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Functional Signatures of non-coding RNAs Plasmacytoma Variant Translocation 1(PVT-1) and miR-135 in COVID-19 Patients

Medhat M. Elsayed[1*], Hatem A. El-mezayen[1], Olfat G. Shaker[2], Yasmine Abdelfatah[3], Sara M. Abdo[1]

[1]*Biochemistry Division, Chemistry Department, Faculty of Science, Helwan University, 11759 Cairo, Egypt*
[2]*Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Cairo University, 12613 Giza, Egypt*
[3]*Internal medicine Department, Faculty of Medicine, Cairo University, 12613 Giza, Egypt*

Abstract

Globally, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic had a major impact on the populations, and different responses implemented to control its spread. Limited and controversial data are available regarding the involvement of lncRNAs in COVID-19 pathogenesis. This study aims to relation between Plasmacytoma variant translocation 1 (PVT-1) and MicroRNA 135 (miR-135) expression levels and COVID-19 patients. Furthermore, to investigate the reliable relations of these non-coding RNAs (ncRNAs) with other laboratory indices and clinical characteristics of COVID-19 patients. The methods of this study included 30 COVID-19 patients and 20 healthy controls. For all subjects, full medical investigations and laboratory analysis were performed. The expressions of candidate ncRNA; sPVT-1 and miRNA-135 were assessed by real-time quantitative polymerase chain reaction (RT-qPCR). Results: Among COVID-19 patients versus healthy individuals, PVT-1, expression levels were significantly up-regulated, while miRNA-135 expression was down-regulated. Besides miR-135 were negatively correlated. ROC curve analysis indicated diagnostic performances for both miR-135 (AUC = 0.96, $p < 0.05$) in COVID-19. After this study concluded the PVT-1and miRNA-135 expression levels to be employed as biomarkers to detect severity of COVID-19.

Keywords: Non-coding RNAs plasmacytoma variant translocation 1(PVT-1), miR-135.

1. INTRODUCTION

One class of virus is the corona virus. There are numerous varieties, and some of them are disease-causing. A respiratory disease pandemic known as COVID-19 was caused by the corona virus SARS-CoV-2, which was discovered in 2019. Based on the epidemiological update by the WHO, 5 SARS-CoV-2 VOCs have been identified since the beginning of the pandemic: Alpha, Beta, Gamma , Delta and Omicron: First reported in South Africa in November 2021 [1]. COVID-19 includes clinical features that present in varying ways with respect to frequency and severity and vary by age, vaccination status and variants of concern. Symptoms that are absent at the onset of illness may develop over time with disease progression. [2]. During the Omicron wave that began in November 2021, those who have had at least 2 vaccinations reported milder symptoms; typical symptoms reported during the Omicron wave included runny nose, headache, sneezing, and sore throat. This response is different than the predominant symptoms earlier in the pandemic, which included fever, cough, chills and muscle pain. When fever occurred in Omicron cases, it was more frequently reported in unvaccinated than in vaccinated cases. [3].

As in SARS and MERS, the diagnosis of 2019 n-CoV infection is based on a history of detailed contact and travel and precise laboratory testing. The diagnostic tools are molecular methods, serology and viral culture. The most common diagnostic methods are molecular methods as RT-PCR (reverse transcription) or real-time PCR, which are made using RNA from respiratory samples such as oropharyngeal swabs, sputum, nasopharyngeal aspirate, deep tracheal aspirate, or bronchoalveolar lavage. In particular, lower respiratory tract samples can offer significantly higher viral load and genome fraction than upper respiratory tract samples. [4].

Treatment of Coronaviruses, Due to the many side effects and the presence of medicinal residues of the chemical drugs for the treatment of viral diseases, especially respiratory viruses, attention has been paid to medicinal plant derived

*Corresponding author e-mail: mdhat.mido93@yahoo.com.; (Medhat M. Elsayed).
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products has increased. There are several plants for the treatment of respiratory viruses, including (Human Respiratory Syncytial Virus (RSV), Human Parainfluenza Viruses (HPIV), Human Metapneumovirus (HMPV), Rhinovirus (HRV), Respiratory Adenoviruses (HadV), Human Coronaviruses Unrelated to SARS (CoV), SARS Coronavirus (SARS-CoV), and Human Bocavirus(HBoV), Which prevent or decrease infection via various mechanisms. [5].

