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miRNA expression in COVID-19

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is regarded as a challenge in health system. Several studies have assessed the immune-related aspect of this disorder to identify the host-related factors that affect the course of COVID-19. microRNAs (miRNAs) as potent regulators of immune responses have gained much attention in this regard. Recent studies have shown aberrant expression of miRNAs in COVID-19 in association with disease course. Differentially expressed miRNAs have been enriched in pathways related with inflammation and antiviral immune response. miRNAs have also been regarded as potential therapeutic targets in COVID-19, particularly for management of pathological consequences of COVID-19. In the current review, we summarize the data about dysregulation of miRNAs in COVID-19.

1. Introduction

From late 2019, the arrival of coronavirus disease 2019 (COVID-19) caused by SARS Coronavirus 2 (SARS-CoV-2) has produced a serious health problem all over the world (Ammad Ud Din and Boppana, 2020). This virus is from the β subfamily of Coronaviridae family and Nidovirales order (Pal et al., 2020). The single strand RNA of this virus has a size of about 30 kb with 5’cap and 3’ poly A tail. The structural proteins of SARS-CoV-2 are represented as S, E, M and N proteins corresponding to spike glycoprotein, envelope, membrane and nucleocapsid, respectively. Being cleaved to two subunits, S protein facilitates virus attachment to angiotensin-converting enzyme 2 (ACE2) and its entry to target cells (Wan et al., 2020). This virus can also bind to transmembrane protease serine 2 (TMPRSS2) employing this protease for priming of its S protein (Hoffmann et al., 2018). COVID-19 is associated with dysregulation of immune responses, over-production of pro-inflammatory cytokines and impairment of the balances in the percentage of naïve/memory helper T cells and Tregs (Noroozi et al., 2020).

MicroRNAs (miRNAs) are small-sized RNA molecules that are involved in fine regulation of gene expression mainly via binding with 3’ UTR of target transcripts (Macfarlane and Murphy, 2010). In addition to the living cells, miRNAs are produced by DNA viruses and possibly RNA viruses. Yet, miRNA biogenesis by RNA viruses is debated because they are replicated within the cytoplasm and do not attain the nuclear miRNA machine (Fani et al., 2021).

Living cells attacked by viruses produce miRNAs at the initial stage of infection as a part of antiviral reaction (Fani et al., 2018). SARS-CoV-2 genome has been predicted to be targeted by a number of cellular miRNAs. Fig. 1 depicts SARS-CoV-2 genome and its components and their relationship with host miRNAs during SARS-CoV-2 infection. In a recent study, Arisan et al. have shown that miR-8066, miR-5197, miR-3611, mir-3934-3p, miR-1307-3p, miR-3691-3p and miR-1468-5p are significantly linked with cellular pathways participating in viral pathogenicity and host response. Notably, SARS-CoV-2 related changes in cellular transcriptome have been similar to the target pathways of these miRNAs (Arisan et al., 2020).

Another in silico method has led to identification of numerous potential human antiviral miRNAs that can affect expression of SARS-CoV-2 genes and also SARS-CoV-2-encoded miRNAs predicted to target host genes. Comparison of SARS-CoV-2 miRNA binding profiles of viruses isolated from different regions and normalized SARS-CoV-2 mortalities has revealed that up-regulation of cellular miRNAs might confer both
advantage and disadvantage to the host immune responses. Moreover, SARS-CoV-2 viral miRNAs has been revealed to target immune-related signal transduction (Khan et al., 2020).

In the current review, we summarize the data about dysregulation of miRNAs in COVID-19.

2. Dysregulated miRNAs in COVID-19

An in vitro study has implied the impact of SARS-CoV-2 as an exogenous competing RNA for enhancing expression of endogenous targets. miR-1207-5p has been shown to target CSF1 gene, a gene that is up-regulated in epithelial cells after SARS-CoV-2 infections. CSF1 can enhance recruitment and stimulation of macrophages in acute inflammatory responses during the course of COVID-19. Cumulatively, SARS-CoV-2-induced dysregulation of miR-1207-5p targets might be involved in uncontrolled inflammatory responses in COVID-19 (Bertolazzi et al., 2020).

A high throughput study in peripheral blood samples has identified 35 up-regulated and 38 down-regulated miRNAs in patients with COVID-19. Notably, miR-16-5p has been the most over-expressed miRNA in patients. Furthermore, miR-6501-5p and miR-618 levels have been 1.5 times higher in these patients compared with healthy donors. On the other hand, miR-627-5p has been the most under-expressed miRNA in patients (Li et al., 2020).

