Rationale and Study Design of an Early Care, Therapeutic Education, and Psychological Intervention for the Management of Post-intensive Care Syndrome and Chronic Pain After Coronavirus Disease 2019 (PAIN-COVID): Study protocol for a randomized controlled trial

Antonio Ojeda  
Hospital Clinic de Barcelona Servei d'Anestesiologia Reanimacio i Tractament del Dolor

Andrea Calvo  
Hospital Clinic de Barcelona Servei d'Anestesiologia Reanimacio i Tractament del Dolor  
https://orcid.org/0000-0001-8249-1226

Tomas Cuñat  
Hospital Clinic de Barcelona Servei d'Anestesiologia Reanimacio i Tractament del Dolor

Ricard Mellado Artigas  
Hospital Clinic de Barcelona Servei d'Anestesiologia Reanimacio i Tractament del Dolor

Oscar Comino-Trinidad  
Hospital Clinic de Barcelona Servei d'Anestesiologia Reanimacio i Tractament del Dolor

Jorge Aliaga  
Hospital Clinic de Barcelona Servei d'Anestesiologia Reanimacio i Tractament del Dolor

Marilyn Arias  
Hospital Clinic de Barcelona Servei d'Anestesiologia Reanimacio i Tractament del Dolor

Maribel Ahuir  
Hospital Clinic de Barcelona

Carlos Ferrando  
Hospital Clinic de Barcelona Servei d'Anestesiologia Reanimacio i Tractament del Dolor

Christian Dürsteler  
Hospital Clinic de Barcelona Servei d'Anestesiologia Reanimacio i Tractament del Dolor

Study protocol

Keywords: COVID-19, Randomised controlled trial, protocol, Post ICU Syndrome, Chronic Pain, critical illness.
Abstract

Background: Critically ill patients with COVID-19 disease are an especially susceptible population to develop Post-intensive Care Syndrome (PICS) due to acute respiratory distress syndrome (ARDS). Patients can suffer acute severe pain and may have long-term deterioration in mental, cognitive, and functional health after discharge. However, few controlled trials are evaluating interventions for the prevention and treatment of PICS. The study hypothesis is that a specific care program based on early therapeutic education and a psychological intervention improves the quality of life of patients at risk of developing PICS and chronic pain after COVID-19 disease. The primary objective is to determine if the program is superior to standard-of-care on health-related life quality at six months after hospital discharge. The secondary objectives are to determine if the intervention is superior to standard care, evaluating the health-related life quality, the incidence of chronic pain and the degree of functional limitation, the incidence of anxiety, depression, and post-traumatic stress syndrome at 3 and 6 months after hospital discharge.

Methods: The PAINCOVID trial is a unicentric randomized, controlled, patient blinded superiority trial with two parallel groups. The primary endpoint is the health-related quality of life at six months after hospital discharge, and randomization will be performed with a 1:1 allocation. This paper details the methodology and statistical analysis plan of the trial and was submitted before outcome data were available.

The sample size calculated is 84 patients, 42 for each arm. Estimating a loss of follow up of 20%, a sample size of 102 patients is necessary (51 each group).

Discussion: This is the first randomized clinical trial assessing the effectiveness of an early care therapeutic education, and psychological intervention for the management of PICS and Chronic Pain after COVID-19. The intervention will serve as a sample of the need to implement early care programs on early stages, having an incalculable impact given the current scenario of the pandemic.

Trial registration: This study is being in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors’ institutional review board Comité Ético de Investigación Clínica del Hospital Clinic de Barcelona (approval number: HCB/2020/0549) and was registered on May 9, 2020 at clinicaltrials.gov (NCT04394169).

