Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Gene Reports 28 (2022) 101641

Contents lists available at ScienceDirect

Gene Reports

journal homepage: www.elsevier.com/locate/genrep

miRNA expression in COVID-19

Kiarash Roustai Geraylow [a], Romina Hemmati [a], Sepideh Kadkhoda [b], Soudeh Ghafouri-Fard [c,*]

[a] Student Research Committee, Semnan University of Medical Sciences, Semnan, Iran
[b] Department of Medical Genetics, Tehran University of Medical Sciences, Tehran, Iran
[c] Department of Medical Genetics, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ARTICLE INFO

Keywords:
miRNA
COVID-19
SARS-CoV-2

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

Abbreviations: COVID-19, Coronavirus disease 2019; miRNAs, microRNAs; ACE2, Angiotensin-converting enzyme 2; TMPRSS2, Transmembrane protease serine 2; TLR, Toll-like receptor; ARDS, Acute respiratory distress syndrome; ROC, Receiver operating characteristic; UTR, Untranslated region; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; ORF, Open reading frame; HMVEC, Human Lung Microvascular Endothelial Cells; HDAC, Histone deacetylate; hBMEC, Human brain microvascular endothelial cells.

* Corresponding author.
E-mail address: s.ghafourifard@sbmu.ac.ir (S. Ghafouri-Fard).

https://doi.org/10.1016/j.genrep.2022.101641
Received 29 October 2021; Received in revised form 25 June 2022; Accepted 10 July 2022
Available online 16 July 2022

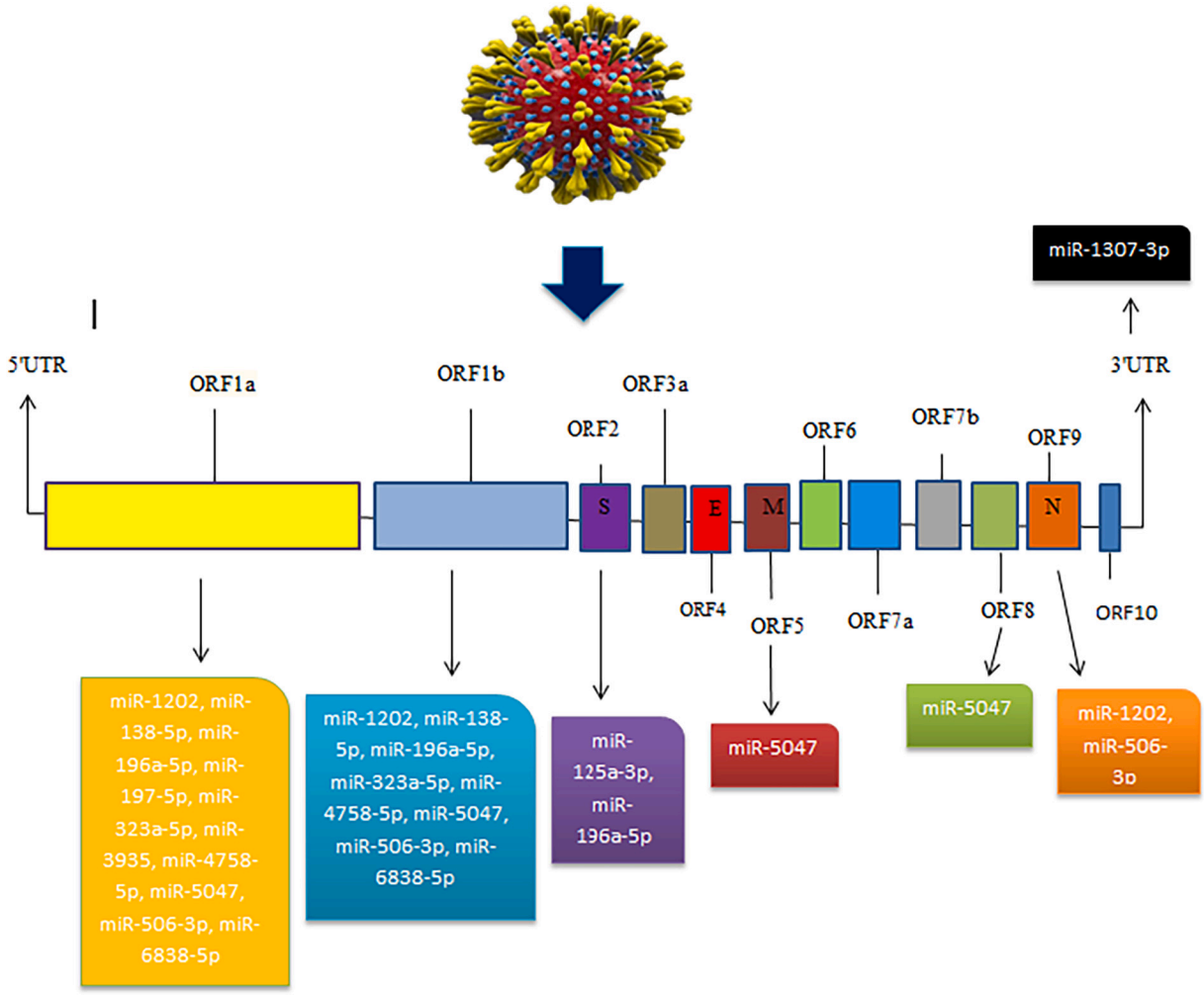

Fig. 1. The schematic image of the SARS-CoV-2 genome and its components and their relationship with host miRNAs during SARS-CoV-2 infection. miRNAs that interact with each element are shown in boxes below each element.

