Rodolfo Furlan Damiano

Manifestações psicopatológicas e cognitivas associadas à infecção pelo vírus SARS-CoV-2

Tese apresentada à Faculdade de Medicina da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Programa de Psiquiatria

Orientador: Prof. Dr. Euripedes Constantino Miguel

Coorientador: Orestes Vicente Forlenza

(Versão corrigida. Resolução CoPGr 6018/11, de 1 de novembro de 2011. A versão original está disponível na Biblioteca da FMUSP)

São Paulo

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PSYCHOPATHOLOGICAL AND COGNITIVE MANIFESTATIONS ASSOCIATED WITH SARS-CoV-2 VIRUS INFECTION

Doctoral Thesis, by Rodolfo Furlan Damiano, MD

UNIVERSIDADE DE SÃO PAULO

FACULDADE DE MEDICINA

Programa de Pós-graduação em Ciências Médicas: Psiquiatria

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Esta tese é parte do Programa Tripartite de Pós-Graduação em Neurociências do Desenvolvimento Translacional. Este programa é executado por Programas de Pós-Graduação em Psiquiatria e Saúde Mental brasileiros considerados de nível internacional pelo Ministério da Educação do Brasil de três Universidades (Universidade Federal de São Paulo, Universidade de São Paulo, e Universidade Federal do Rio Grande do Sul). O programa Tripartite visa formar os principais pesquisadores do país com conhecimento avançado em metodologias de campo inovadoras em áreas estratégicas como neurociência populacional, fenomenologia baseada em evidências, neurociência clínica, neurociência integrativa e prevenção de transtornos mentais baseada em evidências.

O cuidado é a essência da vida, e o amor a essência do cuidado

Dedicatória

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RESUMO

Damiano RF. Manifestações psicopatológicas e cognitivas associadas à infecção pelo vírus SARS-CoV-2 [tese]. São Paulo: Faculdade de Medicina, Universidade de São Paulo; 2023.

Introdução: Estudos preliminares com pacientes infectados com o vírus SARS-CoV-2 indicam acometimento de diferentes órgãos e sistemas, incluindo o sistema nervoso central (SNC). As alterações no SNC incluem manifestações agudas e crônicas envolvendo expressões clínicas de natureza psiquiátrica, neurológica ou neuropsiquiátrica. Nesta presente tese, nosso objetivo visa caracterizar as alterações psicopatológicas e cognitivas após 6-11 meses da infecção por SARS-CoV-2. **Objetivos:** a. Descrever as manifestações psicopatológicas e cognitivas em pacientes após 6-11 meses da infecção por SARS-CoV-2; b. Identificar variáveis na linha de base que possam prognosticar manifestações psicopatológicas e cognitivas em pacientes após 6-11 meses da infecção por SARS-CoV-2; c. Investigar a associação de alterações de olfato e paladar na linha de base com as manifestações psicopatológicas e cognitivas em pacientes após 6-11 meses da infecção por SARS-CoV-2; d. Correlacionar as manifestações biológicas agudas na linha de base e após 6-11 meses da infecção por SARS-CoV-2, medidas por meio de exames de sangue gerais e painel de citocinas com as manifestações psicopatológicas e cognitivas 6 a 11 meses depois. **Métodos:** Foram avaliados cerca de 700 indivíduos adultos com diagnóstico confirmado laboratorialmente de COVID-19. Tais indivíduos tiveram diversos dados e marcadores biológicos coletados durante a internação, sendo subsequentemente avaliados multidisciplinarmente, de 6-11 meses após a alta. Neste momento, materiais biológicos foram novamente coletados. Esta tese versa primariamente sobre os dados coletados a partir de uma entrevista psiquiátrica estruturada aliada a diversas escalas de avaliação sintomatológica e uma bateria de testes neuropsicológicos a fim de acessar a cognição. **Resultados:** Os resultados desta tese são apresentados em 3 artigos. No Artigo 1, que envolve os objetivos 1 e 2 encontramos: os diagnósticos de 'depressão', 'transtorno de ansiedade generalizada' e 'transtorno de estresse pós-traumático' foram observados, respectivamente, em 8%, 15,5% e 13,6% da amostra. O declínio da memória foi relatado subjetivamente por 51,1% dos pacientes. Os desfechos psiquiátricos ou cognitivos não foram associados a nenhuma variável clínica relacionada à gravidade da doença em fase aguda, nem a estressores psicossociais relacionados à doença. Os resultados do artigo 2 se referem ao objetivo 3, ou seja: a perda olfatória e gustativa moderada/grave concomitante durante a fase aguda da COVID-19 foi significativamente associada ao pior desempenho na tarefa de memória da lista de palavras. Finalmente, descrevemos a seguir os resultados do artigo 3, que ser referem ao objetivo 4. A análise multivariada encontrou sexo, idade, etnia, escolaridade, comorbidade, fragilidade e atividade física significativamente associados à cognição geral. Análise bivariada constatou que diversos marcadores biológicos (ex.: G-CSF, IFN-alfa2, IL13, IL15, IL1-RA, EL1-alfa, IL45, IL5, IL6, IL7, TNF-Beta, VEGF, Proteína C Reativa e D-Dímero) do follow-up foram consideravelmente associados com a cognição geral. No entanto, após uma análise de regressão multivariada (LASSO), tais marcadores

inflamatórios e citocinas não se mantiveram expressivamente associadas à cognição. **Conclusão:** Nossos dados sugerem que os transtornos mentais são frequentes após 6-11 meses da infecção por SARS-CoV-2, notadamente os transtornos depressivo, de ansiedade generalizada e de estresse pós-traumático. Além destes, cerca de metade da amostra relata declínio de memória. No entanto estes achados não foram associados a nenhuma variável clínica relacionada à gravidade da doença em fase aguda, nem a estressores psicossociais relacionados à doença. Por outro lado, observamos que alterações quimiossensoriais se correlacionaram com pior desempenho em tarefas de memória. Finalmente, nossos dados não confirmaram a hipótese de que marcadores inflamatórios e citocinas (tanto na fase aguda como tardia) pudessem predizer ou estar associados aos déficits psiquiátricos ou cognitivos na COVID-Longa.

Palavras-chave: COVID-19. SARS-CoV-2. Estudos de coortes. Cognição. Citocinas. Internação hospitalar. Psiquiatria comunitária.

ABSTRACT

Damiano RF. Psychopathological and cognitive manifestations associated with SARS-CoV-2 virus infection [thesis]. São Paulo: "Faculdade de Medicina, Universidade de São Paulo"; 2023.

Introduction: Preliminary studies with patients infected with the SARS-CoV-2 virus indicate involvement of different organs and systems, including the central nervous system (CNS). Changes in the CNS include acute and chronic manifestations involving clinical expressions of psychiatric, neurological or neuropsychiatric nature. In this present thesis, our objective is to characterize psychopathological and cognitive alterations after 6-11 months of SARS-CoV-2 infection. **Objectives:** a. To describe psychopathological and cognitive manifestations in patients after 6-11 months of SARS-CoV-2 infection; b. Identify baseline variables that may predict psychopathological and cognitive manifestations" in patients after 6-11 months of SARS-CoV-2 infection; c. To investigate the association of smell and taste changes at baseline with psychopathological and cognitive manifestations in patients after 6-11 months of SARS-CoV-2 infection; d. Correlate the acute biological manifestations at baseline and after 6-11 months of SARS-CoV-2 infection, as measured by general blood tests and cytokine panel, and correlate them with psychopathological and cognitive manifestations at 6 to 11 months after. **Methods:** About 700 adult individuals with laboratory-confirmed diagnosis of COVID-19 were evaluated. Such individuals had several data and biological markers collected during hospitalization, being subsequently evaluated multidisciplinary, from 6 to 11 months after discharge. At this time, biological materials were again collected. This thesis deals primarily with data collected from a structured psychiatric interview combined with several symptom assessment scales and a battery of neuropsychological tests in order to assess cognition. **Results:** The results of this thesis are presented in 3 articles. In Article 1, which involves objectives 1 and 2, we found: the diagnoses of 'depression', 'generalized anxiety disorder' and 'post-traumatic stress disorder' were observed, respectively, in 8%, 15.5% and 13 .6% of the sample. Memory decline was subjectively reported by 51.1% of patients. Psychiatric or cognitive outcomes were not associated with any clinical variables related to the severity of the illness in the acute phase, nor with psychosocial stressors related to the illness. The results of article 2 refer to objective 3, that is: concomitant moderate/severe olfactory and gustatory loss during the acute phase of COVID-19 were significantly associated with worse performance in the word list memory task. Finally, we describe below the results of article 3, which refer to objective 4. The multivariate analysis found gender, age, ethnicity, education, comorbidity, frailty and physical activity significantly associated with general cognition. Bivariate analysis found that several biological markers (eg, G-CSF, IFN-alpha2, IL13, IL15, IL1-RA, EL1-alpha, IL45, IL5, IL6, IL7, TNF-Beta, VEGF, C-Reactive Protein and D -Dimer) at follow-up were significantly associated with general cognition. However, after a multivariate regression analysis (LASSO), such inflammatory markers and cytokines did not remain significantly associated with cognition. **Conclusion:** Our data suggest that mental disorders are frequent after 6-11 months of SARS-CoV-2 infection, notably depression, generalized anxiety and post-traumatic stress disorders. In addition to these, about half of the sample report memory decline. However, these findings were not associated with any clinical variable related to the severity of the disease in the acute phase, nor with psychosocial stressors related to the disease. On the other hand, we observed that chemosensory changes correlate with worse performance in memory tasks. Finally, our data did not support the hypothesis that inflammatory markers and cytokines (both in the acute and

late phases) could predict or be associated with psychiatric or cognitive deficits in Long COVID.

Keywords: COVID-19. SARS-CoV-2. Cohort studies. Cognition. Cytokines. Hospitalization. Community psychiatry.

Introdução

No início de março de 2020, a Organização Mundial da Saúde (OMS) declarou a infecção pelo novo coronavírus (SARS-CoV-2) uma doença pandêmica com consequências desconhecidas (1). Pouco mais de um ano depois, havia mais de cento e cinquenta milhões de infectados e mais de 3 milhões mortes em todo o mundo causadas *pelo Coronavirus Disease* 2019 COVID-19 (dados de 5 de Maio de 2021) (2). Dados recentes, de março de 2023, mostram cerca de 675 milhões de infectados, quase 7 milhões de mortes e cerca de 13 bilhões de doses de vacinas aplicadas (2). A magnitude da disseminação da doença em algumas regiões tornou o Brasil um dos países com a maior taxa de transmissão e de mortalidade pelo vírus em todo o mundo (2, 3).

O primeiro estudo sobre os efeitos do SARS-CoV-2 no corpo humano foi realizado por Zhou et al. (4) e publicado na *Nature* em meados de 2020. No início, apenas sintomas pulmonares foram identificados (4, 5), pensando em se tratar de uma afecção exclusivamente respiratória. Entretanto, logo começaram a ser divulgados novos sintomas, com destaque para as manifestações no sistema nervoso central (SNC) (6). Ao longo do tempo, evidências acumuladas sugeriram que as a fisiopatologia aguda e crônica da doença promove (ou suscita) complicações neuropsiquiátricas importantes, com altas taxas de depressão, ansiedade, transtorno do estresse pós-traumático (TEPT), bem como alterações neurológicas e cognitivas (7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20).

A primeira meta-análise referente aos efeitos neuropsiquiátricos da COVID-19 foi conduzida por Rogers et al. (21) e mostrou que, da mesma forma que outros coronavírus (SARS-CoV-1 e MERS), o SARS-CoV-2 pode afetar o SNC de várias formas, incluindo agravos psiquiátricos e cognitivos, agudos e crônicos. Estudos longitudinais de outras

infecções por coronavírus mostraram uma prevalência média de depressão de 14,9%, ansiedade de 14,8%, TEPT de 32,2%, e alterações de memória de 18,9% (21).

Na conjuntura atual da pandemia de COVID-19, os sintomas psiquiátricos, neurológicos e neuropsiquiátricos agudos são diversos (22). Os sintomas psiquiátricos mais prevalentes na fase aguda de pacientes infectados pela SARS-CoV-2 foram sintomas ligados ao estresse (96,2%) (23), depressivos (29,2%) e ansiosos (20,8%), sendo a prevalência de depressão entre os infectados significativamente maior do que entre os indivíduos em quarentena (não infectados) (24). Achado similar, exceto pela adição dos sintomas psicóticos, foi encontrado por outro estudo que identificou 16,8% de incidência de sintomas psiquiátricos novos em pacientes durante a fase aguda, sendo os mais comuns sintomas psicóticos (43%) e sintomas de transtornos de humor (17%) (10). Outros agravos neuropsiquiátricos comuns são delirium e alterações de memória, o que alguns pesquisadores chamaram de síndrome "demência-like" (26%), caracterizada por alterações de memória, atenção e função executiva (10, 25). Em uma coorte retrospectiva chinesa, a incidência geral de delirium foi de 7,5%, com uma incidência muito maior (14,8%) em casos graves (26). Outro estudo encontrou uma prevalência de 26% de "demência-like" (10). Alterações de atenção e memória também foram identificadas em outro estudo com pacientes tanto com infecção severa por SARS-SoV-2 (27) quanto com infecções leves (28).

A definição de COVID-Longa

Ao longo do tempo, diversos sintomas persistentes importantes foram identificados em pacientes que contraíram o vírus da SARS-CoV-2. Tais sintomas incluem manifestações psicopatológicas, cognitivas, otorrinolaringológicas, respiratórias, cardiovasculares, renais, fadiga, entre outros (19, 29, 30). Esse conjunto de

agravos diversos fez os especialistas criarem um termo de COVID-Longa, ou mais especificamente *Post-Acute Sequelae of COVID-19* (PASC) (31). Nesta tese, consideraremos o diagnóstico de PASC proposto por Soriano e colaboradores (31). De acordo com os autores, que se basearam em um consenso Delphi, PASC pode ser definida pela existência de sintomas relacionados à COVID-19 que não podem ser explicados por outros diagnósticos, que tenham início em até 3 meses após a infecção aguda e que durem por pelo menos 2 semanas.

Em um estudo de nosso grupo com os dados da mesma fonte que aqueles coletados para esta tese, investigamos os sintomas mais frequentemente associados com o diagnóstico de PASC em pacientes pós-hospitalizados utilizando um modelo de variáveis latentes em *Item Response Theory* (32). Surpreendentemente, encontramos que os sintomas mais associados (maiores coeficientes [coef] de associação em ordem decrescente) com o diagnóstico de COVID-Longa foram: fadiga, transtorno do estresse pós-traumático, depressão, perda de memória, ansiedade, dificuldade de concentração e insônia.

Como o objetivo da tese busca esmiuçar as alterações psicopatológicas e cognitivas tardiamente (a partir de 6 meses) à infecção por SARS-CoV-2, assim como fatores clínicos e biológicos precoces preditores de tais manifestações tardias, focaremos próximos itens nessas questões. Na presente tese, o uso do intervalo de 6 meses após infecção foi dado pela logística implementada na coleta de dados, que demorou 6 meses para começar a partir do início da pandemia.

Efeitos Psicopatológicos Crônicos da COVID-19

Inúmeros estudos com diferentes metodologias foram produzidos nos últimos anos avaliando os efeitos psicopatológicos da COVID-19. Apesar disso, ainda há um debate na literatura referente ao impacto da pandemia da COVID-19 na saúde mental da população (11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 33). Inicialmente, verificou-se prevalência elevadas de depressão, ansiedade, fadiga e TEPT na população durante o período pandêmico (34, 35, 36, 37, 38, 39), ao passo que estudos posteriores detectaram um declínio da prevalência desses sintomas nos 2 meses subsequentes ao início da pandemia (40, 41). O mesmo padrão de diminuição foi encontrado no Brasil em um grande estudo de coorte (ELSA) nos sintomas depressivos, ansiosos e de estresse após 7 meses do início da pandemia (42). Meta-análises recentes investigando o impacto da pandemia na população geral têm encontrado um declínio nos transtornos mentais ao longo da pandemia, apresentando dados de prevalências ainda menores do que aqueles pré-pandêmicos (43). Entretanto, os estudos longitudinais apresentam excessiva heterogeneidade (I^2s>90%) relacionada à mudança (pré e pós pandemia) nos sintomas e diagnósticos psiquiátricos, sendo difícil tirar conclusões inequívocas (11, 43). O mesmo fenômeno tem sido discutido em termos de suicídio (44); uma meta-análise recente revelou que na população geral da maioria dos países, as taxas de suicídio tenderam a diminuir ou se estabilizar ao longo dos meses que se seguiram à pandemia (45). Importante observar que esses dados são preliminares e em sua maioria ecológicos, além de não separarem por extratos populacionais (46).

Por outro lado, os achados contraditórios observados pelas revisões sistemáticas descritas acima, não são supreendentes. Os impactos de uma pandemia na população são resultado da soma inúmeros fatores, entre eles: localização geográfica (16), sexo predominante (47, 48), etnia predominante (49), idade média da população estudada (48), nível sócio-econômico, políticas públicas durante a pandemia (50), gravidade do

acometimento populacional pelo vírus durante a pandemia (51), impacto econômico (52), situação de vulnerabilidade da população estudada (49), entre outros. Além disso, tais estudos dão uma perspectiva geral da saúde mental da população e não distinguem indivíduos infectados dos não infectados. Dessa forma tornam-se necessários estudos cujo objetivo seja averiguar real impacto da infecção na saúde mental dos indivíduos, foco específico deste estudo.

Referente ao tema em questão, meta-análises atuais têm demonstrado que, embora a prevalência geral de depressão e ansiedade tenham diminuído durante a pandemia da COVID-19, houve um crescimento paralelo de depressão nos indivíduos infectados (47). Estudos iniciais 6 meses após a infecção por SARS-CoV-2, mostraram que cerca de um terço dos pacientes (33,62%) apresentou algum tipo de sintoma psicopatológico residual persistente, sendo que cerca de 12,8% tiveram novos diagnósticos. Desses, os mais incidentes foram os de transtornos de humor, de ansiedade ou psicóticos (8,63%), transtornos do sono (2,53%) e síndromes demenciais (0,67%). Importante ressaltarmos que os diagnósticos neuropsiquiátricos foram significativamente mais numerosos para indivíduos que contraíram COVID-19 do que para aqueles que contraíram Influenza no mesmo período, destacando o possível papel etiológico do SARS-CoV-2 nas manifestações da doença no SNC (53).

Corroboram esta hipótese a observação de que, durante a pandemia, países em que houve precária gestão em saúde (incluindo manejo de medidas preventivas, indicações de tratamento e vacinação) tiveram um número mais expressivo de mortes. Concomitantemente, a saúde mental dos habitantes desses países teve maior impacto psicopatológico durante a pandemia esses dois anos epidemia de COVID-19. Este achado foi confirmado por diversos estudos em múltiplos países, em que se avaliaram diversos

parâmetros de gestão pública durante a pandemia e seu impacto na psicopatologia da população (50, 54, 55, 56, 57).

Em se tratando de estudos populacionais Brasileiros, cumpre-nos ressaltar a coorte ELSA (Estudo Longitudinal de Saúde do Adulto). O estudo ELSA, que avaliou mudanças psicopatológicas antes e após o início da pandemia, não encontrou um aumento de transtornos mentais (42). Entretanto**,** cabe-nos ressaltar alguns vieses importantes para esse estudo, tais como a não separação de indivíduos infectados dos não infectados pelo SARS-CoV-2 e a perda de 50% da onda anterior, que poderia representar os indivíduos mais impactados pela pandemia nos mais diferentes níveis. O mesmo grupo de pesquisa, avaliando dados da mesma coorte, também encontrou um aumento da densidade da rede de sintomas psicopatológicos (associação mais forte entre os diferentes sintomas), o que pode predizer um futuro aumento da frequência de transtornos mentais (12).

Dentro desse escopo das alterações cognitivas em pacientes com COVID-Longa, havia diversas limitações no momento de planejamento do estudo, tais como a predominância de desenho transversal com pequeno número amostral (58), com avaliação do estado mental baseada em pequenas matrizes de sintomas neuropsiquiátricos, (59) frequentemente representada por questionários de autorrelato (escalas dimensionais) (60) ou impressão clínica (64, 69, 70) Por isso, um dos objetivos desta tese versa sobre a implementação de um protocolo robusto de avaliações cognitivas amplas desenhado por neuropsicólogos e com escalas dimensionais e estruturadas, além da possibilidade de uma melhor caracterização dos sintomas.

Efeitos Cognitivos Crônicos da COVID-19

Se há uma indefinição quanto aos possíveis efeitos da pandemia da COVID-19 na saúde mental, certamente não é sua influência na cognição. Desde o início da pandemia estudos têm demonstrado consistentemente impactos da SARS-CoV-2 nos domínios cognitivos dos pacientes infectados (61). Estudos em sobreviventes de COVID-19 apontaram para deficiências em vários domínios cognitivos nas formas agudas da doença (37, 62, 63), particularmente memória episódica, atenção e funções executivas (e.g., flexibilidade cognitiva), que foram interpretadas como secundárias ao processo inflamatório sistêmico. (62). Em um estudo inicial, Jaywant et al. (64) avaliaram o comprometimento cognitivo antes da alta hospitalar em uma coorte transversal de 57 pacientes internados em unidades de reabilitação após terem contraído COVID-19 grave (definido por dificuldades de mobilidade ou prejuízo a outras atividades de vida diária e que portanto necessitem reabilitação hospitalar). Apesar do pequeno tamanho da amostra, os autores encontraram altas taxas de prejuízo à atenção e disfunções executivas, que não foram associadas ao tempo de intubação, tempo decorrido desde a extubação até a avaliação, diagnósticos psiquiátricos ou pré- comorbidades metabólicas ou cardiovasculares existentes, sugerindo que todos os casos graves de COVID-19 estão em risco de comprometimento cognitivo. Do mesmo modo, Woo e colaboradores (28) investigando indivíduos adultos que contraíram uma forma leve de COVID-19, encontraram uma alta prevalência de alterações de memória de curto prazo, atenção e concentração, sendo que estas não estavam associadas com a gravidade da doença na linha de base, sugerindo um impacto específico do SARS-CoV-2 no Sistema Nervoso Central.

Tais sintomas foram identificados inicialmente em estudos epidemiológicos (53, 65). Em um importante estudo, Taquet et al. (53) mostraram que a incidência de diagnósticos de demência nos indivíduos após a infecção por SARS-CoV-2 foi maior do

que após outras infecções durante o mesmo período (tais como Influenza ou outras doenças do sistema respiratório). O mesmo autor encontrou uma prevalência de 0,67% de novos casos de demência após 6 meses do diagnóstico de COVID-19 e uma associação positiva entre a gravidade da doença e a sintomatologia neuropsiquiátrica, usando um grande registro eletrônico de saúde. Diversos estudos já identificaram declínio cognitivo em sobreviventes da COVID-19 (33), seja em portadores de formas leves (66) ou severas da COVID-19 (67). Ademais, estudos utilizando dados médicos eletrônicos populacionais confirmam tais achados e apontam para uma necessidade urgente de que pesquisadores se debrucem sobre esse tema (68). Finalmente, uma vez confirmada a associação entre o SARS-CoV-2 e manifestações no SNC, o próximo passo será a elucidação de possíveis mecanismos para explicá-la.

Mecanismos Propostos de Associação

Ao longo do tempo diversos estudos foram publicados propondo diferentes mecanismos para explicar a associação entre os sintomas relacionados com alterações do SNC e a infecção por SARS-CoV-2 (69, 70, 71, 72). Um importante estudo publicado no JAMA *Psychiatry* apontou que a infecção pelo SARS-CoV-2 pode causar sintomas neuropsiquiátricos por mecanismos diretos e indiretos, tais como dano neuronal direto, lesão cerebral vascular endotelial, disfunção no sistema de neurotransmissão por mecanismos diretos e/ou sistêmicos, além de eventos trombóticos (71). A descoberta do RNA do coronavírus no tecido cerebral de pacientes falecidos levantou a possibilidade de um mecanismo de lesão cerebral direta (73). Essa observação foi corroborada pelo achado do vírus em células neurais e endoteliais em tecidos do lobo frontal (74), e no líquido cefalorraquidiano de indivíduos infectados (75, 76, 77). Além disso, o SARS-CoV-2 foi encontrado em astrócitos de todos os pacientes falecidos com lesão cerebral,

sugerindo que o cérebro pode ser um santuário para o SARS-CoV-2 (37). Um estudo encontrou o vírus SARS-CoV-2 no tecido cerebral 53% de pessoas analisadas que morreram por COVID-19, embora as lesões cerebrais fossem inespecíficas e não pudessem ser atribuídas ao vírus diretamente (78). O RNA SARS-CoV-2, no entanto, raramente é identificado em amostras de Líquido Cefalorraquidiano (LCR) de pacientes com COVID-19 (79), e a maioria dos casos de sintomas neurológicos associados à COVID apresentam PCR negativo para SARS-CoV-2 no líquor, incluindo encefalopatias (7, 80, 81).

Entretanto, a despeito dos mecanismos diretos, a análise do LCR de pacientes com sintomas neurológicos mostrou imunorreatividade para SARS-CoV-2, resultante do vazamento de anticorpos séricos para o LCR, ao invés da produção intratecal de anticorpos (82, 83), sugerindo mecanismos indiretos. Vários desses mecanismos indiretos são descritos, como um estado de hipercoagulabilidade, neuroinflamação, alterações imunológicas e epigenéticas (22). Estudos sugerem, por exemplo, que a ruptura da barreira hematoencefálica está associada à encefalopatia, favorecendo a teoria da neuroinflamação (83, 84). Um possível mecanismo para essa teoria pode ser a hiperativação dos receptores P2X7 e consequente estimulação do inflamassoma NLRP3, desencadeando a cascata inflamatória. (85). A tempestade de citocinas, que gera uma resposta inflamatória ao SARS-CoV-2 no SNC, é mediada pela liberação maciça de citocinas de células gliais como IL1b, IL6 e TNF-alfa, encontradas no plasma de pacientes com COVID-19 (71, 86, 87, 88, 89, 90).

O conhecimento adquirido de outros surtos de coronavírus (SARS-CoV e MERS-CoV) sugeriu potenciais rotas neuroinvasivas para explicar alguns dos mecanismos envolvendo a ação direta do vírus no SNC. Sabe-se que a passagem pelas vias aéreas

superiores e o neuroepitélio olfatório são as etapas iniciais para a identificação do odor (91, 92). As células olfatórias expressam a isoforma 2 da enzima de conversão da angiotensina (ACE-2) e a serina protease tipo II (TMPRSS-2), que podem representar o ponto de entrada viral no SNC (93). Vários vírus de RNA podem sofrer transporte axonal para diferentes estruturas cerebrais, causando encefalite aguda (94, 95, 96). Um estudo recente apontou para a interface neural-mucosa na mucosa olfatória como uma potencial porta de entrada do SNC para SARS-CoV-2 (97).

Além da passagem pela via do neuroepitélio nasal, independentemente da passagem das vias aéreas inferiores, acumulam-se evidências sugerindo que o vírus infecta inicialmente os terminais nervosos periféricos e entra no SNC por meio de um mecanismo transsináptico, (98). Rotas transsinápticas foram relatadas em diferentes coronavírus (CoVs), como HEV67 (99, 100) e no vírus da bronquite aviária (101, 102). A infecção direta dos gânglios da raiz dorsal em ratos resultou na presença de SARS-CoV no SNC (100). Dados de microscopia eletrônica confirmaram a presença do vírus nas vesículas neuronais. A invasão viral do SNC pode ocorrer pela via transsináptica mediada pelo nervo vago, por meio da inoculação intranasal do vírus influenza (101). Animais vagotomizados parcialmente (unilateralmente) inoculados com o vírus apresentaram presença viral nos gânglios da raiz, bilateralmente. O vírus atingiu o gânglio contralateral à de-aferentação primeiro, sugerindo um transporte menos eficaz após a lesão do nervo vago. No SARS-CoV-2, os mecanismos transnasais e transsinápticos podem permitir que o vírus invada o bulbo olfatório e o tronco cerebral, sendo ambos possíveis locais iniciais para a invasão do SNC (103). Uma vez que no SNC, o vírus afeta neurônios, microglia, oligodendrócitos e, especialmente, astrócitos, minando a viabilidade dos neurônios (37, 103, 104).

Da mesma forma e contribuindo para a fisiopatologia do SARS-CoV-2 nos quadros demenciais, Abate et al. (68) revisou os diferentes mecanismos pelos quais a infecção por SARS-CoV-2 pode aumentar o risco da doença de Alzheimer (DA), que podem ser extrapolados para outras manifestações envolvendo alterações cognitivas. A neuroinvasão viral direta, como hipotetizado acima, e sua associação com a expressão de ACE-2 no cérebro, especialmente em células gliais, pode levar ao estresse oxidativo e perda neuronal devido à ativação da microglia e astrócitos, além do aumento da produção de óxido nítrico (NO). **(105, 106)**. Estudos pré-clínicos mais recentes apontaram para prejuízos cognitivos em ratos após inoculação de proteína spike de SARS-CoV-2 direto em hipocampo de ratos (107). As descobertas de que SARS-CoV-2 infecta astrócitos (37) e do seu papel na deposição de β-amiloide (βA) ressaltam uma possível ligação entre a infecção por COVID-19 e a DA. Foi demonstrado também que o βA atua como um peptídeo antimicrobiano que pode ser superproduzido a partir de um mecanismo imunológico (108). Já se sabe que os indivíduos com o alelo ApoE3 podem ser mais suscetíveis a formas graves da doença COVID-19 (109), agora a conexão entre o genótipo ApoE4, neuroinflamação e patologia da DA ainda precisa ser melhor investigada (110). De fato, estudos recentes apontaram para similaridades neuropatológicas entre Doença de Alzheimer e o declínio cognitivo relacionado à PASC (111), incluindo uma série de marcadores genéticos da DA (e.g., FERMT2, HLA-DRB1, GNA15, STAB1, ICA1L, COLGALT1, TNFAIP2, ITGAM, VASP, IDLIA, PVR, TECPR1) (112), e diversos biomarcadores séricos (i.e. GFAP, NFL, P-tau 181, UCH, NSE, and S100B) (111). Ademais, os estados hipercoaguláveis mencionados acima podem precipitar doenças microvasculares e consequentemente induzir demência vascular e DA (113). Todos esses fatores merecem ser estudados e podem contribuir concomitantemente para o

desenvolvimento de sintomas tanto psicopatológicos quanto cognitivos da SARS-CoV-2 (71).

Até onde temos conhecimento, apenas um estudo avaliou a associação de alterações de paladar e olfato com manifestações psicopatológicas e cognitivas nos pacientes pós-COVID-19, apontando para evidências de uma via direta de entrada do SARS-CoV-2 no SNC (114). Os autores encontraram uma associação positiva entre sintomas ansiosos, depressivos e perda de paladar e olfato. No entanto, o estudo tem limitações e vieses, tais quais a utilização de testes de rastreio de sintomas psiquiátricos, uma amostra pequena, e realização de avaliações apenas durante a fase aguda da COVID-19. Por isso, um dos objetivos desta tese versa sobre a implementação de um protocolo robusto com avaliações cognitivas e psicopatológicas amplas, além de uma avaliação otorrinolaringologia em uma ampla gama de pacientes.

Fatores Preditivos

Poucos estudos se debruçaram em entender os fatores que predigam o desenvolvimento de maior ou menor morbidade psiquiátrica e cognitiva a longo prazo na infecção por COVID-19. Assim como descrito nos tópicos acima, a possível associação entre a morbidade psiquiátrica e a maior gravidade da doença (tempo de hospitalização, necessidade de intubação orotraqueal, uso de drogas vasoativas, necessidade de leito em unidade de terapia intensiva) foi aventada e debatida em diversos estudos, porém ainda sem uma definição segura (28, 53, 64, 65). Da mesma forma, estudos de longo prazo de pacientes com formas agudas graves da doença (caracterizada por necessidade de hospitalização em leito de Unidade de Terapia Intensiva (UTI) por insuficiência respiratória, choque séptico ou cardiogênico) e síndrome do desconforto respiratório

agudo apontam para maior incidência de declínio cognitivo e disfunção executiva nesses indivíduos (115, 116).

Um outro fator importante a ser discutido é a relação com maior ou menor tempestade inflamatória (117). Existe evidência crescente de uma associação entre o aumento de citocinas pró-inflamatórias e diversos transtornos psiquiátricos, tais como depressão (118, 119), transtorno de ansiedade generalizada (120) e TEPT (121). (117). Além disso, diferentes estudos que investigaram doenças neurodegenerativas associaram marcadores inflamatórios e declínio cognitivo (122), especialmente em pacientes com Doença de Alzheimer (123, 124) e Infecções Virais Crônicas (e.g., HIV, HCV) (125, 126, 127, 128, 129)**.** As principais citocinas envolvidas são IL6 e o Fator de Necrose Tumoral – alfa (TNF-alfa).

A identificação de alterações clínicas e biológicas com importância preditiva pode levar a possíveis intervenções precoces**.** No entanto, poucos estudos avaliaram simultaneamente a presença de marcadores inflamatórios séricos na linha de base e o aparecimento de sintomas psiquiátricos e cognitivos após a infecção por SARS-CoV-2 (130). Um primeiro estudo avaliando marcadores inflamatórios hematológicos que não incluiu citocinas séricas, encontrou resultados positivos entre o Índex de Inflamação Sistêmica (IIS) e sintomas depressivos, ansiosos e TEPT (131). Zhou et al., avaliando 29 pacientes, encontraram uma relação positiva entre maiores índices de fatores inflamatórios e sintomas de prejuízo cognitivo (62). Um outro estudo trouxe uma séries de casos que apontam também para uma possível associação entre IL-6 e sintomas depressivos (132), mas que ainda precisa ser melhor investigada, inclusive para avaliar a importância de se utilizar bloqueadores de IL-6 no contexto de doenças clínicas e seu impacto na morbidade psiquiátrica e cognitiva (133). Um estudo testou a hipótese da

influência do uso de agentes bloqueadores de citocinas (ABC) (Anakinra e Tocilizumabe) no impacto inflamatório e sintomas depressivos e de TEPT meses após a alta (134). Os autores encontraram que os pacientes tratados com ABC tiveram uma menor incidência de sintomas depressivos (mas não de TEPT) na alta, sendo moderado por menores níveis de IIS, sugerindo que a tempestade de citocinas possa ter contribuído para os sintomas depressivos na amostra avaliada. Esse estudo preliminar, com pequena amostra (n = 84), uso de escalas apenas sintomáticas e ausência de uso de medidas cognitivas precisa ser ampliado e replicado com melhores instrumentos. Por fim, um estudo recente apresentou dados relevantes associando resistência insulínica e inflamação com sintomas neuropsiquiátricos em uma coorte de indivíduos com COVID-Longa, mas necessita de outros estudos confirmatórios (135).

Assim como referimos acima sobre as alterações psiquiátricas e cognitivas, no que diz respeito aos fatores preditivos, havia diversas limitações no momento de planejamento do estudo tais como predominância de desenho transversal com pequeno número amostral (62, 132), com avaliação de poucas citocinas inflamatórias (62, 132), e com escassa caracterização dos sinais e sintomas clínicos durante a internação (28). Por isso, um dos objetivos desta tese versa sobre a implementação de um protocolo robusto com avaliações cognitivas amplas, desenhado por neuropsicólogos, com possibilidade de uma melhor caracterização dos sintomas, além de um perfil amplo de citocinas inflamatórias e outros marcadores séricos a fim de permitir uma melhor associação das variáveis em questão.

Limitações gerais dos estudos anteriores no momento de planejamento deste protocolo

No início do planejamento deste estudo, em meados de 2020, havia uma necessidade urgente de uma melhor caracterização do perfil de morbidade psiquiátrica e

neuropsicológica aguda e crônica entre as vítimas da COVID-19 e o papel desempenhado pelos múltiplos componentes fisiopatológicos relacionados à doença (além do impacto destes e outros fatores na predição de gravidade e estadiamento da doença) a partir de estudos de coorte mais detalhadamente desenhados do ponto de vista metodológico. O conhecimento disponível sobre a chamada hipótese de "neurocovid" tinha sido amplamente construída a partir da análise clínica de séries de casos e estudos não controlados realizados em meio à crise pandêmica. Apesar das dificuldades metodológicas inerentes à realização de pesquisas nesse contexto, o corpo de evidências sobre a morbidade neuropsiquiátrica relacionada à COVID-19 era limitado e incentivava a implementação de protocolos de avaliação de sintomas mais refinados para abordar esse assunto em maior profundidade. Entre as limitações metodológicas dos estudos no início do planejamento deste protocolo destacavam-se: predominância de desenho transversal (58) e a falta de padronização do diagnóstico da infecção por SARS-CoV-2 **(136)** e de marcadores de gravidade (59). Além disso, a avaliação do estado mental era, em geral, baseada em pequenas matrizes de sintomas neuropsiquiátricos (59)**,** frequentemente representada por questionários de autorrelato (60) ou pela impressão clínica do médico assistente, (10) portanto, na ausência de entrevistas estruturadas de diagnóstico psiquiátricos (39, 40). Todas essas limitações justificavam a implementação de um estudo de coorte com um grande número de participantes pós hospitalizados, com uma ampla e profunda identificação dos sintomas cognitivos e psiquiátricos, com o objetivo de caracterizar as alterações psicopatológicas e cognitivas após 6-11 meses da infecção por SARS-CoV-2.

Objetivos

Objetivo Geral

Caracterizar as alterações psicopatológicas e cognitivas após 6 meses da infecção por SARS-CoV-2.

Objetivos Específicos

1. Descrever as manifestações psicopatológicas e cognitivas em pacientes após 6-11 meses da infecção por SARS-CoV-2.
2. Identificar variáveis na linha de base que possam predizer manifestações psicopatológicas e cognitivas em pacientes após 6-11 meses da infecção por SARS-CoV-2., tais como tempo de hospitalização, comorbidades, tempo de permanência em UTI, funcionalidade, estado geral de saúde e necessidade de terapia dialítica;
3. Investigar a associação de alterações de olfato e paladar na linha de base com as manifestações psicopatológicas e cognitivas em pacientes após 6-11 meses da infecção por SARS-CoV-2.
4. Correlacionar as manifestações neurobiológicas agudas na linha de base e após 6-11 meses da infecção por SARS-CoV-2, medidas por meio de exames de sangue gerais e painel de citocinas com as manifestações cognitivas 6 a 11 meses depois.

Hipóteses

1. As prevalências de transtornos depressivo, de ansiedade generalizada, TEPT (por extensão), e de transtornos cognitivos nos pacientes infectados por SARS-CoV-2 serão aumentadas em comparação com aquelas encontradas na população geral, porém menor do que as aventadas em outros estudos que utilizam escalas dimensionais de sintomas;
2. Há uma relação direta entre gravidade da infecção (maior tempo de hospitalização, necessidade de UTI, maior tempo de permanência em UTI, necessidade de Intubação Orotraqueal, Necessidade de Diálise) e incidência de transtornos mentais (depressão, ansiedade e TEPT) e cognitivos (alterações da atenção e função executiva) em pacientes após 6-11 meses da infecção por SARS-CoV-2;
3. Há uma associação positiva entre a ocorrência de manifestações psicopatológicas e cognitivas associadas ao SARS-CoV-2 e a presença de alterações de olfato e paladar persistente em pacientes após 6-11 meses da infecção por SARS-CoV-2
4. Há uma associação entre níveis de citocinas pró-inflamatórias (IL1,2,6,7 e TNF) e de marcadores inflamatórios séricos (PCR, CPK e Dímero-D) com manifestações cognitivas persistentes associadas ao COVID-19 em relação àqueles sem estas manifestações.

Metodologia Geral

Abaixo faremos uma descrição geral dos métodos que não podem ser encontrados nos manuscritos descritos nos resultados. Para maiores detalhes os leitores podem consultar a metodologia do artigo de Busatto e colaboradores (137), em que está esmiuçada a metodologia inicialmente planejada para a coleta de dados geral. Abaixo, faremos uma descrição resumida.

Todos os pacientes acima de 18 anos, sem demência, com diagnóstico laboratorial confirmado de SARS-CoV-2 (por meio de PCR ou Sorologia) e que ficaram hospitalizados por pelo menos 24 horas no Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP) durante o ano de 2020 foram considerados elegíveis para a participação no estudo (n=3.751). Após a exclusão dos pacientes sem COVID-19 e daqueles que faleceram durante a internação, aproximadamente 1.800 pacientes foram planejados para ser contactados pelos pesquisadores do estudo. Considerando inicialmente as perdas oriundas do estudo, era esperado que 800 pacientes participassem das visitas presenciais que seriam realizadas de 6 a 11 meses após a alta da internação hospitalar. As visitas foram realizadas no complexo HCFMUSP e contou com a participação de equipe multiprofissional com secretárias, enfermeiros, neuropsicólogos e médicos, esses últimos das seguintes especialidades: clínica médica, fisiatria, psiquiatria, pneumologia, neurologia e otorrinolaringologia. Uma série de avaliações e exames laboratoriais (incluindo coleta de plasma para citocinas) foi realizada por toda a equipe, como pode ser visto na figura 1.

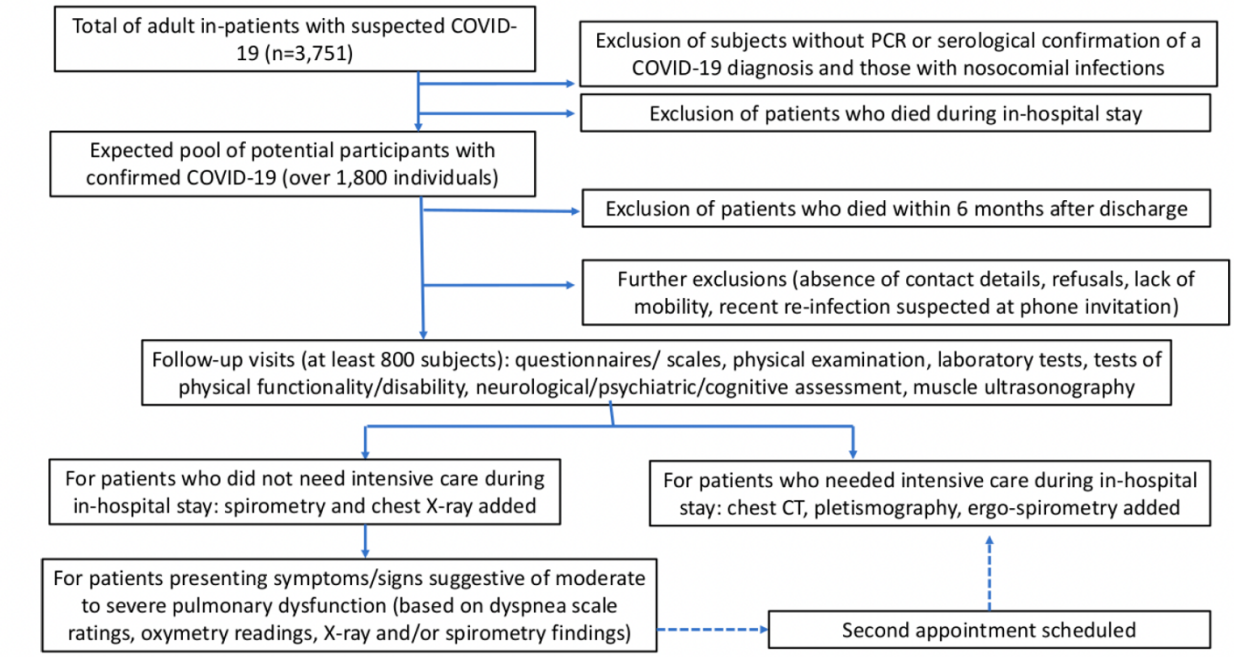

Figura 1. Fluxograma e avaliação dos potenciais participantes aos 6-11 meses após alta hospitalar

Após o fim da coleta de dados, o fluxograma foi atualizado no sentido de caracterizar a amostra dos pacientes avaliados durante o estudo por todos os grupos (figura 2). Na figura 2 podemos verificar que 870 pacientes foram avaliados, sendo que 749 foram na modalidade presencial e 121 por teleconsulta, 157 pacientes faleceram pós alta, e 930 pacientes foram excluídos do estudo por diversos motivos (e.g. falta de contato, falta, doenças clínicas, etc). É importante salientar que a equipe da psiquiatria realizou a avaliação completa (dados psicopatológicos e cognitivos) apenas dos pacientes presenciais, pois foi decidido que esta equipe não realizaria a avaliação por teleatendimento pela dificuldade logística oriunda dos testes e escalas estruturadas; o que justifica o menor número de indivíduos avaliados.

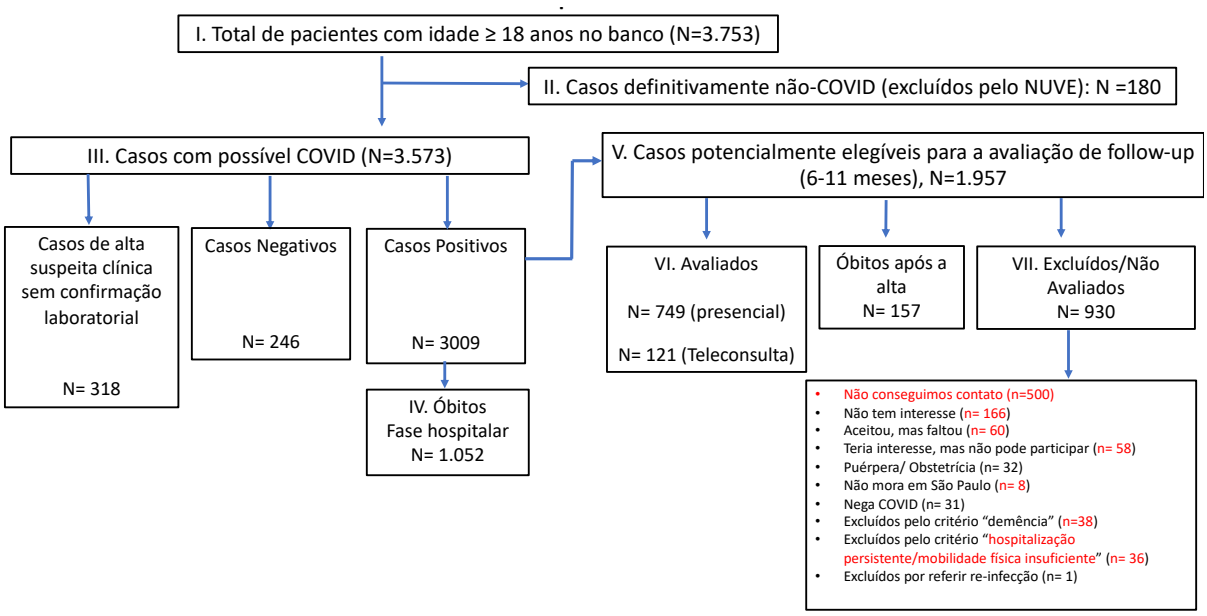

Figura 2. Fluxograma atualizado dos pacientes participantes do estudo

Além disso, pode ser visto na figura 3 que, erroneamente, foram incluídos na amostra total (presencial/teleconsulta), 69 pacientes que previamente preenchiam os critérios de exclusão: alta suspeita clínica e sem confirmação laboratorial (n=37), casos com demência prévia (n=12), menores de 18 anos (n=2) e COVID negativos (n=18). Tais sujeitos foram posteriormente excluídos dos estudos ou justificados nos métodos/limitações de cada manuscrito descrito nos resultados.

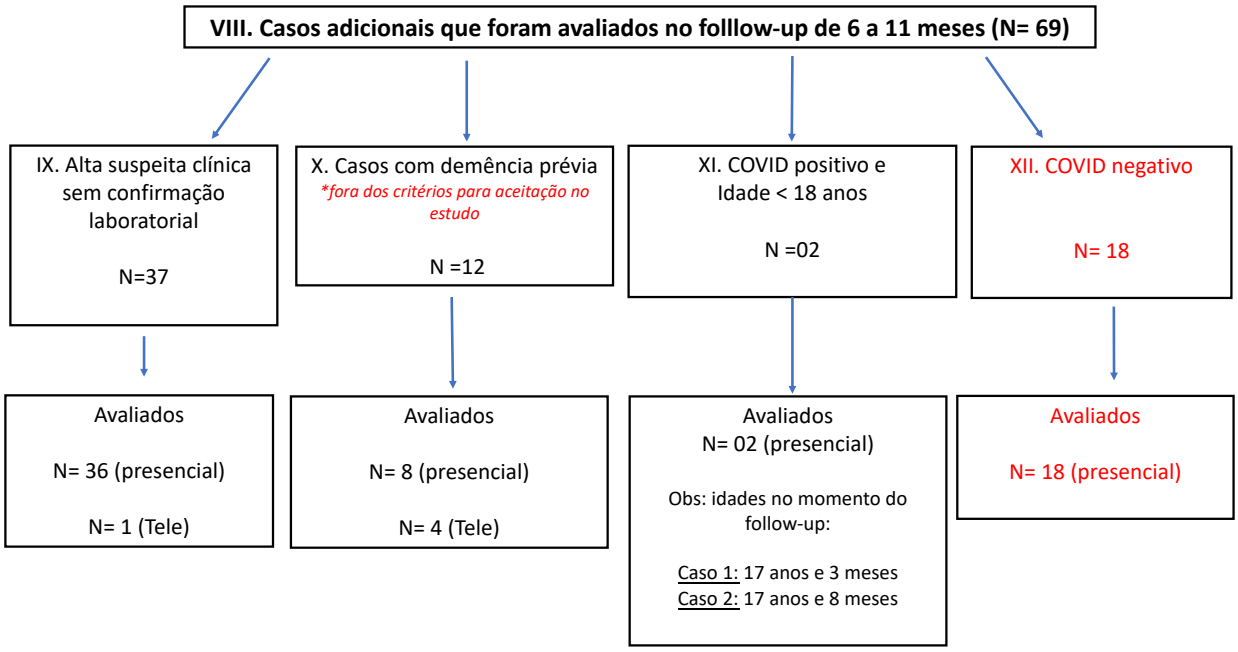

Figura 3. Fluxograma final com casos que preencheram critérios de exclusão que foram avaliados no seguimento de 6 a 11 meses

Resultados

Os resultados podem ser encontrados nos artigos decorrentes da presente tese, como seguem abaixo:

Artigo 1 (relativo aos Objetivos 1 e 2)

O artigo referente aos objetivos 1 e 2 (a. Descrever as manifestações psicopatológicas e cognitivas em pacientes após 6- meses da infecção por SARS-CoV-2; b. Identificar variáveis na linha de base que possam predizer manifestações psicopatológicas e cognitivas em pacientes infectados pelo COVID-19, tais como tempo de hospitalização, comorbidades, tempo de permanência em UTI, funcionalidade, estado geral de saúde, necessidade de terapia dialítica) foi publicado na *General Hospital Psychiatry* (FI: 7.587) e encontra-se a seguir. Cumpre-nos ressaltar que o referente artigo foi o mais citado pela agência FAPESP no ano de 2022 (www.namidia.fapesp.br).

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Post-COVID-19 psychiatric and cognitive morbidity: Preliminary findings from a Brazilian cohort study

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ABSTRACT

Objective: The present study aims to investigate the occurrence of psychiatric and cognitive impairments in a cohort of survivors of moderate or severe forms of COVID-19.
Method: 425 adults were assessed 6 to 9 months after hospital discharge with a structured psychiatric interview, psychometric tests and a cognitive battery. A large, multidisciplinary, set of clinical data depicting the acute phase of the disease, along with relevant psychosocial variables, were used to predict psychiatric and cognitive outcomes using the 'Least Absolute Shrinkage and Selection Operator' (LASSO) method.
Results: Diagnoses of 'depression', 'generalized anxiety disorder' and 'post-traumatic stress disorder' were established respectively in 8%, 15.5% and 13.6% of the sample. After pandemic onset (i.e., within the previous year), the prevalence of 'depression' and 'generalized anxiety disorder' were 2.56% and 8.14%, respectively. Memory decline was subjectively reported by 51.1% of the patients. Psychiatric or cognitive outcomes were not associated with any clinical variables related to the severity of acute-phase disease, nor by disease-related psychosocial stressors.
Conclusions: This is the first study to access rates of psychiatric and cognitive morbidity in the long-term outcome after moderate or severe forms of COVID-19 using standardized measures. As a key finding, there was no significant association between clinical severity in the acute-phase of SARS-CoV-2 infection and the neuropsychiatric impairment 6 to 9 months thereafter.

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1. Introduction

There is an urgent need for a better characterization of the profile of acute and chronic psychiatric and neuropsychological morbidity among COVID-19 victims and the role played by multiple pathophysiological components related to disease severity/staging and individuals' clinical characteristics. Cross-sectional studies addressing the incidence of psychiatric and cognitive abnormalities in the acute and severe cases of SARS-CoV-2 infection highlight the occurrence of delirium, encephalopathy, cognitive impairment, insomnia, psychosis and mood symptoms [1]. Regarding chronic symptoms, longitudinal studies conducted in post-COVID-19 cohorts have presented preliminary evidence of a high prevalence of psychiatric symptoms in the 'long phase' of the disease, namely anxiety, depression, fatigue, and post-traumatic stress disorder (PTSD) [2–6], though recent studies indicated that these symptoms tend to wane in the following months [7]. These large longitudinal studies are important but fail in differentiating infected from non-infected individuals as well as patients with asymptomatic, mild, moderate, and severe cases, who might present with different phenomenological characteristics [8,9].

