REVIEW ARTICLE

COVID-19 and its long-term sequelae: what do we know in 2023?

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ABSTRACT

Post-viral syndrome is a well-known medical condition characterized by different levels of physical, cognitive, and emotional impairment that may persist with fluctuating severity after recovering from an acute viral infection. Unsurprisingly, COVID-19 may also be accompanied by medium- and long-term clinical sequelae after recovering from a SARS-CoV-2 infection. Although many clinical definitions have been provided, "long-COVID" can be defined as a condition occurring in patients with a history of SARS-CoV-2 infection, developing 3 months from the symptoms onset, persisting for at least 2 months, and not explained by alternative diagnoses. According to recent global analyses, the cumulative prevalence of long-COVID seems to range between 9% and 63%, and is up to 6-fold higher than that of similar postviral infection conditions. Long-COVID primarily encompasses the presence of at least 1 symptom, such as fatigue, dyspnea, cognitive impairment/brain fog, postexertional malaise, memory issues, musculoskeletal pain/spasms, cough, sleep disturbances, tachycardia/palpitations, altered smell/taste perception, headache, chest pain, and depression. The most important demographic and clinical predictors to date are female sex, older age, cigarette smoking, pre-existing medical conditions, lack of COVID-19 vaccination, infection with pre-Omicron SARS-CoV-2 variants, number of acute phase symptoms, viral load, severe/critical COVID-19 illness, as well as invasive mechanical ventilation. Concerning the care for long-COVID patients, the greatest challenge is the fact that this syndrome cannot be considered a single clinical entity, and thus it needs an integrated multidisciplinary management, specifically tailored to the type and severity of symptoms.

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Current epidemiology of COVID-19 COVID-19 is a life-threatening infectious disease sustained by SARS-CoV-2, the virus first identified in the Chinese town of Wuhan in November 2019. Thereafter, it has spread rapidly worldwide, and the World Health Organization (WHO) has finally classified it as a pandemic disease in March 2020.[1]

The accurate characterization of the ongoing COVID-19 epidemic is challenging for countless reasons. First, the number of official cases of SARS-CoV-2 infection is underestimated mainly because of undertesting and under-reporting all around the world, making it impossible to provide accurate measures of its current frequency.[2] Then, although it is undeniable that the clinical severity of COVID-19 has considerably declined over time due to either immunity (natural, vaccine-elicited, or both) or the virus attenuation,[3] the overall number of deaths and the mortality rate are also substantially underestimated. According to recent epidemiologic evidence from the WHO, the global number of COVID-19–related deaths may be up to 3-fold higher than officially reported,[4] with ample variations in the volume of excess deaths worldwide (eg, the underestimation bias may even exceed 50% in certain South American regions). Likewise, a debate is fueling over the fact that the way COVID-19–related deaths are counted in some countries may not reflect the real scenario, with several million deaths missed by official statistics.[5] That said, and with the apparent preamble that pandemic numbers are largely biased and will continue to grow in the foreseeable future (COVID-19 seems now

TABLE 1 World Health Organization clinical case definition of long-COVID developed with Delphi methodology

• Occurs in patients with a history of probable or confirmed SARS-CoV-2 infection
• Develops 3 months from the symptoms onset
• Persist for at least 2 months afterward
• Could not be explained by alternative diagnoses
• The main symptoms: – Develop after initial recovery from acute SARS-CoV-2 infection or persist from the original illness – May fluctuate or even relapse over time – Impact everyday functioning – Encompass (in descending order of ≥50% agreement): ▪ Fatigue (78%) ▪ Dyspnea (78%) ▪ Cognitive impairment/brain fog (74%) ▪ Postexertional malaise (67%) ▪ Memory issues (65%) ▪ Muscle pain/spasms (64%) ▪ Cough (63%) ▪ Sleep disorders (62%) ▪ Tachycardia/palpitations (60%) ▪ Altered smell/taste (57%) ▪ Headache (56%) ▪ Chest pain (55%) ▪ Joint pain (52%) ▪ Depression (50%)

almost unstoppable in China), the official figures published by the WHO in its regularly updated COVID-19 dashboard are still concerning, approximating 650 million official cases of SARS-CoV-2 infection and over 6.6 million COVID-19–related deaths at the end of 2022.[6]

