

O Impacto da Reabilitação Respiratória e Funcional na Recuperação de Doentes Internados em Contexto de Infecção por SARS-COV-2: Implementação de um Programa para Obtenção de Ganhos em Saúde Pública

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DE INFECÇÃO POR SARS-COV-2: IMPLEMENTAÇÃO DE UM
PROGRAMA PARA OBTENÇÃO DE GANHOS EM SAÚDE
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Os artigos acima listados, que integram esta tese, não foram e não serão incluídos noutras teses ou trabalhos semelhantes.

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O médico que só sabe de Medicina, nem de Medicina sabe.

Abel Salazar

A saúde pública é um capital da Nação, que esta tem o dever de vigiar e auxiliar com o mesmo carinho e zelo com que protege todas as suas outras riquezas.

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À memória da minha mãe.

ABSTRACT

Abstract

An outbreak of acute community-acquired atypical pneumonia of unknown etiology was reported in Wuhan, the capital of Hubei province in central China, in December 2019. The subsequent investigation led to the detection of a novel coronavirus, that would be named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease caused by the SARS-CoV-2 was named as coronavirus disease 2019 (COVID-19).

It would take forty-one days between the World Health Organization declared the novel coronavirus outbreak a public health emergency of international concern, on 30 January 2020, to the declaration of COVID-19 pandemic, on 11 March 2020. That declaration led to unprecedented measures all over the world, namely social isolation, prevention of contacts and changes in the healthcare organization.

It soon became clear that the patients with severe COVID-19 would be a great concern to the healthcare services. A small percentage of COVID-19' patients require intensive care and reliance on ventilators, but, unlike other diseases, when these patients need this kind of treatment, they will need it for a longer period than more typical uses of intensive care units. This rose a major concern: the recovery from the consequences of severe respiratory illness and the secondary disabilities that result from intensive care treatments.

In fact, care in the intensive care unit (ICU) is usually intense due to the serious medical conditions themselves, use of life-sustaining equipment, sedatives, pain and other medications that have mind-altering effects. The exposure to these stressors may impact several aspects of the patient. The disability that persists in the patients who survive critical illness is recognized as the post-intensive care syndrome (PICS) and it is a physical, cognitive, and mental disorder that occurs during ICU stay or after ICU or hospital discharge and includes the long-term prognosis of ICU patients and effects on the patient's family.

As SARS-CoV-2 was spreading through the world, the number of patients that had been subjected to ICU treatment and survive was increasing due to the success of critical care medicine in reducing mortality. The medical community realized that the size of this post-ICU cohort would be unprecedented, with a large number of patients vulnerable to PICS and other consequences of intensive care. Therefore, there were many calls to action for the medical community to apply all the resources available to optimize the COVID-19 survivorship experience and lessen the impact of PICS on the health burden. Due to past

evidence, the implementation of rehabilitation programs that begin in the ICU appeared to be one of the most promising tools for this purpose.

This thesis intends to design and evaluate the impact of the implementation of a multidisciplinary rehabilitation program in patients subjected to ICU treatment due to COVID-19, in Centro Hospitalar Ente Douro e Vouga. The multidisciplinary rehabilitation program was designed on the basis of the best evidence available in published literature, and following the recommendations issued by the Portuguese Society of Physical Rehabilitation Medicine. The following paragraphs describe the specific objectives defined for this thesis:

- *Development of a study protocol to conduct a randomized controlled double-blind, double-arm clinical trial.*

A study protocol to conduct a randomized controlled double-blind, double-arm clinical trial was designed and published (Paper I). Although some minor modifications had to be made to the original protocol in order to preserve its feasibility, the implementation of the study protocol was successful, and we were able to include a number of patients higher than the minimum value established.

- *Evaluate the impact on physical and respiratory outcomes of the multidisciplinary rehabilitation program.*

It was possible to verify that the multidisciplinary rehabilitation programme in the ICU had beneficial outcomes for the patients, in their functional and respiratory functions (Paper II). The intervention group showed significantly better results than the control group in the main outcome – the 6 minute walking test, both on the 4- and 12-week follow-up assessment. The intervention group also had a significantly shorter length of stay in the ICU.

- *Evaluate the impact on mental health and quality of life related outcomes of the multidisciplinary rehabilitation program.*

The effects of the multidisciplinary rehabilitation program on the health-related quality of life (HRQoL) and mental health of the patients included in the trial were analyzed (Paper III). The group that received a multidisciplinary rehabilitation had higher score in the mental component summary measure of the 12- Item Short-Form Health Survey and a

greater number of patients in the intervention group presented low levels of anxiety and depression.

In conclusion, the results of this thesis show that it is possible and safe to implement multidisciplinary rehabilitation program in the ICU context. Further, the impact on physical, respiratory, mental and quality of life related outcomes of the multidisciplinary rehabilitation program was positive, but it was not possible to prove superiority in relation to standard of care in all these outcomes.

RESUMO

Resumo

Em Dezembro de 2019 foi reportado um surto de pneumonia atípica adquirida na comunidade de etiologia desconhecida em Wuhan, capital da província de Hubei, no centro da China. A investigação subsequente conduziu à descoberta de um novo coronavírus, que foi denominado *severe acute respiratory syndrome coronavirus 2* (SARS-CoV-2). A doença causada pelo SARS-CoV-2 foi denominada doença causada pelo coronavírus 2019 (COVID-19).

Decorreram quarenta e um dias desde que a Organização Mundial da Saúde declarou o surto do novo coronavírus como uma emergência de saúde pública de âmbito internacional, no dia 30 de janeiro de 2020, e a declaração da pandemia de COVID-19, no dia 11 de março de 2020. Esta declaração desencadeou medidas sem precedentes, em todo o mundo, nomeadamente no que diz respeito a isolamento social, prevenção de contactos e alterações na organização dos cuidados de saúde.

Em pouco tempo tornou-se evidente que os doentes com COVID-19 grave se tornariam numa fonte de preocupação para os serviços de saúde. Apesar de apenas uma pequena percentagem dos doentes com COVID-19 necessitar de internamento em unidades de cuidados intensivos e ventilação invasiva, quando estes pacientes necessitam deste tipo de tratamento, vão necessitar durante um período mais longo do que as condições clínicas previamente conhecidas. Este facto originou uma grande preocupação dentro da comunidade médica: a recuperação das consequências da doença respiratória grave e das incapacidades secundários aos tratamentos prestados na unidade de cuidados intensivos.

Os tratamentos prestados nas unidades de cuidados intensivos são geralmente intensos, devido às próprias condições clínicas graves, ao uso de equipamentos de suporte de vida, sedativos, analgésicos e outros fármacos com efeitos psicotrópicos. Estas exposições podem afectar vários aspectos da saúde do doente. A incapacidade que persiste nos doentes que sobrevivem à doença crítica é reconhecida como o síndrome pós cuidados intensivos, e consiste num distúrbio físico, cognitivo e mental que ocorre durante o internamento em unidade de cuidados intensivos ou após a alta. Inclui o prognóstico a longo prazo e os efeitos na família do doente.

À medida que o SARS-CoV-2 se espalhava pelo mundo, o número de pacientes que foram submetidos a tratamento em unidades de cuidados intensivos e sobreviveram aumentava, devido ao sucesso dos avanços da medicina intensiva na redução da mortalidade. Ficou claro para comunidade médica que o tamanho desta coorte pós-unidade cuidados intensivos seria sem precedentes, ficando um grande número de doentes vulneráveis ao síndrome pós-cuidados intensivos. Foram realizados vários apelos à comunidade médica para que aplicasse todos os recursos disponíveis para minimizar as consequências resultantes da COVID-19 grave com necessidade de tratamento intensivo e para diminuir o impacto do PICS nos cuidados de saúde. Tendo em conta a evidência existente, a implementação de programas de reabilitação com início na unidade de cuidados intensivos apresentava-se como uma das ferramentas mais promissoras para este fim.

Esta tese pretende elaborar e avaliar o impacto da implementação de um programa de reabilitação multidisciplinar em doentes submetidos a tratamento em unidades de cuidados intensivos por COVID-19, no Centro Hospitalar Entre Douro e Vouga. O programa de reabilitação multidisciplinar foi concebido com base na melhor evidência disponível na literatura publicada e seguindo as recomendações da Sociedade Portuguesa de Medicina Física e Reabilitação. Os parágrafos seguintes descrevem os objetivos específicos definidos para esta tese:

- *Desenvolvimento de um protocolo de estudo para a realização de um ensaio clínico randomizado, controlado, duplamente cego e de braço duplo.*

Foi elaborado e publicado um protocolo para a realização de um ensaio clínico randomizado, controlado, duplamente cego e de braço duplo (Artigo I). Embora algumas pequenas modificações tenham sido realizadas ao protocolo original para preservar a sua viabilidade, a implementação do protocolo foi bem-sucedida e foi possível incluir um número de doentes superior ao valor mínimo estabelecido.

- *Avaliar o impacto do programa de reabilitação multidisciplinar nos outcomes das funções física e respiratória*

Foi possível verificar que o programa de reabilitação multidisciplinar aplicado na unidade de cuidados intensivos demonstrou efeitos benéficos nas funções física e respiratória dos doentes (Artigo II). O grupo de intervenção mostrou resultados significativamente

melhores do que o grupo de controlo no *outcome* principal, *6-minute walking test*, nas avaliações realizadas às 4 e 12 semanas de seguimento. O grupo de intervenção apresentou também uma duração de internamento em unidade de cuidados intensivos significativamente menor.

- *Avaliar o impacto do programa de reabilitação multidisciplinar nos outcomes relacionados com a saúde mental e qualidade de vida*

Foram analisados os efeitos do programa de reabilitação multidisciplinar na qualidade de vida relacionada com a saúde e com a saúde mental dos doentes incluídos no ensaio clínico (Artigo III). O grupo de intervenção apresentou uma pontuação mais alta no componente de saúde mental do *12-item short form health survey*, e um maior número de doentes deste grupo apresentou baixos níveis de ansiedade e depressão.

Em conclusão, os resultados desta tese demonstram que é possível e seguro implementar um programa de reabilitação multidisciplinar no contexto de unidade de cuidados intensivos. O impacto do programa de reabilitação multidisciplinar nos *outcomes* relacionados com as funções físicas, respiratória, saúde mental e qualidade de vida foi positivo, mas não foi possível comprovar superioridade em relação ao tratamento *standard* em todos eles.

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ABBREVIATIONS

Abbreviations

ACE2 - Angiotensin-converting enzyme 2

ARDS - Acute respiratory distress syndrome

BMI – Body mass index

CatB - Cysteine proteases cathepsin B

CatL - Cysteine proteases cathepsin L

COVID-19 - Coronavirus Disease 2019

CPM - Continuous passive motion

DEMMI - De Morton Mobility Index

ECMO - Extracorporeal membrane oxygenation

HHD - Hand held dynamometry

HIV - Human immunodeficiency virus

HRQoL – Health related quality of life

ICF - International Classification of Functioning, Disability and Health

ICU – Intensive care unit

ICU-AW – Intensive care unit-acquired muscle weakness

LRT - Lower respiratory tract

MAS - Modified Ashworth Scale

MERS-CoV - Middle East Respiratory Syndrome

MRC - Medical Research Council sum score

NAAT - Nucleic acid amplification test

NSA - Modified Nottingham Sensory Assessment

PICS - Post-intensive care syndrome

PICS-F – Post-intensive care syndrome for families

PTSD - Post-traumatic stress disorder

RASS - Richmond Agitation Sedation Scale

RCT – Randomized controlled trial

RNA – Ribonucleic Acid

ROM – Range of motion

rRT-PCR - real-time reverse-transcription polymerase chain reaction

RTC - Replication and transcription complex

SARS - Severe Acute Respiratory Syndrome

SARS-CoV - Severe Acute Respiratory Syndrome Coronavirus

SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2

S5Q - Standardized Five Questions

TRS - Transcription regulatory sequences

URT - Upper respiratory tract

VOC – Variant of concern

WHO – World Health Organization

CHAPTER I
INTRODUCTION

Introduction

1. COVID-19

In December 2019, a group of pneumonia cases was reported in Wuhan, a city located in China's Hubei province, which was later found to be caused by a novel coronavirus, temporarily named 2019-nCoV (1-3). Later, it was found that the new coronavirus is related to the SARS virus (SARS-CoV) that swept China in 2002, with a fatality rate of 9,7%, and both belong to a "species" category called severe acute respiratory syndrome-related coronavirus (3, 4). Therefore, the virus was renamed as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (4). The World Health Organization (WHO) named the disease caused by the SARS-CoV-2 as coronavirus disease 2019 (COVID-19) (5).

The WHO, on 30 January 2020, declared the novel coronavirus outbreak a public health emergency of international concern, WHO's highest level of alarm (6). On 24 February 2020, the WHO acknowledged that the SARS-CoV-2 had the potential to spread globally and cause a pandemic outbreak, and, on 11 March 2020, the WHO declared the COVID-19 a pandemic (6).

After three years, on 5 May 2023, the WHO declared an end to COVID-19 as a public health emergency (7). Until that date, the cumulative cases worldwide stood at 765,222,932, with nearly seven million deaths (7). However, the Director-General of WHO warned that the risk remains of new variants emerging and causing new surges in cases and deaths (7).

1.1. SARS-CoV-2 virology

Due to the crown-like spikes on their surface, that can be observed when viewed under an electron microscope, coronaviruses were given their name from the Latin word corona, which means crown or halo (8). Coronaviruses are enveloped viruses containing an unsegmented single-stranded positive-sense RNA genome of approximately 32 kilobases, thus making it the largest known genome for an RNA virus (9, 10). They belong to the subfamily Coronavirinae, of the family Coronaviridae, of the order Nidovirales (8, 11). The Coronavirinae subfamily consists of four genera: alphacoronavirus, betacoronavirus, deltacoronavirus and the gammacoronavirus, with the SARS-CoV-2 strain being classified under the betacoronavirus genus based on the genome sequence analysis (11-13). Whereas alphacoronaviruses and betacoronaviruses exclusively infect mammalian species, gammacoronaviruses and deltacoronaviruses have a wider host range that includes avian species (14). Human and animal coronavirus infections mainly result in respiratory and enteric diseases (15).

Long-known human coronaviruses like HCoV-229E and HCoV-OC43, as well as the more recently discovered HCoV-NL63 and HCoV-HKU1, are responsible for the seasonal and mostly mild respiratory tract infections known as the "common cold" symptoms (15). In contrast, the coronaviruses responsible for the severe acute respiratory syndrome (SARS-CoV), Middle East respiratory syndrome (MERS-CoV), and SARS-CoV-2, which have all been detected in people over the past 20 years, are extremely pathogenic (15, 16).

The coronavirus virion consists of four main structural proteins, namely spike (S), envelope (E), membrane (M), nucleocapsid (N) (figure 1) (9, 17). The positive-sense, single-stranded RNA genome is encapsidated by N, whereas M and E ensure its incorporation in the viral particle during the assembly process (10, 15). S trimers protrude from the host-derived viral envelope and provide specificity for cellular entry receptors (18).

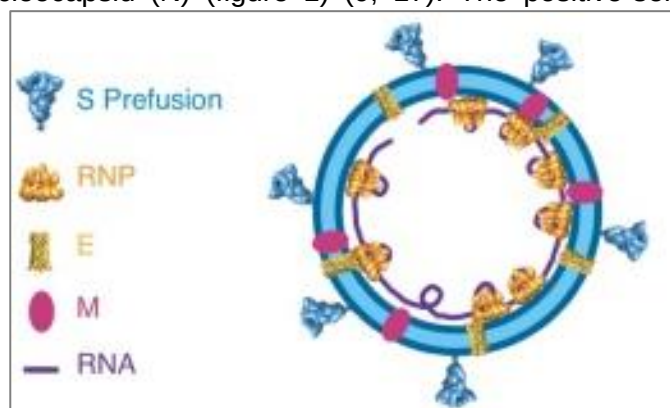


Figure 1 – Schematic model of SARS-CoV-2 virion. Reproduced from Hardenbrook et al. (2022).

Angiotensin-converting enzyme 2 (ACE2) and other cellular receptors interact specifically

with coronavirus particles (18, 19). These interactions, along with host factors like the cell surface serine protease TMPRSS2, facilitate viral uptake and fusion at the cellular or endosomal membrane (19, 20). Coronavirus S proteins are homotrimeric class I fusion glycoproteins that are divided into two functionally distinct parts (S1 and S2) (15, 18). The receptor-binding domain of the surface-exposed S1 controls the pathogenicity and cell tropism of the virus by specifically attaching to the receptor of the host cell (15, 18). Heptad repeat sections and the fusion peptide, which are found in the transmembrane S2 domain, facilitate the fusing of viral and cellular membranes after severe conformational rearrangements (15, 18). In addition to receptor interaction, the coronavirus S proteins must be cleaved by host cell-derived proteases in order for fusion to occur (20). Although the endosomal cysteine proteases cathepsin B (CatB) and cysteine proteases cathepsin L (CatL) can also help in this process, it has been demonstrated that SARS-CoV uses the cell-surface serine protease TMPRSS2 for priming and entrance (19). In agreement, SARS-CoV entrance into in vitro cell cultures is effectively blocked by the concurrent suppression of TMPRSS2, CatB, and CatL29 (19). Since the human respiratory tract expresses TMPRSS2, it significantly aids in the pathogenesis and dissemination of the SARS-CoV (15).

A complicated program of viral gene expression that is tightly controlled in both space and time begins when the coronavirus genome is released into the host cell cytoplasm upon entry (15). Two polyproteins, pp1a and pp1ab, are created by the translation of ORF1a and ORF1b from the genomic RNA (15). Following proteolytic cleavage by two cysteine proteases present in nsp3 (papain-like protease; PLpro) and nsp5 (chymotrypsin-like protease), sixteen non-structural proteins are produced from pp1a (nsp1-11) and pp1ab (nsp1-10, nsp12-16) (10).

Since nsp1's proteolytic release is known to happen quickly, it can target the host cell's translational machinery (15). The viral replication cycle is controlled by interactions between Nsp2–16, which make up the viral replication and transcription complex (RTC), and host cell components at specific subcellular sites (21). Nsp12–16 are thought to contain the essential enzymatic activities involved in RNA synthesis, RNA proofreading, and RNA modification (21). In contrast, nsp2–11 are thought to provide the supporting functions required to accommodate the viral RTC, such as modulating intracellular membranes, host immune evasion, and providing cofactors for replication (21). The RNA-dependent RNA polymerase nsp12 and its two cofactors nsp7 and nsp8, the latter of which has suggested primase or 3'-terminal adenylyltransferase activity, synthesize RNA (22).

