Minerva Anestesiologica 2022 January-February;88(1-2):72-9
DOI: 10.23736/S0375-9393.21.16032-8

EXPERTS' OPINION

Long-term complications of COVID-19 in ICU survivors: what do we know?

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has caused more than 175 million persons infected and 3.8 million deaths so far and is having a devastating impact on both low and high-income countries, in particular on hospitals and Intensive Care Units (ICU). The ICU mortality during the first pandemic wave ranged from 40% to 85% during the busiest ICU period for admissions around the peak of the surge, and those surviving are frequently faced with impairments affecting physical, cognitive, and mental health status, complicating the postacute phase of COVID-19, which in the pre-COVID period, were defined collectively as postintensive care syndrome (PICS). Long COVID is defined as four weeks of persisting symptoms after the acute illness, and post-COVID syndrome and chronic COVID-19 are the proposed terms to describe continued symptomatology for more than 12 weeks. Overall, 50% of ICU survivors suffer from new physical, mental, and/or cognitive problems at 1 year after ICU discharge. The prevalence, severity, and duration of the various impairments in ICU survivors are poorly defined, with substantial variations among published series, and may reflect differences in the timing of assessment, the outcome measured, the instruments utilized, and thresholds adopted to establish the diagnosis, the qualification of personnel delivering the tests, the resource availability as well diversity in patients' case-mix. Future longitudinal studies of adequate sample size with repeated assessments of validated outcomes and comparison with non-COVID-19 ICU patients are needed to fully explore the long-term outcome of ICU patients with COVID-19. In this article, we focus on chronic COVID-19 in ICU survivors and present state-of-the-art data regarding long-term complications related to critical illness and the treatments and organ support received.

(*Cite this article as:* Rasulo FA, Piva S, Latronico S. Long-term complications of COVID-19 in ICU survivors: what do we know? Minerva Anestesiol 2022;88:72-9. DOI: 10.23736/S0375-9393.21.16032-8)

Key words: COVID-19; Intensive Care Units; Respiratory distress syndrome.

Infection caused by severe acute respiratory syndrome related Coronavirus-2 (SARS-CoV-2), initially discovered in November 2019 in Wuhan, China, has spread to the entire planet over the past 18 months, resulting in the worst healthcare crisis of this century with more than 175 million persons infected and 3.8 million deaths.[1]

On the February 18, 2020, the first COVID-19 patient occupied an ICU bed in Codogno, Lombardy, Italy, and on April 3, 2020, just 44 days later, the total number of ICU beds rose to 4068, making Italy the hardest hit country after China at the time.

The associated human disease, Coronavirus disease 2019 (COVID-19), was declared a global pandemic on March 11, 2020, by the World Health Organization. COVID-19 overlaps with three pre-existing pandemics, obesity, undernutrition, and climate change, which affect most people worldwide. This synergy of pandemics, called syndemic, makes the health consequences far more alarming than COVID-19 epidemic alone.[2]

Consequences of COVID-19 have been devasting also in high-income countries, with a huge impact on hospitals and Intensive Care Units (ICU). Early statistics indicate that 20% of infected subjects are hospitalized,[3] and 3% to 81% are admitted to an ICU,[4] with most of these critically ill patients experiencing acute respiratory distress syndrome (ARDS) and requiring mechanical ventilation.[5] Mortality in the ICU was high during the first pandemic wave, above 40%[6, 7] and up to 85% in some series,[8] and was highest during the busiest ICU period for admissions around the peak of the surge.[7] For the clinicians suddenly faced with the task of treating a new disease, knowledge was a day-by-day process during which clinicians gained experience, hospitals improved organization and resource availability, and the entire medical community struggled to provide new effective treatments for hospitalized patients such as steroids and tocilizumab, resulting in a significant reduction of mortality also in ICU patients.[8-11] However, this may come at a cost because there is likely to be an untold burden of ICU survivors with long-lasting, multi-dimensional impairments affecting physical, cognitive, and mental health status, which, in the pre-COVID period, have been defined collectively as postintensive care syndrome (PICS). Since PICS is common and well defined among non-COVID ICU survivors, it has been recommended to unify post-COVID-19 research aims with those of PICS research.[12] However, the multisystem nature of SARS-CoV-2 infection leaves little doubt that myriads of pulmonary, cardiovascular, neuropsychiatric, hematologic, endocrine, gastrointestinal, dermatologic and renal problems may complicate the postacute phase of COVID-19,[13, 14] with a disproportionate effect on people from ethnic minority groups, or living in rural areas and low-income countries.[15, 16] This would require a multi-disciplinary approach and dedicated post-COVID-19 clinics. In fact, the NHS in England has established post-COVID-19 clinics to offer comprehensive assessment and guide patients to access specialist services.[16]