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-16-2-3p 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	TMPRSS2		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				Histone deacetylate (HDAC) pathway.	miR-335-5p and miR-26b-5p are affected by Spike, ACE and histone deacetylate network.	(Teodori et al., 2020)
miR-1202	Bioinformatics		7362			A single nucleotide polymorphism of miR1202 (rs140092351) is associated with COVID-19 and also interacts with several exposure factor.	(Zhang et al., 2021)
miR-451a	In vivo		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-28-3p	In vitro		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-155	In vitro		Vero E6, Calu-3, Caco-2 and H1299	Human epithelial cell line Calu-3		Induction of miR-155 and stimulation of the innate immune responses in SARS-CoV-2 is twice as high as in SARS-CoV.	(Wyler 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		The mentioned miRNAs are decreased in the elderly and diabetic groups and can directly inhibit the expression of S protein and the replication of SARS-CoV-2 virus.	(Wang et al., 2021)
aly-miR396a-5p, rlcv-miR-rL1–28-3p	In vitro		LLC1, macrophage cell lines, Vero E6 cells, A549 U937		Suppression of Nsp12 and spike genes	Ginger exosome miRNAs (aly miR396a 5p and rlcv miRrL1 28 3p) suppressed the expression of NSP12 and spike genes, which are key mediators of lung inflammation in SARS-CoV-2 infection.	(Teng et al., 2021)
miR-219a-2-3p, miR-30c-5p, miR-378d, miR-29a-3p, miR-15b-5p	In vitro & bioinformatics		Human lung cell line A549	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	(Siniscalchi et al., 2021)

(*continued on next page*)

Table 1 (*continued*)

microRNA	Study design	Participants	Number of samples/cell type	Targets/regulators	Signaling pathway	Study highlights	Ref
						protective capacity of cells.	
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	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					Immune modulatory		
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-429, hsa-miR-15a-5p, and hsa-miR-20a-5p	Bioinformatics				MAPK 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, NFYB, BRF1, HES2, NFYB, MED12L, MAFG, 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-193b-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				TMPRSS2			
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.	(Roganović, 2021b)
	Bioinformatics			ORF1ab			

(*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-4778-5p and hsa-miR-4531hsa-miR-6844 hsa-miR627-5p hsa-miR-3674						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)
miR-9-5p, miR-218-5p let-7d-5p, -7e-5p, miR-494-3p, miR-382-3p, miR-181c-5p	Bioinformatics			ACE2 TMPRSS2		miRNAs regulates SARS-CoV-2 infectivity in human cells through attachment of host	(Pierce et al., 2020)
miR-361-5p, miR-410-3p				IFN-α		miRNAs to the SARS-CoV-2 genome and	
miR-23a, miR-29a, -29c, miR-151a, -151b (S), miR-4707-3p (S), miR-298 miR-7851-3p, miR-8075				SARS-CoV-2 ORFs		modulation of the transcripts of viral entry proteins, ACE2 and TMPRSS2, and modulation by their upstream IFN modulators.	
hsa-miR-499a-3p hsa-miR-4532 hsa-miR-6763-3p hsa-miR-26b-5p	Bioinformatics			ACE2		SNP of microRNAs influence susceptibility to COVID-19 s and response to anti-viral drug by regulating *ACE2* expression.	(Paniri et al., 2021)
miR-30c and miR-200c				ACE2/TMPRSS2		Intestinal microRNAs (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	Bioinformatics					miR-2 This miRNA has the highest probability of attachment of human coronavirus RNAs and is increased in mice lung during SARS-CoV infection.	(Nersisyan et al., 2020a)
miR-24	In vitro		hBMEC	Transmembrane Glycoprotein Neuropilin-1		miR-24 targets Neuropilin-1.	(Mone et al., 2021)
hsa-miR-146a and hsa-miR-126-3p	In vivo	Hospitalized Covid-19 patients				Small-EVs, hsa-miR-146a and hsa-miR-126-3p are considerably down-regulated with COVID-19 severity.	(Mitchell et al., 2021)
miR-148a and miR-590	In vitro		HEK-293 T and human microglial cell line (CHME3)	USP33 and IRF9		Novel pathway for induction of neuroinflammatory damages that begins with Spike induced exosome production (exosomes loaded with miR-148a and miR-590).	(Mishra and Banerjea, 2021)
miR-4485	Clinical and bioinformatics	50 IgG (−) and 30 IgG (+) fracture patients	80 bone marrow specimens	TLR4		SARS-CoV-2 inhibits osteogenic differentiation and affects fracture healing by overexpressing miR-4485.	(Mi et al., 2021)
miR-2392	Both in vitro human and in vivo hamster 103 models			Mitochondrial and inflammatory pathways associated with SARS-CoV-2		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
						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.	
hsa-miR-1236–3p, zof-miR2673b	Bioinformatics			'GGAAGAG' in 5024 SARS-CoV-2 3′UTR		The target of these microRNAs represents a region concentrated in the SARS CoV 2 genome that may become a promising target for the fight against COVID 19.	(Mangukia et al., 2021)
miR-200c	In vitro		Neonatal rat cardiomyocytes (NRCMs) and Neonatal rat cardiac fibroblasts (NRCFs)	ACE2		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.	(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						These microRNAs commonly bind to SARS-CoV, MERS-CoV, and SARS-CoV-2.	
mir-21, mir-124, and mir-146a (anti-neuroinflammatory)	Bioinformatics and in vivo			IL-12p53, Stat3, and TRAF6		Expression of anti-neuroinflammatory miRNAs was decreased and their targeted mRNAs were increased, and the relative expression of pro-neuroinflammatory miRNAs was increased.	(Keikha and Jebali, 2021)
mir-326, mir-155, and mir-27b (pro-inflammatory)				PPARS, SOCS1, and CEBPA			
hsa-miR-31-3p, hsa-miR-29a-3p, and hsa-miR-126-3p	Bioinformatics In vivo and bioinformatics	Covid patients	19 blood sample	*ZMYM5*, *COL5A3*, 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, COL5A3, 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 of 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	(Karakas Celik et al., 2021)

(*continued on next page*)

Table 1 (*continued*)

microRNA	Study design	Participants	Number of samples/cell type	Targets/regulators	Signaling pathway	Study highlights	Ref
						response and lung damage repair	
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.	(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.	(Demiray et al., 2021)
hsa-miR-340-3p, hsa-miR-652-3p, hsa-miR-4772-5p, hsa-miR-192-5p, and hsa-miR-1291	Bioinformatics				Autophagy	These miRNAs may be markers to forecast alterations in mild SARS-CoV-2 infection. 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 candidate targets for the regulation of ACE2 respiratory system cell.	(Bozgeyik, 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-432-5p, 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-Hosseinabadi et al., 2021)
miR-124-3p	Bioinformatics					A ceRNA network involving one miRNA (miR-124-3p), one mRNA (Ddx58), one lncRNA (Gm26917) and two circRNAs (Ppp1r10, C330019G07RiK) in SARS-CoV infected cells is predicted.	(Arora et al., 2020)
miRs8066, 5197, 3611, 3934-3p, 1307-3p, 3691-3p, 1468-5p	Bioinformatics			KEGG pathways		7 key-microRNAs with remarkable association to KEGG pathways associated to viral pathogenicity and host response are detected.	(Arisan et al., 2020)
miR-486-3p	In vivo, bioinformatics		10	HCN4		MiR-486-3p inhibits HCN4 and markers involved in immune response.	(Aminu et al., 2021)
	In vivo					These micro RNAs contribute to the	(Tang et al., 2020b)