Full-length negative-sense genomic copies, which serve as templates for the production of fresh positive-sense genomic RNA, are produced to start viral genomic replication (23, 24). These freshly created genomes are either assembled into fresh virions or used for translation to produce more nsps and RTCs (23, 24). The RTC halts transcription when it comes into contact with transcription regulatory sequences (TRSs), which are found upstream of the majority of ORFs in the 3' one-third of the viral genome (23, 24). The production of negative-strand RNA halts at these TRS elements, also known as the TRS "body," and is restarted at the TRS next to a leader sequence, which is situated about 70 nucleotides from the 5' end of the genome (23, 24). The interaction between the complementary TRSs of the developing negative strand RNA (negative-sense TRS body) and the positive strand genomic RNA (positive-sense TRS-L) is what causes this discontinuous step of coronavirus RNA synthesis (23, 24). A negative strand copy of the leader sequence is added to the developing RNA to finish the synthesis of negative-strand sgRNAs when RNA synthesis is restarted at the TRS-L region (15). Negative-strand sgRNAs are created during the discontinuous step of negative strand RNA synthesis, and these sgRNAs are employed as templates to create a

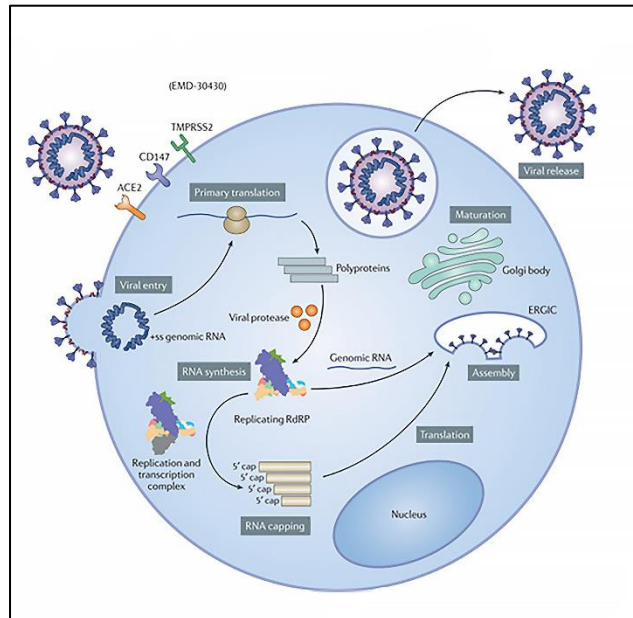


Figure 2 – SARS-CoV-2 life cycle. Adapted from Yang et al. (2021).

distinctively nested set of positive-sense sg mRNAs, which are then translated into structural and auxiliary proteins (15). Finally, virions are secreted from the infected cell by exocytosis (15).

Critical molecular interactions with host proteins that are repurposed to fulfill the needs of the virus are always necessary for an intracellular coronavirus life cycle to succeed (15). This includes host factors necessary for viral RNA synthesis and virus assembly (such as endoplasmic reticulum and Golgi components and associated vesicular trafficking pathways), factors necessary for the translation of viral mRNAs (such as critical translational initiation factors), and factors necessary for viral RNA entry (such as the entry receptor and host cell proteases) (15).

1.2 SARS-CoV-2 origin, transmission and evolution

SARS-CoV-2 is the ninth documented coronavirus that infects humans and the seventh identified in the last 20 years (25). All previous human coronaviruses, like the great majority of human viruses, have zoonotic origins (figure 3) (25). Several traces of these earlier zoonotic occurrences can be seen in the emergence of SARS-CoV-2 (25, 26). It displays clear similarities to SARS-CoV that spilled over into humans in Foshan, Guangdong province, China in November 2002, and again in Guangzhou, Guangdong province in 2003 (26). The previously identified animal reservoirs include bats, mice, rats, chickens, dogs, cats, horses, and camels (27). Bats have been reported to be the primary carrier and reservoir for a vast range of viruses, including the coronavirus, thus making the animal–human species barrier cross highly probable due to the large number of bats that congregate within the community and their ability to travel long distances (17, 28). Due to their replication process and the absence of viral RNA polymerase proofreading activity, RNA viruses, including the coronavirus, influenza virus, and HIV, are known to have exceptionally high mutation rates (29).

It was reported the possibility of SARS-CoV-2 to have jumped the species barrier from bats sold at the Huanan South China Seafood Market in Wuhan, Hubei Province, China (30). Nonetheless, our knowledge on the animal origin of SARS-CoV-2 remains incomplete to a large part, since the reservoir hosts of the virus have not been clearly proven (30, 31).

The main form of human-to-human transmission occurs through respiratory droplets expelled by an infected individual (32, 33). Evidence indicates that infectious

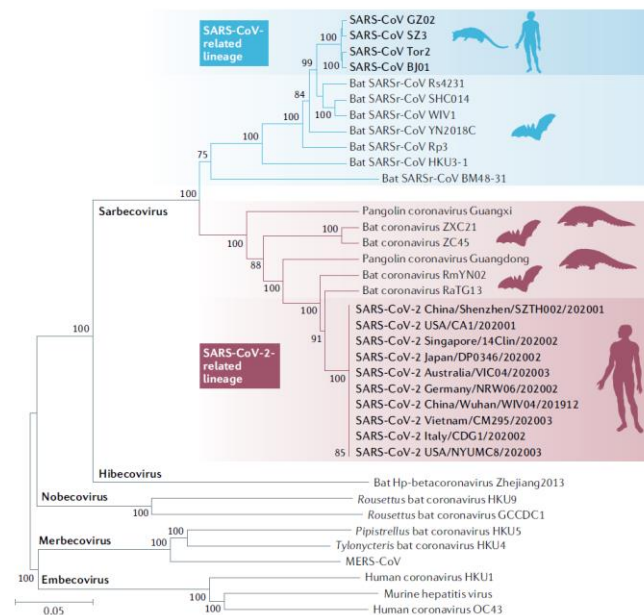


Figure 3 - Phylogenetic tree of the full-length genome sequences of SARS-CoV-2, SARSr-CoVs and other betacoronaviruses. Reproduced from Hu et al. (2021)

virus can be found in aerosols and in exhaled breath samples, hence, coughing and sneezing renders SARS-CoV-2 airborne, putting non-infected individuals at risk of contracting the disease (34). There is currently no conclusive evidence for fomite or direct

contact transmission of SARS-CoV-2 in humans (33). As for vertical transmission, the studies conducted suggest that it rarely occurs (33).

Due to their replication process and the absence of viral RNA polymerase proofreading activity, RNA viruses, including the coronavirus, influenza virus, and HIV, are known to have exceptionally high mutation rates (29). The first months of evolution after SARS-CoV-2 infected humans were characterized by limited adaptation and phenotypic change relative to its later evolution (35). The first notable change arose early in the pandemic and gave subsequent variations a growth advantage of about 20% (36). Novel and significantly altered SARS-CoV-2 strains started to appear in October 2020 (37). Higher amounts of non-synonymous mutations in the spike protein—especially in the case of Omicron—as well as unique behavioral characteristics, such as increased transmissibility and antigenicity, set these variations apart from one another (37). To date, five SARS-CoV-2 variants have been declared variants of concern (VOCs) by the WHO (and national public health agencies) on the grounds that they have significantly altered transmissibility or immune evasion, necessitating vigilant surveillance (37, 38). Each VOC showed transmission advantages over preceding variants and became dominant, either regionally or globally (37, 38).

Compared with previously dominant Alpha, Beta, Gamma and Delta lineages, the most recent Omicron lineages demonstrate a wide spectrum of mutations and sub-lineages with high immune escape and upper airway tropism (39). Omicron variants have out-competed others, but in systematic reviews are associated with lower risk of hospitalization, intensive care unit (ICU) admission, oxygen therapy, ventilation and death compared with Delta variants (40-42).

1.3 COVID-19 – pathophysiology

The SARS-CoV-2, which is acquired through respiratory aerosols, enters the human body through the nasal epithelial cells (43-45). It binds with ACE2 receptors and releases its RNA inside the epithelial cells (ECs) (43, 44). The immunological response produced at this stage, which lasts a few days, is only mild (43, 44). The patients are highly contagious despite having a low viral load at this time, and the incubation period of COVID-19, which is the time period from exposure to the virus to symptom onset, is 5–6 days, but can be up to 14 days. (43, 44). The majority of patients do not progress beyond this phase as the mounted immune response is sufficient to contain the spread of infection (43-45).

In about one-fifth of the cases, the virus evades the immunological response and spreads from the nasal channel to the alveolar portion of the lung (43-45). The virus-laden pneumocytes now release a variety of cytokines and inflammatory markers, including CXCL-10, monocyte chemoattractant protein-1, macrophage inflammatory protein-1, tumour necrosis factor, and IFN- γ (44). These include interleukins (IL-1, IL-6, IL-8, IL-120, and IL-12) (44).

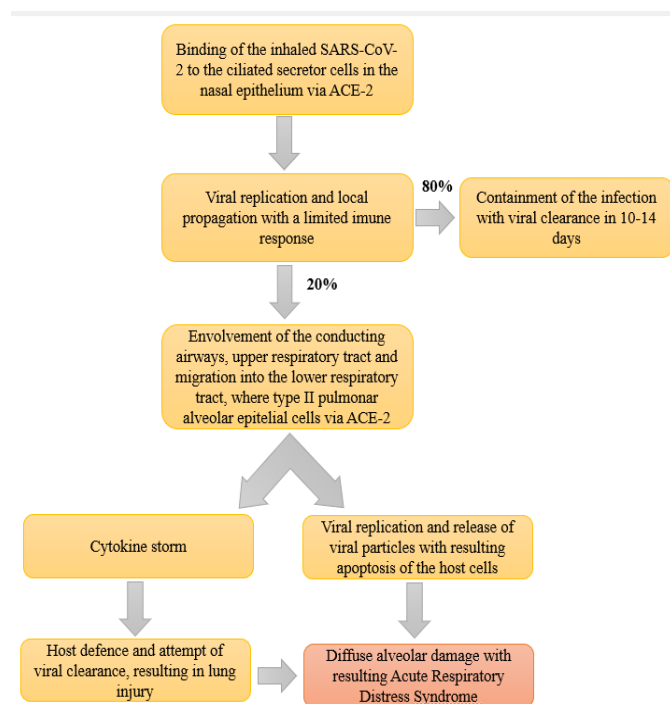


Figure 4 – Pathophysiology of COVID-19. Adapted from Parasher (2021).

The neutrophils, CD4 helper T cells, and CD8 cytotoxic T cells that are chemoattracted by this "cytokine storm" start to get sequestered in the lung tissue (44). These cells are in charge of warding off the virus, but in doing so, they also cause inflammation and lung damage (43, 44). New virus particles are released as the host cell undergoes apoptosis, infecting the nearby type 2 alveolar epithelial cells in the same way (43, 44). Diffuse alveolar damage results from the ongoing harm brought on by the sequestered inflammatory cells and viral replication, which causes the loss of both type 1 and type 2 pneumocytes and leads to pulmonary edema, activation of disseminated

intravascular coagulation, pulmonary ischemia, hypoxic respiratory failure, and progressive lung damage (43, 44, 46).

The most notable acute histological features, according to autopsy results, are pulmonary involvement with diffuse alveolar destruction, hyaline membrane formation, and pulmonary micro-emboli (47). In fatal cases, these characteristics were frequently linked to elevated levels of inflammatory cytokines and enhanced angiogenesis (48). The hyaline membrane was thought to be caused by an accumulation of hyaluronic acid in the alveolar space, which resulted in the trapping of a large amount of water, and an increase in vascular permeability (referred to as a "bradykinin storm") (49). Additionally, a high throughput extracellular antigen profiling study discovered serum autoantibodies against numerous immunomodulatory proteins, including cytokines, chemokines, complement activation components, and cell surface proteins, which may increase the tissue damage caused by immune complex deposition and complement (49). By preventing immunoreceptor signaling, these autoantibodies may also compromise virological regulation and immune system performance (50). These autoantibodies, particularly those against interferons, are substantially correlated with the severity of the disease (50).

1.4 COVID-19 diagnosis

The pathogens, their components, and the stages of their life cycles all have a role in the diagnosis of pathogenic illnesses, as well as the host response, which includes the production of micro or macro metabolites (43). Standard confirmation of acute SARS-CoV-2 infections is based on the detection of unique viral sequences by nucleic acid amplification tests (NAATs), such as real-time reverse-transcription polymerase chain reaction (rRT-PCR). The assays' targets include regions on the E, RdRP, N and S genes (51).

Once an individual has been infected by the virus, the mean time it takes to develop symptoms (incubation period) is 5-6 days, with a range of between 1- and 14-days following exposure (52-54). Before any symptoms appear, the virus may be found in the upper respiratory tract (URT) 1–3 days in advance (53, 54). Around the time that symptoms first appear, the SARS-CoV-2 concentration in the URT peaks before gradually declining (55-57). In comparison to patients with mild sickness, patients who are very ill often have greater viral loads, according to certain research (56, 58).

During the second week of an illness, viral RNA is more likely to be found in the lower respiratory tract (LRT) and, for a small percentage of people, in the feces (59). The viral RNA may only be detectable in some individuals for a few days, whereas it may be detectable in other patients for several weeks or even months (60). Long-term viral RNA persistence does not always imply long-term infectiousness. According to a few studies, a lower infectiousness is correlated with an extended number of days between the onset of symptoms and their resolution, a decrease in the viral load in respiratory secretions, and an increase in neutralizing antibodies (61, 62).

False-negative PCR results can occasionally occur as a result of the compositional variability of respiratory secretions and the inadequacy of collection efforts (63, 64). Viral RNA may be found in LRT secretions, such as sputum or bronchoalveolar lavage, in patients for whom SARS-CoV-2 infection is strongly suspected and URT swabs are negative (65).

In a small number of patients, feces or rectal swabs have been revealed to contain SARS-CoV-2 RNA, and some investigations have suggested that this positivity lasts longer than it does in respiratory tract specimens (65, 66). SARS-CoV-2 RNA has been

found in blood samples from certain patients, and some studies have shown that this finding is related to the severity of the disease (67, 68).

The optimal specimen depends on clinical presentation and time since symptom onset (51). At minimum, respiratory specimens should be collected (51). Upper respiratory specimens are adequate for testing early-stage infections, especially in asymptomatic or mild cases (69). Testing combined nasopharyngeal and oropharyngeal swabs from one individual has been shown to increase sensitivity for detection of respiratory viruses and improve the reliability of the result (70). Lower respiratory specimens are advised if collected later in the course of the COVID-19 disease or in patients with a negative URT sampling and there is a strong clinical suspicion of COVID-19 (69). LRT specimens can consist of sputum, if spontaneously produced and/or endotracheal aspirate or bronchoalveolar lavage in patients with more severe respiratory disease (69).

The decision to test should be based on both clinical and epidemiological factors (51). Rapid collection of appropriate specimens from and accurate laboratory diagnosis of patients in whom SARS-CoV-2 infection is strongly suspected are the two priorities to support clinical management of patients and infection control measures (51). If required for case management, patients should also be tested for other pathogens, as recommended in local clinical management guidelines, but this should never delay testing for SARS-CoV-2 (39). Co-infections of SARS-CoV-2 with other pathogens have been reported, thus a positive test for another pathogen does not rule out COVID-19 and vice versa (71). There is a risk of false positive or false negative SARS-CoV-2 results, if testing is not performed with adequate assays or not done under adequate conditions (51).

Optimal diagnostics consist of a NAAT assay with at least two independent targets on the SARS-CoV-2 genome, however, in areas with widespread transmission of SARS-CoV-2, a simple algorithm might be adopted with one single discriminatory target (39). When using a one-target assay, it is recommended to have a strategy in place to monitor for mutations that might affect performance (39).

Rapid diagnostic tests that detect the presence of SARS-CoV-2 viral proteins (antigens) in respiratory tract specimens are available, typically take about 30 minutes to be completed, and are most used in the context of self-testing (51). In contrast to NAATs, there is no amplification of the target that is detected, making antigen tests less sensitive (39). Additionally, false-positive results may occur if the antibodies on the test strip also recognize antigens of viruses other than SARS-CoV-2, such as other human coronaviruses

(39). When used in settings with higher pre-test probability, such as in places where there is ongoing community transmission or when an individual is at high likelihood of exposure the positive predictive value of the test is high (39). When used in a low pre-test probability setting the positive predictive value of self-testing is lower, which will lead to increased false-positive results (39).

Serological assays that detect antibodies produced by the human body in response to infection with the SARS-CoV-2 can be useful in various settings (51). Serology should not be used as a standalone diagnostic to identify acute cases in clinical care or for contact tracing purposes (51).

1.5 COVID – clinical manifestations

The most common symptoms of COVID-19 are fever (83-99%), cough (59-82%), fatigue (44-70%), anorexia (40-84%), shortness of breath (31-40%) and myalgias (11-35%). (72-74). Other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhoea, nausea and vomiting, have also been reported (74). Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms has also been reported (75). Older people and immunosuppressed patients, in particular, may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, confusion, and absence of fever (76, 77).

According to the WHO, COVID-19 can manifest as mild, moderate, severe and critical disease (39). A meta-analysis of 94 studies suggested that asymptomatic infection represents 32% (95% CI 25.3–39.5%) of all SARS-CoV-2 infection, with 20% (17–25%) of people remaining asymptomatic throughout the course of infection (78). In 2020, when population testing rates were high early in the pandemic, asymptomatic infection amongst nursing home residents was 43–67% of all SARS-CoV-2 infection, and amongst obstetric patients was 45–100% (79). The proportion of cases that are asymptomatic declines with age, which may explain some of the wide variation between cohorts of individuals, and across geographies (80).

Data from 2020 demonstrated that amongst symptomatic patients, most developed only mild (40%) or moderate (40%) disease and approximately 15% developed severe disease which requires oxygen support (72, 76). Critical disease occurred in 5%, with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multi-organ failure, including acute kidney injury and cardiac injury (74).

