

Long COVID-19 Syndrome and Frailty: Cause or Consequence or Both?

Ray Marks^{1,*}

¹Department of Health and Behavior Studies, Teachers College, Columbia University, New York, NY 10027, USA

Corresponding author:

Ray Marks, Department of Health and Behavior Studies, Teachers College, Columbia University, New York, NY 10027, USA

Keywords:

COVID-19, Frailty, Long COVID, Intervention, Post-acute COVID, Prevention

Received: Jan 16, 2023

Accepted: Jan 17, 2023

Published: Jan 19, 2023

Abstract

Background: Many older adults remain vulnerable to COVID-19 infections. They are also often at risk for frailty and poor health outcomes.

Aim: This exploratory review examines the correlates of long COVID and frailty and their association insofar as the older adult's wellbeing may be jeopardized.

Methods and procedures: Articles that emerged between January 1 2022 and 2023 in major electronic data bases that addressed the current topic of interest were sought using the key words: *Long COVID* and *Frailty*. Those deemed relevant were duly downloaded, analyzed and summarized in narrative form.

Results: A high proportion of older adults can be expected to remain vulnerable to COVID-19 long term impacts, plus new variants of infection, along with frailty as both an outcome and mediator. Many too are at risk for persistent long COVID-19 complications and a low life quality if more concerted preventive and rehabilitation efforts to avert frailty early on are not forthcoming in a timely manner.

Conclusion: Prompt and continuing frailty assessments of older adults at risk for COVID-19 or recovering from this disease, especially those with long COVID manifestations who are frail or may become frail are strongly indicated.

Introduction

For more than three years, the pandemic known as COVID-19 has ravaged the lives of many older adults, including reducing their expected lifespan, as well as their independence and life quality [1-3]. Those deemed frail at the inception of the COVID 19 pandemic in December 2019 and who were in the higher age groups were later observed to be especially at risk [4]. At the same time, those older surviving adults who were not deemed frail at the time they became infected with COVID-19, but survived this illness, may have acquired a pre frail or emergent frailty characterization state due to both impacts of COVID-19 itself on clinical well being and deterioration and its multisystem adverse influences [1, 5]. Even when it appeared the pandemic had been attenuated to some degree, the emergence of what has since been termed the long COVID-19 syndrome [6], a complex post acute COVID set of negative health attributes, was observed in a fair percentage of COVID survivors that continued to exacerbate the debility of the individual, especially those who were classified as being frail at the time of acquiring an incident COVID-19 infection [7]. They were also observed to have a worse clinical disease course than those who were not frail [8], a situation thought to heighten the persistence of post-COVID long term health ramifications [7].

Given the growing need for health providers and others to assist older adults to avoid preventable illnesses or disability states, as well as an excess public health and human resources burden-now linked to COVID-19 prevalence and severity [9] and low life quality, as well as to enable them to age more successfully than not, it appears there may indeed be some merit to examining those factors other than mainstream determinants that could arguably help to mitigate the rate and degree of downward spiraling of the older adults' health as well as their COVID-19 survival status such as frailty [10, 11].

In this regard, this mini review elected to selectively focus on establishing if there is some evidence to support the view that the development of a complex health state termed long COVID illness can be observed in cases deemed frail at the inception of an acute COVID infection, and/or whether any of these complications may independently or collectively foster frailty, which in turn can predictably engender a high rate of secondary infections, adverse health outcomes, and immense social costs even though it was not explicitly listed as being among the most common of 50 post acute COVID symptoms [12, 13]. However, very few long COVID analyses include aging adult samples to any degree, and those who were initially frail may not report this as relevant to COVID-19 recovery processes, and many may have passed away since they were infected. Instances of emergent frailty due to long COVID physical activity challenges may also take time to unfold and may not yet be evident [14], but may be deemed to continue to occur if COVID-19 mitigation efforts are largely unsuccessful.

Aim

In light of the importance of helping older adults to maintain a high level of wellness and one free from excess preventable health issues, this mini review sought to establish whether there is a role for improvements in frailty prevention both before, or after exposure, to COVID-19 disease or its variants, and especially in the face of long COVID-19 complications among vulnerable older adult COVID survivors and populations and that include, shortness of breath, fatigue, fever, headaches, "brain fog" and other neurological problems.

A parallel aim was not only to establish if more should be done in this regard, but if desirable, in what respect?

Hypothesis

It was hypothesized that a possible bidirectional relationship would be found to exist between frailty-deemed a

measure of biological aging-[15], COVID infections, and a moderate proportion of long COVID symptoms in sizeable numbers of older community dwelling adults and others due to their oftentimes heightened state of ill health and morbidity risk. Moreover, it was believed a link between the presence of a frailty state and COVID-19 infection risk would appear to be an apparent, albeit possibly preventable, important disabling correlate among a high number of older adults wherever they reside, thus health care costs would be undesirably increased and resources strained beyond measure if not addressed in a timely comprehensive manner.

Relevance

Long coronavirus disease 2019 or long COVID-19 is a health complication defined by the World Health Organization as one that occurs in individuals with a history of probable or confirmed severe acute respiratory syndrome coronavirus-2 infection, usually within 3 months from the onset of COVID-19 illness, and with symptoms that last for at least two months and possibly considerably longer that cannot readily be explained by an alternative diagnosis is currently of major concern to public health policy makers and others. In the elderly population, apart from its typical symptoms (fatigue, cough, or dyspnea), its main consequences include the findings of multiple functional declines that can induce muscle wasting and mass declines, while fostering frailty, and disability [16].

Frailty, a potentially preventable serious health state and undisputed impediment to well-being among many older populations, regardless of any COVID-19 presence or risk, not only impact vulnerability to infectious agents such as the coronavirus19, but its associated impacts on reductions in physical activity participation and various degrees of anxiety, and depression can collectively impact disease resistance [17]. Unsurprisingly, frailty is a multi-dimensional construct and embodies multiple physical, mental, and social dimensions of health adversely, including those that align with descriptions of long COVID disease. Alternately, the presence of long COVID-19 disease complications may exacerbate or foster a frail state [18], especially if long COVID symptoms of fatigue and muscle pain emerge [19].