(*continued on next page*)

Table 1 (*continued*)

microRNA	Study design	Participants	Number of samples/cell type	Targets/regulators	Signaling pathway	Study highlights	Ref
miR-146a-5p, miR-21-5p, miR-142-3p, and miR-15b-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.	
hsa-let-7e / hsa-mir-125a and hsa-mir-141 / hsa-miR-200	Bioinformatics			ACE2 and TMPRSS2 genes		JARID1B inhibits the transcription of hsa-let-7e / hsa-mir-125a and hsa-mir-141 / hsa-miR-200 and indirectly affect ACE2 / TMPRSS2 expression	(Nersisyan et al., 2020b)
miR-147-3p	Bioinformatics, in vivo			EXOC7, RAD9A, and TFE3		miR147-3p was overexpressed in SARS-COV-2 infected cells.	(Liu et al., 2021)
miR-776-3p miR-1275 miR-4742-3p, miR-31-5p and miR-3215-3p	In vivo		10 COVID-19 patients sampled and 10 healthy control			miR-776-3p and miR-1275 were decreased, and miR-4742-3p, miR-31-5p and miR-3215-3p were over-expressed.	(Farr et al., 2021)

level in treatment-responsive COVID-19 patients (Keikha et al., 2021). Notably, miR-29 family has been shown to contain numerous binding regions in the SARS-CoV-2 genome (Jafarinejad-Farsangi et al., 2020).

miRNA levels have also been correlated with clinical responses of COVID-19 cases to the anti-IL-6 receptor agent Tocilizumab. Non-responder COVID-19 patients have exhibited decreased levels of miR-146a-5p in their sera after receiving a single dose of this drug. Notably, among non-responders, the lowermost expression amounts of miR-146a-5p have been correlated with the poorest outcome (Sabbatinelli et al., 2021). miR-146a has also been among the topmost miRNAs affecting expression of differentially expressed genes in lungs of COVID-19 patients (Jafarinejad-Farsangi et al., 2020).

Peripheral expressions of miR-21, miR-126, miR-155, miR-208a, and miR-499 have been analyzed in two cohorts of patients including COVID-19 cases needing mechanical ventilation, healthy persons and Influenza- acute respiratory distress syndrome (ARDS) patients. In both cohorts, serum levels of miR-21, miR-155, miR-208a and miR-499 have been abnormally increased in COVID-19 cases compared with healthy subjects (Garg et al., 2021).

Expression analysis of miR-200c-3p in mildly affected COVID-19 patients, COVID-19 patients with respiratory disorders and severely affected COVID-19 cases has shown highest levels of this miRNA in the latter group. 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 been 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/c/e, miR-6080, miR-181a-5p, miR-199a-3p, and miR-339 are highly specific for determination of severity and mortality rate of COVID-19 (Gustafson et al., 2022). In addition, Wilson et al. have shown correlations between levels of CCL20, IL-6, IL-10, and miR-451a and mortality of COVID-19 patients (Wilson et al., 2022). Besides, miR-133a and miR-122 have been found to be correlated with 28 day mortality of COVID-19 patients. Mechanistically, these two miRNAs reflect inflammation-

Table 2
Diagnostic role of miRNAs in COVID-19.

microRNA	Biomarker role	Sample number	Area under curve	Sensitivity (%)	Specificity (%)	References
miR-148a-3p, miR-486-5p and miR-451a	Discriminating ward vs. ICU patients	84	0.89 (0.81–0.97			(Gonzalo-Calvo et al., 2021)
miR-148a-3p, miR-486-5p and miR-451a	COVID-19 severity		From 0.72 (0.59–0.84) to 0.90 (0.82–0.97)			
miR192-5p and miR-323a-3p	Mortality during the ICU stay		0.80 (0.64–0.96)			
miR-155 miR-208a miR-499	Distinguish between the COVID-19 and the influenza-associated ARDS	33	1.00 0.79 0.86		100	(Garg et al., 2021)
miR-19a-3p, miR-19b-3p, and miR-92a-3p	Diagnostic biomarker for SARS-CoV-2-infection	33	0.81 0.87 0.85	88 89 90	85 86 87	(Fayyad-Kazan et al., 2021)
miR-29a-3p miR-146a-3p miR-155-5p	Biomarker for COVID-19 diagnosis	33	0.91 0.87 0.90	83.3 83.3 83.3	93.3 73.3 100	(Donyavi et al., 2021)
miR-26a-5p miR-29b-3p miR-34a-5p	Best power to discriminate the COVID-19 group from healthy subjects	19	0.82 0.81 0.70			(Centa et al., 2020)
miR-195-5p miR-423-5p, miR-23a-3p and miR-195-5p	COVID-19 case identification	7 COVID-19 samples and 10 control	0.90 1.00	72 99.9	95 99.8	(Farr et al., 2021)