The mild cases are self-limited, primarily affecting the upper airway with limited involvement of the lungs (73, 74, 81). Moderate disease is characterized by the evidence of pneumonia (73, 74, 81). Severe disease is characterized by severe pneumonia, which consists of clinical signs of pneumonia (fever, cough, dyspnea) plus one of the following: respiratory rate >30 breaths/min, severe respiratory distress, or SpO₂ < 90% on room air (73, 74, 81). Critical infection is characterized by respiratory failure, septic shock, and multisystem organ dysfunction, and often complicated by ARDS (73, 74, 81). A small percentage of COVID-19 patients requires intensive care and reliance on ventilators, but, unlike other diseases, when these patients need this kind of treatment, they will need it for

a longer period than more typical uses of ICU (82). This fact rose a major concern: the recovery from the consequences of severe respiratory illness and the secondary disabilities that result from intensive care treatments (82).

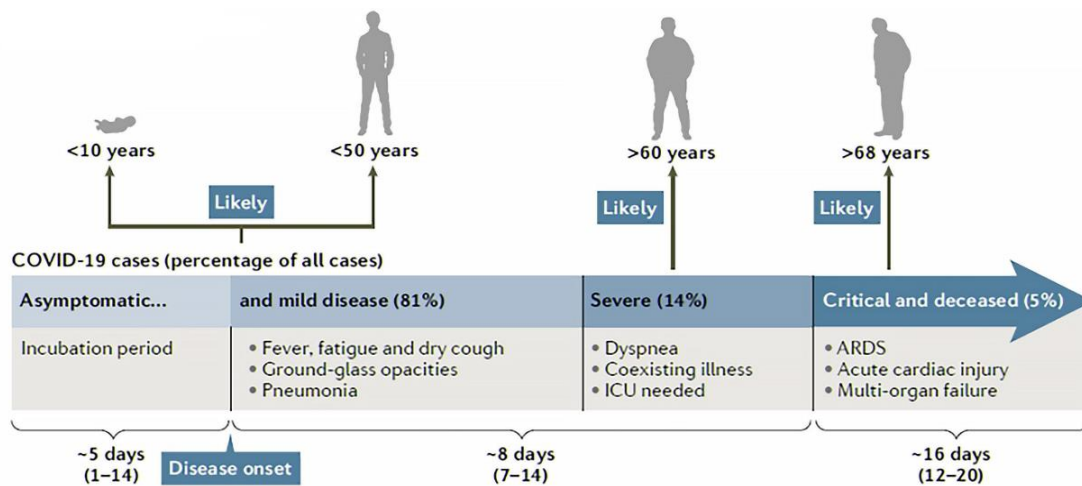


Figure 5 – Likely clinical features of COVID-19 according to age. Adapted from Hu et al. (2021).

The study conducted by Zhang et al. found that age, male gender and the presence of comorbidities are factors of an increased risk for severe Covid-19-related disease and/or mortality (83). Patients with one or more of the following comorbid conditions are at higher risk of developing severe illness or being admitted to the ICU when compared to non-severe COVID-19 patients: chronic obstructive pulmonary disease, diabetes, cerebrovascular disease, coronary heart disease, hypertension, and cancer (84). Smoking history is an additional factor linked to COVID-19 severe ICU cases (85). Another epidemiological risk factor for poor prognosis is obesity (86). Young patients with a body mass index (BMI) over 30 were two times more likely to be hospitalized in a study by Lighter et al. that differentiated patient age and BMI (87). Additionally, it was discovered that young patients with BMIs of 30-34 and 35 had an elevated rate of ICU admission of 1,8 and 3,6, respectively (87).

1.6 COVID-19 severe disease

Severe and critical cases represented 15% and 5% of laboratory-confirmed COVID-19 patients, respectively (88). These posed a high burden to the healthcare system as it consumed most of its medical resources and contributed to the majority of deaths (88). Most of the global ICUs had to be reorganized to face the COVID-19 pandemic (89). When possible, some ICUs were reserved only for these patients, and there was an incremental demand for equipment such as ventilators, consumable materials, therapeutics and as well as human force as healthcare workers (89). Although only a small percentage of COVID-19 patients requires intensive care and reliance on ventilators, occurs that, unlike other diseases, when these patients need this kind of treatment, they will need it for a longer period than more typical uses of ICU (82). This fact rose a major concern: the recovery from the consequences of severe respiratory illness and the secondary disabilities that result from intensive care treatments (82).

Currently, although rates of disease have fallen and outcomes have improved, driven in part by temporal changes in global immunity resulting from natural and vaccine exposure, the concern with critical ill patients maintains (39). The development of vaccines and treatment for COVID-19 has substantially reduced hospitalization, severity of disease, and mortality, but the virus continues to evolve with variable infectivity, immune escape and disease severity (39). This has led to changes in the protection afforded by vaccines, and the loss of activity of some previously effective drugs (39). In fact, there remains a substantial risk for severe illness, since Omicron caused more than 1,2 million deaths in 2022, and vaccine effectiveness reduces over time (39, 90). Clinically vulnerable population remain at high risk, including people at the extremes of age, those with comorbidities, frailty, and people who remain unvaccinated (39).

2. Intensive Care

The ICU is a specialist hospital facility that provides treatment and monitoring for people who are seriously ill and in need of both life supporting interventions and intensive monitoring (91). Critical illness can result from surgery, trauma, infection, or an exacerbation of a medical condition and results in malfunction of at least one organ, requiring medical, nursing, therapeutic, psychological, social, and/or technical support (92). Critical care medicine has advanced significantly in the last years, resulting in reduced mortality and, consequently, increased survival rates (92-94). This ability to increase survival has resulted in the global expansion of ICU services, which now provide vital support such as that needed after life-saving and complex surgical procedures, after severe wounds, burns, poisonings, and overdoses, as well as to support patients who are suffering from deteriorating cardiovascular and renal disorders, respiratory disorders, and other diseases (92-94).

For patients who in the past might not have survived their medical condition or treatment, a successful ICU discharge is a positive development (93). However, it has become increasingly clear that recovering from an ICU may involve managing a number of newly acquired or worsening impairments in one or more areas of physical, psychological, cognitive, or social functioning in addition to recovering from the primary presenting ailment (95-97). These limitations are frequently severe, frequently unrelated to the presenting disease, and collectively, they are a challenge for survivors (95-97). The fact that such deficits affect more than half of adult ICU patients is concerning (97, 98).

2.1 Post-intensive care syndrome

In 2012, the Society of Critical Care Medicine held a stakeholder conference to address subacute/chronic physical and psychological problems after ICU discharge, in which post-intensive care syndrome (PICS) was proposed (99).

PCIS refers to the disability that persists in the patients who survives critical illness, and it is a physical, cognitive, and mental disorder that occurs during ICU stay or after ICU or hospital discharge and includes the long term prognosis of ICU patients and effects on the patient's family (99). Six attributes make up this syndrome: multidimensional impairments that are new or worsening, physical dysfunction, psychiatric disorder, cognitive impairment, unsuccessful social reconstruction, and impaired symptoms that last after ICU discharge (93). The main characteristics of PICS are characterized by four defining characteristics (physical dysfunction, psychosocial illnesses, cognitive impairments, and unsuccessful social reconstruction), that interact and have an impact on one another (93).

It is not possible to estimate the frequency of PICS with accuracy, partly due to the lack of consensus on the assessment tools used for its diagnosis and evaluation, but it has been reported that more than half of ICU survivors will exhibit at least one symptom from the cognitive, physical, or psychological sphere (100-102).

The risk factors for the development of PICS are not well understood and vary across studies, but they can be broadly divided into two groups: those that are related to pre-existing conditions, such as neuromuscular or neurological disease, other severe comorbidities, or a history of mental illness, and those that are related to the intensive care unit, such as the presence of delirium, the dosage of sedatives administered, and the presence of acute respiratory distress syndrome (94, 103).

Patients with PCIS may have a variety of symptoms, including cognitive symptoms, mental symptoms and physical symptoms. These symptoms start after the critical illness, persist after discharge from the ICU and can last for weeks, months and even years. Physical impairment after critical illness is a recognized part of PICS, affecting about one-third of ICU survivors (103, 104).

Much of the prolonged physical impairments of PICS arise from ICU-acquired muscle weakness (ICU-AW), defined as a diffuse symmetrical decrease in skeletal muscle strength for which other causes have been excluded (105). Clinical signs of ICU-AW may include difficulty weaning off the ventilator, difficulties speaking or swallowing, and generalized limb weakness (104, 106). Critical illness myopathy, critical illness polyneuropathy, and muscular deconditioning are further subcategories of ICU-AW (104, 106).

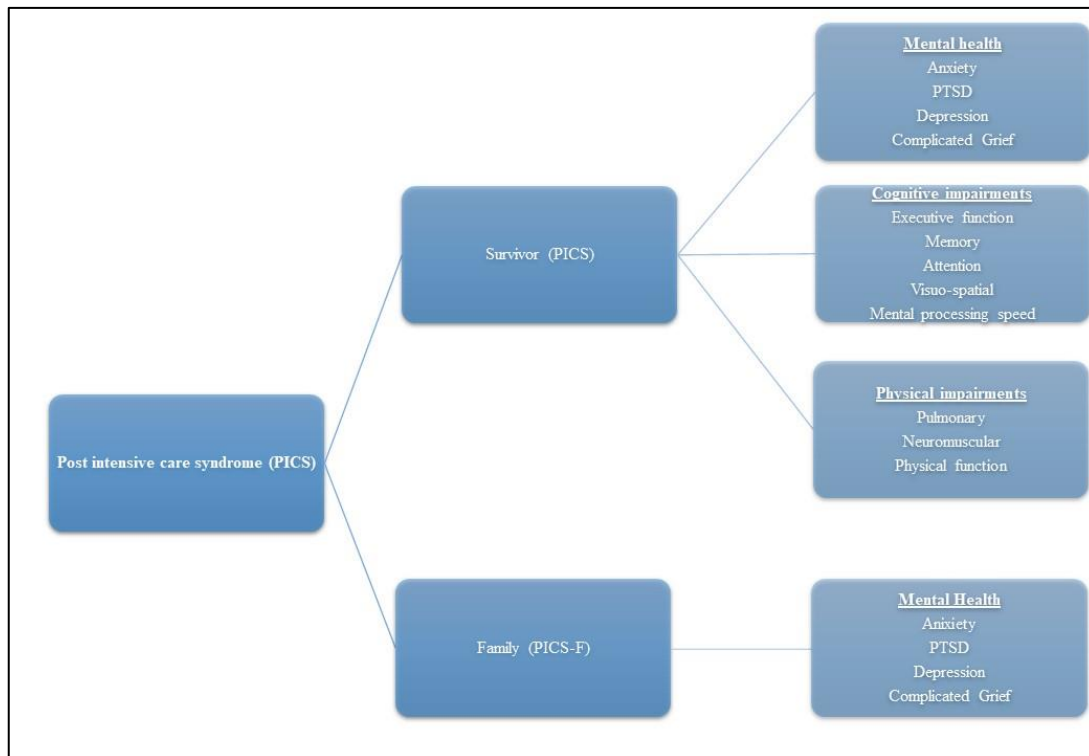


Figure 6 – Conceptual diagram of PICS. PTSD – post traumatic stress disorder.

Due to automatic unloading brought on by mechanical ventilation, the respiratory musculature rapidly deteriorates, and in as little as two days, a CT scan will show diaphragmatic thinning (107). Tracheal intubation and mechanical ventilation tolerance can typically only be achieved with the use of opiates and sedatives, which worsen atrophy caused by disuse by reducing the neuronal activation of the respiratory musculature (106, 108). Furthermore, weakness brought on by neuromuscular blockers may persist for up to a week after their discontinuation and mimic the myopathy seen after spinal or other denervation injuries if they are used to help patients and ventilators synchronize, as in ARDS (106, 108). Inflammatory mediators, electrolyte imbalances, endocrine dysfunction, and poor nutritional status frequently also contribute to the myopathy of ICU-AW by decreasing protein synthesis and promoting proteolysis, in addition to skeletal muscle atrophy from inactivity (104, 108). In addition, the evolution of

ischemia in the microvascular level of the muscle and supplying nerves that can damage cellular ion channels and mitochondria (104, 108).

The cognitive impairment of PICS may manifest as deficits in memory, processing speed, or attention that persist up to years following ICU discharge (109, 110). Risk factors for these deficits in ICU survivors include prolonged or frequent periods of hyper- or hypoglycemia and pre-existing cognitive deficits (94, 111). Additionally, there is a strong correlation between ICU delirium and the ensuing cognitive abnormalities in PICS (101).

PICS also includes impairments in mental health function, including depression, anxiety, and post-traumatic stress disorder (PTSD) (94, 109). These psychological problems are usually accompanied by fatigue, loss of interest, loss of appetite, feelings of despair, disturbed sleep, and sexual dysfunction (103, 112). Disease in and of itself, along with its complications, prolonged bed rest, drug side effects, medical and nursing procedures, and restricted physical function and autonomy, results in a physical impairment that also impacts mood and mental health (103). ICU discharge is therefore followed by depression and anxiety (113). Risk factors for the development of mental health problems following an ICU stay include a personal history of psychiatric illness, female gender, and younger age (105). There is also evidence to suggest that hypoglycemia and hypoxia not only increase the risk of cognitive dysfunction in ICU survivors but may contribute to depressive symptoms as well (114).

PICS is recognized as a growing public health burden due to the associated neuropsychological and functional disability (115). The cognitive impairment and psychiatric disorders clearly have substantial direct and indirect economic effects, not only for the patients themselves, but also for their families (116). These impairments have a negative impact on work productivity, work capacity and life satisfaction, as well as they increase health-related medical costs (115). The patients themselves are not the only ones affected by PICS as caregivers are essential in patients' recovery, and are also exposed to many stressors, like fearfulness, financial pressure and work overload (117, 118). In consequence, caregivers experience also an extensive burden, with impact on quality of life, financial status and psychological well-being (116, 118). Therefore, PICS has also been recognized for families (PICS-F) and is defined by the presence of new physical or psychological symptoms in the relatives of patients treated and discharged from the ICU (99). The causes and factors that increase the risk of PICS-F include patient and family characteristics and ICU characteristics (119). Predisposing factors include advanced age, inadequate knowledge of ICU care, prolonged ICU stay, poor staff

communication, visiting restrictions, low income, increased financial strain from caring for patients, prior history of anxiety and depression, particularly requiring medication, and prior personal ICU experience (118, 119).

2.2 The role of rehabilitation in PICS

The level of health burden associated with PICS suggests that the prevention of PICS symptoms from ICU admission is more important and effective than intensive treatment of PICS following ICU discharge (94, 105). In the United States, the ABCDEF bundle of care is an evidence-based approach to preventing PICS that has been incorporated into the ICU care at over 70 major hospitals, as part of the ICU Liberation Collaboration (120):

- A- Assessment, management, and prevention of pain
- B- Both spontaneous breathing trials and spontaneous awakening trials
- C- Choice of sedation and analgesia (maintain a relatively light level of sedation and avoid benzodiazepines)
- D- Delirium assessment, prevention, and management
- E- Early mobility and exercise
- F- Family engagement and empowerment

Early mobility is an element of the ABCDEF bundle. With physical impairments being predominantly contributing to PICS, it has been proposed to start as early as possible with rehabilitation in the ICU (121, 122). The effects of rehabilitation strategies on different aspects of functioning and disabilities can be measured and classified according to the domains of the International Classification of Functioning, Disability and Health (ICF) (123, 124). The ICF framework consists of 3 core domains to describe the level of functioning: (1) body functions and structures, (2) activities, and (3) participation (124). Safe treatment methods and precise physical functioning evaluations based on the ICF framework are necessary for the implementation of physical therapy in an ICU setting. In fact, rehabilitation targets different outcomes depending on the stage of recovery, domains of bodily processes and structures (muscle wasting, exercise capacity, and strength) and exercises (walking ability and transfers) (123).

Early rehabilitation is supposed to begin as soon as possible (34, 49–52). However, in clinical practice, there are a number of practical obstacles to the application of rehabilitation for critically sick patients in the ICU, in addition to safety concerns (125). According to research in the field, significant impediments to early rehabilitation in the ICU include a shortage of staff and time, potential risks of airway obstruction and dislocation of intravenous and arterial lines, as well as monitoring (125, 126).

2.3 Rehabilitation applied in ICU

Sommers et al. presented the first evidence-based, expert driven and practical statement for the rehabilitation clinical reasoning process regarding motor functions and activities of ICU patients (127). This evidence statement provides evidence-based clinical recommendations regarding safety precautions, as well as the evaluation and treatment of musculoskeletal and cardiopulmonary functioning in ICU regardless of the medical diagnosis for which the patient was admitted to the ICU. In this chapter, we summarize Sommers et al recommendations, as they reflected the best evidence available in the period before COVID-19.

Early mobilization and activation of ICU patients is challenging due to their critical respiratory and hemodynamic conditions, which call for medicines and intrusive equipment. As a result, it is crucial to monitor patients' safety both before and during mobilization and activation. As part of the clinical reasoning process, every patient should be screened for the presence of red flags (contra-indications) and relative contra-indications to consider (potential) risks and benefits before and during every rehabilitation treatment session. According to the evidence in published literature, the strength of evidence of the recommendations for red flags is Level 1 (table 1) and for 'relative contra-indications' Level 3 and 4 evidence (table 2) (127).

Table 1- Contra-indications to rehabilitation.

Domain	Contra-indications (red flags)
Heart rate	Recent myocardial ischemia Heart rate < 40 or > 130 beats/min
Blood pressure	Mean Arterial Pressure (MAP) < 60 mmHg or > 110 mmHg
Oxygen saturation	≤ 90%
Parameters of ventilation	Fractional concentration of inspired oxygen (FiO ₂) ≥ 0,6 Positive End Expiratory Pressure (PEEP): ≥ 10 cm H ₂ O
Respiratory frequency	Respiratory frequency > 40 breath/min
Level of consciousness of patient	Richmond Agitation Sedation Scale (RASS) score: -4, -5, 3, 4
Doses inotropic	High inotrope doses (Dopamine ≥ 10 mcg/kg/min; Nor/adrenaline ≥ 0,1 mcg/kg/min)

Temperature	$\geq 38.5^{\circ}\text{C}$ $\leq 36^{\circ}\text{C}$
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Table 2 – Relative contra-indications to rehabilitation.

