Title: Cardiovascular implications of miRNAs in COVID-19

Carmine Izzo*¹, Valeria Visco*¹, Jessica Gambardella²,³, Germano Junior Ferruzzi¹, Antonella Rispoli¹, Maria Rosaria Rusciano¹, Anna Laura Toni¹, Nicola Virtuoso⁴, Albino Carrizzo¹,⁵, Paola Di Pietro¹, Guido Iaccarino², Carmine Vecchione¹,⁵, Michele Ciccarelli¹

1 Department of Medicine, Surgery and Dentistry, University of Salerno, Baronissi, Italy.
2 Department of Advanced Biomedical Sciences, "Federico II" University, Naples, Italy.
3 Department of Medicine, Einstein-Sinai Diabetes Research Center, The Fleischer Institute for Diabetes and Metabolism, Einstein Institute for Aging Research, Albert Einstein College of Medicine, New York, NY.
4 Cardiology Unit, University Hospital “San Giovanni di Dio e Ruggi d’Aragona”, Salerno, Italy.
5 Vascular Physiopathology Unit, IRCCS Neuromed, Pozzilli, Italy.

*Equally contributed

ADDRESS FOR CORRESPONDENCE:

Michele Ciccarelli, MD, PhD
Department of Medicine, Surgery and Dentistry, University of Salerno
Via Salvador Allende
84081 Baronissi, Salerno, Italy
mciccarelli@unisa.it;
Phone: +390899965021

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic continues to be a global challenge due to resulting morbidity and mortality. Cardiovascular (CV) involvement is a crucial complication in COVID-19 and no strategies are available to prevent or specifically address CV events in COVID patients. The identification of molecular partners contributing to CV manifestations in COVID-19 patients is crucial for providing early biomarkers, prognostic predictors and new therapeutic targets. The current report will focus on the role of miRNAs in CV complications associated with COVID-19. Indeed, miRNAs have been proposed as valuable biomarkers and predictors of both cardiac and vascular damage occurring in SARS-CoV-2 infection.

Keywords: COVID-19; miRNA; biomarkers; cardiovascular disease

SIGNIFICANCE STATEMENT

It is essential to identify the molecular mediators of COVID-19 cardiovascular (CV) complications. This report focused on the role of miRNAs in CV complications associated with COVID-19, discussing their potential use as biomarkers, prognostic predictors, and therapeutic targets.
1 Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Table 1) pandemic is still a global health challenge with serious effects on people's health, cultures, and economies (Ayoub, Mumtaz et al. 2021). Because of COVID-19-related complications and mortality, this pandemic has astonished the world. However, the exact pathogenesis of this disease and virus-host interactions are still unknown; as a result, it is critical to continue researching the biological and molecular mechanisms involved in clinical complications, in order to identify new prognostic and therapeutic targets and prevent hospitalizations and sanitary emergencies (Visco, Vitale et al. 2022). In this context, mounting evidence has suggested miRNAs as a class of powerful biomarkers.

