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REVIEW

The long-term cardiovascular impairment of COVID 19: need for clarity in definition and terminology

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ABSTRACT

Clinical experience and several large studies in the field have found that SARS-CoV-2 infection can cause long-term persistent cardiovascular (CV) impairment beyond the acute phase of the disease. This has resulted in a major public health concern worldwide. Regarding COVID-related long-term involvement of various organs and systems, using specific definitions and terminology is crucial to point out time relationships, lingering damage, and outcome, mostly when symptoms and signs of CV disease persist beyond the acute phase. Due to a lack of a common standardized definition, investigators have used interchangeable terms such as "long COVID," "post-COVID," or "post-acute sequelae of COVID-19" to describe CV involvement, thus causing some confusion. For the sake of clarity, the aim of this paper is to discuss the definition and terminology used in defining sequelae after the acute phase of COVID-19, thus pointing out the meaning of definitions like acute cardiac injury, post-acute sequelae of COVID-19, long COVID syndrome, and increased risk of atherosclerotic cardiovascular disease.

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KEY WORDS: Heart injuries; Post-acute COVID-19 syndrome; Cardiovascular abnormalities.

Several large longitudinal studies on COVID-19 affected people have found that SARS-CoV-2 infection can result in long-term cardiovascular (CV) impairment beyond the acute phase. This has become a major public health concern.[1-3] Current knowledge of the pathophysiological mechanisms responsible for delayed complications is limited. Many symptoms (like breathlessness, chest pain, fatigue, headaches, brain fog, and palpitations) and signs of CV issues (like ventricular dysfunction and arrhythmias) are reported. Still, there are no definitive indicators that suggest that long-lasting cardiac involvement is developing.[4, 5] A new syndrome is emerging.

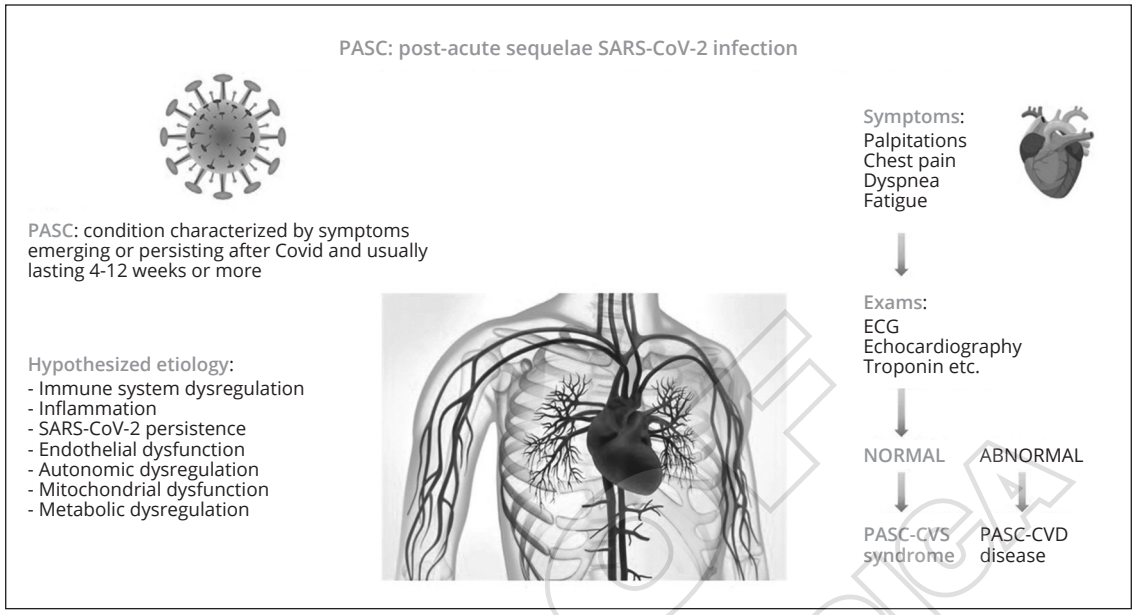

Figure 1.—Graphical abstract.

