Title: Impact on Mental, Physical, And, Cognitive functioning of Critical care Time due to COVID-19 (IMPACCT-COVID19): protocol for a multicentre, prospective cohort study

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ABSTRACT (290/300)

Introduction: Intensive care unit (ICU) survivors and their families present a variety of mental, cognitive and physical impairments lasting years. The ongoing pandemic could affect the duration, variety, and severity of these impairments. Our aim is to determine the impact of the COVID-19 pandemic on the physical, mental, and cognitive health of survivors, their families and their treating healthcare professionals in the long-term.

Methods and analysis: Prospective cohort in seven Chilean ICUs with a qualitative component. Sample: 450 adults, able to walk independently, in ICU and mechanical ventilation >48 hours with and without COVID-19. Assessments: Only at ICU discharge, Clinical Frailty Scale, Charlson comorbidity index, mobility (FSS-ICU) and muscle strength (MRC-SS). Cognitive functioning (MOCA-blind), anxiety and depression (HADS), post-traumatic stress (IES-R) symptoms, disability (WHODAS 2.0), quality of life (EQ-5D-3L), employment, and survival will be assessed at ICU discharge, 3 and 6 months. Physical activity (GPAQ and actigraphy) will be measured in a sample at 6 months after ICU discharge. The perceptions of family members regarding the ICU stay and the later recovery will be explored 3 months after discharge. Health care professionals will be invited to discuss the challenges faced during the pandemic using semi-structured interviews.

Ethics and dissemination: The “Impact on Mental, Physical, And, Cognitive functioning of Critical care Time due to COVID-19” (IMPACCT-COVID19) study was approved by the local Research and Clinical Trials Unit, the local Ethics Committee (2020-78) and each participating site. All eligible patients will receive

verbal and written information about the study before signing an informed consent form. A leaflet containing information about post-intensive care syndrome and rehabilitation alternatives will be provided to all participants. Study findings will be published in peer-reviewed journals following standard guidelines and disseminated through social media and conference meetings.

Keywords: COVID-19, critical care, postintensive care syndrome, rehabilitation, follow-up studies

Strengths and limitations of this study:

- The mental, physical and cognitive consequences related to the post-intensive care syndrome could be greater in periods of high occupancy during the pandemic and even more in patients infected with COVID-19.
- This is the first Chilean multicentre follow-up study assessing functional outcomes of mechanically ventilated patients discharged from intensive care unit (ICU).
- This study will also explore the views and experiences of family members/ next of kin and health care professionals working during the pandemic.

INTRODUCTION

Post-intensive care syndrome (PICS) is a common consequence of an intensive care unit (ICU) stay and can last up to 5 years.[1–3] The family members are often affected, reporting diminished quality of life and mental health related quality of life.[4] About 80% of family members become informal carers and 33% of families

see a significant reduction of income the first 6 months after discharge.[5] The extent to which these problems will be modified by the pandemic and coronavirus disease 2019 (COVID-19) remains unknown.

If under normal circumstances, an ICU stay has detrimental effects, the pandemic added two extra factors. Firstly, a rapid and exponential increase in acute care bed capacity might have affected the quality of care delivered by spreading too thin highly skilled healthcare staff. Secondly, COVID-19 involves a new disease with great uncertainties regarding treatment, prognosis and long-term effects. Early reports suggest that 64% of patients who were discharged from ICU after severe COVID-19 have at least one symptom of PICS at 6 months after discharge[6] and 32% had anxiety or depression symptoms,[7] which suggests these patients will have similar impairments to what has been reported for other ICU survivors previously.[8,9] Additionally, infection control protocols meant that healthcare staff had to wear personal protective equipment and family visiting was restricted.[10] These factors add another layer of potential negative effects due to challenges in communication with patients and their family members. Therefore, we hypothesize that the prevalence and severity of mental, physical, and cognitive impairments will be higher in patients treated in periods of higher bed occupancy and those who had severe COVID-19. In the case of family members, we expect that the experience of having a next of kin in the ICU during pandemic would be stressful and traumatic, but those with social support will cope better. In the case of staff members, their experiences will vary greatly depending on their profession and workplace, but we expect places with a more open/ less hierarchical structure to have coped better with the increase in demand.