Analysis of the human genome has revealed that almost 60% of human DNA is transcribed into non-coding RNAs (ncRNAs) (Venter, Adams et al. 2001, Frith, Pheasant et al. 2005). MicroRNAs are the most studied ncRNAs, consisting of 19–24 nucleotides in length and able to bind complementary target mRNA to overpower translation or to induce mRNA degradation (Guterres, de Azeredo Lima et al. 2020, Tang, Gao et al. 2020, Satyam, Bhardwaj et al. 2021). It is estimated that MicroRNAs are involved in regulating the expression of more than 60% of protein-coding genes in mammals. Hence, MicroRNAs play a key role in a plethora of physiological and pathological mechanisms, including the antiviral response (Saçar Demirci and Adan 2020). For instance, host cellular microRNAs can bind the coding regions of the genome in RNA viruses (e.g., HIV, hepatitis C virus, dengue virus, and influenza virus), thus exerting an antiviral effect (Guterres, de Azeredo Lima et al. 2020) (Chan, Choi et al. 2020, Fulzele, Sahay et al. 2020). In the context of COVID19, MicroRNAs targeting the S, M, N, E, and ORF1ab genes might suppress SARS-CoV-2 invasion into the cell, limiting its replication (Saçar Demirci and Adan 2020). Furthermore, several miRNAs are key regulators of inflammation-related mediators, appearing to be essential in some inflammatory diseases (Chandan, Gupta et al. 2019), including viral-mediated inflammation. More broadly, both innate and adaptive immune responses can be regulated by miRNAs (Saçar Demirci and Adan 2020). Given this evidence, miRNAs could be important players in determining the susceptibility to Sars-Cov2 infection and the entity of immune response to it, directly affecting the cell damage induced by the virus or by cytokine storm (Chandan, Gupta et al. 2019). On the other hand, miRNAs are implicated in regulating COVID19 complications, especially cardiovascular (CV) events. Indeed, miRNAs dysregulation has been associated with a variety of CV alterations, suggesting their role as causal factors in disease progression (Paul, Chakraborty et al. 2018). The current report will focus on the role of miRNAs in CV complications associated with
COVID-19, discussing their potential use as biomarkers and prognostic predictors in COVID-19 patients.

2 Cardiovascular complications in COVID-19

The primary clinical manifestations of COVID-19 are respiratory; however, CV involvement is a crucial complication. Indeed, COVID-19 can significantly affect patients' CV system, and myocardial injury can occur in approximately 12% of hospitalized patients with COVID-19 infection (Clerkin, Fried et al. 2020). Associated with a high inflammatory burden due to cytokine release, SARS-CoV-2 can induce vascular inflammation, acute myocardial injury, myocarditis, arrhythmias, venous thromboembolism, heart failure, and Kawasaki disease (Chang, Toh et al. 2021, Tajbakhsh, Gheibi Hayat et al. 2021). Significantly, the incidence of acute cardiac injury has been reported to be about 13-fold higher in ICU/severe patients compared with non-ICU/severe patients (Li, Yang et al. 2020). Moreover, patients with COVID-19 and pre-existing CV disease have an increased risk of severe presentations. Accordingly, death and mortality from COVID-19 are deeply associated with CV disease, including diabetes and hypertension, (Azevedo, Botelho et al. 2021, Chang, Toh et al. 2021). Finally, therapies used for COVID-19 may have CV side effects, like arrhythmia (Chang, Toh et al. 2021) (Azevedo, Botelho et al. 2021). To date, there is no effective strategy to address the adverse CV events related to COVID-19 infection except for the management of symptoms (Tajbakhsh, Gheibi Hayat et al. 2021); consequently, the identification of molecular players contributing to the CV impact of COVID-19 is crucial for providing new early biomarkers and prognostic predictors for these patients.

In the context of CV involvement in COVID-19, we should consider myocardial damage: acute ischemic injury (type 1 myocardial infarction) (Bangalore, Sharma et al. 2020), non-ischemic injury (i.e., myocarditis) (Inciardi, Lupi et al. 2020), stress cardiomyopathy (van Osch, Asselbergs et al. 2020), heart failure (HF) (Chitsazan, Amin et al. 2021) and myocardial fibrosis. Moreover, we should consider vascular damage: thromboembolism, vascular inflammation and Kawasaki disease (Chang, Toh et al. 2021).