As such, developing specific definitions and appropriate terminology regarding time relationships, lingering damage, and the outcome is imperative, mainly when symptoms and signs of heart problems persist over time (Figure 1).[4-6]

Literature search

Due to a lack of a standard standardized definition of the syndrome regarding time relationship the most, recently a few investigators have published state for art papers on "long COVID," "post-COVID" or "post-acute sequelae of COVID-19" (PASC) in patients with CV involvement.

We have conducted a systematic search on the most frequent scientific information platforms to clarify how the above-stated terminology is used and which clinical picture and symptomatology it refers to.

Our search strategy has been designed to create this review relating to the terminology used to define the chronic post-COVID-19 syndrome. We have searched MEDLINE, Scopus, and Web of Science databases.

Firstly, we have searched the single MESH terms: "long COVID," "post-COVID" and "post-acute sequelae of COVID-19" (PASC). Second, we have used their combination.

We included papers published last year up to December 4th, 2022. For studies to be included in this review, they have had to report on primary research, be published in peer-reviewed journals, and be written in English. The present review briefly analyses terminology and the related clinical symptoms.

Search for the term "long COVID" has identified 188 articles, of whom 36 have been classified as review. Search for the term "post-COVID" has identified 1140 documents, of whom 124 have been classified as review. A search for "post-acute sequelae of COVID-19" (PASC) has identified 104 articles, and 20 of them have been classified as review.[7-10] Interestingly, in some manuscripts, the terms Long COVID and Post-COVID have been used to describe the same patients, clinical conditions, and symptoms, thus highlighting some confusion. Recently, a state-of-the-art paper on 'long-COVID: Post-acute sequelae of COVID-19 with a cardiovascular focus' has been published. The American College of Cardiology released a 2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults as guidance on the evaluation of cardiovascular symptoms after covid-19 to help clinicians diagnose and manage PASC.[4, 5] Other manuscripts have emphasized

Reported symptoms	%
Fever	8-16
Cough	10-14
Headache	13-27
Myalgia/fatigue	10-20
Sore throat/rhinorrhea	11-26
Dysgeusia/anosmia	4-15
Cardiovascular symptoms	4-8
Neurological symptoms	2-4
Gastro-intestinal symptoms	2-16

Figure 2.—Main aspects of the SARS-CoV-2 pandemic in terms of symptoms in Italy.

that persistent cardiac injury and COVID-19-related increased CV risk need further comments.[11]

Our understanding of long COVID needs to be continuously updated to provide timely information for public policy and guidance for post-COVID-19 care since the latter is a distinct entity compared to the acute phase of SARS-CoV-2 infection[5, 11-14] (Figure 2).[15, 16]

Many words are shared: "persistent," "sequelae," "long COVID," and "risk factor" In terms of terminology, all of them are linked to different concepts.

Definition of COVID 19 in the chronic phase

At the pandemic's beginning, scientists addressed critical knowledge gaps around COVID-19. They needed to learn about long COVID. One of the first reports was from Italy. The authors stated, "We assessed persistent symptoms in patients discharged from the hospital after recovery from COVID-19. Common symptoms included cough, fever, dyspnea, musculoskeletal symptoms (myalgia, joint pain, and fatigue), gastrointestinal symptoms, and anosmia/dysgeusia. However, information is lacking on symptoms that persist after recovery."[17, 18] These patients were called 'long haulers.' The term was initially coined by a patient and inspired several people to study long COVID, also known as post-COVID conditions.[19]

Several definitions have subsequently been introduced. The Centers for Disease Control and Prevention has defined "post-COVID conditions" as a broad range of symptoms presents 4 or more weeks after the first infection, which include LC (symptoms lasting weeks to months) and persistent post-COVID syndrome.[2] Based on the chronicity of symptoms post COVID-19 infection, Nalbandian *et al.* classified post-acute COVID-19 as follows: "post-acute COVID-19 syndrome" (presence of subacute or persistent symptoms up to 12 weeks from the initial episode) and "chronic post-COVID syndrome" (symptoms present beyond 12 weeks).[19]

