U.PORTO

DOUTORAMENTO

INVESTIGAÇÃO CLÍNICA E EM SERVIÇOS DE SAÚDE

Implicações neurológicas de infeções respiratórias críticas e seu impacto funcional: uma análise comparativa entre SARS-CoV-2 e outras etiologias infeciosas

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Ao meu marido e aos meus pais,

O meu núcleo duro

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INDÍCE

LISTA DE ABREVIATURAS, SIGLAS E ACRÓNIMOS

ARDS – *Acute Respiratory Distress Syndrome*

BHE – Barreira Hematoencefálica

COVID-19 – Doença Coronavírus 2019

CVD – *Cerebrovascular disease*

DVC – Doença Vascular Cerebral

ECA2 – Enzima de Conversão da Angiotensina 2

FMACI – Fraqueza Muscular Adquirida nos Cuidados Intensivos

ICU – *Intensive Care Unit*

LCR – Líquido Cefalorraquidiano

MERS - *Middle Eastern Respiratory Syndrome*

MFR – Medicina Física e de Reabilitação

OMS – Organização Mundial de Saúde

PRM – *Physical and Rehabiltiation Medicine*

RASS – *Richmond Agitation-Sedation Scale*

RT-PCR - *Reverse Transcription Polymerase Chain Reaction*

SARS - *Severe Acute Respiratory Syndrome*

SDRA – Síndrome de Dificuldade Respiratória Aguda

SDTCS – Sinais de disfunção do trato cortico-espinhal

SNC – Sistema Nervoso Central

SNP – Sistema Nervoso Periférico

SPICI – Síndrome Pós Internamento em Cuidados Intensivos

UCI – Unidade de Cuidados Intensivos

VMI – Ventilação Mecânica Invasiva

LISTA DE FIGURAS

LISTA DE PUBLICAÇÕES

A presente tese de Doutoramento baseia-se nas seguintes publicações, apresentadas subsequentemente em secção própria:

ARTIGOS PRINCIPAIS:

1. Teixeira-Vaz A, Rocha JA, Costa A, Simões Moreira T, Almeida E Reis D, Oliveira M, Silva AI, Paiva JA. What is the impact of previous cerebrovascular disease on critical COVID-19 patients' mortality? A prospective cohort study. J Neurol Sci. 2022 Nov 15;442:120382. doi: 10.1016/j.jns.2022.120382. Epub 2022 Aug 24. PMID: 36037666; PMCID: PMC9400379. [2º quartil, *Scimago*]
2. Teixeira-Vaz A, Rocha JA, Reis DAE, Oliveira M, Moreira TS, Silva AI, Monteiro-Soares M, Paiva JA. Critical COVID-19 and neurological dysfunction - a direct comparative analysis between SARS-CoV-2 and other infectious pathogens. Rev Bras Ter Intensiva. 2022 Nov 4;34(3):342-350. doi: 10.5935/0103-507X.20220229-pt. PMID: 36351066; PMCID: PMC9749094. [2º quartil, *Scimago*]
3. Teixeira-Vaz A, Rocha JA, Oliveira M, Almeida E Reis D, Simões Moreira T, Silva AI, Paiva JA. The PRINCOVID Retrospective Study: A Predictive Model of Pressure Injuries for Critical COVID-19 Patients. Am J Phys Med Rehabil. 2023 Aug 1;102(8):707-714. doi: 10.1097/PHM.0000000000002195. Epub 2023 Jan 22. PMID: 36722899; PMCID: PMC10368159. [1º quartil, *Scimago*]
4. Teixeira-Vaz A, Rocha JA, Oliveira M, Simões-Moreira T, Reis DAE, Silva AI, Paiva JA. Surviving critical COVID-19: How functionality, physical, mental and cognitive outcomes evolve? PLoS One. 2023 Jun 23;18(6):e0284597. doi: 10.1371/journal.pone.0284597. PMID: 37352178; PMCID: PMC10289386. [1º quartil, *Scimago*]

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RESUMO

A doença COVID-19 representa uma importante ameaça à saúde numa escala global, constituindo, até ao momento atual, a maior crise de saúde pública do século XXI.

Estima-se que 85 a 90% dos casos correspondam a infeções pauci-sintomáticas ou ligeiras. No entanto, até 15% das infeções são graves exigindo, eventualmente, admissão em Serviços de Medicina Intensiva / Unidades de Cuidados Intensivos (UCI).

As infeções graves são aquelas que se revelam mais impactantes tanto pela morbilidade provocada, como pelo acréscimo na letalidade associada à doença. São múltiplos os fatores descritos como predisponentes de maior mortalidade pela COVID-19. No entanto, e apesar da plausibilidade biológica para um efeito particularmente adverso das comorbilidades neurológicas na mortalidade atribuível à COVID-19 crítica, a literatura é escassa no que se refere a estudos especificamente desenhados para avaliar este impacto.

Por este motivo, consideramos importante avaliar o efeito da presença de comorbilidades neurológicas, especificamente a doença vascular cerebral (DVC), na mortalidade de doentes críticos COVID-19.

Para tal, desenvolvemos um estudo de coorte prospetivo incluindo consecutivamente 178 doentes COVID-19 críticos. A DVC prévia, presente em cerca de 10% da amostra, revelou-se um fator independente para mortalidade em UCI no contexto da doença COVID-19 crítica, consubstanciando-se com um risco de morte 2,51 vezes superior.

A doença COVID-19 cursa primariamente com sinais e sintomas respiratórios, cuja severidade é o principal determinante da gravidade da doença. No entanto, sinais, sintomas e síndromes neurológicos foram descritos em todo o espetro clínico da COVID-19, apontando para um eventual neurotropismo vírico e potencial neuro-invasivo. No contexto de UCI, independentemente do diagnóstico de admissão, existe também um risco acrescido de se verificarem complicações neurológicas relacionadas com a própria doença crítica e com o seu tratamento.

Neste sentido, é relevante investigar se, em doentes críticos COVID-19, a disfunção neurológica é apenas um epifenómeno da doença crítica ou se está diretamente relacionada com o potencial neurotropismo e neuro-invasividade do SARS-CoV-2.

Por este motivo, desenvolvemos um estudo de coorte prospetivo incluindo consecutivamente 54 doentes internados em UCI por Síndrome de Dificuldade Respiratória Aguda (SDRA) de etiologia infeciosa. Neste trabalho, foram diretamente comparados doentes com SDRA a SARS-CoV-2 (n=27) com doentes com SDRA a outros patógenos infeciosos (n=27), no que se refere à prevalência e características da disfunção neurológica. Um total de 61% dos doentes incluídos apresentaram pelo menos um sinal, sintoma ou síndrome neurológica durante o internamento em UCI. Nos doentes COVID-19 verificou-se um risco 1,98 vezes superior de desenvolver estas complicações, em comparação com os casos que tinham sido admitidos por SDRA a outros patógenos infeciosos.

Na abordagem ao doente crítico, um outro aspeto que consideramos fundamental foi o da avaliação e intervenção por Medicina Física e de Reabilitação (MFR), como determinante de redução da morbilidade e da mortalidade associada à doença. O desenho e implementação de programas de MFR pode ser influenciado por múltiplas condicionantes, como sendo as lesões por pressão. Apesar da prevalência, impacto clínico e económico das lesões por pressão no doente crítico, os modelos preditivos de risco desta complicação nos doentes COVID-19 críticos são escassos.

Assim, desenvolvemos um estudo de coorte retrospetivo incluindo consecutivamente 205 doentes COVID-19 críticos, em que foram avaliados múltiplos potenciais preditores acessíveis à admissão na UCI, visando identificar fatores de risco para o desenvolvimento desta complicação. A prevalência de lesões por pressão na amostra incluída foi elevada, afetando mais de 50% dos doentes. Identificamos quatro preditores independentes para o desenvolvimento de lesões por pressão em doentes COVID-19 críticos: sexo masculino, hipertensão (comorbilidade) e valores mais baixos de hemoglobina e albumina à admissão na UCI. Estes fatores constituíram o modelo PRINCOVID. De modo a facilitar a aplicabilidade deste modelo num contexto real de prática clínica, convertemo-lo num *score*. O *score* PRINCOVID varia entre 0 e 15 pontos, com dois grupos de risco distintos: “em risco” (≤ 7 pontos) e “alto risco” (> 7 pontos). Foi também feita a comparação direta entre o PRINCOVID e o *standard* da prática clínica (escala de *Braden*), sendo que o modelo PRINCOVID apresentou um poder preditivo significativamente superior.

Uma vez que os doentes mais graves são também os que apresentam, *à priori*, uma probabilidade superior de desenvolver sequelas relacionadas com a COVID-19, o impacto a longo prazo da doença nesta população é muito importante. De facto, o elevado número de sobreviventes à doença COVID-19 crítica tem criado um peso significativo nos sistemas de saúde

ao longo do contínuo de cuidados, com ulterior necessidade de políticas estruturais de reorganização dos mesmos. No entanto, a extensão, evolução temporal e características das sequelas da doença crítica COVID-19 encontra-se pouco documentada na literatura.

Exatamente por este motivo, definimos também como objetivo desta investigação caracterizar as consequências clínicas e funcionais da doença COVID-19 crítica após alta da UCI. Para tal, desenvolvemos um estudo de coorte prospetivo incluindo 42 sobreviventes de internamento em UCI por SDRA a SARS-CoV-2. Estes doentes foram avaliados em consulta de MFR aos seis e doze meses após a alta da UCI. Nestas avaliações clínicas foram caracterizados os domínios físico, mental e cognitivo da Síndrome Pós Internamento em Cuidados Intensivos, através do exame objetivo e múltiplas escalas de avaliação. Além disso, foi também avaliada a funcionalidade destes doentes. Os resultados deste estudo revelaram que, aos seis e doze meses após alta da UCI, sobreviventes de COVID-19 crítica apresentam alterações consideráveis nos domínios físico, mental e cognitivo, apesar de se ter verificado uma evolução positiva significativa em todos estes domínios ao longo do período de seguimento. De realçar ainda que apenas cerca de metade da amostra estava autónoma seis meses após a alta da UCI, valor que aumentou em cerca de 20% nos seis meses subsequentes.

Em suma, esta investigação visou contribuir para a melhor compreensão do doente crítico COVID-19, numa abordagem "antes, durante e depois da UCI", com particular enfoque na disfunção neurológica e no impacto clínico e funcional da doença. Assim, foi explorado o efeito de comorbilidades neurológicas na mortalidade em UCI, avaliado se a disfunção neurológica é, ou não, mais comum em doentes críticos COVID-19 (em comparação com doentes com SDRA por outros patógenos infeciosos), e analisado o impacto a longo termo da doença crítica COVID-19 nos domínios mental, físico e cognitivo e na funcionalidade. Ademais, foi também desenvolvido um modelo preditor de risco de lesões por pressão para esta população, dado o impacto de programas de MFR na prevenção destas complicações e o potencial efeito da presença de lesões por pressão no desenho e implementação de programas de MFR.

SUMMARY

COVID-19 disease poses an important health threat on a global scale, thereby constituting the most significant public health crisis of the 21st century, so far.

Indeed, 85 to 90% of COVID-19 patients have paucisymptomatic or mild infections. Nevertheless, up to 15% have severe diseases, some requiring admission to Intensive Care Units (ICU).

Severe infections are the most impactful, not only because of the morbidity caused but also due to the presumed increase in the disease-associated lethality. In the hitherto literature, there are several described risk factors for higher mortality from COVID-19. However, and despite the biological plausibility of a particularly adverse effect of neurological comorbidities on mortality due to critical COVID-19, the literature is scarce regarding this topic.

For this reason, we considered important to evaluate the effect of neurological comorbidities, specifically cerebrovascular disease (CVD), on the mortality of critically ill COVID-19 patients.

Accordingly, we performed a prospective cohort study with consecutive inclusion of 178 critical COVID-19 patients. Previous CVD, present in about 10% of the sample, was an independent risk factor for mortality. The presence of this comorbidity was associated with a 2.51-fold higher risk of death during an ICU stay.

This virus mainly causes respiratory signs and symptoms, which are the main determinants of disease severity. Nevertheless, neurological signs, symptoms, and syndromes have been reported in the full clinical spectrum of COVID-19, pointing towards a viral neurotropism and potential of neuro-invasiveness. In an ICU setting, there is an inherent risk of neurological complications regardless of the admission diagnosis. These complications may be related to the critical illness itself and/or the required treatment.

As so, one of the most pressing questions in this area is whether neurological dysfunction in critically ill COVID-19 patients is just an epiphenomenon of the critical illness or directly related to the alleged neurotropism and neuro-invasiveness of SARS-CoV-2.

For this reason, we developed a prospective cohort study including consecutively 54 patients admitted to ICU due to infectious Acute Respiratory Distress Syndrome (ARDS). In this analysis, patients with ARDS due to SARS-CoV-2 (n=27) were directly compared with patients with

ARDS due to other infectious pathogens (n=27), regarding the prevalence and characteristics of neurological dysfunction. A total of 61% of the sample had at least one neurological sign, symptom, or syndrome during ICU stay. COVID-19 patients presented a 1.98-fold higher risk of developing these complications when compared to cases admitted with ARDS due to other infectious pathogens.

In the treatment of critically ill patients, Physical and Rehabilitation Medicine (PRM) intervention is of paramount importance. Indeed, PRM programs have a significant effect on the reduction of both morbidity and mortality associated with COVID-19 disease. The design and implementation of PRM programs pends on several factors and considers multiple constraints, namely the presence of pressure injuries. Despite the prevalence, clinical and economic impact of pressure injuries, predictive risk models are scarce for this complication in critical COVID-19 patients.

Thus, we developed a retrospective cohort study with consecutive inclusion of 205 critical COVID-19 patients, in which multiple potential predictors accessible at ICU admission were evaluated, aiming to identify risk factors for developing this complication.

The prevalence of pressure injuries was high, affecting more than 50% of the sample. Four factors were identified as independent predictors for developing pressure injuries in critically ill COVID-19 patients: male gender, hypertension (comorbidity), and lower values of hemoglobin and albumin at ICU admission. These factors constituted the PRINCOVID model. To facilitate the applicability of this model in a real-life clinical context, we converted it into a score. The PRINCOVID score varies between 0 and 15 points, with two distinct risk groups: “at risk” (≤ 7 points) and “high risk” (> 7 points). Furthermore, a direct comparison between the PRINCOVID and the standard of clinical practice (Braden scale) was performed: the PRINCOVID model presented a significantly higher predictive power.

Since severe patients are also those who have, *a priori*, a higher probability of developing COVID-19-related sequelae, the long-term impact of the disease in this population is very important. In fact, the high number of survivors of critical COVID-19 has created a significant burden on health systems along the continuum of care, with a further need for structural policies to reorganize them. However, the extent, clinical path, and characteristics of COVID-19-related sequelae are poorly documented in the literature.

In accordance, we also defined as an objective of this investigation to characterize the clinical and functional consequences of critical COVID-19 illness after ICU discharge.

As so, we developed a prospective cohort study including 42 survivors of critical ARDS due to SARS-CoV-2. These patients were evaluated in a PRM ambulatory appointment at six and twelve months after ICU discharge. The physical, mental, and cognitive domains of Post Intensive Care Syndrome were characterized through physical examination and multiple scales. In addition, the functionality of these patients was assessed. This study highlights that six and twelve months after ICU discharge, survivors of critical COVID-19 have considerable impairments in the physical, mental and cognitive domains, despite a significative positive evolution in all these domains throughout the first year after ICU discharge. Furthermore, only about half of the sample was independent six months after discharge from the ICU, a value that increased by around 20% in the subsequent six months.

In brief, this investigation aimed to contribute to a better understanding of the critically ill COVID-19 patient, in a “before, during, and after ICU” approach, with an essential focus on the topics of neurological dysfunction and the clinical and functional impact of the disease. Indeed, we have explored the impact of neurological comorbidities in ICU mortality of COVID-19 patients, assessed whether neurological dysfunction is more frequent in critical COVID-19 patients (in comparison with patients with ARDS due to other infectious pathogens), and analyzed the long-term impact of critical COVID-19 in the mental, physical and cognitive domains and in the functionality. Furthermore, we have also developed a predictive model for pressure injuries in this population due to the effect of PRM programs in the prevention of this complication and the potential impact of pressure injuries in the design and implementation of PRM programs.

INTRODUÇÃO

A DOENÇA COVID-19: O MOMENTO EM QUE A NOSSA VIDA MUDOU

Em dezembro de 2019, o *Hubei Integrated Chinese and Western Medicine Hospital*, na cidade chinesa de *Wuhan*, reportou um surto de pneumonia grave de etiologia vírica provável. Nos trinta dias seguintes foi possível a identificação do vírus SARS-CoV-2, tendo-se constatado uma disseminação rápida da doença a nível global, a qual foi subsequentemente designada Doença Coronavírus 2019 (COVID-19)[1, 2].

Pela propagação massiva da doença foi declarado em março de 2020, pela Organização Mundial de Saúde (OMS), o estado de pandemia por COVID-19[3]. Atualmente, três anos depois, foram reportados mais de 765 903 278 casos a nível mundial e de 5 582 987 casos em Portugal[4].

A COVID-19 alterou o paradigma da área da saúde, tendo tido também um impacto significativo na sustentabilidade socioeconómica global[5]. O impacto social da pandemia, essencialmente pela alteração dos padrões de vivência em comunidade e na sociedade, foi muito significativo tanto no modo, como na qualidade de vida da população mundial, algo que se relaciona diretamente com o efeito das adaptações existentes a nível psico-emocional[6]. Além disso, também o impacto económico desta situação foi devastador em múltiplos contextos, designadamente nos setores primários (agricultura, pecuária, indústria do petróleo), secundários (envolvidos na génese dos produtos finais, como a indústria da manufaturação) e terciários (que incluem os Serviços, como a educação, indústria financeira, turismo, imobiliária, entre outras)[7].

Numa perspetiva histórica, em dois momentos prévios nos últimos vinte anos os Coronavírus já haviam desencadeado quadros infeciosos que se revelaram importantes ameaças à saúde pública globalmente: o *Severe Acute Respiratory Syndrome* (SARS) em 2002-2003 e o *Middle Eastern Respiratory Syndrome* (MERS) em 2012[8-10]. Apesar dos agentes etiológicos destas três entidades pertencerem à mesma família filogenética, são múltiplas as características que os distinguem tanto no que se refere à sua patogénese, como à apresentação clínica[10, 11]. É, contudo, de destacar que a mais relevante diferença clínica entre estes micro-organismos é a maior prevalência de portadores assintomáticos da infeção por SARS-CoV-2[10, 12].

A significativa proporção de indivíduos assintomáticos, aliada ao facto de a apresentação da COVID-19 ser dinâmica e frequentemente distinta entre doentes, conduz a inerentes dificuldades no diagnóstico precoce, contribuindo assim para a disseminação desta doença[13].

Adicionalmente, a ausência de imunidade protetora e a capacidade do SARS-CoV-2 para ultrapassar mecanismos de imunidade inata, constituíram também aspetos essenciais na propagação deste vírus[14].

A transmissibilidade do SARS-CoV-2 ocorre, essencialmente, através de aerossóis, os quais podem permanecer no ar, nas mãos e em superfícies[15]. O tempo mediano de incubação do SARS-CoV-2 varia entre dois e doze dias, sendo que a transmissão por indivíduos assintomáticos foi já amplamente descrita[16, 17]. Parecem existir alguns fatores predisponentes para um risco acrescido de contrair esta infeção, designadamente de índole sociodemográfica (idade avançada, sexo masculino, estado civil casado, maior número de elementos no agregado familiar) e comorbilidades (fatores de risco vasculares, patologia oncológica, patologia psiquiátrica)[18].

Estas particularidades de propagação e transmissibilidade do SARS-CoV-2 foram o substrato essencial para o planeamento e operacionalização das medidas de prevenção primária, implementadas com o objetivo fundamental de reduzir a taxa de incidência da COVID-19[19]. Entre as medidas com maior eficácia presumível, destaque para o distanciamento físico, o isolamento e restrição de circulação, a utilização de material de proteção da via aérea e a identificação e isolamento de casos e contactos, as quais condicionaram uma diminuição global no índice de transmissibilidade, na taxa de incidência da COVID-19 e na mortalidade atribuível à doença[19, 20].

Ao longo do tempo verificou-se uma significativa desaceleração na transmissibilidade, na gravidade e na mortalidade associada à COVD-19, algo que se encontra provavelmente indexado a estas estratégias de saúde pública de base populacional, à vacinação, à otimização da capacidade diagnóstica, aos avanços terapêuticos e à modificação adaptativa do vírus[21].

O *gold-standard* para o diagnóstico da COVID-19 é a análise da *Reverse Transcription Polymerase Chain Reaction* (RT-PCR) do SARS-CoV-2 em amostras recolhidas através de zaragatoa naso- e oro-faríngea (via preferencial), aspirado traqueal ou lavado bronco-alveolar[22]. A especificidade deste método de diagnóstico é muito elevada, no entanto a sua sensibilidade varia entre 40 e 60%[23]. Além do método de RT-PCR, a análise de amostras recolhidas da via aérea pode também ser feita com recurso a testes de antigénio, os quais apresentam um poder diagnóstico inferior, particularmente nas novas variantes víricas, em doentes pauci-sintomáticos e nos primeiros dias após a infeção em que existe uma reduzida carga vírica sistémica[24, 25].

Globalmente, estima-se que 85 a 90% dos casos de COVID-19 correspondam a infeções pauci-sintomáticas ou ligeiras[22]. No entanto, até 15% das infeções são graves, cursando com

falência respiratória e, por vezes, disfunção multiorgânica, condicionando assim a necessidade de admissão em Serviços de Medicina Intensiva / Unidades de Cuidados Intensivos (UCI)[26].

A capacidade de predição da gravidade e da mortalidade atribuível à doença é extraordinariamente importante na priorização correta dos doentes, particularmente ao nível das UCI[27]. Vários modelos preditivos de gravidade e mortalidade associada à COVID-19 foram sendo descritos na literatura, incluindo variáveis sociodemográficas, comorbilidades, sinais e sintomas à admissão hospitalar, complicações relacionadas com a doença, entre outros factores[28-32]. A existência destes modelos reveste-se de particular importância na otimização dos cuidados de saúde prestados[33].

O limitado número de vagas em UCI impôs desafios organizacionais significativos, em termos de dotação de camas e de recursos humanos. Globalmente, verificou-se um impacto negativo significativo da pandemia COVID-19 na abordagem a doentes não COVID-19, especificamente no que se refere à acessibilidade a métodos de rastreio, diagnóstico precoce e tratamento atempado[34, 35]. Apesar do presumível efeito deletério desta situação pandémica na mortalidade por outras doenças além da COVID-19, é de realçar que, entre os doentes admitidos em UCI por outras doenças críticas na era pandémica, não se verificou uma diferença significativa na sua mortalidade, em comparação com os resultados da era pré-pandémica[35, 36].

Existindo a necessidade de admissão em UCI, os cuidados clínicos preconizados neste contexto são basilares na redução da mortalidade associada à doença[22]. As taxas de mortalidade por COVID-19 são variáveis entre diferentes países, estando relacionadas com a saturação das UCI, o seu nível de preparação e grau de diferenciação, bem como com a eficácia das estratégias de prevenção primária de base populacional, incluindo a vacinação, e com a implementação de intervenções terapêuticas dirigidas[8, 22, 37, 38].

No que se refere ao tratamento em fase de doença aguda, na vasta maioria dos casos a abordagem é conservadora, no domicílio, com medidas primariamente sintomáticas[39]. No entanto, a hospitalização e a eventual admissão em UCI podem ser necessárias de acordo com a gravidade do quadro clínico e características do doente[39].

O tratamento dos casos graves de COVID-19 inclui, fundamentalmente, medidas farmacológicas e tratamentos de suporte[8, 39-43].

Apesar da ampla investigação clínica na área da terapêutica farmacológica dirigida à COVID-19, e da existência de recomendações em constante atualização pela OMS, ainda não se

encontram claramente definidas linhas de abordagem terapêutica farmacológica preferencial[8, 43]. Globalmente, as intervenções farmacológicas dirigidas à doença COVID-19 podem ser categorizadas em três grupos: 1) agentes antivíricos, 2) terapêuticas com alvo no hospedeiro (como os anticorpos neutralizantes) e 3) outros agentes[8, 44].

Para além das intervenções farmacológicas, o tratamento de suporte é algo determinante na melhor abordagem a estes doentes[45, 46]. O suporte ventilatório (com métodos de ventilação não invasiva, invasiva e *extracorporeal membrane oxygenation*), renal (com terapêutica de substituição desta função), cardiovascular (através do suporte vasopressor, inotrópico ou *extracorporeal membrane oxygenation*), nutricional, entre outros, são alguns dos métodos incluídos neste âmbito[41]. Além destas intervenções mais específicas da Medicina Intensiva, também a Medicina Física e de Reabilitação (MFR) têm um papel primário na prevenção e na gestão de potenciais complicações na doença aguda COVID-19, configurando-se como uma abordagem de suporte adjuvante muito relevante[47].

A DOENÇA COVID-19: MAIS DO QUE UMA DOENÇA RESPIRATÓRIA

O vírus SARS-CoV-2 causa, essencialmente, sinais e sintomas respiratórios, cuja severidade é o principal determinante da gravidade da doença[48]. Entre os indivíduos afetados, cerca de 20% desenvolve quadros de pneumonia, os quais podem ter características compatíveis com Síndrome de Dificuldade Respiratória Aguda (SDRA)[49].

De acordo com a definição de *Berlin,* a SDRA consiste num quadro de inflamação pulmonar aguda com aumento da permeabilidade alvéolo-capilar, associado a hipoxemia e opacidades bilaterais objetiváveis em imagem de tórax, sem evidência de insuficiência cardíaca esquerda[50, 51]. De acordo com o nível de oxigenação, a SDRA é categorizada em ligeira (PaO_2/FiO_2 entre 200-300 mmHg, PEEP ou CPAP ≥ 5 cmH_20), moderada (PaO_2/FiO_2 entre 100-200 mmHg, PEEP ≥ 5 cmH_20) ou grave (PaO_2/FiO_2 ≤ 100 mmHg, PEEP ≥ 5 cmH_20)[50, 51].

Na COVID-19, a progressão para a SDRA ocorre em vários estádios, sendo caracterizada inicialmente por alterações na perfusão pulmonar, no contexto da hiper-inflamação, hipercoaguabilidade e embolização pulmonar, com envolvimento mínimo dos espaços aéreos. Posteriormente, existe um estado de progressivo edema inflamatório e subsequente consolidação parenquimatosa, sendo esta fase mais similar à SDRA clássica em termos de mecânica pulmonar e resposta ao suporte respiratório[48, 52].

No início da pandemia, a suspeita clínica de COVID-19 surgia mediante a apresentação de sintomas respiratórios. No entanto, atualmente é conhecido que sinais, sintomas e síndromes atribuíveis à disfunção dos sistemas nervoso, cardiovascular, digestivo, hematológico, endócrino, entre outros, podem constituir parte do quadro clínico da COVID-19[13]. Assim, apesar da disfunção respiratória ser a característica-chave da doença, a COVID-19 pode ter uma afeção multisistémica, conforme detalhado na Figura 1.

A presença de manifestações multiorgânicas na COVID-19 prende-se, essencialmente, com o tropismo que o SARS-CoV-2 apresenta para o recetor da Enzima de Conversão da Angiotensina 2 (ECA2)[13]. Especificamente, pensa-se que a entrada deste vírus nas células do hospedeiro seja mediada pelo recetor da ECA2, sendo este o seu alvo primário[53, 54]. A lesão multiorgânica surge por eventuais fenómenos ulteriores de toxicidade vírica direta, lesão das células endoteliais, trombo-inflamação, desregulação da resposta imune e do sistema renina-angiotensina-aldosterona[55].

Apesar da diversidade de órgãos e sistemas afetados pela doença, verifica-se uma lesão preferencial de determinados tecidos[56]. Pensa-se que esta predileção se relaciona diretamente com a expressividade relativa dos recetores da ECA2, mais presentes no epitélio da via aérea, parênquima pulmonar, células renais, intestino delgado, endotélio vascular e sistema nervoso[56].

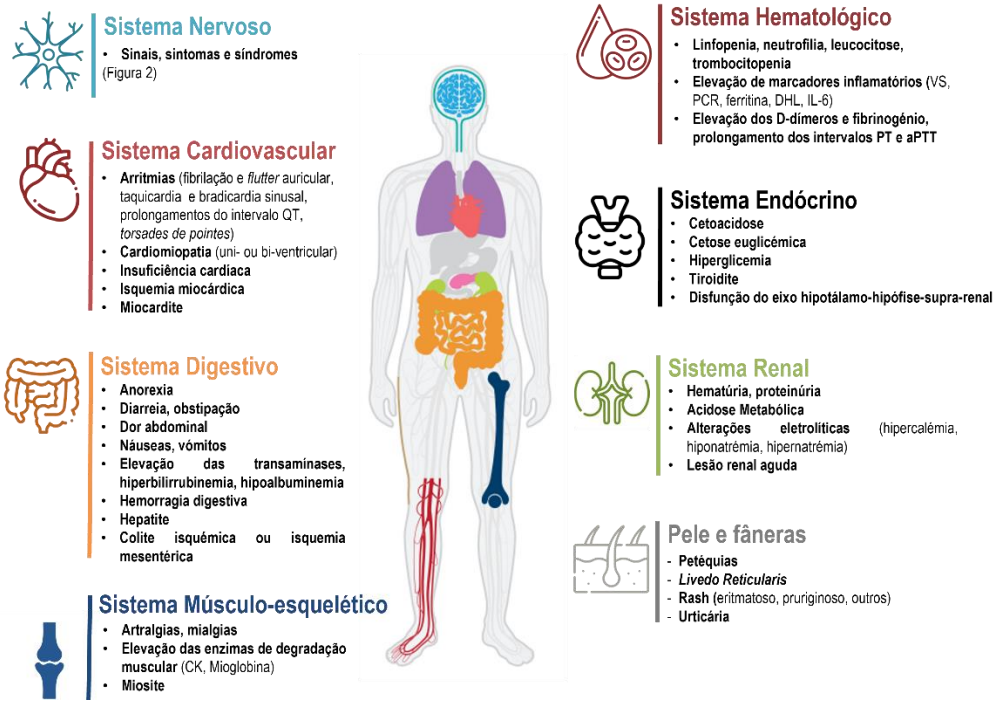

Figura 1. Afeção multiorgânica da doença COVID-19: exemplificação do envolvimento extra-respiratório

Legenda: DHL: Desidrogenase láctica; IL-6: Interleucina 6; CK: Creatina Quinase; PCR: Proteína C Reativa; VS: Velocidade de Sedimentação; PT: Tempo de Protrombina; aPTT: Tempo de Tromboplastina Parcial Ativado (adaptado de *Cayman Chemical ©)*

A DOENÇA COVID-19: O UNIVERSO DO SISTEMA NERVOSO

Os sinais, sintomas e síndromes neurológicos são particularmente comuns nos doentes COVID-19, estando presentes em até 90% dos casos sintomáticos[57].

As manifestações neurológicas podem ocorrer à apresentação da doença, ou durante o seu curso, tendo sido reportadas em todo o espectro clínico da COVID-19[57, 58]. Inclusivamente, a disfunção neurológica foi descrita como manifestação clínica única em doentes COVID-19[59].

No que se refere à sua base fisiopatológica, globalmente existem duas teorias principais: a da disseminação hematogénica sistémica e a da disseminação neuronal retrógrada.