COVID-19 can severely damage the CV system, but its involvement is not yet understood. Acute myocardial COVID-19 injury is identified as a sudden rise in troponin levels, and many studies correlated with a worse patient outcome, but the aetiology is still unclear. It is unknown whether the myocardial damage is due to a direct action of the virus toward the heart and vessels or a phenomenon secondary to severe general impairment of all systems due to an advanced septic state (Lombardi, Carubelli et al. 2020).
Although initially, it seemed that the virus could cause severe direct myocardial damage, recent evidence undermined this hypothesis. According to these studies’ histological results of myocardial tissue, a multifactorial aetiology of myocardial injury appears more likely. In particular, the inflammatory infiltrate is consistent with myocarditis, with multifocal lymphocyte infiltrate evident only in a few cases (Basso, Leone et al. 2020). In most patients, the predominant autopsy finding was a diffuse monocyte-macrophage infiltrate without related cardiomyocyte damage. This is non-pathognomonic for viral myocarditis as it is frequently found in many severe pathological conditions. This finding appears to be more attributable to inflammatory heart damage in sepsis than to direct viral tropism (Babapoor-Farrokhran, Gill et al. 2020). To date, the most accredited hypothesis is that myocardial injury is secondary to multiple events generated during the massive inflammatory response in COVID-19 diseases, such as cytokine storm, endothelial and microvascular damage and increased metabolic demands in patients with a reduced coronary reserve. Unlike other presentations of pneumonia, however, the SARS-Cov2 syndrome has a marked prothrombotic tendency, with a greater risk of venous thrombosis and pulmonary thromboembolism, which can affect the prognosis negatively (Guzik, Mohiddin et al. 2020). The origin of myocardial damage is plausibly multifactorial due to hypoxia combined with an increase in oxygen requirements, the massive release of inflammatory mediators and a procoagulant state.

The long-term effects of COVID-19 infection are still largely unknown. LONG-COVID is defined as the permanence of mostly vague symptoms beyond the acute phase of the disease for about 3 weeks. Instead, the prolonged symptoms for over 12 weeks is called CRONIC-COVID (Halpin, O'Connor et al. 2021). Fatigue, dyspnea and orthostatic intolerance are among the most frequent symptoms. It is also hypothesized that orthostatic hypotension may result from a dysfunction of the autonomic nervous system (Dani, Dirksen et al. 2021).

Numerous miRNAs have primary roles in modulating clinical manifestations of CV diseases, including cardiac hypertrophy, fibrosis, and myocardial infarction (Plowman and Lagos 2021); as a result, research has been encouraged to explore the role of miRNAs in regulating CV complications of COVID-19 involvement (Figure 1).

2.1 Cardiac Damage in COVID19 and miRNA involvement

The mechanisms behind SARS-CoV-2 cardiac damage are multiple, including direct infection of cardiac-cell, systemic inflammatory response, respiratory dysfunction, hypoxia, and endothelial
dysfunction (Tajbakhsh, Gheibi Hayat et al. 2021). These conditions induce different clinical manifestations such as myocarditis, acute coronary syndrome, arrhythmias, and heart failure (Calabrese, Garofano et al. 2021). The mechanisms underlying the heterogeneity in CV manifestations are unclear yet, but miRNAs could be critical players (Babapoor-Farrokhran, Gill et al. 2020). For instance, the miRNA-200 family is an emblematic case; indeed, this miRNA family is associated with increased ACE2 expression in cardiomyocytes and consequent higher exposure to the virus aggression (Lu, Chatterjee et al. 2020). Interestingly, patients with the critical illness show low levels of miRNA-200b (Wicik, Eyileten et al. 2020).