According to the report in the literature, the post-acute sequelae of SARS-CoV-2 infection (PASC) represent a heterogeneous clinical disorder without an unanimously accepted definition for its widely varying presentations. Patients with PASC have symptoms after SARS-CoV-2 infection, usually persisting over 4-12 weeks (without ACI) in the post-acute period (in the past, the latter was called "convalescence").[4, 5, 11] Twelve weeks after the acute phase of infection,

the 'chronic period' starts, and patients with symptoms not explained by an alternative diagnosis should have long COVID syndrome. This distinction is important and is related to several complex underlying mechanisms. These patients should be evaluated on an individual basis.[4, 5, 11] Irrespective of the definition used by different medical societies or health organizations, it is essential to remember that even individuals with mild form may still develop PASC in the days or weeks after infection and even chronic long COVID.[2, 4, 5, 20-22]

PASC into two groups: those with objectively distinguishable cardiovascular disease (PASC-cardiovascular disease, PASC-CVD) and those with test results normal or unable to fully explain reported symptoms (PASC-cardiovascular syndrome, PASC-CVS). Cardiovascular manifestations of PASC are frequent[23] and mainly affect non-elderly individuals.[24] Many patients, including those with cardiovascular diagnoses, suffered from exercise intolerance, describing fatigue even during activities of daily living and severe post-exertional dyspnea. However, in patients with cardiopulmonary symptoms suspected of having a cardiac etiology, tests led to a cardiovascular diagnosis in only 23% of cases. Specifically, the diagnosis included new cardiomyopathy, ischemia, arrhythmias, and myocardial involvement. On the contrary, in most cases (77%), no cardiovascular disease was found.[25]

The potential pathophysiological mechanisms of PASC remain unknown. However, the mechanisms implicated in PACS have been hypothesized to be consequences of altered physiological pathways and mechanical/anatomical damage to the cardiac system during the acute phase of COVID-19. These mechanisms include impaired regulatory mechanisms of the immune system, residual post-inflammatory damage, and inadequate and underlying antibody response during acute infection.[26, 27]

Pandemic-induced stress was included among the possible pathophysiological mechanisms and triggers.[28]

Stress induces several effects on the cardiovascular system: endothelial dysfunction, vasoconstriction, increased sympathetic activity, plaque activation, increased atrioventricular conduction velocity, platelets activation, increased systemic inflammation, and reduce immune system function.[28] All these factors have been called into question to explain the pathophysiological mechanism leading to the development of PASC. Furthermore, systemic vascular involvement may explain nearly all patients' fatigue. The mechanisms involved in PASC are like those of the acute phase. Still, vascular systemic involvement can determine different symptoms and slow and insidious disease evolution.[27, 28]

Anxiety has been associated with neurocognitive-PASC (neuro-PASC); a syndrome characterized by persistent neurocognitive symptoms.[29]

Several studies found females significantly more likely to report persistent neurocognitive symptoms following SARS-CoV2 infection. Discrepancies in sex hormones related to inflammatory processes may contribute to this difference. However, non-biological factors may also be associated with female sex and contribute to the observed associations.[30]

CV outcomes and COVID 19

Acute cardiac injury (ACI) is a known major complication of the infection. However, until the study's publication by Lu *et al.*, it was unknown whether ACI acquired during COVID-19 recovers or not.[6] The authors investigated the incidence of ACI over a follow-up period of 2.5 months following hospitalization. ACI was defined as serum troponin-T (TNT) level >99th percentile upper reference limit during hospitalization, and recovery was defined as TNT below this cut-off 2.5 months after admission. ACI incidence rate was 39.7% among hospitalized patients. Among the survivors, 55.8% exhibited persistent cardiac dysfunction. Predicting ACI recovery post-discharge using the top predictors (TNT, creatinine, lymphocyte, sodium, lactate dehydrogenase, lymphocytes, and hematocrit) at discharge yielded 63.73-75.73% accuracy. Although 2.5 months is a short definition, the term long-COVID (cardiac) condition may be applied to this setting.[6] Researchers from Washington University and the Veterans Administration Health Care System in St. Louis have reported that one year after COVID-19 infection some

patients were still at higher risk of CV disease, including ischemic heart disease, myocarditis, pericarditis, heart failure, arrhythmias, cerebrovascular disorders, and thromboembolic disease.[11] Patients with mild COVID-19 infection who had not been hospitalized were also at risk, and the risk increased with the severity of the infection. Patients with a diagnosis of COVID-19 disease had a 72% increased risk of developing heart failure, a 63% increased risk of myocardial infarction, and a 52% increased risk of stroke compared with healthy controls. This was regardless of age, race, sex, and other cardiovascular risk factors, including obesity, hypertension, diabetes, chronic kidney disease, and hyperlipidemia, even in individuals without any underlying CV disease.[11]