Na teoria da disseminação hematogénica sistémica, postula-se que após a infeção das células da via aérea, o vírus possa transitar através da barreira epitelial e ganhar acesso à corrente sanguínea, acedendo ao sistema nervoso através da infeção ativa das células endoteliais da barreira hematoencefálica (BHE) e/ou do plexo coroideu. Adicionalmente, por um mecanismo tipo "cavalo de Tróia", o SARS-CoV-2 poderá infetar diretamente outras células, designadamente os leucócitos, os quais podem migrar para múltiplos outros tecidos corporais e aí atravessar a BHE, ganhando desta forma acesso ao SNC[60]. Em ambas as hipóteses, pensa-se que existe um compromisso da integridade estrutural e/ou funcional da BHE, levando à morte de células neuronais pela viremia[59]. Neste sentido, é possível encontrar RNA vírico no líquido cefalorraquidiano (LCR), de acordo com o inicialmente postulado por *Moriguchi et al*[61]. No entanto, tal nem sempre se verifica, uma vez que a deteção de marcadores víricos no LCR requer um certo limiar, o qual não é comummente atingido mesmo que na presença de conteúdo vírico, além de que a presença de produtos hemáticos no LCR pode interferir com a capacidade de deteção de partículas víricas[59].

Relativamente à teoria da disseminação neuronal retrógrada, esta postula que existe entrada do SARS-CoV-2 através do bolbo olfativo, via mecanismos primariamente celulares, com subsequente transmissão superior por via transcribiana, e ulterior atingimento encefálico[62]. Além destas vias principais, foram também descritas vias ancilares, designadamente por afeção primária dos nervos periféricos[63].

Independentemente da via de entrada no organismo, e particularmente no sistema nervoso central (SNC), destaca-se que a predileção por este sistema e o potencial neuro-invasivo do SARS-CoV-2 está previsivelmente relacionado com o tropismo do vírus pelo recetor da ECA2. De

facto, nas células da glia, nos neurónios, nas células endoteliais e do músculo liso arterial encefálico, existe uma elevada expressividade desde recetores, o que torna o sistema nervoso um alvo preferencial do SARS-CoV-2[64, 65]. Em termos estruturais, a preponderância destes recetores é máxima ao nível da substância *nigra*, dos ventrículos, do giro temporal médio, do córtex cingulado posterior e do bolbo olfativo, algo que constitui a possível base estrutural explicativa de alguns dos sinais, sintomas e síndromes neurológicos mais comuns nesta infeção[56].

Em suma, e apesar de as vias e bases fisiopatológicas para o neurotropismo e neuro-invasividade do SARS-CoV-2 ainda não se encontrarem totalmente esclarecidas, a existência de afeção neurológica pelo SARS-CoV-2 é, atualmente, clara[60, 66]. Na literatura, a descrição de sinais, sintomas e síndromes neurológicos é vasta, conforme explicitado na Figura 2.

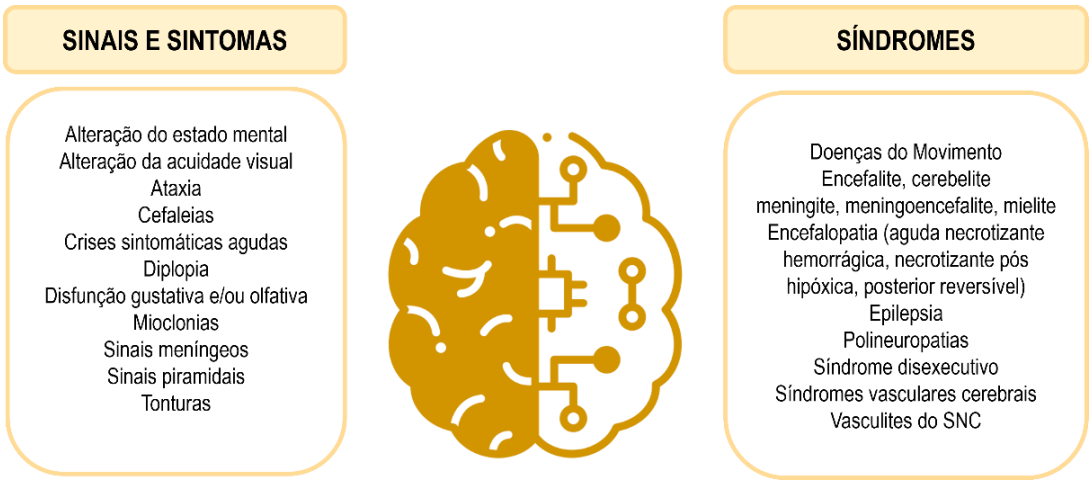

Figura 2. Sinais, sintomas e síndromes neurológicos da doença COVID-19 descritos na literatura.

Legenda: SNC: Sistema Nervoso Central

No que se refere à relação entre a gravidade da doença COVID-19 e a probabilidade de apresentar disfunção neurológica, a literatura não é unânime. Em alguns estudos, a prevalência de disfunção neurológica não é significativamente diferente entre doentes críticos e doentes pauci-sintomáticos[67]. No entanto, em outros trabalhos, os doentes mais graves parecem apresentar um risco superior de alterações neurológicas[68]. Estudos dirigidos à população de doentes críticos no âmbito do estudo da disfunção neurológica e do seu impacto são escassos. Na população de doentes COVID-19 críticos, uma das questões fundamentais é se as manifestações neurológicas são apenas um epifenómeno da doença crítica ou se estão diretamente relacionadas com o neurotropismo do SARS-CoV-2.

Além das amplas descrições clínicas de alterações neurológicas nesta população, já previamente explicitadas e ilustradas na Figura 2, destaca-se que alterações estruturais em

estudos de imagem do SNC têm sido também detalhadas. Múltiplos padrões foram descritos, incluindo micro-hemorragias, alterações hipóxico-isquémicas, alterações da substância branca, variações da perfusão cerebral, alterações do realce lepto-meníngeo, entre outras[69]. No que se refere à topografia destas lesões, na substância cinzenta as áreas mais frequentemente descritas como afetadas foram os gânglios da base e o cerebelo, ao passo que na substância branca parece haver um predomínio pelo trato cortico-espinhal, seguido pelo corpo caloso[70]. O trato cortico-espinhal é uma via *major* de substância branca, que conecta estruturas corticais a estruturas subcorticais críticas (como o tálamo e os gânglios da base), sendo também uma via primordial de conexão cortico-medular[71]. A sua função é, assim, essencial na veiculação de informação referente ao controlo motor voluntário[72]. Consequentemente, a afeção desta via associa-se à presença de alterações do controlo e função motora, objetiváveis clinicamente como défices de força muscular. Adicionalmente, a lesão desta via pode estar também associada a alterações da integridade do arco reflexo, ilustradas clinicamente pela presença de reflexos miotáticos hiperativos e clónus. Ademais, este tipo de lesões pode condicionar alterações do tónus muscular, como sendo a espasticidade. Por último, uma lesão do trato cortico-espinhal pode conduzir à desrepressão de reflexos primitivos segmentares, entre os quais se enquadra o reflexo cutâneo-plantar em extensão (sinal de *Babinski)*[71, 72]. Por outro lado, o corpo caloso desempenha um papel fundamental na comunicação inter-hemisférica, sendo que lesão desta estrutura pode condicionar défices cognitivos multi-domínios e síndromes disconectivos[73]. Apesar da potencial relevância neste âmbito destaca-se, contudo, a marcada carência de estudos neuro-imagiológicos funcionais, incluindo avaliações tratográficas, conectómicas e com paradigmas de ativação funcional.

Adicionalmente, também em estudos eletrofisiológicos, foram já documentadas várias alterações em doentes COVID-19 críticos, incluindo neuropatias agudas e subagudas, sensitivas, motoras ou mistas, de predomínio axonal e/ou desmielinizante, com afeção de um ou mais do que um nervo periférico[74, 75].

Além da elevada prevalência e possível morbilidade associada, a disfunção neurológica parece ter também um impacto na mortalidade associada à doença COVID-19[76, 77]. De facto, não só doentes com alterações neurológicas em fase aguda, como também doentes com patologias neurológicas prévias, parecem ter um maior risco de morte pela doença COVID-19[78]. No entanto, especificamente em doentes críticos, o impacto da doença neurológica prévia na mortalidade intra-hospitalar ainda não se encontra esclarecido, ao contrário do que já acontece com outras comorbilidades, como a hipertensão arterial, a dislipidemia, a diabetes *mellitus*, a doença pulmonar obstrutiva crónica, a patologia cardíaca, renal e oncológica[79, 80].

As interconexões neuro-respiratórias podem ser a justificação para o impacto negativo da patologia neurológica nos doentes com infeções respiratórias. De facto, a presença de uma lesão neurológica pode ser, por si só, um fator de agravamento da disfunção respiratória, nomeadamente na presença de lesões com afeção regional do tronco cerebral (por disfunção dos centros cardiorrespiratórios)[81-85]. Adicionalmente, esta relação pode também ser explicável pelo facto de a função respiratória estar diretamente relacionada com o sistema nervoso autónomo e com o controlo central da respiração[82].

A DOENÇA COVID-19: O FOCO NO DOENTE CRÍTICO

No doente crítico, independentemente do seu diagnóstico principal de admissão, existe um risco inerente de complicações relacionadas com o sistema nervoso, nomeadamente as lesões de nervos cranianos, neuropatias periféricas, lesões encefálicas e/ou medulares adquiridas (de etiologia tóxica, metabólica, vascular ou traumática)[86, 87]. De facto, um em cada três doentes admitidos por patologia não neurológica em UCI desenvolve complicações neurológicas, as quais podem surgir no contexto da própria doença crítica e/ou do seu tratamento (por iatrogenia) [86,88].

A existência de complicações neurológicas em doentes críticos associa-se a um aumento para o dobro da duração do internamento e a um risco de mortalidade duas vezes superior[86, 88].

No doente COVID-19 crítico, a importância destas alterações é ainda maior, uma vez que além da afeção do sistema nervoso potencialmente indexada à doença crítica e/ou ao seu tratamento, múltiplos sinais, sintomas e síndromes neurológicos foram descritos como características integrantes da infeção por SARS-CoV-2.

Assim, o exame neurológico tem particular relevância na avaliação clínica destes doentes, especificamente num contexto de diagnóstico, orientação terapêutica e prognóstico[89, 90]. Está, pois, recomendada a avaliação neurológica de todos os doentes admitidos em UCI, incluindo a avaliação do nível e conteúdo da consciência, da cognição, dos nervos cranianos, da função do tronco cerebral, da capacidade motora e vestíbulo-cerebelosa[90]. No entanto, estas avaliações podem revelar-se difíceis dado o contexto da doença crítica[86, 89].

Como tal, a suspeição clínica deve ser elevada e a presença de respostas anómalas deve ser particularmente valorizada[86]. Entre outros, o exame detalhado e rigoroso dos sinais de disfunção do trato cortico-espinhal (SDTCS), onde se inclui a apreciação dos reflexos miotáticos, dos reflexos cutâneos e do tónus, é criticamente importante neste contexto. A avaliação dos

reflexos miotáticos permite a rápida distinção entre patologia do primeiro e segundo neurónio motor (respetivamente, aumento ou diminuição/ausência da resposta reflexogénica)[91]. A presença de clónus e do sinal de *Babinski* (reflexo cutâneo-plantar em extensão) são sinais característicos de lesão do primeiro neurónio motor[91]. A avaliação dos SDTCS é um componente do exame neurológico cuja execução é rápida, informativa e sem necessidade de significativa colaboração do doente. Esta questão é particularmente relevante no contexto da atividade clínica em UCI, nomeadamente por ser uma avaliação aplicável em doentes sedo-analgesiados[91].

No entanto, a literatura é escassa no que se refere à prevalência de SDTCS no contexto de UCI, bem como à sua relevância clínica[92-94]. De facto, a influência real da iatrogenia farmacológica e da própria doença crítica nestes sinais encontra-se ainda por caracterizar[92-94]. Além disso, algumas complicações diretamente relacionadas com o internamento em UCI, entre as quais o exemplo paradigmático é a Fraqueza Muscular Adquirida nos Cuidados Intensivos (FMACI), podem mascarar a expressão destes sinais uma vez que, classicamente, esta entidade se associa a uma redução do tónus e à diminuição ou abolição dos reflexos miotáticos[95-97].

Assim, a inclusão do exame neurológico, e em particular da avaliação dos SDTCS, na avaliação sistemática do doente crítico é importante uma vez que, além da possibilidade de gerar a suspeição clínica de uma eventual afeção do sistema nervoso, é também fundamental para a eventual adaptação da intervenção de MFR realizada a estes doentes, especificamente no que se refere aos seus objetivos, estratégias e componentes.

A DOENÇA COVID-19: A REABILITAÇÃO EM FASE AGUDA

No doente crítico, independentemente de a etiologia da doença ser a COVID-19 ou não, o estado de doença hiper-aguda, a disfunção multiorgânica, a iatrogenia medicamentosa e técnica, a desregulação da cronobiologia e o afastamento da família são fatores predisponentes ao desenvolvimento de múltiplas complicações, designadamente neurológicas, músculo-esqueléticas, cardiovasculares, respiratórias, vesico-esfincterianas, cutâneas, entre outras[98, 99].

Estas complicações podem ser evidentes logo durante o internamento em UCI, ou apenas após a alta da unidade. Independentemente do *timing* do diagnóstico, mas particularmente nos casos em que se verifiquem complicações precoces relacionadas à doença crítica, programas integrados, multimodais e abrangentes de MFR têm demonstrados benefícios clínicos e funcionais a curto, médio e longo prazo[98, 100-104]. De facto, a implementação de programas de MFR em doentes críticos associa-se a uma melhoria da função física (respiratória, motora, manutenção da

integridade do revestimento cutâneo) e qualidade de vida, bem como à redução do número de dias sob ventilação mecânica invasiva (VMI) e da duração do internamento em UCI e hospitalar[98, 100-105].

Numa perspetiva histórica, apenas nos últimos 20 anos começou a surgir mais evidência relativamente ao impacto da MFR na abordagem ao doente crítico. No entanto, na última década, tem-se verificado um crescimento exponencial da quantidade e qualidade de estudos nesta área do conhecimento, acompanhando assim os avanços técnico-científicos da Especialidade[106, 107].

De facto, a avaliação e intervenção por MFR está preconizada como parte dos *standards* de abordagem clínica ao doente crítico em múltiplas recomendações internacionais[103, 105, 108]. Apesar de não se encontrarem totalmente estabelecidos os critérios de seleção e a "dose" ótima desta intervenção, existe consenso relativamente aos seguintes factos: 1) a mobilização precoce é segura e pode reduzir os custos associados aos cuidados de saúde; 2) devem existir critérios de segurança para o início do programa; 3) devem ser adotadas abordagens protocoladas e estruturadas; 4) é recomendada uma intervenção multimodal e multiprofissional, com profissionais capacitados e diferenciados para a intervenção neste contexto; 5) o doente e a família devem ser envolvidos na intervenção e 6) a avaliação dos resultados do programa e a valorização de medidas de resultado são um componente-chave da intervenção[108, 109].

Globalmente, a intervenção de MFR na UCI tem como objetivo principal reduzir a prevalência da FMACI, resultando num impacto positivo na autonomia, capacidade funcional, qualidade de vida e sobrevida[100, 102]. Adicionalmente, existe também evidência do impacto da reabilitação respiratória na redução do tempo sob VMI, na duração do desmame ventilatório e na mortalidade[104, 110, 111]. Especificamente no doente crítico com disfunção neurológica, a intervenção de MFR é particularmente importante, devendo ser iniciada o mais precocemente possível com vista a evitar adicionais sequelas estruturais e funcionais[98].

Particularizando ao doente COVID-19 crítico com aparente ou confirmada disfunção neurológica, a abordagem da MFR, em conformidade com os *standards* da Especialidade, deve ser feita de acordo com a Classificação Internacional da Funcionalidade, com objetivos e intervenções dirigidos à estrutura e função, atividades e participação[112, 113]. A implementação de estratégias de mobilização e verticalização precoce, combinada com reabilitação respiratória, cognitiva e abordagens multissensoriais, integrados num programa abrangente e multimodal, têm efeitos na função neurológica, respiratória e global nestes casos, com benefícios expressivos no que se refere à morbilidade e à mortalidade[98]. A existência de protocolos de reabilitação dirigidos

a doentes críticos COVID-19 na literatura, conforme detalhado nos estudos de *Levy et al.* e *Curci et al.* é particularmente importante na homogeneização das avaliações e intervenções realizadas[114-116]. Apesar da existência destes protocolos, orientados essencialmente para a disfunção respiratória característica da doença, realça-se a ausência de protocolos estandardizados que entrem em linha de conta, e apresentem intervenções dirigidas, à disfunção neurológica possivelmente indexada à COVID-19.

Para a implementação de programas de MFR em doentes críticos é imperativa a presença de determinados critérios de segurança[109]. As condicionantes respiratórias (incluindo estado e parâmetros ventilatórios e necessidade de terapêuticas adjuvantes), cardiovasculares (compreendendo a estabilidade hemodinâmica e a necessidade de dispositivos e/ou terapêuticas adjuvantes) e neurológicas (referentes ao estado de consciência e à pressão intracraniana) são basilares no que se refere à segurança para iniciar o programa de MFR[109].

Os efeitos adversos relacionados com a intervenção de MFR são raros (<4%), pelo que é relativamente unânime que os benefícios superam os potenciais riscos associados[109]. Realce para o facto de determinadas condições poderem não ser inviabilizadoras do início do programa de MFR, mas serem impactantes no seu desenho e implementação. Um exemplo clássico é o das lesões por pressão.

As lesões por pressão são definidas, em conformidade com o consenso do *National Pressure Ulcer Advisory Panel* de 2016, como lesões localizadas na pele e/ou tecidos moles sob uma proeminência óssea ou relacionadas com a presença de determinados dispositivos, como resultado de pressão intensa e/ou prolongada ou pressão em combinação com cisalhamento[117]. As lesões por pressão estão associadas a resultados desfavoráveis em saúde (relacionados com a morbimortalidade) e a um aumento dos custos em saúde[118]. Os doentes críticos são particularmente propensos ao desenvolvimento destas lesões, com prevalências duas vezes superiores aos doentes hospitalizados em enfermaria[119-121].

Na SDRA por SARS-CoV-2, esta complicação é ainda mais comum[122]. A maior prevalência de lesões por pressão em doentes COVID-19 críticos parece estar na dependência de múltiplos fatores, nomeadamente os que estão diretamente relacionados com a infeção por SARS-CoV-2, com a própria doença crítica e com o ambiente da UCI. No que se refere à infeção vírica, nestes casos o característico estado de coagulopatia sistémica e inflamação, combinado com a oclusão e lesão trombogénica microvascular, parece contribuir de modo significativo para o desenvolvimento destas complicações. Ademais, a própria doença crítica, pela hipotensão,

hipoxemia e compromisso na perfusão tecidular potencia o desenvolvimento de lesões por pressão. Adicionalmente, a limitação nos posicionamentos pela instabilidade hemodinâmica ou hipoxemia profunda resultantes da doença crítica, pode também resultar no desenvolvimento de alterações cutâneas no contexto da permanência de períodos temporais prolongados na mesma posição. Por último, o ambiente da UCI exerce também uma influência significativa na manifestação destas lesões cutâneas tanto pelas associadas alterações nutricionais, como pela utilização de tecnologias médicas, como sendo as cânulas de traqueostomia, os sistemas de oxigenoterapia, as sondas oro- e naso-gástricas, os cateteres urinários, as linhas e cateteres arteriais e venosos, entre outros[123-127].

A importância clínica e socioeconómica das lesões por pressão torna essencial a identificação precoce de doentes de risco acrescido, visando a atempada adoção de estratégias preventivas e de monitorização, incluindo programas de MFR, com o objetivo de reduzir a incidência desta complicação, particularmente no contexto de UCI. Destaca-se ainda que, pelo facto de as lesões por pressão poderem consubstanciar-se com um fator condicionante no início, estrutura e execução de programas de MFR em UCI, a sua prevenção de importância *major.*

A DOENÇA COVID-19: E DEPOIS DA ALTA?

O estado de saúde a longo termo dos sobreviventes de um internamento em UCI tem sido objeto de interesse e estudo crescente nos últimos anos[128]. Independentemente do diagnóstico de admissão, os sobreviventes a um internamento em UCI apresentam classicamente sequelas a curto, médio e longo termo[128]. Estas estão relacionadas com a doença crítica, com o tratamento e suporte de órgãos recebido, e com o próprio ambiente da UCI[128]. Além da morbilidade, sabe-se também que os sobreviventes da doença crítica têm um aumento significativo do risco de mortalidade nos anos subsequentes[129].

O elevado número de sobreviventes à doença crítica tem criado um peso significativo nos sistemas de saúde ao longo do contínuo de cuidados, sendo tal particularmente exemplificado com o advento da doença COVID-19. De facto, o impacto das sequelas a longo termo nos sobreviventes à COVID-19 parece ser tão ou mais significativo do que em outros doentes críticos[130].

Classicamente os doentes com COVID-19 crítica, em comparação com outros doentes críticos, têm um maior número de dias de internamento, sob VMI e sob sedo-analgesia e bloqueio neuromuscular[131-133]. Estes doentes têm, também, no contexto da sua doença de base e da

necessidade terapêutica associada, maior carga de fatores de risco para desenvolverem Síndromes Pós Internamento em Cuidados Intensivos (SPICI)[131-133]. Além disso, pelo menos na primeira vaga pandémica havia alguma incerteza por parte dos profissionais de saúde na segurança dos programas terapêuticos de MFR em doentes COVID-19 internados em UCI, com quadros clínicos de elevada gravidade[134]. Por todos os anteriores motivos, poderia pensar-se que a prevalência e gravidade das sequelas da doença crítica seria maior nesta população, em conformidade com alguns estudos da literatura[135]. No entanto, num estudo comparativo realizado por *Hodgson et al*, não foi encontrada uma diferença significativa na prevalência, severidade e impacto da SPICI entre doentes com COVID-19 e outros doentes críticos[136]. De destacar que, além da dúvida existente relativamente ao efeito da etiologia da doença crítica nas características da SPICI (especificamente quando nos referimos à comparação direta entre doentes com e sem COVID-19), a prevalência da síndrome nesta população de sobreviventes a uma infeção crítica a SARS-CoV-2, a sua evolução temporal, bem como a necessidade (ou não) de alteração da definição e nomenclatura da síndrome dado o contexto epidemiológico, não se encontram ainda totalmente esclarecidas[137].

A SPICI é um termo "guarda-chuva" para a presença de alterações, de novo ou agravadas, nos domínios físico, mental e cognitivo, com impacto na autonomia, funcionalidade e qualidade de vida, em sobreviventes de doença crítica[138].

No que se refere ao domínio físico, o achado predominante desta síndrome é a FMACI. Esta entidade consiste na perda combinada de massa e função muscular. Na sua base patofisiológica, está incluída a combinação de fenómenos miopáticos e (poli)neuropáticos[128, 139].

Quanto ao domínio mental, os principais achados incluem a ansiedade, a depressão e os sintomas de *stress* psicológico (incluindo *stress* pós-traumático), algo que está primariamente relacionado com a iatrogenia medicamentosa e com o próprio ambiente da UCI [140-142].

As alterações cognitivas incluem a disfunção em um ou múltiplos domínios, sendo os mais comummente afetados a memória, funcionamento executivo e a velocidade de processamento[143]. Os principais fatores de risco para disfunção cognitiva neste contexto são a hipoxemia, a hipotensão, a desregulação glicémica, a iatrogenia medicamentosa (especificamente por sedo-analgésicos) e as encefalopatias agudas secundárias[144].

A SPICI é uma entidade comum, sendo a prevalência de afeção do domínio físico de 25 a 80%, de afeção do domínio mental de 8 a 57% e de disfunção cognitiva de 30 a 80%[145-147]. Além

dos amplos intervalos de prevalência de disfunção de cada um dos domínios, destaca-se que existe também uma heterogeneidade significativa nas descrições da extensão, intensidade e duração dos sintomas de SPICI[128]. Esta variabilidade poderá estar relacionada com os critérios de diagnóstico utilizados e *timing* da sua aplicação, com a disparidade das características estruturais e funcionais dos centros onde decorrem os estudos existentes, bem como com características metodológicas destas investigações.

No que se refere à abordagem a esta entidade, existem algumas estratégias preventivas que se encontram recomendadas e, como tal, são idealmente implementadas durante o internamento em UCI. A redução da intensidade da sedação, tanto no que se refere à sua duração como às classes farmacológicas utilizadas (evitando, sempre que possível, o uso extenso de benzodiazepinas), a otimização nutricional, a instituição precoce de programas de MFR e a inclusão das famílias com liberalização das visitas aos doentes enquanto internados em UCI, são alguns dos exemplos mais característicos [148-150].

Especificamente no que se refere à intervenção de MFR, esta encontra-se preconizada em doentes críticos, desde a UCI até ao retorno à comunidade[151]. Efetivamente, e logo na UCI, a precocidade da intervenção associa-se a maiores benefícios clínicos e funcionais [101, 130, 152]. Dada a persistência e impacto a médio e longo prazo da SPICI, o seguimento clínico multidisciplinar, incluindo por MFR, encontra-se preconizado[153]. Ademais, a intervenção por MFR deve ser, idealmente, prolongada no tempo de acordo com a necessidade do doente[153].

Nos doentes COVID-19 a presença de uma doença crítica é de facto impactante: aproximadamente um em cada quatro sobreviventes à COVID-19 crítica que eram previamente independentes apresenta, à data de alta hospitalar, um estado de dependência funcional de novo[130]. Exatamente por isto, o seguimento e intervenção por MFR após a alta da UCI revela-se extraordinariamente importante. No entanto, existe ainda muito por esclarecer neste âmbito, especificamente no que se refere à evolução temporal do perfil da SPICI COVID-19 e aos programas de MFR ideais a implementar na prática clínica nesta população.

A DOENÇA COVID-19: A MINHA VISÃO E MOTIVAÇÃO

A minha ligação a esta linha de investigação que aborda o doente crítico COVID-19, nas vertentes da indexada disfunção neurológica e do impacto funcional da doença, surgiu de dificuldades práticas e desafios diagnósticos e terapêuticos na abordagem a estes doentes no início da pandemia COVID-19.

Nesta fase, o nível de conhecimento relativamente às características da doença e às abordagens terapêuticas com eventual eficácia era parco. A confrontação com esta realidade no âmbito da avaliação e intervenção por MFR do doente internado por COVID-19, nomeadamente do doente COVID-19 crítico, revelou-se um desafio. Deste modo, as questões de investigação de cada um dos trabalhos constituintes desta Tese surgiram de dúvidas clínicas e de dificuldades reais, pelo que o objetivo último desta dissertação é o de melhorar a qualidade na prática clínica, especificamente os cuidados prestados a estes doentes.

De facto, a atividade multidisciplinar e multiprofissional reveste-se de particular importância na otimização dos cuidados prestados nos Serviços de Saúde. Particularmente no doente crítico, a avaliação etiológica e diagnóstica, a instituição de medidas de prevenção de complicações e o tratamento atempado das mesmas, assenta em princípios de abrangência e integração na abordagem clínica.

A clara noção da imprescindibilidade da abordagem a estes doentes num âmbito multidisciplinar, com a inclusão na avaliação dos doentes COVID-19 de várias Especialidades além da Medicina Intensiva, nomeadamente a MFR, funcionou como um catalisador do presente Doutoramento. Adicionalmente, o meu particular interesse na reabilitação do doente neurológico e do doente crítico e a compreensão profunda dos desafios na abordagem a estes doentes, constituíram também uma alavanca para o desenho e desenvolvimento dos trabalhos constituintes desta Tese.

Assim, esta dissertação pretende contribuir para a expansão do conhecimento em torno destas temáticas, particularmente no âmbito da avaliação clínica, funcional e da predição de complicações no doente COVID-19 crítico enquanto internado em UCI, bem como na orientação destes casos após a alta da UCI.

OBJETIVOS

Compreendendo o impacto da doença crítica COVID-19, no que se refere à amplitude e importância clínica e funcional das suas manifestações (quer na fase aguda, quer a médio e longo prazo), e efeito na mortalidade, este projeto de investigação centrou-se principalmente nesta população de doentes.

A corrente investigação pretendeu estudar os doentes COVID-19, numa perspetiva de "antes, durante e depois" do internamento em UCI, com particular enfoque na disfunção neurológica e seu impacto clínico e funcional, de acordo com o fluxograma explicitado na Figura 3.

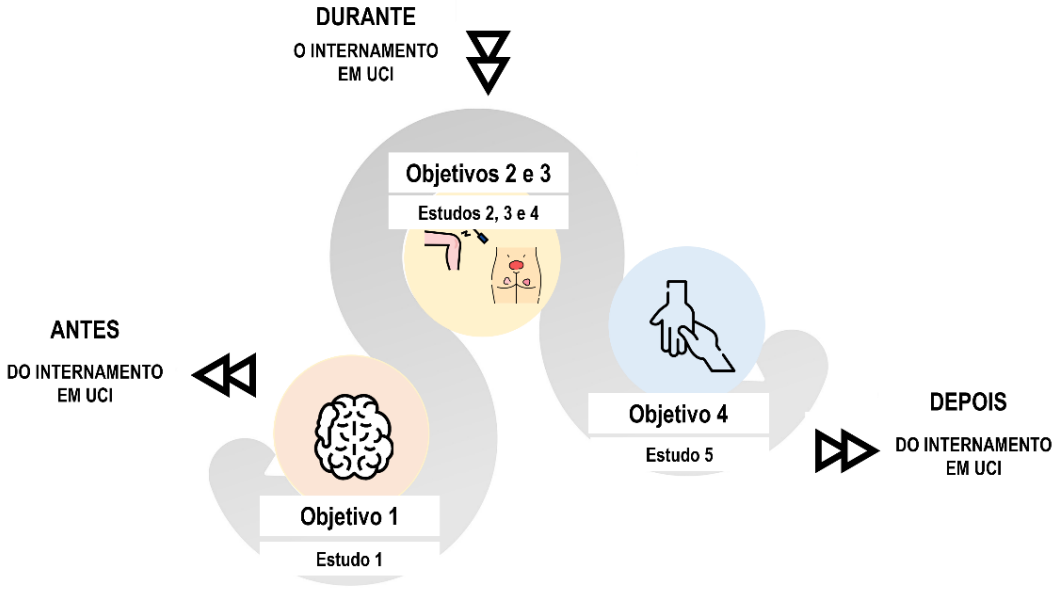

Figura 3. Fluxograma da organização dos objetivos e estudos da Tese.

Em suma, os objetivos específicos deste projeto foram:

1) Avaliar o impacto de comorbilidades neurológicas, especificamente a doença vascular cerebral (DVC) prévia, na mortalidade de doentes críticos COVID-19;
2) Investigar se a doença crítica por SARS-CoV-2 cursa, mais frequentemente, com sinais, sintomas e síndromes neurológicos, em comparação com SDRA causados por outros patógenos infeciosos:
    a. Descrever os principais sinais, sintomas e síndromes neurológicos existentes nesta população;

b. Identificar a prevalência destas alterações em UCI, comparando entre doentes com e sem COVID-19 crítica;
c. Identificar outros fatores, além da etiologia da doença crítica, potencialmente associados à disfunção neurológica em UCI;

3) Identificar fatores preditivos de outras complicações comuns em UCI, designadamente das lesões por pressão, dadas as suas consequências clínicas e potencial impacto no desenho e implementação de programas de MFR em doentes críticos COVID-19:
   a. Caracterizar as lesões por pressão, no que se refere à sua prevalência, severidade e topografia, em doentes críticos COVID-19;
   b. Identificar fatores preditivos, à admissão da UCI, para o desenvolvimento destas complicações;
   c. Desenvolver um modelo preditivo para este evento adverso;
   d. Converter o modelo num *score* de risco, visando facilitar a sua aplicação na prática clínica;
4) Caracterizar as consequências a longo termo da infeção crítica a SARS-CoV-2
   a. Descrever as consequências físicas, mentais e cognitivas, bem como o seu impacto na funcionalidade;
   b. Monitorizar a evolução temporal destas consequências.