Assessment of miRNA profile of lung tissues of SARS-CoV infected mice has shown up-regulation of miR-21-3p in this tissue, endorsing the probability of miR-21-3p binding with the human coronavirus transcripts (Nersisyan et al., 2020a).

Tang et al. have assessed miRNA landscape in laboratory-confirmed COVID-19 patients with moderate or severe disease course compared with healthy subjects. They have reported consistent down-regulation of miR-146a-5p, miR-21-5p and miR-142-3p as well as consistent up-regulation of miR-3605-3p in COVID-19 cases. Moreover, miR-15b-5p, miR-486-3p and miR-486-5p have been shown to be over-expressed only in severely affected COVID-19 cases, while miR-181a-2-3p, miR-31-5p, and miR-99a-5p have been only down-regulated in this subtype of COVID-19 cases. Differentially expressed miRNAs have been enriched in pathways related with inflammation, antiviral immune response, Toll-like receptor (TLR) signaling and IFN-related pathways (Tang et al., 2020a).

In a cross-sectional study, Keikha et al. have miRNAs profile of peripheral blood of COVID-19 patients with various disease grades in the course of their hospitalization. They have reported down-regulation of hsa-miR-31-3p, hsa-miR-29a-3p, and hsa-miR-126-3p while up-regulation of hsa-miR-17-3p in these patients parallel with increase in the disease grade. Expression of mRNA targets of these miRNAs has been inversely correlated with their expression levels. These alterations in expression of these miRNAs and mRNAs have been also perceived during hospitalization of COVID-19 cases who have not responded to treatment. However, expressions of transcripts have been returned to the normal
### Table 1: Dysregulated miRNAs in COVID-19.

