Role of microRNAs in cognitive decline related to COVID-19 (Review)

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Abstract. The likelihood and severity of cognitive decline related to coronavirus disease 2019 (COVID-19) have been shown to be reflected by the severity of the infection and concomitant alterations in specific biomarkers. The present review discusses the role of microRNAs (miRNAs/miRs) as biomarkers in COVID-19 and the potential molecular mechanisms of cognitive dysfunction related to COVID-19. A systematic search of published articles was carried out from January 31, 2000 to December 31, 2022 using the PubMed, ProQuest, Science Direct and Google Scholar databases, combining the following terms: 'COVID-19' OR 'SARS-CoV-2' OR 'post-COVID-19 effects' OR 'cognitive decline' OR 'neurodegeneration' OR 'microRNAs'. The quality of the evidence was evaluated as high, moderate, low, or very low based on the GRADE rating. A total of 36 studies were identified which demonstrated reduced blood levels of miR-146a, miR-155, Let-7b, miR 31 and miR-21 in patients with COVID-19 in comparison with a healthy group. The overexpression of the Let-7b may result in the downregulation of BCL-2 during COVID-9 by adjusting the immune responses between chronic inflammatory disease, type 2 diabetes, COVID-19 and cognitive impairment. The reduced expression of miR-31 is associated with cognitive dysfunction and increased microcoagulability in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). miR-155 mediates synaptic dysfunction and the dysregulation of neurotransmitters due to acute inflammation, leading to brain atrophy and a subcortical cognitive profile. The downregulation of miR-21 in patients with COVID-19 aggravates systemic inflammation, mediating an uncontrollable immune response and the failure of T-cell function, provoking cognitive impairment in patients with SARS-CoV-2. On the whole, the present review indicates that dysregulated levels of miR-146a, miR-155, Let-7b, miR-31, and miR-21 in the blood of individuals with COVID-19 are associated with cognitive decline, the chronic activation of immune mechanisms, the cytokine storm, and the vicious cycle of damage and systemic inflammation.

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Contents

1. Introduction

Coronavirus disease 2019 (COVID-19), as the cause of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a multi-organ disease with subacute and long-term effects and a wide range of clinical manifestations, including in the central nervous system (CNS) (1,2). Following a 4-month follow-up

of patients hospitalized due to COVID-19, 30-40% of patients were found to have memory dysfunction, attention, or dysexecutive syndrome (3). Currently, 'COVID-19 brain fog' is defined as a non-specific mental syndrome following infection with COVID-19, that consists of fatigue, low attention span, memory disability, a loss of motivation and difficulty with long working hours. A young age has been found to increase the likelihood of COVID-19-related cognitive decline, regardless of severe disease (4). Thus far, the progression of cognitive symptoms is associated with COVID-19 (5). However, it remains obscure whether the neurological deficits of patients with COVID-19 can be long-lasting (>6 months) or even gradual, conceivably expanding the likelihood of cognitive damage. Another unanswered issue is whether COVID-19 infection accentuates the nature of dementia in individuals with pre-existing conditions. Direct brain infection may be a potential pathway through which SARS-CoV-2 affects cognitive ability (6).

A main unresolved issue that persists is whether the cognitive symptoms reported in patients with COVID-19 are explained by (7) i) the exacerbation of a systemic inflammatory response/cytokine storm; ii) encephalitis after the SARS-CoV-2 attack in the brain, or both; iii) COVID-19 may provoke tissue hypoxia and microvascular lesions, destroying the cerebral perfusion and the integrity of the blood-brain barrier, which may impair the function and cognition of brain areas such as the hippocampus; iv) the onset of the autoimmune cascade; or v) peripheral organ deterioration. Defective cognition may affect lifetime occupation and physical function following recovery from COVID-19, initiating a vicious cycle of adverse mental health and cognitive decline. The investigation of cognitive decline related to COVID-19 mechanisms is crucial to adopt the proper strategies with which to prevent subsequent cognitive decline. This evidence underlines the necessity for the evolution of biological indicators to evaluate therapeutic interventions in the disease course.

A biomarker is defined as 'a characteristic that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention' (8). Taking account of i) the invasive procedures for *in vivo* brain specimens; and ii) the reflection of brain-related events in the cerebrospinal fluid (CSF), the latter may be the perfect origin for biomarkers for uncovering and surveilling diverse pathophysiological procedures. Consequently, it is imperative to discover slightly invasive and disease-specific diagnostic biomarkers that will permit the prompt recognition of pathologic protein aggregation (9). Thus far, previous meta-analyses with protein biomarkers (α-synuclein, Aβ42, Tau and pTau 181) in the CSF, blood and saliva of patients with Parkinson's disease (PD) have yielded inconsistent conclusions (10-14).

