CHAPTER 124

The importance of early diagnosis of delirium in elderly patients with Covid-19

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ABSTRACT
Introduction: Delirium is a transient neuropsychiatric syndrome considered a geriatric emergency, related to prolonged periods of hospitalization and which contributes to an increase in the mortality rate, especially in the elderly affected by SARS-CoV-2. Objective: To carry out an integrative review of the literature in order to list factors of importance of screening, anamnesis and physical examination to contain the early manifestation of delirium in elderly patients affected by Covid-19. Methodology: This is an integrative literature review carried out by searching for scientific articles in Pubmed (NCBI), Latin American and Caribbean Health Sciences (Lilacs) and Scientific Electronic Library Online (SciELO) databases.). For this, the descriptors were used: Coronavirus, Delirium, Elderly and the filter "PUBLICATION DATE" was selected with the option "5 YEARS", in the aforementioned databases. The articles selected through the PICO strategy were submitted to methodological rigor and level of evidence analysis. Results: 155 scientific articles were found; however, 17 articles were selected after analyzing the inclusion and exclusion criteria. Of this sample, 41, 17% of the selected studies reported that delirium is associated with high mortality and morbidity, in addition to being often underreported. Screening using tools such as the Chart-Based Delirium Identification Instrument is essential for early detection of delirium. Conclusion: Multiprofessional team work aligned with medical work is necessary for early intervention of delirium in elderly patients with Covid-19.

Keywords: Coronavirus, Delirium, Elderly.

1 INTRODUCTION

Delirium, also known as acute confusional state, is a transient neuropsychiatric syndrome. It is called deficiencies in several aspects, such as attention, consciousness and cognitive function. Most presentations are preceded by nonspecific signs and symptoms, characterized by restlessness, anxiety, irritability and sleep disturbances (Maldonado, 2017).

Because it is the most prevalent acute confusional cognitive disorder in the elderly, an epidemiological and pathophysiological study is needed to reduce the risk of complications in these patients. The highest prevalence of delirium occurs in men who are approximately 65 years of age or older and have triggering factors for the development of delirium (Moraes-Júnior et al., 2019).

Among the triggering factors of delirium, we highlight associations with infections, water electrolysis disorders, some drugs such as antiallergic and sedatives, and cardiovascular and endocrine system diseases are also common (Moraes-Júnior et al., 2019). Emmerton and Abdelhafiz (2020) relate the

occurrence of delirium to the presence of comorbidities, multisystem dysregulation, diseases of the neurological system and the environment in which the patient lives.

Delirium is considered a geriatric emergency and is related to prolonged periods of hospitalization, in which mortality rates are higher. The diagnosis is made through anamnesis and physical assessment of the patient, and therefore knowing their clinical characteristics and performing a detailed physical examination is crucial for assertiveness in the analysis (Unicovsky; Santarem, 2020).

From the emergence of the infection caused by SARS-CoV-2, called by the World Health Organization (WHO) of Covid-19, in December 2019, in the city of Wuhan, China, it was observed that patients infected by this disease had severe respiratory symptoms, consistent with a respiratory distress syndrome (SAR), as well as the effects on the incidence of delirium in hospitalized patients, showing that delirium can be triggered by isolated factors and that SARS-CoV-2 infection can be an important trigger (Bosco et al., 2020).

There is a high incidence of elderly people who have preexisting comorbidities, making them more fragile, increasing the risk of worsening the patient with Covid-19 and, consequently, prolonged hospitalization, which presupposes a worse prognosis for the patient. Based on this information, it is important to research and establish delirium screening in patients with Covid-19, in order to reduce the risk of this clinical condition and facilitate early intervention and improve future outcomes (Emmerton; Abdelhafiz, 2020). Thus, it is essential to understand the relationship between Covid-19 and delirium, especially in the elderly population, in order to minimize the effects arising from this relationship. In this context, the objective was to carry out an integrative review of the literature, in order to relate the importance of screening in elderly patients who were affected by Covid-19, who needed prolonged hospitalization, and its evolution with the early occurrence of delirium.

