Original article

Postintensive care syndrome in COVID-19. Unicentric pilot study. Calm does not come after the storm

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A B S T R A C T

Introduction: Postintensive care syndrome (PICS) is the physical, cognitive or psychiatric deterioration that appears after a critical illness and persists beyond hospital admission. The objective of this study was to describe the prevalence of PICS in the patients with coronavirus disease 2019 (COVID-19) admitted to the intensive care unit of the Consorcio Hospital General Universitario de Valencia.

Patients: They benefited from a standardized assessment, addressing health-related quality of life (EuroQol-5D-3L), a physical status (6 MWT, "test up and go" and hand dynamometer), a nutritional assessment (MUST and the Global Subjective Assessment), cognitive impairment (MoCA), mental health disorders (HADS and Davidson Trauma Scale) and pain (visual analogue scale and DN4).

Results: From March to June 2020, 59 patients with SARS-CoV-2 were admitted to our ICU. 29 of these were recruited for the study. The stay in the ICU and the mechanical ventilation time were long (24 days [IQR 12–36], and 18 days [IQR 7–31] respectively). The SOFA upon admission to the ICU was high (3 [IQR 3–5]). Tracheostomy was performed in 52% and pronation in 93%. 90% had some abnormal test. 20% had post-traumatic stress syndrome.

Conclusions: We found that 9 out of 10 survivors of SARS-CoV-2 admitted had at least one PICS alteration at 4–6 weeks from discharge from the Hospital. Six out of 19 patients presented with two or more affected evaluated areas.

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Síndrome post cuidados intensivos en COVID-19. Estudio piloto unicéntrico. La calma no llega tras la tempestad

R E S U M E N

Antecedentes y objetivo: El síndrome post cuidados intensivos (SPCI) es el deterioro físico, cognitivo o psiquiátrico que aparece después de una enfermedad crítica y persiste tras el ingreso hospitalario. El objetivo es evaluar la prevalencia de SPCI en los pacientes con enfermedad por coronavirus 2019 (COVID-19) ingresados en la unidad de cuidados críticos (UCI) del Consorcio Hospital General Universitario de Valencia.

Pacientes: Se evaluó la calidad de vida subjetiva (EuroQol-5D-3L), el estado funcional (test de marcha de 6 min, «levanta y anda» y dinamómetro de mano); nutricional (Malnutrition Universal Screening Tool [MUST] y Valoración subjetiva global [VSG]); montreal cognitive assessment (MoCA); mental (escala de ansiedad y depresión hospitalaria [HADS] y escala de Trauma de Davidson) y de dolor (escala visual analógica y detección de dolor neuropático-DN4).

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Resultados: Del 1 de marzo al 30 de junio del 2020 ingresaron en UCI 59 pacientes por SARS-CoV-2. Contactamos con los 29 supervivientes a las cuatro a seis semanas del alta hospitalaria. La estancia en UCI (24 días [IQR 12−36]) y el tiempo de ventilación mecánica (18 días [IQR 7−31]) fueron prolongados. El Sequential Organ Failure Assessment (SOFA) al ingreso en UCI fue elevado (3 [IQR 3−5]). Se realizó traqueostomía en el 52% y pronación al 93%. En cuanto al SPCI, el 90% tenía algún test alterado. Presentaron dos o más test alterados seis de cada 10. Un 20% presentó el test para detección del trastorno de estrés postraumático (TEPT) patológico.

Conclusiones: Encontramos que nueve de cada 10 supervivientes de una neumonía por SARS-CoV-2 ingresados en UCI tenían al menos una alteración de SPCI a las cuatro a seis semanas del alta hospitalaria. Los problemas de SPCI concurrentes (dos o más) estuvieron presentes en más de seis de cada 10. Seis de los pacientes presentaron TEPT.