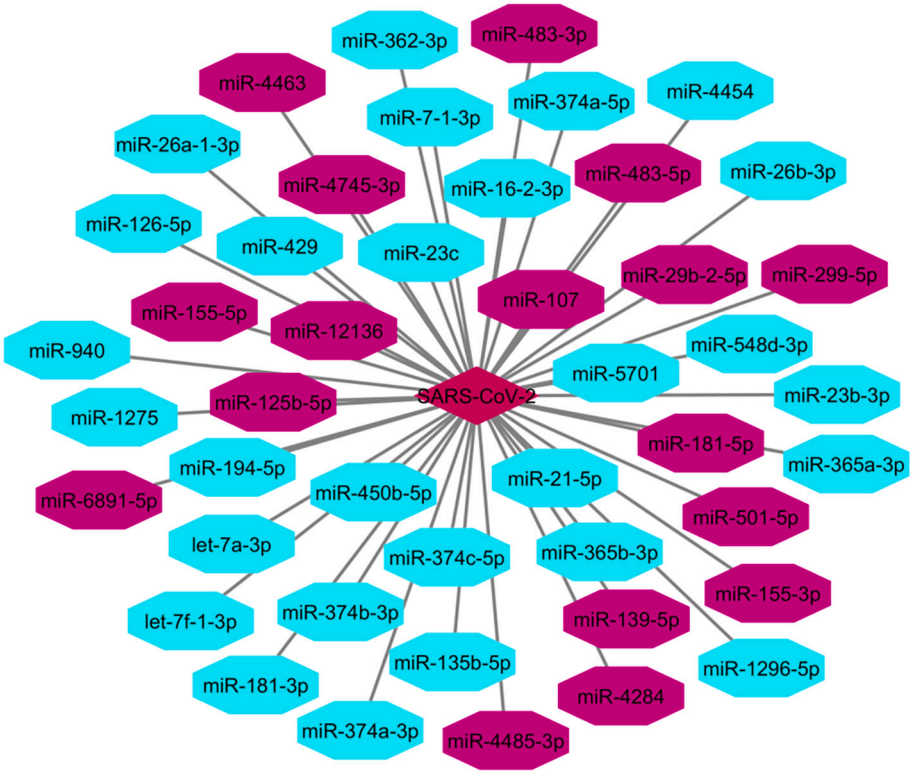

Fig. 2. The miRNA-infection network. Significantly up- and down-regulated miRNAs in SARS-CoV-2 according GSE148729 analysis. The purple and green hexagons represent up and down-regulated miRNA respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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 demised 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 expression 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 distinct 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, Balmeh 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 (Balmeh 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-200 family miRNAs that target 3′ UTR of ACE2 mRNA as well as TMPRSS2 targeting miRNAs hsa-let-7e-5p (Nersisyan et al., 2020b) and miR-98 (Matarese et al., 2020). Consistent with this speculation, the inhibitory effect of miR-200c on ACE2 has been verified in rat primary cardiac cells as well as human iPSC-derived cardiomyocytes (Lu et al., 2020).

Fig. 2 depicts the miRNA-infection network in COVID-19 based on assessment of GSE148729 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 (Roganović, 2021a).

The influence of viral miRNAs on activity of several immune-related pathways such as Wnt, IFN, NF-κB, 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 (Narożna and Rubiś, 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.

References

Aminu, A.J., Petkova, M., Atkinson, A.J., Yanni, J., Morris, A.D., Simms, R.T., Chen, W., Yin, Z., Kuniewicz, M., Holda, M.K., Kuzmin, V.S., Perde, F., Molenaar, P., Dobrzynski, H., 2021. Further insights into the molecular complexity of the human sinus node - the role of 'novel' transcription factors and microRNAs. Prog. Biophys. Mol. Biol. 166, 86–104.

Ammad Ud Din, M., Boppana, L.K.T., 2020. An update on the 2019-nCoV outbreak. Am. J Infect Control 48, 713.

Arghiani, N., Nissan, T., Matin, M.M., 2021. Role of microRNAs in COVID-19 with implications for therapeutics. Biomed. Pharmacother. 144, 112247.

Arisan, E.D., Dart, A., Grant, G.H., Arisan, S., Cuhadaroglu, S., Lange, S., Uysal-Onganer, P., 2020. The prediction of miRNAs in SARS-CoV-2 genomes: hsa-miR databases identify 7 key miRs linked to host responses and virus pathogenicity-related KEGG pathways significant for comorbidities. Viruses 12.

Arora, S., Singh, P., Dohare, R., Jha, R., Ali Syed, M., 2020. Unravelling host-pathogen interactions: ceRNA network in SARS-CoV-2 infection (COVID-19). Gene 762, 145057.

Bagheri-Hosseinabadi, Z., Ostad Ebrahimi, H., Bahrehmand, F., Taghipour, G., Abbasifard, M., 2021. The relationship between serum levels of interleukin-2 and IL-8 with circulating microRNA-10b in patients with COVID-19. Iran J. Immunol. 18, 65–73.

Balmeh, N., Mahmoudi, S., Mohammadi, N., Karabedianhajiabadi, A., 2020. Predicted therapeutic targets for COVID-19 disease by inhibiting SARS-CoV-2 and its related receptors. Inf. Med. Unlocked 20, 100407.

Banaganapalli, B., Al-Rayes, N., Awan, Z.A., Alsulaimany, F.A., Alamri, A.S., Elango, R., Malik, M.Z., Shaik, N.A., 2021. Multilevel systems biology analysis of lung transcriptomics data identifies key miRNAs and potential miRNA target genes for SARS-CoV-2 infection. Comput. Biol. Med. 135, 104570.

Barreda-Manso, M.A., Nieto-Díaz, M., Soto, A., Muñoz-Galdeano, T., Reigada, D., Maza, R.M., 2021. In silico and in vitro analyses validate human microRNAs targeting the SARS-CoV-2 3'-UTR. Int. J. Mol. Sci. 22.

Bertolazzi, G., Cipollina, C., Benos, P.V., Tumminello, M., Coronnello, C., 2020. miR-1207-5p can contribute to dysregulation of inflammatory response in COVID-19 via targeting SARS-CoV-2 RNA. Front. Cell. Infect. Microbiol. 10, 586592.

Bozgeyik, I., 2021. Therapeutic potential of miRNAs targeting SARS-CoV-2 host cell receptor ACE2. Meta Gene 27, 100831.

Bruscella, P., Bottini, S., Baudesson, C., Pawlotsky, J.-M., Feray, C., Trabucchi, M., 2017. Viruses and miRNAs: more friends than foes. Front. Microbiol. 8, 824.

Centa, A., Fonseca, A.S., Ferreira, S., Azevedo, M.L.V., Vaz de Paula, C.B., Nagashima, S., Machado-Souza, C., Miggiolaro, A., Baena, C.P., De Noronha, L., Cavalli, L.R., 2020. Deregulated miRNA expression is associated with endothelial dysfunction in post-mortem lung biopsies of COVID-19 patients. Am. J. Phys. Lung Cell. Mol. Phys. 320, L405-12.

Chow, J.T.-S., Salmena, L., 2020. Prediction and analysis of SARS-CoV-2-targeting MicroRNA in human lung epithelium. Genes 11, 1002.

De Gonzalo-Calvo, D., Benítez, I.D., Pinilla, L., Carratalá, A., Moncusí-Moix, A., Gort-Paniello, C., Molinero, M., González, J., Torres, G., Bernal, M., 2021. Circulating microRNA profiles predict the severity of COVID-19 in hospitalized patients. Transl. Res. 236, 147–159.