| microRNA         | Study design       | Participants                | Number of samples/cell type | Targets/regulators | Signaling pathway | Study highlights                                                                                                                                                      | Ref                                      |
|------------------|--------------------|-----------------------------|-----------------------------|--------------------|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| miR-146-5p       | In vivo            | Hospitalized patients       | 30                          |                    |                   | Decreased serum level of miR-146a is associated with not responding to tocilizumab and adverse outcomes in COVID-19 patients.                                          | (Sabbatinelli et al., 2021)              |
| miR-98           | In vitro           | HMVEC-L, HUVEC              |                |                    |                   | miR-98 modulates TMPRSS2 expression in the endothelial cells                                                                                                         | (Matarese et al., 2020)                 |
| miR-1207-5p      | In vitro           | Human alveolar and bronchial epithelial cells |                | CSF1               |                   | miR-1207-5p influences inflammation by targeting genes in severe COVID-19 cases.                                                                                   | (Bertolazzi et al., 2020)               |
| miR-200c-3p      | In vivo            |                               | 111                        |                    |                   | miR-200c-3p might be a predictor of COVID-19 severity independent of known risk factors.                                                                           | (Pimenta et al., 2021a)                |
| miR-27a-3p, miR-26b-5p, miR-10b-5p, miR-302c-5p, hsa-miR-587, hsa-miR-1305, hsa-miR-200b-3p, hsa-miR-124-3p, hsa-miR-16-5p | Bioinformatics | | | ACE2             |                   | The mentioned miRNAs are modulators of ACE2 network and virus-associated proteins.                                                                                | (Wicik et al., 2020)                    |
| miR-335-5p and miR-26b-5p | Bioinformatics | | 7362 | ACE2 | Histone deacetylase (HDAC) pathway. | miR-335-5p and miR-26b-5p are affected by Spike, ACE and histone deacetylase network. A single nucleotide polymorphism of miR1202 (rs140092351) is associated with COVID-19 and also interacts with several exposure factor. | (Teodori et al., 2020) |
| miR-1202         | Bioinformatics     |                             | 5                           |                    | IL-6R translation | Down regulation of miR-451a, is negatively associated with IL-6/IL-6R-related cytokines storm in COVID-19 cases.                                                         | (Yang et al., 2021)                     |
| miR-451a         | In vivo            |                             | 293 T cells                 |                    | Disintegrin and metalloproteinase 17 and ADAM17 | miR-28-3p inhibits ADAM17-dependent ACE2 ectodomain shedding, making it a potential target in the prevention and management of COVID-19 patients. | (Xu and Li, 2021)                      |
| miR-28-3p        | In vitro           | Vero E6, Calu-3, Caco-2 and H1299 | 141                        | S protein          | Plasmid-driven Spike expression Viral translation and replication | The study indicates use of antiviral miRNAs as a treatment or preventive strategy for COVID-19 patients by increasing the replication of SARS-CoV-2 virus. | (Teng et al., 2021)                    |
| miR-155          | In vitro           | Vero E6, Calu-3, Caco-2 and H1299 | 141                        | S protein          | Plasmid-driven Spike expression Viral translation and replication | The study indicates use of antiviral miRNAs as a treatment or preventive strategy for COVID-19 patients by increasing the replication of SARS-CoV-2 virus. | (Teng et al., 2021)                    |
| miR-7-5p, miR-24-3p, miR-145-5p, miR-223-3p | In vivo | Young group elderly group healthy group diabetic group | 141                        | S protein          | Plasmid-driven Spike expression Viral translation and replication | The study indicates use of antiviral miRNAs as a treatment or preventive strategy for COVID-19 patients by increasing the replication of SARS-CoV-2 virus. | (Teng et al., 2021)                    |
| microRNA | Study design | Participants | Number of samples/cell type | Targets/regulators | Signaling pathway | Study highlights | Ref |
|----------|--------------|--------------|-----------------------------|--------------------|-------------------|------------------|-----|
| miR-21, miR-23b, miR-28, miR-29a, miR-29c, miR-98 and miR-326 | In vivo | 6 Uninfected pregnant women and 15 SARS-CoV-2-infected pregnant women | 21 (Plasma, PBMCS and Placenta Biopsy) | | Antiviral | protective capacity of cells. miRNA profiles in plasma and placenta of pregnant women infected with COVID-19 shows that the combination of miRNA and antiviral/immune elements could modulate the infection and the abnormal function of immune reactions of SARS-COV-2. | (Saulle et al., 2021) |