MicroRNAs (miRNAs/miRs) are small, phylogenetically conserved non-coding RNAs (19-23 nucleotides in length) that regulate protein expression by interacting with complementary sequences in the 3-untranslated region (3'-UTR) of their target mRNAs and then exerting their functions by degrading mRNAs or inhibiting protein translation (9,15). miRNAs are involved in RNA silencing and the post-transcriptional regulation of gene expression. In cells from humans and other animals, miRNAs have been shown to primarily function by destabilizing mRNAs. This RNA silencing consists of the following steps: i) The cleavage of the mRNA strand into two fragments; ii) the destabilization of the mRNA by shortening its poly(A) tail; or iii) reducing the translation of the mRNA into proteins (16). To date, >2,500 miRNAs have been found in humans (miRbase), controlling vital functions, such as lipid metabolism, apoptosis, differentiation, organ development and cell death (9,17). The dysregulated expression of miRNAs has been found to be associated with inflammatory, degenerative and autoimmune disorders, cancer, cardiovascular diseases, diabetes mellitus, and rheumatic and neurodegenerative diseases such as PD (18-20). Essentially, miRNAs have recently been designated as novel mediators of cell-cell communications, being cell-secreted in different biological fluids (blood, CSF, saliva and urine) (21-23). These features also characterize miRNAs as plausible biomarkers for PD (13,23,24). Several miRNAs have been associated with PD, as they modulate the expression of critical proteins implicated in pathophysiology, such as synuclein alpha, leucine-rich repeat kinase 2, glucosylceramidase beta and nuclear receptor-related-17 (24,25). A recent meta-analysis identified several miRNAs with a highly significant differential expression in the brain and blood of patients with PD (26).

The present review discusses the underlying mechanisms that link COVID-19 to cognitive decline. miRNAs in serum, plasma, CSF, extracellular vesicles and exosomes may have an impact on disease pathogenesis and may be useful as biomarkers or therapeutic targets. There is an unmet need to unravel post-COVID-19-associated factors in the early stages in order to substantially improve the quality of care and therapy. It is crucial to detect the changes in plasma biomarkers in diverse cognitive types, since cognitive decline is one of the most disabling post-COVID effects. Hence, the present review provides an update the role of circulating miRNAs as diagnostic biomarkers for COVID-19-related cognitive damage as future therapeutic tools and prognostic predictors in clinical practice for neurologists.

2. Data collection methods

The present study was conducted following the Patient, Intervention, Comparison, and Outcome (PICO) and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (27). The PRISMA flowchart used herein (Fig. 1).

Search strategy. A search was performed for related studies using the Scopus, MEDLINE/PubMed, Embase, OVID, Science Direct, LILACS and EBSCO databases, using these medical subject headings (MeSH Terms): 'COVID-19' OR 'SARS-CoV-2' OR 'post-COVID-19 effects' OR 'cognitive decline' OR 'neurodegeneration' OR 'miRNAs' OR 'Lt-7b', OR 'miR-31', OR 'miR-155', OR 'miR-21'. The articles derived from this search were subjected to a further selection process for relevancy.

Inclusion and exclusion criteria, study quality and risk of bias. The quality of scientific evidence was classified as high, moderate, low, or very low, according to the GRADE scale (28). The inclusion criteria were as follows: 1) Human biological