The mechanism by which the virus causes long-term damage to the heart and blood vessels is the subject of debate and research. Potential tools include persistent damage from a previous direct viral invasion of endothelium and cardiac tissue; elevated levels of proinflammatory chemical messengers called cytokines that lead to heart scarring due to chronic infection; depression of the immune system; loneliness in quarantine; and genetic predisposition.[31, 32]

The distinction between the persistence of an ACI condition and PASC is simple if the two are separated by complete healing. Still, it is not simple if symptoms and complications continue soon after the infection and then persist.[4-7] Again, distinguishing between long-term CV consequences and increased risk of atherosclerotic cardiovascular disease (ASCVD) following COVID-19 infection is also difficult.

Some individuals with CV risk factors such as obesity and chronic kidney disease may have an increased risk of acquiring SARS-CoV-2 infection leading to worse CV outcomes after COVID-19.[33] However, Al-Aly *et al.* have noted that disease severity and related outcomes are similar across study subgroups suggesting that SARS-CoV-2 infection leads to *de-novo* CV disease due to a chronic latent inflammatory trigger.[11] The authors of this study have not compared symptomatic versus asymptomatic infections, a potential area for further research.[11]

Similarly, Kuehn has reported that young patients with COVID-19 were 166% more likely to receive a new diagnosis of diabetes than were age- and sex-matched patients without COVID-19.[34]

Without a standard definition and the lack of specific guidance on how to manage patients recovering from the acute phase of the illness and the wide range of similar symptoms as well, it is certainly challenging to distinguish among the different conditions and assign the label of persistent ACI, PASC, long COVID and increased risks of ASCVD.

Governments and health systems worldwide

TABLE I.—*Definitions and clinical presentation of COVID-19.*[45-49]

Definitions and clinical presentation of COVID-19
• Asymptomatic (or paucisymptomatic): it refers to an individual who tests positive for SARS-CoV-2 infection but has no symptoms or non-specific symptoms consistent with COVID-19
• Mild illness: it refers to an individual who has symptoms or signs of COVID-19 (*e.g.* fever, cough, sore throat, and malaise), without dyspnoea or abnormal chest imaging
• Moderate illness: individual who has lower respiratory disease (*e.g.* pneumonia) with oxygen saturation equal to or over 94% on room air at sea level
• Severe illness: individual who has lower respiratory disease with oxygen saturation <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, a respiratory rate >30 breaths per minute, or infiltrates involving >50% of the lung fields on chest imaging
• Critical illness: individual who has lower respiratory disease with respiratory failure, septic shock, and/or multiple organ dysfunction, without or with different heart participation
• Myocarditis: condition defined by the presence of cardiac symptoms (*e.g.* chest pain, dyspnoea, palpitations, syncope), elevated cardiac troponin, and abnormal electrocardiographic, echocardiographic, CMR, and/or histopathological findings on biopsy or post-mortem evaluation in the absence of flow-limiting coronary artery disease
• Myocardial involvement: condition defined by abnormal myocardium as elicited by electrocardiographic, echocardiographic, CMR and/or histopathological findings, with or without symptoms and with or without an elevated troponin
• Myocardial injury: condition defined by a troponin level above the 99th percentile upper reference limit
• Post-acute sequelae COVID of (PASC): condition defined by a collection of symptoms that emerge or persist after recovery from COVID-19, usually lasting for 4-12 weeks and beyond

TABLE II.—*Definitions of different form of PASC*.[27, 38-41]

Definitions of different form of PASC
• Neuro-PASC: persistence of neurocognitive symptoms
• PASC-cardiovascular disease (PASC-CVD): subjects with objectively distinguishable cardiovascular disease
• PASC-cardiovascular syndrome (PASC-CVS) subjects in which test results normal or unable to fully explain reported cardiovascular symptoms

should be prepared to deal with the likely significant contribution of the COVID-19 pandemic to a rise in the burden of CV diseases.[35-38]