Psychiatric and cognitive morbidity following SARS-CoV-2 infection may emerge from multiple factors as part of what is being referred to as post-acute COVID-19 syndrome (PACS) or "long COVID" [10]. Psychosocial stress represents an important mechanism that predisposes COVID-19 victims to emotional suffering, some of whom will ultimately present with signs and symptoms of major psychiatric disorders [11]. However, recent evidence indicates that neuropsychiatric outcomes may also represent features of systemic and central nervous system (CNS) involvement in the pathophysiology of COVID-19, resulting largely from indirect mechanisms mediated by inflammation, hypercoagulability, vascular, and immunological pathways, in addition to possible direct invasion of the brain by the coronavirus [4,12]. According to current knowledge, the interaction of multiple COVID-19-related pathophysiological mechanisms disrupts brain homeostasis, causing dysfunctions/injuries that will ultimately present as symptoms of mental and cognitive impairment ('neurocovid') [13]. A recent perspective piece suggested that, in vulnerable populations (particularly the elderly), SARS-CoV-2 infection may hasten underlying brain pathologies and increase the risk of late-life cognitive decline and progression to dementia [14].

The available knowledge on the so-called 'neurocovid' hypothesis was largely built from the clinical analysis of case series and uncontrolled studies conducted amidst the pandemic. In spite of the inherent methodological difficulties of carrying out research in this context, the current body of evidence about COVID-19-related neuropsychiatric morbidity does encourage the implementation of more refined symptom assessment protocols to address this matter in greater depth. Most studies so far have methodological limitations, such as cross-sectional design [15] and lack of standardized SARS-CoV-2 infection determination [16] and lack of severity markers [17]. Furthermore, the assessment of the mental state has been generally based on small arrays of neuropsychiatric symptoms [18], frequently assessed by self-report questionnaires [19], electronic databases [20], or by the attending physician's clinical impression [1], therefore restricted to dimensional or non-validated symptomatic scales [5,7,21]. Finally, most of the available literature was published in populations from Eastern and European countries, which may constrain the generalizability of findings [5].

The primary objective of the present study is to ascertain the mental and cognitive state of COVID-19 survivors after 6 to 9 months of the acute episode, with emphasis on the assessment of patients who recovered from moderate or severe forms of the disease requiring hospitalization, using a comprehensive protocol composed by objective and validated psychometric instruments. As a secondary and exploratory goal, we determined the extent to which these impairments were correlated with the severity of the acute disease, as well as with the occurrence of stressful events related to the COVID-19 pandemic, trying to predict potential variables associated with a worse neuropsychiatric morbidity.

2. Methods

2.1. Study design and setting

The study was conducted at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), a tertiary, university-based medical facility that is responsible for providing care for moderate and severe cases of the COVID-19 in Brazil. The 'HCFMUSP post-COVID-19 cohort' was constituted to facilitate multidisciplinary studies addressing long-term medical, functional and neuropsychiatric outcomes among adults and elders who survived moderate or severe forms of COVID-19. Subjects were assessed 6–9 months after hospital discharge (mean interval of 207 days, SD 20.4) through structured interviews and assessment protocols pertaining to an interdisciplinary medical team. A full description of our methodology as well a flowchart can be seen at Busatto et al. [22]. In the present communication, we will report on the assessment of psychiatric and cognitive outcomes.

This research protocol has been approved by the Ethics Committee at HCFMUSP (CAPPesq-HC), and registered at the Brazilian Registry of Clinical Trials (ReBEC) under the registration number 4.270.242 (RBR-8z7v5wc) and will be reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. [23]

2.2. Participants

All patients hospitalized at HCFMUSP for at least 24 h due to moderate or severe forms of COVID-19 between March and September 2020 ($n = 3751$) were regarded as eligible for this 'post-COVID-19 cohort'. The requirement of hospital treatment was used to ascertain moderate forms of COVID-19, and the need of intensive care unit (ICU) treatment was used to define severe cases. We present herein a preliminary analysis of the first 2009 individuals who were invited to participate (compared with the total cohort sample described above and in Busatto Filho et al., 2021). From hospital registries, we ascertained all patients aged 18 years or older who were discharged from hospital in this time period, excluding the deceased ($n = 1803$). Diagnostic confirmation was based on clinical presentation combined with Polymerase Chain Reaction (PCR) tests to detect viral RNA or enzyme-linked immunosorbent assays to detect the presence of anti-SARS-CoV-2 serum antibodies (in subjects for whom a RT-PCR test collected up to the 10th day of symptom onset was not available). We also included 6 patients with highly suspected COVID-19 (based on clinical and chest-CT findings) without PCR confirmation. These patients were contacted by telephone and enrolled in this follow-up study. In case of acceptance, an appointment was made at an outpatient clinic dedicated to the assessment of this cohort. From all contacted patients, a small number of patients declined participation, reporting being too impaired to visit the clinic ($n = 18$). Further exclusions were due to failed telephone contact ($n = 645$), refusal to participate in the study as expressed by the patient or his/her informant upon telephone contact ($n = 297$), inability to comply with the assessment protocol due to pre-existing dementia or severe intellectual deficiency ($n = 10$), or unknown reasons (i.e., subjects who did not show at the scheduled appointment) ($n = 408$). A total of 425 volunteers signed informed consent and completed neuropsychiatric assessments between October/2020 and January/2021. A flow-chart can be seen in Supplementary Fig. 1.

2.3. Assessment protocol

A set of data relative to the acute stage of the disease was retrieved from hospital charts and databases, providing baseline information on duration of hospital stay; requirement/duration of ICU care; requirement of orotracheal intubation, mechanical ventilation, or dialysis; and

any available information about previous diagnoses, comorbidities, and relevant clinical symptoms. There was no systematic capture of neuropsychiatric and/or cognitive symptoms at baseline, except for recorded information about incident delirium, seizures, or any signs suggestive of encephalopathy or cerebrovascular events during the acute phase of the disease.

Evaluation of mental state and global cognitive function was done in face-to-face interviews by a dedicated team of psychiatrists, psychologists, neuropsychologists, and undergraduate medical students using the following instruments (details provided on Supplementary Table 1): Clinical Interview Schedule - Revised (CIS-R), Structured Clinical Interview for DSM-5 Disorders, Research Version (SCID-5-RV), Hospital Anxiety and Depression Scale (HAD), Ask Suicide-Screening Questions (ASQ), Post-Traumatic Stress Disorder Checklist (PCL-C), Alcohol Use Disorder Identification Test (AUDIT), Memory Complaint Scale (MCS), Temporal and Spatial Orientation (as obtained from the Mini-Mental State Examination), Trail Making Test (TMT) – A, Verbal Fluency Test (VFT), – Clinical Frailty Scale (CFS), International Physical Activity Questionnaire (IPAQ) – Short Version. All examiners attended the training sessions on the assessment protocol in order to standardize procedures and maximize the reliability of psychometric measures. Prior to examination, a score sheet was completed to gather information about the patient's mental health antecedents (personal and family history of psychiatric disorders) and occurrence of psychosocial/stressful events related to the COVID-19 pandemic (e.g., death of close family members; financial problems; and other relevant life-events or stressors). Questions regarding substance use and general health status (GHS) were also included. The latter variable was acquired upon completion of a questionnaire presented to the participants during clinical examination. This variable had five possible ratings in a Likert scale relative to the patient's perception of global health, yielding five categorical GHS ratings, i.e., very bad; bad; average; good; or very good. The assessment protocol required on average 90 min to be completed, comprising a structured interview with psychometric and cognitive screening tests, as described below.

2.4. Statistical analysis

For descriptive statistics, we calculated percentages, mean, median, standard deviation, and the upper and lower limits of the 95% confidence interval to the percentage. For inferential statistics we used linear regression for numeric variables, binary logistic regression for binary variables, and Poisson distribution for trail making and verbal fluency. For selecting predictive variables to include in our analysis we used the LASSO (Least Absolute Shrinkage and Selection Operator) method in order to reduce the number of selected variables predicting new data with small error [24]. LASSO is reputed as a very sensitive machine learning method for increasing the quality of prediction by shrinking regression coefficients [25]. Each LASSO was repeated at least ten times in order to reduce its instability and possible effect of confounding factors.

After LASSO, the following variables were included as possible predictors: age, education level, temporo-spatial orientation score in Mini Mental State Examination (MMSE), general health status (GHS) and pre−/post-COVID-19 frailty (CFS), persistent cough, duration of hospitalization during acute phase of infection, length of stay in ICU, requirement of hemodialysis or orotracheal intubation, and presence of medical/neurological comorbidities (such as systemic arterial hypertension, diabetes mellitus, cancer, hepatic steatosis or cirrhosis, chronic renal disease, gastric ulcer, bleeding ulcer, rheumatoid arthritis, rheumatological disease, stroke and dementia).

3. Results

Data from an interim sample of 425 patients were used in the present analysis. The mean age of participants was 55.7 years (median 56.4), and 51.5% were women. Overall educational level was low, with 55.5% of participants not having completed high school (less than 12 years of education) (Table 1). Table 2A displays the characteristics of the sample during the acute phase of COVID-19 (hospital treatment), with emphasis on variables that could potentially predict unfavourable neuropsychiatric outcomes. Supplementary Table 2 describes the clinical profile of patients during hospital stay, with emphasis on the diagnosis of medical comorbidities and the requirement of intensive-care treatment.

Table 1 also presents an estimate of their subjective memory complaints (MCS score). The characterization of symptoms according to psychometric scales (HADS, ASQ, AUDIT, MCS) and cognitive screening tests (MMSE-orientation, TMT-A and VFT) at 6-month follow-up after COVID-19 infection is summarized in Table 2B. Table 3 presents the diagnostic classification according to CIS-R, SCID-5-RV (for the assessment of psychotic symptoms) and changes in substance use behaviour. Notably, we found evidence of psychotic symptoms according to SCID-5-RV schedule, with 8.7% of participants reporting hallucinations and 12.5% reporting delusions of any kind lifetime. Furthermore, we calculated both chronic diagnosis (all time) and new diagnosis (symptoms starting within less than one year). Noteworthy, when looking only to new diagnosis, we found a prevalence of 2.56% of 'depression' (1.16% severe depression), 2.79% of 'specific phobia', 8.14% of 'generalized anxiety disorder' and 1.4% of 'obsessive-compulsive disorder'.

Table 4 displays linear regression analyses searching for predictors of the psychiatry outcomes 'anxiety' and 'depression' according to HAD, and Table 4B displays predictors of the CIS-R outcome 'common mental disorder' (please see a complete definition in Supplementary Table 1), six months after the acute phase of COVID-19. In all instances, only two variables were able to predict the occurrence of these psychiatric diagnoses, namely 'current frailty' (according to CFS) and 'general health status' (GHS scale). 'Common mental disorder' was positively associated with GHS across all levels, i.e., better general health associated with better psychiatric outcomes. As compared to those with 'very bad' general health, patients with 'regular' health were 86% less likely to be diagnosed with a 'common mental disorder' ($p = 0.016$), similar to those

Table 1
Sociodemographic, psychosocial variables and subjective memory complaints.

		%	95%CI
Age (years)	< 60	58.49	53.74–63.09
mean: 55.7, SD 14.2	≥ 60	41.51	36.92–46.26
	Female	48.47	43.75–53.21
Sex	Male	51.53	46.79–56.25
	No formal education	4.47	2.84–6.92
	Incomplete Elementary School	33.41	29.09–38.03
	Elementary School	11.06	8.40–14.42
	Incomplete High School	6.59	4.57–9.39
	High School	27.76	23.72–32.21
	Incomplete Bachelor	4.71	3.03–7.20
	Bachelor	8.00	5.75–11.00
Education	Post-Graduation	4.00	2.47–6.36
	No	36.94	32.49–41.63
	Little	16.24	13.02–20.05
	Moderate	11.06	8.40–14.42
	A lot	24.47	20.62–28.78
Financial Problems[a]	Extreme	11.29	8.61–14.68
Death of Family	No	92.24	89.27–94.45
Member[a]	Yes	7.76	5.55–10.73
	Similar or better	48.93	44.17–53.7
	Slightly worse	35.80	31.36–40.5
MCS–1	Much worse	15.27	12.13–19.05
	Similar or better	53.06	43.25–62.64
	Slightly worse	35.71	26.92–45.59
MCS–2	Much worse	11.22	6.22–19.15

[a] Psychosocial stress due to or related to COVID-19. MCS, Memory Complaint Scale; MCS-1, self-assessment (patient); MCS-2, assessment provided by a family member.

Table 2
(A) Clinical variables that could potentially impact the incidence of neuropsychiatric symptoms. (B) Neuropsychiatric symptoms among patients with moderate or severe COVID-19 in assessment 1 post-discharge.

		N	Mean (SD)	Min.	1stQ	Median	3rdQ	Max.	95%CI
A	Duration of hospitalization (days)	424	16.53 (16.31)	1	7	11	21	142	15.12–18.25
	Duration of ICU stay (days)	210	13.62 (14.24)	0	6	9.5	15.75	126	11.99–15.93
	Length of orotracheal intubation (days)	128	10.77 (8.66)	0	6	8	13.25	52	9.46–12.49
	Length of hemodialysis (days)	45	14.38 (10.38)	0	5	13	21	36	11.54–17.55
	Frailty (CFS) prior to COVID-19	405	2.54 (1.13)	1	2	3	3	7	2.43–2.65
	Frailty (CFS) post-COVID-19	404	3.12 (1.24)	1	2	3	4	7	3.00–3.25
	Duration of cough (days)	126	112.80 (168.27)	1	15	61	191	1586	92.04–157.77
	Current O_2 saturation	418	96.30 (2.33)	81	96	97	98	100	96.05–96.50
	Current Body Mass Index (BMI)	419	31.90 (6.94)	17.68	27.47	30.55	35.09	61.57	31.26–32.59
	HADS Anxiety	425	6.18 (5.10)	0	2	5	10	21	5.71–6.68
	HADS Depression	425	4.81 (4.52)	0	1	4	8	19	4.39–5.25
	ASQ	425	0.60 (1.55)	0	0	0	0	11	0.47–0.77
	AUDIT	425	1.56 (3.65)	0	0	0	1	29	1.25–1.95
	MCS	425	5.29 (4.15)	0	2	5	8	14	4.90–5.69
	MMSE (orientation score, range 0–10)	425	9.33 (1.44)	0	9	10	10	10	9.18–9.45
	TMT-A (completion time, seconds)	422	69.10 (51.10)	0	37.08	53.58	84.75	350	64.60–74.39
	TMT-A (number of errors)	422	1.86 (20.98)	0	0	0	1	429	0.76–6.92
	VFT (number of words)	424	15.39 (5.30)	0	12	15	18	39	14.90–15.91
	VFT (number of errors)	417	0.04 (0.24)	0	0	0	0	2	0.02–0.07
B	VFT (number of perseverations)	421	0.76 (1.16)	0	0	0	1	8	0.66–0.88

ICU, Intensive Care Unit; CFS, Clinical Frailty Scale; HADS, Hospital Anxiety Depression Scale; ASQ, Ask Suicide-Screening Questions; AUDIT, Alcohol Use Disorder Identification Test; MCS, Memory Complaint Scale; MMSE, Mini-Mental State Examination; TMT, Trail Making Test; VFT, Verbal Fluency Test (animals).

Table 3
Prevalence of psychiatric diagnoses according to the CIS-R schedule, changes in substance use behaviour, and presence of psychotic symptoms according to the SCID-5 interview, among participants in the 'HCFMUSP post-COVID-19 cohort'.

Diagnosis	Onset at any time (%)	Onset less than 1-year (%)	Onset 1-year or more (%)
Mild Depression without somatic symptoms	1.65	0.70	0.95
Mild Depression with somatic symptoms	1.65	0.47	1.18
Moderate Depression without somatic symptoms	1.41	0.23	1.18
Moderate Depression with somatic symptoms	1.88	0.00	1.88
Severe Depression	1.41	1.16	0.25
Depression - Total	8.00	2.56	5.44
Panic Disorder	0.94		
Agoraphobia without Panic	0.71		
Agoraphobia with Panic	0.71		
Social Phobia	0.71		
Specific Phobia - Without COVID	2.82		
Specific Phobia - With COVID	3.76	2.79	0.97
Generalized Anxiety Disorder	14.12	8.14	5.98
Obsessive Compulsive Disorder	3.53	1.40	2.13
Mixed anxiety-depressive disorder	15.53		
Common Mental Disorder	32.24		
Post-Traumatic Stress Disorder	13.65		
Started or increased use of Alcohol post-COVID19	1.42		
Started or increased use of Tobacco post-COVID19	1.65		
Started or increased use of Cannabis post-COVID19	0.48		
Started or increased use of Sedative Drugs post-COVID19	6.27		
Started or increased use of Opioids post-COVID19	1.42		
Started or increased use of other drugs post-COVID19	2.38		
Delusions	12.47		
Hallucinations	8.71		

Table 4
(A) Linear regression analysis addressing the impact of general health status (GHS) subsequent to COVID-19 on the psychiatric outcome (anxiety or depression) after six months, as defined by the CIS-R interview. (B) Binary logistic regression for Common Mental Disorder (outcome variable) according to different categories of general health status (GHS) subsequent to COVID-19 (predicting variable).

A	Predicting variable	Coefficient	SE	95%CI	p-value
Anxiety	(Intercept)	9.15	1.72	5.77–12.52	<0.001
	GHS – Bad	−1.82	1.74	−5.24–1.60	0.296
	GHS – Average	−4.13	1.56	−7.20 to −1.06	0.008
	GHS – Good	−5.84	1.57	−8.93 to −2.75	<0.001
	GHS – Very Good	−6.81	1.72	−10.20 to −3.42	<0.001
	Current CFS score	0.58	0.21	0.16–0.99	0.006
Depression	(Intercept)	7.69	1.47	4.81–10.58	<0.001
	GHS – Bad	−1.63	1.48	−4.54–1.93	0.274
	GHS – Average	−4.56	1.33	−7.18 to −1.94	<0.001
	GHS – Good	−6.02	1.34	−8.66 to −3.38	<0.001
	GHS – Very Good	−6.38	1.47	−9.27–3.48	<0.001
	Current CFS score	0.67	0.18	0.32–1.02	<0.001

B	Predicting variable	OR	SE	95%CI	p-value
Common Mental Disorder	(Intercept)	1.39	2.41	0.28–10.35	0.71
	GHS - Bad	1.15	2.55	0.14–6.67	0.89
	GHS - Average	0.14	2.26	0.02–0.59	0.02
	GHS - Good	0.09	2.28	0.01–0.37	0.003
	GHS - Very Good	0.07	2.51	0.01–0.35	0.003
	Current CFS score	1.33	1.11	1.09–1.63	0.01

GHS, General Health Status; CIS-R, Clinical Interview Schedule – Revised; CFS, Clinical Frailty Scale.

with 'good' (91.5%, $p = 0.003$) and 'very good' general health (94.4%, p = 0.003). The same was true for frailty scores, where each additional point on the CFS increased the chance for having a 'common mental

disorder' in 32.5% ($p = 0.006$). The Area under the ROC curve of 0.72, indicating good quality of the model. Regarding 'depression' and 'anxiety', the occurrence of symptoms within these affective domains was associated with a worse estimate of general health (i.e., lower GHS) and frailty (i.e., higher CFS scores) (Table 4A). Psychiatric symptoms could not be associated with any clinical measure at the time of COVID-19 infection or psychosocial variables related to effect of COVID-19 pandemic.

Table 5 summarizes data relative to linear regression analysis addressing the effect of socio-demographic and clinical variables on the prediction of cognitive outcomes, i.e., temporo-spatial orientation (MMSE), attention (TMT-A) and verbal fluency (VFT with semantic restriction). Previous history of stroke or pre-existing dementia at baseline assessment (i.e., prior to the acute phase of COVID-19) were associated with worse performance in the orientation task of the MMSE ($R^2 = 0.283$). Older age and disorientation (according to MMSE) were associated with a worse performance in the TMT-A ($R^2 = 0.114$). Finally, older age, higher frailty (CFS) scores prior to COVID-19 and temporo-spatial disorientation (MMSE) in the current assessment were associated with a worse performance in the VFT; as opposed to that, higher education was (as expected) associated with better performance in the VFT. Curiously, individuals who had been submitted to hemodialysis due to COVID-19 complications during hospitalization had a better performance in this cognitive task. The aforementioned models explained 28%, 11% and 24% of the variability in new diagnoses of cognitive impairment according to the MMSE, TMT-A and VFT, respectively.

Supplementary Table 3 compares the results from cognitive tests (TMT-A and VFT) obtained in the present sample with Brazilian norms. In our sample, patients performed worse in TMT-A across all ages (19–39: 34.37 vs 48.03 s; 40–59: 39.91 vs 60.8 s; 60–75: 43.62 vs 81.86 s). However, no apparent differences were found between our sample and Brazilian norms regarding VFT, unless a better performance of our sample in individuals under 65 years old (13.79 vs 16 words).

Finally, the comparison of baseline (in-hospital) clinical and socio-demographic variables of participants and non-participants showed striking similarities in mean age (55 years in both groups), gender distribution (53% and 51% of males, respectively), body mass index (32,5 and 30,8) and duration of symptoms upon hospital admission (8 days for both groups). Participants had in fact a higher number of medical comorbidities, longer hospital stay (14 vs. 9 days) and a higher proportion of them required ICU treatment (65% vs. 42%) or orotracheal intubation (43% vs. 29%), subsuming that the actual participants had experienced more severe forms of the acute disease as compared to non-participants (data not shown).

4. Discussion

The present study provides original data highlighting the high prevalence of neuropsychiatric impairment in the long-term outcome of moderate or severe forms of SARS-CoV-2 infection. To the best of our knowledge, the objective assessment of mental state with the aid of validated diagnostic instruments is a relevant and original contribution in the characterization of psychiatric and cognitive impairments among COVID-19 survivors; most of the previous studies dedicated to the assessment of long-term post-COVID-19 neuropsychiatric morbidity were based solely on unstructured questionnaires, self-report tests, telephone-based interviews or other forms of remote assessment, yielding at best a preliminary overview of complaints and symptoms. Moreover, studies that proposed to assess potential predictors of psychiatric and cognitive morbidity included only a few variables, most of them assessed retrospectively. The protocol that we used in the present study was built to provide diagnostic classification and to depict a more detailed symptomatic profile of post-COVID-19 psychiatric and cognitive morbidity. A comprehensive array of clinical and functional variables that had been previously tabulated during hospital treatment, along with a set of COVID-19 related psychosocial stressors, were used to evaluate the contribution of these acute-phase variables to the long-term psychiatric outcomes.

The CIS-R diagnoses of 'common mental disorder', 'anxiety' and 'PTSD' were highly prevalent. Also, we found that roughly one-third of the new diagnoses of 'depression' and 'obsessive-compulsive disorder', and the majority of diagnoses of 'generalized anxiety disorder' were established within the previous year in our sample of post-COVID-19 survivors. This is in line with previous studies that called attention to the high prevalence of mental health problems in the course of COVID-19 [26,27]. The prevalence of 'common mental disorder' in this post-COVID-19 cohort (32.2%) was higher than previously reported in the Brazilian general population (26.8%), as indicated by epidemiological studies using the CIS-R schedule' [28]. Regarding the CIS-R diagnosis of 'depression', prevalence in the present sample (8.0%) was higher than expected in epidemiological studies concerning high- and low-income countries (respectively 5.5% and 5.9%, 12-month prevalence), as well as in general Brazilian population using the same instrument (around 4 and 5%) [29]. The CIS-R diagnosis of 'generalized anxiety disorder' (GAD) in the present sample (14.1%) was considerably higher than the

Table 5
Linear regression analysis displaying statistically significant effects of variables predictive on cognitive outcome, according to the assessment of MMSE temporo-spatial orientation, attention (TMT-A) and verbal fluency (VFT).

Cognitive outcome	Predicting variable	Coefficient	SE	95%CI	p-value
MMSE (orientation)	(Intercept)	9.49	0.059	9.37–9.60	< 0.001
	Previous Stroke	−1.31	0.277	−1.85 to −0.76	< 0.001
	Previous Dementia	−6.44	0.486	−7.39 to −5.48	< 0.001
	(Intercept)	97.63	21.572	55.23–140.03	< 0.001
TMT-A	Age (years)	0.97	0.168	0.64–1.30	< 0.001
	MMSE (orientation score)	−8.77	1.813	−12.34 to −5.21	< 0.001
	(Intercept)	8.79	2.348	4.18–13.41	< 0.001
	Hemodialysis required	1.45	0.733	0.01–2.90	0.049
	Frailty pre-COVID	−0.60	0.222	−1.04 to −0.16	0.007
	Age (years)	−0.04	0.019	−0.08 to −0.004	0.030
	Education level:				
	Incomplete Elementary	0.80	1.15	−1.45–3.06	0.49
VFT	Elementary School	1.82	1.30	−0.74–4.37	0.16
	Incomplete High School	2.03	1.42	−0.76–4.83	0.15
	High School	2.58	1.23	0.16–5.00	0.04
	Incomplete Bachelor	4.72	1.59	1.60–7.84	0.00
	Bachelor's degree	4.56	1.40	1.81–7.31	0.00
	Post-Graduation	5.41	1.65	2.17–8.66	0.00
	MMSE (orientation score)	0.88	0.18	0.53–1.23	< 0.001

MMSE, Mini-Mental State Examination; TMT-A, Trail Making Test (A); VFT, Verbal Fluency Test (semantic restriction: "Animals").

12-month prevalence in the European general population (0.2–4.3%) [30], in Brazilian general population (9.9%) and in Brazilian individuals with coronary heart disease (10.2%), both using the same instrument [31]. A recent study using the same structured interview (CIS-R) in representative sample of Brazilian general population during COVID-19 pandemic found lower rates than reported in this manuscript, with 21.1% of common mental disorders, 2.8% of depressive disorders and 8% of anxiety disorders, highlighting high prevalence in our sample [32].

Even though the cross-sectional nature of the psychiatric data acquisition precludes the assessment of incidence rates, we were able to determine the prevalence of new psychiatric diagnoses. Our data indicate a high prevalence of new diagnoses of 'depression', 'generalized anxiety disorder' and 'obsessive compulsive disorder', contrasting with the findings of a recent meta-analysis of longitudinal studies that found only a small increase on mental health issues among general population pre- and post-COVID-19 pandemic [33]. Noteworthy, our sample is older and represented by COVID-19 survivors, and therefore more prone to be clinically impaired. We understand that the high proportion of new psychiatric diagnoses in our sample can be related to the severity of COVID-19 morbidity, but may also contain an indirect effect of controversial policies in Brazil during the COVID-19 crisis [34], given that the appropriateness of public policies has been shown to moderate mental health burden in the general population during COVID-19 pandemic [35]. The impact of the actual COVID-19 infection on new psychiatric diagnoses was challenged by a recent meta-analysis, although not controlling for the severity of the acute disease [36].

We found high rates of lifetime delusions (8.7%) and hallucinations (12.5%) in the present sample. Even though there are some reports of psychotic symptoms following COVID-19 [37], there are several reports indicating high rates of lifetime psychotic symptoms in the general population, ranging from 7.2 to 12.5% [38,39], consistent with our findings. In our study, 'delusions of religious content' accounted for a substantial proportion of the latter classification (6.15%), and we perceived that, in many such cases, non-delusional religious beliefs (e.g., acknowledging any form of spiritual interference or guidance as key to surviving the disease) could have led to an overestimation of this item. Therefore, after withdrawing 'delusions of religious content' from the former estimate, the overall prevalence of delusions was downgraded to 6.35%.

Impairments in several cognitive domains were found in our sample, especially executive and attentional deficits. Likewise, previous studies in COVID-19 survivors have pointed out to impairments in several cognitive domains in acute forms of the disease [4,40], particularly logical memory and executive functions (attention and cognitive flexibility), which were interpreted as possibly related to the systemic inflammatory process [40]. Long-term studies following patients with severe acute illnesses and acute respiratory distress syndrome point to cognitive decline and executive dysfunction as well [41,42]. Contrary to what we expected, cognitive morbidity after six months of SARS-CoV-2 infection was unrelated to any of the multiple clinical parameters relative to the acute phase of the disease, nor to any of psychiatric diagnoses that were established after six months of hospital discharge. Disorientation was only associated with pre-existing dementia or stroke, presumably reflecting cognitive impairment prior to COVID-19. Older age and disorientation (according to MMSE) were associated with worse performance in attention and verbal fluency tasks, and lower scores in verbal fluency were associated with frailty. In a recent study, Jaywant et al. [43] evaluated cognitive impairment prior to hospital discharge in a cross-section of 57 inpatients recovering from severe COVID-19, and, similar to our findings, the authors found high rates of attention and executive dysfunction unrelated to clinical severity. Conversely, Taquet et al. [20] in a large retrospective cohort study, found a positive association between disease severity and neuropsychiatric symptomatology using a large electronic health record.

The presence and severity of psychiatric manifestations were unrelated to two important psychosocial stressors (i.e., 'death of a close relative' or 'financial loss'), nor to any of the multiple clinical parameters relative to the acute phase of the disease. Psychosocial stressors [11] such as death of a close relative [44] or major financial loss [45] are reputed to be powerful triggers of psychiatric morbidity; however, these variables were not associated with a worse neuropsychiatric outcome in our sample. In the absence of any such associations between risk factors and observed outcomes, psychiatric and cognitive impairments observed in the long-term after moderate or severe COVID-19 could be viewed either as an expression of SARS-CoV-2 effects on brain homeostasis or a representation of non-specific psychiatric manifestations secondary to diminished general health status, given that these disorders are correlated with general health status regardless of the cause of diminished general health [46].

Surprisingly though, patients who had been submitted to hemodialysis during ICU treatment for COVID-19 performed better on the verbal fluency test. We do not have a prompt interpretation for this putative 'protective' effect of hemodialysis on this specific cognitive domain, although the beneficial effect of dialysis on the clearance of systemic toxins could be regarded as advantageous in relation to severely ill patients who remained at pre-dialytic states. Previous studies have shown that individuals discharged from ICU [47] (especially those with acute respiratory distress syndrome) may present with symptoms compatible with *post-intensive care syndrome* (PICS) [48], which consists in a combination of psychological, physical and cognitive impairments following conditions that did require critical care, and may persist for up to five years after ICU discharge [49].

We must also acknowledge the limitations of the present study. First, the assessment of psychiatric and cognitive impairment in this cohort was performed after 6–9 months of the acute episode, in the absence of a similar protocol implemented at baseline, and thus precludes the characterization of changes secondary to this viral disease. However, it is noteworthy that a myriad of detailed information regarding clinical, laboratory and supplementary tests were accessible at baseline. Second, selection bias might remove relevant cases from the study sample, given that patients with more severe consequences of the disease may be less prone to accept enrolment to the study and/or to comply with the procedures. Regarding psychiatric diagnoses, we acknowledge that the CIS-R interview focuses predominantly on mood and affective symptoms, without covering other relevant psychiatric domains. Because of that, we tried to buffer our assessment battery with other questionnaires and psychometric tests. In this regard, the assessment of psychotic symptoms based on the SCID-5-RV (Module B, Psychotic and Associated symptoms) may have been too specific to be implemented in a non-psychiatric sample. Even though all raters were trained for reliability, it is plausible that the lack of experience in the assessment of psychotic patients may have biased the completion of this questionnaire, particularly among less educated patients, to whom culture-bound and religious beliefs may have influenced their responses, causing the overrating of psychotic symptoms. Also, we did not include pre-existing psychiatric illness in our analysis due to lack of availability in the current dataset, though we plan to include this parameter in future analyses. Furthermore, comparison of these results to general population prevalence rather than to the prevalence of these conditions in other patients recovering from serious illness limits one's ability to assess the specificity of these findings. Furthermore, the category of 'new diagnosis' might be biased by memory recall bias. Finally, 6 patients with high clinical suspicion of COVID-19, but without laboratory confirmation by PCR, were included. These individuals had been admitted as inpatients within the first 6 weeks after the initial preparation of HCFMUSP as a COVID-only facility, and the decision to include them was based on the fact that the in-hospital RT-PCR testing setup was not yet fully operational at that time. Nonetheless, the clinical picture of these cases was highly compatible with COVID-19 and they were treated as such throughout hospitalization.

In summary, we found a high prevalence of psychiatric and cognitive

impairments following SARS-CoV-2 infection, specifically common mental disorders, depression, anxiety, PTSD, executive and attentional cognitive impairments. These deficits seem unrelated to psychosocial stressors or clinical risk factors documented in the acute-stage of COVID-19. The present findings should encourage longitudinal studies addressing changes in mental and cognitive state among COVID-19 survivors across distinct ranges of severity.

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Declaration of Competing Interest

Authors Declare no Conflict of Interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.genhosppsych.2022.01.002.

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Artigo 2 (relativo ao Objetivo 3)

O manuscrito referente ao objetivo 3 (c. Investigar a associação de alterações de olfato e paladar na linha de base com as manifestações psicopatológicas e cognitivas em pacientes com COVID-19) foi publicado no *European Archives of Psychiatry and Clinical Neuroscience* (FI: 5.760) e encontra-se na íntegra a seguir.

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ORIGINAL PAPER

Association between chemosensory impairment with neuropsychiatric morbidity in post-acute COVID-19 syndrome: results from a multidisciplinary cohort study

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Abstract
Preliminary methodologically limited studies suggested that taste and smell known as chemosensory impairments and neuropsychiatric symptoms are associated in post-COVID-19. The objective of this study is to evaluate whether chemosensory dysfunction and neuropsychiatric impairments in a well-characterized post-COVID-19 sample. This is a cohort study assessing adult patients hospitalized due to moderate or severe forms of COVID-19 between March and August 2020. Baseline information includes several clinical and hospitalization data. Further evaluations were made using several different reliable instruments designed to assess taste and smell functions, parosmia, and neuropsychiatric disorders (using standardized psychiatric and cognitive measures). Out of 1800 eligible individuals, 701 volunteers were assessed on this study. After multivariate analysis, patients reporting parosmia had a worse perception of memory performance ($p < 0.001$). Moderate/severe hypogeusia was significantly associated with a worse performance on the word list memory task ($p = 0.012$); Concomitant moderate/severe olfactory and gustatory loss during the acute phase of COVID-19 was also significantly associated with episodic memory impairment ($p = 0.006$). We found a positive association between reported chemosensory (taste and olfaction) abnormalities and cognition dysfunction in post-COVID-19 patients. These findings may help us identify potential mechanisms linking these two neurobiological functions, and also support the speculation on a possible route through which SARS-CoV-2 may reach the central nervous system.

Keywords COVID-19 · Mental health · Cognition · Gustatory · Olfactory

Introduction

SARS-CoV-2 [1], the virus responsible to cause the new coronavirus disease 2019 (COVID-19), affects several systems such as the pulmonary, cardiovascular, hematological, neurological, psychiatric, and otorhinolaryngological ones.

Members of the HCFMUSP COVID-19 study group are listed in the Acknowledgements section.

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According to recent data, around 260 million people have been infected throughout the world [2] and, of these, many individuals suffer from disease sequelae, named as long-COVID [3] or post-acute COVID-19 syndrome (PASC) [4].

Moreover, the pathophysiology of COVID-19 might be involved in the onset or aggravation of chemosensory disorders (taste and smell) [5, 6]. Besides them, parosmia which is an abnormal olfactory perception where subjects perceive differently the same smell may appear during the chemosensory loss recovery phase [6]. Although these dysfunctions are common in the early stages of infection, they are often overlooked by patients as perceived as harmlessness and common, with rates of approximately 3–20% of those who are affected by COVID-19, with a large severity range [7]. COVID-19 patients present rates of olfactory and gustatory disfunction of 41.0% and 38.2% [8], respectively, with some studies presenting prevalence as high as 83.9% [9]. Although complete recovery is common, 5% of the patients report no chemosensory recovery [10]. Interestingly, smell and taste losses were shown to be presented in 63.4% of patients underwent COVID-19 infection even after complete vaccination [11]. Parosmia, which is related to smell recovery [12], was find in 40% of COVID-19 patients assessed 6 months after the disease [13]. These sequelae may have a negative impact on the quality of life and functional capacity of survivors.

Moreover, psychiatric disorders and cognitive impairment are common acute- and post-clinical manifestations of SARS-CoV-2 infection [5, 14, 15]. Rogers et al. [16], reviewing the association between psychiatric and neuropsychiatric presentations and severe coronavirus infections, highlighted that depression, anxiety, fatigue, post-traumatic stress disorder, and rarer neuropsychiatric syndromes might develop in the longer term of the disease. Huang et al. [17] in an ambidirectional cohort study found an incidence of 23% of anxiety or depression in patients 6 months after their discharges from a hospital. Taquet et al. [5] also described a 33·62% incidence of neurological and psychiatric outcomes (e.g., dementia, mood disorder, anxiety disorder, and psychotic disorders) 6 months after SARS-CoV-2 infection. Moreover, these sequelae were more common in patients with previous SARS-CoV-2 infection than in patients who had influenza or other respiratory tract infections, stressing the impact of SARS-CoV-2 to brain homeostasis [5].

There is limited information on the association between olfactory/taste dysfunction and psychiatric symptoms in association with COVID-19. Speth et al. showed a positive correlation between severities of smell and taste loss, depression, and anxiety in a sample of COVID-19 survivors [18]. However, the study is limited to the small sample size, using only dimensional scales to depict psychiatric symptoms and no information regarding cognitive impairment. Thus, the objective of the present study is to analyze the association between olfactory and gustatory dysfunctions and neuropsychiatric morbidity, in a large cohort of moderate and severe COVID-19 recovered patients, using a large body of dimensional and structured questionnaires, as well as a systematized cognitive assessment.

Methods

Study design and population

This study was carried out at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), a tertiary university hospital that has been a key element in the care of moderate to severe cases of coronavirus. All patients hospitalized at HCFMUSP for at least 24 h due to moderate or severe forms of COVID-19 between March 30th and August 30th, 2020 were regarded as eligible for this study. Moreover, we included 36 patients with highly suspected COVID-19 (based on clinical and chest-CT findings) without laboratory confirmation. These individuals had been admitted as in-patients within the first 6 weeks after the initial preparation of IC-HCFMUSP as a COVID-only facility, and the decision to include them was because the in-hospital RT-PCR testing setup was not yet fully operational at that time, thus increasing the risk of false-negative results. To a better description of the study design, please see Busatto Filho et al. [19].

In this study, we excluded those who did not complete neuropsychiatric and otorhinolaryngological batteries, presented previous diagnoses of end-stage cancer, subjects living in long-term facilities, or insufficient physical mobility to leave home after 6 months of hospital discharge, suspected reinfection at the time of follow-up and those who refused to participate in the study, thus reporting a total of 701 volunteers who signed informed consent and fulfilled the neuropsychiatric assessments between October/2020 and April/2021. This study has been approved by the Ethics Committee at HCFMUSP (CAPPesqHC), and registered at the Brazilian Registry of Clinical Trials (ReBEC) under the registration number 4.270.242 (RBR-8z7v5wc), and is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [20].

Assessment protocol and data collection

Hospital charts and databases were used to obtain information on duration of hospital stay; requirement/duration of ICU care; requirement of orotracheal intubation, mechanical ventilation, or dialysis; and any available information about previous diagnoses, comorbidities, and relevant

clinical symptoms. All assessment were made in face-to-face sequential interviews, with a team of psychiatrists, psychologists, neuropsychologists, and medical students for psychiatric and cognitive battery, and otolaryngologists, for the olfactory and taste questionnaires including visual analogue scale regarding either chemosensory, parosmia and recovery rates. To standardize procedures and maximize the reliability of the tests made, all examiners were submitted to training sections before starting the data collection. We also evaluated the global health status (visual analogue scale), physical exercise (using International Physical Activity Questionnaire [21]), and frailty—current and before COVID-19 (using the Clinical Frailty Scale [22]). Further evaluations were made using those following instruments (better descripted in Supplementary Material 1): (A) Olfactory and Taste Assessment: The evaluation of integrity of olfactory and gustatory function (according to the patients' subjective impression) was performed with the aid of Visual Analogue Scale developed by authors, as reported in the previous studies [23, 24]. In brief, the patients were asked to indicate their perception of change in the previous ability to recognize (a) smell or (b) taste in a numeric scale ranging from 0 to 10, where higher scores represent better function [0 = unable to identify any (a) smell or (b) taste; 10 = no impairment in (a) smell or (b) taste sensitivity]. These scales were administered upon objective, multidisciplinary reassessment of patients 6–11 months after hospital discharge to depict patients' current perception of impairment in smell or taste identification, and also retrospectively to estimate the occurrence of any such impairments during the acute phase of COVID-19. Cut-off scores were used to allocate participants into distinct categories according to magnitude of olfactory and/or gustatory impairment, i.e., severe impairment (0–4); moderate impairment (8–5); mild impairment (9); or no impairment (10) in these chemosensory functions. Subjects presenting with moderate/severe impairment were compared with those reporting mild/no impairment to verify the association of these conditions with neuropsychiatric outcomes. Subjects were also inquired about the presence parosmia in a binary question (yes/no); (B) Structured Psychiatric Interview: Clinical Interview Schedule-Revised (CIS-R), and Structured Clinical Interview for DSM-5 Disorders, Clinical Version (SCID-5-CV) for psychotic disorders; (C) Psychiatric Assessment Scales: Hospital Anxiety and Depression Scale (HAD), Ask Suicide-Screening Questions (ASQ), Post-Traumatic Stress Disorder Checklist (PCL-C), and Alcohol Use Disorder Identification Test (AUDIT); (D) Cognitive Assessment: Memory Complaint Scale (MCS), Temporal and Spatial Orientation of Mini-Mental State Examination (MMSE), Trail Making Test (TMT), digit symbol substitution test (DSST), and Neuropsychological Battery CERAD.

Statistical analysis

The sample of patients was described using frequency, mean, standard deviation, and confidence interval of demographic characteristics and clinical variables. The main variables of interest were defined as olfactory and gustatory dysfunctions, namely, parosmia; hyposmia, i.e., moderate and severe current olfactory loss (those who pointed out fewer than 8 in self-report); hypogeusia, i.e., moderate and severe current gustatory loss (those who pointed out less than 8 in self-report); and hyposmia/hypogeusia, i.e., moderate and severe current olfactory and gustatory loss (those who pointed out less than 8 in both self-reports). Univariate analyses were performed to identify covariates and factors associated with the variables of interest at a 10% significance level, since this is an exploratory study [25]. To evaluate this association in discrete factors and covariates, χ^2 and Mann–Whitney tests were used, respectively. For statistical significance analysis, we adopted p value and Bonferroni adjusted p value. Multivariate analyses were performed for combinations of covariates that showed significant univariate association with the variables of interest. This association was evaluated through stepwise Logistic Regression at a significance level of 5%. The covariates and factors analyzed include sociodemographic parameters (age and gender), baseline hospitalization parameters (need of ICU, Intubation or Dialysis, length of hospitalization), social issues (financial problems following COVID-19 and Death of Close relatives), global health status (physical exercise using IPAQ questionnaire, Global health Status, and Frailty), and Psychiatric and Cognitive Measures.

Results

A total of 701 patients answered questionnaires. Table 1 describes main sample's sociodemographics and clinical characteristics. The mean age was 55.3 years (SD: 14.6), with 52.4% of males and a mean duration of hospitalization of 17.6 days (SD: 17.6). Regarding specific care, 56.4% needed ICU care, 37.4% intubation, and 12.7% hemodialysis. Regarding the general health status, 10.1% of the subjects described their health as 'bad or very bad', 38.5% as 'average', and 51.4% as 'good or very good'. Furthermore, 38.3% declared being sedentary, with only 3.9% of subjects perceiving themselves as 'very active'. Interestingly, we found 12 people with olfactory hallucinations and nine individuals with gustatory hallucinations. Of those, 72.7% of subjects with olfactory and 87.5% of those with gustatory

Table 1 Sociodemographic and clinical characteristics ($n = 701$)

Variable	Mean (SD)	Percent	95%CI.lo	95%CI.hi
Age (years)	55.3 (14.6)		54.3	56.3
Male sex		52.4	49.0	55.8
Length of hospitalization (days)	17.6 (17.6)		16.5	18.9
ICU		56.4	53.0	59.8
Length of ICU (days)	13.7 (13.5)		12.6	15.1
OTI		37.5	34.2	40.9
Length of OTI (days)	10.6 (8.7)		9.6	11.8
Dialysis		12.1	10.0	14.5
Length of dialysis (days)	13.0 (11.1)		11.1	15.5
General health status				
Very bad		2.3	1.4	3.6
Bad		7.8	6.2	9.9
Average		38.5	35.2	41.9
Good		41.1	37.8	44.6
Very good		10.3	8.3	12.6

SD standard deviation, *ICU* intensive care unit, *OTI* orotracheal intubation, *95%CI.lo* 95% confidence interval—lower bound, *95%CI.hi* 95% confidence interval—upper bound

hallucinations reported that these symptoms were not present prior to COVID-19.

Hereinafter, in this paragraph, descriptive statistics of the neuropsychiatric variables will be present. First, CIS-R diagnoses prevalence of our sample are depression 7.5%; panic disorder 0.8%; agoraphobia 1.5%; social phobia 0.8%; specific phobia 2.1%; generalized anxiety disorder 15.1%; obsessive–compulsive disorder 3.1%; mixed depressive and anxiety disorder 13.5%; common mental disorder 30%. Besides CIS-R diagnosis, we found the following results on psychiatric assessment: PTSD prevalence 13.4%; last-year suicidal attempt: 2.4%; last 4 weeks suicidal ideation 10.1%; HAD anxiety mean 6.0 (SD: 5.1); HAD depression mean 4.8 (SD: 4.6); AUDIT score mean 1.56 (SD: 3.5). Regarding cognitive outputs, we found: MCS mean 5.2 (SD: 4.16); MMSE orientation score mean 8.27 (SD: 3.25); TMT-A mean 65.5 s (SD: 48.0 s); verbal fluency mean 15.57 (SD: 5.43); DSST mean 32.2 (SD: 19.3); Boston naming test mean 13.15 (SD: 2.27); word list mean 15.35 (SD: 4.7); constructional praxis mean 8.26 (SD: 2.55); word list recall mean 4.86 (SD: 2.25); and word list recognition mean 7.88 (SD: 2.77).

Moderate/severe chemosensory impairments with reported onset during the acute phase of COVID-19 were significantly associated with long-lasting moderate/severe olfactory and/or gustatory symptoms, as observed after 6–11 months of follow-up. Univariate analyses (Table 2) indicate several statistically significant associations of dependent variables with the distinct subtypes of chemosensory impairment (olfactory, gustatory, or concomitant olfactory/gustatory impairment). Parosmia was significantly associated with the magnitude of cognitive complaints (MCS) and impairment in naming ability (Boston), as well as with the occurrence of psychiatric symptoms (ASQ) and CIS-R diagnoses ('anxiety disorder' and 'common mental disorder'). Moderate/severe hyposmia was associated with older age and with worse cognitive performance, as shown by the TMT-A (longer time of execution), DDST (more incorrect answers) and CERAD's word list memory task (small number of recalled words). Moderate/severe hypogeusia was also related to a worse performance on the memory task. Finally, patients presenting with moderate or severe impairments in both chemosensory functions (i.e., concomitant olfactory and gustatory dysfunction) were older, and had more psychiatric symptoms and a worse overall cognitive performance. In this sub-sample of post-COVID survivors, we found statistically significant associations with diagnoses of 'mixed anxiety and depressive disorder' and 'common mental disorder', and with the occurrence of memory complaints according to the MCS. These patients also had lower scores in the TMT-A, DSST, VFT, and CERAD's word list recall.

Table 3 presents a multivariate analysis between variables showing statistically significant associations with the four a priori chosen dependent variables (i.e., parosmia; moderate/severe hyposmia; moderate/severe hypogeusia; concomitant moderate/severe hyposmia and hypogeusia). Therefore, variables identified as significant in univariate analysis (Table 2) were included in the stepwise Logistic Regression analysis. Moderate/severe chemosensory losses during the acute phase of COVID-19 remained significantly ($p < 0.001$) associated with current moderate/severe chemosensory losses. Patients reporting parosmia had a worse perception of memory performance (as shown by higher scores in the MCS; $p < 0.001$). Moderate/severe hypogeusia

Table 2 Univariate analysis between chemosensory and clinical and neuropsychiatric morbidity, only significant associations

Referred chemosensory symptoms (prevalence)	Independent variable	*p* value	Bonferroni adjusted *p* value
Parosmia (9%)	MCS	0.001	0.004
	Boston	0.017	0.087
	ASQ	0.024	0.120
	Anxiety Disorders	0.037	0.185
	CMD	0.056	0.280
Moderate and severe current olfactory deficit (18%)	COVID-19 olfactory deficit	0.000	0.000
	TMT-A	0.008	0.033
	Digit-symbol	0.009	0.037
	Word List Memory Task	0.041	0.166
	Age	0.092	0.367
Moderate and severe current gustatory deficit (20%)	COVID-19 gustatory deficit	0.000	0.000
	Word List Memory Task	0.010	0.020
Moderate and severe current olfactory and gustatory deficit (11%)	COVID-19 olfactory and gustatory deficit	0.000	0.000
	Word List Memory Task	0.002	0.020
	Digit-symbol	0.006	0.057
	TMT-A	0.013	0.126
	Verbal Fluency	0.015	0.155
	Age	0.020	0.201
	Mixed Anxiety/Depressive Disorder	0.040	0.397
	Word list recall	0.053	0.532
	CMD	0.058	0.577
	MCS	0.079	0.794

MCS, Memory Complaint Scale; CMD, Common Mental Disorder; TMT-A, Trail Making Test – A

Table 3 Multivariate analysis between chemosensory and clinical and neuropsychiatric morbidity

Referred chemosensory symptoms (prevalence)	Independent variables	B	S.E.	Wald	df	Sig	Exp(B)
Parosmia (9%)	MCS	0.105	0.032	10.975	1	0.001	1.110
	Constant	− 2.953	0.251	138.115	1	0.000	0.052
Moderate and severe current olfactory deficit (18%)	COVID-19 olfactory deficit	− 0.024	0.003	54.016	1	0.000	0.977
	Constant	− 0.790	0.123	41.192	1	0.000	0.454
Moderate and severe current gustatory deficit (20%)	COVID-19 gustatory deficit	0.858	0.238	12.992	1	0.000	2.358
	Word List Memory Task	− 0.052	0.021	6.275	1	0.012	0.950
	Constant	− 1.228	0.364	11.393	1	0.001	0.293
Moderate and severe current olfactory and gustatory deficit (11%)	COVID-19 olfactory and gustatory deficit	3.035	0.597	25.884	1	0.000	20.808
	Word List Memory Task	− 0.074	0.027	7.545	1	0.006	0.928
	Constant	− 3.440	0.691	24.784	1	0.000	0.032

MCS Memory Complaint Scale

was significantly associated with a worse performance on the memory test (CERAD's word list recall, $p = 0.012$); Concomitant moderate/severe olfactory and gustatory loss during the acute phase of COVID-19 was also significantly associated with memory impairment according to CERAD's word list memory task ($p = 0.006$).

Discussion

To our knowledge, this is the first study to demonstrate associations between neuropsychiatric dysfunction with chemosensory functions (smell and taste) in a large

prospective cohort of post-COVID individuals. Upon multivariate analysis, certain cognitive variables (such as subjective memory complaints and performance on the word list recall) remained significantly associated with poor post-COVID-19 olfactory and gustatory functions. Although preliminary analyses identified in association with chemosensory deficits, psychiatric symptoms (or diagnoses) did not retain statistical significance after controlling for multiple covariates in logistic regression. We found several interesting and promising associations that could help clinicians and researchers better understand the link between COVID-19, chemosensory (taste and smell impairments), and brain functions as well as to extend to other connections between olfactory and gustatory functions and neuropsychiatric symptoms.

Neuropsychiatric impairments following COVID-19 are multiple, but greater attention have been given to the cognitive function and the higher risk for dementia [5, 26]. In our sample, a worse memory perception was positively associated with parosmia 6–9 months following COVID-19 infection. Interestingly, both worse current gustatory and olfactory function were associated with a reduced performance in the word list memory test. The word list memory test evaluates episodic memory [27], a cognitive function heavily impaired in Alzheimer's Disease (AD) and strongly related to the hippocampus and connections. It is important to stress is that episodic memory is the capacity to learn, reserve, and retrieve subjective daily life information [28], being associated with several brain structures within the hippocampus and parahippocampal regions (such as perirhinal, entorhinal, and parahippocampal cortices) [29]. Even though, in our sample, cognitive dysfunction was not associated with isolated olfactory impairment, it was significantly associated with gustatory loss and gustatory plus olfactory losses. The subdivision of between taste and smell seems to be more theoretical than practical, seen that the major cause of taste impairment is olfactory dysfunction [30].

Complex interaction of several inter-related brain structures might also explain our findings regarding chemosensory loss and decrease in memory function in long-COVID. There is a possibility that anterograde pathogenic transmission of SARS-CoV-2 infected with the olfactory system may cause symptoms in the brain [31]. Although very small but apparently, human olfactory neurons with SARS-CoV-2 infection have been reported in autopsy [32] and in vitro [33], linking chemosensory dysfunction to brain impairment. Since reaching the nervous system, SARS-CoV-2 might induce a cascade of several different cellular and molecular processes producing neuropathological impairments with similar features of some neurodegenerative diseases [34]. Anatomically, the olfactory network is involved by the pathological process of AD. It is well known that olfactory dysfunction is a common feature of AD even in its initial phase [35–41], possible related to the presence of beta-amyloid deposits and neurofibrillary tangles from the olfactory bulb to the brain regions that receive neuronal projections directly or indirectly from the olfactory bulb, including the piriform cortex, amygdala, hippocampal and entorhinal cortex, and orbitofrontal cortex [42, 43]. The piriform cortex has a spatial and connectivity relationship with the transentorhinal cortex, the region primarily affected in most AD cases, and with the hippocampus, the structure most directly related to episodic memory [44, 45]. This complex interaction of several inter-related brain structures might explain our findings regarding chemosensory loss and decrease in memory function in long-COVID.