Introduction

A series of cases of pneumonia caused by a new coronavirus (SARS-CoV-2) were identified in Wuhan (China) in December 2019, giving rise to a global pandemic due to the disease called COVID-19. As of August 2021, 196 million cases had been confirmed worldwide. Five percent of these patients may require admission to critical care units (ICU)[1], although this percentage may be modified by the new variants and by the recent introduction of vaccination.

Over the last three decades, a significant development in both technology and knowledge has made possible to reduce the short-term mortality of patients admitted to the ICU. There is little data on mid- and long-term recovery after a severe episode of COVID-19, although this pathology shares patterns that also occur after other critical conditions[2–4].

Survivors of severe conditions with ICU admission often experience worsening health that lasts beyond hospital discharge, known as post-intensive care syndrome (PICS). PICS is defined as the onset or worsening of physical status (impaired mobility, recurrent falls, or quadri/tetra-paresis), cognitive status (impaired attention, memory, executive functions, mental speed), or mental health status (anxiety, depression, post-traumatic stress disorder [PTSD]) affecting the quality of life in survivors of critical conditions. The morbidity resulting from PICS has wide-ranging public health and socio-economic implications, such that it prevents people from returning to their family and professional roles[5–7]. Currently, there is no standardized PICS follow-up model[8].

The aim of the study was to describe the prevalence of PICS in the cohort of patients who were admitted to an adult medical-surgical anaesthesia ICU between 1 March and 30 June 2020 with severe SARS-CoV-2 pneumonia. Quality of life, physical, cognitive, psychiatric, nutritional and pain-related changes were evaluated. Secondary objectives were the characteristics of ICU admission, proposals for follow-up by other specialists, readmissions and mortality.

Material and methods

Descriptive and prospective study of the prevalence of PICS in the cohort of patients admitted for COVID-19 in the Anaesthesia ICU of the Consorcio Hospital General Universitario de Valencia (CHGUV) between March 1st and June 30th, 2020. Approved by the Drug Research Ethics Committee (number 90/2020).

The inclusion criteria were all surviving patients four to six weeks after hospital discharge who had been admitted to our ICU with severe respiratory failure secondary to SARS-CoV-2 pneumonia confirmed by PCR (pharyngeal and/or pulmonary bronchoaspirate) and who had at least one of the following criteria: bilateral pneumonia, mechanical ventilation for more than two days, septic shock, multi-organ dysfunction syndrome, or acute respiratory distress syndrome. Exclusion criteria were pre-vious neurological or neuromuscular disease, dependency status, previous psychiatric condition or cognitive deficit, or short life expectancy (Appendix A Annex).

Participation in the study was explained in a specific multidisciplinary visit (consisting of Anaesthesiology, Internal Medicine, Physical Medicine and Rehabilitation, Psychiatry and Endocrinology) and informed consent was obtained.

Patient characteristics, level of education, comorbidities, consultations with other departments, data on ICU admission, mortality and degree of satisfaction were collected.

At the time of writing there are no validated tests to measure PICS. Validated tests were selected for the evaluation of each section and are shown in Table 1 (full description in the Annex):

1. The assessment of health-related quality of life (EuroQol-5D-3L) in which the individual assesses his or her own health status. The descriptive system contains five health dimensions (mobility, self-care, activities of daily living, pain/discomfort and anxiety/depression) and each of them has three levels of severity (no problems, some problems or moderate problems and severe problems). The second part of the EQ-5D-3L is a 20 cm millimetre-divided vertical visual analogue scale (VAS) ranging from 0 (worst imaginable health status) to 100 (best imaginable health status). The individual should mark the point on the vertical line that best reflects his or her current overall health status assessment.

The functional assessment consisted of:

2. The six-minute walk test assesses in an integral way the response of the respiratory, cardiovascular, metabolic, musculoskeletal and neurosensory systems to the stress imposed by exercise by measuring the maximum distance an individual can walk, as fast as possible, over a period of six minutes. It is a reliable tool in the diagnosis, staging, prognosis and follow-up of people with chronic respiratory diseases.