| miR-17, miR-92, miR-146, miR-150, miR-155, miR-223 | In vivo | 6 Uninfected pregnant women and 15 SARS-CoV-2-infected pregnant women | 21 (Plasma, PBMCs and Placenta Biopsy) | | Immune modulatory | Human host cell | |
| hsa-miR-15b-5p | In vitro | RNA template component of the SARS-CoV-2 RdRp structure | | | | This miRNA inhibits viral infection and proliferation by targeting the RNA template component of SARS-CoV-2 RNA-dependent RNA polymerase. | (Sato et al., 2021) |
| hsa-miR-1267, hsa-miR-1-3p, hsa-miR-5683 | In-silico, Vmir analyzer, bioinformatics | Human host cell | | | | hsa-miR-1267, hsa-miR-1-3p and hsa-miR-5683 were common between five viral SARS-CoV2 miRNAs. These associations partake in the functions of genes specific for immune complex production, and enzyme binding with roles in the virus-host interactions. | (Sarma et al., 2020) |
| hsa-miR-1-3p, hsa-miR-17-5p, hsa-miR-199a-3p, hsa-miR-15a-5p, and hsa-miR-20a-5p | Bioinformatics | MAFK signaling pathway | The mentioned miRNAs were down-regulated and were shown to have anti-viral impact in respiratory diseases. Therefore, they can be used as novel drug targets. | | | (Sardar et al., 2020) |
| miR-6741-3p | In vitro and in silico bioinformatics | 20 of COVID patients with kidney disease | 40 Samples of nasopharyngeal swabs | APOL1-associated genes, SWT1, NPYB, BRF1, HES2, NPYB, MED12L, MAPG, GTF2H5, TRAF3, PRSS23 | | This study shows an effective association between miR-6741-3p and renal disease susceptibility. | (Safdar et al., 2021) |
| miR-193b-3p, miR-503-5p, miR-455-5p, miR-31-3p, miR-1938-5p, miR-2355-5p | In vitro and bioinformatics | 23 HNSCC and Lung cancer cells and one COVID19 patients who underwent operation for HNSCC | TMPRSS2 protease | | | Anti-correlation between the expression of microRNAs and the expression of their target TMPRSS2 in a SARS-CoV-2 infected tissue. | (Sacconi et al., 2020) |
| miR-125a-5p, miR-125b-5p, miR-574-5p, and miR-936 | Bioinformatics, in silico | ACE2 expression | | | | The study indicates possible use of miRNAs in the diagnosis of male infertility after infection with SARS-CoV-2. | (Sabetian et al., 2021) |
| miR-204-5p | | TMRPSS2 | | | | | |
| SARS-CoV-miR-029, miR-055, miR-084, miR-027, miR-005, miR-077, miR-060, miR-007 | In silico | Human genes | Expression of human genes mediated by SARS CoV 2 miRNAs affects adaptive hypoxia, neuronal invasion, hormonal imbalances, and induction of cancer pathways. | | | (Roy et al., 2021) |
| miR-146a, miR-155 | Bioinformatics | Patients with periodontitis and type2 diabetes | ACE2 | | | Increased miR 146a, miR 155 due to diabetes and periodontitis in the oral cavity upregulates angiotensin converting enzyme 2 expression and modulates the host antiviral response. | (Roganovic, 2021b) |
| microRNA Study design | Participants | Number of samples/cell type | Targets/regulators | Signaling pathway | Study highlights | Ref |
|----------------------|--------------|-----------------------------|--------------------|-------------------|-----------------|-----|
| hsa-miR-4778-5p and hsa-miR-4531hsa-miR-6844 hsa-miR627-5p hsa-miR-367 | Bioinformatics | | | | miR-6844 is associated with the ORF1ab gene of SARS-CoV-2. The mentioned miRNAs have a possible involvement in inflammatory responses. In addition, a significant difference in the characteristics of SARS-CoV-2 between Indonesia and Wuhan was shown by evaluating the host miRNAs. (Rahmadi et al., 2021) |
| let-7d-5p, -7e-5p, miR-494-3p, miR-382-3p, miR-181c-5p | | | | | miR-4778-5p and hsa-miR-6844 | (Rahmadi et al., 2021) |
| miR-361-5p, miR-410-3p | Bioinformatics | | ACE2 | | miRNAs regulates SARS-CoV-2 infectivity in human cells through attachment of host miRNAs to the SARS-CoV-2 genome and modulation of the transcripts of viral entry proteins, ACE2 and TMPRSS2, and modulation by their upstream IFN modulators. | (Pierce et al., 2020) |
| miR-23a, miR-29a, -29c, miR-151a, -151b (S), miR-4707-3p (S), miR-298 miR-7851-3p, miR-8075 | | | | | miR-361-5p, miR-410-3p | (Rahmadi et al., 2021) |
| hsa-miR-499a-3p hsa-miR-4532 hsa-miR-6763-3p hsa-miR-26b-5p | Bioinformatics | | ACE2 | | miRNAs regulates SARS-CoV-2 infectivity in human cells through attachment of host miRNAs to the SARS-CoV-2 genome and modulation of the transcripts of viral entry proteins, ACE2 and TMPRSS2, and modulation by their upstream IFN modulators. | (Pierce et al., 2020) |
| miR-30c and miR-200c | Bioinformatics | | ACE2 | | miR-30c and miR-200c regulate ACE2/TMPRSS2 genes and are involved in the pathogenesis of coronavirus infection and acute respiratory distress syndrome | (Nersisyan et al., 2020c) |
| miR-21-3p | Biocomputational | | ACE2 | | miRNAs regulates SARS-CoV-2 infectivity in human cells through attachment of host miRNAs to the SARS-CoV-2 genome and modulation of the transcripts of viral entry proteins, ACE2 and TMPRSS2, and modulation by their upstream IFN modulators. | (Nersisyan et al., 2020a) |
| miR-24 | In vitro | | ACE2 | | miR-24 targets Neurilpin-1. | (Mone et al., 2021) |
| hsa-miR-146a and hsa-miR-126-3p | In vivo | Hospitalized Covid-19 patients | | | miR-24 targets Neurilpin-1. | (Mone et al., 2021) |
| miR-2392 | Clinical and bioinformatics | | | | miR-2392 suppressed mitochondrial gene expression, increased inflammation, glycolysis, and hypoxia as well as | (McDonald et al., 2021a) |