As such, it is clear that although poorly studied, a better understanding of any link between frailty, the acquisition of COVID-19 and possible long COVID complications may have immense social and fiscal implication in terms of intervening on and comprehending if these conditions produce a cycle of negative events that threatens to undermine the ability of many older adults to age successfully, while limiting their disease resistance-even if vaccinated. Since frailty alone is a key COVID-19 risk factor, and one that predicts the need for hospitalization [20], more upstream efforts to prevent this state among aging adults have been advocated [21]. At the same time, to minimize the social and public health burden that appears to be emerging and converging, the serious nature of potentially preventable cycle of interacting events that can result in multiple long lasting COVID complications as well as possible re infections and hospitalizations, must clearly raise the strong possibility of an urgent need for more timely and intense upstream preventive efforts, plus resources that may be needed but have not been allocated in recent budgets, or have been allocated elsewhere [22].

Methods and procedures

In accord with the aims of this report, well established data bases including the **PUBMED, PUBMED CENTRAL, SCIENCE DIRECT** and **GOOGLE SCHOLAR** believed to house salient topical peer reviewed articles on the issue of long COVID and frailty among aging adults were carefully sought. Key terms used alone or in combination included, 'COVID-19', 'elderly', 'frailty', 'frail elderly', 'frailty syndrome', 'long COVID', 'older adults', 'post-acute COVID syndrome'. The time period of interest was predominantly January, 1 2022- January 10, 2023, although data from 2020-2021 was accepted if

relevant.

After scanning the listed articles, those deemed relevant were examined for their key findings and incorporated into a broad based narrative given the novel topic and an obvious lack of any well designed prospective study on this relatively new and emergent syndrome. Excluded were foreign articles, proposals for future studies, nursing home studies, those focusing on long term rather than long COVID-19 issues, telehealth issues, intervention approaches for addressing long COVID, and issues related to long COVID-19 other than frailty and its correlates. A comprehensive prior overview of COVID-19 frailty impacts published between 2020 and January 2022 can be found at: <https://medcraveonline.com/IPMRJ/IPMRJ-07-00299.pdf> [23]

Results

Although a widely publicized and studied topic for more than four decades, and a fairly strong predictor of COVID-19 risk in the older adult population, it is clear very little is currently written about frailty, a condition featuring muscle weakness, low physical activity ability, and fatigue, among other declining functional and cognitive features, as far as either fostering the emergence or persistence of long COVID-19 complications that may include one or more of these aforementioned attributes. However, it appears plausible to suggest that COVID-19 cases who show post acute evidence of fatigue/muscle weakness, difficulty with breathing, and discomfort, anxiety/depression and impaired concentration in more than 20% of survivors may be impacted by the presence of preclinical frailty. Moreover, these older adults who survive COVID-19 and exhibit one more long term adverse health symptoms, may be expected to either develop a frail state or to experience a worsening frail state if this situation is not anticipated or addressed in a timely manner as indicated by Anaya et al. [19]. As observed by Huang et al. [24] frailty, a predictor of mortality after a COVID-19 infection among vulnerable older adults [25], is also associated with having a poor mental health one year after hospital discharge for COVID among survivors [26] and among the long term COVID syndrome features are multiple reports of new or persistent features of depression and anxiety [19].

Zamora et al. [27] who collected data on cases testing positive for COVID-19 between March - June 2020, as well as at a three-month follow-up time period between June to September 2020 showed COVID-19 positive residents did tend to present with worse functionality, higher frailty levels and malnutrition risks compared to those designated non-COVID-19 residents,. Damanti et al. [8] who studied COVID survivor cases 65 years and older found frailty was significantly associated with: (i) confusion, as a presenting symptom of COVID-19; (ii) malnutrition, a heightened risk of muscle mass losses, impaired muscle performance, mobility complaints, challenges in self-care, and in performing usual activities of daily living at 1-month follow-up; (iii) dyspnea and risk of sarcopenia at 3-month follow-up was also noted; and (iv) difficulties in self-care at the 6-month follow-up remained or increased. Moreover, in a subgroup of patients (78 individuals), the prevalence of frailty increased at the 1-month follow-up compared to baseline.

It thus seems the emergent features mentioned by Damanti et al. [8] such as the incidence and prevalence of sarcopenia or muscle mass losses associated with frailty states may not only predict a high risk of long COVID but many of the possible long COVID complications that have been seen to emerge [28], or heighten the degree of adverse COVID-19 manifestations [29]. Tosato et al. [3] report that several additional mechanisms that may be involved in long COVID syndrome, including chronic inflammation, metabolic perturbations, endothelial dysfunction, and gut dysbiosis, may be pathogenic mechanisms that overlap with those of the aging process and may aggravate pre-existing degenerative conditions, including those associated with frailty states. It is also plausible that the frailty state seen in long COVID cases, developed even in otherwise healthy older adults during the height of COVID-19 pandemic consequent

to public health efforts to keep the older adult 'safe' and that involved social isolation and oftentimes a reduced availability of health services, and possibly access to sound nutrition, sunlight, and physical activity opportunities.

With their weakened immune system they may have deteriorated further if hospitalized, while their susceptibility to excess muscle mass and bone loss vulnerability was potentially exacerbated [30]. Those with pre existing comorbid health conditions, and those recovering from severe COVID-19 may have been at highest risk for frailty, as well as long COVID complications, for example if they lost weight due to swallowing problems. According to Di Girolama et al. [31], aging, often characterized by sarcopenia or sarcopenic obesity that is not averted in a timely manner raises the risk for acquiring both severe acute COVID-19 as well as long-COVID complications.

In short, therefore, although the literature on the current topic of interest is neither robust, nor conclusive, it appears hard to refute the need for the application of both timely as well as effective intervention strategies to prevent or reduce frailty among older vulnerable adults who have been exposed to COVID-19 and have not fully recovered, as well as those who are vulnerable. This may not only help to reduce the chances of a future secondary infection [30], and an accelerated aging process, but may foster an unanticipated and ongoing presence of persistent immune-metabolic systems dysfunction [32]. Unresolved, in a timely way, this series of interacting events may heighten frailty, and its risk for falls as well as fears of falling common among frail older adults [23, 33], as well as any ongoing long COVID symptoms, as well as excess degrees of premature mortality [15].

According to Covino et al. [34] adults over 80 years of age and have been hospitalized for a bout of acute COVID-19 illness should routinely undergo a frailty assessment as indicated because this could effectively stratify the degree of prevailing risk of premature death after discharge, as well as the acquisition of long COVID complications, and possibly help to direct resources to mitigate any probable long-term worsening of any identified frailty accordingly, particularly in cases with a pre-existing reduced state of health that clearly exposes the sufferer to a multitude of potentially preventable adverse health outcomes [35]. In addition, due to associated increases in numbers of older adults living to higher ages, older adults who survive an acute COVID-19 episode, and are found to have long COVID-19 symptoms should receive carefully tailored long term interventions.