The primary objective of this study is to compare the trajectory of mental, physical and cognitive impairments at ICU discharge, 3 and 6 months of mechanically ventilated adult patients who survived an ICU stay due to severe COVID-19 or other causes, during the pandemic. Secondary objectives are:

- To compare the disability, quality of life and survival rate at ICU discharge, 3 and 6 months of patients who were admitted to ICU due to severe COVID-19 or other causes during high and low bed occupancy in the pandemic;
- To describe the sedentary behaviour and physical activity levels in a sample of ICU survivors during the COVID-19 pandemic using a one-week actigraphy protocol;
- To explore the psychological and emotional experiences reported by family members/next of kin of patients admitted to the ICU during the COVID-19 pandemic;
- To explore the emotional, intellectual, physical and administrative challenges faced by the participating ICU staff during the COVID-19 pandemic;
- To evaluate the feasibility of the follow-up from ICU discharge to 3 and 6 months during the pandemic.

METHODS

Study design and setting

The “Impact on Mental, Physical, And, Cognitive functioning of Critical care Time due to COVID-19” (IMPACCT-COVID19) is a prospective, multicentre, cohort study in seven Chilean academic medical-surgical ICUs. This study also involves a

qualitative component including semi-structured interviews with family members/next of kin of ICU survivors and with ICU staff from the participating centres. Participating sites are four public and three private hospitals comprising a pooled bed capacity of about 200 ICU beds for both COVID-19 patients and patients admitted for other causes. The IMPACCT-COVID19 study started in October 2020. Data collection is planned until November 2021 to achieve completion of the study in February 2022.

Study population and eligibility criteria

Adult patients (≥18 years old) who are mechanically ventilated for at least 48 hours in one of the participating ICUs and do not meet any of the exclusion criteria (**Table 1**) will be invited to participate.

Table 1. Exclusion and stopping follow-up criteria

Exclusion criteria	**Rationale**
Unable to walk independently 2 weeks prior to ICU admission (with or without a gait aid)	Potential confounding factor
S5q < 5 or CAM-ICU positive within 72 hours after ICU discharge	Unable to evaluate
Patient who do not understand or speak Spanish	Unable to evaluate
Patient unable to communicate verbally	Incomplete assessment data
Burn or severe trauma as admission diagnosis	Incomplete assessment data
Any neurological disorder (i.e. spinal cord injury, stroke and brain tumours) as admission diagnosis	Potential confounding factor
Transferred to a non-participating study centre before ICU discharge assessment	Unable to evaluate
Recent prolonged hospital stay (extended by more than 3 months)	Potential confounding factor
Criteria to stop follow-up	
Re-admission after being ICU discharged	Potential confounding factor
Withdrawal of consent	Incomplete assessment data
Death before 3 or 6 months from ICU discharge	Incomplete assessment data

ICU, intensive care unit; s5q, simple 5 questions scale; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit

Procedure

The planned flow of participants throughout the study is presented in **Figure 1**. Daily, patients will be screened to identify those who could potentially be discharged from the ICU. Each site coordinator, which is a clinician physiotherapist responsible for the site, will check that the patient is delirium-free (CAM-ICU negative) and cooperative (i.e. using 5 standardised questions: open [close] your eyes; look at me; open your mouth and stick out your tongue; nod your head; raise your eyebrows when I have counted up to five[11]) within 72 hours from ICU discharge. Every patient deemed eligible will be invited to participate and will receive verbal and written information about the study. Patients will be assessed at ICU discharge (T1, defined by the point between medical decision of discharge until 72 hours after), 3 months (T2) and 6 months after ICU discharge (T3). Fifty-eight physiotherapists were trained for the assessments at ICU discharge, which included in-person measurements and self-administered questionnaires. Physiotherapists had to be working in one of the participating ICUs at the time of the training. Training for standardising T1 assessments was delivered by experienced physiotherapists and researchers (ACM, CMO and FGS). For the follow-up assessments (T2 and T3), patients will be contacted via email or telephone to schedule a phone call evaluation performed by trained interviewers.

