

Impacts on cognition of older adults infected by COVID-19: a literature review

Impactos na cognição de pessoas idosas infectadas pela Covid-19: uma revisão de literatura

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ABSTRACT

One of the sequelae of COVID-19 infection is cognitive deficits. The older population is characterized as a high-risk group, making it important to determine the cognitive impacts of the disease in this group. The aim of the present study was to identify the impacts on cognition in older survivors of COVID-19. An integrative literature review was carried out in May 2022. The search was conducted in PubMed, Scopus, Web of Science and BIREME databases, using the following descriptors: “cognition”, “COVID-19”, “older adults” and “aging”. The search yielded 1.958 potentially relevant titles. After excluding duplicates and applying the exclusion criteria to the title and abstracts of the articles selected, 44 studies were read in full, with five included in the final review. The results showed that older survivors of COVID-19 had cognitive deficits ranging from mild to severe impairment. The predominant cognitive impacts in this population were memory functions, verbal functioning, encoding and executive functions. These cognitive impairments affect daily activities of older survivors of COVID-19, highlighting the need for actions to prevent the disease in this population.

Keywords: Aged. Aging. Cognition. COVID-19.

RESUMO

Uma das sequelas que a infecção da Covid-19 causou foram os déficits cognitivos na população acometida. Sendo a população idosa caracterizada como grupo de risco, é importante conhecer os impactos cognitivos causados pela infecção nesse grupo. Este estudo tem como objetivo identificar os impactos na cognição em indivíduos idosos acometidos pela Covid-19. Trata-se de uma revisão de literatura do tipo integrativa, realizada no mês de maio de 2022. Foram consultadas as bases de dados PubMed, Scopus, Web of Science e BIREME, aplicando os seguintes descritores “cognition”, “Covid-19”, “aged” e “aging”. A busca rendeu um total de 1.958 títulos potencialmente relevantes. Após a exclusão das duplicatas e a aplicação dos critérios de exclusão na seleção por título e resumo, foram lidos na íntegra 44 estudos e cinco destes compuseram a amostra final desta revisão. Os resultados obtidos evidenciaram que as pessoas idosas acometidas pela Covid-19 apresentaram déficits cognitivos que variaram entre comprometimento leve a grave. Foi possível identificar os impactos cognitivos nessa população, principalmente em se tratando das funções da memória, da função verbal, da codificação e das funções executivas, além de associar esses comprometimentos cognitivos ao impacto das atividades diárias dos idosos, o que evidencia a necessidade de ações de prevenção da doença, especialmente nessa população.

Palavras-chave: Cognição. Covid-19. Envelhecimento. Idoso.

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INTRODUCTION

Coronavirus is a disease which causes respiratory infections in those affected (Lima, 2020). To date, many different types of coronavirus have been described. SARS-CoV, one of the types studied, causes Severe Acute Respiratory Syndrome (SARS). The novel coronavirus, referred to as SARS-CoV-2, was the strain responsible for the outbreak of COVID-19 (Ferreira & Corrêa, 2020), first detected in 2019 in the city of Wuhan, China (Ministry of Health, 2020).

Neurological sequelae and cognitive impairment are symptoms observed after infection by COVID-19, secondary to multiple factors and direct or indirect interactions of the virus with the cortical and systemic structure of the brain (Ritchie, Chan & Watermeyer, 2020). In individuals with acute respiratory distress syndrome (ARDS), a more severe form of COVID-19, the prevalence of cognitive impact is greater, in which around 20% of patients present long-term cognitive impairment (Sasanejad, Ely & Lahiri, 2019). Additionally, the older population are at highest risk of death from COVID-19, with mortality risk rising with age and the presence of comorbidities (Lloyd-Sherlock, Ebrahim, Geffen & McKee, 2020).

The older population (aged ≥ 60 years, as defined by the Brazilian Statute of Elders, Law 10.741/2003 - Brazil, 2003), is classified as a high-risk group given the greater likelihood of presenting comorbidities and/or compromised immune systems (Costa et al., 2020). Comorbidities associated with worse disease outcomes include cardiovascular diseases, diabetes mellitus and arterial hypertension (Yang et al., 2020).