Protracted severe disability in large numbers of patients, if confirmed, can be as disrupting for health care systems as the acute stage of COVID. Long COVID, defined as four weeks of persisting symptoms after the acute illness, is estimated to occur in approximately 10% of people infected,[17] so there are likely more than 17 million people affected globally. Post-COVID syndrome[16] and chronic COVID-19[13] are the proposed terms to describe continued symptomatology for more than 12 weeks but estimates of prevalence of these conditions and long-term course in the surviving population are yet unknown. In this article, we focus on chronic COVID-19 in ICU survivors and present state of the art data regarding long-term pulmonary complications as well as complications related to critical illness and the treatments and organ support received.[18]

The PICS framework

The term PICS describe a constellation of new or worsening clinical signs and symptoms arising in ICU survivors after the exposure to critical illness and its treatment.[19] Long-lasting deficits tend to cluster into domains that are categorized as physical, cognitive, and mental health domains. However, co-occurrence of conditions is common (*i.e.*, symptoms in two or more domains),[20] and hence, the approach to post-ICU patients is necessarily multi-dimensional, because it is the entire person that is involved – his/her body, mind and spirit – not just his/her organs. Also, it is not only “the etiology of ICU admission” that matters in determining prognosis.[21] Admission diagnoses and severity of the acute disease are certainly important but pre-existing comorbidities and frailty are also strongly associated with post-ICU health problems.[22-24] The socio-economic context also is a key determinant of prognosis, because well-organized health-care systems in high-income countries meet population needs more easily than health-care systems in low- and middle-income countries where 30% to 50% of health care financing comes from out-of-pocket payments, and fragmented governance, inadequate drugs and medical supplies, lack of equipment, bureaucracy and emigration of doctors and nurses are major constraints.[25]

Overall, 50% of ICU survivors suffer from new physical, mental, and/or cognitive problems at one year after ICU discharge,[23] and ARDS survivors shows a marked reduction in nearly all PICS domains.[26, 27] We have proposed that the "A" of ARDS should also indicate "after," to emphasize "the need to address early survivorship care aimed at preventing disability after ICU with the same high priority that is given to the treatment of the acute lung injury to reduce mortality."[28]

Physical impairment

The World Health Organization International Classification of Functioning (ICF) conceptualizes functioning as the interactions between three domains or constructs: personal factors at the body level and at the level of the whole person, and environmental factors (the whole person in a social context), and disability as involving the dysfunction of one or more of these same levels: impairments (the body), activity limitations (the person) and participation restrictions (the person in the societal context) (Table I).[28, 29] Some authors further separate the activity limitations assessed in a standardized environment from those assessed in the usual environment.[29, 30]

Physical impairments have long been recognized as a major health problem in patients surviving ARDS or other critical conditions.[22] In her seminal study, Herridge reported that 22% of ARDS survivors at three months had significant muscle weakness, with a 12% average loss of body weight, and a median six-minute walked distance that was less than half the predicted value.[31] Fan found similar results with significant muscle weakness associated with impairments in physical function and health-related quality of life at three months that persisted at 24 months.[32] Needham reported substantial impairments for six-minute-walk distance and SF-36 physical function outcome measures in survivors of acute lung injury assessed at six and 12 months.[33] Fatigue was reported by 70% of ARDS survivors at six months and 12 months.[34]

To date, no study has provided comprehensive data on physical impairments in ICU patients after COVID-19. Evaluation of the physical components of the syndrome requires in-person assessment of patients, which has been limited or prevented by the hospital access restrictions put in place to support infection prevention and control measures to reduce the spread of infection. In a preliminary analysis of 6-month data from our center,[35] we found that MRC sum score below 48 indicating significant muscle weakness was present in only two patients (4%); handgrip dynamometry was below 80% of the predicted value in 40 patients (71%), but none had a reduction of grip strength below the cut-off values indicating ICU-acquired muscle weakness; median distance walked in six

TABLE I.—*World Health Organization International Classification of Functioning (ICF).*

