



Post-COVID-19 global health strategies: the need for an interdisciplinary approach

Gemelli Against COVID-19 Post-Acute Care Study Group¹

Received: 15 May 2020 / Accepted: 30 May 2020 / Published online: 11 June 2020
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Abstract

For survivors of severe COVID-19 disease, having defeated the virus is just the beginning of an uncharted recovery path. What follows after the acute phase of SARS-CoV-2 infection depends on the extension and severity of viral attacks in different cell types and organs. Despite the ridiculously large number of papers that have flooded scientific journals and preprint-hosting websites, a clear clinical picture of COVID-19 aftermath is vague at best. Without larger prospective observational studies that are only now being started, clinicians can retrieve information just from case reports and or small studies. This is the time to understand how COVID-19 goes forward and what consequences survivors may expect to experience. To this aim, a multidisciplinary post-acute care service involving several specialists has been established at the Fondazione Policlinico Universitario A. Gemelli IRCCS (Rome, Italy). Although COVID-19 is an infectious disease primarily affecting the lung, its multi-organ involvement requires an interdisciplinary approach encompassing virtually all branches of internal medicine and geriatrics. In particular, during the post-acute phase, the geriatrician may serve as the case manager of a multidisciplinary team. The aim of this article is to describe the importance of the interdisciplinary approach—coordinated by geriatrician—to cope the potential post-acute care needs of recovered COVID-19 patients.

Keywords COVID-19 · Personalized medicine · Post-acute care · Health care organization

Introduction

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by SARS-CoV-2 that mainly affects the respiratory system, as interstitial pneumonia and acute respiratory distress syndrome (ARDS) [1]. Infectious disease physicians, pneumologists, and intensive care physicians are the medical specialists primarily involved in the management of the acute phase of COVID-19. However, as the number of confirmed COVID-19 cases exceeds five million globally, the share of patients who have survived the disease is scaling up. Clinicians and pathologists are now trying to better characterize the site(s), nature, and severity of damage caused by

SARS-CoV-2. Although the lungs are definitely the first target organ of SARS-CoV-2 infection, accumulating evidence indicates that the virus can spread to many different organs, including the heart, blood vessels, kidneys, gut, and brain [2]. For this reason, a multidisciplinary approach becomes crucial for the evaluation and the follow-up of patients with COVID-19 disease (Fig. 1).

Although a substantial body of studies on short-term outcomes of COVID-19 inpatients has already been produced, the literature is void of data on long-term outcomes of patients who survive the acute phase of the disease [3]. It may be assumed that the majority of survivors with a mildly symptomatic presentation (80%) will not be presenting long-term sequelae and will eventually fully recover. No mid-term complications have been reported also for patients with moderately severe symptomatic presentation that required hospitalization but not mechanical ventilation. On the other hand, it may be expected that patients with severe symptomatic presentation requiring mechanical ventilation will be experiencing long-term complications and incomplete recovery (e.g., reduced exercise capacity).

Members of the Gemelli Against COVID-19 Post-Acute Care Study Group are listed in acknowledgement section.

