many years to come, whether that be via acute infection or Long COVID. Multiple CV injuries and disorders have been documented in patients demonstrating that COVID-19 can have a prolonged damaging effect on the CV system. With the risk of AMI being twice as likely to occur in those diagnosed with COVID-19 [17], comprehensive strategies must be in place to screen patients and effectively manage the conditions to improve functional status and quality of life. However, to ease pressure on current healthcare systems to develop effective management strategies, governments and policymakers need to prioritise developing and installing prevention methods to reduce conditions which pose a risk to population health.

Figure Captions:

Fig 1: The prevalence of CV complications following an acute COVID-19 infection.

Central Illustration Legend: The prevalence and risk of serious cardiac event and/or mortality following an infection with Sars-CoV-2 has increased at an alarming rate. There is a need to implement effective prevention and management strategies to reduce the risk to population health and wellbeing.

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