Noteworthy, regarding the impact of chemosensory deficits on mental health, even though we found associations between smell and taste alterations with psychiatric diagnoses (mostly anxiety and common mental disorders), the statistical significance of these associations was not sustained upon multivariate analysis. Previous studies suggested a link between hyposmia/anosmia and the development of major depressive disorder [46–51], but apparently individuals with unipolar depression tend to recover their olfactory function after symptomatic remission, contrary to individuals with bipolar depression [52]. Neuroimaging studies suggested that smaller volumes of the olfactory bulb could be associated with depression [53, 54]. In rodents, depressive states induced by olfactory bulbectomy is related to several abnormalities in neurochemical processes in the hippocampus [55], which points out to a potential causative link.

We must acknowledge the limitations of the present study. First, although participants in this cohort were evaluated after 6–11 months after the acute phase of COVID-19, the characterization of neuropsychiatric symptoms and chemosensory symptoms at baseline was retrospective and, therefore, not provided by a standardized protocol. Nonetheless, we had access to a large body of clinical data relative to the hospital treatment phase, based on which we were able to build a substantial database to ascertain the impact of these variable on mental health outcomes. Second, given the voluntary participation in the study, one must consider that some individuals with higher degrees of cognitive and/or psychiatric impairments may have been less prone to accept enrolment or to comply with the whole assessment, which could generate a selection bias. Third, we have no objective data regarding previous participants' mental and/or cognitive health impairments. Finally, we did not use psychophysical measures to objectively determine chemosensory symptoms; rather, we used self-response questionnaires to estimate the patients' perception of the integrity of smell and taste abilities. Although this approach may be less accurate and prone to recall bias when estimating these functions retrospectively, we

understand that the substantial size of the present sample may render this approach based on self-reported questionnaires acceptable [23].

In sum, this study is the first to characterize the association between olfactory and gustatory symptoms and neuropsychiatric status in a large cohort of post-COVID-19 individuals. We found a positive association between reported chemosensory abnormalities and few neuropsychiatric symptoms, particularly those illustrating cognition dysfunction. These findings may help us identify potential mechanisms linking these two neurobiological functions, and also support the speculation on a possible route through which SARS-CoV-2 may reach the central nervous system and lead to neurocognitive impairment thereafter. Furthermore, we suggest a stronger link between taste and cognition that deserver further investigation.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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Artigo 3 (relativo ao Objetivo 4)

O manuscrito referente ao objetivo 4 (d. Correlacionar as manifestações neurobiológicas agudas na linha de base e após 6-11 meses, medidas por meio de exames de sangue gerais e painel de citocinas em pacientes infectados pelo COVID-19 com as manifestações psicopatológicas e cognitivas 6 a 9 meses depois) foi aprovado para publicação no periódico *Frontiers in Immunology* (FI: 8.786) e encontra-se na íntegra a seguir.

Cognitive Impairment in Long-COVID and its association with persistent dysregulation in inflammatory markers

Long-COVID Cognitive symptoms and Inflammation

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Abstract

Objective: To analyze the potential impact of sociodemographic, clinical and biological factors on the long-term cognitive outcome of patients who survived moderate and severe forms of COVID-19. **Methods:** We assessed 710 adult participants (Mean age = 55 ± 14; 48.3% were female) 6 to 11 months after hospital discharge with a complete cognitive battery, as well as a psychiatric, clinical and laboratory evaluation. A large set of inferential statistical methods was used to predict potential variables associated with any long-term cognitive impairment, with a focus on a panel of 28 cytokines and other blood inflammatory and disease severity markers. **Results:** Concerning the subjective assessment of cognitive performance, 36.1% reported a slightly poorer overall cognitive performance, and 14.6% reported being severely impacted, compared to their pre-COVID-19 status. Multivariate analysis found sex, age, ethnicity, education, comorbidity, frailty and physical activity associated with general cognition. A bivariate analysis found that G-CSF, IFN-alfa2, IL13, IL15, IL1.RA, EL1.alfa, IL45, IL5, IL6, IL7, TNF-Beta, VEGF, Follow-up C-Reactive Protein, and Follow-up D-Dimer were significantly ($p<.05$) associated with general cognition. However, a LASSO regression that included all follow-up variables, inflammatory markers and cytokines did not support these findings. **Conclusion:** Though we identified several sociodemographic characteristics that might protect against cognitive impairment following SARS-CoV-2 infection, our data do not support a prominent role for clinical status (both during acute and long-stage of COVID-19) or inflammatory background (also during acute and long-stage of COVID-19) to explain the cognitive deficits that can follow COVID-19 infection.

Keywords: COVID-19; SARS-CoV-2; Cognition; Inflammation; Infectious Disease; Cohort Study.

Introduction

Our continued experience with COVID-19 has led to the identification of numerous extrapulmonary consequences of SARS-CoV-2 infection (Gupta et al., 2020). Of particular relevance to the present report are the psychiatric and cognitive symptoms associated with this infection. Such symptoms were initially identified in large epidemiological studies (Taquet et al., 2021a, Taquet et al., 2021b). However, epidemiological studies do not address whether these symptoms are related to the specific pathological consequences of the infection itself, or the social situations of the individuals who contract the virus. More recent cohort COVID-19 studies have demonstrated a significant increase in psychiatric and cognitive symptoms in individuals previously infected by COVID-19, irrespective of the severity of the acute disease; this is true in both mild (Del Brutto et al., 2021) or more severe forms (Duindam et al., 2022) of the disease.

Numerous studies have documented the effect of SARS-CoV-2 infection on cognition (Damiano et al., 2021, Ceban et al., 2022). Preclinical studies in mice have demonstrated cognitive deficits in mice after injection of SARS-CoV-2 spike protein directly into the hippocampus (Oh et al., 2022). In humans, higher cognitive impairment has been reported in post-COVID-19 survivors. Indeed, these post-acute sequelae syndrome (PASC) has been termed long-COVID-19; defined as displaying COVID-19 related symptoms that persist after 3 months following initial infection and lasting for more than 2 weeks. Critically, this impairment is not related to any pre-existing clinical or emotional disturbances (Damiano et al., 2022a). Further, a recent report has shown a potential link between a deficit in cognitive performance and chemosensory impairment in long-COVID-19 patients (Damiano et al., 2022b, Soriano et al., 2022). Finally, population studies assessing electronic medical records of over a million individuals

confirm the importance of cognitive impairment among post-COVID19 patients (Wulf Hanson et al., 2022) and point to an urgent need for gathering researchers and public leaders to better understand and more effectively face the long-COVID-Challenge (Abate et al., 2020).

One of the most puzzling aspects associated with this research area is the role of inflammation during the acute and post-acute COVID-19 phase and its impact on cognition (Lyra et al., 2022). In general, studies across numerous brain-based disorders have demonstrated a convincing relationship between inflammatory markers and cognitive decline (Singh-Manoux et al., 2014), especially in patients with Alzheimer's disease (Heneka et al., 2015) and chronic viral infections (e.g., HIV, HCV) (Hoare et al., 2020, Alford and Vera, 2018, Solinas et al., 2015, Rubin et al., 2018, Weinstein et al., 2019). However, studies assessing the relationship between COVID-19 and inflammation remain preliminary in nature. Preclinical data in hamsters are consistent with post-mortem brain data from COVID-19 victims; that is, neural inflammation is one of the core symptoms of SARS-CoV-2 exposure (Klein et al., 2021). This is relevant because a recent human COVID-19 cohort study has documented an important association between inflammation and cognitive deficits (Mazza et al., 2021). Clear data such as these are complicated by other findings; higher levels of C-reactive protein (CRP) are associated with the post-acute sequelae syndrome of COVID-19 (PASC), but not with cognition itself (Busatto et al., 2022).

The COVID-19 pandemic has brought about a great deal of new research, but additional larger, well-designed studies are still needed (Munblit et al., 2022) (Alvarez et al., 2022). This is particularly the case for COVID-19 studies addressing cognitive outcomes. Though informative, existing studies have had to rely on small sample sizes (Diana et al., 2022), a restricted set of predictor variables (Serrano-Castro et al., 2022), a

low number of analyzed cytokines (Zhou et al., 2020), or a lack of objective psychiatric tools administered by trained professionals (e.g., neuropsychological battery, psychiatric interview) (Biagianti et al., 2022, Evans et al., 2021). Thus, the aim of the present study was to analyze the potential impact of sociodemographic, clinical and biological factors on the long-term cognitive outcome of patients who survived moderate and severe forms of COVID-19. To this end, we utilized a large, hospital-based dataset to identify a cohort in the acute phase of the disease, and then completed a longitudinal follow-up of this cohort using a comprehensive set of clinical, neuropsychological and laboratory tools.

Methods

Study Design and Setting:

This is a single center, cohort study conducted at *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* (HCFMUSP), a university-based, tertiary medical facility that provided care for moderate and severe cases of the COVID-19 during the acute phase of the first wave of the pandemic, i.e., prior to the onset of vaccination protocols. The 'HCFMUSP post-COVID-19 cohort' was constituted to facilitate multidisciplinary studies addressing long-term medical, functional and neuropsychiatric outcomes among adults and elders who survived moderate or severe forms of COVID-19. Previously we reported a preliminary assessment of psychiatric and cognitive outcomes in an interim sample of 425 patients (i.e., half the size of the present test group) indicating high rates of mood and cognitive symptoms 6-11 months following infection (Damiano et al., 2022a). Details about the methodological protocol can also be found elsewhere (Busatto Filho et al., 2021).

This research protocol has been approved by the Ethics Committee at HCFMUSP (CAPPesq-HC), and registered at the Brazilian Registry of Clinical Trials (ReBEC) under the registration number 4.270.242 (RBR-8z7v5wc) and will be reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement (von Elm et al., 2007).

Participants:

All patients that were hospitalized at HCFMUSP for at least 24 hours due to moderate or severe forms of COVID-19 between March and August 2020 (n=3,753) were regarded as eligible for this 'post-COVID-19 cohort'. From hospital registries, we ascertained all patients aged 18 years or older who were discharged from the hospital in this time period, excluding the deceased (n=1,052). Diagnostic confirmation was based on clinical presentation combined with either: a Polymerase Chain Reaction (PCR) tests to detect viral RNA or an enzyme-linked immunosorbent assays to detect the presence of anti-SARS-CoV-2 serum antibodies (in subjects for whom a RT-PCR test collected up to the 10th day of symptom onset was not available). These patients were contacted by telephone and enrolled in this follow-up study. In total, 1,957 patients were eligible for assessment (supplementary figure 1). Of these, some declined to participate (n=172); could not be contacted by telephone (n-=512); or did not show on their day of evaluation (n=62). An additional 12 potential participants were excluded due to a co-morbid dementia diagnosis; 26 were excluded for being evaluated in tele-appointments (i.e., lack of complete cognitive assessment) and 204 were excluded for having missing cognitive data. The missing cognitive data was due to a second COVID-19 wave that occurred during the protocol; meaning professionals were not readily available for research purposes. A further 157 individuals died and 102 were excluded for other reasons (e.g.,

missing data, lack of psychiatric protocol), leaving a total of 710 participants in the final sample.

Assessment protocol:

All participants signed consent forms and were assessed 6-11 months after hospital discharge (days; mean = 223; median = 202; SD 55.1) through structured interviews and assessment protocols administered by to an interdisciplinary medical team (from October/2020 to January/2021). Evaluation of mental state and global cognitive function was done in face-to-face interviews by a dedicated team of psychiatrists, psychologists, neuropsychologists, and undergraduate medical students. A set of data relative to the acute stage of the disease was retrieved from hospital charts and databases, providing baseline information on duration of hospital stay; requirement/duration of ICU care; requirement of orotracheal intubation, mechanical ventilation, or dialysis; and any available information about previous diagnoses, comorbidities, relevant clinical symptoms, and laboratory exams (after 72 hours of hospitalization). Severity of acute phase of COVID-19 was determined using the World Health Organization (WHO) criteria (Marshall et al., 2020) ranging from 1 (less severe) to 4 (most severe). There was no systematic capture of neuropsychiatric and/or cognitive symptoms at baseline, except for recorded information about incident delirium, seizures, previous psychiatric disease (diagnosed by a specialist), or any signs suggestive of encephalopathy or cerebrovascular events during the acute phase of the disease. The complete description of the assessment protocol can be seen at Supplementary Table 2, but a brief description is provided below:

a) General Evaluation: Educational background ("no study ever" to post-graduation), Ethnicity, Socioeconomic Status (from the Brazilian Economic Classification Criterion – ABEP) ranging from A (best ranked) to E (worst ranked), Patient's mental health, and occurrence of psychosocial/stressful events

related to the COVID-19 pandemic (i.e., death of close family members; financial problems; and other relevant life-events or stressors).

b) Psychiatric Interview: Clinical Interview Schedule - Revised (CIS-R), Structured Clinical Interview for DSM-5 Disorders, Research Version (SCID-5-RV) for psychotic symptoms, Hospital Anxiety and Depression Scale (HAD), Ask Suicide-Screening Questions (ASQ), Post-Traumatic Stress Disorder Checklist (PCL-C), and Alcohol Use Disorder Identification Test (AUDIT).

c) Cognitive Assessment: Memory Complaint Scale (MCS) for both the patient and the closest informant. Here, we added a question to rank how the patients perceive themselves cognitively after COVID-19 (Similar or Better; Slightly Worse; or Much Worse). Temporal and Spatial Orientation (as obtained from the Mini-Mental State Examination, MMSE), Trail Making Test (TMT) – A, Verbal Fluency Test (VFT), Digit-Symbol Substitution Test (DDST), and the Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (CERAD), including Boston Naming Test, Word List Learning, Word List Recognition, Word List Recall, Constructional Praxis and Delayed Constructional Praxis.

d) Clinical Evaluation: An internal physician evaluated global health status (visual analogue scale), Clinical Frailty Scale (CFS) both pre- and post-COVID-19, International Physical Activity Questionnaire (IPAQ) – Short Version, presence of comorbidity (to calculate Charlson Score – (Roffman et al., 2016)), Functional Assessment of Chronic Illness Therapy (FACIT) Scale to measure chronic fatigue, Smell and Taste function from visual analogue scale (0 to 100), body mass-index (BMI), pulse oximetry (to assess blood oxygen), and spirometry (for calculating forced vital capacity, FVC).

e) Cytokines: Plasma samples collected during follow-up of 389 out of the 710 participants were centrifugated and used for the analysis of 28 cytokines and chemokines. We employed the Human Cytokine/Chemokine Magnetic Bead Panel (Merck-Millipore, Cat. HCYTMAG-60K-PX30), according to the manufacturer's instructions. 25 ul of serum were used. Analytes were detected on the Magpix® instrument (Luminex Corp., Austin, TX 78727, USA). The calibration of the equipment was performed before use and followed all the manufacturer's recommendations. The concentrations of cytokines and chemokines in each sample was calculated using a calibration curve obtained for each individual experiment with the diluent of each sample as vehicle, when necessary. When cytokines were not detected, we calculated the average of the detection limits for that factor and divided the value by the square root of two. The resulting value was assigned to that cytokine. To minimize inter-batch variation effects, cytokines were transformed using a R code (ComBat: Adjust for batch effects using an empirical Bayes framework in sva: Surrogate Variable Analysis. https://rdrr.io/bioc/sva/man/ComBat.html. Accessed 25 August 2022.).

Statistical analysis:

To facilitate data analysis, we transformed the objective cognitive assessments into Latent Cognitive Dimensions (LCD). First, we transformed the output of cognitive assessment tests into z-scores, as per cognitive domains. Second, we performed a Confirmatory Factor Analysis (CFA) to create LCD (see Supplementary Figure 1). We used CFA rather than Exploratory Factor Analysis (EFA) because previous literature supports the use of the cognitive dimensions measured here (Lezak et al., 2004). Third, according to each factor loading we calculated an score for each of the following dimensions based on the indicated tests: a) Orientation (Spatial and Temporal Orientation

from MMSE); b) Attention (TMT Time; TMT Errors; and DSST correct answers); c) Language (Boston Naming Test and Verbal Fluency – number of words); d) Episodic Memory (Word List Learning; Word List Recognition; and Word List Recall); e) Visuospatial Ability (Constructional Praxis and Delayed Constructional Praxis); and f) Global Cognition (composite score of all sub-dimensions).

For descriptive statistics, we calculated percentages, mean, median, standard deviation, and the upper and lower limits of the 95% confidence interval. We first conducted bivariate analysis between two groups (cytokines x non-cytokines) in order access potential selection bias. Then we performed a bivariate analysis (Pearson's product-moment correlation, Kendall's rank correlation tau, Student's t test, One-way ANOVA, or Pearson's Chi-squared test) between each sub-dimension and potential predictors, and those that reached $p<.10$ were selected for next steps. Linear regression with each cognitive dimension was performed using only independent variables from baseline. Any variable assessed in the follow-up was analysed using two different models; EFA (using Varimax Rotation) with continuous variables and cytokines (log-transformed) that reached significance with global cognitive dimension, to understand each PASC cluster; and Least Absolute Shrinkage and Selection Operator (LASSO) regression model with all cytokines, inflammatory markers, and follow-up potential associated and confounder variables. LASSO is reputed to be a very sensitive machine learning method for increasing the quality of prediction by "shrinking" regression coefficients (Musoro et al., 2014), particularly when there are multiple independent variables potentially associated with distinct outcomes. Therefore, it is suitable for exploratory studies, due to its greater prediction accuracy as compared to other regression models (Vasquez et al., 2016). Each LASSO was repeated at least ten times in order to reduce any instability and possible effect of confounding factors.

Results

Out of the 710 subjects that comprised our sample, 48.3% were female, with a mean age of 55 years (SD: 14.1). Regarding ethnicity, 65% identified as white, 8% as Black, 23.3% as Brown, and 0.4% as Yellow (further unknown). The WHO severity scores were normally distributed (Shapiro-Wilk p<.001), with a mean of 2.65 (SD: 1.12). The Charlson scores were also normally distributed (Shapiro-Wilk p<.001), with a mean of 3.10 (SD: 1.85). The mean duration of hospitalization was 17.6 days (SD 19.4). More than half of the patients (54.3%) required Intensive Care Unit (ICU) care (mean duration of ICU stay: 14.2 days, SD 13.8); 37.2% required orotracheal intubation (mean 10.8 days, SD: 8.77), and 12.5% required haemodialysis (mean 13.3 days, SD 11.2). Only 3.7% of participants reported a previous history of psychiatric disorders (i.e., any diagnosis prior to COVID-19 onset). That said, upon follow-up reassessment, we found a high prevalence of mood- and anxiety disorders (as indicated by the CIS-R schedule), including Generalized Anxiety Disorder (GAD, 14.6%), Depression (7.4%), and Common Mental Disorder (CMD, 30.2%). Concerning the self-assessment of cognitive performance (as indicated by participants or their caregivers), 49.3% endorsed being unaffected by COVID-19, 36.1% reported a slightly poorer overall performance in memory, and 14.6% reported being severely impacted, compared to their pre-COVID-19 status.

Persistent post-COVID-19 general health symptoms were often reported by participants, complying with the definition of PASC. Twenty percent of the patients reported having 1 or 2 persistent symptoms, whereas multiple symptoms were reported by the majority of the sample, i.e., 26% had 3-5 symptoms, and 45% of participants had more than 5 symptoms. Only 9% of the study group reported having no post-COVID-19 symptoms. Tiredness was the most frequent complaint (51%), followed by dizziness

(36%), body aches (33%), dyspnoea (30%), severe muscular/joint pains (27%), nocturia (24%), chest pain (20%), cough (19%), oedema (17%), taste loss (16%), nasal obstruction (16%), skin problems (15%), smell loss (14%), tinnitus (14%), hearing loss (14%), abdominal pain (14%), appetite loss (13%), diarrhoea (6%), and nausea/vomiting (3%).

The following drugs were used for the pharmacological treatment of COVID-19 in the acute phase of the disease: vasopressors (5.5%), antiaggregant (19.3%), corticosteroids (60.6%), antiviral (33.9%), immunosuppressors (4.4%), antibiotics (92.6%), antifungals (6.5%), antiparasitic (7.1%), non-steroidal anti-inflammatories (23.2%), angiotensin-converting enzyme inhibitors (19.8%), angiotensin-II receptor antagonists (22.2%).

Bivariate analysis comparing two groups (cytokines x non-cytokines) found non-significant ($p>.05$) differences between groups regarding age, length of hospitalization, any cognitive dimension (general cognition, attention, orientation, episodic memory, language, visuospatial ability), comorbidity (Charlson severity), education level, socioeconomic status (ABEP), or previous psychiatric disease. A significant difference ($p<.05$) was found regarding sex (cytokines: male 46.9%, female 53.1%; non-cytokines: male 56.5%, female 43.5%) and WHO severity (cytokines: class 1, 9.3%, class 2, 38.4%, class 3, 3.6%, class 4, 48.7%; non-cytokines: class 1, 14.6%, class 2, 45%, class 3, 5%, class 4, 35.4%). CFA presented good fit (Standardized Root Mean Square Residual - SRMR = 0.04) reaching all five sub-dimensions. Bivariate analysis between cognitive dimensions and independent variables can be seen in Supplementary tables 3 and 4. To test if our assumption was correct (i.e., individuals who claimed to be worse after COVID-19 were in fact cognitively worse), we performed two tests. First, patient and informant reports concerning patient cognition after COVID-19 were significantly associated

(p<.001). Second, patients' perceptions about changes in their cognitive state after COVID-19 were associated with their actual performance in objective tests addressing episodic memory (p=.002), orientation (p=.022), and global cognition (p=.026); but not for attention (p=.284), language (p=.184) and visuospatial ability (p=.539).

Tables 1-5 presents linear regression models using baseline variables as predictors and each cognitive subdimension as outcomes. Supplementary Table 5 presents a similar approach using global cognitive dimension as an outcome. We found statistically significant relationships between cognitive outcomes (orientation and attention, in particular) and socio-demographic variables (i.e., sex and education level).

All factors were significantly associated with higher educational profile as a protective factor, whereas male sex, in turn, was a protective factor for all but visuospatial ability and episodic memory. Older age was significantly associated as a risk factor for all variable except orientation. Comorbidity (Charlson severity score) was associated with all but orientation and visuospatial ability as risk factors. Several other variables were associated with specific independent variables. First, *orientation* was significantly associated previous psychiatric disease and pre-COVID-19 frailty as risk factors. A*ttention* was not associated with any other variable. Brown ethnicity was associated with *Language*, as a risk factor, which in turn, was also associated with low physical activity as a protective factor. *Episodic memory* was associated with COVID-19 severity and low socioeconomic status as a risk factors. *Visuospatial ability*, in turn, was associated with pre-COVID-19 frailty as risk factor; and finally, *Global cognition* was associated with Brown ethnicity and pre-COVID-19 frailty as risk factors and low physical exercise as a protective factor.

Supplementary Table 6 presents a model to better understand PASC clusters in our sample. We found five different clusters with a total explained variance of 58.6% (i.e., only loadings > 0.4):

factor 1: IL4, IL5, IL1-RA, IL1-alpha, IL13, IL6, IL15, and TNF-beta*;*

factor 2: VEGF, IL7, IFN-alpha2, G-CSF, IL1-RA, and IL15*;*

factor 3: chronic fatigue, MCS patient, depression, PTSD, and anxiety*;*

factor 4: orientation, attention, language, episodic memory, and visuospatial ability*;*

factor 5: smell and taste.

Finally, LASSO regression with all follow-up variables, inflammatory markers and cytokines did not find any significant variables associated with any cognitive sub-dimension or the global cognitive dimension.

Discussion

Here we present a diverse set of sociodemographic, clinical and biological variables associated with cognitive impairment in a cohort of survivors of moderate and severe forms of SARS-CoV-2 infection. First, we identified sociodemographic variables associated with poor cognitive performance; such as older age, female sex, ethnicity endorsed as Brown, and a lower educational profile. Second, clinical variables associated with poorer global cognition were: high comorbidity, low physical exercise, and a more severe frailty pre-COVID-19. Third, though we identified five clusters associated with post-COVID-cognitive disturbances, cognition appeared as a separate and individual factor. And fourth, a LASSO analysis did not identify any clinical or biological

(inflammatory markers and cytokines during follow-up) associated with poorer cognitive performance for any cognitive dimension, or for global cognition in general.

There is no debate that post-COVID-19 patients can develop a persistent spectrum of cognitive disturbances (Ceban et al., 2022), which some authors liken to an Alzheimer's Disease (AD)-type cognitive impairment (Fu et al., 2022). In fact, recent studies have pointed out several neuropathological similarities of PASC Cognitive Syndrome with AD (Alvarez et al., 2022); including, numerous elevated AD marker genes (e.g., FERMT2, HLA-DRB1, GNA15, STAB1, ICA1L, COLGALT1, TNFAIP2, ITGAM, VASP, IDLIA, PVR, TECPR1) (Fu et al., 2022), several circulatory biomarkers (i.e. GFAP, NFL, P-tau 181, UCH, NSE, and S100B) (Alvarez et al., 2022), and the presence of Apolipoprotein E ε4 allele (APOE4) (Kurki et al., 2021, Xiong et al., 2021), consistent with other reports (Damiano et al., 2021). Curiously, in LASSO regression modelling, we did not find a link between inflammatory cytokines and cognitive disturbances, as has been previously reported (Lyra et al., 2022, Vanderheiden and Klein, 2022, Ceban et al., 2022). These data suggest that future research might focus on additional AD biomarkers, rather than solely on inflammatory cytokines.

Although LASSO regression modelling did not find significant relationships between cognitive impairments and cytokine levels, bivariate analysis between cognitive sub-dimensions (Supplementary Table 3) suggested several cytokines that may be involved in cognitive function and may warrant further investigation. In particular, IL-1RA, IL-7, and G-CSF were associated with attention, language, episodic memory, and cognition dimensions. These factors have previously been implicated in cognitive function. For example, in adults with multiple sclerosis, a higher serum concentration of the anti-inflammatory marker IL-1RA was associated with better social-cognitive functioning (Turner et al., 2021). A study of 42 adults with bipolar disorder found that

IL-7 levels were significantly associated with measures of cognition, showing higher levels in the cognitively unimpaired group and a positive correlation with cognitive performance (Strawbridge et al., 2021). Further, preclinical studies indicate that treatment with G-CSF, a growth factor involved in neuroprotection and plasticity, may contribute to improved cognitive function in a model of traumatic brain injury (He et al., 2020). However, the potential role of IL-1RA, IL-7, and G-CSF in long COVID outcomes is unknown. In a previous study, IL-1RA and IL-7 were reported to be higher in the plasma of patients who recovered from COVID-19 compared to healthy controls and patients with acute COVID-19, however, G-CSF did not differ between control patients and patients recovered from COVID-19 (Loretelli et al., 2021). IL-1RA is an anti-inflammatory cytokine due to its IL-1 antagonistic actions inhibiting IL-1α and IL-1β signaling. G-CSF has neuroprotective properties as it inhibits apoptosis and inflammation in the brain, and also stimulates neurogenesis (Rahi et al., 2021).

We acknowledge that the lack of statistically significant associations between inflammatory markers and cognitive impairment was unexpected. This negative finding might be explained by several reasons: first, the effect of confounding variables, such as psychiatric, fatigue and pulmonary symptoms. This in line with a previous study conducted by our group, in which we found a significant association between "long-COVID" (defined as a latent dimension) and higher levels of C-reactive protein and d-dimer, but not with any specific psychiatric or cognitive symptom (Busatto et al., 2022). This is an interesting finding giving that in Busatto et al., latent PASC is dominated by fatigue, insomnia, psychiatric and cognitive symptoms. We hypothesize that the interaction among all symptoms increase the strength of association, especially in a sample of severe individuals (post-hospitalized); and highlights that the lack of association does not exclude the potential role of inflammation impacting the cognition

of these individuals. Second, the fact that cytokines were determined only in a subset (n=389) of the total follow-up sample (n=710). The inclusion of participants in this sub-sample was not random; rather, it prioritized the occurrence of general PASC symptoms (including, but not restricted to, cognitive symptoms), rendering the analysis prone to selection bias. Third, the LASSO regression per se, which may have supressed the significance of weaker associations between variables through the "shrinking" process. Finally, the fact that cytokines were not determined at baseline, precluding its comparison with follow-up values. This may be particularly relevant in the light of the frequent prescription of corticosteroids to post-COVID-19 patients, along with studies showing that this intervention may actually attenuate the so-called "cytokine storm" (Langarizadeh et al., 2021).

Moreover, we did not observe a significant association between observed clinical (i.e., pulmonary disorder, fatigue, smell and taste impairment, and COVID-19 severity) and psychiatric disorders (i.e. depression, GAD, PTSD, and CMD) and cognitive disturbances. The EFA data were consistent with this notion; cognitive impairment is a separate and specific cluster of the PASC syndrome. Instead, after controlling for multiple variables, we found that the presence of higher comorbidity and more severe frailty pre-COVID-19, as well as lower physical exercise in the weeks prior to the follow-up assessment, predicted poorer cognitive performance. The first two variables (comorbidity and frailty) have been previously discussed (Damiano et al., 2022a, Ceban et al., 2022), however, the latter variable (physical exercise) is a new finding that might be an important target for neuropsychological rehabilitation techniques in PASC patients. Such a strategy would be consistent with the protective effect of physical exercise observed in individuals with AD (Cámara-Calmaestra et al., 2022), particularly those who carry the

Apolipoprotein E ε4 allele (Jensen et al., 2019) that modulates AD biomarkers (Frederiksen et al., 2018).

One of the most robust findings in the present study was the observed relationship between different sociodemographic phenotypes and cognitive decline in long-COVID-19. Older age, female sex, ethnicity endorsed as Brown, and a lower educational profile predicted lower cognitive performance, with educational profile having the greatest effect size. Several other studies have reported poorer cognitive performance in PASC individuals who are older and female (Ceban et al., 2022). A lower educational profile comprises one of the main factors related to cognitive reserve and might be one of the main risk factors following acute stressors (Contador et al., 2022, Ihle et al., 2019) such as COVID-19 (Costas-Carrera et al., 2022, Devita et al., 2022). It is noteworthy that, in the present sample, the significant association between cognitive performance and lower educational profile was not accompanied by an association with socioeconomic status, given the fact that these two variables are often intertwined. We hypothesize that this lack of association in the present analysis may be due to a floor effect, given that 73.81% of our sample was raked as pertaining to lower socioeconomic classes (C-E).

It is important to point out to some limitations. First, we did not have a pre-COVID cognitive assessment. However, we did demonstrate that patients who claimed that their mental faculties were worse post-SARS CoV-2 infection, were in fact cognitively worse. Other qualifiers of the present study include: a) this is a single-centre study from a single country, which might limit its generalizability, b) our cohort is made up of relatively older individuals, which might increase the likelihood of a ceiling effect, reducing potentially significant associations, and c) cytokines were analysed 6-11 months after COVID-19 infection and not in acute phase, which could have influenced our results. However, our

stated aim was to analyse long-term inflammatory markers, in order to fill this gap in literature.

In summary, here we highlight the importance of several sociodemographic characteristics that might protect against cognitive impairment following SARS-CoV-2 infection. Our data do not find a prominent role for clinical status (both during acute and long-stage of COVID-19) or inflammatory background (also during acute and long-stage of COVID-19) to explain cognitive deficits following infection. These findings will require further validation by other centres. These results also point to possible interventions for cognitive impairment following COVID-19 (e.g., exercise) that future studies might address.

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Table 1. Linear Regression between baseline variables and Orientation

	Coefficient	SE	Lower CI	Upper CI	p-value
(Intercept)	-0.374	0.362	-1.085	0.336	0.301
Age	-0.004	0.003	-0.011	0.002	0.213
Sex [Male]	0.136	0.067	0.005	0.268	0.042
Ethnicity [Yellow]	0.570	0.496	-0.403	1.544	0.250
Ethnicity [Black]	0.097	0.121	-0.142	0.335	0.427
Ethnicity [Brown]	-0.079	0.079	-0.234	0.076	0.318
ABEP [B1]	0.115	0.240	-0.356	0.586	0.631
ABEP [B2]	0.214	0.223	-0.225	0.653	0.339
ABEP [C1]	0.186	0.223	-0.252	0.623	0.405
ABEP [C2]	0.052	0.227	-0.393	0.498	0.818
ABEP [D-E]	0.037	0.249	-0.451	0.525	0.882
Education [Uncompleted Elementary/Middle School]	0.426	0.180	0.073	0.779	0.018
Education [Completed Elementary/Middle School]	0.818	0.201	0.422	1.214	< 0.001
Education [Uncompleted High School]	0.525	0.212	0.108	0.942	0.014
Education [Completed High School]	0.801	0.194	0.421	1.182	< 0.001
Education [Uncompleted Undergraduation]	0.826	0.234	0.367	1.285	< 0.001
Education [Completed Undergraduation]	0.866	0.224	0.425	1.306	< 0.001
Education [Post-graduation]	0.927	0.264	0.408	1.445	< 0.001
Charlson Severity Score	-0.006	0.024	-0.053	0.040	0.789
Previous psychiatric disease [Yes]	-0.373	0.166	-0.700	-0.046	0.026
Severity WHO [2]	0.110	0.101	-0.088	0.307	0.277
Severity WHO [3]	0.176	0.174	-0.167	0.518	0.315
Severity WHO [4]	0.098	0.112	-0.123	0.319	0.384
Basal C-protein	0.000	0.000	-0.001	0.001	0.560
Basal D-dimer	0.000	0.000	0.000	0.000	0.577
Pre-COVID-19 frailty	-0.100	0.032	-0.162	-0.039	0.002
IPAQ [Irregularly Active]	0.112	0.086	-0.057	0.282	0.194
IPAQ [Active]	0.105	0.079	-0.050	0.260	0.182
IPAQ [Very Active]	0.216	0.176	-0.129	0.560	0.220

Table 2. Linear Regression between baseline variables and Attention

	Coefficient	SE	Lower CI	Upper CI	p-value
(Intercept)	0.447	0.447	-0.432	1.325	0.318
Age	-0.023	0.004	-0.031	-0.015	< 0.001
Sex [Male]	0.187	0.083	0.025	0.350	0.024
Ethnicity [Yellow]	0.075	0.601	-1.105	1.256	0.900
Ethnicity [Black]	0.029	0.150	-0.265	0.324	0.845
Ethnicity [Brown]	-0.134	0.101	-0.332	0.064	0.184
ABEP [B1]	-0.077	0.291	-0.648	0.495	0.793
ABEP [B2]	0.056	0.272	-0.478	0.589	0.837
ABEP [C1]	-0.029	0.270	-0.559	0.500	0.913
ABEP [C2]	-0.223	0.276	-0.765	0.318	0.418
ABEP [D-E]	-0.305	0.302	-0.899	0.288	0.312
Education [Uncompleted Elementary/Middle School]	0.519	0.228	0.070	0.968	0.023
Education [Completed Elementary/Middle School]	1.093	0.253	0.595	1.592	< 0.001
Education [Uncompleted High School]	1.298	0.267	0.772	1.823	< 0.001
Education [Completed High School]	1.676	0.243	1.198	2.154	< 0.001
Education [Uncompleted Undergraduation]	2.228	0.293	1.653	2.803	< 0.001
Education [Completed Undergraduation]	2.138	0.280	1.589	2.688	< 0.001
Education [Post-graduation]	2.413	0.325	1.774	3.052	< 0.001
Charlson Severity Score	-0.089	0.029	-0.146	-0.032	0.002
Previous psychiatric disease [Yes]	-0.239	0.192	-0.616	0.138	0.213
Severity WHO [2]	0.085	0.123	-0.156	0.327	0.488
Severity WHO [3]	-0.094	0.218	-0.522	0.334	0.667
Severity WHO [4]	0.022	0.138	-0.248	0.293	0.872
Basal C-protein	0.000	0.000	-0.001	0.001	0.977
Basal D-dimer	0.000	0.000	0.000	0.000	0.916
Pre-COVID-19 frailty	-0.075	0.040	-0.153	0.003	0.060
IPAQ [Irregularly Active]	0.099	0.106	-0.111	0.308	0.355
IPAQ [Active]	0.110	0.097	-0.080	0.300	0.255
IPAQ [Very Active]	0.098	0.212	-0.319	0.515	0.645

Table 3. Linear Regression between baseline variables and Language

	Coefficient	SE	Lower CI	Upper CI	p-value
(Intercept)	-0.068	0.363	-0.781	0.645	0.851
Age	-0.013	0.003	-0.020	-0.006	< 0.001
Sex [Male]	0.223	0.068	0.089	0.356	0.001
Ethnicity [Yellow]	-0.020	0.504	-1.009	0.969	0.968
Ethnicity [Black]	0.062	0.122	-0.178	0.302	0.614
Ethnicity [Brown]	-0.201	0.080	-0.358	-0.044	0.012
ABEP [B1]	-0.271	0.244	-0.750	0.207	0.266
ABEP [B2]	-0.081	0.229	-0.531	0.369	0.724
ABEP [C1]	-0.286	0.226	-0.731	0.158	0.207
ABEP [C2]	-0.154	0.232	-0.609	0.301	0.506
ABEP [D-E]	-0.046	0.251	-0.539	0.447	0.855
Education [Uncompleted Elementary/Middle School]	0.607	0.176	0.262	0.952	< 0.001
Education [Completed Elementary/Middle School]	1.124	0.196	0.739	1.508	< 0.001
Education [Uncompleted High School]	1.233	0.210	0.821	1.646	< 0.001
Education [Completed High School]	1.319	0.190	0.946	1.691	< 0.001
Education [Uncompleted Undergraduation]	1.678	0.231	1.224	2.131	< 0.001
Education [Completed Undergraduation]	1.779	0.221	1.344	2.213	< 0.001
Education [Post-graduation]	1.894	0.260	1.382	2.405	< 0.001
Charlson Severity Score	-0.065	0.024	-0.112	-0.018	0.007
Previous psychiatric disease [Yes]	-0.283	0.180	-0.640	0.073	0.118
Severity WHO [2]	0.136	0.102	-0.063	0.336	0.181
Severity WHO [3]	-0.107	0.181	-0.462	0.249	0.555
Severity WHO [4]	0.139	0.113	-0.084	0.361	0.221
Basal C-protein	0.000	0.000	-0.001	0.001	0.515
Basal D-dimer	0.000	0.000	0.000	0.000	0.854
Pre-COVID-19 frailty	-0.046	0.032	-0.110	0.017	0.154
IPAQ [Irregularly Active]	0.193	0.088	0.021	0.365	0.028
IPAQ [Active]	0.123	0.080	-0.033	0.280	0.122
IPAQ [Very Active]	0.068	0.176	-0.277	0.413	0.698

Table 4. Linear Regression between baseline variables and Episodic Memory

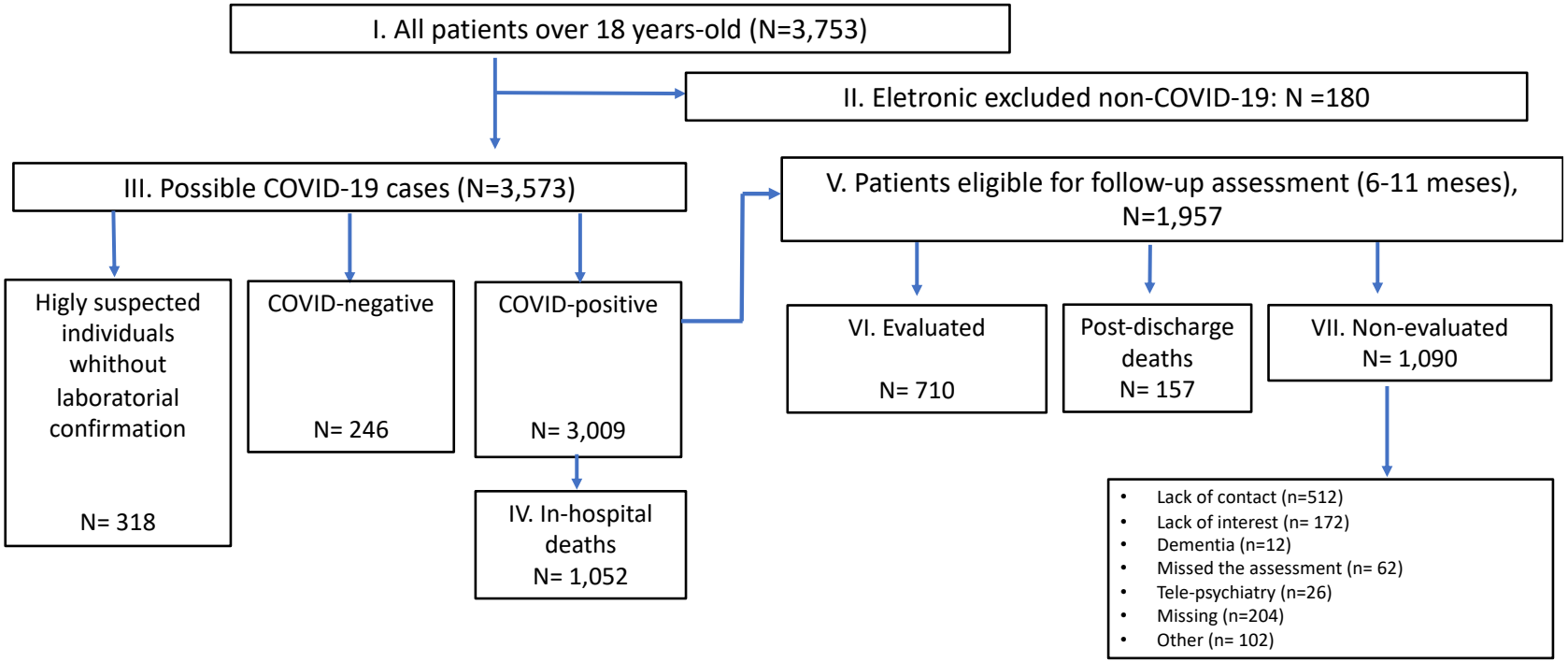
	Coefficient	SE	Lower CI	Upper CI	p-value
(Intercept)	2.051	0.686	0.704	3.399	0.003
Age	-0.038	0.006	-0.051	-0.025	< 0.001
Sex [Male]	0.078	0.129	-0.175	0.332	0.544
Ethnicity [Yellow]	0.030	0.948	-1.831	1.892	0.975
Ethnicity [Black]	-0.161	0.231	-0.614	0.293	0.487
Ethnicity [Brown]	-0.163	0.152	-0.462	0.136	0.285
ABEP [B1]	-0.939	0.457	-1.837	-0.041	0.040
ABEP [B2]	-0.730	0.425	-1.566	0.105	0.087
ABEP [C1]	-0.729	0.422	-1.558	0.099	0.084
ABEP [C2]	-0.957	0.431	-1.803	-0.111	0.027
ABEP [D-E]	-1.137	0.470	-2.059	-0.214	0.016
Education [Uncompleted Elementary/Middle School]	0.412	0.331	-0.238	1.063	0.214
Education [Completed Elementary/Middle School]	1.011	0.368	0.288	1.733	0.006
Education [Uncompleted High School]	1.279	0.396	0.502	2.056	0.001
Education [Completed High School]	1.323	0.359	0.617	2.029	< 0.001
Education [Uncompleted Undergraduation]	1.226	0.435	0.372	2.079	0.005
Education [Completed Undergraduation]	1.410	0.420	0.584	2.235	< 0.001
Education [Post-graduation]	2.199	0.491	1.234	3.163	< 0.001
Charlson Severity Score	-0.128	0.045	-0.216	-0.039	0.005
Previous psychiatric disease [Yes]	-0.457	0.363	-1.180	0.267	0.212
Severity WHO [2]	0.388	0.193	0.010	0.766	0.044
Severity WHO [3]	0.394	0.337	-0.268	1.056	0.243
Severity WHO [4]	0.141	0.216	-0.282	0.565	0.512
Basal C-protein	0.000	0.001	-0.001	0.002	0.618
Basal D-dimer	0.000	0.000	0.000	0.000	0.352
Pre-COVID-19 frailty	-0.034	0.061	-0.155	0.086	0.574
IPAQ [Irregularly Active]	0.288	0.166	-0.038	0.614	0.084
IPAQ [Active]	0.174	0.150	-0.121	0.470	0.246
IPAQ [Very Active]	0.457	0.332	-0.194	1.108	0.169

Table 5. Linear Regression between baseline variables and Visuospatial Ability

	Coefficient	SE	Lower CI	Upper CI	p-value

(Intercept)	-0.491	0.505	-1.482	0.500	0.331
Age	-0.020	0.005	-0.029	-0.011	< 0.001
Sex [Male]	0.127	0.094	-0.058	0.312	0.179
Ethnicity [Yellow]	1.530	0.714	0.128	2.932	0.032
Ethnicity [Black]	0.129	0.169	-0.202	0.460	0.445
Ethnicity [Brown]	-0.141	0.111	-0.359	0.076	0.203
ABEP [B1]	0.357	0.336	-0.302	1.016	0.288
ABEP [B2]	0.237	0.314	-0.379	0.854	0.450
ABEP [C1]	0.083	0.312	-0.529	0.695	0.789
ABEP [C2]	0.013	0.318	-0.611	0.638	0.966
ABEP [D-E]	0.138	0.348	-0.546	0.821	0.693
Education [Uncompleted Elementary/Middle School]	1.131	0.245	0.650	1.613	< 0.001
Education [Completed Elementary/Middle School]	1.653	0.273	1.117	2.188	< 0.001
Education [Uncompleted High School]	1.661	0.293	1.086	2.236	< 0.001
Education [Completed High School]	2.020	0.266	1.499	2.542	< 0.001
Education [Uncompleted Undergraduation]	2.381	0.321	1.750	3.012	< 0.001
Education [Completed Undergraduation]	2.494	0.310	1.886	3.103	< 0.001
Education [Post-graduation]	2.751	0.362	2.040	3.462	< 0.001
Charlson Severity Score	-0.011	0.033	-0.077	0.054	0.738
Previous psychiatric disease [Yes]	-0.223	0.234	-0.686	0.240	0.343
Severity WHO [2]	0.035	0.141	-0.241	0.311	0.801
Severity WHO [3]	-0.236	0.246	-0.720	0.248	0.339
Severity WHO [4]	0.072	0.157	-0.235	0.380	0.645
Basal C-protein	0.000	0.001	-0.001	0.001	0.430
Basal D-dimer	0.000	0.000	0.000	0.000	0.531
Pre-COVID-19 frailty	-0.114	0.046	-0.203	-0.025	0.013
IPAQ [Irregularly Active]	0.148	0.122	-0.091	0.387	0.226
IPAQ [Active]	0.005	0.110	-0.211	0.222	0.961
IPAQ [Very Active]	0.170	0.244	-0.310	0.649	0.487

Supplementary Table 1. Flow-chart of evaluated individuals in cognitive assessment of the cohort



Supplementary Table 2. Instruments Used in the Follow-up Evaluation

Scale	Characteristic	References
A. Diagnostic Interview		
Clinical Interview Schedule - Revised (CIS-R)	It is a structured psychiatric interview developed by Lewis et al. (1992) and culturally adapted to the Brazilian population by Nunes et al. (2011). It consists of 14 sections addressing: somatic symptoms; fatigue; sleep problems; irritability; physical health worries; depression; depressive ideas; worry; anxiety; phobias; panic; compulsive behaviors; obsessive thoughts; forgetfulness/concentration problems, yielding 5 psychiatric categories based on ICD-10: generalized anxiety disorder, depressive episode, all phobias (agoraphobia, social phobia, and simple phobia), obsessive-compulsive disorder, and panic disorder. The diagnosis of a common mental disorder can be established if the participant scores ≥12 in the sum of all 14-dimensional symptoms. It presents good psychometric characteristics even when compared with more robust instruments such as the Structured Clinical Interview for DSM-5 Disorders (SCID-5).	Lewis G, Pelosi AJ, Araya R, Dunn G. Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. Psychological medicine 1992; 22(2): 465-86. Nunes MA, Alves MGdM, Chor D, Schmidt MI, Duncan BB. Adaptação transcultural do CIS-R (Clinical Interview Schedule - Revised Version) para o português no estudo longitudinal de saúde do adulto (ELSA). 2012 2012; 31(4). Jordanova V, Wickramesinghe C, Gerada C, Prince M. Validation of two survey diagnostic interviews among primary care attendees: a comparison of CIS-R and CIDI with SCAN ICD-10 diagnostic categories. Psychological medicine 2004; 34(6): 1013-24. Pez O, Gilbert F, Bitfoi A, et al. Validity across translations of short survey psychiatric diagnostic instruments: CIDI-SF and CIS-R versus SCID-I/NP in four European countries. Soc Psychiatry Psychiatr Epidemiol 2010; 45(12): 1149-59.
Structured Clinical Interview for DSM-5 Disorders, Research Version (SCID-5-RV)	The assessment of psychotic symptoms was done with the aid of an excerpt of the SCID-5-RV schedule, i.e., Module B, Psychotic and Associated Symptoms (items B2 to B19). The SCID-5-RV is a semi-structured psychiatric interview that follows the diagnostic criteria established by the American Psychiatric Association (APA)'s Diagnostic and Statistical Manual for Mental Disorders, 5th Edition (DSM-5). Given that the target population comprised subjects with no (a priori) previous history of psychotic disorders, and to render the interpretation of responses easier for the examiners, this assessment was limited to nineteen objective questions yielding yes/no answers (i.e., symptom present or absent). Thirteen of those questions address different types of delusions, while the remaining six assess auditory, visual, tact, taste, olfactory and somatic hallucinations.	First M, Williams J, Karg R, Spitzer R. Structured Clinical Interview for DSM-5 Disorders, Clinician Version (SCID-5-CV). . Arlington, VA: American Psychiatric Association; 2016.

B. Self-Report Measures		
Hospital Anxiety and Depression Scale (HAD)	It is a self-assessment scale developed by Zigmond and Snaith (1983) and validated to Brazilian clinical population by Botega et al. (1995). The HAD is a widely used reliable instrument to determine the levels of anxiety, depression and emotional disorders in hospitalized and post-hospitalized patients, due to its focus on psychological rather than somatic symptoms of depression. The scale is composed of 14 questions scored from 0-3, subdivided in two domains (anxiety and depression) of seven questions each. Total score ranges from 0 to 21, higher scores indicating more severe symptoms. We used cut off of ≥8 for both subscales, which supposedly yields 82% sensitivity for the identification major depressive disorder (MDD) and 78% for generalized anxiety disorder (GAD), along with 74% specificity for MDD and GAD.	Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67(6): 361-70. Botega NJ, Bio MR, Zomignani MA, Garcia Jr C, Pereira WAB. Transtornos do humor em enfermaria de clínica médica e validação de escala de medida (HAD) de ansiedade e depressão. Revista de Saúde Pública 1995; 29: 359-63. Brennan C, Worrall-Davies A, McMillan D, Gilbody S, House A. The Hospital Anxiety and Depression Scale: A diagnostic meta-analysis of case-finding ability. Journal of Psychosomatic Research 2010; 69(4): 371-8.
Ask Suicide-Screening Questions (ASQ)	The ASQ is a four-item self-report questionnaire to screen for suicide risk. It evaluates the occurrence of suicidal ideation in the previous four weeks, in addition to any previous attempts. The questions address the 'wish to die', the feeling of 'leaving one's family better off if dead', the presence of suicidal thoughts, and any previous suicide attempts. The first three answers range from never to daily (0-3), implying the risk of suicide. The scale further estimates the number of suicide attempts, if any, in the previous year. Studies in pediatric emergency settings indicated good psychometric properties, with 96.9% sensitivity, 87.6% specificity, and negative predictive value (NPV) of 99.7%.39 The ASQ has also been validated for use among adults, representing a good tool for the screening of suicidal risk behavior with specificity and NPV rates of 89% and 100% respectively. For this study, we used a score (sum of questions 1, 2, 3, 4 and 6) in order to produce a continuous variable.	Horowitz LM, Bridge JA, Teach SJ, et al. Ask Suicide-Screening Questions (ASQ): a brief instrument for the pediatric emergency department. Arch Pediatr Adolesc Med 2012; 166(12): 1170-6. Horowitz LM, Snyder DJ, Boudreaux ED, et al. Validation of the Ask Suicide-Screening Questions for Adult Medical Inpatients: A Brief Tool for All Ages. Psychosomatics 2020; 61(6): 713-22.