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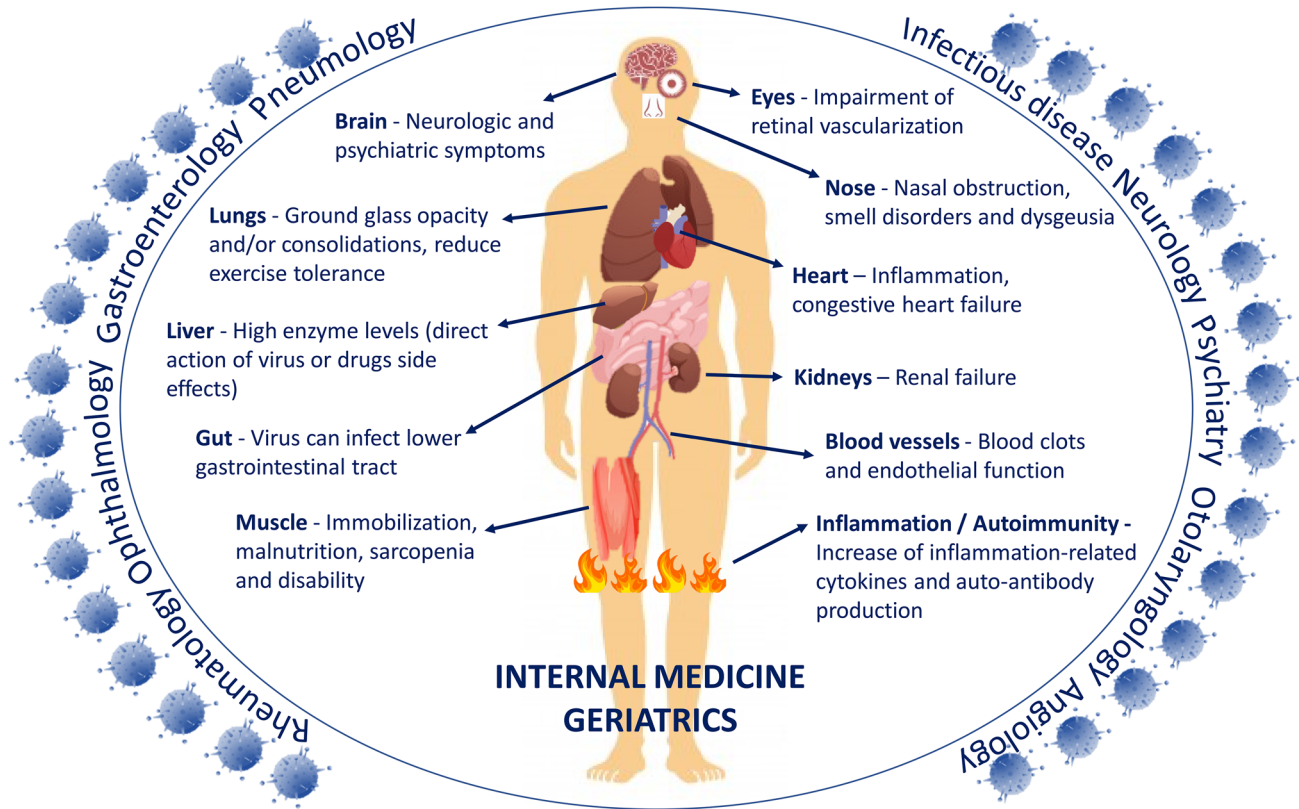


Fig. 1 Multi-organ impairment caused by SARS-CoV-2 infection: holistic approach coordinated by internal medicine–geriatrics

The follow-up of people who have recovered from COVID-19 should be as comprehensive as possible in order to collect all the necessary information to better define the clinical and care needs. This comprehensive assessment should be linked to information on the acute phase of illness (signs and symptoms suffered during the hospital stay) and may be used to redefine the healthcare organizational model and plan what is necessary in the medium and long term. It therefore appears appropriate to propose a detailed model for the first assessment (minimum data set for the assessment of COVID-19 patients), providing that subsequent stages can be customized based on the initial findings (Table 1).

The most important open question to be answered is as follows: “Once recovered from COVID-19 what happens to patients, and how has the virus impacted their body?” To answer this question, the Fondazione Policlinico Universitario A. Gemelli IRCSS (Rome, Italy) has set up a multidisciplinary healthcare service called “Post-COVID-19 Day Hospital.” The specialist assessments offered to patients are outlined in the following sections. Furthermore, the important role of geriatrician acting as a care manager of patients who suffered COVID-19 disease is described. In fact, the geriatrician is the specialist who best can manage the multidimensional health problems, with a great aptitude and skill to cope multimorbid and complex patients.

Second, geriatricians are the doctors who best know the principles of teamwork in close collaboration with the other health care professionals and family. In particular, the geriatrician is able to manage the onset of the most important syndromes, such as sarcopenia, malnutrition, depression, and delirium.

The study protocol was approved by the Ethics Committee of the Università Cattolica del Sacro Cuore (Rome, Italy). Written informed consent has been obtained from the participants. Due to possible contamination, a photograph was taken of the sheet and it was eliminated as a hazardous material.