Domain	Relative contra-indications
Clinical view	Decreased level of awareness/consciousness Sweating Abnormal face color Pain Fatigue
Fractures	Unstable fractures
Neurological instability	Intra Cranial Pressure (ICP) ≥ 20 cmH ₂ O Presence of lines that make mobilization unsafe.

The type of physical rehabilitation interventions is dependent on the patient's level of consciousness. Active interventions are recommended for patients able to follow instructions, and passive interventions are recommended for patients unable to follow instructions (127). Changes in safety parameters should be monitored during each treatment session (127).

For unconscious patients the range of motion for joint contractures and muscle tone using passive joint movements should be monitored daily (127). In patients who are at risk for, or already have, joint contractures, stretching, splinting or passive movements using continuous passive motion (CPM) should be applied for 20 minutes daily (127). In addition, passive cycling, CPM or electrical muscle stimulation should be applied daily to stimulate muscle contractions (127).

For patients who are conscious and able to follow instructions, active therapy modalities in a functional context are recommended (127). For the prevention of joint contractures and muscle tone a sequence of five active range of motion exercises are recommended daily (127). To prevent muscle atrophy and improve muscle strength, active exercises (building up training referring to FITT components: frequency, intensity, type and time, repetitions from eight till ten and sets from one till three), as well as 20 minutes of active cycling are recommended (127).

The recommended assessment tools are described on table 3.

Table 3 – Recommended assessment tools and their definition.

Name	Definition
Richmond Agitation Sedation Scale (RASS)	Screening of global mental functions, i.e. patients responsiveness and consciousness;
Standardized Five Questions (S5Q)	Assessing patients' ability to cooperate;
Goniometry	Measuring range of joint motion (ROM)
Medical Research Council sum score (MRC)	Measuring manually localized muscle strength as well as the summation of total muscle strength;
Hand held dynamometry (HHD)	Measuring localized muscle strength in muscles with MRC > 3;
Modified Ashworth Scale (MAS)	Assessing muscle tone;
Modified Nottingham Sensory Assessment (NSA)	Evaluating sensory function;
De Morton Mobility Index (DEMMI)	Measuring functional ability (e.g. transfers in and out of the bed, standing balance and walking;
The Borg Score	Monitoring exertion during exercise (in conscious patients)

More recently, in 2023, Renner et al. published a guideline on multimodal rehabilitation for patients with post-intensive care syndrome (128). The recommendations in this statement present three levels of evidence, as stated in table 4 (128).

Table 4 – Recommendations of rehabilitation in the ICU, according to level of evidence.

Rehabilitation ought to be applied
Early mobilization ought to be started within the first few days in the ICU, adapted to the patient's resilience and general condition.
Interventions for delirium prophylaxis ought to include multimodal sensory, cognitive and emotional stimulation (mobilization, purposeful stimulation and engagement, aids for orientation, contact to family members).
ICU diaries ought to be implemented for reducing the risks of symptoms of anxiety,

depression, and PTSD in critically ill patients after discharge from the ICU.

In post-ICU care, ICU diaries ought to be worked on with health care professionals.

Rehabilitation is recommended and should be considered

Training of the inspiratory muscles using an inhalation trainer should be used to increase the strength of the inspiratory muscles and the quality of life in the short term as an adjunct to standard physical therapy.

As dysphagia is frequent in patients with tracheostomy, standardized swallowing assessment should be performed before oral nourishment is initiated.

Computer-based learning of attention functions and/or therapy aiming at improvement of cognition should be performed with critically ill patients and in further rehabilitation.

Interventions for stress reduction (pain, anxiety, sleep, noise), improvement of communication and family care should be applied.

Critically ill patients with adaptation disorders such as anxiety and depression benefit from psychological interventions. These should be offered already in the ICU and/or early rehabilitation and, if possible, also to relatives.

Post-traumatic stress reactions should be treated by interventions such as psychoeducation and psychotherapy.

Access to professional support and aftercare should be offered in the first 12 months after discharge aiming at mental stabilization.

Rehabilitation is an option, can be considered

Supplemental use of ergometers (bed cycling) in addition to early mobilization can be considered.

Wheelchair cycle ergometer training can be used in addition to the standard physical therapy to improve muscle strength and cardiovascular fitness.

Strength training can be used as an adjunct to standard physical therapy to increase walking speed.

Electrical stimulation of the ventral thigh musculature can be used to strengthen the muscles.

2.4 Literature evidence on rehabilitation in ICU

Clinical trials investigating early mobilization and rehabilitation have yielded inconsistent results, with some studies exhibiting notable benefits and others not (129-132). For example, a quasi-RCT demonstrated that early mobilization, started within 48 hours of intubation, led to a markedly decreased number of days before the patient was first mobilized out of bed and a decreased ICU and hospital length of stay (129). Similar to the above, in a two-center RCT, beginning rehabilitation early (at a median of 1,5 days after intubation) led to a reduction in the amount of time patients spent in delirium and on mechanical ventilation as well as a significantly higher level of functional independence at hospital discharge (130). Nonetheless, in a single-center RCT in patients in the ICU for ≥ 5 days, intensive exercise in the ICU (started at a median of 7 days from admission), along with more intensive exercise on the hospital ward and in the outpatient setting, did not improve patient outcomes compared with usual care over a 1-year follow-up (131). The physical functioning of patients in a five-center RCT who began an intense program at a median of 8 days after intubation did not improve at the 1-, 3-, or 6-month follow-up, either (132). It is important to notice that in both these last trials the rehabilitation intervention began later than in the two first mentioned trials.

The contradictory results are present also in meta-analysis studies. The study by Fuke et al. revealed that early rehabilitation significantly improved short-term physical function in patients with critical illness, as assessed by the MRC scoring system and the incidence of ICU-AW, but it did not significantly improve the patients' cognitive and mental status-related outcomes (133). Moreover, the study by Kayambu et al. concluded that there is evidence that early rehabilitation has beneficial effects on muscle strength, physical function, health-related quality of life (HRQoL), ventilator-free days, and lengths of stay in the ICU and hospital (122). It is important to notice that the methods used to assess quality of life were different, as Kayambu et al. used the Medical Outcomes Study 36-Item Short Form survey score, and Fuke et al. used the EQ-5D (122, 133). The meta-analysis conducted by Zang et al. indicated that early mobilization was effective in preventing the occurrence of ICU-AW, shortening the length of ICU and hospital stay, and improving the functional mobility (134). However, it had no effect on the ICU mortality rate and ventilator-free days (134). Similar results were reported by Wang et al., whose analysis showed that physical rehabilitation improved physical function at hospital discharge, reduced ICU length of stay by 0,8 days and hospital length of stay by 1,75 days (135).

In addition to the lack of consensus in the literature about the effects of rehabilitation on PICS, according to Balas et al., there is little evidence that mobility interventions are routinely used in critical care (136). Jolley et al reported that only 8% of German patients receiving mechanical ventilation received out-of-bed mobilization, and across Australian and New Zealand hospitals only 3% achieved sitting at the side of the bed, with none progressing to standing or walking (137). Due to the lack of consensus in the literature about the beneficial effects of rehabilitation on PICS, more randomized controlled trials to clarify this issue.

2.5 COVID-19 pandemic and the need to implement effective rehabilitation strategies

As SARS-CoV-2 spread through the world, it came to notice that a great number of patients would be subjected to ICU treatment, and that the size of this post-ICU cohort will be unprecedented, with a large number of patients vulnerable to PICS and other consequences of intensive care (82, 138).

In fact, several authors recommended the implementation of a rehabilitation program to improve these patients' outcomes (82, 139, 140). Stam et al. published a call to action, and claimed that was therefore important to turn to the resources of rehabilitation hospitals and specialists in rehabilitation medicine and their multiprofessional teams who are equipped and experienced in providing the necessary interventions for mental, cognitive and physical impairments of the consequences of intensive care and mechanical ventilation (82).

Koh et al. described a number of effective rehabilitative strategies that can be used in this widespread emergency in a study that was published in March 2020. To permit supervision of therapy without running the danger of contracting the virus, they advise adopting telerehabilitation as a first resort, if practical (141). The study further recommended that healthcare teams that work directly with patients should be divided into subteams, with each subteam having the necessary skills to take over for the others in the event of an absence (141).

McNeary et al. (142) encouraged rehabilitation involvement (in a safe environment, ensuring protection of staff and patients) for sequelae resulting from ARDS, ECMO, and prolonged prone position (posterior reversible encephalopathy syndrome, neuromuscular illness, plantar flexion contractures, and wounds), always taking account of respiratory distress, which might not allow the patient to tolerate intense therapies.

The study by Stutz et al. (139) highlighted the feasibility of early rehabilitation for critically ill patients with COVID-19.

In the context of the COVID-19 pandemics the topic of rehabilitation in ICU became more relevant, since the healthcare professionals faced an unknown disease and had limited physical and human resources. Lacking an effective pharmacological

treatment, interventions that could optimize patients's recover and diminish length of stay in ICU were important.

CHAPTER II

AIMS

Aims

This research thesis aimed to design and evaluate the impact of the implementation of a multidisciplinary rehabilitation program in patients subjected to ICU treatment due to COVID-19.

To achieve these aims, we have addressed three specific objectives:

- A) Development of a study protocol to conduct a randomized controlled double-blind, double-arm clinical trial. (Paper I)
- B) Evaluate the impact on physical and respiratory outcomes of the multidisciplinary rehabilitation program. (Paper II)
 - B1) Test the superiority of the multidisciplinary rehabilitation program in relation to standard of care.
- C) Evaluate the impact on mental and quality of life related outcomes of the multidisciplinary rehabilitation program. (Paper III)
 - C1) Test the superiority of the multidisciplinary rehabilitation program in relation to standard of care.

A detailed description of the methods is provided in the protocol of the randomized controlled trial (Paper I), and in each of the articles/manuscripts addressing the objectives.

CHAPTER III

PAPER I

LETTER

Open Access



Therapeutic respiratory and functional rehabilitation protocol for intensive care unit patients affected by COVID-19: a structured summary of a study protocol for a randomised controlled trial

Ana Cristina Carvalho^{1*}, Jorge Moreira², Pedro Cubelo², Pedro Cantista³, Catarina Aguiar Branco^{2,4} and Bruno Guimarães^{2,5,6,7*}

Abstract

Objectives: The primary objective of the presented study is to analyze the respiratory and functional effects of a rehabilitation program in patients affected by hospitalization in Intensive Care Unit (ICU) due to COVID-19, in comparison with the group treated with standard of care, at discharge endpoint.

The secondary objectives of the presented study are to evaluate different outcomes of the rehabilitation program in comparison to standard of care regarding: functional performance at 4-week and 12-week post-discharge mark; health-related quality of life, the impact on the health services (namely days of hospitalization), the cost-effectiveness of the intervention proposed.

Trial design: This is a randomized, controlled, double-blind, double-arm clinical trial of treatment, with an allocation ratio 1:1 and framework of superiority.

Participants: The study will be conducted at Centro Hospitalar Entre Douro e Vouga, Santa Maria da Feira, Portugal. Potential participants will be adult patients (≥18 years old) hospitalized in ICU with respiratory insufficiency due to COVID-19, who are referred to respiratory and functional rehabilitation. Only patients approved by physical rehabilitation doctors to perform respiratory and functional rehabilitation will be considered potential participants. To be eligible for inclusion participants must have been independent in their activities of daily living before the onset of critical illness (verbal statement by their proxy) and have to meet the safety criteria defined by the Portuguese Society of Physical Rehabilitation Medicine.

(Continued on next page)

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(Continued from previous page)

Intervention and comparator: Both groups will receive usual medical and nursing care in the ICU, which involves assessment and treatment of the respiratory system and may include positioning, hyperinflation techniques and suctioning. The physical function of the patient is assessed, and active bed exercises and mobility are encouraged as soon as possible and may include sitting out of bed.

The intervention group will receive a functional and respiratory multidisciplinary rehabilitation protocol (that includes medical, nursing, physiotherapy and occupational therapy interventions) during their entire hospital stay. After reassurance that the patients fulfil the safety criteria, they will initiate the rehabilitation protocol, individualized to each patient based on the clinical status. The rehabilitation interventions and exercises implemented will be consistent with recommendations from the Portuguese Society of Physical Rehabilitation Medicine.

The intervention will occur 6 days per week (Monday to Saturday), fifteen minutes, twice per day for each participant. Throughout all activities, progression will be increased successively, depending on the individual's tolerance and stability.

After discharge, the intervention group will continue with rehabilitation exercises, prescribed by physical rehabilitation doctors. These exercises are designed for the patient to do at home, and then report their execution to rehabilitation nurses through teleconsultation, until 12 weeks after ICU discharge.

Main outcomes: Baseline descriptive data collection will include age, sex, comorbidities and date of admission to ICU. The need of mechanical ventilation and length of use, as well as the need for oxygen therapy, length of ICU stay (days/hours), incidence of ICU readmission, discharge destination and survival will also be recorded.

Prior to intervention, every two days and at discharge, participants will be evaluated using the following scales: Glasgow Coma Scale, Richmond Agitation Sedation Scale, Chelsea Critical Care Physical Assessment, 5 standardized questions for cooperation, Medical Research Council Sum-Score, Handgrip strength test and Medical Research Council dyspnea scale. At discharge, Borg Rating of Perceived Exertion will be evaluated.

The primary outcome measure will be functional capacity using the 6-Minute Walk Test, and it will be measured at discharge and at the 4-week and 12-week mark. Medical Research Council Sum-Score, Handgrip strength test, Medical Research Council dyspnea scale and Borg Rating of Perceived Exertion will also be re-evaluated at the 4-week and 12-week mark. The health related quality of life will also be used as an outcome measure, using the 12-Item Short Form Survey, at 12 weeks of follow-up.

Randomisation: Participants will be divided into two groups, standard care and intervention, by means of balanced randomization at a 1:1 ratio using blocks of 10 participants. The randomization sequence is going to be created using a free software (<http://www.randomized.org/>). In order to ensure the confidentiality of the randomisation sequence, this process will be conducted by an assessor external to the study.

Blinding (masking): The evaluators in the study will be blinded during the entire process. The evaluators will be unaware of the study objectives and the randomized distribution of patients to study groups and will not have access to the randomization sequence. Although blinding for patients will not be possible to achieve completely, subjects will be unaware of other treatment modalities, and they will not know if they belong to the intervention or standard group. As for the treating physiotherapists and ICU staff, blinding will not be possible to achieve, but they will not be responsible for assessing outcomes.

Numbers to be randomised (sample size): We plan to randomise 40 participants to each group. 80 participants in total.

Trial Status: This is the second and definitive protocol version, dated from 26th February 2021. Recruitment started on 8th March 2021. Participants will be recruited between March 8, 2021, and June 8, 2021. Study completion is expected to be October 2021.

Trial registration: ReBEC [RBR-7rvhpq9](#). Registry name: The effect of rehabilitation in hospitalized COVID-19 patients. Registered on 17 March 2021. Retrospectively registered.

Full protocol: "The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest in expediting dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol".

Keywords: COVID-19, Randomized controlled trial, protocol, intensive care unit, post-intensive care syndrome, functional rehabilitation, respiratory rehabilitation

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13063-021-05210-y>.

Additional file 1. Full study protocol.

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Not applicable.

Authors' contributions

All the procedures for recruiting, intervening, and evaluating the participants are carried out by personnel attached to this group. ACC is the principal investigator and has contributed to the concept and study design, provided clinical expertise and contributed to the manuscript development. JM, PC, PCA and CAB contributed to the protocol development and provided clinical expertise. BG contributed to the protocol development, provided clinical expertise and he is responsible for designing the statistical procedures. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request. The data will be available after the main publication of them; for other circumstances, they should consult the corresponding author. Any data required to support the protocol can be supplied on request.

Declarations

Ethics approval and consent to participate

This study complies with the Helsinki guidelines for human research, and it has been approved by the Commission of Ethics for Health of Centro Hospitalar Entre Douro e Vouga, reference CA-081/2021-0t_MP/CC. All study participants will sign an informed consent approved by the ethics committee. The identification of each individual will remain concealed based on the ethical principles of confidentiality and privacy. Any reason for compensation will be covered by professional liability insurance. Informed consent is available in the portuguese language from the corresponding author on request. There is no anticipated harm and compensation for trial participation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Supplementary Material – Full study protocol

Therapeutic respiratory and functional rehabilitation protocol for intensive care patients affected by COVID-19: study protocol for a randomized controlled trial

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Abstract

Background: The coronavirus disease 2019 (COVID-19), declared pandemic on 11th March 2020 by the World Health Organization, has led to an increasing number of patients in the intensive care units (ICU) around the world. The size of this post-ICU cohort will be unprecedented, with many patients vulnerable to post-intensive care syndrome. The implementation of rehabilitation programs that begin in the ICU may play a role in reducing these harmful consequences. The primary objective of the presented study is to analyze the respiratory and functional effects of a rehabilitation program in patients affected by the COVID-19 hospitalized in ICU, in comparison with the group subjected to standard of care, at discharge endpoint.

Methods: A randomized, controlled, double-blind, double-arm clinical trial will be conducted in Centro Hospitalar Entre Douro e Vouga. Patients who fulfil the eligible criteria will be recruited and randomized to one of two groups: standard of care and intervention group. The intervention group will receive a functional and respiratory rehabilitation protocol. Baseline demographic and clinical data will be collected. Functional and respiratory capacities will be evaluated using the following scales: Glasgow Coma Scale, Richmond Agitation Sedation Scale, Chelsea Critical Care Physical Assessment, 5 standardized questions for cooperation, Medical Research Council sumscore, Handgrip strength test, Medical Research Council dyspnea scale and Borg Rating of Perceived Exertion. The primary outcome measure evaluated at discharge, 4-week and 12-week of follow-up, is functional capacity using the 6-Minute Walk Test. The health related quality of life will be evaluated at 12-week mark after discharge, using the 12-Item Short Form Survey.

Discussion: In this prospective, single-center, allocation-concealed and assessor-blinded randomized controlled trial we expect the intervention group to achieve better functional and respiratory outcomes, less days of hospitalization and an improvement in health related quality of life, comparing to the standard of care group.

Trial registration: RBR-7rvhpq9. Retrospectively registered.