Ferrara et al. [36] who aimed to assess transitions in frailty status in older adults who survived hospitalization for COVID-19 using a longitudinal panel study design for the evaluation of individuals discharged alive, after hospitalization due to COVID-19 found 61 patients (34.5%) scored worse frailty scores on a validated instrument at follow-up compared to hospital admission, and 22 cases (12.4%) became frail.

Fumagalli et al. [37] found that at 12 months, 40.5% of their patient sample reported at least one adverse health symptom, the most common being fatigue, experiencing exertion associated breathlessness, having a persistent cough, and bowel complaints. Most common psycho-emotional symptoms reported were insomnia, confusion, fear, and depression. Age, gender, frailty, multiple symptoms at baseline and chronic obstructive pulmonary disease were associated with symptom persistence. Furthermore, frailty, pulmonary disease and multiple symptoms at baseline were associated with increased risk of somatic symptoms at 12 months, while age and gender were associated with emotional factors.

This set of aforementioned complex scenarios appear very important to examine further and mitigate accordingly given that Prampart et al. [9] found that of 318 cases of COVID-19 who had been hospitalized, 75 or almost half of the cases studied described long-term symptoms that prevailed at three months after their incident infection. Of those deemed to be frail at the 3-months follow-up, data revealed that 30% were not initially frail at baseline. Moreover, increasing frailty defined by a worse frailty state between baseline and 3 months occurred in 41 cases (26.8%). Although the reasons for the observed frailty attributes were not clear, it does appear that its correlates of muscle weakness and a

loss of muscle mass during COVID hospitalization and their impact on functional ability and the adoption of a more sedentary lifestyle may be implicated [38].

Köller [4] indicates that patients over 80 years of age suffering from COVID-19 not only show a 3.6-fold increase in the risk of mortality compared to the group aged 18-49 years, but the risk of being frail (or having frailty CFS scores ranging from 6-9) is three times higher than those for robust patients (CFS scores 1-3). It was also reported that a frailty cut-off score of 6 or more clearly tended to correlate with a high risk of mortality among COVID-19 patients older than 65 years, thus what we know about frailty among COVID-survivors remains of key import to continue to examine and minimize. This is highlighted by the fact that mid-term and long-term survival after COVID exposure is observed to be determined by the degree of frailty that existed before acquiring COVID-19 illness, rather than by the severity of the disease. Patients over 60 years appear particularly at risk for developing a rapid loss of muscle mass during moderate or severe COVID-19 bouts of illness, thus should be specifically targeted, along with those being treated on intensive care units who are found to lose 20-30% of their thigh extensor muscle mass within 10 days, and the extent of the ensuing muscle mass loss associated with COVID-19 is found decisive in determining the course of the disease.

To address these above mentioned overlapping emergent and ongoing health issues, in addition to acting to avert muscle losses during periods of COVID hospitalization, several authors [eg., 30, 38] now advocate for home-based strategies to include resistance exercises, higher/desirable protein intakes and supplementation in an effort to minimize any persistent adverse post-COVID-19 disease ramifications and frailty onset or progression. Palmer et al. [39] in agreement with Holland et al. [12] suggest less emphasis be placed on isolation type practices because these appear to especially impact the vulnerability of the older frail individual with a pre existing health condition very significantly, while possibly jeopardizing the sustainability of multiple healthcare systems. Advocated in this regard are more thoughtful integrated needs based strategies aimed at safeguarding frail and non frail vulnerable older adults as far as this is possible. Most authors however, did not appear to anticipate the emergence of long COVID additional health issues, among COVID survivors, nor their additional human and economic costs. Data may also underestimate the nature of the impact and association of COVID-19 survival and frailty among older adults, for example if they have not been hospitalized and have a medical record, symptoms may be confused with those of aging health related conditions, and only limited COVID-19 rather than its variants have been well examined.

Since this syndrome known to be associated with more than 200 health complaints among survivors has not been extensively studied, long COVID syndrome remains hard to prevent, define, and what is published may not be generalized because several reports stem from mobile or online health surveys of the post COVID survivor [that not all older adults may be able to negotiate technically or if they remain very impaired], or medical records where information cannot be readily validated.

However, it does appear that even if cases of mild COVID-19 are expected to recover within a year, adults over the age of 70 can be expected to be more vulnerable than youth in this regard and since at least 20% of COVID survivors may be at risk in this regard, should be studied independently [13, 22]. Until then, providing vulnerable older adults with continued access to health services during periods of any desired lockdown is strongly indicated, especially given that frailty is associated with a reduced ability to walk any distance within a given time frame as has been observed in survivors who incurred a COVID-19 infection and that has enormous health services implications [40]. Alternately, most available data tend to point to the probability that those older adults who do not receive adequate ongoing and comprehensive tailored treatments are also likely to be more frail than those who do [41], and are likely to impact the prevailing social costs of dealing with COVID-19 ramifications quite markedly [42].

In addition, since lockdowns and service restrictions in their own right may have induced excess rates of frailty among many vulnerable adults, Mansell et al. [2] argue that the disruptive effects of COVID-19 for older people should not be underestimated as contributing to an observed excessive mental and physical health decline and possibly the onset and perpetuation of frailty from long COVID complications, such as cardiovascular and cognitive health challenges, and their added disability burden and costs. Although Taniguchi et al. [43] did not discuss COVID long term frailty implications, they observed one in five COVID-19 patients admitted to the intensive care ward were already frail, thus survivors - if any- would likely be at high risk for adverse outcomes unless clinicians consider frailty alongside sociodemographic and clinical attributes can impact a COVID prognosis in the context of critical care where acute hospitalization with bed rest could possibly intensify an ensuing or emergent sarcopenic or muscle mass loss process, as well as the emergence or exacerbation of neurological symptoms [44, 45]. Weihe et al. [46] observed that among a cohort of 204 six-month survivors, frailty was evident in 20% of these surviving cases at 6 months, and for 18% at 12 months. Fatigue was reported by 52% at 6 months, and by 47% of cases at 12 months, while moderate, severe, or extreme health problems were reported by 28% of the survivors at 6 months, and by 25% at 12 months.