Infectious disease assessment

One of the most important problems to be addressed is the possibility of a SARS-CoV-2 reinfection. Some reports suggest that COVID-19 could relapse in patients who were considered to have recovered from the disease [4]. However, there are no definite data about possible SARS-CoV-2 reinfection. Understanding the potential protective immunity to SARS-CoV-2 and its duration in time would represent a major scientific achievement both at the individual level and in a global health perspective.

The role of the infectious disease physician is extremely important to evaluate the following: (a) the output and

Table 1 Comprehensive COVID-19 post-acute assessment

Visit	Domain	Assessment
# 1	General assessment Venous sampling Electrocardiogram Clinical history Infectious disease assessment	Nasopharyngeal swab and Immunoglobulin evaluation (capillary blood point of care) Oxygen saturation, heart rate, blood pressure Physical performance (hand grip and chair stand test) Sociodemographic characteristics Epidemiological link Flu and pneumococcal vaccinations Allergy Medical and medication history Lifestyle (physical activity, diet, alcohol consumption) Past and present signs and symptoms of COVID-19 Treatment received for COVID-19 (supplemental oxygen, antibiotics, anti-retroviral, hydroxychloro- quine, immunomodulators) Psychiatric history and quality of life assessment
# 2	Gastroenterology Pneumology Rheumatology Otolaryngology Ophthalmology	Stool and urine analysis Gastrointestinal symptoms Irritable bowel syndrome symptom severity score Respiratory symptoms Blood gas analysis Spirometry (lung capacity for carbon monoxide) 6-min walking test Immuno-rheumatologic assessment and capillaroscopy ENT clinical history, VAS, General ENT exam Olfactometry/olfactometry Visual acuity (BCVA) Fundus photo retinography, OCT of posterior pole, OCT angiography
# 3	Ultrasound Neurology Psychiatry Pediatric Nutrition Internal medicine and geriatrics	Echocardiography and lung ultrasound Vascular ultrasound for current and/or previous deep vein thrombosis, endothelial function, athero- sclerotic burden Central and peripheral nervous system Skeletal muscular manifestations Psychiatric disorders Pediatric epidemiologic link Anthropometric evaluation (BMI, calf circumference) Bioelectric impedance analysis Case management Comprehensive geriatric assessment Physical performance (Short Physical Performance Battery) Planning of successive follow-up visits
# 4	Radiology Other assessments	Chest X-ray and or chest CT scan Renal or liver function

implications of nasopharyngeal swab for SARS-CoV-2 performed one month after two negative ones; (b) clinical and laboratory findings in patients with a recent diagnosis of COVID-19 stratified according to clinical presentation (mild–moderate VS severe ARDS); (c) the immunologic response (IgG and IgA/IgM serum levels) in patients who have overcome the acute phase of the disease at different times during the follow-up (1 month after the onset of symptoms and at 3, 6, and 12 months); (d) the viral load in patients with a positive nasopharyngeal swab to understand the possible viral activity and contagiousness; (e) the possibility of reinfection and the proportion of adverse reactions after hospital discharge; and (f) the possible development of other viral and/or bacterial infections.

Pneumological assessment

Common findings in COVID-19 hospitalized patients are respiratory failure, dry cough, dyspnoea, and CT scan lung abnormalities appearing as ground glass opacities and/or consolidations. During the acute phase, exercise tolerance cannot be assessed using standard tests like the 6-min walking test. Moreover, some patients still need oxygen therapy or have respiratory symptoms at discharge. A respiratory follow-up is of pivotal importance to evaluate lung function, alveolar–arterial gas exchange, and exercise tolerance in recovered non-infective COVID-19 patients [5]. Nothing is known about long-term respiratory sequelae in COVID-19 patients.

The pneumological evaluation is also important to decide for whom and when to order a high-resolution lung CT scan to evaluate radiological resolution of pneumonia or the possible fibrotic evolution.