PUBLICAÇÕES

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"What is the impact of previous cerebrovascular disease on critical COVID-19 patients' mortality? A prospective cohort study."

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What is the impact of previous cerebrovascular disease on critical COVID-19 patients' mortality? A prospective cohort study

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ABSTRACT

Objectives: We aimed to evaluate the effect of previous cerebrovascular disease (CVD) on mortality rates of critically ill COVID-19 patients.
Materials & methods: A prospective cohort study was performed between May/2020 and May/2021, at a tertiary-care-center. We consecutively included adult patients admitted to intensive care units (ICU) having as primary diagnosis Acute Respiratory Distress Syndrome due to SARS-CoV-2, requiring invasive mechanical ventilation for >48 h. We considered as exposure the diagnosis of previous CVD and as main outcome the in-ICU mortality.
Results: The study sample included 178 patients: 74.2% were males, with a mean age of 63 ± 12.4 years-old(yo). Previous CVD was documented in 17 patients (9.6%). During the study period, the mortality rate at ICU was of 33.1% ($n = 59$). The proportion of mortality at ICU was higher in patients with prior CVD (58.8% vs 30.4%; $p = 0.02$). Also, older patients (66 ± 11.4 yo vs. 62 ± 12.7 yo, $p = 0.04$) and those with higher score at SAPSII at ICU admission (47.8 ± 15.4 vs. 40.7 ± 15.9; $p = 0.01$) had a higher ICU deathrate. Patients with previous CVD had a 2.70 (95%CI = 1.36–5.39) higher likelihood of dying compared to those who had no previous CVD. After adjustment (for gender, age, SAPSII and total length of stay), multivariate Cox analysis revealed that previous CVD remained a strong predictor for in-ICU death in critically ill COVID-19 patients (*HR = 2.51; 95%CI = 1.15–5.51*).
Conclusions: Previous CVD was significantly associated to higher mortality in critical COVID-19 patients. We suggest that, in patients with previous CVD, prioritization of vaccination strategies should be implemented alongst with higher surveillance when infected with SARS-CoV-2.

1. Introduction

COVID-19 firstly emerged in December 2019, with a report of severe flu-like-illness in China [1]. After the disease spread to over 110 countries, a global pandemic was declared on March 2020 and as of that date the number of cases has been increasing daily, posing a severe health threat at a global scale [2]. After almost two years, this novel disease has provoked over 5 million deaths [3].

Most infected patients are asymptomatic or paucisymptomatic. Nevertheless, up to 15% have severe disease and around 5% became critically ill requiring ventilatory support [4].

Part of the biomedical research has focused on identifying risk factors associated with greater severity or higher mortality in COVID-19 patients, in order to improve preventive and therapeutic strategies. Demographic factors, such as age and gender, as well as comorbidities, such as diabetes, obesity, and cardiovascular diseases, were repeatedly associated with higher mortality [5]. Regarding the association between previous cerebrovascular disease (CVD) and mortality due to COVID-19, most studies have found a positive association [6–8]. Nevertheless, prior studies included both ambulatory and hospitalized patients, and thus were not directed to critically ill COVID-19 patients.

As so, we aimed to access the impact of previous CVD on the

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mortality rates of critically ill COVID-19 patients.

2. Materials and methods

2.1. Study design and definitions

Prospective cohort study including patients admitted to Intensive Care Units (ICU) of an Intensive Care Medicine Department of a tertiary-care center in Portugal, from May 2020 to May 2021. The sample recruitment methodology was systematic, with consecutive inclusion of all eligible patients.

Inclusion criteria encompassed the diagnosis of Acute Respiratory Distress Syndrome (ARDS) due to SARS-CoV-2 requiring ICU admission and invasive mechanical ventilation for >48 h, and age > 18 years-old (yo).

The study was approved by our institutional review board and performed in accordance with Helsinki declaration.

A COVID-19 case was assumed when a positive result on real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens was depicted before ICU admission.

ARDS was defined as an acute syndrome of lung inflammation and increased alveolar-capillary permeability associated with severe hypoxia and bilateral infiltrates on chest radiographs, with no evidence of left heart failure, in line with the Berlin definition [9].

Invasive mechanical ventilation (IMV) was defined as a form of artificial ventilation that included an endotracheal tube (ETT) and a mechanical ventilator [10].

We included under the label "previous CVD" any past cerebral infarction (ischemic strokes and silent infarctions), transient ischemic attacks and intracerebral hemorrhages (stroke and silent intracerebral hemorrhages), in accordance with the American Heart Association/American Stroke Association definitions [11,12].

The cause of death was determined using a pre-specified set of syndromes defined a priori, based on the review of the existing literature [13]. COVID-19 related multiple organ dysfunction syndrome (MODS) was defined as the dysfunction of two or more systems/organs, including pulmonary, hematologic, cardiac, neurological, renal, hepatic, and gastrointestinal, that were not existent before SARS-CoV-2 infection [14]. ICU-acquired infections were defined according to confirmed microbiological assessment or strong clinical suspicion without microbiological assessment. Indeed, we have considered secondary infection as a cause of death according to (1) the existence of a secondary infection, and (2) a compatible clinical course with clinical deterioration occurring after a transient improvement following admission [13]. Refractory hypoxemia was identified in case of a PaO2 < 60 mmHg for >1 h while receiving a FiO2 of 1.0 that led to intractable hypoxemia and/or hypercapnia [15]. Fatal mesenteric or limb ischemia, fatal myocardial infarction, pulmonary embolism leading to cardiac arrest and major strokes accounted for fatal thromboembolic events [13].

2.2. Data collection methods

The main investigator was responsible for the assessment of electronic clinical records (ECR) of included patients. Previous CVD was considered in the presence of confirmed clinical and/or neuroimagiological (including computed tomography and magnetic resonance imaging, reported by senior neuroradiologists of our center) findings. Data from selected patients were gathered on an anonymized electronic database and each patient received a unique code number to secure their anonymity.

2.3. Predictive variables and outcomes

Mortality at ICU was the main outcome. Data regarding the severity of the disease (including number of days at ICU and total length of stay; number of days under IMV, extracorporeal membrane oxygenation (ECMO), renal replacement therapy and vasopressor support) were also evaluated. The predictive variables were the following: age, gender, previous functional status assessed through the modified Ranking scale (mRS), comorbidities (including hypertension, diabetes *mellitus*, hyperlipidemia, obesity, smoking habits, atrial fibrillation, ischemic heart disease, heart failure, peripheral vascular disease, chronic pulmonary obstructive disease (CPOD), asthma, sleep apnea, chronic kidney disease, psychiatric pathology, oncologic pathology and immunosuppression [6,16]), previous cerebrovascular disease (type) and a severity score at ICU admission (the *Simplified Acute Physiology Score* (SAPS) II).

2.4. Sample size calculation and Statistical analysis

Due to lack of data on the effect of previous CVD on mortality in critical COVID-19 patients, we used data from a population-based cohort [6]. Considering an expected prevalence on the unexposed patients of 0.10, a relative risk of 3, a power of 80% and a level of significance of 0.05, we estimated that a total sample size of 118 patients would be required.

Statistical analysis was performed using SPSS program version 27 (IBM® Corporation, Armonk, NY). Categorical variables are summarized as frequencies and percentages, and continuous variables as mean and standard deviation (variables with normal distributions). Normal distribution was checked using histogram visual inspection. Chi-square test or Fisher's exact test were used, as appropriate, to compare categorical variables. Continuous variables were compared between groups using independent samples *t*-test. For the time-to-event analyses regarding the main outcome (mortality), cumulative incidence of event curves was estimated for each group (previous CVD versus no previous CVD). They were considered separately by using the Kaplan-Meier method and were compared statistically by using the log-rank test. We fitted a multivariable Cox proportional regression model, with the time unit being the number of ICU days until death. The model was adjusted for all covariates with a significant association with the dependent variable using the Backward-Wald methodology (cut-off for entry = 0.05; cut-off for exclusion = 0.10). All reported *p*-values are two-tailed, with a p-value <0.05 indicating statistical significance.

3. Results

The study sample consisted of 178 eligible patients admitted to the ICU during the study period, with a mean age of 63 ± 12.4 years-old (yo), 74.2% were men. Cases with previous CVD were 17 (9.6%), mostly ischemic strokes (47.1%), followed by transient ischemic attacks (23.5%), silent (17.6) and hemorrhagic (11.8%) strokes. Socio-demographic data, comorbidities and characteristics regarding critical respiratory illness, with a comparative analysis between cases with and without previous CVD, are summarized in Table 1.

Patients with previous CVD were more frequently dyslipidemic and had more often a history of ischemic heart disease. Patients with previous CVD had higher SAPS II at ICU admission; nevertheless, no significant differences were found regarding other parameters used as metrics of the severity of critical illness, as the number of days at the ICU and the total length of stay, number of days under IMV, ECMO, renal replacement therapy and vasopressor support.

During the study period, the mortality rate at the ICU was of 33% (n = 59). ICU deathrates at 30 and 90 days were 64.4% (n = 38), and 84.7% (n = 50), respectively. After ICU discharge, there were 2 additional deaths (one on the first 90 days, and another on the first 180 days).

A total of 58.8% (n = 10) of cases with previous CVD died during ICU stay, compared to 30.4% (n = 49) of the patients without previous CVD (p-value = 0.018). The median time to death was 25 days for patients with previous CVD and 116 days for patients without this comorbidity.

Causes of in-ICU death of the sample were the following: COVID-19 MODS (n = 26, 44.1%), ICU acquired infections (n = 20, 33.9%),

Table 1
Sociodemographic, comorbidities and characteristics regarding the critical illness of the sample.

Characteristic	Total cohort (n = 178)	No previous CVD (n = 161)	Previous CVD (n = 17)	p-value
Sociodemographic characteristics				
Male gender, n(%)	132 (74.2)	117 (72.7)	15 (88.2)	0.25
Age, mean (SD)	63.1 (12.4)	62.7 (12.5)	67.8 (10.6)	0.11
mRS, n(%)				0.18
0	176 (98.9)	160 (99.4)	16 (94.1)	
1	0 (0)	0 (0)	0 (0)	
2	2 (1.1)	1 (0.6)	1 (5.9)	
3	0 (0)	0 (0)	0 (0)	
4	0 (0)	0 (0)	0 (0)	
5	0 (0)	0 (0)	0 (0)	
Comorbidities				
Hypertension, n(%)	108 (60.7)	96 (59.6)	12 (70.6)	0.38
Diabetes *Mellitus*, n(%)	69 (38.8)	59 (36.6)	10 (58.8)	0.07
Hyperlipidemia, n(%)	89 (50.0)	76 (47.2)	13 (76.5)	0.02
Obesity, n(%)	78 (43.8)	73 (45.3)	5 (29.4)	0.21
Smoking habits, n(%)	6 (3.4)	6 (3.7)	0 (0.0)	1.00
Atrial fibrillation, n(%)	13 (7.3)	13 (8.1)	0 (0.0)	0.62
Ischemic heart disease, n(%)	12 (6.7)	8 (5.0)	4 (23.5)	<0.01
Heart failure, n(%)	10 (5.6)	8 (5.0)	2 (11.8)	0.25
Peripheral vascular disease, n(%)	19 (10.7)	17 (10.6)	2 (11.8)	1.00
CPOD, n(%)	7 (3.9)	7 (4.3)	0 (0.0)	1.00
Asthma, n(%)	10 (5.6)	9 (5.6)	1 (5.9)	1.00
Sleep apnea, n(%)	20 (11.2)	18 (11.2)	2 (11.8)	1.00
Chronic kidney disease, n (%)	12 (6.7)	9 (5.6)	3 (17.6)	0.09
Psychiatric pathology, n(%)	28 (15.7)	27 (16.8)	1 (5.9)	0.48
Oncologic pathology, n(%)	20 (11.2)	18 (11.2)	2 (11.8)	1.00
Immunosuppression, n(%)	13 (7.3)	12 (7.5)	1 (5.9)	1.00
>3 comorbidities[a], n (%)	104 (58.4)	12 (70.6)	92 (57.1)	0.29
Characteristics regarding critical respiratory illness				
SAPS II, mean (SD)	43.0 (16.0)	41.4 (14.7)	58.6 (20.7)	<0.01
ICU length of stay (days), median (IQR)	28.5 (199)	30 (199)	19 (100)	0.17
Hospital length of stay (days), median (IQR)	42 (309)	43 (260)	33 (306)	0.23
Number of days under IMV, median (IQR)	20 (197)	20 (197)	19 (101)	0.21
Number of days under vasopressors, median (IQR)	5 (130)	5 (130)	3 (38)	0.56
Number of days under ECMO support, median (IQR)	51 (193)	53 (193)	22 (81)	0.79
Number of days under renal replacement therapy, median (IQR)	21 (71)	22 (71)	13 (31)	0.87

Legend: CVD = Cerebrovascular disease; CPOD = Chronic pulmonary obstructive disease; ECMO = extracorporeal membrane oxygenation; mRS = modified Rankin scale; n = number of patients; SD = Standard deviation.
[a] Including all aforementioned comorbidies.

refractory hypoxemia ($n = 11$, 18.6%) and fatal thrombotic events (n = 2, 3.4%). No significative differences were found regarding the causes of death between patients with and without previous CVD. COVID-19 MODS was the cause of death in 23 patients without previous CVD (46.9%) and in 3 patients with previous CVD (30%; p-value = 0.08). A total of 16 patients without previous CVD (32.7%) and 4 patients with previous CVD (40%) died from ICU acquired infections (p-value = 0.27). Refractory hypoxemia was responsible for 9 deaths (18.4%) in the group of patients without previous CVD and for 2 deaths (20%) in the group with previous CVD (p-value = 0.60). The remaining cases (2 patients without previous CVD and 1 patient with previous CVD) died from fatal thrombotic events (p-value = 0.31).

Regarding the two patients that died after ICU discharge, none had previous CVD; in one patient, the cause of death was a fatal thrombotic event whereas in the other patient cause was death was not captured (out-hospital death).

Having a previous CVD was associated with an increased likelihood of dying in the ICU of 2.70 (95% Confidence interval (95%CI) 1.36–5.39) – Fig. 1A, compared to critically ill COVID-19 patients without this comorbidity.

We also found that older age (66 ± 11.4 yo vs. 62 ± 12.7 yo, p-value = 0.04) and higher Simplified Acute Physiology Score (SAPS) II at admission (47.8 ± 15.4 vs. 40.7 ± 15.9; p-value = 0.007) were associated with higher mortality (Table 2). Additionally, patients that survived ICU had a significantly higher ICU (34 (199) vs 18 (194); p-value = 0.02) and total length of stay (49 (309) vs. 23 (201); $p < 0.01$) (Table 2).

Using multivariate survival Cox analysis to adjust for the effect of gender (male gender; HR = 2.59; 95%CI = 1.12–5.97; p-value = 0.026), age (HR = 1.02; 95%CI = 0.93–1.04; p-value = 0.165), SAPS II at admission (HR = 0.99; 95%CI 0.98–1.01; p-value = 0.568) and total length of stay (HR = 0.95; 95%CI = 0.93–0.96; p-value<0.01), previous CVD remained independently associated with an increased risk of death in critically ill COVID-19 patients (HR = 2.51; 95%CI = 1.15–5.51; p-value = 0.021) – Fig. 1B.

In order to address specifically the impact of CVD on in-ICU mortality, we have also performed a subanalysis to access if patients without previous CVD that presented a similar level of ischemic disease (previous ischemic heart disease) also had higher mortality rates. Indeed, in our sample, the presence of ischemic heart disease was not significantly associated with a higher ICU deathrate (41.7% vs 32.5% p-value = 0.54).

4. Discussion

Our study revealed that, amongst critically ill COVID-19 patients, having previous CVD more than doubled the risk of death during ICU stay, irrespective of age, gender, severity of disease at ICU admission (SAPS II score) and total length of stay. The positive association of CVD with COVID-19 mortality has been previously described in some studies [6–8], but not unanimously [17]. Indeed, patients with previous CVD, possibly due to weaker immune functions (namely post stroke immunosuppression) and poorer organ functions, are thought to have higher risk of severe infections and mortality, according to Zhang L et al[8]. Also, and according to Lazcano U et al population-based study, individuals with previous CVD might carry a higher risk of mortality due to a previous impaired functional status or to their higher risk of cardiovascular events that can be precipitated by the setting of infection and hypercoagulability related to COVID-19 [6]. Nevertheless, data specifically regarding critically ill COVID-19 patients still lacks in the hitherto literature.

Our investigation differs from previous studies, as most of these were retrospective cohorts including ambulatory and hospitalized patients, and none was an exclusively ICU patients' prospective analysis. Additionally, previous studies have shown lack of standardization regarding CVD definition using broader and less well-specified definitions [18,19]. Indeed, our study used the international definitions, endorsed by institutions of reference of this area of knowledge [11,12]. Moreover, our study included data regarding the cause of death in the ICU patients, which was also not captured in previous analysis [6,20].

Several mechanisms have been proposed to explain the increased risk of mortality amongst critical respiratory patients with previous CVD. The presence of brain medullary cardiorespiratory or autonomic nervous system dysfunction may potentially cause circulatory and respiratory dysfunction, which can increase the risk of contracting

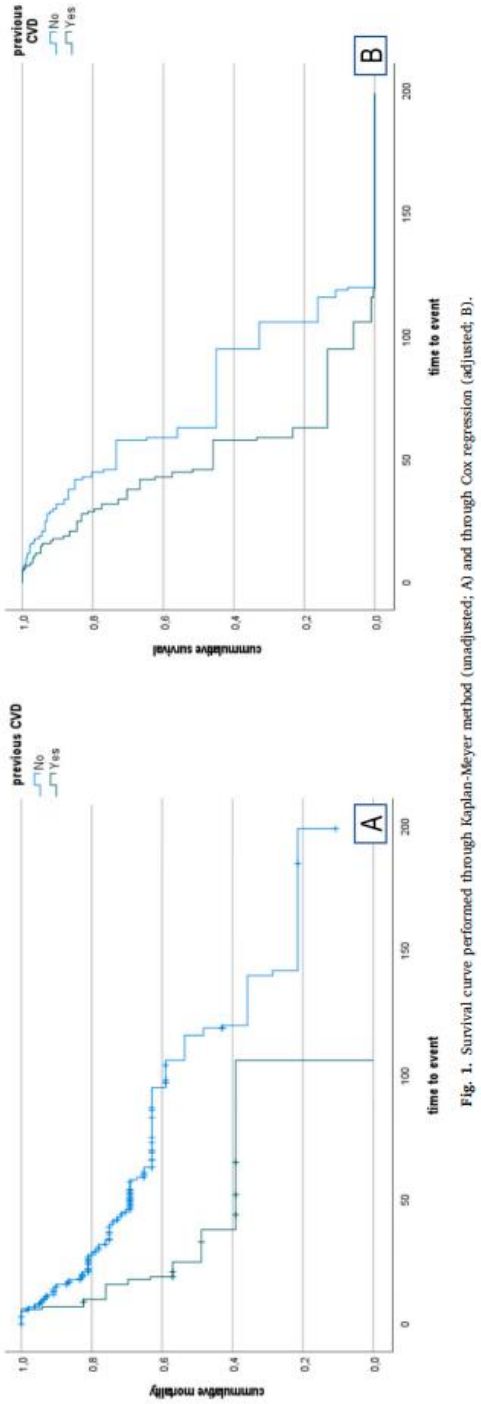

Fig. 1. Survival curve performed through Kaplan-Meyer method (unadjusted; A) and through Cox regression (adjusted; B).

Table 2
Bivariate analysis of characteristics associated with mortality in the ICU.

Characteristic	Total cohort (n = 178)	Survivor (n = 119)	Non survivor (n = 59)	p-value
Sociodemographic characteristics				
Male gender, n(%)	132 (74.2)	87 (73.1)	45 (76.3)	0.65
Age, mean (SD)	63.1 (12.4)	61.7 (12.7)	65.8 (11.4)	0.04
mRS, n(%)				1.00
0	176 (98.9)	118 (99.2)	58 (98.3)	
1	0 (0)	0 (0)	0 (0)	
2	2 (1.1)	1 (0.8)	1 (1.7)	
3	0 (0)	0 (0)	0 (0)	
4	0 (0)	0 (0)	0 (0)	
5	0 (0)	0 (0)	0 (0)	
Comorbidities				
Hypertension, n(%)	108 (60.7)	74 (62.2)	34 (57.6)	0.56
Diabetes *Mellitus*, n(%)	69 (38.8)	47 (39.5)	22 (37.3)	0.78
Hyperlipidemia, n(%)	89 (50.0)	61 (51.3)	28 (47.5)	0.63
Obesity, n(%)	78 (43.8)	57 (47.9)	21 (35.6)	0.12
Smoking habits, n(%)	6 (3.4)	5 (4.2)	1 (1.7)	0.67
Atrial fibrillation, n(%)	13 (7.3)	9 (7.6)	4 (6.8)	1.00
Ischemic heart disease, n(%)	12 (6.7)	7 (5.9)	5 (8.5)	0.54
Heart failure, n(%)	10 (5.6)	6 (5.0)	4 (6.8)	0.73
Peripheral vascular disease, n (%)	19 (10.7)	13 (10.9)	6 (10.2)	0.88
CPOD, n(%)	7 (3.9)	4 (3.4)	3 (5.1)	0.69
Asthma, n(%)	10 (5.6)	9 (7.6)	1 (1.7)	0.17
Sleep apnea, n(%)	20 (11.2)	14 (11.8)	6 (10.2)	0.75
Chronic kidney disease, n(%)	12 (6.8)	7 (5.9)	5 (8.5)	0.53
Psychiatric pathology, n(%)	28 (15.7)	21 (17.6)	7 (11.9)	0.32
Oncologic pathology, n(%)	20 (11.2)	13 (10.9)	7 (11.9)	0.85
Immunosuppression, n(%)	13 (7.3)	6 (5.0)	7 (11.9)	0.75
Previous CVD, n(%)	17 (9.6)	7 (5.9)	10 (16.9)	0.02
Characteristics regarding critical respiratory illness				
SAPS II, mean (SD)	43.0 (16.0)	40.7 (15.9)	47.8 (15.4)	<0.01
ICU length of stay (days), median (IQR)	28.5 (199)	34 (199)	18 (194)	0.02
Hospital length of stay (days), median (IQR)	42 (309)	49 (309)	23 (201)	<0.01
Number of days under IMV, median (IQR)	20 (197)	21 (159)	18.5 (197)	0.80
Number of days under vasopressors, median (IQR)	5 (130)	5 (130)	5 (123)	0.73
Number of days under ECMO support, median (IQR)	49 (193)	46 (155)	74 (192)	0.08
Number of days under renal replacement therapy, median (IQR)	21 (71)	18.5 (50)	22.5 (71)	0.83

Legend: CPOD = Chronic pulmonary obstructive disease; CVD = Cerebrovascular disease; mRS = modified Rankin scale; n = number of patients; SD = Standard deviation.

opportunistic infections (viral and bacterial) [21]. Another possible hypothesis is the relative immobility of post-stroke patients, which increases the risk for hypercoagulable state that culminates in thrombus formation [22]. Additionally, emerging evidence demonstrates that extrapulmonary viral invasion, including of the central nervous system, causes substantial neuronal damage [23]. Indeed, it seems extremely plausible that, in patients with lower neurological reserve, an infectious pathogen with neurotropism can lead to higher damage, in comparison with patients with absence of previous neurological dysfunction. Moreover, acute stroke patients with COVID-19 seem to have higher mortality rates than stroke patients without this infection, in accordance with Harrison SL *et al* study [24].

Patients with previous CVD were similar to patients without previous

CVD in most characteristics, with the exception of having significantly higher rates of hyperlipidemia and ischemic heart disease, in line with previous studies [6,20]. Moreover, we analyzed which factors were associated with higher mortality rates: asides from CVD, older age and higher scores on SAPS II were also significantly associated with higher mortality. These data are also in line with previous studies outside the ICU setting [8,17,19].We found a higher mortality rate in patients with previous CVD compared to other studies, which probably stems from restricting the study sample to critically ill COVID-19 patients who have, a priori, a higher risk of death than those admitted to other hospital medical wards. Indeed, our data also suggests that previous CVD is an independent risk factor for ICU mortality on COVID-19 patients, which is in line with Lazcano U et al population-based study [6]. Also, not only previous CVD critical COVID-19 patients had higher mortality rates, but also had a lower median number of days until this adverse event, also in accordance with the literature [6].

Our study presents some limitations. Sample size was calculated based on rates in the general population, given the absence of studies in ICU patients. This study data was abstracted from ECR, and as blinding of data collectors to previous DVC status of patients was not possible, an ascertainment bias could not be excluded. Nonetheless, all information was collected following a prespecified standardized form. We are aware of the fact that ethnicity information was not incorporated, and non-White ethnicity has been found to be a risk factor for COVID-19 mortality in population-based studies [7]. Also, and due to the fact that not all patients have performed neuro-imaging studies, additional cases of silent CVD could be overlooked, with an underestimation of the real prevalence of this entity. Likewise, cases of transient ischemic attacks could also have been underestimated due to underreporting. Furthermore, and given the pandemic effect on the ICU rates of admission, this earlier and higher rate of mortality of the CVD population can also be an overestimation since in critical COVID-19 patients with severe comorbidities (as previous CVD patients), the therapeutic roof could not be the same to patients without any prior comorbidities. Nonetheless, our sample had mostly often previous functional independence on all daily-life activities, in line with the ICU setting of the study.

5. Conclusions

We believe that our study provides valuable information with implications on clinical practice. As we report a higher rate of mortality amongst critical COVID-19 patients with previous CVD, even after adjusting for diseases' severity at admission and length of stay, we conclude that prioritizing vaccination and heightened surveillance in this subgroup of COVID-19 patients should be implemented. Additionally, we encourage prognostic research to include CVD as a component of prognostic models. Further studies, ideally multicentric, are warranted to access the possible differential impact of previous CVD between critical and non-critical COVID-19 patients.

Statements

I confirm that our Institution Ethics Review Board (Comissão de Ética para a Saúde – Centro Hospitalar Universitário de São João, Faculdade de Medicina da Universidade do Porto), approved this study (n° 169/20). Also, on behalf of all authors I deny any potential conflicts of interests and sources of funding. Regarding data sharing, the data that support the findings of this study are available from the corresponding author upon reasonable request.

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"Critical COVID-19 and neurological dysfunction - a direct comparative analysis between SARS-CoV-2 and other infectious pathogens."

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Critical COVID-19 and neurological dysfunction - a direct comparative analysis between SARS-CoV-2 and other infectious pathogens

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ABSTRACT

Objective: To evaluate whether critical SARS-CoV-2 infection is more frequently associated with signs of corticospinal tract dysfunction and other neurological signs, symptoms, and syndromes, than other infectious pathogens.

Methods: This was a prospective cohort study with consecutive inclusion of patients admitted to intensive care units due to primary infectious acute respiratory distress syndrome requiring invasive mechanical ventilation > 48 hours. Eligible patients were randomly assigned to three investigators for clinical evaluation, which encompassed the examination of signs of corticospinal tract dysfunction. Clinical data, including other neurological complications and possible predictors, were independently obtained from clinical records.

Results: We consecutively included 54 patients with acute respiratory distress syndrome, 27 due to SARS-CoV-2 and 27 due to other infectious pathogens. The groups were comparable in most characteristics. COVID-19 patients presented a significantly higher risk of neurological complications (RR = 1.98; 95%CI 1.23 - 3.26). Signs of corticospinal tract dysfunction tended to be more prevalent in COVID-19 patients (RR = 1.62; 95%CI 0.72 - 3.44).

Conclusion: Our study is the first comparative analysis between SARS-CoV-2 and other infectious pathogens, in an intensive care unit setting, assessing neurological dysfunction. We report a significantly higher risk of neurological dysfunction among COVID-19 patients. As such, we suggest systematic screening for neurological complications in severe COVID-19 patients.

Keywords: SARS-CoV-2; COVID-19; Respiratory distress syndrome; Coronavirus infections; Neurological manifestations; Pyramidal tract; Intensive care

INTRODUCTION

Coronavirus disease 2019 (COVID-19) poses a severe health threat on a global scale. Most infected patients are asymptomatic or paucisymptomatic. Nevertheless, up to 15% have severe disease, and approximately 5% become critically ill.[1]

This virus causes mainly respiratory signs and symptoms, whose seriousness greatly determines the severity and mortality of the disease. Nevertheless, neurological signs, symptoms and syndromes have been reported in the full clinical spectrum of COVID-19.[1,2] Descriptions include olfactory and gustatory dysfunction, cranial nerve and peripheral neuropathies, signs of corticospinal tract dysfunction (CSTD), cognitive impairment, *delirium*, seizures, meningitis, encephalitis, myelitis and acute cerebrovascular disease.[2-5]

Conflicts of interest: None.

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It remains unclear whether neurological dysfunction is solely an epiphenomenon of respiratory illness or directly related to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[3,5] The paucity of comparative studies designed to assess neurological dysfunction between COVID-19 and non-COVID-19 patients is the main reason for the persistence of this gap in knowledge.

We aimed to identify whether SARS-CoV-2 is more frequently associated with signs of CSTD and other neurological signs, symptoms, and syndromes, than other pathogens causing severe respiratory failure.

METHODS

Study design and definitions

This was a prospective cohort study with consecutive inclusion of patients admitted to four intensive care units (ICUs) of an intensive care department in a tertiary-care center between May 2020 and September 2021.

Inclusion criteria were age older than 18 years old and ICU admission diagnosis of infectious acute respiratory distress syndrome (ARDS), requiring invasive mechanical ventilation (IMV) for more than 48 hours.

Acute respiratory distress syndrome was defined in accordance with the Berlin definition as an acute syndrome of lung inflammation and increased alveolar-capillary permeability associated with severe hypoxia and bilateral infiltrates on chest radiographs, without evidence of left heart failure.[6]

Exclusion criteria were the presence of previous known central or peripheral neurologic pathologies reported in electronic clinical records (ECR) and death or discharge before the first 24 - 72 hours after ventilatory weaning.

The study was approved by our institutional review board (*Comissão de Ética* of the *Centro Hospitalar Universitário de São João* of the *Faculdade de Medicina, Universidade do Porto* - n° 169/20) and performed in accordance with the Helsinki Declaration. Written informed consent was waived considering the study setting, so verbal consent was obtained before clinical evaluation.

Sampling consisted of consecutive inclusion of all eligible patients until the calculated sample size was achieved.

A COVID-19 ARDS case was assumed when a positive result on a real-time reverse-transcriptase polymerase chain reaction (RT–PCR) assay of nasal and pharyngeal swab specimens was found during the first 24 hours after hospital admission. Other infectious ARDS cases were assumed when there was a primary ARDS due to other pathogens (identified through respiratory tract samples, blood, or urine cultures), with a negative RT–PCR assay for SARS-CoV-2.

