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Research Article

Correlation between MicroRNA-155 Expression and Viral Load in Severe COVID-19 Patients

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I N F O

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A B S T R A C T

Background: The SARS-CoV-2 virus causes COVID-19, a respiratory syndrome. It causes inflammation and damages several organs in the body. miRNAs play a role in regulating the infection resulting from SARS-CoV-2. MicroRNA-155, a kind of microRNA linked to viral defences, can affect the immune responses during COVID-19.

Objectives: Examination of the involvement of microRNA-155 in the development and severity of COVID-19, as well as finding the correlation between microRNA-155 and viral load (copies/mL) in severe cases of the disease.

Materials and Method: A case-control research study was performed between October 2022 and June 2023. It included a cohort of 120 hospitalised individuals with severe cases of COVID-19, together with 115 individuals with mild cases of COVID-19 and apparently healthy individuals. A real-time PCR procedure was applied to determine microRNA-155 expression in the studied groups and the viral load (copies/mL) in severe cases of the disease.

Results: MicroRNA-155 was expressed in severe cases threefold more than its expression in mild cases of COVID-19 and healthy individuals. Also, a strong association was demonstrated between microRNA-155 and viral load (copies/mL) in severe COVID-19.

Conclusion: MicroRNA-155 could be used as a biomarker for severe COVID-19 conditions and could have a role in disease severity and infectious particles of the virus. Since it is positively correlated with viral load (copies/mL) in severe cases of the disease.

Keywords: Microrna-155, Mir-155, Covid-19, Viral Load, SARS-CoV-2

Introduction

COVID-19 is a pulmonary illness resulting from SARS-CoV-2 virus exposure, causing inflammation, and affecting multiple organs in the body.[1] SARS-CoV-2 infiltrates lung cells and specifically targets the lower respiratory tract, where it is strongly conjugated to angiotensin-converting enzyme receptors.[2,3] Activation of cells of the immune system such as neutrophils and macrophages takes place when an infection happens in the lower respiratory tract. These cells secrete several chemokines and cytokines, which subsequently stimulate the immunological response, including B and T cells. Nonetheless, the atypical immune

system response can lead to excessive production and accumulation of cytokines which is in most cases referred to as cytokine storms or hypercytokinemia.[4] This could result in the individual suffering from acute respiratory distress syndrome owing to the presence of pneumonia in several lungs and its complications being very diverse with some consequential psychological trauma in the future.[1,5]

For effective management of COVID-19, the determination of the viral load circulating in the blood of infected individuals is an important factor.[6] Viral load is defined as the amount of virus capable of replication that is measured in the body. This tool is used for the diagnosis and monitoring of pathological changes of viral infection in the respiratory system and for evaluating the progression and treatment response of the disease.[7] Through the use of real-time reverse transcription-PCR (RT-PCR) analysis, the viral load can be determined through the quantification of viral RNA in the samples collected from the patient, with emphasis on the cycle-threshold (Ct) value. The lower the Ct values, the more viral load is noticed in the patient's samples.[8] It is however cautionary to state that not much research has been done on the correlation between the viral load and disease severity in patients suffering from COVID-19. This fact has to do with the fact that among COVID-19 patients who were critically ill and needed an intensive level of care, they had significantly greater virus load as shown in the results. In addition, it has been found that among patients within large networks of hospitals, more virus particles correlate with higher mortality odds.[9]

In recent times, microRNAs (miRs) have attracted a great deal of attention because of their ability to inhibit viral entry and replication and to affect local and systemic immune and inflammatory responses.[10] Also, from this vast collection of human microRNAs, which have been described to be more than ten thousand microRNA-155 was found to be more interesting. Such is the typical representation of a microRNA, loaded with diverse functional potentials. It has been established that microRNA-155 acts as a regulatory factor in signalling pathways. Hemopoiesis, heart diseases, inflammation, immunology, and cancer are all involved in pathological abnormalities and/ or physiological processes.[11] Recent findings have shown that microRNA-155 is involved in the mechanisms of several viral diseases, such as respiratory, circulatory, and neuroviruses.[12]

This study aimed to quantify the level of microRNA-155 expression in patients with severe COVID-19, mild COVID-19 cases, and healthy individuals for comparison. The goal of our research was to analyse the impact of microRNA-155 on the development and severity of COVID-19 infection. Also, we performed additional analysis to test the correlation between the load of the virus in severe COVID-19 cases and microRNA-155 expression in epithelial cells derived from nasopharyngeal swabs. This study was performed to examine how microRNA-155 might affect the course of COVID-19 disease.