Post-Traumatic Stress Disorder Checklist (PCL-C)	It is an instrument developed for the assessment of PTSD, based on DSM-III-R diagnostic criteria that has a validated Brazilian Portuguese version. The scale takes into account the severity of symptoms reported by the subject in the previous month, utilizing a grading scale ranges from 'nothing' to 'extremely' (1-5). For PTSD diagnosis, the patient needs to have at least moderate symptoms (score ≥3) in one or more criteria listed in cluster B, three in cluster C, and two in cluster D. Raters were instructed to score only if suspected PTSD symptoms occurred after COVID-19 onset.	Weathers F, Litz B, Herman D, Huska JA, Keane T. PTSD Checklist: Reliability, validity, and diagnostic utility. Proceedings of the 9th Annual Meeting of the International Society for Traumatic Stress Studies (ISTSS) 1993. Berger W, Mendlowicz MV, Souza WF, Figueira I. Equivalência semântica da versão em português da Post-Traumatic Stress Disorder Checklist - Civilian Version (PCL-C) para rastreamento do transtorno de estresse pós-traumático. Revista de Psiquiatria do Rio Grande do Sul 2004; 26: 167-75.
Alcohol Use Disorder Identification Test (AUDIT)	The AUDIT is a widely used instrument developed by the World Health Organization to estimate Alcohol Use Disorder (AUD). It is a comprehensive 10-item self-report screening tool, with total score ranging from 0 to 40, indicating 'low risk' (0-7), 'increasing risk' (8-15), 'higher risk' (16-19) and 'possible dependence' (20 or more). A Brazilian Portuguese version has been validated for use in urban populations, with good psychometric proprieties.	Reinert DF, Allen JP. The Alcohol Use Disorders Identification Test (AUDIT): A review of recent research. Alcoholism: Clinical and Experimental Research 2002; 26(2): 272-9. World Health O. AUDIT: the Alcohol Use Disorders Identification Test : guidelines for use in primary health care / Thomas F. Babor ... [et al.]. 2nd ed ed. Geneva: World Health Organization; 2001. Lima CT, Freire AC, Silva AP, Teixeira RM, Farrell M, Prince M. Concurrent and construct validity of the audit in an urban brazilian sample. Alcohol Alcohol 2005; 40(6): 584-9.
C. Cognitive Assessment		

Memory Complaint Scale (MCS)	The MSC carries out a systematic search for memory complaints. It is composed of seven self-reported items with graded responses where higher scores indicate greater intensity (0, 1 and 2). The memory complaints are ranked as 'absent' (0-2), 'mild' (3-6), 'moderate' (7-10) and 'severe' (11-14). This instrument explores the frequency and the degree to which the memory complaints impact on daily activities; compares the current memory to that of a younger age, and to that of others within the same age range. The scale has two identical versions (A and B), the latter dedicated to capture the informant's report (if available) about the subject's memory complaints. Previous research suggested that subjective memory complaints may be a proxy of poor cognitive function in older adults. After completion of the MCS schedule, participants were additionally asked to rank their overall memory performance in the light of COVID-19.	Vale FAC, Balieiro-Jr AP, Silva-Filho JH. Memory complaint scale (MCS): Proposed tool for active systematic search. Dementia & Neuropsychologia 2012; 6: 212-8. Amariglio RE, Townsend MK, Grodstein F, Sperling RA, Rentz DM. Specific subjective memory complaints in older persons may indicate poor cognitive function. J Am Geriatr Soc 2011; 59(9): 1612-7.
Digit Symbol Substitution Test (DDST)	The DDST is a widely used test in neuropsychology. It consists in a series of numbers and symbols where participants are asked to fill out blank spaces in two minutes. In our test, we asked to fill out the respective number looking for each specific symbol. The score consists of summing the right answers (right numbers) in two minutes.	Jaeger J. Digit Symbol Substitution Test: The Case for Sensitivity Over Specificity in Neuropsychological Testing. Journal of clinical psychopharmacology. 2018;38(5):513-9.

Temporal and Spatial Orientation of Mini Mental State Examination (MMSE)	This study utilizes the temporal and spatial orientation section of the mini-mental state examination (MMSE) composed of 10 questions for which answers were classified as either correct or incorrect. It is asked that the patient specify the day of the week, the day of the month, which month, which year and at what time the interview is being conducted. The spatial orientation is determined by assessing if the patient is able to correctly name the following items: the specific location the interview is being conducted at; the building he or she is in; the neighborhood or any close by streets; the country and the state. The choice for this part of the instrument was meant to discriminate severe forms of dementia, which could impact our final outcome and interpretation.	Bernard BA, Goldman JG. MMSE - Mini-Mental State Examination. In: Kompoliti K, Metman LV, eds. Encyclopedia of Movement Disorders. Oxford: Academic Press; 2010: 187-9.
Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery (CERAD)	Developed by the Consortium to Establish a Registry for Alzheimer's Disease and adapted to Brazilian population by Bertolucci et al., it consists in a large cognitive battery assessing different cognitive domains. We uded the following instruments from CERAD: Boston Naming Test, Word List Learning, Word List Recall, Constructional Praxis and Delayed Constructional Praxis.	Welsh K, Butters N, Hughes J, Mohs R, Heyman A. Detection of abnormal memory decline in mild cases of Alzheimer's disease using CERAD neuropsychological measures. Arch Neurol. 1991;48(3):278-81. Bertolucci PHF, Okamoto IH, Brucki SMD, Siviero MO, Toniolo Neto J, Ramos LR. Applicability of the CERAD neuropsychological battery to Brazilian elderly. Arquivos de Neuro-Psiquiatria. 2001;59:532-6.
D. Clinical Assessment		
Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale	FACIT is a self-report scale developed to measure chronic fatigue following clinical or psychiatric ilnessess. It is a 13-item scale, with a 4-point likert (ranging from 4 = not at all fatigued to 0 = very much fatigued). It demonstrated good psychometric proprieties and a translated version has been used in Brazilian samples.	Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage. 1997;13(2):63-74. Bianchi WA, Elias FR, Pinheiro Gda R, et al. Analysis of the association of fatigue with clinical and psychological variables in a series of 371 Brazilian patients with rheumatoid arthritis. Rev Bras Reumatol. 2014;54(3):200-207.

Clinical Frailty Scale (CFS)	The CFS was developed for use in the Canadian Study of Health and Aging (CSHA), and described by Rockwood et al. It is composed of a 7-item scale that clinicians have to ascertain for the vulnerability of each patient, where 1 represents very fit (robust, active, energetic) and 7 severely frail (completely dependent). It has demonstrated good accuracy, being able to predict death or entry in institutional care of elderly individuals.	Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. Canadian Medical Association Journal 2005; 173(5): 489-95.
Smell and Taste Evaluation	The evaluation of integrity of olfactory and gustatory function (according to the patients' subjective impression) was performed with the aid of Visual Analogue Scale developed by authors, as reported in previous studies. In brief, the patients were asked to indicate their perception of change in the previous ability to recognize (a) smell or (b) taste in a numeric scale ranging from 0 to 10, where higher scores represent better function (0 = unable to identify any (a) smell or (b) taste; 10 = no impairment in (a) smell or (b) taste sensitivity). These scales were administered upon objective, multidisciplinary reassessment of patients 6-11 months after hospital discharge in order to depict patients' current perception of impairment in smell or taste identification, and also retrospectively to estimate the occurrence of any such impairments during the acute phase of COVID-19. Cut-off scores were used to allocate participants into distinct categories according to magnitude of olfactory and/or gustatory impairment, i.e., severe impairment (0-4); moderate impairment (8-5); mild impairment (9); or no impairment (10) in these chemosensory functions. Subjects presenting with moderate/severe impairment were compared with those reporting mild/no impairment in order to verify the association of these conditions with neuropsychiatric outcomes. Subjects were also inquired about the presence of anosmia, parosmia, cacosmia and fluctuations in smell functions.	McCormack HM, Horne DJ, Sheather S. Clinical applications of visual analogue scales: a critical review. Psychological medicine. 1988;18(4):1007-19. Sayin İ, Yaşar KK, Yazici ZM. Taste and Smell Impairment in COVID-19: An AAO-HNS Anosmia Reporting Tool-Based Comparative Study. Otolaryngol Head Neck Surg. 2020;163(3):473-9.

International Physical Activity Questionnaire (IPAQ) – Short Version	Developed by an international board of World Health Organization in 1998, the IPAQ was broadly used and validated in several countries, presenting good psychometric proprieties, including Brazil We used the short version consisting in four questions (with A and B sections) and generated four different levels of physical activity: sedentary, irregularly active, active ad very active.	Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc 2003; 35(8): 1381-95. Matsudo S, Araújo T, Matsudo V, et al. Questionário Internacional de Atividade Física (IPAQ): Estudo de Validade e Reprodutibilidade no Brasil. Rev Bras Ativ Fis Saúde 2001; 6(2).

Supplementary Table 3. Bivariate Analysis between potential predictors and cognitive sub-dimensions with continuous variables.

Dependent	Independent	Correlation	Lower CI	Upper CI	p-value
Orientation	Age	-0.235	-0.302	-0.165	< 0.001
Orientation	Charlson Score	-0.220	-0.289	-0.149	< 0.001
Orientation	Basal C-Reactive Protein	-0.034	-0.109	0.042	0.386
Orientation	Basal D-Dimer	-0.056	-0.133	0.023	0.164
Orientation	Pre-COVID-19 Frailty	-0.303	-0.368	-0.235	< 0.001
Orientation	EGF	-0.004	-0.107	0.100	0.946
Orientation	Eotaxin	0.036	-0.067	0.139	0.495
Orientation	G-CSF	0.054	-0.049	0.156	0.306
Orientation	GM-CSF	0.055	-0.048	0.157	0.296
Orientation	IFN-alfa2	0.052	-0.052	0.154	0.327
Orientation	IFN-gama	0.056	-0.048	0.158	0.291
Orientation	IL10	-0.018	-0.121	0.085	0.728
Orientation	IL12-p40	0.049	-0.055	0.151	0.356
Orientation	IL12-p70	-0.031	-0.133	0.073	0.561
Orientation	IL13	-0.010	-0.113	0.093	0.844
Orientation	IL15	0.064	-0.040	0.166	0.227
Orientation	IL17	0.047	-0.056	0.150	0.369
Orientation	IL1.RA	0.007	-0.096	0.110	0.891
Orientation	IL1-alfa	0.001	-0.102	0.104	0.982
Orientation	IL1-beta	0.023	-0.080	0.126	0.658
Orientation	IL2	0.023	-0.080	0.126	0.658
Orientation	IL4	0.000	-0.103	0.103	1.000
Orientation	IL5	-0.007	-0.110	0.096	0.894
Orientation	IL6	-0.023	-0.126	0.080	0.658
Orientation	IL7	0.066	-0.037	0.168	0.207
Orientation	IL8	-0.045	-0.147	0.059	0.395
Orientation	IP10	-0.017	-0.120	0.087	0.752
Orientation	MCP1	0.073	-0.031	0.175	0.167
Orientation	MIP1-alfa	-0.216	-0.312	-0.115	< 0.001
Orientation	MIP1-beta	0.003	-0.101	0.106	0.961
Orientation	TNF-alfa	0.070	-0.033	0.172	0.183
Orientation	TNF-beta	0.001	-0.102	0.104	0.987
Orientation	VEGF	0.082	-0.021	0.184	0.117
Orientation	Follow-up C-Reactive Protein	-0.018	-0.091	0.054	0.625
Orientation	Follow-up D-Dimer	-0.007	-0.080	0.065	0.842
Orientation	Socioeconomic Status (ABEP)	-0.172	-0.242	-0.100	< 0.001
Orientation	Education	0.235	0.114	0.350	< 0.001
Orientation	COVID-19 Severity	-0.036	-0.108	0.037	0.275
Orientation	IPAQ	0.082	0.009	0.153	0.012
Attention	Age	-0.490	-0.544	-0.433	< 0.001
Attention	Charlson Score	-0.438	-0.497	-0.376	< 0.001

Attention	Basal C-Reactive Protein	-0.029	-0.105	0.048	0.460
Attention	Basal D-Dimer	-0.126	-0.203	-0.047	0.002
Attention	Pre-COVID-19 Frailty	-0.302	-0.368	-0.233	< 0.001
Attention	EGF	-0.057	-0.160	0.047	0.283
Attention	Eotaxin	-0.068	-0.171	0.037	0.203
Attention	G-CSF	0.148	0.045	0.248	0.005
Attention	GM-CSF	0.101	-0.003	0.203	0.057
Attention	IFN-alfa2	0.107	0.002	0.208	0.045
Attention	IFN-gama	0.087	-0.017	0.189	0.102
Attention	IL10	-0.020	-0.124	0.084	0.704
Attention	IL12-p40	0.070	-0.035	0.172	0.191
Attention	IL12-p70	0.019	-0.085	0.123	0.720
Attention	IL13	0.145	0.041	0.245	0.006
Attention	IL15	0.082	-0.022	0.185	0.122
Attention	IL17	0.019	-0.086	0.123	0.725
Attention	IL1-RA	0.166	0.063	0.266	0.002
Attention	IL1-alfa	0.133	0.029	0.233	0.012
Attention	IL1-beta	0.005	-0.099	0.109	0.921
Attention	IL2	0.042	-0.062	0.145	0.431
Attention	IL4	0.176	0.073	0.275	< 0.001
Attention	IL5	0.122	0.018	0.223	0.022
Attention	IL6	0.102	-0.002	0.204	0.055
Attention	IL7	0.196	0.093	0.294	< 0.001
Attention	IL8	0.021	-0.083	0.125	0.690
Attention	IP10	-0.092	-0.194	0.013	0.085
Attention	MCP1	0.046	-0.058	0.149	0.388
Attention	MIP1-alfa	-0.039	-0.142	0.066	0.466
Attention	MIP1-beta	-0.099	-0.201	0.005	0.063
Attention	TNF-alfa	0.087	-0.018	0.189	0.103
Attention	TNF-beta	0.135	0.032	0.236	0.011
Attention	VEGF	0.154	0.051	0.254	0.004
Attention	Follow-up C-Reactive Protein	-0.150	-0.221	-0.077	< 0.001
Attention	Follow-up D-Dimer	-0.123	-0.195	-0.050	< 0.001
Attention	Socioeconomic Status (ABEP)	-0.299	-0.365	-0.230	< 0.001
Attention	Education	0.360	0.244	0.465	< 0.001
Attention	COVID-19 Severity	-0.045	-0.118	0.029	0.123
Attention	IPAQ	0.121	0.048	0.193	< 0.001
Language	Age	-0.420	-0.478	-0.358	< 0.001
Language	Charlson Score	-0.381	-0.442	-0.316	< 0.001
Language	Basal C-Reactive Protein	-0.025	-0.101	0.051	0.516
Language	Basal D-Dimer	-0.108	-0.185	-0.030	0.007
Language	Pre-COVID-19 Frailty	-0.321	-0.385	-0.253	< 0.001
Language	EGF	-0.042	-0.145	0.061	0.424
Language	Eotaxin	0.022	-0.081	0.125	0.676
Language	G-CSF	0.116	0.013	0.217	0.027
Language	GM-CSF	0.107	0.004	0.208	0.042

Language	IFN-alfa2	0.088	-0.016	0.189	0.096
Language	IFN-gama	0.129	0.025	0.229	0.015
Language	IL10	0.033	-0.071	0.136	0.537
Language	IL12-p40	0.088	-0.016	0.190	0.096
Language	IL12-p70	0.018	-0.086	0.121	0.735
Language	IL13	0.134	0.031	0.234	0.011
Language	IL15	0.136	0.033	0.236	0.010
Language	IL17	0.078	-0.025	0.180	0.139
Language	IL1-RA	0.126	0.023	0.226	0.017
Language	IL1-alfa	0.132	0.029	0.232	0.012
Language	IL1-beta	0.030	-0.074	0.133	0.570
Language	IL2	0.076	-0.027	0.178	0.149
Language	IL4	0.133	0.030	0.233	0.012
Language	IL5	0.108	0.005	0.209	0.041
Language	IL6	0.082	-0.022	0.183	0.123
Language	IL7	0.157	0.054	0.256	0.003
Language	IL8	0.041	-0.062	0.144	0.437
Language	IP10	-0.045	-0.148	0.059	0.394
Language	MCP1	0.076	-0.028	0.178	0.152
Language	MIP1-alfa	-0.073	-0.175	0.031	0.169
Language	MIP1-beta	0.022	-0.081	0.125	0.676
Language	TNF-alfa	0.090	-0.013	0.192	0.088
Language	TNF-beta	0.131	0.028	0.231	0.013
Language	VEGF	0.139	0.037	0.239	0.008
Language	Follow-up C-Reactive Protein	-0.080	-0.152	-0.008	0.030
Language	Follow-up D-Dimer	-0.023	-0.096	0.049	0.529
Language	Socioeconomic Status (ABEP)	-0.218	-0.286	-0.147	< 0.001
Language	Education	0.275	0.156	0.387	< 0.001
Language	COVID-19 Severity	-0.025	-0.098	0.047	0.380
Language	IPAQ	0.104	0.031	0.175	< 0.001
Epimemory	Age	-0.467	-0.522	-0.408	< 0.001
Epimemory	Charlson Score	-0.416	-0.475	-0.352	< 0.001
Epimemory	Basal C-Reactive Protein	-0.027	-0.103	0.049	0.489
Epimemory	Basal D-Dimer	-0.088	-0.166	-0.009	0.028
Epimemory	Pre-COVID-19 Frailty	-0.259	-0.326	-0.188	< 0.001
Epimemory	EGF	-0.119	-0.220	-0.016	0.024
Epimemory	Eotaxin	-0.042	-0.145	0.063	0.434
Epimemory	G-CSF	0.129	0.025	0.229	0.015
Epimemory	GM-CSF	0.021	-0.083	0.125	0.690
Epimemory	IFN-alfa2	0.091	-0.013	0.193	0.085
Epimemory	IFN-gama	0.095	-0.009	0.197	0.072
Epimemory	IL10	-0.004	-0.108	0.100	0.941
Epimemory	IL12-p40	0.065	-0.039	0.168	0.220
Epimemory	IL12-p70	-0.018	-0.122	0.086	0.735
Epimemory	IL13	0.050	-0.054	0.153	0.345
Epimemory	IL15	0.088	-0.016	0.190	0.097

Epimemory	IL17	0.014	-0.090	0.117	0.795
Epimemory	IL1-RA	0.115	0.011	0.216	0.030
Epimemory	IL1-alfa	0.042	-0.062	0.146	0.425
Epimemory	IL1-beta	-0.020	-0.124	0.084	0.703
Epimemory	IL2	0.039	-0.065	0.142	0.461
Epimemory	IL4	0.065	-0.039	0.168	0.218
Epimemory	IL5	0.044	-0.061	0.147	0.412
Epimemory	IL6	0.012	-0.092	0.116	0.820
Epimemory	IL7	0.132	0.029	0.233	0.012
Epimemory	IL8	0.023	-0.081	0.127	0.659
Epimemory	IP10	-0.041	-0.144	0.063	0.443
Epimemory	MCP1	0.061	-0.043	0.163	0.253
Epimemory	MIP1-alfa	-0.150	-0.250	-0.047	0.005
Epimemory	MIP1-beta	-0.024	-0.128	0.080	0.648
Epimemory	TNF-alfa	0.064	-0.040	0.167	0.227
Epimemory	TNF-beta	0.068	-0.036	0.171	0.199
Epimemory	VEGF	0.146	0.042	0.246	0.006
Epimemory	Follow-up C-Reactive Protein	-0.086	-0.158	-0.013	0.021
Epimemory	Follow-up D-Dimer	-0.099	-0.171	-0.027	0.008
Epimemory	Socioeconomic Status (ABEP)	-0.199	-0.268	-0.127	< 0.001
Epimemory	Education	0.236	0.114	0.351	< 0.001
Epimemory	COVID-19 Severity	-0.024	-0.097	0.049	0.404
Epimemory	IPAQ	0.115	0.042	0.186	< 0.001
Visuoability	Age	-0.388	-0.449	-0.325	< 0.001
Visuoability	Charlson Score	-0.322	-0.387	-0.254	< 0.001
Visuoability	Basal C-Reactive Protein	-0.002	-0.078	0.074	0.965
Visuoability	Basal D-Dimer	-0.112	-0.190	-0.034	0.005
Visuoability	Pre-COVID-19 Frailty	-0.290	-0.356	-0.221	< 0.001
Visuoability	EGF	-0.097	-0.199	0.007	0.067
Visuoability	Eotaxin	-0.048	-0.151	0.056	0.364
Visuoability	G-CSF	0.014	-0.090	0.117	0.792
Visuoability	GM-CSF	-0.017	-0.120	0.087	0.748
Visuoability	IFN-alfa2	-0.008	-0.112	0.096	0.879
Visuoability	IFN-gama	-0.012	-0.116	0.091	0.814
Visuoability	IL10	-0.056	-0.159	0.048	0.290
Visuoability	IL12-p40	-0.022	-0.125	0.082	0.685
Visuoability	IL12-p70	-0.029	-0.133	0.074	0.579
Visuoability	IL13	0.055	-0.049	0.158	0.296
Visuoability	IL15	0.022	-0.082	0.125	0.680
Visuoability	IL17	-0.057	-0.160	0.047	0.281
Visuoability	IL1-RA	0.041	-0.063	0.144	0.435
Visuoability	IL1-alfa	0.041	-0.062	0.145	0.434
Visuoability	IL1-beta	-0.041	-0.144	0.063	0.437
Visuoability	IL2	-0.022	-0.126	0.081	0.673
Visuoability	IL4	0.060	-0.044	0.163	0.256
Visuoability	IL5	0.054	-0.050	0.157	0.309

Visuoability	IL6	0.044	-0.060	0.147	0.407
Visuoability	IL7	0.069	-0.035	0.172	0.192
Visuoability	IL8	0.060	-0.044	0.162	0.261
Visuoability	IP10	-0.146	-0.246	-0.043	0.006
Visuoability	MCP1	0.054	-0.050	0.157	0.307
Visuoability	MIP1-alfa	-0.019	-0.122	0.085	0.723
Visuoability	MIP1-beta	0.030	-0.074	0.133	0.577
Visuoability	TNF-alfa	0.043	-0.061	0.146	0.418
Visuoability	TNF-beta	0.057	-0.047	0.159	0.286
Visuoability	VEGF	0.057	-0.047	0.159	0.284
Visuoability	Follow-up C-Reactive Protein	-0.042	-0.114	0.031	0.262
Visuoability	Follow-up D-Dimer	-0.021	-0.094	0.052	0.570
Visuoability	Socioeconomic Status (ABEP)	-0.230	-0.299	-0.159	< 0.001
Visuoability	Education	0.270	0.150	0.382	< 0.001
Visuoability	COVID-19 Severity	-0.033	-0.105	0.040	0.267
Visuoability	IPAQ	0.081	0.008	0.153	0.005
Cognition	Age	-0.537	-0.588	-0.482	< 0.001
Cognition	Charlson Score	-0.488	-0.543	-0.429	< 0.001
Cognition	Basal C-Reactive Protein	-0.021	-0.098	0.056	0.591
Cognition	Basal D-Dimer	-0.133	-0.211	-0.054	0.001
Cognition	Pre-COVID-19 Frailty	-0.347	-0.411	-0.280	< 0.001
Cognition	EGF	-0.068	-0.171	0.037	0.205
Cognition	Eotaxin	-0.037	-0.142	0.068	0.486
Cognition	G-CSF	0.132	0.028	0.234	0.013
Cognition	GM-CSF	0.086	-0.019	0.190	0.106
Cognition	IFN-alfa2	0.106	0.001	0.208	0.049
Cognition	IFN-gama	0.099	-0.006	0.201	0.066
Cognition	IL10	-0.009	-0.114	0.096	0.862
Cognition	IL12-p40	0.074	-0.031	0.177	0.169
Cognition	IL12-p70	-0.009	-0.113	0.096	0.874
Cognition	IL13	0.150	0.046	0.251	0.005
Cognition	IL15	0.119	0.014	0.221	0.026
Cognition	IL17	0.027	-0.078	0.131	0.614
Cognition	IL1-RA	0.157	0.052	0.257	0.003
Cognition	IL1-alfa	0.138	0.034	0.239	0.010
Cognition	IL1-beta	0.010	-0.095	0.114	0.856
Cognition	IL2	0.064	-0.041	0.168	0.232
Cognition	IL4	0.164	0.060	0.264	0.002
Cognition	IL5	0.129	0.024	0.231	0.016
Cognition	IL6	0.108	0.003	0.210	0.044
Cognition	IL7	0.175	0.072	0.275	< 0.001
Cognition	IL8	0.049	-0.056	0.153	0.358
Cognition	IP10	-0.102	-0.205	0.003	0.057
Cognition	MCP1	0.090	-0.015	0.193	0.094
Cognition	MIP1-alfa	-0.073	-0.176	0.032	0.173
Cognition	MIP1-beta	-0.040	-0.144	0.065	0.456

Cognition	TNF-alfa	0.096	-0.009	0.199	0.072
Cognition	TNF-beta	0.146	0.042	0.247	0.006
Cognition	VEGF	0.167	0.063	0.267	0.002
Cognition	Follow-up C-Reactive Protein	-0.123	-0.195	-0.049	0.001
Cognition	Follow-up D-Dimer	-0.086	-0.158	-0.012	0.023
Cognition	Socioeconomic Status (ABEP)	-0.291	-0.357	-0.221	< 0.001
Cognition	Education	0.357	0.241	0.464	< 0.001
Cognition	COVID-19 Severity	-0.037	-0.110	0.037	0.208
Cognition	IPAQ	0.126	0.052	0.198	< 0.001

Supplementary Table 4. Bivariate Analysis between potential predictors and cognitive sub-dimensions with categorical variables.

Dependent	Independent	Statistic	df	p-value
Orientation	Sex	-2.227	694.9	0.026
Orientation	Ethnicity	2.238	3, 703	0.083
Orientation	Delirium	1.600	340	0.111
Orientation	Previous Psychiatric Disease	1.259	509	0.209
Attention	Sex	-1.947	647.1	0.052
Attention	Ethnicity	2.318	3, 684	0.074
Attention	Delirium	1.839	331	0.067
Attention	Previous Psychiatric Disease	-1.214	491	0.225
Language	Sex	-2.681	726	0.008
Language	Ethnicity	3.883	3, 700	0.009
Language	Delirium	2.881	339	0.004
Language	Previous Psychiatric Disease	-0.412	506	0.681
Epimemory	Sex	-0.205	721	0.838
Epimemory	Ethnicity	1.154	3, 695	0.327
Epimemory	Delirium	2.680	334	0.008
Epimemory	Previous Psychiatric Disease	-0.955	501	0.340
Visuoability	Sex	-1.396	721	0.163
Visuoability	Ethnicity	3.358	3, 695	0.018
Visuoability	Delirium	0.978	334	0.329
Visuoability	Previous Psychiatric Disease	-0.961	501	0.337
Cognição	Sex	-1.877	704	0.061
Cognição	Ethnicity	2.859	3, 678	0.036
Cognição	Delirium	2.210	327	0.028
Cognição	Previous Psychiatric Disease	-0.875	485	0.382

Supplementary Table 5. Linear Regression between baseline variables and Global Cognition

	Coefficient	SE	Lower CI	Upper CI	p-value
(Intercept)	0.903	1.129	-1.315	3.120	0.424
Age	-0.069	0.010	-0.090	-0.049	< 0.001
Sex [Male]	0.591	0.210	0.179	1.002	0.005
Ethnicity [Yellow]	1.453	1.520	-1.533	4.438	0.340
Ethnicity [Black]	0.120	0.375	-0.617	0.857	0.749
Ethnicity [Brown]	-0.497	0.251	-0.990	-0.004	0.048
ABEP [B1]	-0.595	0.736	-2.041	0.851	0.419
ABEP [B2]	-0.234	0.687	-1.583	1.115	0.734
ABEP [C1]	-0.592	0.682	-1.933	0.748	0.386
ABEP [C2]	-0.890	0.698	-2.260	0.480	0.202
ABEP [D-E]	-0.889	0.764	-2.388	0.611	0.245
Education [Uncompleted Elementary/Middle School]	2.255	0.569	1.138	3.372	< 0.001
Education [Completed Elementary/Middle School]	4.127	0.632	2.885	5.368	< 0.001
Education [Uncompleted High School]	4.423	0.669	3.109	5.737	< 0.001
Education [Completed High School]	5.231	0.607	4.038	6.423	< 0.001
Education [Uncompleted Undergraduation]	6.137	0.732	4.699	7.575	< 0.001
Education [Completed Undergraduation]	6.404	0.703	5.022	7.785	< 0.001
Education [Post-graduation]	7.481	0.820	5.870	9.092	< 0.001
Charlson Severity Score	-0.224	0.073	-0.367	-0.080	0.002
Previous psychiatric disease [Yes]	-1.022	0.543	-2.098	0.054	0.062
Severity WHO [2]	0.490	0.312	-0.123	1.102	0.117
Severity WHO [3]	0.085	0.559	-1.012	1.182	0.879
Severity WHO [4]	0.308	0.349	-0.378	0.994	0.378
Basal C-protein	0.000	0.001	-0.002	0.003	0.686
Basal D-dimer	0.000	0.000	0.000	0.000	0.890
Pre-COVID-19 frailty	-0.241	0.101	-0.439	-0.043	0.017
IPAQ [Irregularly Active]	0.646	0.270	0.116	1.176	0.017
IPAQ [Active]	0.391	0.245	-0.090	0.872	0.111
IPAQ [Very Active]	0.703	0.538	-0.352	1.759	0.191

Supplementary Table 6. Exploratory Factor Analysis (EFA) with continuous variables from follow up.

Factor Loadings

	Factor					
	1	**2**	**3**	**4**	**5**	**Uniqueness**
VEGF		0.756				0.3863
IL7		0.809				0.2658
IL4	0.879					0.1515
IFN-alpha2	0.336	0.717				0.3608
G-CSF		0.857				0.1855
IL5	0.761					0.3357
IL1-RA	0.419	0.774				0.2181
IL1-alpha	0.936					0.0592
IL13	0.941					0.0454
IL6	0.930					0.0841
IL15	0.484	0.564				0.4464
TNF-beta	0.907					0.0934
Smell					0.791	0.3322
Chronic Fatigue			-0.678			0.4808
Taste					0.750	0.4003
C-protein						0.9291
D-Dimer						0.9906
Orientation				0.426		0.7996
Attention				0.793		0.3547
Language				0.807		0.3341
Epi Memory				0.616		0.5940
MCS Patient			0.633			0.5623
FVC						0.9543
Visuoability				0.726		0.4668
Depression			0.823			0.2997
Blood O2						0.9585
PTSD			0.878			0.2153
Anxiety			0.840			0.2875

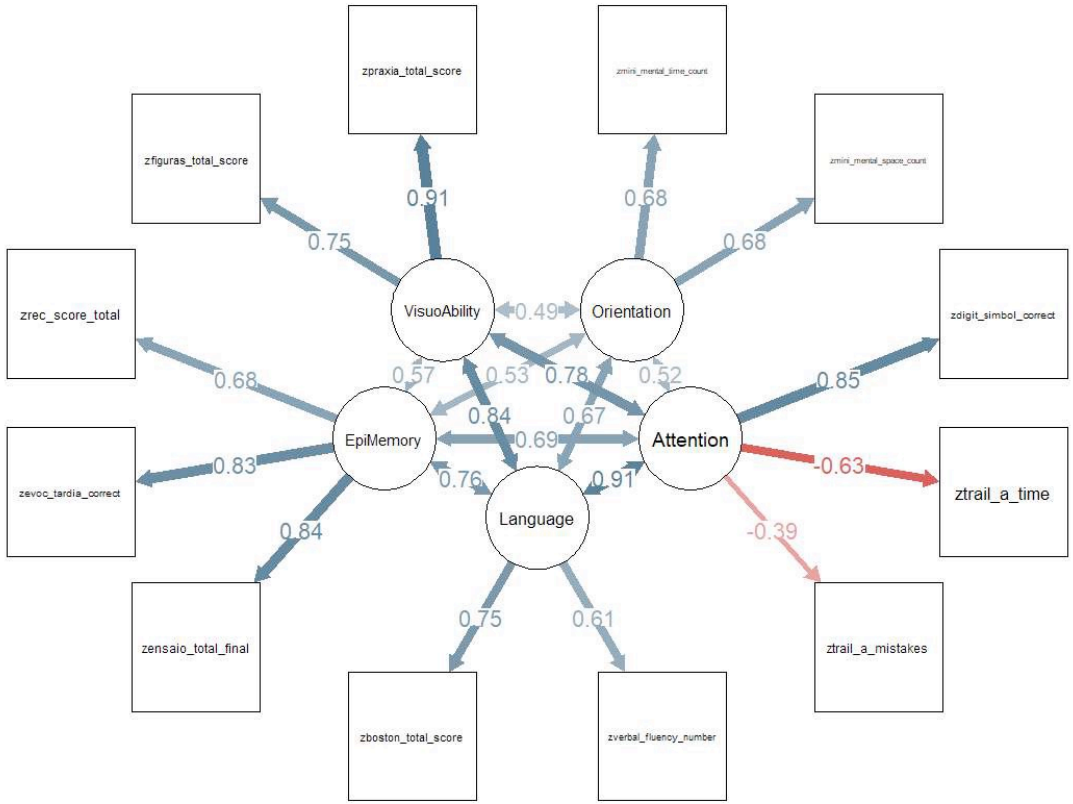
Note. 'Minimum residual' extraction method was used in combination with a 'varimax' rotation

Factor Loadings

	Factor					
	1	2	3	4	5	Uniqueness

Factor	SS Loadings	% of Variance	Cumulative %
1	5.54	19.77	19.8
2	3.84	13.72	33.5
3	3.16	11.28	44.8
4	2.58	9.22	54.0
5	1.29	4.61	58.6

Supplementary Figure 1. Confirmatory Factor Analysis (CFA) for Latent Cognitive Dimensions (LCD).



Discussão e Considerações Finais

O presente estudo contribuiu para o desenvolvimento do conhecimento na área de estudos em COVID-Longa, principalmente pela escassez de estudos relacionados em países de baixa e média renda (16). Os principais achados versam sobre os 4 principais objetivos e serão melhor discutidos adiante, tais como: a) alta prevalência de transtornos psiquiátricos (depressão, ansiedade, TEPT) e de prejuízos cognitivos em pacientes com COVID-Longa quando comparados a outros estudos com população geral e/ou clinicamente similar; b) Ausência de associações entre marcadores de gravidade da COVID-19 na linha de base e a sintomatologia psicopatológica e cognitiva 6-11 meses após infecção pela SARS-CoV-2; c) Associação significativa entre maiores déficits quimiossensoriais e sintomatologia psicopatológica e cognitiva 6-11 meses após infecção pela SARS-CoV-2; d) Ausência de associação significativa entre maior sintomatologia cognitiva no follow-up e marcadores inflamatórios 6-11 meses após infecção pela SARS-CoV-2.

A seguir, discutiremos os achados de acordo com os 4 objetivos desta tese.

Objetivo 1: Prevalência de Sintomas Psiquiátricos e Cognitivos na COVID-Longa

Este estudo encontrou altas taxas de sintomas depressivos, ansiosos e de TEPT na amostra avaliada. Ao olhar apenas para novos diagnósticos, encontramos uma prevalência de 2,6% de 'depressão' (1,2% depressão grave), 2,8% de 'fobia específica', 8,1% de 'transtorno de ansiedade generalizada' e 1,4% de Transtorno Obsessivo-Compulsivo (TOC). TEPT foi encontrado em 13,65% da amostra. Importante salientar que consideramos apenas os sintomas de TEPT relacionados à pandemia da COVID-19 (isolamento, hospitalização, infecção). Relacionado aos sintomas cognitivos, ao redor de 50% dos pacientes dizem estar piores da memória 6 a 11 meses

após a infecção pela SARS-CoV-2; fato corroborado em sua grande maioria pelos familiares mais próximos.

A prevalência de 'transtorno mental comum' nesta coorte pós-COVID-19 (32,2%) foi maior do que a relatada anteriormente na população geral brasileira (26,8%), conforme indicado por estudos epidemiológicos utilizando o instrumento CIS-R (138). Em relação ao diagnóstico de 'depressão', a prevalência na presente amostra (8,0%) foi maior do que o esperado em estudos epidemiológicos em países de alta e baixa renda (respectivamente 5,5% e 5,9%, prevalência de 12 meses), bem como na população brasileira em geral utilizando o mesmo instrumento (em torno de 4 e 5%) (139). O diagnóstico CIS-R de 'transtorno de ansiedade generalizada' na presente amostra (14,1%) foi consideravelmente superior à prevalência de 12 meses na população geral europeia (0,2-4,3%) (140, 141). Estudo recente utilizando a mesma entrevista estruturada (CIS-R) em amostra representativa da população geral brasileira durante a pandemia de COVID-19 encontrou taxas menores do que as relatadas neste manuscrito, com 21,1% de transtornos mentais comuns, 2,8% de transtornos depressivos e 8% de transtornos de ansiedade, destacando alta prevalência em nossa amostra (42).

Referente ao achado impactante de que mais de 50% da amostra dizerem estarem piores da memória 6 a 11 meses após a infecção pela SARS-CoV-2, os estudos subsequentes com populações com COVID-Longa corroboram nossos achados, evidenciando o papel de protagonismo que os déficits cognitivos apresentam nos pacientes com sintomas persistentes da infecção por SARS-CoV-2 (61). De fato, estudos recentes apontaram várias semelhanças neuropatológicas da síndrome cognitiva da COVID-Longa com a Doença de Alzheimer (111).

Uma discussão mais aprofundada pode ser encontrada nos manuscritos 1, 2 e 3 onde discutimos diversas vias fisiopatológicas da morbidade cognitiva associada a COVID-Longa.

Objetivo 2: Marcadores de Gravidade dos Sintomas Psiquiátricos e Cognitivos na COVID-Longa

Nosso estudo identificou diversos fatores preditivos de pior saúde mental e cognição global. 'Estado Geral de Saúde' e 'Fragilidade pós-COVID-19' estiveram associadas com maiores sintomas depressivos, ansiosos e de transtorno mental comum. Piores índices de Cognição Global estiveram associados com maior idade, sexo feminino, etnia parda, menores índices educacionais, maior número de comorbidades, fragilidade pré-COVID e menores índices de atividade física prévia. Digna de nota foi a ausência de associação entre gravidade da infecção por SARS-CoV-2 em linha de base e de prejuízos financeiros ou perda de familiares.

Do ponto de vista cognitivo, os achados até o presente momento (principalmente elevado prejuízo em memória episódica, funções executivas e atencionais) também já foram excessivamente estudados em amostras de pacientes com COVID-Longa (29, 61, 67, 111, 142, 143). Estudos que avaliam a associação de gravidade da doença com maior sintomatologia cognitiva em pacientes com COVID-Longa ainda são inconclusivos, majoritariamente pela falta de estudos sistematizados com pacientes com sintomas leves ou assintomáticos (143). Observando tal ausência de associação do ponto de vista do acometimento psicopatológico, os resultados são mais robustos, apesar de ainda inconclusivos (144, 145). Curiosa é a ausência de associação entre gravidade e estressores psicossociais (perda de familiares ou prejuízos financeiros), já que tais associações já tinham sido exaustivamente estudadas em estudos com diferentes populações, evidenciando o papel negativo e significativo da perda de pessoas próximas (luto patológico) e de prejuízos financeiros na saúde mental (115, 116, 146, 147).

Ademais, de acordo com recente estudo avaliando pacientes que contraíram COVID-19 (148), a trajetória dos sintomas depressivos e ansiosos está fortemente associada à infecção (presença ou ausência) e à sintomatologia da COVID-19, incluindo seu tempo de sintomas. Tal fato corrobora os achados neste estudo (muito embora não exclua a hipótese que associa maior gravidade da COVID com maior acometimento) que encontrou altas taxas de sintomas ansiosos e depressivos na amostra, não associadas a nenhum outro preditor de maior gravidade, além de fragilidade e estado geral de saúde. Ambos os fatores já foram amplamente analisados em outros estudos avaliando seus impactos na cognição (149, 150, 151, 152).

A ausência de associação encontrada pode ser explicada por diferentes vias. Inicialmente podemos pensar que, de fato, a infecção por SARS-CoV-2 por si só é responsável pela alta prevalência de sintomas encontrada (psicopatológicos e/ou cognitivos), seja por seus mecanismos diretos ou indiretos, discutidos com maior profundidade nos manuscritos da presente tese. Uma segunda hipótese é que a alta prevalência pode estar associada a sintomas desenvolvidos posteriormente e não avaliados por nós, ou mesmo por outras variáveis não avaliadas da linha de base. Uma terceira hipótese aborda o efeito teto (distribuição assimétrica dos sintomas, com a maior parte dos indivíduos situando-se nos níveis superiores), já que nossa coorte foi composta por pacientes todos hospitalizados, com elevada morbidade neuropsiquiátrica. A quarta hipótese supões que devido à maior gravidade prévia de nossa amostra, que é composta por indivíduos já previamente clinicamente graves, o que pode diminuir a variabilidade entre os participantes.

Objetivo 3: Associação dos sintomas cognitivos e quimiosensoriais (paladar e olfato)

A presente tese identificou que, em indivíduos com PASC, prejuízos cognitivos estiveram associados com alterações de olfato e paladar. De acordo com o que sabemos até então, apenas um

estudo avaliou a associação de alterações de paladar e olfato com manifestações psicopatológicas nos pacientes pós-COVID-19, encontrando uma associação positiva entre sintomas ansiosos, depressivos e perda de paladar e olfato (114). Tal achado se mostra relevante à luz do conhecimento atual, seja na identificação precoce do possível comprometimento cognitivo, seja na aplicação de medidas preventivas para tais indivíduos, ou na extrapolação de tais dados para outras doenças infecciosas virais agudas. Entretanto, a não utilização de testes objetivos de avaliação de olfato e paladar pode ter comprometido nossos resultados, haja vista que indivíduos mais globalmente comprometidos podem confundir seus sintomas ou tender a hipovalorizá-los, como podemos ver na revisão sistemática de Hannum e Colaboradores (153). Nesse sentido, sugerimos que novos estudos possam ser realizados utilizando testes objetivos de avaliação de olfato e paladar (por exemplo 'odor threshold tests' ou 'Sniffin' sticks test') (153). Tal achado está mais bem discutido no segundo manuscrito da presente tese.

Objetivo 4: *Inflamação e Identificação de clusteres longitudinais de PASC*

O terceiro artigo produzido pela presente tese identificou diversos fatores inflamatórios (citocinas) associados a prejuízos cognitivos; entretanto, tais citocinas não sobreviveram após análise multivariada. Pouquíssimos estudos se debruçaram em avaliar tal questão em uma população grande de pacientes com COVID-Longa. Entretanto, estudos com doenças crônicas apresentaram resultados interessantes; em particular estudando as Interleucinas IL-1RA, IL-7, e G-CSF. Em estudos prévios, tais fatores já foram implicados na função cognitiva. Por exemplo, em adultos com esclerose múltipla, uma maior concentração sérica do marcador anti-inflamatório IL-1RA foi associada a um melhor funcionamento sócio-cognitivo (154) Um estudo de 42 adultos com transtorno bipolar descobriu que os níveis de IL-7 estavam significativamente associados com

medidas de cognição, mostrando níveis mais elevados no grupo cognitivamente preservado e uma correlação positiva com o desempenho cognitivo (155). Além disso, estudos pré-clínicos indicam que o tratamento com G-CSF, um fator de crescimento envolvido na neuroproteção e plasticidade, pode contribuir para a melhoria da função cognitiva em um modelo de lesão cerebral traumática (156). No entanto, o papel potencial da IL-1RA, IL-7 e G-CSF em desfechos COVID longos é desconhecido.

Diversos motivos podem explicar o contraste do encontrado no presente estudo da ausência de associação e o reportado acima. O primeiro deles é que, de fato, a despeito do apresentado em pequenas amostras, o estado inflamatório persistente causado pela COVID-Longa não é suficiente para verificarmos um aumento nos sintomas cognitivos a longo prazo. Entretanto, não foram associadas citocinas de linha de base, sendo que a hipótese inicial da "Tempestade de Citocinas" não pode ser descartada. Um outro motivo pode ser o efeito teto, já que todos os pacientes podem estar excessivamente inflamados. Porém, a ausência de parâmetros clínico-laboratoriais para normatização dos resultados impede-nos de tirar essa conclusão.

Clusteres em COVID-Longa

Neste estudo, utilizando Análise Fatorial Exploratória, 5 clusteres foram identificados em pacientes portadores de PASC:

- *Fator 1*: IL4, IL5, IL1_RA, IL1_alpha, IL13, IL6, IL15, e TNF_beta*;*

- *Fator 2:* VEGF, IL7, IFN_alpha2, G_CSF, IL1_RA, e IL15*;*

- *Fator 3:* Fadiga, Queixa de Memória, Depressão, TEPT e Ansiedade*;*

- *Fator 4:* Orientação, atenção, linguagem, memória episódica e habilidade visuoespacial.

- *Fator 5:* Paladar e olfato.

Pode-se observar claramente que, entre os pacientes com PASC, há 2 *clusteres* inflamatórios, que não se associam com nenhum dos sintomas clínicos estudados. O terceiro fator envolve sintomas psicopatológicos como fadiga e queixa de memória. Fadiga crônica tem sido associada com sintomas psicopatológicos em diversos estudos (157); sendo que o mesmo pode-se observar das queixas de memória/cognitivas (158, 159) que, neste estudo, têm maior ligação com sintomas psicopatológicos do que com os sinais objetivos de prejuízo de memória. Os dois *clusteres* restantes são de prejuízos cognitivos e de alterações quimiosensoriais, os quais também se mostram isolados de outros sintomas. Em suma, em nossa amostra há 4 *clusteres* de COVID-Longa: a) Inflamatório; b) Psicopatológico; c) Cognitivo; d) Quimiossensorial. A identificação desses *clusteres* abre espaço para o acompanhamento e o direcionamento de abordagens terapêuticas individualizadas, evitando a generalização de apenas uma doença homogênea chamada PASC e dessa forma ampliando o escopo para uma visão sindrômica. Entretanto, tais *clusteres* se diferenciam com os estudos existentes até agora (160, 161); enquanto Wong-Chew e colaboradores separaram os sintomas apenas por meio da localização por sistema (respiratório, cardiovascular, etc.) (160), Kenny e cols. (161), utilizando Análise de Correspondência Múltipla, encontrou clusteres mais ligados a sintomas físicos (diversos dos analisados aqui). Haverá. No futuro, necessidade de Revisões Sistemáticas (RS) e Meta Análises (MA) avaliando tal temática, porém não existem RS/MA que sistematizem o conhecimento no campo até então. Sugerimos assim que mais estudos possam se debruçar no entendimento dos grupos de PASC/COVID-Longa.

Limitação do Presente Estudo e Sugestões para Estudos Futuros

O estudo presente possui uma série de limitações que necessitam ser elencadas:

1. A avaliação dos sintomas psiquiátricos e cognitivos foi realizada de 6 a 11 meses após a alta hospitalar, sem protocolo similar pré-infecção, o que nos impede de concluir a etiologia das alterações aqui encontradas.
2. Viés de seleção pode ter-se excluído pacientes com consequências da doença mais severa, já que os mesmos poderiam ser mais propensos a se recusarem de participar por não conseguirem responder à bateria proposta e a apresentar manifestações psicopatológicas e cognitivas;
3. Falta de inclusão de pacientes com sintomas leves e assintomáticos;
4. Falta de grupo controle com pacientes que apresentem hospitalização por doença respiratória viral aguda não COVID-19 ou para Doenças Respiratórias Crônicas;
5. A escala utilizada (CIS-R) foca sua avaliação em transtornos ansiosos e de humor, não acessando outros transtornos psiquiátricos importantes, tais como psicóticos;
6. A avaliação foi realizada por neuropsicólogos e estudantes de medicina com treinamento prévio, porém, sem a realização de um estudo de confiabilidade. Isso pode ter acarretado vieses de avaliação que por sua vez impactariam nos resultados, principalmente na avaliação de pacientes menos escolarizados que por sua vez foram os mais afetados pela COVID-19.

Considerando o exposto acima e o estado da arte atual das pesquisas com COVID-19, abaixo elenco algumas sugestões para pesquisas futuras:

1. Desenvolvimento de estudos de coorte prospectivos (pré e pós) a infecção pelo SARS-CoV-2;

2. Realização de estudos com maior tamanho amostral, que minimizaria as perdas pelo viés de seleção; ou até mesmo a adoção de protocolos robustos de avaliação à distância (Telemedicina);
3. Inclusão de pacientes leves e assintomáticos (pareados por sexo, idade e comorbidade), que realizem a mesma bateria de avaliação dos demais grupos;
4. Estudos controlados (com um grupo controle com doença crônica, ou mesmo outro quadro viral agudo com sequelas persistentes);
5. Adoção de escalas mais completas e robustas, como a Structured Clinical Interview for DSM Disorders (SCID);
6. Estudos que possam permitir uma melhor confiabilidade, como treinamento com casos supervisionados e testes de confiabilidade (entre avaliadores).

Conclusão

Nossos dados sugerem que os transtornos mentais são frequentes após 6-11 meses da infecção por SARS-CoV-2, notadamente os transtornos depressivo, de ansiedade generalizada e de estresse pós-traumático (Objetivo 1). Além destes, cerca de metade da amostra relata declínio de memória (Objetivo 1). No entanto estes achados não foram associados a nenhuma variável clínica relacionada à gravidade da doença em fase aguda, nem a estressores psicossociais relacionados à doença (Objetivo 2). Por outro lado, observamos que alterações quimiossensoriais se correlacionaram com pior desempenho em tarefas de memória (Objetivo 3). Finalmente, nossos dados não confirmaram a hipótese de que marcadores inflamatórios e citocinas (tanto na fase aguda como tardia) pudessem predizer ou estar associados aos déficits psiquiátricos ou cognitivos na COVID-Longa (Objetivo 4).

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Apêndice 01

Nas próximas páginas, iremos apresentar publicações que ocorreram durante o período do doutorado do candidato e que, apesar de não serem diretamente oriundas de seus objetivos, contaram com a liderança ou participação direta do mesmo e versam sobre a mesma temática proposta neste projeto de doutorado.

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Clinical, sociodemographic and environmental factors impact post-COVID-19 syndrome

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Background Sociodemographic and environmental factors are associated with incidence, severity, and mortality of COVID-19. However, little is known about the role of such factors in persisting symptoms among recovering patients. We designed a cohort study of hospitalized COVID-19 survivors to describe persistent symptoms and identify factors associated with post-COVID-19 syndrome.

Methods We included patients hospitalized between March to August 2020 who were alive six months after hospitalization. We collected individual and clinical characteristics during hospitalization and at follow-up assessed ten symptoms with standardized scales, 19 yes/no symptoms, a functional status and a quality-of-life scale and performed four clinical tests. We examined individual exposure to greenspace and air pollution and considered neighbourhood´s population density and socioeconomic conditions as contextual factors in multilevel regression analysis.

Results We included 749 patients with a median follow-up of 200 (IQR = 185-235) days, and 618 (83%) had at least one of the ten symptoms measured with scales. Pain (41%), fatigue (38%) and posttraumatic stress disorder (35%) were the most frequent. COVID-19 severity, comorbidities, BMI, female sex, younger age, and low socioeconomic position were associated with different symptoms. Exposure to ambient air pollution was associated with higher dyspnoea and fatigue scores and lower functional status.

Conclusions We identified a high frequency of persistent symptoms among COVID-19 survivors that were associated with clinical, sociodemographic, and environmental variables. These findings indicate that most patients recovering from COVID-19 will need post-discharge care, and an additional burden to health care systems, especially in LMICs, should be expected.

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By November 2021, COVID-19 caused more than 250 million cases, with more than five million deaths worldwide [1]. Cohort studies of hospitalized patients identified risk factors for poor outcomes and revealed mortality rates ranging from 25% to 49% [2-5]. In addition, among recovering patients, reports of persistent symptoms emerged, first by patients on social media and later defined as "post-COVID-19 syndrome" when symptoms persist after 12 weeks [6].

Recent data show that persistent symptoms affect more than half of recovering patients [7-9]. Fatigue, dyspnoea, sleep disturbances [8], and psychiatric and cognitive symptoms [10] are the most common. Patients that had more severe forms of COVID-19 [8] and females [7,8] are at higher risk of persistent

symptoms. Our knowledge on the mechanisms involved, other potential risk factors and treatment options for these symptoms are still limited.

Besides clinical features, there is evidence that sociodemographic and environmental risk factors can influence the incidence, severity, and mortality of COVID-19. Socioeconomic disparities were associated with differences in mortality in Brazil [3], and in Sao Paulo, low-income communities had higher risk of hospitalization and death [10]. Population density also appears to have an impact on morbidity and mortality [11]. Furthermore, the risk of infection and death is not only higher in the poorest neighbourhoods, but also among the poorest individuals [12], suggesting an interaction between individual and contextual socioeconomic factors [13].

Evidence also exists linking air pollution with increased COVID-19 incidence and mortality [14]. Chronic exposure to air pollution impairs lung function and increases vulnerability to respiratory diseases, particularly infections [15]. On the other hand, studies have indicated that exposure to greenspace may play a role in reducing risk of mortality in COVID-19 [16]. This beneficial effect might be related to reduced exposure to air pollution, greater diversity of microbial exposure and enhanced immunity [17].

Sao Paulo was the epicentre of COVID-19 cases in Brazil and, like other megacities of low-and middle-income countries (LMIC), copes with important socioeconomic disparities, irregular distribution of greenspace, high levels of air pollution and complex urban arrangements [18], offering an appropriate setting to evaluate post-COVID-19 syndrome. We hypothesized that, in this city, not only individual but sociodemographic, and environmental factors could be associated with the persistence of symptoms in COVID-19. Identifying such factors is important in order to create health policies to prevent or mitigate long term health consequences and provide patient-centred care for a growing number of survivors worldwide. Therefore, we designed a cohort study of hospitalized COVID-19 survivors, to describe clinical characteristics and persistent symptoms after six months of hospitalization and identify clinical, sociodemographic, and environmental factors associated with post-COVID-19 syndrome.