Garg et al. have recently shown that inflammation and cardiac myocyte-specific miRNAs are upregulated in critically ill COVID-19 patients. Specifically, serum concentrations of miR-21, miR-155, miR-208a, and miR-499 are significantly increased in COVID-19 patients compared to healthy controls (Garg, Seeliger et al. 2021). The upregulation of these miRNAs is associated with increased fibroblasts survival resulting in cardiac fibrosis and hypertrophy. miRNA-499 is associated with hypoxic damage and impairment of repair mechanisms mediated by cardiac stem cells (van Rooij, Quiat et al. 2009). miRNA-21 has a key role in several CV diseases (Cheng, Ji et al. 2007, Ji, Cheng et al. 2007). MiR-21 exerts an antiapoptotic effect, altering cardiac fibroblasts' ERK–MAP kinase signalling pathway. Thus, its upregulation, recorded in severe COVID-19 patients, could support fibroblasts proliferation, causing fibrosis, hypertrophy, and dysfunctions (Kukreja, Yin et al. 2011, Zhou, Jin et al. 2018). miRNA-208 is produced by cardiomyocytes and regulates β-myosin heavy chain expression in stress conditions. In murine models, miR-208 knockout prevents fibrosis and hypertrophy induced by aortic ligation (Gupta 2007, van Rooij, Quiat et al. 2009). In the contest of severe Sars-Cov 2 infection, upregulation of miR-208 has been associated with an increased proinflammatory and prothrombotic state, resulting in a high risk of ischemic CVs manifestations, including early STEMI in COVID-19 patients (Dou, Wei et al. 2020, Modin, Claggett et al. 2020).

Heart failure is a frequent condition in COVID-19 patients and is related to a poor prognosis (Dou, Wei et al. 2020). Increased levels of miRNA-155 in COVID-19 patients have been associated with significant endothelial inflammation, fibroblasts proliferation, and cardiomyocyte pyroptosis. These mechanisms induce hypertrophy and ventricular dysfunction, resulting in heart failure 32140622 28129114 (Wang, Zhang et al. 2017). Contextually, the expression of miR-29 is lower in patients with severe COVID-19 phenotype. Indeed, miRNA-29 is expressed explicitly by cardiac fibroblasts and promotes the TGF-β pathway. Hence, its downregulation in COVID-19 patients favours the proliferation of fibroblasts, and extracellular matrix deposition, with consequent cardiac

A cardiac arrhythmia occurs in more than 15% of hospitalized Covid-19 patients, with a higher prevalence in patients with severe symptoms and requiring intensive care (Guo, Fan et al. 2020, Wang, Hu et al. 2020). Direct damage to cardiomyocytes and electrical conduction alterations, either caused by ischemia originating from microvascular disease or re-entry ventricular arrhythmia induced by myocardial fibrosis, could orchestrate the onset of the arrhythmia in COVID-19 patients (Greco, Madè et al. 2020). In this setting, miR-15b is upregulated in critically ill COVID-19 patients, and its levels are associated with a higher incidence of arrhythmias, representing a possible marker of heart damage (Liu, Yang et al. 2018, Dou, Wei et al. 2020, Niu, Xu et al. 2020, Zhang, Amahong et al. 2021).

2.2 Vascular damage in COVID-19 and the role of miRNAs

Severe COVID-19 is associated with coagulation abnormalities that mimic other sepsis-related systemic coagulopathies such as disseminated intravascular coagulation or thrombotic microangiopathy, which result in a rise in mortality in these patients (Levi, Thachil et al. 2020).