Materials and Method

Study Design

Between October 2022 and June 2023, research employing a case-control study was conducted. The current study enrolled a cohort of 120 hospitalised patients with a severe course of COVID-19 in combination with 115 patients suffering from mild forms of COVID-19 and healthy individuals of all genders and ages who served as the control group. From Ibn Al-Khatteeb Hospital in Baghdad, Iraq, samples of severe COVID-19 cases were collected. For this objective, nasopharyngeal swabs were obtained. Subsequently, the samples were subjected to centrifugation at a speed of 5000 g/min for five minutes to prepare them for the qPCR technique.

Ethics

The study protocol and proposal received approval from the Iraqi Ministry of Health and Environment and the University of Baghdad's Ethical Committee (reference: CSEC/0922/0083). Written informed consent was obtained from each participant. The study conformed to the Code of Ethics outlined by the World Medical Association's Declaration of Helsinki.

RNA Extraction and Quantitation

After collecting the samples, RNA was extracted and purified from the sputum using the ReliaPrep Viral Nucleic Acid Extraction Kit (Promega). In order to completely separate the nucleoprotein complex, 300 µL of the substance was combined with 600 µL of Trizol reagent in a 1.5 mL microcentrifuge tube and left to incubate for 10 minutes at a temperature of 25 °C. Each 1.5 mL tube was supplemented with 20 µL of Proteinase K Solution and 200 µL of Cell Lysis Buffer. The samples were subjected to incubation at a temperature of 56 °C for a duration of 10 minutes using a heat block device. Subsequently, a vortex was generated and 250 µL of pure isopropanol (100%) was introduced within a span of 10 seconds. The contents of the tube were transferred into the ReliaPrep Binding Column, and the centrifuge was operated at its maximum speed of 1200 rpm for one minute. A 500 µL solution was used to wash the column, and a centrifuge was operated at 1200 rpm for 3 minutes. The residue is discarded. The eluates were stored in 1.5 mL tubes for further processing. A quantum fluorometer is utilised to quantify the quantity of extracted RNA from the samples and ascertain its concentration.

MicroRNA-155 Primers Design

The microRNA-155 sequence was acquired and specifically targeted using three different types of primers. The primers

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used for the expression of microRNA-155 were obtained from Macrogen (Korea). The components consist of a forward primer, an adaptor primer, and a universal reverse primer (Table 1). The U6 reference gene was utilised as the endogenous control in the current study (Table 2).

Table 1.Sequences of MicroRNA-155 Primers

Primer	Sequence
Stemloop primer (adaptor)	3′- GTC GTA TCC AGT GCA GGG TCC GAG GTA TTC GCA CTG GAT ACG ACAACCCC -5′
Forward primer	3′- CGCGCGTTAATGCTAATC-5′
Universal reverse primer	5′-CCA GTG CAG GGT CCG AGG TA-3′

Table 2.Sequences of U6 Reference Gene Primers[13]

Primer	Sequence
Forward Primer	5′-GCTTCGGCAGCACATATACTAAAAT-3′
Reverse Primer	5′- CGCTTCACGAATTTGCGTGTCAT-3′

Performing Real-Time PCR

Isolated RNA was transformed into cDNA by Luna-Script RT Super-Mix Kit from Biolabs, UK. The reaction mixture was subjected to a single cycle of incubation for two minutes at 25 °C (primary annealing), fifteen minutes at 55 °C (reverse transcriptase, cDNA synthesis), and one minute at 90 °C (heat inactivation). At Sacycler, Saccac, Italy, we performed quantitative RT-PCR (qPCR) using the LunaScript RT Master Mix Kit (5X) from BioLabs, a company located in England. The RT-PCR mixture consisted of 0.5 µL of both the forward primer and reverse primer, together with 10 µL of the master mix. Following the addition of 5 µL of cDNA from each sample, primers and reverse primers were also added. Additionally, 4 µL of nuclease-free water was included to increase the total amount to 20 µL. The U6 gene served as the endogenous control. Real Time-PCR was applied for a duration of one minute at a temperature of 95 °C in order to initiate the activity of the polymerase enzyme. Subsequently, the double-stranded cDNA was denatured for 15 seconds at 95 °C and then annealed for 20 seconds at 60 °C using channel scanning, repeating this process 45 times. The separation properties of double-stranded cDNA during cycles with increasing denaturing TM were examined using melting curve analysis. The Ct value of miRNA-155 was standardised using the U6 reference gene. The expression of microRNA-155 was assessed using a relative quantitative technique, which involved the comparative Ct formula and the 2^-ΔΔCT analysis.[14]