Introduction

Since the initial outbreak of COVID-19 in December 2019, there have been more than 14.3 million cases of infection with the SARS-Cov-2 virus reported worldwide.(1) This has led to a large number of hospital admissions testing the capability of many healthcare systems. Among hospitalized patients, 10-20% are admitted to the intensive care unit (ICU) and from those, more than 70% require invasive mechanical ventilation with an overall mortality over 30%.(2)(3)(4)
Critical care survival has been reported as 16-37%, and this will result in an unimaginable size of a cohort of critical care survivors given the number of global infections, these patients can present a significant worsening of their health status and deterioration in the quality of life. (5) In 2012 the Society of Critical Care defined a new term, the Post-intensive Care Syndrome (PICS) defined the syndrome as the appearance or worsening of the physical, mental or cognitive state after a critical illness that was maintained beyond hospitalization. Consequently, Health-related quality of life (HRQoL) and Post-Intensive care syndrome (PICS) is becoming the focus of intensive care medicine rather than survival rate alone.(6,7) As psychological dysfunction can persist up years after ICU discharge, its management is becoming an important strategy to improve quality of life as well as the early detection of posttraumatic stress disorder and anxiety and depression.(8) Moreover, there is evidence that patients who survive to a critical illness have a high prevalence of moderate to extreme chronic pain being an essential factor affecting the ability to return to work and to restore quality of life up to 5 years following discharge. (9) However, few controlled trials have evaluated interventions for the prevention and treatment of PICS. (10)

Patients with COVID-19 disease are an especially susceptible population to develop PICS due to acute respiratory distress syndrome (ARDS). Patients can suffer acute severe pain and may have long-term deterioration in mental, cognitive, and functional health after discharge. However, pain is a conscious experience by definition, thus, sedated patients can suffer a high nociceptive input inadvertently. (5) Although, there are recent publications describing nervous system involvement after infection with SARS-CoV-2.(11)(12) Thus, chronic pain could potentially appear as a complication or sequel after COVID-19. However, as far as we know, there are no studies related to chronic pain care after critical illness, and specifically in patients with COVID19.(13)

We hypothesize that a specific care program based on early therapeutic education and a psychological intervention improves the quality of life of patients at risk of developing PICS and chronic pain after COVID-19 disease.

**Primary outcome**

The primary objective is to determine if a specific care program based on early therapeutic education and a psychological intervention improves the health-related quality of life (HRQoL), compare to standard care at six months after hospital discharge.

**Secondary Outcomes**

The secondary objectives are to determine if the intervention is superior to standard-of-care, evaluating:

- The HRQoL at three months after hospital discharge.
- The incidence of chronic pain and the degree of functional limitation at three and six months after hospital discharge.
- The incidence of anxiety and depression at three and six months after hospital discharge.
Methods

Study Design

The PAIN-COVID trial is a comparative, prospective, single-centre randomized controlled trial that will include 102 patients. (Figure 1. Summary of Patient flow diagram). The trial has been designed in accordance with the fundamental principles established in the Declaration of Helsinki, the Convention of the European Council relating to human rights and biomedicine, and the Universal Declaration of UNESCO on the human genome and human rights, and with the requirements established by Spanish legislation in the field of biomedical research, the protection of personal data, and bioethics, registered on May 9, 2020 at http://www.clinicaltrials.gov with identification no. (NCT04394169). Approval of the final protocol by the Comité Ético de Investigación Clínica del Hospital Clinic de Barcelona – approval number: HCB/2020/0549, Chairperson: Prof Joaquin Fores Viñeta, on May 14, 2020.

This study followed the “Standard Protocol Items: Recommendations for Interventional Trials, The SPIRIT 2013 Statement” provides evidence-based recommendations for the minimum content of a clinical trials protocol. (Figure 2)

Study Population

Adults patients will be enrolled if they fulfilled at least one of the following criteria: 1) had confirmed SARS-CoV-2 infection from a respiratory tract sample using PCR-based tests, 2) had Acute Physiology And Chronic Health Evaluation (APACHE) II score over 14, 3) ICU stay over 10 days, 4) Acquired weakness in ICU (14)(Supplement, Definition D1), 5) Delirium during ICU (14) (Supplement Definition, D2). 6) Acceptance to participate in the study signing informed consent.