2 METHODOLOGY

This is a descriptive-exploratory research with the objective of investigating, through screening, the potential for delirium manifestation in the elderly, who needed prolonged hospitalization due to Covid-19, allowing the construction of an integrative literature review, following the model described by Soares et al. (2006). Bibliographic searches were carried out in the virtual databases: Pubmed (NCBI), Latin American and Caribbean Literature on Health Sciences (Lilacs) and the *Scientific Electronic Library Online* (SciELO) from April 7 to June 28, 2022 For this, the descriptors were used: *Coronavirus, Delirium, Elderly* , joining them through the Boolean operator " *AND* ".

The scientific question that guided the search strategy of the present study was developed by the authors and followed the guidelines of the PICO strategy, being: *What is the importance of screening for delirium in elderly patients who had Covid-19 and required hospitalization?* With the inclusion criteria, full scientific articles available *online were adopted* that contained the descriptors in the title or abstract,

written in Portuguese, Spanish and English, using the filter “PUBLICATION DATE” and selecting the option “5 YEARS”, in the aforementioned databases.

Works that did not meet the central theme and duplicated works were also excluded. In addition, the articles included in this study were evaluated for methodological rigor, using an instrument adapted from the *Critical Appraisal Skills Program* (CASP), of the *Public Health Resource Unit* (PHRU, 2006). This adapted tool (Chart 2) presents 10 items (maximum 10 points) and classifies the works according to this score: 6 to 10 points, good methodological quality and reduced bias; 5 points or less, satisfactory methodological quality with increased risk of bias. In the selected studies, a second instrument from the US *Agency for Healthcare and Research and Quality* (AHRQ) was also applied. This, in turn, according to Stillwell et al. (2010) presents the hierarchical classification according to seven levels of evidence according to the research design.

