UNIVERSIDADE CESUMAR - UNICESUMAR
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EFEITOS DE UM MODELO MULTIPROFISSIONAL DE INTERVENÇÃO SOBRE PARÂMETROS DE APTIDÃO FÍSICA RELACIONADOS A SAÚDE E BIOMARCADORES DE PESSOAS COM EXCESSO DE PESO OU OBESIDADE PÓS COVID-19

MARIELLE PRISCILA DE PAULA SILVA LALUCCI

TESE DE DOUTORADO

MARINGÁ
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Orientador: Prof. Dr. Braulio Henrique Magnani Branco.

Coorientadora: Prof. Dr. Solange Marta Franzói de Moraes.

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Tese apresentada ao Programa de Pós-Graduação em Promoção da Saúde da Universidade Cesumar, como requisito final para obtenção do título de Doutor em Promoção da Saúde pela Comissão julgadora composta pelos membros:

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Aprovado em: 13 de março de 2024

DEDICATÓRIA

Aos meus pais, Luiz Sergio e Sandra, que sempre me incentivaram na busca pelo conhecimento.

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EPÍGRAFE

"Trabalhar na área da saúde é um princípio: permite ser útil à sociedade com toda a força e conhecimento que se tem. Este serviço à sociedade deve ser consequência da vocação e do compromisso ao graduar-se."

Jacinto Convit

RESUMO

Em dezembro de 2019, surgiu a doença chamada de novo Coronavírus (COVID-19), sendo decretado posteriormente estado de pandemia. O espectro clínico da COVID-19 varia de infecção assintomática a doença crítica. As manifestações clínicas da COVID-19 são divididas de acordo com sua gravidade: leve (sem evidência de pneumonia viral ou hipóxia); moderada (sinais clínicos de pneumonia, mas nenhum sinal de pneumonia grave); grave (sinais clínicos de pneumonia mais um dos seguintes: frequência respiratória >30 respirações/min, dificuldade respiratória grave, ou $SatO_2$ <90%) e crítica (Síndrome do Desconforto Respiratório Agudo (SDRA), sepse, choque séptico ou trombose aguda). A obesidade é um fator de risco conhecido para a COVID-19 grave. Portanto, indivíduos com excesso de peso com diagnóstico positivo para COVID-19 têm um risco aumentado de complicações, hospitalizações, admissão em Unidade de Terapia Intensiva (UTI), além de maior necessidade de ventilação mecânica invasiva (VMI), risco de morte e desenvolvimento da Síndrome de COVID-19 Longa, onde os indivíduos afetados não se recuperam por várias semanas ou meses após o início dos sintomas. Sendo assim, estratégias multiprofissionais de reabilitação dos sobreviventes da COVID-19 são indispensáveis para combater uma condição com diferentes sequelas. O objetivo geral deste trabalho foi analisar os efeitos de uma intervenção multiprofissional sobre parâmetros de aptidão física relacionados a saúde e biomarcadores de pessoas com excesso de peso e obesidade, após alta da COVID-19 em diferentes graus de comprometimento. No primeiro artigo, "*Obesity as a risk factor for complications and mortality in individuals with SARS-CoV-2: a systematic review*", foram analisados os estudos disponíveis que identificaram o excesso de peso e/ou obesidade como fator de risco para mortalidade, uso de suporte de oxigênio e alterações em marcadores bioquímicos, em indivíduos hospitalizados com SARS-CoV-2. Já, no segundo manuscrito, "*Effects of 8 and 16 weeks of multi-professional intervention on body composition, physical fitness, and biomarkers in overweight survivors of COVID-19: a clinical trial*", foram investigado os efeitos de uma intervenção multiprofissional (intervenção de exercícios físicos, intervenção nutricional e psicoeducação) na composição corporal, aptidão física e biomarcadores em 59 indivíduos sobreviventes de COVID-19 com sobrepeso, divididos em três grupos de acordo com a sintomatologia [grupo leve (n = 31), moderado (n = 13) e grave (n = 15)]. Os grupos experimentais foram submetidos a um programa multiprofissional composto por exercícios físicos (força muscular e exercícios aeróbicos, ou seja, treino simultâneo) realizados duas vezes por semana, intervenção nutricional e psicoeducação, realizados uma vez por semana cada. Os participantes foram avaliados no início do estudo (pré-intervenção), após oito semanas (pós-8 semanas) e após 16 semanas de intervenção (pós-16 semanas). Após as oito semanas, foram observados os seguintes resultados: valores significativamente maiores para massa magra, massa musculoesquelética, força de pressão manual isométrica máxima, força máxima de tração lombar, flexão de braços, teste de sentar e levantar, e distância percorrida no teste de caminhada de seis minutos (p<0,05) e redução significativa de triglicerídeos, lipoproteína de baixa densidade e hemoglobina glicada (p<0.05). Após 16 semanas, a pressão arterial sistólica e diastólica reduziram significativamente nos três grupos experimentais (p<0,05). Diante disso, o modelo de intervenção multiprofissional proposto promoveu a melhoria de parâmetros de aptidão física relacionados à saúde, aspectos hemodinâmicos e bioquímicos dos sobreviventes da COVID-19.

Palavras-chave: diagnóstico laboratorial; doenças crônicas; doença por 2019-nCoV; equipe de cuidados de saúde; enfermidade transmissível; interdisciplinaridade; obesidade.

ABSTRACT

In December 2019, the disease called the new Coronavirus (COVID-19) emerged and was subsequently declared a pandemic. The clinical spectrum of COVID-19 ranges from asymptomatic infection to critical illness. The clinical manifestations of COVID-19 are divided according to their severity: mild (no evidence of viral pneumonia or hypoxia); moderate (clinical signs of pneumonia but no signs of severe pneumonia); severe (clinical signs of pneumonia plus one of the following: respiratory rate >30 breaths/minute, severe respiratory distress, or $SatO_2$ <90%); and critical (Acute Respiratory Distress Syndrome (ARDS), sepsis, septic shock, or acute thrombosis). Obesity is a known risk factor for severe COVID-19. Therefore, overweight individuals diagnosed positive for COVID-19 have an increased risk of complications, hospitalizations, admission to the Intensive Care Unit (ICU), in addition to a greater need for invasive mechanical ventilation (IMV), risk of death and development of Long COVID-19, where affected individuals do not recover for several weeks or months after the onset of symptoms. Therefore, multidisciplinary rehabilitation strategies for COVID-19 survivors are essential to combat a condition with different consequences. The general objective of this study was to analyze the effects of a multi-professional intervention on health-related physical fitness parameters and biomarkers of people with overweight and obesity, after discharge from COVID-19 in different degrees of impairment. In the first article, "Obesity as a risk factor for complications and mortality in individuals with SARS-CoV-2: a systematic review", the available studies that identified over weight and/or obesity as a risk factor for mortality, use of oxygen support and changes in biochemical markers in individuals hospitalized with SARS-CoV-2 were analyzed. In the second article "Effects of 8 and 16 weeks of multi-professional intervention on body composition, physical fitness, and biomarkers in overweight survivors of covid-19: a clinical trial", the effects of a multi-professional intervention (physical exercise intervention, nutritional intervention and psychoeducation) on body composition, physical fitness and biomarkers in 59 overweight COVID-19 survivors, divided into three groups according to symptomatology [mild group (n = 31), moderate group (n = 13) and severe (n = 15)], were investugated. The experimental groups underwent a multi-professional program consisting of physical exercise (muscle strength and aerobic exercise, i.e., simultaneous training) twice a week, nutritional intervention and psychoeducation once a week each. Participants were assessed at the beginning of the study (pre-intervention), after eight weeks (post-8 weeks) and after 16 weeks of intervention (post-16 weeks). After eight weeks, significantly higher values for lean mass, musculoskeletal mass, maximum isometric hand grip strength, maximum lumbar traction strength, arm flexion, sit-to-stand test, distance covered in the six-minute walk test (p<0.05), significant reduction in triglycerides, low-density lipoprotein and glycated hemoglobin (p<0.05) were observed. After 16 weeks, systolic and diastolic blood pressure were significantly reduced in the three experimental groups (p<0.05). Therefore, the proposed multi-professional intervention model promoted the improvement of health-related physical fitness parameters, hemodynamic and biochemical aspects of COVID-19 survivors.

Keywords: laboratory diagnosis; chronic diseases; disease by 2019-nCoV; health care team; communicable disease; interdisciplinarity; obesity.

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LISTA DE ABREVIATURAS E SIGLAS

ALT	Alanina aminotransferase
ANVISA	Agência Nacional de Vigilância Sanitária
AST	Aspartato aminotransferase
ATP	Adenosina Trifosfato
AVC	Acidente Vascular Vertebral
BT	Bilirrubina Total
COVID-19	Coronavírus-2019
CoVs	Coronavírus
CT	Colesterol Total
DCNTs	Doenças Crônicas Não Transmissíveis
DCVs	Doenças Cardiovasculares
DM2	Diabetes Mellitus tipo 2
DRCs	Doenças Renais Crônicas
ECA2	Enzima conversora de angiotensina 2
ECMO	Oxigenação por membrana extracorpórea
FA	Fosfatase Alcalina
FC	Frequência cardíaca
GAD-7	Transtorno de Ansiedade Generalizada
Gama-GT	Gama-glutamiltransferase
HAS	Hipertensão arterial sistêmica
Hb	Hemoglobina
HbA1c	Hemoglobina Glicada
HDL	*High Density Lipoprotein*
HOMA-IR	Avaliação do modelo de homeostasia - Resistência à insulina
IDR	Ingestão Diária Recomentada
IES-R	Impacto da Escala de Evento Revisada
IFN-γ	Interferon-gama
IgA	Imunoglobulina-A
IL-6	Interleucina -6
IMC	Índice de Massa Corporal
IR	Insuficiência Respiratória

kb	Kilobases
LDL	*Low Density Lipoprotein*
LRA	Lesão Renal Aguda
MERS-CoV	Síndrome Respiratória do Oriente Médio Coronavírus
MHC-SF	Continuum de Saúde Mental
MG	Massa gorda
MLG	Massa livre de gordura
MM	Massa magra
MME	Massa musculoesquelética
OMS	Organização Mundial de Saúde
PA	Pressão arterial
PAD	Pressão arterial diastólica
PCR	Reação em Cadeia da Polimerase
PCR	Proteína C Reativa
PFA	Proteína de Fase Aguda
PHG-9	Questionário de Saúde do Paciente-9
QM	Quilomícrons
SARS-CoV	Síndrome Respiratória Aguda Grave Coronavírus
$SatO_2$	Saturação de oxigênio
SDRA	Síndrome do Desconforto Respiratório Agudo
SM	Síndrome Metabólica
SNC	Sistema Nervoso Central
SNP	Sistema Nervoso Periférico
SpO_2	Saturação periférica de oxigênio
SRAA	Sistema Renina-angiotensina-aldosterona
TAB	Tecido Adiposo Branco
TG	Triglicérides
TNF-α	Fator de Necrose Tumoral Alfa
TOTG	Teste Oral de Tolerância à Glicose
UTI	Unidade de Terapia Intensiva
VLDL	*Very Low Density Lipoprotein*
VMI	Ventilação Mecânica Invasiva
VO_2 pico	Consumo máximo de oxigênio
VR	Valor de referência

α-CoV	Alfacoronavírus
β-CoV	Betacoronavírus
γ-CoV	Gammacoronavírus
δ-Cov	Deltacoronavírus
%GC	Percentual de gordura corporal

LISTA DE SÍMBOLOS

%	Porcentagem
β	Beta
α	Alfa
γ	Gamma
δ	Delta
>	Maior que
<	Menor que
≥	Maior ou igual que
≤	Menor ou igual que
±	Mais ou menos
Kg	Quilograma
g	Grama
mg	Miligrama
µg	Microgramа
ng	Nanogramas
pg	Picograma
m	Metro
cm	Centímetro
m^2	Metro quadrado
mm^3	Milímetro cúbico
L	Litro
mL	Mililitro
µL	Microlitro
dL	Decilitro
U/L	Unidades por litro
µmol	Micromol
mmol	Milimol
mmHg	Milímetro de mercúrio

SUMÁRIO

CAPÍTULO I

1. INTRODUÇÃO

Parte dos sobreviventes do Coronavírus-2019 (COVID-19) tem apresentado sequelas de ordem respiratória; descondicionamento físico, com perda da massa musculoesquelética e redução da força e resistência muscular, assim como a diminuição da capacidade cardiorrespiratória; redução da qualidade de vida; problemas emocionais, dentre outros (Carda *et al*., 2020; CDC, 2021). Diferente dos sinais e sintomas da COVID-19, as complicações da síndrome pós COVID longa não são bem esclarecidas. Para alguns indivíduos, as complicações podem afetar múltiplos órgãos e persistir por meses, independentemente da gravidade da doença no início. Porém, indivíduos com maior grau de acometimento da COVID-19 têm maior risco de morte nos 12 meses após a doença (Mainous III *et al*., 2021).

A gravidade da doença dependerá da intensidade da resposta imune desencadeada pelo vírus (Romão *et al*., 2022). Portanto, os sinais e sintomas de longo prazo dependem da extensão e gravidade da infecção viral, dos órgãos afetados e da chamada "tempestade de citocinas" durante a fase aguda da COVID-19 (Landi *et al*., 2020). A síndrome pós-COVID longa ou condição pós-COVID-19 inclui fadiga, dispneia, dor torácica, perda de paladar e/ou olfato, alterações cognitivas, artralgias e diminuição da qualidade de vida (Groff *et al*., 2021). À vista disso, o atendimento multiprofissional, com a atuação de médicos, fisioterapeutas, profissionais de educação física, nutricionistas, enfermeiros, biomédicos, psicólogos e outras áreas afins torna-se indispensável para recuperar globalmente a saúde e qualidade de vida dos indivíduos afetados pela doença (Price *et al*., 2023).

Um estudo realizado em ambulatório na Itália com 143 indivíduos observou que, no momento da internação 35% deles apresentavam hipertensão arterial sistêmica; 18,2% problemas na tireoide; 11,2% desordem imunológica; e 9,1% doença pulmonar obstrutiva crônica. Ainda, 32% deles apresentavam um ou dois sintomas referentes à COVID-19 e 55% tinham três ou mais sintomas, sendo também observada piora na qualidade de vida em 44% dos avaliados (Carfì *et al*., 2020). Huang *et al*. (2021) descreveram as consequências a longo prazo da COVID-19 em 1.733 indivíduos após 6 meses de alta hospitalar. Os autores observaram que 63% ainda apresentavam fadiga ou fraqueza muscular, 26% tinham dificuldade para dormir, ansiedade ou depressão, que foi relatada

em 23% dos indivíduos. Os participantes que apresentaram maior gravidade da doença relataram maiores problemas de mobilidade, dor ou desconforto e 58 indivíduos sem histórico autorrelatado de diabetes mellitus tipo 2 (DM2) foram diagnosticados com a doença no acompanhamento após a alta hospitalar.

Soma-se ainda a obesidade como doença pró-inflamatória, correlacionada com aumento da prevalência de outras Doenças Crônicas Não Transmissíveis (DCNTs), como a DM2, hipertensão arterial sistêmica (HAS), dislipidemias, síndrome metabólica, dentre outras patologias (Maffetone; Laursen, 2020). O excesso de gordura corporal promove um estado de inflamação de baixo grau, comprometendo a homeostase imunológica, com consequente risco aumentado para DCNTs e infecções de diferentes naturezas (Maffetone; Laursen, 2020). A obesidade também é conhecida como fator de risco para COVID-19 grave, já sendo descrita na literatura a relação dose-resposta entre o índice de massa corporal (IMC) mais alto e o agravamento da COVID-19, visto que cada aumento de 1 unidade de IMC pode estar relacionado a um aumento de 12% no risco de COVID-19 grave (De Bandt; Monin, 2021; Pranata *et al*., 2021; Freire *et al*., 2022).

A prática regular de atividade física e uma alimentação adequada estão relacionadas com a resposta imune às infecções virais (Minuzzi *et al.*, 2021). Indivíduos ativos apresentam melhor resposta imunológica no reconhecimento e eliminação de antígenos, uma vez que a duração e intensidade da atividade física são fatores responsáveis nas diferentes alterações no sistema imunológico, bem como na melhora da função cardiorrespiratória, capacidade funcional e da qualidade de vida (Lira *et al*., 2021). Nesse sentido, para a recuperação das condições de saúde de pessoas com obesidade pós-COVID-19, são imperativas intervenções multiprofissionais, haja vista a complexidade multifatorial das doenças crônicas, com a indispensabilidade de realização de avaliações periódicas, visto que os impactos a longo prazo pós-COVID-19 não foram, ainda, tão bem elucidados pela ciência.

2. REVISÃO DA LITERATURA

2.1 CORONAVÍRUS-2019

Os Coronavírus (CoVs) são normalmente associados a infecções virais do trato respiratório, hepático, gastrointestinal e sistema nervoso central, pertencentes à ordem *Nidovirales*, família dos *Coronaviridae*, subfamília *Coronavirinae*, compostos por quatro

gêneros: *alfacoronavírus* (α-CoV), *betacoronavírus* (β-CoV), *gammacoronavírus* (γ-CoV) e *deltacoronavírus* (δ-Cov), podendo infectar várias espécies de hospedeiros (Cui; Li; Shi, 2019; Luk *et al*., 2019). O genoma dos CoVs é um RNA de fita simples, variando de 29,0 kb a 30,2 kilobases (kb) de sentido positivo (+ ssRNA) com estrutura de capa 5' e cauda 3' poli-A (Zhou *et al*., 2020). Eram conhecidos por infectar humanos, seis CoVs causadores de infecções respiratórias suaves, enquanto a Síndrome Respiratória Aguda Grave Coronavírus (SARS-CoV) e Síndrome Respiratória do Oriente Médio Coronavírus (MERS-CoV), pertencentes ao gênero β-CoV, podem infectar o trato respiratório inferior de humanos de forma grave (Hussain *et al*., 2020; Chen; Liu; Guo, 2020).

Em 31 de dezembro de 2019, a Organização Mundial de Saúde (OMS) foi notificada sobre um surto de pneumonia viral na China, província de Hubei, sendo declarada emergência de saúde pública de interesse internacional e, posteriormente, em 11 de março de 2020, estado de pandemia, a doença chamada de novo Coronavírus – 2019 (COVID-19) ou Síndrome Respiratória Aguda Grave Coronavírus 2 isolado Wuhan-Hu-1 (SARS-CoV-2-WH-HU1: MN908947.3) (Cárdenas - Conejo *et al*., 2020). Foi a primeira pandemia desencadeada por um Coronavírus, espalhando-se rapidamente para a maioria dos países (Hu *et al*., 2021; O'Leary *et al*., 2021).

O SARS-CoV-2 é o sétimo Coronavírus a infectar humanos e a terceira doença β-coronavírus zoonótica conhecida, depois da SARS e da MERS (Sun *et al*., 2020). Embora a taxa de mortalidade seja relativamente menor, quando comparado ao SARS (9,6%) e MERS (34%) (Baud *et al*., 2020; Hussain *et al*., 2020), o grande problema do novo Coronavírus é a alta disseminação, sendo mais rápida e ampla (Baud *et al*., 2020; Hussain *et al*., 2020).

Estudos apontam que o SARS-CoV-2 está relacionado ao Coronavírus de morcego isolado de *Rhinolophus sinicus* em 2015 na China (Bat-CoV-RaTG13: MN 996532.1), apoiando a teoria de que a cadeia de transmissão começou dos morcegos (reservatório natural) para os homens, embora o reservatório intermediário ainda não tenha sido esclarecido (Benvenuto *et al*., 2020; Zhang *et al*., 2020; Zhou *et al*., 2020).

Devido à sua alta disseminação, a COVID-19 está presente em todos os países, com exceção da Antártida, com total de 676.609.955 casos (10/03/2023). Os Estados Unidos, Brasil e Índia são os países com maior número de casos do novo Coronavírus, com um total de 6.881.955 mortes (10/03/2023), sendo os Estados Unidos, Brasil e México os países com mais mortes pela COVID-19 (JHU, 2021). A transmissão da COVID-19 pode ser feita de forma direta, por meio de gotículas e aerossóis infecciosos e

contato direto com a pessoa infectada, e pela forma indireta, no contato com superfícies contaminadas (fômites) (Sommerstein *et al*., 2020). Sendo assim, pessoas infectadas com a COVID-19 podem contribuir para a disseminação da doença (Meselson, 2020). As partículas inaladas e de aerossol se depositam em diferentes locais do trato respiratório. As partículas inspiráveis ou inaladas, devido ao seu diâmetro (10 a 100 µm), são depositadas nas regiões do trato respiratório superior, enquanto as partículas respiráveis ou aerossolizadas com diâmetro ≤10µm depositam-se no trato respiratório inferior (Tellier *et al*., 2019).

O espectro clínico da COVID-19 varia de infecção assintomática a doença crítica (Gandhi; Lynch; Del Rio, 2020). As manifestações mais comuns da COVID-19 são febre, mialgia, fadiga, falta de ar e tosse seca (Wang *et al*., 2020a). Alguns sintomas não específicos, como dor de garganta, congestão nasal, dor de cabeça, diarreia, náuseas, vômitos, anosmia e ageusia, também foram relatados (WHO, 2020). Indivíduos idosos (com idade igual ou superior a 60 anos) e com doenças crônicas pré-existentes podem desenvolver formas mais graves da doença, progredindo rapidamente para Síndrome do Desconforto Respiratório Agudo (SDRA) (Du *et al*., 2020; Wu *et al*., 2020). Entre os indivíduos sintomáticos, o período médio de incubação é de aproximadamente 4 a 5 dias, e 97,5% apresentam sintomas dentro de 11,5 dias após a infecção (Gandhi; Lynch; Del Rio, 2020).

As manifestações clínicas da COVID-19 são divididas de acordo com sua gravidade: leve (sem evidência de pneumonia viral ou hipóxia); moderada (sinais clínicos de pneumonia, mas nenhum sinal de pneumonia grave); grave (sinais clínicos de pneumonia mais um dos seguintes: frequência respiratória >30 respirações/min, dificuldade respiratória grave, ou $SatO_2$ <90%) e crítica (SDRA, sepse, choque séptico ou trombose aguda) (WHO, 2023). O SARS-CoV-2 usa o receptor da enzima conversora de angiotensina 2 (ECA2) para se ligar às células do hospedeiro, sendo que esse receptor é amplamente distribuído no corpo humano, podendo afetar diversos órgãos (Berger, 2020). Além das doenças respiratórias, a lesão renal aguda (LRA) tem sido relatada como uma complicação comum entre indivíduos hospitalizados com COVID-19, sendo o rim o segundo órgão mais comumente afetado pela doença (Xu *et al*., 2021). A causa mais comum de LRA é a lesão glomerular e tubular (Ng *et al*., 2020; Pfister *et al*., 2021).

A COVID-19 pode levar a lesão miocárdica aguda, insuficiência cardíaca e complicações arrítmicas (Madjid *et al*., 2020). O SARS-CoV-2 pode alterar as vias de sinalização da ECA2, levando a lesão aguda do miocárdio e pulmão. Também pode

aumentar a circulação de citocinas pró-inflamatórias, levando à falência de múltiplos órgãos, além de apresentar interação com o sistema renina-angiotensina-aldosterona (SRAA), aumentando eventos taquicardíacos (Babapoor-Farrokhran *et al*., 2020; Bansal, 2020). Outros mecanismos propostos de lesão cardíaca incluem relação demanda-oferta de oxigênio ao miocárdio, espasmo coronário, ruptura da placa e trombose coronária e efeitos adversos de várias terapias (Mahenthiran, Mahenthiran, Mahenthiran; 2020).

Complicações neurológicas, como dor de cabeça, tontura, hipogeusia (diminuição da sensação relacionada ao paladar), hiposmia (diminuição do olfato) são as mais relatadas, porém, em estados mais graves da doença, também são relatados: acidente vascular cerebral (AVC), problemas de consciência e hemorragia intracraniana (Hess, Eldahshan, Rutkowski, 2020; López-Blanco, 2020). A doença neurológica pode ser consequência de insuficiência cardiorrespiratória generalizada e fatores metabólicos, desencadeados pela infecção, invasão direta do vírus devido ao seu tropismo com o sistema nervoso central (SNC) e periférico (SNP), ou uma resposta autoimune do vírus (Berger, 2020; Paybast *et al*., 2020).

Além disso, foram relatadas complicações gastrointestinais (dilatação segmentar, estenose do intestino delgado, degeneração, necrose e descamação da mucosa gastrointestinal) devido à possibilidade da transmissão fecal-oral e lesão hepática durante o curso da doença (Tian *et al*., 2020). O vírus infecta o trato gastrointestinal pelo ligamento da proteína viral com seu receptor ECA2 presente nos enterócitos do íleo e do cólon (Cha, REgueiro, Sandhu, 2020). A lesão hepática em indivíduos infectados pode ser causada por infecção viral nos hepatócitos, hepatotoxicidade induzida por drogas e inflamação sistêmica induzida pelo aumento de citocinas circulantes ou hipóxia associada à pneumonia (Cha, Regueiro, Sandhu, 2020; Lee, Huo, Huang, 2020). Hipercoagulabilidade e complicações trombóticas também foram relatadas (Haimei, 2020). As complicações clínicas decorrentes do SARS-CoV-2 ainda não estão bem esclarecidas, mas é possível observar que a doença causa inúmeras complicações graves.

Um grande desafio para conter a disseminação da COVID-19 é que indivíduos assintomáticos e pré-sintomáticos transmitem o vírus. Os indivíduos podem ser infecciosos 1 a 3 dias antes do início dos sintomas, e 40 a 50% dos casos podem ser atribuídos à transmissão de pessoas assintomáticas ou pré-sintomáticas. Com o início dos sintomas, os indivíduos apresentam altos níveis virais nasofaríngeos, que caem em um período de 1 a 2 semanas. Os indivíduos podem ter o vírus detectável por semanas a meses, sendo recomendada a suspensão do isolamento 10 dias após o início dos sintomas

se a febre estiver ausente por pelo menos 24 horas e outros sintomas tiverem diminuído (Gandhi; Lynch; Del Rio, 2020). O teste de diagnostico para COVID-19 envolve a detecção do ácido nucleico SARS-CoV-2 por meio de ensaio de Reação em Cadeia da Polimerase (PCR). A especificidade da maioria dos ensaios de PCR é de quase 100% (Gandhi; Lynch; Del Rio, 2020).

Embora não existam tratamentos aprovados no Brasil para o SARS-CoV-2, várias outras medidas preventivas têm sido sugeridas, como uso de máscaras faciais, a lavagem regular das mãos com sabão, uso de álcool 70%, distanciamento social e a quarentena (Onyeaka *et al*., 2021). Por se tratar de uma doença respiratória, o uso de máscaras faciais reduz a disseminação e transmissão de partículas, contendo o vírus, sendo seu uso adotado pela população em geral (Ball *et al*., 2021).

2.2 COVID-19 E OBESIDADE

A obesidade é uma doença crônica não transmissível (DCNT) caracterizada pelo acúmulo de gordura corporal, associada ao aumento do risco de doenças, como diabetes *mellitus* tipo 2 (DM2), hipertensão arterial sistêmica (HAS) e doenças cardiovasculares (DCV) (Mariath *et al*., 2007; Gadde *et al*., 2018). O índice de massa corporal (IMC) é determinado pela fórmula (peso corporal em kg/estatura m^2), sendo esta ainda a mais utilizada para definir excesso de peso (IMC $\geq$ 25 kg/m^2) e obesidade (IMC $\geq$ 30 kg/m^2) (WHO, 1998).

A OMS estima que mais de 1,9 bilhão de indivíduos adultos apresentem excesso de peso, dos quais 650 milhões são obesos. Estima-se que 61,4% da população adulta brasileira apresentem excesso de peso, dos quais mais de 41 milhões (24,3%) de pessoas são classificadas como obesas (IBGE, 2021, BRASIL, 2023). A obesidade é um fator de risco conhecido para COVID-19 grave (Kompaniyets *et al*., 2021), já tendo sido descrita, na literatura, a relação dose-resposta entre IMC mais alto e agravamento da COVID-19. Portanto, indivíduos com excesso de peso com diagnóstico positivo para COVID-19 têm um risco aumentado de complicações, hospitalizações, admissão em unidade de terapia intensiva (UTI), além de maior necessidade de ventilação mecânica invasiva (VMI) e risco de morte (Kompaniyets *et al*., 2021). Essas ocorrências devem-se ao aumento da expressão de ECA2 pelos adipócitos, promovendo a invasão e proliferação do vírus e a desregulação da resposta imune inata e adaptativa, associadas ao aumento na produção de citocinas pró-inflamatórias e adipocinas, levando a uma resposta hiperinflamatória (De

Bandt; Monin, 2021; Barbalho *et al*., 2023).

Diversos estudos vêm demostrando a prevalência de hospitalização de pacientes obesos com COVID-19 (Hamer et al., 2020; Kalligeros *et al*., 2020; Palaiodimos *et al*., 2020). Rottoli *et al*. (2020) realizaram um estudo em um hospital em Bolonha, na Itália, cujo objetivo foi analisar se o IMC representava fator de risco para insuficiência respiratória (IR), admissão em UTI e óbito. Dos 482 indivíduos admitidos, 176 (36,5%) tinham excesso de peso e 104 (21,6%) eram obesos. Entre os indivíduos com obesidade, 51,9% apresentaram IR, 36,4% foram internados na UTI, 25% necessitaram de ventilação mecânica e 29,8% morreram em 30 dias a partir do início dos sintomas. Por sua vez, o estudo realizado por Somonnet e colaboradores (2020), em um hospital na França, avaliou a relação entre obesidade e SARS-CoV-2 e a necessidade de VMI em 124 pacientes admitidos em UTI. A obesidade (IMC $\geq$ 30 kg/m^2) e obesidade grave (IMC $\geq$ 35 kg/m^2) representaram 74,6% e 28,2% dos indivíduos internados, respectivamente. A proporção de indivíduos que necessitaram de IMV aumentou na mesma proporção que o IMC e foi maior em pessoas com IMC $\geq$ 35 kg/m^2 (85,7%).

Petrilli *et al*. (2020) descreveram em sua pesquisa as características clínicas e laboratoriais associadas à gravidade da COVID-19 em indivíduos internados em hospitais, nos Estados Unidos da América. Dos 2.741 indivíduos internados com a doença, 34,3% apresentaram IMC $\geq$ 25 kg/m^2, havendo 32,8% com IMC $\geq$ 30 kg/m^2 e 6,7% com IMC $\geq$ 40 kg/m^2. Por sua vez, Gao *et al*. (2020) investigaram a associação entre obesidade e gravidade da COVID-19 em três hospitais chineses. Das 150 pessoas internadas, 65 foram diagnosticadas com sobrepeso ($\geq$ 25 kg/m^2). Os indivíduos obesos apresentaram permanência hospitalar prolongada e evolução para a forma grave da doença. Os pesquisadores puderam observar que cada aumento de 1 unidade (kg/m²) no IMC também foi associado a um aumento de 12% no risco de COVID-19 grave. Com esses estudos, observa-se que a obesidade é realmente um fator de risco para a gravidade da COVID-19, portanto, é necessária maior atenção às medidas preventivas.

2.3 COVID-19 E BIOMARCADORES

A replicação rápida e intensa do SARS-CoV-2 desregula o sistema imune, aumentando a produção de citocinas pró-inflamatórias, o que contribui para a patogênese da COVID-19. Além dos níveis elevados de citocinas, exames laboratoriais relacionados à

hiperinflamação e dano tecidual têm sido apontados como um fator preditor de gravidade da doença (Fajgenbaum; June, 2020). Estudos clínicos demonstraram que níveis alterados de alguns marcadores sanguíneos podem estar relacionados à gravidade e mortalidade dos indivíduos com COVID-19 (Skevaki *et al*., 2020).

2.3.1 Perfil lipídico

O colesterol é precursor dos hormônios esteroides (sexuais e do córtex suprarrenal), dos ácidos biliares e da 25OH vitamina D. Além disso, como constituinte das membranas celulares, o colesterol atua na fluidez destas e na ativação de enzimas presentes (SBC, 2017). O colesterol existente nos tecidos e no plasma sanguíneo pode apresentar-se sob a sua forma livre, ou sob a forma de ésteres, que resultam da combinação da molécula de colesterol com um ácido graxo de cadeia longa, sendo ambas as formas transportadas ligadas às lipoproteínas (Berg; Tymoczko; Stryer, 2014).