Although the role of frailty in fostering premature mortality after sustaining an acute COVID-19 infection, when a patient is discharged from the health care setting is unclear, Andrew et al. [47] suggest strong and coordinated surveillance and research focused on vulnerable long term care frail residents is duly required and strongly indicated even in the absence of a well defined science base. These efforts should include, but should not be limited to, careful frailty assessments using tools such as the chronic frailty syndrome survey [CSF], and rigorous reporting of morbidity and mortality in long term care facilities, but again this group did not discuss or predict a role for long COVID complications in this regard even though most adverse symptoms in this respect, plus frailty associated with exhaustion is an established falls risk predictor in the elderly [48].

According to Pires et al. [49], additional musculoskeletal manifestations encountered by the older adult in the context of post COVID infections are falls leading to hip fractures and other sites, increased mortality after sustaining a hip fracture, reduced bone mineral density and osteoporosis, acute sarcopenia, various forms of muscle pathology, fibromyalgia, osteonecrosis, and necrotizing autoimmune myositis. Undoubtedly, one or more of these residual forms of dysfunction involving the musculoskeletal system, can be anticipated to predictably and markedly affect the life quality of the affected person, while engendering a decrease in any previously established pre COVID disability-adjusted life years.

In addition, Zhu et al. [50] imply that aging-related changes, including multimorbidity, along with a weakened immunity status and frailty, may render older people more susceptible to severe infection, even if they have been vaccinated or survived an acute incident bout of COVID-19 illness, thus placing them at higher risk of morbidity and mortality and possible long term multiple adverse COVID consequences, including possible increases in one or more of their existing chronic health conditions. Older persons who experience frailty or multiple chronic disease may also adapt poorly to both their altered health state, as well as any altered health care system approaches such as replacing face to face care with remote health care, and that could have unanticipated detrimental consequences on their physical and mental health that may well raise the risk of incurring secondary infections and other health vulnerabilities, including chronic pain and sleep challenges.

Indeed, Ferrara et al. [36] showed that at least one third of older adults previously hospitalized for COVID-19 had an unfavorable frailty transition score over a median follow-up period of almost 6 months. In addition, as put forth by Braude et al. [51] those COVID survivors found to be frail were also found to present with significant psychiatric problems and an overall reduced wellbeing within one year after incurring an acute COVID-19 diagnosis requiring

hospital admission.

Ramirez-Valez et al. [52] report that limb muscle wasting, common among COVID-19 cases and a key factor in fostering probable declines in daily activity and exercise participation, appeared likely to account for the lower absolute and relative muscle strength measurements that were recorded for those post acute-COVID long term syndrome sufferers they recently studied. Moreover, those who were already frail at the outset of the pandemic may have been especially vulnerable to COVID infection as a result of probable lower levels of vaccination protection [53], and because they may then have required prolonged hospitalization, and a more pronounced decline in muscle mass loss than anticipated, and possible slower COVID recovery rates.

Along with a poorer than desired response to COVID-19 vaccination, and a high mortality rate, older adults who exhibit frailty may present with a weakened immune system that places them at a higher risk of undesired outcomes such as severe COVID and/or long COVID syndrome if they survive this illness [54, 55]. This is possibly due to the common frailty correlates of skeletal muscle weakness and poor exercise tolerance [56], and other manifestations affecting mobility, including fatigue, joint and muscle pain, and poor physical performance that may slow COVID recovery rates [49]. for up to 12 months in approximately 40% of COVID survivors [37]. At the same time, the most common somatic long COVID symptoms of fatigue, breathlessness with activity, along with psycho-emotional symptoms of insomnia, confusion, fear, and depression may exacerbate any existing frailty or prevailing tendency to become frail, a state identified as being associated with long COVID symptoms persistence. Thus, even though no specific form of intervention has been advocated to date to mitigate long COVID complications, it seems rehabilitation programs based on multiple forms of physical activity [57] and associated programs that foster adequate nutrition may be useful for preventing or improving post-COVID-19 efforts to minimize excess muscle mass losses and frailty, as well as the risk of future respiratory infections.

Discussion

Since the onset of the COVID-19 pandemic in December 2019, global efforts to mitigate its immense impact have been implemented in all countries. Only partially successful to date, the impact of this emergent viral infection has markedly reduced the ability of an older adult to age successfully and with limited signs of dysfunction. In this regard, this current review elected to explore the possible continuum between vulnerability to COVID-19 infections and frailty as a potentially preventable determinant as well as outcome of COVID-19 disease exposure, especially among vulnerable older adults [58]. The impact as well as the persistence or emergence of frailty in older adult populations which may be due to illness associated muscle mass declines, or social isolation impacts and others, and its possible heightened risk of disability, and infections, plus a high degree of pre or post recovery cognitive impairments or symptoms were hypothesized to place the older surviving pre frail or frail adult at high risk for long term COVID complications and persistent infection risk.

On the other hand, while not definitive, and needing more careful study, a role for primary and secondary as well as more focused tertiary prevention efforts was anticipated as being advanced to reduce both the risk of acquiring COVID-19 infections, plus long COVID complications in surviving older adults, especially among those with poorer than desired health status who acquire or demonstrate a history of frailty. Indeed, Antonelli et al. [59] advocate that in addition to persistent attention to vaccination approaches, at-risk populations such as the older frail adult must be specifically targeted in efforts to boost vaccine effectiveness and deter infection risk, such as providing for their nutrition needs, while applying caution in exercising severe isolating measures in the post-vaccination era. Frail older adults and

individuals living in more deprived areas, including those who have received steroids when hospitalized for COVID-illness who may develop bone mass and vascular changes, those who exhibit gastro intestinal problems that may foster weight loss, and those with a preclinical musculoskeletal condition associated with pain and falls injuries, even if these individuals are vaccinated, are deemed especially vulnerable in this respect [49, 69, 70].

As well, proactive, rather than reactive interventions in this regard appear highly indicated because persistent multi-organ dysfunction that predicts COVID susceptibility as well as frailty states, and can be induced or exacerbated by COVID-19 exposure and illness may well set even previously healthy older individuals on an unanticipated potentially irreversible trajectory towards frailty and excess disease manifestations among a large proportion of aging individuals who are recovering from COVID-19 [5]. Frailty itself should be a key target in this regard, because researchers show when present, it strongly influences the prevailing degree of recovery resilience by an affected older adult in the post COVID recovery period [60]. Frailty may also impact the need for and excess use of prescriptions for analgesia, antidepressants, antihypertensives, steroids for breathing issues, and oral hypoglycemics among those who are recovering, and especially among those older adults who sustain persistent long-COVID complications that exhaust their remaining personal resources.