Ophthalmologic assessment

SARS-CoV-2 infection affects the vasculature likely through immune-mediated reaction. Occlusive phenomena of intravascular coagulation are expected to be more evident in smaller vascular districts [6]. In this scenario, ophthalmological assessment is particularly important to evaluate the degree of impairment of retinal vascularization in COVID-19 survivors. Indeed, the ophthalmologist will evaluate possible damages that COVID-19 infection may have inflicted to the retina. It will be important to correlate the degree of retinal impairment with cerebrovascular and/or cognitive impairment. All patients should be offered complete ophthalmology evaluation including visual acuity assessment, anterior segment and ocular fundus photograph, 3D optical coherence tomography (OCT), and OCT angiography (OCTA). OCTA provides vascular analysis *in vivo* without dye injection. Macula and optic nerve analyses are also performed to assess the degree of macula/optic nerve vascular impairment. The analysis of the fundus and the study of vascular detail with the OCTA technique may help evaluate the involvement of retinal layers from the most superficial to the deepest.

Otolaryngologic assessment

All recovered COVID-19 disease patients need to be investigated about nasal, hearing, and vestibular function. The ear–nose–throat (ENT) evaluation consists of a complete physical inspection of the nose, throat, and ears, especially aimed at nasal cavities through anterior rhinoscopy [7]. Five parameters are assessed: nasal mucosae, nasal septum, presence of polyps, degree of turbinate hypertrophy, and integrity of the olfactory cleft. Each patient is asked to complete a visual analog scale (VAS) for three symptoms: nasal obstruction, dysosmia, and dysgeusia. Symptom severity during the acute phase and during the recovering period is collected and compared. Scores range from 0 (total dysfunction) to 4 (normal function). The degree of olfactory and taste dysfunctions is also assessed by means of the chemosensory complaint score, a validated questionnaire, ranging from 0 to 16. All patients perform the identification test using the Sniffin' Sticks test [8], which consists of 16 blue pens with black numbers. Each pen is presented only once and an interval of at least 30 s is observed between each presentation to avoid olfactory desensitization. For each odorant pen, the patient is requested to choose from a list of four written proposals. The identification score corresponds to the number

of correct responses. Lastly, the refill taste strips are used to measure the taste ability. The test consists of four containers in the highest concentrations of sweet, sour, salty, and bitter. Taste strips are applied by placing them on the tongue and asking the patient to close the mouth. To assess gustatory sensitivity of specific tongue areas, the mouth stays open and the strip is placed in contact only with this area until the patient can provide an answer.

Neurologic assessment

SARS-CoV-2 may infect nervous system and skeletal muscles [9]. Neurologic features have been grouped into three categories: central nervous system (CNS) manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system (PNS) manifestations (taste impairment, smell impairment, vision impairment, and nerve pain), and skeletal muscular injury manifestations [10].

During the post-acute care assessment, neurologic signs and symptoms occurred during the acute phase of SARS-CoV-2 infection are retrospectively investigated to evaluate their persistence in the post-COVID-19 phase. The follow-up of COVID-19 patients also includes a specific neuropsychological assessment in order to evaluate cognitive functions (especially attention, memory, and language) and the interaction with psycho-behavioral aspects.

Psychiatric assessment

Patients recovered from COVID-19 have passed through a dramatic experience, not only because of illness severity but also because of the peculiar conditions of their hospitalization. Long-lasting fever, pain, difficulties of breathing, and exhaustion set up feelings of despair, hopelessness, and depression in most patients. In patients admitted to the intensive care unit, fear of dying reached a concrete and paroxysmal expression. In any case, during the hospitalization, they were forced to live isolated because of the biological risk. The isolation was generally long and intense. Patients spent hours and days alone, meeting a few nurses or doctors for short time, which increased their sufferance and feelings of loneliness. Some patient felt to be considered like plague and the fear of being contagious accompanied them even after hospital discharge. Risk of dying, social isolation, illness severity, and sleep problems increase the risk of mental disorders such as anxiety, mood, and thought as well as acute and post-traumatic stress disorders. In addition, objective social isolation and subjective feelings of loneliness are associated with a higher risk of death, in general, and suicide, in particular. In light of the above considerations, mental health support is provided during the post-COVID-19 phase to prevent

the possible future development of severe psychiatric disorders [11].