Aphasia was defined as an impairment of comprehension or formulation of language, including semantic, grammar, phonology, morphology or syntax impairments.[7] Dysarthria was considered when there was a motor speech impairment causing slowness, weakness and/or imprecision in speech ability[8] and dysphonia when there was an impairment in voice production.[9] Focal weakness was assumed when there was a muscle strength deficit involving one or more limbs.[10] *Delirium* was defined as an alteration of attention, consciousness, and cognition, with a reduced ability to focus, sustain or shift attention.[11] A seizure was considered a change in the level of consciousness, behavior, memory, or feelings related to uncontrolled and/or abnormal electrical activity of the brain.[12] In accordance with the American Heart Association (AHA),[13,14] cerebrovascular diseases were classified as: (1) transient ischemic attack (TIA), a transient episode of neurological dysfunction caused by focal brain ischemia; (2) ischemic stroke, when there was an episode of neurological dysfunction caused by focal cerebral infarction and (3) hemorrhagic stroke, when a focal accumulation of blood within the brain parenchyma or ventricular system, that was not caused by trauma, occurred. Encephalopathy refered to dysfunction of the level or contents of consciousness due to brain dysfunction, possibly resulting from global brain insults or a focal lesion in relation to primary neurological or systemic conditions.[15] Encephalitis was assumed when there was an acute infection of brain parenchyma characterized clinically by fever, headache, and an altered level of consciousness,[16] and myelitis when there was an inflammatory disorder of the spinal cord, characterized by acute or subacute dysfunction affecting the motor, sensory, and/or autonomic systems.[17] Peripheral neuropathies encompassed disorders of peripheral nerve cells and fibers, including mononeuropathies, multifocal neuropathies and polyneuropathies.[18]

Data collection methods

The main investigator, supported by two senior physicians of physical medicine and rehabilitation (PMR) and intensive care medicine, was responsible for assessing the ECR of all patients admitted to the ICU daily. This assessment was used to identify patients fulfilling eligibility criteria for the study and to evaluate the timing of their ventilatory weaning (withdrawal from ventilatory support).

All patients were extubated at the time of the clinical evaluation. Data from patients who fulfilled eligibility criteria were gathered on a database, and each patient received a code number to secure their anonymity.

Eligible patients, 24 - 72 hours after ventilatory weaning, were randomly assigned through a computer-generated allocation sequence to one of three independent investigators for clinical assessment. The investigators were blinded to the patients' characteristics and to the study research question and aims. These investigators were PMR physicians with specific training on critical care and neurological rehabilitation. To ensure common evaluation methods, an educational session taught by a board certificated PMR specialist was attended before the study began. Clinical evaluation included assessment of level of sedation (using Richmond Agitation-Sedation Scale - RASS) and the evaluation of signs of CSTD, namely enhanced deep tendon reflexes (DTR) and the Babinski sign. Each patient was evaluated by the same investigator in the first 24 - 72 hours after ventilatory weaning and re-evaluated every 24 - 72 hours, until three observations were completed.

Deep tendon reflexes were evaluated using a predefined T-shaped reflex hammer at the following locations: biceps, triceps, brachioradialis, patellar and Achilles tendons. The grading of reflex response was performed in accordance with an adapted form of the National Institute of Neurological Disorders and Stroke (NINDS) myotatic reflex scale as follows: 0 - absent, 1 - hyporeflexia, 2 - normoreflexia, 3 - hyperreflexia, 4 - hyperreflexia with unsustained clonus (< 5 beats), and 5 - hyperreflexia with sustained clonus (> 5 beats).[19]

The Babinski sign was evaluated using the reflex hammer dull point by running up, with light pressure, the lateral plantar side of the foot, from heel to toe. The response of each hallux and toe was recorded as extensor (Babinski sign), flexor or neutral.[20]

Both on DTR and on Babinski sign evaluations, when in doubt, the investigators repeated each evaluation up to three times, recording the most consistent response. The investigators registered the anonymized measurements through an anonymized electronic form.

Outcomes and predictors

The primary outcomes were the presence of signs of CSTD and the presence of other neurological signs, symptoms, or syndromes (aphasia, dysarthria, dysphonia, focal weakness, *delirium*, seizures, stroke, transient ischemic attack, encephalopathy, encephalitis, myelitis, peripheral neuropathies). Signs of CSTD were defined as the presence of a Babinski sign in at least one extremity or hyperreflexia in at least two extremities.[21] We considered that signs of CSTD were present when identified in all clinical evaluations. Information regarding other neurological signs, symptoms or syndromes was recorded from the ECR. First, we analyzed the presence of each neurological complication individually. Moreover, we performed further analysis considering a combined dichotomic endpoint (neurological dysfunction composite). This composite considered, for each patient, the presence of at least one neurological sign, symptom, or syndrome, regardless of the number of neurological manifestations.

Several other data were extracted from the ECR by the main investigator before assessing data regarding clinical examination, namely, age; sex; previous autonomy on daily-life activities assessed through the modified Rankin scale (mRS); comorbidities (hypertension, diabetes mellitus, hyperlipidemia, obesity, smoking habits, atrial fibrillation, ischemic heart disease, heart failure, peripheral vascular disease, chronic pulmonary obstructive disease, asthma, sleep apnea, psychiatric pathology, oncologic pathology and immunosuppression); number of days in the ICU and total length of stay; number of days under IMV, noninvasive ventilation and oxygen therapy; need for prone sessions; need, type and number of days under extracorporeal membrane oxygenation (ECMO); and need and number of days under renal replacement therapy, vasopressors, sedanalgesics, neuromuscular blockers and corticosteroids.

The presence of other complications during the ICU stay was also recorded. Cardiovascular complications included bradyarrhythmia, tachyarrhythmia (atrial fibrillation, flutter, other tachyarrhythmias), tachycardia-bradycardia syndrome, secondary myocardial injury, cardiac arrest, pericarditis, pericardial effusion, endocarditis, acute heart failure and cardiogenic chock. Abdominal complications included hepatitis, elevated liver enzymes, gastrointestinal bleeding, pseudo-obstruction and obstruction, diarrhea, and constipation. Infectious complications were considered when ICU-acquired infections were observed, irrespective of admission diagnosis. Muscular weakness was assessed six to nine days after ventilatory weaning through the Medical Research Council-Sum Score (MRC-SS).

Sample size calculation and statistical analysis

Due to a lack of data on the characteristics and significance of DTR assessment in the ICU setting, data from a general population study were used.[4,22] Considering an expected prevalence of the unexposed of 0.36, a relative risk (RR) of 2, a power of 80% and a level of significance of 0.05, we estimated a total sample size of 54 patients (27 per group).

Statistical analysis was performed using Statistical Pakage for the Social Sciences (SPSS) software, version 27. Categorical variables are summarized as frequencies and percentages, and continuous variables are summarized as the mean and standard deviation (variables with normal distribution) or median and interquartile range (variables with skewed distributions). Normal distribution was checked using histogram visual analysis. The chi-square test or Fisher's exact test was used, as appropriate, to compare categorical variables. Continuous variables were compared between groups using independent samples t test or the Mann–Whitney U test, in accordance with the variable distribution. The RR, its standard error and its 95% confidence interval (95%CI) were calculated according to Altman et al.[23] Binary logistic univariate analysis was also performed, using the composite of neurological complications as the dependent variable. All reported p values are two-tailed, with a p value < 0.05 indicating statistical significance.

RESULTS

A total of 207 patients diagnosed with primary infectious ARDS were admitted to the ICU during the study period. Were excluded 153 patients: 89 died, 42 were transferred to other hospitals before neurological assessment, and 22 had previous neurological pathology. Fifty-four patients were consecutively included in accordance with the sample size calculation: 27 with ARDS due to COVID-19 and 27 with ARDS due to other infectious pathogens.

Regarding the group with ARDS due to other infectious pathogens, most agents (56%) were *Gram*-negative bacteria (*Serratia, Rickettsia, Pseudomonas, Moraxella, Legionella, Klebsiella, Escherichia coli, Haemophilus influenzae*), but other agents, including gram-positive bacteria (*Staphylococcus, Streptococcus, Enterococcus*) and fungal pathogens (*Pneumocystis, Aspergillus*), were also identified.

Table 1 details the sample's sociodemographic and clinical characteristics. Despite being comparable in most characteristics, COVID-19 patients were immunosuppressed less often (0% *versus* 26%: p value = 0.010). Immunosuppression in the ARDS due to other infectious pathogens group was due to posttransplant status (n = 3), alveolar proteinosis (n = 1), ANCA-MPO vasculitis (n = 1), neoplasms (n = 1) and human immunodeficiency virus infection (n = 1).

Regarding characteristics related to critical respiratory illness (Table 1), the groups were also comparable. Nevertheless, COVID-19 patients had a significantly higher number of days in the ICU (p value = 0.006) under IMV (p value = 0.039), sedoanalgesia (p value = 0.025), and corticosteroids (p value = 0.004), with higher rates of prone positioning (p value < 0.001).

Regarding the primary outcome, 61% of the sample presented at least one neurological sign, symptom, or syndrome. Nevertheless, each neurological complication was *per se* rare (< 5%), except for *delirium* (30%) and signs of CSTD (33%).

We compared the groups on the presence of each neurological complication and on the neurological dysfunction composite. We identified significant differences between groups when analyzing the composite (p value = 0.002), with COVID-19 patients presenting with an RR 1.98-fold higher (95%CI 1.23 - 3.26) than patients admitted for ARDS due to other etiologies (85% *versus* 43%). In the analysis of each complication, our data did not reach statistical significance (Table 2). Moreover, 44% of COVID-19 patients presented signs of CSTD, while in non-COVID patients, its prevalence was 27%. Although signs of CSTD tended to be more prevalent in COVID-19 patients (RR = 1.62; 95%CI 0.72 - 3.44), this difference did not reach statistical significance (p value = 0.20). Regarding the RASS at the time of neurological examination, no differences were found between groups for any of the evaluations (p values: 1st observation: 0.649; 2nd observation: 0.093; 3rd observation: 0.170).

To identify factors potentially associated with neurological complications, we performed a univariate analysis (Table 3), in which no other variables, apart from COVID-19 diagnosis, were associated with this adverse event.

Moreover, we analyzed whether there were differences between groups in nonneurological complications (Table 2). No significant differences were observed, except for infectious complications (p value < 0.001): COVID-19 patients had a 3.29-fold higher risk (95%CI 1.70 - 6.34).

Table 1 - Sociodemographic and clinical features

	Total (n = 54)	COVID-19 ARDS (n = 27)	Other infectious ARDS (n = 27)	p value
Sociodemographic features				
Age	62 ± 12	65 ± 12	59 ± 13	0.07*
Men	38 (70)	18 (67)	20 (74)	0.55†
Modified Rankin scale				1.00‡
0	53 (98)	27 (100)	26 (96)	
3	1 (2)	0 (0)	1 (4)	
Comorbidities				
Hypertension	25 (46)	14 (52)	11 (41)	0.41†
Diabetes Mellitus	22 (41)	11 (41)	11 (41)	1.00†
Hyperlipidemia	19 (35)	13 (48)	6 (22)	0.05†
Obesity	15 (28)	11 (41)	4 (15)	0.05†
Smoking habits	11 (20)	3 (11)	8 (30)	0.09‡
Atrial fibrillation	4 (7)	3 (11)	1 (4)	0.61‡
Ischemic heart disease	3 (6)	0 (0)	3 (11)	0.24‡
Cardiac insufficiency	5 (9)	1 (4)	4 (15)	0.35‡
Peripheral vascular disease	6 (11)	5 (19)	1 (4)	0.19‡
CPOD	6 (11)	1 (4)	5 (19)	0.19‡
Asthma	3 (6)	3 (11)	0 (0)	0.24‡
Sleep apnea	7 (13)	2 (7)	5 (19)	0.42‡
Psychiatric disorders	11 (20)	7 (26)	4 (15)	0.31†
Cancer	10 (19)	5 (19)	5 (19)	1.00†
Immunosuppression	7 (13)	0 (0)	7 (26)	0.01‡
Characteristics regarding critical respiratory illness				
APACHE	20 ± 7	19 ± 5	22 ± 8	0.14*
SAPS II	44 ± 16	40 ± 15	47 ± 16	0.15*
Days on ICU	17 (185)	22 (185)	13 (42)	0.01§
Total length of stay	36 (228)	38 (228)	31 (69)	0.09§
Days under IMV	11 (157)	14 (157)	9 (36)	0.04§
Days under NIV	2 (13)	3 (13)	1 (7)	0.06§
Days under HFNO therapy	0.5 (30)	1 (10)	0 (30)	0.11§
Prone position	31 (57)	21 (78)	10 (37)	< 0.01†
ECMO	10 (19)	6 (22)	4 (15)	0.48†
Days under ECMO	27 (146)	63 (146)	17 (31)	0.26§
Corticosteroids	33 (61)	22 (82)	11 (41)	< 0.01†
Days under corticosteroids	7 (28)	10 (24)	0 (28)	< 0.01§
Vasopressor need	48 (89)	24 (89)	24 (89)	1.00†
Days under vasopressor support	5 (75)	7 (75)	5 (22)	0.16§
Renal replacement therapy	9 (17)	3 (11)	6 (22)	0.47‡
Days under renal replacement therapy	14 (53)	23 (47)	10 (40)	0.38§
Neuromuscular block > 24 hours	49 (91)	26 (96)	23 (85)	0.35‡
Days under neuromuscular block	5 (93)	7 (93)	4 (9)	0.09§
Sedoanalgesia	54 (100)	27 (100)	27 (100)	---
Days under sedoanalgesia	11 (184)	15 (184)	9 (32)	0.03§

ARDS - acute respiratory distress syndrome; CPOD - chronic pulmonary obstructive disease; APACHE - Acute Physiology and Chronic Health Evaluation; SAPS - Simplified Acute Physiology Score; ICU - intensive care unit; IMV - invasive mechanical ventilation; NIV - noninvasive ventilation; HFNO - high flow nasal oxygen; ECMO - extracorporeal membrane oxygenation; IQR - interquartile range. * Independent samples t test; † Pearson chi square test; ‡ Fisher exact test; § Mann-Whitney U test. Results expressed as mean ± standard deviation; n (%); or median (interquartile range).

Table 2 - Complications of critical respiratory illness

	Total (n = 54)	COVID-19 ARDS (n = 27)	Other infectious ARDS (n = 27)	RR (95%CI)	p value
Neurological complications					
Delirium	16 (30)	9 (33)	7 (26)	1.28 (0.56 - 2.95)	0.55*
Seizures	2 (4)	2 (7)	0 (0)	5.00 (0.25 - 99.52)	0.49†
Transient ischemic attack	1 (2)	1 (4)	0 (0)	3.00 (0.13 - 70.54)	1.00†
Encephalopathy	1 (2)	1 (4)	0 (0)	3.00 (0.13 - 70.54)	1.00†
Encephalitis	0 (0)	0 (0)	0 (0)	--	--
Myelitis	0 (0)	0 (0)	0 (0)	--	--
Peripheral neuropathy	2 (4)	2 (7)	0 (0)	5.00 (0.25 - 99.52)	0.49†
Aphasia	1 (2)	1 (4)	0 (0)	3.00 (0.13 - 70.54)	1.00†
Dysarthria or dysphonia	1 (2)	1 (4)	0 (0)	3.00 (0.13 - 70.54)	1.00†
Focal weakness	0 (0)	0 (0)	0 (0)	--	--
Signs of CSTD‡	18 (33)	11 (44)	7 (27)	1.62 (0.72 - .44)	0.20*
Composite of neurological complications§	33 (61)	22 (85)	11 (43)	1.98 (1.23 - 3.26)	< 0.01*
Overlap with other infections	30 (56)	23 (85)	7 (26)	3.29 (1.70 - 6.34)	< 0,01*
Abdominal complications	22 (41)	11 (41)	11 (41)	1.00 (0.53 - 1.90)	1.00*
Cardiovascular complications	15 (28)	10 (37)	5 (19)	1.53 (0.68 - 3.45)	0.13*

ARDS - acute respiratory distress syndrome; RR - relative risk; 95%CI - 95% confidence interval; CSTD - corticospinal tract dysfunction. * Pearson chi square test; † Fisher exact test; ‡ defined as the presence of the Babinski sign in at least one extremity or other pyramidal tract signs in at least 2 extremities(21); § including all described neurological complications. Results expressed as n (%).

Table 3 - Univariable logistic analysis of possible factors associated with neurological complications

Composite for neurological complications	Odds ratio (95%CI)	p value*
Age	1.03 (0.99 - 1.08)	0.16
Men	2.00 (0.60 - 6.64)	0.26
Modified Rankin scale	--	--
Hypertension	0.78 (0.25 - 2.39)	0.66
Diabetes Mellitus	0.73 (0.23 -2.28)	0.59
Hyperlipidemia	2.05 (0.60 - 7.05)	0.25
Obesity	0.91 (0.27 - 3.11)	0.89
Smoking habits	0.70 (0.16 - 3.05)	0.63
Atrial fibrillation	1.97 (0.19 - 20.32)	0.57
Ischemic heart disease	0.29 (0.03 - 3.43)	0.33
Cardiac insufficiency	0.93 (0.14 - 6.12)	0.94
Peripheral vascular disease	0.13 (0.01 - 1.25)	0.08
CPOD	---	---
Asthma	1.27 (0.10 - 14.9)	0.85
Sleep apnea	0.41 (0.08 - 2.08)	0.29
Psychiatric disorders	1.17 (0.29 - 4.64)	0.83
Cancer	2.52 (0.47 - 13.6)	0.28
Immunosuppression	0.59 (0.11 - 3.24)	0.54
APACHE	1.01 (0.93 - 1.11)	0.67
SAPS II	0.98 (0.95 - 1.02)	0.44
Days on ICU	1.01 (0.99 - 1.03)	0.25
Total length of stay	0.96 (0.96 - 1.00)	0.21
Days under IMV	1.01 (0.98 - 1.03)	0.59
Days under NIV	1.20 (0.94 - 1.54)	0.15
Days under oxygen therapy	1.09 (0.91 - 1.30)	0.32
Prone position	0.97 (0.31 - 3.04)	0.96
ECMO	1.31 (0.29 - 5.95)	0.73
Days under ECMO	1.01 (0.95 - 1.05)	0.59
Corticosteroids	1.91 (0.61 - 5.97)	0.27
Days under corticosteroids	1.00 (0.92 - 1.09)	0.93
Vasopressor need	1.71 (0.31 - 9.42)	0.54
Days under vasopressor support	1.00 (0.96 - 1.04)	0.98
Renal replacement therapy	2.52 (0.47 - 13.58)	0.28
Days under renal replacement therapy	1.68 (0.65 - 4.35)	0.28
Neuromuscular block > 24 hours	2.65 (0.40 - 17.44)	0.31
Days under neuromuscular block	1.03 (0.96 - 1.10)	0.47
Sedoanalgesia > 24 hours	---	---
Days under sedoanalgesia	1.01 (0.99 - 1.03)	0.49
MRC-SS	1.03 (0.97 - 1.09)	0.31
COVID-19 ARDS	5.73 (1.65 - 19.91)	< 0.01

95% CI - 95% confidence interval; CPOD - chronic pulmonary obstructive disease; APACHE - Acute Physiology and Chronic Health Evaluation; SAPS - Simplified Acute Physiology Score; ICU - intensive care unit; IMV - invasive mechanical ventilation; NIV - noninvasive ventilation; ECMO - extracorporeal membrane oxygenation; MRC-SS - Medical Research Council Sum Score; ARDS - acute respiratory distress syndrome. * Obtained through binary logistic analysis.

DISCUSSION

Critical COVID-19 patients presented a 1.98-fold higher risk of developing neurological complications than patients admitted to the ICU for other infectious ARDS. To our knowledge, this is the first study comparing the presence of signs of CSTD and other neurological signs, symptoms and syndromes, between COVID-19 and non-COVID-19 critical ARDS patients.

Several signs, symptoms and syndromes of neurological dysfunction have been reported in up to 80% of COVID-19 patients on the disease's full clinical spectrum. These findings have generated considerable concern due to their possible impact on mortality, morbidity, disability, and quality of life.[24]

Clinical and preclinical data have shown that SARS-CoV-2 has some degree of neurotropism, and different mechanisms have been suggested to account for this.[25,26] First, it is thought that SARS-CoV-2 exploits the angiotensin converting enzyme 2 receptor to enter cells, namely, in the respiratory system and in neurological tissue.[26] Nonetheless, non angiotensin converting enzyme 2 pathways have not been excluded. Both a direct transsynaptic route via the olfactory bulb and a blood circulatory pathway, through which systemic inflammation compromises the blood–brain barrier, have been proposed.[27] Another possible explanation is that the combination of hypoxia and neuroinflammation damages hippocampal and cortical areas, resulting in neuropsychiatric effects.[25]

Indeed, multiple studies have addressed the frequency and characteristics of neurological dysfunction among COVID-19 patients,[28,29] but there is still a substantial gap in knowledge in several domains, specifically regarding critically ill patients. Both central and peripheral nervous system involvement have been extensively reported in ICU patients, either as a manifestation of systemic critical illness or its treatment.[30] Furthermore, one in three patients admitted due to nonneurological pathology in the ICU develop neurological complications, which doubles the length of stay and mortality rate, increasing postdischarge disability.[30] As such, critical COVID-19 patients could be prone to develop not only possible disease-associated neurological dysfunction (neuro-COVID) but also ICU-related neurological complications.

In our study, both groups were comparable regarding most baseline characteristics. Nonetheless, COVID-19 patients were immunosuppressed less often than non-COVID-19 patients. Additionally, COVID-19 patients had a higher number of days in the ICU, under IMV and under sedoanalgesia. As these factors could possibly influence the rates of neurological dysfunction, we analyzed whether any were associated with neurological dysfunction, and no significant differences were found. Additionally, when assessing the between-group differences in the RASS, we also aimed to identify the impact of those characteristics on the clinical status at the time of clinical examination, and again, no significant differences were found. Thus, COVID-19 patients had a higher risk of neurological complications regardless of the critical illness severity or its treatment.

In our sample, the overall prevalence of neurological dysfunction was 85% among COVID-19 patients, similar to the literature.[24] Each neurological complication was *per se* rare, which is also similar to the Deana et al. study.[31] Nevertheless, *delirium* (33%) and signs of CSTD (44%) were common complications, with a lower prevalence in comparison to other studies.[32] Regarding *delirium*, despite its frequency and impact, the use of screening tools remains low, leading to a potential underestimation of its real prevalence in our sample. Additionally, regarding the signs of CSTD, its prevalence in our sample was also lower than that in previous studies, which could be due to the application of different diagnostic criteria (in relation to the absence of a standard).

In our study, we assessed signs of CSTD as an objective measure of neurological involvement. In the ICU, a detailed neurological examination can be extremely difficult to perform. However, the evaluation of signs of CSTD can be an important tool since it does not require patient collaboration, which is frequently compromised in this setting. DTR assessment allows a rapid and clear distinction between upper and lower motor neuron pathology (enhanced and depressed/absent reflexes, respectively), and the presence of the Babinski sign is a characteristic finding of upper motor neuron pathology.[33] Few studies have evaluated the prevalence of CSTD in the ICU setting and its clinical relevance, as well as the real influence of iatrogenesis (namely, neuromuscular blockage) on this manifestation.[4,34,35] Moreover, intensive care unit acquired weakness (ICUAW), which can have an increased prevalence in this population as risk factors are significantly more common, can also mask the presence of signs of CSTD because, when ICUAW is present, the DTR response is reduced or absent, so an underestimation of CSTD can be present in our analysis given the study setting.[4,36-38] However, magnetic resonance imaging studies of COVID-19 patients showed that corticospinal tract lesions were the most common lesions of the white matter.[39] Indeed, in our analysis, COVID-19 patients tended to have higher rates of CSTD signs, with a 1.2-fold higher RR.

Regarding ICU complications, there were no differences in the rates of muscular weakness, cardiovascular and abdominal complications, data consistent with the literature.[40]

We highlight that this is the first comparative study in the ICU setting, aimed at assessing neurological dysfunction, that established a direct comparison between ARDS due to COVID-19 and other pathogens. The study design and methodological strengths reinforce our major findings. To assure the external validity of our results, there was a consecutive sampling of participants and inclusion of patients from different ICU. Regarding the internal validity of our data, we stress that the main investigator collected the predictive variables before assessing data regarding neurological bedside examination and that the three associated investigators were independent (so blinded to the patients' characteristics). Additionally, regarding the evaluation method, the same material (to decrease the risk of instrumental biases) was used, and the investigators were trained by the same expert to ensure common evaluation techniques. Additionally, to evaluate possible confounding factors, we performed a univariate analysis that confirmed that no factor other than COVID-19 diagnosis was significantly associated with the presence of neurological dysfunction.

Our study presents some limitations. Sample size was calculated based on CSTD rates in the general population, given the absence of studies in ICU patients when our study's recruitment started. Nevertheless, Helms et al.'s data, published during our recruitment period, reveals a higher prevalence of signs of CSTD in the COVID-19 population, which is probably related to the heterogeneity of the criteria for defining CSTD.[4]

Indeed, in critical ARDS patients, neuromuscular blockage is used as a standard of care, and ICUAW is present in more than 50% of cases. As the effect of both on the DTR response is thought to be its reduction or abolition, this should be fully considered when these examinations are performed in the ICU.[34,35] Moreover, in our sample size calculation, we considered an RR of 2, so the absence of differences in our population regarding the CSTD signs may be because the relative risk is 19% lower than expected. As such, CSTD rates in the ICU setting may be lower, and thus, the sample size may have been underestimated. Additionally, DTR assessment and rating are dependent on subjective judgment and are operator dependent, implying inter- and intraobserver variability, the extent of which has been rarely reported.[41] Moreover, the signs, symptoms and syndromes of neurological dysfunction included in the composite (aphasia, dysarthria, dysphonia, focal weakness, *delirium*, seizures, stroke, transient ischemic attack, encephalopathy, encephalitis, myelitis, peripheral neuropathies) were only considered when registered in medical records; thus, registration bias must be considered.

Given the higher percentage of neurological dysfunction among COVID-19 patients, we suggest that patients with severe forms of COVID-19 should be systematically screened for neurological complications. Moreover, it is thought that patients with neurological complications during index hospitalization have significantly worse 6-month functional outcomes.[42] Early evaluation of physical medicine and rehabilitation may allow early diagnosis of neurological complications and implementation of tailored therapeutic interventions to reduce the long-term impact of these sequelae.[32,42]

Further studies are warranted to assess the long-term impact of neurological dysfunction in COVID-19 patients. The relationship between the signs of CSTD and neurological syndromes, as well as inter- and intraobserver reliability for CSTD, remains to be characterized in the ICU setting. Additionally, a causal relationship between disease severity and frequency and the characteristics of neurological involvement remains controversial.

CONCLUSION

In brief, critical COVID-19 patients presented a significantly higher risk of developing neurological complications than patients admitted to the intensive care unit due to other infectious acute respiratory distress syndromes. Thus, we suggest that patients with severe forms of COVID-19 should be systematically screened for neurological complications due to its impact on patient morbidity and quality of life.

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“Complex regional pain syndrome after severe COVID-19 - A case report.”

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Case report

Complex regional pain syndrome after severe COVID-19 – A case report

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HIGHLIGHTS

- In an intensive care unit, neurological complications are frequently encountered.
- CRPS may occur after peripheral nerve injuries, leading to increased disability.
- The systemic hyperinflammation of severe COVID-19 may contribute to neuronal sensitization.
- Peripheral and central neuronal sensitization can lead to chronical and disproportionate pain.
- A multidisciplinary approach is important in prompt diagnosis and treatment.

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ABSTRACT

Neurological complications are frequently reported in an intensive care unit (ICU), as a manifestation of a critical systemic illness or of its treatment. On the specific setting of COVID-19 patients, peripheral nerve lesions can have a multiplicity of causes, such as post-infectious neuropathy, positioning-related neuropathy or iatrogeny. An unusual but potentially disabling complication of any peripheral nerve lesion is Complex Regional Pain Syndrome (CRPS). Although there have been no mechanistic studies assessing how SARS-CoV-2 might directly impact nociception, it is hypothesized that the systemic hyperinflammation seen in severe COVID-19 may contribute to peripheral and central neuronal sensitization, possibly increasing the risk of developing CRPS. This case report highlights the potential hazards and consequences of peripheral nerve injuries on an ICU setting in COVID-19 patients, as well as the importance of a multidisciplinary approach for an early diagnosis and treatment, which are directly related to a better prognosis.

1. Introduction

Neurological complications are frequently reported in an intensive care unit (ICU), as a manifestation of a critical systemic illness or of its treatment [1]. These complications may present during the ICU stay (stroke, anoxic-ischemic injuries, peripheral nerve injuries, delirium, seizures) or after ICU discharge (Post-traumatic Stress Disorder and depression) [1]. Specifically on COVID-19 patients, peripheral nerve lesions (PNL) most commonly occur as a manifestation of SARS-CoV-2 infection (post-infectious neuropathy), a sequela of COVID-19 critical illness (positioning-related neuropathy) or as consequence of a treatment (iatrogenic lesions) [2].

Peripheral nerve lesions usually follow a well-recognized clinical course, depending on lesions' topography and severity, but if there is a superimposed development of Complex Regional Pain Syndrome (CRPS), a diverse array of clinical features may develop [3, 4]. This syndrome is characterized by regional pain, seemingly disproportionate to the usual course of any known lesion, usually associated with a distal pattern of abnormal sensory, motor, sudomotor, vasomotor and/or trophic findings [3]. It may be clinically diagnosed through the Budapest Criteria and its severity could be accessed using the CRPS Severity Score (CSS) [3, 5]. The present therapeutic standard-of-care is a multimodality approach including patient education, rehabilitation, psychological support, and pharmacological intervention [4].

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2. Case report

We report a case of 35-year-old woman, right-handed, previously independent in all basic and instrumental daily-life activities (DLA), with history of congenital confluent pink spots located on the dorsal surface of the hands and forearms, asthma and morbid obesity. The patient was admitted to an Infectious Diseases-ICU due to acute respiratory distress syndrome (ARDS) 5 days after the diagnosis of SARS-CoV-2 infection. The progressive respiratory failure led to the need of respiratory and vasopressor support. Invasive mechanical ventilation was started on the 6th ICU Day and by that time an arterial line was placed on the left brachial artery by an experienced physician (through the antecubital fossa, guided by superficial anatomy references).

Twenty-four-hours later, the patient presented with a hematoma next to the line insertion site and absence of radial pulse. An upper-limb-doppler was requested, depicting a reduction of both radial and ulnar arteries flow. As so, the line was removed, and anticoagulation was started. A favorable clinical evolution was observed, and the patient was weaned from ventilation at the 12th ICU Day.

Ten days later, the neuro-motor examination revealed an asymmetric muscular strength impairment affecting mainly the left upper limb - according to Medical Research Council (MRC) scale, the score for the segments of the right upper and lower limbs strength was 4/5, also 4/5 for the left shoulder abduction and 3/5 for the left elbow flexion and extension, wrist flexion and extension and palmar prehension - with normal passive and active range of motion on all segments of the upper and lower limbs, normal deep tendon reflexes and muscular tonus, without any superficial sensorial alterations or complaints.

Due to the asymmetric muscular strength impairment, an electromyography was requested, depicting severe axonal lesion of the median nerve on the forearm. On nerve conduction studies, a significantly increased latency and decreased amplitude was reported on the left limb, both on the segments wrist-abductor pollicis brevis and elbow-wrist. On needle electromyography, signs of acute partial denervation on the left abductor pollicis brevis, first dorsal interosseous and flexor carpi radialis were identified. No other peripheral nerve injuries were identified.

An ultrasonographic evaluation was then performed, excluding the presence of hematomas on the nerve path or on other accessible plans on the superior left upper limb. Regarding pharmacological treatment, we highlight the absence of neurotoxic medications administered previously and during the hospital stay, as reported on Table 1. After sustained clinical stability, the patient was transferred to a rehabilitation facility.

On the clinical appointment three months after discharge, the patient presented with moderate pain of the left hand (Numeric Scale of Pain: 4/10), pinprick hyperesthesia on the dorsal surface of the hand, regional temperature and skin color asymmetry (with increased regional

Table 1. Pharmacological treatment administered to the patient.

