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Evaluation of miR-195-5p Expression and Determine Some Immunological Markers in Hospitalized Patients with Severity COVID-19

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Abstract: COVID-19 pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a unique global health crisis that ended up causing considerable morbidity and mortality in all age groups worldwide. This analysis tried to explore the regulation expression of endogenous miR-195-5p and its impact in levels of IL-6, IL-8 and TNF-α. This study includes 50 severe COVID-19 patients against a control population of 25 healthy controls. The results indicated that the highest number of patients' group ranged between 40-50 years and this represented by 20((40.00%) followed by the patients' group who was between >50 years old which was 19 (38.00%) and 11(22.00%) in patients with <40 years, on the other hand; ELISA assay showed there were a highly significance in IL-6 (5.582 ±0.29 ng/ml) and TNF-α showed (151.82 ±13.19 ng/ml), when compared to healthy control group (2.664 ±0.21 ng/ml) and (54.63 ±8.87 ng/ml)respectively, while there were a significant increase in IL-8 levels (29.73 ±5.56 ng/ml) compared to healthy control group (22.65 ±1.14 ng/ml). The Expression of the miR-195-5p gene was decreased in high significantly decrease (P≤0.01) in patients (0.374 ±0.18) fold compared to control that recorded (1.00 ±0.00). In conclusion, the decreased expression of miR-195-5p in severity COVID-19 patients can contribute in increment of IL-6, IL-8 and TNF-α levels because the lack its role consequently increase the cytokine storm.

Key points: COVID-19; miR-195-5p; IL-6, IL-8, TNF- α.

Introduction:

The World Health Organization (WHO, 2019) initiated the coronavirus disease (COVID-19) as a global health emergency that was first noted in 2019. Ever since its advent, the pandemic has left millions of confirmed cases and had a high mortality rate across the globe. Even though SARS-CoV-2 can infect a large number of individuals with no to mild symptoms, other affected people do get severe clinical outcomes, such as pneumonia, acute respiratory distress syndrome (ARDS), and even death (Chen et al., 2020; Kumar et al., 2020). A broad spectrum of clinical manifestations of a SARS-CoV-2 infection exists, including asymptomatic carriers and those with life-threatening developing respiratory failure. Cytokines are the small mediators of protein that are central to intercellular communications and coordinate immune responses (Mangalmurti and Hunter, 2020). Nevertheless, too much immune activation may cause a loss of control over the production of pro-inflammatory cytokines, also referred to as the cytokine storm (CS) (Coperchini et al., 2020). Many studies have also highlighted the importance of host immune response in establishing the severity and path of COVID-19. In particular, hyperinflammatory states associated with high concentrations of cytokines and chemokines (i.e., interleukin (IL)-6, IL-8, and tumor necrosis factor-alpha (TNF-α)), lymphopenia, and the infiltration of immune cells into afflicted tissues, have been determined as the major factors contributing to poor clinical outcomes (Mehta et al., 2020; Zhang et al., 2020; Huang et al., 2020; Xu). MicroRNAs (miRNAs) are small non-coding RNA nucleotide molecules

crucial to the posttranscriptional regulation (of gene expression). miRNAs are usually known to exert their regulatory contributions to repression of target messenger RNAs (mRNAs) through binding to the three untranslated regions (3-UTRs) resulting in degradation or translation repression of the latter (Bartel, 2018). miRNAs May influence more than 60 percent of all protein-coding genes in humans (Friedman et al., 2009). The miRNAs, because of their large-scale regulatory functions, participate in numerous physiological and pathological processes such as immune responses and inflammations. This study aimed to investigate the expression of endogenous miR-195-5p in patients with severe COVID-19 and its correlation with patient age and selected immunological markers, specifically interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-alpha).

Materials and Methods:

Patients and sampling:

The present study was performed during the period between from December 2021 to March 2022. Blood samples of (50) patients with Severity COVID-19 were collected from Al-Zahraa Teaching Hospital in Wasit, Iraq. Male patents of different ages, (25) individuals samples used as control group, all them apparently healthy. All the patients are hospitalized cases of covid-19. From the confirmed positively infected persons, 5 ml of blood was divided into two parts:4 ml in a gel tube for serum collection and 1ml in EDTA tube for gene expression determine. The serum was yield by centrifugation (5000 rpm for 5 min). The supernatants were collected carefully and frozen at -20°C.