Exclusion criteria are: 1) Patients with non-confirmed SARS-CoV-2 infection according to WHO guidance(15), 2) Central Nervous System degenerative diseases Terminal illness (Supplement, Definition D3), 3) Terminal illness (Supplement, Definition D4)(16), 4) Insufficient understanding of the Spanish language, 5) Patients in whom it would be difficult to complete follow-up, 6) Not having informed consent.

Methods of randomization and bias minimization

Once informed consent has been obtained, the patient will be assigned by the investigator to either the control or intervention group in a 1:1 proportion, according to the allocation sequence generated by the
randomization programme, only the researchers who signed the inform consent had access to this list which was concealed from the primary investigator.

The data for the screening will be obtained from the clinical records program of the hospital clinic de Barcelona, where the patients who have required admission to the ICU, as well as days of admission, will be reviewed by the members of the research team destined to this is to verify who meets the inclusion criteria.

Screening for patients will be done monthly. Enrolment is expected to take 3 to 6 months. Baseline visit will take place between 4 to 6 weeks after hospital discharge. Follow-up visits will take place at 3 and 6 months after discharge, Figure 2.

The patient will be encouraged to maintain the participation in the study during each interview, giving the feedback about the importance of your collaboration, as well as the participant who decides does not completely follow up will be asked about reason and all of these answers will be consigned.

Database will paper-based and electronic data entry will be used through the FileMaker programme, only three researcher team members will obtain access to this programme, also, form (CRF) will be stored in the hospital files and all data will be available on the web when the study has been finished.

Blinding

This is a simple blind study. Visits will be carried out by an investigator with sufficient training in questionnaires. This investigator will not participate in the intervention or the evaluation of the results. The intervention will be performed by two researchers (pain physician and psychologist). These researchers will not participate in the questionnaire and baseline data collection or in the data analysis. Researchers who analyse the results will not participate in the questionnaire and baseline data collection or program intervention.

General Procedures

The study subjects will be divided into two arms, and the intervention program will be compared to the standard-of-care clinical practice. Baseline visit will take place four to six weeks after hospital discharge, and two follow-up visits will take place at 3 and 6 months after.

The intervention program will consist of an early care therapeutic education on prevention and management of PICS and chronic pain during the three scheduled medical visits within the first six months after hospital discharge, and psychological treatment in patients at risk for emotional distress.

Recruitment and participant timeline

Patients who are eligible for the study will be contacted at 1 month after discharge from the hospital, they will be informed about the study and they will be asked for their participation. Those who accept to
participate will be visited the following week (baseline visit). Informed consent will be obtained by one of the investigators just from the patients themselves. (Supplement, Figure F2).

**Baseline visit**

The baseline visit will take place between 4 to 6 weeks after hospital discharge. Information regarding the study will be given to the patient, and informed consent will be obtained. After that, the patient will be randomized. During this first visit, demographic data, medical history and ICU and hospitalization variables will be collected to all the included patients, independently of the randomization arm. All patients will undergo a series of questionnaires to evaluate the quality of life and the presence of anxiety, depression, post-traumatic stress disorder. It will also be evaluated the presence of pain and their influence on the patient’s life.

**Intervention group**

The intervention consists of a program that includes early patient care, therapeutic education, and psychological intervention. It will be performed along the three medical visits scheduled as follows:

- Visit 1 Intervention Group, four to six weeks after hospital discharge.
- Visit 2 Intervention Group, eight weeks after hospital discharge.
- Visit 3 Intervention Group, 18 weeks after hospital discharge.