Cardiovascular assessment

SARS-CoV-2 impacts the cardiovascular system in multiple ways, although it is presently unclear whether the virus exacerbates pre-existing cardiovascular disease (CVD) or causes new cardiovascular abnormalities. Many cardiac conditions have been described in COVID-19 patients, including heart failure and cardiomyopathy [12]. Heart failure is especially highly prevalent in hospitalized patients. Cardiomyopathy was also reported and is thought to develop direct effects of the virus and/or toxic effects of the cytokines that are released during the infection. In many patients, a prothrombotic state develops during the acute phase, which may lead to pulmonary embolism, intracardiac thrombus, and exacerbation of coronary artery disease [13]. Moreover, patients with cardiovascular risk factors, including male sex, diabetes, hypertension, and obesity, as well as pre-existing CVD are at highest risk of negative outcomes. Echocardiography has an important role in managing critically ill patients, but the prolonged and close contact with patients makes it difficult to perform a detailed examination during the acute phase of disease. For these reasons, a complete trans-thoracic echocardiography is performed during the post-acute phase to explore the effects of SARS-CoV-2 infection on the heart.

COVID-19 is also recognized as a cause of severe vascular complications, mainly secondary to the inflammatory cytokine storm and rapidly progressing systemic inflammation [14]. These last conditions may lead to endothelial dysfunction, which in turn may promote the development of atherosclerosis, plaque instability, and myocardial infarction. Furthermore, COVID-19 patients show significant abnormalities in the coagulation pathway and are at increased risk of venous thromboembolic events. Based on these elements, ultrasonographic evaluation is important to investigate the following: (a) the endothelial function, by evaluating the brachial artery reactivity, which is a well-established technique used in adults (endothelium-dependent vasodilation) [15]; (b) the prevalence of current and/or previous deep vein thrombosis events; and (c) the whole atherosclerotic burden, using specific scores for carotid and lower limb districts as previously reported.

Nutritional assessment

Nutrition is a major determinant of health. In COVID-19, nutritional status is a crucial factor across all disease stages, especially in people at risk for negative outcomes, such as older adults and those with multimorbidity. It is widely acknowledged that malnutrition is both a cause and a consequence of immune dysfunction. In addition, in COVID-19 patients, low levels of circulating markers of nutritional

status (e.g., albumin, pre-albumin, and lymphocyte counts) are associated with worse outcomes [16]. Prolonged intensive care unit stays are a well-established risk factor for malnutrition and lead to striking decline in muscle mass and strength and overall physical function. Following SARS-CoV-2 infection, overactive inflammation may exacerbate catabolic processes and anorexia. These phenomena may, in turn, aggravate malnutrition and be responsible for poor recovery, loss of independence, disability, and reduced quality of life after ICU discharge. Not surprisingly, expert consensus recommends accurate and timely nutritional assessment and interventions to improve clinical outcomes in people at risk of malnutrition, including persons with chronic/severe diseases across healthcare settings [17, 18]. Recently, the European Society for Clinical Nutrition and Metabolism (ESPEN) developed a practical guide for the nutritional management of patients with SARS-CoV-2 infection [19]. According to ESPEN recommendations, nutritional screening, assessment and therapy should be considered as an integral part of the continuum of care for COVID-19 patients. In this multidisciplinary post-acute care service, a comprehensive nutritional assessment is implemented according to the most recent guidelines. In particular, body composition changes (assessed through anthropometry and bioelectrical impedance analysis) as well as energy/protein intake is evaluated, and specific nutritional recommendations are provided to support the functional recovery of post-acute COVID-19 patients.

Gut assessment

Gastrointestinal involvement is common in COVID-19, as reflected by a prevalence of anorexia, diarrhoea, vomiting, nausea, abdominal pain, and/or gastrointestinal bleeding as high as 50% (varying from 3 to 79% according to different reports), even in the absence of respiratory manifestations [20]. Indeed, infectious SARS-CoV-2 has been detected in stool specimens, and ACE2 receptors, which the virus uses to entry in host cells, are expressed in esophagus, stomach, small bowel, colon, liver, and pancreas. Viral infections may cause post-infectious gastrointestinal disorders as well. Moreover, drugs with potential gastrointestinal, pancreatic, and hepatobiliary side effects, such as antibiotics, antivirals, hydroxychloroquine, and biologics, are frequently used to treat patients affected by COVID-19. The role of the gastroenterologist is to recognize COVID-19 digestive manifestations, to make proper differential diagnosis, and to manage the infection-related complications and adverse drug events.