3. The "timed up & go" test has clinical utility as a screening tool for the risk of falls, without providing detailed information as to the specific area of disability that is directly influencing the risk.

4. The hand dynamometer is an evaluation tool used to measure hand grip strength. The value of the manual digital dynamometry is in % of normal. The measurement is made in newtons of the average force of the maximum grip forces. Through a database stratified by age and sex, the percentage with respect to normal values is established.

For the nutritional assessment, the following were used:

5. The *Malnutrition Universal Screening Tool* (MUST): Recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the British Association of Parenteral and Enteral Nutrition (BAPEN). It is a five-step screening tool designed to identify adults who are malnourished, at risk of malnutrition (malnutrition), or obese.

6. The Global Subjective Assessment (GSA) is a widely used nutritional assessment tool, with the aim of identifying malnourished patients and predicting morbidity in surgical patients,

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Table 1
Tests and test results.

Test	Evaluation	Results
Average health-related quality of life		
Euroqol-5D-3L test	Mobility	1.5
1 = "no (I do not have) problems"		
2 = "some or moderate problems"		
3 = "a lot of problems"		
	Personal care	1.1
	Daily activities	1.6
	Pain or discomfort	1.6
	Anxiety or depression	2
	EQ-VAS	> 60%
Physical status assessment		
Exercise capacity assessment: 6-minute walk test (6MWT)		< 350 m in 5 patients
Normal: 400 and 700 m in 6 minutes		
Pathological: less than 350 m in 6 minutes		Mean 419 SD 77
Physical Function Assessment: Timed Up & Go test		
< 20 s: normal		> 20 s in 1 patient
> 20 s: increased risk of fall		
Muscle status assessment: Hand dynamometer* Right/left (no.° of patients)		
	Normal > 90%	6 / 8
	Slightly altered 80–90%	2 / 5
	Significantly altered < 80%	21 / 16
Cognitive status assessment		
Cognitive impairment (MoCA)	Pathological < 26 points	< 26 in 18 patients (62%)
Mental status assessment		
Hospital Anxiety and Depression Scale (HADS)	Pathological > 11 points in both anxiety and depression	HADS > 11 in 8 patients (28%)
Davidson Trauma Scale	Cut-off > 40 points	> 40 in 6 patients (20%)
Nutritional status assessment		
«*Malnutrition Universal Screening Tool*» (MUST)	1 point: 6 patients (21%)	
Global risk of malnutrition:		
0 points: low risk / 1 point: intermediate risk	0 points: 79%	
2 or more points: high risk		
Malnutrition Screening Global Subjective Assessment (GSA)		
A: Well nourished		
B: Mild/moderate malnutrition	A = 100%	
C: Severe malnutrition / cachexia/ sarcopenia		
Pain assessment		
Visual analogue scale (VAS)	Moderate pain with score > 5	≥ 5 in 4 patients (14%)
Neuropathic pain detection scale (DN4)	Neuropathic pain with a score > 4	> 4 in 6 patients (21%)

EQ-VAS: global health status assessment; MoCA: Montreal cognitive assessment.
Normal quantitative variables are expressed as mean and standard deviation (SD) and non-quantitative variables as median and interquartile range (IQR).
  * Percentage relative to the reference values using a digital dynamometer that measures the average newtons of the maximum grip strength performed, indexed by age and gender.

although it has subsequently been applied in many other populations.

For the assessment of cognitive function, the following was performed:

7. The Montreal Cognitive Assessment (MoCA) test, which is designed for the detection of mild neurocognitive disorders and early stages of dementia. It assesses the following cognitive dimensions: attention and concentration; executive functions, memory, language, visuospatial skills, conceptual reasoning, calculation, and orientation.

