AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

MOLECULAR SIGNATURES OF IMMUNE AND VASCULAR DYSREGULATION IN LONG COVID

Agzamxodjayeva N.U., Abidova D.E.,

Ruzibakieva M.R., Islamova R.K.

PhD, Profi University, Associate Professor at the

Department of Propedeutics of Internal Diseases. Tashkent, Uzbekistan.

E-mail: nozimaulugbekovna@mail.ru; ORCID: 0000-0001-5593-1740

DSc, Physician at the Outpatient Department, Republican

Specialized Scientific-Practical Medical Center of Cardiology.Tashkent, Uzbekistan.

E-mail: abidova.dilorom@bk.ru.; ORCID: 0009-0000-9786-5710.

DSc, Leading Researcher, Department of Cellular Therapy, Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan, Tashkent, Uzbekistan. E-mail: malika-ruz@hotmail.com; ORCID: https://orcid.org/0000-0002-5982-945X

Head of the Department of Propedeutics of Internal Diseases, Profi University, Tashkent, Uzbekistan. E-mail: islamovaranokarimovna@gmail.com; ORCID: 0000-0003-1663-8669

Abstract

Background. Post-COVID syndrome (Long COVID) is a multisystem condition in which persistent inflammation, endothelial dysfunction, and dysregulation of the immune response play a significant role, particularly in patients with concomitant arterial hypertension.

Objective. To investigate the expression patterns of microRNAs (miR-155 and miR-28) and the distribution of gene polymorphisms AGT T174M, JAK2 V612P, IL6 −174G>C, and EDN1 Lys198Asn in patients with Long COVID depending on the presence of arterial hypertension.

Materials and Methods. A total of 174 individuals were examined: patients with Long COVID and arterial hypertension (n=50), patients with Long COVID without arterial hypertension (n=52), and a control group of healthy donors (n=72). MicroRNA expression was assessed by real-time PCR, and genotyping was performed using allele-specific PCR. Statistical analysis included nonparametric tests, correlation analysis, and ROC analysis.

Results. Patients with Long COVID and arterial hypertension demonstrated a significant decrease in miR-155 and miR-28 expression ($p<0.001$), associated with the presence of TM and MM genotypes of AGT T174M, as well as GG and GT genotypes of JAK2 V612P. IL6 and EDN1 polymorphisms did not exert a significant effect on microRNA levels. ROC analysis revealed high predictive value of ΔCt miR-155 and miR-28 for stratifying patients according to JAK2 genotype (AUC >0.95).

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

Conclusions. Comprehensive evaluation of microRNAs and genetic polymorphisms enables the identification of molecular markers associated with the severity of Long COVID in patients with arterial hypertension, opening prospects for personalized monitoring and prognosis.

Keywords: Long COVID, microRNA, arterial hypertension, AGT, JAK2, genetic polymorphism.

Introduction

Post-COVID syndrome (Long COVID) is currently regarded as one of the most significant consequences of the COVID-19 pandemic, exerting a prolonged impact on public health and healthcare systems worldwide. According to the World Health Organization, Long COVID is defined as a condition characterized by the persistence or emergence of new symptoms 12 weeks or more after acute SARS-CoV-2 infection, which cannot be explained by an alternative diagnosis. The clinical heterogeneity of Long COVID, encompassing cardiovascular, neurological, respiratory, and metabolic manifestations, highlights the complex and multilayered pathogenesis of this condition.

In recent years, particular attention has been directed toward cardiovascular involvement in Long COVID. Large cohort studies have demonstrated that a substantial proportion of patients develop de novo arterial hypertension, blood pressure instability, tachycardia, endothelial dysfunction, and an increased risk of thrombotic complications during the post-COVID period. These alterations may persist for months or even years after infection, significantly reducing patients' quality of life and increasing the risk of adverse cardiovascular outcomes.