2.3. Enzyme Linked Immunosorbent Assay:

The evaluate the levels of IL-37 and IL-35 in patients and control group the Enzyme Linked Immunosorbent Assay was done according to the manufacturer's instructions. The Human IL-6, IL-8 and TNF-α was carried out according to manual manufacture of *BT-LAB* Company/ China.

RNA Extraction and cDNA. Synthesis:

Each sample was extracted with TRIzol(r) LS Reagent in TOTAL RNA extraction and as per the manufacturer protocol. Reverse-transcribed cDNA was then synthesized with the Easyscript (r) cDNA synthesis kit in a final volume of 20mL. The reverse transcription was carried out with the following thermal cycling conditions, 25 ℃-10 minutes, 42 ℃-10 minutes, 85 ℃-5 minutes and a hold at 4 ℃ until the reaction was complete.

Primers:

The miR-195-5p primer, U6 primer and EzOmics SYBR qPCR kit were purchased from Biomics Biotechnologies Inc. (Jiangsu, China). The U6 primer used as an internal control was:5′GTCCTATCCAGTGCAGGGTCCGAGGTGCACTGGATACGACAAAATATGGAAC-3′ (stem-loop primer) 5′-TGCGGGTGCTCGCTTCGCAGC-3′ (sense) and 5′-CCAGTGCAGGGTCCGAGGT-3′ (antisense) (Luo et al.,2014) .For amplification of miR-195-5p, 100 ng RNA was used in a 25-µl reaction system containing 12.5 µl 2X Master Mix, 0.5 µl 50X SYBR-Green, 0.5 µl reverse transcription primer (10 µM), 0.5 µl sense and 0.5 µl antisense primers (10 µM). One Step PCR parameters for miRNA quantification were as follows: 37°C for 60 min for reverse transcription, 10 min at 95°C, and then 40 cycles of 20 sec at 95°C, 30 sec at 62°C and 30 sec at 72°C. Each sample was tested in triplicate.

Quantitative analysis of extracted RNA:

After RNA extraction, NanoDrop (NP80 Implen, Germany) device was used to quantify it. In this way, 1–2 µL of the sample was placed in the mentioned device and the samples were read at 260/280 and 260/230 wavelengths.

Statistical Analysis:

The Statistical Packages of Social Sciences-SPSS (2019) program was used to detect the effect of difference groups in study parameters. T-test was used to significant compare between means. Chi-Square test was used to significant compare between percentage in this study. The gene expression

was evaluated according to the Livak and Schmittgen equation [2001], ΔCT and ΔΔCT were computed.

Results and Discussion:

Distribution of patients according to age:

The result of distributing the covid-19 patients' samples according to age, indicated that the highest number of patients' group ranged between 40-50 years and this represented by 20((40.00%) followed by the patients' group who was between >50 years old which was 19 (38.00%) and 11(22.00%) in patients with <40 years, table-

Table 1: Distribution of cases according to Age in patients

Factor		Patients No. (%)	Control No. (%)	P-value
Age groups (year)	<40 yr.	11 (22.00%)	21 (84.00%)	0.0001 **
	40-50 yr.	20 (40.00%)	4 (16.00%)	
	>50 yr.	19 (38.00%)	0 (0.00%)	
	Total	50	25	
	Mean ±SE	47.06 ±1.24	32.00 ±1.18	0.0001 **
** (P≤0.01), NS: Non-Significant.				

Immunological Markers assay results

Interleukin-6, interleukin-8 and Tumor necrosis factor- α were included as significant immunological indicators. ELISA kits were used to estimate the levels of IL-6, IL-8 and TNF-α. Table -2 showed a highly significance in IL-6 (5.582 ±0.29 ng/ml) and TNF-α showed (151.82 ±13.19 ng/ml), when compared to healthy control group (2.664 ±0.21 ng/ml) and (54.63 ±8.87 ng/ml) respectively, while there were a significant increase in IL-8 levels (29.73 ±5.56 ng/ml) compared to healthy control group (22.65 ±1.14 ng/ml)

Table 2: Comparison between patients and control groups in IL-6, IL-8 and TNF-α

Group	**Means ±SE**		
	IL-6 (ng/ml)	**IL-8 (ng/ml)**	**TNF-α (ng/ml)**
Patients	5.582 ±0.29	29.73 ±5.56	151.82 ±13.19
Control	2.664 ±0.21	22.65 ±1.14	54.63 ±8.87
T-test	0.873 **	6.013 *	39.33 **
P-value	0.0001	0.0494	0.0001
* (P≤0.05), ** (P≤0.01).			