As lipoproteínas são macroagregados moleculares de forma esférica constituídos de um núcleo hidrofóbico, que contém principalmente colesterol esterificado e triglicérides (TG), envolvido por uma monocamada constituída de fosfolipídios e colesterol livre, lipídeos anfifílicos e proteínas, denominadas apolipoproteínas (Gondim *et al*., 2017, SBC, 2017). As apolipoproteínas têm diversas funções no metabolismo das lipoproteínas, como a formação intracelular das partículas lipoproteínas, atuação como ligantes a receptores de membrana que as captam para o interior da célula (apo B-48, apo B-100 e E), ou cofatores enzimáticos (apo C-II, C-III e A-I) (SBC, 2017).

Existem quatro grandes classes de lipoproteínas separadas em dois grupos: as mais ricas em TG, maiores e menos densas (quilomícrons – QM e *very low density lipoprotein* – VLDL) e as ricas em colesterol (*low density lipoprotein* – LDL e *high density lipoprotein* – HDL) (SBC, 2017).

Atualmente, o colesterol demonstrou ser um fator importante nas infecções por SARS-CoV-2 (Wang *et al*., 2021). Hilser *et al*. (2021) investigaram a relação entre a gravidade da COVID-19 e os níveis de HDL-c. Segundo a pesquisa, entre os 1.117 indivíduos com COVID-19 incluídos, 968 apresentaram níveis de HDL-c significativamente mais baixos (50 ± 18 mg/dL) e 1.050 indivíduos apresentaram triglicerídeos mais altos. Corroborando em parte o estudo anterior, os níveis mais baixos de HDL-c estão associados ao desfecho grave da doença, porém os níveis de triglicerídeos

foram significativamente maiores em indivíduos com COVID-19, principalmente, em casos graves da doença (Masana *et al*., 2021).

2.3.2 Enzimas hepáticas

O fígado é a maior víscera do corpo humano, sendo responsável pela produção e metabolismo de várias substâncias (Schinoni, 2006). O fígado atua na digestão de gorduras provenientes dos alimentos através da produção da bile, no armazenamento e liberação da glicose, na produção de proteínas, na eliminação de toxinas, na produção de colesterol e no armazenamento de vitaminas e minerais (Guyton, 2011).

Devido à importância do papel que o fígado desempenha, foram desenvolvidos vários marcadores bioquímicos para mensurar o desempenho, bem como apontar possíveis lesões nesse órgão: aspartato aminotransferase (AST), alanina aminotransferase (ALT), gama-glutamiltransferase (Gama-GT), fosfatase alcalina (FA) e albumina (Gomes, 2014).

As transaminases (AST e ALT) são encontradas no citosol dos hepatócitos e liberadas na corrente sanguínea após ruptura da membrana celular (Marchese *et al*., 2018). A AST é uma enzima mitocondrial encontrada no fígado, no tecido cardíaco, muscular esquelético, renal, cerebral, pancreático, enquanto a ALT é uma enzima encontrada principalmente no citoplasma do hepatócito, sendo esta mais específica para lesões hepáticas, pois não é encontrada em outros órgãos ou tecidos (Barbosa *et al*., 2005).

A Gama-GT é encontrada no interior dos hepatócitos e nas células epiteliais biliares, estando envolvida no transporte de aminoácidos e peptídeos para as células, na síntese proteica e na regulação dos níveis de glutationa tecidual (Telli; Grigeri; Mello, 2016). É considerada um importante marcador de lesão hepatobiliar de alta sensibilidade, porém de baixa especificidade, podendo sofrer alterações por uso de fármacos, álcool e várias condições patológicas, como infarto agudo do miocárdio, insuficiência renal e diabetes (Silva; Neves; Costa, 2021).

A fosfatase alcalina é uma proteína de membrana envolvida no transporte de metabólitos através das membranas celulares, apresentando quatro subtipos de acordo com sua localização (intestinal, placentária, células germinativas e fígado/osso/rim) (Barbosa *et al*., 2005). No fígado, a FA está presente nas células que formam a parede dos ductos biliares, onde participa da digestão de lipídios (Barbosa *et al*., 2005). Níveis elevados dessa enzima ocorrem em lesões expansivas, hepatite viral, mononucleose infecciosa,

câncer de cabeça de pâncreas, tumores e fraturas ósseas (Telli; Grigeri; Mello, 2016).

A albumina é a proteína mais abundante no plasma, constituindo cerca de 60% do total das proteínas séricas, exercendo função oncótica (Malisano; Auler Júnior, 1998). Sua síntese ocorre exclusivamente no fígado através da transcrição de seu gene no braço longo do cromossomo 4, estando sua concentração reduzida na disfunção hepática (Nicholson; Wolmarans; Park, 2000). Uma vez sintetizada, a albumina é rapidamente liberada no sangue através dos capilares sinusoides, sendo que 30-40% é mantida na circulação e 60-70% é distribuída no interstício, músculo e pele (Santos *et al*., 2004). A albumina é degradada principalmente pelos músculos, fígado, rins e, em menor porcentagem, pelo trato gastrointestinal (Caraceni *et al*., 2013).

Pela presença do receptor da ECA2 no fígado, a disfunção hepática devido à infecção por COVID-19 pode estar relacionada à infecção grave, lesão hepática induzida por inflamação, hepatotoxicidade associada a medicamento e hipóxia (Luglio *et al*., 2020). Zhang *et al*. (2020), ao analisar 663 indivíduos hospitalizados com COVID-19, observou aumento das transaminases ALT (n = 151) e AST (n = 171), estando estas relacionadas com a gravidade da COVID-19 e mortalidade. Outro estudo, com 1.099 indivíduos com COVID-19, observou um aumento de 22,2% e 21,3% da AST e ALT, respectivamente, também relacionado à gravidade da doença, em 39,4% e 28,1% dos casos, respectivamente (Guan *et al*., 2020).

Outros biomarcadores hepáticos também estão associados com a gravidade da COVID-19. Entre uma coorte de 799 indivíduos, as concentrações de ALT, AST, bilirrubina total (BT), FA e Gama-GT foram marcadamente maiores em indivíduos falecidos, se comparados àqueles recuperados. Porém, 65% dos indivíduos falecidos desenvolveram hipoalbuminemia, devido à albumina ser um reagente de fase aguda negativa, cuja síntese é regulada negativamente por citocinas inflamatórias (Chen *et al*., 2020).

2.3.3 Marcadores de função renal

Os rins são órgãos responsáveis por garantir a excreção de dejetos metabólicos, controle das concentrações de sais nos tecidos e células (osmorregulação) e produção de hormônios. Portanto, a diminuição progressiva da função renal pode comprometer outros órgãos (Schrier, 2016). Doenças renais crônicas (DRCs) são um termo geral para

alterações que afetam tanto a estrutura como a função dos rins. Em vista disso, o declínio da função renal está associado ao aumento da morbimortalidade, limitação ou perda da qualidade de vida. Dessa forma, diversos novos marcadores têm sido propostos para diagnosticar e monitorar as doenças renais (Malta *et al*., 2019).

A creatinina é derivada, principalmente, do metabolismo da creatina e da fosfocreatina (Dusse *et al*., 2017). A transformação da creatina em creatinina ocorre no tecido muscular. Portanto, sua produção é diretamente proporcional à massa muscular, ocorrendo variações com a idade, sexo, etnia, estado nutricional e massa muscular (Bastos, 2011). O consumo de carne também pode elevar os níveis de creatinina, visto que a carne contém creatina, que pode ser convertida em creatinina pelo cozimento (Dusse *et al*., 2017).

A ureia é uma substância produzida no fígado, sendo o principal metabólico nitrogenado derivado da degradação de proteínas pelo organismo (Sodré; Costa; Lima, 2007). Após a metabolização, 90% da ureia circulante no sangue são filtradas e excretadas pelos rins e o restante eliminado pelo trato gastrointestinal e pele (Almeida *et al*., 2021). Por isso, deve ser dosada e avaliada simultaneamente com a creatinina para melhor avaliação da função renal (Dusse *et al*., 2017). Marcadores de função renal apresentam-se elevados em casos graves da COVID-19, sugerindo que a doença pode danificar o rim, devido à alta expressão de ECA2 nas células glomerulares (Xiang *et al*., 2020).

Estudos demostraram níveis significativamente mais elevados de marcadores renais em casos graves de COVID-19 (Henry; Lippi, 2020, Cheng *et al*., 2020). Cheng *et al.* (2020), ao analisarem 701 indivíduos com COVID-19, revelaram que os níveis elevados de creatinina e ureia na admissão hospitalar se correlacionaram com a gravidade da doença. Os autores descobriram que a incidência de mortalidade hospitalar de indivíduos com creatinina elevada (33,7%) foi significativamente maior do que naqueles com creatinina normal (13,2%).

Concordando com estudo anterior, amostras clínicas de 28 indivíduos com COVID-19 apresentaram níveis significativamente mais elevados de ureia e creatinina sérica em casos graves. Portanto, para os autores, os biomarcadores renais (ureia, creatinina, cistatina C, bilirrubina direta, colinesterase, lactato desidrogenase) podem ser usados para distinguir casos graves dos casos leves da COVID-19 (Xiang *et al*.,2020).

2.3.4 Eletrólitos

Os eletrólitos sanguíneos, como cálcio, fósforo e magnésio, são substâncias inorgânicas provenientes da alimentação, estando envolvidos em vários processos fisiológicos, como desenvolvimento ósseo, formação do sangue, síntese hormonal e regulação do batimento cardíaco (Lobo; Tramonte, 2004). Sua deficiência na concentração plasmática pode reduzir o papel do sistema imunológico, que é a principal linha de defesa para infecções (Kumar *et al*., 2021).

O cálcio é o mineral mais abundante no corpo humano, representando cerca de 99% do que é encontrado nos ossos (Gooldman; Gilman, 2018). Esse mineral está envolvido em diversas funções biológicas, como a contração muscular, coagulação sanguínea, funções cardíacas, transmissão de impulsos, suporte estrutural do esqueleto e mediação de vários hormônios (Pereira *et al*., 2009). A absorção do cálcio ocorre principalmente no trato gastrointestinal, e apenas 500 mg/dia do cálcio ingerido é absorvido (Pereira *et al*., 2009). De acordo com a Agência Nacional de Vigilância Sanitária (ANVISA), a ingestão diária recomentada (IDR) de cálcio para adultos é de 1000 mg/dia, tendo como recomendação máxima de 1200 mg/dia para gestantes e 1000 mg/dia para lactantes (BRASIL, 2005).

O fósforo é o segundo mineral mais abundante no corpo humano e, juntamente com o cálcio, participa da estrutura óssea. Também é vital para a produção de energia (ATP), funcionamento dos músculos e nervos e para o equilíbrio ácido-básico (Bridges, 2021). Sua fonte é proveniente da alimentação, como feijão, nozes, cereais, laticínios, carnes e ovos, sendo rapidamente absorvido no intestino (Ramos; Cuppari, 2019; Mason; Booth, 2020). Cerca de aproximadamente 75% do fósforo é encontrado nos ossos e dentes, 10% nos músculos, 1% no tecido nervoso e 1% na corrente sanguínea (Mason; Booth, 2020). A IDR de fósforo para adultos é de 700 mg/dia, tendo como recomendação máxima de 1250 mg/dia para gestantes e lactantes (BRASIL, 2005).

O magnésio é o segundo cátion intracelular, após o potássio, mais abundante no corpo humano, estando envolvido nos processos inflamatórios e defesa imune, síntese de ácidos nucleicos e proteínas, alergia, crescimento e estresse, excitabilidade cardíaca e pressão arterial (Noronha; Matuschak, 2012). Cerca de 60% do magnésio está presente nos ossos, 27% nos músculos, 19% nos tecidos moles, 1% nos glóbulos vermelhos e plasma sanguíneo, e sua fonte está diretamente relacionada à ingestão de água potável e alimentação (folhas verdes ricas em clorofila, cereais, grãos, nozes e leguminosas)

(Swaminathan, 2003; Motoyama *et al*., 2005). A IDR de magnésio para adultos é de 260 mg/dia, tendo como recomendação máxima de 220 mg/dia para gestantes e 270 mg/dia para lactantes (BRASIL, 2005).

Observa-se, portanto, que as concentrações dos eletrólitos dentro dos limites plasmáticos aceitáveis são essenciais para a regulação adequada do bom funcionamento do sistema imunológico. Sendo assim, a ingestão de uma alimentação saudável, composta por alimentos *in natura* que contenham sais minerais e vitaminas, é necessária para um sistema imunológico saudável, capaz de combater a COVID-19 (Jayawardena *et al*., 2020). Dessa forma, estudos de revisão sistemática mostram que a gravidade da COVID-19 está associada a concentrações séricas mais baixas dos eletrólitos sanguíneos (Lippi; South; Henry, 2020; Kumar *et al*., 2021).

Ao analisar 127 indivíduos com COVID-19, os autores mostraram uma diminuição nos níveis plasmáticos do cálcio em todos os casos da doença (leve, moderado, grave/crítico). Porém, os casos graves/críticos mostraram níveis de cálcio significativamente mais baixos (Zhou *et al*., 2020). Para os autores, o cálcio pode ser considerado um biomarcador de gravidade clínica no início dos sintomas da COVID-19 e está associado a lesões em múltiplos órgãos (Zhou *et al.*, 2020).

Xue *et al.* (2020) analisaram 32 indivíduos com COVID-19 (12 casos leves e 20 casos graves/críticos), verificando que os níveis de fósforo sérico dos indivíduos graves/críticos foram menores do que dos indivíduos considerados casos leves. Portanto, acredita-se que a hipofosfatemia possa estar relacionada à gravidade da COVID-19. Grande estudo americano com 1.685 indivíduos internados com COVID-19 relatou que 21% deles apresentavam hipermagnesemia, estando estes indivíduos envolvidos em maior incidência de choque séptico, insuficiência respiratória com uso de ventilação mecânica e insuficiência renal aguda (Stevens *et al*., 2021). Destarte, o monitoramento dos níveis de cálcio, fósforo e magnésio, como outros minerais séricos em indivíduos com COVID-19 em estado grave/crítico, é importante para um melhor prognóstico.

2.3.5 Marcadores de função pancreática

O pâncreas é um órgão classificado como uma glândula anfícrina, por possuir uma porção endócrina e outra exógena (BRASIL, 2021). A porção endócrina ou hormonal é formada pelas Ilhotas de *Langerhans*, que são responsáveis pela produção de insulina e

glucagon, ambos reguladores dos níveis de glicose no sangue (Montenegro; Chaves; Fernandes, 2016). Sua porção exógena é responsável pela síntese do suco pancreático, atuando na digestão de carboidratos (amilase), lipídios (lípase) e proteínas (proteases) (BRASIL, 2021).

A amilase é uma isoenzima produzida pelo pâncreas exócrino e glândulas salivares, atuando na digestão do amido e glicogênio proveniente dos alimentos (Telli, 2016). A lipase é uma enzima digestiva secretada pelas células acinares do pâncreas e atua removendo os ácidos graxos dos triglicerídeos da alimentação, produzindo monoglicerídeos e ácidos graxos de cadeia longa saturada e polissaturada (Lunagariya *et al*., 2014).

A amilase e a lipase séricas são largamente utilizadas como marcadores de inflamação pancreática (Ferreira *et al*., 2008). O diagnóstico definitivo de pancreatite segue as diretrizes do *American College of Gastroenterology,* requerendo a presença de, pelo menos, duas das seguintes características: 1) dor abdominal, 2) amilase e/ou lipase superior a três vezes os níveis normais e 3) achados de imagem (Banks; Freeman, 2006).

A expressão da ECA2 nas células pancreáticas torna o pâncreas um alvo para a COVID-19. O vírus pode causar danos às ilhotas pancreáticas, resultando em diabetes aguda e danos às glândulas exócrinas, causando pancreatite aguda (Correia de Sá; Soares; Rocha, 2021). Inamdar *et al*. (2020) analisaram 189 indivíduos hospitalizados com pancreatite, e apenas 32 indivíduos apresentaram o teste positivo para COVID-19. O tempo de internação (26,91%), necessidade de ventilação mecânica (9%) e mortalidade (4%) foram maiores entre os indivíduos com pancreatite e COVID-19, em comparação com aqueles que não apresentaram COVID-19 positivo.

Um estudo realizado em Wuhan/China analisou 55 indivíduos hospitalizados com COVID-19 em estado crítico na UTI, e três indivíduos apresentaram pancreatite aguda, 29 indivíduos tinham enzimas pancreáticas elevadas e 23 indivíduos apresentaram os valores das enzimas dentro dos pontos de corte. Os níveis elevados das enzimas pancreáticas foram associados à ventilação mecânica e lesão renal aguda (Ding *et al*., 2021). Outro estudo realizado na China observou que nove (17%) indivíduos, dos 52 internados, apresentavam lesão pancreática, sendo seis aqueles que apresentaram níveis anormais de glicose no sangue (Wang *et al*., 2021). Esses achados mostram potenciais lesões pancreáticas em indivíduos com COVID-19, podendo estar relacionadas à alta expressão da ECA2 nas células pancreáticas.

2.3.6 Perfil Glicêmico

O DM é uma síndrome decorrente da falta e/ou incapacidade da insulina para regular os níveis de glicose sanguínea, resultando em hiperglicemia crônica (Mclellan *et al*., 2009). A hiperglicemia causa liberação de citocinas pró-inflamatórias e estresse oxidativo, favorecendo infecções em pessoas com DM (Anghebem; Rego; Picheth, 2020). Segundo a Sociedade Brasileira de Diabetes, os exames laboratoriais para o diagnóstico de DM são: glicose em jejum, glicemia duas horas após teste oral de tolerância à glicose (TOTG) e hemoglobina glicada (HbA1c) (SBD, 2019).

A glicose é uma molécula obtida por meio da alimentação ou da degradação do glicogênio armazenado no corpo, e sua quantidade na circulação sanguínea é regulada pela insulina e glucagon, hormônios produzidos no pâncreas (Silva; Freitas Filho; Freitas, 2018). O exame de glicemia tem a finalidade de quantificar os níveis de glicose na circulação sanguínea, após jejum de 8 horas (Lima, 2016).

A HbA1c refere-se a um conjunto de substâncias formadas com base em reações entre a hemoglobina (Hb) A1, cujo terminal valina da cadeia beta está ligado à glicose por meio de uma ligação estável e irreversível (Bem; Kunde, 2006; Netto *et al*., 2009). A quantidade de glicose ligada a Hb é diretamente proporcional à concentração média de glicose no sangue (Sumita; Andriolo, 2008). A determinação dos níveis de HbA1c é a melhor opção para a avaliação do controle glicêmico em médio e longo prazos (Bem; Kunde, 2006).

Indivíduos diabéticos têm risco aumentado para infeções diversas, incluindo casos mais graves da COVID-19 (Lim *et al*., 2021). A glicose alta na circulação sanguínea facilita a hiperinflamação observada na tempestade de citocinas, característica típica decorrente da infecção da COVID-19 (Correia de Sá; Soares; Rocha, 2021), sendo que o vírus SARS-CoV-2 também pode causar danos às ilhotas pancreáticas, responsáveis pela regulação glicêmica, além de alterações na coagulação e na resposta imune (Logette *et al*., 2021).

Ao analisar 364 indivíduos internados com COVID-19 (114 com DM e 250 sem DM), Xu *et al*. observaram que os indivíduos com DM necessitaram mais de terapia VMI/ECMO, quando comparados aos indivíduos sem DM, e 23,7% daqueles com DM faleceram. Pessoas com DM podem ser suscetíveis a infecções graves por COVID-19, podendo a infecção viral influenciar negativamente no prognóstico daqueles acometidos pela COVID-19 (Xu *et al*., 2020).

Wang *et al*. (2020b) analisaram 28 indivíduos com DM2 e COVID-19 e observaram que os níveis de HbA1c foram semelhantes entre os internados na UTI e aqueles internados na enfermaria de isolamento. Entre os diabéticos, 22,2% foram admitidos na UTI e 5,9% admitidos na enfermaria, indicando que a COVID-19 associada com o DM2 tem maior probabilidade de evolução para os casos graves.

Corroborando o estudo anterior, Shauly-Aharonov e colaboradores (2021) observaram que os níveis de glicose em jejum e HbA1c foram significativamente maiores entre os indivíduos com diagnóstico positivo para COVID-19 com DM2, como também naqueles sem DM2, estando, em ambos os casos, relacionados com a gravidade da doença. Portanto, a glicemia aumentada pré-infecção é um fator de risco para COVID-19.

2.3.7 Proteína C Reativa

A proteína C reativa (PCR) é um tipo de proteína de fase aguda (PFA) cálcio-dependente da família das pentatraxinas, sintetizada nos hepatócitos em resposta à interleucina-6 (IL-6), sendo esta estimulada pelo Fator de Necrose Tumoral Alfa (TNF-α), liberado no tecido adiposo branco (TAB) (Agostinis Sobrinho *et al*., 2015) e causando aumento em resposta às infecções ativas ou em processos inflamatórios agudos (Aguiar *et al*., 2013). Além do seu papel como biomarcador inflamatório, a PCR também atua como parte do mecanismo de defesa contra inflamação e invasão de patógenos (Wu *et al*., 2015).

A elevação dos níveis de PCR inicia-se em média seis horas após um processo inflamatório, duplicando a cada 8 horas e atingindo seu pico entre 36 e 50 horas. Porém, em indivíduos com excesso de peso ou obesidade, a resposta inflamatória pode ser precoce, uma vez que eles possuem valores de PCR basais normalmente elevados (Wagmacker *et al*., 2015).

Níveis elevados desse marcador inflamatório têm sido associados à obesidade e relacionam-se diretamente à quantidade de gordura corpórea, através do IMC, obesidade visceral, circunferência abdominal, resistência insulínica, Síndrome Metabólica (SM) e DM (BRASIL *et al*., 2007; Gomes *et al*., 2010). Níveis elevados também têm sido observados em indivíduos com COVID-19 grave devido ao sistema imune inato desregulado pela presença de citocinas inflamatórias (Wang *et al*., 2020c).

Na admissão hospitalar, foram frequentes níveis de PCR acima do ponto de corte

(≥10 mg/L) (SBC, 2017) em pessoas com COVID-19. Chen *et al*. (2020) observaram que 86% dos indivíduos hospitalizados com a doença apresentaram aumento nos níveis de PCR (51,4 ± 41,8 mg/L). Dados semelhantes também foram observados por Cao *et al*., (2020), dos 102 indivíduos admitidos no hospital com COVID-19, 51% apresentaram aumento nos níveis de PCR na admissão, aumentando esse valor durante a hospitalização (62,7%). Dos 17 indivíduos que evoluíram para óbito, todos apresentaram valores de PCR superiores a 100 mg/L.

Diversos estudos vêm demostrando a correlação do aumento nos níveis de PCR com a severidade da COVID-19 (Ali, 2020; Smilowitz *et al*., 2021; Wang *et al*., 2020c). Zhao e colaboradores (2021), ao analisarem 77 indivíduos hospitalizados com COVID-19 em um hospital de Beijing, observaram que 64,9% apresentaram aumento nos valores de PCR. Quanto à gravidade da doença, 56,1% dos indivíduos categorizados como não graves e 90% dos considerados graves tiveram aumento nos valores de PCR. Condizendo com o estudo anterior, Guan *et al*. (2020) observaram 1.099 indivíduos hospitalizados em 552 hospitais da China e constataram que 60,7% apresentaram aumento nos resultados de PCR, dos quais 56,4% dos indivíduos considerados não graves e 81,5% daqueles considerados graves apresentaram aumento nos valores de PCR. Portanto, os níveis de PCR são fortes indicadores para a presença e evolução da infecção por COVID-19, uma vez que este é um dos primeiros biomarcadores a serem alterados.

2.3.8 Valores de Referência

Os valores de referência (VRs) considerados nos artigos apresentados seguem diretrizes nacionais.

Os pontos de corte utilizados para o perfil lipídico serão os propostos pela nova Diretriz Brasileira de Dislipidemias e Prevenção da aterosclerose (SBC, 2017), em que se tem valores desejáveis em jejum de colesterol total (CT) < 190 mg/dL, HDL-c > 40 mg/dL, TG < 150 mg/dL e LDL-c < 130 mg/dL. Para as enzimas hepáticas os valores de corte utilizados serão os determinados pelo fabricante do *kit* Gold Analisa Diagnóstico, sendo ALT < 45 U/L para homens e < 37 U/L para mulheres, AST < 39 U/L para homens e < 37 U/L para mulheres, fosfatase alcalina < 43 U/L, Gama-GT < 60 U/L para homens e < 40 U/L para mulheres e albumina entre 3,5 a 5,5 g/dL (ANALISA, 2020). Os valores de corte para a função renal serão estabelecidos de acordo com a Sociedade Brasileira de Nefrologia, sendo creatinina entre 0,6 e 1,3 mg/dL e ureia entre 20 e 40 mg/dL (Bastos,

2011). Os pontos de corte para Eletrólitos serão os determinados pelo fabricante do *kit* Gold Analisa Diagnóstico, sendo cálcio 8,8 a 11 mg/dL, fósforo 2,5 a 4,8 mg/dL e magnésio 1,6 a 2,6 mg/dL (ANALISA, 2020). Os pontos de corte para função pancreática serão os determinados pelo fabricante do *kit* Gold Analisa Diagnóstico, sendo amilase direta entre 25 e 125 U/L e lipase direta entre 13 e 60 U/L (ANALISA, 2020). Os pontos de corte utilizados para o controle glicêmico serão estabelecidos de acordo com a Sociedade Brasileira de Diabetes (SBD, 2019), em que valores < 100 mg/dL de glicose em jejum são considerados como glicemia normal; entre ≥ 100 e < 126 mg/dL pré-diabetes ou risco aumentado para DM e ≥ 126 mg/dL diabetes estabelecido e HbA1c < 5,7% normal; entre ≥ 5,7 e < 6,5% pré-diabetes ou risco aumentado para diabetes mellitus e ≥ 6,5% DM. Para proteína C reativa o ponto de corte será de 1,0 a 5,0 mg/dL (encontrado em infecções virais e processos inflamatórios leves), de 5,1 a 20,0 mg/dL (encontrado em infecções bacterianas e processos inflamatórios sistêmicos) e acima de 20,0 mg/dL (encontrado em infecções graves, grandes queimados e em politraumatismo) (Fleury, 2022).

2.4 SÍNDROME DE COVID-19 LONGA

A síndrome da COVID-19 longa ou condição pós-COVID-19 é a condição em que os indivíduos afetados não se recuperam por várias semanas ou meses após o início dos sintomas sugestivos de COVID-19 (Nabavi, 2020). Evidências cientificas tem demonstrado que indivíduos que necessitaram de internação em UTI e/ou suporte ventilatório durante casos graves parecem ter um risco aumentado de desenvolver síndrome de COVID-19 longa (Davis *et al*., 2021). A OMS estimou que 10 a 20% dos pacientes com COVID-19 apresentaram sintomas persistentes por meses após a infecção e reconheceu que a condição é claramente uma preocupação de saúde pública, dado o impacto substancial que tem na sociedade, variando do aumento dos custos de saúde à economia e perda de produtividade (WHO, 2022).

Em relação aos sintomas persistentes, Miranda *et al*. (2022) analisaram 646 indivíduos positivos internados para COVID-19, os dados foram coletados através de entrevistas realizadas pessoalmente ou por meio de plataforma virtual uma vez por mês, por até 14 meses após o diagnóstico confirmado. De toda a população, 50,2% apresentaram síndrome de COVID longa, com 23 sintomas diferentes relatados; os mais frequentes foram fadiga (35,6%), tosse persistente (34%), dispneia (26,5%), perda de

olfato/paladar (20,1%), dores de cabeça frequentes (17,3%), transtornos mentais (20,7%), alteração da pressão arterial (7,4%) e trombose (6,2%). O estudo de Huang *et al*. (2021) descreveu as consequências a longo prazo da COVID-19 em 1.733 indivíduos, após 6 meses de alta hospitalar. Os autores observaram que os sobreviventes da COVID-19 apresentavam principalmente fadiga ou fraqueza muscular (63%), dificuldade de sono (26%) e ansiedade ou depressão (23%). Os participantes que apresentaram maior grau da doença relataram maiores problemas de mobilidade, dor ou desconforto e 58 indivíduos sem histórico autorrelatado de DM2 foram diagnosticados com a doença no acompanhamento após a alta hospitalar. Estes resultados apoiam que indivíduos com COVID-19 grave necessitam de cuidados pós-alta hospitalar.

Alguns estudos avaliaram o impacto da síndrome COVID-19 longa de acordo com sua sintomatologia. Perli *et al*. (2023) avaliaram a composição corporal, aptidão cardiopulmonar e os sintomas de longo prazo de indivíduos com excesso de peso afetados pela COVID-19. Os 90 participantes foram divididos em três grupos de acordo com a gravidade da doença: casos leves (sem internação), moderados (internação, sem suporte de oxigênio) e casos graves/críticos (internados em UTI). Os sintomas mais prevalentes no longo prazo foram déficit de memória (66,7%), falta de concentração (51,7%), fadiga (65,6%) e dispneia (40%). O teste de Bruce apresentou efeito do tempo com aumento da distância percorrida após 1 ano apenas para o grupo grave/crítico. A saturação periférica de oxigênio (SpO_2) foi significativamente menor no grupo grave/crítico, quando comparado ao grupo leve. Foi observado efeito de tempo para composição corporal, com aumento de massa magra (MM), massa musculoesquelética (MME), massa livre de gordura (MLG), e MM apenas para o grupo grave/crítico após 1 ano. Com isso, reavaliar e identificar as sequelas mais prevalentes no longo prazo é essencial para realizar intervenções de promoção da saúde mais precisas.

Estudo semelhante foi realizado por Lemos *et al*. (2022), no qual os autores avaliaram a composição corporal (bioimpedância elétrica) e a aptidão cardiorrespiratória (protocolo de Bruce, com análise direta das trocas gasosas) de pessoas com excesso de peso ou obesidade após COVID-19. Os 171 voluntários foram alocados em três grupos: pessoas não hospitalizadas/sintomas leves, pessoas hospitalizadas e pessoas internadas na UTI. Os indivíduos hospitalizados apresentaram valores significativamente maiores de massa gorda (MG) e percentual de gordura corporal (%GC) do que indivíduos não hospitalizados. Foram encontrados valores significativamente maiores para frequência cardíaca (FC) e consumo máximo de oxigênio (VO_2 pico) para indivíduos que não foram

internados, quando comparados aos internados em UTI. Após o teste cardiorrespiratório, foram observados valores mais elevados de SpO_2 nos indivíduos não hospitalizados do que em todos os indivíduos hospitalizados. A pressão arterial diastólica (PAD) foi significativamente maior no 10º e 15º minutos pós-teste de Bruce em participantes hospitalizados do que em participantes não hospitalizados. Com base nesses resultados, a monitorização da FC, SpO_2 e PA é necessária durante a reabilitação para evitar possíveis complicações físicas. Dado o menor condicionamento físico entre todos os grupos, propostas de recuperação dos problemas de saúde são urgentes e indispensáveis para os sobreviventes da COVID-19.

A síndrome da COVID-19 longa pode causar perda de produtividade dos sobreviventes. Davis *et al*. (2021) analisaram 3.762 indivíduos com COVID-19 por até 7 meses após o diagnóstico, os autores observaram que a maior área de impacto relatada foi no trabalho, com 86,2% dos indivíduos que trabalhavam sentindo-se de leve a gravemente incapazes de trabalhar, sendo 45,2% os que precisavam de um horário de trabalho reduzido em comparação com antes da doença, e outros 22,3% não estavam trabalhando no momento da pesquisa como resultado direto de sua doença. Também, 89,1% dos participantes relataram experimentar mal-estar pós-esforço físico ou mental, diante disto, o estudo demonstrou o grande impacto que os sintomas têm na capacidade dos indivíduos de trabalhar e realizar tarefas diárias.