Keywords: COVID-19, Randomized controlled trial, protocol, intensive care unit, post-intensive care syndrome, functional rehabilitation, respiratory rehabilitation

Introduction

In December 2019, a group of pneumonia cases was reported in Wuhan, China, which was later found to be caused by a novel coronavirus, temporarily named 2019-nCoV (1-3). Later, it was found that the new coronavirus belongs to a “species” category called severe acute respiratory syndrome-related coronavirus (SARS-CoV) and is related to the virus that swept China in 2003 (3). Therefore, the virus was renamed as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the World Health Organization (WHO) named the disease caused by the SARS-CoV-2 as coronavirus disease 2019 (COVID-19) (4). Since then, the infection has spread all over the world, and on the 11th March 2020, WHO declared the state of pandemics, which led to unprecedented measures all over the world, namely social isolation, prevention of contacts and changes in the healthcare organization (5). Prior to the implementation of any public health interventions, the basic reproduction number of SARS-CoV-2 was estimated to be as high as 5,7, meaning that each infected individual had the potential to transmit the disease to as many as 5 to 6 new individuals (6). As of 27th January 2021, the virus has resulted in over 98,2 million cases and over 2,1 million deaths all over the world, with significantly worse outcomes and higher mortality in the elderly (7).

The most common symptoms of COVID-19 are fatigue, fever, dry cough, and anosmia (2, 4, 8-10). According to the WHO (4), COVID-19 can manifest as mild, moderate, severe, and critical disease. Approximately 80% of cases are mild and self-limited, primarily affecting the upper airway with limited involvement of the lungs (9-11). Moderate disease is characterized by the evidence of pneumonia (9-11). Severe infection, characterized by dyspnea, tachypnea, hypoxemia, cardiovascular sequelae, and extensive lung disease, occurs in 15% of cases (9-11). Critical infection, characterized by respiratory failure, septic shock, and multisystem organ dysfunction, and often complicated by acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulopathy (DIC), occurs in 5% of cases (9-11). This small percentage of COVID-19 patients requires intensive care and reliance on ventilators, but, unlike other diseases, when these patients need this kind of treatment, they will need it for a longer period than more typical uses of intensive care unit (ICU) (12). This raises a major concern: the recovery from the consequences of severe respiratory illness and the secondary disabilities that result from intensive care treatments (12).

In 2012, the Society of Critical Care Medicine held a stakeholder conference to address subacute/chronic physical and psychological problems after ICU discharge, in which post-

intensive care syndrome (PICS) was proposed (13). PICS refers to the disability that persists in the patients who survives critical illness, and it is a physical, cognitive, and mental disorder that occurs during ICU stay or after ICU or hospital discharge and includes the long term prognosis of ICU patients and effects on the patient's family (13-15). PICS is recognized as a growing public health burden due to the associated neuropsychological and functional disability (16). The cognitive impairment and psychiatric disorders clearly have substantial direct and indirect economic effects, not only for the patients themselves, but also for their families (17). These impairments have a negative impact on work productivity, work capacity and life satisfaction, as well as they increase health-related medical costs (16).

Patients with PICS may have a variety of symptoms, including functional, respiratory and cognitive symptoms (14, 15). These symptoms start after the critical illness, persist after discharge from the ICU and can last for weeks, months and even years. Intensive care unit-acquired weakness (ICU-AW) is one factor related to muscle weakness (18, 19). It is defined as the acute muscle weakness of the extremities in a symmetric pattern, which is caused by critical illness, and it has an important contribution to prolonged mechanical ventilation, increased ICU and hospital lengths of stay, and mortality (18, 19). Currently, there is no consensual intervention applied to improve the outcomes of ICU-AW, but early physical rehabilitation, neuromuscular electrical stimulation and glucose control are some of the preventive measures that have been applied (20). PICS components should be identified before ICU discharge and rehabilitation should be started as soon as possible (17).

The level of health burden associated with PICS suggests that the prevention of PICS symptoms from ICU admission is more important and effective than intensive treatment of PICS following ICU discharge (14). There is no consensus in the literature about the beneficial effects of rehabilitation on PICS, with some studies showing beneficial effects, and others showing no effects (20-22). Also, the dose–response of physical rehabilitation for clinical outcomes is unknown (14). Therefore, more randomized controlled trials are needed to clarify the effect of physical rehabilitation on PICS.

As SARS-CoV-2 is spreading through the world, the number of patients that have been subjected to ICU treatment and survive is increasing due to the success of critical care medicine in reducing mortality (23). The size of this post-ICU cohort will be unprecedented, with a large number of patients vulnerable to PICS and other consequences of intensive care (12, 23). Therefore, it is of great importance that the

medical community apply all the resources available to optimize the COVID-19 survivorship experience and lessen the impact of PICS on the health burden, and the implementation of rehabilitation programs that begin in the ICU appears to be one of the most promising tool for this purpose (23, 24).

Objectives

The primary objective of the presented study is to analyze the respiratory and functional effects of a rehabilitation program in patients affected by the COVID-19 hospitalized in ICU, in comparison with the group subjected to standard of care, at discharge endpoint.

The secondary objectives of the presented study are to evaluate different outcomes of the rehabilitation program in comparison to standard of care regarding:

- Functional performance at 4-week and 12-week post- discharge mark,
- Health-related quality of life.
- The impact on the health services (namely days of hospitalization),
- The cost-effectiveness of the intervention proposed.

Methods and Design

We will conduct a controlled, randomized, double-blind, double-arm clinical trial of treatment in the tertiary, interdisciplinary ICU of Centro Hospitalar Entre Douro e Vouga. The study has been approved by the Commission of Ethics for Health of Centro Hospitalar Entre Douro e Vouga, reference CA-081/2021-0t_MP/CC. This trial adheres to the recommendations from the Consolidated Standards of Reporting Trials (CONSORT) statement (25).

Participants

Potential participants will be adult patients (≥ 18 years old) hospitalized at ICU of Centro Hospitalar Entre Douro e Vouga, with respiratory insufficiency due to COVID-19, who are referred to respiratory and functional rehabilitation. Only patients approved by physical rehabilitation doctors to perform respiratory and functional rehabilitation will be considered potential participants. To be eligible for inclusion, participants must have been independent in their activities of daily living before the onset of critical illness (verbal statement by their proxy) and have to meet the safety criteria defined by the Portuguese Society of Physical Rehabilitation Medicine (26) namely:

- A. Assessment of respiratory system
 - i. Respiratory Rate equal to or less than 30 breaths/min
 - ii. Oxygen Saturation equal to or greater than 90%
 - iii. Inspired oxygen concentration less than or equal to 60%
 - iv. Positive end-expiratory pressure less than or equal to 10 cmH₂O
 - v. Absence of dyssynchrony between ventilator and patient
- B. Assessment of cardiovascular system
 - i. Systolic Blood Pressure between 90 and 180 mmHg
 - ii. Mean Arterial Pressure between 65 mmHg and 110 mmHg
 - iii. Blood Pressure variability less than 20%
 - iv. Heart rate between 40 and 120 beats per minute
 - v. Absence of arrhythmias or rhythm abnormalities de novo with impact on hemodynamic stability
 - vi. No new antiarrhythmic drugs in the last 24 hours
 - vii. No signs of recent acute coronary syndrome, particularly in the last 48 hours
 - viii. No continuous perfusion of vasopressors or no recent increase in the dose of vasopressors, namely in the last 2 hours

- ix. No continuous perfusion of vasodilators
 - x. No signs of shock accompanied by serum lactate greater than or equal to 4 mmol/L
 - xi. Absence of deep venous thrombosis or pulmonary thromboembolism in the last 24 hours and, in the presence of these entities, with anticoagulation instituted at least 24 hours ago
 - xii. Absence of severe aortic stenosis with impact on hemodynamic stability
- C. Assessment of neurological system
- i. Intracranial pressure less than 20 cmH₂O
 - ii. No need for increased sedation in the last 30 minutes
- D. Hematological and laboratory evaluation
- i. Stable hemoglobin level greater than 7 g/dL
 - ii. Platelet level above 20000 / mm³
- E. Other safety criteria:
- i. No need of prone position
 - ii. Absence of unstable limb or spine fracture
 - iii. No signs of hepatic or kidney failure
 - iv. No signs of active bleeding
 - v. Body temperature between 36 and 38.5 ° C

Potential participants will be excluded if they don't met the safety criteria. Further exclusion criteria are prior muscle weakness (such as a preexisting neurological or neuromuscular disease), prior pulmonary diseases that condition forced expiratory volume on 1 second (FEV₁) and/or Tiffeneau-Pinelli index (such as pulmonary obstructive disease or restrictive pulmonary diseases), acute thrombosis, contraindications to cycling (such as fractures or recent surgical procedures to the lower limbs, preexisting open wounds, and body weight of more than 120 kg) and patients with a diagnosis on admission that excludes the possibility of walking at hospital discharge.

Interventions

Both groups will receive usual medical and nursing care in the ICU, which involves assessment and treatment of the respiratory system and may include positioning, hyperinflation techniques and suctioning. The physical function of the patient is assessed, and active bed exercises and mobility are encouraged as soon as possible and may include sitting out of bed.

The intervention group will receive a functional and respiratory multidisciplinary rehabilitation protocol (that includes medical, nursing, physiotherapy and occupational therapy interventions) during their entire hospital stay.

After reassurance that the patients fulfil the safety criteria, they will initiate the rehabilitation protocol, individualized to each patient based on the clinical status. The rehabilitation interventions and exercises implemented will be consistent with recommendations from the Portuguese Society of Physical Rehabilitation Medicine (26).

The intervention will occur 6 days per week (Monday to Saturday), fifteen minutes, twice per day for each participant. Throughout all activities, progression will be increased successively, depending on the individual's tolerance and stability.

All adverse events will be noted, which includes any event that occurs during or up to fifteen minutes, after intervention, and persists despite therapy interruption and constitute criteria for discontinuing intervention.

After discharge, the intervention group will continue with rehabilitation exercises, prescribed by physical rehabilitation doctors. These exercises are designed for the patient to do at home, and then report their execution to rehabilitation nurses through teleconsultation, until 12 weeks after ICU discharge.

Outcomes

Baseline descriptive data collection will include age, sex, comorbidities and date of admission to ICU. The need of mechanical ventilation and length of use, as well as the need for oxygen therapy, length of ICU stay (days/hours), incidence of ICU readmission, discharge destination and survival will also be recorded.

Prior to intervention, participants will be evaluated using the following scales:

- oGlasgow Coma Scale (GCS) – it is based on motor responsiveness, verbal performance, and eye opening to appropriate stimuli, and was designed and should be used to assess the depth and duration coma and impaired consciousness (27).

- oRichmond Agitation Sedation Scale (RASS) - it is a commonly utilized and validated sedation assessment scale, that was designed to assess the level of alertness and agitated behavior in critically ill patients (28). It is a 10-point scale ranging from -5 to +4 (28). Levels -1 to -5 denote 5 levels of sedation, starting with “awakens to voice” and ending with “unarousable” (28) Levels +1 to +4 describe increasing levels of agitation (28). The lowest level of agitation starts with apprehension and anxiety, and peaks at combative and violent. RASS level 0 is “alert and calm” (28).

- oChelsea Critical Care Physical Assessment (CPAx) – it is a test used on patients in ICU to assess physical and respiratory function impairments and morbidity (29). It is a pictorial composite of 10 numerical evaluations of pertinent functions and impairments, namely, respiratory function, cough, moving within the bed, supine to sitting on the edge of the bed, dynamic sitting, standing balance, sit to stand, transferring from bed to chair, stepping, grip strength (29).
- o5 standardized questions for cooperation (S5Q) – it assesses patients' ability to cooperate, and it consists of five commands, and 1 point is attributed for each command that the patient is able to perform (30).
- oMedical Research Council sum score (MRC-SS) - it evaluates global muscle strength. Manual strength of six muscle groups (shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion) is evaluated on both sides using MRC scale (31). Summation of scores gives MRC-sum score, ranging from 0 to 60 (31).
- oHandgrip strength test – it uses a handgrip dynamometer to assess muscle strength (31).
- oMedical Research Council dyspnea scale (mMRC) – it is the test most frequently used in clinical practice to evaluate dyspnea (32). It summarizes the score of five offered statements about breath possibility during the daily activities, and patients choose the one which describes their problems in the best manner (32). It is easy to perform and correlates with clinical parameters and parameters of respiratory function (32).

Every two days and at discharge of intervention the following scales will be re-evaluated: GCS, RASS, CPAX, S5Q, MRC-SS, handgrip strength test, mMRC. At discharge, Borg Rating of Perceived Exertion (BRPE) will be evaluated. It is a widely used and reliable indicator to monitor and guide exercise intensity, that allows individuals to subjectively rate their level of exertion during exercise or exercise testing (33). MRC-SS, BRPE, handgrip strength test and mMRC will also be evaluated at 4-week and 12-week mark.

The primary outcome measure evaluated at discharge, as well as, in the follow-up at 4-week and 12-week mark, is functional capacity using the 6-Minute Walk Test (6MWT). The 6MWT is a practical and simple test that measures the distance a person can quickly walk on a flat, hard surface in 6 minutes (34). It is self-paced and submaximal and reflects the functional exercise level for daily physical activities (34).

The health related quality of life (HRQoL) will be evaluated at 12-week mark after discharge using 12-Item Short Form Survey (SF-12) (35, 36). It is a self-reported outcome measure assessing the impact of health on an individual's everyday life (35). It has eight

domains: limitations in physical activities because of health problems, limitations in social activities because of physical or emotional problems, limitations in usual role activities because of physical health problems, bodily pain, general mental health (psychological distress and well-being), limitations in usual role activities because of emotional problems, vitality (energy and fatigue) and general health perceptions (35).

The data will be collected by evaluators attached to the research group who have previously been instructed in the procedures to follow and do not know the group to which the patients belong.

The schedule for enrolment, data collection, intervention and outcome measures is described on table 1.

Data for the economic analysis

A cost-consequences economic evaluation will evaluate the effectiveness of the intervention compared to standard of care practice. Costs will be incurred at the patient level, in delivering the intervention. The cost of intervention refers to the resources applied to the implementation of the rehabilitation program to individual patient care. Variable resource use associated with the intervention (time spent, number of resources) will be recorded for each patient.

The economic impact related to the hospitalization of the analyzed patients was calculated based on the Case Mix Groups (CMGTM), according to the Portuguese health system guidance. The CMG system defines and identifies homogeneous groups of inpatient based on most responsible diagnosis and taking in consideration the age, length of stay, and health care resources.

Sample size

The sample size was estimated using the Winpepi® program (<http://www.brixtonhealth.com/pepi4windows.html>), with an estimated alfa risk of 5%, a power of 95%, a minimum expected difference of 10%, a rate of follow-up losses of 10%, a proportion in group B (standard of care) of 20% and proportion in group A (intervention) of 60%, for which 40 subjects are required in each group. We will include 80 patients who will be divided into two groups.

Recruitment, Randomization and Blinding

The participants will be recruited using the hospital computer system, after consultation of patient identification, confirmation of medical diagnosis (respiratory failure with a confirmed PCR test for SARS-CoV-2 positive), and current clinical condition by an assessor, who is going to evaluate patient's eligibility.

Reasons for nonrecruitment will be noted in a daily screening log. Eligible patients will be asked to participate. Written informed consent from the patient or their next of kin will be sought. If the next of kin provides initial consent, the participant will be asked to consent once they are able to do so. Trial participation will have no effect on routine management of their underlying condition or any other healthcare requirements. Participants have the right to withdraw from the trial at any given time. If unwilling to participate or withdrawing from the trial, patients will be excluded from the study and asked if the data that has already been collected may be retained.

Participants will be then divided into two groups, standard care and intervention, by means of balanced randomization at a 1:1 ratio using blocks of 10 participants. The randomization sequence is going to be created using a free software (<http://www.randomized.org/>). In order to ensure the confidentiality of the randomization sequence, this process will be conducted by an assessor external to the study.

The evaluators in the study will be blinded during the entire process. The evaluators will be unaware of the study objectives and the randomized distribution of patients to study groups and will not have access to the randomization sequence. Although blinding for patients will not be possible to achieve completely, subjects will be unaware of other treatment modalities, and they will not know if they belong to the intervention or standard group. As for the treating physiotherapists and ICU staff, blinding will not be possible to achieve, but they will not be responsible for assessing outcomes.

Participants' timeline

Table 1 – Schedule for enrolment, data collection, intervention and outcome measures.

Timepoint	Enrolment	Allocation	Post allocation			
			ICU stay (every 2 days)	Discharge	Follow-up (4 weeks)	Follow-up (12 weeks)
Eligibility screen	×					
Informed consent	×					
Clinical Evaluation and Inclusion-Exclusion criteria	×					
Demographic and diagnostic data		×		×		
Assessments:						
GCS		×	×	×		
RASS		×	×	×		
CPAx		×	×	×		
S5Q		×	×	×		
MRC-SS		×	×	×	×	×
Handgrip strength test		×	×	×	×	×
mMRC		×	×	×	×	×
BRPE				×	×	×
6MWT				×	×	×
SF12						×

GCS - Glasgow Coma Scale; RASS - Richmond Agitation Sedation Scale; CPAx - Chelsea Critical Care Physical Assessment; S5Q - 5 standardized questions for

cooperation; MRC – SS - Medical Research Council sum score; mMRC - Medical Research Council dyspnea scale; BRPE - Borg Rating of Perceived Exertion; 6MWT - 6-Minute Walk Test; SF-12- 12-Item Short Form Survey.

Statistical Analysis

The statistical analysis will be carried out through the SSPS®, version 25.0 (SSPS Inc., Chicago, IL, USA). Continuous variables will be expressed as mean and standard deviation or standard error, or as median and interquartile range. Categorical variables will be expressed as absolute and relative frequencies.

The Kolmogorov-Smirnov test will be used to evaluate the normal distribution of the continuous variables. We will analyze the hypothesis contrast inference by Student's t test for independent variables with parametric distributions and Mann-Whitney's U for non-parametric distributions. The confidence level used will be 95% (0,05), and the power of the study will be 90% (0,1). If the rate of loss to follow-up were observed greater than 15%, we will perform an intention-to-treat analysis. A sub-analysis will be carried out, depending on the age of the patients, sex, and clinical status.

Discussion

As of 31st January 2021, Portugal had 6869 hospitalized patients due to COVID-19, 865 of them in ICU, with increasing tendency (37). This number of ICU patients occupies 84% of the total 1021 ICU vacancies available in Portugal for all kinds of pathologies. This situation represents a huge burden on the national health system and also raises public health concerns, as care in the ICU is usually intense due to the serious medical conditions themselves, such as the use of life-sustaining equipment, sedatives, pain and other medications that have mind-altering effects, and this exposure to stressors impacts several aspects of the patient (14). The prevention and reduction of PICS is a health problem with growing relevance in this context.