Given that some lncRNAs have been reported to have the potential to encode small proteins or micro-peptides, the latest definition of lncRNA is a class of transcripts of over 200 nucleotides that have no or limited coding capacity.Less than 2% of the human genome is translated into protein-coding RNAs (mRNAs), whereas almost 60% is translated into RNAs without the ability to code for proteins (ncRNAs).Non-coding RNAs can be divided into two groups based on their transcript size: small non-coding RNAs (small ncRNAs) and long non-coding RNAs (lncRNAs).

MicroRNAs (miRNAs) and long ncRNAs, which also include circular RNAs, are the most researched small ncRNAs (circRNAs) [6]. Long non-coding RNAs (LncRNAs) are non-coding RNAs (ncRNAs) that control the transcription and translation of the expression of protein-coding genes. They have certain characteristics with coding genes, including the existence of epigenetic markers, the presence of introns and splice variants, and the transcription being regulated by promoter elements.[7]. Plasmacytoma variant translocation 1 (PVT-1) has an inflammatory response and regulation ability through multiple pathways. [8].

The microRNA-135 have a role in vascular disorders, particularly those brought on by viral infections. Our goal was to determine the expression of miRNA-135 in COVID-19 patients who had severe respiratory injury. [9]. Up to date, employing ncRNAs as biomarkers for viral diseases has not been extensively investigated in COVID-19. The present study aimed to assess the association between miR-135, and PVT-1 in COVID-19 and evaluate the diagnostic efficacy of their expression levels as potential biomarkers. Additionally, To highlight relationships between these non-coding RNAs and other laboratory data as well as the clinical traits of COVID-19 patients.

2. SUBJECTS AND METHODS

2.1 Study design and subjects

This study was carried out in the Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Cairo University, Cairo, Egypt. This is a prospective case-control study that included a total of 50 subjects classified into two groups Group I: 30 patients that have COVID-19 (17 Males and 13 females; with ages ranging from 42 to 81 years), Group II: 20 subject healthy control (8 Males and 12 females; with ages ranging from 46 to 80 years). Informed consents were obtained from participants prior their enrollment. The study protocol was approved by the Ethical Committee of Faculty of Medicine, Cairo University (N-448-2023).

For all the samples, clinical, biochemical, imaging criteria and histopathological confirmation were performed. The COVID-19 patients were diagnosed using RT-qPCR Detection Kit (Taq Path™ COVID-19 CE-IVD RT- PCR; Thermo Fisher) and underwent a comprehensive history taking, in addition to, thorough clinical examination and routine laboratory investigations. Peripheral blood (10 mL) was drawn into EDTA anticoagulated tubes (BD Vacutainer) from COVID-19 patients at the time of diagnosis and from healthy volunteers and kept at 4 °C until further processing (within two hours of collection). Plasma samples were subjected to a two-step centrifugation protocol (2500 ×g and 16,000 ×g; 10– 10 min, 4 °C) to obtain plasma. After separation, the cell-free plasma samples were homogenized, aliquoted, and stored at −80 °C until further analysis.

Total RNA extraction was performed from plasma samples using GeneJET RNA Purification Kit (Thermo Fisher Scientific, Inc.) following the instruction. Checking of RNA quality was done using NanoDrop® 1000 spectrophotometer (NanoDrop Technologies, Inc. Wilmington, USA). Then, synthesis of complementary DNA (cDNA) was done using the High- Capacity cDNA Reverse Transcription Kits (Thermo Fisher Scientific) according to the instructions. Subsequently, real time-qPCR was performed for amplification of the genes of PVT-1and mir-13, using SYBR Premix Ex TaqTM II (Perfect Real Time, TaKaRa, Japan).

PCR reaction conditions were as follows: 95°C for 5 min, then 40 cycles of 95°C for 15 seconds and 60°C for 60 seconds. The 2-ΔΔCt method was applied to quantitatively analyze the results with normalization to U6 snRNA GAPDH for the rest of the genes as internal controls.