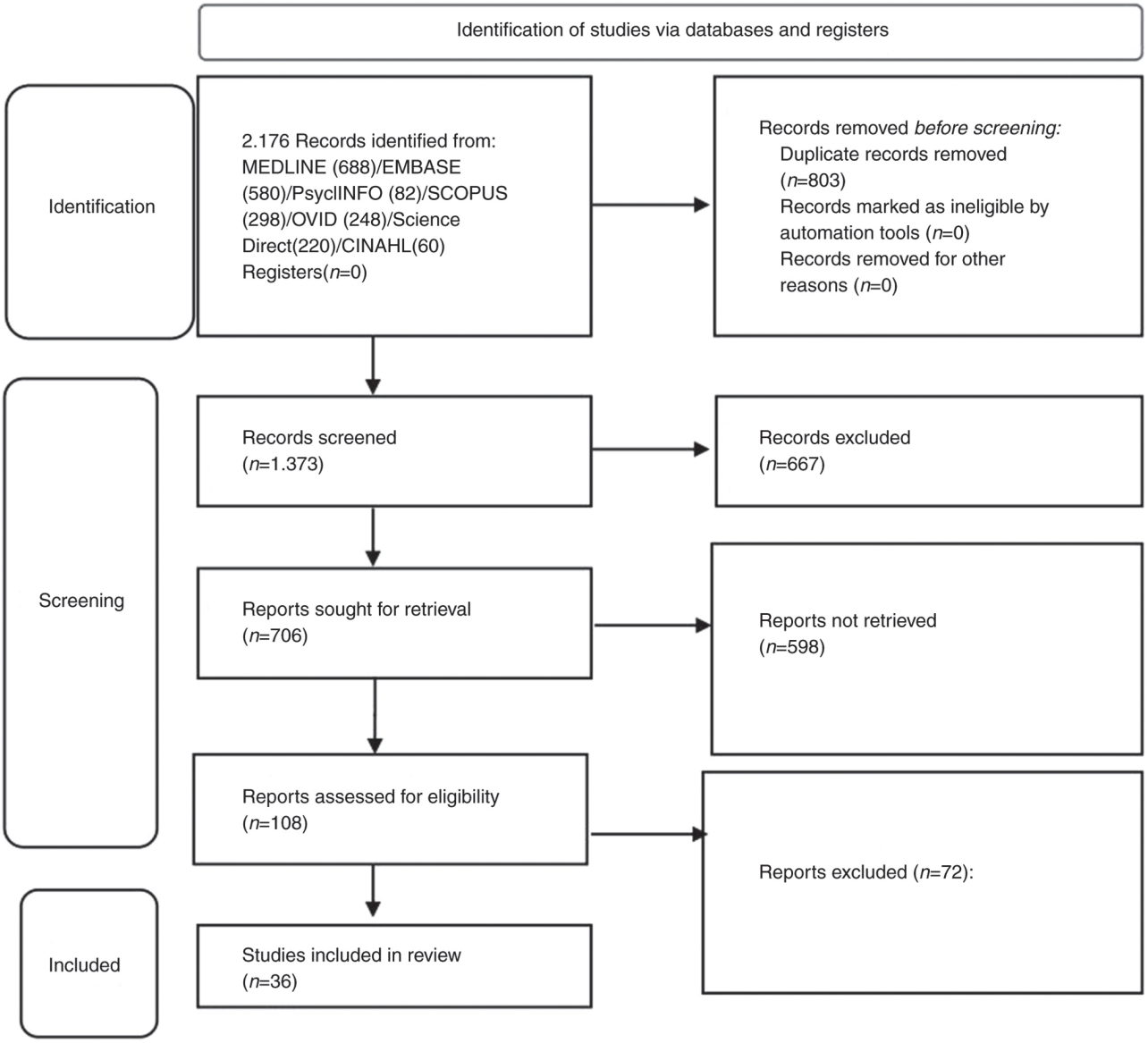

Figure 1. PRISMA flowchart of the study selection process used in the present review.

samples; ii) a sample size >15 biological samples; iii) studies with an accuracy (%) of quantitative polymerase chain reaction (qPCR) measurements >50%; iv) studies controlled by biological samples from patients with Alzheimer's disease (AD), mild cognitive impairment (MCI), frontotemporal lobar degeneration and dementia with Lewy bodies. The exclusion criteria included reviews, meta-analyses, theses and case reports. Of note, only qualitative syntheses was performed, due to the high heterogeneity and small sample size of the studies, exposure assessment methods and covariate adjustments. The main miRNAs in cognitive decline related to COVID-19 and the relevant pathophysiological mechanisms are summarized in Fig. 2.

3. miR-146a

Exosomal miR-146a (Fig. 3) originates from bone marrow-derived mesenchymal stem cells and is then taken up by activated astrocytes of the hippocampal region, indicating a neuroprotective role in seizure-associated cognitive damage (29). Lower blood levels of circulating miR-146a in AD cause neuroinflammation (30). The overexpression of miR146a in microglia has been found to play a neuroprotective role in learning/memory issues, diminished neuroinflammation and amyloid plaque by lessening NF-κB nuclear translocation and therefore, T-cell adhesion molecules. miR-146a also affects microglial phenotype switching, decreasing the levels of pro-inflammatory cytokines, and enhancing the clearance of β-amyloid and tau (31). Thus, serum miR-146a may be considered a biomarker for the progression of AD (32,33). The downregulation of microRNA-146a in chronic diseases, such as diabetes, obesity and hypertension may be associated with severe COVID-19 (34). The overproduction of IL-6 inactivates anti-COVID drugs, such as tocilizumab (35). However, larger longitudinal studies are required to elucidate the pathogenetic paths of the function of miR-146a in the COVID-19-mediated cognitive decline as a circulating prognostic biomarker, given its overexpression in dementia and SARS-CoV-2 infection,