METHODS

Study design and location

This is a cohort study conducted at Hospital das Clínicas from the University of Sao Paulo Medical School (HCFMUSP). The study protocol was published elsewhere [19]. In brief, the largest building of an academic hospital was turned into a dedicated facility for COVID-19 patients, transferred from health services across the metropolitan area of Sao Paulo, where approximately 23 million people live. A total of 900 beds were made available, and over 3000 patients were admitted from March 30th to August 31st, 2020.

Study population

We aimed at very broad inclusion criteria, hoping to include as many survivors of the first wave of COVID-19 as possible. Thus, the inclusion criteria were survival six months after hospitalization, hospital stay of at least 24 hours, age >18 years and confirmed COVID-19. Hospital stays shorter than 24 hours were not included because for those patients we did not have complete baseline data. Exclusion criteria were nosocomial COVID-19 infection, given that they were admitted to the hospital for other severe acute conditions, previous diagnosis of dementia or end-stage cancer, subjects living in long-term care facilities or with insufficient mobility to leave home after six months of hospital discharge, since the performance of some of the tests and scales would not be feasible for such patients, suspected reinfection at the time of follow-up and refusal to participate in the study.

Patients were invited to participate in the study by telephone and those who accepted were scheduled for in-person visits. Visits were scheduled for within three weeks of the six-month mark after hospitalization. However, patients who agreed to participate but were unavailable at that window had their appointments rescheduled and were evaluated later (see Appendix S1 in the **Online Supplementary Document**).

This study integrates the results of several research projects led by health specialist teams within HCFMUSP. All projects were approved by the Ethics Committee (approval numbers: 4.270.242, 4.502.334, 4.524.031, 4.302.745 and 4.391.560). Informed consent was obtained from all participants.

Sociodemographic variables

Age, sex, years of education, socioeconomic position and race were collected. Socioeconomic position was measured by a standardized questionnaire validated for the Brazilian population which classified individuals

in seven categories (A-most affluent, B1, B2, C1, C2, D and E) [20]. Race was self-declared, using the official Brazilian categories (white, mixed, black, Asian, indigenous). (More details in Appendix 1 the **Online Supplementary Document**).

We also collected information on population and average per capita income for each participant's neighbourhood. We divided the population by the area of each neighbourhood to compute the population density. The average income (in US$) was used as an indicator of the socioeconomic conditions of the neighbourhood.

Clinical assessments

We registered comorbidities at hospital admission with the Charlson comorbidity index [21]. Post COVID-19-symptoms were obtained with standardized scales, when available, or by direct question and a yes/no answer. We assessed 10 symptoms measured by standardized scales, 19 yes/no symptoms, a functional status scale, a quality-of-life scale, and performed four tests (spirometry, chest x-ray, 1-minute sit-to-stand test and hand grip strength test).

We present results for all symptoms, scales and tests performed but focused on four outcomes representative of the post-COVID-19 syndrome and which were measured with standardized scales to minimize bias: dyspnoea, assessed with the Medical Research Council (MRC) scale [22]; fatigue, assessed with the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT) [23]; anxiety and depression, assessed with the Hospital Anxiety and Depression scale (HADS) [24]; and functional status, assessed with the Post-COVID-19 Functional Status (PCFS) Scale [25].

A full list detailing evaluations and instruments is presented in Table S1 in the **Online Supplementary Document**.

Environmental variables

To estimate exposure to greenspace and air pollution, each participant´s residential address was georeferenced and a 300 m buffer area around each address was created. We used satellite images of the Sao Paulo metropolitan region for 2018 and 2020, to classify and quantify the land covered by greenspace. The 300 m buffer corresponds to approximately five min walking distance from the household and is recommended by the WHO [26].

Gridded satellite estimates of annual mean levels of air pollution ($PM_{2.5}$ – particulate matter up to 2.5μm diameter) were obtained for 2018, and we averaged the gridded values for the same buffer areas and these values were assigned to each participant. Further details of the greenspace and air pollution exposure assessment are in Appendix 1 in the **Online Supplementary Document**.

Data collection

Study data were collected and managed using a secure, web-based platform (REDCap – Research Electronic Data Capture) [27]. The results are reported in accordance with the Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) guidelines [28].

Statistical analysis plan

We did not perform a sample size estimation, and instead aimed at recruiting as many survivors of the large cohort of COVID-19 hospitalized patients as possible, using broad inclusion criteria, minimizing exclusion criteria and implementing a well-organized recruitment strategy.

We describe the prevalence of symptoms and present the results of several clinical evaluations at follow up. Categorical variables are expressed as count and percentage, and continuous variables, as mean and standard deviation, or median and interquartile range (IQR) as appropriate. We created histograms to visualize the variable´s distribution followed by the Shapiro-Wilk test to check for normality.

We conducted a multilevel regression analysis using a generalized linear mixed model with random intercepts at the neighbourhood level to identify whether clinical, sociodemographic, and environmental factors were associated with the four selected outcomes. In the multilevel models, individual variables were included in the first level and the contextual characteristics of neighbourhoods (population density and per capita income) in the second level. The variance inflation factor (VIF) was used to check the multicollinearity of the variables.

We first examined each variable in univariate models, then we fitted multivariate models with variables that showed an association with at least one of the outcomes in the univariate analysis. We retained the two contextual variables (population density and neighbourhood socioeconomic conditions) and the environmental expo-

sures (air pollution and greenspace) in the multivariate models regardless of their significance in the univariate models. We dropped the variable education as our indicator of socioeconomic position already included education. We present the adjusted estimates of changes in each outcome variable for a unit change in each predictor.

All tests were two-tailed with a significance level of 0.05 and performed using the Rstudio software [29]. Missing data was minimal for clinical characteristics and no imputation methods were used.

Ethics approval and consent to participate

This study integrates the results of several research projects within HCFMUSP. All projects were approved by the HCFMUSP Ethics Committee (approval numbers: 4.270.242, 4.502.334, 4.524.031, 4.302.745 and 4.391.560). Informed consent was obtained from all participants.

RESULTS

Of 3009 patients with COVID-19 who were admitted to the hospital between March 30 and August 31, 2020, 1957 survived hospitalization and 749 were included in the study (**Figure 1**). The median number of days after discharge for follow-up assessments was 200 (IQR=185-235) days.

Comparisons between patients who participated in the study and those excluded are shown in Table S2 in the **Online Supplementary Document**. While demographic characteristics were comparable, participants had higher body mass index (BMI), more previous hypertension, and more severe disease, indicated by longer duration of hospitalization and more need for ICU and intubation during hospitalization.

Table 1 shows sociodemographic and clinical characteristics during hospitalization for all participants. Approximately half were male, with age of 55±14 years-old, predominantly white, with low education, and middle to low socioeconomic position. Almost 60% were admitted to the ICU during hospitalization.

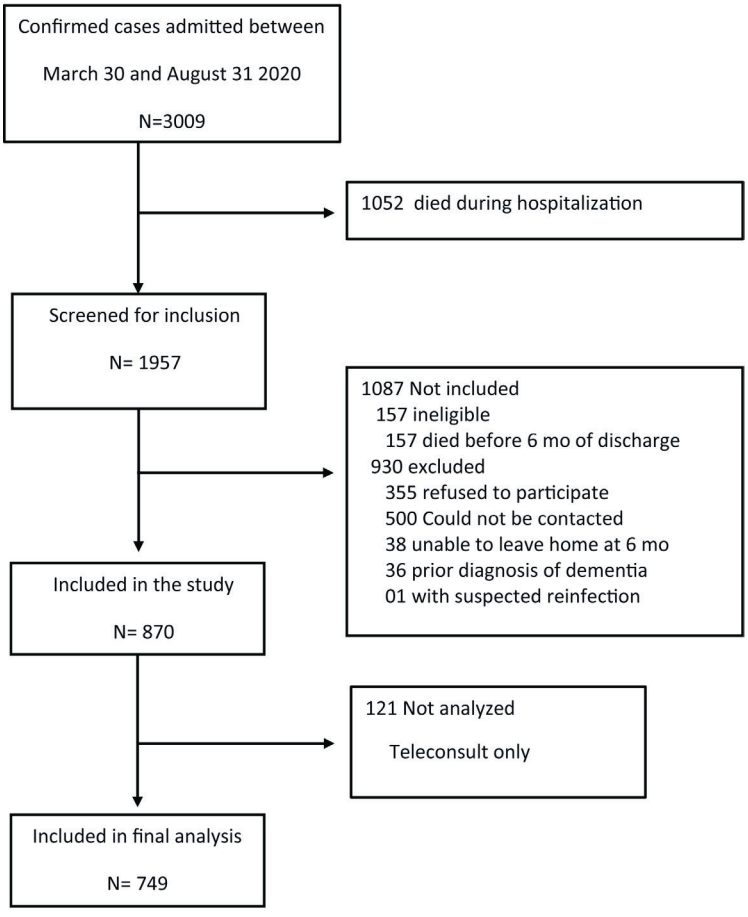

Figure 1. Study participant flow. Legend: Flow of potentially eligible participants in the study, and final numbers included and analysed.

At follow-up, 618 (83%) had at least one of the ten symptoms measured with standardized instruments (Figure S1 in the **Online Supplementary Document**), and the median number of symptoms was 2 (IQR=1-5). **Table 2** shows the results of scales and tests performed at follow-up. Pain, fatigue, posttraumatic stress disorder (PTSD), and memory impairment were the most common symptoms. Diagnostic tests showed impairment in muscle strength for almost two thirds and pulmonary function abnormalities in one third of patients. Table S3 in the **Online Supplementary Document** shows the prevalence of additional symptoms.

To examine whether timing of evaluation at follow-up had an impact on our findings, we compared patients evaluated before 200 days of hospitalization (the median) and those evaluated after 200 days. We found that patients evaluated later were less likely to have developed acute renal failure during hospitalization, and had shorter ICU and hospital stay (Table S4 in the **Online Supplementary Document**). They also had a higher prevalence of anxiety, depression, dyspnoea, severe muscle/joint pain, and loss of smell at follow-up (Table S5 in the **Online Supplementary Document**).

Figure 2, Panel A, shows that participants came from several neighbourhoods and different cities across the metropolitan region of Sao Paulo. The maps also show the population density in each neighbourhood (**Figure 2**, Panel B), the average per capita income of the neighbourhoods (**Figure 2**,

Table 1. Baseline and hospitalization characteristics of participants

Characteristic	All (N = 749)
Age, y, mean ± SD	55 ± 14
Male	397 (53%)
Body mass index, kg/m^2, median (IQR)	31·1 (27·5-36·6)
Race*	
White	342 (47%)
Asian	10 (1%)
Mixed	273 (37%)
Black	102 (14%)
Indigenous	7 (1%)
Education	
<4 y	265 (36%)
4-8 y	142 (19%)
8-12 y	202 (27%)
>12 y	134 (18%)
Socioeconomic position†	
A+B1+B2 (high)	196 (27%)
C1+C2 (medium)	470 (64%)
D+E (low)	73 (10%)
Smoking history, yes	284 (38%)
Charlson comorbidity index, median (IQR)	3 (2-4)
Duration of symptoms at admission, median (IQR), d	8 (6-11)
Acute renal failure during hospitalization	315 (42%)
ICU stay	445 (59%)
Intubation	305 (41%)
Duration of hospitalization, median (IQR), d	12 (7-23)

SD – standard deviation, IQR – interquartile range, y – years
Data are presented as counts (percentage) unless otherwise stated.
*The categories represent the Brazilian official race categories.
†Brazilian official socio-economic classes, based on household assets, access to public services, and educational level of the head of the family, with A being the higher income class and E the lower income class. We collapsed categories A+B1+B2 (high), C1+C2 (medium) and D+E (low) for the present analysis. Body mass index missing for 9 (1%) patients. Race missing for 15 (2%) patients. Education level missing for 6 (1%) patients. Socioeconomic position missing for 10 (1%) patients. Charlson comorbidity index missing for 30(4%) patients. Smoking history missing for 6 (1% patients). PM2.5 missing for 1 (0%) patient. Duration of symptoms missing for 1 (0%) patient. Acute renal failure was defined and staged according to the KDIGO definition using serum creatinine criteria.

Table 2. Symptoms, scales, and test results at follow-up*

	All (N = 749)	Percent abnormal
Objective symptoms		
Muscle/joint pain, VAS (0-100) (abnormal if ≥65)	40 (10-65)	41%
Fatigue, score (0-52) (abnormal if ≤39)	42 (33-47)	38%
Posttraumatic stress disorder, score (0-85), (abnormal if ≥30)	24 (19-36)	35%
Memory impairment, score (0-14) (abnormal if ≥7)	4 (1-8)	35%
Insomnia, score (0-28) (abnormal if ≥8)	6 (2-11)	32%
Dyspnoea, score (0-5), (abnormal ≥2)	1 (0-2)	30%
Anxiety, points (0-21) (abnormal if >8)	5 (2-9)	26%
Loss of taste, VAS (0-100), (abnormal if ≤80)	100 (85-100)	23%
Depression, points (0-21) (abnormal if >8)	3 (1-7)	22%
Loss of smell, VAS (0-100), (abnormal if ≤80)	100 (84-100)	21%
Scales		
Post COVID functionality, points (0-4), (abnormal if ≥2)	1 (0-2)	32%
Quality of Life, VAS (0-100)	80 (60-90)	NA
Diagnostic tests		
Muscle strength, kgf, (abnormal if <25% age percentile)	19 (10-28)	64%
SpO2 at rest, % (abnormal if <92%)	97 (95-98)	7%
SpO2 at the end of sit-to-stand test % (abnormal if decrease ≥4% from baseline)	96 (95-98)	10%
Forced vital capacity, % predicted (abnormal if <80% of predicted value)	84 (74-94)	32%
Abnormal X Ray (according to radiologist)	NA	29%

SpO2 – peripheral saturation of oxygen measured at rest and at the end of the sit-to-stand test, HADS – hospital anxiety and depression scale
*Values are median (interquartile range) and percentage of the total population with abnormal results according to cut off values shown in Table S1 in the **Online Supplementary Document**. Scales and instruments used to measure each symptom or test are shown in Table S1 in the **Online Supplementary Document**. Dyspnoea was missing for 8 participants; SpO2 at rest was missing for 3 participants; sit-to-stand test was missing for 73 participants; forced vital capacity was missing for 108 participants; x-ray was missing for 122 participants; HADS was missing for 78 participants; posttraumatic stress disorder scale was missing for 14 participants; post COVID functionality was missing for 3 participants; insomnia was missing for 3 participants; fatigue was missing for 3 participants; muscle/joint pain was missing for 15 participants; loss of smell was missing for 22 participants; loss of taste was missing for 34; muscle strength was missing for 23; quality of life was missing for 4.

Panel C), the distribution of greenspace (**Figure 2**, panel D), and air pollution levels (**Figure 2**, Panel E). The median exposure to $PM_{2,5}$ of participants was 14.4μg/m^3 (range = 12.5-20.8) and the median greenspace exposure in the 300m buffers was 17.0% (range = 2.2%-99.7%).

Univariate analysis (Table S6 in the **Online Supplementary Document**) indicated that sociodemographic characteristics were significantly associated with the outcomes examined. Comorbidities, BMI, and indicators of COVID-19 severity also showed to be predictors of symptom persistence. Smoking and race were not associated with the selected outcomes. Exposure to air pollution showed a statistically significant association only with dyspnoea, but the direction of the associations was consistent for all outcomes. On the other hand, exposure to greenspace showed an inconsistent pattern, acting either as a protective or risk factor, but was not statistically associated with the outcomes.

Table 3 presents the multilevel linear multivariate estimates for sociodemographic, clinical, and environmental factors associated with each predefined outcome. Female sex was associated with increased dyspnoea, lower functional status, increased fatigue, and higher anxiety and depression scores. Younger age was associated with higher anxiety and depression, while lower socioeconomic position was associated with increased dyspnoea, increased fatigue, and worse functional status.

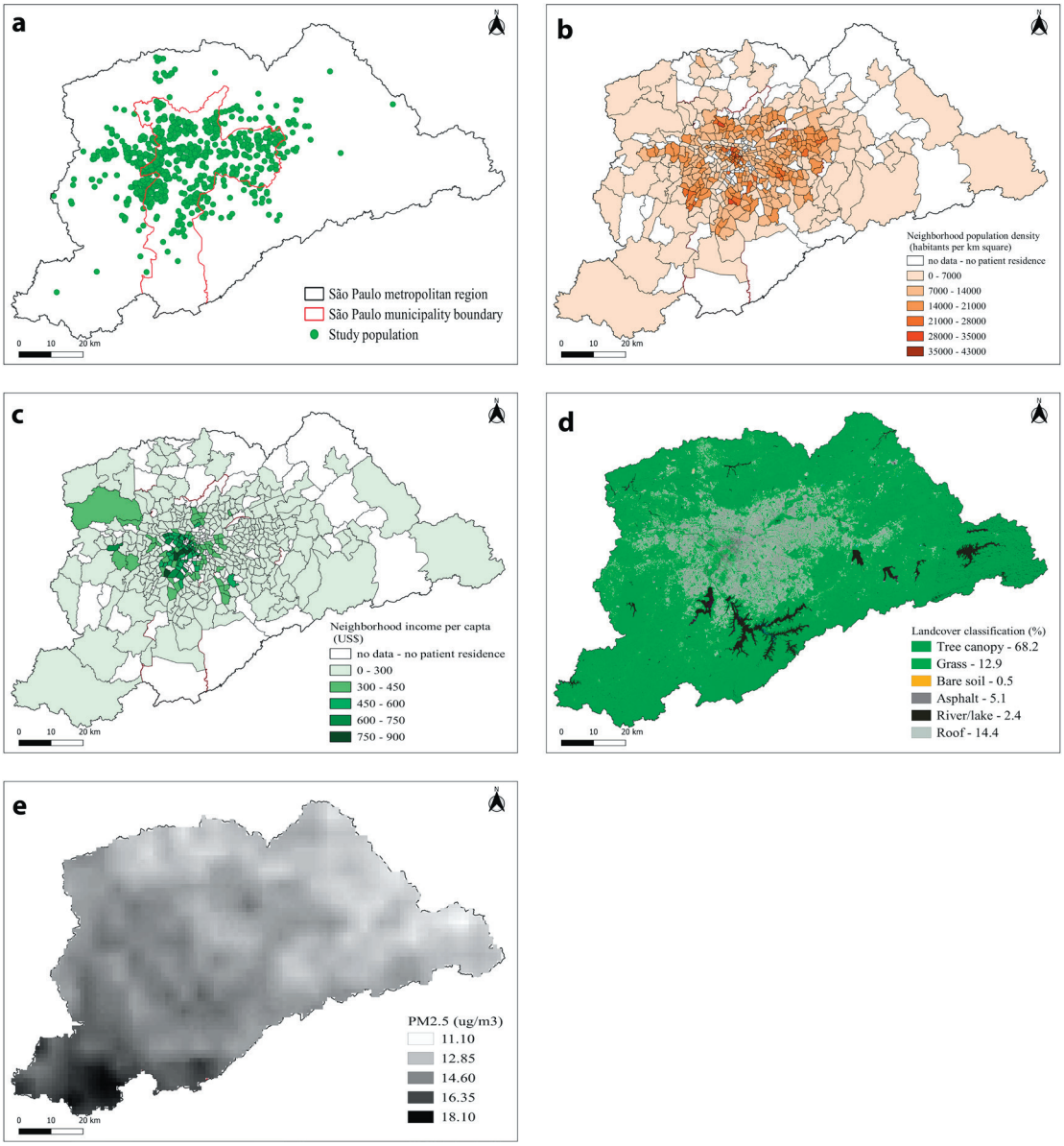

Figure 2. Patients place of residence, sociodemographic and environmental characteristics of the Sao Paulo Metropolitan Region. Legend: Maps of the Sao Paulo Metropolitan Region, comprising 39 municipalities and where approximately 23 million people live. a) green dots represent the origin (residency) of each participant. The red line represents the borders of the city of Sao Paulo; b) population density in each neighbourhood; c) the average per capita income of the neighbourhoods; d) the distribution of greenspace; e) air pollution levels.

More comorbidities at admission were associated with increased dyspnoea, increased fatigue, and lower functional status at follow-up. BMI was associated with increased dyspnoea and intubation during hospitalization with decreased fatigue and with lower scores for anxiety and depression. Hospital length of stay was associated with increased fatigue and worse functional status (**Table 3**).

Neighbourhood per capita income and population density, and individual exposure to greenspace did not show any statistically significant association with any of the outcomes studied while exposure to ambient air pollution was associated with increased dyspnoea, lower functional status, and increased fatigue.

DISCUSSION

In this observational study of COVID-19 survivors hospitalized in the largest public tertiary care hospital in Sao Paulo, Brazil, during the first surge of cases in 2020, we found that 83% of patients persisted with symptoms 6 months after hospitalization. The most prevalent symptoms were joint/muscle pain and fatigue. Diagnos-

Table 3. Regression estimates for sociodemographic, clinical, and environmental factors associated with selected persistent symptoms and functional scale in patients with Covid-19 at follow-up

		Dyspnoea		Fatigue		Functional status		Anxiety/depression	
		Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value
Sex	Female	-		-		-		-	
	Male	-0.39 (-0.55, -0.23)	<0.001	4.79 (3.37-6.20)	<0.001	-0.39 (-0.56, -0.23)	<0.001	-4.93 (-6.24, -3.61)	<0.001
Age		0.00 (-0.01, 0.01)	0.93	0.06 (-0.01, 0.13)	0.08	0.00 (-0.01, 0.01)	0.76	-0.08 (-0.14, 0.01)	0.02
Socioeconomic position	High	-		-		-		-	
	Medium	0.31 (0.13-0.50)	<0.001	-0.07 (-1.70, -1.56)	0.94	0.10 (-0.09, 0.29)	0.29	0.71 (-0.81, 2.22)	0.36
	Low	0.59 (0.30-0.88)	<0.001	-2.66 (-5.27, -0.06)	0.05	0.38 (0.08-0.69)	0.01	1.93 (-0.50, 4.35)	0.12
Charlson score		0.08 (0.02-0.14)	0.01	-0.87 (-1.39, -0.36)	<0.001	0.09 (0.03-0.15)	0.01	0.18 (-0.30, 0.66)	0.47
Body mass index		0.02 (0.01-0.03)	<0.001	-0.06 (-0.16, 0.03)	0.20	0.00 (-0.01, 0.01)	0.56	0.03 (-0.06, 0.12)	0.51
Intubation	No	-		-		-		-	
	Yes	-0.12 (-0.31, 0.07)	0.21	2.11 (0.45-3.78)	0.01	-0.11 (-0.31, 0.08)	0.25	-1.81 (-3.35, -0.26)	0.02
Length of hospital stay		0.00 (-0.01, 0.01)	0.76	-0.04 (-0.09, -0.00)	0.05	0.01 (0.01-0.02)	<0.001	0.00 (-0.04, 0.04)	0.85
$PM_{2.5}$ (air pollution)		0.16 (0.01-0.32)	0.03	-1.43 (-2.73, -0.12)	0.03	0.16 (0.01-0.31)	0.03	0.50 (-0.71, 1.72)	0.42
Greenspace		0.00 (-0.01, 0.01)	0.66	0.00 (-0.05, 0.05)	0.92	0.00 (-0.01, 0.01)	0.93	0.00 (-0.05, 0.05)	0.92
Per capita income		0.00 (-0.00, 0.00)	0.12	0.00 (-0.00, 0.00)	0.16	0.00 (-0.00, 0.00)	0.45	0.00 (-0.00, 0.00)	0.82
Population density		0.00 (-0.00, 0.00)	0.80	0.01 (-0.01, 0.02)	0.34	0.00 (-0.00, 0.00)	0.48	0.00 (-0.01, 0.01)	0.68

95% CI – 95% confidence interval

We collapsed socioeconomic position categories A+B1+B2 (high), C1+C2 (medium) and D+E (low) for the present analysis. Estimates are coefficients from the multilevel regression. P values obtained with a multilevel model.

tic tests showed that two thirds of the patients had impairment of muscle strength and almost one third had pulmonary function abnormalities. In addition, we found that clinical, sociodemographic, and environmental characteristics were associated with post-COVID-19 syndrome.

The prevalence of persistent symptoms in our study is higher than what has been found elsewhere. For example, a large Chinese and a French cohort reported prevalence of 76% and 51% respectively [8,9]. Our higher estimate may be due to the severity of the acute disease among our participants, as noted by the high rate of ICU admission and need for mechanical ventilation. In addition, it may reflect a degree of selection bias since participants in our study had higher severity of disease compared to those who did not participate. However, a high prevalence of long-term health consequences after COVID-19 should not be a surprise. Previous studies showed that a significant proportion of survivors of acute respiratory distress syndrome (ARDS) have persistent physical disability or cognitive impairment one year after discharge [30], with fatigue, dyspnoea and PTSD being commonly reported. Yet, survivors of ARDS typically endure several days of hospitalization, while persistent symptoms in COVID-19 have been reported in cohorts including mild cases [31]. This suggests that a large number of recovered cases of COVID-19 are expected to present persistent symptoms, which will require specialized health attention, causing a significant burden on health care services.

The high prevalence of symptoms after hospital discharge is probably influenced by peculiarities of the health care system in Sao Paulo, and in LMICs in general. It is known that the burden of critical illness is higher in LMICs [32] and large epidemiological studies found an elevated mortality for patients under mechanical ventilation [33] or with sepsis [34] in Brazil. The interplay between structural deficiencies in the health care system, more severe disease at admission [5], lower access to health care before and after the COVID-19 hospitalization, and socioeconomic factors may lead to worse overall health and exacerbate the impact of the COVID-19 after hospital discharge.

Our observed prevalence of joint/muscle pain, fatigue, dyspnoea, and of neuropsychiatric symptoms, such as PTSD, memory impairment, sleep disturbances, anxiety and depression were slightly higher or comparable to previous studies [7-9]. Post-COVID-19 functional status was abnormal in approximately one third of participants, similar to what was previously observed [35] and underscores the impact in daily life of COVID-19 survivors several months after hospital discharge.

The multivariate analysis identified several factors associated with the persistence of symptoms, including clinical (comorbidities, hospital length of stay and intubation), sociodemographic (sex, age, BMI, and socioeconomic position), and environmental (air pollution) factors. Preexisting comorbidities were associated with increased dyspnoea, fatigue and lower functional status at follow-up, in line with findings by a meta-analysis of long-term outcomes of COVID-19 [31], although available evidence still precludes us from determining the reasons for such association [31]. Severity of the acute disease has been implicated with persistent symptoms

in other studies [7,8,35]. However, the underlying mechanism is not clear and likely to be multifactorial and include the direct effects of viral infection, immunological response, corticosteroid therapy and ICU stay [8]. Surprisingly, in our study we observed that intubation was associated with decreased anxiety and depression and decreased fatigue at follow up, which should be further explored in future studies.

Female sex was associated with all the selected outcomes examined. While mortality rates due to COVID-19 are higher in males [2-5], female sex has been reported as a risk factor for long-term symptoms in previous studies [7,8,36], and more specifically, associated with stress, depression, anxiety, fatigue, and dyspnoea [8]. The underlying mechanism for this finding is unknown, and likely multifactorial.

Although age was not associated with most outcomes examined in this study, younger patients were at higher risk of anxiety and depression at follow-up, in line with previous findings of a study focusing specifically on mental health in COVID-19 survivors [36]. Such a finding could be related to the impact of the pandemic on work availability, social isolation and other daily life impacts, as shown by a survey in China which found that younger people suffered a greater psychological impact during the pandemic [37]. While age is one of the most important predictors of the severity and lethality of COVID-19, there is no consensus about its role in the persisting symptoms [9,31,38].

We found a positive association between BMI and dyspnoea similar to a finding in a smaller German cohort [39]. BMI has been associated with worse outcomes in acute COVID-19, and possible mechanisms to explain our finding include more severe acute disease and worse overall health and exercise tolerance as BMI increases.

Race was not significantly associated with any outcome in our analysis. This contrasts with reports of disproportionate burden of infection and death from acute COVID-19 among African Americans and Hispanics in the US [40] and in Brazil [3].

Socioeconomic disparities have deeply affected the course of COVID-19 in Brazil with vulnerable regions suffering a disproportionate higher burden of morbidity and mortality [10,41]. We now provide novel information showing that socioeconomic conditions are also strong predictors of symptoms of Post-COVID-19 syndrome. The mechanisms behind greater susceptibility to infection and severe disease among deprived populations are likely to be the same involved in the persistence of symptoms. Chronic socioeconomic deprivation can impact overall health through different pathways including greater food insecurity, limited access to health care, and unhealthy lifestyles [42].

We have tested, by multilevel analysis, whether neighbourhood characteristics such as mean income, population density, percentage of green areas and air pollution levels could have an impact on different post COVID-19 symptoms. We observed that ambient levels of $PM_{2.5}$ were associated with persistent dyspnoea, increased fatigue, and lower functional status at follow-up. To the best of our knowledge, this is the first study examining the role of air pollution in post-COVID-19 syndrome, although evidence is increasing on its role on the incidence and severity of this disease [14]. Air pollution is known to have acute and chronic systemic effects and particularly affects the lungs by mechanisms involving oxidative stress and inflammation, adversely affecting responses to viral infections [15,43]. A debilitated respiratory tract is prone to present more serious outcomes of COVID-19 [43] and thus, potentially predispose individuals to persisting symptoms. Although these potential mechanisms can explain the association between $PM_{2.5}$ exposure and persistent dyspnoea, the association with fatigue and functional status is less clear. Thus, further studies may help us confirm this novel and important impact of air pollution on health.

The lack of effect of green areas on persistent symptoms could be related to the fact that we examined individual exposure based on the presence of green areas, but not the accessibility of individuals to these areas, an indicator probably more related to the expected beneficial effects of green areas on disease recovery. Similarly, population density might be important to enhance transmissibility and mortality [44] but not persistence of symptoms.

Our study has limitations. First, it was performed at a single academic hospital and, thus, results may not be generalizable. However, patients from this cohort were transferred from the entire Sao Paulo Metropolitan Region, which comprises 39 municipalities with 21 million inhabitants. Second, given that our hospital was the primary reference hospital for COVID-19 in the metropolitan area of Sao Paulo, the assessed patients possibly represented the most severe cases, hence, our results may not apply to less severe cases of COVID-19. In addition, subjects who agreed to participate in this study also had more severe acute disease and were more likely to have been admitted to the ICU and needed intubation than those who refused to participate. Therefore, patients included in our study probably represent a subset of more severe cases of COVID-19 patients who needed hospitalization and survived, and one should be cautious when extrapolating our findings to all

COVID-19 survivors. Third, our findings are likely to be impacted by the higher burden of disease in LMICs and structural deficiencies of our health care system, and therefore may not be generalizable to other settings.

The study also has strengths, such as its large sample size and minimal missing data, which allows for more precise estimation of outcomes. In addition, we used standardized, validated instruments to detect symptoms, and objective tests whenever available. Patients were evaluated by a multidisciplinary team, allowing for more precise detection of symptoms. This cohort of patients will continue to be followed up and the multiple assessments already performed will be examined in greater depth, in order to confirm the present results, and thus, deepen the knowledge about Post-COVID-19 Syndrome. This will be important to better deal with the sequelae of this disease in the future.

CONCLUSIONS

Through a multidisciplinary and integrated approach, we identified a high frequency of persistent symptoms 6 months after hospitalization in a large cohort of COVID-19 survivors. These persistent symptoms were associated with clinical, sociodemographic, and environmental variables.

With more than 200 million cases of the disease diagnosed worldwide, an increasing burden on health care systems, including mental health and rehabilitation services, is expected to occur, especially in megacities of LMICs, where structural problems in health care and high air pollution levels may pose additional challenges to the provision of health care for post-COVID syndrome.

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Additional material

Online Supplementary Document

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INVITED REVIEW

Cognitive decline following acute viral infections: literature review and projections for post-COVID-19

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Abstract
Recently, much attention has been drawn to the importance of the impact of infectious disease on human cognition. Several theories have been proposed, to explain the cognitive decline following an infection as well as to understand better the pathogenesis of human dementia, especially Alzheimer's disease. This article aims to review the state of the art regarding the knowledge about the impact of acute viral infections on human cognition, laying a foundation to explore the possible cognitive decline followed coronavirus disease 2019 (COVID-19). To reach this goal, we conducted a narrative review systematizing six acute viral infections as well as the current knowledge about COVID-19 and its impact on human cognition. Recent findings suggest probable short- and long-term COVID-19 impacts in cognition, even in asymptomatic individuals, which could be accounted for by direct and indirect pathways to brain dysfunction. Understanding this scenario might help clinicians and health leaders to deal better with a wave of neuropsychiatric issues that may arise following COVID-19 pandemic as well as with other acute viral infections, to alleviate the cognitive sequelae of these infections around the world.

Keywords Cognition · Alzheimer's disease · Virus · Dementia · COVID-19 · Prevention

Introduction

Cognitive impairment is a vital healthcare problem worldwide. Population studies have shown that 3–19% of the population older than 65 years meet criteria for mild cognitive impairment (MCI) [1, 2]. Of these, more than 50% will develop dementia [2]. Global prevalence of dementia in the population is 1.3%, and 7.3% in people aged 65 years or more [3], which is similar to those found in Latin American population [4]. Many studies have shown a direct influence of viral infections on cognition, especially in the development of MCI and dementia [5–7]. The high prevalence and the overlap of both conditions underscore the importance of a better understanding of the role of viral infections in the pathogenesis of dementia [8, 9].

Viral infections significantly impact world's global burden of medical and neurological diseases [8]. In the last decades, the role of viral infections in cognitive impairment following has been widely discussed [5]. Viruses, such as herpes viruses, cytomegalovirus, human immunodeficiency virus (HIV), Varicela zoster virus (VZV), Epstein–Barr virus (EBV), and Hepatitis C virus, have been implicated in Alzheimer's disease pathogenesis [7, 10]. Mechanisms underlying viral pathogenesis in these conditions may include a direct viral effect or indirect mechanisms, such as inflammation, epigenetic changes, and hypercoagulable changes, that may impact on brain structure and function in healthy or in cognitively impaired individuals [6, 11–15]. Previous reviews have also addressed this topic; however, most of them are not specific to acute viral infections [6],

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restricted to few viral infections (e.g. Herpes virus) [7] or letter to editors [5].

In this context, emerging infectious diseases, especially those affecting the population on a pandemic scale, should be monitored for potential neuropsychiatric compromise. This may be the case of coronavirus disease 2019 (COVID-19), which currently challenges physicians and health care professionals not only for its high mortality and severity of clinical manifestations, but also for emergence of atypical and unexpected clinical presentations [16], such as cognitive impairment [17]. Some experts worldwide [18], including those from the Alzheimer's Association, have been interested in studying this potential association, reviewing the most updated evidence towards this topic and proposing a cross-cultural prospective study to assess individuals reporting cognitive impairment and other neuropsychiatric complaints [19]. However, there is still a need of further theoretical studies, especially using a multi-specialist approach, to discuss further this matter and guide for future interventional studies.

To address this matter, we conducted a comprehensive literature review with different specialists (neurologists, geriatrists, psychiatrists, neuropsychologists), to address the available studies that investigated the occurrence of cognitive decline following the most prevalent acute viral infections. Moreover, understanding about the pathophysiology of the cognitive impairment following other viral infections will help to better understand the emergence of neuro-cognitive symptoms among COVID-19 survivors. Post-COVID cognitive impairment may represent an important clinical feature of the disease, and may impose an additional and long-lasting burden, especially psychiatric and cognitive issues, particularly among older adults. Recognizing cognitive impairment following COVID-19 may be essential to promote preventive and therapeutic interventions and help clinicians worldwide to identify and treat this condition. This narrative review aims to bridge this gap, presenting the literature about the impact of viral infections on cognition, as well as to develop a theoretical framework on how COVID-19 impacts in the CNS function and may cause cognitive impairment.

Methods

We conducted a narrative review of literature following international guidelines for writing narrative reviews [20, 21]. First, two authors have searched three databases (PubMed, Scielo and EMBASE) using the following keywords: "Cognition", "Cognitive Impairment", "Cognitive Decline", "Dementia", Alzheimer's Disease", "Virus", "Acute", "Viral Infection", "Infection", and "Infectious Disease", with restriction of title, abstract and keyword. We selected additional disease-specific parameters ("Herpes simplex type 1", "varicella-zoster", "West Nile virus", "Influenzae", "Japanese encephalitis", "aseptic meningitis", "Acute respiratory distress syndrome"), adding the name of the parameter to the Boolean search. Selected articles were also searched for references. We accepted only articles in English, Spanish, Italian, and Portuguese. Selected articles were discussed with all authors and then included in the review.

Pathophysiology and types of the cognitive impairment following viral infections

First, it is important to give clear definitions about cognitive decline (or cognitive impairment), mild cognitive impairment, dementia and Alzheimer's disease, respectively. Cognitive decline can be understood as the loss of cognitive performance. It can be linear and natural or can have a non-linear and accelerated characteristic of loss [22]. The latter, when not impact activities of daily life, is called mild cognitive impairment (MCI), whereas dementia notably interferes on daily life [2]. The most common cause of dementia is the Alzheimer's disease, which can be defined as a chronic neurodegenerative disorder, characterized by the accumulation in brain of amyloid-β (Aβ) and tau protein [23]. Cognitive impairment may be caused by viral infections associated with direct invasion of the central nervous system [11, 24], or as an indirect effect of systemic infections not typically causing CNS infection (e.g. cytokine storm, neuro-inflammation, hypercoagulability) [11, 24].

Moreover, encephalitis is defined as an inflammation of the brain parenchyma associated with neurologic dysfunction, which usually manifests clinically with seizures, encephalopathy, focal neurologic signs and symptoms. In 2013, the International Encephalitis Consortium issued standardized and now widely case definitions for encephalitis. Diagnosing encephalitis requires demonstration of altered mental status decreased or altered level of consciousness, lethargy or personality change) lasting > 24 h, combined with at least two minor criteria (fever, new-onset seizures, focal signs, CSF pleocytosis, parenchymal abnormalities on neuroimaging, or typical electroencephalogram findings) for possible encephalitis, and three minor criteria for probable encephalitis [25]. For aseptic meningitis, Brighton Collaboration case definitions are widely used. Diagnosing aseptic meningitis requires clinical evidence of meningitis (fever, headache, vomiting, nuchal rigidity), and CSF pleocytosis, and negative CSF culture [26]. Distinguishing between meningitis and encephalitis is often elusive, given the shared disease mechanisms and clinical overlap. To avoid such confusion, the more encompassing term "meningoencephalitis" is frequently used interchangeably with meningitis and encephalitis.

Below, we will summarize the most important findings regarding six viruses that causes acute infections and its impact on cognition.

Herpes simplex virus type 1

Molecular biology and epidemiology

Herpes simplex virus type 1 (HSV-1) is a double-stranded DNA virus of the herpesviridae family. It is the leading cause of acute infectious encephalitis worldwide [27–29]. The incidence of HSVE is estimated to be between 2 and 4 cases/1,000,000, without clear regional differences [30, 31].

Mechanisms of infection

HSV primary infection involves skin or mucosae. Following primary infection, the virus infects sensory neurons and, ultimately, the dorsal root ganglia, via axonal transport. After prolonged latent infection, the virus may access the central nervous system by retrograde transport through trigeminal or olfactory nerves [32]. The predilection for involvement of mesiotemporal and limbic cortices may be explained by the intense connectivity between the olfactory nerves and the limbic system [33].

Clinical manifestation

Acute herpes simplex encephalitis presents commonly with prodromal symptoms, such as fever and respiratory symptoms, which progress over several days to encephalopathy, focal neurological signs and seizures [32, 34]. Neuroimaging shows characteristic but variable degrees of restricted diffusion, T2/FLAIR hyper-intensities and contrast enhancement in the mesial temporal lobes, orbito-frontal, insular and anterior cingulate cortices, frequently bilateral and asymmetrical [32, 34]. Typical CSF findings include mild-to-moderate pleocytosis (10–200 WBC/mm^3), mildly elevated protein (50–100 mg/dL) and normal glucose [32].

Impacts on cognition

Herpesviridae viruses can be implicated in late-onset Alzheimer's disease pathogenesis [35, 36], probably due to the increased amyloid-β amyloidosis [37]. Early reports from the pre-acyclovir era describe severe anterograde amnesia due to bilateral hippocampal damage in surviving HSV-1 patients [38]. A few patients followed longitudinally over long periods [39–46], display persistent severe anterograde and retrograde amnesia, with relatively preserved remote memories, the hallmark of bilateral hippocampal lesions. The severity of retrograde amnesia in HSV-1 patients is possibly associated with greater involvement of temporal lobe structures, including the temporal poles and temporal neocortical regions [43].

Memory deficit severity correlates with the extent of medial temporal lobe involvement and is the most important late finding in HSV encephalitis [47]. Bilateral lesions are associated with more profound cognitive deficits, involving semantic memory impairment and visual agnosia [42, 48]. Executive dysfunction, possibly due to orbito-frontal and anterior cingulate cortices damage is also recognized in HSV-1 encephalitis [49].

Although HSV-1 survivors may show improved cognition over time, cognitive impairment is an enduring long-term consequence of brain damage. Severe memory impairment is recognized in 40–58% of patients one year after the encephalitis [50–52], and 80% of patients display persistent mild cognitive deficits three years after the acute episode [53]. The advent of acyclovir, in the late 1980s, considerably modified the prognosis of HSV-1 encephalitis [54–56]. Mortality rates have dropped below 20% [34, 57]. Cognitive impairment, however, remains very common in acyclovir-treated patients [52].

Varicella zoster virus

Molecular biology and epidemiology

Varicella zoster virus (VZV) is a ubiquitous exclusively human DNA virus of the herpeviridae family and is the second cause of encephalitis worldwide [27, 29, 58].

Mechanisms of infection

Following primary infection, the VZV remains latent in cranial, dorsal root, and autonomic ganglia [59]. Iatrogenic immunosuppression and advanced age are associated with decreased cell-mediated immunity, which leads to VZV reactivation and neurological complications [60]. VZV reactivation shares many mechanisms with HSV-1 reactivation, and retrograde axonal transport within sensory neurons plays an important role [61].

Clinical manifestation

VZV can cause miscellaneous central nervous system diseases, including as meningitis, encephalitis, myelitis and CNS vasculopathy which frequently overlap [60]. Most frequently, VZV reactivates as shingles, and the infection is limited to the peripheral nervous system, with rash resolution over a few weeks. Occasionally, especially in immunocompromised patients, meningoencephalitis occurs. Clinical presentation is similar to other encephalitis syndromes, with varying degrees of encephalopathy, seizures, and headache. CSF studies show the typical profile

of viral meningoencephalitis, with 50–300 WBC/mm^3, and 40–150 mg/dL of protein [62, 63]. In encephalitis cases, neuroimaging shows encephalitic abnormalities nearly as frequently as signs of intracranial vasculitis [62].

Impacts on cognition

Studies assessing prognosis using hard endpoints in the post-acyclovir era showed neurological impairment in 20–60% of patients upon hospital discharge [62–64], 55% after one month, 51% after three months and 71% after one year [62, 65] after the acute episode. Recent attention has been drawn to potential long-term effects of herpes virus infection on cognition in the absence of an acute neurological syndrome. Viral presence in the CNS may interfere with pathogenic mechanisms related to neurodegenerative diseases, such as Alzheimer's disease (AD) [7, 10]. According to the 'viral hypothesis of AD', this interaction may be non-specifically associated with up-regulation of inflammatory responses and oxidative stress, which are secondary, but relevant components of the amyloid cascade. This interaction may also operate through a specific mechanism within the core pathogenesis, hastening amyloid overproduction [10, 12].

Japanese encephalitis

Molecular biology and epidemiology

Japanese encephalitis (JE) is the most common cause of encephalitis in Asia, affecting mainly children. Adult cases are increasingly reported [66]. JE is also a relevant cause of encephalitis in the western pacific, and JE cases have also been reported in Australia [67]. The disease is caused by the Japanese Encephalitis virus (JEV), a mosquito-borne single-stranded RNA virus of the flaviviridae family. The disease is usually transmitted to humans following the pig–mosquito–human route [68].

Mechanisms of infection

Following subcutaneous inoculation, the JE virus infects various parts of the brain, suggesting a hematological route of infection, which could be explained by infection of endothelial cells and subsequent transcellular transport into the brain parenchyma, and paracellular leakage through damaged blood–brain barrier or blood–CSF barrier [69].

Clinical manifestation

Only one in 25 to one in 1000 infections are symptomatic [70]. Patients typically present with fever and encephalopathy, often associated with seizures and moderate CSF pleocytosis. Neuroimaging may reveal specific abnormalities in the thalami in 22% of cases [71].

Impacts on cognition

Around 45–64% of survivors show neurological sequelae on hospital discharge [72–74]. In a Chinese retrospective series of 50 JE patients [66], 12% died during hospital admission, 75% had significant functional limitations upon discharge, and 39% of survivors had major limitations after 18 months.

These findings are in agreement with an early study conducted in Japan that found that 29% of patients had "detectable neurological sequelae" one year after the encephalitis episode [75], as well as with recent studies conducted in India and Japan, showing that 100% of patients had neurologic deficits on hospital discharge [76], 44% of patients had at least one neurological CNS sequel one to two years post encephalitis [74]. Cognitive deficits, especially intellectual disability and memory loss have been presented both in children and adults [72, 74] as well as memory learning in rats [77].

West Nile virus encephalitis

Molecular biology and epidemiology

West Nile virus (WNV) is a single-stranded RNA virus of the flaviridae family. The primary hosts are birds, and humans can be infected through transmission by mosquitoes. WNV is enzootic in Africa, Europe and Asia, and is also endemic in the United States, where over three million infections have occurred between 1999 and 2010 [78]. In endemic regions, WNV accounts for a significant proportion of encephalitis cases [28, 79]. In the United States, WNV was the second leading cause of viral encephalitis in the 2000–2010 period [28]. WNV can also cause massive outbreaks worldwide [80]. In Europe, the incidence of WNV disease rose sevenfold in 2018 (from the previous year), with a total 181 deaths [81]. A severe outbreak was also experienced in Romania, where incidence peaked at 1.5/100,000 in the year of 1996.

Mechanisms of infection

Although the exact disease mechanism is unknown, current hypothesis suggests the WNV enters the CNS hematogenously after crossing the blood–brain barrier, by endothelial replication or through transneuronal axonal transport within olfactory or peripheral somatic nerves [82].

Clinical manifestations

Most cases are mild or asymptomatic. Nervous system involvement (meningitis, encephalitis, acute flaccid paralysis) occurs in 1% of patients. Acutely, WNV encephalitis (WNE) patients usually present with fever and encephalopathy. Movement disorders, including myoclonus and parkinsonism, and motor weakness are common [83]. Mortality rates can be as high as 15–20%, with older adults at a higher risk [84].

Impacts on cognition

WNE patients experience significant morbidity during the initial months following acute infection. Most cases require rehabilitation [85, 86]. Movement disorders persist for months to years [83, 87–91]. Eighty percent of WNE patients report persistent WNV-related symptoms one year after infection.

Using comprehensive neuropsychological assessment tools, [88] showed that patients with neuro-invasive WNV disease displayed mild cognitive deficits in immediate and delayed memory, and more significant cortical thinning than controls on magnetic resonance imaging [88]. These findings were supported by another study conducted in Canada [89].

Aseptic meningitis

Molecular biology and epidemiology

Although the exact cause is unknown in many cases, viral meningitis is a leading cause of aseptic meningitis (AM) worldwide. Viral meningitis accounts for roughly 40% of all AM cases [92, 93]. The rates of detection of causative pathogens, particularly viruses, increases as more molecular and immunological testes are used [94], and the diversity of AM-causing viruses is ever-increasing [95], so many physicians consider AM of unknown cause as presumably of viral etiology [96]. Enteroviruses, VZV and herpes simplex virus type 2 are common causative agents.

Mechanisms of infection

In aseptic meningitis, mechanisms of infection are specific to the underlying infection associated. Herpes simplex and VZV-associated aseptic meningitis are usually associated to reactivation and its associated mechanisms, as described above. Human enteroviruses, a major cause of AM worldwide, are primarily acquired through the fecal–oral or fecal–hand–oral route (and occasionally by aerosolized oral secretions). Following infection in the oropharynx, the virus spreads to the gastrointestinal tract. The following viremia is occasionally followed by entry to the central nervous system through hematogenous spread [97, 98]. Once the virus enters the cerebrospinal fluid, it triggers accumulation of inflammatory cells, release of inflammatory cytokines, such as interleukin (IL)-1B, IL-6 and tumor necrosis factor (TNF)-alpha, which leads to increased permeability of the blood–brain barrier and additional inflammation, leading to typical symptoms of meningeal irritation [97].

Clinical manifestation

AM encompasses a clinical syndrome including patients with clinical and laboratory signs of meningitis, such as headache and nuchal rigidity, for which a bacterial cause of meningitis is excluded [26]. These symptoms of meningitis frequently follow prodromal systemic symptoms that are specific to the associated infection: shingles in VZV-disease, respiratory symptoms in enterovirus D68, diarrhea and hand-foot-and-mouth syndrome in other human enteroviruses [99]. The hallmark that differentiates AM from encephalitis is absence of altered mental status, which is the major diagnostic criterion for encephalitis, which is usually accompanied by absence of parenchymal abnormalities on neuroimaging and electroencephalogram studies [25].

Impacts on cognition

Acute AM is usually considered a benign condition not associated with long-term neurological sequelae. The perceived benign course may reflect, in fact, an underestimation of cognitive impairment in acute viral meningitis, due to the paucity of studies assessing quality of life and neuro-cognitive outcomes in this condition, as compared to the widely recognized consequences of acute bacterial meningitis (BM) and acute viral encephalitis (VE) [100].

Longitudinal studies in AM did not report a significant morbidity in the long term [24, 100, 101]. The inclusion of comprehensive tools for mental status and cognition revealed that AM patients might present with subtle visual memory and cognitive processing speed impairment [24], and worse global mental health status, compared to healthy controls. [101, 102].

Influenza viruses

Molecular biology and epidemiology

Influenza viruses are single-stranded RNA viruses of the Orthomyxoviridae family. Influenza types B and C infect predomonantly humans and typically do not cause pandemics. Influenza type A viruses may infect other mammals and avians, which leads to mixing genetic material and epidemics in naïve populations. Influenza viruses, including the most common subtypes A (H1N1), A (H3N2), B (Victoria),

and B (Yamagata) are common causes of acute lower respiratory infections in humans [103], accounting for at least four large-scale pandemics in the last century [104]. An important complication of influenza infection (but not exclusive of it) is the acute respiratory distress syndrome (ARDS), which affects 200,000 patients yearly in the United States, accounting for more than 10% of total ICU admissions, with a hospital mortality risk of 30–40% [105].

Mechanisms of infection

Influenza virus is transmitted primarily by infection of epithelial cells within the respiratory tract following inhalation. The virus then spreads to the upper and lower respiratory tracts causing the flu or viral pneumonia. The pathogenesis of both ANE and encephalopathy associated with influenza are poorly understood. Although some researchers suggested a direct role for brain infection in encephalopathy, viral particles are seldom recovered from CSF or brain samples [106]. Alternatively, encephalopathy patients frequently show high levels of serum and CSF cytokines, suggesting cytokine-mediated inflammation/cytokine storm as a potential cause [107–109].

Clinical manifestation

Influenza causes uncomplicated flu in a majority of cases. Although influenza viruses were not consistently shown to cause infective encephalitis in humans or animal models, they occasionally cause encephalopathy, usually presenting with normal CSF profile [110]. Rarely, influenza infections lead to severe encephalopathy with coma, extensive abnormalities on neuroimaging and high mortality rates, a syndrome called acute necrotizing encephalopathy, which affects largely children but also adults [111].

Impacts on cognition

Experimental studies show that the injection of Influenza A virus in mice's olfactory bulb caused cognitive impairment 14–20 weeks after the infection [112] as well as hippocampal morphology changes [113]. A case of severe amnesia with hippocampal imaging abnormality following Influenza A infection has been reported [114]. Other studies showed that Amyloid-β protein has antimicrobial properties [115], specifically against Influenza A [116], which can explain its increased deposition in susceptible individuals (in special older adults) exposed to Influenza viruses. Additionally, influenza vaccination may decrease dementia risk in patients with chronic diseases [117, 118], underscoring a potential role of Influenza in human dementia.

Furthermore, cognitive impairment is very common in ARDS survivors. Seventy to 100% of ARDS patients are cognitively impaired on hospital discharge, 46–80% one-year post-discharge, and 20% after five years [119, 120]. Moreover, one-year post-discharge, ARDS survivors show high rates of anxiety, depression, executive dysfunction and post-traumatic stress disorder [121, 122]. Persistent cognitive impairment was reported after a 2-year follow-up: roughly half of patients displayed signs of cognitive impairment [123]. Putative biological mechanisms underlying long-term cognitive impairment in ARDS patients include hypoxia, cytokine-mediated damage, cerebral autoregulation disruption, and blood–brain barrier damage-associated decrease in Amyloid-β clearance [124].