There is a general consensus in the literature that older people undergo a natural process of biological aging which leads to morphological, biochemical and psychological changes in the body. Cognition is also affected, typically showing some decline with aging, with the extent of these impairments varying widely between individuals (Stern, Barnes, Grady, Jones & Raz, 2019).

Cognition involves the processing of knowledge, which occurs through the integration of different mental functions such as attention, perception, memory, reasoning, language, problem-solving, execution and expressing

of information (Harvey, 2019). Cognitive impairment, depending on its severity, can have major impacts, such as reduced capacity to perform self-care, engage in daily activities, or drive (Stern et al., 2019). Given the importance of cognitive functioning in daily living, determining the impacts on cognition among older survivors of COVID-19 is paramount. Although numerous sequelae of COVID-19 have been documented, further complications continue to be identified by researchers as time goes on. In this sense, the objective of the present integrative review was to identify the impacts of COVID-19 on cognition in older individuals infected by the virus.

MATERIALS AND METHODS

The present study entailed an integrative-type review of the literature. This approach seeks to consolidate the results found in samples on a given topic in an ordered and systematic manner (Ercole, Melo & Alcoforado, 2014). The following research question was devised to guide the study: "What are the impacts on the cognition of older adults infected by COVID-19?".

The search was conducted in May 2022. The criteria for inclusion were empirical articles in English, Portuguese or Spanish, and studies addressing cognitive impacts in the older population infected by COVID-19. The exclusion criteria were: studies involving older adults with other diseases affecting cognition; studies failing to report cognitive status of sample in results; studies investigating the effects of lockdown due to the pandemic and/or addressing other impacts of the pandemic not related to COVID-19 infection; literature reviews, letters, congress or conference abstracts, posters, reports, dissertations, theses and book chapters; and off-topic (not related to guiding question) studies.

A search of the literature held on the following databases was conducted: PubMed, Scopus, Web of Science and BIREME. The search strategy employed the following descriptors: "cognition", "COVID-19", "aged", "aging", extracted from Medical Subject Headings (MeSH) and from Health Science Descriptors (DeCS) (Table 1).

Table 1
Search strategy for each individual database.

Databases	Descriptors	Number of studies retrieved
BIREME	cognition AND COVID-19 AND (aged OR aging)	262
PubMed	cognition AND COVID-19 AND aged	1025
Scopus	cognition AND COVID-19 AND aged	486
Web of Science	cognition AND COVID-19 AND aged	185

Source: The authors.

The data were keyed into spreadsheet (Microsoft Office - Excel®) tables to aid article screening and selection. The information extracted from the articles reviewed was synthesized in the form of a table containing the study parameters (references, title, sample, objectives, assessment instruments, results of cognitive assessments). References were created and managed using the Mendeley software package.