Demiray, A., Sarı, T., Çalışkan, A., Nar, R., Aksoy, L., Akbubak, İ.H., 2021. Serum microRNA signature is capable of predictive and prognostic factor for SARS-COV-2 virulence. Turk. J. Biol. 46, 245.

Donyavi, T., Bokharaei-Salim, F., Baghi, H.B., Khanaliha, K., Alaei Janat-makan, M., Karimi, B., Sadri Nahand, J., Mirzaei, H., Khatami, A., Garshasbi, S., Khoshmirsafa, M., Jalal Kiani, S., 2021. Acute and post-acute phase of COVID-19: analyzing expression patterns of miRNA-29a-3p, 146a-3p, 155-5p, and let-7b-3p in PBMC. Int. Immunopharmacol. 97, 107641.

Fajnzylber, J., Regan, J., Coxen, K., Corry, H., Wong, C., Rosenthal, A., Worrall, D., Giguel, F., Piechocka-Trocha, A., Atyeo, C., 2020. SARS-CoV-2 viral load is associated with increased disease severity and mortality. Nat. Commun. 11, 1–9.

Fani, M., Zandi, M., Rezayi, M., Khodadad, N., Langari, H., Amiri, I., 2018. The role of microRNAs in the viral infections. Curr. Pharm. Des. 24, 4659–4667.

Fani, M., Zandi, M., Ebrahimi, S., Soltani, S., Abbasi, S., 2021. The role of miRNAs in COVID-19 disease. Futur. Virol. https://doi.org/10.2217/fvl-2020-0389.

Farr, R.J., Rootes, C.L., Rowntree, L.C., Nguyen, T.H.O., Hensen, L., Kedzierski, L., Cheng, A.C., Kedzierska, K., Au, G.G., Marsh, G.A., Vasan, S.S., Foo, C.H., Cowled, C., Stewart, C.R., 2021. Altered microRNA expression in COVID-19 patients enables identification of SARS-CoV-2 infection. PLoS Pathog. 17, e1009759.

Farshbaf, A., Mohtasham, N., Zare, R., Mohajertehran, F., Rezaee, S.A., 2021. Potential therapeutic approaches of microRNAs for COVID-19: challenges and opportunities. J. Oral. Biol. Craniofac. Res. 11, 132–137.

Fayyad-Kazan, M., Makki, R., Skafi, N., el Homsi, M., Hamade, A., el Majzoub, R., Hamade, E., Fayyad-Kazan, H., Badran, B., 2021. Circulating miRNAs: potential diagnostic role for coronavirus disease 2019 (COVID-19). Infect. Genet. Evol. 94, 105020.

Fulzele, S., Sahay, B., Yusufu, I., Lee, T.J., Sharma, A., Kolhe, R., Isales, C.M., 2020. COVID-19 virulence in aged patients might be impacted by the host cellular microRNAs abundance/profile. Aging Dis. 11, 509.

Gambardella, J., Coppola, A., Izzo, R., Fiorentino, G., Trimarco, B., Santulli, G., 2021a. Role of endothelial miR-24 in COVID-19 cerebrovascular events. Crit. Care 25, 306.

Gambardella, J., Coppola, A., Izzo, R., Fiorentino, G., Trimarco, B., Santulli, G., 2021b. Role of endothelial miR-24 in COVID-19 cerebrovascular events. Crit. Care 25, 306-306.

Garg, A., Seeliger, B., Derda, A.A., Xiao, K., Gietz, A., Scherf, K., Sonnenschein, K., Pink, I., Hoeper, M.M., Welte, T., Bauersachs, J., David, S., BäR, C., THUM, T., 2021. Circulating cardiovascular microRNAs in critically ill COVID-19 patients. Eur. J. Heart Fail. 23, 468–475.

Giuliani, A., Matacchione, G., Ramini, D., Di Rosa, M., Bonfigli, A.R., Sabbatinelli, J., Monsurrò, V., Recchioni, R., Marcheselli, F., Marchegiani, F., 2022. Circulating miR-320b and miR-483-5p levels are associated with COVID-19 in-hospital mortality. Mech. Ageing Dev. 202, 111636.

Gonzalo-Calvo, D., Benítez, I.D., Pinilla, L., Carratalá, A., Moncusí-Moix, A., Gort-Paniello, C., Molinero, M., González, J., Torres, G., Bernal, M., Pico, S., Almansa, R., Jorge, N., Ortega, A., Bustamante-Munguira, E., Gómez, J.M., González-Rivera, M., Micheloud, D., Ryan, P., Martinez, A., Tamayo, L., Aldecoa, C., Ferrer, R., Ceccato, A., Fernández-Barat, L., Motos, A., Riera, J., Menendez, R., Garcia-Gasulla, D., Peñuelas, O., Torres, A., Bermejo-Martin, J.F., Barbe, F., 2021. Circulating microRNA profiles predict the severity of COVID-19 in hospitalized patients. Transl. Res. 236, 147–159.