U6 snRNA and GAPDH were selected as internal reference genes due to their stable expression in plasma samples, as validated in previous ncRNA studies. [10].

PVT1: forward primer 5′-TGG CTG AGA GGG TTG AGA TC-3′ and reverse primer 5′-GCT GTA TGT GCC AAG GTC AC-3′.mir-135: forward primer 5′-TTG GTC TTG TTT CCC GGT CC-3′ and reverse primer 5′-TCA CAG CTC CAC AGG CTA AC-3′.

2.2 Statistical analysis

Data Analysis was performed using statistical package of social science (SPSS v23). For quantitative parametric data, independent student t-test was used to compare measure of 2-independent groups as well as One-way ANOVA test was used for comparing more than 2-independent groups with Benferroni Post-Hoc to test significance at p-value <0.05.

While for quantitative non-parametric data, Kruskalwallis test and Mann-whitney test were used to compare more than 2-independent groups. For measuring the correlation between qualitative data, Bivariate Pearson correlation test to find out the association between different groups with a two-tailed to test the significance. Sensitivity and specificity test were generated for testing a new test with ROC Curve (Receiver Operating Character). P-value<0.05 was considered as a cutoff value for significance [11].

3. 3. RESULTS

3.1 Demographic, Clinical, and laboratory characteristics of COVID-19 Patients: According to demographic data, there is no statistically significant difference between COVID-19 patients and the controls in age, with a mean of 61.46±10.72 and 59.70±9.02 respectively. Also, the sex within the patients group shows no statistically significant difference as regards to the control group with regard to the health group. Additionally, the COVID-19 patients exhibited significant up-regulation in PVT-1 expression levels and statistically significant down regulation in miRNA-135 expression levels, as compared to the control group as shown in Table (1).

3.2. Relationship between PVT-1 and miR-135 expression levels versus different characteristics in COVID-19 patients: Regarding PVT-1 and the clinical investigations performed on the patients, results showed that there are statistical significance differences as regards to the duration of admission, heart rate, diabetes mellitus, GGO, nodal enlargement and Chest CT distribution. Regarding miR-135 there are statistical significance differences in miR-135 and the clinical investigations performed on the patients including the heart rate, hypertension and Chest CT distribution. as shown in Table (2).

3.3. Significant correlations of PVT-1 and miR-135 expression levels with descriptive/laboratory and clinical data of COVID-19 patients: The miR-135 was directly correlated with serum CRP levels (r=0.38, p=0.035). While, significant positive correlations were reported between PVT-1 versus INR, sodium and PT (p< 0.05). as shown in Table (3).

3.4. Diagnostic performances of miR-135 and PVT-1 among COVID-19 patients: Receiving operating characteristic analysis curves and the corresponding area under the curve were calculated for providing the diagnostic performances of miR-135 and PVT-1 in COVID-19 patients. ROC curve analysis for miR-135 revealed the best diagnostic performance to differentiate healthy controls and COVID-19 patients at a cut-off value of 0.34 fold with AUC = 0.96, sensitivity about 96.7% and specificity 98.8% as shown in (Table 4).

Table 1: Demographic, clinical and laboratory characteristics of studied participants

Parameters	COVID-19 (N=30)	Control (N=20)	P-value
Age (years)	61.46±10.72	59.70±9.02	0.30
Gender **Female** **Male**	13 (43.3%) 17 (56.7%)	12 (60%) 8 (40%)	0.25
Systolic blood pressure	132.07±27.42	103.50±10.89	**0.001***
Diastolic blood pressure	79.87±12.56	70.0±7.25	**0.032***
RBCs	4.32±0.85	4.90±0.05	**0.004***
Hemoglobin	11.75±2.60	12.28±1.30	**0.001***
Hematocrit (%)	36.03±7.36	38.90±0.85	**0.001***
MCV (fL)	83.35±5.45	83.97±4.74	0.55
MCH (pg)	27.03±2.20	27.58±1.97	0.281
MCHC (g/dL)	32.40±1.29	34.29±0.57	**0.001***
PLTs	212.60±78.46	290.75±60.18	**0.0001***

