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Expression analysis of lncRNA *Morrbid* and *NeST* lncRNA in patients with Coronavirus disease 2019 and their clinical signs

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Abstract

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remains a major global health challenge because of its heterogeneous clinical manifestations and the need for reliable molecular markers to better understand disease pathogenesis. Long non-coding RNAs (lncRNAs) have emerged as important regulators of gene expression and immune responses, participating in both innate and adaptive immunity during viral infections. Among them, the immune-related lncRNAs Morrbid and NeST have been implicated in the regulation of immune cell survival and interferon-mediated antiviral responses, suggesting their potential involvement in COVID-19.

In the present study, we investigated the expression levels of Morrbid and NeST in peripheral blood mononuclear cells (PBMCs) obtained from COVID-19 patients and healthy controls. Total RNA was extracted, complementary DNA (cDNA) was synthesized, and gene expression was quantified using quantitative real-time polymerase chain reaction (qRT-PCR). Compared with healthy controls, COVID-19 patients exhibited significantly higher expression of Morrbid (median = 34.693 vs. 15.590; $p = 0.008$) and NeST (median = 252.172 vs. 92.272; $p = 0.046$).

These findings demonstrate that both lncRNAs are significantly upregulated in PBMCs of COVID-19 patients and suggest that they may represent candidate biomarkers associated with the host immune response to SARS-CoV-2 infection. However, given the observed variability in gene expression, larger independent cohorts together with complementary functional and molecular validation studies are required to confirm their biological and potential diagnostic significance.

Keywords: COVID-19, lncRNA *Morrbid*, *NeST* lncRNA, biomarker, adaptive immunity

Statements and Declarations

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

This study was ethically approved by Fasa University of Medical Sciences [Ethical Code: IR.FUMS.REC.1399.097].

Informed consent

Written informed consent was obtained from all participants before their enrollment in the study. Participants were informed about the study objectives, procedures, potential benefits, and their right to withdraw from the study at any time without any consequences.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

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Author Contributions

Ghazal Ghaznavi contributed to study conceptualization, data collection, laboratory experiments, data analysis, and preparation of the original manuscript draft as part of her master's thesis. Ali Ghanbari Asad and Yaser Mansoori conceived and supervised the study, designed the research methodology, interpreted the data, secured resources, and critically revised the manuscript. Raziye Ranjbar and Fateme Zarei assisted with laboratory procedures, molecular analyses, and data collection. Abdolreza Daraei contributed to study methodology, scientific consultation, data interpretation, and manuscript revision. Yosef Gholampoor, Jalal Karimi, Amir Ansari, and Zahra Montaseri participated in patient recruitment, clinical assessment, sample collection, and acquisition of clinical data. Mojtaba Sohrabpour contributed to data interpretation and critical revision of the manuscript. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

1. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19), emerged in late 2019 and rapidly developed into a global pandemic. The infection primarily affects the respiratory system, producing clinical symptoms that range from mild, cold-like manifestations to severe pneumonia and multi-organ dysfunction (1, 2). The World Health Organization (WHO) officially designated the virus as SARS-CoV-2 because of its genetic similarity to previously identified SARS-CoV and MERS-CoV (3, 4). Coronaviruses are enveloped, positive-sense, single-stranded RNA viruses capable of infecting both humans and animals (5). Their genome, approximately 26–32 kb in length, encodes several structural proteins, including the nucleocapsid (N), spike (S), membrane (M), and small membrane (SM) proteins, as well as additional glycoproteins such as hemagglutinin esterase (HE) (6). SARS-CoV-2 infection activates both innate and adaptive immune responses. In many patients, these responses lead to excessive inflammatory reactions such as cytokine storms, which substantially contribute to disease severity (7). Approximately 97% of the human genome does not encode proteins but gives rise to a wide spectrum of non-coding RNAs (ncRNAs) that play critical roles in gene regulation (8). Among these, long non-coding RNAs (lncRNAs), defined as transcripts exceeding 200 nucleotides, have become prominent for their regulatory functions in transcription, RNA processing, and epigenetic modification (9). Emerging evidence suggests that lncRNAs play essential roles in immune regulation, including the activation and differentiation of macrophages,

$CD4^+$ and $CD8^+$ T cells, regulatory T cells (Tregs), and natural killer (NK) cells (10). Dysregulation of these molecules has been implicated in autoimmune diseases and cancers (11), as well as viral infections (12).