(continued on next page)
### Table 1 (continued)

| microRNA          | Study design         | Participants               | Number of samples/cell type | Targets/regulators | Signaling pathway | Study highlights                                                                                                                                                                                                 | Ref                     |
|-------------------|----------------------|----------------------------|-----------------------------|--------------------|-------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| hsa-miR-1236-3p, zof- miR2673b | Bioinformatics       | 'GGAAGAG' in 5024 SARS-CoV-2 3' UTR |                             |                    |                   | Promoted many COVID-19 associated symptoms. miR-2392 is expressed in the blood and urine of COVID-19 cases, but not identified in COVID-19 negative patients.                                                               | (Mangukia et al., 2021) |
| miR-200c          | In vitro             | Neonatal rat cardiomyocytes (NRCMs) and Neonatal rat cardiac fibroblasts (NRCFs) | ACE2                        |                    |                   | The target of these miRNAs represents a region concentrated in the SARS-CoV-2 genome that may become a promising target for the fight against COVID-19. MiR-200c modulates ACE2 expression in both rat and human cardiomyocytes, which can be used to treat cardiovascular complications of COVID-19. | (Lu et al., 2020)      |
| miR-155, miR-130a | Clinical             | Recovered COVID-19 patients and healthy | 70 Blood samples            |                    |                   | miR-155 and miR-130a levels were higher in the mild/moderate group compared to the severe/critical                                                                                                                | (Li et al., 2021)       |
| hsa-miR-15b-5p, hsa- miR-195-5p, hsa-miR- 221-3p, hsa-miR-140-3p, and hsa-miR-422a | In vitro and bioinformatics | Hamster lung tissues |                             |                    |                   | Hsa-miR-15b-5p, hsa-miR-140-3p, and hsa-miR-422a have been decreased, and hsa-miR-195-5p and hsa-miR-221-3p have been increased in affected specimens. These miRNAs commonly bind to SARS-CoV, MERS-CoV, and SARS-CoV-2. | (Kim et al., 2020)      |
| hsa-miR-15a-5p, hsa- miR-15b-5p, hsa-miR-195-5p, hsa-miR-16-5p, and hsa-miR-196a-1-3p | Bioinformatics and in vivo | IL-12p53, Stat3, and TRAF6 | PFARS, SOCS1, and CEBPA |                    |                   | Expression of anti-inflammatory miRNAs was decreased and their targeted miRNAs were increased, and the relative expression of pro-inflammatory miRNAs was increased.                                                                 | (Keikha and Jebali, 2021) |
| hsa-miR-31-3p, hsa- miR-29a-3p, and hsa-miR-126-3p | Bioinformatics and in vivo | Covid patients | 19 Blood sample | ZMYM5, COLS3, and CAMSAP1 |                   | Hsa-miR-31-3p, hsa-miR-29a-3p, and hsa-miR-126-3p have been down-regulated and the levels of their mRNA targets (ZMYM5, COLS3, and CAMSAP1) have been enhanced with the increase of disease grade. | (Keikha et al., 2021)  |
| hsa-miR-17-3p     |                      |                            |                             |                    | DICER1            | Hsa-miR-17-3p has been increased and DICER1 level has been down-regulated with the increase of disease grade.                                                                                               |                       |
| hsa-miR-214, hsa-miR- 98 and hsa-miR-32 | In vitro             | Tmprss2                    |                             |                    |                   | Hsa-miR-214, hsa-miR-98 and hsa-miR-32 have a potential for silencing Tmprss2 and can be used to prevent the SARS-CoV-2 viral transmission and replication.                                                      | (Kaur et al., 2021)    |
| miR-516a-3, miR-720 and miR-328 | Bioinformatics       | 27 SNPs were demonstrated to affect miRNA binding for cytokine receptors genes. These miRNAs play a major role in the regulation of immune |                             |                    |                   |                                                                                                  | (Karacaks Celik et al., 2021) |
| microRNA            | Study design     | Participants                        | Number of samples/cell type | Targets/regulators                          | Signaling pathway | Study highlights                                                                 | Ref                      |
|---------------------|------------------|-------------------------------------|----------------------------|---------------------------------------------|-------------------|-----------------------------------------------------------------------------------|--------------------------|
| miR-21, miR-16, let-7b, let-7e, and miR-146a | In silico        |                                    |                            | Several differentially expressed genes (DEGs)                          |                    | miR-21, miR-16, let-7b, let-7e, and miR-146a have been the most important miRNAs targeting DEGs. | (Jafarinejad-Farsangi et al., 2020) |
| miR-24              | In vivo          | Patients hospitalized for COVID-19   | 369 plasma                 | EC-EV miR-24 is associated with cerebrovascular complications in COVID-19. |                    | miR-21, miR-16, let-7b, let-7e, and miR-146a have been the most important miRNAs targeting DEGs. | (Gambardella et al., 2021a) |
| hsa-miR-190a        | In vivo          |                                    | 50                         | hsa-let-7d, hsa-miR-17, hsa-miR-34b, hsa-miR-93, hsa-miR-200b, hsa-miR-200c, hsa-miR-223 expression levels were decreased and hsa-miR-190a and hsa-miR-203 increased in COVID-19 patients. |                    | hsa-let-7d, hsa-miR-17, hsa-miR-34b, hsa-miR-93, hsa-miR-200b, hsa-miR-200c, hsa-miR-223 expression levels were decreased and hsa-miR-190a and hsa-miR-203 increased in COVID-19 patients. | (Demiray et al., 2021)    |
| hsa-miR-340-3p, hsa-miR-4772-5p, hsa-miR-192-5p, and hsa-miR-1291 | Bioinformatics   |                                    |                            | Autophagy                                                                 |                    | hsa-miR-1291 is a potential biomarker to forecast the beginning of severe symptoms in SARS-CoV-2 infection. | (Mi et al., 2021)        |
| miR-200c-3p         | Bioinformatics   |                                    |                            | ACE2                                                                 |                    | miR-200 family members are strong candidates for the regulation of ACE2 respiratory system cell. | (Borseyik, 2021)         |
| miR-3941 and hsa-miR-138-5p | In silico, in vitro, bioinformatics |                                    |                            | SARS-CoV-2 3′UTR                                                                 |                    | These microRNAs show antiviral or protective effects in the host cells, making them potential candidates for therapeutic treatment | (Barreda-Manso et al., 2021) |
| hsa-miR-342-5p, hsa-miR-98-5p and hsa-miR-17-5p | Bioinformatics   |                                    |                            | Host genes (MYC, IL6, ICAM1 and VEGFA) and SARS-CoV2 gene (ORF1ab) |                    | These miRNAs target multiple host and SARS-CoV2 genes and can be novel personalized therapeutic targets for COVID-19 patients. | (Banaganapalli et al., 2021) |
| miR-10b             | In vivo          | COVID-19 patients and healthy subjects | 62 Blood samples           | IL-2 and IL-8                                                                 |                    | miR-10b is downregulated in the blood samples of COVID-19 patients and can contribute to cytokine storms by increasing IL-2 and IL-8 | (Bagheri-Hoseinzadeh et al., 2021) |
| miR-124-3p          | Bioinformatics   |                                    |                            | A ceRNA network involving one miRNA (miR-124-3p), one mRNA (Ddx58), one IncRNA (Gm26917) and two circRNAs (Ppp1r10, C330019G07Rik) in SARS-CoV infected cells is predicted. |                    | A ceRNA network involving one miRNA (miR-124-3p), one mRNA (Ddx58), one IncRNA (Gm26917) and two circRNAs (Ppp1r10, C330019G07Rik) in SARS-CoV infected cells is predicted. | (Arora et al., 2020)      |
| miR-486-3p          | Bioinformatics   | KEGG pathways                       |                            | 7 key-microRNAs with remarkable association to KEGG pathways associated to viral pathogenicity and host response are detected. |                    | miR-486-3p inhibits HCN4 and markers involved in immune response. | (Aminu et al., 2021)     |
| miR-8066, 5197, 3611, 3934-3p, 1307-3p, 3691-3p, and 1468-5p | Bioinformatics   | KEGG pathways                       |                            | 7 key-microRNAs with remarkable association to KEGG pathways associated to viral pathogenicity and host response are detected. |                    | miR-486-3p inhibits HCN4 and markers involved in immune response. | (Aminu et al., 2021)     |
| miR-486-3p          | In vivo, bioinformatics |                                    | 10                         | HCN4                                                                 |                    | These micro RNAs contribute to the | (Tang et al., 2020b)      |
| miR-486-3p          | In vivo          |                                    |                            |                                                                                       |                    |                                                                                      |                          |