2.5 INTERVENÇÕES PARA PREVENCÃO, MANEJO, REABILITAÇÃO E PROMOÇÃO DA SAÚDE PÓS COVID-19

A COVID-19 é uma infecção respiratória com manifestações multissistêmicas, assim, estratégias de reabilitação dos sobreviventes da COVID-19 são indispensáveis para combater uma condição com diferentes sequelas (Bonay; Abdelkarim; Ammar, 2023). Mohamed e Alawna (2021) realizaram um estudo na Turquia onde foi investigado o efeito do exercício aeróbico de intensidade moderada nos marcadores imunológicos, gravidade e progressão da doença em 30 indivíduos com COVID-19 leve ou moderada. Os indivíduos foram divididos aleatoriamente em dois grupos (grupo de exercício e controle), cujas sessões de exercícios ocorreram três vezes por semana, com duração de aproximadamente 40 minutos/sessão, durante 2 semanas. As medições foram realizadas no início do estudo e após as 2 semanas de atividade física. Os autores observaram que antes das duas semanas de exercício aeróbico não houve diferença significativa entre os grupos na pontuação total

da escala de Wisconsin (qualidade de vida específica da doença orientada ao paciente), leucócitos, linfócitos, IL-6, IL-10, imunoglobulina-A (IgA) e TNF-α, mas, após a intervenção, a escala de Wisconsin diminuiu significativamente no grupo do exercício, enquanto os marcadores imunológicos aumentaram significativamente no grupo do exercício. Diante disso, o exercício aeróbico de intensidade moderada diminuiu a gravidade e progressão dos distúrbios associados à COVID-19 e à qualidade de vida, afetando positivamente a função imunológica do indivíduo.

Um estudo semelhante, realizado em Portugal, analisou os efeitos de um programa de treinamento combinado durante a pandemia da COVID-19 na composição corporal, perfil metabólico (perfil glicêmico e lipídico), aptidão cardiorrespiratória, qualidade de vida e estresse, em 31 trabalhadores sedentários. Os indivíduos foram divididos aleatoriamente em dois grupos (grupo treinamento combinado e controle, que mantiveram seu estilo de vida), em que as sessões de exercícios concorrentes (resistidos e aeróbios) ocorreram três vezes/semana em dias alternados, com duração de aproximadamente 55 minutos/sessão, durante 16 semanas. As sessões de treinamento foram realizadas presencialmente até a oitava semana e, nas semanas seguintes, as sessões foram realizadas remotamente. As avaliações ocorreram pré e pós-intervenção. Após o período de intervenção, o grupo de treinamento concorrente apresentou valores significativamente menores de circunferência de quadril e cintura, em relação ao grupo controle. O grupo controle aumentou significativamente o perfil glicêmico (glicemia em jejum e HOMA-IR) após 16 semanas. Também foi observado pelos autores que o grupo de treinamento concorrente apresentou melhores resultados nos níveis de estresse percebido, nos domínios físicos, psicológicos e ambientais da qualidade de vida e na percepção da satisfação com a vida. Com isso, os resultados sugerem que os indivíduos que permaneceram fisicamente ativos durante o confinamento referente à pandemia foram capazes de diminuir os efeitos deletérios associados ao sedentarismo (Silva *et al*., 2022).

Com foco na reabilitação de indivíduos pós-COVID-19, Sordi *et al*. (2023) avaliaram o efeito de uma intervenção multiprofissional (intervenção nutricional, psicoeducativa e intervenção de exercício físico), na composição corporal, aptidão física e biomarcadores em sobreviventes de COVID-19 com sobrepeso (IMC $\geq$ 25kg/m^2), em diferentes sintomatologias. Os 35 indivíduos foram divididos em três grupos de acordo com a sintomatologia (grupo controle, COVID-19 moderada e COVID-19 grave). O grupo controle foi composto por aqueles que nunca haviam adquirido a doença. Todos os participantes realizaram exercícios de treinamento concorrentes, com foco na melhora da

aptidão cardiorrespiratória e neuromuscular, duas sessões/semana, com duração de 60 minutos/sessão, durante 8 semanas. Após as intervenções os autores relataram que o grupo COVID-19 moderada apresentou melhora da força dinâmica de membros inferiores e membros superiores, isometria máxima lombar - força de tração, flexibilidade, marcadores como albumina, PCR, glicemia de jejum e triglicerídeos; para o grupo COVID-19 grave, foram observados melhoras na força dinâmica da parte inferior do corpo e valores mais baixos de PCR e triglicerídeos; e, para o grupo controle, foram identificadas melhora nas repetições de abdominais, redução da PCR, glicemia de jejum, CT e triglicerídeos. Sendo assim, 8 semanas de intervenção multiprofissional pode ser uma ferramenta eficiente para reverter o processo inflamatório e promover melhorias nas atividades diárias e na qualidade de vida em sobreviventes da COVID-19 (Sordi *et al*., 2023).

Jimeno-Almazán *et al*. (2022) realizaram um estudo na Espanha para avaliar a reabilitação de indivíduos pós-COVID-19, onde compararam os resultados de indivíduos com condição pós-COVID-19 submetidos a intervenção de exercício terapêutico supervisionado de intensidade baixa e moderada. Os 39 voluntários foram aleatoriamente designados para dois grupos: grupo dos exercícios multicomponente personalizado e supervisionado em três sessões/semana ou grupo controle (não supervisionado) que seguiu as diretrizes da OMS para reabilitação após COVID-19, sendo recomendado exercício aeróbico de 20 a 30 minutos, 5 dias por semana, além de exercício de força em três sessões, ambos os grupos com duração de 8 semanas. Após o acompanhamento, houve mudanças nos resultados físicos em ambos os grupos, tendo uma melhora significativa no grupo dos exercícios multicomponentes para os marcadores cardiovasculares e de força (VO_2 máximo, teste de sentar e levantar, teste de carga submáxima progressiva utilizando maquina Smith para os exercícios de supino e agachamento), e na qualidade de vida. Ao comparar os dois grupos, o exercício supervisionado é uma intervenção mais eficaz, segura e bem tolerada em condições pós-COVID-19.

Devido ao isolamento social e ao impacto do luto, a pandemia está intimamente associada com sequelas psicoemocionais (mazza *et al.,* 2020). Ryal *et al*. (2023) investigaram os efeitos de um modelo de intervenção multiprofissional na saúde mental de sobreviventes de meia idade da COVID-19, e com excesso de peso. Os 135 voluntários com excesso de peso ou obesidade foram distribuídos em quatro grupos experimentais: COVID leve, moderada, grave e grupo controle. Foram utilizados os seguintes questionários como instrumento para coleta de dados antes e após 8 semanas de intervenção: Continuum de Saúde Mental – MHC-SF (avaliar o bem-estar emocional,

social e psicológico dos participantes), Impacto da Escala de Evento Revisada – IES-R (rastreamento de sintomas pós-traumáticos), Transtorno de Ansiedade Generalizada – GAD-7 (rastrear os níveis de ansiedade dos participantes) e Questionário de Saúde do Paciente-9 – PHG-9 (verifica a presença de cada um dos sintomas de um episódio de depressão). Os resultados indicaram apenas um efeito temporal, com um aumento significativo nas pontuações globais MHC, bem-estar emocional, bem-estar social e bem-estar psicológico, bem como detectaram uma redução significativa nas pontuações globais do IES-R, intrusão, evitação e hiperexcitação, além de redução nos escores GAD-7 e PHG-9. Com isso, foi possível identificar que as intervenções psicoeducacionais reduziram a ansiedade, a depressão e os sintomas de estresse pós-traumático em pacientes pós-COVID-19.

Diante disso, as intervenções multiprofissionais podem ser uma ferramenta eficiente para reverter o processo inflamatório e promover melhorias nas atividades diárias e qualidade de vida para indivíduos acometidos pela COVID-19.

3. JUSTIFICATIVA

O mundo está enfrentando um grave cenário de pandemia decorrente do novo Coronavírus (COVID-19), sendo que, até a presente data (10/03/2023), foram confirmados 676.609.955 casos e 6.881.955 mortes, baseados nos dados estatísticos da Universidade John Hopkins, Estados Unidos da América (JHU, 2021). No Brasil, o primeiro caso confirmado de COVID-19 foi em 26 de fevereiro de 2020, sendo a primeira morte registrada no mês seguinte (Cavalcante *et al*., 2020). Cerca de três anos após o relato do primeiro caso no Brasil, já foram registrados 37.085.675 casos e 699.310 mortes (10/03/2023) (JHU, 2021). O Estado do Paraná, com aproximadamente 11.444.380 habitantes, ocupa a 3ª posição em número de casos acumulados (2.966.772 casos) e o 4º lugar em número de óbitos (46.509 mortes) (21/11/2023) (IBGE, 2022; FIOCRUZ, 2021).

A metanálise publicada por Hussain et al. (2020) aponta que a obesidade é um fator de risco considerável para a mortalidade decorrente do novo Coronavírus. Destarte, políticas públicas que busquem prevenir e combater a obesidade durante os ciclos da vida, via intervenções multiprofissionais, são substanciais para a promoção da longevidade saudável e redução dos custos de tratamento hospitalares e não hospitalares dessa DCNT (Bolognese *et al*., 2020; Magnani Branco *et al*., 2020). A condução de intervenções

multiprofissionais para o combate à obesidade é indispensável, dado que essa DCNT apresenta característica multifatorial, podendo ser influenciada pela ansiedade, depressão, compulsão alimentar, baixa autoestima, falta de apoio familiar, má alimentação e atividade física esporádica (Branco *et al*., 2018, Branco *et al*., 2019; Costa *et al*., 2019; Bolognese *et al*., 2020; Magnani Branco *et al*., 2020).

Em virtude dos aspectos supraelencados, enfatiza-se que os impactos da COVID-19 em pessoas com obesidade vão além do risco aumentado para os casos graves da doença (Stefan; Birkenfeld; Schulze, 2021). Em vista disso, as pessoas obesas hospitalizadas por COVID-19 propendem a perder grande proporção da massa magra devido à inatividade física, pela terapia nutricional hospitalar, bem como pela inflamação de baixo grau (Gualtieri *et al*., 2020). Adicionalmente, verifica-se também a redução da capacidade cardiorrespiratória em pessoas obesas internadas pela COVID-19 (Zbinden-Foncea *et al*., 2020). Consequentemente, fundamentado na etiologia da obesidade, intervenções multiprofissionais que objetivem recuperar as condições de saúde biopsicossociais de pessoas com obesidade são relevantes para a promoção da saúde nessa grande parcela da população brasileira, que já apresenta prevalência de excesso de peso de 61,4% e obesidade de 24,3%, em pessoas com idade igual ou superior a 18 anos (BRASIL, 2023).

4. OBJETIVOS

4.1 Objetivo Geral

Analisar os efeitos de uma intervenção multiprofissional sobre parâmetros de aptidão física relacionados a saúde e biomarcadores de pessoas com excesso de peso e obesidade, após alta da COVID-19 em diferentes graus de comprometimento.

4.2 Objetivos Específicos

1) Analisar aspectos relacionados ao cuidado aos indivíduos com excesso de peso ou obesidade na COVID-19 (via revisão de literatura – revisão sistemática).

2) Investigar os efeitos de uma intervenção multiprofissional em pessoas com excesso de peso e/ou obesidade, após alta da COVID-19, sobre a aptidão física

relacionada à saúde, respostas hemodinâmicas e biomarcadores.

3) Verificar os efeitos de uma intervenção multiprofissional em pessoas com excesso de peso e/ou obesidade, após a alta da COVID-19, na aptidão física relacionada à saúde e biomarcadores, sobre as diferentes sintomatologias (casos leves, moderados e graves).

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CAPÍTULO II

Artigo 1: "*OBESITY AS A RISK FACTOR FOR COMPLICATIONS AND MORTALITY IN INDIVIDUALS WITH SARS-COV-2: A SYSTEMATIC REVIEW*"

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OBESITY AS A RISK FACTOR FOR COMPLICATIONS AND MORTALITY IN INDIVIDUALS WITH SARS-COV-2: A SYSTEMATIC REVIEW

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Abstract

This systematic review aimed to analyze the available studies that identified overweight and/or obesity as a risk factor for mortality, use of respiratory support, and changes in biochemical markers in adults hospitalized with SARS-CoV-2. Using PRISMA guidelines, PubMed, Web of Science, and Scopus databases were searched until January 2024. The protocol was registered with PROSPERO (code: CRD42024501551). Of the 664 articles, only 8 met the inclusion criteria (e.g., adult individuals aged 18 or over diagnosed with COVID-19 individuals with overweight and/or obesity). In addition, the Downs & Black tool was used to assess the quality of the studies). The studies analyzed totaled 9,782 adults hospitalized for COVID-19, indicating that overweight and obesity are present in more than half of adults. Diseases such as diabetes mellitus and hypertension are more prevalent in adults with obesity. The systematic review also highlighted that a higher incidence of respiratory support is related to a higher incidence of hospitalization in intensive care units and that adults with overweight and obesity have a higher risk of mortality from COVID-19. Biochemical markers such as procalcitinin, C-reactive protein, and interleukin-6 are associated with the severity of COVID-19 infection. This systematic review exposed overweight and/or obesity as a risk factor for COVID-19 worsening COVID-19, as well as for the need for intensive care, respiratory support, mortality, and changes in essential blood markers.

Keywords: COVID-19; Overnutrition; Hospitalization; Oxygen Inhalation Therap; Clinical Laboratory Techniques.

1. Introduction

In recent years, the infection caused by the SARS-CoV-2 virus has caused one of the biggest public health problems in the world [1]. The pandemic spread rapidly and caused several health problems, resulting in excess morbidity and mortality, reaching 6.881.955 deaths [2,3]. COVID-19 is characterized by infection of the respiratory tract, flu-like symptoms are predominant; however, the infection can affect several areas (i.e., social, psychological, economic, and educational, among others), leading to cardiovascular (vasculitis, venous thrombosis, acute myocardial infarction and myopericarditis) and pulmonary (pulmonary embolism, pulmonary fibrosis, pleurisy and pneumonia) sequelae [4,5], as well as psychological sequelae, substantially affecting mental health [6].

The rapid and intense replication of SARS-CoV-2 deregulates the immune system, increasing the production of pro-inflammatory cytokines contributing to the pathogenesis of COVID-19 [7]. In addition to high cytokine levels, laboratory tests related to hyperinflammation and tissue damage have been identified as predictors of disease severity [8]. Clinical studies have shown that altered levels of some blood markers may be related to the severity and mortality of individuals with COVID-19 [9].

The angiotensin-converting enzyme 2 (ACE2), the receptor used by SARS-CoV-2 to enter the host's cells, is widely distributed throughout the human body, targeting various organs, so the blood markers used to attest to the efficiency of these organs are altered [9,10]. The expression of ACE2 in pancreatic cells makes the pancreas a target for the virus, which can cause damage to the pancreatic islets, resulting in acute diabetes, and to the exocrine glands, causing acute pancreatitis, thus altering their blood markers [11]. Altered fasting glucose facilitates the hyperinflammation observed in the cytokine storm due to the deregulation of the innate immune system [11]. Elevated levels of inflammatory markers, such as C-reactive protein (CRP), have also been observed in individuals with COVID-19, as well as changes in renal markers due to the high expression of ACE2 in glomerular cells [12].

Although COVID-19 is a multisystem disease, obesity has been associated with the worst prognosis for this disease, supposedly as a result of inflammation, hormonal dysregulation, and indirectly through underlying diseases such as hypertension and diabetes [13-14]. Therefore, obesity has been reported as a significant risk factor for the SARS-CoV-2 virus [2]. As a result, these changes may predestine the management of COVID-19 disease [1]. The myriad concerns around the world have prompted public health providers to work to minimize the harmful effects and mitigate the impact of increased morbidity and mortality associated with COVID-19 infection in people with obesity, as some studies show that hospitalization, mortality, and mechanical ventilation rates are increased in individuals with overweight [13,15]. In addition, class II obesity ($\geq$ 35 kg/m^2) was associated with a higher risk of ICU admission and the need for IMV [16]. The risk of mortality in individuals with obesity was higher compared to the non-obesity population [15].

Given the aspects listed, it is emphasized that the impacts of COVID-19 on people with obesity go beyond the increased risk for severe cases of the disease [17]. In this sense, people with obesity hospitalized for COVID-19 tend to lose a large proportion of lean mass due to physical inactivity, hospital nutritional therapy, as well as low-grade

inflammation [18]. In addition, there is also a reduction in cardiorespiratory capacity in people with obesity hospitalized for COVID-19 [19-21]. Considering the above, this systematic review aimed to analyze the available studies that identified overweight and/or obesity as a risk factor for mortality, use of respiratory support, and changes in biomarkers in adults hospitalized with SARS-CoV-2.

2. Materials and Methods

2.1. *Protocol and registration*

The conduct of this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol [22], which correspond to a checklist of 27 items designed to facilitate the development and reporting of a robust protocol for systematic reviews or meta-analyses. The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under: CRD42024501551.

2.2. *Inclusion and Exclusion Criteria*

The inclusion criteria for this systematic review were: *(i)* original articles written in English, Spanish, or Portuguese; *(ii)* published until January 2024; *(iii)* that recruited adult individuals aged 18 or over of both sexes; *(iv)* that included individuals who were overweight and/or obesity, according to the definitions presented by the studies based on BMI; *(v)* that included hospitalized individuals with a confirmed diagnosis of COVID-19 by real-time polymerase chain reaction (real-time PCR); *(vi)* that presented studies with an experimental design: cross-sectional, retrospective and/or prospective; *(vii)* that the object of study included individuals with overweight and/or obesity as a risk factor for COVID-19 complications; and *(viii)* studies with 60% or more of the total score on the Downs & Black scale was determined for more considerable reliability of the results [23,24]. On the other hand, the exclusion criteria were: *(i)* duplicate articles; *(ii)* case studies; *(iii)* Mendelian randomization analysis; *(iv)* studies linking COVID-19 with other underlying diseases (cancer, diabetes mellitus, hepatic steatosis, cardiovascular diseases, polycystic ovary, anorexia, influenza, human immunodeficiency virus, tuberculosis) or with pregnant women; *(v)* studies with associated interventions (e.g. psychological intervention, bariatric surgery), psychological intervention, bariatric surgery; vaccination; nutritional therapy/support); and *(vi)* studies with partial data from individuals without COVID-19.

2.3. *Search Strategy*

The search process was conducted in January 2024, using PubMed, Web of Science (core Collection) and Scopus. The Medical Subject Headings (MeSH) of the National Library of Medicine of the United States of America used unbiased language terms related to COVID-19, obesity, and biomarkers. The search string used was as follows: ("biomarkers" OR "inflammation" OR "lipid metabolism" OR "lipid metabolism disorders" OR "diabetes mellitus" OR "glycemic control" OR "C-reactive protein" OR "kidney function tests" OR "liver function tests" OR "electrolytes" OR "pancreatic function tests") AND ("COVID-19" OR "SARS-CoV-2" OR "post-acute COVID-19 syndrome") AND ("body composition" OR "body fat" "sarcopenia" OR "muscle strength" OR "muscles" OR "body mass index" OR "nutritional status" OR "anthropometry") AND ("obesity" OR "obesity, abdominal" OR "overweight" OR "excess weight"). Citation alarms were set so that the principal researcher automatically received emails about the latest updates to the search terms used in the database (to include the most recent studies in the review). These updates were received daily (if available), and the studies were eligible for inclusion until the start of manuscript preparation (January 11, 2024). After the formal systematic searches, additional manual searches were carried out by consulting the reference lists of the included studies, and previous reviews and meta-analyses were reviewed to detect studies potentially eligible for inclusion.

2.4. *Study selection and data extraction*

The studies were exported to the EndNote reference manager (version X9, Clarivate Analytics, Philadelphia, PA, USA). Three authors (MPPSL, DCSM, and BHMB) carried out the process independently. Possible disagreements between reviewers on study conditions were resolved by a fourth author (PV-B). Subsequently, potentially eligible studies were reviewed in full text, and the reasons for excluding those not meeting the selection criteria were reported. Data (authors and year of publication, country of origin of the study, study design, study period, age group or the average age of the sample, gender, sample size, mortality rate, nutritional status, use of respiratory support, biomarkers, and main results obtained) from the studies were extracted by three authors (MPPSL, DCSM, and BHMB) independently, using a form created in Microsoft Excel (Microsoft Corporation Redmond, WA, USA).

2.5. *Methodological quality assessment*

This phase aimed to detect the methodological quality in the selected studies through the Downs & Black [25] tool, which could eventually lead to the exclusion of the selected studies. Two authors (MPPSL and DCSM) carried out this process independently. A third author (BHMB) resolved possible disagreements between the reviewers. This reliable tool has been widely used in health research [25]. The instrument consists of 27 items, relating to reporting (10 items), external validity (3 items), internal validity bias (7 items), internal validity confounding (selection bias) (6 items) and statistical power (1 item), allowing a study to be rated between 0 and 32 points. The complete list is usually applied for randomized studies, while for non-randomized studies, it is reduced to 17 criteria after excluding items 9, 13, 14, 17, 19, 22, 23, 24, 26, and 27, which are not applicable in non-randomized studies, with a maximum score of 17 points [26]. In this way, the original non-randomized controlled trials and descriptive studies positively evaluated in 60% (10 points or more out of 17) criteria were selected and included in the subsequent analyses since they presented a moderate to high methodological quality [23,25,26].

2.6. *Data Extraction*

The following data was obtained and analyzed from the selected studies: *(i)* authors and year of publication, *(ii)* country of origin of the study, *(iii)* study design, *(iv)* study period, *(v)* age group or the average age of the sample, *(vi)* gender, *(vii)* sample size, *(viii)* mortality rate, *(ix)* nutritional status, *(x)* use of respiratory support, *(xi)* biomarkers, and *(xii)* main results obtained.

3. Results

3.1. *Study Selection*

The search process is shown in Figure 1. A total of 664 records were found in the study identification phase in PubMed (n = 316), Web of Science (n = 311), and Scopus (n = 37). In the screening phase, duplicate studies (n = 236) and non-original studies (n = 107) were excluded. A total of 321 full-text studies were analyzed, 185 of which were excluded because they did not meet the object of systematic review, 16 because they were studies with children under 18 years old, 3 because they were studies on medication (drugs), 13 because they were studies related to COVID-19 vaccination, 4 studies were not retrieved, and 65 studies were excluded because they were relating COVID-19 to other underlying diseases. The remaining 35 studies were assessed for methodological quality

using the Downs & Black scale. Of them, 27 were excluded due to low methodological quality, leaving 8 studies that met all the selection criteria [27-34].

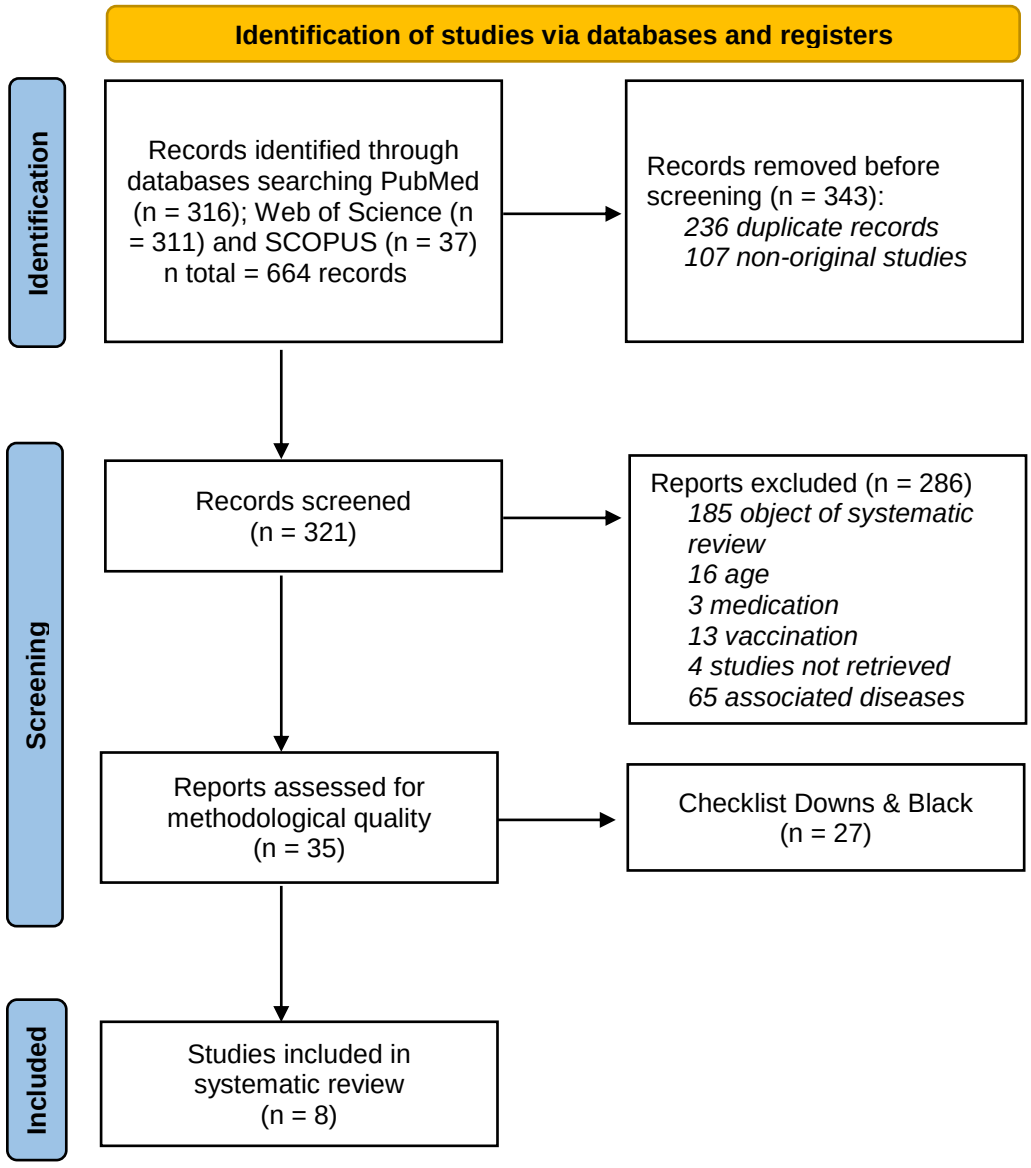

Figure 1. Flowchart of the study selection process*

3.2. *Methodological Quality Assessment*

Of the 35 studies selected for the methodological assessment using the Downs & Black scale [27-61], one study scored 6/17 [35], 3 scored 7/10 [36-38], 11 scored 8/17 [39-49], 12 scored 9/17 [50-61], 7 scored 10/17 [27-30,32-34], and one study scored 11/17 [31]. Only 8 studies obtained 60% or more of the total scale score (17 points) [27-34]; therefore, they were selected to be analyzed in this systematic review (see Supplementary File S1).

3.3. *Study characteristics*

One study was carried out in Serbia [29], one in Turkey [30], one in Brazil [31], one in China [33], and 4 in the United States of America [27,28,32,34]. These studies analyzed nutritional status, use of oxygen support, mortality rate, and biochemical profiles in adults hospitalized with SARS-CoV-2.

Regarding the main comorbidities of COVID-19 positive adults, diabetes mellitus (DM) was also present in 8 studies with a prevalence ranging from 2% to 53% [27-34], chronic obstructive pulmonary disease was present in 8 studies, ranging from 3.2% to 25.6% [27-34], systemic arterial hypertension (SAH) was present in 7 studies, ranging from 31% to 83% [27,29-34], and cardiovascular diseases (acute myocardial infarction, congestive heart failure, chronic heart disease, coronary artery disease, and atrial fibrillation) were also present in 7 studies ranging from 5.3% to 32.5% of the sample [27,28,30-34].

3.4. *Sample characteristics*

The studies analyzed totaled 9,782 adults hospitalized for COVID-19, with an average age of 63.3 years, with 51.1% of male participants and a mortality rate of 17.9%. The characteristics of the studies and the sample are shown in Table 1.

Table 1. Characteristics of the studies and the sample.

Study	Country	Study design	Study period	Age group or mean (years)	Sex (%)	Adults	Mortality (%)
Zahid et al. [27]	United States	Retrospective study	03/2020 - 06/2020	64	F 39.0 M 61.0	1.274	NR
Salvy et al. [28]	United States	Retrospective study	03/2020 - 01/2021	< 65 e ≥ 65	F 48.5 M 51.5	3.861	8.6
Stevanovic et al. [29]	Serbia	Prospective observational study	10/2021 - 12/2021	67	F 37.0 M 63.0	216	16.7
Agca et al. [30]	Turkey	Observational, cross-sectional, and retrospective study	03/2020 - 05/2020	54	F 42.6 M 57.4	284	8.0
Gil et al. [31]	Brazil	Prospective observational study	03/2020 - 10/2020	59.0 ± 15.0	F 50.0 M 50.0	186	6.5
Naaraayan et al. [32]	United States	Retrospective study	03/2020 - 05/2020	71	F 43.4 M 56.6	348	40.5
Zeng et al. [33]	China	Retrospective cohort study	02/2020 - 04/2020	58.5 ± 14.3	F 49.3 M 50.7	3.019	2.2
Nakeshbandi et al. [34]	United States	Retrospective cohort study	03/2020 - 04/2020	68.0 ± 15.0	F 48.0 M 52.0	504	43.0

Note: F = female; M = male; NR = not reported.

3.5. *Categorization by nutritional status and use of respiratory support*

Seven studies analyzed in this systematic review categorized BMI according to the cut-off points adopted by the World Health Organization (WHO) [27-32, 34], in which adults are classified as: *(i)* underweight: < 18.5 kg/m^2, *(ii)* normal weight: 18.6-24.9 kg/m^2, *(iii)* overweight: 25-29.9 kg/m^2, *(iv)* obesity class I: 30-34.9 kg/m^2, *(v)* obesity class II: 35-39.9 kg/m^2 and *(vi)* obesity class III: > 40 kg/m^2 [62]. The study of Zeng et al. [33] is in line with the Chinese consensus on nutritional status, in which underweight is defined as BMI: ≤ 18.5 kg/m^2, normal weight: 18.5-23.9 kg/m^2, overweight: ≥ 24-27.9 kg/m^2 and obesity is defined as: ≥ 28 kg/m^2 [63] (Table 2).

Of the 8 studies selected, only 2 did not report the use of respiratory support [32,33]. The use of respiratory support reached 91.9% of adults hospitalized due to COVID-19 [29]. Stratification of the use of oxygen support occurred in 5 selected studies, with one article reporting the use of mechanical ventilation (MV) in 34% [27] and IMV in 11% of hospitalized adults [30], the use of orotracheal intubation as oxygen support was reported in 2 studies, in 3.6% and 22% of adults respectively [28,34]. Only 1 study stratified respiratory support into more than one type. Gil et al. [31] reported using oxygen therapy in 55.9%, non-invasive mechanical ventilation (NIMV) in 7.5%, and IMV in 3.8% of adults, where the data presented above can be seen in Table 2. Stevanovic et al. [29] found that 91.9% of hospitalized adults used respiratory support, of which 38.4% were overweight and 39.3% were obese. Nakeshbandi et al. [34] found that 74.1% of inpatients were on respiratory support, and 45.9% were obese.

Table 2. Characteristics of nutritional status and use of respiratory support in the studies.

Studies	BMI (mean)	Categorization by BMI	Respiratory support (%)[a]
Zahid et al. [27]	28.7	Overweight, 4.9% Obesity, 42.2%	34.0
Salvy et al. [28]	<65 years: 25.8 ≥65 years: 26.0	Overweight, 30.7% Obesity, 35.6%	3.6
Stevanovic et al. [29]	NR	Overweight, 38.4% Obesity, 39.3%	91.9
Agca et al. [30]	25.9	Overweight, 41.0% Obesity, 24.0%	11.0
Gil et al. [31]	29.5 ± 6.9	Obesity, 40.9%	Oxygen therapy, 55.9 NIMV, 7.5 IMV, 3.8
Naaraayan et al. [32]	NR	Overweight, 35.3% Obesity, 34.8%	NR
Zeng et al. [33]	NR	Overweight, 38.6%	NR

		Obesity, 13.2%	
Nakeshbandi et al. [34]	NR	Overweight, 30.0% Obesity, 43.0%	22.0

Note: BMI = body mass index, NIMV = non-invasive mechanical ventilation, IMV = invasive mechanical ventilation, NR = not reported; a = respiratory support results represent the whole group, without division by BMI.