For mental assessment:

8. The Hospital Anxiety and Depression Scale (HADS) is a widely used tool to assess symptoms of anxiety and depression in the hospital setting

9. The Davidson Trauma Scale measures the frequency and severity of post-Traumatic stress

For pain assessment:

10. The VAS allows measurement of the intensity of pain reported by the patient with maximum interobserver reproducibility. It consists of a 10 cm horizontal line, with the extreme expressions of a symptom at each end.

11. Neuropathic pain with the DN4 score consisting of seven items referring to symptoms and three referring to examination. A total score of 4/10 or greater suggests neuropathic pain.

The degree of patient satisfaction was also evaluated, readmissions and mortality were recorded during the study period.

Statistical analysis was performed with R software version 4.0.3 (http://www.R-project.org/). The normal distribution of the variables was assessed through the Kolmogorov-Smirnov test. The continuous variables that met the normality criteria are expressed as mean and standard deviation (SD) (age and body mass index) and the variables that did not meet this hypothesis, as median and interquartile range (IQR). Hypothesis testing for parametric variables was performed using Student's *t* and non-parametric

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Table 2
Characteristics of the patients and their admission to the ICU-anaesthesiology department.

Patient characteristics (n = 29)	
Age	63 SD 10
body mass index	28 SD 5
Gender	Male 16 (55.2%)
Studies	
Basics	15 (52%)
Bachelor	4 (14%)
University students	10 (35%)
Comorbidities	
HTN	12 (41%)
DM	4 (14%)
DLP	10 (35%)
Hypothyroidism	4 (14%)
Other	14 (48.3%)
No known previous pathology	7 (24%)
Characteristics of admission to the ICU-anaesthesiology dpt.	
ICU days	24 (IQR 12−36)
SOFA ICU admission	3 (IQR 3−5)
Total ventilation days	18 (IQR 7−31)
NIMV	0
HFO	62% (18)
Non-rebreather mask	21% (6)
Tracheostomy	52% (15) 8 (IQR 0−23)
Proning	93% (27) 3 (IQR 3−4)
RRT	10% (3)
Corticosteroids	83% (24)
Hyperglycaemia	14% (4)
Vasoactive drugs	66% (19)
Neuromuscular relaxation	38% (11)
Dysfunction of 2 or more organs	45% (13)
Remdesivir	3.4% (1)
Anakinra	6.9% (2)
Hyperimmune plasma	0
Tocilizumab	69% (20)

Normal quantitative variables are expressed as mean and standard deviation (SD) and non-quantitative variables as median and interquartile range (IQR).
DM: diabetes mellitus; DLP: dyslipidaemia; HTN: hypertension, HFO: high-flow oxygen; SOFA: *Sequential Organ Failure Assessment*; RRT: renal replacement therapy; ICU: critical care unit; IMV: days of invasive mechanical ventilation; VMK: oxygen through mask; NIMV: non-invasive mechanical ventilation.

variables were analysed using the Wilcoxon signed-rank test. Proportions were compared using Fisher's test. Two-tailed analysis was considered statistically significant when p < 0.05.

Results

From 1 March to 30 June 2020, 64 patients with positive PCR for SARS-CoV-2 were admitted to the Anaesthesia ICU, 59 for pneumonia and five for other pathologies. Thirty patients died within six weeks of hospital discharge. We contacted the remaining 29 within four to six weeks of hospital discharge. The characteristics of the patients and their admission to the ICU are shown in Table 2. Male prevalence (55%) and overweight (mean body mass index 28 (SD 5), as well as hypertension are the most common comorbidities. There was no previous pathology in 24%. ICU stay and time on mechanical ventilation were prolonged (median 24 days [IQR 12−36] and 18 days [IQR 7−31], respectively). The *Sequential Organ Failure Assessment* (SOFA) on ICU admission was high (median 3 [IQR 3−5]). Tracheostomy was performed in 52% and proning 93%. 69% received tocilizumab.