Boun Kim Tan et al., in a meta-analysis of 102 studies (64503 patients), showed a higher prevalence of thrombotic vascular complications in hospitalized patients with severe infection, predominantly venous thromboembolism (Tan, Mainbourg et al. 2021). It is well known that angiotensin-converting enzyme 2 (ACE2) plays a crucial role in the development of CV complications, especially in thromboembolic events (Ziegler, Allon et al. 2020). Indeed, high expression of ACE2 in COVID-19 patients leads to RAAS overactivation (Ziegler, Allon et al. 2020); as a result, excessive vasoconstriction and blood flow acceleration augment the risk of thrombosis and hypertension (Reynolds, Adhikari et al. 2020). COVID-19 causes a profoundly pro-inflammatory state, as suggested by high levels of C-reactive protein, lactate dehydrogenase, ferritin, interleukin-6 and D-dimer. The cytokine hyperproduction in COVID-19 includes IL-6, IL-7, TNF, and inflammatory chemokines such as CCL2, CCL3, and soluble IL-2 receptor. This so-called "cytokine storm" promotes thrombosis through multiple mechanisms, including activation of monocytes, neutrophils, and endothelium, finally inducing vascular injury (Abou-Israil, Diamond et al. 2020). In this scenario, endothelial dysfunction is a leading actor, as suggested by several reports (Evans, Rainger et al. 2020, Libby and Lüscher 2020, Sardu, Gambardella et al. 2020, Gambardella and Santulli 2021, Okada, Yoshida et al. 2021). SARS-CoV-2 accesses host cells via the binding of its spike glycoprotein to angiotensin-converting enzyme 2 (ACE2), sialic acid
receptor, transmembrane serine protease 2 (TMPRSS2), and extracellular matrix metalloproteinase inducer (CD147); cathepsin B and L also participate in virus entry (Sardu, Gambardella et al. 2020). Notably, endothelial cells express all the cofactors necessary for the internalization of SARS-CoV-2 in human host cells (Gambardella and Santulli 2021), supporting the hypothesis of direct and primary damage of the endothelium. Accordingly, a significant morphological change in endothelial cells was observed, including disruption of the intercellular junction, cell swelling and loss of contact with the basement membrane, as well as the presence of intracellular viruses and disrupted cell membranes; of course, these alterations cause an increased vascular hypercoagulability (Ackermann, Verleden et al. 2020, Connors and Levy 2020).

A specific miRNA signature has also been associated with the prothrombotic phenotype of COVID-19 patients. In the study of Gambardella et al., downregulation of miR-103a, miR-145, miR-885, and upregulation of miR-424 were detected in the group of patients with high D-dimer, marker of high thrombotic risk (Winstein, Stein et al. 2016). Accordingly, downregulation of miR-103a was observed in another study of non-COVID-19 deep venous thrombosis patients compared to healthy controls (Sun, Chai et al. 2020). Furthermore, miR-145 is a modulator of coagulation response through the activity of tissue factor, which is a critical component of clot formation and the restoration of miR-145 expression in a thrombotic animal model reduces tissue factor activity, decreasing thrombogenesis (Sahu, Jha et al. 2017, Grover and Mackman 2018). On the other hand, miR-885 is thought to target the von Willebrand factor (vWF), another key component of the clotting cascade (Winstein, Stein et al. 2016, Zhang, Guo et al. 2019).

Finally, miR-320 is upregulated in COVID-19 patients and has been associated with a high incidence of thrombotic and ischemic events. Indeed, miRNA-20 targets and inhibits the mRNA of the heat shock protein (Hsp20), thereby increasing platelet aggregation and decreasing vasorelaxation (Ren, Wu et al. 2009, Kukreja, Yin et al. 2011, Fayyad-Kazan, Makki et al. 2021).

3 miRNAs as potential prognostic and predictive markers for CVs in COVID-19 patients

The ongoing fight against COVID-19 requires the identification of biomarkers for clinical use. In this regard, miRNAs show suitable characteristics as a non-invasive tool with high sensitivity and specificity. Moreover, laboratory processing is feasible due to miRNAs’ long half-life in plasma and economically sustainable thanks to modern rapid and cost-effective technologies (Terrinoni, Calabrese et al. 2019).
Different small studies have investigated the use of miRNAs as a reliable prognostic biomarker in COVID-19. An initial miRNA panel was assessed comparing patients with and without COVID-19. This first study highlighted 35 over-expressed and 38 under-expressed miRNAs in COVID-19 patients compared to controls. Of these, miRNA-16, miRNA-618, and miRNA-6501 showed a significant over-expression. On the other hand, miRNA-627, miRNA-183, and miRNA-144 showed a significant under-expression (Li, Hu et al. 2020). These miRNAs are associated with the immune-inflammatory system during the host's antiviral response, like miRNA-16 and miRNA-618, and with vascular homeostasis like miRNA-183 (Rossato, Affandi et al. 2017, Jafarinejad-Farsangi, Jazi et al. 2020, Wang, Song et al. 2020).