Arterial hypertension, as one of the most prevalent cardiovascular diseases, is considered not only a comorbid condition but also a potential modifier of Long COVID progression. Patients with hypertension more frequently exhibit pronounced post-COVID symptoms, experience prolonged recovery, and demonstrate poorer functional outcomes. This underscores the relevance of investigating the molecular mechanisms underlying the interaction between Long COVID and arterial hypertension.

Current concepts of Long COVID pathogenesis emphasize the pivotal role of chronic low-grade inflammation, dysregulation of innate and adaptive immune responses, and persistent endothelial dysfunction. Epigenetic mechanisms of gene expression regulation, particularly microRNAs—short non-coding RNAs capable of modulating the expression of multiple target genes involved in inflammation, vascular tone, and tissue remodeling—are increasingly recognized as central players in these processes.

MicroRNA miR-155 is considered a key regulator of immune and inflammatory responses. It is actively involved in T-cell differentiation, macrophage activation, and regulation of pro-inflammatory cytokine production, including IL-6 and TNF-α. Several studies have demonstrated that dysregulated miR-155 expression is associated with chronic inflammation and cardiovascular disease. In the context of COVID-19 and Long COVID, miR-155 is regarded as a potential mediator of persistent inflammation and vascular dysfunction.

MicroRNA miR-28, in turn, is implicated in angiogenesis, apoptosis regulation, and cellular responses to hypoxia. Altered expression of miR-28 may contribute to endothelial dysfunction

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

and impaired vascular reactivity, which is particularly relevant in patients with arterial hypertension during the post-COVID period.

Alongside epigenetic mechanisms, genetic factors play an important role in individual susceptibility to Long COVID. Polymorphisms in genes involved in the regulation of the renin-angiotensin-aldosterone system, inflammatory responses, and vascular tone may influence the severity and clinical features of post-COVID syndrome. Specifically, the AGT T174M polymorphism has been associated with altered renin-angiotensin system activity and increased risk of arterial hypertension. The JAK2 V612P polymorphism affects the JAK/STAT signaling pathway, which is crucial for immune regulation and cytokine-mediated responses. Variants of the IL6 (−174G>C) and EDN1 (Lys198Asn) genes are also considered potential determinants of inflammatory and vascular changes.

Despite accumulating evidence on the role of microRNAs and genetic factors in COVID-19, their integrated investigation in patients with Long COVID, particularly in combination with arterial hypertension, remains insufficient. The lack of systematized data limits opportunities for early risk stratification and the development of personalized approaches to patient monitoring and management.

In this context, conducting a comprehensive molecular-genetic study aimed at evaluating the expression of key microRNAs and the distribution of genetic polymorphisms in patients with Long COVID appears both timely and scientifically justified.

The aim of the present study was to evaluate the association between the expression of miR-155 and miR-28 and the polymorphisms of the AGT, JAK2, IL6, and EDN1 genes in patients with Long COVID, taking into account the presence of arterial hypertension.

Materials and Methods. This study was designed as a prospective case–control investigation conducted in accordance with biomedical ethics and approved by the local institutional review board. A total of 174 individuals were examined, including 50 patients with Long COVID and arterial hypertension, 52 patients with Long COVID without hypertension, and 72 healthy donors serving as controls. All participants were between 18 and 65 years of age, had a documented history of SARS-CoV-2 infection confirmed by PCR or antigen testing, and presented with persistent or newly developed symptoms lasting at least 12 weeks after the acute phase, consistent with the WHO definition of Long COVID. Patients with acute infections, autoimmune disorders, malignancies, chronic systemic diseases other than hypertension, as well as pregnant or lactating women, were excluded. Clinical evaluation included medical history, physical examination, and measurement of blood pressure, heart rate, and body mass index, while laboratory tests comprised complete blood count, biochemical profile, and inflammatory markers such as C-reactive protein, IL-6, and TNF-α. For molecular analysis, total RNA was isolated from peripheral blood mononuclear cells, reverse transcription was performed with specific stem-loop primers, and quantitative real-time PCR was used to assess the relative expression of miR-155 and miR-28 with U6 snRNA as an internal control. Genotyping of AGT T174M, JAK2 V612P, IL6 −174G>C, and EDN1 Lys198Asn polymorphisms was carried out using allele-specific PCR, with agarose gel electrophoresis for visualization and sequencing confirmation in selected samples. Statistical analysis was performed using SPSS v.25.0; descriptive statistics were expressed as mean ± SD or median with interquartile range, group

