Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Post-acute COVID-19 Syndrome (PACS): A public health emergency

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The *Anaesthesia Critical Care and Pain Medicine* journal reacted quickly to the emergence of SARS-CoV-2 Infection (COVID-19), reporting in early April the two-week outcomes of Intensive Care Unit (ICU) patients [1] and anticipating the devastating consequences of COVID-19 beyond China [2,21]. Simultaneously, other journals reported the need for standardised therapies [2,3] and the need for a personalised approach before the RECOVERY trial data [4] suggested that patients requiring oxygenation support may benefit from dexamethasone treatment. Moreover, building on the personalised treatment of COVID-19 patient argument, two different severe phenotypes in patients who underwent mechanical ventilation were identified [2].

Lower respiratory tract infections (LRTI), including influenza, have been the most frequent cause of infectious death during the last two decades worldwide, indeed [5]. Among survivors, persistent inflammation was associated with long-term systemic complications, reducing 1-year survival (particularly due to cardiovascular events), and with important quality-of-life impairment [6]. As those that do not know their past are doomed to repeat, we should remember what was known before the COVID-19 pandemic regarding long-term complications after recovery from pulmonary infections [7]. For instance, major adverse cardiovascular events (MACE) were well known to occur acutely and up to ten years after a patient presented CAP [8]. The higher risk for developing these complications was the first 30 days after the acute pneumonic episode; however, MACE could happen several years thereafter [9]. Importantly, disease severity was directly linked with the development of these complications, being patients with severe CAP at higher risk of developing MACE [10]. The mechanisms associated with MACE in CAP patients have been partially dissected in patients with CAP due to *Streptococcus pneumoniae* and influenza virus [8]. These pathogens have a specific tropism for the heart and can induce necroptosis, a highly pro-inflammatory cell-death pathway, in cardiomyocytes. Moreover, there is evidence that the acute pneumococcal insults into the heart during the CAP caused heart scarring, which might be responsible for the long-term MACE documented in patients admitted due to severe CAP [11]. Therefore, the fact that COVID-19 patients might develop long-term consequences independently of the disease severity is not surprising and should invite researchers to identify the underlying mechanisms to identify potential therapeutic targets.

Thus, it should not be surprising that at least one out of ten COVID-19 symptomatic survivors develop Post-acute COVID-19 Syndrome (PACS) [12], and it should be considered a public health emergency. ICU survivors often live with cognitive, psychological, and physical sequelae months after ICU discharge, despite of intense rehabilitation, with a significant impact on quality of life. In 2010, the Society of Critical Care Medicine (SCCM) organised a conference defining the post-intensive care syndrome (PICS) as "new or worsening impairment of cognition, mental health or physical function after critical illness, persisting beyond the acute care hospitalisation" [13]. In 2014, a second conference [14] addressed barriers to clinical practice and identified resources and research gaps. Symptoms may reflect immunologic alterations depending on personal genotypes or vasculitis involvement, adverse therapy effects, prolonged immobilisation, and mitochondrial dysfunction. Depression, sleep disturbances, and cognitive impairment are serious consequences. Thus, it is crucial to implement follow-up programs after ICU discharge [15] to identify and improve care for these patients, but the actual incidence remains hidden.

Taking into account the potential long-term impact and systemic complications in patients that survive COVID-19, several organisations, including the World Health Organization (WHO) and the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC), have launched multinational collaborative efforts to define, characterise and determine the frequency of these complications. The authors endorse the participation in these research protocols [16], which should address PACS after ICU admission, ward hospitalisation, and outpatient care.