Moreover, miRNA-nsp3-3p was able to predict a week in advance the disease progression from mild to moderate with an accuracy of 97% (Donyavi, Bokharaei-Salim et al. 2021, Fu, Wang et al. 2021), and a similar role was observed for miRNA-29a, miRNA-146a, miRNA-155, and miRNA-let-7b. These same miRNAs were also associated with specific symptoms like fever, dry cough, and anosmia (Donyavi, Bokharaei-Salim et al. 2021). During COVID-19 follow-up the patient's rehabilitation occurs alongside a progressive downregulation of miRNA-7b, miRNA-103a, miRNA-200c, and miRNA-2115 (Zheng, Xu et al. 2020).
To note that also miRNAs associated with CV complications of COVID-19, including miRNA-21, miRNA-126, miRNA-155, miRNA-208a, and miRNA-499 (some of which have been already mentioned above), showed a crucial prognostic value (Garg, Seeliger et al. 2021). Cardiometabolic miRNAs like -122 and -133a have also been proposed as predictors of inflammation-induced cardiomyocyte damage and COVID-19 severity, in particular as 28-day mortality prediction (Gutmann, Khamina et al. 2022).

Prediction of treatment response was also achieved with CV miRNAs. Mirna-146a, associated with endothelial activation and pro-inflammatory response, was influential in predicting therapy-responsiveness of severe patients after 3 days of tocilizumab administration (Hou, Wang et al. 2009, Cheng, Sivachandran et al. 2013, Ramkaran, Khan et al. 2014, Sabbatinelli, Giuliani et al. 2021). Interestingly, miRNA-146a downregulation also occurred in elderly and type 2 diabetic patients, conditions associated with the worst COVID-19 prognosis (Mensà, Giuliani et al. 2019). Likewise, under-expression of miRNA126 associated with lung microvascular endothelial loss was used to identify patients not responding to redeliver successfully and favipiravir treatment in ICU (Tian, Xu et al. 2019) (Luo, Dong et al. 2015, Cao, Mikosz et al. 2020, Keikha, Hashemi-Shahri et al. 2021).

Overall, miRNAs predictive potential is still to be enhanced. Its understanding is at a beginning stage, and no predictive miRNAs have been found for identifying Long COVID or Chronic COVID. Moreover, there are no studies, at present times, highlighting gender differences in miRNAs expression in COVID patients.

4 miRNAs as potential therapeutic targets for CV complications of COVID-19

Although the FDA has not approved the use of miRNA for therapeutic purposes, its research had begun some years before COVID-19. Therapy based on miRNA has been mainly used for viral infection treatment, like influenza viruses and HCV (Chauhan, Jaggi et al. 2021). The hope for expanding miRNAs' therapeutic use to COVID-19 is driven by their crucial role in modulating the expression of both host and viral components, (Schmidt 2014). The therapeutic use of miRNA has advantages due to particle size, specific biological pathway regulation, and multi-gene targeting (Rupaimoole, Han et al. 2011, Hanna, Hossain et al. 2019). Association therapies could also be an alternative, reducing drug resistance and improving sensitivity (Hanna, Hossain et al. 2019).

In 2015, miRNA-2911 was used to suppress viral influenza viruses targeting multiple viral genes (Zhou, Li et al. 2015). This approach may represent a valuable strategy for COVID-19 treatment as
well. miRNA-155 antagonist drugs were used to reduce inflammatory damage in the influenza-infected lung (Woods, Doolittle et al. 2020). Up-regulation of miRNA-155 has been highlighted in also in COVID-19 patients, leading to a viable therapeutic option (Desjarlais, Wirth et al. 2020, Pierce, Simion et al. 2020).

