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REVIEW ARTICLE

Long COVID, Non-COVID19 Excess Deaths, and Post-Pandemic Cardiovascular Disease Risks: Mechanistic Links and Intervention Opportunities

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ABSTRACT

Persistent non-COVID19 excess mortality is a major post-pandemic health crisis without clear explanation. In current review, the hypothesis of Long COVID's causal link to the non-COVID19 excess mortality was studied by applying time-lag correlation analysis between the excess death with COVID19 and the excess death without COVID19 in Australia between Jan 2020 and Mar 2023, which revealed a remarkable correlation that coincided with the disease severity of the corresponding variants including Delta, Omicron BA.1-BA.3, and Omicron BA.4-BA.5 waves. Based on the correlating epidemiological findings, known immunity-mediated pathologies of Long COVID such as endothelial damage, thrombosis, and bleeding were explored in contemplating acute coronary syndrome as a precipitating mechanism of the non-COVID19 excess death. The identified mechanistic linkage of non-COVID19 excess mortality to Long COVID paves ways for its countermeasures. Additional measures of using nasal hygiene products to curb the airborne infection risks, reserved physical exercise in the months after the recovery of COVID19, closer management of cardiovascular diseases (CVD) and diabetic risk factors, and root-level Long COVID treatments tailored to treating the dysfunctional immunity around macrophages and neutrophils are proposed to reduce the non-COVID19 excess deaths.

Keywords: COVID19, excess mortality, excess death, CVD, cardiovascular diseases, hypertension, blood pressure, hypercholesterolemia, dyslipidemia, cholesterol, microvascular rarefaction, SARS-CoV-2, blood clots, thrombosis, neutrophils, macrophage, immunity, immune dysfunction, Long COVID, acute coronary syndrome, ACS

Introduction

Excess non-COVID19 mortality in current COVID19-endemic era is an imminent global concern with many nations reporting persistent 5% or higher excess deaths[1] (**Fig. 1**). Taking United Kingdom (UK) as an example, the excess death comprised CVD and other circulatory diseases as two of the most common cited causes during the pandemic through to the endemic period up to June 2023 with nearly 100,000 excess deaths from CVD as of June 2023, making CVD the single largest contributor to the recorded excess deaths among other disease areas[2]. Independently, a recent 18 months follow-up study on UK Biobank data showed that COVID19 infection drastically escalated the risks of CVD and all-cause mortality risks in both acute phase and in long-term[3], confirming the epidemiological linkage between past COVID19 infection and the long-term escalated risks of CVD and non-COVID19 excess deaths.