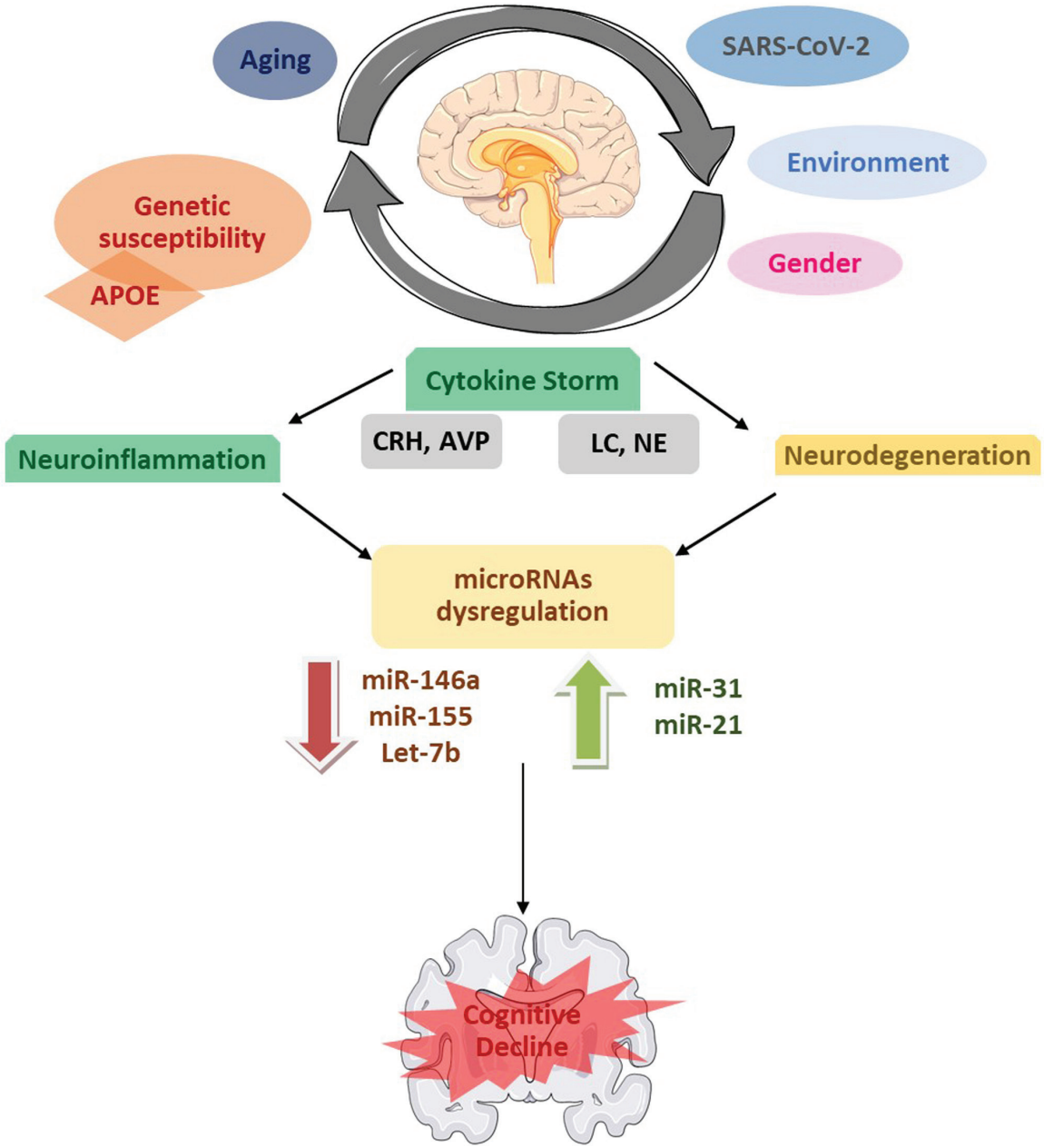

Figure 2. Schematic diagram providing a visual summary of the key findings, including the main miRNAs studied, and their associations with cognitive dysfunction and other diseases and co-existing factors. Parts of this image were derived from the free medical site http://smart.servier.com/(accessed on November 15, 2023) by Servier, licensed under a Creative Commons Attribution 3.0 Unported Licence. miRNA/miR, microRNA; APOE, apolipoprotein E; CRH, corticotrophin-releasing hormone; AVP, arginine-vasopressin; LC, locus coeruleus; NE, norepinephrine; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

as well as its role as an anti-neuroinflammatory, therefore, therapeutic tool.