3.6. *Biochemical and hematological markers*

Blood biochemical markers were present in 6 studies (Table 3), with C-reactive pro-tein (CRP) showing a variation in the results measured in patients, with values ranging from 2.33 mg/L to 100 mg/dL, being the most cited in the analyzed studies [28,30-34], followed by D-Dimer present in 5 studies, with results ranging from 2383.8 ng/mL to 1.5 mg/dL [27,30-33], lactate dehydrogenase (LDH) present in 4 studies with results ranging from 179.10 U/L to 780 U/L [27,29,30,33], ferritin in 3 studies [27,29,30] and creatinine in 3 studies [27,31,33] with results ranging from 219.8 ng/mL to 877 ng/mL, and 64.5 µmol/L to 1.4 mg/dL, respectively. Albumin [30,33], fasting blood glucose [30,33], urea [31,33] and procalcitonin (PCT) [29,30], both markers present in 2 studies each, with results of 31.26 g/L and 39 g/dL; 4.89 mmol/L and 127 mg/dL; 51.8 mg/dL and 4.41 mmol/L; 0.089 µg/L and 0.142 µg/L respectively. The biochemical markers analyzed in three studies were alanine aminotransferase (ALT) (23.3 U/L) [33], aspartate aminotransferase (AST) (19.8 U/L) [33], total bilirubin (9.50 U/L) [33], interleukin-6 (IL-6) (67.0 pg/mL) [29], gamma-glutamyl transferase (GGT) (30.2 U/L) [33], fibrinogen (6.59) [29], calcium (8.86 mmol/L) [29], direct bilirubin (3.30 U/L) [33], uric acid (287.43 µmol/L) [33], prothrombin time (PT) (12.83 seconds) [33], partially activated thromboplastin time (aPTT) (28.03 seconds) [33] and Hemoglobin A1c (6.6%) [27].

The hematological markers were present in 4 studies (Table 3), with the absolute lymphocyte count [27,30,31,33], with values of $1.3x10^3/mm^3$, $1.2x10^9/L$, 26.28% and 0.9 K/µl respectively, the absolute neutrophil count [27,30,31,33], with values of $6.6x10^3/µL$, $3.78x10^9/L$, 63.3% and 6.1 K/µl respectively, hemoglobin [30,31,33] with values of 12.6 g/L, 123.93 g/L and 13.2 g/dL respectively, and absolute total leukocyte count in 3 studies [27,30,33] with results of $5.70x10^9/L$, $5.9x10^9/L$ and 7.7 K/µl respectively. Only 4 studies did not analyze blood parameters [28,29,32,34].

Table 3. Characteristics of the biochemical markers and hematological markers in the studies.

Studies	Laboratory tests
Zahid et al. [27]	Biochemical markers = CRP: 112 mg/L - creatinine: 1.2 mg/dL - LDH: 484 µ/L - D-dimer: 524 ng/mL - ferritin: 756.05 ng/mL - Hemoglobin A1c: 6.6% Hematological markers = leukocytes: 7.7 K/µl - lymphocytes: 0.9 K/µl - neutrophil: 6.1 K/µl
Salvy et al. [28]	NR
Stevanovic et al. [29]	Biochemical markers = CRP: 100.0 mg/dL - IL-6: 67.0 pg/mL - ferritin: 877.0 ng/mL - LDH: 780.0 U/L - fibrinogen: 6.59 - PCT: 0.142 µg/L
Agca et al. [30]	Biochemical markers = Glycemia: 127.0 mg/dL - albumin: 39.0 g/dL - calcium: 8.86 mmol/L - LDH: 267.0 U/L - D-dimer: 0.61 µd/L - CRP: 47.7 mg/mL - PCT: 0.089 µg/L - ferritin: 219.8 ng/mL Hematological markers = leukocytes: 5.9 10^9/L - Hb: 13.2 g/dL - platelets: 214 10^9/L - lymphocytes: 1.2 10^9/L - neutrophil: 3.78 10^9/L
Gil et al. [31]	Biochemical markers = CRP: 92.3 mg/dL - urea: 51.8 mg/dL - D-dimer: 2383.8 ng/mL - creatinine: 1.4 mg/dL Hematological markers = Hb: 12.6 g/L - neutrophil: 6.6 10^3/mm³ - lymphocytes: 1.3 10^3/mm³ - platelets: 255.8 10^3/mm³
Naaraayan et al. [32]	Biochemical markers = CRP: 176.4 mg/L - D-dimer: 1.5 mg/dL
Zeng et al. [33]	Biochemical markers = CRP: 2.33 mg/L - uric acid: 287.43 µmol/L - creatinine: 64.5 µmol/L - glycemia: 4.89 mmol/L - urea: 4.41 mmol/L - albumin: 37.26 g/L - ALT: 23.30 U/L - AST: 19.80 U/L - GGT: 30.20 U/L - LDH: 179.10 U/L - TBIL: 9.50 U/L - DBIL: 3.30 U/L - TP: 12.83 seg. - TTPa: 28.03 seg. - D-dimer: 0.42 mg/L Hematological markers = leukocytes: 5.70 10^9/L - Hb: 123.93 g/L - platelets: 234.01 10^9/L - lymphocytes: 26.28% - neutrophil: 63.3%
Nakeshbandi et al. [34]	NR

Note: PCT = procalcitonin, LDH = lactate dehydrogenase, CRP = reactive protein C, IL-6 = interleukin-6, Hb = hemoglobin, ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase; TBIL = total bilirubin, DBIL = direct bilirubin, PT: prothrombin time, TTPa = partially activated thromboplastin time, NR = not reported.

4. Discussion

Considering that this systematic review aimed to analyze the available studies that

identified overweight and/or obesity as a risk factor for mortality, use of respiratory support, and changes in biochemical markers in adults hospitalized with SARS-CoV-2. The following outcomes in this systematic review were observed: *(i)* male adults are more likely to be admitted to hospital; *(ii)* overweight and obesity were present in more than half of all adults of the analyzed studies; *(iii)* pre-existing diseases were more prevalent in adults with obesity; *(iv)* hypertension is the main comorbidity found among adults with COVID-19; *(v)* diabetes mellitus was the second most common comorbidity among adults; *(vi)* it was observed that a higher incidence of respiratory support use was related to a higher incidence of ICU admission; *(vii)* adults with overweight or obesity had an increased risk of mortality from COVID-19 and (viii) inflammatory markers such as PCT, CRP and IL-6 are associated with the severity of COVID-19 infection

Our systematic review was based on data from 8 studies with COVID-19 positive adults [27-34]. All the selected studies showed that males are more likely to be admitted to hospital, around 51.1% of all adults with COVID-19. Similar results were also presented by Huang et al. [64], who found that males are more likely to be infected than females. This response may occur because the sex hormone may play a role in the expression of the ACE2 receptor [65]. Older people and adults with pre-existing diseases are more susceptible to SARS-CoV-2, which may be associated with a higher frequency of comorbidities [66].

Chronic diseases, such as obesity, share several standard characteristics with infectious diseases, such as a pro-inflammatory state and attenuation of the innate response [67]. According to the WHO, obesity is a pandemic [68]. Estimates for global levels of overweight (BMI $\geq$ 25 kg/m^2) suggest that more than 4 billion people could be affected by 2035, reflecting an increase from 38% of the world's population [69]. Obesity (BMI $\geq$ 30 kg/m2) alone will increase from 14% to 24% of the population over the same period, so one in four people will live with the disease [69]. In the Americas, 47% of all men and 49% of all women will be obese by 2035 [69]. In the European region, 35% of all women and 39% of men will be obese in the same period [69]. The projected annual growth of adults with obesity between 2020 and 2035 is 28%, which could cause a financial impact on the health sector of 19.2 billion dollars in 2035 [69]. Overweight and obesity will likely cost the global economy more than 4 trillion in potential income by 2035, almost 3% of global gross domestic product (GDP) [69].

Obesity is associated with a poor prognosis of COVID-19; excess body fat reduces the response to antiviral agents through deficient functions of T cells and macrophages

[70]. The risk of health problems and death from COVID-19 is up to 4 times higher in adults with obesity [71]. Studies have shown the prevalence of hospitalization of individuals with obesity COVID-19. Rottoli et al. [72] analyzed that 36.5% of hospitalized adults were overweight, and 21.6% were obese. In turn, Petrilli et al. [73] overweight and obesity accounted for 34.3% and 32.8% of inpatients, respectively. Gao et al. [74] described a 12% increase in the risk of severe COVID-19 for each unit increase in BMI. In this systematic review, overweight and obesity were present in more than half of adults, with values ranging from 30% to 41% and 13.2% to 43%, respectively.

As previously described, obesity is a risk factor for the onset of other diseases, and these comorbidities are mainly responsible for increased mortality rates, decreased life expectancy, and quality of life, and when associated with COVID-19, can lead to the development of severe COVID-19. Paravidino et al. [75] described that comorbidities for both adults aged < 60 years and ≥ 60 years were more prevalent in adults with normal weight/overweight or obesity, with hypertension (55% and 77.9%) and diabetes mellitus (31.4% and 48.7%) respectively standing out. Adults with multiple underlying medical conditions have a higher risk of severe COVID-19 diseases [76]. In this systematic review, the comorbidities of adults with COVID-19 were analyzed, but only three studies analyzed the correlation between BMI and comorbidities. The studies reported that all pre-existing diseases were more prevalent in adults with obesity compared to the overall study population [30,33,34].

Systemic arterial hypertension (SAH) is currently the leading risk factor for morbidity and mortality worldwide and is a condition often observed in association with obesity [77,78]. Hypertension is the most frequent comorbidity in adults with COVID-19 and has been identified as a significant risk factor for the increased severity and mortality associated with COVID-19 [76]. Hypertension plays a vital role in regulating the renin-angiotensin-aldosterone system (RAAS) and immune responses, leading to the release of cytokines and increased inflammation [79]. Obesity aggravates hypertension by activating the RAAS, leading to increased formation of angiotensin II, which induces vasoconstriction and aldosterone production, leading to salt and water retention [77]. A study analyzing 138 hospitals in China showed that the prevalence of hypertension was 31.2% among adults with COVID-19; in addition, 58.3% of hypertensive adults were admitted to the ICU, compared to 21.6% of normotensive adults [80]. A French study included 134,209 adults hospitalized with COVID-19, where 49.6% had hypertension and one in four had obesity (23.9%). IMV was recurrent in hospitalized adults with obesity [81]. This

systematic review shows that hypertension is the main comorbidity found among adults with COVID-19, with values ranging from 62% to 67.6%, but none of these studies correlated the prevalence of hypertensive adults with BMI [27,29,31,32]. In contrast to previous studies, Agca et al. [30], Zeng et al. [33], and Nakeshbandi et al. [34] correlated hypertension with BMI, with values ranging from 27% to 85% for overweight people and 44% to 87% for people with obesity.

In addition to SAH, studies have reported a higher risk of severe COVID-19 in diabetic adults due to the impairment of the immune system [82,83]. Diabetes mellitus (DM) is a chronic syndrome of multiple etiology resulting from the lack and/or inability of insulin to exert its effects adequately [84]. Diabetic adults have increased ACE2 expression, leading to a higher risk of infection by the COVID-19 virus since ACE2 is the receptor for SARS-CoV-2 [85]. ACE2 is expressed in pancreatic beta cells, which are responsible for hormones such as insulin, which control blood glucose [86]. In addition, furin protease, which mediates furin endoprotease and cleaves the virus's S protein, is expressed at high levels in diabetic patients [84,87].

The results showed that DM was the second most common comorbidity found in this systematic review, with the incidence of DM in adults with obesity ranging from 20.6% to 57% [27,30,33,34]. A previous meta-analysis of 33 studies with 16,003 adults showed that diabetic adults with COVID-19 are twice as likely to develop severe COVID-19 and die compared to non-diabetics. They are thus more likely to develop Acute Respiratory Distress Syndrome (ARDS), need IMV, and be admitted to the ICU [88]. Another meta-analysis of 40 studies involving 18,012 adults with COVID-19 showed that DM leads to a 2.3-fold increase in symptom severity and a 2.5-fold increase in mortality associated with COVID-19 [89].

The increase in respiratory complications resulting from COVID-19, the need for ICU admission, and the use of mechanical ventilation appear to be associated with increased BMI [90]. Physiologically, increased body weight increases mechanical pressure on the chest and abdomen, thus compromising lung function [91]. Thus, oxygen consumption decreases and, consequently, causes a decrease in expiratory reserve volume, functional capacity, and lung compliance [92,93]. The abnormal release of cytokines in obesity can impair the immune response and influence the lung parenchyma and bronchi [94].

A retrospective cohort study of 200 COVID-19 positive adults seen in a United States emergency room found that adults with severe obesity were more likely to undergo

in-tubation as BMI progressed, with 16.4% of adults with a BMI ≥ 25 kg/m^2 and 34.8% of adults with a BMI ≥ 35 kg/m^2 undergoing intubation [95]. Simonnet et al. [96] confirmed the results found previously; the proportion of adults who required IMV increased with BMI categories and was higher in adults with BMI ≥ 35 kg/m^2, reaching almost 90% of adults. A systematic review supporting the above information found that the rate of oxygen support use ranged from 3.6 to 91.9%, where the higher incidence of oxygen support use was related to a higher incidence of ICU stay [29]. Nakeshbandi et al. [34] observed that the highest prevalence of intubation is related to overweight and adults with obesity, with an incidence of 24% and 28%, respectively.

Obesity is known to contribute to an increased risk of severity and mortality from COVID-19 infection [15]. Obesity alters the mechanical properties of the lungs and chest wall, thus promoting fibrosis, contraction, and vasoconstriction [97,98]. Obesity can also increase the inflammatory process caused by COVID-19 by up-regulating cytokines, contributing to worse outcomes in adults with COVID-19 [99,100]. In addition, increased production of these cytokines is associated with alveolar damage [101]. Obesity is associated with hypercoagulation and an increased risk of arterial thrombosis and venous thromboembolism [102,103]. Finally, increased expression of ACE2 receptors in adipose tissue increases susceptibility to SARS-CoV-2 infection, risk of severe disease, and mortality in adults with obesity [104,105].In our systematic review, overweight or adults with obesity had an increased risk of mortality from COVID-19, with values ranging from 4% to 40% in adults with obesity; however, a higher rate in overweight adults, reaching 54% of deaths [30,33,34]. In a study covering 142 countries, a robust positive association was observed between the percentage of adults with obesity populations and COVID-19 mortality [106]. In another cohort study involving 200 adults, it was observed that during hospitalization, 24% died, with higher rates among adults with severe obesity (34.8%) [95]. In another American study, similar results were also observed, with severe obesity being associated with higher mortality from COVID-19 [107].

Finally, several biomarkers are being used to predict the severity of COVID-19. Inflammatory markers such as PCT, CRP, and IL-6 are reported to be associated with the severity of COVID-19 infection [108]. Markers such as ferritin, D-dimer, LDH, liver enzymes (ALT, AST, GGT, alkaline phosphatase (ALP) and total bilirubin), and kidney functions (creatinine, albumin, and total serum protein) are also monitored in patients suffering from COVID-19 [109]. Increased pro-inflammatory cytokines, such as IL-6 and TNF-α, have been observed in adults with severe COVID-19 and are significantly

associated with mortality [110]. PCT is an inflammatory marker of the critical phase of COVID-19 infection; high PCT values have been associated with an approximately five-fold increased risk of severe COVID-19 [109]. The many pathological processes in COVID-19 include hyper-inflammation, cytokine storms, and deregulation of the coagulation pathway, among others. Therefore, Laboratory tests can help assess the prognosis of the disease, determine appropriate therapeutic options, and scrutinize the response to treatment.

Adults with COVID-19 are likely to need rehabilitation intervention during and directly after hospitalization [111]. Rehabilitation is a multidisciplinary intervention that aims to improve functional capacity, increase quality of life, facilitate social reintegration after hospitalization, reduce persistent symptoms, and improve the ability to perform activities of daily living [112]. Sordi et al. [113] evaluated the effect of a multi-professional intervention (nutritional, psychoeducational, and physical exercise intervention) on body composition, physical fitness, and biochemical markers in overweight COVID-19 survivors (BMI $\geq$ 25kg/m^2) with different symptoms. After the interventions, the authors re-ported that the moderate COVID-19 group showed improvement in dynamic muscle strength of lower and upper limbs, maximum lumbar isometry - traction force, flexibility, markers such as albumin, CRP, fasting glycemia and triglycerides, for the severe COVID-19 group, improvements were seen in dynamic muscle strength lower limbs and lower CRP and triglyceride values, and for the control group, improvements were seen in abdominal repetitions, a reduction in CRP, fasting glucose, TC and triglycerides.

In another study, Perli et al. [21] assessed the body composition, cardiorespiratory fitness, and long-term symptoms of overweight adults affected by COVID-19. The most prevalent long-term symptoms were memory deficit (66.7%), lack of concentration (51.7%), fatigue (65.6%) and dyspnea (40%). The Bruce test showed a time effect with increased distance covered after 1 year only for the severe/critical group. Percutaneous oxygen saturation (SpO_2) was significantly lower in the severe/critical group up to 5 min after the Bruce test when compared to the mild group, and diastolic blood pressure at the end of the Bruce test was significantly higher in the severe/critical group when compared to the mild group. A time effect was observed for body composition, with increased lean mass, skeletal muscle mass, fat-free mass, and lean mass only for the severe/critical group. Because of this, multi-professional interventions can be an efficient tool for reversing the inflammatory process and promoting improvements in daily living activities and quality of

life [21].

Among the limitations of this systematic review are *(i)* the populations studied differed in their comorbidities and severity, *(ii)* body weight and height were self-reported or reported by family members at the time of hospital admission, *(iii)* the definition of BMI categories is not consensual, WHO defines overweight as BMI ≥ 25 kg/m^2 and obesity as BMI ≥ 30 kg/m^2. However, the cut-off values for the Chinese population define overweight as BMI 24.0 - 27.9 kg/m^2 and obesity as BMI ≥ 28 kg/m^2, *(iv)* some covariates had missing data, which could have influenced the results, and *(v)* only three studies presented their data according to BMI. In terms of strengths, we found *(i)* methodological quality above 60% in the studies analyzed, *(ii)* methodological processes that followed the PRISMA, PROSPERO, and Downs & Black tools, and *(iii)* the use of three databases: PubMed, Scopus, and Web of Science (core collection).

Consequently, these results may help draw up public health policies, especially in countries with a higher prevalence of individuals with obesity, as well as directing the actions of health professionals towards care aimed at integrality and humanization, promoting educational actions capable of making the population aware of the importance of self-care and healthy lifestyles.

5. Conclusion

This systematic review exposed overweight and/or obesity as a risk factor for the worsening of COVID-19, as well as for the need for intensive care, respiratory support, mortality, and changes in significant blood markers. It should be noted that obesity is a chronic non-communicable disease present in all age groups, that it can be prevented, and that healthy lifestyles can reduce the severity of COVID-19 infection.

Thus, it is understood that health professionals should pay special attention to overweight and obesity individuals. Adopting healthy lifestyles, such as adequate and healthy eating and physical activity, is essential for maintaining and recovering a healthy weight. Individuals hospitalized with obesity must be carefully monitored and managed quickly and effectively so that therapeutic interventions by a multidisciplinary team can be carried out in the best way, promoting a reduction in morbidity and mortality in these individuals.

6. Practical applications

The etiology of obesity is complex and multifactorial, resulting from the

interaction of genes, environment, lifestyle, and emotional factors. It is, therefore, essential to assess the causes that lead people to gain body weight, to investigate possible associated morbidities, and, above all, to discuss actions that seek to promote the health of people with overweight and obesity. All interventions that treat obesity in all its forms must be multidisciplinary. Food and nutritional guidance for people who are overweight and/or obesity, aimed at reducing the consumption of foods rich in sugar and fat, combined with regular physical activity, are essential strategies in the treatment of obesity. Given this, governmental and non-governmental strategies in the early phases of life are recommended to reduce the impact caused by chronic diseases, significantly obesity. Besides that, micro, meso, and macro strategies are recommended with the creation of specialized treatment centers disciplines with an approach about health in general, how to improve health, and how to promote health promotion in primary and secondary education, as well as in the college and university. Many diseases could be avoided by education. Thus, the educational approach should be considered in the life cycle, i.e., children, adolescents, young adults, middle-aged adults, and older adults. Finally, our efforts may also be directed at pregnant women and children (more extended actions), trying to change unhealthy habits and focusing on health education.

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Supplementary File S1. Methodological quality assessment*

Criteria	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Total
AlBahrani et al. [36]	0	1	0	N/D	1	1	0	N/D	1	1	1	N/D	0	1	1	N/D	0	7
Torrego-Ellacuría et al. [37]	1	1	0	N/D	1	0	0	N/D	1	1	0	N/D	0	1	1	N/D	0	7
Tong [38]	1	1	0	N/D	1	0	1	N/D	0	1	0	N/D	0	1	1	N/D	0	7
Tonietto et al. [50]	1	1	1	N/D	1	0	1	N/D	1	1	0	N/D	0	1	1	N/D	0	9
Yamamoto et al. [39]	1	1	0	N/D	1	0	1	N/D	1	1	0	N/D	0	1	1	N/D	0	8
Zahid et al. [27]	1	1	1	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	**10**
Caccialanza et al. [40]	0	1	1	N/D	1	1	0	N/D	1	1	0	N/D	0	1	1	N/D	0	8
Palaiodimos et al. [51]	1	1	1	N/D	1	1	1	N/D	0	1	0	N/D	0	1	1	N/D	0	9
Salvy et al. [28]	1	1	1	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	**10**
Stevanovic et al. [29]	1	1	1	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	**10**
Agca et al. [30]	1	1	1	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	**10**
Al-Salameh et al. [52]	1	1	1	N/D	1	1	0	N/D	1	1	0	N/D	0	1	1	N/D	0	9
Azarkar et al. [41]	0	1	1	N/D	1	1	0	N/D	1	1	0	N/D	0	1	1	N/D	0	8
Cai et al. [53]	1	1	0	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	9
Gao et al. [35]	0	0	0	N/D	0	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	6
Gil et al. [31]	1	1	1	N/D	1	1	1	N/D	1	1	1	N/D	0	1	1	N/D	0	**11**
Jayanama et al. [54]	1	1	0	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	9
Kang et al.[42]	1	1	0	N/D	0	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	8
Le Guen et al. [55]	1	1	0	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	9
Lucar et al. [56]	1	1	0	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	9
Martínez Urbistondo et al. [43]	1	1	0	N/D	0	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	8
Martinuzzi et al. [44]	1	0	1	N/D	0	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	8
McNeill et al. [45]	1	1	1	N/D	0	0	1	N/D	1	1	0	N/D	0	1	1	N/D	0	8
Naaraayan et al. [32]	1	1	1	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	**10**
Ninomiya et al. [57]	1	1	1	N/D	0	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	9
Okauchi et al. [58]	0	1	1	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	9
Pérez-Cruz et al. [46]	1	1	0	N/D	1	1	0	N/D	1	1	0	N/D	0	1	1	N/D	0	8
Ye et al. [59]	0	1	1	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	9
Zeng et al. [33]	1	1	1	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	**10**
Al-Sabah et al. [47]	0	1	0	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	8
Anderson et al. [48]	1	1	0	N/D	1	1	0	N/D	1	1	0	N/D	0	1	1	N/D	0	8

Kaeuffer et al. [60]	1	1	0	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	9
Mostaghim et al. [61]	1	1	0	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	9
Nakeshbandi et al. [34]	1	1	1	N/D	1	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	**10**
Rao et al. [49]	1	0	1	N/D	0	1	1	N/D	1	1	0	N/D	0	1	1	N/D	0	8

* According to the Downs & Black checklist13. N/D: not determined; 1: complies; 0: does not comply. Criteria: 1: Is the hypothesis/objective of the study clearly described? 2: Are the main outcomes to be measured clearly described in the introduction or methods section? 3: Are the characteristics of the patients included in the study clearly described? 4: Are the interventions of interest clearly described? 5: Are the distributions of the main confounding factors in each group of subjects to be compared clearly described? 6: Are the main findings of the study clearly described? 7: Does the study provide estimates of random variability in the data for the main outcomes? 8: Have all important adverse events that may result from the intervention been reported? 9: Have actual probability values (e.g. 0.035 instead of <0.05) been reported for the main outcomes, except when the probability value is less than 0.001? 10: Are the sample selection procedures clearly described? 11: Were the study participants representative of the population from which they were recruited? 12: Was there an attempt to blind those who measured the results of the intervention? 13: Was it clear whether any of the study results were based on data mining (i.e. misuse of data analysis to present them as statistically significant)? 14: Were appropriate statistical tests used to assess the main outcomes? 15: Were accurate (valid and reliable) main outcome measures used? 16: Were patients in different intervention groups (trials and cohort studies) or cases and controls (case-control studies) recruited from the same population? 17: Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?

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3. Author 1, A.; Author 2, B. Title of the chapter. In *Book Title*, 2nd ed.; Editor 1, A., Editor 2, B., Eds.; Publisher: Publisher Location, Country, Year; Volume 3, pp. 154–196.
Unpublished materials intended for publication:
4. Author 1, A.B.; Author 2, C. Title of Unpublished Work (optional). Correspondence Affiliation, City, State, Country. year, *status* (*manuscript in preparation*; *to be submitted*).
5. Author 1, A.B.; Author 2, C. Title of Unpublished Work. *Abbreviated Journal Name* year, *phrase indicating stage of publication* (*submitted*; *accepted*; *in press*).
Unpublished materials not intended for publication:
6. Author 1, A.B. (Affiliation, City, State, Country); Author 2, C. (Affiliation, City, State, Country). Phase describing the material, year. (phase: Personal communication; Private communication; Unpublished work; etc.)
Conference Proceedings:
7. Author 1, A.B.; Author 2, C.D.; Author 3, E.F. Title of Presentation. In *Title of the Collected Work* (if available), Proceedings of the Name of the Conference, Location of Conference, Country, Date of Conference; Editor 1, Editor 2, Eds. (if available); Publisher: City, Country, Year (if available); Abstract Number (optional), Pagination (optional).
Thesis:
8. Author 1, A.B. Title of Thesis. Level of Thesis, Degree-Granting University, Location of University, Date of Completion.
Websites:
9. Title of Site. Available online: URL (accessed on Day Month Year). Unlike published works, websites may change over time or disappear, so we encourage you create an archive of the cited website using a service such as **WebCite**. Archived websites should be cited using the link provided as follows:
10. Title of Site. URL (archived on Day Month Year).
See the **Reference List and Citations Guide** for more detailed information.

Preparing Figures, Schemes and Tables

- File for Figures and Schemes must be provided during submission in a single zip archive and at a sufficiently high resolution (minimum 1000 pixels width/height, or a resolution of 300 dpi or higher). Common formats are accepted, however, TIFF, JPEG, EPS and PDF are preferred.

- *Nutrients* can publish multimedia files in articles or as supplementary materials. Please contact the editorial office for further information.
- All Figures, Schemes and Tables should be inserted into the main text close to their first citation and must be numbered following their number of appearance (Figure 1, Scheme 1, Figure 2, Scheme 2, Table 1, etc.).
- All Figures, Schemes and Tables should have a short explanatory title and caption.
- All table columns should have an explanatory heading. To facilitate the copy-editing of larger tables, smaller fonts may be used, but no less than 8 pt. in size. Authors should use the Table option of Microsoft Word to create tables.
- Authors are encouraged to prepare figures and schemes in color (RGB at 8-bit per channel). There is no additional cost for publishing full color graphics.

Original Images for Blots and Gels Requirements

For the main text, please ensure that:

- All experimental samples and controls used for one comparative analysis are run on the same blot/gel.
- Image processing methods, such as adjusting the brightness or contrast, do not alter or distort the information in the figure and are applied to every pixel. High-contrast blots/gels are discouraged.
- Cropped blots/gels present in the main text retain all important information and bands.
- You have checked figures for duplications and ensured the figure legends are clear and accurate. Please include all relevant information in the figure legends and clearly indicate any re-arrangement of lanes.

In order to ensure the integrity and scientific validity of blots (including, but not limited to, Western blots) and the reporting of gel data, original, uncropped and unadjusted images should be uploaded as Supporting Information files at the time of initial submission.

A single PDF file or a zip folder including all the original images reported in the main figure and supplemental figures should be prepared. Authors should annotate each original image, corresponding to the figure in the main article or supplementary materials, and label each lane or loading order. All experimental samples and controls used for one comparative analysis should be run on the same blot/gel image. For quantitative analyses, please provide the blots/gels for each independent biological replicate used in the analysis.

Supplementary Materials, Data Deposit and Software Source Code

MDPI Research Data Policies

MDPI is committed to supporting open scientific exchange and enabling our authors to achieve best practices in sharing and archiving research data. We encourage all authors of articles published in MDPI journals to share their research data including, but not limited to protocols, analytic methods, raw data, processed data, code, software, algorithms, and study material. The data should be FAIR – findable, accessible, interoperable, and reusable – so that other researchers can locate and use the data.

We recommend that data and code should be deposited in a trusted repository that will allow for maximum reuse (see the Data Preservation section below). If this is not possible, authors are encouraged to share the specific reason in the Data Availability Statement and make this material available upon request to interested researchers. In addition, research materials necessary to enable the reproduction of an experiment should be indicated in the Materials and Methods section. Individual journal guidelines can be found at the journal 'Instructions for Authors' page. Data sharing policies concern the minimal dataset that supports the central findings of a published study. Generated data should be publicly available and cited in accordance with journal guidelines.

MDPI data policies are informed by **TOP Guidelines**.

Where ethical, legal, or privacy issues are present, data should not be shared. The authors should clarify the availability status of the data upon submission and make any limitations or exceptions clear in the Data Availability Statement. Authors should ensure that the data shared is in accordance with consent provided by participants on the use of confidential data. Authors should ensure that the publication of such data does not compromise the anonymity of the participants or breach local data protection laws.

In situations where access is restricted to protect confidential or proprietary information, authors will be requested to clearly explain the restrictions on the dataset and make the data available upon request, with permission for the purposes of peer review.

MDPI recognizes that some institutions and funding agencies only require the retention of research data for a finite period after a project's completion or publication. However, there are no such limits specified within the MDPI Data Availability Policy and, therefore, we encourage the authors to archive their research data through appropriate data repositories or provide us with minimal datasets within Supplementary Material.

Data availability statements

Data availability statements are required for all articles published with MDPI. During the peer-review and editorial decision process, authors can be asked to share existing datasets or raw data that have been analyzed in the manuscript, and whether they will be made available to other researchers following publication. Authors will also be asked for the details of any existing datasets that have been analyzed in the manuscript.

Below are the recommended Data Availability Statements:

Data availability status	**Recommended Data Availability Statement**
Data available in a publicly accessible repository	The data presented in this study are openly available in [repository name, e.g., FigShare] at [doi], reference number [reference number].
Data available in a publicly accessible repository that does not issue DOIs	Publicly available datasets were analyzed in this study. This data can be found here: [link/accession number].
Data available on request due to restrictions (e.g., privacy, legal or ethical reasons)	The data presented in this study are available on request from the corresponding author (accurately indicate status).
3rd Party Data	Restrictions apply to the availability of these data. Data were obtained from [third party] and are available [from

	the authors/at URL] with the permission of [third party].
Embargo on data due to commercial restrictions	The data that support the findings will be available in [repository name] at [URL / DOI link] following an embargo from the date of publication to allow for commercialization of research findings.
Restrictions apply to the datasets:	The datasets presented in this article are not readily available because [include reason, e.g., the data are part of an ongoing study or due to technical/ time limitations]. Requests to access the datasets should be directed to [text input].
Data derived from public domain resources:	The data presented in this study are available in [repository name] at [URL/DOI], reference number [reference number]. These data were derived from the following resources available in the public domain: [list resources and URLs]
Data sharing is not applicable (only appropriate if no new data is generated or the article describes entirely theoretical research.	No new data were created or analyzed in this study. Data sharing is not applicable to this article
Data is contained within the article or supplementary material:	The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.
Dataset available on request from the authors.	The raw data supporting the conclusions of this article will be made available by the authors on request.

Data preservation

MDPI acknowledges that researchers, institutions, journals, and data repositories have a shared responsibility to ensure long-term data preservation, and MDPI encourages authors to select data repositories with this goal in mind.