The results of the tests are shown in Table 1. The perception of health status with the EurQol-5D-3L test was "no problems" (severity level 1) in all variables except anxiety/depression, which was referred to as "moderate problems". Likewise, all of them scored above 60 on the assessment of their global health status (EQ-VAS).

In the performance status assessment, 17% (five patients) had an altered six-minute walk test and only one patient took more than 20 s to perform the "timed up and go" test. Assessment of muscle status with the hand dynamometer was markedly impaired in the right hand in 72% and in 55% in the left hand (21 and 16 patients, respectively).

Cognitive impairment was present in 62% (18 patients with a MoCA test <26 points), anxiety or depression in 27% (eight patients), with a prevalence of anxiety scores), and PTSD in 20% (six patients).

Regarding nutrition, 20% (six patients) had an intermediate risk of malnutrition (MUST test) and, according to the ESR, 100% had an A pattern (well nourished).

On pain assessment, four patients had VAS scores >5 and the neuropathic pain detection score (DN4) was >4 in 21%. Three patients demonstrated no impairment in any of their test results. Ninety per cent (26 patients) showed some kind of impairment in some of the tests and 28% (eight patients) showed impairment in three or four tests. Proposals for follow-up were made in 35.7% (10 patients) after the PICS clinic visit which were distributed as follows: 17% to the Psychiatry Department (five patients), 21% to the Pain Control Unit (Anaesthetics) (six patients) and 3% to Nutrition (Endocrinology) (one patient). There were no readmissions or deaths during the study period. Satisfaction surveys showed a result of satisfactory or very satisfactory in all ratings.

Discussion

We found that nine out of 10 survivors of severe SARS-CoV-2 pneumonia requiring ICU admission had at least one PICS disorder four to six weeks after hospital discharge. Concurrent PICS conditions (two or more) were present in more than six cases out of 10. 20% had a pathological post-traumatic stress test.

Over the past 15 years, studies of cognitive, physical, and mental function among survivors of critical conditions report that a significant proportion of these patients suffer from new or worsening impairments and disabilities, giving rise to the concept of PICS. The long-term effects of surviving COVID-19 have become a new focus for researchers due to concerns about the harmful late effects of a previously unknown virus. Although there are few data on recovery after a severe episode of COVID-19, this pathology could share common patterns with other viremias. Recently, Rousseau et al.[9], described the results of a cohort of 38 patients diagnosed with COVID-19 who were assessed at months 1, 3 and 12 after hospital discharge. At three months, 87.5% had not recovered their previous performance status, and only 6.2% had normal levels on the MoCA, Barthel, and the Impact of Event Scale-Revised. The investigators observed combined impairments in 40.6% of the patients. On the other hand, fear of a new disease and isolation could contribute to PICS. Data reported in follow-up studies of ARDS survivors due to other viral infections with high morbidity and mortality (Middle East respiratory syndrome [MERS] and avian influenza virus [H7N9]) show a significant impairment in long-term quality of life. Thus, in studies assessing recovery in survivors of severe H7N9 and H1N1 infection, quality of life at 1–1.5 years was lower than in a general population sample. Other studies find 64% and 56% in one or more impairments in PICS dimensions at three and 12 months, respectively[10–13].

Of the tests performed for functional assessment (exercise capacity, physical function and muscle status) in our patients, muscle status was the most affected. Some publications suggest a mechanism of myopathy or myositis due to involvement of the peripheral nervous system, with a pattern compatible with demyelination and axonal neuropathy in the electrophysiological study, without cerebrospinal fluid abnormalities[14]. The vast majority of our patients received corticosteroid therapy and

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neuromuscular relaxation, factors that also contribute to this involvement.