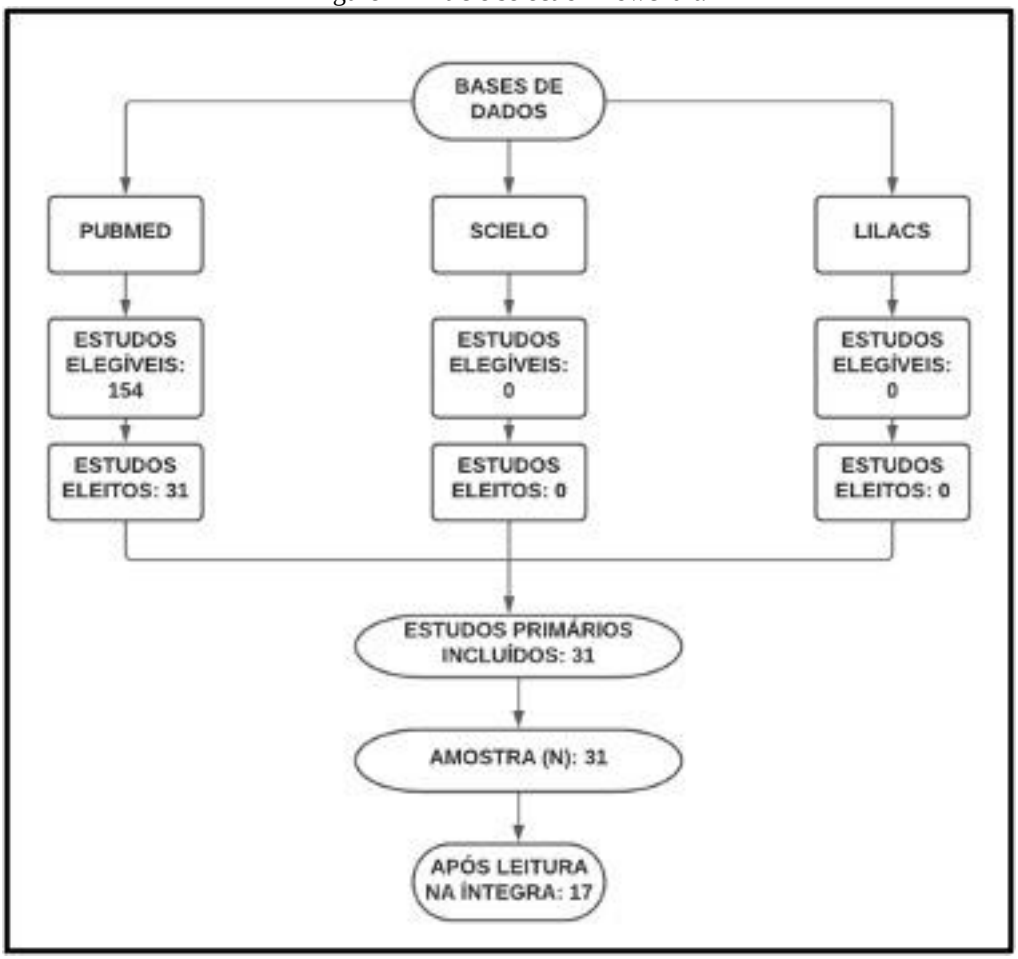
3 RESULTS

Based on the search strategy used, 154 scientific articles were obtained, all from the Pubmed database.

After the first analysis, 31 primary articles (20.1%) were selected for full reading. Subsequently, the articles underwent a final analysis, regarding the adequacy to the theme of the review and exclusion of duplicates, which resulted in the final selection of 17 articles ((11%) (**Figure 1**).

The selected works were analyzed allowing to extract from each of the works their main results and conclusions obtained that allowed answering the question of this review. Finally, the articles were numbered from N1 to N17, in order to include the essential information of each work, such as: title, year, author, type of study and results (**Table 1**).

Figure 1- Article selection flowchart.



Source: Authors, 2022.

Table 1 - Synthesis of articles included in this study (n=17), 2022.

Number/Article	Kind of study	Results and Conclusions
N1 . Alkerydy et al. *Journal of the American Geriatrics Society, 2020.*	Case report.	Falls and delirium are considered atypical presentations of Covid-19. Recognition of these conditions is critical for an effective diagnosis and the provision of appropriate care.
N2 . Benussi et al. *Neurology, 2020.*	Single-center retrospective cohort study.	Study carried out with 173 patients, 56 were elderly and contracted Covid-19. It was observed that in-hospital mortality and delirium rates were significantly higher in this group.
N3 . Garcia-Grimshaw et al. *Journal of the Academy of Consultation-Liaison Psychiatry, 2019.*	Retrospective cohort study.	A study was carried out with 1,017 patients with Covid-19, with 164 confirmed cases with a diagnosis of delirium. Patients who developed delirium had dyspnea and muscle pain more often than those without delirium. Improving preventive measures can reduce the risk of functional and cognitive sequelae over time associated with this neuropsychiatric complication.

N4. Helms et al. *Critical care (London, England), 2020.*	Bicentric cohort study.	It is suggested that severe acute coronavirus syndrome can also invade the central nervous system and be responsible for neurological diseases. Thus, it is considered that delirium may be secondary to systemic inflammation to SARS-Co V-2.
N5. Kennedy et al. *JAMA network open, 2020.*	Multicenter cohort study.	Delirium is associated with high mortality and morbidity and is often undiagnosed. In this study, 28% of elderly patients with Covid-19 had delirium as the sixth most common symptom. Patients who presented delirium in the framework of Covid-19 have a worse prognosis, including ICU stay and hospital death.
N6. Marengoni et al . *Age and ageing, 2020.*	Retrospective cohort study.	A study of 91 patients showed that 25 patients had delirium. 72% of patients with delirium died compared with 31.8% of those without delirium. Patients with delirium were older and more likely to be frail. Patients with delirium were four times more likely to die during hospitalization when compared to those without.
N7. Mattace-Raso et al. *Clinical interventions in aging, 2020.*	Retrospective cohort study.	A study of 123 patients aged 60 years or older showed that 47 had signs and symptoms of delirium. Of these, 39 developed delirium during hospitalization. Delirium screening was done using the Delirium *Observation Screening Scale* (DOSS). A score greater than or equal to three indicative of delirium was followed by a medical evaluation.
N8. Mcloughlin et al. *European geriatric medicine, 2020.*	Point prevalence study.	Two non-modifiable risk factors for delirium presented were age group and male gender. Delirium was prevalent in hospitalized patients with Covid-19, however, it was not always detected, suggesting that it is a clinical complication and the sequelae deserve quality follow-up.
N9. Duggan.; Van; Ely. *Critical care clinics, 2021.*	Review article.	The elderly are more likely to develop delirium due to predisposing risk factors, which include: dementia, hearing, visual and functional impairment and age group. Thus, for the prognosis to be positive, it is essential to perform screening for early identification and optimize non-pharmacological measures, reducing the suffering of patients and family members.
N10. Forget et al. *Clinical interventions in aging, 2021.*	Retrospective cohort study.	This study was conducted with 127 patients hospitalized with Covid-19 and aged 65 and over. Delirium was highly prevalent and was a frequent early manifestation. In addition, it was the main initial clinical presentation of Covid-19 in 10% of cases. However, 49% of patients developed delirium during disease manifestation. Associated with this, high CRP levels in the first 3 days of hospitalization were linked to a higher risk of developing this syndrome. Added to this, it was a predominant initial neurological