Researchers have been steadily gathering important insights into the effects of two years of the COVID-19 pandemic on long-term direct and indirect lingering damage of biological processes and are raising concerns about the deterioration of many organs, CV system included.[27, 39-41] Long COVID-19 is a vast area that involves many different fields of medicine, and different viral variants may cause various long COVID-19 manifestations.[42, 43]

Given the large number of people with COVID-19 globally, multi-omics approaches to the disease might help understand the multifaceted expression of SARS-CoV-2 disease. Integrating different omics data types is often used to elucidate potential causative changes that lead to different phenotypes, diseases, and/or treatment targets.[44]

In conclusion, COVID-19 represents a complex entity not only regarding its acute phase but also concerning its consequences in the short and long term. The present paper tries to shed some light on the aftermaths of COVID-19 in terms of terminology to tackle confusion around them (Table I,[45-49] Table II).[27, 38-41]

Key messages

• COVID-related long-term involvement of various organs and systems, using specific definitions and terminology is crucial to point out time relationships, lingering damage, and outcome, mostly when symptoms and signs of CV disease persist beyond the acute phase.

• PASC into two groups: those with objectively distinguishable cardiovascular disease (PASC-cardiovascular disease, PASC-CVD) and those with test results normal or unable and those with test results normal or unable to fully explain reported symptoms (PASC-cardiovascular syndrome, PASC-CVS).

• The mechanism by which the virus causes long-term damage to the heart and blood vessels is the subject of debate and research.

References

1. Logue JK, Franko NM, McCulloch DJ, McDonald D, Magedson A, Wolf CR, *et al.* Sequelae in Adults at 6 Months After COVID-19 Infection. JAMA Netw Open 2021;4:e210830.

2. Venkatesan P. NICE guideline on long COVID. Lancet Respir Med 2021;9:129.

3. Cecchini E, Schino S, Gambadoro N, Ricciardi L, Trio O, Biondi-Zoccai G, *et al.* Facing the pandemic with a smile: the case of Memedical and its impact on cardiovascular professionals. Minerva Cardiol Angiol 2022. [Epub ahead of print]

4. Raman B, Bluemke DA, Lüscher TF, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. Eur Heart J 2022;43:1157–72.

5. Gluckman TJ, Bhave NM, Allen LA, Chung EH, Spatz ES, Ammirati E, *et al.*; Writing Committee. 2022 ACC Expert Consensus Decision Pathway on Cardiovascular Sequelae of COVID-19 in Adults: Myocarditis and Other Myocardial Involvement, Post-Acute Sequelae of SARS-CoV-2 Infection, and Return to Play: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2022;79:1717–56.

6. Lu JQ, Lu JY, Wang W, Liu Y, Buczek A, Fleysher R, *et al.* Clinical predictors of acute cardiac injury and normalization of troponin after hospital discharge from COVID-19. EBioMedicine 2022;76:103821.

7. Frontera JA, Sabadia S, Yang D, de Havenon A, Yaghi S, Lewis A, *et al.*; NYU Neurology COVID-19 Study Team. Life stressors significantly impact long-term outcomes and post-acute symptoms 12-months after COVID-19 hospitalization. J Neurol Sci 2022;443:120487.

8. Bughrara MS, Swanberg SM, Lucia VC, Schmitz K, Jung D, Wunderlich-Barillas T. Beyond COVID-19: the impact of recent pandemics on medical students and their education: a scoping review. Med Educ Online 2023;28:2139657.

9. Pellegrino R, Chiappini E, Licari A, Galli L, Marseglia GL. Prevalence and clinical presentation of long COVID in children: a systematic review. Eur J Pediatr 2022;181:3995–4009.

10. Allard N, Miller A, Morgan M, Chakraborty S. Post-COVID-19 syndrome/condition or long COVID: persistent illness after acute SARS CoV-2 infection. Aust J Gen Pract 2022;51:952–7.

11. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. Nature 2021;594:259–64.

12. Mattioli AV, Coppi F, Nasi M, Pinti M, Gallina S. Long COVID: A New Challenge for Prevention of Obesity in Women. Am J Lifestyle Med 2022;17:164–8.