Gustafson, D., Ngai, M., Wu, R., Hou, H., Schoffel, A.C., Erice, C., Mandla, S., Billia, F., Wilson, M.D., Radisic, M., 2022. Cardiovascular signatures of COVID-19 predict mortality and identify barrier stabilizing therapies. EBioMedicine 78, 103982.
Gutmann, C., Takov, K., Burnap, S.A., Singh, B., Ali, H., Theofilatos, K., Reed, E., Hasman, M., Nabeebaccus, A., Fish, M., 2021. SARS-CoV-2 RNAemia and proteomic trajectories inform prognostication in COVID-19 patients admitted to intensive care. Nat. Commun. 12, 1–17.
Gutmann, C., Khamina, K., Theofilatos, K., Diendorfer, A.B., Burnap, S.A., Nabeebaccus, A., Fish, M., McPhail, M.J., O'Gallagher, K., Schmidt, L.E., 2022. Association of cardiometabolic microRNAs with COVID-19 severity and mortality. Cardiovasc. Res. 118, 461–474.
Hoffmann, M., Hofmann-Winkler, H., Pöhlmann, S., 2018. Priming time: how cellular proteases arm coronavirus spike proteins. In: Activation of Viruses by Host Proteases, pp. 71–98.
Hum, C., Loiselle, J., Ahmed, N., Shaw, T.A., Toudic, C., Pezacki, J.P., 2021. MicroRNA mimics or inhibitors as antiviral therapeutic approaches against COVID-19. Drugs 81, 517–531.
Jafarinejad-Farsangi, S., Jazi, M.M., Rostamzadeh, F., Hadizadeh, M., 2020. High affinity of host human microRNAs to SARS-CoV-2 genome: an in silico analysis. Noncoding RNA Res. 5, 222–231.
Karakas Celik, S., Cakmak Genc, G., Dursun, A., 2021. A bioinformatic approach to investigating cytokine genes and their receptor variants in relation to COVID-19 progression. Int. J. Immunogenet. 48, 211–218.
Kaur, T., Kapila, S., Kapila, R., Kumar, S., Upadhyay, D., Kaur, M., Sharma, C., 2021. Tmprss2 specific miRNAs as promising regulators for SARS-CoV-2 entry checkpoint. Virus Res. 294, 198275.
Keikha, R., Jebali, A., 2021. The miRNA neuroinflammatory biomarkers in COVID-19 patients with different severity of illness. Neurologia. https://doi.org/10.1016/j.nrl.2021.06.005. Online ahead of print.
Keikha, R., Hashemi-Shahri, S.M., Jebali, A., 2021. The relative expression of miR-31, miR-29, miR-126, and miR-17 and their mRNA targets in the serum of COVID-19 patients with different grades during hospitalization. Eur. J. Med. Res. 26, 75.
Khan, M.A., Sany, M.R.U., Islam, M.S., Islam, A., 2020. Epigenetic regulator miRNA pattern differences among SARS-CoV, SARS-CoV-2, and SARS-CoV-2 world-wide isolates delineated the mystery behind the epic pathogenicity and distinct clinical characteristics of pandemic COVID-19. Front. Genet. 11, 765.
Kim, W.R., Park, E.G., Kang, K.W., Lee, S.M., Kim, B., Kim, H.S., 2020. Expression analyses of MicroRNAs in hamster lung tissues infected by SARS-CoV-2. Mol. Cells 43, 953–963.
Li, C., Hu, X., Li, L., Li, J.-H., 2020. Differential microRNA expression in the peripheral blood from human patients with COVID-19. J. Clin. Lab. Anal. 34 e23590-e23590.
Li, S., Duan, X., Li, Y., Li, M., Gao, Y., Li, T., Li, S., Tan, L., Shao, T., Jeyarajan, A.J., Chen, L., Han, M., Lin, W., Li, X., 2021. Differentially expressed immune response genes in COVID-19 patients based on disease severity. Aging (Albany NY) 13, 9265–9276.
Liu, Z., Wang, J., Ge, Y., Xu, Y., Guo, M., Mi, K., Xu, R., Pei, Y., Zhang, Q., Luan, X., Hu, Z., Chi, Y., Liu, X., 2021. SARS-CoV-2 encoded microRNAs are involved in the process of virus infection and host immune response. J. Biomed. Res. 35, 216–227.
Lu, D., Chatterjee, S., Xiao, K., Riedel, I., Wang, Y., Foo, R., Bär, C., Thum, T., 2020. MicroRNAs targeting the SARS-CoV-2 entry receptor ACE2 in cardiomyocytes. J. Mol. Cell. Cardiol. 148, 46–49.
Macfarlane, L.-A., Murphy, P.R., 2010. MicroRNA: biogenesis, function and role in cancer. Curr. Genomics 11, 537–561.
Mangukia, N., Rao, P., Patel, K., Pandya, H., Rawal, R.M., 2021. Identifying potential human and medicinal plant microRNAs against SARS-CoV-2 3'UTR region: a computational genomics assessment. Comput. Biol. Med. 136, 104662.
Matarese, A., Gambardella, J., Sardu, C., Santulli, G., 2020. miR-98 regulates TMPRSS2 expression in human endothelial cells: key implications for COVID-19. Biomedicines 8.
McDonald, J.T., Enguita, F.J., Taylor, D., Griffin, R.J., Priebe, W., Emmett, M.R., McGrath, M., Sajadi, M.M., Harris, A.D., Clement, J., Dybas, J.M., Aykin-Burns, N., Guarnieri, J.W., Singh, L.N., Grabham, P., Baylin, S.B., Yousey, A., Pearson, A.N., Corry, P.M., Saravia-Butler, A., Aunins, T.R., Nagpal, P., Meydan, C., Foox, J., Mozsary, C., Cerqueira, B., Zaksas, V., Singh, U., Wurtele, E.S., Costes, S.V., Galeano, D., Paccanaro, A., Meinig, S.L., Hagan, R.S., Bowman, N.M., Wolfgang, M. C., Altinok, S., Sapoval, N., Treangen, T.J., Frieman, M., Vanderburg, C., Wallace, D. C., Schisler, J., Mason, C.E., Chatterjee, A., Meller, R., Beheshti, A., 2021. The Great Deceiver: miR-2392's Hidden Role in Driving SARS-CoV-2 Infection. bioRxiv.
McDonald, J.T., Enguita, F.J., Taylor, D., Griffin, R.J., Priebe, W., Emmett, M.R., Sajadi, M.M., Harris, A.D., Clement, J., Dybas, J.M., 2021b. Role of miR-2392 in driving SARS-CoV-2 infection. Cell Rep. 37, 109839.
Mi, B., Xiong, Y., Zhang, C., Zhou, W., Chen, L., Cao, F., Chen, F., Geng, Z., Panayi, A.C., Sun, Y., Wang, L., Liu, G., 2021. SARS-CoV-2-induced overexpression of miR-4485 suppresses osteogenic differentiation and impairs fracture healing. Int. J. Biol. Sci. 17, 1277–1288.
Mishra, R., Banerjea, A.C., 2021. SARS-CoV-2 spike targets USP33-IRF9 Axis via exosomal miR-148a to activate human microglia. Front. Immunol. 12, 656700.
Mitchell, M.I., Ben-Dov, I.Z., Liu, C., Ye, K., Chow, K., Kramer, Y., Gangadharan, A., Park, S., Fitzgerald, S., Ramnauth, A., Perlin, D.S., Donato, M., Bhoy, E., Manouchehri Doulabi, E., Poulos, M., Kamali-Moghaddam, M., Loudig, O., 2021. Extracellular Vesicle Capture by AnTibody of CHoice and Enzymatic Release (EV-CATCHER): a customizable purification assay designed for small-RNA biomarker identification and evaluation of circulating small-EVs. J. Extracell Vesicles 10, e12110.