Irrespective of the substantial harm caused by an acute SARS-CoV-2 infection, with clinical severity spanning from virtually asymptomatic infection to a systemic disease needing intensive care (occasionally leading to death),[7] convincing evidence has emerged that the clinical burden of COVID-19 may be extended far beyond the acute infective period, with medium- and long-term consequences that may have a substantial impact on the quality of life of the affected individuals, and thus representing a paramount global health challenge.[8] Overall, this condition has been defined as "long-COVID" and is associated with substantial organic dysfunction placing further pressure on already strained health care systems.[9] It may also exert a remarkable social impact as emphasized by recent studies, revealing limitations in the post-COVID quality of life and daily work capacity.[10] In fact, it may manifest in many patients recovering from SARS-CoV-2 infection, with 11% to 70% of all such patients being unable to return to work within 6 months after recovering.[11]

Definition of long-COVID Although many clinical definitions have been proposed for the long-term, often permanent, sequelae of COVID-19,[12] we should now refer to that endorsed by the WHO, which has been developed using Delphi methodology (ie, involving scientists and patients from all worldwide regions), and including up to 12 different clinical domains. According to the consensus reached, long-COVID is defined as a condition occurring in patients with a history of probable or confirmed SARS-CoV-2 infection, which typically develops 3 months from the onset of symptoms, persists for at least 2 months, and cannot be explained by alternative diagnoses. The symptoms may develop after initial recovery from an acute SARS-CoV-2 infection or persist from the original disease, fluctuate or even relapse over time, and usually impact everyday functioning,[13,14] as summarized in TABLE 1. According to this universally agreed definition, in summary, long-COVID could be defined as a clinical syndrome characterized by the presence of at least 1 typical COVID-19 symptom which has not disappeared 3 months after recovering from an acute SARS-CoV-2 infection (the period from recovery to 3 months afterwards will hence be defined as "post-COVID" syndrome) or may have newly developed after such period (FIGURE 1). Importantly, a core outcome set has also been defined (ie, minimum set of agreed outcomes that could be measured in COVID-19 patients),[8] encompassing 4 domains (physiological or clinical outcomes, life impact outcomes, survival, and outcome from the previous end points), declined through 11 outcomes: cardiovascular functioning, symptoms and conditions; fatigue or exhaustion; pain; nervous system functioning, symptoms and conditions; cognitive functioning, symptoms and conditions; mental functioning, symptoms and conditions; respiratory functioning, symptoms and conditions; postexertion symptoms; work or occupational and study changes; survival; and recovery from the previous end points.

Prevalence and predictors of long-COVID The accurate estimation of the epidemiologic burden of long-COVID, as well as of its predictors, remains challenging. This is inherently attributable to the use of different definitions and variable follow-up time, as well as to the inclusion of heterogenous populations with various demographical (ie, age, sex, ethnic origin) and clinical (illness severity, comorbidities, vaccination status) characteristics (TABLE 2). Although many studies and meta-analyses have attempted to estimate the prevalence of long-COVID, we will briefly describe in this narrative review the most relevant points.

The burden of long-term health consequences of long-COVID has been recently (early 2023) summarized in a systematic literature review and meta-analysis by O'Mahoney et al.[15] Briefly, the authors reviewed a total of 194 studies published until January 2022, totaling over 700 000 participants, with 5 of such studies performed in patients younger than 18 years, and with a follow-up between 28 and 387 days (ie, slightly over 1 year) after recovering from acute SARS-CoV-2

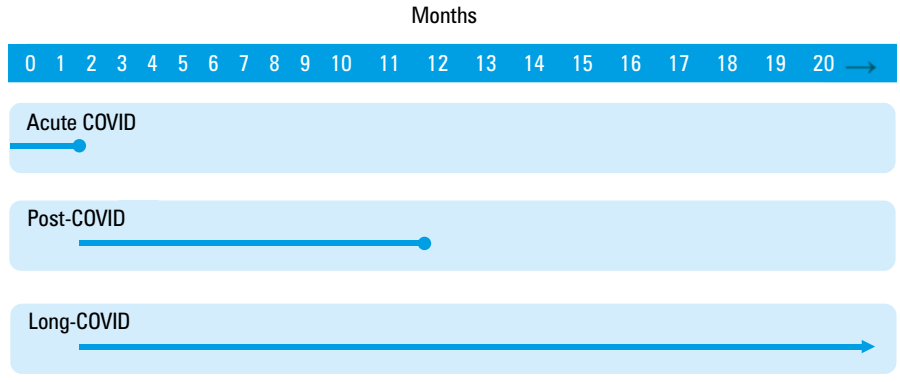

FIGURE 1 Persistent symptoms after diagnosis (months) of SARS-CoV-2 infection

TABLE 2 Leading demographic and clinical predictors of long-COVID

• Female sex
• Older age
• Cigarette smoking
• Pre-existing medical conditions
• No COVID-19 vaccination
• Infection with former SARS-CoV-2 variants (ie, pre-Omicron)
• Number of acute phase symptoms
• Viral load
• Severe/critical COVID-19
• Invasive mechanical ventilation