(continued on next page)
level in treatment-responsive COVID-19 patients (Keikha et al., 2021). Notably, miR-29 family has been shown to contain numerous binding sites affecting expression of differentially expressed genes in lungs of COVID-19 patients (Keikha et al., 2021). Up-regulation of miR-200c-3p and systemic arterial hypertension have been identified as independent factors for severe COVID-19. Cumulatively, miR-200c-3p expression level has suggested as a predictor of COVID-19 course (Pimenta et al., 2021b).

Gambardella et al. have reported a significant association level of miR-24 in endothelial cells/extracellular vesicles and cerebrovascular disorders, suggesting a possible mechanism for pathoetiology of cerebrovascular complications in COVID-19 (Gambardella et al., 2021b). In a recent study, Gustafson et al. have identified a number of miRNAs whose expression in the peripheral blood has been associated with severe COVID-19 mortality. Their results have indicated that miR-30b/30c, miR-133a and miR-451a are highly specific for determination of severity and mortality rate of COVID-19 patients (Wilson et al., 2021b). Besides, miR-339 and miR-339-5p have been found to be correlated with 28 day mortality of COVID-19 patients. Mechanistically, these two miRNAs reflect inflammation-related pathways.

### Table 1 (continued)

| microRNA       | Study design     | Participants        | Number of samples/cell type | Targets/regulators | Signaling pathway | Study highlights                          | Ref        |
|----------------|------------------|---------------------|----------------------------|--------------------|-------------------|------------------------------------------|------------|
| miR-16a-5p     | Moderate and severe COVID-19 |                      |                            |                    |                   | pathoetiology of disease and can possibly be used as markers of disease severity and therapeutic targets for COVID-19 patients. (Nersisyan et al., 2020b) |
| hsa-let-7e / hsa-mir-125a and hsa-mir-141 / hsa-mir-200 | Bioinformatics | ACE2 and TMPRSS2 genes | JAB21B inhibits the transcription of hsa-let-7e / hsa-mir-125a and hsa-mir-141 / hsa-mir-200 and indirectly affect ACE2 / TMPRSS2 expression | miR147-3p was overexpressed in SARS-CoV-2 infected cells. miR-776-3p and miR-1275 were decreased, and miR-4742-3p, miR-3215-3p were over-expressed. (Farr et al., 2021) |
| miR-147-3p     | Bioinformatics, in vivo | EXOC7, RAD9A, and TFE3 | miR147-3p was overexpressed in SARS-CoV-2 infected cells. miR-776-3p and miR-1275 were decreased, and miR-4742-3p, miR-3215-3p were over-expressed. (Farr et al., 2021) |
| miR-776-3p     | In vivo | 10 COVID-19 patients sampled and 10 healthy control |                                     |                    |                   |                                         |            |