Before hospitalization	During Hospitalization	After discharge
Desogestrel 0.075 mcg/day	**Bronchodilators**	Desogestrel 0.075 mcg /day
Fluticasone/Salmeterol 250 mcg/50 mcg 1 inhalation on demand	Ipratropium Bromide, 80 mcg; 4/day; 28 days Salbutamol, 100 mcg; 3/day; 30 days	Fluticasone/Salmeterol 250 mcg/50 mcg 1 inhalation on demand
	Corticosteroids Dexamethasone, 7.5mg; 1/day; 10 days Prednisolone, 20mg; 1/day; 2 days	
	Antivirals Oseltamivir, 75mg; 2/day; 5 days	
	Non-steroidal anti-inflammatory drugs Ketorolac, 30mg; 1/day; 4 days Diclofenac, 75mg; 1/day; 4 days Ibuprofen, 400mg; 3/day; 2 days Parecoxib, 40mg; 1/day; 4 days	
	Anti-thrombotic Aspirine, 100mg; 1/day; 10 days Enoxaparine, 60mg, 1/day, 5 days; 80mg, 3/day; 15 days; 120mg; 1/day; 5 days	
	Antibiotics Ampicilin, 2000mg; 2/day; 3 days Ceftriaxone, 1000mg; 1/day; 6 days Piperacillin/tazobactam, 4000 + 500mg, 1/day; 5 days Vancomicine, 1000mg; 2/day; 5 days	
	Proton pump inhibitors Pantoprazole, 40mg; 1/day; 19 days	
	Antiemetics Ondansetron, 8mg; 1/day; 6 days Metoclopramide, 10mg; 3/day; 6 days	
	Diuretics Furosemide 40mg; 2/day; 2 days -> 20mg; 1/day; 16 days Spironolactone 50mg; 1/day; 3 days	
	Laxatives Bisacodyl, 10mg; 3/day; 4 days Lactulose, 15ml; 3/day; 5 days	
	Neuromuscular block Rocuronium bromide, 7 days	
	Sedative-Hypnotic Propofol, 11 days Fentanil, 13 days Dexmedetomidine, 6 days Zolpidem, 10mg; 1/day; 2 days	
	Vasopressor support Noradrenaline, 7 days	

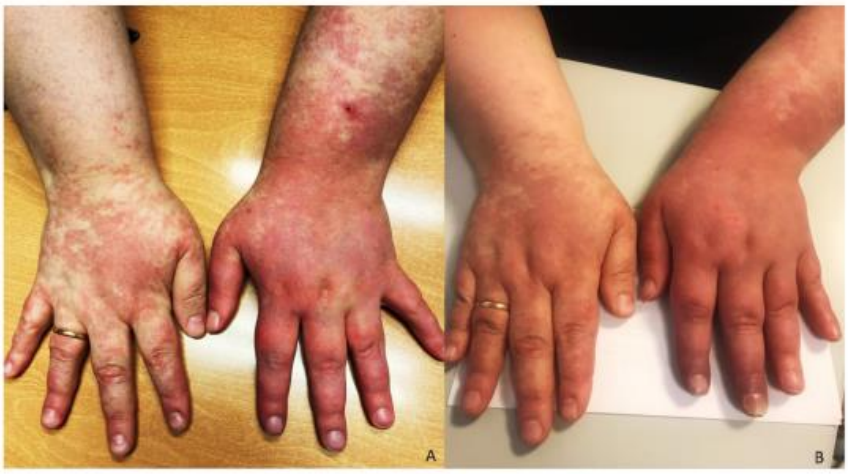

Figure 1. A: Clinical presentation on the first appointment. B: Clinical presentation on the second appointment, after multimodality therapeutic intervention.

temperature and redness on the affected hand), trophic changes (absence of nails growth and altered skin texture - thickness), hand edema and a "pointing finger" deformity, maintaining the muscular strength impairment with predominant involvement of the distal left upper limb (Figure 1A). These complains impacted the performance of some DLA, namely driving, shopping and manual tasks requiring fine motor control (e.g. preparing food, management of financial matters and medication). Due to these clinical manifestations, and in accordance with Budapest Criteria, CRPS was diagnosed, with a severity score of 14 according to CSS (Table 1).

A multimodality therapeutic approach was started, including patient education, rehabilitation and pharmacologic intervention. The patient education was performed by a Neurologist and a Physical Medicine and Rehabilitation doctor, in accordance with the European Federation of Pain recommendations [4]. The rehabilitation approach included twice-a-week one-hour sessions of occupational therapy with the following techniques: contrast baths, joint mobilization of the hand and wrist, manual isometric muscular strengthening of intrinsic and extrinsic hand muscles, mirror visual feedback therapy, fine motor control reeducation and analgesic massage. The pharmacologic intervention consisted of a 2-week cycle of ibuprofen 400mg three-times a day.

After eight weeks and fifteen rehabilitation sessions, there was a significative improvement on the patients' subjective complains and on objective measurements. Regarding subjective complains, the patient suffered paroxysmal pain less frequently, reported a subjective muscular strength increase that was confirmed on neuro-motor examination (scoring 4/5 on the MRC on the hand and wrist segments and 5/5 on the proximal segments of the left upper limb), maintaining the "pointing finger" deformity and an asymmetric vaso/sudomotor pattern. On objective measurements, the CSS was 7 points lower (Figure 1B), which represented as significant improvement in accordance with CSS smallest real difference value (4,9 points) [5]. Moreover, the patient was already able to perform all basic DLA and almost all instrumental DLA, including shopping, driving for small distances, managing financial matters and medication. Nonetheless, the patient still reported some disability on some steps of food preparation and heavy domestic work due to the lack of manual dexterity. Consequently, the therapeutic approach was further tailored, focusing specially on muscular strengthening and stretching, as well as on normalization of hand use and gesture reeducation, alongst with the prescription of ibuprofen on demand. Follow-up appointments were scheduled each 8–12 weeks to evaluate patients' evolution and optimize therapeutic interventions.

3. Discussion

Irrespective of the admission diagnosis, PNL are not rare in the ICU setting, and can occur after intravenous or intra-arterial line placement or removal. The most frequently affected nerves are the superficial branch of the radial nerve, the medial and lateral antebrachial cutaneous nerves and the radial and ulnar dorsal sensory branches of the hand [1]. PNL may result from pressure neuropraxia secondary to fluid extravasation or hematoma near the cannulation site, from chemical damage from medications or it can be directly inflicted by the needle [1]. CRPS is an unusual (incidence of 0.82/100000 person-years) but potentially disabling complication of any PNL, typically classified as type 2 in this context [4]. Given the heterogeneous and labile nature of the syndrome, clinical presentations may differ substantially between patients and even for the same patient time; therefore, assessment, tracking of changes and therapeutic planning may be challenging in the setting of CRPS.

To our knowledge, this is the first report of CRPS after an iatrogenic nervous lesion on a critically ill COVID-19 patient. Although there have been no dedicated mechanistic studies at how the SARS-CoV-2 virus might directly impact nociception, the broad systemic hyperinflammation seen in severe COVID-19 may contribute to peripheral and central neuronal sensitization, leading to chronic and possibly disproportionate pain, which can be a possible explanation for the development of CRPS on this case [2].

4. Conclusions

This case highlights a potential hazard of arterial puncture of the brachial artery - peripheral nervous lesions -, even under controlled conditions, specifically on COVID-19 patients. Although unusual, CRPS may occur after a peripheral nerve injury, leading to potentially significant function losses. An effective multidisciplinary approach is extremely important to attain a prompt diagnosis and successful treatment. We highlight the need of an increased awareness of this syndrome and its diagnostic and therapeutic approaches, both on acute and subacute stages after an injury [6]. This knowledge is critically important, because early diagnosis and treatment are associated with better prognosis [4, 7].

Declarations

Author contribution statement

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Additional information

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4

"*The PRINCOVID retrospective study - a predictive model of pressure injuries for critical COVID-19 patients*."

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The PRINCOVID Retrospective Study

A Predictive Model of Pressure Injuries for Critical COVID-19 Patients

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Objective: The aim of the study is to characterize pressure injuries, identify risk factors, and develop a predictive model for pressure injuries at intensive care unit admission for critical COVID-19 patients.

Design: This study was a retrospective analysis of a consecutive sample of patients admitted to intensive care unit between May 2020 and September 2021. Inclusion criteria encompassed the diagnosis of acute respiratory distress syndrome due to SARS-CoV-2, requiring invasive mechanical ventilation more than 48 hrs. The following predictors were evaluated: sociodemographic characteristics, comorbidities, as well as clinical and laboratory findings at intensive care unit admission. The primary outcome was the presence of pressure injuries.

Results: Two hundred five patients were included, mostly males (73%) with a mean age of 62 yrs. Pressure injury prevalence was 58%. On multivariable analysis, male sex, hypertension, hemoglobin, and albumin at intensive care unit admission were independently associated with pressure injuries, constituting the PRINCOVID model. The model reached an area under the receiver operating characteristic curve of 0.71, surpassing the Braden scale ($P = 0.0015$). The PRINCOVID score ranges from 0 to 15, with two risk groups: "at risk"(≤7 points) and "high risk"(>7 points).

Conclusions: This study proposes PRINCOVID as a multivariable model for developing pressure injuries in critical COVID-19 patients. Based on four parameters (sex, hypertension, hemoglobin, and albumin at intensive care unit admission), this model fairly predicts the development of pressure injuries. The PRINCOVID score allows patients' classification into two groups, facilitating early identification of high-risk patients.

Key Words: Pressure Injuries, Pressure Ulcers, COVID-19, Critical Illness

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The data sets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Data from the abstract of this article was presented at the International, European and Portuguese Congress of Physical Medicine and Rehabilitation (ISPRM/ESPRM/SPMFR), which took place in Lisbon, Portugal, in July 2022. This work was awarded with the prize "Best Oral Communication of the Portuguese Society of Physical and Rehabilitation Medicine."

Ana Teixeira-Vaz, Mafalda Oliveira, David Almeida e Reis, and Tiago Simões Moreira are in training.

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What Is Known

- Pressure injuries (PIs) interfere with physical, psychological, and social well-being, increasing length of stay and health-related costs. In critical COVID-19 patients, this issue is even more pressing.

What Is New

- Because the standardly used Braden scale has a lower predictive value in COVID-19 patients, a score for PI prediction (the PRINCOVID) that includes four easily assessable parameters (male sex, hypertension, and values of hemoglobin and albumin at intensive care unit admission) was developed. The PRINCOVID score ranges from 0 to 15 points, with two PI risk groups: "at risk" (≤7 points) and "high risk" (>7 points). In comparison with the standardly used Braden scale, the PRINCOVID is of easy and rapid application, including only four parameters that are standardly included in medical records. Moreover, this model has a significantly higher area under the receiver operating characteristic curve in this population, when compared with the Braden scale.

COVID-19 firstly emerged in December 2019, with a report of severe flu-like illness in China.[1] After the disease spread to more than 100 countries, a global pandemic was declared on March 2020 and, as of that date, the number of cases has been increasing daily, posing a severe health threat on a global scale.[2] Most infected patients are asymptomatic or paucisymptomatic. Nevertheless, up to 15% have severe disease, and approximately 5% become critically ill, requiring ventilatory support.[3]

COVID-19 patients are susceptible to several complications due to the primary disease and its treatment (iatrogeny), mainly if critically ill. A common problem resulting from sepsis and prolonged intensive care unit (ICU) stays is the development of pressure injuries (PIs).[4] Pressure injuries are frequent in critically ill COVID-19 patients and demand 3 times more care than in other hospitalized patients.[5] Several factors have been pointed out for the increased risk of PI in COVID-19 patients: hypoxia, hypotension, systemic thrombogenic microvascular injury, poor perfusion, and immobility.[6]

As PI are a significant problem associated with several adverse health outcomes (morbimortality) and increased healthcare costs, its prevention is a relevant goal.[7]

Our investigation aimed to characterize PI in critically ill COVID-19 patients, identify risk factors, and develop a

predictive model to identify COVID-19 patients with a higher risk of developing PI at ICU admission.

MATERIAL AND METHODS

A retrospective cohort study was performed, including patients admitted to four ICUs of a tertiary care center in Portugal from May 2020 to September 2021.

Patients with the diagnosis of acute respiratory distress syndrome (ARDS) due to SARS-CoV-2 infection requiring ICU admission and invasive mechanical ventilation for more than 48 hrs and age older than 18 yrs were consecutively included. The clinical reasoning for the cutoff of the invasive mechanical ventilation minimal length was to ensure similar levels of respiratory disease (ARDS) severity.

A COVID-19 case was assumed if a positive result on real-time reverse-transcriptase polymerase chain reaction assay of nasal and pharyngeal swab specimens was depicted before ICU admission.

Acute respiratory distress syndrome was defined as an acute syndrome of lung inflammation and increased alveolar-capillary permeability, associated with severe hypoxia, and bilateral infiltrates on chest radiographs, with no evidence of left heart failure, in line with the Berlin definition.[8]

Invasive mechanical ventilation was defined as a form of artificial ventilation that included an endotracheal tube and a mechanical ventilator.[9]

This investigation was approved by our institutional review board and performed following the Helsinki declaration. Verbal informed consent was obtained in accordance with our institutional review board authorization. This study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines and reports the required information accordingly (see Supplementary Checklist, Supplemental Digital Content 1, http://links.lww.com/PHM/B965).

The main investigator was responsible for assessing inclusion criteria. Data were obtained from electronic clinical records. The evaluated variables were grouped as outcomes or predictors. Data were therefore gathered on an anonymized electronic database, and each patient received a unique code number to secure anonymity.

The presence of PI was the primary outcome. A PI was defined following the National Pressure Ulcer Advisory Panel consensus of 2016[10] as a localized damage to the skin and/or underlying soft tissue over a bony prominence or related to medical or other devices as a result of intense and/or prolonged pressure or pressure in combination with shear.[10] Data regarding PI location and severity were also evaluated. Based on the Revised Pressure Injury Staging System,[10] PI severity was graded in the four categories: (1) grade 1: intact skin with a localized area of erythema (nonblanchable or blanchable) or changes in skin sensation, temperature, or firmness; (2) grade 2: partial-thickness loss of skin with the exposed dermis, with a wound bed that was viable, pink or red, and moist; (3) grade 3: full-thickness skin loss, in which adipose tissue was visible in the ulcer and granulation tissue; and (4) grade 4: full-thickness skin and tissue loss with exposed or directly palpable fascia, muscle, tendon, ligament, cartilage, or bone in the ulcer.[10] The study sample was recruited from a population of critically ill patients admitted to specialized ICUs where the standard of care comprises several measures to prevent PI risk, including routine risk assessment and implementation of preventive measures, such as adequate nutritional support, proper positioning and repositioning (2-hourly turns, alternating sides, pending on the general medical condition, skin condition, and comfort), early mobilization (with the collaboration of a rehabilitation team), proper skin care and use of ICU-specific beds, mattresses, and pressure-redistributing surfaces.

Skin injuries registered as vascular, surgical, traumatic, or neoplastic were not considered PI, heeding the applied definition.

Several possible predictors were evaluated, namely, sociodemographic characteristics (age and sex), comorbidities (hypertension, diabetes mellitus, hyperlipidemia, obesity, smoking habits, cardiac pathology [atrial fibrillation, ischemic heart disease, heart failure], peripheral vascular disease, respiratory pathology [chronic pulmonary obstructive disease, asthma, sleep apnea], neurological disorders [previous cerebrovascular disease, traumatic brain injury, migraine and other forms of headache, Parkinson disease and other movement disorders, epilepsy and cognitive impairments], psychiatric disorders and oncologic pathology), clinical status at ICU admission (evaluated through the Simplified Acute Physiology Score II and the Acute Physiology and Chronic Health Evaluation [APACHE II] scores) and laboratory findings at ICU admission (including hemoglobin, leucocytes, platelets, total proteins, albumin, creatinine, glucose, C-reactive protein [CRP], lactates, lactate dehydrogenase, procalcitonin, myoglobin, creatine kinase [CK] and CK-MB). Laboratory values were compiled from the first laboratory study performed after ICU admission, including exclusively evaluations conducted in the first 48 hrs of ICU stay.

The score on the Braden scale at ICU admission was also evaluated. The Braden scale for predicting PI risk is a widely and standardly used instrument that contains six subscales (sensory perception, activity, mobility, moisture, nutrition, and friction/shear). It classifies patients according to the global punctuation in "at risk" (total scores of 15–18), "moderate risk" (total scores of 13–14), "high risk" (total scores of 10–12), and "very high risk" when total scores are of 9 or less.[11,12] This instrument is a standardized, evidence-based assessment that accurately predicts PI risk, with a moderate predictive validity with good sensitivity and low specificity in adult critically ill patients.[13,14]

Statistical analysis was performed using SPSS version 27 (IBM Corporation, Armonk, NY) and the MedCalc (Version 20.112) software. Categorical variables are summarized as frequencies and percentages, and continuous variables as means and standard deviations (variables with normal distributions) or medians and interquartile ranges (variables with skewed distributions). Normal distribution was examined using histogram visual inspection. As appropriate, the χ^2 test or Fisher exact test were used to compare categorical variables. Continuous variables were compared using independent samples t test or Mann-Whitney U test, in agreement with the variable distribution. Variables were independently tested in univariable Cox proportional hazard regression models, with the dependent variable being the occurrence of PI. Exponentials of regression coefficients were interpreted as hazard ratios (HRs). Independent variables with at least marginal association with the outcome variable ($P < 0.100$) in univariable analyses were included in the multivariable logistic regression model. Therefore, the final multivariable regression model (PRINCOVID) included all covariates with a significant association with the dependent

variable after adjustment for other independent variables using the Backward-Wald methodology (cutoff for entry = 0.05; cutoff for exclusion = 0.10). The number of points associated with each variable/category (score points) was obtained by multiplying the adjusted regression coefficients by three and rounding the result to the nearest unit.[15] To facilitate the score computation, continuous variables included in the multivariate model were categorized: hemoglobin was grouped into <8 g/dl; 8–10 g/dl; >10 g/dl, and albumin was grouped into <34 and ≥34 g/dl. Receiver operating characteristic (ROC) curve analysis for the model was performed to assess its' forecasting accuracy. The comparison of ROC curves to test the significance of the difference between the areas under ROC curves (PRINCOVID and Braden scale) was performed according to the method of DeLong et al.[16] In addition, we performed a classification tree (based on χ^2 statistic determination and with a significance level of 0.05 for node splitting) to define possible cutoffs for the PRINCOVID score. To perform internal validation, 5-fold cross-validation of the score results was performed, as well as of the "risk groups" identified by the classification tree ("at-risk" and "high-risk" groups). All reported *P* values are two-tailed, with a *P* value less than 0.05 indicating statistical significance.

RESULTS

A total of 205 patients were included, mostly males (73%) with a mean age of 62 yrs (SD, 13.1). Most patients presented at least one comorbidity. Hypertension (55.1%), hyperlipidemia (46.3%), and obesity (39.5%) were the most commonly identified. Table 1 illustrates the characteristics of the included sample.

The prevalence of PI was 58% (n = 118), and multiple (two or more) PI were depicted in 61 patients (51.7% of the patients with PI). Regarding its severity, most of the PI were grade 2 (45.2%), with 16.6% (n = 34) of patients having severe PI (graded as a 3 or 4). In patients with severe PI, the majority (91.2%) were approached with dressing care, with two cases requiring antibiotic therapy combined with dressings and one case requiring surgical intervention. Pressure injuries were depicted in 11 locations, most often on the sacrum (64%) and face (61%), as detailed in Figure 1.

Several potential predictors for PI development were analyzed, including sociodemographic characteristics, comorbidities, and clinical and laboratory findings at ICU admission (Table 1).

Regarding sociodemographic characteristics, male sex was significantly associated with the occurrence of PI (P = 0.009); in our sample, males had an HR 2.29 folds higher of having PI (95% confidence interval [CI], 1.22–4.26). Oppositely, age was not significantly associated with PI (P = 0.118). Nevertheless, PIs were more prevalent in patients with older age (prevalence: <65 yrs, 54%; 65–75 yrs, 57%; >75 yrs, 73%). However, on univariate analysis, age older than 75 yrs was not significantly associated with PI development (P = 0.054; HR, 2.21; 95% CI, 0.97–5.04).

Several comorbidities were also evaluated: our data revealed that hypertension (P = 0.048; HR, 1.76; 95% CI, 1.01–3.08) was significantly associated with the presence of PI. No other comorbidity was statistically associated with PI development. Nonetheless, patients with obesity tended to present PI more often (44.9% vs. 32.2%), although statistical significance was not reached (P = 0.065; HR, 1.72; 95% CI, 0.96–3.06).

The APACHE and Simplified Acute Physiology Score II scores were used as metrics of disease severity. None of the scores were significantly associated with a higher risk of PI, although a tendency was found in the APACHE score. Patients with PI had higher APACHE scores at ICU admission (20.1 vs. 18.2; P = 0.087).

Likewise, laboratory findings at ICU admission were considered as possible predictors for PI. Lower values of hemoglobin (11.8 vs. 12.6 g/dl, P = 0.006) and albumin (27.9 vs. 29.6 g/dl, P = 0.009) and higher values of CRP (186.7 vs. 155.1 mg/l, P = 0.039) and CK-MB (1.7 vs. 1.2 µg/l, P = 0.012) were significantly associated with PI development.

On multivariable analysis, we included in the regression model all the predictors that had a P value less than 0.100. As so, male sex, hypertension, obesity, APACHE score, hemoglobin, albumin, total proteins, CRP, and CK-MB at ICU admission were included.

After adjustment, male sex (HR, 4.30; 95% CI, 1.92–9.64), hypertension (HR, 2.08; 95% CI, 1.04–4.14), and value of hemoglobin (HR, 0.86; 95% CI, 0.71–1.03) and albumin (HR, 0.93; 95% CI, 0.86–0.99) at ICU admission were all independently associated with PI (Table 2). To facilitate the score computation, hemoglobin and albumin were then categorized to their introduction in the score. Finally, we multiplied the adjusted regression coefficients of those variables by three and rounded the results to the nearest integer to determine the number of points for each variable for the final score (Table 2). Based on that, we developed the PRINCOVID score, which ranges from 0 to 15 points (male sex: 4 points; hypertension: 2 points; hemoglobin <8 g/dl: 6 points; hemoglobin of 8–10 g/dl: 4 points; albumin <34 g/dl: 3 points).

The score presented a fair discriminative power and good accuracy when tested against the outcome variable, reaching an area under the ROC curve (AUC-ROC) of 0.71 (95% CI, 0.64–0.78; P < 0.01).

Subsequently, we compared the PRINCOVID with the standardly used Braden scale. The score on the Braden scale was significantly lower (indicating higher risk) in patients with PI (12.3 vs. 13.8, P = 0.007). Hence, we assessed the predictive value (AUC-ROC) of the Braden scale for PI in this population. The Braden scale had an AUC-ROC of 0.51, which indicates a poor predictive index. When comparing both models, the PRINCOVID AUC-ROC surpassed the Braden scale with statistical significance (0.71 vs. 0.51, P = 0.0015; Fig. 2).

To define possible cutoff points for the PRINCOVID score, we tested it in a classification tree, which identified two groups with different PI risks (Fig. 3): "at risk" (≤7 points; PI risk, 45%) and "high risk" (>7 points; PI risk, 72%). The percentage of correct predictions according to this classification was 63%. We used cross-validation to test this risk classification against the occurrence of PI, obtaining an AUC-ROC of 0.64 (95% CI, 0.56–0.71).

DISCUSSION

We propose the PRINCOVID as a multivariable model that includes four parameters (sex, hypertension, value of

TABLE 1. Sample characteristics and univariate analysis of potential factors associated with the development of pressure injuries

Characteristic	Total Cohort	Presence of PI	Absence of PI	HR (95% CI)	P
Sociodemographic characteristics					
Male sex, *n* (%)	149 (72.7)	94 (79.7)	55 (63.2)	2.28 (1.22–4.26)	0.009
Age, mean (SD)	61.9 (13.1)	63.2 (12.5)	60.3 (13.8)	—	0.118
Age >75 yrs, *n* (%)	33 (16.1)	24 (20.3)	9 (10.3)	2.21 (0.97–5.04)	0.054
Comorbidities					
Hypertension, *n* (%)	113 (55.1)	72 (61.0)	41 (47.1)	1.76 (1.03–3.08)	0.048
Diabetes mellitus, *n* (%)	72 (35.1)	36 (30.5)	36 (41.4)	0.62 (0.35–1.11)	0.107
Hyperlipidemia, *n* (%)	95 (46.3)	54 (45.8)	41 (47.1)	0.95 (0.54–1.65)	0.847
Obesity, *n* (%)	81 (39.5)	53 (44.9)	28 (32.2)	1.72 (0.96–3.06)	0.065
Smoking habits, *n* (%)	8 (3.9)	6 (5.1)	2 (2.3)	2.28 (0.45–11.6)	0.471
Atrial fibrillation, *n* (%)	14 (6.8)	9 (7.6)	5 (5.7)	1.35 (0.44–4.19)	0.598
Ischemic heart disease, *n* (%)	12 (5.9)	7 (5.9)	5 (5.7)	1.03 (0.32–3.38)	0.956
Heart failure, *n* (%)	10 (4.9)	5 (4.2)	5 (5.7)	0.75 (0.20–2.59)	0.621
Peripheral vascular disease, *n* (%)	20 (9.8)	10 (8.5)	10 (11.5)	0.71 (0.28–1.80)	0.471
Neurological pathology, *n* (%)	31 (15.1)	17 (14.4)	14 (16.1)	0.89 (0.40–1.89)	0.739
COPD, *n* (%)	7 (3.4)	3 (2.5)	4 (4.6)	0.54 (0.12–2.48)	0.461
Asthma, *n* (%)	12 (5.9)	5 (4.2)	7 (8.0)	0.51 (0.16–1.65)	0.251
Sleep apnea, *n* (%)	21 (10.2)	13 (11.0)	8 (9.2)	1.22 (0.48–3.09)	0.671
Psychiatric pathology, *n* (%)	32 (15.6)	21 (17.8)	11 (12.6)	1.50 (0.68–3.29)	0.315
Oncologic pathology, *n* (%)	23 (11.2)	14 (11.9)	9 (10.3)	1.17 (0.49–2.83)	0.733
Severity scores at ICU admission					
SAPS II, mean (SD)	42.8 (16.6)	44.0 (15.8)	41.2 (17.6)	—	0.251
APACHE, mean (SD)	19.3 (7.6)	20.1 (7.4)	18.2 (7.8)	—	0.087
Laboratory findings at ICU admission					
Hemoglobin, mean (SD), g/dl	12.2 (2.2)	11.8 (2.4)	12.6 (1.8)	—	0.006
Leukocytes, mean (SD), cells/l	9.2 (4.6)	9.0 (4.5)	9.49 (4.8)	—	0.503
Platelets, mean (SD), cells/l	212.1 (89.8)	213.1 (97.3)	210.5 (79.0)	—	0.834
Total proteins, mean (SD), g/l	60.1 (6.8)	59.4 (6.4)	61.1 (7.4)	—	0.087
Albumin, mean (SD), g/l	28.6 (4.8)	27.9 (4.3)	29.6 (5.2)	—	0.009
Creatinine, median (IQR), U/l	190.4 (94.2)	0.9 (7.3)	0.79 (16.1)	—	0.241
Glucose, mean (SD), mmol/l	173.3 (108.8)	190.8 (102.3)	190.0 (82.9)	—	0.955
C-reactive protein, mean (SD), mg/l	1.41 (0.63)	186.7 (114.6)	155.1 (98.1)	—	0.039
Lactates, mean (SD), mmol/l	478.9 (207.2)	1.43 (0.6)	1.40 (0.7)	—	0.746
Lactate dehydrogenase, mean (SD), U/l	0.32 (247.0)	465.4 (175.9)	497.5 (243.4)	—	0.280
Procalcitonin, median (IQR), ng/ml	111.1 (6450.4)	0.33 (13.8)	0.31 (246.9)	—	0.270
Myoglobin, median (IQR), µg/l	162 (7608)	116.3 (4151.4)	96.55 (6450.4)	—	0.487
Creatine kinase, median (IQR), µg/l	1.50 (44.9)	180.5 (7608)	118.5 (4003)	—	0.332
Creatine kinase-MB, median (IQR), µg/l	1.50 (44.9)	1.7 (24.9)	1.2 (44.9)	—	0.012

COPD, chronic obstructive pulmonary disease; IQR, interquartile range; SAPS, Simplified Acute Physiology Score.

hemoglobin and albumin at ICU admission) easily assessable at ICU admission. This score ranges from 0 to 15 and fairly predicts the risk of PI in critically ill COVID-19 patients. Patients with a PRINCOVID score >7 have a risk of developing PI during ICU stay of 72%. In comparison with the standardly used Braden scale, the PRINCOVID is an easy and rapidly appliable tool, which includes only four parameters that are standardly available in electronic clinical records. Moreover, this model has a significantly higher AUC-ROC in this population.

Pressure injuries are associated with adverse health outcomes (morbimortality) and increased health costs. In the United States, the treatment of hospital-acquired pressure injuries represents incremental costs of up to $10.708 per patient, totalizing $26.8 billion annually, based on 2.5 million reported cases.[17] Hence, its' prevention is of maximum importance, so models that are easy to apply and that accurately predict the risk of this complication are required.

Pressure injuries are a more pressing concern in critically ill patients than in other hospitalized or nursing home patients. This concern becomes even more relevant when the critical illness is due to SARS-CoV-2 infection, in comparison with non–COVID-19 patients.[18] Several etiological factors have been pointed out to justify this increased risk of PI development in critically ill COVID-19 patients. Those factors have been generally grouped as (1) directly related to the viral infection, illustrated by the status of systemic coagulopathy and inflammation, combined with microvascular occlusion and thrombogenic microvascular lesioning (decreasing the potential of wound healing

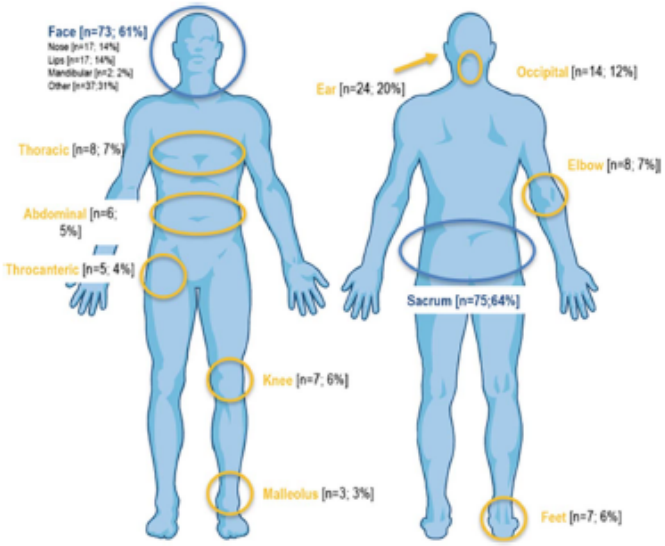

FIGURE 1. Pressure injury distribution per anatomic region. Edited from a Shutterstock image (license: 111679070).

significantly[19]); (2) related to the critical illness, by the presence of hypotension, hypoxia, poor perfusion, and the possible need for vasopressor medications (which reduce peripheral tissue perfusion); and (3) related to in-hospital care, as the limited repositioning due to hemodynamic instability or profound hypoxia, the use of prone position, and the use of medical devices (tracheostomy tubes, feeding tubes, oxygen delivery devices, central lines, catheters).[6,20,21] In addition, the role of immobilization and nutritional depletion is highlightable.[6] In short, COVID-19 patients have higher rates of PI, as well as unusual presentations, multiple PIs, earlier onset, and lesions of higher severity.[22]

Moore et al.[23] systematic review estimated that the average prevalence of PI among published studies in Europe ranges from 4.6% to 27.2%. Nevertheless, studies in an ICU setting report a higher prevalence, ranging up to 40% of patients.[24–26] In our population, the prevalence of PI was slightly higher than in other ICU studies with COVID-19 patients.[5,25]

Regarding PI locations, the sacrum was the most common location in our sample, which is compatible with the literature.[20] In addition, the face was also commonly affected by this complication, with higher rates than in pre–COVID-19 studies, though in line with studies launched since the beginning of the pandemic.[27] Indeed, in this population, facial lesions were extremely common in relation to the use of external devices (such as feeding devices, endotracheal tubes, high-flow, and standard nasal cannula) and prone positioning. The prevalence of PI in other locations was also in line with the literature.[24]

The rate of severe PI in our population was high (16.6% of all patients with PIs). Theoretically, the same thrombogenic vascular changes related to COVID-19 that occur in the skin may occur in the underlying soft tissues, making these tissues less tolerant to the damaging effects of pressure and shear.[6] Nevertheless, the clinical impact regarding possible interventions of more severe

TABLE 2. Binary logistics analysis of potential factors associated with the development of pressure injuries

	Regression Coefficient	HR (95% CI)	*P*	Score Points
Male sex	1.458	4.30 (1.92–9.64)	<0.001	4
Hypertension	0.732	2.08 (1.04–4.14)	0.037	2
Hemoglobin, g/dl		0.10 (0.71–1.02)	0.092	
<8	2.107	8.22 (0.95–78.70)	0.053	6
8–10	1.402	4.06 (1.03–16.02)	0.047	4
>10[a]	[a]	[a]		0
Albumin, g/l		0.93 (0.86–1.00)	0.050	
<34	1.113	3.05 (0.93–9.95)	0.041	3
>34[a]	[a]	[a]		0

[a] Reference category.