infection. The main results of this comprehensive meta-analysis are as follows: (1) the cumulative prevalence of COVID-19 survivors reporting at least 1 unresolved symptom 4 months after recovery was as high as 45%, irrespective of the hospitalization status; (2) fatigue and weakness were the most frequent complaints, followed by dyspnea, impaired usual activity, taste and/or smell dysfunction, depression, muscular and/or joint pain, affected sleep, anxiety, cough and headache; (3) the prevalence of all symptoms 120 days after the index date was higher in hospitalized than nonhospitalized patients (53% vs 35%). A parallel meta-analysis was conducted by Chen et al.[16] It encompassed 50 studies, published up to March 2022, with 1 680 003 COVID-19 patients (67 161 hospitalized, 4165 nonhospitalized, and 1 608 677 with no reported hospitalization status). Similarly as in the meta-analysis by O'Mahoney et al[15], the pooled prevalence of post-COVID-19 symptoms was 43% (95% CI, 39%–46%), and it was substantially higher in the hospitalized than nonhospitalized patients (54% vs 34%). Importantly, the prevalence was higher in women (49% vs 37%). The most frequent health complaint was fatigue, followed by memory impairment, dyspnea, sleep issues, and musculoskeletal pain. A third meta-analysis was published by Notarte et al,[17] and it included 37 peer-reviewed studies and 1 preprint screened through September 15, 2022. Most of the reviewed articles found that the symptoms of long-COVID-19 were associated with older age (though not reaching statistical significance in the meta-analysis; $P = 0.17$), female sex ($P = 0.01$), and pre-existing medical conditions, especially pulmonary disease, diabetes, obesity, and organ transplantation.

Additional investigations were published after these 3 systematic literature reviews, which merit attention. Arjun et al[18] followed-up for up to 223 days (ie, 7.4 months) a cohort of 371 Indian adults aged 18 years or older who received a laboratory diagnosis of SARS-CoV-2 infection. Overall, long-COVID could be identified in 9.4% (95% CI, 6.7%–12.9%) of such patients after 6 months of the follow-up. Regarding the predictors, long-COVID was found to be more frequent in patients with pre-existing medical conditions (odds ratio [OR], 2.00; 95% CI, 1.16–3.44) and in those who experienced severe/critical COVID-19 (OR, 5.71; 95% CI, 3.00–10.89). Notably, neither age ($P = 0.86$) nor sex ($P = 0.36$) were significant predictors of long-COVID in this study. The most frequent complaints were fatigue (54%), breathing difficulties (29%), and cough (17%). Nearly half of such patients (46%) reported to be modestly limited in their daily activities.

Important evidence has then emerged from the PHOSP-COVID (Post-hospitalization COVID-19) Collaborative Group study,[19] involving 2320 adult patients from the United Kingdom, discharged from the hospital after COVID-19, who were re-assessed at 5 and 12 months. In keeping with previous evidence, nearly half (49%) of such patients did not feel to have completely recovered from COVID-19. Lower likelihood of reporting full recovery of COVID-19 symptoms was associated with female sex (OR, 0.68; 95% CI, 0.46–0.99), obesity (OR, 0.50; 95% CI, 0.34–0.74) and the need of invasive mechanical ventilation during hospitalization (OR, 0.42; 95% CI, 0.23–0.76).