Baseline data collection

After the patient agreed to participate and signed the informed consent form, the following baseline data will be collected from the patient clinical records: age, gender, body mass index (BMI), highest educational level achieved (no formal

education, primary school, secondary school, undergraduate or postgraduate), admission diagnosis, Charlson Comorbidity Index, duration of mechanical ventilation, length of hospital stay before ICU admission, ICU length of stay, number of intubations and the maximum level of organ system support received.[12]

Measurement Outcomes

The assessment points and measurement instruments are presented in **Table 2**. Measurement instruments were selected according to the recommended Core Outcome Measurement Set for critical illness survivors.[13,14]

Table 2. Schedule of enrolment and follow-up of the IMPACCT-COVID19 study

	Study period		
	Enrolment	**Follow-up**	
	ICU discharge	3 months from enrolment	6 months from enrolment
Eligibility screening			
Inclusion and exclusion	X		
Invitation to participate			
Informed consent	X		
Patient characteristics			
Age, gender, BMI	X		
Data related to hospitalisation			
Diagnosis, MV days, ICU LOS	X		
Maximum level of organ system support	X		
Pre-admission health and functioning			
Charlson Comorbidity Index	X		
Educational level	X		
Employment status	X	X	X
Clinical Frailty Scale	X	X	X
Physical functioning			
MRC Sum Score	X		
FSS-ICU	X		
Cognitive functioning			
MoCA blind	X	X	X

Mental functioning			
IES-R	X	X	X
HADS	X	X	X
Disability and quality of life			
WHODAS 2.0	X	X	X
EQ-5D-3L		X	X
Sedentary behaviour and physical activity			
Actigraphy			X
GPAQ			X
Survival rate	X	X	X

ICU, intensive care unit; BMI, body mass index; MV, mechanical ventilation; LOS, length of stay; FSS-ICU, Functional Status Score for the Intensive Care Unit; MRC, Medical Research Council; MoCA, Montreal Cognitive Assessment; IES-R, Impact of Event Scale Revised; HADS, Hospital Anxiety and Depression Scale; WHODAS, World Health Organization Disability Assessment Schedule; EQ-5D-3L, European Quality of Life Health Questionnaire 5 domains; GPAQ, Global Physical Activity Questionnaire

When available, we used the Chilean version of each instrument, otherwise, the validated version in Spanish. Trained physiotherapists will take an estimated maximum time of 70 minutes to perform the assessment at ICU discharge (T1). A trained interviewer will take an estimated maximum time of 20 minutes to apply the questionnaires by telephone at 3 (T2) and 6 months (T3) after ICU discharge.

The primary outcome measure is disability assessed at 6 months after ICU discharge using the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) which is recommended for critical illness survivors.[8] The WHODAS 2.0 is a self-reported disability questionnaire based on the International Classification of Functioning, Disability, and Health (ICF). It includes 36 questions, organised under six domains (cognition, mobility, self-care, getting along, life activities and participation). Each question must be answered based on the perceived difficulty for performing activities using a 5-point scale (none, mild, moderate, severe and extreme).[15] We will use the Spanish version freely

available at https://apps.who.int/iris/handle/10665/170500.[16] The estimated response time ranges from 5 to 10 minutes when evaluated in-person at ICU discharge and 10 to 20 minutes when evaluated by telephone at 3 and 6 months after ICU discharge.

Secondary outcomes measures

Clinical Frailty Scale

The Clinical Frailty Scale (CFS) is a clinical judgment based tool developed for the Canadian Study of Health and Aging to evaluate the degree of frailty in elderly patients.[17] Currently, it is also used for critically ill patients.[18] The CFS evaluates specific domains including physical functioning, activities of daily living (ADL), instrumental ADL, assistance for personal care, comorbidities, and cognition to generate a frailty score using a 9-point scale ranging from 1 (very fit) to 9 (terminally ill). A score greater than 4 is considered fragile.[17] We will use the Spanish version and recommended training material by the developers at the Dalhousie University.[17,19]) The estimated scoring time ranges from 1 to 5 minutes evaluated in-person at ICU discharge considering the status 2 weeks before the onset of symptoms.