Coronaviruses and COVID-19

To our knowledge, no articles have investigated cognitive decline/impairment following the middle east respiratory syndrome (MERS) or the severe acute respiratory syndrome-coronavirus-1 (SARS-CoV-1). Although several studies have reported neuropsychiatric symptoms associated with the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) [13, 125], evidence of SARS-CoV-2 impact on human cognition remains scarce. Coronavirus disease 2019 (COVID-19) is caused by a RNA virus of the Coronaviridae family, and has been initially recognized as an agent of severe acute respiratory syndrome-related coronavirus (SARS-CoV) [126]. Although initially regarded as affecting the respiratory system with occasional gastrointestinal symptoms [127], subsequent reports showed that COVID-19 may also affect other major body organs, including renal, cardiovascular, and central nervous systems (CNS) [16, 125, 128].

COVID-19 has been recognized as a disease with pandemic consequences by World Health Organization in early March, 2020 [129]. Thenceforth, it has been infected almost 200 million people and killed more than 2.6 million people around 223 countries the world [130]. Especially in low- and middle-income countries, such as Brazil, due to the lack of vaccines, this number is still rising [130]. Furthermore, lack is known about the effect of the vaccine on new variants of SARS-CoV-2 [131].

Based on a review of the available literature, some authors predicted a high incidence of psychiatric morbidity following the COVID-19 pandemic, such as depression, anxiety and post-traumatic stress disorder [132]. Emotional symptoms can be related to COVID-19 through interaction with major life events and psycho-social stressors [133–135] or arise from disruption of brain function and damage to nervous tissues [17, 136]. Recent reports highlighting the risk for neuropsychiatric impairments secondary to COVID-19 showed that SARS-CoV-2 infection is associated with non-negligible incidence of neurological and psychiatric

manifestations and provided evidence that neuropsychiatric and cognitive symptoms may arise as a direct CNS infection by the virus also [17, 136].

Most studies on cognitive changes following SARS-CoV-2 infection focused on acute changes, mainly acute encephalopathy [137–139]. The occurrence of persistent cognitive deficits resulting from COVID-19 infection remains uncertain. Preliminary studies of convalescent COVID-19 patients using comprehensive neuropsychological assessment showed cognitive impairment two to four weeks after infection. Attentional deficits were the most relevant changes [140, 141]. A recent population-based study showed that 26% of all those with neuropsychiatric disorders due to COVID-19 had a dementia-like syndrome, with a median patient age of 71 years [136]. Another study showed that cognitive impairment (mainly attention and executive dysfunctions) has been reported in 28–56% of patients with mild or asymptomatic COVID-19, which was correlated with decreased cortical thickness in the right gyrus rectus, and in language associated areas [17]. A recent article showed changes in working memory, set-shifting, divided attention, and processing speed in a cohort of 57 patients recovering from moderate/severe patients with COVID-19, not being associated with intubation length, psychiatric and clinical diagnosis [142].

MRI studies have shown brain structural and microstructural changes in COVID-19 patients [143–146], such as acute necrotizing encephalopathy [145], cortical signal intensity abnormalities and unilateral FLAIR or diffusion hyper-intensities in medial the temporal lobe (MTL) [144, 146] and hippocampal abnormalities [143, 147]. A small case series of COVID-19 patients with acute encephalopathy suggested that the disease may be associated with a specific frontal hypo-metabolism pattern on FDG-PET [148] that differs from usual findings in delirium [149]. These abnormalities are associated with encephalitis and may at least partially explain cognitive impairment in COVID-19.

SARS-CoV-2 may cause neuropsychiatric symptoms by various indirect mechanisms, such as a hypercoagulable state, neuro-inflammation, immunological and epigenetic changes [132]. Several studies implied that blood–brain barrier disruption is associated with encephalopathy, favoring the neuro-inflammation theory [150, 151]. A possible mechanism for this theory might be hyper-activation of P2X7 receptors and a consequent NLRP3 inflammasome stimulation, triggering the inflammatory cascade [152]. The finding of coronavirus RNA in brain tissue of deceased patients raised the possibility of a direct brain injury mechanism [153]. This observation was corroborated by the finding of the virus in neural and endothelial cells in frontal lobe tissues [154], and in the cerebral spinal fluid of infected individuals [147, 155, 156]. Additionally, SARS-CoV-2 was found in astrocytes of all deceased patients with brain damage, underscoring the fact that brain may be a sanctuary for SARS-CoV-2 [17]. A recent article found SARS-CoV-2 virus in 53% of brain tissues of people who died by COVID-19, even though brain lesions were non-specific and could not be attributed to SARS-CoV-2 lesions directly [157]. SARS-CoV-2 RNA, however, is rarely identified in CSF samples of COVID-19 patients [158], and most cases of COVID-associated neurological symptoms are CSF-RT-PCR-negative, including encephalopathic patients [128, 137, 159]. CSF analysis of patients with neurological symptoms showed SARS-CoV-2 immunoreactivity, resulting from serum antibody leakage to the CSF, rather than to intrathecal antibody production [150, 160].

Knowledge acquired from other CoVs outbreaks (SARS-CoV and MERS-CoV) has suggested potential neuro-invasive routes. The upper airways and the olfactory neuroepithelium, are the initial step for odor identification [161, 162]. Olfactory cells express angiotensin-converting enzyme isoform 2 (ACE-2) and type II serine protease (TMPRSS-2), which may represent the viral entry point to the CNS [163]. Several RNA viruses can undergo axonal transport to different brain structures causing acute encephalitis [164–166]. A recent study pointed out to the neural–mucosa interface in olfactory mucosa as a potential port of CNS entry for SARS-CoV-2 [167]. Finally, the cytokine storm theory proposes that SARS-CoV-2 inflammatory response in the CNS is mediated by the massive glial cell cytokine release, such as IL1b, IL-6, and IFN I-III [168, 169]. Low ACE-2 expression is noted in both neurons and glial cells [170].

Intranasal SARS-CoV-1 inoculation (80% homology to SARS-CoV-2) in K18-hACE2 mutant mice (with the human form of ACE-2) resulted in the viral presence throughout the CNS, and was associated with local inflammatory mediators, respiratory dysfunction, and high mortality, with only mild lung infection [171, 172]. These findings suggest the importance of a CNS mechanism in virus-induced evolution and respiratory complications. CNS expression of ACE-2 expression in the CNS cells cannot isolatedly account for susceptibility to infection. Lungs and intestines usually show significant signs of viral infection and inflammation, which may be associated with high ACE-2 levels in pneumocytes and enterocytes. However, endothelial cells, which also express high ACE-2 levels do not display correspondingly high SARS-CoV infection levels [173].

In addition to the passage through the nasal neuro-epithelium route, independently from lower airway passage, evidence is accumulating suggesting that the virus initially infects peripheral nerve terminals and, through a trans-synaptic mechanism, enters the CNS [174]. Trans-synaptic routes have been reported in different coronaviruses (CoVs), such as HEV67 [175, 176] and in the avian bronchitis virus [177, 178]. Direct dorsal root ganglia infection in rats resulted in the presence of SARS-CoV in the CNS

[176]. Electron microscopy data confirmed the presence of the virus in neuronal vesicles. CNS viral invasion can occur through vagus nerve mediated trans-synaptic route, through intranasal inoculation of the influenza virus [177]. Partially (ipsilaterally) vagotomized animals inoculated with the virus showed viral presence in the root ganglia, bilaterally. The virus reached the ganglion contralateral to the de-afferentation first, suggesting a less effective transport after vagus nerve injury. In SARS-CoV-2, trans-nasal and trans-synaptic mechanisms might allow the virus to invade the olfactory bulb and brainstem, with both being the possible initial site for CNS invasion [179]. Once the virus enters the CNS, it affects neurons, microglia, oligodendrocytes, and especially astrocytes, undermining neurons viability [17, 179, 180].

Abate et al. [18] reviewed the different mechanisms by which SARS-CoV-2 infection might increase Alzheimer's disease (AD) risk, which could be extrapolated to other cognitive diseases. Direct viral neuro-invasion, as hypothesized above, and its association with ACE-2 expression in brain, especially in glial cells, could lead to oxidative stress and neuronal loss, due to both microglia and astrocyte activation, and increased nitric oxide (NO) production. [181, 182]. The finding that SARS-CoV-2 infects astrocytes [17] and its role with amyloid-β (Aβ) deposition, underscores a possible link between COVID-19 infection and AD. Aβ has also been shown to act as an antimicrobial peptide that may be overproduced in an immunologic mechanism [115]. Additionally, individuals with the ApoE3 allele may be more susceptible to severe forms of COVID-19 disease [183]. The connection between ApoE4 genotype, neuro-inflammation, and AD pathology should be further investigated [184]. Additionally, hypercoagulable states may induce micro-vascular disease and induce vascular dementia and AD [185]. Figure 1 summarizes the neurobiological impact of SARS-CoV-2 on cognition.

Clinical implications

It is important that health professionals be aware of the potential impact of COVID-19 in Central Nervous System, especially in cognition. It could impact not only older individuals with cognitive impairment, but also healthy individuals more susceptible to it. More studies should be done to identify these susceptible individuals, its relationship with disease severity, the pathophysiological mechanisms of this impairment, as well as to understand the long-term consequences of the cognitive deficits. Health managers should also promote campaigns and continuing education programs to help physicians and other health professionals to identify and deal with these emerging issues.

Moreover, the need of an approach to deal with these cognitive impairments is urgent. The spread of cognitive rehabilitation techniques is indispensable, as it has been showed to be effective and can be used through several different cognitive deficits and etiologies [186]. Also, the use of therapeutic agents to prevent and treat cognitive impairment following virus infections has been recently proposed. Wozniak and Itzhaki [187] in a narrative review, pose the provocative question whether it is time to initiate using antiviral agents for AD. Previous research has found that the development of anti-herpes medications had a positive impact, reducing the incidence of AD [56]. Current randomized controlled trials (RCTs) are investigating the effect of antiviral therapy for

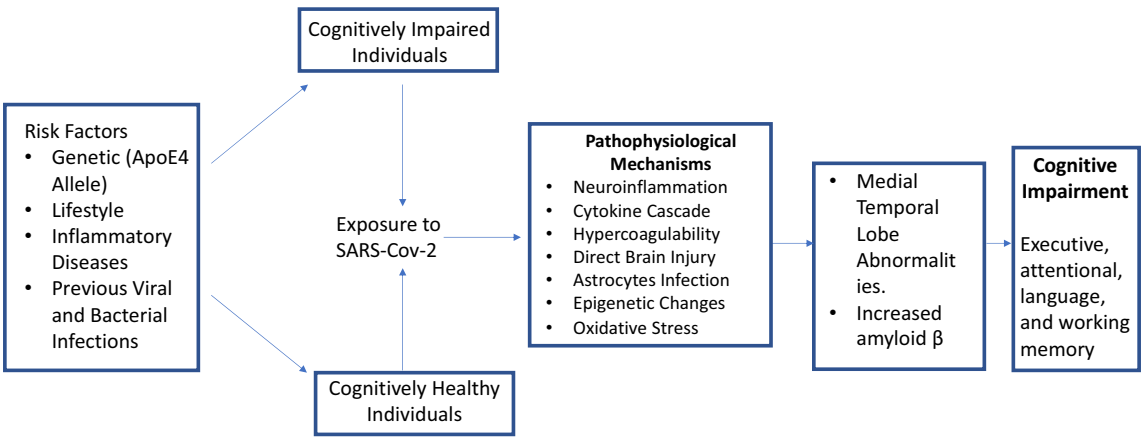

Fig. 1 Proposed pathophysiological mechanisms of the impact of SARS-CoV-2 infection on human cognition. First, risk factors, such as genetic, lifestyle, inflammatory diseases and previous viral and bacterial infections, might interact with exposure to SARS-CoV-2 in brains of both cognitively healthy and impaired individuals. It may induce several different mechanisms, such as neuro-inflammation, cytokine cascade, hypercoagulability, direct brain injury, astrocytes infection, epigenetic changes and oxidative stress, which together may induce medical-temporal lobe abnormalities and/or increased amyloid-β. These different pathways might induce a cognitive impairment, mainly in executive, attentional, language and working memory areas

the treatment of AD [188]. Antibacterial therapy has also been suggested as an alternative for the treatment of senile dementia [10].

Some authors have suggested that due to anti-inflammatory properties, antimalarial drugs could be used to prevent neuropsychiatric COVID-19 complications [189]. Additionally, anticholinergic agent was proposed to reduce cytokine storm and Aβ deposition [190]. Furthermore, adamantane agents were suggested to play a potential neurocognitive protective effect in cognitively impaired patients [191]. So far, these agents were not proven to reduce mortality or morbidity due to SARS-CoV-2 infections.

Limitations

This paper has several limitations. First, due to the narrative nature of this review, there is a selection bias of articles. Second, we chose only six out of several different acute viral infections and virus-related syndromes. Our intent was to provide a wide scenario including both ubiquitous viruses causing disease worldwide (HSV-1, VZV, Influenzae), and viruses with marked regional relevance (WNV, JEV). Third, COVID-19 is an ongoing and dynamic epidemic. Many new articles are published daily, which makes reviewing this ever-changing field challenging. For instance, we made projections about post-COVID-19, because long-term studies on cognitive outcomes are largely lacking. We hope these projections will soon be confronted with original data from ongoing studies.

Conclusion

In sum, several viral agents have been shown to affect human cognition by distinct pathogenetic mechanisms. Some of these pathogens may cause long-term cognitive impairment, including parenchymal brain damage due to the direct CNS infection or to indirect mechanisms leading to disrupted brain function, such as hypercoagulable states and neuroinflammation. Recently, a wide body of evidence has shown that COVID-19 might lead to neuropsychiatric issues, especially cognitive impairments. However, lack is known about the pathophysiological mechanisms. Thus, it is crucial to understand the cognitive impact of acute viral infections and how it could be incorporate in the understanding of clinical impairments of COVID-19 in central nervous system. This knowledge may help us understand and predict possible long-term cognitive outcomes of COVID-19, helping both patients and health providers to cope better with this still unknown disease.

Declarations

Conflict of interest The authors declare no conflict of interest.

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COVID-19 highlights negligence with psychiatry patients in Brazilian general hospitals: a call for action

COVID-19 evidencia a negligência com pacientes psiquiátricos em hospitais gerais brasileiros: uma chamada para a ação

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DEAR EDITOR,

It is well known that due to multiple factors, psychiatric patients experience almost a decade of delay until intervention (DUI) to initiate a mental health treatment[1]. Moreover, some authors have already pointed out to a marked increase in mortality rate in individuals with mental disorders, highlighting a worse and delayed quality of healthcare for psychiatric patients with non-psychiatric illnesses[2]. Considering the fact that acutely mentally ill patients can be challenging, especially for untrained health staff, alongside with all the psychological and environmental stress precipitated by the COVID-19 pandemic, psychiatric patients are currently under even higher risk of medical negligence and larger DUI.

In order to overcome such a bleak state of affairs, we propose a combined intervention on three levels. First, there is the education of health professionals to-be. A recent multicenter controlled study[3] proposed an antistigma intervention curriculum (ASIC), where medical students were submitted to clinical encounters with people living with serious mental illnesses followed by supervised small group discussions. Authors found that ASIC was effective in reducing stigma and also in changing attitudes toward psychiatry as a career choice.

Second, regarding treatment delivery, programs such as ASIC should be made available to professionals working at any health service potentially involved in the care of psychiatric patients. Besides, it is imperative that before overburdening the health staff with further responsibilities (courses, training, extra work hours, etc.), that health administrators take a time to remember usually forgotten practices that promote stress buffering and facilitates the emotional ventilation amongst professionals, in order to create a safe and healthy working environment.

Last, but not least, there is a well-known juxtaposition between psychiatric symptoms precipitated by stress and symptoms from general medical conditions, such as tremors, tachycardia, sweating, shortness of breath, and fatigue. However, such symptoms are not all equally modulated by the mental status[4]. For instance, chronic fatigue is known for having a low placebo response[5] and could be a more reliable indicator of respiratory compromise than self-reported dyspnea in pre-acute pulmonary failure. Considering the paucity of evidence in that regard, we acknowledge that such statement is highly speculative, but that should not stop us from inquiring into the merits of identifying red flags that may help health care providers discriminating psychiatric symptoms from symptoms indicating the need for urgent clinical intervention. In fact, it should be an incentive for fostering more research initiatives in the realm of liaison psychiatry services. This knowledge might promote better quality of care, reducing the DUI of psychiatric patients and consequently reduce their high mortality.

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Thus, COVID-19 pandemic evidence the worse quality of care that people living with severe mental illnesses might suffer in our general hospitals. Therefore, it is time to change teaching, clinical and research settings in order to promote the best quality of care to patients with psychiatric illnesses. Treating the most vulnerable individuals of our society, especially those with severe mental diseases is urgent and addressing this issue will help not only patients with mental illnesses but all the community.

INDIVIDUAL CONTRIBUTIONS

Rodolfo Furlan Damiano – Contributed with the design, writing and review.
Hermano Tavares – Contributed with the design, writing and review.

CONFLICT OF INTERESTS

Authors declare having no conflict of interests.

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Letter to the Editor

COVID-19 specific phobia: A new psychiatric entity?

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Specific Phobia

Dear Editor,

Case Vignette: "M.R., 64 year-old woman with no previous history of psychiatric disorders, started with a strong and recurrent fear of being infected with COVID-19, both herself and her relatives. She would have a panic attack every time she thought about her husband or children going back to work or even leaving home for whatever reason. Due to this fear, she sought help at the hospital emergency room several times, thinking she could have been infected. She accepted to have an appointment with a psychiatrist because, even though she understood her fear as plausible, the degree to which it filled her mind and impacted on her life 'was driving her crazy' (as she said). She could not refrain from going repeatedly to the hospital ER to run additional tests, in spite of being aware of the risk of the contact visiting COVID-19 patients and, therefore, being actually exposed to the risk of contamination.

The pandemic caused by SARS-CoV-2, the virus responsible for the Coronavirus Disease 2019 (COVID-19), has caused biological, economic, social, cultural and psychological impacts on the world's population (Bauchner, 2020). Fear and anxiety are common and expected psychological responses during situations like this, however sometimes under specific circumstances some anxiety-related disorders can emerge (Taquet et al., 2021).

Anxiety disorders represent the most common group of psychiatric disorders and one of the most important causes of disability worldwide (Craske et al., 2017). The most common diagnoses under this group are Specific Phobia, Generalized Anxiety Disorder, and Social Anxiety Disorder (Baxter et al., 2013). Specific Phobia has an estimated 12-month prevalence around 7% and consists of excessive and persistent fear in the face of a specific situation or object (Craske et al., 2017). The situation or object is usually avoided by the individual, when possible, but if the exposure occurs, the anxiety develops quickly and can intensify to the risk of a panic attack. Several situations related due to COVID-19 might be important predictors for developing fear and specific phobia (Mertens et al., 2020).

To the best of our knowledge, no study has yet described a specific phobia related to the fear of catching COVID-19. In our large cohort investigating 712 individuals who underwent hospitalization due to COVID-19 in a large Brazilian city (Busatto Filho et al., 2021), and using a well validated psychiatric interview instrument (CIS-R) (Lewis et al., 1992) to capture psychiatric diagnoses 6-9 months after remission of the acute phase of the disease, we found a prevalence of 2.66% (n=19) of participants with any Specific Phobia, one fifth of whom could be viewed as having COVID-19 Specific Phobia (0.56% - (n=4) of the total sample). Although less frequent than other forms of psychiatric morbidity that pertain to 'long-COVID', the public health impact of this specific feature of anxiety disorders may be substantial given the massive numbers of the pandemic.

Symptoms may vary from autonomic symptoms when facing fearful and stressful situations to avoidance of any feature that might remind this situation – in this case, the COVID-19 pandemic. Patients may avoid leaving home, touching objects, talking with people, including their own family. Symptoms may persist even in non-stressful places, affecting quality of life. However, we should be cautious when interpreting and generalizing this finding. It might be only an artifact from CIS-R output and, in fact, represent symptoms from related disorders. For instance, in this case the fear seems to be more elaborated than the usual immediate fears in simple phobia (the infection involves not only her but her family members) and can happen at any time (e.g., going to work or even alone), without the exposure to the virus being necessary a triggering factor. It involves repetitive thoughts (repetitions of aversive thinking) that could be better conceptualized as obsessions and repetitive reassurance, seeking help in the hospital repetitively, which could be seen as a compulsive behavior. Not mentioned here, however, avoidance behaviors may also develop as frequently seen in phobias and OCD (Stein et al., 2019). Additional differential diagnoses should also include Post-Traumatic-Stress Disorder (PTSD) (Schillaci et al., 2009) and other Anxiety-Related Disorders (Craske et al., 2017).

This differentiation is important because it will guide the rationale of the treatment. Nevertheless, it also raises the importance of COVID-19 in the psychopathology of this year and perhaps of this decade. Thus, more studies should be done regarding this clinical entity in order to confirm and/or deny it and also to understand possible therapeutic strategies targeted to these individuals, helping them to deal and overcome this important and stressful entity.

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Declaration of Competing Interest

Authors Declare no Conflict of Interest.

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REVIEW ARTICLE

Mental health interventions following COVID-19 and other coronavirus infections: a systematic review of current recommendations and meta-analysis of randomized controlled trials

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Objective: To review the most common mental health strategies aimed at alleviating and/or preventing mental health problems in individuals during the coronavirus disease 2019 (COVID-19) and other coronavirus pandemics.
Methods: We conducted a systematic review of the literature assessing three databases (PubMed, SCOPUS, and PsycINFO). A meta-analysis was performed with data from randomized controlled trials (RCTs). For non-RCT studies, a critical description of recommendations was performed.
Results: From a total of 2,825 articles, 125 were included. Of those, three RCTs were included in the meta-analysis. The meta-analysis revealed that the interventions promoted better overall mental health outcomes as compared to control groups (standardized mean difference [SMD] = 0.87 [95%CI 0.33-1.41], $p < 0.001$, $I^2 = 69.2\%$), but did not specifically improve anxiety (SMD = 0.98 [95%CI -0.17 to 2.13], $p > 0.05$; $I^2 = 36.8\%$). Concerning the systematic review, we found a large body of scientific literature proposing recommendations involving psychological/psychiatric interventions, self-care, education, governmental programs, and the use of technology and media.
Conclusions: We found a large body of expert recommendations that may help health practitioners, institutional and governmental leaders, and the general population cope with mental health issues during a pandemic or a crisis period. However, most articles had a low level of evidence, stressing the need for more studies with better design (especially RCTs) investigating potential mental health interventions during COVID-19.

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Keywords: Community mental health; prevention; management; coronavirus; COVID-19; pandemic

Introduction

Pandemics have historically been more destructive and devastating in terms of morbidity and mortality than any other type of world disaster, rivaled only by human-made disasters of war and genocidal murder. Nevertheless, empirical data on mental health impacts of pandemics has been meager in comparison to what has been reported for natural or human-made disasters. Though disaster-related mental health research has increased in recent years, most pandemics in the last century have generated limited study.[1]

In early March 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) outbreak a pandemic with unpredictable consequences.[2] Almost 1 year later, more than 112 million individuals have been infected, with almost 2.5 million deaths worldwide caused by the new severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.[3] Furthermore, even though COVID-19 was initially described mainly as a respiratory disease, accumulating evidence suggests that several other systems are affected, and neuropsychiatric complications may play an important role in the overall disease burden.[4,5]

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A recent meta-analysis has shown that, similar to other coronaviruses (severe acute respiratory syndrome coronavirus 1 [SARS-CoV-1] and Middle East respiratory syndrome [MERS]), SARS-CoV-2 may affect the central nervous system (CNS) in many different ways, including acute, subacute, and chronic neurological and psychiatric impairments.[6] Many acute neuropsychiatric events have been described, such as encephalopathy, delirium, anosmia, and ageusia[7]; the former two presumably relate to systemic/indirect insults to the brain, whereas the latter may reflect a specific mechanism through which the virus would directly affect nerve cells and/or damage support cells in the neuroepithelium.[8-11] Higher rates of depression, anxiety, suicidal behavior, and post-traumatic stress disorder (PTSD) have been associated with prior viral pandemics including SARS and MERS, suggesting similar patterns may emerge with COVID-19.[6,12,13] A recent study[14] investigating a clinical sample of COVID-19 survivors 1-month after hospital discharge reported high rates of mental health symptoms, such as depression, anxiety, PTSD, insomnia, and obsessive-compulsive symptoms, which were directly related to baseline immune inflammation of exposed individuals during hospitalization.[14]

There are several processes through which a coronavirus can cause neuropsychiatric diseases. Potential neuropathological mechanisms include acute injury to nasal and gustative cells with trans-synaptic flow into the brain, as well direct viral injury to brain tissue via blood-brain barrier (BBB) diapedesis, which generates a glial neuroinflammatory response. Even without viral transfer into the brain itself, there may be indirect CNS effects when cytokine storm results from breaches in the BBB, particularly via fenestrated endothelium and endotheliitis. This neuroinflammatory cascade can promote a hypercoagulability state leading to CNS thrombotic events and further injury to the BBB.[6,7,15] Moreover, there are also possible environmental reasons for psychiatric morbidity. For example, individuals may develop stress due to social isolation, loneliness, economic burden, and unemployment following the pandemic, stigma, and several others.[16-22]

Given the fact that more than 20 million individuals have been infected, many of whom will develop psychiatric symptoms, it is possible that we might face a wave of neuropsychiatric diseases in the upcoming months and years.[7] Within this context, experts around the world have proposed preventive and therapeutic strategies to manage mental health sequelae, largely based on their personal experiences and on the knowledge derived from other pandemics.[23-26]

Understanding the current evidence obtained through randomized controlled trials (RCTs) is crucial to guide mental health and other health practitioners. Likewise, understanding the opinions of mental health experts could potentially help in the development of future guidelines and in the design of clinical trials in order to minimize the mental health burden in this and future pandemic crises. However, at the present moment, there is a lack of systematic evidence and a scarcity of evidence-based practice recommendations regarding mental health preventive and management strategies in the COVID-19 pandemic, both individually and at a population level. Such evidence could possibly guide clinicians and health managers worldwide, helping to mitigate the mental health consequences of this and other pandemics.

Thus, the goal of this study was to review the current scientific literature regarding the most common mental health strategies available with the aim of alleviating and/or preventing mental health problems (e.g., depression, anxiety, PTSD, and suicidal behavior) in individuals during COVID-19 and other coronaviruses pandemics. Moreover, we investigated the possible effectiveness of mental health interventions, as compared to control groups, based on a meta-analysis of randomized controlled clinical trials.

Methods

The present study was based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[27,28] A meta-analysis was performed with RCT results, and for non-RCT studies a critical description of recommendations was performed with all included articles. The study was registered on the PROSPERO[29] platform under registration CRD42020190212.

Eligibility criteria

The following criteria were applied for inclusion of studies in this review: articles addressing preventive and/or management strategies to handle mental health issues in laypersons and health professionals during the COVID-19, SARS, or MERS pandemics. For the meta-analysis, only RCTs reporting effect sizes and/or full data on means, standard deviations (SD), and sample sizes for each group were included; whereas for the descriptive analysis, all articles (letters to the editor, editorials, opinion essays, guidelines, observational studies) were included. No language or date restrictions were applied.

Exclusion criteria were non-coronavirus-related articles and articles that did not describe interventions or provide recommendations for the prevention or management of mental health concerns.

Search strategy

The literature search was conducted in three databases (PubMed, SCOPUS, and PsycINFO) from inception to June 3, 2020. Moreover, a hand search was performed on three pre-print databases (medRxiv, bioRxiv, PsyArXiv) in order to find additional articles. Key words were derived from meetings of the researchers and based on literature reviews, including a recent literature review on the prevalence of mental health problems due to COVID-19 infections.[6] Keywords were grouped using the following Boolean operators and adjusted according to each database: ''(mania OR manic OR dysthymia OR dysthymic OR anxiety OR anxious OR suicidal OR euphoria OR suicide OR affective OR depression OR depressive OR bipolar OR post-traumatic stress disorder OR PTSD OR mood OR mental health) AND (covid-19 OR coronavirus OR SARS-Cov-2 OR SARS OR MERS OR severe

acute respiratory syndrome OR SARS-Cov OR middle east respiratory syndrome)."

Study selection

The selection of studies was conducted in three stages.

Stage 1

Two independent authors (RFD and TDS) screened simultaneously all references in the three databases using the search strategies described earlier. Duplicates were excluded using the Endnote software. Both authors determined eligibility based on title and/or abstract. Any article suggesting or recommending mental health interventions or presenting original data regarding any kind of interventions that might help mental health practitioners, governmental leaders, and educators around the world deal with the emergent mental health crisis were considered and included. Any disagreements between researchers were discussed with a third party (GL), and a final decision was made. All included articles on stage 1 were available to stage 2.

Stage 2

The selected articles were read in full by the same independent researchers (RFD and TDS). Both authors independently analyzed the data focusing on the eligibility criteria and extracted the following variables: authors, first author, year of publication, journal, language, type of study, type of intervention (preventive or management), targeted population (health care workers, laypersons, etc.), and category of recommendation. Articles that did not meet eligibility criteria in stage 2 were excluded. In the descriptive analysis, the authors grouped the most common mental health interventions and recommendations and, based on this information, they determined the following groups: psychological/psychiatric interventions, complementary and alternative therapies, self-care, technology and media, education, governmental programs, general recommendations, spirituality and religiousness, health care institutions, and physical intervention. Each article could have more than one category of recommendation, and any disagreement between researchers was again discussed with a third party (GL).

Stage 3

All information was compiled, and an expert summary provided. RCTs meeting the inclusion criteria were included for meta-analysis. Practical recommendations for laypersons, mental health care workers, and agencies were summarized.

Quality assessment

Each RCT was assessed using the Cochrane Back Review Group Criteria List for Methodological Quality Assessment[30] by two independent authors (RFD and TDS). This assessment covers the following methodological items: A = randomization method; B = allocation concealed; C = similar baseline; D = patient blinded; E = provider blinded; F = assessor blinded; G = cointervention avoided; H = acceptable compliance; I = acceptable drop out; J = timing of outcome of assessment similar; and K = intention to treat analysis. A score ranging from 0 to 11 was used.

Meta-analysis

The software Meta-Essentials was employed for the meta-analysis. All outcomes provided by each article were included. For studies that had more than one outcome group (e.g., anxiety, depression, somatization), analyses were carried out separately for each group, with studies labeled with a letter in parentheses (e.g., "b") for each of these comparisons.

Effect size was based on the mean, SD and sample size of the intervention and control groups for each comparison. For the meta-analyses that compiled different scales, effect size was calculated as the standardized mean difference (SMD = Cohen *d*) with its 95% confidence interval (95%CI). This approach enabled inclusion of different outcome measures in the same synthesis.

Random effects model meta-analyses were conducted for all studies that had full data assessing mental health in general, and a sub-analysis was carried out for anxiety. A p-value < 0.05 was adopted as significant and heterogeneity was determined using I^2.

Results

Figure 1 summarizes the steps of the systematic review. We found 2,825 articles through database searching: 877 from PubMed, 1,562 from EMBASE, and 386 from Psyc INFO. No other studies were found in additional databases (i.e., medRxiv, bioRxiv, PsyArXiv). After excluding duplicates, a total of 2,070 articles remained for the first screening. From those, 13 were automatically excluded due to the lack of title.

From 2,057 references screened, 154 were accepted for full-text reading. After full-text reading, 29 additional articles were excluded, leaving a total of 125 articles that were included in the final analysis. Of these, four were RCTs.[31-34] However, only three were included in the meta-analysis,[32-34] because one provided only absolute numbers and percentages rather than means and standard deviation.[31]

Descriptive analysis of the articles included in the systematic review

A total of 125 articles published from 2003 (first article) to 2020 regarding mental health interventions for COVID-19 and other coronaviruses (SARS and MERS) were found.

Table 1 summarizes our results. More than 90% of the articles were published in 2020 and were about COVID-19, while the remaining minority included SARS-CoV-1 (6.4%), MERS (0.8%), and more than one coronavirus (0.8%). The majority of studies were conducted in China (28.8%), the United States (14.4%), and the United Kingdom (12%), followed by Italy (5.6%), India (4.8%), and

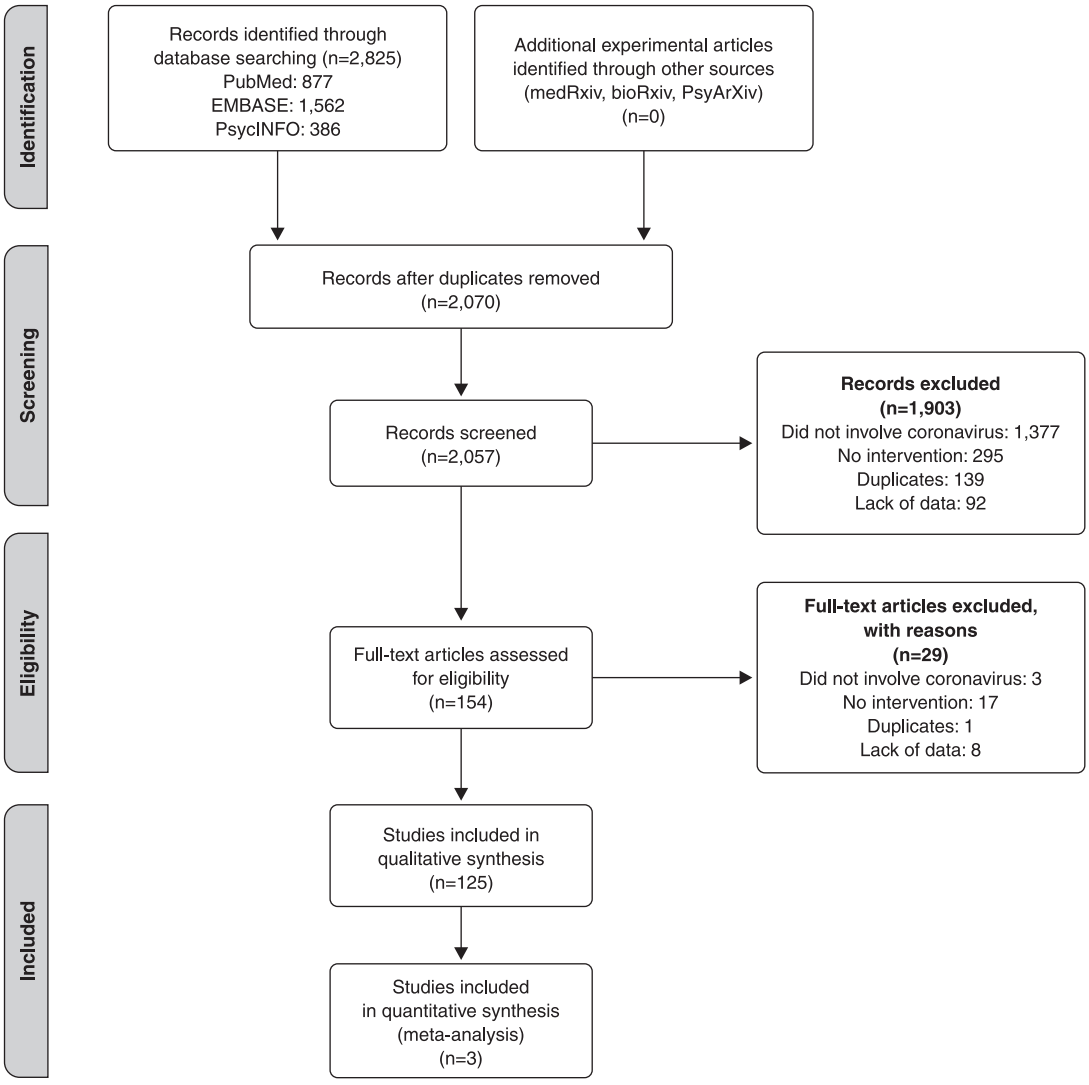

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

Australia (3.2%). Most of these publications were letters to the editors (33.6%) and review articles (28%), followed by original research articles, largely cross-sectional in design (9.6%). The remaining articles (28.8%) included editorials, reports, experimental studies, cohort studies, consensus statements, meta-analyses, opinion, and quasi-experimental studies. Almost 70% included recommendations for the lay public and 20.8% for health care professionals.

Mental health interventions

Table 2 summarizes the descriptive analysis of the 125 articles addressing preventive or interventional strategies for mental health symptoms in individuals during coronavirus pandemics. Recommendations regarding any kind of preventive and/or management interventions were made by 86.4 and 58.4% of all included articles respectively. More than one intervention was proposed in 69.6% of these articles, with 21.6% proposing more than five different interventions. The most common combined interventions were psychological and psychiatric (12.8%), technology and media (7.2%), and the combination of both (6.4%). Regarding each intervention, psychiatric and psychological were the most frequently reported, followed by self-care and educational interventions.

Meta-analysis

For the meta-analysis, three RCTs were included,[32-34] for a total of 128 participants. The meta-analysis revealed improved mental health in intervention groups as compared to control groups for a combination of outcomes analyzed together (improved anxiety,[32-34] depressive symptoms,[33,34] sleep quality,[32] hostility,[33] and somatization[33]) (SMD = 0.87 [95%CI 0.33-1.41], $p < 0.001$, $I^2 = 69.2\%$) (three studies included, with eight comparisons) (Figure 2). Due to the limited number of studies, an individual meta-analysis was only possible for anxiety,

Table 1 Descriptive analysis of articles proposing mental health interventions for COVID-19 and other coronaviruses

	No. articles (%)
Year	
2020[12,25,31,32,34,35-145]	116 (92.8)
2003-2019[33,146-153]	9 (7.2)
Journal	
Asian Journal of Psychiatry[38,64,71,75,81,97,106,109,114,119,125]	11 (8.8)
Lancet Psychiatry[12,55,67,73,88,95,140]	7 (5.6)
Psychiatry Research[47,83,104,116,126,141,144]	7 (5.6)
Clinical Neuropsychiatry[65,99,112,131]	4 (3.2)
Other	96 (76.8)
Type of study/article	
Letter to the editor[12,25,36,37,41,43-45,47,50,53-55,61,62,65-67,71-73,75,77-79,81,85,88,92,95,103-105,109,114,122,123,126,130,140,141,144]	42(33.6)
Review[40,42,46,58,60,64,69,70,90,91,93,94,96-98,100,101,107,108,111-113,115-119,121,124,125,134,136,137,142,148]	35 (28.0)
Cross-sectional[38,49,52,102,106,110,128,135,138,146,150,151]	12(9.6)
Editoria[35,48,51,84,89,99,127,129,139,145]	10 (8.0)
Report[39,57,59,63,68,76,80,83,131,152]	10 (8.0)
Experimental[32-34,132]	4 (3.2)
Quasi-experimental[31,147,153]	3 (2.4)
Cohort[143,149]	2 (1.6)
Consensus[82,86]	2 (1.6)
Meta-analysis[87,120]	2 (1.6)
Opinion[74,133]	2 (1.6)
Protocol[56]	1(0.8)
Country of the corresponding author	
China[32-34,38,43,47,52,55-57,67,77,78,80,83,92-95,120,125-127,132,134-136,138,142-144,148-151,153]	36 (28.8)
United States[25,39,50,51,54,69,79,86,91,101,107,108,114,121,123,124,140,141]	18 (14.4)
United Kingdom[12,42,48,49,59,62,70,73,74,89,96,102,122,129,137]	15 (12.0)
Italy[53,63,65,99,112,116,139]	7 (5.6)
India[64,71,75,97,98,119]	6 (4.8)
Australia[85,87,111,145]	4 (3.2)
Others	39 (31.2)
Coronavirus	
SARS-Cov-2[12,25,31,32,34-57,59-145]	115 (92.0)
SARS-Cov-1[33,146-151,153]	8 (6.4)
MERS[152]	1 (0.8)
More than one coronavirus[58]	1 (0.8)
Population included or targeted for recommendations	
General population[12,25,31,32-38,44-47,50,51,53,54,58,60-71,73,75,76,78-81,84-86,88-95,97,98,100-112,114,116-120,125-128,130,131,140-145,148-153]	88 (70.4)
Health care workers[39,41-43,48,49,52,55,57,59,72,74,87,96,121,122,124,132,133,135-139,146,147]	26 (20.8)
General population and health care workers[40,77,82,83,99,113,115,123,129,134]	10 (8.0)
Children/adolescents[56]	1 (0.8)

COVID-19 = coronavirus disease 2019; MERS = Middle East respiratory syndrome; SARS-CoV = severe acute respiratory syndrome coronavirus.

without any differences detected between the intervention and control groups (SMD = 0.98 [95%CI -0.17 to 2.13], $p > 0.05$; $I^2 = 36.8\%$) (three studies included, with three comparisons). Other comparisons were not possible due to the lack of data.

Moreover, a quality assessment of clinical trials was carried out for the three included articles (Table 3). In general, the articles were of low quality, with a general score ranging from 3 to 7 (Table 1).

The first clinical trial was a 2006 study of a 1-day group debriefing technique, Strength-Focused and Meaning-Oriented Approach for Resilience and Transformation (SMART), based on Asian philosophies and traditional Chinese medicine[33] applied for people with chronic diseases 1 month after the SARS pandemic. The authors found that the intervention group reported improved depressive symptoms, but no difference was detected in anxiety, hostility, and somatization symptoms. Two other intervention studies were administered to patients with COVID-19. Liu et al.[32] evaluated the effects of progressive muscle relaxation, 30 min daily for 5 days, for patients with COVID-19 in an isolation ward. Subjects who received the intervention improved significantly in anxiety and sleep quality measures. Another Chinese group investigated the impact of an internet-based intervention for depressive and anxiety symptoms in COVID-19 patients.[34] This 2-week trial consisted of daily 50-minute practices of breath relaxation techniques, mindfulness, ''refuge skill,'' and a ''butterfly hug.'' The authors found a significant improvement in mild depressive symptoms and anxiety symptoms after the 1st and 2nd weeks of the intervention.

Table 2 Mental health interventions for COVID-19 and other coronaviruses proposed by articles included in the systematic review

	No. articles (%)
Preventive recommendations	109 (86.4)
Management recommendations	73 (58.4)
Combined interventions	
Psychological/psychiatric interventions	16 (12.8)
Technology/media	9 (7.2)
Psychological/psychiatric interventions + technology/media	8 (6.4)
Education	8 (6.4)
Self-care	7 (5.6)
Governmental programs	7 (5.6)
Psychological/psychiatric interventions + technology/media + education	5 (4.0)
Psychological/psychiatric interventions + governmental programs	5 (4.0)
Psychological/psychiatric interventions + education	4 (3.2)
Others	56 (44.8)
Number of recommendations proposed per article	
1	38 (30.4)
2	28 (22.4)
3	11 (8.8)
4	11 (8.8)
5	10 (8.0)
More than 5	27 (21.6)
Psychological/psychiatric interventions	
Individual psychotherapies[33,36-38,52,55,56,59,80,82,87,99,100,108,118-121,125,127,136,137,139,142,148,153]	26 (20.8)
Hotline[12,36,37,42,43,45,55,72,75,81,84,102,109,113,114,125,133,136,137,139,142,144,145,153]	24 (19.2)
Support groups[35,38,39,42,48,55,57,59,63,72,74,76,88,96,119,126,127,129,139,146,148]	21 (16.8)
Psychological first aid[59,70,72,83,92,118,119,131,136]	9 (7.2)
Art therapy[50,60,61]	3 (2.4)
Enhancing optimism intervention[33,148]	2 (1.6)
Post-COVID-19 support[73,150]	2 (1.6)
Home brain stimulation[54]	1 (0.8)
Music therapy[57]	1 (0.8)
Psychopharmacology[127]	1 (0.8)
Home care[68]	1 (0.8)
Prisoner mental health care[89]	1 (0.8)
Complementary and alternative therapy	
Mindfulness[34,42,44,46,51,57,65,75,80,86,118,121,139]	13 (10.4)
Breathing techniques[34,40,51,121]	4 (3.2)
Yoga[40,51,60]	3 (2.4)
Qigong[69]	1 (0.8)
Self-care	
Sleep hygiene[40,42,44,48,57,58,66,86,96,97,101,117,119,121,126,128,135,138,143]	19 (15.2)
Time with family/friends[25,40,42,44,58,75,78,86,97,101,117,119,126,128,133]	15 (12.0)
Exercise[25,75,86,97,101,110,117-119,121,126,128,132,143]	14 (11.2)
Eating[40,42,57,58,75,86,96,97,101,110,117,119,128]	13 (10.4)
Leisure time[40,42,44,51,52,58,66,75,86,97,119,126,128]	13 (10.4)
Health preventive measures[12,66,86,106,117,119,123,128]	8 (6.4)
Establishing a routine[25,66,75,86,97,105]	6 (4.8)
Listening to music[42,128]	2 (1.6)
Altruism/helping others[121,133]	2 (1.6)
Technology and media	
Telehealth[12,31,60,63,68,71,72,77-79,81-83,91-93,98,102,104,108,109,111,113,114,119,125]	26 (20.8)
Time of exposure in media[25,38,40,42,51,70,75,86]	8 (6.4)
WhatsApp/chat support groups[57,78,81,95,119,125,126]	7 (5.6)
Specific media recommendations[47,64,84,145]	4 (3.2)
Education	
Accurate dissemination of COVID-19 info[62,63,76,84,87,99,102,112,113,116,123,125,126,129,133,134,144,148]	18 (14.4)
Stress management courses[87,99,101,102,106,112,113,117-119,121,123,137-139,142]	16 (12.8)
Keeping scientifically updated[42,48,52,59,63,82,87,116,123,124,129]	11 (8.8)
Web courses[34,44,49,55,63,94,113,129,142,145]	10 (8.0)
Recommendations to school/universities[85,140,141]	3 (2.4)

Continued on next page

Table 2 (*continued*)

	No. articles (%)
Governmental programs	
Social and economic support[12,25,64,67,76,88,90,92,96,99,103,117,119,127,133,135,148,150,151]	19 (15.2)
Increased mental health services[12,25,41,43,53,64,65,67,76,82,92,99,107,127,136,148,152]	17 (13.6)
Supporting victims of domestic violence[12,25,107,113]	4 (3.2)
General recommendations	
Avoid the term "social distancing"[90,99,101,130]	4 (3.2)
Clinical tips[70,77,90,93]	4 (3.2)
Spirituality and religiousness	
Pray[42,128]	2 (1.6)
Religious practices[94]	1 (0.8)
Health care institutions	
Safe environment/protective equipment[12,42,48,52,59,76,82,87,96,121,122,124,147]	13 (10.4)
Balanced shift rotations[12,42,48,76,82,87,96,122,129]	9 (7.2)
Place to rest[42,48,76,87,96,122,124]	7 (5.6)
Avoiding moral injury[74,89,122,129]	4 (3.2)
Role models[48,122]	2 (1.6)
Provide housing[96,124]	2 (1.6)
Physical intervention	
Muscle relaxation[32]	1 (0.8)

COVID-19 = coronavirus disease 2019.

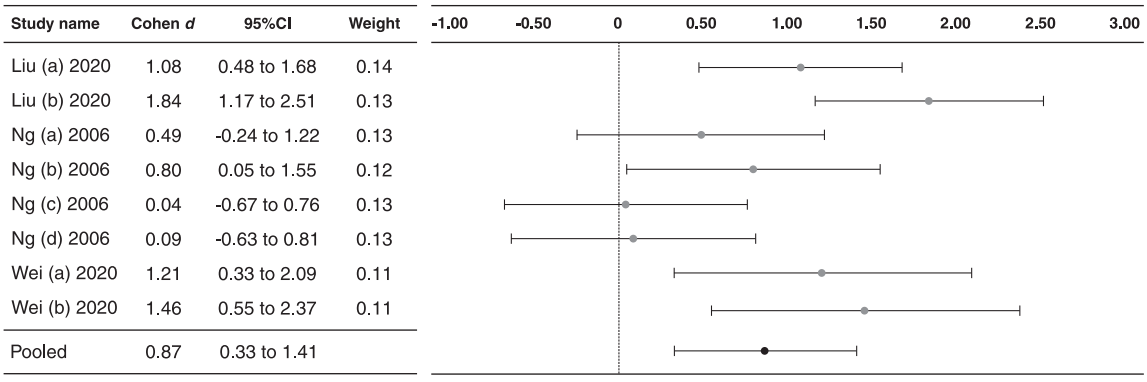

Figure 2 Meta-analysis of mental health intervention for coronavirus disease 2019 (COVID-19) and other coronaviruses. Pooled effect size: Cohen *d* = 0.87 (95% confidence interval [95%CI] 0.33-1.41), $p < 0.001$, $I^2 = 69.2\%$. Liu[32] (a) = anxiety; Liu[32] (b) = sleep quality; Ng[33] (a) = anxiety; Ng[33] (b) = depression; Ng[33] (c) = somatization; Ng[33] (d) = hostility; Wei[34] (a) = depression; Wei[34] (b) = anxiety.

Discussion and clinical recommendations

To the best of our knowledge, this is the first study to systematically evaluate interventions designed to improve mental health outcomes during and after coronaviruses infections. In the meta-analysis, interventions were effective in improving the general mental health outcomes (anxiety, depressive symptoms, sleep problems, hostility, and somatization) of individuals, but only when aggregated. When analyzing interventions for impact specifically on anxiety symptoms, the results were not significant.

Concerning the descriptive systematic review, we found a large body of scientific literature proposing mental health interventions, mostly based on low-quality levels of evidence (i.e., expert opinions or cross-sectional studies). Most articles were from China and the United States and focused on the novel SARS-CoV-2 infection. Below, we will discuss the most important findings from these studies for each intervention group, as well as propose future interventions for mental health practitioners, general clinicians, educators, and governmental leaders.

Psychological/psychiatric interventions

Psychiatric and psychological interventions were, by far, the most common strategies recommended. Most recommendations were aimed at preventing the development of PTSD,[154-156] given the increased risk of PTSD reported in other coronaviruses[6] and the H1N1 epidemic.[157] Notably, most experts recommended individual psychotherapies,[55,87] but also stressed the importance of hotlines[24,158] and peer support groups.[59,148] Certain individual interventions have more evidence for people facing acute stress,[159,160] such as Trauma-Focused Cognitive Behavioral

Table 3 Quality assessment of controlled randomized trials

Author	n	A	B	C	D	E	F	G	H	I	J	K	Total
Ng[33]	51	-	+	+	-	-	-	?	?	+	+	?	4
Liu[32]	51	?	?	+	-	-	-	?	?	+	+	?	3
Wei[34]	26	+	+	+	?	?	?	+	+	+	+	?	7

n = number of participants; A = randomization method; B = allocation concealed;
C = similar baseline; D = patient blinded; E = provider blinded; F = assessor blinded;
G = cointervention avoided; H = acceptable compliance; I = acceptable drop out;
J = timing of outcome of assessment similar and; K = intention to treat analysis.
+ indicates information provided; - indicates information not provided; ? indicates not possible to determine.

Therapy[161] and Prolonged Exposure Therapy.[162,163] Psychological First Aid (i.e., initial crisis interventions with the aim to stabilize survivors from disasters) is a subset of interventions that requires more investigation. Ng et al.[33] found a negative association of a debriefing technique with depressive symptoms 1 month after stress exposure. However, several other studies and expert consensus guidelines suggest that debriefing interventions following an acute stressor may be contraindicated, highlighting a greater risk of developing PTSD.[164]

Early psychopharmacological interventions were also recommended in some articles.[127] While there is a lack of studies investigating pharmacological interventions specifically for acute stress,[160] it is important to underscore the importance of avoiding iatrogenic contributors. For example, several studies have pointed out an increase of PTSD symptoms following the use of benzodiazepines for acute stress.[165,166] Thus, experts suggest that clinicians avoid using benzodiazepines to treat mild symptoms (e.g., mild anxiety, insomnia) of acute stress and adjustment disorders,[167] but more studies should be done to investigate these controversies.

Complementary and alternative therapies

Meditation, especially mindfulness,[34,46] yoga,[40,51] and breathing techniques,[34,121] were the most recommended complementary practices. There is a large body of evidence of the positive effects of these practices in mental health.[168] Mindfulness meditation has been used and validated for acute stress situations,[169] including those related to COVID-19.[34] It has been shown to have an effect on mood and anxiety, inducing neurobiological changes, even after 8-week meditation programs.[170,171] A recent systematic-review[172] did highlight possible adverse effects from meditation practices and meditation-based therapies, however, such as the emergence of depressive and anxiety symptoms, cognitive anomalies, and suicidal behavior. Based on these studies, we suggest that complementary and alternative practices (especially mindfulness) should be encouraged as a good and low-cost practice to alleviate and/or prevent mental health issues following traumatic periods/experiences. However, attention should be paid especially to moderate and severe cases, where these practices could be detrimental if not enhanced with specialized mental health care.

Self-care

Engaging in self-care practices is essential in promoting positive mental health. Several authors have pointed out the importance of exercise, eating habits, leisure time, sleep hygiene, establishing a routine, reducing alcohol intake, and spending more time with family and friends.[25,35] There is a large body of evidence that self-care behaviors can decrease the development of mental health issues and stimulate positive mental health in the general population, but also in in mental health practitioners.[173-175] Interestingly, two authors stressed the importance of altruistic behaviors in promoting mental health.[121,133] Previous articles have shown a positive relationship between altruistic behaviors and mental health outcomes,[176] though a recent cross-sectional study investigating the effect of altruism on mental health showed a negative relationship between high levels of altruism and negative affect during the COVID-19 pandemic.[177] This finding was corroborated by a large population-based study,[178] which can be explained due to the fact that highly altruistic people might engage less in self-care practices.