Other studies have also been recently published that extended the follow-up of SARS-CoV-2 infection for up to 2 years. The first was authored by Huang et al,[20] and included 1119 adult Chinese patients (median age, 57 years) who participated in a visual interview 2 years after recovering from an acute SARS-CoV-2 infection. In this large cohort of recovered patients, the persistence of at least 1 sequelae symptom remained as high as 55% after 2 years, with fatigue and sleep disturbances being the most

frequent complaints, followed by joint pain, palpitations, dizziness, cough, and headache. The most important predictors of symptoms persistence after 2 years from recovery were older age (OR, 1.08; 95% CI, 1.02–1.15), female sex (OR, 1.65; 95% CI, 1.41–1.92), cigarette smoking (OR, 1.26; 95% CI, 1.04–1.54), and disease severity (OR, 1.40; 95% CI, 1.02–1.91). The second study, published by Helmsdal et al,[21] included 170 adult patients from the Faroe Islands, who were followed-up for nearly 2 years (23 months). Importantly, persistent symptoms were reported by 38% of such patients, with up to one-fourth (24%) complaining of incomplete recovery. The prevalence of long-COVID was found to be significantly associated with aging (P = 0.03), the number of acute phase symptoms (P = 0.001), and clinical severity (P <0.05). The third study, published by Fernández-de-Las-Peñas et al,[22] included 668 adult Spanish patients (360 needing hospitalization), who were interviewed 2 years after recovering from an acute SARS-CoV-2 infection. Overall, 427 patients (63.3%) reported at least 1 post-COVID-19 symptom, with such prevalence being significantly and surprisingly higher in those who did not need hospitalization (67.5% vs 59.7%), thus indicating that the hospitalization per se may not play a role in the risk of developing COVID-19 clinical sequelae. In both cohorts, fatigue, pain, and memory loss were the most frequent complaints. The fourth prospective cohort study, published by Millet et al,[23] involved as many as 173 adults from the United States who recovered from COVID-19 (91 needing hospitalization), and who were re-assessed 2 years afterward. Overall, 23% of these patients reported at least 1 persistent symptom, the most common of which was dyspnea, followed by fatigue, difficulty focusing / brain fog, memory loss, and anxiety. The risk of having at least 1 persistent symptom was higher in women (53.6% vs 31.3%), as well as in inpatients as compared with outpatients (52.9% vs 48.0%). Finally, Kalak et al[24] followed-up 166 Israeli patients for up to 18 months after COVID-19 onset, and reported that although the prevalence of most COVID-19 symptoms decreased between 3 and 18 months post-COVID, fatigue (21.2%), dyspnea (15.8%), and brain fog (7.3%) remained considerably prevalent. Importantly, dyspnea at admission, intensive treatment, and intubation were significant predictors of the symptoms persistence after 18 months.

Important evidence has also emerged from a recent study by Girón Pérez et al,[25] who re-evaluated 70 adult COVID-19 patients 3 months after recovery. The authors found that the number of symptoms reported by the patients was directly associated with the initial viral load (r = 0.74; P <0.001). Thus, measuring the viral load (either with SARS-CoV-2 molecular or antigen assays) may be advisable for defining the basic infectivity and predicting the clinical course of the disease, but also for anticipating the risk of long-term consequences after an acute SARS-CoV-2 infection.[26]

A population-based study exploring the prevalence and risk factors of post-COVID syndrome in children and adolescents has also been recently published by Dumont et al.[27] The authors followed-up for at least 12 weeks a total number of 1034 Swiss patients aged 6 months to 17 years, 570 (55.1%) of whom displayed anti–SARS-CoV-2 antibodies. In seropositive children, the rate of persistent symptoms was 9.1% (95% CI, 6.7%–11.8%). Likewise in most adult studies, the most important predictors of post-COVID symptoms were older age (prevalence ratio, 1.1; 95% CI, 1.0–1.3), pre-existing chronic health conditions (prevalence ratio, 3.5; 95% CI, 2.0–6.1), especially asthma, and lower economic status (prevalence ratio, 3.0; 95% CI, 1.5–6.2).

Besides long-COVID, it seems also important to mention here that SARS-CoV-2 infection may substantially impact physiological function, boosting the aging-related decline. Specifically, an interesting longitudinal study published by Ferrara et al,[28] encompassing 177 patients aged 65 years or older followed up for a median period of 6 months, evidenced a significant decline in the clinical frailty scale after recovering from COVID-19 in nearly one-third of all participants, and revealed that over 12% of such patients became frail during the relatively short follow-up.