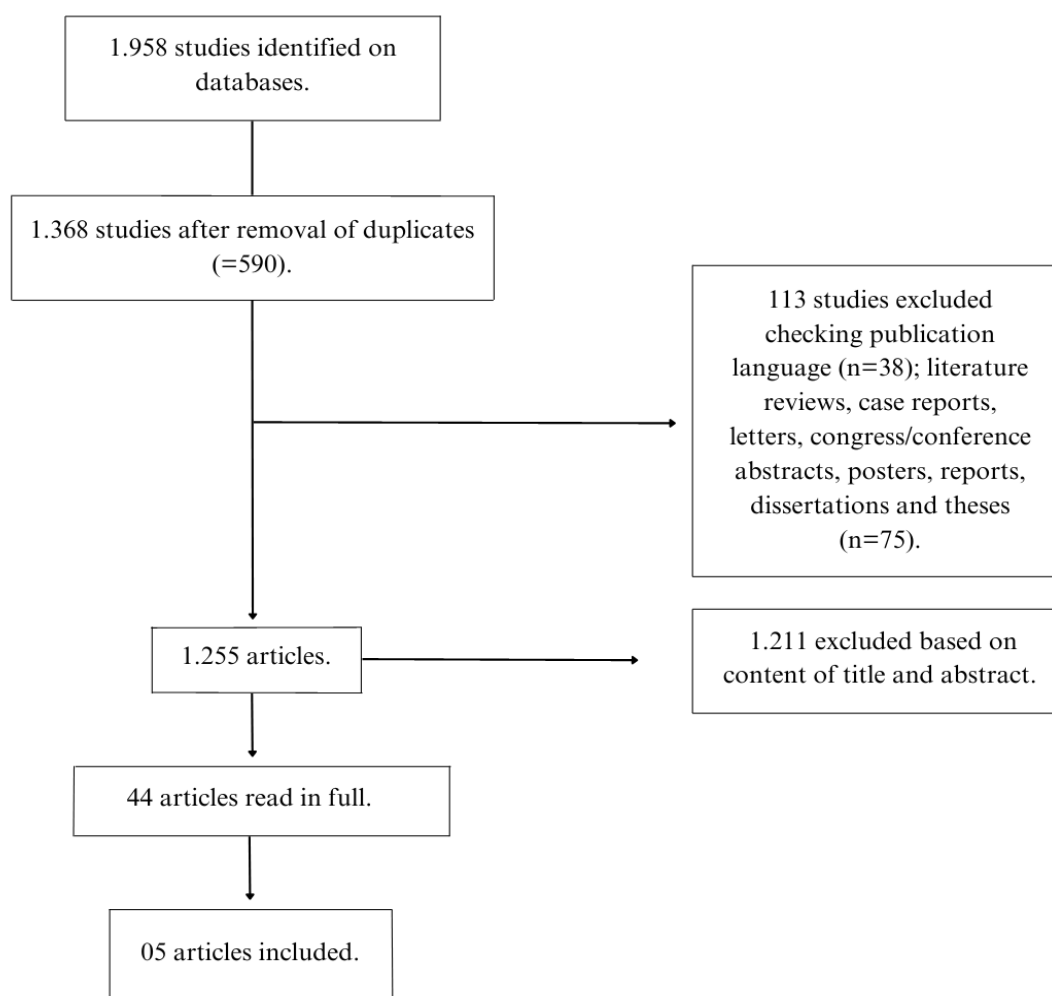
All article screening and evaluation processes were performed independently by one of the authors. In the

event of doubt over the eligibility of studies for inclusion, another researcher examined the study and a consensus was reached on the selection.

The initial search resulted in the retrieval of 1.958 articles. After exclusion of duplicates using the EndNote software, exclusion criteria were applied based on title and abstract, leading to the selection of 44 articles for full reading. Following analysis, a final total of five studies were included in the review (Figure 1).

Figure 1

Flow diagram of article selection process for inclusion in integrative review of the literature.



Source: The authors.

RESULTS AND DISCUSSION

A total of five studies were selected for inclusion in the review. Regarding country of publication, two of the studies were conducted in China (Liu et al., 2021, 2022), while one article was published in Italy (Devita et al., 2021), one in the USA (Whiteside et al., 2021), and one in Sweden (Larsson et al., 2021). For the design of the studies reviewed, one was a retrospective, observational clinical study (Devita et al., 2021), one was a cohort study (Liu et al., 2022), one was a cross-sectional longitudinal study (Liu et al., 2021), one was a case series (Whiteside et al., 2021) and one was a cross-sectional prospective

descriptive study (Larsson et al., 2021).

The parameters of author, year of publication, sample, objective, instruments used for assessing cognition, and main cognitive performance results are presented in Table 2. Given the recency of the topic, the studies reviewed were all published within the 2021-2022 window. Each of the studies was published in a different journal: *Molecular Neurodegeneration* (Liu et al., 2021), *International Journal of Environmental Research and Public Health* (Larsson et al., 2021), *Clinical Neuropsychologist* (Whiteside et al., 2021), *JAMA Neurology* (Liu et al., 2022), and *Frontiers in Psychiatry* (Devita et al., 2021).

Table 2

Characteristics of studies for author, publication year, sample, objective, cognitive assessment instruments and cognitive performance results.