Bearing in mind this review is limited both by the lack of depth in the reports that prevail and their limited time lines and samples, among other factors, and included all forms of study with no due regard for flaws, there seems to be little disagreement COVID-19 and its repercussions remain highly serious public health concerns in 2023. As such, while how this pandemic will impact older populations as time proceeds is unknown, it appears that to avert a 'legacy of post COVID long lasting ill health' [61], efforts to avert iatrogenic frailty impacts among the older hospitalized COVID-19 patient even after hospital discharge, are highly indicated, among other approaches. While almost no attention has been given to heightening upstream preventive approaches in this regard, there is ample related past work to support Piotrowicz et al. [44] who advocate for a multidisciplinary approach including nutritional support, early physical as well cardio-pulmonary rehabilitation, and psychological support and cognitive training to foster the health of the post-COVID survivor. Indeed, despite a lack of robust scientific evidence, this proposed holistic and early management of the post acute COVID-19 patient does appear to hold considerable probable benefits for the older client as well as society in general, as far as minimizing the disastrous functional outcomes of failing to do this and allowing the possible emergence of multiple potentially persistent and far reaching adverse long COVID-19 syndrome complications, including frailty. At present, almost no other alternatives have been put forth to address long COVID implications in older adult groups or frailty subgroups. What is clear however is that the sole application of strict isolation measures, while possibly saving some lives, can be expected to advance any vulnerability or risk among the older adult population towards frailty, as well as its possible impact on COVID vaccination potency and infection risk, plus the trajectory of desired post-acute COVID recovery processes. Similarly, scarce resources that limit geriatric rehabilitation or actions to prioritize groups other than the older adult COVID survivor are imperative to avoid [62, 63], especially for hospitalized COVID-19 cases [64] and for those who were non frail when they developed COVID-who are found to transition towards frailty and excess disability at high rates [65], including a higher vulnerability to stress and stressors [66], plus a higher odds of incident and persistent mental disorders [67], as well as physical challenges [48, 49, 69, 70].

To counter the multiple persistent ill effects currently observed specifically among older COVID 19 survivors the most promising approaches examined in prior randomized studies might be helpful. These include, but are not limited to various forms of assistance to build muscle mass or prevent its decline including physical activity; physical activity combined with nutrition; avoidance of steroids and opioids, falls risk prevention instruction, and psychological rehabilitation as indicated, along with comprehensive periodic follow up assessments and should apply to frail as well as non frail older

adult COVID survivors using an integrated rather than a fragmented approach. On the other hand, since COVID infections in their own right are not only increasing in numbers in the elderly, frailty which appears associated with COVID vulnerability to a high degree, if not prevented throughout adulthood in a dedicated manner, can undoubtedly be expected to increase in incidence and prevalence in coming years, thus exposing the vulnerable older adult to a life of premature or excess disability, as well as a high chance of death in those with severe frailty who are susceptible to COVID-19 and its variants, along with a high rate of hospital readmissions in the mild-moderately severe frail case [66, 68].

To enable more older adults to be more resistant across time to COVID and its variants, it seems funds to be harnessed to avert all forms of frailty among older adults, especially the most vulnerable, plus the development of sound and precise evidence based preventive strategies against COVID-19 and its long term impacts will be highly fruitful. To this end, researchers and clinicians are encouraged to continue to pool and extend their collective observations to include more diverse samples, sub groups exhibiting various degrees of frailty, the role of age, and gender, including those who are not vaccinated. Extending the current evidence base and modes of research design in order to better understand why some older adults are more vulnerable to both frailty as well as COVID-19 than others, and what is needed in this regard to more effectively protect against long COVID complications and how these can be eradicated will undoubtedly advance this emergent realm of geriatric care and practice for many who remain vulnerable for years to come.

In the interim, applying the most promising potentially preventable modes of maximizing immune system status, as well as bone and muscle status, along with emotional health attributes, key COVID and frailty antecedents using actionable preventative approaches remain strongly indicated by several research groups. It also appears there must surely be improved practical efforts to educate older adults and their significant others, and how they can help to avert infection risk as well as averting frailty states. Based on the current literature, it also appears a focus on heightening positive cognitions, provider knowledge, countering the multiple negative mythologies of aging as purely a declining and negative economic state that can lead to a downward spiral of COVID associated impacts, personalized interventions, social support, and the provision of access to safe indoor and outdoor environments, non medical pain relief approaches, hand washing and masking, plus access to needed nutrients will be especially helpful in all likelihood in this regard and even if more profound anti-COVID measures prevail.

Conclusions

While this current scoping review is not without limitations and may not be inclusive, based on a high percentage of prevailing data published since January 2021, it is concluded that:

- The long term consequences of COVID-19 experienced by many COVID-19 survivors should not be underestimated and may foster frailty states that heighten COVID-19 secondary infection risk as well as morbidity and premature mortality especially among adults in the highest age groups and those with emotional health challenges.
- Frail older adults, especially women with multi morbidities on the other hand are more likely to be susceptible to COVID-19 infections than those who are deemed healthy and experience more severe and long term often dire health consequences, even if vaccinated.

Carefully construed up and downstream public health measures, including vaccinations, and interventions to address both frailty and multi morbidity risk or its presence among vulnerable older adult groups, have the probable potential to improve the lives of many frail, as well as non frail older adults, while reducing COVID-19 complications, including the emergence of frailty states, and their immense impact on wellbeing.

As with past research in multiple spheres dealing with health across the lifespan, those living in poverty, those with low educational levels, those older adults living alone, those who may have lost a spouse to COVID, those who are

underweight, as well as those with diabetes, poor exercise tolerance, functional disability, those who are food insecure, frail or pre frail, plus those who have respiratory challenges, and/or depression should be prioritized.

Anticipated are enhancements in life quality and enormous reductions in health care social and economic costs, more effective innate protection against COVID variants, better vaccination protection, less possible harm in response to some vaccinations, less potential to spread COVID-19 infectious agents, adverse use of drugs and exposure to COVID drug reactions, and reduced overall health resource needs.