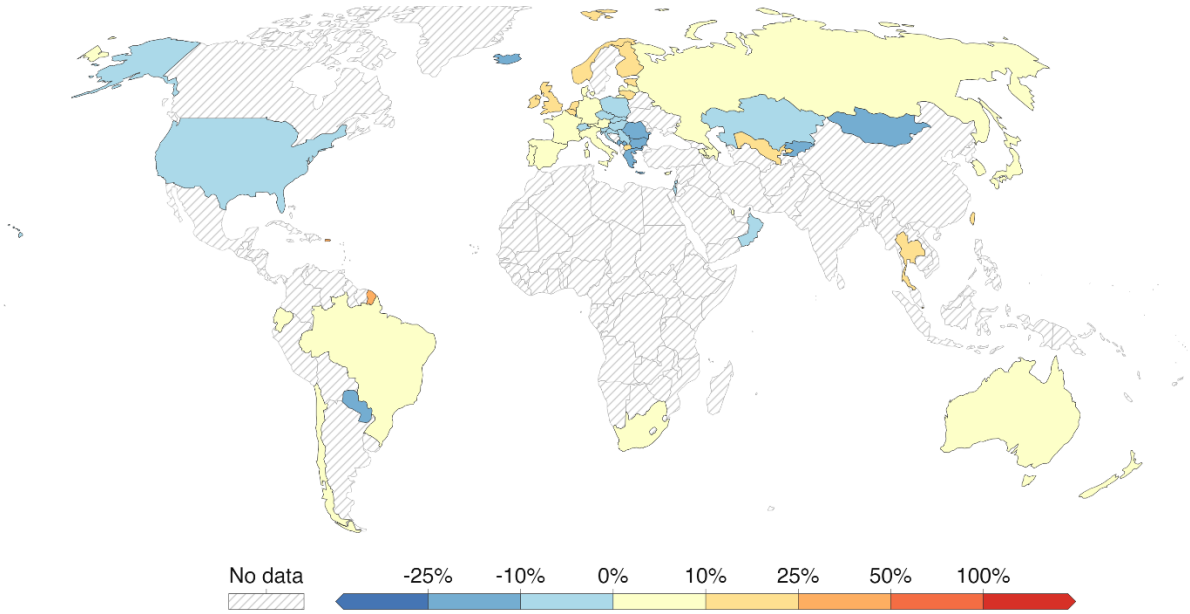

Figure 1. Excess mortality: Deaths from all causes compared to projection in the week of Jun 18, 2023[55-57]. Global excess mortality heatmap image was generated using OurWorldInData (https://ourworldindata.org/excess-mortality-covid). The percentage difference between the reported number of weekly or monthly deaths and the projected number of deaths for the same period based on previous years. The reported number might not count all deaths that occurred due to incomplete coverage and delays in reporting

To develop countermeasures against the escalated CVD risks and the non-COVID19 excess deaths, their mechanistic linkage to the long-term effects of COVID19 needs to be first identified. Long COVID, also known as post-acute sequelae SARS-CoV-2 infection (PASC), is a highly prevalent long-term syndrome with estimated incidence at 10–30% among non-hospitalized cases and 50–70% among hospitalized cases[4]. Coincidentally, a recent 1-year comparative cohort study of 13,435 US adults with Long COVID and 26,870 matched adults without Long COVID reported 133% increased all-cause mortality in the Long COVID cohort (2.8% in the Long COVID cohort vs. 1.2% of controls), as well as increased incidences of cardiac arrythmias (relative risk [RR]=2.35; 95% CI, 2.26-2.45), pulmonary embolism (RR=3.64; 3.23-3.92), ischemic stroke (RR=2.17; 1.98-2.52), coronary artery disease (RR=1.78; 1.70-1.88), heart failure (RR=1.97; 1.84-2.10), chronic obstructive pulmonary disease (RR=1.94; 1.99-2.00), and asthma (RR=1.95; 1.86-2.03)[5]. Given these close resemblances between the presented findings on the Long COVID cohort study[5] and the CVD-driven non-COVID19 excess mortality patterns[2], a linkage between the two phenomena may be stipulated. As partial mechanisms of Long COVID pathologies and their potential therapeutic intervention methods have been identified, confirmation of this linkage may lead to countermeasures to the non-COVID19 excess death problem.

A plausible epidemiological link between Long COVID and non-COVID19 excess deaths revealed in Australian Bureau of Statistics (ABS) data.

While there has not been any published evidence or proposal for the link between Long COVID and