Author/year	Sample	Objective	Instruments used	Results
Devita et al. (2021)	299 participants aged 18-90 years; 90 individuals \geq 65 years.	To evaluate the differences in cognitive and psychological sequelae of COVID-19 between younger and older adults, regardless of being admitted to the ICU or not.	MoCA and PCL	The only significant MoCA score predictors were age, with cognitive performance decreasing as age increases, and the duration of hospitalization. Of the whole sample, 30.7% suffered from cognitive frailties (i.e., difficulties in memory and/or in focusing attention) after COVID-19 infection.
Whiteside et al. (2021)	Three individuals aged 62-75 years	To investigate cognitive sequelae of 3 patients in acute rehabilitation post-COVID-19.	WAIS-IV, RDS, HVLTR, RBANS, BDAE, O-TMT, TSAT, ILS, BAI and GDS	The three patients all demonstrated deficits on formal neuropsychological testing, ranging from mild to severe. The worst deficits found were in encoding, verbal fluency and executive functions. The anxiety symptoms found may have contributed to cognitive difficulties.
Larsson et al. (2021)	211 patients with mean age = 65.1 years (114 \geq 65 years).	To evaluate physical function, cognitive functioning, and daily activities in patients hospitalized during the 1 st and 2 nd waves and to investigate differences depending on age and ICU admission	MoCA and TMT	The older patients (\geq 65 years) demonstrated lower cognitive function than the younger patients. There was no significant difference in cognitive function between the patients depending on ICU admission. The ability to perform daily activities was significantly lower in the older age group.
Liu et al. (2021)	1539 patients and 466 control individuals, aged $>$ 60 years.	To assess current cognitive status and longitudinal cognitive decline in older patients recovered from COVID-19.	TICS-40 and IQCODE	Compared with controls, both severe and non-severe COVID patients had cognitive decline. Compared with non-severe patients, severe cases had higher educational levels.
Liu et al. (2022)	1438 patients and 438 control individuals, aged 66-74 years.	To investigate the 1-year trajectory of cognitive changes in older survivors of COVID-19	TICS-40 and IQCODE	COVID-19 survivors had lower TICS-40 scores than control individuals at both 6 months and 12 months after patient discharge. More severe patients had lower TICS-40 scores than non-severe cases and control individuals.

Source: The authors.

Note. BAI = Beck Anxiety Inventory. BDAE = Boston Diagnostic Aphasia Examination. GDS = Geriatric Depression Scale. HVLTR = Hopkins Verbal Learning Test – Revised. IQCODE = Informant Questionnaire on Cognitive Decline in the Elderly. ILS = Independent Living Scale. MOCA = Montreal Cognitive Assessment. O-TMT = Oral Trail Making Test. PCL = Post-traumatic Stress Disorder Checklist. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status. RDS = Reliable Digit Span. TICS-40 = Telephone Interview for Cognitive Status. TSAT = Test of Sustained Attention and Tracking. ICU = Intensive Care Unit. WAIS-IV = Wechsler Intelligence Scale for Adults.

The results of this review corroborated the presence of cognitive impairment in older adults after COVID-19 infection (Devita et al., 2021; Larsson et al., 2021; Liu et al., 2021; Whiteside et al., 2021; Liu et al., 2022). The studies which specifically addressed the cognitive functions affected reveal reduced performance for memory and/ or attention, encoding of new information, verbal fluency, and executive functions (Devita et al., 2021; Whiteside et al., 2021). These impaired functions after infection negatively affect the life of the older population, who experienced difficulties managing daily activities, despite being able to take care of themselves (Larsson et al., 2021). Difficulty with activities of daily living was also addressed in Stage III of the cognitive functioning model developed by Whiteside et al. (2021). Another two studies showed lower cognitive performance on the assessments

applied (Liu et al., 2021, 2022).

Devita et al. (2021) found lower scores on the MoCA for the older population, i.e. poor performance compared to the younger adults included in the study sample. Over 30% of the sample had cognitive deficits, affecting cognitive functions such as memory and/or attention after COVID-19 infection. The factors in the study that proved significant predictors of MoCA score were age and duration of hospitalization.