WBCs	8.97±6.53	5.68±1.51	**0.033***
INR	1.41±0.40	1.01±0.03	**0.0001***
Neutrophil (L)	7.53±5.94	7.12±1.01	0.51
Lymphocyte (L)	0.965±0.53	1.15±0.127	0.68
Monocyte (L)	0.473±0.25	0.48±0.06	0.37
ALBUMIN	2.90±0.53	4.50±0.21	**0.003***
ALT	72.71±16.64	13.35±1.12	**0.0001***
AST	74.70±16.54	16.40±1.42	**0.0001***
LDH	455.03±214.08	161.50±26.21	**0.002***
PT	20.34±7.29	11.50±0.51	**0.0001***
Creatinine	1.98±0.44	0.65±0.28	**0.004***
miR-135	0.310±0.071	0.98±0.001	**0.002***
PVT-1	5.55±1.92	1.11±0.01	**0.0001***

Data are expressed as mean ± SD. P-value < 0.05 is considered statistically significant.
RBCs Red blood cells, MCV Mean corpuscular volume, MCH Mean corpuscular hemoglobin, MCHC Mean corpuscular hemoglobin Concentration, PLTs Platelets, WBCs White blood cells, INR International normalized ratio, ALT Alanine aminotransferase, AST Aspartate aminotransferase, LDH Lactate dehydrogenase, PT Prothrombin time, CRP C-reactive protein, RDW(%) Red cell distribution width, PH potential of hydrogen, miR-135 MicroRNA-135, PVT-1 Plasmacytoma Variant Translocation 1.

Table 2: Relationship between PVT-1and miR-135 expression levels versus different characteristics in COVID-19 patients

Parameters		**PVT-1 mean±SE**	**p-value PVT-1**	**mir-135 mean±SE**	**p-value mir-135**
Age	≤60 years (N=12) >60 years (N=18)	7.87±4.07 4.0±1.75	0.085	0.19±0.07 0.38±0.10	0.214
Duration of admission	≤10 days (N=23) >10 days (N=7)	7.05±2.43 0.61±0.45	**0.030***	0.32±0.086 0.26±0.121	0.737
Heart Rate	<60 bpm (N=1)	0.293±0.001	0.608a	0.254±0.001	0.97a
	Between 60 and 100 bpm (N=22)	6.74±2.58	0.436b	0.247±0.05	0.737b
	>100 (N=7)	2.56±0.96	**0.049c**	0.513±0.26	**0.002c**
RSNA	Typical (N=28)	5.33±2.01	0.761	0.311±0.07	0.414
	Indetermined (N=2)	8.58±8.38		0.290±0.064	
Drug treatment	Negative (N=22)	5.03±1.83	0.288	0.292±0.088	0.824
	Positive (N=8)	6.97±5.43		0.357±0.118	
Comorbidity					

Hypertension	Negative (N=6)	6.39±2.85	0.264	0.236±0.04	**0.010***
	Positive (N=24)	4.29±2.32		0.419±0.161	
Diabetes mellitus	Negative (N=18)	8.13±7.33	**0.05***	0.218±0.057	0.205
	Positive (N=12)	4.90±1.68		0.33±0.08	
CT Findings					
GGO	Negative (N=21)	4.34±1.50	**0.006***	4.34±1.50	**0.006***
	Positive (N=9)	8.36±5.51		8.36±5.51	
Consolidation	Negative (N=27)	5.75±2.13	0.298	5.75±2.13	0.298
	Positive (N=3)	3.77±1.80		3.77±1.80	
mixed GGR and consolidation	Negative (N=13)	6.69±3.84	0.137	6.69±3.84	0.137
	Positive (N=17)	4.67±1.82		4.67±1.82	
pl effusion	Negative (N=23)	6.00±2.42	0.389	6.00±2.42	0.389
	Positive (N=7)	4.07±2.35		4.07±2.35	
nodal enlargement	Negative (N=18)	7.31±3.04	**0.039***	7.31±3.04	**0.039***
	Positive (N=12)	2.91±1.41		2.91±1.41	
Pattern bronchial dilatation	Negative (N=28)	5.32±2.01	0.778	5.32±2.01	0.778
	Positive (N=2)	8.71±8.24		8.71±8.24	
Chest CT distribution	Central (N=4)	7.89±6.90	**0.002x**	7.89±6.90	**0.002x**
	Peripheral (N=10)	1.95±0.78	0.754y	1.95±0.78	0.754y
	Mixed (N=16)	7.21±3.17	**0.024z**	7.21±3.17	**0.024z**
No. of lobe affected	0 (N=1)	0.44±0.0001	>0.05aa	0.44±0.0001	>0.05aa