4. miR-155

In addition to hyperphosphorylated tau protein, the primary expressed chromosome 21 miRNA in Down's syndrome-related dementia is miR-155 overexpression in the CNS (36). By regulating inflammatory cytokines, such as interferon (IFN)-λ and IFN-β, miR-155 functions as a crucial modulator of pro-inflammatory responses in the CNS and activates microglia (Fig. 3). The inflammatory effect of miR-155 in the CNS is mediated in macrophages and microglia by NF-κB following the releasee of IFN-γ. Targeting anti-inflammatory regulators, such as SH2 domain-containing inositol-5'-phosphatase 1, activator protein 1, signal transducer and activator of transcription 5, suppressor of cytokine signaling 1 and IL-13 receptor alpha 1 may exacerbate inflammation and compromise the anti-inflammatory response (37). Additionally linked to the advancement of cognitive impairment, is the stimulation of CNS T-cell responses by miR-155. β-amyloid accumulation and consequent cognitive impairment are caused by T-cell activation, IFN-γ production and CNS infiltration (38). In mouse models of traumatic brain injury, knockout experiments have demonstrated that miR-155 exerts a pro-neuroinflammatory effect by reducing neuroinflammation, improving cognition and promoting rapid recovery (39).

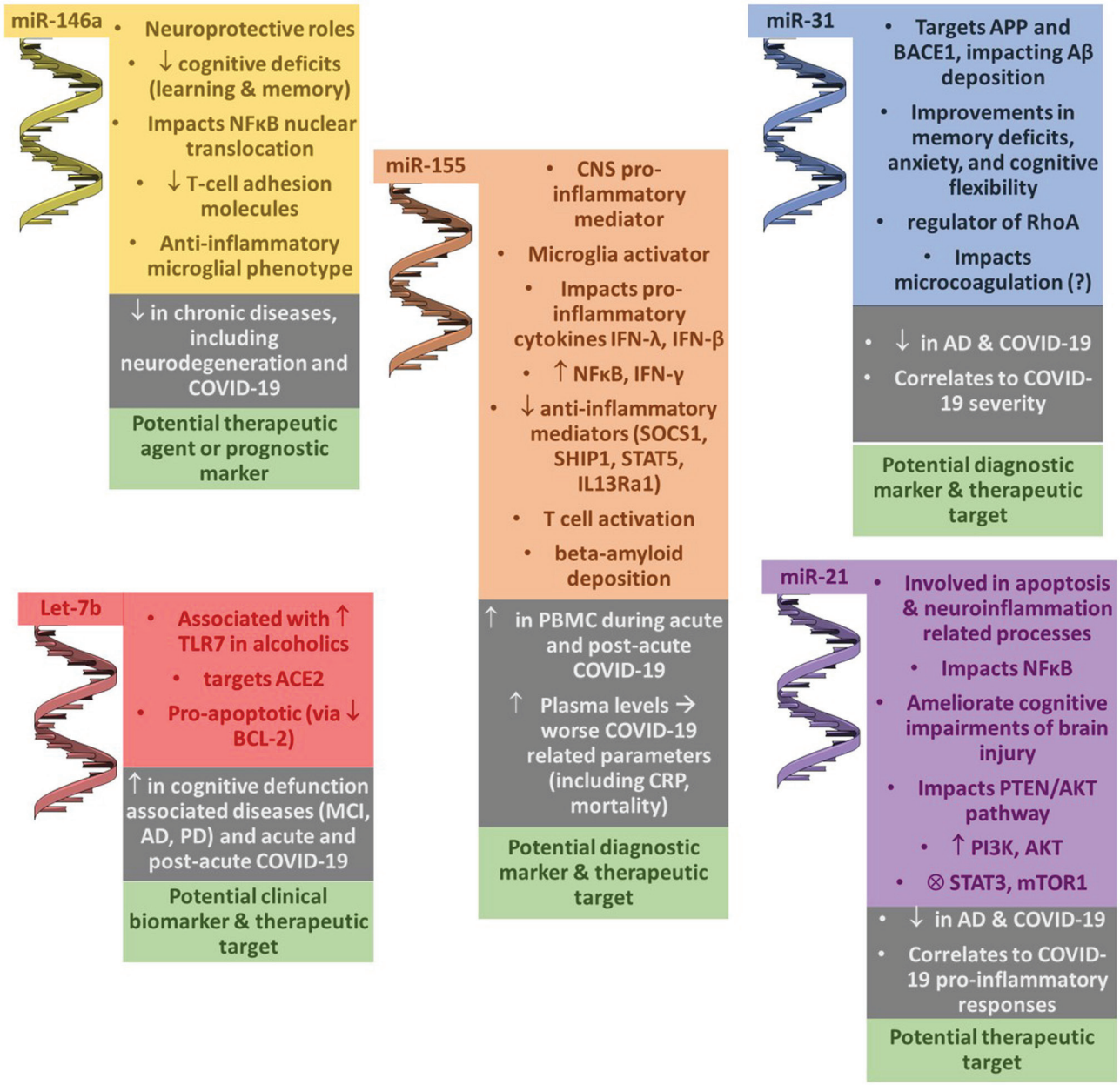

Figure 3. Schematic diagram of the main miRNAs studied and their associations with cognitive dysfunction and physiopathological and molecular processes, and other diseases and observations in patients with COVID-19; potential uses as of miRNAs as markers or therapeutic targets. Please refer to the text for further details. Parts of this image derived from the free medical site http://smart.servier.com/(accessed on November 15, 2023) by Servier, licensed under a Creative Commons Attribution 3.0 Unported Licence. ↓, decrease; ↑, increase; ⓧ, inhibition; ACE2, angiotensin-converting enzyme 2; AD, Alzheimer's disease; AKT, protein kinase B; BACE1, beta-site amyloid precursor protein cleaving enzyme 1; BCL2, B-cell lymphoma 2; CNS, central nervous system; IFN, interferon; IL13Ra1, IL-13 receptor alpha 1; MCI, mild cognitive impairment; mTOR1, mammalian target of rapamycin 1; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; PD, Parkinson's disease; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; RHoA, Ras homolog family member A; SHIP1, SH2 domain-containing inositol 5'-phosphatase 1; SOCS1, suppressor of cytokine signaling 1; STAT5, signal transducer and activator of transcription 5; TLR7, Toll-like receptor 7.

Moreover, increased concentrations of miR-155 have been found in blood-derived monocytes and monocyte-derived macrophages, demonstrating an inadequate cell migration and the clearance of β-amyloid in patients with AD (40). Promoting neuroinflammation and blood-brain barrier membrane permeability to neuroinflammatory cells, miR-155 likely leads to brain atrophy and progressive cognitive impairment (41). Elevated levels of serum miR-155 in peripheral blood mononuclear cells (PBMCs) from individuals experiencing acute COVID-19 infection suggest its potential as a COVID-19 diagnostic biomarker (42). Similarly, during the post-acute COVID-19 phase, miR-155 expression has been found to be elevated in PBMCs from patients with COVID-19 (43). Furthermore, there appears to be a substantial association between plasma miR-155 levels and clinical markers of COVID, including biochemical results and chest computed tomography scans. miR-155 has been shown to have a high sensitivity (90%) and specificity (100%) as a biomarker for the identification of COVID-19, and a 76% sensitivity and specificity for the severity of COVID-19 (44).