In the study of Whiteside et al. (2021), the sample included three patients, comprising two men aged 62 and 75 years, and one woman aged 73 years, while education of patients ranged from 12-14 years. The three patients had comorbidities, with all presenting hypertension and hyperlipidemia, while comorbidities included coronary artery disease, obstructive sleep apnea, type II diabetes,

Guillen-Barre, among others. All of the patients had severe COVID-19 symptoms and received long-term ICU treatment for 20-42 days, and two patients were intubated for 14 and 18 days, respectively. On administration of a neuropsychological battery over the telephone, the three patients showed performance deficits on neuropsychological tests ranging from mild to severe for different cognitive functions such as encoding, verbal fluency, executive functions, attention and language.

The patients assessed in the study by Whiteside et al. (2021) exhibited deficits in encoding new information and had below expected scores given the patients' educational history. In two out of the three patients, the authors noted emotional issues and anxiety and/or depression that may have been another contributory factor impacting cognitive performance. According to the authors, all of the patients met criteria for multiple-domain mild cognitive impairment. The results showed cognitive deficits after severe COVID-19 infection and hospitalization, with greatest impact on encoding, verbal fluency and executive.

Whiteside et al. (2021), in the same study, proposed a three-stage model of cognitive functioning after infection called Cognitive COVID-19. Stage I involves individuals with no detectable cognitive deficits associated with COVID-19 infection; Stage II includes individuals presenting mild cognitive symptoms associated with COVID-19 infection and/or treatment, generally patients who had prolonged mechanical ventilator and/or ICU treatment; and lastly, Stage III involves individuals with moderate-to-severe cognitive symptoms associated with COVID-19 infection. This last stage includes patients with associated complications, such as hypoxia, ARDS, stroke, etc. These individuals are likely to have difficulty with activities of daily living, such as returning to work, driving, or being independent. The authors point out that individuals may move in either direction between stages.

The study by Larsson et al. (2021) involved a total sample of 221 individuals, of which 114 were older adults ≥ 65 years. There was a greater number of men (79 males) than women (35 females) in the cohort assessed. Of this overall sample, 51 patients were admitted to the ICU and 31 were intubated during the hospital stay. Mean length of ICU stay was 18.5 days. Mental state was assessed using the MoCA, where older patients scored below the cut-off for cognitive impairment, suggesting difficulties performing cognitive tasks. There was no significant difference in cognitive function between the patients depending on ICU admission. The authors found that the ability to perform daily activities was significantly lower in the older age group compared to the younger age group, due to cognitive impairment post-infection impacting daily activities of these individuals. A concern raised by the study was the different time points of assessment during the hospital stay and that this timing may have influenced results. Moreover, the study suggested that older patients

may manifest cognitive impairment at hospital discharge after COVID-19 infection.

The study by Liu et al. (2021) investigated a sample of 1.539 COVID-19 patients aged ≥ 60 years and a control group of 466 uninfected spouses. The cognitive assessment was performed over the telephone using the TICS-40 and IQCODE. Results showed that severe COVID-19 patients were older, had a higher proportion of males and more frequently had hypertension, a history of stroke, coronary heart disease, and chronic obstructive pulmonary disease (COPD). Severe COVID-19 patients had comparable frequencies of diabetes mellitus and hyperlipidemia relative to controls. Compared with non-severe COVID-19 patients, severe cases had higher educational levels and also higher frequencies of ICU admission, receiving mechanical ventilation, high-flow oxygen therapy and higher incidences of *delirium* during hospitalization.

The authors also reported an analysis of current cognitive status and status at six months in older patients with COVID-19. At the first timepoint, patients had lower scores on the TICS-40 relative to the control group, while severe patients had even lower scores than non-severe patients. After hospital discharge, patients had higher scores on the IQCODE compared with the control group, suggesting greater cognitive decline. Also, results showed that patients with severe COVID-19 infection scored higher than non-severe cases.

In the same study by Liu et al. (2021), the authors constructed regression models to investigate the potential risk factors for cognitive impairment at first and second assessment in COVID-19 patients. The univariate regression analyses revealed the factors age, COVID-19 severity, ICU admission history, *delirium*, history of stroke, coronary heart disease and COPD were associated with cognitive impairment at the first and assessment, whereas the factors age, lower educational level, COVID-19 severity, ICU stay, *delirium*, hypertension, diabetes, history of stroke, coronary heart disease and COPD were associated with long-term cognitive decline.