non-COVID19 excess deaths to the best of my knowledge, a simple time-lag correlation analysis of a recent ABS data on excess mortality with or without COVID19 corroborates a epidemiologic association between the COVID19 variant waves and non-COVID19 excess deaths[6] (**Fig.2**). Briefly, the analysis was performed to test the hypothesis that the non-COVID19 excess deaths were mechanistically linked to Long COVID, assuming the number of excess COVID19 deaths at a given time point as a preceding indicator of Long COVID incidence at later time points. The assumptions were justified by the strength of the correlation between COVID19 case numbers and the acute COVID19 deaths[7], and by the WHO definition of Long COVID as a delayed disorder of COVID19 infection[8]. Under the assumptions, the second wave pandemic excess death spike with COVID19 was used as the reference point for aligning the excess death without COVID19 at 3 months displacement, which is the WHO-defined time of Long COVID development upon infection[8] (**Fig. 2B**). Using the 3 months displaced data pair between the excess mortality with COVID19 and the excess mortality without COVID19, correlation plots were generated for Delta [June 2021-Nov 2021][9] (**Fig. 2C**), Omicron BA.1 – BA.3 [Dec 2021 – Sep 2022][10] (**Fig. 2D**), and Omicron BA.4-BA.5 waves [Oct 2022 – Dec 2022][9] (**Fig. 2E**). The resulting correlation plots showed strong positive association toward non-COVID19 excess deaths 3 months after Delta and Omicron BA.4 – BA.5 waves, and strongly negative association after 3 months of the Omicron BA.1-BA.3 waves, indicating that the non-COVID19 excess deaths follow the same temporal manifestation pattern as those in Long COVID patients. Furthermore, each variant wave's directionality and strength of the association to the non-COVID19 excess deaths was consistent with the reported Long COVID propensity and symptoms severity from each variant wave, as Omicron BA.1 was reported with up to 76% less propensity for developing Long COVID and reduced mortality versus Delta[11,12]. Also, Omicron BA.5 was reported with greater hospitalization rate (HR=1.24[0.91-1.69]) and mortality rate (OR=1.55[0.78-3.08]) than Omicron BA.2[13], indicative of more long-term complications from the Omicron BA.5 variant infection cases versus BA.1/BA.2. Taken together, these overlapping findings support the validity of the assumption used in the analysis, implicating a mechanistic link between Long COVID and the ongoing non-COVID19 excess deaths. Furthermore, given the common involvement of CVD and other circulatory diseases as the primary presented features in both the non-COVID19 excess deaths and in Long COVID, candidate pathological mechanisms were contemplated.

Immunity-mediated endothelial damage mechanisms of Long COVID that help account for the non-COVID19 excess deaths pathologies.

While the pathological mechanism for the non-COVID19 excess deaths or the CVD involvement thereof has not been clarified, several immunological endothelial damage mechanisms have been identified in explaining the cause and the CVD-thrombosis pathologies of Long COVID involving neutrophil activation, macrophage/monocyte activation, and/or T-cell activation with persistent SARS-CoV-2 antigen exposure.

Neutrophils are the primary mediators of the rapid innate host defense against viral, bacterial, and fungal pathogens, but its excessive activation can lead to local and systemic inflammation and subsequent damages to the endothelium of capillaries, contributing to an increased incidence of thrombotic events[14]. In patients with persistent pulmonary Long COVID, signatures of chronic and excessive neutrophil activation such as increased in-blood chemokines, proteases, and markers of neutrophil extracellular traps (NETS) that were suggestive of endothelial dysfunctions and vascular inflammation[15] have been reported. NETS are neutrophil-secreted complex structures consisting of DNA, histones, and granular proteins that trap and kill pathogens, but it can also cause endothelial damages including vascular inflammation, coagulation, and endothelial dysfunctions. NETS have been also shown to play key roles in arterial and venous thrombosis, and as well as in the development of acute coronary syndrome (ACS) that can cause heart failure, arrythmia, and sudden deaths[16].

Macrophages/monocytes are another major mediators of innate host immunity involved in the detection, destruction, and clearance of bacterial, viruses, and other harmful organisms, but unlike neutrophil its excessive activation can also lead to overproduction of chemokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), interferons (IFNs), interleukin-1 (IL-1), and monocyte chemotactic protein-1 (MCP-1) that can collectively induce microvascular vasoconstriction, oxidative stress, and platelet aggregation[17] in mounting endothelial and tissue inflammatory damages. In fact, multiple preclinical and clinical studies have shown that SARS-CoV-2 Spike protein directly interacts with macrophages/monocytes and reprograms them into the pathologically activated macrophages that are characteristically seen in the patients with acute COVID19[18,19], Long COVID[20],

post-COVID myocarditis and pericarditis[21], and in other COVID19-related autoimmune syndromes such as MIS-C[22] and MIS-A[23]. The COVID-reprogrammed macrophages were shown to maintain its pathologically activated status for over 8 months in clinical studies[24], making the COVID-reprogrammed macrophage a prime suspect that drives the sustained microvascular rarefaction leading to multitude of sustained Long COVID pathologies[25], and possibly the non-COVID19 excess deaths[26] and the non-COVID19 CVD-excess deaths reported[2,27].