**Components:**

- Interview and physical examination.
- Therapeutic education about the PICS, orally and with specific documents that will be delivered at the end of the visit. PICS fact-sheet developed by the investigators and a rehabilitation manual recommended by the Follow-up and Rehabilitation Committee of the Argentine Society of Intensive Care, SATI.(14)
- Therapeutic education about pain (if the patient reports pain). Include: pain neurophysiology’s explanation, rational use of drugs prescribed by other specialists, information about how to manage daily life activities, importance of pre-emptive pain management for proper rehabilitation.

A psychological intervention will be performed if the following criteria are met: a score higher than 8 on the hospital anxiety and depression (HAD) test depression subscale (supplement, questionnaire Q1)(17). The intervention protocol consists of 7 weekly sessions lasting one hour and a half (supplement, Table 1). The intervention in depression is based on Rehm’s model of self-control.

**Control group**

Standard-of-care: patient follow-up will be carried out by their referring physicians (primary care physicians or specialists) who will not be involved in the study. After the baseline visit, the second and third visits will take place through a phone call at 3 and 6 months after hospital discharge.
Outcomes measurements

Demographic data will be collected at baseline visit, including age, gender, body mass index, tobacco use, socioeconomic level, work status, civil state. Barthel index and Medical history will also be recorded, especially psychiatric disorders, chronic pain, opioid usage and previous ICU admission. (Supplement, Table 2).

Data regarding ICU and hospital admission will be also collected: Acute Physiology and Chronic Health disease Classification System (APACHE) II and Sequential Organ Failure Assessment Score (SOFA) severity scores, days under invasive or non-invasive mechanical ventilation, presence of sepsis(18) (Supplement Definition, D5), need for tracheostomy, use of vasoactive drugs, acute kidney injury (Supplement Definition, D6) and need for renal replacement therapy, stress hyperglycaemia and hypoglycaemia, (Supplement Definition, D6, D7) corticoid use, use of neuromuscular blocking agents, days under sedation, ICU acquired weakness, delirium presence, maximum value of ferritin, d-dimer and C reactive protein, and ICU and hospital length of stay. Mini-mental state exam (MMSE) test, which is a widely used test of cognitive function among the elderly that analyses orientation, attention, memory, language and visual-spatial skills, will be evaluated before answering the questionnaires.(19)

The impact of the intervention program on health-related quality of life reported by the patient will be assessed through the European quality of life 5 dimensions/5 levels (supplement, questionnaire Q2)(20). The questionnaire assesses the quality of life in study participants according to 5 domains: mobility, self-care, usual activities, pain/discomfort, anxiety/depression, each scored according to a scale of 1 (no problems) to 5 (indicating extreme problems) and generating a 5-digit code corresponding to quality of life. The visual analogue scale of the same test will also be assessed (from 0 -the worst imaginable health- to 100 -the best imaginable health). The questionnaire provides a simple descriptive profile of a respondent's health state. Quality of life will be assessed during baseline visit and at 3 and 6 months after discharge.

Pain, (presence and intensity) will be assessed by the Brief Pain Inventory (BPI) questionnaire (supplement, questionnaire Q3)(21) during the baseline visit, and at 3 and 6 months after discharge. This questionnaire is a multidimensional questionnaire that evaluates pain intensity in the last 24 hours (worst, lowest, average) and current (right now). It also assesses the impact of pain on daily activities (general activity, encouragement, work, relationships with other people, sleep, enjoying life and the ability to walk). The questions are rated on a scale from 0 to 10, with 10 being the worst possible value. Subsequently, the average intensity score (BPI intensity score) and average interference score (BPI interference score) is calculated. Following IMMPACT recommendations, a clinically significant pain will be defined if the mean intensity score (BPI intensity score) is greater than or equal to 3.(22)

If BPI is positive for pain, pain catastrophizing will be assessed by the Pain Catastrophizing Scale (PCS) (supplement, questionnaire Q4)(23) and patients will also undergo Douleur Neuropathique en 4 Questions test (DN4) (supplement, questionnaire Q5) to screen for neuropathic pain.(24) PCS consists of 13 questions that explore the frequency of thoughts and feelings that the interviewees have in the presence
of current or anticipated pain, which are grouped into three scoring subscales (magnification, rumination and defencelessness). Each question is rated on a 5-point scale (0: not at all; 4: all the time). Being the maximum total score of 52 points. A score greater or equal than 30 will be considered as clinically relevant level of catastrophizing.