MDPI encourages authors to commit to preserving their datasets on their laboratory or institutional servers, for at least five years after publication. If, during that time, the repository to which the data were originally submitted disappears or experiences data loss, we may ask the authors to upload the data to another repository and publish a correction or update to the original publication.

If authors remove their data from the original public repository or change access criteria in a manner that is inconsistent with the publication, we may ask authors to notify the editorial office as soon as possible.

How to choose an appropriate data repository

MDPI encourages the submission of data to community-recognized data repositories where possible. We recommend the authors visit **re3data.org** or **fairsharing.org** to help identify registered and certified data repositories relevant to their subject area if no community resource is available. If the authors' institution has its generalist data repository this can be

used to host authors' data as long as the repository can mint **DataCite DOIs**, and allows for data to be shared under open terms of use (for example the **CC0 waiver**).

Data repository criteria

The following criteria should be considered when selecting an appropriate repository, ensuring that platforms:

- Ensure long-term persistence and preservation of datasets in their published form;
- Provide stable identifiers for submitted datasets (DOIs in most cases);
- Allow public access to data without barriers, such as logins or paywalls;
- Support open licenses (CC0 and CC-BY, or their equivalents, are required in most cases);
- Provide confidential review of submitted datasets without the requirement for reviewers to provide identifying information.

Data citation

Authors are encouraged to formally cite any datasets stored in external repositories that are mentioned within their manuscript, including the main datasets that are the focus of the submission, as well as any other datasets that have been used in the work. For previously published datasets, authors should cite both the related research articles and the datasets themselves. Appropriate citation of data is checked and enforced by *Journal Editorial* staff before publication.

Computer Code and Software

For work where novel computer code was developed, authors should release the code either by depositing in a recognized, public repository or uploading as supplementary information to the publication. The name and version of all software used should be clearly indicated.

Supplementary Material

Additional data and files can be uploaded as "Supplementary Files" during the manuscript submission process. The supplementary files will also be available to the referees as part of the peer-review process. Any file format is acceptable, however we recommend that common, non-proprietary formats are used where possible. For more information on supplementary materials, please refer to **https://www.mdpi.com/authors/layout#_bookmark83**.

Unpublished Data

Restrictions on data availability should be noted during submission and in the manuscript. "Data not shown" should be avoided: authors are encouraged to publish all observations related to the submitted manuscript as Supplementary Material. "Unpublished data" intended for publication in a manuscript that is either planned, "in preparation" or "submitted" but not yet accepted, should be cited in the text and a reference should be added in the References section. "Personal Communication" should also be cited in the text and reference added in the References section. (see also the MDPI reference list and citations style guide).

Remote Hosting and Large Data Sets

Data may be deposited with specialized service providers or institutional/subject repositories, preferably those that use the DataCite mechanism. Large data sets and files greater than 60 MB must be deposited in this way. For a list of other repositories specialized in scientific and

experimental data, please consult databib.org or re3data.org. The data repository name, link to the data set (URL) and accession number, doi or handle number of the data set must be provided in the paper. The journal **Data** also accepts submissions of data set papers.

Deposition of Sequences and Expression Data

New sequence information must be deposited to the appropriate database prior to submission of the manuscript. Accession numbers provided by the database should be included in the submitted manuscript. Manuscripts will not be published until the accession number is provided.

- *New nucleic acid sequences* must be deposited into an acceptable repository such as **GenBank**, **EMBL**, or **DDBJ**. Sequences should be submitted to only one database.
- *New high throughput sequencing (HTS) datasets* (RNA-seq, ChIP-Seq, degradome analysis, …) must be deposited either in the GEO database or in the NCBI's Sequence Read Archive.
- *New microarray data* must be deposited either in the GEO or the ArrayExpress databases.The "Minimal Information About a Microarray Experiment" (MIAME) guidelines published by the Microarray Gene Expression Data Society must be followed.
- *New protein sequences* obtained by protein sequencing must be submitted to UniProt (submission tool SPIN).

All sequence names and the accession numbers provided by the databases should be provided in the Materials and Methods section of the article.

References in Supplementary Files

Citations and References in Supplementary files are permitted provided that they also appear in the reference list of the main text.

Research and Publication Ethics

Research Ethics

Research Involving Human Subjects

When reporting on research that involves human subjects, human material, human tissues, or human data, authors must declare that the investigations were carried out following the rules of the Declaration of Helsinki of 1975 (**https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/**), revised in 2013. According to point 23 of this declaration, an approval from the local institutional review board (IRB) or other appropriate ethics committee must be obtained before undertaking the research to confirm the study meets national and international guidelines. As a minimum, a statement including the project identification code, date of approval, and name of the ethics committee or institutional review board must be stated in Section 'Institutional Review Board Statement' of the article.

Example of an ethical statement: "All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of XXX (Project identification code)."

For non-interventional studies (e.g. surveys, questionnaires, social media research), all participants must be fully informed if the anonymity is assured, why the research is being conducted, how their data will be used and if there are any risks associated. As with all research involving humans, ethical approval from an appropriate ethics committee must be obtained prior to conducting the study. If ethical approval is not required, authors must either provide an exemption from the ethics committee or are encouraged to cite the local or national legislation that indicates ethics approval is not required for this type of study. Where a study has been granted exemption, the name of the ethics committee which provided this should be stated in Section 'Institutional Review Board Statement' with a full explanation regarding why ethical approval was not required.

A written informed consent for publication must be obtained from participating patients. Data relating to individual participants must be described in detail, but private information identifying participants need not be included unless the identifiable materials are of relevance to the research (for example, photographs of participants' faces that show a particular symptom). Patients' initials or other personal identifiers must not appear in any images. For manuscripts that include any case details, personal information, and/or images of patients, authors must obtain signed informed consent for publication from patients (or their relatives/guardians) before submitting to an MDPI journal. Patient details must be anonymized as far as possible, e.g., do not mention specific age, ethnicity, or occupation where they are not relevant to the conclusions. A **template permission form** is available to download. A blank version of the form used to obtain permission (without the patient names or signature) must be uploaded with your submission. Editors reserve the right to reject any submission that does not meet these requirements.

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If the study reports research involving vulnerable groups, an additional check may be performed. The submitted manuscript will be scrutinized by the editorial office and upon request, documentary evidence (blank consent forms and any related discussion documents from the ethics board) must be supplied. Additionally, when studies describe groups by race, ethnicity, gender, disability, disease, etc., explanation regarding why such categorization was needed must be clearly stated in the article.

Ethical Guidelines for the Use of Animals in Research

The editors will require that the benefits potentially derived from any research causing harm to animals are significant in relation to any cost endured by animals, and that procedures followed are unlikely to cause offense to the majority of readers. Authors should particularly ensure that their research complies with the commonly-accepted '3Rs [1]':

- Replacement of animals by alternatives wherever possible,
- Reduction in number of animals used, and
- Refinement of experimental conditions and procedures to minimize the harm to animals.

Authors must include details on housing, husbandry and pain management in their manuscript.

MDPI endorses the ARRIVE guidelines (**arriveguidelines.org/**) for reporting experiments using live animals. Authors and reviewers must use the ARRIVE guidelines as a checklist, which can be found at **https://arriveguidelines.org/sites/arrive/files/documents/Author%20Checklist%20-%20Full.pdf**. The journal *Nutrients* requires authors to submit the completed checklist at submission, and it will be made available to reviewers. Editors reserve the right to reject submissions that do not adhere to these guidelines based on ethical or animal welfare concerns, or if the procedure described does not appear to be justified by the value of the work presented.

For further guidance authors should refer to the Code of Practice for the Housing and Care of Animals Used in Scientific Procedures [2], American Association for Laboratory Animal Science [3] or European Animal Research Association [4].

If national legislation requires it, studies involving vertebrates or higher invertebrates must only be carried out after obtaining approval from the appropriate ethics committee. As a minimum, the project identification code, date of approval and name of the ethics committee or institutional review board should be stated in Section 'Institutional Review Board Statement'. Research procedures must be carried out in accordance with national and institutional regulations. Statements on animal welfare should confirm that the study complied with all relevant legislation. Clinical studies involving animals and interventions outside of routine care require ethics committee oversight as per the American Veterinary Medical Association. If the study involved client-owned animals, informed client consent must be obtained and certified in the manuscript report of the research. Owners must be fully informed if there are any risks associated with the procedures and that the research will be published. If available, a high standard of veterinary care must be provided. Authors are responsible for correctness of the statements provided in the manuscript.

If ethical approval is not required by national laws, authors must provide an exemption from the ethics committee, if one is available. Where a study has been granted exemption, the name of the ethics committee that provided this should be stated in Section 'Institutional Review Board Statement' with a full explanation on why the ethical approval was not required.

If no animal ethics committee is available to review applications, authors should be aware that the ethics of their research will be evaluated by reviewers and editors. Authors should provide a statement justifying the work from an ethical perspective, using the same utilitarian framework that is used by ethics committees. Authors may be asked to provide this even if they have received ethical approval.

1. NSW Department of Primary Industries and Animal Research Review Panel. Three Rs. Available online: **https://www.animalethics.org.au/three-rs**
2. Home Office. Animals (Scientific Procedures) Act 1986. Code of Practice for the Housing and Care of Animals Bred, Supplied or Used for Scientific Purposes. Available online: **https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/388535/CoPanimalsWeb.pdf**
3. American Association for Laboratory Animal Science. The Scientific Basis for Regulation of Animal Care and Use. Available online: **https://www.aalas.org/about-aalas/position-papers/scientific-basis-for-regulation-of-animal-care-and-use**

4. European Animal Research Association. EU regulations on animal research. Available online: **https://www.eara.eu/animal-research-law**

Research Involving Cell Lines

Methods sections for submissions reporting on research with cell lines should state the origin of any cell lines. For established cell lines the provenance should be stated and references must also be given to either a published paper or to a commercial source. If previously unpublished *de novo* cell lines were used, including those gifted from another laboratory, details of institutional review board or ethics committee approval must be given, and confirmation of written informed consent must be provided if the line is of human origin.

An example of Ethical Statements:

The HCT116 cell line was obtained from XXXX. The $MLH1^{+}$ cell line was provided by XXXXX, Ltd. The DLD-1 cell line was obtained from Dr. XXXX. The DR-GFP and SA-GFP reporter plasmids were obtained from Dr. XXX and the Rad51K133A expression vector was obtained from Dr. XXXX.

Research Involving Plants

Experimental research on plants (either cultivated or wild) including collection of plant material, must comply with institutional, national, or international guidelines. We recommend that authors comply with the **Convention on Biological Diversity** and the **Convention on the Trade in Endangered Species of Wild Fauna and Flora**.

For each submitted manuscript supporting genetic information and origin must be provided. For research manuscripts involving rare and non-model plants (other than, e.g., *Arabidopsis thaliana*, *Nicotiana benthamiana*, *Oryza sativa*, or many other typical model plants), voucher specimens must be deposited in an accessible herbarium or museum. Vouchers may be requested for review by future investigators to verify the identity of the material used in the study (especially if taxonomic rearrangements occur in the future). They should include details of the populations sampled on the site of collection (GPS coordinates), date of collection, and document the part(s) used in the study where appropriate. For rare, threatened or endangered species this can be waived but it is necessary for the author to describe this in the cover letter.

Editors reserve the rights to reject any submission that does not meet these requirements.

An example of Ethical Statements:

Torenia fournieri plants were used in this study. White-flowered Crown White (CrW) and violet-flowered Crown Violet (CrV) cultivars selected from 'Crown Mix' (XXX Company, City, Country) were kindly provided by Dr. XXX (XXX Institute, City, Country).

Arabidopis mutant lines (SALKxxxx, SAILxxxx,…) were kindly provided by Dr. XXX, institute, city, country).

Clinical Trials Registration

Registration

MDPI follows the International Committee of Medical Journal Editors (ICMJE) **guidelines** which require and recommend registration of clinical trials in a public

trials registry at or before the time of first patient enrollment as a condition of consideration for publication.

Purely observational studies do not require registration. A clinical trial not only refers to studies that take place in a hospital or involve pharmaceuticals, but also refer to all studies which involve participant randomization and group classification in the context of the intervention under assessment.

Authors are required to pre-register clinical trials with an international clinical trials register and cite a reference to the registration in the Methods section. Suitable databases include **clinicaltrials.gov**, **the EU Clinical Trials Register** and those listed by the World Health Organisation **International Clinical Trials Registry Platform**.

Approval to conduct a study from an independent local, regional, or national review body is not equivalent to prospective clinical trial registration. MDPI reserves the right to decline any paper without trial registration for further peer-review. However, if the study protocol has been published before the enrolment, the registration can be waived with correct citation of the published protocol.

CONSORT Statement

MDPI requires a completed CONSORT 2010 **checklist** and **flow diagram** as a condition of submission when reporting the results of a randomized trial. Templates for these can be found here or on the CONSORT website (**http://www.consort-statement.org**) which also describes several CONSORT checklist extensions for different designs and types of data beyond two group parallel trials. At minimum, your article should report the content addressed by each item of the checklist.

Dual Use Research of Concern

MDPI follows the practical framework defined in **Guidance for Editors: Research, Audit and Service Evaluations** and introduced by the Committee on Publication Ethics (COPE). Research that could pose a significant threat, with broad potential consequences to public health or national security, should be clearly indicated in the manuscript, and potential dual-use research of concern should be explained in the cover letter upon submission. Potential areas of concern include but are not limited to biosecurity, nuclear and chemical threats, and research with a military purpose or application, etc. For these manuscripts to be considered for peer review, the benefits to the general public or public health must outweigh the risks. The authors have a responsibility to comply with relevant national and international laws.

Sex and Gender in Research

We encourage our authors to follow the **'Sex and Gender Equity in Research – SAGER – guidelines'** and to include sex and gender considerations where relevant. Authors should use the terms sex (biological attribute) and gender (shaped by social and cultural circumstances) carefully in order to avoid confusing both terms. Article titles and/or abstracts should indicate clearly what sex(es) the study applies to. Authors should also describe in the background, whether sex and/or gender differences may be expected; report how sex and/or gender were accounted for in the design of the study; provide disaggregated data by sex and/or gender, where appropriate; and discuss respective results. If a sex and/or gender analysis was not conducted, the rationale should be given in the Discussion. We suggest that our authors consult the full **guidelines** before submission.

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Potential disputes over borders and territories may have particular relevance for authors in describing their research or in an author or editor correspondence address, and should be respected. Content decisions are an editorial matter and where there is a potential or perceived dispute or complaint, the editorial team will attempt to find a resolution that satisfies parties involved.

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The editors of this journal enforce a rigorous peer-review process together with strict ethical policies and standards to ensure to add high quality scientific works to the field of scholarly publication. Unfortunately, cases of plagiarism, data falsification, image manipulation, inappropriate authorship credit, and the like, do arise. The editors of *Nutrients* take such publishing ethics issues very seriously and are trained to proceed in such cases with a zero tolerance policy.

Authors wishing to publish their papers in *Nutrients* must abide to the following:

- Any facts that might be perceived as a possible conflict of interest of the author(s) must be disclosed in the paper prior to submission.
- Authors should accurately present their research findings and include an objective discussion of the significance of their findings.
- Data and methods used in the research need to be presented in sufficient detail in the paper, so that other researchers can replicate the work.
- Raw data should preferably be publicly deposited by the authors before submission of their manuscript. Authors need to at least have the raw data readily available for presentation to the referees and the editors of the journal, if requested. Authors need to ensure appropriate measures are taken so that raw data is retained in full for a reasonable time after publication.
- Simultaneous submission of manuscripts to more than one journal is not tolerated.
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- If errors and inaccuracies are found by the authors after publication of their paper, they need to be promptly communicated to the editors of this journal so that appropriate actions can be taken. Please refer to our **policy regarding Updating Published Papers**.
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  Reuse of text that is copied from another source must be between quotes and the original source must be cited. If a study's design or the manuscript's structure or language has been inspired by previous works, these works must be explicitly cited.

  All MDPI submissions are checked for plagiarism using the industry standard software iThenticate. If plagiarism is detected during the peer review process, the manuscript may be rejected. If plagiarism is detected after publication, an investigation will take place and action taken in accordance with our policies.

- **Image files must not be manipulated or adjusted in any way** that could lead to misinterpretation of the information provided by the original image.

  Irregular manipulation includes: 1) introduction, enhancement, moving, or removing features from the original image; 2) grouping of images that should obviously be presented separately (e.g., from different parts of the same gel, or from different gels); or 3) modifying the contrast, brightness or color balance to obscure, eliminate or enhance some information.

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Our in-house editors will investigate any allegations of publication misconduct and may contact the authors' institutions or funders if necessary. If evidence of misconduct is found, appropriate action will be taken to correct or retract the publication. Authors are expected to comply with the best ethical publication practices when publishing with MDPI.

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Authors should not cite advertisements or advertorial material.

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Artigo 2: "*EFFECTS OF 8 AND 16 WEEKS OF MULTI-PROFESSIONAL INTERVENTION ON BODY COMPOSITION, PHYSICAL FITNESS, AND BIOMARKERS IN OVERWEIGHT SURVIVORS OF COVID-19: A CLINICAL TRIAL*"

Artigo elaborado conforme as normas do periódico científico: *Medicine.* Disponível em: https://journals.lww.com/md-journal/Pages/Instructions-for-Authors.aspx

EFFECTS OF 8 AND 16 WEEKS OF MULTI-PROFESSIONAL INTERVENTION ON BODY COMPOSITION, PHYSICAL FITNESS, AND BIOMARKERS IN OVERWEIGHT SURVIVORS OF COVID-19: A CLINICAL TRIAL

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COVID-19= Coronavirus-2019

BMI= body mass index

NCDs= chronic non-communicable diseases

CONSORT= *Consolidated Standards of Reporting Trials*

RT-PCR= reverse transcriptase polymerase chain reaction

REBEC= Brazilian Clinical Trials Registry Platform

BP= blood pressure

SBP= systolic blood pressure

DBP= diastolic blood pressure

HR= heart rate

%SpO_2= peripherical oxygen saturation

6MWT= 6-min walk test

EDTA= ethylenediamine tetraacetic acid

HbA1c= glycated hemoglobin

TC= total cholesterol

HDL-c= high-density lipoprotein

LDL-c= low-density lipoprotein

TGL= triglycerides

ALT= alanine aminotransferase

AST= aspartate aminotransferase

GGT= gamma-glutamyl transferase

ALP= alkaline phosphatase

CRP= C-reactive protein

MIHS= maximal isometric handgrip strength

MILTS= maximal isometric lumbar-traction strength

VO_2 peak= peak oxygen consumption

CBT= cognitive behavioral theory

SD= standard deviation

FM= fat mass

BFP= body fat percentage

ACE2= Angiotensin-Converting Enzyme 2

IL= interleukin

IFN-γ= Interferon-gamma

TNF-α= Tumor Necrosis Factor Alpha

aPTT= Activated Partial Thromboplastin Time

PT= prothrombin time

WHO= World Health Organization

ABSTRACT

Objective: To analyze the effects of a multi-professional intervention on body composition, physical fitness, and biomarkers in overweight COVID-19 survivors with different symptomatology.

Methods: This clinical trial included 59 volunteers, allocated into three parallel groups according to SARS-CoV-2 symptomatology [mild group (n=31), moderate group (n=13), and severe group (n=15)]. The groups underwent a multi-professional program consisting of physical exercise, nutritional, and psychoeducation interventions for 16 weeks, and the volunteers performed anthropometric and body composition as the first outcome and physical fitness and biochemical tests as the second outcome. The groups were analyzed by a two-way mixed-measures analysis of variance (before, post-8, and post-16 weeks of intervention).

Results: After the 8 weeks, the following results were observed: significantly higher values ($p<0.05$) for fat-free mass and musculoskeletal mass, as well as significantly lower values ($p<0.05$) for fat mass, body fat percentage, and abdominal circumference ($p<0.05$). For physical tests were observed after 8 weeks of intervention: higher values ($p<0.05$) for maximal isometric handgrip strength, maximal lumbar-traction strength, arm flexion, strength-endurance abdominal repetitions, sit-to-stand test, peak oxygen consumption, and walked distance in 6-min walk test ($p<0.05$). Biochemical tests showed a significant reduction of triglycerides, low-density lipoprotein, and glycated hemoglobin after 8 weeks of intervention ($p<0.05$). No significant differences were observed for 16 weeks of intervention ($p>0.05$). Therefore, 8 weeks of intervention promoted significant improvements in anthropometrics, body composition, physical fitness tests, and a significant reduction in lipid profile and glycated hemoglobin. After 16 weeks, the systolic and diastolic blood pressure significantly reduced in three experimental groups ($p<0.05$).

Conclusion: The multi-professional intervention model promoted benefits for the post-COVID-19 patients, independent of the severity of symptoms.

The study was registered in the Brazilian Clinical Trials Registry Platform (REBEC) under RBR-4mxg57b.

Keywords: Coronavirus; Interdisciplinary Study; Health Promotion.

INTRODUCTION

Part of Coronavirus-2019 (COVID-19) survivors have presented sequelae of respiratory order; physical deconditioning, with loss of musculoskeletal mass and reduced muscle strength and endurance, as well as decreased cardiorespiratory capacity; reduced quality of life; emotional problems, among others.[1] Unlike the signs and symptoms of COVID-19, the complications of acute post-COVID-19 are not well understood.[2] For some persons, complications may affect multiple organs and persist for months, regardless of the severity of the disease at onset. However, persons with a higher degree of COVID-19 involvement have a higher risk of death within 12 months of illness.[3]

The severity of the disease depends on the intensity of the immune response triggered by the virus. Therefore, long-term signs and symptoms are subject to the extent and severity of the viral infection, the organs affected, and the so-called "cytokine storm" during the acute phase of COVID-19.[4] The acute post-COVID-19 syndrome or post-COVID-19 state includes fatigue, dyspnea, chest pain, loss of taste and/or smell, cognitive changes, and arthralgias are factors that affect work and daily functioning for a long time due to COVID-19.[5,6] Thus, rehabilitation strategies for COVID-19 survivors are indispensable to combat a condition with different sequelae and significant impacts on the population, the health of persons, and the economy.[5-8]

It is well established in the scientific literature that obesity is a risk factor for severe COVID-19, with a dose-response relationship between higher body mass index (BMI) and worsening of the disease.[6,7,9] Obesity is a pro-inflammatory disease correlated with the increased prevalence of other chronic non-communicable diseases (NCDs), such as type 2 diabetes mellitus, hypertension, dyslipidemia, and metabolic syndrome, among other pathologies.[10] Therefore, the application of interventions aimed at patient recovery by providing physical activity, healthy eating, and psychoeducation can reduce the sequelae of the disease and the complications resulting from the post-COVID syndrome in overweight persons.[5-8]

In this sense, recovering the health conditions of people with obesity after COVID-19 is urgent and indispensable.[6,7] For this reason, interventions with physical exercise, dietary reeducation, and psychoeducation in post-COVID-19 patients after 8 weeks showed promising responses of multi-professional intervention with a significant reduction (p = 0.003) in C-reactive protein, a significant increase (p = 0.0005) in serum albumin and a significant improvement in the sit-to-stand test in those who were hospitalized.[5] However, the multi-professional intervention for patients surviving

COVID-19 for more than 12 weeks, considering the specific symptoms (mild, moderate, and severe/critical),[11,12] is still unknown to the present study's authors. Therefore, considering the symptoms between the groups may be relevant to promoting assertive interventions and recovery prognoses. Besides that, Sordi et al.[5] observed little changes for the severe group after a multi-professional intervention focused on recovery health-related physical fitness of post-COVID-19 patients.

Therefore, this study aimed to analyze the effects of multi-professional intervention on anthropometry, body composition, physical fitness (health-related physical fitness, flexibility, maximal isometric strength tests, dynamic muscle strength-endurance, cardiorespiratory fitness), and biochemical parameters in overweight and obese COVID-19 survivors after 16 weeks discharge from COVID-19 at different degrees of impairment. Based on previous studies,[5,13] as a primary outcome, the authors of this study propose that the 16 weeks of multi-professional intervention can improve body composition and physical fitness and, as a secondary outcome, biomarkers parameters.

METHODS

Experimental approach to the problem

This study is an uncontrolled parallel-group clinical trial, with repeated measures over 16 weeks, carried out from January to October 2022, following *Consolidated Standards of Reporting Trials* (CONSORT).[14] The experimental groups (mild COVID-19 group, moderate COVID-19 group, and severe/critical COVID-19 group) underwent a multi-professional program consisting of physical exercises (muscle strength and aerobic exercises, i.e., concurrent training), nutritional intervention, and psychoeducation. Participants were assessed at the beginning of the study (pre-intervention), after eight weeks (post-8 weeks), and after 16 weeks of intervention (post-16 weeks). Those interested contact the multi-professional team from the Interdisciplinary Health Promotion Intervention Laboratory in the university facilities.

The assessments included anthropometry, body composition, health-related physical fitness, flexibility, maximal isometric strength tests, dynamic muscle strength-endurance, cardiorespiratory fitness, and biochemical parameters. All assessments were conducted in the morning (between 7:00 and 11:30 h) and in the exact location (laboratory, with the control of variables, temperature, and investigators that applied the devices in pre- and post-assessments). The patients did not present pain before the assessments or during the training sessions, without presenting musculoskeletal and/or

cardiorespiratory injuries during the intervention.

Subjects

Participants were recruited through the Maringá, Paraná, Brazil, Municipal Health Department, the Maringá Municipal Hospital, and TV, radio, and social media advertising. One hundred and forty-six volunteers of both sexes were invited to take part in the study according to the following inclusion criteria: *(i)* male and female participants aged between 19 and 65 years; *(ii)* BMI > 25.0 kg/m^2, *(iii)* positive diagnosis confirmed by RT-PCR (reverse transcriptase polymerase chain reaction) for COVID-19; *(iv)* having received medical authorization to participate in this study; *(v)* have received the first dose of the COVID-19 vaccine; *(vi)* be available to participate in multi-professional interventions twice a week for sixteen weeks; and *(vii)* have contracted COVID-19 between January 2, 2021 and September 22, 2021. Exclusion criteria included the following: *(i)* debilitating neurological diseases (i.e., Alzheimer's or Parkinson's); *(ii)* contraindications for physical exercise; and *(iii)* pregnancy. Following Jensen et al.[15], 15 participants per group would be sufficient for α = 0.05 and β = 0.80%.

The present study was approved by the Local Research Ethics Committee (protocol n° 4.546.726/2021) and followed the Declaration of Helsinki. The study was registered in the Brazilian Clinical Trials Registry Platform (REBEC) under RBR-4mxg57b. All subjects were informed about the purposes of the study and signed an informed consent form.

Procedures

Seventy-five volunteers were accepted to take part in the program and were allocated according to their COVID-19 symptoms (mild, moderate, or severe/critical symptoms) (15), following the groups: mild COVID-19 (n = 41); moderate COVID-19 (n = 18) and severe/critical COVID-19 (n = 16). Baseline measurements were taken over two days. First, the subjects underwent a clinical assessment by a pulmonologist and an intensive care physician, consisting of the participant's clinical history (history of surgery, pre-existing chronic non-communicable diseases, continuous use of medication, main signs and symptoms showing possible sequelae of COVID-19, and type and length of stay in hospital (ward/room or intensive care unit)) (appendix A), anthropometric and body composition assessment, and blood collection for biochemical analyses.

On the second day, the following data were collected: *(i)* blood pressure [BP –

systolic blood pressure (SBP) and diastolic blood pressure (DBP)] after 5 min of rest, according to the VIII Guideline on Arterial Hypertension;[16] *(ii)* measurement of heart rate (HR) and peripherical oxygen saturation (%SpO_2), both at rest; *(iii)* posterior chain flexibility test on the Wells bench (sit and reach test); *(iv)* maximal isometric strength tests with specific dynamometers; *(v)* sit-up test; *(vi)* 30-s chair-stand-test; *(vii)* push-up (adapted) and *(viii)* 6-min walk test (6MWT). After the 6MWT, the following variables were collected: BP, HR, and %SpO_2. All tests are described in the sections below. After the clinical assessment, the self-reported signs and symptoms were considered for the non-randomized allocation of participants in the experimental COVID-19 groups according to the "*Clinical Management of COVID-19: Living Guidance*".[11]

Over the 16 weeks, 16 participants dropped out of the study for different reasons. Figure 1 presents the flowchart of the present study's participants based on the CONSORT Guidelines,[14] and Figure 2 illustrates the methodology used for the 16-week intervention.

Figure 1 near here

Figure 2 near here

Anthropometry and Body Composition

The participants' height was measured using a stadiometer attached to a scale with a capacity of 2.2 m and an accuracy of 0.1 cm (Welmy R-110®, Santa Bárbara D' Oeste, São Paulo). Abdominal circumference was measured using a tape measure (model T87-2®, Florianópolis, Santa Catarina, Brazil), with a measuring capacity of 2 meters and precision of 0.1 cm, following the specifications proposed by Heyward.[17] The participant's body composition was measured using tetrapolar bioimpedance (*InBody* 570®, Biospace Co Ltd., Seoul, Korea), with a capacity of 250 kg and an accuracy of 100 g, according to the manufacturer's instructions, following recommendations to improve validity.[18] All participants were previously instructed on the recommendations. The following parameters were measured: BMI (kg/m^2), lean mass (kg), fat mass (kg), body fat percentage (%), and skeletal muscle mass (kg).[19]

Biochemical analyzes

The blood collection procedures followed the guidelines of the Clinical and Laboratory Standards Institute.[20] Participants were previously instructed on how to prepare for the collections that took place at the Clinical Analysis Laboratory of the University facilities, and after collection, participants were instructed to press on the puncture site to avoid bruising. The collected blood samples were dispensed into Vacuplast® collection tubes containing stacking gel with an activator and tubes with the anticoagulant ethylenediamine tetraacetic acid (EDTA) K2. Subsequently, to obtain serum, the samples containing an activator were centrifuged in a Centrilab® analog centrifuge at 3.500 rpm (relative centrifugal force) for 15 minutes at room temperature. The following laboratory tests were analyzed: glycemic control [glycated hemoglobin: (HbA1c)]; lipid profile [total cholesterol (TC), high-density lipoprotein (HDL-c), low-density lipoprotein (LDL-c), and triglycerides (TGL)], liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) alkaline phosphatase (ALP) and albumin], C-reactive protein (CRP), markers of renal function (creatinine and urea), electrolytes (magnesium, total calcium, and phosphorus), and markers of pancreatic function (amylase and lipase). The analyses used the Gold Análise Diagnóstica kits (Belo Horizonte, Minas Gerais, Brazil) in the automatic biochemical and turbidimetric analyzer device URIT 8021® from MHLab. All analyses were performed in triplicate. The Finecare® FIA Meter Plus analyzer from WONDFO was used for HbA1c.

Physical fitness

Health-related physical fitness tests

The chosen physical tests to evaluate the outcomes of the COVID-19 survivors follow the order: *(i)* sit and reach test; *(ii)* MIHS, MILTS; *(iii)* sit-up test for abdominal strength-resistance; *(iv)* 30-s chair-stand-test for lower limbs; *(v)* push-up test for upper limbs and *(viii)* 6MWT.[1] The participants were instructed about the procedures for all physical tests, and the researchers respected a rest between the tests. Furthermore, the choice of physical tests was based on promoting the assessment of physical fitness test parameters in places with low resources and clinics, public hospitals, gyms, and others.

Flexibility assessment

The sit and reach test was employed to evaluate the flexibility of the posterior chain using the Wells Bench. Participants were instructed according to previously

described procedures.[21] The test was repeated three times, with a 60-s interval between attempts. The highest value obtained was recorded and expressed in cm.

Maximal isometric strength tests

To assess MIHS, a TKK 5101 dynamometer (Takei Physical Fitness Test®, Tokyo, Japan) with a capacity of 100 kg was used. MILTS was evaluated using a Takei dynamometer (Takei Physical Fitness Test®, Back Strength Dynamometer, type 2, Japan) with a capacity of 300 kg. According to previous recommendations, three trials were performed for both tests, lasting 3–5 s with a 1-min rest between trials.[22] The highest value was recorded in kg.

Dynamic muscle strength-endurance assessment

To assess dynamic muscle, sit-up, 30-s chair-stand, and push-up tests for upper limbs were performed according to the procedures described in previous studies.[23,24] For the sit-up and push-up tests, the maximum number of repetitions achieved in 60 s was recorded, and for the 30-s chair-stand test, the muscular endurance of the lower limbs was evaluated from the maximum number of repetitions performed in 30 s.