Mone, P., Gambardella, J., Wang, X., Jankauskas, S.S., Matarese, A., Santulli, G., 2021. miR-24 targets the transmembrane glycoprotein neuropilin-1 in human brain microvascular endothelial cells. Noncoding RNA 7.
Narożna, M., Rubiś, B., 2021. Anti-SARS-CoV-2 strategies and the potential role of miRNA in the assessment of COVID-19 morbidity, recurrence, and therapy. Int. J. Mol. Sci. 22, 8663.
Nersisyan, S., Engibaryan, N., Gorbonos, A., Kirdey, K., Makhonin, A., Tonevitsky, A., 2020a. Potential role of cellular miRNAs in coronavirus-host interplay. PeerJ 8, e9994.
Nersisyan, S., Shkurnikov, M., Turchinovich, A., Knyazev, E., Tonevitsky, A., 2020b. Integrative analysis of miRNA and mRNA sequencing data reveals potential regulatory mechanisms of ACE2 and TMPRSS2. PLoS One 15, e0235987.
Nersisyan, S.A., Shkurnikov, M.Y., Osipyants, A.I., Vechorko, V.I., 2020c. Role of ACE2/TMPRSS2 genes regulation by intestinal microRNA isoforms in the covid-19 pathogenesis. Bull. Russ. State Med. Univ. 16–18.
Noroozi, R., Branicki, W., Pyrc, K., Łabaj, P.P., Pospiech, E., Taheri, M., Ghafouri-Fard, S., 2020. Altered cytokine levels and immune responses in patients with SARS-CoV-2 infection and related conditions. Cytokine 133, 155143.
Pal, M., Berhanu, G., Desalegn, C., Kandi, V., 2020. Severe acute respiratory syndrome Coronavirus-2 (SARS-CoV-2): an update. Cureus 12 e7423-e7423.
Paniri, A., Hosseini, M.M., Moballegh-Eslam, M., Akhavan-Niaki, H., 2021. Comprehensive in silico identification of impacts of ACE2 SNPs on COVID-19 susceptibility in different populations. Gene Rep. 22, 100979.
Paul, S., Vázquez, L.A.B., Reyes-Perez, P.R., Estrada-Meza, C., Alburquerque, R.A.A., Pathak, S., Banerjee, A., Bandyopadhyay, A., Chakraborty, S., Srivastava, A., 2022. The role of microRNAs in solving COVID-19 puzzle from infection to therapeutics: a mini-review. Virus Res. 308, 198631.
Pierce, J.B., Simion, V., Icli, B., Perez-Cremades, D., Cheng, H.S., Feinberg, M.W., 2020. Computational analysis of targeting SARS-CoV-2, viral entry proteins ACE2 and TMPRSS2, and interferon genes by host MicroRNAs. Genes (Basel) 11.
Pimenta, R., Viana, N.I., Dos Santos, G.A., Candido, P., Guimarães, V.R., Romão, P., Silva, I.A., De Camargo, J.A., Hatanaka, D.M., Queiroz, P.G.S., Teruya, A., Echenique, L., Besen, B., Leite, K.R.M., Srougi, V., Srougi, M., Reis, S.T., 2021. MiR-200c-3p expression may be associated with worsening of the clinical course of patients with COVID-19. Mol. Biol. Res. Commun. 10, 141–147.
Pimenta, R., Viana, N.I., Dos Santos, G.A., Candido, P., Guimarães, V.R., Romão, P., Silva, I.A., De Camargo, J.A., Hatanaka, D.M., Queiroz, P.G.S., Teruya, A., Echenique, L., Besen, B.A.M.P., Leite, K.R.M., Srougi, V., Srougi, M., Reis, S.T., 2021. MiR-200c-3p expression may be associated with worsening of the clinical course of patients with COVID-19. Mol. Biol. Res. Commun. 10, 141–147.
Rahmadi, A., Fasyah, I., Sudigyo, D., Budiarto, A., Mahesworo, B., Hidayat, A.A., Pardamean, B., 2021. Comparative study of predicted miRNA between Indonesia and China (Wuhan) SARS-CoV-2: a bioinformatics analysis. Genes Genomics 43, 1079–1086.
Roganović, J., 2021. Downregulation of microRNA-146a in diabetes, obesity and hypertension may contribute to severe COVID-19. Med. Hypotheses 146, 110448.
Roganović, J.R., 2021. microRNA-146a and -155, upregulated by periodontitis and type 2 diabetes in oral fluids, are predicted to regulate SARS-CoV-2 oral receptor genes. J. Perinatol. 92, 35–43.
Roy, S., Sharma, B., Mazid, M.I., Akhand, R.N., Das, M., Marufatuzzahan, M., Chowdhury, T.A., Azim, K.F., Hasan, M., 2021. Identification and host response interaction study of SARS-CoV-2 encoded miRNA-like sequences: an in silico approach. Comput. Biol. Med. 134, 104451.
Sabbatinelli, J., Giuliani, A., Matacchione, G., Latini, S., Laprovitera, N., Pomponio, G., Ferrarini, A., Svegliati Baroni, S., Pavani, M., Moretti, M., Gabrielli, A., Procopio, A. D., Ferracin, M., Bonafe, M., Olivieri, F., 2021. Decreased serum levels of the inflammaging marker miR-146a are associated with clinical non-response to tocilizumab in COVID-19 patients. Mech. Ageing Dev. 193, 111413.
Sabetian, S., Castiglioni, I., Jahromi, B.N., Mousavi, P., Cava, C., 2021. In silico identification of miRNA-lncRNA interactions in male reproductive disorder associated with COVID-19 infection. Cells 10.
Sacconi, A., Donzelli, S., Pulito, C., Ferrero, S., Spinella, F., Morrone, A., Rigoni, M., Pimpinelli, F., Ensoli, F., Sanguineti, G., Pellini, R., Agrawal, N., Izumchenko, E., Ciliberto, G., Giannì, A., Muti, P., Strano, S., Blandino, G., 2020. TMPRSS2, a SARS-CoV-2 internalization protease is downregulated in head and neck cancer patients. J. Exp. Clin. Cancer Res. 39.
Safdar, M., Khan, M.S., Karim, A.Y., Omar, S.A., Smail, S.W., Saeed, M., Zaheer, S., Ali, M., Ahmad, B., Tasleem, M., Junejo, Y., 2021. SNPs at 3'UTR of APOL1 and miR-6741-3p target sites associated with kidney diseases more susceptible to SARS-COV-2 infection: in silco and in vitro studies. Mamm. Genome 1–12.
Sardar, R., Satish, D., Gupta, D., 2020. Identification of novel SARS-CoV-2 drug targets by host MicroRNAs and transcription factors co-regulatory interaction network analysis. Front. Genet. 11, 571274.
Sarma, A., Phukan, H., Halder, N., Madanan, M.G., 2020. An in-silico approach to study the possible interactions of miRNA between human and SARS-CoV2. Comput. Biol. Chem. 88.
Sato, A., Ogino, Y., Tanuma, S.I., Uchiumi, F., 2021. Human microRNA hsa-miR-15b-5p targets the RNA template component of the RNA-dependent RNA polymerase structure in severe acute respiratory syndrome coronavirus 2. Nucleosides Nucleotides Nucleic Acids 40, 790–797.
Saulle, I., Garziano, M., Fenizia, C., Cappelletti, G., Parisi, F., Clerici, M., Cetin, I., Savasi, V., Biasin, M., 2021. MiRNA profiling in plasma and placenta of SARS-CoV-2-infected pregnant women. Cells 10.
Siniscalchi, C., di Palo, A., Russo, A., Potenza, N., 2021. Human MicroRNAs interacting with SARS-CoV-2 RNA sequences: computational analysis and experimental target validation. Front. Genet. 12, 678994.