This article presents a detailed description of a randomized controlled trial designed to analyze the results of the implementation of a respiratory and functional rehabilitation program, applied in patients affected by COVID-19 hospitalized in ICU. This trial has the strength of having a pragmatic design of early initiation of a rehabilitation protocol that allows the prospective inclusion of patients, and also the follow-up of participants up to 12 weeks after discharge. The implementation of the protocol, if it proves superior to standard care, in the daily routine of the ICU will be simple, and it could constitute the foundation for the development of new treatment guidelines. Limitations of this study are the intervention being performed only in one center and the impossibility of blinding the ICU staff, nonetheless the assessors responsible for randomization and outcome measures will be completely blinded to group allocation. The treating professionals have been given formation about the possible adverse events that can happen during the intervention and the importance of reporting them.

We expect the intervention group to achieve better functional and respiratory outcomes, less days of hospitalization and an improvement in health related quality of life, comparing to the standard of care group. The results will be communicated to the Portuguese health authorities internally and to other relevant groups through publications in medical journals.

Trial status

This is the second and definitive protocol version. Participants will be recruited between March 8, 2021, and June 8, 2021. Study completion is expected to be October 2021. The study protocol has been submitted before the end of the recruitment and before the last patient.

Abbreviations

SARS-CoV - severe acute respiratory syndrome-related coronavirus

SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2

WHO - World Health Organization

COVID – 19 - coronavirus disease 2019

ARDS - acute respiratory distress syndrome

DIC - disseminated intravascular coagulopathy

ICU - intensive care unit

PICS - post-intensive care syndrome

ICU – AW - Intensive care unit-acquired weakness

GCS - Glasgow Coma Scale

RASS - Richmond Agitation Sedation Scale

CPAx - Chelsea Critical Care Physical Assessment

S5Q - 5 standardized questions for cooperation

MRC - Medical Research Council

MRC – SS - Medical Research Council sum score

mMRC - Medical Research Council dyspnea scale

BRPE - Borg Rating of Perceived Exertion

6MWT - 6-Minute Walk Test

HRQoL - The health related quality of life

SF-12- 12-Item Short Form Survey

CMG - Case Mix Groups

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Not applicable.

Authors' contributions

All the procedures for recruiting, intervening, and evaluating the participants are carried out by personnel attached to this group. ACC is the principal investigator and has contributed to the concept and study design, provided clinical expertise and contributed to the manuscript development. JM, PC, PCA and CAB contributed to the protocol development and provided clinical expertise. BG contributed to the protocol development,

provided clinical expertise and he is responsible for designing the statistical procedures. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request. The data will be available after the main publication of them; for other circumstances, they should consult the corresponding author. Any data required to support the protocol can be supplied on request.

Ethics approval and consent to participate

This study complies with the Helsinki guidelines for human research, and it has been approved by the Commission of Ethics for Health of Centro Hospitalar Entre Douro e Vouga, reference CA-081/2021-0t_MP/CC. All study participants signed an informed consent approved by the ethics committee. The identification of each individual will remain concealed based on the ethical principles of confidentiality and privacy. Any reason for compensation will be covered by professional liability insurance. Informed consent is available in the portuguese language from the corresponding author on request. There is no anticipated harm and compensation for trial participation.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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CHAPTER IV

PAPER II



Multidisciplinary rehabilitation in intensive care for COVID-19: randomised controlled trial

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Shareable abstract (@ERSpublications)

This study analysed the respiratory and functional effects of a multidisciplinary rehabilitation programme in #COVID19 intensive care patients, and obtained encouraging results on its beneficial outcomes and future implementation <https://bit.ly/3BQTJZ9>

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Abstract

Coronavirus disease 2019 (COVID-19) has led to an increasing number of patients in intensive care units (ICUs). The size of this post-ICU cohort will be unprecedented, with many patients vulnerable to post-intensive care syndrome. We analysed the respiratory and functional effects of a multidisciplinary rehabilitation programme on functional performance, in patients hospitalised in the ICU due to COVID-19. We conducted a randomised controlled clinical trial. 96 patients who fulfilled the eligibility criteria were randomised into control or intervention group. The control group received standard of care in the ICU, and the intervention group received a functional and respiratory rehabilitation protocol that included medical, nursing, physiotherapy and occupational therapy interventions.

At discharge, the intervention group showed significantly better muscular strength and respiratory capacity, and significantly fewer days of hospitalisation (12.90 ± 5.8 versus 15.60 ± 6.7 days, $p=0.037$). At the 4- and 12-week follow-up, we applied our main outcome measure, the 6-min walk test (6MWT). The intervention group had significantly better results than the control group on the 6MWT at the 4-week follow-up (604 ± 67 versus 571 ± 57 m, $p=0.018$) and at the 12-week follow-up (639 ± 53 versus 611 ± 67 m, $p=0.025$).

These results support the role of a multidisciplinary rehabilitation programme in COVID-19 patients hospitalised in the ICU and adds evidence that the implementation of rehabilitation programmes in ICUs could result in beneficial outcomes for critically ill patients.

Introduction

Coronavirus disease 2019 (COVID-19) is a highly infectious disease, caused by the severe acute respiratory syndrome coronavirus 2, which leads to respiratory, physical and psychological dysfunction in patients [1]. The most common symptoms of COVID-19 are fever and cough [2, 3]. Additional symptoms include weakness, dyspnoea, fatigue, nausea, vomiting, diarrhoea and changes to taste and smell [2, 3]. Approximately 80–90% of cases are mild and self-limited, primarily affecting the upper airway with limited involvement of the lungs [2, 3]. The remaining 10–20% will need medical care, and 5% will require admission to the intensive care unit (ICU) and be exposed to the post-intensive care syndrome (PICS) [2, 3].

PICS refers to the disability that persists in patients who survive critical illness; it is the result of a combination of factors related to the intense care in the ICU [4, 5]. PICS is recognised as a growing public health burden due to the associated neuropsychological and functional disability, and the evidence suggests



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that the prevention of ICU admission is more important and effective than intensive treatment of PCIS following ICU discharge [4, 6].

Nowadays, functional and respiratory rehabilitation is increasingly implemented in critically ill patients to prevent or improve pulmonary function [7]. Although there is still no consensus in the literature about the beneficial effects of rehabilitation on PCIS, with some studies showing beneficial effects [8–10], and others showing no relevant effects [11, 12], there is a growing body of evidence that respiratory muscular retraining and early mobilisation are a feasible and safe strategy to improve muscular and functional capacities in critically ill patients [7, 13].

Despite the potential of rehabilitation in ICU, it is difficult to test this complex intervention [14]. However, facing the COVID-19 pandemic and estimating the size of the post-ICU cohort associated with this disease, several authors recommended the implementation of a rehabilitation programme to improve these patients' outcomes, and the study by *Stutz et al.* [15] highlighted the feasibility of early rehabilitation for critically ill patients with COVID-19 [16–20].

The objective of the study presented herein is to analyse the respiratory and functional effects of a rehabilitation programme on functional performance, in patients affected by COVID-19 hospitalised in the ICU, in comparison with a group subjected to standard of care, at discharge end-point and at 4- and 12-week follow-up.

Material and methods

Study design

A randomised, controlled, double-arm clinical trial was conducted in the tertiary, interdisciplinary ICU of Centro Hospitalar Entre Douro e Vouga, Portugal. Ethical approval for this study was provided by the ethical committee of Centro Hospitalar de Entre o Douro e Vouga. This trial is registered with the Brazilian Clinical Trials Registry (identifier RBR-7rvhpq9), and was performed in accordance with the Consolidated Standards of Reporting Trials guidelines.

The participants were divided into two groups (standard care (control) and intervention), by means of balanced randomisation at a 1:1 ratio using free software (www.random.org). Physiotherapists, occupational therapists and rehabilitation nurses other than those who provided usual care performed the trial intervention across the trial continuum. The rehabilitation physicians working in the ICU were not blinded, but the outcome assessor was blinded to group allocation. The complete blinding of the patients was not possible, but they were not aware of other treatment modalities.

Both groups received usual medical and nursing care in the ICU, which involved assessment and treatment of the respiratory system, and active bed exercises and mobility were encouraged as soon as possible. The intervention group received a functional and respiratory multidisciplinary rehabilitation programme (which included medical, nursing, physiotherapy and occupational therapy interventions) during their entire hospital stay, starting within the first 24 h from ICU admission, 15–30 min per session, twice per day, 6 days per week. It was individualised to each patient based on their clinical status and consistent with recommendations from the Portuguese Society of Physical and Rehabilitation Medicine [20]. Progression was increased successively, depending on the individual's tolerance and stability. After discharge from the ICU, the intervention group continued with rehabilitation exercises, prescribed by rehabilitation physicians, which they performed, unattended, whether the patient was discharged home or to an inpatient unit, until 12 weeks after ICU discharge. They reported their execution to the medical team and rehabilitation nurses through teleconsultation. The control group did not receive any further rehabilitation intervention after hospital discharge.

Study subjects

Participants were adult patients (aged ≥ 18 years) with respiratory insufficiency due to COVID-19 hospitalised at the ICU of the Centro Hospitalar Entre Douro e Vouga, who were referred for respiratory and functional rehabilitation by the ICU medical team at this tertiary hospital. Written informed consent was obtained from participants or their authorised representatives.

The inclusion criteria were 1) independent in activities of daily living before the onset of critical illness; 2) fulfil the safety criteria defined by the Portuguese Society of Physical and Rehabilitation Medicine [20], which included a score of ≥ -2 or higher in the Richmond Agitation–Sedation Scale, designed to assess the level of alertness and agitated behaviour in critically ill patients [21]. Patients were excluded if they did not meet these safety criteria. Other exclusion criteria included 1) prior muscle weakness (such as a

pre-existing neurological or neuromuscular disease); 2) prior pulmonary disease affecting forced expiratory volume in 1 s (FEV₁) and/or Tiffeneau–Pinelli index; 3) acute thrombosis; 4) diagnosis on admission that excludes the possibility of walking at hospital discharge; 5) patients transferred from other hospitals.

Assessment

At admission, baseline descriptive data were collected, which included age, sex, body mass, body mass index, smoking status and comorbidities. Other descriptive data, such as the need and length of invasive mechanical ventilation and length of ICU stay (days) were also collected at discharge from the ICU.

Prior to intervention and at discharge participants were evaluated using the following scales: Chelsea Critical Care Physical Assessment tool (CPAx), Medical Research Council sum-score (MRC-SS), handgrip strength test (HST). CPAX is a pictorial composite of 10 numerical evaluations of pertinent functions and impairments used to assess physical and respiratory function impairments and morbidity [22]. MRC-SS evaluates the manual strength of six muscle groups bilaterally [23]. HST uses a handgrip dynamometer to assess muscle strength [23]. At discharge, the Medical Research Council dyspnoea scale (mMRC) was evaluated. mMRC summarises the score of five offered statements about breath possibility during daily activities [24].

The primary outcome measure was functional capacity, evaluated at the 4-week and 12-week marks, using the 6-min walk test (6MWT), which is a practical and simple test that measures the distance a person can quickly walk on a flat, hard surface in 6 min, reflecting the functional exercise level for daily physical activities [25].

The secondary outcome measures included Borg Rating of Perceived Exertion (BRPE), evaluated at the 4-week and 12-week marks, MRC-SS and HST. BRPE is a widely used and reliable indicator to monitor and guide exercise intensity, which allows individuals to subjectively rate their level of exertion during exercise or exercise testing [26]. The option to evaluate 6MWT and BRPE was due to the expected difficulty for patients to perform 6MWT at ICU discharge, as reported by AL CHIKHANIE *et al.* [27].

Statistical analysis

The sample size was estimated using the Winpepi programme with an estimated α risk of 5%, power of 85%, pooled variance of 20%, for which 40 subjects were required in each group. Considering a rate of follow-up losses of 15%, we included 96 patients. We used SSPS (version 27.0; SSPS, Chicago, IL, USA), for all statistical analyses. Categorical variables were expressed as absolute and relative frequencies. Continuous variables were expressed as mean $\pm$ SD. We used the Chi-squared test or Fisher exact test (as appropriate) to compare categorical variables between the two study groups, including the primary end-point, and the t-test to compare continuous variables. Significant differences between groups or across time were reported at $\alpha=0.05$. All reported p-values are two-sided.

Results

Characteristics of participants

96 patients fulfilled the eligibility and inclusion criteria and were enrolled in this study. They were randomly allocated to the intervention group (48 patients) and the standard of care (control) group (48 patients). There were no losses to follow-up (figure 1). Both groups were constituted mainly of females, and the mean age was 68.31 years in the control group and 66.63 years in the intervention group. The demographic and clinical characteristics of participants are presented in table 1.

Functional status at admission and discharge evaluation

The values are presented in table 2. There were no statistically significant differences between the two groups in all the scales used. The percentage of patients who needed invasive mechanical ventilation (with sedation) is presented in table 2. The other patients received oxygen support through noninvasive ventilation, such as noninvasive positive pressure ventilation and high-flow nasal cannula oxygen therapy. The intervention group showed shorter length of stay in ICU and those patients who needed mechanical ventilation had a significantly shorter length of use. Additionally, the intervention group showed a statistically significant better functional status in the MRC-SS, HST and mMRC.

4-week and 12-week follow-up evaluations

The intervention group showed better functional performance in the 6MWT, BRPE and MRC-SS, on both 4-week and 12-week follow-up evaluations, as shown in table 2. No differences were found between the two groups regarding HST.

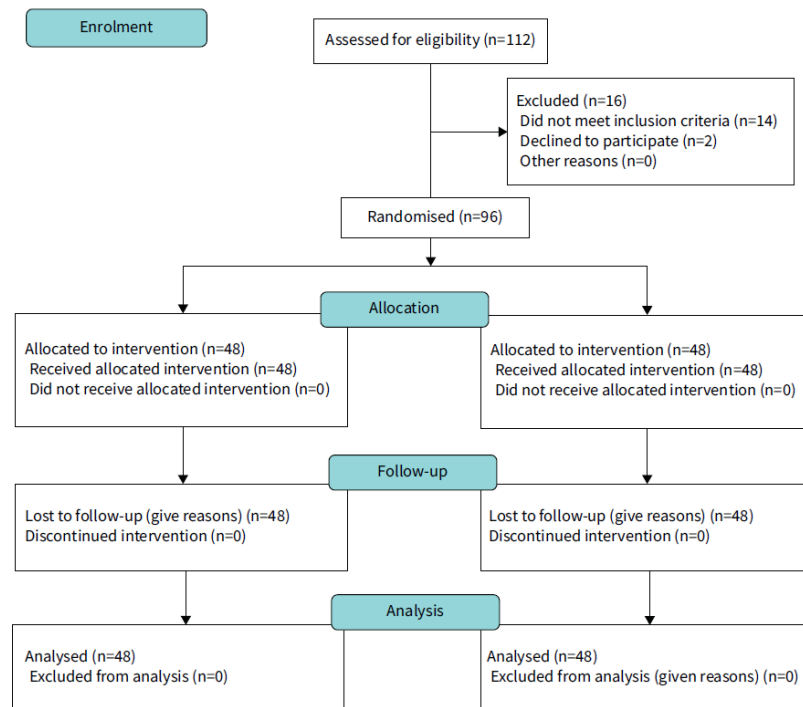


FIGURE 1 Participant flow through the trial.

TABLE 1 Demographic and clinical characteristics of the patients

	Control group	Intervention group	p-value
Patients	48	48	
Female	27 (56.25)	28 (58.33)	0.840
Age years	68.31±12.47	66.63±14.21	0.540
Body mass kg	76.34±8.76	77.49±11.01	0.570
BMI kg·m ⁻²	28.04±3.22	29.17±4.14	0.130
Smokers			
Regular smokers	9 (18.75)	11 (22.91)	0.615
Previous smokers	12 (25.00)	8 (16.67)	0.314
Cormobidities			
Heart failure	6 (12.50)	3 (6.25)	0.293
Hypertension	7 (14.58)	9 (18.75)	0.583
Arrhythmia	2 (4.17)	4 (8.33)	0.399
Myocardial infarction	3 (6.25)	1 (2.08)	0.307
Diabetes	5 (10.41)	3 (6.25)	0.460
Dyslipidaemia	2 (4.17)	3 (6.25)	0.645
Stroke	2 (4.17)	4 (8.33)	0.399
Thyroid disease	1 (2.08)	1 (2.08)	>0.999
Kidney disease	1 (2.08)	3 (6.25)	0.307
Malignancy	8 (16.67)	11 (22.91)	0.442

Data are presented as n, n (%) or mean±sd, unless otherwise stated. BMI: body mass index.

TABLE 2 Clinical evaluations and group comparisons

	Admission			ICU discharge			4-week follow-up			12-week follow-up		
	Control group	Intervention group	p-value	Control group	Intervention group	p-value	Control group	Intervention group	p-value	Control group	Intervention group	p-value
CPAx score 0–60	33.16±9.77	31.33±8.42	0.330	44.02±4.64	41.27±6.07	0.014						
ICU LOS days				15.60±6.70	12.90±5.8	0.037						
Need of IMV during ICU stay				23 (47.92)	21 (43.75)	0.682						
Length of use of IMV days				6.1±4.2	4.1±3.6	0.037						
MRC-SS score 0–60	47.2±7.1	46.7±6.8	0.730	52.1±4.1	54.4±3.7	0.005	57.9±2.3	58.9±1.1	0.008	59.4±0.7	59.6±0.3	0.007
HST kg	14.1±5.6	12.7±7.3	0.290	21.2±4.3	23.3±5.1	0.032	25.9±5.1	27.1±4.4	0.220	26.6±4.9	27.4±4.2	0.393
mMRC						0.031						
mMRC ≤1				16 (33.3)	7 (14.6)							
mMRC ≥2				32 (66.7)	41 (85.4)							
BRPE score 6–20							12.5±1.8	11.7±2.1	0.048	11.9±1.1	11.3±1.6	0.035
6MWT m							571±57	604±67	0.018	611±67	639±53	0.025

Data are presented as mean±s.d. or n (%), unless otherwise stated. ICU: intensive care unit; CPAX: Chelsea Critical Care Physical Assessment; LOS: length of stay; IMV: invasive mechanical ventilation; MRC-SS: Medical Research Council sum-score; HST: handgrip strength test; mMRC: modified Medical Research Council dyspnoea score; BRPE: Borg Rating of Perceived Exertion; 6MWT: 6-min walk test.