Previous literature has demonstrated the interaction between balanced levels of interleukin-6 (IL-6) and the occurrence of respiratory failure in patients infected with SARS-CoV-2 (Chen et al., 2019). The levels of tumor necrosis factor-alpha (TNF-alpha) in this study were significantly elevated in COVID-19 participants compared to healthy controls. These results are consistent with the ones obtained by Halim et al. (2022), who have also proved that the average TNF-a concentration was remarkably higher in the patients with severe COVID-19 than in non-serious cases, thus confirming the findings of the current study.

***miR-195-5p* Folding:**

Expression of the *miR-195-5p* gene was decreased in high significantly decrease (P≤0.01) in patients (0.374 ±0.18) fold compared to control that recorded (1.00 ±0.00). this results were

obtained according to According to the Livak and Schmittgen equation [2001] where: ΔΔCt= ΔCt (target)- ΔCt (control) and Folding= $2^{-\Delta\Delta Ct}$

Table (3): Comparison between *MIR-195-p gene folding in* patient and control groups according to (Folding = $2^{-\Delta\Delta Ct}$)

Groups	Mean ±SE of *miR-195-5p*
Patients	0.429 ±0.07
Control	1.00 ±0.00
T-test	0.210 **
P-value	0.0001
** (P≤0.01).	

miR-195-5p is also a member of miR-15 family that is assumed to control the genes that have been found chiefly to be involved in cell proliferation and apoptosis (Bandi et al., 2009). miR-195 dysregulation is noticed in the backdrop of a number of viral infections, against SARS-CoV-2 as well (Farr et al., 2021). The host miRNA reaction to the severe SARS-CoV-2 infection is deep researched and it has been identified that there exists a great number of changes in the microRNA expression on various levels of COVID-19 development (Farr et al., 2021). Significantly, it has been witnessed that earlier research has shown a common down regulation of a number of miRNAs in the host, especially among the critically affected patients. Among them, miRNAs whose target sequences have been predicted in the SARS-CoV-2 genome miR-195, were significantly dysregulated at the plasma levels of severe cases compared to moderate or asymptomatic infections (Fernandez-Pato et al., 2022).

Even though the exact functional role of miR-195-5p in the context of infection with SARS-CoV-2 is not currently fully understood, it has been suggested that the virus could serve as a molecular sponge- trapping miR-195 in cells that it infects and thus further inhibiting its expression and possible immuno-modulatory bioactivity (Bartoszewski et al., 2020). This hypothesis is also underpinned by the fact that the amount of viral RNA present in infected cells as part of the total resultant RNA can reach up to 50 percent (Blanco-Melo et al., 2020), which implies a high possibility of direct interactions with the host RNA molecules.

Besides, it could be possible that SARS-CoV-2 evolved to include binding sites more of the host microRNAs in an effort to avoid being recognized by immune system (Trobaugh et al., 2014). Since the degradation of microRNA by viral RNA (sequential complementarity) represents a potential risk, and indeed, the inverse correlation between circulating miR-195 and N-gene RNAemia was observed, it could be speculated that the decrease in miR-195 levels identified in this study may be a sequela of such the viral sponging effect (Zhang et al., 2019).

Another possible reason behind the downregulation of miR-195 is the global inhibition of microRNA expression the SARS-CoV infected cells due to the virus-mediated endoplasmic reticulum (ER) stress, which has already been observed during coronavirus infection (Fung and Liu, 2014). Collectively, the mechanisms can have contributed to the reduction of circulating miR-195-5p and its possible role in immune dysregulation in severe COVID-19.

Even though it is unknown whether this decrease in plasma miR-195 concentration is a symptom of COVID-19 pathophysiology or an etiological factor, one can assume that such downregulation can affect the level of severity-related indicators including IL-6 and IL-8. Since in this study all plasma samples were acquired within 48 hours since the time of hospitalization the presence of a decrease in the miR-195 levels may possibly influence the development of severe clinical symptoms in the initial stages of the disease.