Construct (or domain)	Description of construct	Outcome	Outcome measure
Personal factors: body function and structure	Physiology and anatomical structure of the body systems	Anatomical and physiological impairment at the level of individual organs or body systems, including neurological, cardiac, respiratory, and musculoskeletal systems	Impairment of muscle strength assessed with MRC scale or handgrip dynamometry; critical illness neuromyopathy assessed with EMG; fatigue assessed with appropriate scales
Personal factors: activities	Execution of a specific task	Performance-based measurement and self-reported physical measures focused on limitations in specific activities, such as sitting, standing, or walking	Activity limitations assessed with 6-minute walk test, timed up-and-go, SF36 physical functioning
Environmental factors	Participation in everyday life situations	Assessment of participation	Participation restrictions assessed with ADL, IADL, return to work, SF36 role physical

Complete assessment of physical function in ICU survivors should include measurements pertaining to all three ICF domains.
MRC: Medical Research Council; EMG: electromyography; SF-36: 36-Item Short Form Survey; ADL: activities of daily living (*i.e.* dress, bathe, eat, get in and out of bad, walk). IADL: instrumental activities of daily living (*i.e.* use telephone, go shopping, take medications, handle own money). Some authors further separate the activity limitations assessed in a standardized environment (*i.e.* 6-minute walk test; timed up-and-go) from those assessed in the usual environment (*i.e.* ADL, IADL).[28, 29]

minutes was 80% of predicted (median distance walked 450 meters, IQR 405-529); however, severe fatigue was reported by one third of patients and did not improve over time. In a Chinese study in Wuan,[36] the six-minute walk test was 85% of predicted value (median distance walked 479 meters [IQR=434-515]) and 82% of patients reported fatigue or weakness at six months; however, weakness was only assessed as a subjective measure using a questionnaire. In the French COMEBAC study in Paris,[37] the median distance walked in six minutes was 462 meters (IQR=380-523), and muscle weakness "compatible with ICU-related neuromyopathy" was described in 27% patients but ascertainment methods were not reported. Preliminary data from International Severe Acute Respiratory Infection Consortium and RECOVER trial in the UK with retrospective comparison of COVID- and non-COVID mechanically ventilated patients, shows that the prevalence (10.3% [3/29] *vs*. 32.5% [54/166]) and severity (median 2.0/10 *vs*. 5.7/10) of fatigue at six-months is less in the COVID-19 cohort.[38] Taken together, these data suggest that physical impairment in COVID-19 ICU survivors may be less frequent and severe, and recovery may be faster than in non-COVID ICU survivors (Figure 1).

In contrast with these results, a preliminary report from the PHOSP-COVID Collaborative Group study in the UK assessing COVID-19 hospitalized patients at a median of five months after hospital discharge[39] showed that the short physical performance battery (SPPB) was ≤10 in 134 ICU patients (51%) and the median Incremental Shuttle Walk Test (ISWT) was 36% predicted, indicating substantial functional impairment.

Cognitive and mental health impairment, and return to work

Deficits in cognitive function are highly prevalent in ARDS survivors, with 30%[40] to 46%[41] of patients showing generalized cognitive decline at one year. In a mixed population of medical and surgical critically ill patients, 26% and, respectively, 40% of surviving patients assessed at three months had global cognition scores that were similar to scores for patients with mild Alzheimer's disease and moderate traumatic brain injury.[42] Cognitive deterioration at one year was reported in 6% to 13% of patients in a recent series of med-