SARS-Cov-2 Viral Load Determination

Once the real-time PCR thermal cycler reaches the desired duration, the cycle threshold (Ct) records are collected for severe cases of COVID-19. To convert a cycle threshold (Ct) value to a precise viral load, the process involves creating a series of diluted samples with known concentrations of positive control RNA. This allows for the estimation of the viral RNA copies per millilitre. For estimation of the log10 viral load of all the samples tested in the current investigation, the Ct values of all positive controls were collected and plotted along with the log10 viral load. This was done to create a standard curve (Figure 1). The current approach for determining viral load (measured in copies/mL) was developed based on the methodology described by Hill et al.[15]

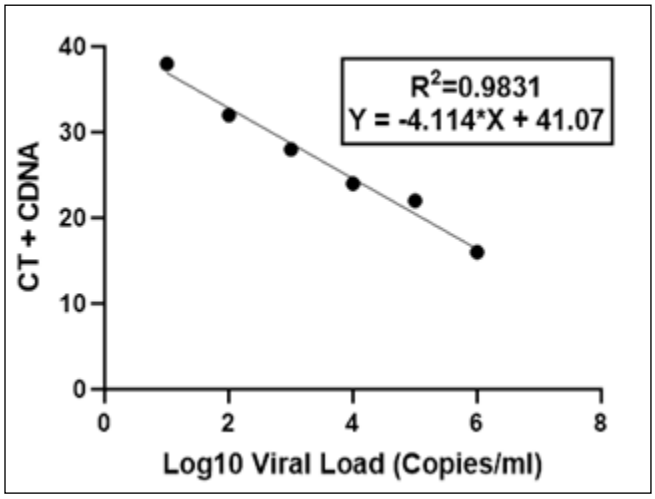

Figure 1.Standard Curve Plotted between Ct Values of Positive Control of SARS-CoV-2 and Log10 Viral Load (Copies/mL)

Statistical Analysis

The raw data sheets from the current study were entered into the computer and analysed using the SPSS programme, specifically version 23. This program includes various well-known statistical characteristics such as the t test, mean, standard deviation, standard error, and others. The significance of the differences is determined by whether they are equal to or less than 0.05. A p value less than 0.01 is considered highly significant. Additionally, the correlation coefficient (r) was calculated for the parameters under study. All of these analyses were done with the aid of the statistical package SPSS version 23.

Results

MicroRNA-155 (miRNA-155) Expression

A real-time PCR assay was utilised to analyse nasopharyngeal samples obtained from severe COVID-19 patients, as well as a control group consisting of individuals with normal health

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and mild cases of COVID-19. The objective was to assess the expression of microRNA-155 in both groups. The U6 gene served as the endogenous control. The Ct value of the target microRNA was normalised to the U6 reference gene. The expression of microRNA-155 was assessed using the relative quantitative technique, employing the comparative Ct formula and the 2^-ΔΔCT analysis to calculate the fold change. Real Time-PCR results indicated that the expression of microRNA-155 was elevated in severe COVID-19 patients compared to the control group consisting of mild and healthy individuals. The average fold number of microRNA-155 expression in severe COVID-19 patients was 4.167970, whereas in the control group, it was only 1.631186. There are substantial changes in the expression of microRNA-155 between severe COVID-19 patients and persons who are mild or healthy ($p = 0.00$, $p < 0.01$) (Table 3).

SARS-CoV-2 Viral Load Estimation

After getting Ct values from the real-time PCR thermal cycler device, the viral load was estimated for 89 confirmed positive severe COVID-19 samples according to the standard curve plotted between Ct values and log10 viral load (Figure 2).