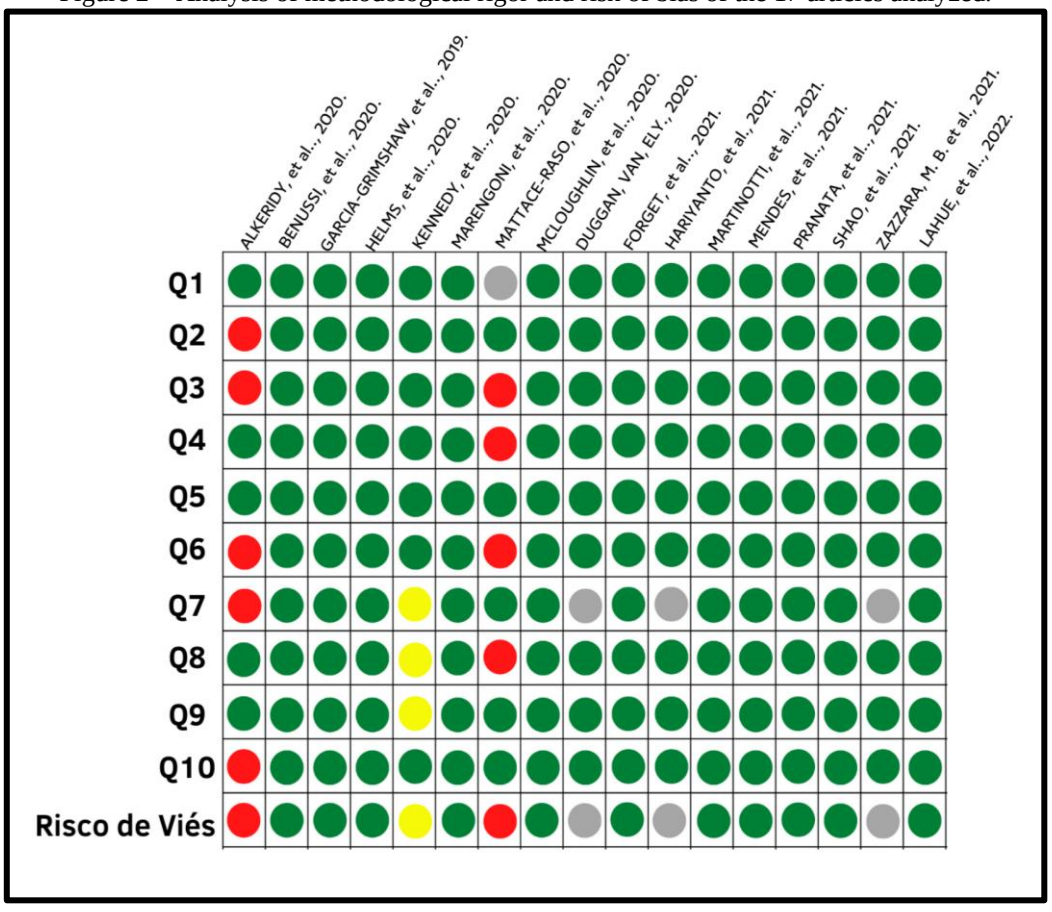
		manifestation of Covid-19 in 10% of patients.
N11. Hariyanto et al. *Journal of psychiatric research, 2021.*	Systematic review.	This analysis from 20 selected studies showed that delirium symptoms on admission were related to poor Covid-19 outcomes, that is, delirium symptoms on admission were associated with a more severe state of the SARS-CoV-2 virus. including possible mortality. It is important for clinicians to add delirium as one of the common presenting symptoms of Covid-19 in the elderly. In this way, it would help to better identify poor outcomes and related mortality.
N12. Martinotti et al. *Neurological Sciences: Official Journal of the Italian Society of Neurology and the Italian Society of Clinical Neurophysiology, 2021.*	And multicenter observational study .	Eighty hospitalized patients with Covid-19, with a mean age of 74.7 years who showed signs of delirium were selected for studies. Thus, 45 patients underwent neuropsychological screening for cognitive deficits on admission. It is concluded that advanced age, cognitive deficit, total number of drugs in use and use of antipsychotics were the most relevant risk factors for the development of delirium.
N13. Mendes et al. *The journals of gerontology. Series A, Biological sciences and medical sciences, 2021.*	Retrospective cohort study.	Of a total of 235 patients aged 65 and over hospitalized with Covid-19, 48 had delirium. This condition was hypoactive in 41.6% of the cases and hyperactive and mixed in 35.4% and 23%, respectively. The presence of delirium did not change the time from onset of symptoms to hospitalization or even length of stay, but it was associated with a higher risk of dying.
N14. Pranata et al. *Archives of gerontology and geriatrics, 2021.*	Systematic review.	The result was an increase in mortality in patients with Covid-19 who had delirium. The methods used to assess confusion were 4AT, *Chart-Based Delirium Identification Instrument*, Diagnostic and Statistical Manual of Mental Disorders 4 and 5. Delirium in patients with Covid-19 was associated with length of hospital stay, need for intensive care and mechanical ventilation . In addition, patients have a worse functional and cognitive outcome after discharge.
N15. Shao et al. *Age and ageing, 2021.*	Systematic review.	The risk of neuropsychiatric complications in the elderly with Covid-19 may be due to viral factors, in which an invasion of the central nervous system occurs, inducing inflammatory mediators, disease and treatment factors. In this systematic review and meta-analysis, it was possible to find that 1 in 3 patients develop delirium and are associated with a threefold higher mortality.