References

1. Perrotta F, Corbi G, Mazzeo G, Boccia M, Aronne L, et al. (2020) COVID-19 and the elderly: insights into pathogenesis and clinical decision-making. *Aging Clin Exp Res.* 32(8):1599-1608. doi: 10.1007/s40520-020-01631-
2. Mansell V, Hall Dykgraaf S, Kidd M, Goodyear-Smith F. (2022) Long COVID and older people. *Lancet Healthy Longev.* 3(12):e849-e854. doi: 10.1016/S2666-7568(22)00245-8.
3. Tosato M, Ciciarello F, Zazzara MB, Pais C, Saveria G, et al; Gemelli Against COVID-19 Post-Acute Care Team. (2022) Nutraceuticals and dietary supplements for older adults with Long COVID-19. *Clin Geriatr Med.* 38(3):565-591. doi: 10.1016/j.cger.2022.04.004.
4. Köller M. (2022) Coronavirus disease 2019 und frailty. *Z Gerontol Geriatr.* 55(7):564-568..
5. Serviente C, Decker ST, Layec G. (2022) From heart to muscle: pathophysiological mechanisms underlying long-term physical sequelae from SARS-CoV-2 infection. *J Appl Physiol* (1985). 132(3):581-592. doi: 10.1152/jappphysiol.00734.2021.
6. Sykes DL, Holdsworth L, Jawad N, Gunasekera P, Morice AH, et al. (2021) Post-COVID-19 symptom burden: what is long-COVID and how should we manage it? *Lung.* 199(2):113-119. doi: 10.1007/s00408-021-00423-z.
7. Holland C, Garner I, Simpson J, Eccles F, Pardo EN, et al. (2021) Impacts of COVID-19 lockdowns on frailty and well-being in older people and those living with long-term conditions. *Adv Clin Exp Med.* 30(11):1111-1114. doi: 10.17219/acem/144135.
8. Damanti S, Cilla M, Cilona M, Fici A, Merolla A, et al. (2022) Prevalence of long COVID-19 symptoms after hospital discharge in frail and robust patients. *Front Med (Lausanne).* 9:834887. doi: 10.3389/fmed.2022.834887.
9. Prampart S, Le Gentil S, Bureau ML, Macchi C, Leroux C, et al. (2022) Functional decline, long term symptoms and course of frailty at 3-months follow-up in COVID-19 older survivors, a prospective observational cohort study. *BMC Geriatr.* 22(1);1-11.
10. Vlachogiannis NI, Baker KF, Georgiopoulos G, Lazaridis C, van der Loeff IS et al. (2022) Clinical frailty, and not features of acute infection, is associated with late mortality in COVID-19: a retrospective cohort study. *J Cachexia, Sarcopenia Muscle.* 13(3):1502-1513. doi: 10.1002/jcsm.12966.
11. [11] Hewitt J, Carter B, Vilches A, Quinn TJ, Braude P, et al. (2020) The influence of frailty on survival following COVID-19. The COPE study (COVID in Older People): a multi-centre, European observational cohort study. *The Lancet Public Health.* 5(8):e444-e451. doi: 10.1016/S2468-2667(20)30146-8.
12. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, et al. (2021) More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep.* 11(1):16144. doi: 10.1038/s41598-021-95565-8.

13. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, et al. (2021) Attributes and predictors of long COVID. *Nat Med.* 2021 Apr;27(4):626-631. doi: 10.1038/s41591-021-01292-y.
14. Humphreys H, Kilby L, Kudiersky N, Copeland R. (2021) Long COVID and the role of physical activity: a qualitative study. *BMJ Open.* 11(3):e047632. doi: 10.1136/bmjopen-2020-047632.
15. Mak JKL, Eriksson M, Annetorp M, Kuja-Halkola R, Kananen L, et al. (2022) Two years with covid-19: the Electronic Frailty Index identifies high-risk patients in the Stockholm GeroCovid Study. *Gerontology.* 1-10. doi: 10.1159/000527206.
16. Rodriguez-Sanchez I, Rodriguez-Mañas L, Laosa O. (2022) Long COVID-19: the need for an interdisciplinary approach. *Clin Geriatr Med.* 38(3):533-544. doi: 10.1016/j.cger.2022.03.005..
17. Soysal P, Veronese N, Thompson T, Kahl KG, Fernandes BS, et al. (2017) Relationship between depression and frailty in older adults: a systematic review and meta-analysis. *Ageing Res Rev.* 36:78-87.
18. Kojima M, Satake S, Osawa A, Arai H. (2021) Management of frailty under COVID-19 pandemic in Japan. *Glob Health Med.* 3(4):196-202. doi: 10.35772/ghm.2020.01118.
19. Anaya JM, Rojas M, Salinas ML, Rodríguez Y, Roa G, et al. (2021) Post-COVID syndrome. A case series and comprehensive review. *Autoimmun Rev.* 20(11):102947. doi: 10.1016/j.autrev.2021.102947.
20. Zhu Y, Sealy MJ, Jager-Wittenaar H, Mierau JO, Bakker SJ et al. (2022) Frailty and risk of hospitalization from COVID-19 infection among older adults: evidence from the Dutch Lifelines COVID-19 Cohort study. *Aging Clin Exptl Res.* 34(11):2693-2702.
21. Lengelé L, Locquet M, Moutschen M, Beaudart C, Kaux JF et al. (2022) Frailty but not sarcopenia nor malnutrition increases the risk of developing COVID-19 in older community-dwelling adults. *Aging Clin Exptl Res.* 34(1):223-234.
22. Ziauddeen N, Gurdasani D, O'Hara ME, Hastie C, Roderick P, et al. (2022) Characteristics and impact of Long Covid: findings from an online survey. *Plos One,* 17(3):e0264331.
23. Marks R. (2022) Covid-19 frailty impacts and implications. *Int Phys Med Rehab J.* 7(1):26-34.
24. Huang C, Huang L, Wang Y, Li X, Ren L, et al. (2022) Functional decline, long term symptoms and course of frailty at 3 -months follow-up in COVID-19 older survivors, a prospective observational cohort study. *BMC Geriatr.* 22(1):542. doi: 10.1186/s12877-022-03197-y.
25. Pagliuca R, Cupido MG, Mantovani G, Bugada M, Matteucci G, et al. (2022) Absence of negativization of nasal swab test and frailty as risk factors for mortality in elderly COVID-19 patients admitted in long-term care facilities. *Eur Geriatr Med.* 13(4):933-939. doi: 10.1007/s41999-022-00657-x.
26. Bourmistrova NW, Solomon T, Braude P, Strawbridge R, Carter B. (2022) Long-term effects of COVID-19 on mental health: A systematic review. *J Affective Dis.* 299:118-125.
27. Cortés Zamora EB, Mas Romero M, Tabernero Sahuquillo MT, Avendaño Céspedes A, Andrés-Petrel F, et al. (2022) Psychological and functional impact of COVID-19 in long-term care facilities: the COVID-A study. *Am J Geriatr Psychiatr.* 30(4):431-443. doi: 10.1016/j.jagp.2022.01.007.
28. Martone AM, Tosato M, Ciciarello F, Galluzzo V, Zazzara MB, et al; Gemelli Against COVID-19 Post-Acute Care Team. (2022) Sarcopenia as potential biological substrate of long COVID-19 syndrome: prevalence, clinical features, and risk factors. *J Cachexia Sarcopenia Muscle.* 13(4):1974-1982. doi: 10.1002/jcsm.12931.