Discussion

The results of our study showed that the group of patients who received a multidisciplinary rehabilitation programme had a significant better functional and respiratory performance than the control group. During the COVID-19 pandemic, we observed that ICUs became overwhelmed in many countries, and this fact raised the need to optimise ICU treatment in terms of length and patient outcome [18, 28]. Some studies have already been conducted to study the influence of rehabilitation in COVID-19 patients [15, 19, 27, 29–32], but to our knowledge, this is the first randomised controlled trial to analyse the impact of the implementation of a rehabilitation programme in COVID-19 patients hospitalised in the ICU.

The main outcome of this study, at the 4-week and 12-week assessments, was the 6MWT. The intervention group showed significantly better results than the control group, both on the 4- and 12-week follow-up assessment. These results are in line with the previous data from LIU *et al.* [17], who reported a significant improvement in 6-min walk distance after 6 weeks of respiratory rehabilitation; those from SCHINDLER *et al.* [32], who reported an improvement in 6MWT performance after rehabilitation; and those from AL CHIKHANIE *et al.* [27], who reported a significantly better performance on the 6MWT of post-ICU COVID-19 patients who performed a rehabilitation programme, compared to post-ICU non-COVID-19 patients who did not undertake any rehabilitation programme. The difference in 6MWT values in the two groups was >30 m, which, according to the study by BOHANNON *et al.* [33], reflects the minimum clinically important difference value for most diseases. These findings suggest that the rehabilitation programme implemented improves functional and respiratory capacity, supported by the fact that at the 4-week follow-up, the intervention group showed significantly lower levels of perceived exertion in the BRPE scale applied after the 6MWT, and the difference between the groups was clinically important (0.8) [34]. BRPE is a widely used and reliable indicator to monitor and guide exercise intensity, which allows individuals to subjectively rate their level of exertion during exercise or exercise testing [26]. Both groups showed better values at the 12-week evaluation than the 4-week evaluation, which is similar to the results reported by DENEHY *et al.* [11], and suggests that changes in functional capacity tend to improve over time, but the rehabilitation programme seems to enhance the recovery time.

In addition, the groups showed significantly different performances on the other secondary outcome measures. In fact, the intervention group showed larger improvements in different assessments compared to the control group. Similar results were observed in the studies by HERMANS *et al.* [23] and DANTAS *et al.* [35], which showed that early rehabilitation interventions (mobilisation and stimulation of activities) in critically ill intensive care patients could influence or even prevent physical impairments. Moreover, this specific difference in the MRC-SS values was also found in the study KAYAMBU *et al.* [36], which analysed the effects of rehabilitation in ICU patients with other medical conditions (not COVID-19). Furthermore, the intervention group had significantly better performances on the mMRC than the control group. The mMRC is moderately correlated with the functional assessments of patients' cardiopulmonary fitness, including FEV₁, being therefore an indirect indicator of respiratory function [24]. Considering the results of the study by LIU *et al.* [17], who conducted a randomised controlled trial to investigate the effects of 6-week respiratory rehabilitation training in elderly patients with COVID-19, in which the intervention group had a significantly better respiratory function (evaluated using FEV₁), and the results from our study, the mMRC might be considered a good indicator of improvement in respiratory function.

There were no significant differences between the two groups in the HST, similar to the results reported by SCHWEICKERT *et al.* [9] and MORRIS *et al.* [10]; therefore, this indicator might not be a reliable measure to evaluate the outcomes of rehabilitation programmes in the ICU setting.

Rehabilitation had an impact on the length of ICU stay, as the intervention group had a significantly shorter length of stay in the ICU, which is in line with findings from IANNACCONE *et al.* [37], who implemented specialised COVID-19 rehabilitation units, with decrease of the hospitalisation in acute COVID-19 patients from 15 days to 10 days. MORRIS *et al.* [38] also reported shorter stay in the ICU in patients that received early mobility. The percentage of patients who needed invasive mechanical ventilation is in line with that reported by WANG *et al.* [39]. Both intervention group and control group presented relatively short mean times of invasive mechanical ventilation, that were probably affected by the inclusion and exclusion criteria, namely the exclusion of patients with previous respiratory diseases. The intervention group needed invasive mechanical ventilation for a shorter period than the control group, which may reflect the impact of the rehabilitation programme on respiratory function and is similar to the results found by SCHWEICKERT *et al.* [9], who reported more ventilator-free days in the group that received a rehabilitation intervention.

Limitations

This study shows beneficial results regarding the effects of a rehabilitation programme on ICU patients, but these must be interpreted in the light of certain limitations. This clinical trial was performed in one centre only. The application of this protocol to a multicentre population might increase the significance of these results. The blinding of the multidisciplinary treatment team was not possible because they needed the knowledge of the group allocation in order to be able to provide the patient the correct intervention. Nonetheless, the assessors responsible for randomisation and outcome measures were completely blinded to group allocation. It was not possible to achieve complete blinding for patients, but subjects were unaware of other treatment modalities, and they did not know if they belonged to the intervention or standard group. Therefore, we cannot completely rule out placebo effects or experimenter bias in the current study.

Future directions

This study strongly indicates that the multidisciplinary rehabilitation programme in the ICU has beneficial outcomes for the patients. Unfortunately, not all ICU units have multidisciplinary professionals, namely rehabilitation physicians, physiotherapists and rehabilitation nurses, available to integrate this kind of programme into the ICU daily routine. However, there is growing evidence that rehabilitation in the ICU can play a major role in patient recovery, thus leading to fewer days of hospitalisation and better outcomes. In this sense, cost-effectiveness studies should be conducted to evaluate the possible benefits associated with the inclusion of these professionals in ICU multidisciplinary teams.

In conclusion, this randomised clinical trial presents beneficial results of a multidisciplinary rehabilitation programme in COVID-19 patients hospitalised in the ICU and adds evidence that the implementation of rehabilitation programmes in the ICU could result in beneficial outcomes for critically ill patients.

This study is registered at <https://ensaiosclinicos.gov.br/> with identifier number RBR-7rvhpq9. Individual participant data that underlie the results reported in this article, after deidentification, will be available, beginning 9 months and ending 36 months after article publication, to anyone who wishes to access the data for any purpose. The study protocol will also be available. Proposals should be directed to cristinapbcarvalho@gmail.com.

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CHAPTER V

PAPER III

The impact of a multidisciplinary rehabilitation program in quality of life and mental health in critical COVID-19 patients – randomized controlled trial

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Abstract

Objective: The coronavirus disease 2019 (COVID-19) has infected more than 100 million people and was responsible for an unprecedented number of patients in the intensive care units (ICU), since about one-fifth of the patients required intensive treatment. We analysed the effects of a rehabilitation program on quality of life and mental health in patients affected by the COVID-19 hospitalized in ICU.

Patients and Methods: A randomized controlled clinical trial was conducted to analyze the effects of a multidisciplinary rehabilitation program on quality of life and mental health in patients affected by the COVID-19 hospitalized in ICU, in comparison with the group subjected to standard of care. Ninety-six patients, who fulfilled the eligible criteria, were randomized into control or intervention group. The control group received standard of care in the ICU, and the intervention group received a functional and respiratory rehabilitation protocol, that included medical, nursing, physiotherapy, and occupational therapy interventions.

Results: In the 12-Item Short-Form Health Survey was verified that the intervention group had better results in the mental component (48.1 ± 9.0 vs. 44.2 ± 10.3 , $p=0.048$) summary measure at 12-week after discharge, but no significant differences were found in the physical component summary measure. The intervention also presented lower prevalence of abnormal values in the Hospital Anxiety and Depression Scale (60.4 vs 37.5%, $\chi^2 = 5.044$, $p=0.024$) at 4-week after discharge.

Conclusion: These results suggest that the implementation of a multidisciplinary rehabilitation program in COVID-19 patients hospitalized in ICU impacts positively their quality of life and mental health.

Keywords: COVID-19, functional rehabilitation, post-intensive care syndrome, respiratory rehabilitation, quality of life, mental health.

This trial is registered with Brazilian Clinical Trials Registry.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the coronavirus disease 2019 (COVID-19) and more than 770 million cases of this disease have been reported [1-3]. COVID-19 severity might vary greatly, from mild disease without evidence of viral pneumonia or hypoxia, to critical disease, with complications such as of respiratory failure, acute respiratory distress syndrome, thromboembolism, sepsis, and/or multiorgan failure [4, 5]. The critical disease occurs in 5–10% of the patients, and they will need ICU admission and, therefore, being subject to increased risk of mortality and morbidity, including post-intensive care syndrome (PICS) [4-6].

It is well recognized that people who recover from serious illness have an increased risk for new or worsening depression, anxiety, post-traumatic stress disorder (PTSD), and cognitive and physical impairment, known collectively as PICS [7, 8]. In fact, the study by Hatch et al. [9] found that approximately half of the patients treated in the ICU showed symptoms of anxiety, depression or PTSD at 3- or 12-months following ICU discharge. The effects of PICS can be long-lasting and account for significant physical, mental, and financial stress on patients, their families, and even society [7, 8, 10]. PICS is recognized as a growing public health burden due to the associated neuropsychological and functional disability [11].

COVID-19 ICU survivors have an experience unique comparing to pre-COVID-19 ICU survivors [12, 13]. Due to the contagious nature of SARS-CoV-2, many of them were isolated from their loved ones, had little contact with medical professionals, and received care in facilities that were overworked and underfunded [12]. Some authors hypothesized COVID-19 ICU survivors may have PICS at higher rates than pre-COVID-19 ICU populations due to their social isolation [12, 13].

Lew et al. [14] claimed that COVID-19 complications could be attenuated by offering interdisciplinary rehabilitation that starts early and continues throughout the hospital stay, educating patients/families on self-care after leaving hospital rehabilitation in acute or subacute wards, and providing ongoing rehabilitation care in outpatient and home settings through either in-person therapy or telehealth. Some studies already conducted in COVID-19 patients to evaluate the effects of rehabilitation in ICU have shown encouraging results regarding physical and respiratory function [15, 16]. In fact, in a previous report, we have found that patients submitted to a multidisciplinary rehabilitation program had significant better functional and respiratory performance than the group that received standard of care [16].

However, there is still little evidence about the role rehabilitation programs may play in the mental domain problems derived from PICS and in the quality of life. The studies by Brummel et al. [17] and Morris et al. [18] found no significant effect of rehabilitation on health-related quality of life (HRQoL). On the other hand, the study by Kayambu et al. [19] showed beneficial results of rehabilitation in the domains related to physical function of Item Short-Form Health Survey (SF-36). The study by Jones et al. [20] found significant lower levels of anxiety and depression in ICU patients that received a structured exercise program.

The objective of the presented study is to analyze the effects of a rehabilitation program on quality of life and mental health in patients affected by the COVID-19 hospitalized in ICU, in comparison with the group subjected to standard of care.

Patients and Methods

We conducted a randomized, controlled, double-arm clinical trial in a tertiary and interdisciplinary ICU. Ethical Committee of the hospital approved this study. This trial is registered with Brazilian Clinical Trials Registry, and was performed in accordance with the CONSORT guidelines.

Study population

Participants ≥ 18 years old hospitalized at ICU, who due to COVID-19 were referred to respiratory and functional rehabilitation by the ICU's medical team of this tertiary hospital, were enrolled. Written informed consent was obtained from participants or their authorized representatives. The inclusion criteria were: (1) independent in their activities of daily living before the onset of critical illness; (2) fulfil the safety criteria defined by the Portuguese Society of Physical Rehabilitation Medicine [21]. Patients were excluded if they did not meet these safety criteria. Other exclusion criteria: (1) prior muscle weakness, (2) prior pulmonary diseases that condition forced expiratory volume on 1 second (FEV1) and/or Tiffeneau-Pinelli index, (3) acute thrombosis, (4) patients with a diagnosis on admission that excludes the possibility of walking at hospital discharge, (5) patients transferred from other hospitals.

We estimated a sample size of 40 subjects in each group, since we considered an alfa risk of 5%, a power of 85%, a pooled variance of 20% and detect differences of 30%. Accounting for possible losses in follow-up, 112 patients were assessed for eligibility and 96 were randomized into intervention group (IG) and standard of care group (CG). The randomization was at 1:1 ratio, using a free software (www.randomization.com).

At admission, baseline descriptive data was collected, which included age, sex, body mass, body mass index (BMI), smoking status and comorbidities (heart failure, hypertension, arrhythmia, myocardial infarction, diabetes mellitus, dyslipidemia, stroke, thyroid disease, kidney disease, malignancy). Other data, such as the need and length of invasive mechanical ventilation, length of ICU stay (days) was also collected from clinical records, at discharge from ICU.

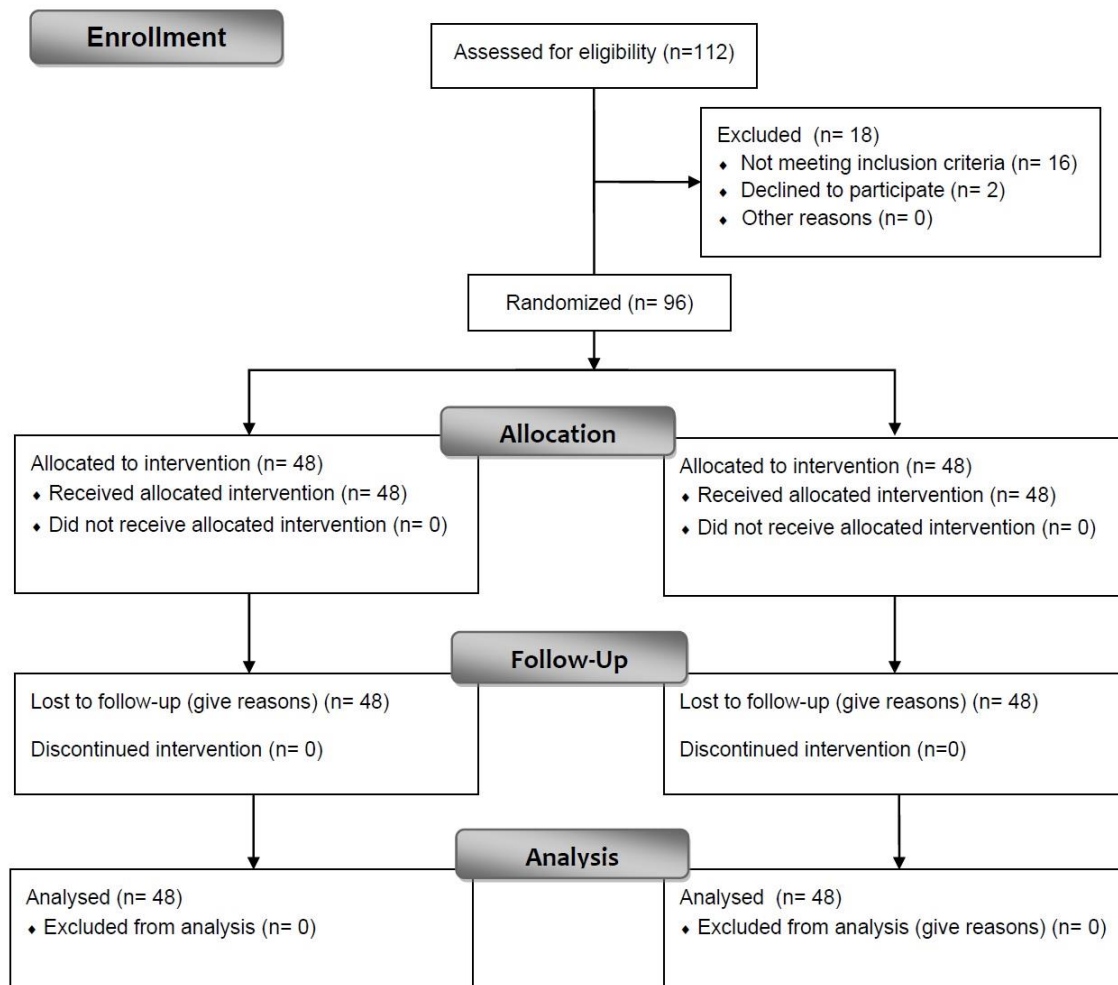


Figure 1- Participant flow through the trial.

ICU rehabilitation program

Physiotherapists, occupational therapists, and rehabilitation nurses other than those who provided usual care performed the trial intervention across the trial continuum. The rehabilitation physicians working in the ICU were not blinded, but the outcome assessor was blinded to group allocation. The complete blinding of the patients was not possible to achieve, but they were not aware of other treatment modalities.

Both groups received usual medical and nursing care in the ICU, which involved assessment and treatment of the respiratory system, and active bed exercises and mobility were encouraged as soon as possible. The IG received a functional and respiratory multidisciplinary rehabilitation program (that included medical, nursing, physiotherapy and occupational therapy interventions) during their entire hospital stay, starting within the first 24 hours from ICU admission, six days per week, 15-30 minutes per session, twice per day. It was individualized to each patient based on the clinical status and consistent with recommendations from the Portuguese Society of Physical Rehabilitation Medicine. Progression was increased successively, depending on the individual's tolerance and stability. After discharge from the ICU, the IG continued with rehabilitation exercises, prescribed by rehabilitation physicians, whether the patient was discharged home or to an inpatient unit, until 12 weeks after ICU discharge. They reported their execution to the medical team and rehabilitation nurses through teleconsultation, twice a week. The CG did not receive any further rehabilitation intervention after hospital discharge.

Outcome measures

The primary outcome measure was self-reported health-related quality of life, measured by 12- Item Short-Form Health Survey (SF-12) at 12-week mark. The SF-36 and its shorter version, the SF-12, are the measures most frequently used to assess HRQoL, and have been translated into more than 140 languages [22]. When the original SF-36 was deemed to be too lengthy and burdensome for respondents, the SF-12 Health Survey

was created as a more compact substitute [23]. Particularly in large-scale research focusing on physical and mental health assessments, the SF-12 maintains the comprehensiveness of the content and psychometric effectiveness [23, 24]. SF-36 was validated in the Portuguese language by Ferreira [25, 26]. Since the SF-12 covers the same 8 health domains as the SF-36 and has a strong correlation with SF-36 summary scores, it offers an accurate representation of these [24].