N16. Zazzara et al. **A** *ge and ageing, 2021.*	Retrospective cohort study.	Adverse outcomes in the face of Covid-19 are associated with frailty and vulnerability to physiological stressors, thus, older adults and comorbid patients have the most severe course of the pathology. Early diagnosis is important, and the 4-AT screening tool is used to detect delirium.
N17. lahue et al. *BMC psychiatry, 2022.*	Single-center retrospective cohort study.	Of a total of 99 diagnosed with Covid-19, 43 patients met the criteria for delirium at any time during their hospitalization. In addition, among patients with delirium, 24 were 65 years of age or younger. In addition, patients who fell into the high Covid-19 severity groups within 24 hours of admission were 7.2 times more likely to develop delirium compared to those in the lowest category.

Source: Authors, 2022.

The evaluation of methodological rigor resulted in 11 works (64.70%) that presented good methodological quality and reduced bias, which scored (**Figure 2** - circles in green). On the other hand, 3 studies showed good quality and low bias (**Figure 2** - gray circles) and only 2 studies (11.76%) showed satisfactory methodological quality with increased potential for bias (**Figure 2** - red circles)

Figure 2 – Analysis of methodological rigor and risk of bias of the 17 articles analyzed.



Source: Authors, 2022.

Regarding the levels of evidence, it was found that 12 studies (70.58%) had level of evidence IV (N2, N3, N4, N5, N6, N7, N8, N10, N12, N13, N16 and N17), 2 (11.76%) had evidence level VI (N1 and N9), another 2 (11.76%) had evidence level V (N11 and N14) and 1 study (5.88%) had evidence level I (N15).