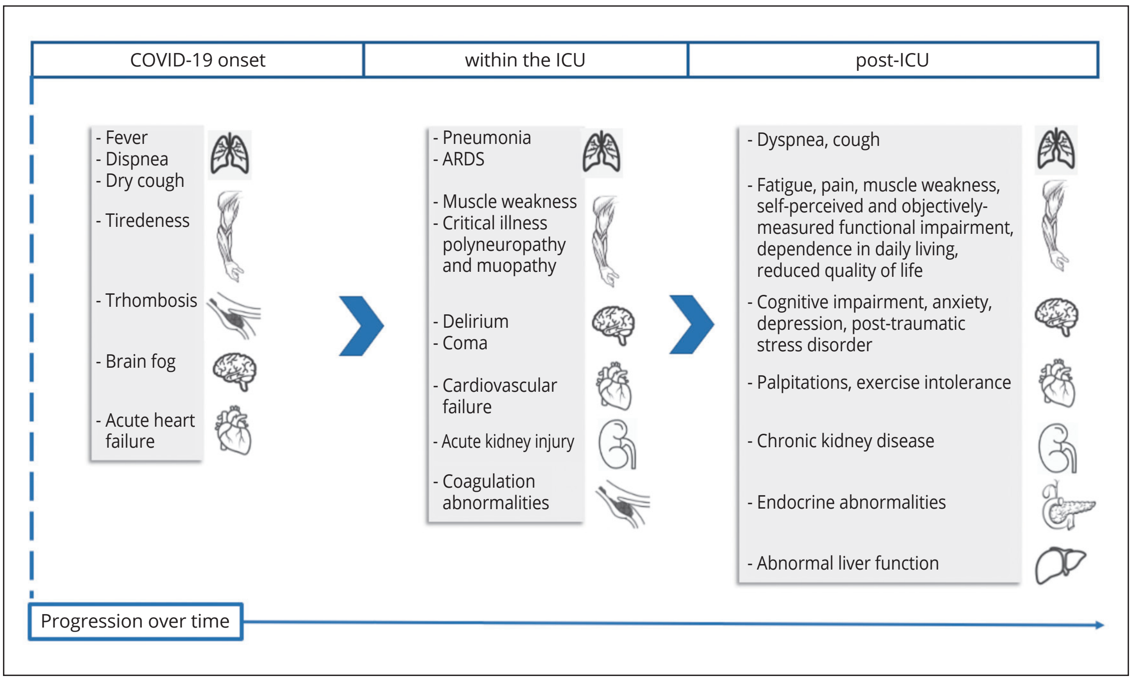

Figure 1.—Progression of COVID-19.

ical, urgent surgical and elective surgery patients with short ICU stay (≥12 hours).[23] However, a recent systematic review reported high prevalence of cognitive impairments, ranging from 35% to 54% in patients assessed with subjective and, respectively, objective tests, and from 36% to 61% in patients assessed with screening tests, such as the Mini-Mental State Examination, and comprehensive cognitive batteries.[43] Mental health impairments are also common in ICU survivors, with reported one-year prevalence of 29% (95% CI: 23-34%) for clinically important depression,[44] 34% (25-42%) for anxiety,[45] and 22% (18-27%) for post-traumatic stress disorders (PTSD).[46] Return to work in previously employed ICU survivors, an important measure of quality of life, ranges between 36% at three months and 60% to 68% at six months to 5 years.[47]

In our series,[35] cognitive function at 6 months was impaired in 26% of COVID-19 ICU patients, with a majority of them showing only mild short-term memory impairment. Mental health impairments with symptoms of anxiety (14%), depression (11%) and PTSD (7%) were also less common than in non-COVID ICU survivors.

In the COMEBAC study,[37] cognitive impairment at 4 months was present in 21 of 50 (42%) intubated patients, and symptoms of anxiety, depression and PTSD were present in 26%, 18% and 10%, respectively.

In the PHOSP-COVID study,[39] 17% of ICU patients had a Montreal Cognitive Assessment (MoCA)<23, indicating at least mild cognitive impairment. Symptoms of anxiety, depression and PTSD were present in 28%, 32% and 16% of patients. Investigators were also able to identify four clusters with different severities of mental and physical health impairment using patient reported outcomes and tests of mental health, cognitive impairment, and physical performance: cluster 1: very severe mental and physical health impairment (17%); cluster 2: severe mental and physical health impairment; cluster 3: moderate mental and physical health impairment with pronounced cognitive impairment (17%); and cluster 4: mild mental and physical health impairment (46%). Details of ICU patients' distribution in these four clusters were not reported; however, the clusters were not strongly related to the severity of acute disease, suggesting that physical, mental and cognitive dysfunction might be due to mechanisms independent from clinical severity.

In our series,[35] the majority of patients (63%) had returned to work with the same employment status as pre-COVID-19 by six months after hospital discharge. Similar results were reported in another Italian series, where 73% of COVID-19 ICU survivors had returned to work by 6 months, although many of them reported reduced work effectiveness.[48] In the PHOSP-COVID study, only 38% of 196 ICU patients had returned to work, whereas the remaining patients were either no longer working or had experienced occupational changes due to health problems.