Medical Research Council Sum Score (MRC-SS)

Limb muscle strength will be assessed using the MRC-SS, which consists in a standardised examination of six muscle groups bilaterally (i.e. shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension and dorsiflexion).[20] All muscle groups are scored using a 6-point scale between 0 and 5 (0 = no visible /

palpable contraction; 1 = visible / palpable contraction or no limb movement; 2 = limb movement, but not against gravity; 3 = movement against the gravity over nearly the entire range of motion; 4 = motion against gravity and resistance, subjectively adjusted for gender and age; 5 = normal force). This scale requires an estimated assessment time of 5 to 10 minutes and will be evaluated only at ICU discharge following the method described by Hermans *et al*.[21]

Functional Status Score for the Intensive Care Unit (FSS-ICU)

The FSS-ICU is a mobility instrument to score the level of physical assistance required when performing five functional activities: rolling, transfer from supine to sit, sitting at the edge of the bed, transfer from sitting to stand, and walking.[22] Each activity is scored using a 7-point scale ranging from 0 (not able to perform) to 7 (complete independence). The resulting overall score ranges from 0 to 35 points. Each evaluation requires between 10 and 30 minutes. It will be assessed at ICU discharge using the available and validated Chilean version.[23,24] Due to the limitations during the pandemic, walking will be evaluated inside the room, forcing the patient to walk with more laps than usual.

Montreal Cognitive Assessment–Blind (MoCA blind)

The MoCA blind is a cognitive screening tool designed to detect cognitive dysfunction in five areas: memory, attention, language, abstraction and orientation. It requires 5 minutes to be completed.[25] Each domain is scored separately for a total score ranging from 0 to 22 points. A score equal to or greater than 18 points is considered normal cognition. To minimize memory bias, the MoCA blind will be

assessed using version 7.1 at ICU discharge (in-person), version 7.2 at 3 months (by telephone) and version 7.3 at 6 months (by telephone),[26,27] following the standardised procedure recommended at https://www.mocatest.org.

Hospital Anxiety and Depression Scale (HADS)

The HADS is an interviewer or self-administered questionnaire designed to identify anxiety and depressive symptoms in a wide variety of in-hospital patients, which requires between 2 and 5 minutes to be completed.[28] The HADS has fourteen questions, seven for anxiety and seven for depressive symptoms. Each question is rated with a 4-point scale ranging from 0 ("absence") to 3 ("extreme presence"), resulting in a sum score of 21 points per subscale. HADS will be evaluated at ICU discharge and by telephone at 3 and 6 months using the Chilean version.[29]

Impact of Events Scale–Revised (IES-R)

The IES-R is an interviewer or self-administered questionnaire designed to measure the subjective distress caused by traumatic events that has been validated for critical illness survivors.[30] It comprises 22 questions divided in three subscales: intrusion, avoidance, and hyperarousal. Questions are rated in a 5-point scale ranging from 0 ("not at all") to 4 ("extremely"). The estimated response time is 6 minutes. It will be evaluated at ICU discharge and by telephone at 3 and 6 months using the available Chilean version.[31]

European Quality of Life Health Questionnaire (EQ-5D-3L)

The EQ-5D-3L is an interviewer or self-administered questionnaire of health status or health-related quality of life, including five domains: mobility, self-care, usual activities, pain/discomfort, anxiety/depression and global health state.[32,33] Each domain is scored based on 3 levels of severity: no problems, some problems, and extreme problems. Additionally, EQ-5D-3L includes a Visual Analog Scale ranging from “best imaginable health state” (100) to “worst imaginable health state” (0). Both parts of the questionnaire take an estimated response time of 2 minutes. It will be evaluated by telephone at 3 and 6 months using the Chilean version.[34]

Employment status

The employment status will be evaluated at ICU discharge, 3 and 6 months using tailored questions regarding current occupation, working hours, and any changes to their employment situation as it has been used elsewhere.[35,36]

Survival

The survival rate will be measured by the percentage of patients still alive at ICU discharge, 3 months, and 6 months after ICU discharge. Information on deaths will be obtained from death certificates from the Chilean National Civil Registry.