4 DISCUSSION

Delirium can be characterized as a clinical syndrome that can cause acute impairment of cognition and attention, it can also lead to hallucinations and behavioral disorders. This clinical picture can be triggered by a general medical condition, environmental factors or the use of some medication (Ito; Pedri, 2013). In addition, its development can start in a short period of time, for example, in hours or days, which makes it different from the symptoms of dementia and other cognitive disorders; it may be reversible because it is an organic cause and fluctuates throughout the day (Ito; Pedri, 2013).

After analyzing the results (Table 1), it is confirmed that the following are non-modifiable risk factors for delirium: male gender, being elderly, the total number of medications in use and use of antipsychotics, in addition to having dementia and/or disability auditory, visual and functional. It may also be associated with poor clinical outcomes, including prolonged hospital stay, admission to long-stay institutions, need for intensive care, use of mechanical ventilation, and loss of independence (García-Grimshaw et al., 2020; Mcloughlin et al. , 2020; Mattace-Raso et al., 2020; Duggan; Van; Ely, 2021; Martinotti et al . 2021).

The elderly have delirium as the sixth most common symptom in Covid-19, and the prevalence was higher in hospitalized patients, however, they are not always diagnosed, suggesting a clinical complication and sequelae that affect the quality of life of these people and may even even favor death, making delirium an important risk marker for identifying a poor prognosis (Marrengoni et al, 2020; Mcloughlin et al., 2020; Kennedy et al., 2020).

Studies confirm that severe acute coronavirus syndrome may be responsible for neurological diseases, due to a direct effect of viral invasion in the central nervous system, to inflammatory mediators induced by the infection, to factors of the disease and of the treatment for Covid-19 itself. Because of this, patients may have altered consciousness and cognition disorders (Benussi et al., 2020; Helms et al., 2020; Hariyanto et al., 2021; Shao et al., 2021; Lahue et al., 2022) .

There are several types of delirium in elderly people hospitalized with Covid-19, the most prevalent being the hypoactive condition, followed by the hyperactive and mixed. Patients with cognitive impairment were more likely to develop delirium compared to those who were cognitively normal before contracting the disease. Another observation made through the studies is that most cases of delirium occurred on the first day of hospitalization, which proves and emphasizes the importance of comprehensive care from the onset of the first symptoms (Forget et al . , 2021; Mendes et al., 2021).

According to the study by Sharon and Inouye (2021), contributors to the development of delirium in Covid-19 are the cytokine storm and immune dysregulation that trigger neuroinflammation (in the brain and meninges) and hypercoagulability. In addition, they state that there are other precipitating factors such as various medications with psychoactive effects, mechanical ventilation, ICU stay, immobility, malnutrition, sleep disruption, social isolation and emotional stress. Therefore, even during the Covid-19 pandemic, delirium can be associated with several reversible factors.

Koftis *et al.* (2020), state that in addition to the causes mentioned above for the development of delirium, they recognize that it can be a manifestation of direct invasion of the central nervous system (CNS) or induction of inflammatory mediators of the CNS. In addition, he understands that it may be a secondary effect of the failure of other organs, an effect of the strategies used for sedation or environmental factors, which include social isolation. Based on experience carried out in the study, it is also believed to be associated with seizures, impaired consciousness, or signs of increased intracranial pressure.

Based on this information, approaches are suggested for the prevention and management of delirium during Covid-19 that can be incorporated into your routine, especially in hospitals. Among them, we can mention: providing communication boards, guidance sheets, remote visits, providing therapeutic activities, encouraging mobility and exercise in the isolation environment, carrying out medication review and educating the team about adverse effects in the elderly, among others. others (Sharon; Inouye, 2021).

According to Leslie et al . (2008), the development of delirium is often associated with functional decline, increased morbidity, increased length of hospital stay, and increased mortality. According to this information, 41.17% (N2, N5, N6, N7, N11, N13 and N15) of the articles analyzed in this study confirm that delirium is associated with high mortality and morbidity and is often not diagnosed.