Rheumatologic assessment

SARS-CoV-2 infection can lead to an abnormal immunologic response causing severe respiratory failure and pneumonia, sustained by the so-called cytokine storm and

thrombo-inflammation. Indeed, several drugs used in severe COVID-19 are immuno-modulators borrowed from the armamentarium of rheumatologic diseases. SARS-CoV-2 infection may also induce the development of autoimmune phenomena, as with other viral infections, and initial reports have described *de novo* development of autoantibodies in COVID-19 patients, in particular, antiphospholipid antibodies, which may contribute to the thrombo-inflammation cascade [21].

In convalescent COVID-19 patients, the role of the immuno-rheumatologist is therefore fundamental for the management of the autoinflammatory and autoimmune aspects of these patients. In particular, convalescent COVID-19 patients deserve an immune-rheumatological evaluation aiming at (a) identifying possible risk factors requiring specific treatments (e.g., presence antiphospholipid antibodies); (b) re-assessing the eligibility for re-treatment of patients with severe pneumonia during hospitalization in a multidisciplinary manner or to integrate with further medications; and (c) managing patients exposed to immunological/immunosuppressant therapies during hospitalization for possible infection risk and adverse events.

Epidemiologic link with young family members

Recent reports document that about 1% of children with COVID-19 develop severe to critical disease. Furthermore, several restrictive measures (parents' smart working and school closures) are heavily affecting the daily life of millions of children and their parents worldwide [22]. While the clinical impact of COVID-19 in children is mild compared with adults, the real epidemiological burden of pediatric COVID-19 is unknown, with several unanswered questions. Do children play a role in this pandemic? Do they play a role in the contagion chain? Children are not infected, or most of them are asymptomatic, but do they spread the infection in family clusters? Moreover, several patients with COVID-19 are keen to understand whether children living in the same household got the infection or not. In order to provide a comprehensive support to families with known SARS-CoV-2 infection and to better understand the epidemiological impact of COVID-19 in children, it is believed that it is important to evaluate with serological studies children whose parents have had a documented SARS-CoV-2 infection. The established post-acute service is a great opportunity to gain insights into the epidemiology of COVID-19 disease among children.

Internal medicine and geriatric assessment

Although no age group is safe from the SARS-CoV-2 infection, the burden is higher and most severe for persons aged 70 years and over, with documented mortality rates of more

than 20% among octogenarians [23]. The presence of multiple pre-existing comorbidities is associated with more severe COVID-19, possibly reflecting the presence of physical and/or cognitive frailty. It is therefore clear that the population more susceptible to negative COVID-19 outcomes involves older adults and/or with those with underlying medical conditions (such as CVD, diabetes mellitus, renal failure, and respiratory diseases), which requires more attention and care [1].

The complexity of patient follow-up, the different medical specialties involved, and the possibility that some patients may develop long-term sequelae call for a multi-domain organization to adequately match the needs of COVID-19 survivors.

In such a complex scenario, the involvement of internists and geriatricians is crucial for the adequate assessment and management of COVID-19 patients. These individuals often experience a worsening of pre-existing medical conditions because of age and COVID-19-associated physical and mental strain and are in need of doctors able to deal with multidimensional health problems. A case manager with great ability and competence in the management of multimorbid and complex patients is therefore needed for optimal post-acute care delivery [24]. In this regard, geriatricians are probably the doctors who best know the principles of teamwork [25]. In this Post-COVID-19 Day Hospital, internal medicine and geriatric specialists are integrated with infectious disease physicians, pneumologists, immuno-rheumatologists, and other specialists into the management of the SARS-CoV-2 infection. This organization allows developing tailored management strategies and the thorough investigation and description of the peculiar clinical consequence of COVID-19 [26, 27].