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

comparisons were conducted with non-parametric tests, correlations were assessed using Spearman's coefficient, and ROC analysis was applied to evaluate the predictive value of ΔCt miR-155 and miR-28 for stratification by JAK2 genotype, with $p<0.05$ considered statistically significant. The study adhered to the Declaration of Helsinki, and all participants provided written informed consent.

Results.

The study included 174 participants divided into three groups: patients with Long COVID and concomitant arterial hypertension (n=50), patients with Long COVID without arterial hypertension (n=52), and a control group of apparently healthy donors (n=72). The groups were comparable in terms of age and sex distribution, with no statistically significant differences observed ($p>0.05$). Patients with arterial hypertension more frequently exhibited clinical signs of autonomic dysfunction and blood pressure instability. Analysis of genetic polymorphisms demonstrated that in patients with Long COVID and arterial hypertension, the frequency of the M allele of the AGT T174M polymorphism was significantly higher compared with the control group (27.0% vs 10.4%, $p=0.0007$), while the TM genotype was detected in 38.0% of cases versus 18.1% in controls ($p=0.0138$). Carriage of the TM genotype was associated with an increased risk of Long COVID in the presence of arterial hypertension (OR=2.78, 95% CI 1.22–6.37). For the JAK2 V612P polymorphism, a trend toward a higher prevalence of the GT genotype was observed in patients with Long COVID and arterial hypertension compared with controls (14.0% vs 4.2%), although the difference reached borderline statistical significance ($p=0.051$). Analysis of the IL6 −174G>C polymorphism revealed a significantly higher frequency of the GG genotype in patients with Long COVID and arterial hypertension compared with the control group (60.0% vs 37.5%, $p=0.014$). In contrast, no statistically significant differences were found in the distribution of EDN1 Lys198Asn genotypes in this subgroup ($p>0.05$). Among patients with Long COVID without arterial hypertension, the most pronounced differences were observed for the EDN1 Lys198Asn polymorphism, with a significantly higher frequency of the T allele compared with controls (36.5% vs 20.8%, $p=0.006$), and carriage of the TT genotype was associated with an increased risk of Long COVID (OR=4.18, $p=0.030$). Analysis of microRNA expression demonstrated significant intergroup differences, with patients with Long COVID and arterial hypertension exhibiting markedly reduced expression of miR-155 and miR-28 compared with patients without arterial hypertension and controls, reflected by increased ΔCt values. The median ΔCt value for miR-155 in hypertensive patients was 6.46 versus 4.23 in non-hypertensive patients ($p<0.001$), while for miR-28 the corresponding values were 7.62 and 4.51, respectively ($p<0.001$). Stratification according to AGT T174M polymorphism showed that carriers of the MM genotype had the lowest expression levels of miR-155 and miR-28 compared with TT and TM genotypes ($p=0.0056$). Analysis of JAK2 V612P demonstrated that the GG genotype was associated with the most pronounced decrease in miR-155 and miR-28 expression ($p=0.0006$ and $p=0.0012$, respectively), whereas no significant associations were found between microRNA expression and IL6 −174G>C or EDN1 Lys198Asn polymorphisms ($p>0.05$). In patients with Long COVID and arterial hypertension, a strong inverse correlation was observed between ΔCt miR-155 and ΔCt miR-28 ($\rho=-0.719$, $p<0.001$), and linear regression analysis indicated that miR-155 expression accounted for 51.7% of the variability in miR-28 expression ($R^2=0.517$). Multivariate regression analysis identified miR-28 expression ($p=0.034$), AGT T174M genotypes ($p<0.05$), and carriage of the JAK2 V612P GG

AMERICAN ACADEMIC PUBLISHER
INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

genotype (p=0.004) as independent predictors of miR-155 expression. ROC analysis demonstrated high diagnostic and prognostic performance of ΔCt miR-155 and miR-28 for stratification of patients with Long COVID and arterial hypertension according to JAK2 genotype, with the area under the ROC curve exceeding 0.95; at optimal cut-off values, the sensitivity and specificity for miR-155 were 95.3% and 100.0%, respectively, and for miR-28 were 97.7% and 100.0%.