13. Farinetti A, Manenti A, Manco G, Roncati L, Coppi F, Mattioli AV. From coronavirus disease 2019 to long coronavirus disease 2019 in vascular pathology. J Vasc Surg 2022;76:1427–8.

14. Chidambaram V, Kumar A, Calcaterra G, Mehta JL. Persistent cardiac injury - An important component of long COVID-19 syndrome. EBioMedicine 2022;77:103892.

15. Barbieri G, Pizzato M, Gögele M, Giardiello D, Weichenberger CX, Foco L, *et al.* Trends and symptoms of SARS-CoV-2 infection: a longitudinal study on an Alpine population representative sample. BMJ Open 2023;13:e072650.

16. Adorni F, Jesuthasan N, Perdixi E, Sojic A, Giacomelli A, Noale M, *et al.*; On Behalf Of The Epicovid Working Group. Epidemiology of SARS-CoV-2 Infection in Italy Using Real-World Data: Methodology and Cohort Description of the Second Phase of Web-Based EPICOVID19 Study. Int J Environ Res Public Health 2022;19:1274.

17. Long CO. Long COVID: let patients help define long-lasting COVID symptoms. Nature 2020;586:170.

18. Centers for Disease Control and Prevention. Post- COVID conditions. https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html. [Accessed January 5th, 2022].

19. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, *et al.* Post-acute COVID-19 syndrome. Nat Med 2021;27:601–15.

20. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ [Accessed on December 6th 2022].

21. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, *et al.*; Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol 2018;72:2231–64.

22. World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus; 2021 [Internet]. https://www.who.int/publications/i/item/WHO-2019-nCoVPost_ COVID-19_condition-Clinical_case_definition-2021.1 [cited 2023 Aug 11].

23. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA 2020;324:603–5.

24. Estiri H, Strasser ZH, Brat GA, Semenov YR, Patel CJ, Murphy SN; Consortium for Characterization of COVID-19 by EHR (4CE). Evolving phenotypes of non-hospitalized patients that indicate long COVID. BMC Med 2021;19:249.

25. Wang SY, Adejumo P, See C, Onuma OK, Miller EJ, Spatz ES. Characteristics of patients referred to a cardiovascular disease clinic for post-acute sequelae of SARS-CoV-2 infection. Am Heart J Plus 2022;18:100176.

26. Elseidy SA, Awad AK, Vorla M, Fatima A, Elbadawy MA, Mandal D, *et al.* Cardiovascular complications in the Post-Acute COVID-19 syndrome (PACS). Int J Cardiol Heart Vasc 2022;40:101012.

27. Lo Tartaro D, Neroni A, Paolini A, Borella R, Mattioli M, Fidanza L, *et al.* Molecular and cellular immune features of aged patients with severe COVID-19 pneumonia. Commun Biol 2022;5:590.

28. Mattioli AV, Coppi F, Nasi M, Gallina S. Stress and cardiovascular risk burden after the pandemic: current status and future prospects. Expert Rev Cardiovasc Ther 2022;20:507–13.

29. Ch'en PY, Gold LS, Lu Q, Ye T, Andrews JS, Patel P. Exploring risk factors for persistent neurocognitive sequelae after hospitalization for COVID-19. Ann Clin Transl Neurol 2023;10:1200–8. [Epub ahead of print]

30. Fernández-de-Las-Peñas C, Martín-Guerrero JD, Pellicer-Valero ÓJ, Navarro-Pardo E, Gómez-Mayordomo V, Cuadrado ML, *et al.* Female sex is a risk factor associated with long-term post-COVID related-symptoms but not with COVID-19 symptoms: the LONG-COVID-EXP-CM multicenter study. J Clin Med 2022;11:413.

31. Bassareo PP, Melis MR, Marras S, Calcaterra G. Learning from the past in the COVID-19 era: rediscovery of quarantine, previous pandemics, origin of hospitals and national healthcare systems, and ethics in medicine. Postgrad Med J 2020;96:633–8.

32. Stein SR, Ramelli SC, Grazioli A, Chung JY, Singh M, Yinda CK, *et al.*; NIH COVID-19 Autopsy Consortium. SARS-CoV-2 infection and persistence in the human body and brain at autopsy. Nature 2022;612:758–63.