	3 (N=1)	0.26±0.0001	0.62bb	0.26±0.0001	0.62bb
	5 (N=28)	5.92±2.05	0.609cc	5.92±2.05	0.609cc

Significant p in bold.significant between- a (<60 bpm, 60-100 bpm), b between (<60 bpm, >100), c between (60-100 bpm, >100). significant between chest CT distribution- x between (central, Peripheral) y between (Central, mixed) z between (Peripheral and mixed) significant between the number of affected lobes-aa between (0, 3) bb between (0,5) cc between (3,5).
RSNA Radiological Society of North America, GGO Ground-glass opacity, Pl Pleural, CT Computed tomography.

Table 3: Correlations of miR-135 and PVT-1 expression levels with descriptive/laboratory and clinical data of COVID-19 patients

Parameters	miR-135 r (p-value)	PVT-1 r (p-value)
Age	0.241(0.199)	-0.182(0.335)
Duration of Hospital Admission	-0.055(0.772)	-0.104(0.584)
Systolic blood pressure	0.114(0.549)	0.049(0.799)
Diastolic blood pressure	-0.016(0.933)	-0.022(0.909)
RBCs	-0.218(0.246)	0.034(0.857)
Hemoglobin	-0.265(0.157)	0.114(0.548)
Hematocrit (%)	-0.272(0.147)	0.078(0.683)
MCV (fL)	-0.197(0.298)	0.070(0.713)
MCH (pg)	-0.188(0.321)	0.191(0.313)
MCHC (g/dL)	-0.067(0.723)	0.298(0.109)
PLTs	-0.044(0.815)	0.178(0.348)
WBCs	0.256(0.172)	0.059(0.755)
INR	-0.210(0.265)	0.390(**0.033***)
Neutrophil	0.291(0.119)	0.014(0.941)
Lymphocyte	-0.026(0.891)	0.103(0.589)
Monocyte	-0.154(0.417)	-0.031(0.872)
ALBUMIN	0.172(0.363)	-0.153(0.420)
ALT	-0.154(0.416)	0.002(0.991)
AST	-0.110(0.561)	-0.165(0.384)
LDH	0.069(0.719)	-0.130(0.493)
PT	-0.202(0.284)	0.377(**0.040***)
Creatinine	0.12(0.499)	-0.14 (0.448)

(r):Spearman'scorrelation coefficient. *Correlation is significant at P ≤ 0.05.
RBCs Red blood cells, MCV Mean corpuscular volume, MCH Mean corpuscular hemoglobin, MCHC Mean corpuscular hemoglobin Concentration, PLTs Platelets, WBCs White blood cells, INR International normalized ratio, ALT Alanine aminotransferase, AST Aspartate aminotransferase, LDH Lactate dehydrogenase, PT Prothrombin time, CRP C-reactive protein, RDW(%) Red cell distribution width.
TSS Total severity score, GGO Ground-glass opacity, CO-RADS coronavirus disease 2019 Reporting and Data System,CXR score chest X-ray score.

Table 4: Diagnostic and prognostic performances of miR-135 and PVT-1among COVID-19 patient groups

	AUC	Cut-off value	Sensitivity	Specificity	95% C.I	Accuracy	p-value
miR-135	0.967	0.34	96.7%	98.8%	0.86 to 1.0	97.75%	**<0.0001***
PVT-1	0.567	5.92	56.7%	99.9%	0.38 to 0.74	78.30%	**0.04***

* Significant (P<0.05).
miR-135MicroRNA-135, PVT-1 Plasmacytoma Variant Translocation 1, AUC Area under curve.