The internal medicine and geriatric specialists have the clinical responsibility of the diagnostic schedule and therapeutic strategies. In particular, geriatricians act as case manager performing the initial assessment of the patients (telephone pre-screening, and clinical and functional assessment), managing health problems that arose from the specific evaluation, monitoring the provision of services, and providing additional diagnostic services when needed. In addition, together with the other specialties, they designed and implemented the individualized care plan and determined the services that each person was eligible for. In this respect, the geriatrician is responsible for the activation of specific rehabilitation and exercise program. Finally, most patients do not need a specific rehabilitation program but a physical activity program; for this reason, a specific exercise protocol based on the SPRINTT project has been implemented [28, 29].

As a whole, the post-acute care service at the Fondazione Policlinico Gemelli aims at expanding the knowledge of COVID-19 and its impact on health status and care needs

as well as at promoting healthcare strategies to treat and prevent the clinical consequence of SARS-CoV-2 infection across different organs and systems.

Conclusion

The rapid spread of SARS-CoV-2 infection pandemic has led to the collection of an impressive amount of observational data addressing the acute phase of the disease. On the other hand, evidence on COVID-19 clinical history following the acute phase is very limited and little is known about mid- and long-term outcomes. It is therefore of utmost importance that healthcare services are put in place to ensure a comprehensive follow-up of people discharged from hospital and the emergency department. Patient follow-up will also offer the extraordinary opportunity to collect data in a standardized manner to better define the global impact of COVID-19, identify specific clinical needs, and devise the organization of comprehensive and individualized care plans.

Acknowledgment The Gemelli Against COVID-19 Post-Acute Care team thanks La Torre R, Brisetti S, Fella L, Sofo MT and all the nurse staff of the “Post-COVID Day Hospital Unit” for their extraordinary dedication and expertise in treating COVID-19 patients. The Gemelli Against COVID-19 Post-Acute Care Study Group is composed as follows: *Steering committee*: Landi F, Gremese E. *Coordination*: Bernabei R, Fantoni M, Gasbarrini A. *Field investigators*: Gastroenterology team: Settanni CR; Geriatric team: Benvenuto F, Bramato G, Carfi A, Ciciarello F, Lo Monaco MR, Martone AM, Marzetti E, Napolitano C, Pagano F, Rocchi S, Rota E, Salerno A, Tosato M, Tritto M, Calvani R, Catalano L, Picca A, Saveria G; Infectious disease team: Cauda R, Tamburrini E, Borghetti A, Di Gianbenedetto S, Murri R, Cingolani A, Ventura G, Taddei E, Moschese D, Ciccullo A; Internal Medicine team: Stella L, Addolorato G, Franceschi F, Mingrone G, Zocco MA; Microbiology team: Sanguinetti M, Cattani P, Marchetti S, Posteraro B, Sali M; Neurology team: Bizzarro A, Lauria A; Ophthalmology team: Rizzo S, Savastano MC, Gambini G, Cozzupoli GM, Culiarsi C; Otolaryngology team: Passali GC, Paludetti G, Galli J, Crudo F, Di Cintio G, Longobardi Y, Tricarico L, Santantonio M; Pediatric team: Buonsenso D, Valentini P, Pata D, Sinatti D, De Rose C; Pneumology team: Richeldi L, Lombardi F, Calabrese A; Psychiatric team: Sani G, Janiri D, Giuseppin G, Molinaro M, Modica M; Radiology team: Natale L, Larici AR, Marano R; Rheumatology team: Paglionico A, Petricca L, Gigante L, Nataello G, Fedele AL, Lizzio MM, Tolusso B, Alivernini S; Vascular team: Santoliquido A, Santoro L, Nesci A, Popolla V.

Data availability All the data and material are available.

Compliance with ethical standards

Conflict of interest None of the participants in the Gemelli Against COVID-19 Post-Acute Care Study Group has any conflict of interest.

Ethics approval The study was approved by the Ethics Committee of the Università Cattolica del Sacro Cuore.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent The author gives consent for publication of this paper.

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