In our series, cognitive impairment was observed in 62%. There are predisposing factors for cognitive impairment after discharge in ICU ventilated patients (gender, age and cognitive reserve). In addition, there are studies on COVID-19 in which the patient's phenotype could improve or worsen this cognitive impairment[15]. It appears that COVID-19 induces a general threat to the entire nervous system through multifactorial pathogenic mechanisms: hypotension-hypoxia, direct central nervous system neuroinvasion, peripheral nervous system and muscle involvement, micro- and macrovascular thrombosis, and post-infectious immune suppression (without evidence of direct central nervous system [CNS] viral infection)[14,16]. Other publications highlight altered images of the quantitative diffusion tensor on brain MRI which appears radiologically normal on other scans; cortical and hippocampal abnormalities could explain the altered mental status seen in many patients. On the other hand, abnormalities in the excitability of brainstem nuclei would provide plausible neuroanatomical substrates to explain the altered sensorium in patients[17,18]. Another study finds a possible anomaly in the microstructure and functional integrity of the brain during the recovery stages of COVID-19, which suggests a potential for SARS-CoV-2 neuroinvasion[19,20].

In addition, 28% had anxiety or depression, with a prevalence of anxiety scores, and PTSD was observed in 20% of patients. Depression is highly prevalent in survivors with ARDS of any origin[21]. In addition, the sequelae could be greater in these patients due to the restriction of visits and the limitations in social support due to the risk of transmission. Despite this, the EQ-5D-3L test showed that most patients did not perceive their health status to be altered at the time of the visit with the exception of the anxiety/depression domain, as also shown by the HADS scale.

Nutritional deficits have an impact on the physical and functional recovery of individuals. Only one patient in the cohort had a nutritional disorder, who was already under follow-up for a previous nutritional condition.

On the other hand, it is estimated that the prevalence of chronic pain after ICU stay varies between 14–77%, depending on the scale, measurement method and variability of the population studied[22]. Repeated prone positioning can lead to brachial plexus injuries, joint subluxations, etc.[23] 21% of our patients had neuropathic pain at the time of the SPCI visit.

The implementation of the "ABCDEFGH package" in the ICU (airway and pain management, daily ventilation windows, care coordination, delirium management, early mobility, family contact, communication, availability of equipment) appears to be associated with better short-term outcomes[24].

This study has several limitations. Given the emergent nature of this critical condition, we were unable to pre-screen the patient. Analysis of data derived from those who did not die during follow-up could have resulted in survival bias. As this was a pilot study, no formal sample size calculation was performed and all consecutive COVID-19 positive patients with pneumonia admitted to the ICU during the first wave of the pandemic were included in the analysis. Another limitation is the small sample size; therefore, these results should be taken with caution and may present problems of external validity as they only include patients from our hospital. A comparative sample of non-COVID patients is not available which could have highlighted some of the characteristics of this disease and serve as a comparison of PICS syndrome in the general ICU population. Medical information on potential predictors that can alter scores in the different dimensions of the PICS is limited. There is no consensus on delirium which has been shown to affect long-term outcomes. There is no consensus on the timing of PICS visits, the number of visits and the type of tests to be used. We were unable to assess the impact on patients' relatives (post-intensive care syndrome-family) and caregivers. Finally, follow-up time was arbitrarily determined, but longer-term follow-up may yield more information.

Conclusion

This study describes preliminary information on physical, cognitive, psychiatric, nutritional and pain-related disorders after a severe episode of COVID-19. We found that nine out of 10 survivors of SARS-CoV-2 pneumonia admitted to ICU had at least one PICS disorder four to six weeks after hospital discharge. Concurrent PICS conditions (two or more) were present in more than six cases out of 10. 20% were found positive for pathological PTSD. Further studies are needed to better define PICS, to identify risk factors and to better understand the clinical, biological, psychological and social factors related to the ability to successfully resist and recover from this critical condition. These data would support the need for follow-up in COVID-19 patients admitted to the ICU.

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Conflict of interests

The authors declare that they have no conflict of interest.

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Appendix A. PICS COVID study group of the Consorci Hospital General Universitari de València (CHGUV)

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Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.medcle.2021.11.013.

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