Research on the applicability of this therapy in COVID-19 started by identifying two binding regions of the SARS-CoV-2 genome for miRNA-3150b and miRNA-602. This finding opened the possibility of designing a specific inhibition of viral replication (Baldassarre, Paolini et al. 2020). In the context of miRNAs-based therapeutic strategies development, computational meta-analysis tools, like “miRNACOVID-19” and “psRNATarget” (Saçar Demirci and Adan 2020, Alam and Lipovich 2021) can be handy. An essential factor of CV susceptibility in COVID-19 patients is the levels of ACE2. Using bioinformatics tools, 24 miRNAs were identified, the most interesting of which is miRNA-200c, already subjected to animal studies (Bozgeyik 2021). The use of antago-miRNA against miRNA-200c in the mouse model of H5N1 infection showed a reduction in lung injury, and the same could be for COVID-19, (Liu, Du et al. 2017).

Worth mentioning is the potential role of SARS-CoV-2 on miRNAs expressed in humans. The sponge effect of the SARS-CoV-2 genome in preliminary studies showed a correlation between miRNA-20a-5p with severe disease manifestation associated with clinical deep vein thrombosis and CV manifestations (Pepe, Guarracino et al. 2022). This new starting point for miRNA study could be a novel tool for better understanding the aetiology of COVID-19 and its different clinical features and for developing more accurate antiviral therapies (Li, Wang et al. 2022).

Unfortunately, this line of research is far from a state of applicability, and much more data is needed to evaluate this possibility in clinical trials (McDonald, Enguita et al. 2021, Visco, Ferruzzi et al. 2021).

5 CONCLUSIONS

Identifying molecular partners involved in CV complications of COVID-19 is crucial for unveiling new prognostic predictors and therapeutic targets. A consistent alteration of troponin occurs only in a low percentage of COVID patients with cardiac abnormalities at CMR (Puntmann, Carerj et al. 2020), indicating that troponin is not a helpful marker of cardiac involvement in COVID-19. This highlights the need for accessible and early biomarkers, such as circulating miRs, which may also predict long-term CV consequences of COVID-19. Prior studies have confirmed dysregulations of
circulating miRNAs in COVID-19 patients associated with patient prognosis, multi-organ damage, and sometimes, mortality.

Table 1: Non-standard abbreviations.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACE2</td>
<td>Angiotensin Converting Enzyme 2</td>
</tr>
<tr>
<td>CCL</td>
<td>Chemokin Ligand</td>
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<tr>
<td>COVID-19</td>
<td>Coronavirus Disease 2019</td>
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<td>CV</td>
<td>Cardiovascular</td>
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<tr>
<td>HCV</td>
<td>Hepatitis C Virus</td>
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<tr>
<td>ICU</td>
<td>Intensive Care Unit</td>
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<td>IL</td>
<td>Interleukin</td>
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<tr>
<td>miRNA/miR</td>
<td>Micro RNA</td>
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<tr>
<td>ncRNA</td>
<td>No coding RNA</td>
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<tr>
<td>ORF</td>
<td>Open reading frame</td>
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<tr>
<td>SARS-CoV-2</td>
<td>Severe acute respiratory syndrome coronavirus 2</td>
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<td>STEM</td>
<td>ST-elevation myocardial infarction</td>
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<td>TGF</td>
<td>Transforming growth</td>
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<tr>
<td>TNF</td>
<td>Tumor necrosis factor</td>
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**FIGURE LEGENDS**

Figure 1: miRNAs in CV complications associated with COVID-19.

**AUTHORSHIP CONTRIBUTIONS**

Izzo, Visco, Gambardella, Ferruzzi, Vecchione, Ciccarelli contributed for the conception of the manuscript.

Izzo, Visco, Gambardella, Ferruzzi, Rispoli, Rusciano, Toni, Virtuoso, Carrizzo, Di Pietro, Iaccarino, Vecchione, Ciccarelli contributed to the literature research and in writing of the manuscript.
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