On the linear regression model adjusted for age and sex, the factors COVID-19 severity, ICU admission, *delirium* and COPD were associated with lower scores on the TICS-40. However, high-flow oxygen therapy proved a protective factor against longitudinal cognitive decline.

The investigation by Liu et al. (2022) involved a study sample of 1.438 older COVID-19 patients and a control group of 438 uninfected spouses. Overall, participant age ranged from 66-74 years, mean educational level was 12 years, and the COVID-19 group comprised predominantly women (747 females; 691 males). Length of hospital stay ranged from 14 to 34 days. Compared with non-severe cases, individuals with severe infection were older, had lower educational level, a greater number of comorbidities (hypertension, diabetes, stroke, coronary

heart disease and COPD), higher frequencies of ICU admission, use of mechanical ventilation, high-flow oxygen therapy and longer length of hospital stay. The authors also analyzed cognitive impairment 12 months after hospital discharge, where COVID-19 survivors had lower TICS-40 scores than controls at both six and 12 months after patient discharge. Individuals with severe disease had lower scores on the assessment than less severe patients, indicating worse cognitive impairment. The overall incidence of cognitive impairment in survivors 12 months after discharge was 12.45%.

In the present review, of the five study samples analyzed, three contained a predominance of males (Devita et al., 2021; Larsson et al., 2021; Whiteside et al., 2021). With regard to hospital stay, the studies reported similar length of stay, ranging from 18 to 40 days (Larsson et al., 2021; Whiteside et al., 2021; Liu et al., 2022).

Some of study samples proved similar for comorbidities, consistent with the study by Yang et al. (2020). The studies by Liu et al. (2021), Whiteside et al. (2021) and Liu et al. (2022) all reported cardiovascular disease and arterial hypertension as comorbidities.

All patients included in the studies reviewed were hospitalized and a proportion of these patients required ICU treatment, were intubated or placed on mechanical ventilation. These interventions were associated with severe cases of COVID-19 and with greater cognitive impairment (Liu et al., 2021, 2022). Regarding ICU admission, there was no significant difference in cognitive performance among patients (Larsson et al., 2021), although other studies have shown that, irrespective of diagnosis, ICU patients present cognitive deficits, with longer ICU stays associated with greater cognitive impairment (Zhan et al., 2020). This correlation was also found in the study by Liu et al. (2021) upon associating risk of cognitive impairment with ICU admission.

Associations between years of education and treatment with high-oxygen therapy were found. In the study by Liu et al. (2021), high educational level was considered a protective factor for cognitive impairment

in the sample where, together with high-flow oxygen therapy intervention, was associated with higher TICS-40 score. This relationship with oxygen therapy is congruent with the theory in the literature on the damage to brain structures caused by the COVID-19 virus, such as hypoxia (Perisse et al., 2022). Hypoxia is low oxygenation in the tissues (Fortis & Nora, 2000), whereby a low percentage of oxygen in the brain may be a factor contributing to neurological impairment, particularly in brain regions more associated with hypoxia, such as the hippocampus (Miskowiak et al., 2021).

In general, there is a need for greater understanding of the clinical condition of older survivors of COVID-19, particularly in view of the rise in cases of cognitive impairment after discharge. Neuroimaging studies should also be conducted to elucidate which aspects promote decline in cognitive abilities and to serve as a time-control post-exposure to the virus, considering the role of neural plasticity after infection by SARS-COV-2. This plasticity may be mediated by components of cognitive reserve or influenced by other factors such as different types of treatment, health care and the process of restoring function in neural networks.

CONCLUSION

Given that COVID-19 has global deleterious effects on the organism, future studies elucidating these impacts should be conducted, with an emphasis on cognitive sequelae that may have short or long-term effects in all population strata, but especially the older population. This review revealed the cognitive impacts in the older population, with the functions of memory, verbal functioning, encoding, and executive functions proving the most affected, and also confirmed the association of these cognitive deficits with impacts on the daily activities of these individuals. Thus, research identifying the impacts of COVID-19 infection on the cognition of older survivors of COVID-19 is essential, where this knowledge can help inform interventions and public policies to promote well-being and health in this population.

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