Cardiorespiratory fitness test

The 6MWT was applied to verify the cardiorespiratory fitness of the present study participants. The 6MWT test was performed per American Thoracic Society guidelines.[25] Volunteers were instructed to walk as fast as possible to achieve the greatest distance at the end of 6 min.[25] The peak oxygen consumption (VO_2peak) was calculated using a previous study.[26]

Multi-professional intervention

Food reeducation protocol

Nutritionists held nutritional orientation meetings in groups, with theoretical and practical activities to promote the change in eating behavior. The classes inspired by the Food Guide for the Brazilian Population[27] were adapted to the new scenario experienced by COVID-19. The aim was to educate participants with dynamic classes on the benefits of healthy eating for health and how to deal with the risks associated with chronic NCDs and long-term symptoms of COVID-19.[5]

The meetings took place once a week for approximately 45 minutes for 16

consecutive weeks. In addition to dynamic classes, printed materials on the theme were prepared to be delivered. The interventions addressed the following themes:

1. Pre- and post-exercise - The theme deals with pre- and post-exercise nutrition, indicating the importance of diet, its role in exercise, examples of foods that can help, required amounts, and response time after consumption.

2. Introduction to healthy eating - builders, regulators, energy foods, food pyramid; healthy eating: explains the builders, regulators, and energy of the different foods, their due quantities, and their position in the food pyramid.

3. How to assemble a healthy dish - The lesson explains the proper amounts of each food group (carbohydrates, proteins, fats, salads, and vegetables) and portions at each meal. The intervention becomes more practical with a demonstration on the plate of how to assemble.

4. Gain of muscle mass - The theme talks about how to add in meals foods that help maintain and gain muscle mass. The class exposes examples of where to find proteins and the importance of gaining and maintaining the amount of muscle mass.

5. Micronutrients (vitamins and minerals) - The class of micronutrients: the importance of vitamins and minerals in adolescent health, nutritional interactions, and examples of where we come from in food.

6. Soluble and insoluble fiber - The class of fibers: the importance of daily fiber consumption, the required amount, the difference between soluble and insoluble fiber, and where to find the different fibers in food.

7. How to read food labels - Food labels: how to read food labels, plus practical examples such as sachet juices, biscuits, and processed foods.

8. Types of hunger (emotional, regulatory, specific, and social) - Physical or emotional hunger: explain in detail how to identify the hunger level and whether it is physical or emotional.

9. Intermediate snacks - This theme explains intermediate snacks, their importance, the necessary amount, and examples that can be applied in the daily routine.

10. Stress and anxiety - a theoretical-practical lesson on stress and anxiety, providing what these problems are and how we identify symptoms and physical and psychological signs. The intervention focuses on self-perception and how to deal with these circumstances with practical breathing activities.

11. How to deal with post-COVID-19 sequelae - due to the various sequelae after COVID-19, the class intends to work on the possible sequelae after the virus and

how nutrition can help treat and decrease symptoms.

12. Mindful eating – The class develops in the participants the ability to eat with mindfulness and develop self-control to deal with thoughts, emotions, physical sensations, and habits related to eating.

13. Diet, light, and typical foods - The class explains the different types of foods, at which time to eat each, and examples of each product.

14. Myths and truths of nutrition - to explain some myths commonly commented about this age, such as "water fasting with slimming lemon," sweating makes you lose weight, and not eating carbohydrates to lose weight, among others.

15. Resume the topics already covered - With a conversation circle, all the topics passed in the speeches. The idea was to provide an environment to clarify possibly unclear doubts and resume the previously reported topics.

16. Ten steps to healthy eating - The last lesson covered the ten steps to healthy eating and how to behave on vacation (without the research group).

Psychoeducation protocol

Psychoeducation is a therapeutic technique with the central aim of preventing and treating mental illness with an educational character. It is applied using concepts and information from psychology, based on cognitive behavioral theory (CBT), added to other areas so that the individual has the possibility of gaining a broad understanding of their situation and other mental illnesses related to their condition, as well as focusing on prevention and health promotion.[8,28,29] 16 interventions were developed and applied in 16 meetings, each lasting 45 minutes and held in groups. The interventions were based on content presentations, conversation circles, and dynamics. The following themes were applied:

1. Opening the mental health interventions, this meeting explained all the rules, the participants' duties, the reason for the interventions, and the topics that would be covered during the interventions.

2. The second intervention focused on the importance of physical exercise to explain and motivate the participants on how beneficial exercise is for a better quality of life and mental health.

3. In this meeting, we worked on anxiety in everyday life, how it can impact daily activities, showing examples, ways of identifying it, and then how to deal with it using techniques based on CBT.

4. Discussions about obesity today. The round table discussion demystified beliefs, prejudices, and stereotypes associated with obesity; this intervention aimed to show participants, in the form of a discussion, how obesity is a multifactorial disease.

5. Understanding the role of food in social, psychological, and physical development. Explain to the participants how food is directly linked to our feelings, explaining the types of hunger: psychological, physical, and social.

6. Information on post-traumatic stress disorder. This intervention aimed to help participants identify the disorder's symptoms; this was done by presenting and explaining each symptom.

7. Promoting a healthy lifestyle. Through daily examples, videos, and conversation circles, participants learned how to lead a balanced life, always seeking physical and mental well-being regardless of their current situation.

8. Reflections on stress. To help participants understand how stress can affect their mental and physical health. In addition, to show techniques and behaviors to relieve this feeling healthily.

9. Reflections on depressive symptoms. Demonstrating the types of depression and their most common symptoms, helping to identify them, and proposing techniques and behaviors that can help prevent and treat this disorder.

10. Reflections on insomnia and relaxation techniques. Explain how good quality sleep can influence physical and mental health. In addition, explain how sleep hygiene can help maintain a good rest and recovery routine.

11. Reflections on denial. This topic aimed to explain how this defense mechanism can influence our behaviors and choices.

12. Reflections on fear. To show how fear can affect our feelings and interpersonal relationships, demonstrate examples from everyday life.

13. Reflections on binge eating. Define, demonstrate, and explain how this disorder works and ways of identifying it.

14. Reflections on behavior change. A critical sense was developed to perceive inappropriate behavior and change it.

15. Reflections on bereavement. The stages of bereavement were presented, as well as a space for people to talk about these events.

16. Reflections on aging. The main changes regarding aging were shown through a content presentation.

To reinforce the interventions applied and disseminate support material to

participants, family members, and the community, we used printed and digital information papers delivered and sent after each intervention.[30,31] The interventions aimed to provide knowledge and enable changes about the psychological consequences of the COVID-19 pandemic, in addition to providing guidance on the essential themes of our century and helping participants to become more aware of the mental disorders caused by the contagion process and the COVID-19 pandemic.

Physical exercise protocol

The physical exercise intervention sessions were held on the university premises twice weekly, lasting approximately 60 minutes. The training protocol consisted of cardiorespiratory and muscle strength exercises (concurrent training) to increase muscle strength and, if necessary, motor coordination and balance. The concurrent training plan consisted of 4 weeks of anatomical adaptation with low volume and intensity, that is, 3 sets of 15 repetitions, with no aerobic exercise at the end of the session, and the remaining weeks of physical exercise (12 more in total) had a gradual progression of volume and intensity (via the classic linear periodization); in other words, the loads used were readjusted over the weeks, as well as the number of sets and repetitions. In weeks 5 to 8, 3 sets of 12 repetitions were performed; in weeks 9 to 12, the training sessions consisted of 4 sets of 12 repetitions; and finally, in weeks 13 to 16, 4 sets of 20 repetitions were performed. About aerobic exercise, 1 set of 5 and 1 set of 10 minutes was performed on weeks 5 to 8; 1 set of 10 and 1 set of 15 minutes was performed on weeks 9 to 12; and finally, on weeks 13 to 16, 1 set of 10 and 1 set of 20 minutes was performed. The training was carried out with resistance exercises focused on large muscle groups and cardiorespiratory fitness performed on a treadmill, vertical/horizontal bicycle, or rowing ergometer, according to the preference and physical condition of the patients. For a third day, the participants were requested to improve their physical activity (especially walking, 1 hour per week - if possible, accompanying the physical training). Table 1 presents the training program performed by the experimental groups during the 16 weeks of multi-professional intervention.

Table 1 near here

Statistical Analysis

The statistical analyses were realized using the SPSS 24 software version (IBM,

USA). Data are presented as the mean ± standard deviation (SD). First, data normality was tested using the skewness-kurtosis test, considering values from 2 to −2 to indicate a need for parametric statistical analyses. The main effect and interaction between groups and time were performed via a two-way mixed-measures ANOVA (for repeated measures). Bonferroni's *post-hoc* test was used when a significant difference was found. The significance level established for all tests was $p < 0.05$. The partial eta square (η^2) was calculated according to the classification by Richardson[32] using the following interpretation scale: 0.0099 [*small*], 0.0588 [*moderate*], and 0.1379 [*large*]. Cohen's (*d*) was also calculated for effect size using the following rating: 0.20 [small], 0.80 [moderate], and >0.80 [large].[33]

RESULTS

Table 2 shows the clinical characteristics of the participants in this study stratified by COVID-19 symptoms: mild ($n = 31$), moderate ($n = 13$) and severe ($n = 15$). No differences were observed for age, sex, BMI, resting heart rate, SBP, BPD, and SpO_2 ($p > 0.05$ for all comparisons). Regarding the persistent symptoms self-reported by COVID-19 patients, memory deficit (mild: 71.0%; moderate: 69.2%; severe: 60.0%), fatigue (mild: 41.9%; moderate: 53.8%; 46.7%) and muscle pain (mild: 32.3%; moderate: 46.2%; severe: 53.3%) were more prevalent. However, there was no significant difference between the groups for memory deficit, fatigue, and muscle pain ($p > 0.05$ for all comparisons). Regarding the participants' medical history, a difference was only observed for heart disease (mild: 19.4%; moderate: 0%; severe: 40.0%; with higher values for the severe group, $p = 0.03$). In addition, no differences were detected for the other clinical characteristics (medication in use, self-reported post-COVID-19 symptoms, smoking, and physical activity: $p > 0.05$).

Table 2 near here

Anthropometric and Body composition measurements

A time effect was observed for abdominal circumference ($F = 5.08$; $p = 0.01$; $\eta^2p = 0.08$ – *moderate effect*), with a significant reduction after 8 weeks ($p = 0.01$), with no significant changes after 16 weeks ($p > 0.05$). No time effects were observed for weight, BMI, fat-free mass, musculoskeletal mass, fat mass (FM), and body fat percentage (BFP) ($p > 0.05$). A group effect was observed for fat mass ($F = 3.91$; $p = 0.03$; $\eta^2p = 0.12$ –

moderate effect), with significantly higher values for the severe group compared to the mild group ($p = 0.02$) and for body fat percentage ($F = 4.54$; $p = 0.02$; $\eta^2p = 0.14$ – *large effect*), with significantly higher values for the severe group when compared to the mild group ($p = 0.04$). No group effects were observed for weight, BMI, and abdominal circumference ($p > 0.05$). None of the variables showed an interaction effect between group and time measurements ($p > 0.05$). Table 3 presents anthropometry and body composition before, after 8, and after 16 weeks of intervention.

Table 3 near here

Health-related physical fitness tests

A time effect was observed for all tests: MIHS of the right side ($F = 14.00$; $p < 0.001$; $\eta^2p = 0.22$ – *large effect*), with a significant increase after 8 weeks ($p = 0.01$); MIHS of the left side ($F = 10.34$; $p < 0.001$; $\eta^2p = 0.17$ – *large effect*), with a significant increase after 8 weeks ($p = 0.01$); flexibility ($F = 25.43$; $p < 0.001$; $\eta^2p = 0.35$ – *large effect*), with a significant increase after 8 weeks ($p = 0.00$) and 16 weeks ($p < 0.001$); MILTS ($F = 4.90$; $p = 0.01$; $\eta^2p = 0.09$ – *moderate effect*), with a significant increase after 8 weeks ($p = 0.029$); push-up test ($F = 18.15$; $p < 0.001$; $\eta^2p = 0.28$ – *large effect*), with a significant increase after 8 weeks ($p < 0.001$); abdominal strength-endurance ($F = 19.54$; $p < 0.001$; $\eta^2p = 0.30$ – *large effect*), with a significant increase after 8 weeks ($p < 0.001$) and sit-stand test ($F = 17.78$; $p < 0.001$; $\eta^2p = 0.26$ – *large effect*), with a significant increase after 8 weeks ($p = 0.00$). None of the variables showed differences between groups or interaction effects between group and time measurements ($p > 0.05$). Table 4 also shows the evolution of the cardiorespiratory fitness parameters assessed in the 6MWT during the intervention period. A time effect was observed for the VO_2peak ($F = 10.94$; $p < 0.001$; $\eta^2p = 0.17$ – *large effect*), with a significant increase after 8 weeks ($p = 0.00$); distance covered ($F = 16.35$; $p < 0.001$; $\eta^2p = 0.25$ – *large effect*), with a significant increase after 8 weeks ($p < 0.001$); pre-test DBP ($F = 12.23$; $p < 0.001$; $\eta^2p = 0.20$ – *large effect*), with a significant reduction after 16 weeks ($p < 0.001$); and final DBP ($F = 16.02$; $p < 0.001$; $\eta^2p = 0.24$ – *large effect*), with a significant reduction after 16 weeks ($p < 0.001$). None of the variables showed significant differences between the groups, and the interaction effect between group and time was insignificant ($p > 0.05$). Table 4 shows the physical and cardiorespiratory tests before, after 8, and 16 weeks of intervention.

Table 4 near here

Biochemical parameters

A time effect was observed for total cholesterol (F = 12.17; $p < 0.001$; $\eta^2p = 0.18$ – *large effect*), with a significant reduction after 8 weeks ($p < 0.001$); LDL-c (F = 18.62; $p < 0.001$; $\eta^2p = 0.25$ – *large effect*), with a significant reduction after 8 weeks ($p < 0.001$); HbA1c (F = 11.71; $p < 0.001$; $\eta^2p = 0.19$ – *large effect*), with a significant reduction after 8 weeks ($p = 0.03$); urea (F = 3.77; $p = 0.03$; $\eta^2p = 0.07$ – *moderate effect*), with a significant reduction after 8 weeks ($p = 0.04$); gamma-glutamyl transferase (F = 7.28; $p = 0.001$; $\eta^2p = 0.12$ – *moderate effect*), with a significant reduction after 16 weeks ($p = 0.00$); lipase (F = 4.47; $p = 0.01$; $\eta^2p = 0.08$ – *moderate effect*), with a significant reduction after 16 weeks ($p = 0.00$); magnesium (F = 10.30; $p < 0.001$; $\eta^2p = 0.19$ – *large effect*), with a significant reduction after 16 weeks ($p < 0.001$). Group effects were observed for creatinine (F = 3.18; $p = 0.04$; $\eta^2p = 0.11$ – *moderate effect*), significantly higher in the severe group when compared to the moderate group ($p = 0.04$); and CRP (F = 3.46; $p = 0.01$; $\eta^2p = 0.19$ – *large effect*), significantly higher in the severe group when compared to the mild group ($p = 0.01$). None of the variables showed an interaction effect between group and time measurements ($p > 0.05$). Table 5 shows the responses of biochemical parameters before, after 8 and 16 weeks of intervention.

Table 5 near here

DISCUSSION

Therefore, this study aimed to analyze the effects of multi-professional intervention on anthropometry, body composition, physical fitness (health-related physical fitness, flexibility, maximal isometric strength tests, dynamic muscle strength-endurance, cardiorespiratory fitness), and biochemical parameters in overweight and obese COVID-19 survivors after 16 weeks discharge from COVID-19 at different degrees of impairment. The following outcomes were observed: *(i)* a time effect (before *vs.* post-8w), with increased values for MIHS for right and left sides; *(ii)* a time effect (before *vs.* post-8w, before *vs.* post-16w), with increased values for flexibility after 8 and 16 weeks; *(iii)* a time effect (before *vs.* post-8w), with increased MILTS, arm flexion, abdominal strength-endurance repetitions, sit and stand test, VO_2peak and distance covered in 6MWT after 8 weeks; *(iv)* a time effect (before *vs.* post-16w), with a reduction in pre-test DBP and final

DBP after 16 weeks; *(v)* a time effect (before *vs.* post-8w), with a reduction in abdominal circumference after 8 weeks; *(vi)* a group effect (mild *vs*. severe), with increased values in FM and BFP in the severe group when compared to the mild group; *(vii)* a time effect (before *vs.* post-8w), with a reduction in total cholesterol, LDL-c, HbA1c and urea after 8 weeks; *(viii)* a time effect (before *vs.* post-16w), with a reduction in GGT, lipase and magnesium after 16 weeks; *(ix)* a group effect (moderate *vs.* severe), with an increase in creatinine in the severe group when compared to the moderate group; *(x)* a group effect (severe *vs.* mild), with increased CRP in the severe group compared to the mild group, it was observed that the 8- and 16-week interventions showed significant improvements in body composition parameters, physical fitness and biomarkers after the intervention periods, that is, both show that exercise improves recovery in COVID-19 survivors.

In contrast, no significant differences were detected in body mass, BMI, final HR, pre-test SBP, final SBP, HDL-c, TGL, ALT, AST, ALP, albumin, amylase, calcium, and phosphorus. These differences were also not found when investigating intergroup differences (time effect) and the degree of COVID-19 impairment (group effect).

There was no significant difference in BMI between the different groups, that is, mild, moderate, and severe symptoms, although there was a significant difference in FM and BFP, with lower values for the mild group. Therefore, to analyze the outcome of COVID-19, all anthropometric and body composition parameters must be analyzed, not just BMI alone.[6,7] It is known that excess body fat promotes the secretion of pro-inflammatory mediators, with a consequent reduction in the immune response.[10] Therefore, it is possible to state that being overweight and obese significantly worsens the symptoms of COVID-19.[5-7] A previous study reported that patients with a severe form of COVID-19 showed higher values of fat mass and body fat percentage than those with a mild form of COVID-19 with the same BMI.[7] FM was significantly higher in severe COVID-19 compared to the mild group; similar data were found by Perli et al.[6] when comparing the different symptoms of the disease; the authors also observed that this difference persisted 1 year after the disease. In this line, regular physical exercise can help control these parameters and promote a better immunological response against COVID-19 infection,[34] regardless of the symptoms of the disease. In our study, we did not collect food records before and after the multi-disciplinary interventions. Therefore, we cannot establish a relationship between the participant's body composition and food intake.

Persons who develop the severe form of COVID-19 need long periods of hospitalization, associated with the frequent use of corticosteroids, use of prolonged

mechanical ventilation, and use of neuromuscular blockers, causing direct impacts on the musculoskeletal system after hospitalization.[35] The practice of physical activity is considered one of the main components of a healthy life, promoting the prevention of overweight, systemic inflammation, and transmissible viral diseases, proving to be an effective therapeutic strategy to reduce a series of metabolic disorders, thus reducing the effects against the "cytokine storm" reported in patients with COVID-19.[36]

Regarding health-related physical fitness tests, significant improvements in hand pressure strength were observed for the mild, moderate, and severe COVID-19 groups after 8 weeks of intervention, corroborating the findings of Everaerts et al.,[37] who found an improvement in manual pressure strength after 16 weeks of post-hospital discharge intervention. The 30-second sit-up and chair-stand test for lower limbs also showed improvement after 8 weeks of intervention for all COVID-19 groups, reinforcing the findings of Li et al.[38] after 8 and 9 weeks of tele-exercises. MILTS showed an improvement in the time effect after 8 weeks (before *vs.* post-8w) in the mild, moderate, and severe COVID-19 groups; our studies partially corroborate the results of Sordi et al.,[5] showing improvement only in the moderate COVID-19 group.

Cardiorespiratory fitness was assessed using VO_2peak, HR, SpO_2, and blood pressure to verify physical capacity, effort tolerance, and possible cardiopulmonary changes.[25] The VO_2peak of the mild, moderate, and severe COVID-19 groups after 8 weeks was higher when compared to after 16 weeks of intervention, in line with Rinaldo et al.[39] showing improvement in VO_2peak in response to concurrent training after hospital discharge for COVD-19. No significant improvement was detected in SpO_2. This finding does not corroborate those of Lemos et al.,[7] who found an improvement in SpO_2 values due to the impact of this disease.

Some biochemical analyses did not show significant changes after the intervention: HDL-c, TGL, ALT, AST, ALP, albumin, amylase, calcium, and phosphorus. However, the patient's biochemical analyses were among normative values at pre-intervention.[40] Significant changes were verified after intervention for TC, LDL-c, HbA1c, urea, creatinine, GGT, lipase, magnesium, and CRP. It was observed that dyslipidemia is a risk factor for severe manifestations of COVID-19.[41] It is known that the lipid profile can change viral infections due to the neutralizing role of lipoproteins, protecting the host;[42] however, in patients with COVID-19, this protection does not appear to occur. After the interventions, there was a significant reduction in TC and LDL-c levels after 8 weeks in all groups (mild, moderate, and severe) and an increase in HDL-c levels in the mild and

moderate groups compared to the 16 weeks of intervention. Our studies corroborate other studies that show that the decrease in HDL-c levels correlates with the severity of COVID-19 cases.[43]

Another risk factor for COVID-19 is the increase in serum HbA1c levels. Diabetic individuals are at increased risk for several infections, including more severe cases of COVID-19.[44] High glucose in the bloodstream facilitates the hyperinflammation observed in the cytokine storm,[45] and the SARS-CoV-2 virus can also cause damage to the pancreatic islets, which are responsible for glucose regulation.[46] In the present study, HbA1c levels in the bloodstream were higher in persons with severe COVID-19 even after 16 weeks of intervention; therefore, people with increased blood glucose levels are more likely to progress to severe cases.

Due to the presence of the Angiotensin-Converting Enzyme 2 (ACE2) receptor in several organs, liver dysfunction resulting from COVID-19 may be related to severe infection.[47] Chen et al.[48] observed that ALT, AST, total bilirubin, ALP, and GGT concentrations were higher in deceased persons than in those recovered from COVID-19. Hepatocyte Steatosis is derived from the accumulation of lipids in hepatocytes, altering serum levels of triglycerides and HDL-c, and is considered one of the most common causes of chronic liver disease in adults;[49] therefore, interventions with physical exercise are necessary for a better prognosis of HS. GGT levels in this study were reduced only after 16 weeks of intervention in the mild, moderate and severe COVID-19 groups, showing that just eight weeks is not enough to improve liver parameters.

Studies on COVID-19 indicate that electrolyte abnormalities, including sodium, potassium, chloride, and calcium abnormalities, are also associated with disease severity in persons with COVID-19,[50,51] presenting an association where patients with more severe COVID-19 tend to present hypocalcemia compared to those with less severe forms of the disease.[51] Due to the severity of the disease, many people tend to remain hospitalized for longer, resulting in a loss of muscle mass and bone mineral mass; in females, this process accelerates after menopause due to low estrogen production.[52] In the present study, magnesium levels after interventions significantly improved in patients with mild, moderate, and severe COVID-19 after 16 weeks.

There was no statistical difference in serum CRP levels, although there was a significant level reduction when comparing the three intervention moments. At the pre-intervention moment, we found a high concentration of CRP in the experimental groups about the reference values (> 5.1 mg/dL), corroborating a previous study that revealed a

high concentration of CRP in persons with severe COVID-19 due to the innate system deregulated by the presence of inflammatory cytokines.[53] CRP concentration was reduced in the severe group (before vs. severe) in response to physical exercise, approaching reference values (< 5.0 mg/dL). High levels in the bloodstream can be found in response to active infections or acute inflammatory processes,[54] but high levels of this marker have been associated with obesity, as, in these persons, the inflammatory response can be precise.[55] Considering the aspects listed, multi-disciplinary interventions that aim to recover the health conditions of overweight and obese people are relevant for promoting health in this significant portion of the Brazilian population, which already has a prevalence of overweight of 61.4% and obesity of 24.3% in people aged 18 or over. Public policies must guide change by integrating multi-disciplinary teams to promote a healthy lifestyle for better rehabilitation of COVID-19 survivors.[56]

The absence of significant differences after 16 weeks in the general variables investigated in the present study could be related to a lower volume and frequency of physical exercises, i.e., twice a week. The primary physical training adaptations during the first weeks (8 and 12) are related to neural adaptations with subsequent plateaus.[57] Thus, the improvement in MIHS, MILTS, push-ups, abdominal strength-endurance, and sit-and-reach tests could be explained by neural adaptations after 8 weeks of physical exercise.[57] Considering muscle hypertrophy, the lack of significant differences for skeletal muscle mass and fat-free mass is probably related to lower volume and lower frequency of strength training[58] in which the main muscle groups must be trained at least twice a week to maximize muscle growth, within a volume and intensity suitable for each person. In general, detrained people tend to expend more energy to do physical exercises when compared to trained people.[59] Therefore, when detrained people start physical exercises, energy expenditure could be higher in the first weeks, but with time, the expenditure tends to reduce.[59] Given this, the stabilization of fat mass and body fat percentage after 16 weeks may be justified by a body adaptation[59] or a lower manipulation in volume, frequency, and intensity of concurrent training.[58] However, considering the health status of the study participants, we were cautious about manipulating some aspects linked to physical exercise.

After 16 weeks, a relevant aspect occurred with the three experimental groups. SBP and DBP were significantly reduced at rest. Pescatello et al.[60] pointed out that chronic exercise may reduce BP around ~5-7 mmHg with the following mechanisms: decrease in cardiac output and/or total peripheral resistance, less sympathetic neural

influence, greater local vasodilator influence, higher lumen diameter and bigger distensibility of the vasculature are structural adaptations to physical training promoting lower peripheral resistance, as well as genetic factors.

Six limitations can be highlighted in this study: *(i)* difficulty in composing a control group, as many persons are asymptomatic; *(ii)* loss of follow-up between groups because participants did not return for final assessments; *(iii)* application of the food record before the intervention, after 8 and 16 weeks; *(iv)* absence of other biochemical measures, such as pro-inflammatory cytokines (IL-1, IL-2, IL-6, IL-8, IL-12, IL-18, interferon-gamma (IFN-γ) and Tumor Necrosis Factor Alpha (TNT-α)) and anti-inflammatory cytokines (IL-10), coagulation factors (D-dimer, Activated Partial Thromboplastin Time (Aptt), prothrombin time (PT) and platelets) and cardiac markers (total creatine kinase, creatine kinase-MB, troponin, brain natriuretic peptide, and myoglobin); *(v)* monitoring of body composition and biomarkers after 16 weeks of this study to verify whether changes in eating habits and physical activity were persistent and *(vi)* to perform fine-tuning in volume, intensity and frequency of physical exercise for study participants.

Finally, new studies with more accurate biochemical parameters to analyze the extent of sequelae caused by COVID-19 may be relevant to identifying possible post-COVID damage in overweight or obese persons. To the knowledge of these authors, this is one of the first studies to consider the effect of a multi-professional intervention for 16 weeks according to the symptomatology proposed by the World Health Organization (WHO). The strengths of this study are physical exercise through concurrent training combined with a multi-professional program with physicians, nutritionists, exercise physiologists, psychologists, physiotherapists, and biomedical professionals, which can help participants to return to their activities of daily living. In addition, the present study highlights the importance of a multi-professional team for recovering the sequelae of COVID-19 survivors. Future studies could consider long-term monitoring responses and the difference in response between sex and age groups to combined exercise. More research is needed to explore other training combinations (aerobic vs. resistance) to understand the pathophysiological responses. Furthermore, incorporating a group without the disease (control group) associated with long-lasting COVID-19 could guide more assertive rehabilitation actions.

We can conclude that 8 weeks of intervention promoted significant improvements in anthropometrics, body composition, and physical fitness tests and a significant

reduction in lipid profile and glycated hemoglobin. After 16 weeks, the variables investigated in the present study were stabilized. Finally, the multi-professional intervention model promoted benefits for the post-COVID-19 patients, independently of the severity of symptoms. The design of the study based on a clinical trial and the presence of patients with different symptoms of COVID-19 confer greater validity to the results and a broader perspective of the effects of a multi-professional program, together with nutritional education to educate individuals about healthy eating, psychoeducation to provide knowledge and the possibility of changes, and results of biochemical tests to assess better the effects, in people with overweight and obesity.

The various sequelae observed in individuals affected by COVID-19 are directly related to the severity of the disease, making the progression of the physical exercise program a limiting factor, which implies the need for individualized training based on the difficulties presented during the initial physical evaluation, so professionals must carry out complete assessments, in addition to physical fitness, but also verify the most recent blood results, to devise a better strategy to improve the quality of life of this individual. This study emphasizes the importance of developing strategies to recover health conditions through physical activity, nutrition, and psychoeducation in COVID-19 survivors, thus seeking the individual's integral care and support. With this, my data will help in the development of multi-professional protocols for the recovery of health conditions in overweight and obese people after discharge from COVID-19.

Practical Applications

Given the clinical relevance, a few points can be highlighted: *(i)* this study showed that an 8-week multiprofessional intervention significantly improved fat-free mass, skeletal muscle mass, fat mass, body fat percentage and abdominal circumference; *(ii)* physical tests also significantly improved, for maximum isometric handgrip strength, maximum lumbar traction strength, arm flexion, abdominal strength endurance repetitions, sit-to-stand test, VO_2 peak and distance covered in the 6-minute walk test, after 8 weeks of intervention; *(iii)* in addition, biochemical tests revealed a significant reduction in triglycerides, low-density lipoprotein and glycosylated hemoglobin after 8 weeks of intervention; *(iv)* systolic and diastolic blood pressure were reduced after 16 week of intervention; *(v)* concurrent training, proposed in this research, is a complete training model that stimulates cardiorespiratory and musculoskeletal fitness that can be used safely in individuals affected by COVID-19, thus promoting improvements in physical fitness

and *(vi)* early interventions with health professionals can reduce the possible impacts (sequelae) of COVID-19.

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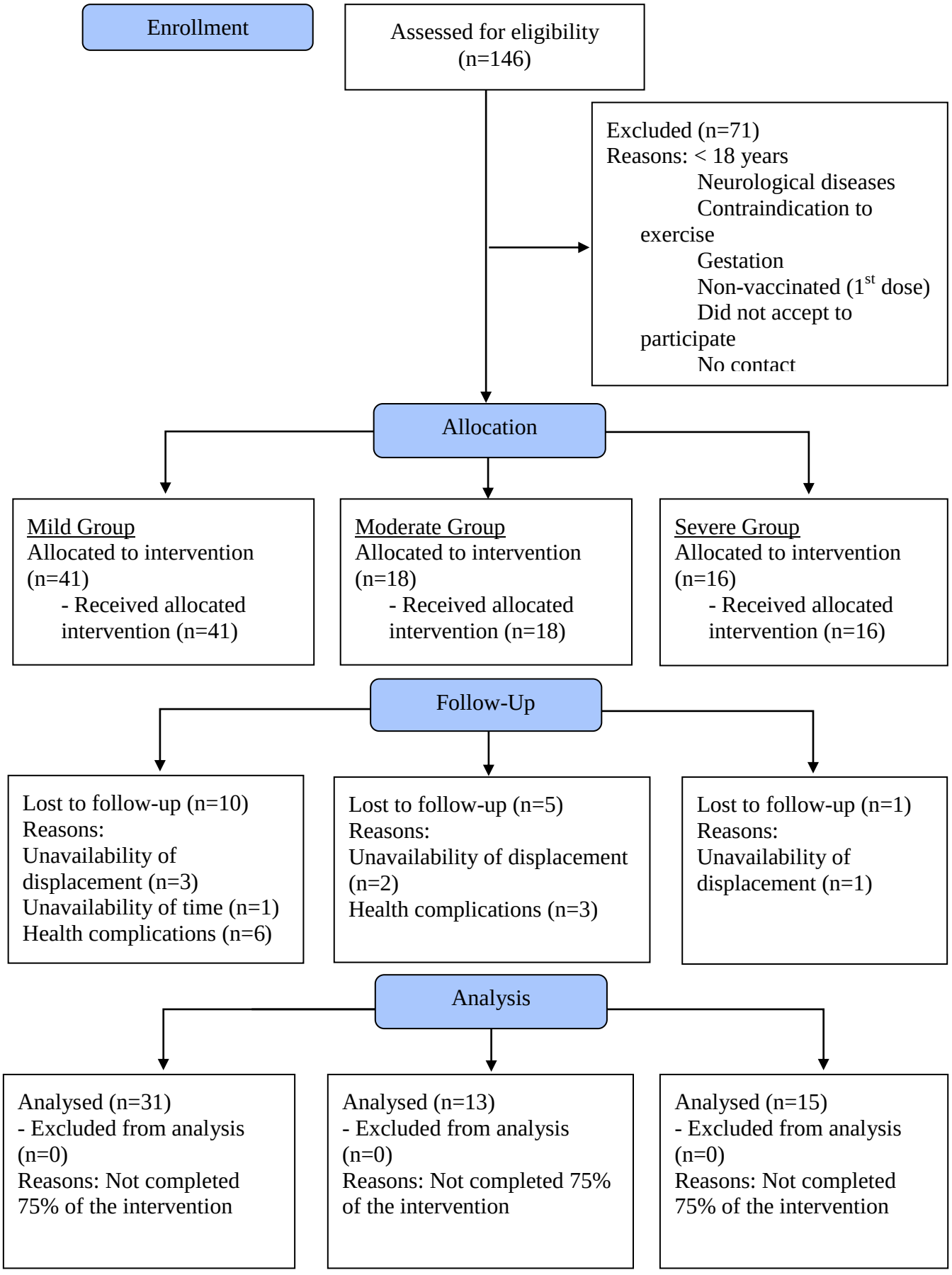

Figure 1. Flowchart diagram of the participants of the present study.