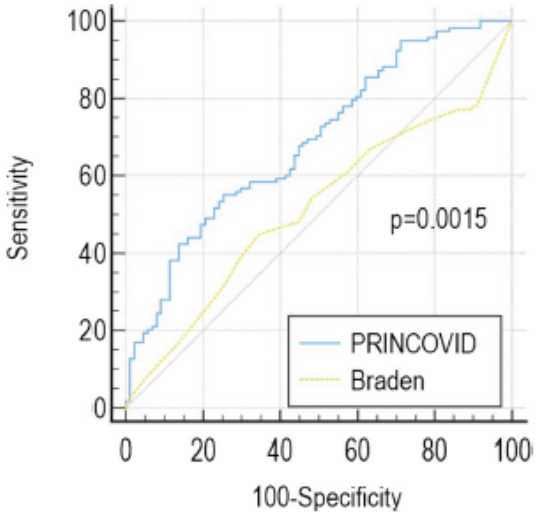

FIGURE 2. Receiver operating characteristic curve comparison between the PRINCOVID model and the Braden scale.

lesions was lower in our population than in the analysis by Ziede et al.,[26] as only one of the patients required surgical intervention.

Thirty-three possible predictors were analyzed in this investigation, including sociodemographic characteristics, comorbidities, and clinical and laboratory findings at ICU admission.

Regarding sociodemographic characteristics, sex (male) was significantly associated with PI development, which is a result that is consistent with some of the previous investigations but unanimously.[19,27–30] Both on univariate and bivariate logistic analysis, this factor was associated with PI development, and in our population, males had an adjusted HR for PI four folds higher than women.

The impact of older age on PI development remains controversial.[5,27] Aging may increase susceptibility to PI by reducing tissue tolerance and inducing cellular changes. The meta-analysis by Serrano et al.[31] identified age as one of the four more critical factors for PI development. In our sample, after age categorization (>75 vs. <75 yrs), there was a tendency to a higher risk in the elderly, in line with the study by Amini et al.,[5] although statistical significance was not reached.

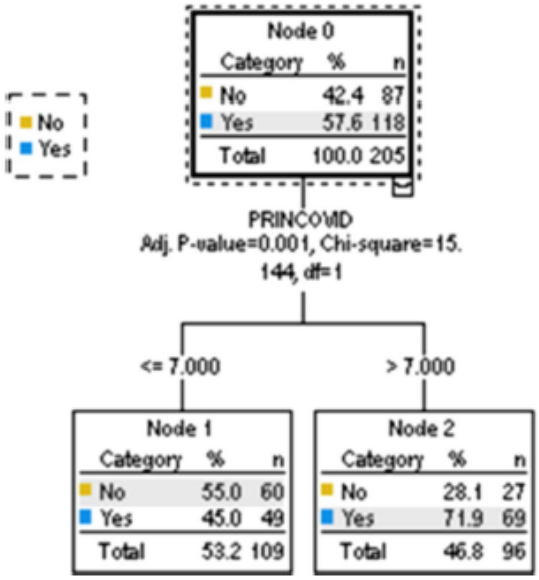

FIGURE 3. Classification tree used to identify cutoffs for the PRINCOVID score, allowing to define groups with different PI risks.

Regarding comorbidities, only hypertension was significantly associated with PI development. Previous investigations also showed that hypertension was a risk factor for developing PI.[20] Other comorbidities previously pointed out as of risk for PI, such as diabetes mellitus and peripheral vascular disease,[5,31] were not associated with PI in our study. This may be explained by the fact that skin lesions caused by mechanisms other than pressure were not considered in our study.

We have also analyzed the impact of the patient's clinical status at ICU admission through the APACHE and Simplified Acute Physiology Score II scores, factors that are usually not associated with PI. However, this information was assessed because of the biological plausibility and the fact that in studies like Challoner et al.,[27] patients with more severe diseases had more frequently PI. No significant association was found, although a tendency for patients with increased disease severity to present skin complications was reported and is also a highlightable fact.

Regarding laboratory findings, 14 parameters were evaluated. Values of hemoglobin and albumin at ICU admission were the only laboratory parameters that were independently associated with the risk of PI development, standing as the main laboratory predictors for this complication.

To evaluate the predictive power of our model, we performed an ROC curve analysis, which depicted an AUC-ROC of 0.71. This value represents a fair discrimination power. For more insight regarding the applicability of our model, we compared it with the Braden scale in the same population. Indeed, the Braden scale is a widely and standardly used score to predict the risk of PI. In our population, we report significantly lower scores on the Braden scale in patients who developed PI, demonstrating some accuracy in predicting the risk of pressure injuries.[3] Nevertheless, the predictive value of this score was poor (AUC-ROC, 0.51). Alderden et al.[32] have previously described a lower predictive value of this scale on the COVID-19 population, in comparison with non–COVID-19 patients, suggesting that clinicians should incorporate factors not included in the Braden scale in the routine assessment of COVID-19 patients. Other studies, namely, McLarney et al.,[19] have identified additional predictive factors for PI besides the Braden scale. Nevertheless, a direct comparison between new models and the standardly used Braden scale have not been previously performed.

In this investigation, a predictive score that fairly predicts the risk of developing a PI in critical COVID-19 patients was developed. The PRINCOVID is easily applicable in a clinical practice setting, including four parameters that are simple to obtain at ICU admission. The PRINCOVID is, to our knowledge, the first score created for application at ICU admission, specifically designed for critically ill COVID-19 patients. In addition, by stratifying the risk of PI, the PRINCOVID seems to be a valuable tool with the potential to optimize critical patients' management.

Our study presents some limitations. As the study data were extracted from electronic clinical records, an ascertainment bias could not be excluded because blinding for the presence of PI was not possible. Nonetheless, all information was collected following a prespecified standardized form. In addition, because of the retrospective design with a data collection method from the electronic clinical records, there may be an underestimation of the prevalence and severity of PI in relation to less documented or lacked care information in an era of hospital overload. Although this is a single-center study, the study took place in a tertiary care center covering a wide geographical referral area, encompassing several specialized ICUs, and receiving several patients transferred from other institutions for advanced ICU care, reaching a higher sample size than most investigations in this field[19,20,27,33]; hence, the external validity of our results is, nonetheless, considerable.

Further studies are warranted for the external validation of the PRINCOVID on other critical COVID-19 samples. In addition, additional investigations would be crucial to evaluate this model's suitability for non-ICU COVID-19 hospitalized and non–COVID-19 ICU patients.

CONCLUSIONS

As PI interfere with physical, psychological, and social well-being and increases the length of stay and health-related costs, the prevention of this complication is of critical importance. This study proposes the PRINCOVID as a multivariable model for the development of PI in critical COVID-19 patients. The PRINCOVID includes four parameters (sex, hypertension, value of hemoglobin and albumin at ICU admission) easily assessable at ICU admission and that fairly predicts the risk of PI in critically ill COVID-19 patients. This model was converted in a score, which ranges from 0 to 15. By classifying patients into two risk groups, our score seems clinically meaningful by creating an opportunity to improve preventive strategies and thereby reduce PI prevalence, especially in high-risk patients. Moreover, the PRINCOVID has a significantly better AUC-ROC than the standardly used Braden scale.

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5

"*Surviving critical COVID-19: how functionality, physical, mental and cognitive outcomes evolve*?"

Ana Teixeira Vaz, José Afonso Rocha, Mafalda Oliveira, Tiago Simões Moreira, David Almeida e Reis, Ana Isabel Silva, José Artur Paiva

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RESEARCH ARTICLE

Surviving critical COVID-19: How functionality, physical, mental and cognitive outcomes evolve?

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Abstract

Purpose

To analyze the long-term consequences of critical COVID-19, regarding physical, mental, cognitive and functional impairments, and to describe its evolution through time.

Methods

Prospective cohort study, with consecutive inclusion of patients admitted due to SARS-CoV-2 to intensive care units(ICU) of a tertiary-care center, between May/2020 and September/2021. All included patients were included in Physical and Rehabilitation Medicine (PRM) inpatient programs during ICU stay. Eligible patients were evaluated on PRM appointments 6 and 12 months after ICU discharge. In each visit, physical examination and a predefined set of scales were applied, aiming to comprehensively evaluate the three domains (physical, mental and cognitive) of post-intensive care syndrome and the patients' functionality. Statistical analysis encompassed descriptive and univariate analysis.

Results

A total of 42 patients were included: 66.7% males, mean age of 62 yo. In the physical domain, 6 months after ICU discharge, there was a significant reduction in quality of life (p-value = 0.034), muscle strength (p-value = 0.002), gait ability (p-value<0.001) and balance (p-values<0.001) and increased fatigue levels (p-value = 0.009), in comparison with reference values. Yet, a significative positive evolution was observed in all referred subdomains (p-values<0.05). Nevertheless, 12 months after discharge, muscle strength (p-value = 0.001), gait (p-value<0.001) and balance (p-value<0.001) were still significantly compromised. Regarding the mental domain, both at 6 and 12 months after discharge, the levels of anxiety and depression were significantly increased (p-values<0.001). Nonetheless, a positive evolution was also found (p-values<0.02). Cognitive performance was significantly impaired in comparison with reference values, both at 6 and 12 months (p-value<0.001). Yet, a global improvement was also depicted (p-value = 0.003). Six months after ICU discharge, 54.8% were autonomous in activities of daily living, a value that improved to 74.0% in the subsequent 6 months (p-value = 0.002).

Conclusion

Critical COVID-19 survivors present significant physical, mental and cognitive impairments 6 and 12 months after ICU discharge, despite their positive evolution through time.

Introduction

Coronavirus Disease 2019 (COVID-19), a primarily respiratory disease caused by the SARS-CoV-2 virus, firstly emerged in December 2019, with a report of severe flu-like illness in China [1]. After the disease spread to over 110 countries, a global pandemic was declared in March 2020 and as of that date the number of cases has been increasing daily, posing a severe health threat at a global scale [2]. Worldwide, there have been more than 759 408 703 confirmed cases, including 6 866 434 deaths [2]. Specifically in Portugal, there have been 5 570 473 confirmed cases of COVID-19 with 26 266 deaths [2].

Most infected patients are asymptomatic or paucisymptomatic. Nevertheless, up to 15% have severe disease requiring admission to intensive care units (ICU). In these cases, appropriate critical care delivery is a cornerstone to reduce mortality, which reaches 75% in some series [3].

Rightfully, the initial focus of COVID-19 research was on acute treatment. However, after three years, the high number of critical COVID-19 survivors has raised emerging questions about mid and long-term outcomes [4, 5].

Regardless of the primary disease, survivors of a prolonged stay in the ICU may experience mid and long-term complications related to the critical illness, to the therapy and to the ICU environment itself [6]. Post-Intensive Care Syndrome (PICS) is defined as new or worsening physical, mental and cognitive disorders that negatively affect daily functioning and quality of life (QoL) in survivors of critical illness [7, 8]. This syndrome seems to be prevalent and impactful in critical COVID-19 survivors, at least in the first year after ICU discharge [6, 9].

A comprehensive description of these patients' follow-up is essential to further assist the design and implementation of rehabilitation interventions and long-term care management for individuals with PICS secondary to COVID-19. Indeed, some previous investigations have addressed the mid and long-term disabilities of critical COVID-19 survivors [10–13]. Yet, there is still a substantial gap in knowledge regarding the extent of the impairments and their evolution through time, specifically in the physical domain and functionality. Also, the characteristics of Physical and Rehabilitation Medicine (PRM) interventions and their impact on the patient's trajectory also require further clarification.

Asso, the primary aim of this study was to describe the long-term consequences of critical COVID-19, regarding physical, mental, cognitive and functional impairments, as well as its evolution through time. As a secondary goal, we intended to characterize PRM intervention in this subset of patients.

Materials and methods

Ethics committee approval statement

This study has been approved by our institutional research ethics committee before started (*Comissão de Ética para a Saúde do Centro Hospitalar Universitário de São João; number of approval: 22/21)*, and it has been conducted in accordance with the principles set forth in the Helsinki Declaration. Written informed consent was obtained from all patients.

Study design

Prospective cohort study with consecutive inclusion of patients admitted to one of four ICU of an Intensive Care Department in a tertiary-care center, between May/2020 and September/2021.

Inclusion criteria were age ≥ 18 years old and ICU admission diagnosis of acute respiratory distress syndrome (ARDS) due to SARS-CoV-2, requiring invasive mechanical ventilation (IMV) for ≥ 48 hours (h). Patients who died during ICU stay were excluded.

After hospital discharge, all patients were reached by telephone and asked to attend a specific post-COVID-19 PRM outpatient appointment. When it was not possible to contact the patients through a single telephonic contact, five more attempts, in different days and at different day hours (from 10am to 5pm, on weekdays) were performed. First PRM appointment was scheduled at six months after ICU discharge. A re-evaluation visit was performed at 12 months after ICU discharge. If any of the appointments were missed, the patient was given two opportunities to reschedule in a one-month period.

The appointments were performed at the outpatient clinic of the PRM department of our center. All participants were interviewed face-to-face by the same PRM physician.

Definitions

ARDS was defined in accordance with the Berlin definition, as an acute syndrome of lung inflammation and increased alveolar-capillary permeability associated with severe hypoxia and bilateral infiltrates on chest radiographs, without evidence of left heart failure [14].

A COVID-19 ARDS case was assumed when a positive result on real-time reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasal and pharyngeal swab specimens was depicted in the first 24h after hospital admission.

Data collection and outcome measures

Data regarding socio-demographic characteristics, functional status, comorbidities, characteristics of the critical respiratory illness and complications during ICU stay were collected by the main investigator from the electronic clinical records (ECR) using a predefined form.

Comorbidities included hypertension, diabetes mellitus, hyperlipidemia, obesity, smoking habits, atrial fibrillation, ischemic heart disease, heart failure, peripheral vascular disease, chronic pulmonary obstructive disease, asthma, sleep apnea, psychiatric pathology, oncologic pathology and immunosuppression.

To describe the characteristics of the critical respiratory illness, information regarding severity scores at ICU admission, namely Acute Physiology and Chronic Health Evaluation (APACHE) and Simplified Acute Physiology Score II (SAPS II) was retrieved. Additionally, data regarding the number of days at the ICU and total length of stay, number of days under IMV, need and number of days under vasopressors, renal replacement therapy, extracorporeal membrane oxygenation (ECMO) and the need for prone positioning were also collected. Several potential complications during ICU stay were assessed, namely neurological, abdominal, cardiovascular, cutaneous and infectious. Neurological complications (signs, symptoms and syndromes) comprised aphasia, dysarthria, dysphonia, dysphagia, focal weakness, delirium, seizures, cerebrovascular diseases, encephalopathy, encephalitis, myelitis, peripheral neuropathies and signs of corticospinal tract dysfunction (CSTD). Cardiovascular complications included bradyarrhythmia, tachyarrhythmia (atrial fibrillation, flutter, others), tachycardia-bradycardia syndrome, secondary myocardial injury, cardiac arrest, pericarditis, pericardial effusion, endocarditis, acute heart failure and cardiogenic chock. Abdominal complications encompassed hepatitis, gastrointestinal bleeding, pseudo-obstruction and obstruction, diarrhea and constipation. Skin complications included the presence of pressure injuries.

Infectious complications were considered in the presence of ICU-acquired infections, superimposed to the primary infectious diagnosis.

Data regarding the aforementioned characteristics was gathered on a database where each patient received a code number to secure their anonymity.

At the PRM appointments (6 and 12 months after discharge), a detailed physical examination was performed, and a predefined set of scales were applied, aiming to comprehensively evaluate the three domains of PICS (physical, mental, and cognitive). Additionally, patients' functionality was systematically assessed. The chosen outcome measures were preferentially the ones recommended by the core outcome set for survivors of acute respiratory failure [15].

Physical examination encompassed the evaluation of the patient's swallowing function, muscle strength, sensory response, signs of CSTD, balance and gait. Data regarding muscle strength, sensory response and signs of CSTD was obtained from physical examination and afterwards formally analyzed through statistical methods. Data regarding swallowing function, balance and gait were analyzed using specific instruments, as described below. Muscle strength was evaluated through manual muscle testing and graded in accordance with the Medical Research Council Sum Score (MRC-SS). The maximum score at this metric is 60 points reflecting maximal strength in all evaluated segments bilaterally, so this value was used as reference category [16]. The sensory exam included the evaluation of light touch sensitivity in all dermatomes from C2-S2 bilaterally. The presence of hyper, hypo or anesthesia, and/or the complains of dys or paresthesia during the sensory examination, were considered as sensory impairments. Signs of CSTD were evaluated through the examination of deep tendon reflexes (DTR) and Babinski sign. Bicipital, tricipital, brachioradialis, patellar and achilles DTR were appraised using a predefined T-shaped reflex hammer. The grading of reflex response was in accordance with an adapted form of the National Institute of Neurological Disorders and Stroke (NINDS) Myotatic Reflex Scale in: 0) absent, 1) hyporeflexia, 2) normal, 3) hyperreflexia, 4) hyperreflexia with unsustain clonus ($\leq$ five beats), 5) hyperreflexia with sustain clonus ($>$ five beats) [17]. Babinski sign was evaluated using the reflex hammer dull point by running up, with light pressure, the lateral plantar side of the foot, from heel to toes. The response of hallux and toes was recorded as extensor (Babinski sign), flexor or neutral [18]. The presence of signs of CSTD was defined as 1) Babinski sign in at least one extremity or 2) hyperreflexia in at least two extremities [19]. All data recorded from the physical examination was included in the physical domain.

To further characterize the physical domain, the European-Quality-of-Life-5-Dimensions-3-Level (EQ-5D-3L) questionnaire was used to measure health-related QoL. The first part of this questionnaire is a three-question component that explores five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is rated on a scale from 1 to 3. In accordance with Larsson IM *et al.* study we have considered the result of at least two points per question as cut-off value for impairment (total score $\geq$ 6) [20]. The second section is a visual analogue scale (EQ-VAS), which is a measure of self-rated overall health status, ranging from 0 to 100%. According to Ferreira PL *et al.* study in the Portuguese population, we have considered values below 75% as an impairment [21].

Fatigue was evaluated using the Portuguese version of Fatigue Assessment Scale (P-FAS) [22]. The P-FAS is a self-reported, 10-item ordinal questionnaire that varies from 10 to 50. A total P-FAS score $\geq$ 22 indicates the presence of fatigue [23].

Swallowing function was evaluated using the Functional Oral Intake Scale (FOIS) and the Portuguese Eating Assessment Tool (P-EAT-10) [24, 25]. FOIS is a continuous scale that ranges from 1 to 7. In accordance with Sassi FC *et al.* analysis, we divided patients in 1) resolved dysphagia, when FOIS levels were of 6 or 7; or 2) non-resolved dysphagia, if the FOIS levels were from 1 to 5 [26]. The P-EAT-10 is a continuous scale, that varies from 0 to 40, with

scores over 3 in each question indicating increase risk of dysphagia, as detailed in Zhang PP *et al.* metanalysis [27]. In accordance, we have considered 30 as the reference value for dysphagia and 0 as the reference for the absence of swallowing complains.

Gait was analyzed and described during physical examination and classified in accordance with the Hauser Ambulation Index (HAI) for analytic purposes [28]. This index ranges from 0 to 9. We have considered 0 as the reference category, thereby classifying patients with scores ≥ 1 as having a gait impairment.

Balance was evaluated objectively in the physical examination and classified accordingly to the Berg Balance Scale (BBS). The BBS assesses the functional balance based on 14 items, with a maximum score of 56 points. In accordance, we have considered that scoring ≤ 55 points was suggestive of having a balance impairment [29]. Additionally, we have considered the cut-off for higher risk of falls (46 points) as reference for the presence of a significative balance impairment [30].

To summarize the obtained results, we have created a composite variable (PICS-physical) that included all subdomains related to the physical function. We have considered that there was an involvement of the physical domain when any of the subdomains was altered.

For the mental domain, we used the Hospital Anxiety and Depression Scale (HADS). We considered 0 points as reference value, thought significant anxiety was defined as HADS-anxiety score ≥ 8 and significant depression as HADS-depression score ≥ 8 [31]. When significant depression or anxiety was reported, an impairment on the mental domain as assumed.

To evaluate the cognitive domain, the Montreal Cognitive Assessment (MoCA) was applied. This score range is 0–30. A cut-off of 26 was used to define cognitive dysfunction in accordance with the literature [32].

Functionality was evaluated through self-reported Functional Independence Measure (FIM). The FIM is a validated and objective assessment of functional status [33]. It is an 18-item ordinal scale, in which the global score varies from 18 to 126 [33]. Since multidisciplinary FIM assessment was not possible in this setting, we have considered self-reported FIM values following previous reports of moderate agreement between self-reported and observed FIM [34]. When the total punctuation at FIM was below 126 points, we considered that the patient was not fully independent on ADL. Even though PICS original definition allocated autonomy on ADL in the physical domain, in our analysis functionality was evaluated separately, since mental, physical and cognitive dysfunction can impact functionality and autonomy on ADL.

Furthermore, information regarding PRM interventions was also collected. Through the ECR, data regarding in-hospital (ICU and wards) rehabilitation programs was retrieved. In each follow-up visit, information concerning PRM programs performed after hospital discharge was obtained, namely, setting (in or outpatient), modalities (uni or multimodal, including rehabilitation nursing, physical therapy, occupational therapy, speech therapy and/or neuropsychology), length (number of months under PRM intervention) and intensity (number of sessions per week and each session duration).

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) statistics software (version 27).

Categorical variables are summarized as frequencies and percentages. Continuous variables are summarized as means and standard deviations (variables with normal distribution) or medians and interquartile ranges (variables with skewed distributions). Normal distribution was checked using histogram visual inspection and the Shapiro–Wilk test.

The chi-square test or Fisher's exact test was used, as appropriate, to compare categorical variables. Continuous variables comparison between "included" and "lost to follow-up" patients was performed with independent sample t-test or the Mann-Whitney U test, according to the variable distribution.

To compare patient's values with normative data (reference category), one sample t-test or one sample Wilcoxon Signed Rank Test were used, in accordance with the variable distribution. Due to the absence of specific cut-offs for the applied scales in this post-critical COVID-19 sample, and the diversity of results (regarding the used metric and the timing of examination) available in the literature, we compared our results with the classic normative values of each scale, as previously referred as the reference category.

Continuous variables were compared regarding its evolution throughout the 6 month follow-up period using paired-samples t-test or related samples Wilcoxon Signed Rank Test, in accordance with the variable distribution.

All reported p values are two-tailed, with a p-value <0.05 indicating statistical significance.

Results

Sample characteristics

A total of 92 critical COVID-19 patients were admitted and discharged alive from our ICU, between May/2020 and September/2021.

Within this eligible sample, 5 patients died after ICU discharge (5.4%), 35 refused to be observed in the appointment (38%) and 10 patients were not reachable (10.9%). As so, 42 patients were included (45.7%). No differences were found between patients included and those lost to follow-up regarding socio-demographic characteristics (gender and age), the severity of disease at admission (APACHE and SAPS II scores), number of days at the ICU and total length of stay (S1 Table).

In the included sample, 66.7% were males with a mean age of 62 years old (standard deviation (SD) = 13.5). All patients were previously independent on ADL. Obesity (57.1%), hypertension (54.8%), and hyperlipidemia (45.2%) were the comorbidities more frequently identified.

The mean SAPS II score was 40.7 (SD = 15.3), with 73.8% (n = 31) of patients scoring over 30 points at ICU admission. Moreover, the median of ICU stay was 31.5 days (interquartile range (IQR) = 15.5–51.3) and the median number of days under IMV was 25 (IQR = 10.0–43.0). During ICU stay, several complications were registered, namely neurological (54.8%), cardiovascular (14.3%), abdominal (42.9%), cutaneous (47.6%) and infectious (71.4%).

Data regarding socio-demographic characteristics, comorbidities, characterization of critical respiratory illness and complications at ICU are detailed in Table 1.

PRM care characterization

Throughout ICU and hospital wards stay, all included patients were evaluated and included in PRM inpatient programs, which consist of one (physical therapy, occupational therapy, speech therapy, and rehabilitation nursing) or more treatment modalities, pending on each patient sequelae. After discharge, 88% (n = 37) maintained PRM treatments: 7 patients (16.7%) were admitted at PRM facilities for inpatient rehabilitation (followed by outpatient rehabilitation), and the remaining 30 patients were included in outpatient rehabilitation programs. A total of 5 patients were not included in PRM programs after hospital discharge since a full recovery in neuromotor domains and autonomy on ADL was achieved. In most cases, PRM outpatient intervention was unimodal (physical therapy; 70.2%; n = 26). The frequency of PRM interventions ranged between 2 to 5 sessions per week, in which each session length of 30 to 60

Table 1. Socio-demographic and clinical characteristics of the sample.

Characteristic	Total cohort (n = 42)
Socio-demographic characteristics	
Male gender, n(%)	28 (66.7)
Age, mean (SD)	61.8 (13.5)
Previous autonomy on ADL, n (%)	42 (100.0)
Comorbidities	
Hypertension, n(%)	23 (54.8)
Diabetes *Mellitus*, n(%)	18 (42.9)
Hyperlipidemia, n(%)	19 (45.2)
Obesity, n(%)	24 (57.1)
Smoking habits, n(%)	1 (2.4)
Atrial fibrillation, n(%)	3 (7.1)
Ischemic heart disease, n(%)	1 (2.4)
Heart failure, n(%)	1 (2.4)
Peripheral vascular disease, n (%)	3 (7.1)
CPOD, n(%)	1 (2.4)
Asthma, n(%)	5 (11.9)
Sleep apnea, n(%)	6 (14.3)
Psychiatric pathology, n(%)	7 (16.7)
Oncologic pathology, n(%)	7 (16.7)
Immunosuppression, n(%)	1 (2.4)
Characteristics regarding the critical respiratory illness	
APACHE II, mean (SD)	18.1 (5.7)
SAPS II, mean (SD)	40.7 (15.3)
SAPS II $\geq$ 30, n (%)	31 (74.0)
Days at ICU, median (IQR)	31.5 (15.5–51.3)
Total length of stay, median (IQR)	41 (28.0–81.5)
Number of days under IMV, median (IQR)	25 (10.0–43.0)
Need for vasopressor support, n (%)	30 (71.4)
Number of days under vasopressors, median (IQR)	7 (2.0–21.5)
Need for renal replacement therapy, n (%)	7 (16.7)
Number of days under renal replacement therapy, mean (SD)	27 (14.9)
Need of ECMO, n (%)	5 (11.9)
Number of days under ECMO, mean (SD)	27.8 (30.4)
Need of prone positioning, n (%)	27 (64.3)
Complications during ICU stay	
Neurological complications[‡], n (%)	
Aphasia, dysarthria or dysphonia	0 (0.0)
Dysphagia	5 (11.9)
Focal weakness	0 (0.0)
Delirium	13 (31.0)
Seizures	0 (0)
Cerebrovascular disease	1 (2.4)
Encephalopathy	2 (4.8)
Encephalitis or myelitis	0 (0.0)
Peripheral neuropathy	2 (4.8)
Signs of CSTD	11 (26.2)
Composite of neurological signs, symptoms, or syndromes	23 (54.8)

(*Continued*)

Table 1. (Continued)

Cardiovascular complications[¥], n (%)	6 (14.3)
Abdominal complications[§], n (%)	18 (42.9)
Cutaneous complications (pressure injuries), n (%)	20 (47.6)
Infectious complications, n (%)	30 (71.4)

APACHE: Acute Physiology and Chronic Health Evaluation; ECMO: extracorporeal membrane oxygenation; ICU: Intensive Care Unit; IQR: Interquartile range; CPOD: Chronic Pulmonary Obstructive Disease; CSTD: Corticospinal tract dysfunction; SAPS: Simplified Acute Physiology Score; SD: Standard deviation.

[|]: Neurological complications included aphasia, dysarthria, dysphonia, dysphagia, focal weakness, delirium, seizures, cerebrovascular disease, encephalopathy, encephalitis, myelitis, peripheral neuropathies and signs of CSTD. The composite of neurological signs, symptoms, or syndromes considered, for each patient, the presence of at least one neurological sign, symptom, or syndrome, regardless of the number of neurological manifestations.

[¥]: Cardiovascular complications included bradyarrhythmia, tachyarrhythmia (atrial fibrillation, flutter, other tachyarrhythmias), tachycardia-bradycardia syndrome, secondary myocardial injury, cardiac arrest, pericarditis, pericardial effusion, endocarditis, acute heart failure, and cardiogenic shock.

[§]: Abdominal complications included hepatitis, elevated liver enzymes, gastrointestinal bleeding, pseudo-obstruction and obstruction, diarrhea, and constipation.

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minutes. At 6 months post-discharge, 62.2% remained under PRM intervention, while at 12 months 32.4% maintained PRM outpatient programs.

PICS analysis

Table 2 details the clinical status at 6 and 12 months, univariate analysis between the achieved scores and the reference values and a comparative analysis ("evolution" between scores at 6 and 12 months.

PICS—Physical domain

PICS physical domain was evaluated through multiple metrics in our analysis. Indeed, 76.2% (n = 32) of our sample had at least one physical impairment at 6 months decreasing to 71.4% (n = 30) at 12 months (p-value = 0.475).

Regarding QoL, at 6 months after ICU discharge, COVID-19 survivors had significantly higher EQ-5D-3L median (7.2 (IQR = 5.0–8.5), p-value = 0.034), and a lower mean EQ-VAS (67.4 ± 21.6, p-value = 0.060), in comparison with reference values. Nevertheless, one year after ICU discharge, we found no difference either in EQ-5D-3L nor in EQ-VAS compared to normative values (p-value = 0.180 and p-value = 0.573, respectively). In both QoL metrics, there was a tendency for improvement through the follow-up period, which was statistically significant only for the EQ-VAS (p-value = 0.038).

Concerning fatigue, COVID-19 survivors had a mean P-FAS of 34.5 ± 32.0 at 6 months, a significantly superior value in comparison with reference values (p-value = 0.009). At 12 months, the median FAS decreased to 18.5 points (SD = 50.0; p-value = 0.043).