29. Ali AM, Kunugi H. (2021) Physical frailty/sarcopenia as a key predisposing factor to coronavirus disease 2019 (COVID-19) and its complications in older adults. *BioMed*. 1(1):11-40.
30. Kirwan R, McCullough D, Butler T, Perez de Heredia F, Davies IG, et al. (2020) Sarcopenia during COVID-19 lockdown restrictions: long-term health effects of short-term muscle loss. *Geroscience*. 42(6):1547-1578. doi: 10.1007/s11357-020-00272-3.
31. Di Girolamo FG, Fiotti N, Sisto UG, Nunnari A, Colla S, et al. (2022) Skeletal muscle in hypoxia and inflammation: insights on the COVID-19 pandemic. *Front Nutr*. 9:865402. doi: 10.3389/fnut.2022.865402.
32. Guaraldi G, Milic J, Cesari M, Leibovici L, Mandreoli F, et al. (2022) The interplay of post-acute COVID-19 syndrome and aging: a biological, clinical and public health approach. *Ageing Res Rev*. 101686.
33. Morley JE. (2020) COVID-19—the long road to recovery. *J Nutr, Hlth & Aging*. 24(9):917-919.
34. Covino M, Russo A, Salini S, De Matteis G, Simeoni B, et al. (2022) Long-term effects of hospitalization for COVID-19 on frailty and quality of life in older adults ≥ 80 years. *J Clin Med*. 11(19):5787. doi: 10.3390/jcm11195787.
35. Sanyaolu A, Okorie C, Marinkovic A, Patidar R, Younis K, et al et al. (2020) Comorbidity and its impact on patients with COVID-19. *SN Comp Clinl Med*. 2(8):1069-1076.
36. Ferrara MC, Zarccone C, Tassistro E, Rebora P, Rossi E, et al; STORM Long-COVID Team. (2022) Frailty and long-COVID: is COVID-19 responsible for a transition in frailty status among older adults who survived hospitalization for COVID-19? *Aging Clin Exp Res*. 1–7. doi: 10.1007/s40520-022-02308-4.
37. Fumagalli C, Zocchi C, Tassetti L, Silverii MV, Amato C, et al; AOU Careggi COVID-19 Follow-up study Group. (2022) Factors associated with persistence of symptoms 1 year after COVID-19: A longitudinal, prospective phone-based interview follow-up cohort study. *Eur J Intern Med*. 97:36-41. doi: 10.1016/j.ejim.2021.11.018.
38. Sagarra-Romero L, Viñas-Barros A. (2020) COVID-19: Short and long-term effects of hospitalization on muscular weakness in the elderly. *Int J Environ Res Public Health*. 17(23):8715. doi: 10.3390/ijerph17238715.
39. Palmer K, Monaco A, Kivipelto M, Onder G, Maggi S, et al. (2020) The potential long-term impact of the COVID-19 outbreak on patients with non-communicable diseases in Europe: consequences for healthy ageing. *Aging Clin Exp Res*. 32(7):1189-1194. doi: 10.1007/s40520-020-01601-4.
40. Townsend L, Dowds J, O'Brien K, Sheill G, Dyer AH, et al. (2021) Persistent poor health after COVID-19 is not associated with respiratory complications or initial disease severity. *Ann Am Thorac Soc*. 18(6):997-1003. doi: 10.1513/AnnalsATS.202009-1175OC.
41. Hirose T, Sawaya Y, Shiba T, Ishizaka M, Onoda K, et al. (2021) Characteristics of patients discontinuing outpatient services under long-term care insurance and its effect on frailty during COVID-19. *Peer J*. 9:e11160. doi: 10.7717/peerj.11160.
42. Kim SG, Kwon HC, Kang TK, Kwak MY, Lee S, et al. (2022) COVID-19 sequelae and their implications on social services. *J Korean Med Sci*. 37(48):e342. doi: 10.3346/jkms.2022.37.e342.
43. Taniguchi LU, Avelino-Silva TJ, Dias MB, Jacob-Filho W, Aliberti MJR. (2022) Association of frailty, organ support, and long-term survival in critically ill patients with COVID-19. *Crit Care Explor*. 4(6):e0712. doi: 10.1097/CCE.0000000000000712.
44. Piotrowicz K, Gąsowski J, Michel JP, Veronese N. (2021) Post-COVID-19 acute sarcopenia: physiopathology and management. *Aging Clin Exp Res*. 33(10):2887-2898. doi: 10.1007/s40520-021-01942-8.