Sedentary Behaviour and Physical Activity

Sedentary behaviour and physical activity will be measured using a standardized one-week actigraphy protocol according to the Chilean National Health Survey [37,38] using the ActiGraph GT3X (ActiGraph, Pensacola, FL, USA) accelerometer

and the Global Physical Activity Questionnaire (GPAQ) in a selected sample of survivors at 6 months after ICU discharge.

Family or next of kin interviews

During the 3-month follow-up call, patients will be asked if a family member or next of kin will be willing to participate in the interview study. Once monthly, we will purposely select a sample of family members to be contacted. The selection will be performed to ensure maximum variation in terms of age, educational level, length of ICU stay, treatment centre and COVID-19 status of the patient that went through ICU. Information about the interview study will be provided over the phone following a script approved by the ethics committee. Once the family members verbally consent, the interview will be scheduled. Interviews will be semi-structured and be recorded for later transcription verbatim. The interviewer is a clinical psychologist with experience conducting interviews and training on providing emotional support for people under distress. We will aim to conduct 18 interviews or more until data saturation is achieved. Interviews will cover four main topic areas: ICU admission, communication during the ICU stay, experience of returning home, and the experience of having a loved one in the ICU. Each transcription will be anonymised, and the recording will be securely deleted.

Critical care staff interviews

Once the bed occupancy in ICU returns to usual levels, recruitment will start. An open call to participate will be made through WhatsApp and Facebook groups of the clinicians working in the participating centres. Additionally, posters will be put in

the rest areas to capture a wider population. We will recruit medics, nurses, healthcare assistants and physiotherapists that normally work in an ICU and have patient-facing clinical duties for more than 96 hours during the pandemic. The invitation to participate will lead to a google form containing information about the study and a short script that constitutes the informed consent. From the list of volunteers, we will purposely sample three professionals per clinical group aiming to maximise variation regarding years of experience and centre where they work. We expect a minimum of 40 interviews, but we will continue recruitment until data saturation is achieved. Interviews will be conducted online or over the phone. Participants will be asked for verbal consent before starting the interview, which will be recorded for later transcription verbatim. Interviews will be semi-structured covering five main topic areas: preparation before the pandemic; intellectual, physical and emotional challenges during the pandemic; and learning for future events.

Follow-up feasibility

The consent rate will be collected, calculating the number of patients who agreed to participate divided by the number of patients who meet selection criteria, expecting a consent rate of > 70%.[39] The feasibility over-time during the follow-up will be measured as cohort retention rate, considering the number of patients who can be contacted and evaluated at 3 and 6 months. [40,41] The reasons for the lack of assessments will be recorded individually.

Sample size calculation

All patients meeting the eligibility criteria discharged from ICU between October 2020 and April 2021 (due to funding constraints) will be invited to participate. Based on bed capacity and patient flow from previous years, we estimated that 20 to 30 mechanically ventilated adult patients are discharged monthly from each centre. This means the sampling universe ranges from 840 to 1260 patients. Hodgson et al (2017) found that a quarter of ICU survivors had severe or moderate disability at 6 months after discharge, and half of them had mild disability.[8] There is no information to estimate how much the prevalence of disability increases during a pandemic; however, the prevalence of mental health issues could be used as a proxy of the expected impact on physical health. Hodgson et al (2017) found that 22% of patients had anxiety or depressive symptoms at 6 months after discharge. Lee et al (2007) found that among survivors of the SARS outbreak, 40% had at least moderate anxiety one year after.[42] This is equivalent to a relative risk of 1.81. Considering that measurement time points are different, we have estimated our sample size assuming a relative risk (RR) of 1.5 or 1.6, which is more conservative than the estimation based on the literature. The different scenarios used for the sample size calculation appear in **Table 3**.

Table 3. Different plausible scenarios for sample size calculation

Outcome	Risk in non-pandemic situation	Risk during the pandemic	Type 1 error	Power	Sample size
WHODAS 2.0	25% severe or moderate disability	40% severe or moderate disability (RR=1.6)	0.05	0.8	343

WHODAS 2.0	40% some degree of disability	64% some degree of disability (RR=1.6)	0.05	0.8	288
WHODAS 2.0	50% mild disability	75% mild disability (RR=1.5)	0.05	0.8	388
HADS	22% anxiety or depressive symptoms	40% moderate anxiety (RR=1.8)	0.05	0.8	226

HADS, Hospital Anxiety and Depression Scale; WHODAS, World Health Organization Disability Assessment Schedule; RR, relative risk

The most plausible scenario is that 40% of ICU survivors discharged in a low demand period will have some degree of disability and this will increase to 64% for those discharged during high-demand periods. Considering loss to follow-up, we estimate 550 patients need to be recruited at ICU discharge; so 413 patients are assessed at 3 months after discharge (25% loss to follow-up) and 289 patients at 6 months (30% lost to follow-up).