Results of the real-time PCR quantitative assay demonstrated a SARS-CoV-2 final dynamic range of 3.00 to 6.289 log10 copies/mL and an average of 4.425 log10 copies/mL. of 60 µL of eluted RNA. RealTime-PCR confirmed the positive samples, depending on the detection of the *ORF1ab* gene. The Ct was plotted against the viral load to create the correlation matrix. Pearson (r) of the positive *ORF1ab* gene were significantly ($p = 0.0001$) different compared to viral load, and there was a negative correlation ($r = - 0.8390$) detected significantly between the Ct of the *ORF1ab* gene of the virus and viral load. Results of log10 viral load results are divided into three categories (< 4 copies/mL, 4–5 copies/mL, and > 5 copies/mL). For the first category (less than 4 copies/mL), males record 17/52 (32.7%) of the virus while females record only 6/37 (16.2%). In contrast, the viral load of the second category (4–5 copies/mL) was revealed in 44.2% of the males tested and 54.1% of the females. SARS-CoV-2 log10 viral load of the third category also showed a dominance of the female results (29.7%) as compared to males (23.1%). Non-significant differences were observed between the viral load results of males and females ($p > 0.05$) in the current study (Figure 3).

The studied sample information included the age of hospitalised patients with COVID-19. Samples categorised the ages into three groups (20–40 years old group, 41–60 years old group, and > 60 years old group). Higher than 60 years old showed a higher viral load number of hospitalised patients of the first category (< 4 copies/mL) of the virus 3/4 (75%). In addition, log10 viral load results demonstrated that 19 out of 34 persons (55.9%) showed 4–5 copies/mL of SARS-CoV-2 in the age group of 41–60 years while the ages between 20 and 40 years showed 47.1% of the same log10 viral load category. The same age group (20–40 years) also showed a higher log10 viral load (> 5 copies/mL) category. The percentage was 29.4%. P value was determined for the age groups, and the result showed no significant difference between the age groups included in the current study ($p > 0.05$) (Figure 4).

Validity of MicroRNA-155 Expression Test (ROC Curve)

The validity of microRNA-155 to reveal whether a COVID-19 patient was considered a positive severe case or not was examined using the ROC test and area under the curve (AUC). This statistical analysis declares that microRNA-155 reached a good level as a biomarker (AUC = 0.651, sensitivity 80%, specificity 68.8%, accuracy 74.48%; $p = 0.00$). This test also determines the cutoff value (31.4), which reflects the threshold of positivity and severity of the disease (Table 4) (Figure 5).

Correlation between MicroRNA-155 Expression and SARS-CoV-2 Log10 Viral Load

A Pearson correlation test (r) was conducted to examine the relationship between the expression of microRNA-155 in severe COVID-19 patients and the log10 viral load (copies/mL) of SARS-CoV-2. The findings indicated a significant positive association ($r = 0.641$; $p = 0.00$) between the expression of microRNA-155 in individuals with severe COVID-19 and the log10 viral load of SARS-CoV-2 (copies/mL). The present analysis revealed highly significant differences ($p < 0.01$) (Figure 6).

Table 3.MicroRNA-155 Expression in Severe COVID-19 Patients and Control

Studied Groups		N	Mean	Std Deviation	Std Error	p Value
Micro RNA-155	Controls	115	31.991	1.6709	0.1558	0.006
	Patients	120	30.692	4.7642	0.4349	
	Total	235	-			
Fold	Controls	115	1.631186	1.6556037	0.1543858	0.001
	Patients	120	4.167970	5.7691001	0.5266444	
	Total	235	-			

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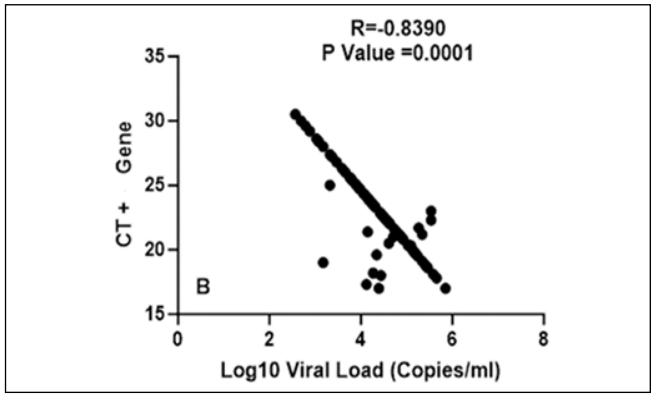