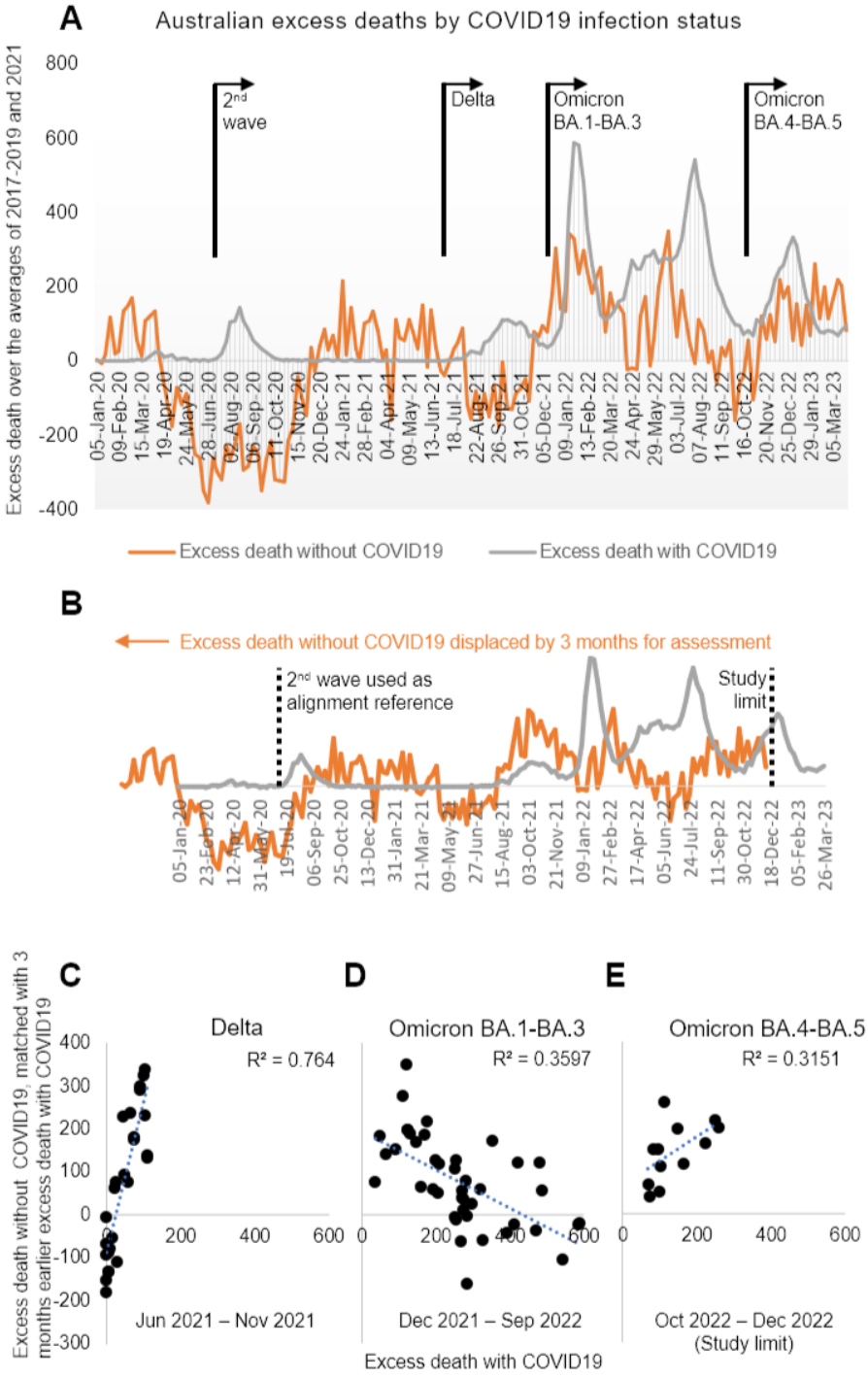

Figure 2. Time-lag epidemiological correlation analysis between the excess mortality with COVID19 and the excess mortality without COVID19 data from ABS data (Jan 2020 – Mar 2023)[6]. (A) the excess mortality data before the application of the time-displacement, noted with the timing of the COVID19 waves and the variants involved. (B) plots of excess mortality data after application of the 3 months' time displacement to the non-COVID19 excess mortality, aligned with respect to the start of 2nd wave. Correlation plots between the excess mortality with COVID19 and the 3 months-displaced non-COVID!9 excess mortality during (C) Delta wave, (D) Omicron BA.1 – BA.3 waves, and (E) Omicron BA.4-BA.5 waves.