The impact of intervention program on anxiety or depression incidence will be assessed by the Hospital Anxiety and Depression test (HAD) (supplement, questionnaire Q1)(17), consisting on 14 questions, with two subscales, one for anxiety and the other for depression, with seven items each and a maximum score of 21 for each subscale. The cut-off points from 0 to 7 imply the absence of clinically relevant anxiety and depression, from 8 to 10 symptoms that it requires consideration, and from 11 to 21 it reports the presence of relevant symptoms, with a very probable diagnosis of anxiety or depression. According to Bjelland's review, a cut-off point equal or greater that 8 will be used as abnormal anxiety or depression´s values. This test will be performed during the baseline visit and at 3 and 6 months.(25)

Finally, post-traumatic stress disorder (PTSD)(26) incidence will be evaluated with the post-traumatic stress disorder checklist questionnaire (PCL-5).(27) It contains 20 questions that correspond to the DSM-V criteria. Participants will rate their symptoms on a scale of 0 (not at all), 1 (slightly), 2 (moderately), 3 (quite) to 4 (extremely), with a score ranging from 0 to 80. The overall severity of the symptoms can be assessed adding the score of each question (interval 0-80). The severity of each symptom can also be evaluated adding the score of the questions. DSM-5 symptom cluster severity scores can be obtained by summing the scores for the items within a given cluster, i.e., cluster B (items 1-5), cluster C (items 6-7), cluster D (items 8-14), and cluster E (items 15-20). A provisional PTSD diagnosis can be made by treating each item rated as 2 = "Moderately" or higher as a symptom endorsed, then following the DSM-5 diagnostic rule which requires at least: 1 B item (questions 1-5), 1 C item (questions 6-7), 2 D items (questions 8-14), 2 E items (questions 15-20). (supplement, questionnaire Q6)

For this analysis, questionnaire licensing was obtained. The validated version in Spanish was used for each of them, except for PCL-5, which being a new questionnaire is not yet validated in Spanish, but it has advantage of screening PTSD according to the DSM-V criteria. The Questionnaires are shown in the supplement.

**Statistical Methods**

**Sample size**

To calculate the sample size of the PAIN COVID clinical trial it is assumed an average of 50 points, in the control group, on the visual analogue scale of the EuroQOL-5D-5L and a clinically relevant difference between the groups of 20%, for distribution of a tail with a type I error of 0.05 and a power of 80%, we have calculated a sample size of 84 patients, 42 for each arm. Estimating a loss of follow up of 20%, we would need a sample size of 102 patients (51 each group).

**Data analysis**
Qualitative variables will be presented as proportions while for quantitative variables, mean (standard deviation) or median (interquartile range), after checking for normality using the Shapiro-Wilk test, will be used. To compare variables across groups, Student t-tests or Mann-Whitney U test for continuous data and Chi-square tests or exact tests for categorical variables will be carried out. Before parametric hypothesis testing, equality of variances will be studied with the use of Levene's test and if assumptions are not met, contrasts will be performed with Welch's test. An intention-to-treat approach will be followed. Two-tailed P-values will be presented and a significance level of 0.05 will be used.

For secondary outcomes, adjustment with the Benjamini-Hochberg procedure will be carried out.

A sub-analysis of the effect of treatment on compliers will be performed for the main outcome. Compliers are defined as those subjects that effectively receive the treatment they are allocated to. For the present study, we will define compliers as individuals that, being randomized to the intervention, complete at least two out of three medical visits and at least five out of seven psychological interventions. For statistical analysis, instrumental variable analysis will be carried out. A two-sided probability (p) value of less than 0.05 will be considered to indicate statistical significance. Statistical analysis was performed using R (https://www.rstudio.com/) statistical software.