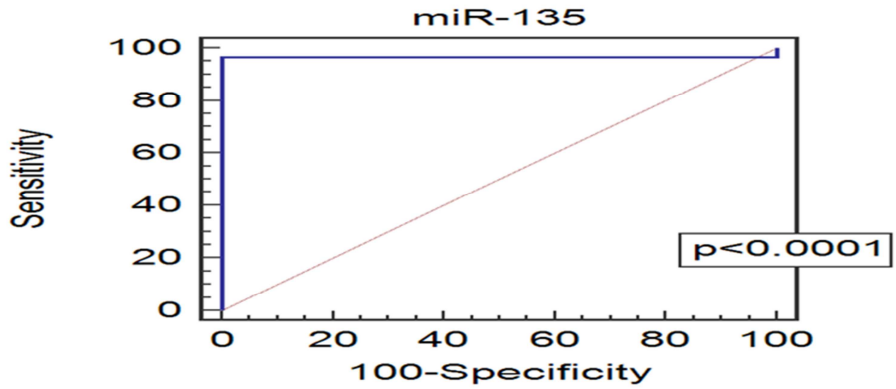

Figure 1: ROC Curve for miR-135 for COVID-19 patient group

4. DISCUSSION

There are many ways to detect severity of COVID-19 in our study we concentrate on certain ways assist us to know the severity of COVID-19 these ways like biomarker genes such as PVT-1 and mir-135.In our study, carried out in the Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Cairo University, this is a prospective case-control study that included a total of 50 subjects classified into two groups: Group I: 30 patients that had COVID-19; Group II: 20 subjects with healthy control analyzing risk factors and outcomes among patients hospitalized with COVID-19.Although the sample size is limited, the high specificity and sensitivity of PVT-1 and miR-135 expressions as a biomarkers suggest a strong potential for future validation in larger cohorts.

4.1 Demographic characteristics and COVID-19 Patients

The study revealed males 56.7% were found to be more infected than females 43.3% this result agrees with de souza et al.,2020. Covid-19 causes a disproportionately high number of deaths in men, prompting the hypothesis that men are more at risk than women. Males are more likely to die from heart disease, diabetes, liver disease, and cancer than females.[12].

4.2 Laboratory indices and COVID-19 patients.

Systolic blood pressure and diastolic blood pressure132.07±27.42 and 79.87±12.56 respectively which is a statistically significant difference between COVID-19 patients and the controls regarding. We notice the Systolic blood pressure and Diastolic blood pressure is increase in covid patient than control is consistent with studies of [13]. Report that one of the processes connecting COVID-19 and hypertension is the immunologic response, which is thought to be dysregulated in both hypertension and SARS-CoV-2 infection. Another study also pointed to the same finding [14]. Reported that compared to non-hypertensive patients, patients with pre-existing hypertension are more likely to be admitted with SARS-CoV-2 infection. Obesity and hypertension are prevalent in hospitalized COVID-19 patients at 50% and 48%, respectively.

The red blood cells (RBCs) (4.32±0.85) were lower than normal, which explains the hypoxia that occurred in COVID-19 patients, whose RBCs are responsible for carrying carry oxygen in the body which is matched with the results reported by [15]. reported that it has been shown that SARS-Co-V2-infection has a considerable effect on the protein and lipid balance of red blood cell (RBC) structural membranes. Increased quantities of glycolytic intermediates were seen in the RBCs of COVID-19 patients, along with membrane protein oxidation and fragmentation. As a result, COVID-19 affects two vital processes that regulate the fine tuning of red cell membranes and hemoglobin oxygen affinity. When moving from the lungs to

the bloodstream, RBCs from COVID-19 patients may not be able to adapt to environmental changes in hemoglobin oxygen saturation and, as a result, may have a reduced ability to transport and deliver oxygen.

Hematocrit and hemoglobin are (36.03±7.36) and (11.75±2.60) respectively were decreased compared to control, which is in agreement with [16] reported that RBCs are significantly altered in size and rigidity by COVID-19; this results in a drop in hematocrit levels and an increase in the RBCs' amplitude, or RDW (red blood cell distribution width), which has been seen [17] reported in COVID-19 that as the disease worsens, the hematocrit and Hb concentration tend to gradually decline, whereas RDW tends to steadily rise in the opposite manner. According to estimates, the RDW increase increases the risk of COVID-19 aggravation by around nine times and the likelihood of severe acute renal injury by sixteen times.