Swallowing function was also analyzed in our sample, as part of the physical domain. Both at 6 and 12 months, the median of FOIS and P-EAT-10 were similar to the reference category. At 6 months after ICU discharge, 5% (n = 2) presented swallowing impairments whereas at 12 months none had this complication.

A total of 31% of COVID-19 survivors had muscle weakness at 6 months, and 28.6% maintained this impairment at 12 months (p-value = 0.002). In brief, both at 6 and 12 months after ICU discharge, median values at MRC-SS were significantly below the normative value (6

Table 2. Scores at 6 and 12 months and comparison with normative values.

	6 months		12 months		p-value (evolution)
	Status	p-value (comparison with reference)	Status	p-value (comparison with reference)	
Physical Domain					
Quality of Life					
EQ-5D-3L, median (IQR) *Reference: 6 points*	7.2 (5.0–8.5)	0.034[a]	6.4 (5.0–7.0)	0.180[a]	0.069[c]
EQ-VAS, mean (SD) *Reference: 75%*	67.4 (21.6)	<0.060[a]	73.3 (18.5)	0.573[a]	0.038[c]
Fatigue					
FAS: mean (SD) *Reference: 22 points*	34.5 (32.0)	0.009[b]	18.5 (50.0)	0.309[b]	0.043[d]
Swallowing function					
FOIS: median (IQR) *Reference: 5 points*	7.0 (7.0)	0.157[b]	7.0 (7.0)	1.000[b]	0.157[d]
EAT10: median (IQR) *Reference: 0 points*	0.0 (0.0)	0.180[b]	0.0 (0.0)	0.317[b]	0.285[d]
Muscle strength					
MRC-SS: median (IQR) *Reference: 60 points*	60.0 (48.0–60.0)	0.001[b]	60 (56.8–60.0)	0.002[b]	0.003[d]
Gait ability					
HAI: median (IQR) *Reference: 0 points*	1.0 (0.0–2.3)	<0.001[b]	0.0 (0.0–1.0)	<0.001[b]	0.026[d]
Balance					
BBS: median (IQR) *Reference: 56 points*	51.0 (42.3–56.0)	<0.001[b]	56 (50.0–56.0)	<0.001[b]	0.010[d]
Sensibility					
Impairment: n (%)	7.0 (16.7)		3.0 (7.1)		0.331[e]
Signs of CSTD					
Present: n (%)	22.0 (52.3)		11.0 (26.2)		<0.001[f]
Phycological Domain					
Anxiety and depression					
HADS–Anxiety: mean (SD) *Reference: 0 points*	5.2 (4.5)	<0.001[a]	4.0 (4.3)	<0.001[a]	0.012[c]
HADS–Depression: mean (SD) *Reference: 0 points*	6.3 (3.7)	<0.001[a]	5.2 (4.9)	<0.001[a]	<0.001[c]
Cognitive Domain					
Cognitive Performance					
MoCA: median (IQR) *Reference: 26 points*	20.0 (11.3–24.8)	<0.001[b]	23.0 (16.0–26.5)	<0.001[b]	0.031[d]
Functionality and autonomy in daily-life activities					
FIM: median (IQR) *Reference: 126 points*	126.0 (125.0–126.0)	0.018[b]	126.0 (126.0)	0.018[b]	0.345[d]

BBS: Berg Balance Scale; CSTD: Corticospinal tract dysfunction; EAT-10: Eating Assessment Tool; FAS: Fatigue Assessment Scale; FIM: Functional Independence Measure; FOIS: Functional Oral Intake Scale; HADS: Hospital Anxiety and Depression Scale; HAI: Hauser Ambulation Index; IQR: Interquartile range; MoCA: Montreal Cognitive Assessment; MRC-SS: Medical Research Council Sum Score; SD: Standard deviation

[a] *One sample t-test;*

[b] *One sample Wilcoxon Signed Rank Test;*

[d] *Paired-samples t-test;*

[e] *Related Samples Wilcoxon Signed Rank Test;*

[f] *Fisher Exact Test;*

[g] *Chi-square test.*

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months: median = 60.0, IQR = 48.0–60.0, p-value = 0.002; 12 months: median = 60.0, IQR = 56.8–60.0, p-value = 0.001). Nonetheless, during the follow-up period, there was a significant improvement on this parameter (p-value = 0.003).

Gait, assessed objectively through the HAI, was also significantly impaired, in comparison with reference values, both at 6 and 12 months after ICU discharge (6 months: median = 1.0, IQR = 0.0–2.3, p-value<0.001; 12 months: median = 0.0, IQR = 0.0–1.0, p-value<0.001). Similarly, there was a significative improvement in this subdomain through the follow-up period (p-value = 0.026).

Regarding functional balance, median BBS was 51.0 (IQR = 42.3–56.0) at 6 months and 56.0 (IQR = 50.0–56.0) at 12 months, values that were significantly reduced in comparison with the reference category (p-values<0.001). Nevertheless, this parameter also evolved positively through time (p-value = 0.001). Moreover, when analyzing the BBS through a cut-off for higher risk of falls, at 6 months 28.6% had a higher risk of this adverse event, a value that decreased to 18.9% at 12 months (p-value = 0.004).

Sensory impairments were present in 16.7% at 6 months and in 7.1% at 12-months. No significant improvement on this subdomain was depicted through the study period (p-value = 0.331).

Signs of CSTD were present in 52.3% (n = 22) at 6 months, and in 26.2% (n = 11) at one year follow-up (p<0.001).

PICS–Mental domain

Overall, at 6 months after ICU discharge, 31.0% (n = 13) had impairments on the mental domain of PICS, value that was reduced to 26.2% (n = 11) at 12 months (p-value = 0.159).

Both at 6 and 12 months after ICU discharge, the mean score at the HADS–Anxiety (5.2 ±4.5 and 4.0±4.3, respectively) and at the HADS–Depression scores (6.3±3.7 and 5.2±4.9, respectively) was significantly superior to the reference value (p-value<0.001). Using the 8 points cut-offs for significant anxiety and depression, a significant difference from our values was also reported (p-value = 0.003 and 0.022), pointing to the absence of significant impairments, despite the presence of alterations. In both anxiety and depression scores, there was a significative positive evolution through the follow-up period (anxiety: p-value = 0.012; depression: p-value<0.001).

PICS—Cognitive domain

The prevalence of cognitive dysfunction at 6 months after ICU discharge was of 79.2%, value that shifted to 64.9% at 12-months (p-value = 0.003). In fact, significant disablement was noted in comparison with reference values both at 6 months (median = 20.0, IQR = 11.3–24.8, p-value<0.001) and 12 months (median = 2.03; IQR = 16.0–26.5; p-value<0.001). Yet, a global improvement in this 1-year follow-up was noted (p-value = 0.0031).

Functionality

In our sample, 54.8% of the patients were fully active on ADL 6 months after ICU discharge, with a median FIM of 126.0 (IQR = 125.0–126.0), a value significantly inferior to the reference category (p-value = 0.018). Moreover, at 12-months after ICU discharge, functionality significantly improved, with 74% of patients being totally independent (p-value = 0.002). Nevertheless, median FIM was still significantly diminished (median = 126.0, IQR = 126.0, p-value = 0.002).

Discussion

Our study revealed that critical COVID-19 survivors present substantial physical, mental and cognitive impairments 6 and 12 months after ICU discharge, and that these impairments seem

to improve through time. Nevertheless, 1 year after ICU discharge, significant disablements in muscle strength, gait ability, balance, psycho-emotional status and cognitive performance persisted. Approximately half of these survivors were fully independent on ADL 6 months after ICU discharge, value that improved by approximately 20% on the subsequent 6 months.

Previous studies have described persistent signs, symptoms and reduced health related QoL after COVID-19 disease in hospitalized patients [10–13]. Irisson-Mora I *et al.* suggested that the grade of severity of disease (critically ill *vs.* hospitalized patients) impacts the prevalence of impairments in COVID-19 survivors [35]. Nonetheless, studies investigating specifically critically ill COVID-19 survivors are still scarce and lack on multidomain assessments and clinical path analysis. Previous investigations were generally limited to describing outcomes in specific time frames, without exploring clinical trajectories [36, 37] or assessing global patient status, not having in consideration PICS main domains and its' impact on functionality [10, 11]. Additionally, part of these studies' methodology included telephone interviews, leading to an absence of physical examination data and to additional biases [10, 11, 37]. Furthermore, most studies that included face-to-face interviews focused on the respiratory and cardiovascular sequelae of critical COVID-19 disease, and not in the physical and cognitive impairments [13, 38]. Our investigation is, to our knowledge, the first to provide a comprehensive analysis of PICS domains trajectory in critical COVID-19 survivors, including not only scales but also physical examination and functionality data.

PICS is known to be a common syndrome after critical care. In this COVID-19 era, due to the marked increase in ICU admissions, the number of patients suffering from this syndrome is rising. Also, critical COVID-19 patients may be particularly prone to develop PICS [39]. Firstly, PICS risk factors are frequent among the COVID-19 critical patient [40]. Secondly, since median ICU and hospital length of stay are usually longer in this population, the subsequent prolonged bed rest and extended hospital stay may contribute to muscular weakness, which is associated with substantial impairments in physical function and health related QoL [41]. Despite the possible increased risk for PICS in the survivors of critical COVID-19, the prevalence of PICS and its definition for this population is still not yet determined [35]. Hence, the possible differential extent and impact of PICS in COVID-19 survivors, in comparison with non-COVID-19 ICU survivors, warrants further clarification. Hodgson CL *et al.* performed a comparative analysis between critical COVID-19 and non–COVID-19 survivors, reporting that the incidence and severity of disabilities, health related QoL, psychological status and cognitive performance at 6 months did not significantly differed between COVID-19 and non–COVID-19 survivors [37]. Nevertheless, this study included a non-matched sample of patients from two different prospective cohorts, in which there were some baseline differences that could affect the results. Also, this study included a single telephone evaluation, so data regarding physical examination and information regarding the clinical path was not included. On the other hand, in-ICU studies, as Rahiminezhad E *et al.*, that compared critical COVID-19 and non-COVID-19 patients regarding functional parameters, reported significantly higher disability in COVID-19 patients [42]. Also, the RECOVID study pointed to a quicker recovery in COVID-19 patients in comparison with patients with other ICU admission motives [43]. Therefore, the real impact of critical COVID-19 on the prevalence, extent and characteristics of PICS warrants further clarification, as this population may have specific needs and different clinical courses.

The baseline characteristics of our sample, namely socio-demographic factors, comorbidities and the characteristics related to the critical respiratory illness, were compatible with previous investigations in this field [10, 37]). We highlight that the mean age of our sample was of 61.8 years old, ranging from 28 to 81 years old. This data is in line with most previous investigations in this field [4, 6, 11–13, 44]. Nevertheless, and as advanced age is not only a risk factor

for higher severity and mortality due to COVID-19, but also a predictor of PICS, we stress that our study data and conclusions should be considered as driven for a cohort of older adults [45, 46].

Regarding PRM intervention, all included patients were evaluated and included in intra-hospitaller PRM programs and all patients who had clinical indication maintained these interventions after hospital discharge. Our data is in line with previous studies, specifically concerning the setting and median duration of PRM programs [35]. The transversal inclusion on PRM programs in this sample, and the maintenance of these interventions for long periods, may be part of the explanation for the significative PICS improvement. Indeed, Berentschot JC *et al.* multicenter prospective cohort study highlighted the impact of post-discharge PRM programs in several physical domains, specifically when performed in multi-modal and comprehensive settings [47]. Nevertheless, direct comparative analysis between different PRM programs regarding its setting, modalities, duration, intensity and other characteristics, still lacks in the hitherto literature. As we have performed an observational analysis, and not an experimental or quasi-experimental study, a clear analysis of the impact of PRM intervention in the multidomain improvement on this sample was not possible to perform. Indeed, it would be clinically relevant to access the specific contribution of PRM intervention in these patients' clinical path, differentiating the rate of improvement that is indexed to the diseases' natural course from the induced by PRM intervention. Nonetheless, our findings emphasize the long-term impact of critical COVID-19, with clear implications for clinical care, specifically in the field of PRM.

In our sample, COVID-19 survivors had significative impairments on QoL at 6 months, with a significative recovery during the first year after ICU discharge. In comparison with Huang L *et al.* study, EQ-VAS was similar at 1-year, yet at 6 months lower scores were noted in our sample [11]. Similarly, significative fatigue at 6 months was noted, which positively evolved until the first year after ICU discharge. In comparison with Hussain N *et al* analysis, our data points out to slightly lower prevalence of this symptom [48].

Swallowing function was also analyzed, as part of the physical domain. Nonetheless, it was not possible to compare our data with follow-up analysis of critical COVID-19 survivors at 6 and 12 months in relation with its absence in the literature.

Muscle strength, gait and balance were also significantly impaired in our sample, both at 6 and 12 months, despite the significantly positive evolution reported through the follow-up period. Since previous studies did not measure these domains, neither at the same timings nor with the same instruments, a comparative analysis with other ICU (ideally COVID-19) studies was not possible.

Sensory impairments were not common in this sample and did not improve significantly over time. Due to the more subjective nature of sensory complains, clinical assessment may have underestimated the prevalence of these complication or its clinical improvement. Most previous studies that have addressed this impairment included only subjective complains and not objective analysis [49]. Nevertheless, according to Pinzon RT *et al.* meta-analysis, sensory impairments were reported in one in each three COVID-19 survivors, a value that exceeds our data by around 50% [49]. The inclusion of specific sensory examinations in follow-up analysis of critical COVID-19 survivors lacks in the literature, which seems to be a significative flaw as a result of the negative impact of these alterations [50].

Regarding signs of CSTD, none of the previous analysis of mid- and long-term morbidities after critical illnesses have analyzed this manifestation. Asso, a direct comparison with a literature was not viable. Nevertheless, there are several reasons to justify the formal search for signs of CSTD. Firstly, these analysis allow a rapid distinction between upper and lower motor neuron pathology [51]. Secondly, as magnetic resonance imaging studies of COVID-19 patients showed that corticospinal tract lesions were the most common lesions of the white matter,

CSTD evaluation may raise clinical suspicion of neurological impairments, allowing earlier diagnosis and treatment [52]. Lastly, as clonus can have a direct impact on gait ability, and therefore influence the patient's functionality, its' active exploration is warranted in the setting of PRM outpatient appointments and therefore should be considered in subsequent investigations that aim to access neurological and functional consequences of critical COVID-19. We have compared this sample rates with the prevalence of CSTD signs in our group cohort of critical COVID-19 patients [53]. We highlight that, despite similar clinical methodology, material and diagnostic criteria, higher rates of CSTD were encountered at 6-months after ICU discharge, which is probably in relation with the impact of intensive care unit acquired weakness on DTR response (its diminishment or abolition) [54]. Nevertheless, the number of patients with signs of CSTD significantly decreased through the follow-up period, highlighting the probably neurological recovery throughout the first year after ICU discharge.

PICS mental domain involvement was inferior when compared to the physical domain in our analysis. Yet, one in each four patients at 1-year maintained psychological complains, data compatible with the literature [9].

Poor cognitive performance after COVID-19 has been previously reported [37]. The proportion of patients who recovered cognitive function over time is in line with previous reports [10]. Nonetheless, in our sample, significative cognitive impairments persisted at 12 months after ICU surpassing previous data from Taniguchi *et al.* study [10]. Miskowiak KW *et al.* postulated that cognitive impairments were associated with the degree of long-term pulmonary dysfunction, increased respiratory symptoms and D-dimer concentrations during acute illness, suggesting a potential link to restricted oxygen delivery to the brain [40]. Since our sample comprises a severe cohort of COVID-19 critically ill patients, the overexpression of this cognitive impairments is most likely in this context.

Overall, PICS was prevalent in our study population, both at 6 and 12 months after ICU discharge. Since there is a significative heterogeneity on PICS diagnostic criteria, direct comparisons between our data and the literature are hard to establish [9]. When analyzing the prevalence of each component of PICS, the main contribution for mid- and long-term impairments was the physical domain, which was confirmed in up to three-fourths of the sample both at 6 and 12 months, data compatible with the literature [12]. Moreover, we highlight the continued recovery of PICS domains throughout our follow up period, data already hypothesized by Zhang H *et al.* [55].

The study design and methodological strengths reinforce our major findings. A prospective cohort study was designed as it clearly indicates the temporal sequence between exposure and outcome, and allows a better characterization of the clinical path. Moreover, this study design allows the examination of multiple effects of a single exposure (namely, and applying to this investigation, the effects of critical COVID-19 on physical, cognitive and mental domains) [56]. To ensure the external validity of our results, there was a consecutive sampling of participants and inclusion of patients from different ICU. To increase patients' engagement, thereby reducing the rates of "lost to follow up", several telephone trials were attempted to recruit the patients, and each patient that missed an appointment was given up to two opportunities to reschedule the visit. Indeed, and in accordance with a prospective cohort study design, the risk of "losses to follow up" was not negligible. We also highlight that a differential loss to follow up could have introduced additional biases. Hence, the rates of "lost to follow up" of our study were in line with previous studies [55]. Moreover, "included" and "lost to follow-up" patients were compared through statistical analysis, emphasizing the external validity of our data. Regarding the internal validity, we stress that all patients were evaluated by a single investigator (a PRM physician), using validated instruments, and thereby ensuring high-quality data and minimizing bias.

Our study presents some limitations. Firstly, we developed a single-center cohort study. The local case-mix may have influenced our results, and its generalization might be limited. Nevertheless, as the study took place in a tertiary care center covering a wide geographical referral area, encompassing several specialized ICU, and receiving several patients transferred from other institutions for advanced ICU care, the external validity of our results is, hence, considerable. Furthermore, and in line with a cohort study design, variables and outcomes were only observed, without any intervention taking place [56]. Secondly, we did not have a contemporaneous control group of critically ill respiratory patients without COVID-19 infection, so we could not distinguish the specific long-term effects of this infection from those that might result from critical illness itself. Also, sample size calculation was not performed due to the lack of data on the chosen outcome measurements available at the literature by the time our recruitment started. Lastly, all patients were evaluated by PRM physicians during hospitalization, and most were included in tailored PRM treatments, which lead to an inability to estimate the impact of PRM programs on PICS trajectory.

Further studies are warranted to characterize the long-term trajectory of PICS in critical COVID-19 patients. Also, predictive models for PICS diagnosis and prognosis are desirable. Moreover, the promising effects of vaccines and other new treatments in PICS need further description in COVID-19 survivors. Furthermore, additional studies, preferably of an experimental nature, designed to assess the impact of different settings, modalities and duration of PRM programs are desirable to further determine the most effective PRM programs in this setting. Finally, future studies should explore the link between brain oxygen delivery and cognitive outcomes and therapies that may attenuate the effect of acute respiratory failure on cognitive impairment.

Conclusion

Critical COVID-19 survivors present significative physical, mental and cognitive impairments 6 and 12 months after ICU discharge, despite their positive evolution through time. Accordingly, at least during the first-year post ICU discharge, but probably for a longer period, COVID-19 patients benefit from PRM evaluations and interventions, since clinical and functional impairments persist.

Supporting information

S1 Table. Comparison between "included" and "lost to follow-up" patients.
(DOCX)

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DISCUSSÃO

A presente investigação propôs-se a contribuir para o aumento do nível de conhecimento sobre a doença crítica COVID-19, especificamente no que se refere ao impacto da mesma em termos clínicos e funcionais, com particular enfoque na associada disfunção neurológica. Desta forma, nos diferentes estudos constituintes desta Tese, foi possível identificar e quantificar o impacto das comorbilidades neurológicas (especificamente a DVC) na mortalidade por COVID-19 crítica, esclarecer que existe um maior risco de disfunção neurológica na doença crítica a SARS-CoV-2, em comparação com outros patógenos infeciosos, analisar o impacto a longo termo da doença nos domínios físico, mental e cognitivo e na funcionalidade, bem como desenvolver um modelo de predição de risco de lesões por pressão para doentes COVID-19 críticos.

Assim, a corrente investigação pretendeu estudar os doentes COVID-19, numa perspetiva de "antes, durante e depois" do internamento em UCI. De acordo com os propósitos inicialmente definidos para os estudos desta Tese, serão de seguida revistos e discutidos os principais achados deste projeto, de acordo com os objetivos listados previamente.

1) Avaliar o impacto de comorbilidades neurológicas, especificamente a DVC prévia, na mortalidade de doentes críticos COVID-19.

Parte da investigação médica realizada no âmbito da doença COVID-19 focou-se na identificação de fatores de risco e no desenvolvimento de modelos preditivos que permitissem identificar uma maior probabilidade de gravidade e mortalidade pela doença[28-32].

A presença de comorbilidades neurológicas, especificamente a DVC prévia, tem inerentemente plausibilidade biológica para um aumento do risco de morte nos doentes COVID-19 críticos[154, 155]. A imunossupressão pós DVC, o pior *status* funcional com subsequente menor reserva global, a presença de disfunção autonómica sequelar à lesão encefálica, o possível atingimento dos músculos inspiratórios e expiratórios com redução global do seu trofismo e força, a afeção dos centros cardio-respiratórios do tronco cerebral em lesões vasculares com esta topografia e o efeito da imobilidade e risco inerente de estados de hipercoaguabilidade são alguns dos possíveis substratos justificativos de um maior risco de complicações, designadamente infeciosas, e de que, na sua presença, exista também maior morbilidade e mortalidade associadas[154-157]. Estes fatores assumem um papel ainda mais preponderante quando nos debruçamos especificamente sobre uma infeção vírica causada por um micro-organismo que apresenta, presumivelmente, neurotropismo e potencial de neuroinvasividade[56, 59, 60, 62, 63, 65, 158].

Como tal, constituiu um dos objetivos desta Tese avaliar se a presença de DVC prévia se associava a maior risco de mortalidade entre doentes críticos COVID-19.

Neste contexto, desenvolvemos um estudo prospetivo numa amostra de doentes COVID-19 críticos. Cerca de 10% da amostra apresentava antecedentes de DVC, a qual foi definida de acordo com as recomendações da *American Heart Association / American Stroke Association*[159, 160]. A definição de critérios de DVC prévia foi particularmente importante neste trabalho em virtude da heterogeneidade existente na sua definição em estudos prévios relacionados com este tópico[161, 162]. Adicionalmente, foi também avaliado, com recurso à escala de *Rankin* modificada, a autonomia prévia de todos os doentes da amostra, com vista a tentar compreender se o impacto na mortalidade era diretamente atribuível à DVC ou imputável às decorrentes alterações da funcionalidade.

Na amostra analisada, a idade, a gravidade da doença à admissão e a DVC prévia associaram-se a uma maior mortalidade pela COVID-19, à semelhança do descrito em estudos prévios realizados fora do contexto de UCI[157, 162, 163]. Nenhuma outra característica sociodemográfica, funcional ou clínica se associou de modo significativo a maior mortalidade nesta amostra. Após ajuste, através de análise multivariada, para a idade e a severidade da doença à admissão da UCI, a DVC prévia manteve-se um preditor independente significativo. De facto, a presença desta comorbilidade resultou num risco 2,51 vezes superior de morte em doentes críticos COVID-19.

É também de destacar que nos doentes com COVID-19 crítica que morreram, o número de dias até à morte foi significativamente menor nos que tinham DVC prévia em comparação com doentes sem esta comorbilidade, achado concordante com a literatura existente[156]. Possivelmente, as alterações estruturais e funcionais relacionadas com as sequelas do evento vascular estão na base desta menor reserva e maior fragilidade, a qual se expressa por uma menor resistência à infeção, com mais rápido envolvimento sistémico.

Na nossa análise, tivemos como objetivo secundário perceber se doentes com outras formas de doença vascular, ilustrados pelos casos com cardiopatia isquémica prévia, tinham também maior risco de morte, ou se este risco era indexado à topografia da lesão vascular (nomeadamente à sua localização no SNC). A presença de doença cardíaca isquémica não se associou de modo significativo a maior mortalidade entre doentes críticos COVID-19, apontando para o impacto específico da topografia da lesão vascular na mortalidade destes doentes, algo que poderá estar na dependência dos potenciais mecanismos causais previamente explicitados.

Além do previamente referido, o nosso estudo acrescenta também de novo à literatura a análise das causas de morte destes doentes, ponto apontado como uma fragilidade em estudos prévios realizados neste âmbito[156, 164]. Uma proporção significativa da nossa amostra teve como causa de morte a disfunção multiorgânica relacionada à COVID-19, tendo sido possível descrever alternativas causas de morte nesta amostra. Não se verificou uma diferença significativa no que se refere às causas de morte dos doentes com e sem DVC prévia.

Foi também feito o seguimento prospetivo dos doentes incluídos que sobreviveram ao internamento em UCI, visando avaliar a eventual existência de letalidade após a alta. No entanto, não foi possível contribuir de modo significativo para o aumento do conhecimento neste âmbito dada a reduzida mortalidade da amostra no tempo de seguimento definido, o qual foi também limitado. Além deste impacto na mortalidade, seria também relevante avaliar se existia uma diferença no que se refere à morbilidade e persistência de sequelas após a alta da UCI.

Concluiu-se, com este estudo, que a DVC prévia é um fator de risco independente para mortalidade em doentes críticos COVID-19, sendo o risco de mortalidade associado à presença desta comorbilidade de 2,51 vezes superior.

No que se refere ao impacto na prática clínica desta análise, a priorização das estratégias de vacinação em sobreviventes de DVC, aliada à sua maior vigilância clínica aquando de uma infeção por SARS-CoV-2, são duas estratégias sugeridas e eventualmente passíveis de implementar nos Serviços de Saúde.

2) Investigar se a doença crítica por SARS-CoV-2 cursa, mais frequentemente, com sinais, sintomas e síndromes neurológicos, em comparação com outros patógenos infeciosos.

No contexto de UCI, o envolvimento do SNC e do sistema nervoso periférico (SNP) foi já extensamente reportado, com uma prevalência descrita de até 33%[86-88, 165]. Especificamente nos doentes com sépsis, a prevalência de disfunção neurológica parece ser mais expressiva, com afeção descrita de dois em cada cinco doentes.[88]

A disfunção neurológica em doentes críticos aumenta para o dobro a duração do internamento hospitalar, sendo considerada um fator *major* para o prolongamento da necessidade de suporte ventilatório[166]. Adicionalmente, a presença destas complicações associa-se a um aumento da taxa de mortalidade em UCI[88].

Quando o contexto de admissão em UCI é a doença COVID-19 esta questão torna-se ainda mais premente, uma vez que este é um vírus com presumível capacidade neurotrópica e neuroinvasiva[56, 59, 60, 62, 63, 65, 158]. De facto, entre doentes críticos COVID-19 as prevalências de disfunção neurológica são variáveis na literatura, com valores descritos entre 12 e 67%[92, 167]. A elevada amplitude deste intervalo relaciona-se provavelmente com o tipo de sinais e sintomas incluídos como parte da disfunção neurológica e com o *timing* da avaliação neurológica, que neste contexto é particularmente importante dadas as alterações do estado mental associadas à iatrogenia medicamentosa. No entanto, era ainda incerto se a disfunção neurológica era apenas um epifenómeno da doença crítica, ou se estava diretamente relacionada à doença COVID-19[168, 169]. Esta incerteza estava essencialmente relacionada com a ausência de estudos comparativos em populações de doentes críticos, com o objetivo de avaliar se existem diferenças na prevalência e características da disfunção neurológica entre doentes COVID-19 e doentes internados com SDRA de outras etiologias.

Por esta razão, desenvolvemos um estudo prospetivo incluindo consecutivamente doentes internados em UCI por SDRA de causa infeciosa. Neste estudo, foram diretamente comparados doentes com SDRA a SARS-CoV-2 com doentes com SDRA a outros patógenos infeciosos, no que se refere à prevalência e características da disfunção neurológica. Como potenciais indicadores de disfunção neurológica, foram considerados os sinais, sintomas e síndromes neurológicas descritos na literatura até à data de início do recrutamento para o estudo, incluindo alterações do SNP e do SNC. Assim, consideramos como sinais e sintomas neurológicos a presença de alterações da fala e da linguagem, défices motores, SDTCS e convulsões. Nas síndromes neurológicas, foi considerada a presença de DVC, *delirium*, encefalopatia, encefalite, mielite e neuropatias periféricas. Deste modo, a presença de sinais e sintomas menos específicos, como as cefaleias, as mialgias e as alterações do olfato e paladar não foram formalmente avaliadas neste contexto, algo também justificável pelo facto de este estudo ter sido feito em doentes internados em UCI, nos quais estas alterações, pelas características clínicas mais frustres e sem presumível impacto direto na morbimortalidade intra-UCI, não são tão frequentemente valorizadas e documentadas.

Um total de 61% da amostra incluída apresentou pelo menos um sinal, sintoma ou síndrome neurológica durante o internamento em UCI. No entanto, cada uma destas manifestações neurológicas foi rara, com exceção do *delirium* e dos SDTCS. Não foi encontrada uma diferença estatisticamente significativa na comparação entre os grupos para cada uma destas manifestações. No entanto, os doentes COVID-19 apresentavam tendencialmente uma maior

prevalência destas alterações. Como tal, foi criada uma variável categórica composta para melhor caracterizar esta questão (*composite of neurological dysfunction)*. Neste contexto, considerou-se que se verificava disfunção neurológica na presença de pelo menos um sinal, sintoma ou síndrome neurológica. Na análise comparativa utilizando esta variável como *outcome*, os doentes COVID-19 apresentaram um risco 1,98 vezes superior de desenvolver estas complicações, em comparação com os casos que tinham sido admitidos por SDRA a outros patógenos infeciosos.

Dada a multiplicidade de potenciais fatores em UCI eventualmente contributivos para a disfunção neurológica, foi também avaliado o possível impacto de características sociodemográficas, comorbilidades, gravidade da doença, e outras complicações com esta relacionadas, no risco de desenvolver complicações neurológicas. Este foi um achado criticamente importante do estudo: nenhum outro fator, além da etiologia da SDRA, se associou de modo significativo ao desenvolvimento de disfunção neurológica.

Realçam-se, ainda, algumas considerações conceptuais relativamente ao estudo desenvolvido para tentar atender ao objetivo estabelecido.

Conforme referido, incluímos doentes com SDRA, a qual foi definida de acordo com os critérios de *Berlin*[51]. Não foi feita a subclassificação da SDRA de acordo com esses critérios (em ligeira, moderada ou grave) uma vez que a SDRA a SARS-CoV-2 é uma entidade nova, em muitos aspetos distinta das SDRA clássicas, na qual a classificação de *Berlin* não parece ser tão adequada para a estratificação dos doentes[170]. Além disto, o *outcome* primário do estudo foi a presença de SDTCS, não existindo evidência do impacto da classificação da SDRA neste domínio. No entanto, e com vista a que fossem incluídos doentes com níveis mínimos de severidade de SDRA similares, foram apenas considerados elegíveis para o estudo doentes com períodos de VMI superiores a 48 horas. Adicionalmente, e para esclarecer a existência de uma eventual relação entre a severidade da doença crítica e a presença de disfunção neurológica, realizamos uma análise comparativa univariada entre potenciais indicadores indiretos de severidade da doença, como sendo a duração do internamento, do suporte ventilatório, vasopressor e renal, e a presença de alterações neurológicas (definidas como a presença de pelo menos um sinal, sintoma ou síndrome neurológico). De facto, não foi encontrada uma associação significativa entre nenhum dos critérios de maior gravidade da doença e a presença de disfunção neurológica.

No que se refere à avaliação clínica dos doentes incluídos no estudo, optou-se por eleger, dentro das várias partes do exame neurológico, a avaliação dos SDTCS como ferramenta a aplicar

no contexto real da prática de investigação clínica. Esta escolha foi feita, essencialmente, porque estas avaliações permitem, de uma forma rápida, sem riscos e sem necessidade de extensa colaboração do doente, precocemente identificar sinais de disfunção neurológica envolvendo o SNC e/ou o SNP[71, 91]. Adicionalmente, e considerando a informação reportada por estudos neuro-imagiológicos, conceptualmente era lógico avaliarmos este domínio dado que o trato cortico-espinhal foi repetidamente referido como a estrutura da substância branca mais frequentemente afetada nesta doença[70, 72].