Figure 2.Standard Curve Plotted between Ct Values of Positive *ORF1ab* Gene and Log10 Viral Load of SARS-CoV-2

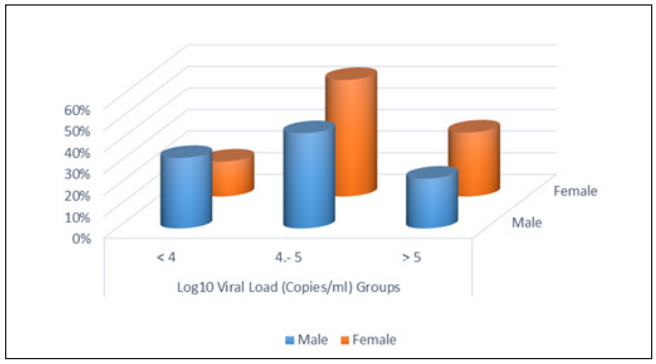

Figure 3.Distribution according to Sex of Log10 Viral Load (Copies/mL) of Severe COVID-19 Cases

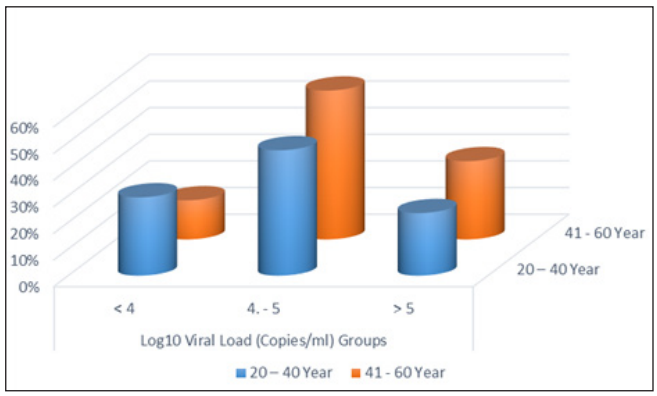

Figure 4.Distribution according to Sex of Log10 Viral Load (Copies/mL) of Severe COVID-19 Cases

Table 4.Validity of MicroRNA-155 Test (ROC Test Details)

Validity of microRNA-155 Test	
Sensitivity	80.00%
Specificity	68.70%
Positive predictive value (PPV)	72.70%
Negative predictive value (NPV)	76.80%
Accuracy	74.48%
Area under the curve (AUC)	0.651
Cutoff value	31.400
p value	0.001

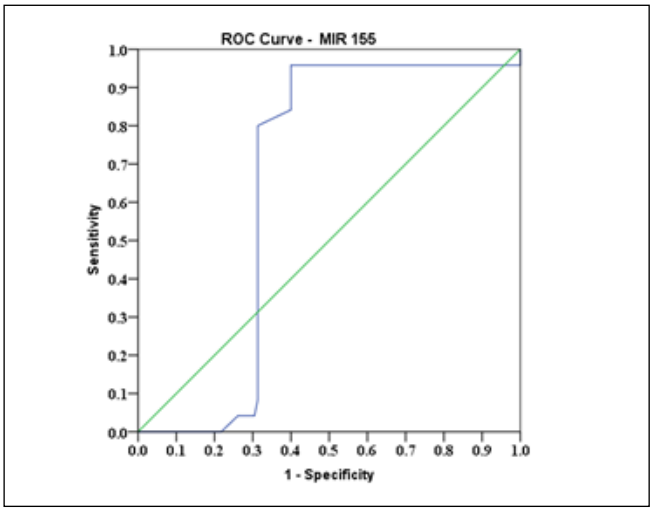

Figure 5.Distributions of Log10 Viral Load (Copies/mL) Groups according to Age Groups