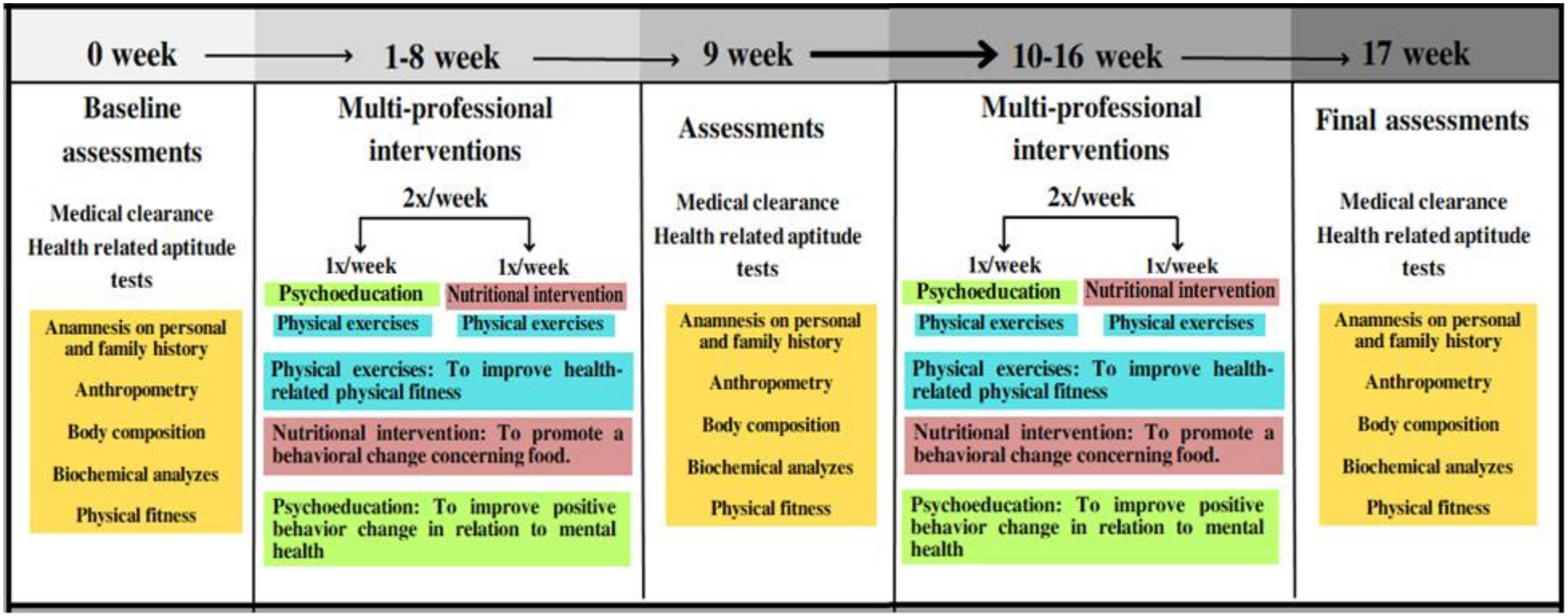

Figure 2. Methodology used for the 16-week intervention.

Table 1. Physical exercise program for mild, moderate, and severe COVID-19 survivors.

Order	Training program A	Training program B
1	Warm-up	Warm-up
2	Plank torso strength	Plank torso strength
3	Rectus abdominis	Rectus abdominis
4	Aerobic exercise	Hip bridge
5	Squat	Leg press
6	Leg extension	Aerobic exercise
7	Bench press	Leg curl
8	Aerobic exercise	Push up
9	Cable pulldown	Cable straight back seated row
10	Dumbbell shoulder press	Front raise
11	Triceps pully	Biceps curl
12	Aerobic exercise	Aerobic exercise

Table 2. Clinical characteristics of patients of three COVID-19 survivors intervention groups.

Variables	Mild (n= 31)	Moderate (n= 13)	Severe (n= 15)	*p*-value
Age (years old)	53.2 ± 12.3	54.3 ± 15.0	50.9 ± 12.9	$p = 0.77$
Sex				$p = 0.33$
Male	18 (58,1%)	4 (30.8%)	15 (66.7%)	
Female	13 (41.9%)	9 (69.2%)	5 (33.3%)	
BMI (kg/m²)	29.5 ± 4.8	31.1 ± 6.2	32.7 ± 4.8	$p = 0.14$
Medical history				
Hypertension	10 (32.3%)	5 (38.5%)	8 (53.3%)	$p = 0.40$
Diabetes	6 (19.4%)	2 (15.4%)	6 (40.0%)	$p = 0.23$
Dyslipidemia	9 (29.0%)	1 (7.7%)	3 (20.0%)	$p = 0.30$
Hypothyroidism	4 (12.9%)	4 (30.8%)	3 (20.0%)	$p = 0.39$
Psychogenic change	9 (29.0%)	2 (15.4%)	0 (0%)	$p = 0.06$
Neuropathy	2 (6.3%)	0 (0%)	2 (13.3%)	$p = 0.39$
Asthma	0 (0%)	1 (7.7%)	0 (0%)	$p = 0.17$
Heart disease	6 (19.4%)	0 (0%)	6 (40.0%)	$\mathbf{p = 0.03}$
Smoking				$p = 0.68$
No	27 (87.1%)	10 (76.9%)	12 (80.0%)	
Past or today	4 (12.9%)	3 (23.1%)	3 (20.0%)	
Medications in use				
Antihypertensive	12 (38.7%)	6 (46.2%)	7 (46.7%)	$p = 0.76$
Antidiabetic	5 (16.1%)	1 (7.7%)	5 (33.3%)	$p = 0.20$
Statin	4 (12.9%)	1 (7.7%)	4 (26.7%)	$p = 0.34$
Antidepressant	5 (16.1%)	3 (23.1%)	1 (6.7%)	$p = 0.49$
Platelet antiaggregant	0 (0%)	1 (7.7%)	1 (6.7%)	$p = 0.33$
Anticonvulsant	1 (3.2%)	1 (7.7%)	1 (6.7%)	$p = 0.79$
Hormone replacement	4 (12.9%)	3 (23.1%)	0 (0%)	$p = 0.16$
Anticoagulant	2 (6.3%)	0 (0%)	1 (6.7%)	$p = 0.65$
Lipid modulator	2 (6.3%)	0 (0%)	2 (13.3%)	$p = 0.39$

Table 2. *(Continued)* Clinical characteristics of patients of three COVID-19 survivors intervention groups.

Variables	Mild (n= 31)	Moderate (n= 13)	Severe (n= 15)	p-value
Antiarrhythmic	1 (3.2%)	0 (0%)	2 (13.3%)	$p = 0.23$
Post-COVID-19 self-reported symptoms				
Fatigue	13 (41.9%)	7 (53.8%)	7 (46.7%)	$p = 0.78$
Dyspnoea	2 (6.3%)	3 (23.1%)	1 (6.7%)	$p = 0.23$
Muscle pain	10 (32.3%)	6 (46.2%)	8 (53.3%)	$p = 0.37$
Joint pain	0 (0%)	0 (0%)	1 (6.7%)	$p = 0.23$
Headache	5 (16.1%)	5 (38.5%)	4 (26.7%)	$p = 0.27$
Cough	7 (22.6%)	2 (15.4%)	4 (26.7%)	$p = 0.78$
Dizziness	6 (19.4%)	4 (30.8%)	5 (33.3%)	$p = 0.54$
Memory déficit	22 (71.0%)	9 (69.2%)	9 (60.0%)	$p = 0.76$
Difficulty concentrating	12 (38.7%)	4 (30.8%)	5 (33.3%)	$p = 0.87$
Anxiety disorder	10 (32.3%)	6 (46.2%)	7 (46.7%)	$p = 0.55$
Depression	4 (12.9%)	4 (30.8%)	2 (13.3%)	$p = 0.33$
Processing speed	12 (38.7%)	6 (46.2%)	4 (26.7%)	$p = 0.57$
A feeling of hearing loss	6 (19.4%)	2 (15.4%)	4 (26.7%)	$p = 0.76$
Hair loss	7 (22.6%)	7 (53.8%)	7 (46.7%)	$p = 0.08$
Loss of smell	1 (3.2%)	0 (0%)	1 (6.7%)	$p = 0.63$
Physical activity ≥ 150 min/week	9 (29.0%)	2 (15.4%)	6 (40.0%)	$p = 0.37$
Baseline vital signs				
HR (bpm)	78.1 ± 10.3	85.1 ± 15.1	81.2 ± 9.9	$p = 0.18$
SBP (mmHg)	126.8 ± 11.9	127.0 ± 10.2	128.0 ± 16.6	$p = 0.95$
DBP (mmHg)	77.7 ± 15.9	82.3 ± 9.3	80.7 ± 16.7	$p = 0.61$
% SpO_2	97.0 ± 1.6	97.4 ± 1.4	96.8 ± 1.6	$p = 0.62$

Note: numerical data are expressed as mean ± standard deviation, and categorical data are expressed as absolute and relative frequency (%); BMI = body mass index; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; %SpO_2 = oxygen saturation; significance level $p<0.05$.

Table 3. Anthropometry and body composition responses before, after 8, and after 16 weeks of intervention in the three COVID-19 survivors' groups.

	Mild (*n* = 31)			**Moderate (*n* = 13)**			**Severe (*n* = 15)**		
Variables	**Before**	**Post-8W**	**Post-16W**	**Before**	**Post-8W**	**Post-16W**	**Before**	**Post-8W**	**Post-16W**
Weight (kg)	84.5 ± 19.4	84.5 ± 19.0	82.7 ± 22.2	80.5 ± 16.1	80.6 ± 15.8	80.7 ± 15.9	100.1 ± 23.1	95.3 ± 27.7	99.1 ± 22.1
BMI (kg/m^2)	29.6 ± 4.9	29.6 ± 4.8	29.5 ± 4.7	31.0 ± 5.9	31.1 ± 6.0	31.1 ± 6.2	33.2 ± 5.3	32.9 ± 5.0	32.7 ± 4.8
AC (cm)*	101.3 ± 13.6	100.5 ± 13.4	100.5 ± 13.2	101.8 ± 14.3	100.7 ± 13.8	100.4 ± 14.2	111.0 ± 14.9	108.7 ± 12.1	109.2 ± 14.0
FFM (kg)	53.0 ± 12.1	53.4 ± 12.2	53.9 ± 13.0	46.2 ± 10.4	45.9 ± 9.9	46.1 ± 10.0	57.6 ± 13.0	55.7 ± 13.9	59.1 ± 13.8
SMM (kg)	29.4 ± 7.2	29.6 ± 7.2	29.9 ± 7.7	25.4 ± 6.3	25.2 ± 6.0	25.3 ± 6.1	32.1 ± 7.7	32.2 ± 7.7	33.0 ± 8.1
FM (kg)‡	31.5 ± 11.5	31.2 ± 10.8	32.0 ± 11.6	34.3 ± 10.7	34.8 ± 11.0	34.6 ± 10.7	42.6 ± 13.3	41.6 ± 13.0	40.0 ± 11.3
BFP (%)‡	36.8 ± 8.1	36.5 ± 7.8	36.1 ± 8.5	42.1 ± 8.4	42.5 ± 8.7	42.3 ± 8.3	43.5 ± 5.2	41.4 ± 7.3	40.1 ± 6.6

Note: Data are presented by mean and standard deviation (±); W = weeks; BMI = body mass index; AC = abdominal circumference; FFM = fat-free mass; SMM = musculoskeletal mass; FM = fat mass; BFP = body fat percentage; * = time effect ($p < 0.05$, before vs. post-8W); ‡ = group effect ($p < 0.05$, mild vs. severe).

Table 4. Physical and cardiorespiratory fitness responses before, after 8, and after 16 weeks of intervention in the three COVID-19 survivors' groups.

	Mild (*n* = 31)			**Moderate (*n* = 13)**			**Severe (*n* = 15)**		
Variables	**Before**	**Post-8W**	**Post-16W**	**Before**	**Post-8W**	**Post-16W**	**Before**	**Post-8W**	**Post-16W**
MIHS-R (kg)*	30.5 ± 11.3	34.6 ± 11.9	34.4 ± 10.9	28.7 ± 12.6	29.6 ± 12.3	31.1 ± 12.1	32.9 ± 13.0	35.7 ± 11.5	36.6 ± 12.8
MIHS-L (kg)*	28.5 ± 10.6	32.4 ± 11.5	33.8 ± 11.2	25.0 ± 8.0	29.0 ± 12.3	30.1 ± 12.0	32.6 ± 12.9	33.7 ± 12.0	34.9 ± 13.3
Flexibility (cm)§	22.2 ± 8.8	24.2 ± 8.9	26.9 ± 7.9	26.8 ± 6.4	29.9 ± 5.9	30.9 ± 3.6	19.4 ± 8.9	21.2 ± 9.8	24.0 ± 9.0
MILTS (kg)*	88.5 ± 38.0	99.9 ± 23.1	104.4 ± 35.2	69.2 ± 19.8	85.5 ± 23.1	83.8 ± 27.8	95.7 ± 34.6	108.5 ± 42.5	108.5 ± 45.0
Push-up (reps)*	19.4 ± 8.9	24.2 ± 10.8	28.3 ± 13.8	15.4 ± 7.1	22.8 ± 8.4	25.3 ± 10.2	15.3 ± 8.5	15.8 ± 6.9	17.6 ± 8.5
Abdominal strength-endurance (reps)*	17.3 ± 8.1	21.0 ± 8.4	26.0 ± 12.2	15.7 ± 8.1	18.9 ± 8.4	23.9 ± 11.3	14.2 ± 8.8	20.0 ± 10.7	18.6 ± 9.8
Sit and reach (reps/min)*	16.3 ± 4.4	19.1 ± 5.9	21.6 ± 5.6	15.8 ± 4.2	20.0 ± 5.9	19.9 ± 4.5	15.8 ± 6.3	17.7 ± 5.6	18.2 ± 5.2

Note: Data are described by mean and standard deviation (±). W = weeks; MIHS = maximal isometric handgrip strength; R = right side; L = left side; MILTS = maximal isometric lumbar-traction strength; 6MWT = 6-minute walk test; VO_2peak = peak oxygen consumption. * = time effect ($p < 0.05$, before *vs.* post-8W); § = time effect ($p < 0.05$; before *vs.* post-8W and post-16W).

Table 4. *(Continued)* Physical and cardiorespiratory fitness responses before, after 8, and after 16 weeks of intervention in the three COVID-19 survivors' groups.

	Mild (*n* = 31)			**Moderate (*n* = 13)**			**Severe (*n* = 15)**		
Variables	**Before**	**Post-8W**	**Post-16W**	**Before**	**Post-8W**	**Post-16W**	**Before**	**Post-8W**	**Post-16W**
6MWT									
VO_2 peak (mL/kg/min)*	16.9 ± 3.6	18.0 ± 3.8	18.6 ± 4.0	16.3 ± 5.4	17.3 ± 5.0	17.7 ± 4.8	16.6 ± 3.8	17.4 ± 4.5	17.8 ± 3.5
Distance (m)*	534.3 ± 69.2	582.8 ± 89.2	595.2 ± 95.8	505.0 ± 109.9	561.1 ± 98.8	562.2 ± 90.5	521.2 ± 108.4	569.1 ± 108.8	553.7 ± 79.7
Final HR (bpm)	78.1 ± 10.2	79.6 ± 10.5	76.0 ± 10.8	80.5 ± 9.8	72.5 ± 9.5	76.9 ± 11.2	79.1 ± 10.3	76.0 ± 11.4	76.5 ± 9.2
SBP pre-test (mmHg)	124.8 ± 12.6	123.6 ± 8.5	123.5 ± 12.3	127.7 ± 13.0	132.0 ± 19.4	131.2 ± 14.2	125.7 ± 11.6	134.0 ± 15.5	127.7 ± 15.0
SBP final (mmHg)	141.6 ± 15.7	148.2 ± 11.5	141.4 ± 18.3	140.8 ± 21.4	148.5 ± 17.3	142.9 ± 18.3	147.9 ± 22.9	147.3 ± 11.0	145.3 ± 12.4
DBP pre-test (mmHg)‡	79.0 ± 9.4	79.1 ± 11.0	75.4 ± 8.7	79.2 ± 12.6	79.9 ± 8.4	75.54 ± 10.8	79.3 ± 12.1	79.7 ± 12.3	76.7 ± 10.5
DBP final (mmHg)‡	84.5 ± 10.6	82.5 ± 13.5	76.5 ± 10.9	86.2 ± 13.9	86.8 ± 8.6	78.4 ± 11.1	85.7 ± 15.1	86.7 ± 11.8	79.2 ± 13.0

Note: Data are described by mean and standard deviation (±). W = weeks; VO2peak = peak oxygen consumption; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure. * = time effect ($p < 0.05$, before *vs.* post-8W) and ‡ = time effect ($p < 0.05$, before *vs.* post-16W).

Table 5. Biochemical parameters responses before, after 8, and after 16 weeks of intervention in the three COVID-19 survivors' groups.

	Mild (*n* = 31)			**Moderate (*n* = 13)**			**Severe (*n* = 15)**		
Variables	**Before**	**Post-8W**	**Post-16W**	**Before**	**Post-8W**	**Post-16W**	**Before**	**Post-8W**	**Post-16W**
TC (mg/dL)*	182.2 ± 48.0	164.6 ± 34.6	168.6 ± 34.9	197.7 ± 56.0	151.7 ± 42.8	159.5 ± 32.5	188.7 ± 61.1	158.5 ± 35.3	156.8 ± 42.0
LDL-c (mg/dL)*	119.4 ± 52.4	87.6 ± 28.4	88.0 ± 29.5	124.6 ± 53.5	74.2 ± 33.7	82.2 ± 27.5	114.9 ± 64.3	84.7 ± 30.5	83.0 ± 45.5
HDL-c (mg/dL)	49.6 ± 12.9	52.4 ± 15.1	56.0 ± 11.2	54.2 ± 14.3	50.0 ± 15.1	53.9 ± 15.4	48.1 ± 7.3	44.6 ± 10.0	48.5 ± 10.9
TGL (mg/dL)	117.8 ± 50.1	124.1 ± 54.1	114.6 ± 54.1	129.9 ± 58.6	112.0 ± 45.7	106.3 ± 45.2	133.8 ± 64.7	141.9 ± 62.9	142.3 ± 85.4
HbA1c (%)*	6.1 ± 0.6	6.0 ± 0.7	5.6 ± 0.4	6.3 ± 1.2	6.0 ± 1.0	5.7 ± 0.5	5.8 ± 0.5	5.7 ± 0.6	5.6 ± 0.4
Creatinine (mg/dL)†	1.2 ± 0.2	1.2 ± 0.3	1.2 ± 0.3	1.1 ± 0.2	1.0 ± 0.4	1.2 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	1.4 ± 0.2
Urea (mg/dL)*	38.4 ± 15.7	35.2 ± 12.9	41.2 ± 11.4	40.9 ± 17.3	29.8 ± 13.5	37.0 ± 11.5	38.1 ± 11.4	32.1 ± 7.5	31.7 ± 9.2
ALT (U/L)	27.5 ± 10.2	27.7 ± 13.2	29.0 ± 13.4	25.7 ± 12.2	26.2 ± 13.2	29.0 ± 13.4	29.4 ± 8.8	33.9 ± 16.8	22.5 ± 8.5
AST (U/L)	29.5 ± 10.6	29.2 ± 10.5	27.1 ± 9.4	22.5 ± 9.0	30.4 ± 10.4	25.8 ± 10.1	31.1 ± 15.4	27.9 ± 7.3	24.6 ± 11.3
ALP (U/L)	51.3 ± 19.5	59.9 ± 21.3	57.0 ± 11.8	59.8 ± 22.8	54.5 ± 20.5	68.3 ± 22.7	60.1 ± 21.3	59.7 ± 16.2	54.5 ± 12.6

Note: Data are described by the mean and standard deviation (±); TC = total cholesterol; LDL-c = LDL cholesterol; HDL-c = HDL cholesterol; TGL = triglycerides; HbA1c = glycated hemoglobin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase and * = time effect ($p < 0.05$, before *vs.* post-8W);); § = time effect ($p < 0.05$, before vs. post-16W); † = group effect ($p < 0.05$, moderate vs. severe) and ‡ = group effect ($p < 0.05$, mild *vs.* severe).

Table 5. *(Continued)* Biochemical parameters responses before, after 8, and after 16 weeks of intervention in the three COVID-19 survivors' groups.

	Mild (*n* = 31)			**Moderate (*n* = 13)**			**Severe (*n* = 15)**		
Variables	**Before**	**Post-8W**	**Post-16W**	**Before**	**Post-8W**	**Post-16W**	**Before**	**Post-8W**	**Post-16W**
GGT (U/L)§	45.7 ± 21.3	39.5 ± 19.4	35.3 ± 16.1	43.7 ± 13.7	43.0 ± 19.8	36.8 ± 14.9	48.0 ± 17.3	42.6 ± 18.2	31.7 ± 11.6
Albumin (g/dL)	4.2 ± 0.6	4.1 ± 0.4	4.0 ± 0.6	3.9 ± 0.7	4.1 ± 0.4	4.1 ± 0.7	4.1 ± 0.4	4.1 ± 0.3	4.2 ± 0.8
Amylase (U/L)	82.8 ± 34.2	76.7 ± 24.1	65.3 ± 29.3	65.5 ± 29.0	59.1 ± 32.8	55.8 ± 17.8	62.7 ± 24.7	63.3 ± 26.1	75.9 ± 38.6
Lipase (U/L)‡	47.6 ± 12.2	53.0 ± 18.3	38.3 ± 11.8	40.3 ± 14.3	45.2 ± 16.8	39.7 ± 14.2	50.9 ± 10.2	45.1 ± 11.6	45.3 ± 15.7
Calcium (mg/dL)	6.4 ± 3.6	6.2 ± 2.5	6.9 ± 3.1	6.0 ± 2.5	7.0 ± 2.8	8.8 ± 3.6	6.8 ± 3.0	7.1 ± 3.5	5.8 ± 3.0
Magnesium (mg/dL)§	2.2 ± 0.6	2.1 ± 0.8	1.6 ± 0.6	2.1 ± 1.2	1.9 ± 0.7	1.9 ± 1.1	2.3 ± 0.6	2.3 ± 0.9	1.4 ± 0.6
Phosphorus (mg/dL)	3.5 ± 1.0	2.5 ± 0.8	3.1 ± 1.0	3.6 ± 0.2	2.9 ± 1.1	2.9 ± 0.6	2.9 ± 0.6	3.2 ± 1.5	3.0 ± 0.8
CRP (mg/dL)‡	6.1 ± 6.9	6.2 ± 5.0	5.2 ± 4.6	9.6 ± 8.6	8.9 ± 7.2	5.9 ± 4.7	13.5 ± 7.5	10.9 ± 5.5	7.0 ± 6.2

Note: Data are described by mean and standard deviation (±); GGT = gamma glutamyltransferase; CRP = C-reactive protein; * = time effect ($p < 0.05$, before *vs.* post-8W); § = time effect ($p < 0.05$, before *vs.* post-16W); † = group effect ($p < 0.05$, moderate *vs*. severe) and ‡ = group effect ($p < 0.05$, mild *vs.* severe).

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- The datasets generated during and/or analyzed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.
- Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.
- All data generated or analyzed during this study are included in this published article [and its supplementary information files].
- The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].

Preprints

Medicine® has no objections to considering preprints for publication. If an author is submitting a manuscript that has been shared as a preprint, authors should include the preprint server name and DOI in the Comments section in the Editorial Manager submission.

Authorship

Medicine® adheres to the Authorship Requirements as defined by the International Committee of Medical Journal Editors (ICMJE). For more information, please visit http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.

Everyone who is listed as an author should have made a substantial, direct, intellectual contribution to the work. For example (in the case of a research report) they should have contributed to the conception, design, analysis and/or interpretation of data.

- Honorary or guest authorship is not acceptable.
- Co-first authorship and co-corresponding authorship is not acceptable.
- Acquisition of funding and provision of technical services, patients, or materials, while they may be essential to the work, are not in themselves sufficient contributions to justify authorship.

Author Name Indexing:

When submitting author names please note that authors should be listed in First Name – Middle Name- Surname order. If an author is submitted as "John R Smith" or "John Robert Smith" the article will publish the authors name as "Smith, J. R."

Be sure to check the proofs prior to publication.

Changes to Authorship

Medicine® considers the final author list to be complete at the time of the first revision submission. **Please be sure to check that all authors are properly listed on the revision submission, this includes the spelling of an author's name, their designated degrees, and order of authors listed.**

Medicine® has a strict policy on changes to authorship and **will not consider authorship change requests after acceptance of the article.**

Author Identification

All submitting Corresponding Authors must provide an ORCID iD when submitting a manuscript to Medicine®. Coauthors are strongly encouraged to provide an ORCID iD but are not required.

Authors can register for an ORCID iD at orcid.org.

CReDIT

Medicine® has integrated CRediT (Contributor Roles Taxonomy) in the editorial manager workflow system. CRediT allows researchers to identify manuscript contributions roles during submission that go beyond just name identification. CRediT enables more transparency to the published work and allows authors to receive credit for individual contributions towards the manuscript.

During submission when a corresponding author adds additional authors to the author list, they can select each individual author's contribution roles from a list of 14 selections. More than one contribution can be selected for each author.

Role	Definition
Conceptualization	Ideas; formulation or evolution of overarching research goals and aims.
Data curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later re-use.
Formal analysis	Application of statistical, mathematical, computational, or other formal techniques to analyse or synthesize study data.
Funding acquisition	Acquisition of the financial support for the project leading to this publication.
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection.
Methodology	Development or design of methodology; creation of models.
Project administration	Management and coordination responsibility for the research activity planning and execution.
Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools.
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components.
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team.
Validation	Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs.
Visualization	Preparation, creation and/or presentation of the published work, specifically visualization/data presentation.
Writing – original draft	Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation).
Writing – review & editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages.

Manuscript Preparation

Necessary files

- **Manuscript**. A single word processing file, including title, authors, abstract, main text, references and figure legends.
- **Figure(s).** Optional
- **Table(s).** Optional
- **Reporting Guidelines Checklist**. Per article type, the corresponding Reporting Guidelines Checklist (and Flow Diagram if applicable). We ask that you use the templates available on Medicine's Editorial Manager site in the "Files & Resources" section of the home page. For more information on Reporting Guidelines, please visit http://www.equator-network.org.

Reporting Guidelines and Article Types

Reporting Guidelines

Medicine® article types are based upon key reporting guidelines, as defined by the EQUATOR Network. Authors should prepare their manuscripts in accordance with the appropriate guidelines(s) and/or checklist(s) for each type of article. We ask that you use the checklist and flow diagram templates for the guidelines outlined below available on Medicine's Editorial Manager site in the "Files & Resources" section of the home page.

The appropriate checklist (and flow diagram, if applicable) must be included with each submission.

For further information regarding reporting guidelines, authors should consult the EQUATOR Network web site (http://www.equator-network.org), which maintains a useful, up-to-date list of guidelines as they are published, with links to articles and checklists.

Article Types

Clinical Trial/Experimental Study (CONSORT Compliant)

Reports of randomized trials must conform to the revised CONSORT guidelines and should be submitted with their protocols and a completed CONSORT checklist. All reports of clinical trials must include a summary of previous research findings and explain how the submitted trial affects this summary of previous findings. Cluster randomized trials should be reported according to extended CONSORT guidelines. Randomized trials reporting harms must be described according to extended CONSORT guidelines. All reports of randomized trials should include a section entitled "Randomization and masking" within the methods section. For information regarding CONSORT guidelines, please visit http://www.consort-statement.org.

Observational Study (STROBE Compliant)*

Observational research comprises several study designs and many topic areas. The STROBE statement should be used when reporting such research. The STROBE recommendations apply to the three main analytical designs used in observational research: cohort, case-control, and cross-sectional studies. The STROBE statement consists of a 22-item checklist. For information regarding STROBE guidelines, please visit http://www.strobe-statement.org.

*Please note that *Medicine*® uses a customized version of the STROBE checklist, available only Medicine's Editorial Manager site in the "Files & Resources" section of the home page.

Systematic Review and Meta-Analysis (PRISMA Compliant)

Systematic reviews and meta-analyses must be reported according to PRISMA guidelines, an evidence-based minimum set of items created to help authors improve the reporting of systematic reviews and meta-analyses. The PRISMA Statement consists of a 27-item checklist, an abstract-specific checklist, and four flow diagrams depending on the type of review (new or updated) and sources used to identify studies. For information regarding PRISMA guidelines, please visit http://www.prisma-statement.org.

Diagnostic Accuracy Study (STARD Compliant)

Investigators reporting studies of diagnostic accuracy should adhere to the STARD statement, part of the STARD initiative to improve the accuracy and completeness of reporting of studies of diagnostic accuracy, to allow readers to assess the potential for bias in a study (internal validity) and to evaluate a study's generalizability (external validity). The STARD statement consists of a 25-item checklist and recommends the use of a flow diagram to describe the design of the study and the flow of patients. For information regarding STARD guidelines, please visit http://www.stard-statement.org.

Economic Evaluation Study (CHEERS Compliant)

Developed by the ISPOR Quality Improvement in Cost-Effectiveness Research Task Force, the CHEERS statement supports the quality, consistency, and transparency of health economic and outcomes research reporting in the biomedical literature. The CHEERS statement includes a 24-item checklist. For more information regarding CHEERS guidelines, please visit http://www.ispor.org/taskforces/EconomicPubGuidelines.asp.

Clinical Case Report (CARE Compliant)

The CARE guidelines provide a framework to support the need for completeness, transparency and data analysis in case reports and data from the point of care. The main tools of CARE are the CARE Statement, CARE checklist, and a Case Report Writing Template. These products offer a rationale and a standardized format for authors to prepare more complete and transparent case reports. For more information regarding CARE guidelines, please visit http://www.care-statement.org/.

Narrative Review (SANRA)

A narrative review is a comprehensive and objective analysis of the literature on a given research topic or problem of interest. Narrative reviews are not systematic in nature but should summarize, synthesize, and integrate findings into writing appropriately. Narrative reviews are evaluated using the Scale for the Assessment of Narrative Review Articles (SANRA), a tool for measuring the quality of a narrative review based on the article's importance to readers, the aims or formulation of questions, the description of the literature search, referencing, scientific reasoning, and presentation of data. For more information about the SANRA tool, please visit: https://www.aerzteblatt.de/down.asp?id=22862.