**Dissemination policy**

Investigators will communicate trial results to participants, healthcare professionals, the public, reporting in results databases. The purpose of the data collection is specific to achieve the objectives defined in the project. The data collected during the study will be included in the investigators file master owned by the centre.

The treatment and communication of personal data of all participants will be in compliance with the Regulation EU 2016/679 of the European Parliament and of the Council of April 27, 2016, on the protection of natural persons as regards to the treatment of personal data and the free circulation of data, being compulsory from May 25, 2018 and to Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights.

**Discussion**

As far as we know, this is the first randomized clinical trial that examines the effectiveness of an early care therapeutic education and psychological intervention for the management of Post-intensive Care Syndrome and Chronic Pain after COVID-19.

Patients who survive a critical illness often experience disturbances in many aspects, being pain one of the most important topics, but unfortunately on many occasions during the stay in the units adequate care is not taken to improve it.(5) This study would quantify the impairment on quality life after ICU admission, as well as the incidence of chronic pain, anxiety, depression and PTSD. The health status derived from our analysis could be used in economic evaluations of healthcare systems and long-term
impact and consequences of the pandemic. Likewise, if the effectiveness of our intervention is verified, it would serve as a sample of the need to implement early care programs that allow the recovery process to be followed from early stages, given the current scenario of the pandemic.

Pain as part of this syndrome should focus its management from the ICU stay, since suffering pain limits and affects quality of life.

This project has some limitations.

The main one is that patients meeting inclusion criteria (especially those who have had a more severe course of the disease), may have a severe limitation of mobility, preventing them to attend trial visits and resulting in a selection bias, as well as the sample size is small given that the study is carried out in a single centre.

In addition, there are risk factors associated with the development of PICS and chronic pain after critical illness. These include older age, low socioeconomic status, female gender, previous mental health problems, negative ICU experiences, and delirium.

Therefore, we will carry out an exploratory analysis of potential associated risk factors to PICS due to COVID-19, although the sample size will be a determining factor in the conclusions.

Thus, future development of multi-centre projects may overcome this limitation.

Eventually, the pandemic situation could limit the correct development by involving face-to-face visits.

Restrictions on mobility may make hospital follow up visits difficult.

**Trial Status**

Protocol version number 1.0 (April 29, 2020)

Recruitment state is currently recruiting (started: May 27, 2020). We anticipate to complete recruitment by September 25, 2020 and complete the study by March 25, 2021.

**List Of Abbreviations**

PICS: Post-Intensive Care Syndrome

ICU: Intensive care unit

HRQoL: Health-related quality of life

ARDS: Acute respiratory distress syndrome

ICU-AW: Intensive care unit-acquired weakness
MMSE: Mini-mental state exam

VAS: Visual analogue scale

EQoL 5D/5L: European quality of life 5 dimensions/5 levels

BPI: Brief pain inventory

HAD: Hospital Anxiety and Depression HAD Scale

Declarations

Ethics approval and consent to participate

The authors certify that this trial was approved by the Ethics Committee of Hospital Clinic de Barcelona – approval number: HCB/2020/0549, Chairperson: Prof Joaquin Fores Viñeta, on May 14, 2020. The authors will obtain written informed consent to participate and publish the results obtained as described in the protocol before participants participate in the study.

Consent for publication

Not Applicable.

Availability of data and materials

The data that support the findings of this study will be available by request to the corresponding author upon reasonable request.

Conflict of Interest Statement:

The authors declare no conflict of interest in relation to this manuscript.

Funding:

The authors received no financial support for the research, the payment for copyright and use of all questionnaire was paid with own resources.