33. Kuehn BM. COVID-19 linked with increased incidence of youth diabetes. JAMA 2022;327:711.

34. Ladds E, Rushforth A, Wieringa S, Taylor S, Rayner C, Husain L, *et al.* Developing services for long COVID: lessons from a study of wounded healers. Clin Med (Lond) 2021;21:59–65.

35. Gaspardone A, Versaci F, Tomai F, Biondi-Zoccai G, Sgueglia GA, Gioffrè G, *et al.* Reduction in emergency access for acute myocardial infarction during the COVID-19 pandemic: a survey from the greater area of Rome. Minerva Cardiol Angiol 2022;70:421–7.

36. Marini M, Zilio F, Martin M, Strazzanti M, Quintarelli S, Guarracini F, *et al.* COVID-19 pandemic and elderly: is the curtain dropped for urgent pacemaker implantations? Minerva Cardiol Angiol 2022;70:298–302.

37. De Rosa S, Spaccarotella C, Basso C, Calabrò MP, Curcio A, Filardi PP, *et al.*; Società Italiana di Cardiologia and the CCU Academy investigators group. Reduction of hospitalizations for myocardial infarction in Italy in the COVID-19 era. Eur Heart J 2020;41:2083–8.

38. Paolisso P, Bergamaschi L, Saturi G, D'Angelo EC, Magnani I, Toniolo S, *et al.* Secondary Prevention Medical Therapy and Outcomes in Patients With Myocardial Infarction With Non-Obstructive Coronary Artery Disease. Front Pharmacol 2020;10:1606.

39. Douaud G, Lee S, Alfaro-Almagro F, Arthofer C, Wang C, McCarthy P, *et al.* SARS-CoV-2 is associated with changes in brain structure in UK Biobank. Nature 2022;604:697–707.

40. Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. Lancet Diabetes Endocrinol 2022;10:311–21.

41. De Gaetano A, Solodka K, Zanini G, Selleri V, Mattioli AV, Nasi M, *et al.* Molecular Mechanisms of mtDNA-Mediated Inflammation. Cells 2021;10:2898.

42. Liao X, Guan Y, Liao Q, Ma Z, Zhang L, Dong J, *et al.* Long-term sequelae of different COVID-19 variants: the original strain versus the Omicron variant. Glob Health Med 2022;4:322–6.

43. Roncati L, Manenti A, Manco G, Farinetti A, Mattioli AV. COVID-19 thromboembolic complications: deepening immunoinflammatory features. J Vasc Surg 2021;74:1048–9.

44. Mercuro G, Bassareo PP, Deidda M, Cadeddu C, Bar-

berini L, Atzori L. Metabolomics: a new era in cardiology? J Cardiovasc Med (Hagerstown) 2011;12:800–5.

45. UK National Health Service. Terminology and Classification; 2023 [Internet]. https://digital.nhs.uk/services/terminology-and-classifications [cited 2023, Aug 11].

46. Cooper LT Jr. Myocarditis. N Engl J Med 2009;360:1526–38.

47. 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 2022;27:1341–53.

48. Babapoor-Farrokhran S, Gill D, Walker J, Rasekhi RT, Bozorgnia B, Amanullah A. Myocardial injury and COVID-19: possible mechanisms. Life Sci 2020;253:117723.

49. Munipalli B, Seim L, Dawson NL, Knight D, Dabrh AM. Post-acute sequelae of COVID-19 (PASC): a meta-narrative review of pathophysiology, prevalence, and management. SN Compr Clin Med 2022;4:90.

Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Giuseppe Calcaterra and Pier P. Bassareo contributed equally to the paper. Conceptualization: Giuseppe Calcaterra, Pier P. Bassareo. Methodology: Anna V. Mattioli, Susanna Sciomer. Resources: Anna V. Mattioli. Writing — original draft preparation: Giuseppe Calcaterra, Pier P. Bassareo, Carmen A. Spaccarotella, Francesco Barillà, Giuseppe Vadalà, Cesare de Gregorio. Writing — review and editing: Francesco Romeo, Jawahar L. Mehta, Anna V. Mattioli. All authors have read and agreed to the published version of the manuscript.

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