Lastly, continued antigen exposures from incomplete viral clearance, viral reactivation, or chronic antigen presentation were reported in some cases of Long COVID, leading to persistent lymphocyte activation involving T cells that damages vascular endothelial cells and tissues[28]. Such persistent antigen exposure is proposed to be a result of non-neutralizing antibodies against the viral antigens in the patients, giving rise to antibody-dependent enhancement (ADE) that leads to sustained pathological inflammation and tissue damage without viral clearance. Another clinically reported mechanism of such pathology was shown in patients suffering from post-COVID19 mRNA vaccination myocarditis presenting SARS-CoV-2 specific T cell activation, where free and antibody-unbound full-length Spike protein that circulated in blood for up to 3 months was reported as the distinguishing feature versus the asymptomatic vaccine recipient controls who only showed antibody-bound Spike proteins in their blood (unpaired t-test; $P<0.0001$)[29]. With the latest variants of SARS-CoV-2 such as Omicron lineages presenting potent immune-evasiveness, reports of ADE by the previous therapeutic antibodies or vaccine-induced antibodies are becoming more common[30]. With current rampant spread of the immune-evasive SARS-CoV-2 variants that continue to evolve in the current endemic-age, this ADE-mediated T-cell driven inflammation mechanism is expected to play increasing roles in future Long COVID and non-COVID19 excess death pathologies. Recently, Omicron BA.4 and BA.5 were reported to display significant immune evasiveness against the antibodies developed against Omicron BA.1[31]. In this regard, it is highly concerning to observe the rapid rise of non-COVID19 excess deaths that correlated with Omicron BA.5 wave (**Fig. 2E**), which deviated away from the 10-months declining pattern in the non-COVID19 excess deaths during the Omicron BA.1-BA.3 waves (**Fig. 2D**). This pathology mechanism could be an imminent threat, rather than a concern for the distant future.

Clinical post-COVID complications common in Long COVID also contribute to ACS: atherosclerosis, hypertension, thrombosis, dyslipidemia, and diabetes.

All three of the above-mentioned immune-mediated endothelial damage mechanisms can each contribute to the development and onset of atherosclerosis[32-34], hypertension[35-37], and thrombosis[38-40], that may collectively precipitate ACS leading to sudden deaths. Indeed, increased incidence of atherosclerosis[41], hypertension (16% of the studied subjects)[42], and thrombosis[43] have been shown in patients after COVID19 infection. Furthermore, other classical high risk factors to ACS such as dyslipidemia[44] and diabetes[45] have been also reported in Long COVID patients, further adding to the risks of ACS in Long COVID patients.

Potential intervention opportunities for tackling the Long COVID and the non-COVID19 excess deaths.

In view of the information presented, the following 5 venues of potential intervention opportunities for tackling the Long COVID and the non-COVID19 excess deaths are proposed.

The first and the foremost is the infection preventative approach, which aims at the root cause of the present problems. Its importance is highlighted by the large-scale retrospective clinical study that found accumulating risk toward more severe disease symptoms, long-term health complications, hospitalizations from all-cause, and all-cause mortality in patients with repeat episodes of COVID19 infection[46]. While the use of N95 or KF94 masks is the backbone countermeasure in preventing the airborne infection from SARS-CoV-2, evolving super-infectivity after each generation of SARS-CoV-2 variant is increasingly compromising their effectiveness. Thus, antiseptic or antiviral measures in forms of nasal spray or nasal rinse that target to protect nasal cavity from airborne pathogens are proposed as the secondary layer protection measure, aside from vigilant practice of standard hygienic measures.