Authors' contributions:

All authors contributed to the study conception and design. The study design was performed by AO. Statistics has been designed by RM. AC, AO and TC have drafted the manuscript protocol. Patient recruitment, acquisition, analysis and interpretation of data will be performed by AC, TC, OC, JA, MA, CD and CF have substantively revised the different contributions of all the authors and collaborated with the structure of this study and submission. All authors read and approved the final version.
This is a single Centre study, coordinated by Dr Ojeda and Dr Calvo, who are responsible for all aspects of organization, including identifying potential recruits and taking consent. Dr Ojeda is supervising the trial and he calls meetings every quarter to evaluate the study, there is not a Public Involvement Group (SPIG) and no other groups overseeing the trial.

**Acknowledgement:**

The authors acknowledge valuable ongoing collaborations with the questionnaires to EuroQol Research Foundation, epprovide™, Fundació Clinic per a la Recerca Biomedica IDIBAPS, MD Anderson Symptom Tools. EuroQol Research Foundation did not have any role in the design of the study, data collection, analysis, or interpretation of data, nor in writing the manuscript.

**References**

1. COVID-19 Map - Johns Hopkins Coronavirus Resource Center [Internet]. [cited 2020 Jul 21]. Available from: https://coronavirus.jhu.edu/map.html

2. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New England Journal of Medicine. 2020 Apr 30;382(18):1708–20.

3. Ferrando C, Mellado-Artigas R, Gea A, Arruti E, Aldecoa C, Bordell A, et al. Características, evolución clínica y factores asociados a la mortalidad en UCI de los pacientes críticos infectados por SARS-CoV-2 en España: estudio prospectivo, de cohorte y multi-céntrico. Revista Española de Anestesiología y Reanimación [Internet]. 2020 Jul [cited 2020 Jul 27];S0034935620301870. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0034935620301870

4. Amrein K, Papinutti A, Mathew E, Vila G, Parekh D. Vitamin D and critical illness: what endocrinology can learn from intensive care and vice versa. Endocrine Connections [Internet]. 2018 Dec [cited 2020 May 28];R304–15. Available from: https://ec.bioscientifica.com/view/journals/ec/7/12/EC-18-0184.xml

5. Kemp HI, Corner E, Colvin LA. Chronic pain after COVID-19: implications for rehabilitation. *Br J Anaesth.* 2020;125(4):436-440. doi:10.1016/j.bja.2020.05.021

6. Elliott D, Davidson JE, Harvey MA, Bemis-Dougherty A, Hopkins RO, Iwashyna TJ, et al. Exploring the Scope of Post-Intensive Care Syndrome Therapy and Care. Critical Care Medicine. 2014 Dec;42(12):2518–26.

7. Inoue S, Hatakeyama J, Kondo Y, Hifumi T, Sakuramoto H, Kawasaki T, et al. Post-intensive care syndrome: its pathophysiology, prevention, and future directions. Acute Medicine & Surgery. 2019 Apr 25;6(3):233.
8. Vlake JH, Van Genderen ME, Schut A, Verkade M, Wils EJ, Gommers D, et al. Patients suffering from psychological impairments following critical illness are in need of information. Journal of Intensive Care. 2020 Jan 9;8(1):6.

9. Lee M, Kang J, Jeong YJ. Risk factors for post-intensive care syndrome: A systematic review and meta-analysis. Aust Crit Care. 2020 May;33(3):287-294. doi: 10.1016/j.aucc.2019.10.004. Epub 2019 Dec 12. PMID: 31839375.

10. Kredentser MS, Blouw M, Marten N, Sareen J, Joseph Bienvenu O, Ryu J, et al. Preventing posttraumatic stress in ICU survivors: A single-center pilot randomized controlled trial of ICU diaries and psychoeducation. Critical Care Medicine. 2018;46(12):1914–22.

11. Li H, Xue Q, Xu X. Involvement of the Nervous System in SARS-CoV-2 Infection. Neurotox Res [Internet]. 2020 May 13 [cited 2020 Jul 28];1–7. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7220627/

12. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T. Neurological associations of COVID-19. Lancet Neurol. 2020 Sep;19(9):767-783. doi: 10.1016/S1474-4422(20)30221-0. Epub 2020 Jul 2. PMID: 32622375; PMCID: PMC7332267.