Lung impairment

Historically, survivors ARDS have been thought as people at greatest risk of persistent pulmonary dysfunction. Initial report emphasized that "residual pulmonary damage might persist for many months following ARDS."[49] It was not until rigorous follow-up studies were performed that it became clear that pulmonary function returns to normal or near-normal within 6-12 months after acute disease, with the exception of a persistent mild reduction in carbon monoxide diffusion capacity. Instead, ARDS survivors have persistent functional limitations mainly as a consequence of muscle wasting and weakness.[31] Physical function remains the single mostly hit health domain.[23]

Ground-glass opacities, fibrotic changes, reduced diffusion capacity, and, more rarely, restrictive pulmonary physiology have been described in COVID-19 survivors.[13] Bilateral ground glass opacities are the most common lung CT pattern in the acute stage of disease, often progressing to mixed areas of ground glass opacities plus consolidations before gradually resolving or persisting as fibrotic areas.[50] Ground glass opacities are also frequently described after the resolution of acute disease in patients seen at follow-up.[37] Progressive pulmonary fibrosis, characterized by excessive extracellular matrix deposition within the lung interstitium and parenchymal destruction,[51] is a much-feared complication of COVID-19 especially in patients with greater severity.[52] In elderly survivors of severe acute respiratory syndrome Coronavirus (SARS) and Middle East respiratory syndrome Coronavirus (MERS), residual pulmonary fibrosis was a common finding;[53] however, most patients recovered within two years and persistent interstitial abnormalities were described in less than 5% of patients after 15 years.[52] Given the similarities between these three syndromes, pulmonary fibrosis might be a common complication of COVID-19. Moreover, fibrosis is a known complication of classical ARDS, particularly in patients with protracted disease (>3 weeks). Therefore, COVID-19 patients with ARDS might be at high risk of developing pulmonary fibrosis. Recent reports support this hypothesis by showing fibrotic lesions and reticulations in 39% and 69% of COVID-19 associated ARDS at 4 months after hospital discharge.[37] Fibrotic-like lung-CT abnormalities were also described in 72% of mechanically ventilated patients four months after COVID-19, and correlated with decrements in lung function, cough and frailty but not with dyspnea.[54]

Conclusions

Persisting physical, cognitive and mental impairments are commonly reported in ICU survivors of COVID-19; however, their prevalence, severity and duration are poorly defined as yet, with substantial variations among published series. This variation likely reflects differences in the timing of assessment, the outcome measured, the instruments utilized, and thresholds adopted to establish the diagnosis, the qualification of personnel delivering the tests, the resource availability as well diversity in patients' case-mix. There are no clear criteria to guide which ICU survivors should be included in follow-up programs, either patients with COVID-19 or other ICU admission causes. Moreover, the PICS framework, as it has been presented here, should be viewed as basic approach to COVID-19 ICU patients. With increasing clinical experience and new research, PICS definition is already expanding to include long-term conditions such as pulmonary and cardiovascular outcomes, endocrine and metabolic disorders (new-onset diabetes), and sexual dysfunctions.[18, 55] Longitudinal studies of adequate sample size and representative patient populations with repeated assessments of validated outcomes, rigorously defined assessment times, and comparison with non-COVID-19 ICU patients are needed to fully explore the long-term outcome of ICU patients with COVID-19.

Key messages

- Physical, cognitive and mental impairments, persisting long after the COVID-19 disease onset, are common in ICU survivors.
- Follow-up programs for patients with PICS, including dedicated post-COVID-19 clinics, should be multidisciplinary and guided by clearer criteria aimed at identifying which ICU survivors would benefit mostly.
- Research, composed of robust studies containing representative patient populations, also in comparison to non-COVID-19 ICU patients, are needed to fully explore the long-term outcome of ICU patients with COVID-19.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions.—Frank A. Rasulo has given substantial contributions to study conception, Simone Piva to literature search, Frank A. Rasulo, Simone Piva and Nicola Latronico to manuscript writing and revision. All authors read and approved the final version of the manuscript.

Comment on: Montini L, Antonelli M. Postacute COVID-19: a new priority for health care systems. Minerva Anestesiol 2022;88:6-7. DOI: 10.23736/S0375-9393.21.16388-6.

History.—Article first published online: October 28, 2021. - Manuscript accepted: October 1, 2021. - Manuscript revised: September 23, 2021. - Manuscript received: July 16, 2021.