Impact of SARS-CoV-2 variants Unlike what has been postulated in the earlier phases of this ongoing pandemic,[29] SARS-CoV-2 (an enveloped coronavirus with nearly 30 000-base long, positive-sense, single-stranded RNA) is subjected to a huge ecologic pressure (ie, mainly host immunity) that fosters progressive incorporation of multiple and often convergent mutations within its genome.[30] According to the most recent update of the Global Initiative on Sharing All Influenza Data consortium,[31] nearly 3000 descendants have originated at the end of 2022 from the original (ie, prototype) 19A clade. Notably, the most recent of these clades, defined as Omicron by the WHO, has already undergone a process of intense mutation and recombination, generating several dozens of sublineages at the end of 2022.[32] Although it is challenging to dissect the effect of natural and vaccination-elicited immunity on the progressive mitigation of viral pathogenicity to explain the attenuated clinical severity seen after the emergence of the Omicron variants, it is undeniable that the clinical impact of these sublineages has considerably decreased over time,[33] together with a COVID-19–related mortality rate that has become even lower than that of common influenza at the end of 2022.[34]

Whether or not an attenuated clinical phenotype in patients with recent SARS-CoV-2 infection would translate into a lower risk of developing long-COVID remains controversial. In an earlier study, Antonelli et al[35] followed nearly 56 000 adults from the United Kingdom diagnosed with

SARS-CoV-2 infection between December 2021 and March 2022, and concluded that the risk of long-COVID was constantly lower in the patients with SARS-CoV-2 Omicron infection than in those infected by SARS-CoV-2 Delta variant. Specifically, across all age groups, the risk of long-COVID among Omicron cases (vs those infected by Delta) was by 74% lower in the individuals vaccinated over 6 months prior to the infection, decreased by 76% in those vaccinated between 3 and 6 months before the infection, and reduced by 50% in those who were vaccinated less than 3 months before the infection. No substantial differences emerged after repeating the same analysis in younger (18–59 years) or older (≥60 years) people. Arjun et al[36] studied 524 Indian adult patients aged 19–90 years, followed-up for a mean period of 73 days, and found the overall prevalence of post-COVID symptoms to be as high as 8.2% in Omicron cases, thus around 3.5-fold lower than that found in the patients who recovered from SARS-CoV-2 Delta infection (29.2%). In a subsequent larger study published by Magnusson et al[37] (1 323 145 Norwegian adults, aged 18–70 years), the risk of developing long-COVID symptoms 3 months after recovering was found to be nearly equivalent in those recovering from SARS-CoV-2 Omicron and Delta infection. Nonetheless, the Omicron cases had a significantly reduced likelihood of experiencing any type of complaint (–43%), musculoskeletal pain (–23%), and fatigue (–11%). Another interesting analysis was published by Taquet et al,[38] who conducted a 2-year retrospective cohort study on as many as 1 487 712 patients from the United Kingdom diagnosed with COVID-19, and found that the risk of developing any neurological or psychiatric outcome or death in those diagnosed with COVID-19 was by 11% lower (OR, 0.89; 95% CI, 0.80–0.98) in the period after vs just before the emergence of the Omicron variant.

Thus, although no definitive conclusions can be made on this matter, it seems reasonable to hypothesize that the infection in the period characterized by the predominance of early sublineages belonging to the Omicron family may be associated with a lower risk of developing post-COVID sequelae and / or long-COVID.

Impact of COVID-19 vaccination With the obvious awareness that the most effective physical preventive measures that have been in place for long during the earlier phases of the COVID-19 pandemic cannot be perpetuated forever (ie, social distancing, lockdown, wearing of face masks), COVID-19 vaccines are now universally recognized as the only reliable means for preventing unfavorable progression of SARS-CoV-2 infection.[39] Nonetheless, interesting evidence is emerging that COVID-19 vaccines would not only be capable of efficiently limiting the risk of developing severe / critical COVID-19, but may also play a role in preventing long-COVID. A recent meta-analysis published by Notarte et al[40] including a total of 11 peer-reviewed studies and 6 preprints (until June 20, 2022) with 17 256 654 participants, concluded that COVID-19 vaccination was globally associated with lower risks of long-COVID, with 2 vaccine doses displaying more favorable result than a single administration. Notably, out of 11 studies investigating the variation of long-COVID symptoms after vaccination, 7 concluded that long-COVID symptomatology may improve after COVID-19 vaccination. These important findings were confirmed in a subsequent and more recent study including 3042 adults from the United States, who completed a questionnaire in order to define their health and fitness after recovering from an acute SARS-CoV-2 infection.[41] In keeping with previous evidence, long-COVID was found to be more frequent in women (OR, 1.84; 95% CI, 1.40–2.42) and in those with pre-existing comorbidities (OR, 1.55; 95% CI, 1.19–2.34). Moreover, as compared with COVID-19 vaccine recipients who received at least a single booster dose, the unvaccinated individuals had an over 40% higher risk of developing long-COVID (OR, 1.41; 95% CI, 1.05–1.91). Similar findings were reported in a concomitant study,[42] showing that the risk of developing long-COVID was inversely associated with the number of COVID-19 vaccine doses, being 42% (95% CI, 37%–47%) in unvaccinated individuals, 30% (95% CI, 7%–65%; OR, 0.86; 95% CI, 0.21–3.49) in those receiving a single vaccine dose, 17% (95% CI, 8%–31%; OR, 0.25 and 95% CI, 0.07–0.87) in those receiving 2 vaccine doses, and 16% (95% CI, 12%–21%; OR, 0.16 and 95% CI, 0.03–0.84) in the recipients of a vaccine booster.