13. Vittori A, Lerman J, Cascella M, Gomez-Morad AD, Marchetti G, Marinangeli F, et al. COVID-19 Pandemic ARDS Survivors: Pain after the Storm? Anesthesia and analgesia. 2020 Apr 27;131(1).

14. Busico M, das Neves A, Carini F, Pedace M, Villalba D, Foster C, et al. Follow-up program after intensive care unit discharge. Medicina Intensiva. 2019 May 1;43(4):243–54.

15. World Health Organization. (2020). Global Surveillance for human infection with novel coronavirus (2019-nCoV): interim guidance, 31 January 2020. World Health Organization. https://apps.who.int/iris/handle/10665/330857. License: CC BY-NC-SA 3.0 IGO

16. SECPAL [Internet]. [cited 2020 Jul 27]. Available from: https://www.secpal.com/biblioteca_guia-cuidados-paliativos-1

17. Herrero MJ, Blanch J, Peri JM, De Pablo J, Pintor L, Bulbena A. A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. General Hospital Psychiatry. 2003;25(4):277–83.

18. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA [Internet]. 2016 Feb 23 [cited 2020 Jul 28];315(8):801-10. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4968574/

19. Creavin ST, Wisniewski S, Noel-Storr AH, Trevelyan CM, Hampton T, Rayment D, Thom VM, Nash KJ, Elhamoui H, Milligan R, Patel AS, Tsivos DV, Wing T, Phillips E, Kellman SM, Shackleton HL, Singleton
GF, Neale BE, Watton ME, Cullum S. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Cochrane Database Syst Rev. 2016 Jan 13;(1):CD011145. doi: 10.1002/14651858.CD011145.pub2. PMID: 26760674.

20. Badia X, Roset M, Montserrat S, Herdman M, Segura A. La versión española del EuroQol: descripción y aplicaciones [The Spanish version of EuroQol: a description and its applications. European Quality of Life scale]. Med Clin (Barc). 1999;112 Suppl 1:79-85. Spanish. PMID: 10618804.

21. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 23(2): 129-138, 1994.

22. Gewandter JS, Dworkin RH, Turk DC, Farrar JT, Fillingim RB, Gilron I, et al. Research design considerations for chronic pain prevention clinical trials: IMMPACT recommendations. Pain. 2015 Jul;156(7):1184-1197. doi: 10.1097/j.pain.0000000000000191. PMID: 25887465; PMCID: PMC5769693.

Research design considerations for chronic pain prevention clinical trials: IMMPACT recommendations. Vol. 156, Pain. Lippincott Williams and Wilkins; 2015. p. 1184–97.

23. Darnall BD, Sturgeon JA, Cook KF, Taub CJ, Roy A, Burns JW, et al. Development and Validation of a Daily Pain Catastrophizing Scale. Journal of Pain. 2017 Sep 1;18(9):1139–49.

24. Perez C, Galvez R, Huelbes S, Insausti J, Bouhassira D, Diaz S, et al. Validity and reliability of the Spanish version of the DN4 (Douleur Neuropathique 4 questions) questionnaire for differential diagnosis of pain syndromes associated to a neuropathic or somatic component. Health and Quality of Life Outcomes. 2007 Dec 4;5:66.

25. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. Journal of Psychosomatic Research. 2002;52(2):69–77.

26. Ruggiero KJ, Del Ben K, Scotti JR, Rabalais AE. Psychometric Properties of the PTSD Checklist - Civilian Version. Journal of Traumatic Stress. 2003 Oct;16(5):495–502.

27. Blanchard EB, Jones-Alexander J, Buckley TC, Forneris CA. Psychometric properties of the PTSD checklist (PCL). Behaviour Research and Therapy. 1996;34(8):669–73.