Quantitative analysis

Categorical variables will be presented as absolute and relative frequencies for each subgroup (i.e. admission diagnosis and treatment centre) and time point (i.e. ICU discharge, 3 and 6 months follow-up). In the case of normally distributed continuous variables, these will be summarised using the mean and standard deviation, while for those non-normally distributed, the median and interquartile range will be used instead.

The trajectory for each outcome measure will be estimated using longitudinal multilevel regression with robust standard errors to account for data coming from

seven treatment centres. If data have a normal distribution, a linear regression model will be chosen. In the case of right skewed data, a Poisson regression will be used. For HADS, IES-R and WHODAS 2.0, data will be analysed as total scores and categories given by each questionnaire.

Survival will be analysed using Kaplan-Meier curves. If the assumption of proportional hazards is met, survival will be compared between patients admitted due to COVID-19 vs. other causes using Cox regression. All analyses will be performed in Stata 16.0 SE.

Qualitative analysis

Data from the interviews with family members and critical care staff will be analysed using framework analysis.[43] Transcription will be aided by the software Scrintal and analysis by Nvivo 12.0. Two coders will listen and read in-full all interviews before meeting to explore potential common topics that were discussed during the interviews. These topics will form the initial coding framework. Through an iterative process these codes will be refined into overarching themes capturing differences and similarities across subgroups. A more advanced coding framework will be reviewed with members of the research team until agreement regarding the final framework is reached.

Themes will be used to explain the experience of family members during the pandemic and, potentially, identify areas where improvements could be made in the future. In the case of critical care staff, the aim is to explore to what extent the approach to the pandemic of each centre influenced the experience of the different clinical groups, and what can be learned for future outbreaks.

Findings will be shared with our participants and with other family members/ critical care staff that did not participate in the interviews to ensure our interpretation reflects their experiences.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this study.

ETHICS AND DISSEMINATION

Ethical considerations

The IMPACCT-COVID19 study is conducted in accordance with the Declaration of Helsinki. Due to the observational nature of this study, patients will not be exposed to any intervention, just observing the evolution of outcomes from ICU discharge to 6 months after. This study was reviewed and approved by the Clínica Alemana Research and Clinical Trials Unit and the Facultad de Medicina Clínica Alemana Universidad del Desarrollo Ethics Committee (registration number 2020-78). The protocol was also reviewed and approved by each participating site ethics committee. All recruited patients will be informed on the study obtaining their written informed consent before the first evaluation. Patients will receive verbal and written information related to post-intensive care syndrome at the ICU discharge evaluation. At the 3- or 6-month evaluation patients with moderate or severe disability (according to the WHODAS 2.0 results) will receive information on rehabilitation alternatives at their nearest hospital.

Dissemination

We will disseminate results to key stakeholders including critical care clinicians, patients, families, rehabilitation staff, research funders and the public.

The knowledge translation of the IMPACCT-COVID-19 study will follow the three end-of-grant knowledge translation strategy categories: *diffusion* (let it happen), *dissemination* (help it happen) and *application* (make it happen).[44] *Diffusion* will be carried out using social media such as Twitter and ResearchGate. *Dissemination* will be carried out through presentation of findings in conference meetings and peer-review journal publications following the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines. Additionally, the progress, preliminary findings and final results will be disseminated on the study's tailored website (https://medicina.udd.cl/kinesiologia-santiago/impacct). *Application* will include workshops, academic meetings and development of useful tool for the follow-up of ICU survivors for both clinicians and researchers.

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Figure caption

Figure 1. IMPACCT-COVID19 study flowchart.

ICU, intensive care unit; COVID-19, coronavirus disease 2019