### Table 2

| microRNA       | Biomarker role                          | Sample number | Area under curve | Sensitivity (%) | Specificity (%) | References                          |
|----------------|-----------------------------------------|---------------|------------------|-----------------|-----------------|--------------------------------------|------------|
| miR-146a-5p, miR-21-5p, miR-142-3p, and miR-15b-5p | Discriminating ward vs. ICU patients | 84            | 0.89 (0.81–0.97) |                  |                  | (Gonzalo-Calvo et al., 2021)        |
| miR-146a-5p, miR-21-5p, miR-142-3p, and miR-15b-5p | COVID-19 severity | From 0.72 (0.59–0.84) to 0.90 (0.82–0.97) |                  |                  |                  | (Garg et al., 2021)                 |
| miR-192-5p and miR-323a-3p | Mortality during the ICU stay | 0.80 (0.64–0.96) |                  |                  |                  | (Garg et al., 2021)                 |
| miR-155 | Distinguish between the COVID-19 and the influenza-associated ARDS | 33 | 1.00 | 100 | (Garg et al., 2021) |
| miR-208a | Diagnostic biomarker for SARS-CoV-2-infection | 33 | 0.81 | 88 | 85 | (Fayyad-Kazani et al., 2021) |
| miR-19b-3p, and miR-92a-3p | Biomarker for COVID-19 diagnosis | 33 | 0.87 | 89 | 86 | (Fayyad-Kazani et al., 2021) |
| miR-29a-3p, miR-146a-3p, miR-155-5p, miR-26a-5p, miR-29B-3p, miR-34a-5p, miR-423-5p, miR-23a-3p and miR-195-5p | COVID-19 case identification | 7 COVID-19 samples and 10 control | 0.90 | 72 | 95 | (Farr et al., 2021) |
| miR-195-5p | Best power to discriminate the COVID-19 group from healthy subjects | 1.00 | 99.9 | 99.8 | (Farr et al., 2021) |


associated myocyte injury and acute phase response of hepatocytes, respectively (Gutmann et al., 2022). In another study by Giuliani et al., miR-320b and miR-483-5p have been validated to be up-regulated in deceased cases compared to those survived. Twenty percent higher serum levels of miR-320b and miR-483-5p has been associated with three-fold higher risk of demise of COVID-19 patients during their hospitalization (Giuliani et al., 2022).

Table 1 shows dysregulated miRNAs in COVID-19.

3. Diagnostic impact of host miRNAs in COVID-19

Donyavi et al. have measured expression levels of let-7b-3p, miR-29a-3p, miR-146a-3p and miR-155-5p in peripheral blood mononuclear cells of COVID-19 patients versus healthy volunteers. Notably, they have reported over-expression of these miRNAs in COVID-19 cases. Moreover, miR-29a-3p, miR-146a-3p and let-7b-3p levels have been different in the post-acute versus acute phase of disease. Assessment of receiver operating characteristic (ROC) curves has confirmed appropriateness of miR-29a-3p, miR-155-5p and miR-146a-3p as diagnostic biomarkers for COVID-19. Furthermore, miR-29a-3p, and miR-146a-3p have been suggested as markers for differentiation of COVID-19 phases, since their levels were different in acute and post-acute phases (Donyavi et al., 2021).

Plasma miRNAs have also been suggested to predict severity of COVID-19. For instance, miR-192-5p and miR-323a-3p could separate ICU non-survivors from survivors. Moreover, expression level of these miRNAs has been correlated with the duration of stay of COVID-19 patients in the ICU (de Gonzalo-Calvo et al., 2021).

Expression levels of miR-155, miR-208a and miR-499 could clearly distinguish between COVID-19 and Influenza-ARDS patients. Moreover, cardiovascular miRNAs signature could separate severely ill, Influenza-ARDS cases needed mechanical ventilation and COVID-19 patients from each other, representing a quite specific involvement of heart tissue in COVID-19 patients (Garg et al., 2021). Table 2 shows the diagnostic role of miRNAs in COVID-19.