Tang, H., Gao, Y., Li, Z., Miao, Y., Huang, Z., Liu, X., Xie, L., Li, H., Wen, W., Zheng, Y., 2020a. The noncoding and coding transcriptional landscape of the peripheral immune response in patients with COVID-19. Clin. Transl. Med. 10, e200.

Tang, H., Gao, Y., Li, Z., Miao, Y., Huang, Z., Liu, X., Xie, L., Li, H., Wen, W., Zheng, Y., Su, W., 2020b. The noncoding and coding transcriptional landscape of the peripheral immune response in patients with COVID-19. Clin. Transl. Med. 10, e200.

Teng, Y., Xu, F., Zhang, X., Mu, J., Sayed, M., Hu, X., Lei, C., Sriwastva, M., Kumar, A., Sundaram, K., Zhang, L., Park, J.W., Chen, S.Y., Zhang, S., Yan, J., Merchant, M.L., Zhang, X., McClain, C.J., Wolfe, J.K., Adcock, R.S., Chung, D., Palmer, K.E., Zhang, H.G., 2021. Plant-derived exosomal microRNAs inhibit lung inflammation induced by exosomes SARS-CoV-2 Nsp12. Mol. Ther. 29, 2424–2440.

Teodori, L., Sestili, P., Madiai, V., Coppari, S., Fraternale, D., Rocchi, M.B.L., Ramakrishna, S., Albertini, M.C., 2020. MicroRNAs bioinformatics analyses identifying HDAC pathway as a putative target for existing anti-COVID-19 therapeutics. Front. Pharmacol. 11, 582003.

Trobaugh, D.W., Klimstra, W.B., 2017. MicroRNA regulation of RNA virus replication and pathogenesis. Trends Mol. Med. 23, 80–93.

Wan, Y., Shang, J., Graham, R., Baric, R.S., Li, F., 2020. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. J. Virol. 94 e00127-20.

Wang, Y., Zhu, X., Jiang, X.M., Guo, J., Fu, Z., Zhou, Z., Yang, P., Guo, H., Guo, X., Liang, G., Zeng, P., Xiao, G., Ma, J., Yin, X., Zhang, L.K., Yan, C., Zhang, C.Y., 2021. Decreased inhibition of exosomal miRNAs on SARS-CoV-2 replication underlies poor outcomes in elderly people and diabetic patients. Signal Transduct. Target. Ther. 6, 300.

Wicik, Z., Eyileten, C., Jakubik, D., Simões, S.N., Martins Jr., D.C., Pavão, R., Siller-Matula, J.M., Postula, M., 2020. ACE2 interaction networks in COVID-19: a physiological framework for prediction of outcome in patients with cardiovascular risk factors. J. Clin. Med. 9.

Wilson, J.C., Kealy, D., James, S.R., Plowman, T., Newling, K., Jagger, C., Filbey, K., Mann, E.R., Konkel, J.E., Menon, M., 2022. Integrated miRNA/cytokine/chemokine profiling reveals severity-associated step changes and principal correlates of fatality in COVID-19. Iscience 25, 103672.

Wyler, E., Mösbauer, K., Franke, V., Diag, A., Gottula, L.T., Arsie, R., Klironomos, F., Koppstein, D., Hönzke, K., Ayoub, S., Buccitelli, C., Hoffmann, K., Richter, A., Legnini, I., Ivanov, A., Mari, T., Del Giudice, S., Papies, J., Praktiknjo, S., Meyer, T.F., Muller, M.A., Niemeyer, D., Hocke, A., Selbach, M., Akalin, A., Rajewsky, N., Drosten, C., Landthaler, M., 2021. Transcriptomic profiling of SARS-CoV-2 infected human cell lines identifies HSP90 as target for COVID-19 therapy. iScience 24, 102151.

Xu, Y., Li, Y., 2021. MicroRNA-28-3p inhibits angiotensin-converting enzyme 2 ectodomain shedding in 293T cells treated with the spike protein of severe acute respiratory syndrome coronavirus 2 by targeting a disintegrin and metalloproteinase 17. Int. J. Mol. Med. 48.

Yang, P., Zhao, Y., Li, J., Liu, C., Zhu, L., Zhang, J., Yu, Y., Wang, W.J., Lei, G., Yan, J., Sun, F., Bian, C., Meng, F., Xu, Z., Bai, C., Ye, B., Guo, Y., Shu, L., Yuan, X., Zhang, N., Bi, Y., Shi, Y., Wu, G., Zhang, S., Gao, G.F., Liu, L., Liu, W.J., Sun, H.X., 2021. Downregulated miR-451a as a feature of the plasma cfRNA landscape reveals regulatory networks of IL-6/IL-6R-associated cytokine storms in COVID-19 patients. Cell. Mol. Immunol. 18, 1064–1066.

Zhang, Y., Yang, H., Li, S., Li, W.D., Wang, J., Wang, Y., 2021. Association analysis framework of genetic and exposure risks for COVID-19 in middle-aged and elderly adults. Mech. Ageing Dev. 194, 111433.