Uma questão particularmente relevante neste âmbito é a da estandardização da definição de SDTCS adotada neste estudo. De facto, noutros estudos em que os SDTCS foram avaliados a sua definição era frequentemente vaga ou não reportada[92, 171]. Deste modo, e visando uniformizar o que foi considerado como sendo patológico, com base no estudo de *Alvarez et al,* definimos a presença de SDTCS como sendo hiperreflexia em pelo menos duas extremidades ou sinal de *Babinski* em pelo menos uma extremidade[172]. A presença de três avaliações clínicas, e a necessidade de existir consistência nestes achados para serem considerados como patológicos, teve como objetivo aumentar o rigor e a validade dos nossos achados.

No entanto, é imperativo destacar algumas dificuldades inerentes neste contexto. De facto, a iatrogenia farmacológica (especificamente a sedo-analgesia e o bloqueio neuromuscular) podem conduzir à subvalorização da presença de SDTCS[92-94, 173]. Além disso, também nos doentes com FMACI, que correspondem a uma significativa percentagem dos doentes em UCI, alguns dos SDTCS podem também não ser objetiváveis, condicionando também uma subestimação da sua prevalência. Como tal, importa salientar que, pelo contexto do estudo, pode ter existido uma global subvalorização da presença de SDTCS, pelo que a interpretação dos nossos resultados deve ser feita com estas ressalvas.

De realçar ainda que, neste estudo, foi utilizada a escala *Richmond Agitation-Sedation Scale (RASS)*, uma escala que avalia o nível de sedação, ao invés de uma escala para avaliar o nível de consciência (como, por exemplo, a Escala de Coma de *Glasgow*)[174]. Esta foi uma escolha ponderada com base no âmbito da sua utilização: no nosso contexto investigacional, e dado o previamente referido impacto potencial da sedo-analgesia na resposta dos reflexos miotáticos, a escala foi essencialmente usada para garantir que as diferenças no grau de sedação não fossem um fator que interferisse de modo significativo na resposta reflexogénica. Ademais, foi também utilizada no âmbito clínico, pela imprescindibilidade de serem cumpridas condições mínimas de colaboração e segurança para a avaliação destes doentes. Apesar de não ter sido diretamente

analisado o impacto do nível de sedação na resposta cortico-espinhal nesta população, foi feita uma análise comparativa da pontuação na escala de RASS entre os dois grupos de doentes avaliados nos três momentos de avaliação clínica, não tendo sido encontradas diferenças significativas entre estes que pudessem justificar as diferenças encontradas no que se refere à prevalência dos SDTCS.

Deste estudo conclui-se que, entre doentes respiratórios críticos, a etiologia da infeção ser o SARS-CoV-2 duplica o risco de complicações neurológicas, comparativamente a outros patógenos infeciosos. Uma vez que a presença destas complicações tem um inerente impacto negativo na funcionalidade a médio e longo prazo, a observação clínica por MFR reveste-se de particular importância[175]. De facto, uma avaliação precoce pela Especialidade poderá permitir o diagnóstico atempado de complicações neurológicas, bem como a implementação de estratégias terapêuticas dirigidas para reduzir o impacto a médio e longo prazo destas alterações[173, 175].

Assim, e no que se refere ao impacto na prática clínica deste trabalho, advoga-se o rastreio sistemático de disfunção neurológica nos doentes críticos COVID-19. Uma abordagem multidisciplinar, com profissionais de Neurologia e MFR capacitados para a avaliação de doentes críticos, suportados por profissionais da Medicina Intensiva, seria idealmente preconizada com o objetivo de precocemente diagnosticar, explorar e intervir nas eventuais complicações neurológicas da doença COVID-19 crítica.

Ainda no contexto da disfunção neurológica em fase aguda no doente COVID-19, e apesar de o enfoque da literatura ser especialmente na patologia do SNC, destaca-se que a patologia do SNP é também muito importante. As lesões nervosas periféricas são comuns no contexto de UCI, apesar de a sua prevalência não estar ainda totalmente esclarecida[176]. Podem surgir no contexto da própria doença critica (polineuropatia do doente crítico) ou do seu tratamento (mono ou polineuropatias por iatrogenia)[176, 177]. A polineuropatia do doente crítico pode advir de alterações microvasculares (vasodilatação, aumento da permeabilidade vascular, edema endoneural, hipoxemia, extravasação), metabólicas (hiperglicemia, desregulação hormonal, ativação de vias proteolíticas) e elétricas (disfunção de canais iónicos, despolarização ou inexcitabilidade celular)[177]. As neuropatias periféricas iatrogénicas podem decorrer de determinados posicionamentos (por compressão), do ato da colocação ou remoção de cateteres e linhas arteriais ou venosas (por extravasamento de fluídos ou por desenvolvimento de hematomas na proximidade do local de canulação levando a uma lesão compressiva, por lesão química induzida pelos fármacos administrados, ou por traumatismo direto pela agulha)[86].

Especificamente no contexto da COVID-19, além dos mecanismos previamente descritos, é possível que exista um tropismo específico do vírus para o SNP, o qual decorre possivelmente de mecanismos de mimetismo molecular, em que se verificam fenómenos de reatividade cruzada entre as imunoglobulinas produzidas em resposta aos antigénios do SARS-CoV-2 com proteínas especificas da mielina, estrutura axonal e junção neuromuscular[178].

As lesões nervosas periféricas apresentam um curso clínico bem esclarecido, dependendo da sua topografia e severidade[179]. No entanto, a recuperação destas lesões é lenta e não raramente incompleta[176]. Além disso, podem destas lesões decorrer complicações graves, das quais o exemplo paradigmático é a Síndrome Dolorosa Regional Complexa[180-183]. Esta síndrome descreve uma panóplia de condições dolorosas caracterizadas por uma dor regional contínua (espontânea ou evocada), associada a alterações tróficas, vasomotoras, sudomotoras, sensitivas e/ou motoras, que são aparentemente desproporcionais, em tempo ou grau, ao evento inicial[182].

Na era pré-pandémica, a literatura era escassa no que se refere à existência de casos com esta complicação em doentes críticos. Apesar da moderada atenção dada aos quadros álgicos pós UCI, a análise específica de quadros de dor neuropática era claramente parca[184].

Com o advento da COVID-19, este tópico tomou particular importância: num estudo de *Ojeda et al* verificou-se que até 50% dos sobreviventes de uma doença COVID-19 crítica podem manifestar quadros álgicos de novo, dos quais até 30% têm características neuropáticas[185]. Estes achados foram ulteriormente reiterados na análise de *Herrero-Montes et al*, que descreveu uma prevalência de sintomatologia neuropática de 25% dos sobreviventes desta doença[186].

Neste contexto, foi possível descrever um dos primeiros casos COVID-19 na literatura com esta entidade, numa abordagem essencialmente focada no diagnóstico precoce e no tratamento multidisciplinar. A presença desta complicação foi posteriormente também descrita por outros autores[187, 188].

Apesar de não existirem estudos mecanísticos dedicados ao impacto do SARS-CoV-2 na nociceção, o estado de hiper-inflamação sistémica existente na COVID-19 crítica pode contribuir para um fenómeno de sensibilização periférica e central, condicionando assim quadros crónicos de dor desproporcional, como sendo a Síndrome Dolorosa Regional Complexa[189].

Com este caso, pretendemos acima de tudo alertar para a possibilidade de esta complicação surgir no contexto de UCI, e exemplificar um programa integrado, multimodal e individualizado de MFR, bem como os seus resultados clínicos e funcionais significativos.

3) Identificar fatores preditivos para o desenvolvimento de lesões por pressão, dadas as suas consequências clínicas e potencial impacto no desenho e implementação de programas de MFR em doentes críticos COVID-19.

As lesões por pressão são complicações comuns nos doentes críticos, com uma prevalência estimada de até 30%[119, 120, 190, 191]. Pela sua significativa prevalência, e associado impacto na morbilidade e mortalidade intra-hospitalar, a prevenção e tratamento destas complicações cutâneas são objetivos clinicamente muito relevantes[192].

No universo de doentes COVID-19 críticos, esta questão é ainda mais importante: a hipoxemia, a hipotensão, a lesão microvascular trombogénica sistémica, as alterações da perfusão e a imobilidade são fatores preponderantes para uma maior predisposição[122, 123]. Deste modo, a prevalência descrita nesta população específica de doentes críticos assume valores marcadamente superiores, de até 80%[121, 123, 193-195].

A MFR apresenta um papel importante na abordagem preventiva e terapêutica às lesões por pressão.

No que se refere à prevenção destas complicações, as mais recentes recomendações clínicas de prevenção de lesões por pressão em contexto de UCI são baseadas nos modelos "ABCDEF" – "*Awaken from sedation, Breathe independently of the ventilator, Choice of sedation, Delirium management, Early Mobilization and Exercise, and Family engagement and empowerment*" – e "PADIS" – "*Pain, Agitation/sedation, Delirium, Immobility (rehabilitation/mobilization), and Sleep (disruptions)*"[196, 197]. Em suma, a intervenção de MFR em UCI é apontada, em ambos os modelos, como um dos fatores-chave na prevenção destas complicações.

Relativamente ao tratamento das lesões por pressão, os programas integrados de MFR, incluindo modalidades como a eletro-estimulação[198], o LASER[199] e os ultrassons[200] constituem uma opção adjuvante pertinente na abordagem terapêutica a esta complicação[201].

Deste modo, existe evidência de benefício das estratégias integradas de MFR na abordagem às lesões por pressão, nomeadamente no âmbito da sua prevenção e tratamento. No entanto, quando os programas de MFR têm como principais objetivos o tratamento de outras sequelas

impactantes na autonomia, funcionalidade e participação, como sendo os défices motores, as alterações do equilíbrio em sedestação e ortostatismo e a incapacidade ou alterações do padrão de marcha, a presença de lesões por pressão implica frequentemente adaptações no desenho e implementação dos programas de MFR. Adicionalmente, existe evidência de que a presença destas complicações se associa a uma maior frequência de interrupção dos programas de MFR, menores ganhos em *outcomes* funcionais (nomeadamente motores) e menor recuperação da autonomia e da qualidade de vida com a intervenção de MFR[202-204]. Neste contexto, é ainda de realçar que a presença de lesões por pressão se associa a uma maior probabilidade de o doente ser institucionalizado após alta hospitalar [203, 204].

Assim sendo, a capacidade de identificar quais os doentes em maior risco de desenvolverem lesões por pressão reveste-se de particular importância. Entre os modelos preditivos de risco existentes, destaca-se a escala de *Braden*[205]. Este é um instrumento estandardizado e validado que prediz adequadamente o risco de lesões por pressão em múltiplos contextos[56]. Especificamente entre doentes críticos, apresenta uma validade preditiva moderada, com elevada sensibilidade, mas reduzida especificidade[206]. No entanto, na população de COVID-19 críticos esta ferramenta não parecer ter o mesmo poder preditivo, pelo que fatores adicionais deverão ser considerados, nomeadamente sociodemográficos (como a idade), comorbilidades (como a hipertensão, a diabetes *mellitus,* a obesidade, entre outros*)*, parâmetros laboratoriais à admissão da UCI (albumina, proteína C reativa, D-dímeros, fibrinogénio, entre outros) e características relacionadas com a gravidade da doença crítica (como a duração do internamento, a necessidade e duração do suporte vasopressor, o nível de oxigenação, entre outras)[127, 193, 207].

A inexistência de modelos preditivos de lesões por pressão para doentes COVID-19 críticos, facilmente aplicáveis à admissão da UCI e com um adequado poder preditivo, foi a motivação para a definição deste objetivo integrado na Tese.

Assim, desenvolvemos um estudo retrospetivo incluindo doentes COVID-19 críticos, em que foram avaliados 33 potenciais preditores da ocorrência de lesões por pressão (socio-demográficos, comorbilidades, fatores clínicos e laboratoriais).

A prevalência de lesões por pressão na amostra analisada foi elevada, com afeção de mais de 50% dos doentes, sendo que na maioria dos casos foram descritas lesões múltiplas e de gravidade considerável. De facto, estes dados são compatíveis com a literatura e consistentes com a perceção de que os doentes COVID-19 críticos apresentam maior prevalência de lesões

por pressão, bem como lesões com apresentações atípicas, múltiplas, de início precoce e de maior gravidade[125].

Em análise multivariada, incluindo no modelo fatores com uma associação no mínimo marginal (p<0,100) à variável de resultado, identificamos como preditores independentes para o desenvolvimento de lesões por pressão quatro fatores: sexo masculino, hipertensão (comorbilidade) e os valores de hemoglobina e albumina à admissão na UCI. Estes fatores constituíram o modelo PRINCOVID. De modo a facilitar a aplicabilidade deste modelo num contexto real de prática clínica, convertemo-lo num *score*, no qual cada um destes preditores tinha uma pontuação específica atribuída: sexo masculino: 4 pontos; presença de hipertensão: 2 pontos; hemoglobina < 8 g/dL: 6 pontos; hemoglobina 8-10 g/dL: 4 pontos; albumina < 34 g/dL: 3 pontos. Assim, o *score* PRINCOVID varia entre 0 e 15 pontos, incluindo quatro preditores independentes facilmente avaliáveis à admissão da UCI.

Pela relevância da identificação precoce de doentes em maior risco de lesões por pressão, construindo e utilizando uma árvore de decisão, foi possível identificar dois grupos de risco distintos: doentes "em risco" (pontuações no PRINCOVID ≤ 7 pontos; risco de 45% de desenvolver uma lesão por pressão) e doentes de "alto risco" (pontuações no PRINCOVID > 7 pontos; risco de 72% de desenvolver uma lesão por pressão).

Neste estudo, fizemos também uma comparação direta entre o PRINCOVID e o *standard* da prática clínica (escala de *Braden*): de facto, o modelo PRINCOVID apresentou um poder preditivo significativamente superior.

Parece-nos, assim, que o *score* PRINCOVID pode ser uma ferramenta potencialmente útil na prática clínica em UCI dada a sua facilidade de aplicação (apenas 4 fatores facilmente identificáveis à admissão na UCI, com pontuações pré-definidas e grupos de risco determinados) e poder preditivo moderado, mas significativamente superior ao instrumento atualmente mais utilizado neste âmbito (escala de *Braden)*.

Essencialmente, e num contexto primariamente clínico, este trabalho acrescenta conhecimento no âmbito da capacidade de identificação precoce (logo à admissão da UCI) de doentes de "alto risco" para desenvolver lesões por pressão. Esta ferramenta poderá assim ser útil na otimização da vigilância das características cutâneas destes indivíduos de elevado risco, e ulterior instituição atempada de medidas adicionais às uniformemente aplicadas em UCI,

minimizando assim o desenvolvimento e a progressão das lesões por pressão em doentes críticos COVID-19.

4) Caracterizar as consequências a longo termo da infeção crítica a SARS-CoV-2

Apesar da extensa investigação clínica realizada no âmbito da COVID-19, o carácter emergente desta doença justifica a menor abundância de estudos dirigidos à avaliação e intervenção nas suas sequelas a médio e longo prazo. No entanto, a importância deste tópico é sustentada pelo crescente número de sobreviventes à infeção por SARS-CoV-2, nomeadamente às formas de doença crítica. De facto, o grau, evolução e duração dos sintomas são alguns dos aspetos que carecem melhor caracterização[208]. Associadamente, o impacto destas sequelas, especificamente de índole física, mental e cognitiva sobre a funcionalidade, autonomia e participação, bem como na qualidade de vida dos doentes, são questões essenciais nesta área do conhecimento[209].

Efetivamente, os doentes críticos têm um risco acrescido de complicações a médio e longo prazo relacionadas com a doença crítica, iatrogenia e/ou com o próprio ambiente da UCI, sendo a SPICI uma entidade cuja prevalência ultrapassa os 50% nos seis meses após a alta da UCI [128, 210].

Nos sobreviventes da doença COVID-19 crítica, parece existir um maior risco de desenvolvimento desta síndrome, no entanto os dados da literatura não são unânimes[135, 211]. Adicionalmente, existem ainda várias questões por esclarecer e esferas por analisar, nomeadamente a análise da extensão e evolução das sequelas, particularmente no domínio físico e na funcionalidade, nesta população[136, 212]. Além disto, também as características da intervenção de MFR e o seu impacto na trajetória clínica e funcional nesta população encontra-se também parcamente explorada e desenvolvida.

Neste sentido, definimos como objetivo desta Tese caracterizar as consequências clínicas e funcionais da doença COVID-19 crítica aos seis e doze meses após alta da UCI. Na nossa perspetiva, a adequada compreensão das características e particularidades das sequelas desta doença, e da sua progressão ao longo do tempo, é importante para adequar as intervenções dirigidas no âmbito da MFR para otimizar o estado clínico e funcional dos sobreviventes à COVID-19 crítica.

Optamos, então, por desenvolver uma análise compreensiva orientada pelos domínios da SPICI (físico, mental e cognitivo) e com particular enfoque na funcionalidade, em conformidade

com o *Stanford Hall consensus*[213]. Nesta declaração de consenso, é realçada a importância de os sobreviventes de uma doença COVID-19 serem alvo de uma avaliação específica da funcionalidade, visando determinar sequelas relevantes e assim direcionar o programa terapêutico de MFR numa perspetiva multidisciplinar, com particular enfoque nos três domínios da SPICI: físico, mental e cognitivo[213].

Para tal, desenvolvemos um estudo de coorte prospetivo incluindo sobreviventes de internamento em UCI por SDRA a SARS-CoV-2. Estes doentes foram avaliados presencialmente em Consulta Externa de MFR aos seis e doze meses após a alta da UCI, sendo que nestas consultas foi utilizada numa abordagem abrangente, compreensiva e estandardizada. Foram avaliados os domínios físico, mental e cognitivo da SPICI, bem como vários dos seus subdomínios, através do exame objetivo e múltiplas escalas, preferencialmente as previstas no "C*ore Outcome Set for Survivors of Acute Respiratory Failure*"[214]. De facto, as características metodológicas deste estudo de investigação constituem uma mais-valia uma vez que a maioria dos estudos publicados até à data baseava-se em avaliações únicas, feitas maioritariamente por via telefónica, portanto sem objetivação e quantificação dos défices possíveis, do seu impacto funcional e da sua evolução temporal[136, 215].

Além da análise detalhada dos três domínios da SPICI, e apesar de a funcionalidade estar classicamente incluída no domínio físico, na nossa análise esta foi considerada separadamente. De facto, as alterações nos três domínios da SPICI podem constituir barreiras à autonomia e consubstanciar-se com alterações na funcionalidade, motivo pelo qual esta vertente foi avaliada separadamente. Uma vez que o contexto das avaliações destes doentes era uniprofissional e em ambulatório, optamos por utilizar a forma auto-reportada da Medida de Independência Funcional. Apesar de esta ser uma limitação do estudo, pelo facto de não ter sido feita a aplicação em contexto de vida real deste instrumento num âmbito idealmente multiprofissional, a sustentação científica proveniente de outras populações de que existe uma correlação moderada entre a avaliação direta e a auto-reportada diminui o ônus desta limitação na validade dos nossos resultados[216].

Os resultados desta investigação revelaram que, aos 6 meses após alta da UCI, sobreviventes de COVID-19 crítica apresentam alterações consideráveis no domínio físico, traduzidas por uma significativa redução na qualidade de vida, força muscular, equilíbrio e capacidade de marcha, e um significativo aumento dos níveis de fadiga. Apesar de todos estes sub-domínios apresentarem uma evolução favorável ao longo do primeiro ano após alta da UCI, foi constatada uma

persistência de défices significativos de força muscular, equilíbrio e capacidade de marcha aos doze meses após alta da UCI. No que se refere ao domínio mental, verificou-se um valor significativamente superior de ansiedade e depressão aos seis e doze meses pós alta da UCI, apesar da melhoria expressiva neste período. Relativamente à cognição, sobreviventes de doença crítica por SDRA a SARS-CoV-2 apresentaram quadros de disfunção cognitiva clinicamente significativa aos seis e doze meses após alta. No entanto, este domínio evoluiu também de modo positivo no período de estudo. No que se refere à análise da funcionalidade, é de realçar ainda que apenas cerca de metade da amostra estava autónoma seis meses após a alta da UCI, valor que aumentou para aproximadamente 70% nos seis meses subsequentes.

De facto, no domínio físico, foi evidente a persistência de sequelas motoras clinicamente significativas ao longo do primeiro ano pós alta da UCI. Estas sequelas, particularmente objetiváveis como défices de força muscular, de equilíbrio e da capacidade de marcha, são abordáveis e tratáveis em programas de MFR, com intervenção de fisioterapia e enfermagem de reabilitação. A atempada integração nestes programas associa-se a benefícios significativos[217].

Destaca-se ainda que este estudo inclui, no domínio físico, a análise de dois subdomínios não comummente explorados na literatura e que se revestem de uma importância eventualmente significativa: as alterações da sensibilidade e os SDTCS.

No que se refere às alterações sensitivas sequelares à COVID-19, foi formalmente questionada na entrevista clínica e avaliada ao exame objetivo a presença de hiperestesia, hipo/anestesia, disestesias e parestesias nos múltiplos dermátomos corporais. Na nossa amostra as alterações sensitivas não foram comuns. Apesar disto, é de destacar que estas alterações não apresentaram uma evolução significativa ao longo do tempo. Este é um dado relevante pois levanta a hipótese de a caracterização e intervenção nesta sequela poder não estar a ser adequada e ajustada às necessidades da população. As alterações da sensibilidade, apesar de potencialmente mais difíceis de avaliar e valorizar clinicamente, são défices neurológicos com um significativo impacto na qualidade de vida e funcionalidade dos doentes[218].

Relativamente aos SDTCS, apesar da sua significativa prevalência em doentes críticos COVID-19 e da documentação de alterações estruturais no trato cortico-espinhal em estudos neuro-imagiológicos realizados em fase aguda, nos sobreviventes de COVID-19 crítica este subdomínio não tem sido analisado formalmente[70, 92, 171]. No entanto, realçamos a importância destas avaliações, e da eventual intervenção dirigida. Por um lado, a alteração da normal resposta clínica na avaliação dos SDTCS pode ser uma pista para o precoce diagnóstico de uma possível

complicação envolvendo o SNC ou o SNP. Por outro, alguns dos SDTCS, nomeadamente as alterações do controlo motor e o clónus, podem ter uma relevância clínica e funcional significativa. A título de exemplo, o clónus da articulação tibiotársica pode interferir com a marcha (especificamente condicionando uma menor cadência, *clearance* ou necessidade de utilizar auxiliares de marcha), com a postura e com o sono[219]. Ademais, pode também condicionar dificuldade nas transferências, fadiga e diminuição da *performance* laboral, com um inerente impacto nas atividades de vida diária[219]. A abordagem a esta sequela deve ser idealmente feita num contexto multiprofissional, com intervenção de médico de MFR para o desenho de um programa integrado de reabilitação, o qual pode incluir a implementação de técnicas cinesiológicas por fisioterapeuta, estratégias farmacológicas, orais ou intra-musculares (como sendo a infiltração de toxina botulínica), entre outras.[220].

Relativamente ao domínio mental, verificou-se também a presença de sintomas compatíveis com quadros ansiosos e depressivos na nossa amostra. Pelo facto de estes sintomas, de acordo com os dados de *Coleman et al*, parecerem ser particularmente prevalentes nos primeiros 120 dias após a infeção por SARS-CoV-2, o rastreio atempado e a ulterior referenciação e/ou discussão em contexto multidisciplinar, revela-se particularmente pertinente[221].

No que se refere ao domínio cognitivo, uma característica também distintiva desta análise foi ter sido formalmente analisada a função cognitiva através de um instrumento de rastreio amplamente validado (o *Montreal Cognitive Assessment)*, ao invés de apenas caracterizada a perceção subjetiva destas alterações[222]. Esta avaliação dirigida permite a melhor compreensão dos domínios afetados, tornando possível a exploração diferencial dos vários domínios possivelmente afetados utilizando ferramentas validadas e específicas para o efeito no âmbito da neuropsicologia. Após este estudo mais alargado, é a adequada caracterização dos domínios mais deficitários que irá ditar os objetivos, componentes e tecnologias utilizadas no âmbito dos programas terapêuticos de MFR, os quais podem ser unimodais com intervenção exclusivamente neuropsicológica, ou multimodais, em conjunto com a intervenção de outras áreas terapêuticas como sendo a terapia da fala e a terapia ocupacional.

Com este estudo conclui-se que existe um impacto físico, mental e cognitivo significativo da doença COVID-19 crítica, sendo este objetivável aos seis e doze meses após alta da UCI. Este impacto apresenta uma clara tradução na funcionalidade, com alterações também expressivas neste contexto. No entanto, parece existir uma evolução paulatina, mas positiva, sustentada e

significativa, de todos os domínios da SPICI e na funcionalidade ao longo do primeiro ano pós alta da UCI.

Como tal, propõe-se com base nos dados desta análise que seja mantida a monitorização, e eventualmente a intervenção, por MFR pelo menos no primeiro ano pós UCI, mas possivelmente por um período mais prolongado. A abrangência da Especialidade, com intervenção num âmbito multiprofissional (incluindo, de acordo com a necessidade, cuidados de enfermagem de reabilitação, de fisioterapia, de terapia da fala, de terapia ocupacional, de ortoprotesia, de neuropsicologia, entre outros) justifica o seguimento destes doentes por MFR. Adicionalmente, a proximidade com outras Especialidades clínicas, decorrente da frequente necessidade de cuidados de MFR nos vários contextos clínicos, poderá garantir o sucesso na comunicação e discussão interdisciplinar de cada caso. Dada a diversidade e amplitude dos défices revelados, propõe-se assim a implementação de uma abordagem individualizada num contexto multiprofissional, integral e abrangente.

Os vários estudos constituintes desta Tese apresentaram limitações.

Em primeiro lugar, destaco a natureza observacional dos estudos constituintes desta Tese. De facto, para tentar atingir os objetivos definidos para os diferentes trabalhos, esta metodologia pareceu-nos adequada. No entanto, o desenho e implementação de estudos experimentais em continuidade com alguns dos trabalhos desenvolvidos seria importante para melhor caracterizar e esclarecer as questões associadas aos mesmos.

Em segundo lugar, é também de realçar o carácter unicêntrico dos estudos como uma limitação. No entanto, realço que o Centro Hospitalar Universitário de São João é um centro terciário, com uma extensa abrangência geográfica, e que inclui várias UCI especializadas recebendo, portanto, doentes de outras instituições para cuidados intensivos mais diferenciados, o que pode potenciar a validade externa dos nossos achados.

Em terceiro lugar, e no que se refere aos métodos de colheita de dados, nos vários estudos realizados parte ou a totalidade dos dados foram recolhidos a partir dos processos clínicos eletrónicos, não permitindo excluir a presença de vieses de medição, de informação e de classificação. Tal facto é particularmente relevante quando nos debruçamos sobre investigação realizada numa época pandémica, em que a sobrelotação das UCI obrigou à maior priorização da avaliação dos doentes em eventual detrimento dos registos clínicos, com potenciais repercussões na extensão, qualidade e completude dos mesmos. De modo a mitigar a existência de adicionais vieses neste processo, a recolha de dados foi feita de modo estandardizado, utilizando formulários pré-definidos.

CONCLUSÕES

Este projeto visou contribuir para uma melhor compreensão do doente crítico COVID-19, especificamente numa abordagem de "antes", "durante" e "depois" do internamento em UCI. A investigação foi essencialmente debruçada sobre os tópicos da disfunção neurológica e do impacto funcional da doença COVID-19 a médio e longo prazo.

Esta dissertação oferece uma perspetiva original, mas fundamentada, sobre estes tópicos. No entanto, reconheço que o projeto não responde a todas as perguntas sobre este tema. Espero, contudo, que possa incentivar e integrar um processo que permita fazê-lo, com o objetivo último de melhorar a qualidade da atividade assistencial prestada a estes doentes.

As principais conclusões deste trabalho foram:

1. A presença de comorbilidades neurológicas, especificamente a DVC prévia, associa-se a um risco de mortalidade 2,51 vezes superior em doentes críticos COVID-19.
    1.1 Esta comorbilidade é um fator de risco independente para maior mortalidade.
2. A doença crítica COVID-19 associa-se a um risco 1,98 vezes superior de desenvolver sinais, sintomas ou síndromes neurológicas, em comparação com outras etiologias infeciosas de SDRA crítica.
3. As lesões por pressão são comuns em doentes COVID-19 críticos. O sexo (masculino), a hipertensão (comorbilidade) e os valores mais baixos de hemoglobina e albumina à admissão da UCI são preditores independentes para o desenvolvimento de lesões por pressão. O PRINCOVID é um modelo multivariado de predição de risco que inclui estes 4 fatores, para os quais está definida uma pontuação a atribuir, o que permite a classificação dos doentes de acordo com o seu risco de desenvolver esta complicação.
    3.1 O modelo PRINCOVID tem maior poder, em comparação com a escala de *Braden*, para predizer lesões por pressão em doentes críticos COVID-19.
4. Os sobreviventes de doença crítica COVID-19 apresentam sequelas nos domínios físico, mental e cognitivo aos seis e doze meses após alta da UCI.
    4.1 Estas sequelas evoluem favoravelmente neste período; no entanto alguns subdomínios físicos, o domínio mental e o domínio cognitivo mantém-se significativamente alterados após este período.

PERSPECTIVAS FUTURAS

A presente dissertação resume um longo trabalho de investigação, centrado num tópico complexo, um caminho feito de imperfeições, desafios constantes e aprendizagem contínua.

Como acredito que deve ocorrer no término de um processo deste tipo, são vários os possíveis caminhos de continuidade desta investigação.

Há duas linhas essenciais de potencial continuidade deste trabalho: a da relação entre a doença COVID-19 e a disfunção neurológica e a do impacto da MFR nas sequelas da doença crítica COVID-19.

Relativamente à relação entre a doença COVID-19 e a disfunção neurológica, destacam-se alguns potenciais objetivos a seguir:

1. Analisar o efeito de outras comorbilidades neurológicas na mortalidade destes doentes;
2. Caracterizar o impacto a longo prazo da presença de manifestações neurológicas durante a permanência em UCI na mortalidade e na funcionalidade;
3. Analisar a relação entre a presença de SDTCS, síndromes clínicas e alterações estruturais em estudos neuro-imagiológicos;
4. Avaliar a concordância inter- e intra-observador na avaliação de SDTCS em contexto de UCI.

No que se refere à potencial continuação da investigação no âmbito do impacto da MFR na doença crítica COVID-19, realçam-se também alguns possíveis objetivos:

1. Validar o *score* PRINCOVID em outras populações de doentes COVID-19 críticos;
2. Analisar a aplicabilidade e poder do modelo PRINCOVID em doentes críticos por outras etiologias;
3. Avaliar a persistência e padrão de evolução da SPICI em doentes COVID-19 críticos após o primeiro ano da alta da UCI;
4. Identificar fatores de risco, e ulteriormente desenvolver modelos preditivos de risco e prognóstico para a SPICI COVID-19;
5. Avaliar o efeito da vacinação e das terapêuticas farmacológicas emergentes na morbilidade a longo prazo dos sobreviventes à COVID-19 crítica;
6. Comparar diferentes programas de MFR para compreender qual é a abordagem mais vantajosa tanto no doente COVID-19 crítico agudo como depois na fase subaguda e crónica, especificamente avaliando a diferença entre programas intensivos de internamento e de

ambulatório, uni e multimodais, bem como o impacto de distintos *timings* de início do programa, sua intensidade e frequência.

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