One of the ways to perform screening for delirium are the *Delirium Observation Screening Scale* (DOSS) methods, the 4-AT tool, the *Chart-Based Delirium Identification Instrument* and the Diagnostic and Statistical Manual of Mental Disorders 4 and 5. However, other methods and signs and symptoms should not be ignored, such as delirium and the absence of typical symptoms of Covid-19 (cough, fever and shortness of breath) . Through early detection, infection and death control in this vulnerable category of patients is facilitated, making care delivery as appropriate as possible (Alkeridy et al., 2020; Hariyanto et al., 2021; Mattace- Raso et al., 2020; Pranata et al., 2021; Zazzara et al., 2021).

Furthermore, Neto et al. (2021) mentions that long-stay institutions for the elderly, in addition to collective environments, have individuals who may be vulnerable to infection by the new coronavirus. The author also mentions that elderly people with delirium, for example, may suffer from the effect of social isolation and confuse this situation with the severity of the Covid-19 infection, making it difficult for caregivers to provide assistance.

Already, for Unikovsky; Santarem (2020), the care of the elderly patient with delirium during the Covid-19 pandemic by the nursing team is fundamental and they should receive training for the early recognition of the signs and symptoms of this condition. Thus, with evidence and other skills in care, it will

be possible to develop safe and comprehensive care. In this sense, the research in question returned 47.05% (N1, N3, N4, N8, N10, N14, N16 and N17) articles which are in line with the research of these authors when referring that the elderly hospitalized with Covid-19 are more likely to develop delirium.

One of the limitations found in this research is the scarcity of studies comparing delirium superimposed on dementia with dementia alone. According to the study by Dugga n; Van and Ely (2021), about 80% of patients with dementia manifest behavioral and psychiatric changes at some point in the establishment of this disease. This can hinder the identification of a possible delirium condition, as the symptoms may be similar. These symptoms can include altered sleep quality, anxiety, paranoia, agitation, hallucinations, and irritability. Thus, it is imperative to understand a patient's initial psychiatric status in order to find out whether one of these clinical presentations is likely to be caused by delirium.

Another limitation found is the difficulty in finding studies that report the diagnostic validity of screening tools for delirium. In this sense, Dugga n; Van and Ely (2021) point out that some of these testing tools that have been validated in patients with dementia previously require patients to be verbal, for example, which can be a barrier to the implementation of this test in ICUs.

Finally, it is worth noting that investigation of the treatment or prevention of delirium is crucial and implements practices for recovery. Thus, it is important for health professionals to assess delirium and monitor symptoms in patients with Covid-19, in order to organize and early diagnosis of these patients, avoiding the high mortality rate (Benussi et al. , 2020; Helms et al., 2020; Hariyanto et al., 2021; Shao et al., 2021; Lahue et al., 2022).

It is worth noting that delirium is considered a public health problem and it is a geriatric emergency that has not yet been explored. This corroborates the lack of extensive studies and confirms the scarcity of materials in some databases, as, for example, only results were found in Pubmed containing the descriptors used for this research.

5 CONCLUSION

From the results presented, it is concluded that the early diagnosis of delirium in patients with Covid-19 is crucial for the patient to have a good prognosis in the face of the adversities presented by the pathologies. Delirium affects mainly elderly males over 65 years of age and its symptoms may not be noticed during this condition. Thus, constant monitoring during the different phases of the day can help detect signs and symptoms of delirium in patients infected with SARS-CoV-2 and avoid worsening prognosis. Thus, screening tools such as the 4-AT, the *Chart-Based Delirium Identification Instrument* and the Diagnostic and Statistical Manual of Mental Disorders 4 and 5 could be consolidated as indispensable for the early detection of delirium.

The integrative review limited the search to only include publications in the last five years, however, due to the SARS-CoV-2 pandemic being more recent, the articles were mostly even more recent, however, it captured the most relevant articles and, therefore, , provides a good overview of the currently available

evidence on the correlation of delirium as an aggravating factor for Covid-19, with a considerable worsening of the prognosis. Future reviews may consider a greater number of evidence through new articles on the topic, including systematic reviews on the topic, as well as the use of other risk of bias assessment and quality assessment tools used in systematic reviews.

Finally, it is important to highlight that future studies should be focused on the search for rapid detection and the evaluation of the effectiveness of delirium prevention strategies in elderly patients with Covid-19.

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