Secondly, therapeutic interventions that normalize the COVID-reprogrammed macrophages and neutrophils may also be considered, as their chronic activation is the root-level driver of the Long COVID systemic and endothelial inflammations, and in turn, ACS pathologies. In support of the proposition, short course of corticosteroid was reported to reduce the symptoms and the macrophage alterations underlying Long COVID for up to 4 months[47], while an independent study reported 51% reduction in death from all-cause among Long COVID patients prescribed with oral corticosteroids[48]. Corticosteroids, however, cannot be used long-term due to their deleterious long-term side effects. Furthermore, corticosteroids may not be applicable in the patients with persistent or hidden COVID infection[28], as they are immunosuppressive. Development of non-steroidal agents with similar benefits is hence warranted.

Thirdly, therapeutic interventions against NETS or its formation (NETosis) may be a promising strategy as

it offers non-steroidal, and non-anticoagulant agents for counteracting the atherosclerosis and thrombosis that drive the symptomatic development of Long COVID and ACS such as DNAse I and enalapril[35,49]. Internal bleeding is a common post-COVID19 complication as SARS-CoV-2 directly compromises vascular integrities by infecting and damaging the vascular endothelial cell linings[43], thereby limiting the use of classical anti-thrombotic agents in patients with recent COVID19 history due to major bleeding risks[50]. Some anti-NETS or NETosis inhibitors offer therapeutic opportunities at resolving atherosclerotic plaques and blood clots without the anti-coagulant activities nor immunosuppression, which would prove valuable when used in patients with Long COVID at risk of ACS development.

Fourth, the use of blood-lipid lowering therapeutic interventions need to be more actively considered in patients with dyslipidemia after COVID19. High incidence of dyslipidemia development featuring varietal increase in blood lipid levels was reported in COVID19 sequelae[44]. Elevated blood lipid is a potent driver of systemic inflammation and inflammatory neutrophil/macrophage activation and an important CVD[51] and ACS[52] risk factor, and its deleterious effects toward Long COVID was clinically confirmed in healthcare workers with obesity[53].

Fifth, advisory against rigorous exercises in patients who recently recovered from COVID19 or with ongoing Long COVID need to be considered. As earlier mentioned, high risks of internal bleeding (IR 1.49: 1.35-1.65), deep vein thrombosis (IR 2.59: 2.12-3.15), and pulmonary embolisms (IR 4.14: 3.44-4.99) have been reported after COVID19 for months[43], likely due to the compromised vascular integrity and endothelial damages suffered[54]. Physical stress is a known trigger of ACS even in healthy young people (HR 3.5 versus no activity: 1.12 – 3.92), and hence the escalation of blood pressure during rigorous exercises may prove catastrophic in the COVID sequelae or in Long COVID patients.

Lastly, vaccination approach at the problem via update, on the other hand, no longer appears feasible as SARS-CoV-2 demonstrated to evolve with increasing immune evasiveness at rates faster than the roll-out of the updated vaccines[31]. Until the news of a successful development of a universal pan-coronavirus vaccine arrives, COVID vaccines based on current technologies may soon become obsolete as the confirming reports of ADE development between the Omicron vaccine antibodies and the latest variants of the virus have come in[29,31].

Conclusion

Post-pandemic problem of persisting non-COVID19 excess deaths can be explained by Long COVID epidemiology and its immune-mediated pathologies. Despite the increasing undercounting of COVID19 infection due to discontinued diagnostic updates and loosened surveillance from endemic policies, this finding suggests that COVID19 may continue to cost millions of lives in unforeseen ways, months after the recovery, disguised as sudden deaths from ACS. However, the present threat may be countered with appropriate additional measures such as nasal hygiene product use for curbing the COVID19 infection, reserved exercises after recovery from COVID19 to reduce ACS risk, development of root-level treatments for Long COVID that aim at COVID-activated macrophages and neutrophils, and closer management of CVD and diabetic risk factors such as obesity, blood lipid level, and blood sugar level.

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