Correlation between *MIR-195-p* and other factors:

The results were obtained recorded the high significant negative correlation between *MIR-195-p and* age (r= -0.46 **,p= 0.0006) and significant positive correlation to IL-6(r=0.27 *,p= 0.0498)

.On other hand; there where negative correlation but non- significant between *MIR-195-p* to IL-8 and TNF-α, table(4).

Table 4: Correlation coefficient of *MIR-195-p* to age and other cytokines

Parameter	Correlation coefficient) r (of *MIR-195-p*	P-value
Age	-0.46 **	0.0006
IL-6	0.27 *	0.0498
IL-8	-0.08 NS	0.505
TNF-α	-0.04 NS	0.796
* (P≤0.05), ** (P≤0.01), NS: Non-Significant.		

According to our results, the level of miR-195-5p in plasma appears to be related to patient age and to certain immunological parameters. The same can be observed in the findings of a study by Giannella et al. (2022), who found that age is significantly negatively correlated with the expression levels of serum miR-224-5p and miR-155-5p in COVID-19 patients. miRNAs downregulation was also associated with subsequent upregulation of their target genes which in COVID-19 may, on the one hand, lead to poor innate and adaptive immune response, severe systemic inflammation, cytokine storm (CS), and predisposition to cardiovascular diseases (Nishiga et al., 2020).

A positive correlation was exhibited between the level of TNF-a and IL-6 in the patients with severe COVID-19 in our study. It aligns with the existing evidence, which postulates that IL-6, as a pyrogenic cytokine released during inflammatory reactions, is a potential TNF-a inducer of production, i.e., it is one of the downstream effects of TNF-a activity (Hunter and Jones, 2017). High IL-6 is commonly accepted as the most important characteristic of the cytokine storm in severe cases of COVID-19 (Wang et al., 2020). In addition, the RNAemia of SARS-CoV-2 has been reported to be associated with plasma levels of IL-6 and its role is suggested in predicting extrapulmonary diseases and worse clinical outcomes (Hogan et al., 2021).

Cytokine storm is a very fast progressing and life-threatening illness that is determined by the unrestrained activation of the immune system and overproduction of the proinflammatory mediators. Such dysregulation might result in tissue destruction, multiorgan failure, and mortality unless timely addressed (Mangalmurti and Hunter, 2020). Some of the major cytokines involved in it include interleukins (IL-6 and TNF-a) which are believed to play catalytic roles in propagating the pathological immune response. It has been repeatedly demonstrated that during COVID-19 patients show extremely high levels of these cytokines in comparison with healthy persons (Coperchini et al., 2020). It has been shown that associations exist between their concentrations and disease severity and that they may represent the basis of the underlying differing immune responses explaining the progression of SARS-CoV-2 infection. An understanding of such immunological signatures could provide interesting facts on the disease pathogenesis as well as the therapeutic target. However, these associations require additional corroboration and should be addressed in future studies on the clinical implications of the links discovered (Zhu et al., 2021; Cesta et al., 2022).

Conclusions:

Based on the results, it can be shown that the concentration of TNF-a and IL-10 in the serum is high in patients with COVID-19 as compared to healthy individuals. Correlation between these cytokines and disease severity has been observed which highlights their possible application as a clinical assessment and follow up means of biomarkers. The discoveries provide important information on the contribution of TNF-a and IL-10 to immune dysregulation, especially when it comes to cytokine storm development in the course of severe COVID-19. A deep deciphering of the background of cytokine kinetics of SARS-CoV -2 infection can guide the establishment of immediate and specific immunomodulatory therapies. Notably, the decreased expression of miR-195-5p can be observed at the initial stages of disease development in severe patients, which opens up new directions in the study of the key molecular actors of pathological immune activation in viral infections. The

discussed regulatory phenomenon might not be peculiar to COVID-19 but could also provide insights into hyperinflammatory response mechanisms in generalized array of infectious and immune-mediated diseases. Further elucidation of the pathways will be of benefit in establishing new diagnostic paradigms and treatment approaches that can be used to prevent modulated pathological immune responses and better patient outcomes.

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