Mean corpuscular hemoglobin concentration (MCHC) equals 32.40±1.29, which is lower than control, which is consistent with [18] reported that in our group, there was progressive anemia with increasing MCV and declining MCHC. The COVID-19 is independently predicted by peak MCV and nadir MCHC.

There is a statistically significant difference between COVID-19 patients and the controls regarding platelet (212.60±78.46) is decreased than control, which is in agreement with [19] reported that lower platelet counts are linked to worse clinical outcomes, and thrombocytopenia has been documented in COVID-19 hospitalized patients.

White blood cells (WBCs) equal (8.97±6.53) that is higher than control, which is consistent with [20] reported White blood cell (WBC) morphologic alterations, which vary between illness phases in COVID-19-positive individuals, are a significant effect of SARS-Co-V2-infection. Also, [21] reported that disease progression and/or more severe disease are associated with loss of these changes in the context of increasing neutrophilia and left-shifted myeloid maturation. The early stages and/or more mild disease are associated with exuberant coalescent monocyte vacuolization and expansion of atypical lymphocytes.

The coagulation profile (INR) is a statistically significant difference 20.34±7.29, which is higher than control. It is in agreement with [22] reported that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that causes the coagulopathy associated with COVID-19 is known to directly interact with endothelial cells, which is at least partially what gives rise to some of the coagulopathy's distinctive characteristics.

Kidney function test (creatinine) is a statistically significant difference with P-value 0.004 and the mean is 1.98±0.44, which is higher than the normal range of 1.4, which results from acute kidney injury (AKI), which is consistent with [23] reported during the coronavirus disease 2019 (COVID-19) pandemic, AKI is one of the most common consequences in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Though atypical pneumonia and severe respiratory failure are the hallmarks of COVID-19, AKI is said to affect 10% of inpatients with the illness.

4.3 Relation between Plasmacytoma variant translocation 1 (PVT-1) and MicroRNA 135 (miR-135) expression levels and COVID-19 patients.

Plasmacytoma variant translocation 1 (PVT-1) gene expression in serum of the COVID-19 group (mean 5.55 and standard deviation 1.92) compared to healthy controls (mean 1.11 and standard deviation 0.01) was reported as statistically highly significant compared to healthy groups with p-values 0.0001. That result is consistent with our findings [24] When H9c2 cells were exposed to hypoxia, cell viability decreased and cell death increased.

We discovered that overexpressing PVT1 exacerbated the hypoxia-induced damage in H9c2 cells. Also [25] finding the expression level of PVT-1 was found to be high in patients who were admitted for less than 10 days, with a mean SE of 7.05±2.43, compared to those who stayed for more than 10 days with a mean SE of 0.61±0.45.

The mir-135 gene expression in serum regarding the COVID-19 group (mean 0.310 and standard deviation 0.071) compared to healthy controls (mean 0.98 and standard deviation 0.001) was reported as statistically highly significant compared to healthy groups with p-values 0.002. It was reported the SARS-CoV-2 genome can be targeted by 128 cellular miRNAs. However, the lung epithelium only expresses a small number of them, if any at all. Let-7a-3p, miR-135b-5p, miR-16-2-3p, and miR1275 were four of the 128 miRNAs that showed downregulation. That result is in agreement with our findings in [26].

5. CONCLUSION

The PVT-1, miRNA-135, Systolic blood pressure, Diastolic blood pressure, RBCs, Hemoglobin, Hematocrit (%), MCHC (g/dL), PLTs, WBCs, INR, ALBUMIN, ALT, AST, LDH, PT and Creatinine assess the diagnostic performances of their expression levels to be employed as biomarkers to detect severity of COVID-19.

COMPETING INTERESTS

No conflict of interest.

AUTHOR CONTRIBUTIONS

All of the authors have agreed to be fully responsible for the submitted manuscript's content and have given their approval for submission.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author.

ETHICAL CONSIDERATIONS

This study was approved by Research Ethics Committee faculty of medicine Cairo University (N-448-2023) and a written informed consent was obtained from all subjects. All methods and experimental protocols were carried out in accordance with relevant guidelines.

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