45. Perna S, Abdulsattar S, Alalwan TA, Zahid MN, Gasparri C, et al. (2022) A cross-sectional analysis of post-acute COVID-19 symptoms. *Ann Ig.* 34(5):478-489. doi: 10.7416/ai.2022.2508.
46. Weihe S, Mortensen CB, Haase N, Andersen LPK, Mohr T, et al. (2022) Long-term cognitive and functional status in Danish ICU patients with COVID-19. *Acta Anaesthesiol Scand.* 66(8):978-986. doi: 10.1111/aas.14108.
47. Andrew M, Searle SD, McElhane J, McNeil SA, Clarke B, et al. (2020) COVID-19, frailty and long-term care: implications for policy and practice. *J Infect Dev Ctries.* 14(5):428-432. doi: 10.3855/jidc.13003.
48. Kim YS, Yao Y, Lee SW, Veronese N, Ma SJ, et al. (2022) Association of frailty with fall events in older adults: a 12-year longitudinal study in Korea. *Arch Gerontol Geriatr.* 102:104747. doi: 10.1016/j.archger.2022.104747.
49. Pires RE, Reis IGN, Waldolato GS, Pires DD, Bidolegui F, et al. (2022) What do we need to know about musculoskeletal manifestations of COVID-19? a systematic review. *JBJS Rev.* 10(6). doi: 10.2106/JBJS.RVW.22.00013.
50. Zhu Y, Liu Y, Jiang H. (2022) Geriatric health care during the COVID-19 pandemic: managing the health crisis. *Clin Interv Aging.* 17:1365-1378. doi: 10.2147/CIA.S376519.
51. Braude P, McCarthy K, Strawbridge R, Short R, Verduri A, et al. (2022) Frailty is associated with poor mental health 1 year after hospitalisation with COVID-19. *J Affective Dis.* May 11.
52. Ramírez-Vélez R, Legarra-Gorgoñon G, Oscoz-Ochandorena S, García-Alonso Y, García-Alonso N, et al. (2023) Reduced muscle strength in patients with long-COVID-19 syndrome is mediated by limb muscle mass. *J Appl Physiol (1985).* 2023;134(1):50-58. doi: 10.1152/jappphysiol.00599.2022.
53. Tang F, Hammel IS, Andrew MK, Ruiz JG. (2022) COVID-19 mRNA vaccine effectiveness against hospitalisation and death in veterans according to frailty status during the SARS-CoV-2 delta (B.1.617.2) variant surge in the USA: a retrospective cohort study. *Lancet Healthy Longev.* 3(9):e589-e598. doi: 10.1016/S2666-7568(22)00166-0.
54. Hussien H, Nastasa A, Apetrii M, Nistor I, Petrovic M, et al. (2021) Different aspects of frailty and COVID-19: points to consider in the current pandemic and future ones. *BMC Geriatr.* 21(1):389. doi: 10.1186/s12877-021-02316-5.
55. Salini S, Russo A, De Matteis G, Piccioni A, Della Polla D, et al. (2022) Frailty in Elderly Patients with Covid-19: A Narrative Review. *Gerontol Geriatr Med.* 8:23337214221079956. doi: 10.1177/23337214221079956.
56. Soares MN, Eggelbusch M, Naddaf E, Gerrits KHL, van der Schaaf M, et al. (2022) Skeletal muscle alterations in patients with acute Covid-19 and post-acute sequelae of Covid-19. *J Cachexia Sarcopenia Muscle.* 13(1):11-22. doi: 10.1002/jcsm.12896.
57. Casas-Herrero Á, Sáez de Asteasu ML, Antón-Rodrigo I, Sánchez-Sánchez JL, Montero-Odasso M, et al. (2022) Effects of Vivifrail multicomponent intervention on functional capacity: a multicentre, randomized controlled trial. *J Cachexia Sarcopenia Muscle.* 13(2):884-893. doi: 10.1002/jcsm.12925..
58. Louise Finlay S. (2022) Frailty: an overview of concepts, risk factors, assessment tools and interventions. *Nurs Older People.* 34(4):35-42. doi: 10.7748/nop.2022.e1394.
59. Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, et al. (2022) Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *Lancet Infect Dis.* 22(1):43-55. doi: 10.1016/S1473-3099(21)00460-6.
60. Guaraldi G, Milic J, Barbieri S, Marchio' T, Caselgrandi A, et al. (2022) 1070. Quality of life and intrinsic capacity in patients with post-acute COVID-19 syndrome is in relation to frailty and resilience phenotypes. In *Open Forum Infectious Dis.* Dec (Vol. 9, No. Supplement_2, pp. ofac492-911). US: Oxford University Press.

61. O'Malley, P. A. (2022) Frailty and disability: predictors or outcomes or both in post COVID-19. *Crit Care Med.* 50 (6):1023-1025.
62. van Dam van Isselt EF, Schols JMGA, Gordon AL, Achterberg WP. (2022) COVID-19, frailty and long-term care: implications for policy and practice. *Post-acute COVID-19 geriatric rehabilitation. Zeitschr für Gerontol und Geriatrie.* 1-5.
63. Chen LK. (2021) COVID-19 vaccination and frailty in older adults. *Arch Gerontol Geriatr.* 104487. doi: 10.1016/j.archger.2021.104487.
64. Tisler A, Stirrup O, Pisarev H, Kalda R, Meister T. (2022) COVID-19, frailty and long-term care: implications for policy and practice. *Post-acute sequelae of COVID-19 among hospitalized patients in Estonia: Nationwide matched cohort study. PLoS One.* 17(11):e0278057. doi: 10.1371/journal.pone.0278057.
65. Taniguchi LU, Avelino-Silva TJ, Dias MB, Jacob-Filho W, Aliberti MJR; COVID-19 and Frailty (CO-FRAIL) Study Group and EPIdemiology of Critical COVID-19 (EPICCoV) Study Group, for COVID Hospital das Clinicas, University of Sao Paulo Medical School (HCFMUSP) Study Group. (2022) Patient-centered outcomes following COVID-19: frailty and disability transitions in critical care survivors. *Crit Care Med.* 50(6):955-963. doi: 10.1097/CCM.0000000000005488.
66. Martí-Pastor A, Moreno-Perez O, Lobato-Martínez E, Valero-Sempere F, Amo-Lozano A, et al. (2023) Association between Clinical Frailty Scale (CFS) and clinical presentation and outcomes in older inpatients with COVID-19. *BMC Geriatrics.* 23(1):1-1.
67. Szlejf C, Suemoto CK, Goulart AC, de Souza Santos I, Bacchi PS, et al. (2023) A pandemic toll in frail older adults: Higher odds of incident and persistent common mental disorders in the ELSA-Brasil COVID-19 mental health cohort. *J Affective Dis.* 2023 Jan 7.
68. Ali AM, Kunugi H. (2021) Physical frailty/sarcopenia as a key predisposing factor to coronavirus disease 2019 (COVID-19) and its complications in older adults. *BioMed.* 1(1):11-40.
69. Agarwala SR, Vijayvargiya M, Pandey P. (2021) Avascular necrosis as a part of 'long COVID-19'. *BMJ Case Rep.* 14 (7):e242101. doi: 10.1136/bcr-2021-242101.
70. Noviello D, Costantino A, Muscatello A, Bandera A, Consonni D, et al. Functional gastrointestinal and somatoform symptoms five months after SARS-CoV-2 infection: a controlled cohort study. *Neurogastroenterol Motil.* 34 (2):e14187. doi: 10.1111/nmo.14187.