Institutions

It is critical that institutions provide a safe and healthy environment in order to foster personal growth and positive mental health outcomes among health care workers. Several experts recommended the importance of protecting health care workers from exposures to coronavirus, providing adequate personal protective equipment, setting balanced shift rotations, creating a comfortable place to rest, providing housing when needed, and providing positive role models for personal growth.[74,124,129] We suggest that institutions and governments should pay attention to and stimulate self-care behaviors of their professionals in order to alleviate their distress and promote better mental health. Special attention should be paid to low- and middle-income countries (LMIC) countries, where health professionals have an extremely high workload and are underpaid. Considerations may include increasing wages, reducing workloads, and affording professionals time to engage in self-care activities.[20]

Technology and media

In the midst of the ''technology era'' in health care services,[179] many online programs have been utilized to

support mental health during the COVID-19 pandemic, and some of them may become standard practices once the pandemic ends. Telehealth services,[145] including online psychological crisis intervention,[142] telephone support services,[102] online mental health services,[95] television-based interventions,[31] smartphone-based e-consults,[71] and the use of social media for psychological interventions[57] are some examples of successful programs developed this year. Leveraging such technologies has the potential to increase access to mental health care, create mentorship between mental health specialists and general practitioners in distant communities, and facilitate dissemination of general mental health recommendations.

Despite the important benefits of technology with regards to mental wellness, there are also some potential downsides. In LMICs, as well as for low-income individuals from developed nations, the lack of access to internet may create larger social and economic disparities. The increased exposure to internet and social media has already been associated with mental health issues, including decline in subjective well-being[180] and increased depressive symptoms.[181] Interestingly, Bessière et al.,[182] in a longitudinal study, found that using the internet for health purposes might be associated with increased depressive symptoms, while using it to communicate with family and friends might be associated with decreased symptoms of depression. The authors suggest that their results could be explained by an increase in rumination, unnecessary alarm, or over-attention to health problems. More studies are needed to explore the potential deleterious effects of telehealth and technology systems in psychiatric and psychological care. Mental health providers should be aware of these problems while evaluating individuals during pandemic situations.

Educational

The use of programs to educate laypersons and health care workers about stress management[137] and to disseminate reliable and scientifically updated information about the disease[63] might be an important strategy to reduce anxiety and increase self-confidence. Furthermore, the importance of maintaining online school and university classes and other web courses was also addressed by many experts[49,141] and seems to be associated with a sense of well-being and accomplishment. However, some concerns emerge in low income countries and low-income areas of other countries, where citizens might face serious economic issues during critical periods, and might not have access to internet or electronic devices.[183] Governments should work to increase access to the internet in low income and vulnerable populations, and mental health professionals are encouraged to develop educational programs for these patients.

Governmental programs

The negative mental health impact of economic crises[19,184] and previous pandemic outbreaks[6] has already been studied by many authors. It is crucial that during crises, government, especially from LMICs,[64] lead initiatives to prevent and address mental health issues, including suicidal behavior,[12] that might arise from distressing situations. Several mental health experts pointed out the importance of governments in lending social and economic support to individuals,[119,151] increasing mental health services,[53] and supporting victims of domestic violence.[25] During the COVID-19 pandemic, countries have developed many different economic interventions in order to ameliorate its impact on health.[185] More studies should be done to understand the exact impact of these initiatives in public health.

Spirituality and religiousness

There is a growing body of evidence highlighting the positive role of spirituality and religiousness in mental health.[186,187] However, few experts recommended spiritual or religious practices as a possible coping mechanism during any coronavirus epidemic. Notably, several groups around the world are developing strategies to deal with the growing spiritual struggle that people might face during a crisis, such as the development of hotlines focused in promoting spiritual care and fulfill the lack of religious support during quarantine.[158,188] However, more empirical studies should be done in order to investigate the exact impact of these religious/spiritual intervention strategies in mental health. Moreover, mental health providers should be aware of the spiritual needs of their patients, identifying if the use of religiousness and spirituality is functional or dysfunctional, and referring to religious leaders or chaplains if appropriate.

Physical interventions

Physical interventions, such as muscle relaxation techniques and yoga exercises, have also been reported by some experts as a tool to curtail anxiety and sleep disturbances during the COVID-19 pandemic. Liu et al.[32] found a positive effect on both anxiety and sleep quality for patients with COVID-19. This finding is consistent with a previous study that used the same technique with pregnant women[189] and breast cancer patients.[190] The underlying mechanism might be the balance between the anterior and hypothalamic nucleus and the reduction of sympathetic nervous system activity,[32] though further studies are needed.

General recommendations

Finally, several general recommendations with clinical tips for mental health practitioners were also published during the COVID-19 and other pandemics.[90,93] Interestingly, many experts recommended the avoidance of the term "social distancing," preferring "physical distancing" in order to reduce feelings of rejection among psychiatric patients.[90,130] To our knowledge, no study has empirically investigated the effect of this recommendation in clinical practice.

Limitations

This study has several limitations. First, we only included three databases, and articles published in other

databases might not have been included. Second, our search strategy is limited to only few mental health issues, potentially limiting generalization. Third, most articles included had a low level of evidence, with a great number of letters to the editor, opinions, editorials, recommendations, and case reports. Forth, due to the dynamic and continuous process of publications during COVID-19 pandemic, new articles may have been published in the months after this review. Fifth, our meta-analysis included only three articles, which could limit our findings. More RCTs are needed in order to overcome this limitation. Finally, we found a high heterogeneity among RCTs, including different intervention populations, different types of interventions, and different outcome measures. Such heterogeneity may have impacted the findings and interpretation of our meta-analysis.

Conclusions

The present review found that there are few clinical trials assessing the effectiveness of interventions to improve the mental health of individuals during coronavirus pandemics. Although the results were superior for the intervention groups as compared to the control groups for general mental health, these results relied on only three studies with limited quality. When analyzing individual outcomes, such as anxiety, the pooled results were not significant. However, in the systematic review, we found a large body of expert recommendations that can help health practitioners, institutional and governmental leaders, and laypersons cope with mental health issues during a pandemic, as well as during periods of social and economic crises. Furthermore, despite the low level of evidence, many of these recommendations can be generalized to routine daily practice in order to improve mental health and wellbeing. This is essential given that in many countries, and especially in developing countries, citizens will face years of social and economic adversity that will have a direct impact on the mental health of populations.

Disclosure

The authors report no conflicts of interest.

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Post-acute sequelae of SARS-CoV-2 associates with physical inactivity in a cohort of COVID-19 survivors

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The aim of this study was to determine whether Post-acute Sequelae of SARS-CoV-2 Infection (PASC) are associated with physical inactivity in COVID-19 survivors. This is a cohort study of COVID-19 survivors discharged from a tertiary hospital in Sao Paulo, Brazil. Patients admitted as inpatients due to laboratory-confirmed COVID-19 between March and August 2020 were consecutively invited for a follow-up in-person visit 6 to 11 months after hospitalization. Ten symptoms of PASC were assessed using standardized scales. Physical activity was assessed by questionnaire and participants were classified according to WHO Guidelines. 614 patients were analyzed (age: 56 ± 13 years; 53% male). Frequency of physical inactivity in patients exhibiting none, at least 1, 1–4, and 5 or more symptoms of PASC was 51%, 62%, 58%, and 71%, respectively. Adjusted models showed that patients with one or more persistent PASC symptoms have greater odds of being physically inactive than those without any persistent symptoms (OR: 1.57 [95% CI 1.04–2.39], $P = 0.032$). Dyspnea (OR: 2.22 [1.50–3.33], $P < 0.001$), fatigue (OR: 2.01 [1.40–2.90], $P < 0.001$), insomnia (OR: 1.69 [1.16–2.49], $P = 0.007$), post-traumatic stress (OR: 1.53 [1.05–2.23], $P = 0.028$), and severe muscle/joint pain (OR: 1.53 [95% CI 1.08–2.17], $P = 0.011$) were associated with greater odds of being physically inactive. This study suggests that PASC is associated with physical inactivity, which itself may be considered as a persistent symptom among COVID-19 survivors. This may help in the early identification of patients who could benefit from additional interventions tailored to combat inactivity (even after treatment of PASC), with potential beneficial impacts on overall morbidity/mortality and health systems worldwide.

COVID-19 pandemic is raising a devastating impact on public health, resulting in millions of hospitalizations and deaths globally[1]. Among survivors, the high occurrence of patients reporting post-acute sequelae of SARS-CoV-2 (PASC) is a great cause of concern, as it threatens health systems worldwide. This condition, also known as "long COVID", is defined as the illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection, usually within 3 months from the onset of COVID-19, with symptoms and effects that last

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	All patients (n = 614)
Age, median (range), years	56 (18–87)
Sex, n (%)	
Female	287 (46.7%)
Male	327 (53.3%)
Race, n (%)	
White	86 (14.0%)
Black	238 (38.7%)
Pardo[a]	283 (46.1%)
Asian	7 (1.2%)
Socioeconomic status, n (%)	
Low	57 (9.3%)
Middle	311 (50.6%)
High	246 (40.1%)
Smoking status, n (%)	
Never	386 (62.9%)
Current/others	228 (37.1%)
Hospital Length of Stay, median (range), days	12 (2–163)
Pre-existing conditions, n (%)	
Hypertension	360 (58%)
Type 2 Diabetes	215 (35%)
Obesity (BMI ≥ 30 kg/m^2)	106 (17%)
ICU Admission, n (%)	338 (55%)
Use of Invasive Mechanical Ventilation, n (%)	231 (37%)

Table 1. Sociodemographic and clinical characteristics of patients. *BMI* Body mass index, *ICU* Intensive care unit. [a]Pardo is the exact term used in Brazilian Portuguese, meaning "mixed ethnicity," according to the Brazilian Institute of Geography and Statistics.

for at least 2 months[2]. Early reports revealed that around 76% of patients reported at least 1 persistent symptom 6 months following hospital discharge[3], with fatigue, dyspnea, cough, headache, loss of taste or smell, and cognitive or mental health impairments (e.g., anxiety or depression) being the most commonly reported symptoms[4–7].

Physical inactivity (i.e., < 150 min/week at moderate-to-vigorous physical activity) is widely recognized as an independent risk factor for impaired functional status[8], musculoskeletal disorders[9], anxiety and depression[10], and all-cause mortality[11]. Only a single study showed that patients who experienced persistent symptoms 6 months after COVID-19 reported lower physical activity levels compared to the pre-infection period[12]. Considering the detrimental effects that physical inactivity may have upon overall health status and quality of life in COVID-19 survivors, it is of public health importance to determine the risk factors related to PASC that may predispose to physical inactivity and help to early identify individuals that are more likely to be physically inactive.

Therefore, we aimed to determine whether PASC are associated with physical inactivity in a cohort of 614 COVID-19 survivors who underwent in-person multidisciplinary assessments conducted 6–11 months following hospitalization in a tertiary hospital in Brazil.

Results

A total of 749 eligible individuals attended the in-person follow-up assessment; 614 had complete data and were included in the analysis. Table 1 shows the characteristics of these patients. The sample comprised patients of both sexes (53% male) aged 56 ± 13 years. The frequency of low, middle, and high socioeconomic status was 9%, 50% and 40%, respectively. This is a similar profile to that of the city of Sao Paulo, according to the National Household Sample Survey (*Pesquisa Nacional por Amostra de Domicílio*—PNADC—2021) from the Brazilian Institute of Geography and Statistics[13]. Thirty-seven percent of the patients were smoking at baseline. Prevalence of current hypertension, type 2 diabetes, and obesity were 58%, 35%, and 17%, respectively. Fifty five percent of the patients required intensive care and 37% used invasive mechanical ventilation. Only 40% of the patients met the physical activity recommendations. Table 2 shows the prevalence of physical inactivity according to sex and age.

Prevalence of physical inactivity in patients exhibiting none, at least 1, 1–4, and 5 or more PASC symptoms were 51%, 62%, 58%, and 71%, respectively. The frequency of physical inactivity in patients reporting different PASC were: dyspnea (77%), fatigue (69%), severe muscle/joint pain (66%), insomnia (66%), post-traumatic stress disorder (65%), memory impairments (65%), anxiety (65%), taste (65%) and smell (63%) loss, and depression (62%). Table 3 details the prevalence of physical inactivity according to the presence of post-acute sequelae of SARS-CoV-2.

The adjusted model controlling for confounders (i.e., age [< 60 and ≥ 60 years old], sex [male or female], intensive care unit admission [yes or no], invasive mechanical ventilation [yes or no], hospital length of stay [< 15 and ≥ 15 days], hypertension [yes or no], type 2 diabetes [yes or no], and obesity [BMI < 30 or BMI ≥ 30]) showed

Physical inactivity (< 150 min/week), n (%)	All patients (n = 614)
Total	369 (60%)
Female	176 (61%)
Male	193 (59%)
< 60 years old	195 (54%)
≥ 60 years old	174 (68%)

Table 2. Prevalence of physical inactivity according to sex and age.

	Physically inactive/physically active (%)
No PASC	51/49
At least 1 symptom	62/38
1–4 symptoms	58/42
5 or more symptoms	71/29
Dyspnea	77/23
Fatigue	69/31
Severe muscle/joint pain	66/34
Insomnia	66/34
Post-traumatic stress disorder	65/35
Memory impairments	65/35
Anxiety	65/35
Taste loss	65/35
Smell loss	63/37
Depression	62/38

Table 3. Relative frequency of physically inactive and active individuals (> 150 min/week) according to the presence of post-acute sequelae of SARS-CoV-2 evaluated 6–11 months following hospitalization. *PASC* Post-acute sequelae of SARS-CoV-2 infection.

that patients with one or more persistent symptoms have greater odds of being physically inactive than those who did not experience any persistent symptoms (OR: 1.57 [95% CI 1.04–2.39], $P = 0.032$) (Fig. 1). In addition, patients reporting 5 or more persistent symptoms showed greater odds of being physically inactive than those without persistent symptoms (OR: 2.38 [95% CI 1.44–3.97], $P = 0.001$) (Fig. 1).

Adjusted models also showed that severe muscle/joint pain (OR: 1.53 [95% CI 1.08–2.17], $P = 0.011$), fatigue (OR: 2.01 [1.40–2.90], $P < 0.001$), post-traumatic stress (OR: 1.53 [1.05–2.23], $P = 0.028$), insomnia (OR: 1.69 [1.16–2.49], $P = 0.007$), and dyspnea (OR: 2.22 [1.50–3.33], $P < 0.001$) were associated with greater odds of being physically inactive (all $P < 0.05$; Fig. 2). Importantly, fatigue and dyspnea remained as statistically significant predictors of physical inactivity, even after adjusting P-value for multiple comparisons (both $P < 0.005$; Fig. 2). Conversely, memory impairments, depression, anxiety, taste, and smell loss did not significantly associate with physical activity (all $P > 0.05$) (Fig. S1).

Discussion

The aim of this study was to examine the associations between PASC and physical inactivity in a cohort of COVID-19 survivors (most of them admitted at ICU with pre-existing comorbidities) 6–11 months following hospitalization. The main findings are severalfold: (i) The frequency of physical inactivity was substantive among patients with PASC (60%); (ii) PASC was associated with 57% greater odds of physical inactivity; (iii) the presence of ≥ 5 persistent symptoms vs. none increased the odds of physical inactivity by 138%; (iv). Namely, dyspnea (132%), fatigue (101%), insomnia (69%), post-traumatic stress (53%), and severe muscle/joint pain (53%) were associated with greater odds of physical inactivity. This study provides novel data suggesting that PASC is associated with physical inactivity, which itself may be considered an expected persistent feature among COVID-19 survivors.

There is a growing body of knowledge calling the attention to a high prevalence of PASC worldwide[4–7]. Indeed, a significant proportion of COVID-19 survivors may still present with physical, mental, or cognitive symptoms 6–12 months after the acute infection, particularly in those following ICU treatment[4,14–18]. Whether PASC are risk factors predisposing to a physically inactive lifestyle was so far unexplored.

In our cohort of patients followed 6–11 months after hospitalization in a tertiary hospital, roughly 60% were physically inactive, which exceeds inactivity estimates of 47% for individuals of similar age observed in a population-based study in Brazil[19]. Interestingly, adjusted models suggested that PASC may predispose to physical inactivity, particularly when multiple symptoms are present. We were also able to identify specific symptoms predicting physical inactivity: severe muscle/joint pain, fatigue, post-traumatic stress, insomnia, and dyspnea.

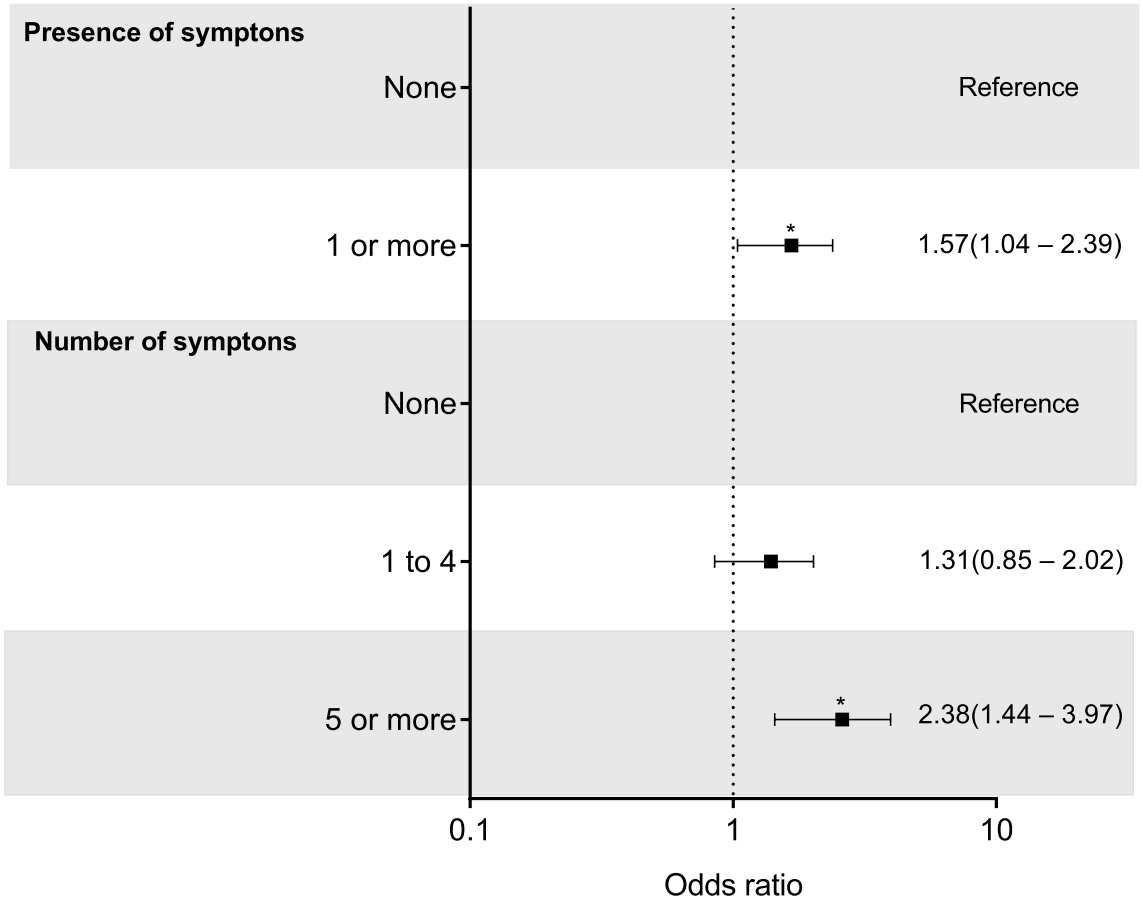

Figure 1. Multivariate-adjusted logistic regression analysis (odds ratio [(95% CI]) of the association between presence and number of persistent symptoms related to COVID-19 (i.e., none, 1–4 and ≥ 5 symptoms) with physical inactivity (< 150 min/week of moderate-to-vigorous activity). *indicates $P < 0.05$;

Importantly, fatigue and dyspnea remained as significant predictors even after adjusting *P*-value using a highly conservative approach (i.e., Bonferroni correction). These results are of relevance as both fatigue and dyspnea are very frequent PASC and, therefore, may increase the odds to physical inactivity and, ultimately, the risk of poor health outcomes. Some caution should be taken when interpreting these findings, as the design of this study does not allow causative inferences, however plausibility does exist to conjecture that these symptoms, especially when combined, may prevent one from achieving the recommended levels of physical activity.

To the best of our knowledge, this study is the first to investigate associations between individual PASC symptoms with physical inactivity. The adjusted regression models showed that not all PASC symptoms were associated with physical inactivity. The significant associations between specific PASC symptoms (i.e. fatigue, pain, dyspnea, and insomnia) and reduced physical activity could be mediated by different COVID-related pathologies, including persistent pulmonary[20], renal[21] or cardiovascular[22] dysfunction. A proportion of PASC cases may also exhibit a form of myalgic encephalomyelitis/chronic fatigue syndrome [23], which is directly associated with signs of persistent systemic inflammation[24] and can potentially lead to hypoactivity. Regarding mental symptoms, the finding that post-traumatic stress was more related to physical inactivity than depression or anxiety is also potentially interesting, indicating that there may be specific psychiatric manifestations that predispose to physical inactivity in PASC.

Independently of the pathophysiological bases underlying the presence of physical inactivity in association with PASC, an inactive lifestyle is a risk factor that has the potential to increase the demand on health systems worldwide, through increasing both the incidence and aggravation of chronic conditions[11]. Moreover, physical inactivity is an independent risk factor strongly associated with increased mortality; estimates using population attributed fractions suggested that physical inactivity can be responsible for 9% of all-cause mortality worldwide[25]. Importantly, distinct clinical populations have demonstrated a sustained decline in physical activity level after hospital discharge[26,27]. For instance, patients with chronic obstructive pulmonary disease hospitalized to treat acute exacerbation showed a reduction of physical activity levels 1 month after hospital discharge, especially those with more pronounced muscle weakness at the end of the hospitalization period[26].Recently, a study observed a significant decrease in self-reported walking time 6 months after the onset of symptoms of COVID-19[12]. In this scenario, if COVID-19, and notably PASC, can result in sustained physical inactivity, patients' survival may be also impacted. Given the multiple types of organ system dysfunctions that may contribute to PASC, further studies are warranted to investigate which of those pathologies may most significantly impact

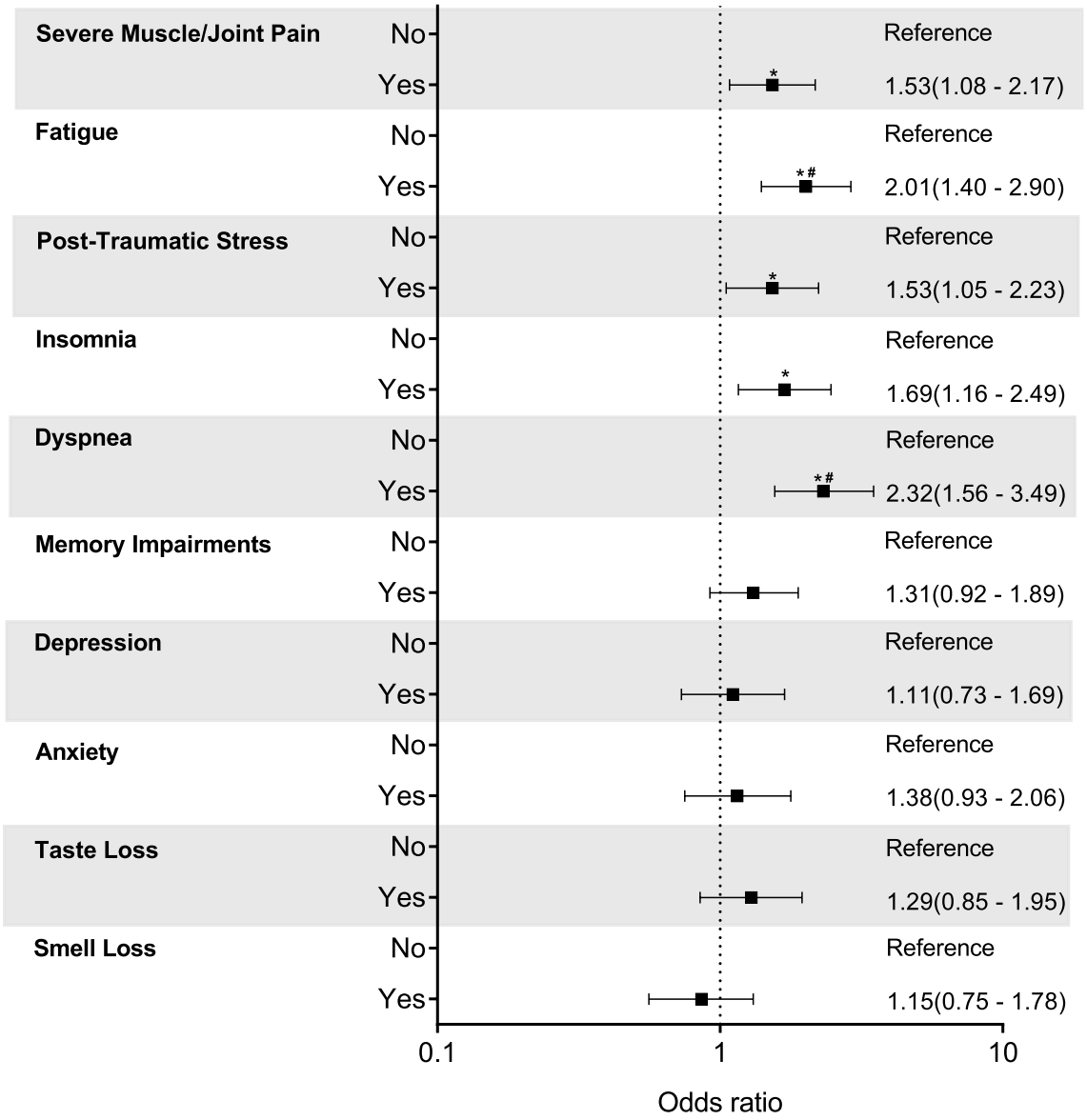

Figure 2. Multivariate-adjusted logistic regression analyses (odds ratio [(95% CI]) of the association between persistent symptoms related to COVID-19 (Severe muscle/joint pain, fatigue, post-traumatic stress, insomnia, dyspnea, memory impairments, depression, anxiety, taste loss, and smell loss) with physical inactivity (< 150 min/week of moderate-to-vigorous activity). *Unadjusted $P < 0.05$; # adjusted $P < 0.005$ (Bonferroni correction).

on the emergence of PASC-related physical inactivity—an emerging risk factor that may lead to higher rates of morbidity and mortality. Of relevance, the reversal of inactivity has the potential to attenuate physical, mental and cognitive symptoms that encompass PASC. Therefore, early identification of individuals that could benefit from interventions specifically tailored to promote physical activity may be key to mitigate, at least partially, the burden associated with PASC. Further studies are also warranted to investigate the accurate prevalence and prognostic value of physical inactivity among COVID-19 survivors, and the potential role of vaccination (and perhaps other therapies) on the prevention of inactivity, as seen with other PASC symptoms[25].

This study is not free of limitations. The observational cross-sectional design hampers establishing cause-and-effect relationships as previously noted, and it may lead to reverse causation bias (i.e., physically inactive individuals may also be prone to PASC, such as fatigue, muscle/joint pain, dyspnea etc.). Physical activity levels were assessed through a questionnaire and reflect the week prior to follow-up assessments. Moreover, the use of questionnaire to assess physical activity is prone to recall bias and overreporting.

In conclusion, among a cohort of COVID-19 survivors showing a high frequency of PASC 6–11 months following hospitalization, the number and type of PASC was predictive of physical inactivity. The novel data provided by this study warrant further investigations to ascertain which COVID-related organ system pathologies may most significantly contribute to the emergence of physical inactivity and help in the early identification of recovering COVID-19 patients who might benefit from interventions to combat inactivity. Considering the

potential impact of this risk factor on overall morbidity and mortality and, hence, health systems, healthcare professionals and policy makers should be concerned about COVID-related physical inactivity.

Methods

Study design and participants. This study is part of HCFMUSP PASC Initiative, which is a prospective, multidisciplinary cohort study of COVID-19 survivors discharged from the largest tertiary hospital of Latin America (Clinical Hospital, School of Medicine of the University of Sao Paulo).

All patients aged ≥ 18 years who had been admitted (for at least 24 h) as inpatients to our hospital due to laboratory-confirmed COVID-19 between March and August 2020 were consecutively invited for a follow-up in-person visit between October 2020 and April 2021. Exclusion criteria were: previous diagnosis of dementia or end-stage cancer, nosocomial COVID-19 infection, living in long-term care facilities or with insufficient mobility to leave home, and suspected reinfection at the time of follow-up assessment. The details on the study protocol and planned measures have been thoroughly described elsewhere[28].

This study was approved by the local Ethics Committee (Ethics Committee Approval Number (approval numbers: 4.270.242, 4.502.334, 4.524.031, 4.302.745 and 4.391.560) and registered at the Brazilian Registry of Clinical Trials (https://ensaiosclinicos.gov.br/). All patients provided written informed consent before entering the study. This manuscript was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement. Furthermore, all methods were performed in accordance with the relevant guidelines and regulations.

Data collection. All patients were evaluated between 6 and 11 months following hospitalization. In brief, patients underwent semi-structured interviewing regarding sociodemographic characteristics, occupational history, lifestyle habits (tobacco and physical activity levels), and self-evaluated health and medical history (with emphasis on previous and present comorbidities, cardiopulmonary symptoms, and medication regimen), and completed a multidisciplinary battery of objective physical assessments and laboratory tests conducted by clinicians and trained non-medical research workers (see reference[28] for details). Smoking status refers to follow-up assessment (6–11 months after hospital discharge), while pre-existing conditions refers to assessments at the time of hospital admission.

Data from interviews, scales and complementary examinations were captured and stored using real-time web-based case report forms developed on a Research Electronic Data Capture (REDCap) system hosted at the hospital[29]. A team of REDCap experts managed the database and provided access for the different research groups to conduct interim and final statistical analyses.

Physical inactivity. Physical activity was assessed during the in-person follow-up visits by experienced researchers using The International Physical Activity Questionnaire-Short Form (IPAQ). In brief, IPAQ inquiries about physical activity in the past 7 days. Time spent in each activity was calculated as the number of days multiplied by the number of hours reported. Participants were classified as physically inactive according to WHO Guidelines (i.e., < 150 min/week of moderate-to-vigorous intensity physical activity).

Post-acute sequelae of SARS-CoV-2 infection. For the present investigation, we used data regarding ten self-reported symptoms deemed as relevant to PASC[9,30] which were evaluated using standardized scales applied by specialized teams during the in-person visits, including: post-traumatic stress disorder[31], anxiety and depression[32], insomnia[33], subjective memory impairment[34], fatigue[35], dyspnea[36], severe muscle/joint pain[36], and taste and smell loss)[37]. For all dependent variables, validated scale cutoffs were used to generate categorical 'yes–no' variables. For all variables but post-traumatic stress, subjects were asked about the presence of symptoms before hospitalization, in order to confirm that the onset of symptoms occurred after COVID-19.

Statistical analyses. Characteristics of patients 6–11 months following hospitalization are presented as absolute (n) and relative (%) frequency. The association of the outcome of interest (physical inactivity) was assessed by means of multivariable logistic regression adjusted by age [< 60 and ≥ 60 years old], sex [male or female], intensive care unit admission [yes or no], invasive mechanical ventilation [yes or no], hospital length of stay [< 15 and ≥ 15 days] and pre-existing conditions (hypertension [yes or no], type 2 diabetes [yes or no], and obesity [BMI < 30 or BMI ≥ 30]). Confounders were selected based on a Direct Acyclic Graph (DAG, www.dagitty.net), which is a causal diagram based on causal relations between the exposure, outcome, and potential confounders[38]. The DAG was developed from a priori knowledge to identify a minimum yet sufficient set of covariates to remove confounding factors from the statistical analysis[39] (Fig. S1). Odds ratios were calculated along their corresponding 95% confidence intervals (95% CI). For associations between each PASC (i.e., post-traumatic stress disorder, anxiety and depression, insomnia, memory impairment, fatigue, dyspnea, severe muscle/joint pain, and taste and smell loss) and physical inactivity, significance level was set at $P \leq 0.005$ (according to Bonferroni correction for multiple tests). All other significance levels were set at $P \leq 0.05$. All analyses were performed in the statistical environment R (version 3.5.3; R Core Team 2020).

Data availability

All background information on individuals and clinical information for patients included in this study are available from corresponding author on reasonable request.

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Author contributions
The authors' contributions were as follows: Designed research: S.G., B.G., R.F.D., F.P., M.I., V.R., E.K., L.R.B., O.V.F., C.R.R.C., G.F.B., H.R.; Conducted research: S.G., A.L.A., G.N.O.J.; Provided essential materials: R.F.D., F.P., M.I., V.R., E.K., L.R.B., O.V.F., C.R.R.C., G.F.B.; Analyzed data/Statistical analysis: S.G., B.G., H.R.; Wrote paper: S.G., B.G., H.R.; Writing—review and editing: A.L.A., G.N.O.J., R.F.D., F.P., M.I., V.R., E.K., L.R.B., O.V.F., C.R.R.C., G.F.B. Primary responsibility for final content: HR. All authors: read and approved the manuscript.

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Competing interests
The authors declare no competing interests.

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Post-acute sequelae of SARS-CoV-2 infection (PASC): a protocol for a multidisciplinary prospective observational evaluation of a cohort of patients surviving hospitalisation in Sao Paulo, Brazil

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ABSTRACT

Introduction COVID-19 may lead to persistent and potentially incapacitating clinical manifestations (post-acute sequelae of SARS-CoV-2 infection (PASC)). Using easy-to-apply questionnaires and scales (often by telephone interviewing), several studies evaluated samples of COVID-19 inpatients from 4 weeks to several months after discharge. However, studies conducting systematic multidisciplinary assessments of PASC manifestations are scarce, with thorough in-person objective evaluations restricted to modestly sized subsamples presenting greatest disease severity.

Methods and analyses We will conduct a prospective observational study of surviving individuals (above 18 years of age) from a cohort of over 3000 subjects with laboratory-confirmed COVID-19 who were treated as inpatients at the largest academic health centre in Sao Paulo, Brazil (Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo). All eligible subjects will be consecutively invited to undergo a 1–2-day series of multidisciplinary assessments at 2 time-points, respectively, at 6–9 months and 12–15 months after discharge. Assessment schedules will include detailed multidomain questionnaires applied by medical research staff, self-report scales, objective evaluations of cardiopulmonary functioning, physical functionality and olfactory status, standardised neurological, psychiatric and cognitive examinations, as well as diagnostic laboratory, muscle ultrasound and chest imaging exams. Remaining material from blood tests will be incorporated by a local biobank for use in future investigations on inflammatory markers, genomics, transcriptomics, peptidomics and metabolomics.

Ethics and dissemination All components of this programme have been approved by local research ethics committees. We aim to provide insights into the frequency and severity of chronic/post-COVID multiorgan symptoms, as well as their interrelationships and associations with acute disease features, sociodemographic variables and

Strengths and limitations of this study

- We have four strengths: first, we will invite consecutively all subjects from a large COVID-19 sample who survived hospitalisation to participate of our systematic, prospective evaluation of multiorgan PASC manifestations.
- Second, the same detailed in-person assessments (surveys using standardised questionnaires/scales and objective assessments of functioning) will be applied to all individuals, rather than being partitioned among subsamples defined based on previous disease severity.
- Third, we will have access to baseline data regarding acute COVID-19 features and details of in-hospital stay that were recorded prospectively.
- Fourth, information regarding potential predictors of outcome will include both individual-level and neighborhood-level environmental variables, in addition to data on medical comorbidities.
- The limitations are that current re-infection will be ruled-out only by the absence of clinical signs and symptoms; and that subjects will be from one single hospital site (although large-sized and homogeneous in its administrative, diagnostic and treatment protocols).

environmental exposures. Findings will be disseminated in peer-reviewed journals and at scientific meetings. Additionally, we aim to provide a data repository to allow future pathophysiological investigations relating clinical PASC features to biomarker data extracted from blood samples.
Trial registration number RBR-8z7v5wc; Pre-results.

INTRODUCTION

COVID-19, caused by infection with the SARS-CoV-2, is a contagious disease with potentially severe and incapacitating manifestations. COVID-19 currently challenges scientific communities worldwide to rapidly produce findings to inform treatment and rehabilitation strategies for both its acute symptoms and possible long-term consequences, with an unprecedented need for multidisciplinary collaboration. Since the SARS-CoV-2 enters host cells via the ACE 2 receptor expressed in several tissues, complications of COVID-19 involving multiple organs are expected. There is emerging evidence that these symptoms may be persistent, characterising what is now being called post-acute sequelae of SARS-CoV-2 infection (PASC). A few reports have suggested that many patients display subacute, multiorgan symptoms 1 month to approximately 3 months from the onset of COVID-19 symptoms,[1–9] when replication-competent SARS-CoV-2 can no longer be isolated.[1] There is also a need for systematic studies to increase knowledge about longer-term PASC (or 'long COVID-19') manifestations, when abnormalities persist beyond 12 weeks of the onset of acute COVID-19 and cannot be explained by other diagnoses.[1 10] In a study that reassessed 1733 patients with COVID-19 after 6 months of in-hospital discharge (in China), 76% of patients reported at least 1 symptom.[11] Findings of multiple organ manifestations were detected, including pulmonary dysfunction, muscle weakness, kidney dysfunction, newly onset diabetes, venous thromboembolism, anxiety, depression and sleep disturbances. In another investigation of COVID-19 inpatients (n=478) conducted in France, persistent manifestations (including dyspnoea, fatigue and cognitive deficits) were also found frequently (in 51% of subjects) 4 months after discharge.[12]

Sao Paulo, Brazil, is one of the most densely populated and urbanised cities from low-income and middle-income countries (LMIC). During the 2020 COVID-19 outbreak, our largest public-funded academic health centre (Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo; HCFMUSP) undertook an operation that turned its main hospital into a fully dedicated inpatient facility for individuals presenting moderate to severe COVID-19.[13] A total of 900 beds were made available at this site, more than 300 of which in intensive care units (ICUs). Over 3500 inpatient admissions due to suspected SARS-CoV-2 infection took place from 30th March through August 2020.

This manuscript describes the methods for an observational prospective follow-up investigation of adult survivors from the above cohort, with two multidisciplinary evaluations planned to be conducted, respectively, at 6–9 months and 12–15 months after in-hospital discharge. Investigations of sequelae after recovery from acute COVID-19 in LMIC settings are relevant to confirm and extend findings of studies conducted elsewhere, and to assist in the planning of local rehabilitation programmes. Our main objectives are to describe the frequency and severity of multidomain symptoms and indices of disability using comprehensive assessment schedules; to investigate significant associations between persistent COVID-19 manifestations and variables related to the acute disease severity, lifestyle habits, COVID-related psychosocial stressors, sociodemographic status and urbanisation-related environmental risk factors; and to assess the potential for reversibility of PASC. Additionally, this multidisciplinary programme will create a data repository to allow further investigations on how different PASC subsyndromes may relate to each other, and future pathophysiological studies relating distinct clinical features of PASC to biomarker data extracted from blood samples obtained from the same subjects.

METHODS

The main components of the protocol were registered at the Brazilian Registry of Clinical Trials (https://ensaiosclinicos.gov.br/). Any relevant changes will be entered at that site.

Study design and setting

We will consecutively invite for the study all eligible adult individuals (≥18 years) who survived moderate or severe COVID-19 requiring hospital treatment for at least 24 hours, and who had their aetiological diagnosis confirmed by reverse-transcriptase PCR (RT-PCR) on swab-collected nasopharyngeal and/or oropharyngeal samples, or by ELISA to detect serum antibodies (in subjects for whom an RT-PCR test collected up to the 10th day of symptom onset was not available). From 3007 confirmed cases of COVID-19, a total of 1998 individuals required ICU care at any point during hospitalisation. Our survival rate immediately after in-hospital stay was over 60% from 30 March 2020 through August 2020, similarly to the figures reported for the Southeastern region of Brazil (where Sao Paulo is located) in retrospective nationwide analyses.[14] This provides a pool of over 1800 potential participants for the current investigation.

Rather than describing a single-study protocol, we summarise herein the methods of an aggregate of several longitudinal projects that were simultaneously proposed and ethically approved by individual research teams at HCFMUSP. These groups were joined together to collect data in an integrated fashion in order to: minimise patient inconvenience (concentrating several assessments on a single day); optimise use of resources; and maximise multidisciplinary interchange of experiences, fostering a comprehensive outlook on the individual health needs of study subjects.[1]

Invitations will begin as of 20 October 2020 and will continue until January 2022.

There are other ongoing research initiatives in the metropolitan region of Sao Paulo with assessments of large groups of individuals with laboratory-confirmed COVID-19 of different degrees of severity, also involving teams based at HCFMUSP.[15–17] Collaboration with these teams may allow us to compare results from our moderate to severe COVID-19 cohort with the findings obtained in demographically matched control groups of mild COVID-19 sufferers who recovered fully within 2–4 weeks after the disease onset. Conversely, we are not currently able to recruit an additional control group of patients admitted to hospital due to other infectious diseases such as community-acquired pneumonia (CAP) or dengue, as HCFMUSP admissions for such conditions have been substantially reduced during the ensuing COVID-19 pandemics.

All reports from this cohort study investigation will follow the principles of the Strengthening the Reporting of Observational Studies in Epidemiology statement.[18]

Patient and public involvement statement

There was no patient or public involvement in the design of this study.

Assessment schedules

A flow chart displaying the steps for the selection and multidisciplinary evaluation of potential participants at 6–9 months after in-hospital discharge is provided in figure 1.

A copy of all interview guides is provided as online supplemental material.

Semi-structured medical interviewing, vital sign and anthropometric measurements, physical and neurological examinations, and assessment of mental health status

A general interview will include selected items from the baseline interview of the Brazilian Longitudinal Study of Adult Health (ELSA-BRAZIL)[19] regarding sociodemographic characteristics, occupational history and retirement status (pre-COVID-19 and post-COVID-19), as well as lifestyle habits (food consumption and smoking) and self-rated health and medical history (with emphasis on previous and present comorbidities, cardiopulmonary symptoms and medication use). Additional questions will cover dermatological, endocrinological, gastrointestinal, haematological, nephrological, otorhinolaryngological and lower urinary tract symptoms, as well as episodes of re-infection and visits to emergency care and other hospital facilities since discharge. The questions in each medical domain were designed to allow self-rated assessments of: pre-COVID-19 symptoms; symptoms that emerged during acute COVID-19; and persistent symptoms since discharge. The interview also includes the Medical Research Council (MRC) Dyspnoea Scale,[20 21] the Clinical Frailty Scale,[22] the short form of the International Physical Exercise Questionnaire[23] and questions regarding current social support.

The interview will be divided in two consecutive subsessions, covering, respectively: its medical domains (conducted by a trained physician) and a brief systematic

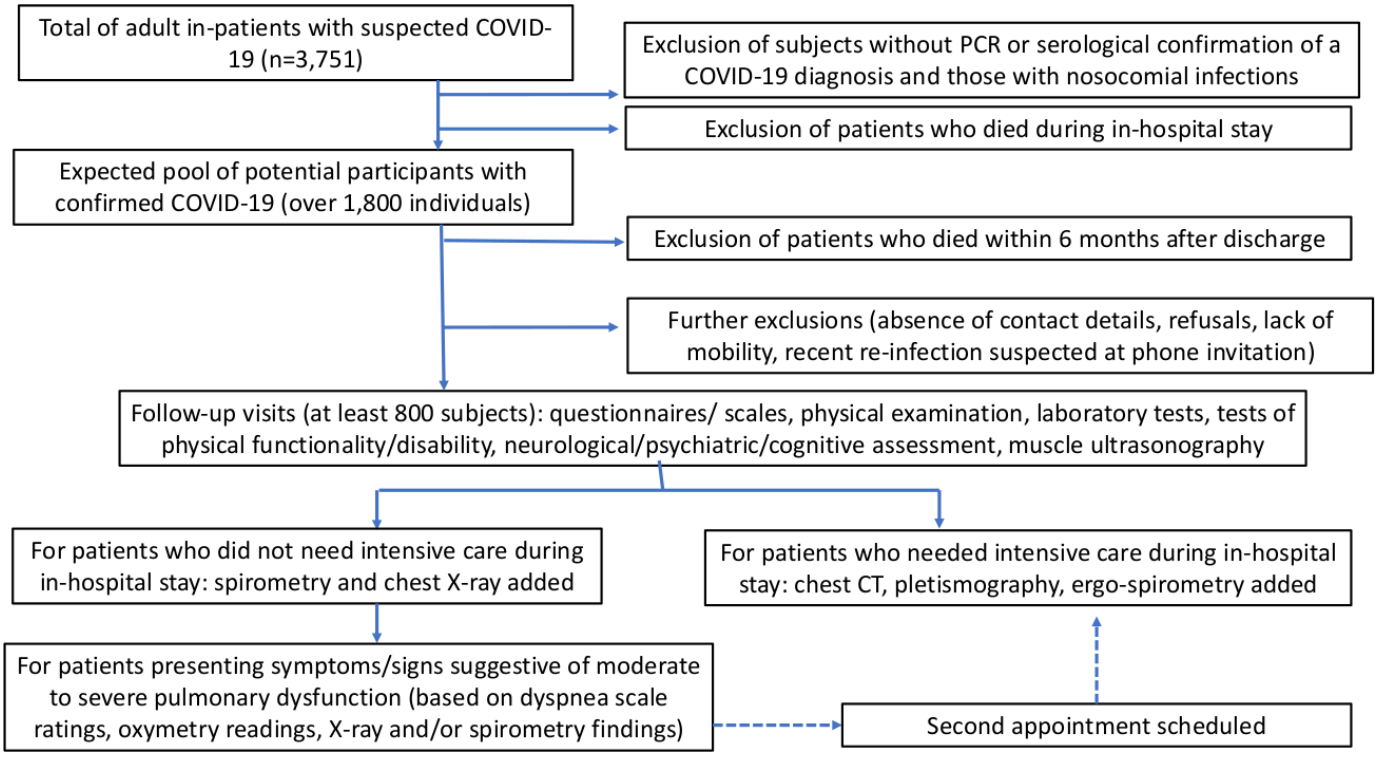

Figure 1 Flow chart and evaluation of potential participants at 6–9 months after in-hospital discharge.

physical examination, and the remaining items, conducted by trained non-medical research workers.

Digital electrocardiographic data will be acquired. Vital sign measurements will include resting arterial blood pressure and heart rate, pulse oxygen saturation, cardiac output, stroke volume, cardiac index, partial pressure of carbon dioxide and partial pressure of oxygen, all obtained with a fingertip device (MTX Cnoga) based on optical technology using colour image sensors.[24] Anthropometric measurements will include body mass index, waist circumference, arm circumference and calf perimeter.

For the neurological assessment, we adapted the WHO screening tool devised for neuroepidemiology investigations in LMIC.[25 26] This included a 15-item questionnaire adapted to account for COVID-related timing of symptoms and a 7-step screening for neurological signs, followed by a deeper, structured neurological examination in all cases, regardless of the results of the screening tool. Subjects will also be inquired about psychiatric manifestations in a comprehensive fashion, using structured instruments for the detection of common mental disorders, anxiety, depression and suicidal thinking,[27–30] post-traumatic stress disorder,[31] alcohol abuse[32] and psychotic symptoms.[33] The mental health assessment will also include questions regarding: the impact of COVID-19 on socioeconomic aspects of the subject's life; changes in patterns of substance use following COVID-19 (alcohol, tobacco, sedative drugs, opioids and others); and sexual dysfunction symptoms.

Laboratory testing and biobank storage of biological samples

Blood samples will be collected for serology COVID-19 testing and diagnostic laboratory tests. Urine samples will be collected for creatinine levels, urinalysis and assessment of kidney injury biomarkers. Remaining material from the samples collected for diagnostic tests will be incorporated by the biobank of the Tropical Medicine Institute (TMI) (which is also a part of HCFMUSP) for use in biomarker-based research investigations; DNA samples will be extracted from lymphocytes, and the PAXgene system will be used for RNA collection. Plasma samples will be extracted from blood collected using EDTA tubes, centrifuged and stored at −80° freezers. This biobank data will be used in future investigations evaluating relationships among PASC manifestations and data on inflammatory markers, genomics, transcriptomics, peptidomics and metabolomics.

Evaluation of disability, quality-of-life and physical functioning

Scales for the assessment of physical functioning, disability and quality-of-life (QOF) will include: the 5-level version of the EQ-5D scale to measure and value generic health;[34] the WHO Disability Assessment Schedule 2.0;[35] the Functional Independence Measure;[36] the Functional Oral Intake Scale;[37] the Post-COVID-19 Functional Status Scale;[38] the Functional Assessment of Chronic Illness Therapy-Fatigue Scale;[39] the Epworth Sleepiness Scale;[40] the Insomnia Severity Index;[41] and the Visual-Analogue Scale for pain.[42]

Structured physical tests will include: manual muscle testing using the MRC strength grading system;[43] the 10-m walk test;[44] the timed up and go test;[45] a measurement of hand grip strength[46] and the 1-minute sit-to-stand test.[47] Oximetry measurements and the Borg Dyspnoea Scale[48] will be undertaken immediately before and after the 1-minute sit-to-stand test, which will not be undertaken with subjects presenting resting pulse oximetry ratings lower than 90%.

Pulmonary function tests and chest imaging exams

Subjects who had been admitted to an ICU during the acute disease stage will undergo a whole-body plethysmography examination and an incremental cardiopulmonary exercise test (CPET), using methods described elsewhere.[49 50] These subjects will also undergo CT imaging of the chest using a 160-detector multi-slice equipment (Aquilion Prime, Canon Medical Systems Corporation, Japan) in the supine position, during end-inspiration and end-expiration without intravenous contrast. Reconstructed images (1-mm slice thickness an 1-mm interval with lung and soft tissue kernels) will be reviewed independently by two experienced thoracic radiologists and any disagreement will be resolved by consensus. The following findings suggestive of COVID-19-related lesions will be documented: ground-glass opacities, consolidation, reticulation, mosaic attenuation, parenchymal bands, atelectasis, architectural distortion, bronchiectasis and honeycomb.[51 52]

Subjects without a history of ICU admission during in-hospital stay will undergo: a frontal and lateral chest X-ray (searching for signs suggestive of COVID-related lesions such as ground-glass opacities, consolidation and linear and reticular opacities)[53]; and a conventional spirometry test using methods described elsewhere.[54] All individuals from this subgroup who fulfil any of the following five criteria will be invited for a second visit to undergo a plethysmography examination, a CPET and a CT scan of the chest: (a) a score on the MRC Dyspnoea Scale equal or greater than 2; (b) a resting pulse oximetry reading of 90% or above; (c) a decrement in the pulse oximetry reading of at least four points during the 1-minute sit-to-stand test; (d) the presence of forced vital capacity lower than 80% of predicted during the spirometry test and/or (e) the presence of pulmonary changes related to COVID-19 as assessed by conventional X-ray.

Muscle ultrasound

Using a 13-MHz GE Healthcare LOGIQe and a 13-MHz FujiFilm SonoSite M-Turbo probe and diagnostic ultrasonography equipment (Wuxi, China, and Bothell, Washington, USA, respectively), measurements of muscle thickness (MT) and echo intensity of the anterior rectus muscle and vastus medialis muscle will be obtained.[55] A strong correlation between conventional radiological

measurements (by MRI or CT) and ultrasound measurements of MT has been previously demonstrated.[56]

Olfactory tests

In addition to the otorhinolaryngological questions included in the interview described in the Semi-structured medical interviewing, vital sign and anthropometric measurements, physical and neurological examinations, and assessment of mental health status section (which will evaluate the presence of hearing loss, tinnitus, vestibulopathy disorders, nasal symptoms, olfactory and taste loss), subjects will undergo the objective 'u-Smell it olfactory test',[57] assisted by a physician. Subjects will be asked to scratch a total of five scents, smell each of them and choose one from five alternatives before moving forward to the next smell, until all five subtests are completed. On completion, a 0–5 smell score will be attributed to each subject. A set of Visual-Analogue Scales will also be applied assessing: the impact on QOF following COVID-related smell and taste loss; and the degree of chemosensitive recovery until the date of the interview.[58]

Cognitive test battery

All individuals will undergo a neuropsychological battery to identify impairments in different cognitive domains, including: the Trail Making Test–part A;[59] the digit-symbol test;[60] the temporo-spatial orientation subtest from the Mini-Mental State Examination[61] and the Consortium to Establish a Registry for Alzheimer's Disease battery.[62 63] Furthermore, we will assess the self-perceived memory status through the Memory Complaint Scale,[64] given both to the patient and a relative (if also present at the appointment).

Environmental exposures

Based on the permanent address of each individual, the following variables will be added to the database: neighbourhood socioeconomic conditions;[65] levels of air pollution and traffic density;[66] and residential greenness, distance to public green spaces and number of street trees.[67]

Procedures

Experienced research staff will make telephone invitations to subjects or close family members (in case of elderly individuals presenting some degree of dependence), followed by written messages using the freeware WhatsApp when no answer is obtained after two telephone attempts. Reasons for non-participation will be recorded.

The series of multidisciplinary assessments described in the Assessment schedules section will be concatenated to take 4–5 hours, with intervals for rest. Selected questions from the semi-structured interview described in subitem Semi-structured medical interviewing, vital sign and anthropometric measurements, physical and neurological examinations, and assessment of mental health status will be undertaken via teleconsultation ahead of the visit, whenever possible and convenient for study subjects and their relatives.