As an example of documenting the long-term consequences of COVID-19, a well-conducted study was published by the COMEBAC (COnsultation Multi-Expertise de Bicêtre Après COVID-19) Study Group [17]. This landmark study was carried out in a third-level hospital in the Paris area and included more than 450 patients. In this study, researchers performed a follow-up visit by phone and an in-person evaluation of the patients who developed persistent symptoms four months after the acute episode. Then, researchers stratified the cohort in patients admitted to the ICU or who remained in the general wards (non-ICU) during the hospital admission. A total of 177 patients (97 ICU and 80 non-ICU patients) were evaluated in the outpatient clinic. During the follow-up, the patients received a comprehensive respiratory assessment (*e.g.*, Chest Tomography, 6-minute walk test, and pulmonary function

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tests) and cardiac assessment (*e.g.,* transthoracic echocardiography and clinical cardiovascular examination), and psychological and cognitive evaluation. Researchers found that the cognitive impairment (34%, 61/177) and psychiatric symptoms (36%, 63/177) were frequent long-term implications of patients that survived the acute COVID-19 episode. Moreover, 25.3% of patients had right ventricular dilation on the echocardiography, and 12.0% had decreased left ventricular ejection fraction. Finally, patients frequently had new-onset dyspnoea, abnormal CT scans (56.4%, 44/78), dysfunctional breathing (17.9%, 14/78), and abnormal diffusion capacity of the lungs for carbon monoxide (69.7%, 23/33). Remarkably, these long-term symptoms and disabilities were documented in both ICU and non-ICU patients. Moreover, the researchers performed a stratified analysis of patients that underwent invasive mechanical ventilation, a surrogate for severity, finding that PACS was evident even in patients with non-severe infection.

The presence of long-term consequences of COVID-19, as previously stated, was not surprising. However, the fact that the frequency and severity of PACS were not directly linked or exclusive to patients with severe disease (*i.e.,* ICU admission or the requirement of invasive mechanical ventilation) is essential to highlight and worth the discussion [18]. Thus, it is urgently needed to identify PACS risk predictors and the potential differences between PACS and PICS, assigning rehabilitation programs to limit the consequences.

Even though the COMEBAC group's study was well conducted, it has important limitations that should be acknowledged before generalising these results. First, this is a monocentric study conducted in a single hospital in France, which severely limits the generalisation of the data. Second, not all patients were assessed in the outpatient clinic; thus, the prevalence of PACS and its characteristics could not be determined by this study. Third, the number of patients is limited with important selection bias as expressed before. Lastly, the lack of a control group [18] is a crucial design weakness. Despite these limitations, this visionary study is of great utility as a hypothesis generator and makes people aware of the existence of PACS as an actual disease.

This study should serve to incentivise the implementation of follow-up programs for all ICU survivors, which should involve a multidisciplinary team of nurses, neurologists, rehabilitation, and mental health specialists, being completed by primary care physicians. We should not miss to identify PICS in family members of survivors of critical illness [19]. Also, the inability to work and their poor quality of life can be devastating for survivors' families. The economic impact of PACS is likely to be huge and needs to be quantified in multi-centric reports of survivors in different countries.

In summary, the PICS epidemic will increase currently with SARS-CoV-2 infected survivors with PACS. Understanding the prevalence with post-ICU follow-up is mandatory, but the lack of ICD-10 codes impedes identification. Researchers lack identification to find funding priorities for policy makers, and providers cannot finance them [20]. Thus, we endorse the call for WHO to create an international classification of disease diagnostic codes for PICS in the COVID-19 era.

Conflict of interest

The authors have no conflicts of interest to declare.

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Jordi Rello[a,b], Arthur James[c,d], Luis Felipe Reyes[e,f,*]

[a]*Vall d'Hebron Institute of Research (VHIR), Barcelona, Spain*

[b]*CHRU Nîmes, France*

[c]*Sorbonne University, GRC 29, AP-HP, DMU DREAM, Department of Anaesthesiology and Critical Care, Pitié-Salpêtrière Hospital, Paris, France*

[d]*SFAR Youth Committee, France*

[e]*Universidad de La Sabana, Chía, Colombia*

[f]*Clínica Universidad de La Sabana, Chía, Colombia*

[*]Corresponding author at: Universidad de La Sabana, Chía, Colombia

E-mail addresses: jrello@crips.es (J. Rello)., luis.reyes5@unisabana.edu.co (L.F. Reyes).

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