On the whole, the overexpression of miR-155 in SARS-CoV-2 infection may partially define the abnormal immune response provoking CNS dysfunction in the frame of COVID-related cognitive decline.

5. Let-7b

Increased Let-7b is a multipurpose miRNA that is differentially expressed in different types of cognitive decline, such as MCI (45), AD (46) and PD (47) (Fig. 3). Increased Toll-like receptor 7 and Let-7b expression have been linked to the post-mortem hippocampal atrophy of alcoholics (48). As a potential clinical biomarker for COVID-19 infection, let-7b levels have been found to be higher in peripheral blood samples during both the acute and post-acute phases of SARS-CoV-2 infection when compared to healthy controls (43). Let-7b is a possible therapeutic weapon against SARS-CoV-2 infection, since it dysregulates angiotensin-converting enzyme 2 and does not increase susceptibility to the virus (49). The overexpression of the Let-7b may result in the downregulation of BCL-2 duringCOVID-9 by adjusting the immune responses between chronic inflammatory disease, type 2 diabetes, COVID-19 and cognitive impairment (50), which may explain the cognitive dysfunction in these patients. These upregulations of Let-7b in SARS-CoV-2 infection are signs of the possible association with cognitive decline; however, small samples and a lack of other respiratory virus-infected groups are major limitations.

6. miR-31

Lower serum levels of miR-31 may be useful as a novel non-invasive biomarker with miR-93 and miR-146a to distinguish AD from vascular dementia (51) (Fig. 3). The lentiviral delivery of miR-31 has been shown to attenuate AD neuropathology by decreasing β-amyloid deposition in both the hippocampus and subiculum of transgenic mouse models (52). miR-31 targets amyloid precursor protein (APP) and β-secretase beta-site amyloid precursor protein cleaving enzyme 1, which further abolishes the pathological alterations in AD. These findings are indicative of memory amelioration, reduced anxiety and improved cognitive flexibility, proposing miR-31 as a therapeutic option of AD. RhoA has been demonstrated to adjust synaptic plasticity, and the inhibition of the RhoA pathway prevent damage in synapses and dendritic spines (53,54). Low serum miR-31 levels have been noted in patients with COVID-19 (55). Low miR31 levels are also indices of severe COVID-19, increasing microcoagulation, thus functioning as an essential prognostic biomarker of COVID-19 and severity (56). Consequently, low levels ofmiR-31 appear to exert a complex effect on cognitive dysfunction and SARS-CoV-2 infection, indicating a possible association between the two disease processes. Conversely, machine learning analysis has revealed that a three-miRNA signature (miR-423-5p, miR-23a-3p and miR-195-5p) can independently classify COVID-19 cases with an accuracy of 99.9% (57). Larger well-designated studies with a more sophisticated mechanistic approach are required however, to elucidate the precise role of miR-31 in the COVID-19-associated cognitive decline.