Medicine® will charge an article publishing fee (APC) of $1450 under a CCBY license for narrative reviews. Narrative reviews submitted to Medicine must include a/n:

- Unstructured abstract (250-word count maximum)
- Include "a review" in the title
- Introduction, Methods, Discussions/Observations, and Conclusions (2,500-5,000 word count maximum)
- References (50-150 reference count maximum)
- Maximum of 5 Figures/Tables

Animal Research and Studies

Medicine® does not consider Animal Research or Animal Studies for publication. Submissions based on animal studies will be rejected without review.

Study Protocols

Medicine® is no longer accepting study protocol submissions. Authors are encouraged to submit their protocols to one of the following journals instead:

International Journal of Surgery Protocols

Medicine: Case Reports and Study Protocols

Formatting

Style

- Text should be 1.5-spaced.
- Typeface should be Times/Times New Roman or similar serif typeface.
- Do not use a sans serif typeface (eg, Arial/Helvetica).
- Body text size should be no smaller than 10 pt and no larger than 12 pt.
- Page size should be US Letter.
- To assist reviewers, please include page numbers in the manuscript file.

Title

Manuscripts must be submitted with both a full title and a short title, which will appear at the top of the PDF upon publication if accepted. Only the full title should be included in the manuscript file; the short title will be entered during the online submission process.

The full title should be specific, descriptive, concise, and comprehensible to readers outside the subject field. Avoid abbreviations if possible. Where appropriate, authors should include the species or model system used (for biological papers) or type of study design (for clinical papers).

Authors and Affiliation

All author names should be listed in the following order:

- First names (or initials, if used),
- Middle names (or initials, if used), and
- Last names (surname, family name)
- Medical and/or highest academic degrees (eg, MD, PhD)

Each author should list an associated department, university, or organizational affiliation and its location, including city, state/province (if applicable), and country.

When a large group or center has conducted the work, the author list should include the individuals whose contributions meet the authorship criteria defined above, as well as the group name. If the article has been submitted on behalf of a consortium, all author names and affiliations should be listed at the end of the article in the Acknowledgements section.

One author should be designated as the corresponding author, and his or her email address should be included on the manuscript cover page. This information will be published with the article if accepted.

For questions regarding authorship requirements, please consult the ICMJE Uniform Requirements for Manuscripts Submitted to Biomedical web page at http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html.

Abbreviations, Nomenclature and Symbols

Abbreviations, nomenclature and symbols should conform to those found in the *AMA Manual of Style*. The use of standard international units is encouraged. Abbreviations should be used sparingly and should be spelled out the first time they are used. A list of abbreviations should be included as part of the manuscript following the title page.

Abstract

A structured abstract should be **no more than 350 words**, summarizing the problem being considered, how the study was performed, the salient results, and the principal conclusions. Specific instructions regarding abstract structure are often included in the relevant reporting guidelines checklist.

Introduction/Materials and Methods/Results/Discussion and Conclusions

The overall structure of your manuscript text should follow the corresponding reporting guideline. For example, a CONSORT compliant manuscript should include the following sections, as defined by the CONSORT checklist:

- Introduction
- Methods
- Results
- Discussion
- Other Information

Acknowledgements

All contributors who do not meet the criteria for authorship should be listed in an 'Acknowledgements' section. Additionally, if the article has been submitted on behalf of a consortium, all author names and affiliations should be listed at the end of the article in the Acknowledgements section. Authors should also disclose whether they had any writing assistance.

References

The style of references conforms to the guidelines set forth by the *AMA Manual of Style*. For Specific examples and information regarding references, see the manual or visit online: http://www.amamanualofstyle.com. EndNote users can access a direct download of the JAMA style at Medicine's Editorial Manager site. Authors using other forms of reference management software should use JAMA style.

- All references cited in the text must be both listed and cited by the reference number (footnotes are not accepted).
- Each reference should be cited in the text, tables, or figures in consecutive numerical order by means of superscript arabic numerals. Use superscript numerals outside periods and commas, inside colons and semicolons. When more than 2 references are cited at a given place in the manuscript, use hyphens to join the first and last numbers of a closed series; use commas without space to separate other parts of a multiple citation (eg, As reported previously,1,3-8,19...The derived data were as follows3,4,12:)
- References should be numbered consecutively in the order in which they are cited in the text.
- References in tables and in figure legends must appear in the reference page(s).
- In listed references, use the author's surname followed by initials without periods. (eg, Doe JF)
- For references with 6 or fewer authors, list all authors. For references with more than 6 authors, list the first 3 authors followed by "et al."
    - 1 author Doe JF.
    - 2 authors Doe JF, Roe JP III.
    - 6 authors Doe JF, Roe JP III, Coe RT Jr, Loe JT Sr, Poe EA, van Voe AE.
    - >6 authors Doe JF, Roe JP III, Coe RT Jr, et al.
- Full-page ranges should be given in expanded form (eg, 426–429, not 426–9).
- If non-English-language titles are translated into English, bracketed indication of the original language should follow the title.

- Abbreviate and italicize names of journals according to the style in PubMed; refer to the National Library of Medicine (NLM) Journals Database (http://www.ncbi.nlm.nih.gov/nlmcatalog/journals) if needed.
- In references to journals that have no volume or issue numbers, use the issue date, as shown in example 1 below. If there is an issue number but no volume number, use the style shown in example 2. Conversely, if there is a volume number but no issue number, follow example 3.

1. Author(s). Article Title. Journal Name. Month Year:inclusive pages.
2. Author(s). Article Title. Journal Name. Year;(Issue No.):inclusive pages.
3. Author(s). Article Title. Journal Name. Year;vol:inclusive pages.

- Papers "submitted for publication" but not yet accepted and citations such as "personal communication" or "unpublished data" are not acceptable as listed references and instead should be included parenthetically in the text. This material, with its date, should be noted in the text as "unpublished data" as follows: (J. F. Doe, MD, unpublished data, January 2010).
- Papers denoted "in press" (accepted for publication) should appear in the references.
- Authors are responsible for the accuracy and completeness of the references.

Tables

Create tables using the table formatting and editing feature of your word processing software. Do not use Excel or comparable spreadsheet programs. Tables should be self-explanatory and should supplement, rather than duplicate, the material in the text.

- Tables are text-only items. Do not embed images within the table file.
- Each table file should include the table title, appropriate column heads, and any legends.
- Save each table in a separate word processing document file and upload individually.
- Do not embed tables within the manuscript file.

- Tables are numbered with arabic numerals (1, 2, 3, etc.) when there is more than one. Do not use roman numerals.
- Cite tables consecutively in the manuscript, and number them in the order in which they are discussed.
- Abbreviations are not permitted in table titles. Any abbreviation(s) used in the body of the table, including dashes, must be defined in a footnote to the table, listed in reading order.
- Many tables include information from other articles and series of patients. In these tables, include the name of the first author of the previous series, and include the reference number and year alongside the author's name. Each series mentioned in a table must be listed in the Reference section.
- For further information on table formatting, please see the *AMA Manual of Style*.

Figures

To ensure the highest-quality reproduction of figures, please follow these guidelines carefully. For further information, please see the "Creating Digital Artwork" file available on Medicine's Editorial Manager site in the "Files & Resources" section of the home page.

Medicine® is not responsible for the quality of images; it is the responsibility of the authors to submit publication-quality, high-resolution images. If you have questions, consult a graphics specialist. The term "Figures" refers to both photographic and computer-generated graphs and charts.

Creating and Saving

- Art should be created/scanned, saved and submitted as TIFF, EPS, or MS Office (DOC, PPT, XLS) files.
- Figures are numbered with arabic numerals (1, 2, 3, etc.) when there is more than one.
- Each file should be saved as the appropriate figure number (eg, Figure 1.tif). Do not include the author name in figure file name.
- Art should be created or scaled to the size intended for publication.
- Use scale markers in the image for electron micrographs, and indicate the type of stain used.
- Image orientation should be the same as intended for publication.
- Artwork generated from office suite programs such as CorelDRAW, MS Word, MS PowerPoint and artwork downloaded from the Internet (low resolution JPEG or GIF files) cannot be used.

Formatting Specifications

- File formats appropriate for figures: TIFF, EPS, or MS Office (DOC, PPT, XLS) files.
- All figures must be designated GRAYSCALE (black and white) or RGB (color).
- Electronic photographs, radiographs, CT scans, and scanned images must have a resolution of at least 300 dpi (dots per inch). Line art (purely black and white figures with no shades of gray) must have a resolution of at least 1200 dpi. Figures that do not meet the resolution requirement will be returned if necessary.
- Digital art files should be cropped to remove non-printing borders (such as unnecessary white or black space around an image) and should not include embedded "legend" text, figure titles, or figure numbers.
- Composite figures may be either submitted as one single print-quality image that is neatly labeled with uppercase letters using Arial/Helvetica bold font or submitted as separate panels

(without labels), eg, Figure 1A.tif, Figure 1B.tif, to be combined during production if accepted for publication.

Submitting

- Attach a separate file for each individual art submission.
- Do not embed figures in the manuscript file.
- Label figures using the Description field provided in the Attach Files section of Editorial Manager (eg, Figure 1, Figure 2). This provides a label for each figure in the PDF generated by Editorial Manager.
- Cite figures consecutively in the manuscript, and number them in the order in which they are discussed.
- Editorial Manager will automatically perform a quality check of all figures submitted, and designate images as either "pass" or "fail."
- Ensure the file format is either TIFF, EPS, or MS Office (DOC, PPT, XLS) files, and the resolution is at least 300 dpi.
- Carefully review the PDF conversion of your submission files to ensure that the figures uploaded without error and appear as intended.

If you experience any difficulties uploading figure images, or have questions regarding submission specifications, please contact the Editorial Office via email: medicine@wolterskluwer.com

Meanwhile, if you do not have figures or a Visual Abstract to summarize your article yet, we encourage you to create one using a tool made for scientists, Mind the Graph. Keep in mind that having a visual element in your paper can increase citations by 120%. Mind the Graph can help you showcase the focal points of your research as easy-to-understand synopses of scientific content in graphical and visual formats. All of this multimedia content link back to the published article so that your work is noticed by the research community, decision makers, and larger society.

Figure Legends

- Legends for all figures should be brief and specific and should appear on a separate page at the end of the manuscript document, following the list of references. Legends should indicate the figure number and must be numbered correctly.
- All symbols or abbreviations appearing in an illustration must be defined in the legend; arrows appearing in a figure should be mentioned in the legend.
- Legends for composite figures should be formatted as a single legend containing necessary information about each part/panel (not separated).
- Credit for any previously published illustration must be given in the corresponding legend and must appear in the style stipulated by the original copyright holder.

For further information on figure legend formatting, please see the *AMA Manual of Style*.

Supplemental Content

Authors may submit supplemental digital content to enhance their article's text. Supplemental digital content may include text documents like questionnaires, graphs, tables, figures, and videos. Supplemental digital content will not appear in the article itself but will appear online,

accessible by a URL embedded in the article. Supplemental digital content files are not copy edited; they will be presented digitally as submitted.

Supplemental content should include a sequential number if submitting more than one (1, 2, 3, etc.). Cite all supplemental digital content consecutively in the text. Citations should include the type of material submitted, should be clearly labeled as "Supplemental Digital Content" or "Supplemental Video," and should provide a brief description of the supplemental content.

Citation Examples:

(see Video, Supplemental Video, which demonstrates the degrees of flexibility in the elbow)

(see Table, Supplemental Content, which illustrates the rise in cost of knee replacement surgery)

Provide a separate set of legends for supplemental digital content at the end of the text, following the figure legend. List each legend in the order in which the material is cited in the text.

Legend Examples:

Supplemental Video. Video that demonstrates the degrees of flexibility in the elbow, 5 minutes, 10MB.

Supplemental Digital Content. Table that illustrates the rise in cost of knee replacement surgery.

Supplemental Content Size and File Type Requirements

- Supplemental digital content may be presented in any format, and should indicate the article title and first author for clarity.
- Supplemental video files should be submitted following these requirements:
    - .wmv, .mov, .flv, .qt, .mpg, .mpeg, .mp4 formats only
    - Video files should be formatted with a 320 x 240 pixel minimum screen size.
    - Videos should not exceed 10 minutes in runtime.
    - Videos must include embedded audio narration in English.
    - Video files too large to upload in Editorial Manager should be submitted via a file transfer website, such as You Send It (https://www.yousendit.com) to medicine@wolterskluwer.com

For more information, please review LWW's requirements for submitting Supplemental Digital Content: http://links.lww.com/A142.

Letters to the Editor

Letters can be responses to articles or other letters published in the journal, or brief comments about issues of importance in general medicine. Letters submitted to the Editor should contain a brief and thoughtful analysis of an original article. Please note that publication is not guaranteed. References, if appropriate, can be provided. Letters to the Editor should be no longer than 500 words.

Letters to the Editor will be posted on the *Medicine* Authors Correspondence Blog and are citable but not indexed in the journal. Authors of the original article may be invited to write a response to one or more letters if the editors deem a response is warranted.

Email letters to medicine@wolterskluwer.com rather than submitting through Editorial Manager.

CAPÍTULO III

CONSIDERAÇÕES FINAIS

A obesidade é um fator de risco conhecido para COVID-19, tendo uma dose-resposta entre IMC mais alto relacionada com o agravamento da COVID-19; portanto, indivíduos com excesso de peso e positivos para COVID-19 tem um risco aumentado de complicações, hospitalizações, admissão em UTI, alterações em marcadores sanguíneos significativos, necessidade de VMI e risco de morte, sendo que os sobreviventes podem desenvolver a Síndrome da COVID-longa, em que os sintomas podem persistir por semanas a meses após a recuperação da COVID-19. Sabe-se que a obesidade é uma doença crônica, presente em todas as faixas etárias, e que através de um estilo de vida saudável, podemos reduzir a gravidade da infecção por COVID-19 em indivíduos com sobrepeso e/ou obesidade.

As sequelas observadas nos indivíduos acometidos pela COVID-19 estão diretamente relacionadas à gravidade da doença. Dessa forma, indivíduos hospitalizados com obesidade e COVID-19 devem ser cuidadosamente acompanhados e manejados de forma rápida e eficaz por uma equipe multidisciplinar, para uma melhor recuperação no pós-COVID. Com base no segundo artigo, concluimos que 8 semanas de intervenção promoveram melhorias significativas nos testes antropométricos, de composição corporal e de aptidão física e uma redução significativa no perfil lipídico e na hemoglobina glicada. Portanto, na reabilitação na Síndrome da COVID-19 longa, os profissionais da saúde devem realizar avaliação completas (aptidão física, composição corporal e marcadores bioquímicos) para traçar uma melhor estratégia para melhorar a qualidade de vida desse indivíduo. Distante disso enfatiza-se a importância de uma equipe multidisciplinar no desenvolvimento de estratégias para recuperação das condições de vida, buscando assim o cuidado integral do indivíduo.

PERSPECTIVAS FUTURAS

Novos estudos podem ser conduzidos considerando algumas lacunas na literatura e outras lacunas observadas na tese. Entretanto, ressalta-se que alguns estudos dependem da fase (aguda ou crônica da doença) e, portanto, podem ser mais ou menos viáveis,

considerando os aspectos ambientais e temporais. Entretanto, abaixo são apontados aspectos que podem ser investigados na COVID-19.

i. Incorporar um grupo sem a doença (grupo controle) associada à COVID-19 de longa duração para orientar ações de reabilitação mais assertivas;

ii. Aplicar o registro alimentar antes da intervenção, após 8 semanas e 16 semanas. No registro alimentar deve ser anotado todos os alimentos e bebidas consumidos ao longo de um ou mais dias, como também alimentos consumidos fora de casa, devendo ser dias alternados e abrangendo um dia de final de semana;

iii. Analisar outros parâmetros bioquímicos mais precisos para avaliar a extensão das sequelas causadas pela COVID-19, tais como citocinas pró-inflamatórias (IL-1, IL-2, IL-6, IL-8, IL-12, IL-18, Interferon-gama (IFN-γ) e fator de necrose tumoral alfa (TNF-α)) e anti-inflamatórias (IL-10), fatores de coagulação (D-dímero, tempo de tromboplastina parcial ativada (TTPa), tempo de protrombina (TP) e plaquetas) e marcadores cardíacos [creatina quinase total, creatina quinase-MB, troponina, mioglobina e peptídeo natriurético cerebral (BNP)] para identificar possíveis danos pós-COVID em pessoas com sobrepeso ou obesidade;

iv. Considerar as respostas de monitoramento a longo prazo e a diferença na resposta entre sexo e grupos de idade ao exercício concorrente;

v. Explorar outras combinações de treinamento (exercício aeróbio *versus* exercício resistido) a fim de compreender as respostas fisiopatológicas;

vi. Conduzir uma intervenção interdisciplinar com seguimento, após 16 semanas deste estudo para verificar se as mudanças nos hábitos alimentares e atividade física foram persistentes para a composição corporal e parâmetros bioquímicos;

vii. Elaborar uma revisão sistemática abordando a aplicação de intervenções multidisciplinares na reabilitação de indivíduos pós-COVID-19.

APÊNDICE A

Anamnese - Projeto pós-COVID - Prevalência e fatores associados

Descrição do formulário

Termo de Consentimento Livre e Esclarecido (TCLE) foi assinado pelo paciente?

- ○ Sim
- ○ Não

Nome do paciente:

Texto de resposta curta

Idade:

Texto de resposta curta

Sexo:

- ○ Masculino
- ○ Feminino

E-mail:

Texto de resposta curta

Telefone:

Texto de resposta curta

Profissão:

Texto de resposta curta

Altura (cm):

Texto de resposta curta

Peso (kg):

Texto de resposta curta

IMC (kg/cm^2):

Texto de resposta curta

Pressão arterial inicial (mmHg) (D/S):

Texto de resposta curta

Saturação de oxigênio inicial (%):

Texto de resposta curta

Frequência cardíaca inicial (bpm):

Texto de resposta curta

Condições e hábitos de vida

Descrição (opcional)

Pratica atividade física regular atualmente? *

- ◯ Sim
- ◯ Não

Quantos dias de atividade física na semana? *

- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ N/A

Duração da atividade física (em minutos): *

- ◯ 15
- ◯ 30
- ◯ 45
- ◯ 60
- ◯ > 60
- ◯ N/A

Praticava atividade física regular antes da COVID? *

- ◯ Sim
- ◯ Não

Quantos dias de atividade física na semana (antes da COVID)? *

- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ N/A

Duração da atividade física (em minutos) antes da COVID: *

- ◯ 15
- ◯ 30
- ◯ 45
- ◯ 60
- ◯ > 60
- ◯ N/A

Tabagista ou ex-tabagista? *

- Sim
- Não

Se tabagista ou ex-tabagista, quantidade de anos x maço? *

- 1-3 anos.maço
- 4-6 ano.maço
- 7-9 ano.maço
- > 9 ano.maço
- N/A

Narguille? *

- Sim
- Não

Se SIM, qual a frequência semanal? *

- 1x/semana
- 2x/semana
- 3x/semana
- > 4x/semana
- N/A

Tempo de tela diário (computado/TV, etc): *

- ◯ < 5h
- ◯ 5-10h
- ◯ > 10h

História mórbida pregressa e medicamentos de uso contínuo

Descrição (opcional)

História clínica (antes da COVID): *

- ☐ Hipertensão arterial
- ☐ Diabetes
- ☐ Dislipidemia (colesterol ou triglicerídeos altos)
- ☐ Asma
- ☐ DPOC/enfisema pulmonar
- ☐ DAC/IAM/revascularização
- ☐ DAC/cateterismo sem revascularização
- ☐ Outra cardiopatia
- ☐ Nenhum
- ☐ Outros...

Algum transtorno psiquiátrico diagnosticado? *

- ◯ Sim
- ◯ Não

Qual transtorno psiquiátrico diagnosticado (se presente)? *

Texto de resposta curta

Algum transtorno de sono diagnosticado? *

- ○ Sim
- ○ Não

Faz uso contínuo de medicamento no momento? *

- ☐ Anti-hipertensivo
- ☐ Anti-diabético
- ☐ Hipolipemiante (colesterol)
- ☐ Medicamento psiquiátrico
- ☐ Nenhum
- ☐ Outros...

COVID-19 e Pós-COVID-19

Descrição (opcional)

Data de diagnóstico da COVID (aproximado): *

Mês, dia, ano

Se internado, data de alta (aproximado):

Mês, dia, ano

Necessitou de ventilação mecânica invasiva?

- ◯ Sim
- ◯ Não

Quantos dias em ventilação mecânica invasiva?

Texto de resposta curta

Pós-COVID-19

Descrição (opcional)

Fadiga persiste atualmente? *

- ◯ Aos PEQUENOS esforços
- ◯ Aos MÉDIOS esforços
- ◯ Aos GRANDES esforços
- ◯ Sem fadiga

Dispneia persiste atualmente? *

- ◯ Aos PEQUENOS esforços
- ◯ Aos MÉDIOS esforços
- ◯ Aos GRANDES esforços
- ◯ Sem dispneia

Tosse persiste atualmente? *

- ◯ Sim
- ◯ Não

Se TOSSE persistiu, durante quanto tempo? *

- ( ) < 2 meses
- ( ) 2 - 4 meses
- ( ) 4 - 6 meses
- ( ) > 6 meses
- ( ) > 1 ano
- ( ) N/A

Outros sintomas persistentes no momento: *

- [ ] Cefaleia
- [ ] Dor muscular
- [ ] Dor articular
- [ ] Déficit de memória
- [ ] Déficit de atenção
- [ ] Velocidade de processamento
- [ ] Queda capilar
- [ ] Nenhum
- [ ] Outros...

TONTURA persiste atualmente?

- ( ) Sim
- ( ) Não

Se a TONTURA persistiu, durante quanto tempo?

- < 2 meses
- 2 meses - 4 meses
- 4 meses - 6 meses
- > 6 meses
- > 1 ano
- N/A

Se a TONTURA persistiu, qual o valor apontado na escala EVA?

- 1
- 2
- 3
- 4
- 5
- 6
- 7
- 8
- 9
- 10
- N/A

ZUMBIDO persiste atualmente?

- Sim
- Não

Se o ZUMBIDO persistiu, durante quanto tempo?

- ◯ < 2 meses
- ◯ 2 meses - 4 meses
- ◯ 4 meses - 6 meses
- ◯ > 6 meses
- ◯ > 1 ano
- ◯ N/A

Se a ZUMBIDO persistiu, qual o valor apontado na escala EVA?

- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5
- ◯ 6
- ◯ 7
- ◯ 8
- ◯ 9
- ◯ 10
- ◯ N/A

OTALGIA persistiu atualmente?

- ◯ Sim
- ◯ Não

Se a OTALGIA persistiu, durante quanto tempo?

- < 2 meses
- 2 meses - 4 meses
- 4 meses - 6 meses
- > 6 meses
- > 1 ano
- N/A

OTORREIA persiste atualmente?

- Sim
- Não

Se a OTORREIA persistiu, durante quanto tempo?

- < 2 meses
- 2 meses - 4 meses
- 4 meses - 6 meses
- > 1 ano
- N/A

PLENITUDE AURICULAR persiste atualmente?

- Sim
- Não

Se a PLENITUDE AURICULAR persistiu, durante quanto tempo?

- < 2 meses
- 2 meses - 4 meses
- 4 meses - 6 meses
- > 6 meses
- > 1 ano
- N/A

PERDA DE SENSAÇÃO AUDITIVA persiste atualmente?

- Sim
- Não

Se a PERDA DE SENSAÇÃO AUDITIVA persistiu, durante quanto tempo?

- < 2 meses
- 2 meses - 4 meses
- 4 meses - 6 meses
- > 6 meses
- > 1 ano
- N/A

Ageusia persiste atualmente?

- Sim
- Não

Por quanto tempo permaneceu com Ageusia?

- ◯ < 2 meses
- ◯ 2 - 4 meses
- ◯ 4 - 6 meses
- ◯ > 6 meses
- ◯ > 1 ano
- ◯ N/A

Anosmia persiste atualmente?

- ◯ Sim
- ◯ Não

Por quanto tempo permaneceu com Anosmia?

- ◯ < 2 meses
- ◯ 2 meses - 4 meses
- ◯ 4 meses - 6 meses
- ◯ > 6 meses
- ◯ > 1 ano
- ◯ N/A

ANEXO 1

CENTRO UNIVERSITÁRIO DE MARINGÁ - UNICESUMAR

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Efeitos de um modelo multiprofissional de intervenção em parâmetros biopsicossociais de pessoas com obesidade pós COVID-19

Pesquisador: Braulio Henrique Magnani Branco

Área Temática:

Versão: 2

CAAE: 39056920.0.0000.5539

Instituição Proponente: Universidade Cesumar

Patrocinador Principal: Universidade Cesumar

DADOS DO PARECER

Número do Parecer: 4.546.726

Apresentação do Projeto:

Trata-se de um ensaio clínico, de grupos paralelos, de medidas repetidas com follow-up. Serão convidados a participar da pesquisa
homens e mulheres com idade entre 19 a 59 anos, com índice de massa corporal (IMC) igual ou superior a 30 kg/m² e com diagnóstico positivo para
a SARS-CoV-2. Os participantes serão subdivididos por sexo e gravidade da COVID (leve, moderada, alta e crítica) de acordo com a história clínica
e um escore calculado com os dados obtidos de cópias dos prontuários das internações. As intervenções iniciarão a partir da alta médica pós
COVID-19. Em consonância com a "Systematic Evidence Review From the Obesity Expert Panel" (U.S. DEPARTMENT OF HEALTH AND HUMAN
SERVICES, 2013), 15 participantes por braço de intervenção serão necessários para a condução do presente estudo. Considerando uma perda
amostral de aproximadamente 30%, serão recrutados 20 participantes por grupo. Assim, 160 participantes, sendo 80 do sexo masculino (COVID
leve, moderada, alta e crítica) e 80 do sexo feminino (COVID leve, moderada, alta e crítica), serão recrutados. Serão realizadas avaliações préparticipação, após 8 semanas de intervenção, após 16 semanas de intervenção e após 16 semanas de follow-up. Serão excluídos participantes
portadores de doença crônica ou aguda que contraindique a realização de exercício físico e/ou

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Bairro: Jardim Aclimação **CEP:** 87.050-390
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altere a resposta à intervenção. As avaliações
consistirão em (1) exame médico com anamnese e exame físico completo; (2) coletas de sangue para o monitoramento de biomarcadores
musculares, renais, hepáticos, pulmonares e metabólicos; (3) mensuração da taxa metabólica basal; (4) avaliação antropométrica e de composição
corporal; (5) testes de aptidão física relacionados à saúde, isto é: força e resistência muscular, flexibilidade e resistência aeróbia e (6) preenchimento
de questionários de saúde, qualidade de vida, nutrição e saúde mental. Serão realizados exercícios físicos (3x/semana), aulas teórico-práticas de
nutrição saudável (2x/semana) e psicoterapia em grupo (1x/semana), ao longo de 16 semanas de intervenções multiprofissionais. Os grupos (adulto
masculino: COVID leve, moderada, grave e crítica e feminino nas mesmas condições) serão avaliados nos momentos (pré, pós 8 semanas, pós 16
semanas e pós 16 semanas de follow-up), via análise de variância (ANOVA) de dois caminhos (grupo x momento), utilizando o post-hoc de
Bonferroni, caso seja identificada diferença significativa, com $p<0,05$. A estatística descritiva envolverá o cálculo das médias, desvios-padrão,
intervalo de confiança a 95%, deltas relativos e absolutos. Acredita-se que a condução da presente pesquisa poderá nortear condutas mais
assertivas frente ao manejo das pessoas com comorbidades recuperadas da COVID-19 e propiciar possibilidades de protocolos de recuperação das
condições de saúde nesse grupo populacional altamente impactado pela pandemia.

Objetivo da Pesquisa:

OBJETIVO GERAL

Investigar os efeitos de uma intervenção multiprofissional em parâmetros biopsicossociais de pessoas com obesidade, após alta da COVID-19 em diferentes graus de comprometimento.

OBJETIVOS ESPECÍFICOS

1) Comparar as respostas biopsicossociais durante e após a intervenção multiprofissional
nos diferentes graus da COVID-19 (leve, moderada, grave e crítica);

2) Analisar os efeitos de uma intervenção multiprofissional de pessoas com obesidade após

alta da COVID-19, na aptidão física relacionada à saúde (força muscular, resistência muscular, resistência cardiorrespiratória, flexibilidade e composição corporal);
3) Verificar os efeitos de uma intervenção multiprofissional de pessoas com obesidade, após alta da COVID-19, no perfil alimentar e de saúde mental;
4) Examinar os efeitos de uma intervenção multiprofissional de pessoas com obesidade após alta da COVID-19 em diferentes biomarcadores (musculares, renais, hepáticos, pulmonares e metabólicos);
5) Correlacionar as respostas biopsicossociais dos participantes do estudo frente ao grau de comprometimento da COVID-19 (leve, moderada, grave e crítica);
6) Contribuir para a elaboração de protocolos multiprofissionais para a recuperação das condições de saúde, em pessoas com obesidade após alta da COVID-19;
7) Desenvolver materiais instrucionais multimeios para a capacitação de profissionais envolvidos na recuperação das condições de saúde, em pessoas com obesidade após alta da COVID-19.

Avaliação dos Riscos e Benefícios:

Riscos:

Os possíveis riscos ou desconfortos decorrentes da participação na pesquisa são tempo dispendido para o preenchimento dos questionários e deslocamento até o Laboratório Interdisciplinar de Intervenção em Promoção da Saúde, possíveis dores musculares durante prática de exercício físico que serão minimizados via exercícios posteriores de relaxamento pela equipe de fisiologia do exercício, possíveis quedas durante a prática de
exercícios físicos, com escoriações e até mesmo fraturas, que serão minimizados com todos os recursos ergonômicos que serão disponibilizadas pela equipe médica e de fisiologia do exercício do Laboratório Interdisciplinar de Intervenção em Promoção da Saúde, além de instruções diárias sobre a utilização da vestimenta adequada para prática de atividade física. Por fim, haverá breve incômodo por conta da punção para coleta de sangue venoso que será minimizada pela equipe biomédica

que é altamente treinada na condução de exames sanguíneos.

Benefícios:

Os possíveis benefícios decorrentes da participação na pesquisa são identificar riscos à saúde dos participantes, recebimento de laudos e relatórios sobre parâmetros de saúde e qualidade de vida, recebimento de intervenções físicas, nutricionais, psicológicas e consultas médicas que direcionarão o voluntário para ações que venham a melhorar a sua respectiva saúde e qualidade de vida, a fim de proporcionar a independência funcional, alimentação saudável, cuidado com a saúde mental e autocuidado.

Comentários e Considerações sobre a Pesquisa:

Trata-se de um Projeto de pesquisa apresentado para a Fundação Araucária ao Programa Pesquisa para o SUS: Gestão Compartilhada em Saúde - PPSUS Edição 2020/2021 Fundação AraucáriaPR/SESAPR/CNPq/Decit/SCTIE/MS.

Considerações sobre os Termos de apresentação obrigatória:

O projeto havia ficado pendente na primeira versão. Após Todas as pendências foram atendidas e todos documentos apresentados estão adequados.

Recomendações:

Não há.

Conclusões ou Pendências e Lista de Inadequações:

Após a leitura do projeto e dos documentos anexados, e de acordo com o disposto na Resolução 466/12, sugere-se que este projeto fique com Parecer APROVADO para que os pesquisadores realizem a coleta dos dados.

Considerações Finais a critério do CEP:

Solicitamos que seja apresentado a este CEP, relatório final da pesquisa, bem como informações relativas às modificações do protocolo, cancelamento, encerramento e destino dos conhecimentos obtidos, através da Plataforma Brasil - no modo:

NOTIFICAÇÃO. Demais alterações e prorrogação de prazo devem ser enviadas no modo EMENDA.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

ANEXO 2

anthea.xie@mdpi.com 10:55
On behalf of Nutrients Editorial Office
To You, +6

Dear Dr. Magnani Branco,

Congratulations on the acceptance of your manuscript, and thank you for submitting your work to Nutrients:

Manuscript ID: nutrients-2861485
Type of manuscript: Systematic Review
Title: Obesity as a Risk Factor for Complications and Mortality in Individuals with SARS-CoV-2: A Systematic Review
Authors: Marielle Priscila De Paula Silva Lalucci, Deborah Cristina de Souza Marques, Pablo Valdes-Badilla *, Leonardo Vidal Andreato, Braulio Henrique Magnani Branco *
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