The secondary outcome measure was psychological outcome using the Hospital Anxiety and Depression Scale (HADS). HADS is a 14-item self-assessment questionnaire that includes a seven-item subscale for anxiety and a seven-item subscale for depression that are each scored on a four-point scale [27]. The two subscales of the HADS are trustworthy indicators of the severity of the emotional disease and can be used to diagnose states of depression and anxiety [28]. The HADS has demonstrated its validity in many acute settings in hospital including the aftermath of a critical illness [9, 29, 30]. The cut-off score >7 was used for each subscale for detecting symptoms of anxiety or depression. Some specifications of the SF-12 and HADS are presented in Table 1.

	Short-Form 12 Health Survey	The Hospital Anxiety and Depression Scale
Type of measure	Generic Self-administered	Generic Self-administered
Author	Ware et al., 1996 [17]	Zigmond and Snaith [27]
Construction	Entirely derived from SF-36	Original
Nº of items	12	14
Nº of subscales	8 (+2 summary scores)	2
Symptoms time frame	Symptoms presented for the last 4 weeks	Symptoms presented for the last week

Subscales/domains	Physical Function; Role Physical; Bodily Pain; General Health; Vitality; Social Function; Role Emotion; Mental Health; Summary measures physical and mental component summary measures (PCS-12 and MCS- 12)	Anxiety and depression
Psychometric properties	TRR: PCS $r = 0.89$; MCS $r = 0.76$ (US sample) [17]; cross-validation: PCS-36 and PCS-12 correlated 0.95; MCS-36 and the MCS-12 correlated 0.97 [16]	TRR: Anxiety $r = 0.75$; Depression $r = 0.75$; The two subscales correlated 0.58 [28].
Scoring and interpretation	Items scored on a 100-point scale – higher score meaning better HRQoL; overall information is computed using specific algorithms to derive the 8 health domains and the summary scores PCS-12 and MCS-12	Items scored on a 21-point scale – higher score meaning a higher level of depression/anxiety.

Table 1 - Specifications of the outcome measures used in the study. PCS-12, Physical component summary measure; MCS-12, Mental component summary measure; TRR, test-retest reliability; HRQoL, Health-related quality of life.

Statistical Analysis

We used SPSS®, version 27.0 (SPSS Inc., Chicago, IL, USA), for all statistical analysis. Categorical variables were expressed as absolute and relative frequencies. Continuous variables were expressed as mean and standard deviation. We used the chi-square test) to compare categorical variables between the two study groups. Independent t-test was used to compare continuous variables. In order to allow for comparisons with other studies, some categorical variables were presented as proportion and confidence interval. Significant differences between groups were reported at the alpha level of 0,05 and reported p-values are two-sided.

Results

Characteristics of participants

Ninety-six patients fulfilled the eligibility and inclusion criteria and were randomly allocated in the intervention group (48 patients) and in the standard of care group (48 patients) (figure 1). Both groups were constituted mainly by females (58.3% in IG and 56.3% in CG). The mean age was 68.3 years old in the CG and 66.6 years old in the IG. The IG showed shorter length of stay in ICU [16]. The demographic and clinical characteristics of participants are detailed in table 2.

	CG (N=48)	IG (N=48)	P-value
Female Sex, N (%)	27 (56.3)	28 (58.3)	0.840
Age in years, mean (SD)	68.3 (12.5)	66.6 (14.2)	0.540
Body mass in kg, mean (SD)	76.3 (8.8)	77.5 (11.0)	0.570
BMI in kg/m², mean (SD)	28.0 (3.2)	29.2 (4.1)	0.130
Smokers, N (%)			
Regular Smokers	9 (18.8)	11 (22.9)	0.615
Previous Smokers	12 (25.0)	8 (16.7)	0.314
Cormobidities, N (%)			
Heart Failure	6 (12.5)	3 (6.3)	0.293
Hypertension	7 (14.6)	9 (18.8)	0.583
Arrhythmia	2 (4.2)	4 (8.3)	0.399
Myocardial infarction	3 (6.3)	1 (2.1)	0.307
Diabetes	5 (10.4)	3 (6.3)	0.460
Dyslipidemia	2 (4.2)	3 (6.3)	0.645
Stroke	2 (4.2)	4 (8.3)	0.399

Thyroid disease	1 (2.1)	1 (2.1)	>0.999
Kidney disease	1 (2.1)	3 (6.3)	0.307
Malignancy	8 (16.7)	11 (22.9)	0.442
Need of IMV during ICU stay, N (%)	23 (47.9)	21 (43.8)	0.682
Length of use of IMV in days, N (%)	6.1 (4.2)	4.1 (3.6)	0.037
LOS in days (SD)	15.6 (6.7)	12.9 (5.8)	0.037

Table 2 - Demographic and clinical characteristics of the patients. CG, control group; IG, intervention group; BMI, body mass index; IMV, Invasive mechanical ventilation; LOS, Length of stay in ICU.

Health-related quality of life

All the ninety-six patients completed the SF-12 quality of life survey at 12-week follow-up. An independent t-test comparison between the two groups found statistical better results in IG for the mental component summary measure of the SF-12 (48.1 ± 9.0 vs. 44.2 ± 10.3 , $p=0.048$). No statistically significant differences were found in the physical component summary measure (45.7 ± 10.2 vs. 42.8 ± 10.7 , $p=0.173$) as shown in table 3.

Hospital anxiety and depression scale

All the ninety-six patients completed the HADS survey at 4-week follow-up. Statistical significant differences were found between the two groups, with a greater number of patients in the IG having low levels of anxiety and depression (60.4 vs 37.5%, $\chi^2 = 5.044$, $p=0.024$), as shown in table 3.

Measurement time point						
	4-week follow-up			12-week follow-up		
	IG	CG	P-value	IG	CG	P-value
HADS			0.024			
Normal, N (%)	29 (60.4)	18 (37.5)				
Abnormal, N (%)	19 (39.6)	30 (62.5)				
SF-12						
PCS-12, Mean (SD)				45.7 (10.2)	42.8 (10.7)	0.173
MCS-12, Mean (SD)				48.1 (9.0)	44.2 (10.3)	0.048

Table 3 - Clinical evaluations and group comparisons. CG, control group; IG, intervention group; 95%CI, 95% confidence interval; HADS, Hospital Anxiety and Depression Scale; SF-12, Short-Form 12 Health Survey; PCS-12, Physical component summary measure; MCS-12, Mental component summary.

Discussion

The results of the present study showed that the group of COVID19 patients that received a multidisciplinary rehabilitation program had significant lower levels of anxiety and depression, as well as better scores for HRQoL. To the best of our knowledge, this is the first randomized control trial to evaluate the impact, on HRQoL and mental health, of the implementation of a multidisciplinary rehabilitation programme in COVID19 patients hospitalized in the ICU.

The IG showed statically better values in the mental component summary measure of SF-12. Similar results were found by Gloeckl et al. [31], whose study showed a significant improvement in the mental health component of SF-36 in severe COVID-19 patients that underwent a rehabilitation program. Liu et al. [32], that conducted a randomized controlled trial in elderly patients with COVID-19 which assessed HRQoL using SF-36 and found a statistically significant improvement after 6 weeks of respiratory rehabilitation. The study by Nopp et al. [2] evaluated the impact of pulmonary rehabilitation in outpatients with long COVID on quality of life using the EuroQol Group 5-dimension 5-level (EQ-5D-5L) questionnaire, and also found a significantly improve in quality of life after rehabilitation, but only 38% of the patients had severe/critical COVID-19. The results of the present study suggest that rehabilitation may have a positive impact in HRQoL of critical COVID-19 patients.

On the other hand, it is well recognized that the ICU treatment may lead to psychological problems, that include anxiety, depression, irritability and panic attacks [33]. The IG showed less prevalence of abnormal values of anxiety and depression, which are in line with other previous studies [31, 34, 35]. These results are similar to those found by Gloeckl et al. [31] that reported a significant improvement in depression in patients with

severe/critical COVID-19 after a rehabilitation program. Liu et al. [32] also found a significant decrease in anxiety in COVID-19 patients after rehabilitation, but not in depression. The study by Kayambu et al. [19] reported a trend towards low levels of anxiety in the group that received a rehabilitation program.

Limitations

This study presents limitations that should be considered. There is a lack of baseline data for mental health because it was not possible to get information about psychological distress before the program implementation. There was only one center where this clinical trial was conducted. The importance of these findings could be increased by using this methodology on a population from many centers. Furthermore, the multidisciplinary treatment team could not be blinded since they need information of the group allocation to give the patient the proper intervention. The assessors in charge of randomization and outcome measurements, however, were fully unaware of group assignment. Patients could not be entirely blinded, however individuals were uninformed of other therapy options and were unsure of their status as participants.

Future directions

This study adds evidence that some psychological problems and decrease in quality of life, which often occur after ICU treatment, could benefit from the implementation of a multidisciplinary rehabilitation program in ICU. However, the results found in this study do not provide enough evidence, and there is a need for more randomized controlled studies to be conducted in this field, ideally multicentre studies. On the other hand, even in the face of strong evidence for the implementation of rehabilitation programs in ICU, this procedure is challenging as many ICU have a lack of specialized rehabilitation staff, such as rehabilitation doctors, physiotherapists, and nurses, who could include this type of program into the everyday operations of the ICU. This is one of the reasons why it

is essential to carry out cost-effectiveness studies to assess the potential advantages of including these specialists in the ICU multidisciplinary teams.

In conclusion, this randomized clinical trial presents a positive impact of a multidisciplinary rehabilitation program in the quality of life and mental health of COVID-19 patients hospitalized in ICU.

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Consent to participate - All study participants signed an informed consent approved by the ethics committee.

Data availability statement - The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

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CHAPTER VI

GENERAL DISCUSSION AND MAIN CONCLUSIONS

General discussion and main conclusions

The aim of this thesis was to design and evaluate the impact of the implementation of a multidisciplinary rehabilitation program in patients subjected to ICU treatment due to COVID-19. This thesis used a methodologically robust randomized controlled trial to show that this multidisciplinary rehabilitation program had a positive impact on patients in the intervention group, and that it showed superiority to the standard of care in respiratory and physical outcomes.

Initially, an extensive review of the published literature on the theme was carried out. Since SARS-CoV-2 was first identified, the scientific knowledge related to COVID-19 has constantly evolved, and so there was a need to keep the characterization of the state of art constantly updating. The emergence of new variants and the development of vaccines were the main events that occurred during the elaboration of this thesis. It is important to notice that the implementation of COVID-19 vaccination had a major impact on the disease natural course, as they revealed themselves as effective tools to prevent severe COVID-19, hospitalization, and death against all variants of concern (143). Our study was conducted in the early phase of COVID-19 vaccination in Portugal, therefore none of the patients included in the trial had been vaccinated.

The multidisciplinary rehabilitation protocol implemented on our trial was designed on the basis of the best evidence available in published literature, and following the recommendations issued by the Portuguese Society of Physical Rehabilitation Medicine (144). A study protocol to conduct a randomized controlled double-blind, double-arm clinical trial was designed and published (Paper I). Our study protocol was published as structured summary, and the full study protocol was published as supplementary information. Although some minor modifications had to be made to the original protocol in order to preserve its feasibility, the implementation of the study protocol was successful, and we were able to include a number of patients higher than the minimum value established.

In paper II it was possible to verify that the multidisciplinary rehabilitation programme in the ICU had beneficial outcomes for the patients, in their functional and respiratory functions. In fact, the intervention group showed significantly better results than the control group in the main outcome – the 6 minute walking test, both on the 4- (604±67 m vs 571±57 m; $p=0,018$) and 12-week follow-up assessment (639±53 m vs

611±67 m; $p=0,025$). In addition, the groups showed significantly different performances on the other secondary outcome measures, namely Borg Rating of Perceived Exertion (11,7±2,1 vs 12,5±1,8; $p=0,048$) and Medical Research Council sumscore (54,4±3,7 vs 52,1±4,1; $p=0,005$). The intervention group also had a significantly shorter length of stay in the ICU (4.1±3.6 days vs 6.1±4.2 days; $p=0,037$).

In paper III we analyzed the effects of the multidisciplinary rehabilitation program on the HRQoL and mental health of the patients included in the trial. The primary outcome measure was self-reported health-related quality of life, measured by 12- Item Short-Form Health Survey (SF-12) at 12-week mark. The results showed that the group that received a multidisciplinary rehabilitation had higher score in the mental component summary measure of the SF-12 (48,18 ± 9,04 vs. 44,22 ± 10,31, $p=0,048$). The secondary outcome measure was psychological outcome using the Hospital Anxiety and Depression Scale (HADS). A greater number of patients in the intervention group presented low levels of anxiety and depression (60,4 vs 37,5%, $\chi^2 = 5,044$, $p=0,024$). To the best of our knowledge, this was the first randomized control trial to evaluate the impact, on HRQoL and mental health, of the implementation of a multidisciplinary rehabilitation programme in COVID19 patients hospitalized in the ICU.

It is important to notice that the analysis of the multidisciplinary rehabilitation protocol could be extended by carrying out an economic analysis. The data obtained so far indicate that the protocol applied in our trial presents a beneficial cost-consequence comparing to standard of care, since the patients in the intervention group had a significant shorter length of ICU stay, which translates into less money spent by the hospital. The increased costs with healthcare professional could not be ascertained, but it is very likely that they represent far less than the amount saved with fewer days of hospitalization. Considering a cost-effectiveness analysis, the results obtained in this study suggest that the patients in the intervention group benefit from more quality of life, but a measure of the quality-adjusted life-years should be carried out.

The main overall limitation of this study is in line with the most frequent limitation in the randomized trials concerning rehabilitation programs, which is the double blinding. The blinding of the multidisciplinary treatment team was impossible because, in order to be able to provide the patient the correct intervention, they needed the knowledge of the group allocation. Nonetheless, the assessors responsible for randomization and outcome measures were completely blinded to group allocation. Blinding for patients was not

possible to achieve completely, but subjects were unaware of other treatment modalities, and they did not know if they belong to the intervention or standard group.

The fact that this clinical trial was only performed in one center is another important limitation of this study. The application of this protocol on a multi-center population might increase the significance of these results. Moreover, to be included in the trial patients had to fulfil the inclusion criteria, and as result it is possible that the results of the program may differ when applied to other patients, although, according to previous research, beneficial outcomes are expected. The present study only considers a time-frame of 12 weeks, and it would be interesting to conduct future trials with a longer time frame.

Although, thanks to the successful vaccination campaign carried out in most countries, severe COVID-19 cases, in need for ICU treatment, have diminished greatly around the world, the results of this thesis play an important part in the future of intensive care treatment. COVID 19 has dramatically increased the numbers of ICU survivors, and both healthcare and ICU were, unprecedentedly, regular subjects of public discourse. The resultant increase in ICU survivors and greater awareness of ICU care provided increased opportunities for dialog about ICU experiences. This might pave the way for a greater exploration of ICU survival experiences and perhaps develop opportunities for PICS research.

This thesis concluded that:

- It is possible and safe to implement multidisciplinary rehabilitation program in the ICU context.
- The impact on physical and respiratory outcomes of the multidisciplinary rehabilitation program was positive, and it was superiority in relation to standard of care.
- The impact on mental and quality of life related outcomes of the multidisciplinary rehabilitation program was positive, but it was not possible to prove superiority in relation to standard of care.

The evidence produced with this thesis was disseminated through academic publications and presentations in scientific conferences.

CHAPTER VII

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APPENDICES

Appendix I
**Development of a rehabilitation protocol for intensive
care patients affected by COVID-19 – study protocol**

Certificate of poster presentation



THE INTERNATIONAL INSTITUTE OF
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This is to Certify that

ANA CRISTINA CARVALHO

has participated with the Poster Presentation titled

**“DEVELOPMENT OF A REHABILITATION PROTOCOL FOR INTENSIVE CARE
PATIENTS AFFECTED BY COVID-19 – STUDY PROTOCOL”**

at

The 7th International Conference on Public Health 2021

**“DRIVING INNOVATIONS IN HEALTHCARE, STRENGTHENING
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Appendix II
**Multidisciplinary rehabilitation in intensive care for
COVID-19 – a randomized controlled trial**

Published abstract

Multidisciplinary rehabilitation in intensive care for COVID-19 - a randomized controlled trial

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Background and Objective: The coronavirus disease 2019 (COVID-19) has led to an increasing number of patients in the intensive care units (ICU). The size of this post-ICU cohort will be unprecedented, with many patients vulnerable to post-intensive care syndrome. PICS is recognized as a growing public health burden due to the associated neuropsychological and functional disability, and the evidence suggests that the prevention from ICU admission is more important and effective than intensive treatment of PCIS following ICU discharge. The objective of this study was to analyze the respiratory and functional effects of a rehabilitation program on functional performance, in patients hospitalized in ICU due to COVID-19. **Methods:** We conducted a randomized controlled clinical trial. Ninety-six patients, who fulfilled the eligible criteria, were randomized into control or intervention group. The control group received standard of care in the ICU, and the intervention group received a functional and respiratory rehabilitation protocol, that included medical, nursing, physiotherapy, and occupational therapy interventions.

Results: At discharge, the intervention group showed significantly better muscular strength and respiratory capacity, and significantly less days of hospitalization (12.90 ± 5.8 vs 15.60 ± 6.7 days, $P=0.037$). At the 4- and 12-week follow-up we applied our main outcome measure – 6-minute walking test. The intervention group had significantly better Results than the control group on the 6-minute walking test at the 4-week follow-up (604 ± 67 vs 571 ± 57 m, $P=0.018$) and at the 12-week follow-up (639 ± 53 vs 611 ± 67 , $P=0.025$). **Conclusions:** These results support the role of a multidisciplinary rehabilitation program in COVID-19 patients hospitalized in ICU and adds evidence that the implementation of rehabilitation programs in ICU could Results in beneficial outcomes for the critical ill patients.

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Appendix III
Multidisciplinary rehabilitation in intensive care for
COVID-19 – a randomized controlled trial

Certificate of oral communication



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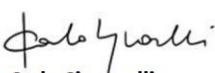
Multidisciplinary rehabilitation in intensive care for COVID-19 - a randomized controlled trial

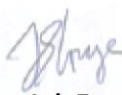
Ana Cristina Carvalho

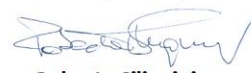
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Has been presented as Oral communication
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Best regards,


Carlo Signorelli
Co - Chair


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