7. miR-21

miR-21 has been shown to significantly modulate apoptosis and neuroinflammation in cognitive decline (59) (Fig. 3). The level of miR-21 in plasma-derived extracellular vesicles is decreased in patients with AD in comparison to those with Lewy body dementia and healthy individuals (60). By functioning as a negative feedback modulator of NF-κB in the anticipation of pro-inflammatory signaling, miR-21 exhibits anti-inflammatory miRNA behavior (61). miR-21 improves dementia associated with brain injury from subarachnoid hemorrhage by modulating the PTEN/AKT pathway and apoptosis in the hippocampus and prefrontal cortex (62). Cell culture AD studies of miR-21 mimics found that miR-21 reduced β-amyloid-induced apoptosis by augmenting the expression of PI3K, AKT and glycogen synthase kinase 3beta (63,64).

Through the inhibition of the mTOR1 pathway, miR-21 restores neurogenesis and reverses cellular senescence in models of vascular dementia, rendering it a promising therapeutic agent for vascular dementia and related cognitive impairment (65). In patients with COVID-19, the relative expression of miR-21 has been found to be downregulated, while that of target pro-inflammatory genes is upregulated (66). The downregulation of miR-21 in patients with COVID-19 aggravates systemic inflammation due to the hyperactive immune response and a lack of T-cell function (67). Increased systemic inflammation may destroy the blood-brain barrier, generating increased neuroinflammation and leading to neurodegeneration. Hence, low miR-21levels may affect the onset and advancement of COVID-associated cognitive decline or may aggravate pre-existing dementia following infection with SARS-CoV-2. The main aspects of the roles of miRNAs included in the present review are summarized in Table I.

8. Limitations to current research

Lack of comprehensive miRNA profiling studies. One of the limitations of current research on the role of miRNAs in cognitive decline related to COVID-19 is the lack of comprehensive miRNA profiling studies. Rigorously designated clinical cohorts with convenient matched controls provide measurements of the whole repertoire, such as serum, plasma, CSF, urine, saliva and exosomes, if feasible. The majority of the existing studies investigating the dysregulation of miRNAs in COVID-19-related cognitive impairment have focused on a limited number of miRNAs. It is crucial to conduct comprehensive profiling studies to identify specific miRNAs that are dysregulated in the context of cognitive decline related to COVID-19. Such studies should encompass a wide range of miRNAs, considering their potential role in neuronal function and neuroinflammation. There is a paucity of comprehensive biofluids analyses assessing CSF, blood levels of multiple inflammatory markers along with CSF levels of other neurodegenerative RNA proteins (apart from miRNAs) as potential biomarkers, such as circular RNAs for comparison.

Inadequate animal models. Another limitation is the inadequacy of relevant animal models for studying the neurological consequences of COVID-19. Current animal models may

Table I. Main aspects of the role of miRNAs included in the present review.

miRNA	Origin	Role	(Refs.)
miR-146a	Bone marrow mesenchymal stem cells activated astrocytes	Neuroprotection anti-neuroinflammatory clearance of β-amyloid and tau	(28-34)
miR-155	As a gene that was transcriptionally activated by promoter insertion in B-cell lymphomas	Modulator of inflammatory cytokines (IFN-λ and IFN-β) clearance of β-amyloid	(35-43)
Let-7b	*Caenorhabditis elegans*	Postmortem hippocampal atrophy of alcoholics; ACE2 dysregulation of BCL-2 downregulation	(44-49)
miR-31	As gene is located on chromosome band 9p21.3	Abolition of β-amyloid pathology by targeting APP and BACE1	(50-56)
miR-21	Human glioblastoma cells	Inhibitor mTOR1 pathway and β-amyloid-induced apoptosis; neurogenesis	(59-64,67)

ACE, angiotensin converting enzyme; APP, amyloid precursor protein; BACE1, beta-site amyloid precursor protein cleaving enzyme 1; BCL-2, B-cell lymphoma 2; IFN, interferon; mTOR1, mammalian target of rapamycin 1.

not fully replicate the complex neurological symptoms and cognitive decline experienced by patients with COVID-19. Therefore, it is essential to develop more accurate animal models that can more closely mimic the long-term neurological complications observed in patients with COVID-19, facilitating a better understanding of the molecular mechanisms underlying cognitive impairment.