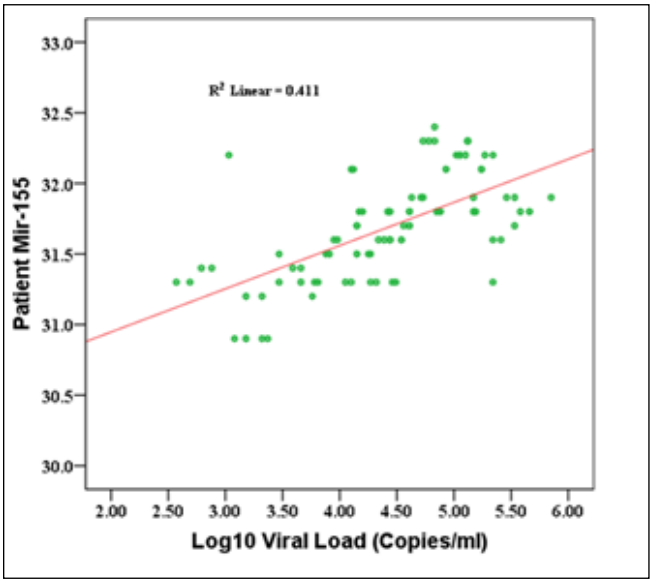

Figure 6.ROC Curve of MicroRNA-155 Expression Test

Discussion

The amount of microRNA-155 produced by both severe COVID-19 subjects and control subjects of mild cases and healthy individuals was measured in our study. The purpose of this study was to study the role of microRNA-155 in relation to the development and severity of COVID-19 disease, as well as evaluate its use in clinical practice as a diagnostic biomarker of COVID-19 disease severity. The study findings indicated that the expression of microRNA-155 was significantly upregulated in the cases of severe COVID-19 compared to moderate and normal

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healthy controls. It is also possible that microRNA-155 might be involved in the development and/ or severity of the clinical form of the disease. Our results agree with those of a study that demonstrated enhanced expression of microRNA-155 in patients infected with COVID-19.[16]

Studies indicated that microRNA-155 correlated with SARS-CoV-2 infection-induced immune response and showed altered engagement.[17] Other findings indicated that microRNA-155-5p levels increased in response to inflammatory stress. This improves the ability of macrophages to produce cytokines and modulates TLR communication in monocytes and macrophages leading to an inflammatory reaction.[18] Our findings corroborate the data presented by Abbasi-Kolli et al., which show that there is a relative increase in the expression of microRNA-155 in patients with acute COVID-19 disease. Many researchers have proved the fact that microRNA-155 expression may be employed as a potential biomarker for SARS-CoV-2 detection and even disease severity.[19,20] This conclusion is consistent with our findings. The supplementary surveys conducted in the current analysis prove that microRNA-155 has a successful score as a biomarker with an accuracy of 74.48%.

Our study found that microRNA-155 is related to the viral load (copies/mL) in patients with severe COVID-19. The viral load fluctuates during the course of SARS-CoV-2 infection. Recently, another study evaluated 17 investigations of 605 patients with upper respiratory tract infections regarding the dynamics of viral load during the infection. Researchers noted marked differences in upper respiratory tract viral load among patients. The unexplained biases in the predicted early or late perturbation of viral loads under immunological control were not captured by body age or gender.[21,22] A more recent study corroborated these results and concluded that patients with severe COVID-19 disease who were placed in intensive care units had even greater viral loads.[9] The microRNA-155 for that has been shown to inhibit/ modulate viral shedding as part of host Response. According to the study, an excessive amount of microRNA-155 among thalassemia patients may ameliorate cardiovascular alteration and offer protection from SARS-CoV-2 infection.[23] Increased concentrations of microRNA-155 and high viral load were observed to accompany the more severe disease. Further studies are required in order to clarify the role of microRNA-155 in influencing the amount of viral load in severe cases of SARS-CoV-2 infection.

Conclusion

The present research is noteworthy in that it has shown that there is an increase in the expression of microRNA-155 in cases of severe COVID-19. Therefore, it may be a suitable candidate for diagnosis in patients with acute disease. In addition, there was a correlation between microRNA-155 and viral load measured in copies per millilitre (copies/mL). Thus, one of these conclusions supports the possibility that microRNA-155 could be critical for the management of patients with severe COVID-19 who require hospitalisation.

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Conflict of Interest: None

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