4. Discussion

Different miRNAs have been found to be altered during the course of COVID-19. Alterations in miRNA levels have been linked to severity of COVID-19 particularly in cases suffering from comorbid conditions (Arghiani et al., 2021).

Both host and SARS-CoV-2 miRNAs can partake in the pathogenesis of COVID-19. In general, miRNAs can affect the dissemination of RNA viruses and pathophysiology of related disorders through directly influencing the viral genome or modulating antiviral immune responses in the host (Trobaugh and Klimstra, 2017). Dysregulated host miRNAs in COVID-19 patients have been consistently related with immune response modulation. Most notably, assessment of miRNA landscape in severely affected COVID-19 patients has shown their relevance with over-activity of the immune responses, defects in T cells functionality, and dysregulation of immune system in these patients (Tang et al., 2020a). miRNAs have also been shown to affect expressions of a number of genes which are implicated in the life cycle of SARS-CoV-2, namely ACE2, TMPRSS2 and Nsp12 (Paul et al., 2022). Thus, miRNAs can be regarded as potential therapeutic targets in COVID-19, particularly for the management of pathological consequences of COVID-19.

Due to unavailability of conclusive experimental data about the role of miRNAs in determination of COVID-19 course, a number of investigators have used in silico methods to find the putative miRNA sites in the SARS-CoV-2 genome. For instance, Balme et al. have reported hsa-miR-1307-3p as a miRNA with the highest affinity to genome of this virus. This miRNA has been found to affect PI3K/Akt pathway and endocytosis (Balme et al., 2020). Another in silico approach has led to identification of more than 800 human miRNAs targeting the SARS-CoV-2 genome with miR-15a-5p, miR-15b-5p, miR-30b-5p, miR-409-3p.
miR-505-3p, and miR-548d-3p having the highest affinity (Fulzele et al., 2020). Although application of these miRNAs in therapeutic approaches requires experimental validation steps, in silico strategies as preliminary steps can facilitate selection of the most important miRNA candidates. After these bioinformatics steps, selected miRNAs can be investigated in knock-in/-down/-out experiments in appropriate cell lines and animal models to find their relevance with the studied diseases.

It has been revealed that viral loads can be used as a factor for recognition of high risk COVID-19 patients (Fajnzylber et al., 2020). Similarly, RNAemia has been found to have comparable efficiency with the most effective protein predictors in prediction of COVID-19 course (Gutmann et al., 2021). miRNAs are also related to viral dissemination and viremia. For instance, miR-2392 has been detected in the circulation of COVID-19 patients and its levels have been found to increase as a function of viral load (McDonald et al., 2021b).

On the other hand, a number of host miRNAs have been predicted to target ACE2. These miRNAs can modulate virus entry. A comprehensive bioinformatics strategy has predicted the interaction between ACE2 and miR-362-5p, miR-421, miR-500a-5p, miR-500b-5p, miR-3909, and miR-4766-5p (Hum et al., 2021), thus suggesting these miRNAs as putative candidates for therapeutic purposes in COVID-19. Other putative candidate miRNAs in this regard are hsa-miR-125a-5p and miR-200c that target SARS-CoV-2 infection. PLoS Pathog. 17, e1009759.

Fig. 2 depicts the miRNA-infection network in COVID-19 based on assessment of GSE418729 dataset (Chow and Salmena, 2020). miRNAs signature might also influence the severity of COVID-19. For instance, the SARS-CoV-2 targeting miRNA miR-146 can regulate TLR signaling, thus limiting disproportionate inflammatory responses to SARS-CoV-2. Decreased levels of miR-146a in patients with diabetes, obesity and hypertension might explain the severity of COVID-19 in these individuals (Reganović, 2021a).

The influence of viral miRNAs on activity of several immune-related pathways such as Wnt, IFN, NF-kB, PI3K/Akt, MAPK and Notch pathways (Bruscella et al., 2017), further suggests miRNA-targeting strategies as possible novel therapeutic methods for combating viral-related disorders. Although not extensively applied in the clinical settings, interference with miRNA synthesis and oligonucleotides that silence endogenous miRNAs are two possible approaches for modulation of expression of miRNAs (Narozho and Rubiš, 2021). On the other hand, a number of host miRNAs that target SARS-CoV-2 genome might be decreased in COVID-19 patients, leading to increase in viral replication. Mimic encoded-miRNAs have been suggested as tools for prevention of deteriorative effects of viral encoded-miRNAs (Farshbaf et al., 2021). Future studies on safety and efficacy of these methods are warranted.

Declaration of competing interest

The authors declare they have no conflict of interest.

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