Conclusions and future perspectives The postviral syndrome, especially postviral fatigue, is a well-known medical condition characterized by different levels of physical, cognitive, and emotional impairment that persists with fluctuating severity after an acute viral infection.[43] It typically involves people of any age and sex, in whom some symptoms of the acute viral infection may not disappear after weeks or months. Thus, it is not surprising that COVID-19 may also be accompanied by medium- and long-term clinical sequelae in those who recover from an acute SARS-CoV-2 infection.

Nonetheless, what differentiates long-COVID from other postviral syndromes, is that the epidemiologic burden of this condition seems to have a much higher prevalence, up to 6-fold higher than that of similar syndromes observed after other viral infections (up to 63% vs around 10%).[44] Notably, the intersection of these figures with the WHO official statistics (650 million diagnoses of SARS-CoV-2 infection up to the end of 2022) would enable us to hypothesize that up to 400 million people worldwide (underestimated) may be already seeking care for long-COVID in the near future, thus putting under unprecedented pressure the already exhausted and drained health care system.

Overall, long-COVID primarily encompasses the presence of at least 1 symptom such as fatigue and / or weakness, dyspnea, impaired functional status, taste and / or smell dysfunction, depression, musculoskeletal and sleep disturbances, anxiety, depression, and headache, while the most important demographical and clinical predictors seem to be female sex, older age, cigarette smoking, pre-existing medical conditions, lack of COVID-19 vaccination, infection with former SARS-CoV-2 variants (ie, pre-Omicron), number of acute phase symptoms, viral load, severe / critical COVID-19 illness, as well as invasive mechanical ventilation. Notably, the search for laboratory-based predictors of long-COVID is still in embryo. This is quite understandable, considering that the study of medium- and long-term consequences of SARS-CoV-2 infection requires time. Nonetheless, this aspect has been recognized as a leading priority by the Working Group and Task Force on COVID-19 of the International Federation of Clinical Chemistry and Laboratory Medicine, emphasizing the need to conduct clinical studies on this matter. In the meantime, promising information is emerging that risk assessment may be supported by the measurement of some selected biomarkers, such as C-reactive protein and other inflammatory cytokines, lymphocyte count, lactate dehydrogenase, interferon γ, tumor necrosis factor α, and even fibrosis biomarkers, such as soluble suppression of tumorigenicity 2 and Krebs von den Lungen 6.[45] To this end, a recent proteomic study has concluded that a significant perturbation of plasma proteome, characterizing differential expression of proteins involved in lipid metabolism, complement and coagulation cascades, atherosclerosis, autophagy, as well as lysosomal function, could predict with 94% accuracy the persistence of COVID-19 symptoms up to 12 weeks after recovery.[46]

As far as the care for patients with long-COVID is concerned, the most important challenge is the fact that this syndrome cannot be considered a single clinical entity. It thus deserves a separate and more focused discussion, and needs an integrated multidisciplinary management tailored explicitly to the type and severity of symptoms.[47] To date, rehabilitation seems the most effective treatment, but the progress of the ongoing research will help to uncover the numerous multifaceted pathogenic mechanisms sustaining the persistence of symptoms over (long) time, and thus will enable us to identify a therapeutic strategy that could be tailored to individual care needs.[48]

The final aspect deserving specific comment is the future risk that the reverse-transcribed SARS-CoV-2 RNA could be integrated within the genome of infected human cells, where it could persist stably, influencing gene expression but also being actively re-expressed after months or years, the consequences of which are as yet completely unpredictable.[49]

ARTICLE INFORMATION

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