Conclusions

In patients with Long COVID and arterial hypertension, a pronounced decrease in the expression of miR-155 and miR-28 was observed; the AGT T174M and JAK2 V612P polymorphisms were associated with altered microRNA expression and may be considered risk factors for vascular complications of Long COVID; the expression of miR-155 and miR-28 demonstrated high prognostic value and can serve as molecular markers for patient stratification; the findings support the feasibility of implementing molecular-genetic approaches in the clinical monitoring of patients with Long COVID.

References

1. Reyes-Long S, Cortés-Altamirano JL, Bandala C, Avendaño-Ortiz K, Bonilla-Jaime H, Bueno-Nava A, Ávila-Luna A, Sánchez-Aparicio P, Clavijo-Cornejo D, Dotor-LLerena AL, Cabrera-Ruiz E, Alfaro-Rodríguez A. Role of the MicroRNAs in the Pathogenic Mechanism of Painful Symptoms in Long COVID: Systematic Review. Int J Mol Sci. 2023 Feb 10;24(4):3574. doi: 10.3390/ijms24043574

2. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV; WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. Lancet Infect Dis. 2022 Apr;22(4):e102-e107. doi: 10.1016/S1473-3099(21)00703-9

3. Ren H, Lin Y, Huang L, Xu W, Luo D, Zhang C. Association of genetic polymorphisms with COVID-19 infection and outcomes: An updated meta-analysis based on 62 studies. Heliyon. 2023 Dec 14;10(1):e23662. doi: 10.1016/j.heliyon.2023.e23662

4. Halas RG, Berceanu Vaduva DM, Radulescu M, Bredicean AC, Mateescu DM, Toma AO, Cotet IG, Guse CE, Marginean A, Margan MM, Lazureanu VE. Long COVID Prevalence and Risk Factors: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. Biomedicines. 2025 Nov 24;13(12):2859. doi: 10.3390/biomedicines13122859

5. Soltani-Zangbar MS, Hajivalili M, Daneshdoust D, Ghadir S, Savari G, Zolfaghari M, Aghebati-Maleki L, Oloufi S, Nouri N, Amini N, Mehdizadeh A, Ghasemi Moghadam H, Mahmoodpoor A, Ahmadian Heris J, Yousefi M. SARS-CoV2 infection induce miR-155 expression and skewed Th17/Treg balance by changing SOCS1 level: A clinical study. Cytokine. 2023 Sep;169:156248. doi: 10.1016/j.cyto.2023

6. Hu J, Huang S, Liu X, Zhang Y, Wei S, Hu X. miR-155: An Important Role in Inflammation Response. J Immunol Res. 2022 Apr 6;2022:7437281. doi: 10.1155/2022/7437281

AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5. No 12. December ,2025

7. Hou Y, Gu T, Ni Z, Shi X, Ranney ML, Mukherjee B. Global Prevalence of Long COVID, Its Subtypes, and Risk Factors: An Updated Systematic Review and Meta-analysis. Open Forum Infect Dis. 2025 Aug 30;12(9):ofaf533. doi: 10.1093/ofid/ofaf533

8. Paval NE, Căliman-Sturdza OA, Lobiuc A, Dimian M, Sirbu IO, Covasa M. MicroRNAs in long COVID: roles, diagnostic biomarker potential and detection. Hum Genomics. 2025 Aug 13;19(1):90. doi: 10.1186/s40246-025-00810-0