On the day preceding the actual visit of subjects to HCFMUSP, subjects will receive a telephone call during which they will be enquired regarding the sudden appearance of symptoms suggestive of SARS-CoV-2 re-infection. Symptomatic individuals will have their visit postponed, and they will be referred to the infectious disease outpatient clinic at HCFMUSP dedicated to the diagnosis and management of acute COVID-19. Subjects or relatives presenting fever on arrival for the scheduled multidisciplinary evaluations will be referred immediately to the same outpatient clinic. Additionally, all subjects will receive guidance at the end of their participation to seek out the infectious disease outpatient clinic in case of suspected re-infection.

Taking into account the long-lasting status of COVID-19 pandemics in Sao Paulo and in order to preserve the safety and social distancing of subjects and their relatives, three additional principles will be applied: (1) subjects will be asked to arrive using private transport, with expenses covered by the research programme; (2) rather than asking subjects and their relatives to circulate around several clinics for the multidisciplinary assessments, all evaluations (except the radiological exams) will be conducted at one single hospital sector, assembling a minimal number of researchers from each collaborating discipline to work on site; and (3) two separate facilities will be used simultaneously for the multidisciplinary assessments of different subjects. Those 2 sites will include: 1 temporary outpatient centre prepared to accommodate up to 8 visits per day of subjects without a history of ICU admission during in-hospital stay; and the clinical research centre of the Instituto do Coração at HCFMUSP, which accommodates up to 10 subjects who had been admitted to an ICU during acute COVID-19 to be evaluated daily. Both facilities are equipped to allow immediate action on any need for emergency interventions.

Data capture and management

Data from interviews, scales and complementary examinations will be captured and stored at real-time using web-based case report forms (CRFs) developed on a Research Electronic Data Capture (REDCap) system hosted at HCFMUSP.[68] A team of REDCap experts will manage the database and provide access for the different research groups to conduct interim and final statistical analyses.

Access to data collected prospectively during inpatient admissions due to acute COVID-19

A REDCap database of information for all cases with suspected COVID-19 during their admission as inpatients in the period between 30 March 2020 through August 2020 at HCFMUSP will be available for the current study. This database includes information on: address, age, sex and race; comorbidities and medications of regular use; acute COVID-19 symptom presentation; vital signs and

laboratory test results at admission; duration of symptoms; duration of hospital stay and treatment protocols used; and indices of disease severity and complications, including use of mechanical ventilation, admission to ICU, tracheostomy, use of vasoactive drugs, acute kidney injury and need for renal replacement therapy, delirium, stroke, pulmonary embolism and other thromboembolic events. Three different procedures were used to feed information in this database, including: automatic data extraction (comorbidities, vital signs, laboratory test results and prescriptions) from our electronic health record system; prospective manual entry of data by research teams during hospital stays; and retrospective extraction of data by a taskforce of researchers who re-evaluated both structured and non-structured fields of electronic CRFs.

Summarisation of clinical information and feedback to participants

Based on the assessments and scale cut-offs proposed by the research teams from the follow-up evaluations after in-hospital discharge, the data gathered will be summarised as short health reports to be used for the benefit of PASC sufferers in need of clinical care. Different specialised outpatient units at HCFMUSP are prepared to immediately provide care for subjects who are detected to display, for instance, significant signs of physical disability or persistent suicidal symptoms at the time of the research assessments. Potentially relevant clinical information will be fed back either directly to the subject and a significant relative via teleconsultation (followed by healthcare advice), or as a written report to be forwarded to the private or public health provider that will continue to care for the individual. A username and password will be provided to allow all individuals to have access to the laboratory and radiological test results in an electronic format.

Sample size estimation and planning for data analysis

Given both the paucity of previous COVID-19 investigations of the kind proposed herein and the continued restrictions imposed by the pandemics in Sao Paulo, Brazil, it is difficult to estimate the number of individuals who will agree to come to the follow-up visits. Given the large number of potential participants (above 1800) and the maximal daily work capacity of our research teams, we estimate that the sample size for the current study will be over 800 subjects (based on a rate of acceptance of at least 45%–50% of invited subjects), providing sufficient numbers to avoid an underpowered investigation. Planned analyses to fulfil the main aims of the study (as outlined at the introduction section of this paper) will include: descriptive statistics, multiple linear and ordinal regression models, and statistical comparisons of subgroups, with correction for multiple testing.

The cohort will be stratified into the three following groups: patients that did not require any oxygen support during in-hospital stay; patients who required supplementary oxygen; and patients who underwent invasive mechanical ventilation. In addition, given the heterogeneity of PASC phenotypes,[1] we will also run separate analyses for subgroups presenting specific types of sequelae (eg, pulmonary sequelae, renal sequelae and endocrine sequelae).

ETHICS AND DISSEMINATION

The Comissão de Ética para Análise de Projetos de Pesquisa (HCFMUSP's institutional review board) gave ethics approval for all protocol components for the study (approval numbers: 4.270.242, 4.502.334, 4.524.031, 4.302.745 and 4.391.560). Informed written consent will be obtained from participants (or their legal guardians) prior to study procedures. Informed written consent will also be given for remaining amounts of blood samples (collected for diagnostic tests) to be incorporated by the TMI biobank, and this has been ethically approved both by HCFMUSP's institutional review board and the Comissão Nacional de Ética em Pesquisa (approval number: B-016). Personal information of participants will be kept confidential.

DISCUSSION

There is a pressing need for observational studies documenting the presence of persistent symptoms and sequelae of COVID-19 after hospitalisation. However, thorough multidisciplinary investigations of large patient samples are still scarce. In a study of PASC that reassessed 1733 patients after 6 months of in-hospital discharge, assessments of multiorgan manifestations were restricted to a 12-item medical questionnaire, physical examination, a cerebrovascular/cardiovascular registration form, scales addressing QOL and dyspnoea, laboratory tests and a 6-minute walking test.[11] Objective assessments (including pulmonary function tests, ultrasonography of lower limb veins and abdomen, and CT of the chest) were conducted in a subsample of 390 patients, including only 76 ICU subjects.[11] In another study of 476 COVID-19 patients investigated 4 months after in-hospital discharge, symptom screening was undertaken by telephone; detailed in-person assessments were restricted to approximately one-third of the sample (those reporting relevant symptoms during the telephone interview and all ICU subjects), including laboratory tests, CT of the chest, cardiopulmonary tests, a 6-minute walking test, and cognitive and psychiatric assessments.[12]

In addition to the large size of our expected sample, one advantage of the study proposed herein is that we will conduct comprehensive symptom surveys and objective assessments of PASC manifestations in all individuals that agree to participate (rather than restricting more detailed schedules to a subsample with greater disease severity).[12] One other potential strength is that we will have access to baseline hospital data that were recorded prospectively. Moreover, rather than advertising the follow-up study

to potentially interested subjects, we will systematically search for individuals fulfilling inclusion criteria for the study. Conversely, one relevant limitation that should be acknowledged is the fact that we will rule out the presence of current re-infection only by the absence of clinical signs and symptoms, rather than by a negative RT-PCR test. Additionally, the fact that the study subjects will be all from one single hospital site might be taken as a further limitation. However, we should consider that HCFMUSP temporarily undertook a substantial multiplication of its capacity to treat cases of respiratory distress in 2020, thus allowing several hundreds of COVID-19 subjects from different city districts to be admitted to our hospital simultaneously. Over approximately 5 months, this setup led to numbers of treated COVID-19 cases comparable to the samples combining several medium-sized or large-sized hospitals included in studies conducted elsewhere. Moreover, our access to one large-sized, single-site sample implies that homogeneous in-stay protocols were used, thus potentially reducing inter-individual differences in outcome due to variations across hospitals regarding administrative, diagnostic and treatment routines.

Another relevant issue regards to the current impracticability to investigate long-term consequences and sequelae in concurrently assessed control groups of inpatients treated at HCFMUSP for other infectious diseases (such as CAP or dengue),[69 70] as stated in the Methods section. Such case–control comparison approach may not be needed for the evaluation of persistent symptoms and signs that are likely to be disproportionately prevalent in COVID-19 sufferers, such as olfactory manifestations.[58] However, the lack of such control groups is an important limitation for other investigations planned on our cohort, and this is a possible protocol change that will be introduced over the course of the study. Nevertheless, the lack of control groups will not jeopardise the validity of analyses investigating significant associations between risk factors and persistent manifestations of COVID-19, or analyses comparing patient subgroups divided according to specific disease features.

The individual interviews at the follow-up assessments will provide critical sociodemographic data that could not be obtained during in-hospital admissions, such as detailed information on educational background and current socioeconomic status. It has been demonstrated that individual-level and neighborhood-level variables provide complementary information about the contribution of socioeconomic conditions to health outcomes,[65] and both will be available to be tested as potentially significant factors associated with COVID-19 outcomes in our sample. The use of such variables should allow us to investigate the extent to which the vulnerability to more severe COVID-19 might be predicted not only by age, ethnicity and medical factors (eg, number of comorbidities)[71] but also socially determined factors such as poor housing conditions, unstable income and delayed access to health services.[72] Once our analyses will be carried out in a large urban LMIC setting, unique information may be gathered regarding the influence of disadvantaged socioeconomic status on specific long-term COVID-19 manifestations.[73]

As in other parts of the world, there is currently in Sao Paulo a commendable pressure from funding agencies, other research sponsors and public universities to ensure that scientific investigations will deliver, as much as possible, evidence-based data to inform real-time solutions to problems related to long-term consequences of COVID-19. Since the observational assessments will be carried out over several months, interim analyses of results may encourage our specialised research teams to plan for nested clinical trials testing the efficacy of short-term interventions targeting specific long-term COVID-19 manifestations. Additionally, we expect that the delivery of general care to the overall cohort will be facilitated by the procedure of summarisation of clinical information and follow-up contacts with participants and their care providers.

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Original Article

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Post-acute sequelae of SARS-CoV-2 infection: relationship of central nervous system manifestations with physical disability and systemic inflammation

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Abstract

Background. Despite the multitude of clinical manifestations of post-acute sequelae of SARS-CoV-2 infection (PASC), studies applying statistical methods to directly investigate patterns of symptom co-occurrence and their biological correlates are scarce.

Methods. We assessed 30 symptoms pertaining to different organ systems in 749 adults (age = 55 ± 14 years; 47% female) during in-person visits conducted at 6–11 months after hospitalization due to coronavirus disease 2019 (COVID-19), including six psychiatric and cognitive manifestations. Symptom co-occurrence was initially investigated using exploratory factor analysis (EFA), and latent variable modeling was then conducted using Item Response Theory (IRT). We investigated associations of latent variable severity with objective indices of persistent physical disability, pulmonary and kidney dysfunction, and C-reactive protein and D-dimer blood levels, measured at the same follow-up assessment.

Results. The EFA extracted one factor, explaining 64.8% of variance; loadings were positive for all symptoms, and above 0.35 for 16 of them. The latent trait generated using IRT placed fatigue, psychiatric, and cognitive manifestations as the most discriminative symptoms (coefficients > 1.5, $p < 0.001$). Latent trait severity was associated with decreased body weight and poorer physical performance (coefficients > 0.240; $p \leqslant 0.003$), and elevated blood levels of C-reactive protein (coefficient = 0.378; 95% CI 0.215–0.541; $p < 0.001$) and D-dimer (coefficient = 0.412; 95% CI 0.123–0.702; $p = 0.005$). Results were similar after excluding subjects with pro-inflammatory comorbidities.

Conclusions. Different symptoms that persist for several months after moderate or severe COVID-19 may unite within one latent trait of PASC. This trait is dominated by fatigue and psychiatric symptoms, and is associated with objective signs of physical disability and persistent systemic inflammation.

Introduction

Symptoms and signs of dysfunction of multiple organ systems may be present during both the acute and post-viral stages of coronavirus disease 2019 (COVID-19) (Al-Aly, Xie, & Bowe, 2021; Bell et al., 2021; Blomberg et al., 2021; Davis et al., 2021; Huang et al., 2021a, 2021b; Lopez-Leon et al., 2021; Menges et al., 2021; Nasserie, Hittle, & Goodman, 2021; Sudre et al., 2021; Writing Committee for the COMEBAC Study Group et al., 2021). Cognitive deficits, anxiety, depression, sleep disturbances, and post-traumatic stress disorder (PTSD) have been frequently shown to persist for weeks to several months after COVID-19 (Abel et al., 2021; Becker et al., 2021; Bourmistrova, Solomon, Braude, Strawbridge, & Carter, 2021; Damiano et al., 2022; Hampshire et al., 2021; Ismael et al., 2021; Mazza et al., 2020, 2021; Søraas et al., 2021; Taquet, Geddes, Husain, Luciano, & Harrison, 2021), highlighting the relevance of central nervous system (CNS) manifestations in the long COVID syndrome (or post-acute sequelae of SARS-CoV-2 infection, PASC).

As in many disorders that present multiple clinical manifestations (Ahmad et al., 2014; Aktas, Walsh, & Rybicki, 2010; Manca, De Marco, Ince, & Venneri, 2021), the detection of specific patterns of symptom clustering may help to elucidate the pathophysiology of PASC, which remains largely unknown. The identification of patterns of co-occurrence of psychiatric and cognitive symptoms with manifestations pertaining to other organ systems could guide hypotheses as to whether CNS symptoms in PASC may emerge under the influence of unifying pathological mechanisms, such as persistent systemic inflammatory and prothrombotic states (Bornstein et al., 2021; Mackay, 2021; Perrin et al., 2020; Phillips & Williams, 2021), or chronic dysfunction of the lungs (Sasannejad, Ely, & Lahiri, 2019) or kidneys (Desmond et al., 2021).

Based on online surveys applied to 3762 subjects with confirmed or suspected COVID-19, one investigation of temporal profiles of PASC symptoms highlighted a cluster combining CNS manifestations with multiple other organ system symptoms, which shared patterns of persistence up to 7 months after acute disease (Davis et al., 2021). Another study applied statistical methods to directly assess patterns of clustering of different PASC manifestations in subjects with moderate or severe COVID-19, based on data from a large sample of adults (n = 1077) evaluated during in-person visits between 2 and 7 months after in-hospital discharge (Evans et al., 2021). The authors of the latter study described four clusters reflecting different levels of PASC severity, and in all clusters there was a close co-occurrence of three CNS symptoms (i.e. depression, anxiety, and PTSD) with manifestations pertaining to other organ systems (i.e. dyspnea, fatigue, and poor physical performance). Cluster severity was directly associated with blood levels of C-reactive protein measured at the same timepoint, possibly reflecting persistent systemic inflammation (Mackay, 2021; Perrin et al., 2020). However, this investigation was limited by the inclusion of only three non-CNS manifestations in the cluster analysis design. Moreover, no analyses were conducted to directly account for the association found between C-reactive protein levels and increased body weight (Evans et al., 2021), or the potentially confounding effects of other pro-inflammatory comorbidities.

In this study, we investigated the patterns of co-occurrence of 30 multi-organ system symptoms (including six psychiatric manifestations and cognitive complaints) in a relatively large sample of adults (n = 749) assessed by multidisciplinary teams at approximately 6–11 months after hospitalization due to COVID-19. We initially conducted an exploratory factor analysis (EFA) on the ratings of all symptoms, with the prediction that one factor would emerge combining cognitive and psychiatric complaints with multiple symptoms pertaining to other organ systems (Davis et al., 2021; Evans et al., 2021). Subsequently, we generated a latent variable combining symptoms of PASC using Item Response Theory (IRT), a statistical approach suitable for scaling multiple health outcomes along one single continuum of severity (latent trait modeling) (Hays, Morales, & Reise, 2000; Krueger et al., 2004). This latent trait of PASC symptoms was used to investigate associations with objective signs of persistent physical disability, pulmonary dysfunction, and kidney function impairment. Finally, we investigated whether latent trait severity would be directly related to levels of blood markers of persistent inflammatory and prothrombotic states measured at the same follow-up assessment (C-reactive protein and D-dimer), accounting for the influence of obesity and other pro-inflammatory comorbidities.

Methods

Study design, participants, and procedures

We consecutively invited for a follow-up visit all adult (⩾18 years) patients that had been admitted for at least 24 h as inpatients to *Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo* (HCFMUSP), Brazil, due to laboratory-confirmed COVID-19, over a period of 5 months (between March and August 2020). Follow-up data collection occurred from October 2020 to April 2021.

Comorbid conditions prior to COVID-19 were identified using a database of information for all cases with suspected COVID-19 during their admission as inpatients at HCFMUSP (Busatto et al., 2021), and we excluded patients with a previous diagnosis of dementia or end-stage cancer. Additional exclusion criteria were nosocomial COVID-19 infection, subjects living in nursing homes or long-term care facilities, and insufficient physical mobility to leave home. Finally, as re-infection by SARS-CoV-2 is possible, we enquired subjects about the emergence of symptoms and signs of infection (e.g. fever) during telephone calls on the day before the follow-up visit and again upon their arrival for the assessments. Any subjects with suspected re-infection had their research visit postponed, and they were referred to the infectious disease outpatient clinic at HCFMUSP dedicated to the diagnosis and management of acute COVID-19.

Online Supplementary material 1 (Methods S1) provides further details on the study period, procedures, and laboratory confirmation of COVID-19. A full description of general procedures for invitations and assessments was provided elsewhere (Busatto et al., 2021).

Data from interviews, scales, and complementary examinations were captured and stored at real-time using web-based case report forms developed on a Research Electronic Data Capture (REDCap) system hosted at HCFMUSP (Harris et al., 2009).

Protocols were approved by the local ethics committee (numbers 4.270.242, 4.502.334, 4.524.031, 4.302.745, and 4.391.560). Informed consent was obtained from all participants or their proxy prior to study procedures.

Evaluation of psychiatric and cognitive symptoms at the follow-up

To assess symptoms of PTSD (Weathers, Litz, Herman, Huska, & Keane, 1993), anxiety and depression (Zigmond & Snaith, 1983), insomnia (Bastien, Vallières, & Morin, 2001), and subjective memory impairment (Vale, Balieiro, & Silva-Filho, 2012), multi-item scales were applied by specialized teams (Busatto et al., 2021). Validated cutoffs were used to generate categorical 'yes-no' variables (see online Supplementary Methods S2 and Table S1 for details). Complaints of impaired concentration were documented using the Clinical Interview Schedule-Revised (CIS-R) (Lewis, Pelosi, Araya, & Dunn, 1992). To identify potentially incident cases, we estimated the date of onset of symptoms using structured questions from the CIS-R; 'no' ratings were applied when symptoms were reported by patients as already present prior to SARS-CoV-2 infection.

Other self-reported symptoms at the follow-up

Additional symptoms previously highlighted as relevant to PASC (Lopez-Leon et al., 2021; Nasserie et al., 2021) (i.e. fatigue, dyspnea, muscle/joint pain, and taste and/or olfaction changes) were also assessed using standardized scales (Bestall et al., 1999; Boonstra, Preuper, Balk, & Stewart, 2014; Brandão Neto et al.,

2021; Webster, Cella, & Yost, et al., 2003) (see online Supplementary Table S1 for details). An adaptation of the WHO screening tool for neuroepidemiology investigations in low-and-middle-income countries (WHO, 1982) was applied by a team of neurologists (Busatto et al., 2021) to assess neurological manifestations including headache, weakness, gait problems, episodes of loss of consciousness, and paresthesia. Finally, subjects were inquired about the presence of 14 persistent post-COVID symptoms covering additional organ-system domains (Busatto et al., 2021) (see full list in online Supplementary Table S1).

The symptoms above, added to those cited in item 2.2, comprised a total of 30 items (online Supplementary Table S1).

Objective assessments of functioning and blood laboratory indices at the follow-up

Objective indices of organ system dysfunction were generated from the following assessments conducted during the same in-person visit (Busatto et al., 2021): anthropometric measurements (including body mass index; BMI); 1 min sit-to-stand and handgrip strength tests (to measure physical disability) (Bohannon, 2015; Litmanovich, Chung, Kirkbride, Kicska, & Kanne, 2020; Strassmann et al., 2013; Vianna, Oliveira, & Araújo, 2007); measurements of resting oxygen saturation, decreased oxygen saturation during the sit-to-stand test, a chest X-ray (Litmanovich et al., 2020), and a spirometry test (Pereira, Sato, & Rodrigues, 2007) (all addressing pulmonary dysfunction); and blood creatinine levels (to estimate glomerular filtration rate, as a measure of kidney function impairment) (Levey et al., 2009).

Details regarding the criteria for rating objective indices of dysfunction as present are provided in online Methods S2 and Table S2 (Supplementary material 1). BMI values were used to detect the presence of clinically relevant weight change after COVID-19 (online Supplementary Table S2), and also to classify study subjects as obese ($\geqslant$30 kg/m^2) or non-obese ($\leqslant$30 kg/m^2) (Table 1).

Missing values for objective signs of dysfunction are provided in online Supplementary Table S3; most of the missing data were due to the fact that some of the assessment protocols were not ready for use at the starting date of data collection.

Methods for measuring C-reactive protein and D-dimer serum levels and information regarding missing data are provided in online Supplementary Methods S3.

Statistical analyses

Identifying symptom dimensions through exploratory factor analysis

Using the binary ratings for the 30 self-reported PASC symptoms outlined in items 2.2 and 2.3 above, we conducted an initial EFA including all symptoms. A total of 203 patients had to be excluded from this analysis (27.1% of the total sample) due to missing values for at least one symptom (see online Supplementary Table S4). Further methodological details and information on missing values are provided in online Methods S4 (Supplementary material 1).

Generation of a unidimensional latent variable through item response theory

Based on previous literature findings (Davis et al., 2021; Evans et al., 2021), we expected that the initial EFA could indicate symptom data to fit an unidimensional latent trait space. Based on this prediction, we chose to generate a latent variable of PASC

Table 1. Baseline and hospitalization characteristics of the sample

Variable	*N* = 749
Age – mean ± s.d., years	55 ± 14
Age groups	
18–39	119 (15.8%)
40–49	156 (20.8%)
50–59	173 (23%)
60–69	190 (25.3%)
$\geqslant$ 70	111 (14.8%)
Sex	
Female	352 (47%)
Male	397 (53%)
Body mass index – median kg/m^2 (IQR)	31.1 (27.5–36.6)
Socioeconomic status[a]	
A	19 (2.5%)
B1	40 (5.4%)
B2	137 (18.5%)
C1	243 (32.8%)
C2	227 (30.7%)
D + E	73 (10%)
Educational level	
<4 years	265 (35.6%)
4–8 years	142 (19%)
8–12 years	202 (27%)
>12 years	134 (18%)
Ethnicity	
White	342 (46.5%)
Asian	10 (1%)
Mixed[b]	273 (37%)
Black	102 (14%)
Indigenous	7 (1%)
Comorbidities	
Hypertension	425 (56.7%)
Diabetes	261 (34.8%)
Obesity[c]	429 (57.5%)
Chronic cardiovascular disease	136 (18.2%)
Chronic respiratory disease	58 (7.7%)
Chronic kidney disease (non-dialytic/dialytic)	49 (6.5%)/35 (4.7%)
Cerebrovascular disease	40 (5.3%)
Cancer	35 (4.7%)
Organ transplantation	35 (4.7%)
Rheumatological disease	31 (4.1%)
Chronic liver disease	26 (3.5%)
HIV	4 (0.5%)
Charlson comorbidity score – mean ± s.d.	3.0 ± 1.8

(*Continued*)

Table 1. (*Continued.*)

Variable	*N* = 749
Smoking	284 (38%)
Duration of COVID-19 symptoms in days – mean ± S.D.	9.0 ± 6.5
Events during hospitalization	
Hospital stay, duration in days – mean ± S.D.	18.6 ± 19.2
Days after hospitalization for the follow-up – median [IQR]	212 [201–254]
Days after hospital discharge for the follow-up – median [IQR]	200 [185–235]
WHO clinical progression scale[d] – frequency in different categories	
3–4	85 (11.3%)
5	327 (43.6%)
6	32 (4.3%)
7–8–9	305 (40.7%)
Renal replacement therapy (yes/no)	96 (12.8%)
ICU stay (yes/no)	445 (59.4%)
Intubation (yes/no)	305 (40.7%)

S.D., standard deviation; IQR, interquartile range; ICU, intensive care unit.
[a]Six categories assessed in accordance to current criteria of the *Associação Brasileira de Empresas de Pesquisa* (ABEP, 2020).
[b]Based on self-reported mixed black and white races.
[c]Rated as present if the body mass index of individuals was equal or higher than 30 kg/m^2, based on self-reported estimates of body weight prior to COVID-19 given by study subjects at the time of the follow-up assessments.
[d]WHO scale categories: 3–4, no continuous supplemental oxygen needed; 5, continuous supplemental oxygen only; 6, continuous positive airway pressure ventilation, bi-level positive airway pressure or high flow nasal oxygen; 7–9, invasive mechanical ventilation and/or extra-corporeal membrane oxygenation (ECMO). WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection (2020).

symptoms using two-parameter logistic IRT modeling (Hays et al., 2000; Krueger et al., 2004), scaling the 30 symptoms of PASC along one single continuum. The IRT approach is suitable for scaling multiple items related to health outcomes along a unidimensional continuum of severity, and it has the additional advantage of being highly flexible for handling missing values (Krueger et al., 2004). In order to classify the 30 multi-organ symptoms included in the latent trait of PASC, we used the property of discrimination as our parameter of interest, referring to the increment in the probability a given symptom to be scored as present as the latent dimension score increased. Further information about the calculation of discrimination indices and IRT details is provided in online Supplementary Methods S5.

We run a sensitivity analysis assessing the properties of all symptoms included in the IRT model after leaving out subjects with comorbidities known to be themselves associated with CNS manifestations (see online Supplementary Methods S6). We also run additional sensitivity analyses including only one psychiatric or cognitive symptom at a time, to test the unique role of each self-reported psychiatric or cognitive symptom within the latent variable (see online Supplementary Methods S6).

Relationships between the latent variable of PASC symptoms, objective signs of organ system dysfunction and laboratory test results

Using two-parameter logistic regression models, we investigated significant associations between the latent variable described above and eight objective signs of organ system dysfunction (see online Supplementary Methods S7).

Additionally, we used a Differential Item Functioning (DIF) analysis approach to investigate relationships between elevated levels of blood tests (C-reactive protein and D-dimer) and the latent variable of PASC symptoms. The DIF approach allowed us to test whether significant relationships between abnormal test results and the latent dimension of PASC were due to different probabilities of endorsing any of the symptoms included in the latent variable (Saha et al., 2010; Penfield & Camilli, 2007). Initially, we investigated the relationship between blood test results and the latent dimension of symptoms under investigation (i.e. syndrome level), with statistical significance assessed using logistic coefficients and 95% confidence intervals. If any significant relationship with the severity of a latent PASC trait was detected, we then tested differential effects at the level of the individual PASC symptoms (i.e. manifestation level) through Mantel–Haenszel tests (see details in online Supplementary Methods S7).

We also conducted sensitivity analyses (logistic regressions) investigating relationships between the latent variable of PASC and blood test results after leaving out subgroups of subjects stratified by sex, age, race, and socio-economic status, in order to verify if the above associations were substantially affected by the influence of any demographic variables on levels of C-reactive protein or D-dimer (see details in online Methods S8, Supplementary material 1). Finally, to take account of the influence of confounding comorbidities on blood laboratory markers, we conducted additional sensitivity analyses after stratifying the sample by the presence of the following diagnoses: obesity; diabetes; chronic lung or heart disease; and additional comorbidities known to affect the blood indices investigated (rheumatic disease, chronic liver or kidney disease, hematological disease; active cancer; and organ transplantation).

Results

Demographics and baseline characteristics

Figure 1 provides the flowchart of potential participants and patient selection (including data on refusals and exclusions). A total of 749 eligible individuals attended the in-person follow-up assessments. Table 1 provides their details regarding demographics, comorbidities, hospitalization events, and time between symptom onset and hospital admission. The mean duration of symptoms characterizing acute COVID-19 prior to hospitalization (as referred by patients and/or relatives upon admission) equaled 9.0 ± 6.5 days (Table 1).

Online Supplementary Table S5 provides results of comparisons between the patients who attended the in-person assessments *v.* the remaining surviving individuals who did not participate (see details also in online Results S1, Supplementary material 1).

Exploratory factor analysis and latent variable modeling

The frequencies of each of the 30 symptoms in the overall sample are provided in online Supplementary Table S4.

One single factor was extracted in the initial EFA (eigenvalue = 4.65), explaining 64.8% of variance. All symptoms presented positive loadings for this factor; loadings >0.35 were found for 16 symptoms, with fatigue, insomnia, psychiatric, and cognitive complaints presenting the highest loadings (>0.5) (see online Supplementary Table S6). One additional factor approached the eigenvalue of one (0.99) and explained an additional amount of 13.8% of data

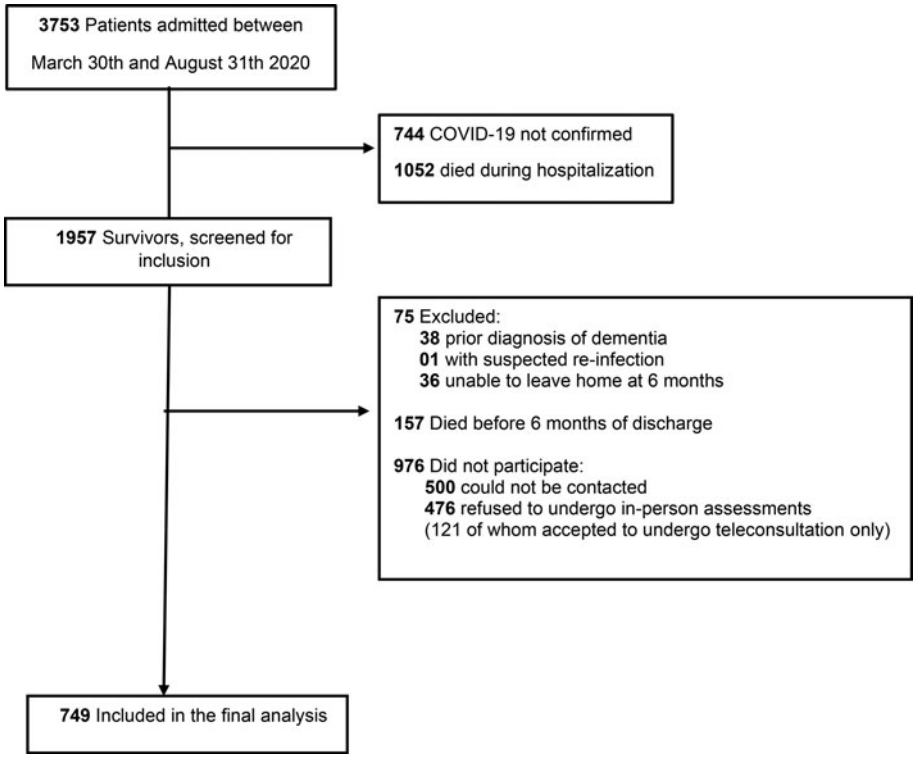

Fig. 1. Potentially eligible subjects and final sample included in the follow-up investigation.

variance, including the symptoms of weakness, gait impairment, and paresthesia, all with loadings above 0.45. Further details related to the EFA results are provided in online Results S2 (Supplementary material 1).

The unidimensional nature of the PASC symptom data, demonstrated by the above EFA, confirmed the validity of using the IRT approach to generate one single latent dimension of PASC. This analysis was conducted with all 749 subjects, taking advantage of the flexibility of the IRT approach for handling missing values. Discrimination properties for each of the 30 manifestations are displayed in Table 2. All 30 symptoms displayed discrimination coefficients from 0.2 to 2.3 ($p \leqslant 0.005$), with highest values for fatigue (2.3) and the six psychiatric and cognitive symptoms (1.5–2.1) (Table 2).

The sensitivity analysis assessing the properties of all symptoms included in the IRT model after leaving out subjects with comorbidities known to be themselves associated with CNS manifestations showed that all psychiatric and cognitive manifestations retained a high degree of discrimination (see online Supplementary Table S7).

In the six IRT analyses including only one psychiatric or cognitive symptom at a time, each of those variables persisted as highly discriminative within the resulting latent variable (see online Supplementary Table S8).

Significant associations between the latent variable of PASC symptoms, objective signs of organ system dysfunction, and laboratory test results

The three following objective signs of organ system dysfunction were significantly associated with the IRT-based latent variable of PASC symptoms: reduced BMI, abnormal sit-to-stand performance, and decreased handgrip strength (Table 3).

Blood levels of C-reactive protein and D-dimer at the follow-up evaluation showed significant direct relationships with the latent PASC dimension, with highest significance for the former (Table 4). There were no differential effects on any of the individual manifestations included in the PASC trait either for C-reactive protein or D-dimer levels (Table 4).

Results of the sensitivity analyses investigating relationships between the latent variable of PASC and blood test results after exclusion of each subgroup stratified by demographic variables are detailed in online Supplementary Results S3; statistical significance was retained in all analyses involving levels of C-reactive protein levels, but not D-dimer. Associations between the latent trait of PASC symptoms and blood biomarkers in each subgroup stratified by demographic variables are detailed in online Supplementary Table S9.

Finally, the sensitivity analyses conducted after excluding subjects with obesity or other comorbidities known to affect values of C-reactive protein and D-dimer showed that associations of the latent variable of PASC remained statistically significant with those two blood biomarkers (online Supplementary Table S10).

Discussion

In this study, we applied statistical methods to document patterns of co-occurrence of several PASC symptoms in a relatively large sample of patients with moderate or severe COVID-19 evaluated 6–11 months after hospitalization, investigating how such symptom co-occurrence was associated with signs of physical disability and persistent inflammation.

We demonstrated that fatigue, insomnia, psychiatric, and cognitive complaints were the symptoms with highest loadings (>0.5) in the single factor extracted by EFA, which explained a large proportion of data variance (64.8%). Several other symptoms presented meaningful loadings in the same EFA factor, and

Table 2. Latent variable modeling of post-acute sequelae of SARS-CoV-2 infection (PASC) using Item Response Theory

	Discrimination			
	Coefficient	*p*	95% CI	
Psychiatric/cognitive symptoms				
Post-traumatic stress	2.110		1.618	2.602
Depression	2.052		1.603	2.502
Memory loss	2.036		1.626	2.445
Anxiety	1.961	<0.001	1.548	2.373
Lack of concentration	1.675		1.328	2.023
Insomnia	1.530		1.225	1.834
Other symptoms				
Fatigue	2.294		1.842	2.745
Nausea/vomiting	1.397		0.838	1.957
Loss of appetite	1.346		0.998	1.694
Dyspnea	1.300		1.024	1.575
Body pain	1.128		0.881	1.374
Hearing loss	1.102		0.804	1.400
Muscle/joint pain	1.085		0.849	1.321
Diarrhea	1.062		0.665	1.458
Loss of smell	1.063		0.795	1.331
Loss of taste	1.033	<0.001	0.773	1.293
Tinnitus	0.971		0.692	1.250
Abdominal pain	0.951		0.668	1.234
Weakness	0.862		0.582	1.143
Nocturia	0.769		0.545	0.993
Nasal obstruction	0.760		0.507	1.012
Gait impairment	0.742		0.460	1.025
Headache	0.704		0.422	0.986
Dizziness	0.695		0.495	0.894
Chest pain	0.680		0.449	0.911
Edema	0.675		0.438	0.918
Paresthesia	0.674		0.428	0.920
Skin problems	0.594	<0.001	0.352	0.835
Cough	0.509		0.289	0.729
Episodes of loss of consciousness	0.664	0.003	0.218	1.109

CI, confidence intervals.

each of them also showed significant discrimination ($p \leqslant 0.005$) along the latent variable of PASC generated using IRT (which allowed the recovery of cases with missing values). These findings confirm the notion that there is a significant degree of co-occurrence of multiple clinical manifestations in COVID-19 patients evaluated several months after hospitalization, suggesting that common underlying pathological mechanisms might influence on the persistence of different organ system symptoms in PASC.

The discriminative role of psychiatric and cognitive symptoms on the IRT-based latent variable of PASC remained high after the exclusion of cases with comorbid conditions themselves known to be associated with psychiatric and cognitive manifestations independently of COVID-19. Moreover, each of those CNS symptoms retained the same level of high discrimination when evaluated in isolation within the IRT model, together with fatigue. The fact that all other symptoms also displayed significant discrimination values in the same latent variable of PASC symptoms indicates that the likelihood of those additional symptoms to be referred by patients was higher in proportion to the presence of fatigue and psychiatric/cognitive complaints. These findings are consistent with the results of previous investigations that traced the trajectory of multiple individual symptoms of PASC over time, as these have indicated an incremental number of symptoms affecting multiple organ systems from approximately 10 weeks after acute COVID-19 onwards, with a prominence of CNS manifestations (Davis et al., 2021).

The latent variable of PASC symptoms was directly related to three objective signs of persistent physical disability, namely low performance on the sit-to-stand test, impaired handgrip strength, and reduced BMI. Conversely, all other indices generated from objective tests of organ system functioning were unrelated to the latent trait of PASC symptoms, including the four signs of persistent respiratory dysfunction. The latter negative findings are consistent with previous observations that fatigue and ill health may be reported by patients several months after acute COVID-19 independently of whether objective signs of respiratory dysfunction are detected at the same timepoint (Townsend et al., 2021a 2021b). The pattern of high discrimination of fatigue, psychiatric, and cognitive symptoms in our latent trait of PASC symptoms, together with its specific association with physical disability, is consistent with the proposed similarity of PASC with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) (Bornstein et al., 2021; Mackay, 2021; Perrin et al., 2020; Phillips & Williams, 2021), a disorder thought to be often triggered by viral disease (Morris, Anderson, Galecki, Berk, & Maes, 2013). Cognitive complaints are listed in the diagnostic criteria for ME/CFS (Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Board on the Health of Select Populations, & Institute of Medicine, 2015). The diagnosis of ME/CFS is also commonly associated with anxiety, depression, and weight loss (Afari & Buchwald, 2003; Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Board on the Health of Select Populations, & Institute of Medicine, 2015).

The latent variable of PASC symptoms described herein was directly associated with persistently elevated blood levels of C-reactive protein at the follow-up assessment, supporting the proposed role for dysregulated inflammatory/immune mechanisms in the pathophysiology of PASC (Mackay, 2021; Perrin et al., 2020). The latent trait of PASC symptoms was also significantly associated with elevated D-dimer levels, suggesting the persistence of a pro-thrombotic state possibly related to inflammatory mechanisms (Nalbandian et al., 2021; Pasini et al., 2021; Townsend et al., 2021a, 2021b). These results extend the findings of Evans et al. (2021), who reported elevated blood levels of C-reactive protein in proportion to the severity of a symptom cluster combining persistent psychiatric manifestations, dyspnea, fatigue, and poor physical performance in COVID-19 patients evaluated between 2 and 7 months after hospital discharge (Evans et al., 2021). Differently from that study, we

Table 3. Associations between the latent variable of PASC symptoms and objective signs of organ system dysfunction

	Latent variable of PASC symptoms			
Objective signs of dysfunction	Coefficient	*p*	95% CI	
Weight loss (⩽ 5% of BMI value prior to COVID-19)[a]	0.258	0.003	0.090	0.426
Reduced resting oxygen saturation (⩽92%)	0.200	0.211	−0.113	0.513
Decreased oxygen saturation during effort[b]	0.029	0.985	−0.303	0.309
Reduced number of repetitions during sit-to-stand test	0.577	<0.001	0.382	0.772
Reduced handgrip strength	0.243	0.007	0.065	0.420
COVID-related abnormalities at X-ray	−0.031	0.727	−0.208	0.145
FVC <80% of predicted at spirometry test	−0.27	0.760	−0.202	0.147
eGFR lower than 60 ml/min/1.73 m^2 (in subjects with no previous history of kidney disease)[c]	0.141	0.277	−0.113	0.394

CI, confidence intervals; BMI, body mass index; FVC, forced vital capacity; eGFR, estimated glomerular filtration rate.
[a]Difference between current BMI measurement and calculated BMI based on self-reported estimates of body weight prior to COVID-19.
[b]Oxygen saturation reduction of ⩾4 points during sit-to-stand test (not undertaken in subjects presenting resting pulse oximetry ratings lower than 90%).
[c]Estimated glomerular filtration rate calculated according to CKD EPI[30].

conducted a set of sensitivity analyses which demonstrated that the association between PASC symptom severity and blood levels of either C-reactive protein or D-dimer remained significant in subgroups excluding patients with conditions known to affect levels of these biomarkers, including obesity, diabetes, and other pro-inflammatory comorbidities. Moreover, findings of the sensitivity analyses using subgroups stratified by demographic variables showed that the significant association between C-reactive protein levels and the latent trait of PASC symptoms was not determined by the influence of these factors (see details in online Discussion S1, Supplementary material 1).

The DIF analyses in our study showed no differential effects of either C-reactive protein or D-dimer levels on the individual symptoms included in the latent variable of PASC symptoms, suggesting that these biomarkers exert a uniform influence on psychiatric, cognitive, and all other symptoms along the overall PASC trait. Persistently elevated levels of these two indices and other inflammatory biomarkers were described in other studies that assessed subjects at variable time points after the onset of acute COVID-19 (Huang et al., 2021b; Mandal et al., 2021; Pasini et al., 2021; Townsend et al., 2021a, 2021b). However, associations with the severity of persistent clinical manifestations were inconsistently reported in those investigations, possibly due to modest sample sizes and the assessment of isolated PASC symptoms, rather than using a unifying latent variable as reported herein.

Peripheral biomarker findings suggestive of systemic inflammation were previously reported in association with symptoms of PTSD (Sankowski, Mader, & Valdés-Ferrer, 2015), mood disorders (Pariante, 2017), anxiety disorders (Michopoulos, Powers, Gillespie, Ressler, & Jovanovic, 2017), and ME/CFS (Montoya et al., 2017). A persistent state of systemic inflammation in PASC may lead to prominent psychiatric, cognitive, and physical dysfunctional manifestations via pro-inflammatory agents entering the CNS by circumventricular organs that have incomplete blood–brain barrier, or via abnormally permeable portions of blood–brain barrier damaged by cytokines (Mackay, 2021; Perrin et al., 2020; Sankowski et al., 2015). Through those pathways, pro-inflammatory agents may affect limbic regions and the hypothalamus, reduce monoamine neurotransmission, and trigger microglia activation and neurotoxicity (Boldrini, Canoll, & Klein, 2021; Mackay, 2021; Perrin et al., 2020).

The findings of this study highlight a multi-symptom dimension of PASC that is dominated by psychiatric manifestations and physical disability, and which may be related to persistent systemic inflammation. However, these results do not rule out the possible existence of additional clinical dimensions of relevance in PASC, combining other symptoms and objective signs of dysfunction. For instance, objectively assessed cognitive deficits (which were not addressed in the present study) may persist after COVID-19 (Becker et al., 2021; Evans et al., 2021; Hampshire et al., 2021) and have been suggested to be independent of psychiatric symptoms and physical disability (Evans et al., 2021); such objective cognitive deficits might be specifically associated with signs of pulmonary dysfunction (Sasannejad et al., 2019) or chemosensory symptoms (Pirker-Kees, Platho-Elwischger, Hafner, Redlich, & Baumgartner, 2021), both of which were prevalent in our sample (online Supplementary Tables S3 and S4). It is also worth noting that our EFA analysis detected an additional trend pattern of symptom co-occurrence involving three neurological manifestations (weakness, gait impairment, and paresthesia) (WHO, 1982). This suggests that there may be different patterns of symptom co-occurrence in PASC involving neurological, psychiatric, and cognitive manifestations, which could emerge under the influence of separate risk factors and underlying brain mechanisms (Boldrini et al., 2021; Taquet et al., 2021). These issues warrant further investigations in large samples of PASC sufferers.

One strength of the present study regards to the use of multi-item scales with validated cutoffs for the assessment of psychiatric manifestations ad other key symptoms (Zigmond & Snalth, 1983), rather than simpler 'yes-no' questions (Blomberg et al., 2021; Huang et al., 2021a, 2021b; Søraas et al., 2021; Sudre et al., 2021; Writing Committee for the COMEBAC Study Group et al., 2021). A study limitation is that subjects were asked at the time of the follow-up assessments about the presence of symptoms before COVID-19, which is prone to recall bias. Therefore, we could not confirm that the onset of symptoms occurred after COVID-19, since subjects did not undergo similar assessments prior to the SARS-CoV-2 infection. Other limitations include: the lack of a control group (Abel et al., 2021); the lack of chest computed tomography imaging and diffusion capacity testing to detect pulmonary involvement in COVID-19 with greater accuracy (Huang et al.,

Table 4. Significant findings from the differential item functioning analysis investigating blood laboratorial predictors of post-acute sequelae of SARS-CoV-2 infection (PASC)

	C-reactive protein > 3.0 mg/l				D-dimer > 2000 ng/ml			
Latent dimension of PASC	Coefficient	*p*	95% CI		Coefficient	*p*	95% CI	
	0.378	<0.001	0.215	0.541	0.412	0.005	0.123	0.702
Clinical manifestations	aOR		95% CI		aOR		95% CI	
Psychiatric/cognitive symptoms								
Loss of memory	0.898	0.75	0.556	1.450	0.950	0.81	0.246	3.662
Anxiety	1.329	0.33	0.798	2.214	0.826	0.99	0.247	2.756
Lack of concentration	0.773	0.34	0.482	1.239	0.681	0.75	0.203	2.276
Post-traumatic stress	1.023	0.93	0.544	1.922	0.454	0.60	0.067	3.051
Insomnia	0.849	0.55	0.538	1.340	0.531	0.47	0.152	1.851
Depression	0.827	0.57	0.490	1.397	2.053	0.33	0.667	6.324
Other symptoms								
Gait impairment	1.795	0.10	0.931	3.461	3.110	0.14	0.960	10.079
Nocturia	1.298	0.33	0.814	2.070	0.645	0.66	0.188	2.221
Dyspnea	1.003	0.92	0.635	1.584	0.674	0.71	0.207	2.199
Fatigue	1.337	0.32	0.807	2.214	0.599	0.44	0.204	1.759
Loss of taste	1.126	0.74	0.685	1.851	0.670	0.78	0.177	2.541
Hearing loss	1.153	0.72	0.658	2.021	2.433	0.21	0.787	7.520
Edema	1.251	0.46	0.751	2.082	0.421	0.41	0.092	1.928
Body pain	1.057	0.88	0.688	1.625	1.351	0.78	0.471	3.874
Loss of appetite	1.353	0.47	0.695	2.635	0.428	0.72	0.049	3.731
Muscle/joint pain	1.117	0.68	0.736	1.696	1.504	0.59	0.542	4.177
Paresthesia	1.114	0.80	0.647	1.917	2.088	0.30	0.705	6.190
Skin problems	0.775	0.41	0.462	1.301	2.412	0.18	0.786	7.404
Weakness	1.060	0.97	0.575	1.956	3.644	0.08	1.106	12.004
Abdominal pain	1.071	0.68	0.736	1.696	1.575	0.69	0.477	5.210
Dizziness	0.927	0.83	0.585	1.467	0.548	0.48	0.172	1.750
Cough	1.222	0.49	0.751	1.990	2.012	0.27	0.746	5.424
Chest pain	1.018	0.96	0.619	1.675	0.249	0.21	0.036	1.745
Episodes of loss of consciousness	1.056	0.87	0.379	2.938	0.820	0.76	0.115	5.826
Loss of smell	0.771	0.40	0.455	1.304	npc	npc	npc	npc
Nasal obstruction	0.857	0.68	0.497	1.475	1.317	0.93	0.376	4.616
Headache	0.724	0.36	0.397	1.320	0.564	0.44	0.204	1.759
Tinnitus	0.652	0.26	0.342	1.243	1.310	0.96	0.358	4.796
Diarrhea	0.558	0.27	0.241	1.295	1.986	0.91	0.303	13.023
Nausea/vomiting	0.495	0.32	0.161	1.519	1.222	0.60	0.074	20.170

CI, confidence interval; aOR, odds ratio adjusted for the relationship between the latent trait score and the other PASC symptoms; npc, not possible to calculate odds ratio and 95%CI.

2020, 2021a); the successful recruitment of only 43% of all patients potentially eligible for in-person visits; and the inclusion of a single hospital site, which may limit the generalizability of our findings. However, it should be noted that the size of our single-site sample was larger than that of most unicentric studies of COVID-19 patients that undertook in-person follow-up assessments to date (Mandal et al., 2021; Mazza et al., 2020; Menges et al., 2021; Sonnweber et al., 2020; Townsend et al., 2020; Writing Committee for the COMEBAC Study Group et al., 2021).

Conclusions and implications

The unidimensional profile of symptom clustering described in this study indicates that multiple persistent manifestations

following moderate or severe COVID-19 may be united within one latent trait of PASC. This latent trait is dominated by fatigue, psychiatric, and cognitive symptoms, and is significantly associated with objective signs of physical disability and persistent systemic inflammation. Further longitudinal studies are needed to evaluate whether these PASC manifestations persist over longer follow-up periods. If confirmed in such additional investigations, our findings would reinforce the need for the development of healthcare services providing focused diagnostic assessments and evaluating the usefulness of tailored treatment programs for PASC sufferers (David, 2021; Heightman et al., 2021). These services could identify patients that do not present long-term, organ-specific sequelae of COVID-19, but who may benefit from multidisciplinary interventions emphasizing physical rehabilitation and mental health-promoting strategies. The present findings also warrant investigations using panels of specific pro-inflammatory and anti-inflammatory markers in large-sized samples of PASC sufferers, in order to ascertain which inflammatory pathways may be most distinctly related to the symptom dimension highlighted herein; the identification of key biomarkers in such investigations may guide randomized clinical trials testing the efficacy of pharmacological interventions to reduce the burden of co-occurring physical disability and neuropsychiatric features of PASC. Finally, the findings of the present study highlight the relevance of full vaccination schemes against SARS-Cov-2, as these have been found to reduce not only the severity of acute COVID-19 but also the risk of PASC manifestations (Antonelli et al., 2022).

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Correspondence

The role of spirituality in the COVID-19 pandemic: a spiritual hotline project

ABSTRACT

Recent correspondence letters to the editor of this journal pointed out to the need of implementing psychological support during the pandemic and post-pandemic period to both general and frontline workers. Especially, they highlighted the importance of religious/spiritual interventions in order to provide an integral and holistic care. In this perspective, an important consequence of the social isolation is the closure of churches and the suspension of religious meetings in order to avoid agglomeration and contagion. However, although this is a very important approach in terms of public health, a question is raised: how to promote spiritual care and help spiritual/religious individuals to cope with their problems while maintaining compliance with social isolation? To address this question, we report the Spiritual Hotline Project, a project designed by many Brazilian healthcare workers intended to give spiritual and religious assistance to people with different cultural background. So far, the hotline was able to assist people from different parts of the world, including Brazil and Portugal as well as with different religious affiliation, in order to provide a spiritual comfort and care during this public health crisis.

Keywords COVID-19, hotline, religion, spirituality, support project

Dear Editor,

We have read with interest the recent previous letter to the editor concerning the need of psychological support[1] and the role of religious interventions in times of COVID-19.[2] It is well-known that the world is facing a disease with unprecedented consequences due to the COVID-19 pandemic, both to physical and to mental health.[3] Thus, developing strategies to prevent and support mental health issues is needed and urgent. Among existed interventions, one of the most widely used strategies to help patients and general population to cope with stress is the use of Mental Health Hotlines (MHH),[4] which are 'emergency lines' where people can talk with a mental health professional using a telephone number and/or an Internet browser.

One of the possible tools that can be used is the utilization of religious and spiritual coping strategies,[5] given that a large part of the population use their religion, spirituality or faith to deal with stress and the negative consequences of life problems and illnesses.[6] As an attempt to address this issue, the São Paulo Medical Spiritist Association (AME-SP), a nonprofit organization with scientific, educational and charitable purposes composed of physicians and other healthcare professionals, has created the 'Spiritual Care Hotline Project – Dr Marlene Nobre', with the objective of offering a free and specialized space for listening and support all persons facing spiritual and religious struggles during this difficult time. For this purpose, a free telephone hotline, an online registration and a scheduling platform were established.

Calls take place from Monday to Friday from 7:00 PM to 9:00 PM with five lines available and a duration of 30 minutes for each call. For this purpose, the attendants, 13 health professionals (e.g. psychiatrists, psychologists) were previously trained by a psychiatrist to handle these spiritual issues, to detect 'red flags' and to make a referral if needed. Basically, this interaction includes (i) **presentation,** (ii) the main **reason** for calling, (iii) compassionate and **affective** listening, (iv) **reading** a short text with reflective content, and (v) **prayer** if the attendee feels comfortable.

The hotline has started on 29 May 2020 and at this moment (14 June 2020), 108 appointments have already been requested and calls were made from 107 Brazilian states and 2 countries (Brazil and Portugal). The general impression of the health professionals and the participants is positive, and there is a backlog of calls that are scheduled.

In conclusion, the development of this hotline aims to bridge a gap, in a moment where people are facing religious

struggle and are coping with stressful conditions such as isolation, closed churches and deaths. This strategy is a first step in order to provide holistic care and to minimize mental health problems related to spiritual issues. We encourage the mental health community to support similar initiatives, but we also stress the need to psychiatrics and mental health professionals around the globe to understand patients' spiritual needs and address it when needed, especially in delicate moments, such as the COVID-19 pandemic.

Conflict of interest

The authors declare no conflict of interest.

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Apêndice 02

Outras Produções Bibliográficas do aluno durante o período do doutorado (2021-até o presente).

1. Artigos Completos Publicados em Periódicos

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