Limited longitudinal studies. The limited number of longitudinal studies focusing on the long-term consequences of COVID-19 is also a significant barrier. Rigorously designated clinical cohorts with convenient matched controls provide measurements of the whole repertoire, such as serum, plasma, CSF, urine, saliva and exosomes, if feasible. Longitudinal studies are vital for tracing the natural history of COVID-19-related cognitive decline, monitoring changes in cognitive function over time, and identifying potential biomarkers for cognitive impairment. Such studies would provide valuable insight into the progression and persistence of cognitive decline in COVID-19 survivors.

Challenges in miRNA detection and quantification. The methodologies used for miRNA detection and quantification present challenges in terms of standardization and accuracy. Current techniques used, such as RT-qPCR and small RNA sequencing have limitations in terms of sensitivity and specificity. The methods of RNA and exosome isolation, and downstream miRNA detection, quantification and normalization methods vary between studies, such as enzyme-linked immunosorbent assay, western blotting and mass spectrometry, leading to conflicting results. Standardizing methods is essential for ensuring reliable and reproducible results across different studies. Robust and validated miRNA detection and quantification methods are imperative for identifying reliable biomarkers of cognitive decline related to COVID-19.

9. Recommendations for future research

Comprehensive miRNA profiling studies. Future research should prioritize conducting comprehensive miRNA profiling studies in patients with COVID-19 with cognitive impairment. These studies can be performed on biological samples, such as plasma, CSF, or brain tissue and should encompass a wide array of miRNAs. Utilizing advanced high-throughput sequencing techniques, such as small RNA sequencing, will enable the identification of specific miRNAs that are dysregulated in COVID-19-related cognitive decline, allowing for a more detailed characterization of the molecular pathways involved.

Functional role studies. To enhance the understanding of the molecular mechanisms underlying cognitive decline related to COVID-19, future research should focus on elucidating the functional roles of dysregulated miRNAs in the pathogenesis of cognitive impairment. Utilizing *in vitro* and *in vivo* models, researchers can assess the impact of miRNA dysregulation on neuroinflammation, neurodegeneration and cognitive function. Understanding the functional roles of miRNAs may lead to the identification of potential therapeutic targets and the development of miRNA-based interventions to mitigate cognitive decline.

Development of accurate animal models. Efforts should be directed towards establishing accurate animal models that accurately mimic the neurological consequences of COVID-19. Such models should replicate the neuroinflammatory and neurodegenerative processes observed in patients with COVID-19. The utilization of genetically modified animal models or non-human primates infected with SARS-CoV-2 may provide a more thorough understanding of the pathophysiology underlying COVID-19-related cognitive decline, facilitating the evaluation of potential therapeutic strategies.

Longitudinal studies on COVID-19 survivors. Conducting well-designed longitudinal studies on COVID-19 survivors to investigate the long-term neurological sequelae is imperative. These studies should involve comprehensive neurological assessments, including cognitive function tests, brain imaging and biomarker analysis. Human studies in cohorts with cognitive decline and genetic predisposition (e.g., APOE) or the

prodromal type of dementia are in their infancy, without any longitudinal studies reported to date, at least to the best of our knowledge. The data collected from longitudinal studies may provide valuable insight into the persistence of cognitive decline, the nature of cognitive deterioration and the identification of potential prognostic factors or biomarkers.

Standardization of miRNAs. Researchers should work towards standardizing and validating miRNA detection and quantification methods. To detect miRNAs, sensitive assays need to be standardized, validated and developed quantitatively, so that they can possibly be used for the assessment of disease progression and the response to disease-modifying therapies. The development and adoption of standardized protocols for miRNA analysis, as well as the implementation of quality control measures, will enhance the accuracy and reproducibility of miRNA-based studies. Robustly validated protocols are required to measure miRNAs in PD samples, taking into account iteration and intra-variability. This standardization is critical for generating robust and reliable miRNA biomarkers for cognitive decline related to COVID-19.

10. Conclusions

The notion related to cognitive damage and COVID-19 is multifactorial; however, large studies to explore this notion are lacking. The discovery of miRNAs as promising biomarkers could accumulate with crucial data for classifying these patients, ameliorating primary care, and providing state-of-the-art personalized therapy in relation to the cognitive decline of the patient. The present review provides an update of the neuropathological COVID-19 related mechanisms and highlights the importance of using circulating miRNAs biomarkers to elucidate these mechanisms. It should be emphasized that thus far, there are no miRNAs that are specific for the different types of dementia.

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Availability of data and materials

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Authors' contributions

AB and VEG conceptualized the study. IGL, VEG, PP, EA, NT, PS, GF, AB and DAS made a substantial contribution to the interpretation and analysis of data from studies to be included in the present review and wrote and prepared the draft of the manuscript. DAS and AB analyzed the data from the studies to be included in the present review, and provided critical revisions. All authors contributed to manuscript revision and have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. The other authors declare that they have no competing interests.

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