Recent studies have shown that lncRNAs can modulate host–virus interactions by shaping antiviral signaling pathways, cytokine production, and immune cell activation (13). Despite this growing knowledge, the functional significance of many immune-related lncRNAs in COVID-19 pathogenesis remains insufficiently understood. Two lncRNAs of particular interest are *Morrbid* and *NeST* (also known as *IFNG-AS1*). *Morrbid* (Myeloid RNA Regulator of Bim-Induced Death) is a long non-coding RNA that regulates the proapoptotic gene *Bcl2l11* (*Bim*) and thereby governs the lifespan of short-lived myeloid cells such as neutrophils and monocytes. By preventing premature apoptosis, it plays a central role in maintaining immune cell homeostasis. *Morrbid* expression is modulated by inflammatory and antiviral signals, particularly those mediated through type I interferons, and its dysregulation has been associated with excessive immune activation and inflammatory disorders (14). *NeST* lncRNA, also known as *Tmevpg1*, is located adjacent to the *IFNG* gene and is a key regulator of immune responses through its epigenetic activation of the interferon-γ (*IFN-γ*) locus. It is predominantly expressed in $CD4^+$ and $CD8^+$ T cells and NK cells and regulates *IFN-γ* transcription by binding to WDR5, a component of the histone H3K4 methyltransferase complex. This interaction increases histone H3 lysine 4 trimethylation at the *IFNG* locus, leading to enhanced *IFN-γ* production and modulation of immune defenses during viral and bacterial infections. Given its capacity to regulate cytokine expression and influence immune cell activity, *NeST* represents a crucial link between lncRNA-mediated epigenetic control and host antiviral responses (15, 16). Collectively, current evidence suggests that lncRNA *Morrbid* and lncRNA *NeST* may both contribute to the immune dysregulation observed in viral infections, particularly COVID-19. Therefore, the present study aimed to investigate the expression levels of lncRNA Morrbid and lncRNA NeST in peripheral blood mononuclear cells (PBMCs) from COVID-19 patients compared with healthy controls. By characterizing the expression profiles of these immune-related lncRNAs, we sought to explore their potential involvement in the host immune response to SARS-CoV-2 infection and to provide preliminary evidence supporting their evaluation as candidate biomarkers associated with COVID-19.

2. Materials & Methods

2.1 Selection of candidate lncRNAs

Candidate long non-coding RNAs (lncRNAs) were selected through an extensive literature review combined with database mining using GeneCards, LncBook, and RNAInter. Immune-related genes implicated in the pathogenesis of COVID-19, particularly those involved in interferon signaling, inflammatory cytokine responses, apoptosis, and myeloid cell homeostasis, were identified. Subsequently, lncRNAs with experimentally validated or strongly predicted regulatory associations with these immune pathways were screened.

2.2 Study Design and Participants

This case–control study evaluated the expression levels of two long non-coding RNAs (lncRNAs) in adults with laboratory-confirmed SARS-CoV-2 infection and in healthy, age- and sex-matched controls. A total of 50 patients with PCR-confirmed COVID-19 and 50 healthy controls were enrolled. Patients were recruited from Vali-asr Hospital (Fasa, Iran). Inclusion criteria included a positive RT-PCR result for SARS-CoV-2 and age $\geq$ 18 years. Individuals with autoimmune disorders, known malignancies, or recent immunosuppressive therapy were excluded.

2.3 Ethical Considerations

The study protocol received approval from the Ethical Committee on Scientific Research of Fasa University of Medical Sciences (FUMS), assigned ethical code IR.FUMS.REC.1399.097. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

2.4 Sample Collection and RNA Extraction

Peripheral blood (5 mL) was collected from each participant into EDTA tubes. Peripheral blood mononuclear cells (PBMCs) were isolated by density gradient centrifugation using Ficoll (Lymphodex, Inno-Train, Germany) in accordance with the manufacturer's instructions. Total RNA was subsequently extracted from isolated PBMCs with TRIzol reagent (Invitrogen, Thermo Fisher Scientific) and treated with DNase I (Thermo Scientific™ DNase I, RNase-free) to remove residual genomic DNA. RNA concentration and purity were assessed spectrophotometrically

using a NanoDrop instrument (Thermo Scientific); integrity was confirmed by agarose gel electrophoresis. Sample purity was evaluated using A_{260}/A_{280} ratios, with values between 2.0 and 2.2 considered indicative of high-quality RNA.

2.5 cDNA Synthesis

Complementary DNA (cDNA) was synthesized from 1 µg of total RNA using the Karmania Pars Gene reverse transcription kit (Cat. CN: KPG-cDNA, LN: KPG-cDNA) following the manufacturer's protocol. Reverse transcription reactions were performed in a final volume of 20 µL. Synthesized cDNA was stored at −20°C until use.

2.6 Quantitative Real-Time PCR (qRT-PCR)

Expression of the target lncRNAs *Morrbid* and *NeST* was quantified by quantitative real-time PCR (qRT-PCR) on an ABI StepOnePlus system using SYBR Green chemistry (SYBR Green master mix with High ROz™; Ampliqon, Cat. No. A325402-25). Primer specificity and amplicon identity were verified by melt-curve analysis, and amplification efficiency was evaluated using standard curve analysis. The specificity of the amplified products was further confirmed by agarose gel electrophoresis. All qRT-PCR reactions were performed in technical triplicates, and ACTB was used as the endogenous reference gene for normalization. The primer sequences used for RT-qPCR are listed in Table 1.

Each 15 µL PCR contained 7.5 µL of SYBR Green master mix, primers at a final concentration of 0.75 µM each, 1 µL of cDNA template, and nuclease-free water to reach the final volume. Thermal cycling comprised an initial denaturation at 95°C for 10 minutes, followed by 45 cycles of denaturation at 95°C for 20 seconds, annealing at 60°C for 30 seconds, and extension at 60°C for 30 seconds. Relative gene expression was calculated using the 2^−ΔΔCt method. ΔΔCt values are reported as mean ± standard deviation, whereas fold change values are reported as medians.

Table 1. Primer sequences used for reverse transcription and quantitative real-time PCR analysis of target lncRNAs and the reference gene

Genes		Sequence 5'-3'	Length
lncRNA NeST	FW	GAGGGGCCAGTTGGGAAAG	115

lncRNA NeST	RW	TTCTTAGGCCTCGGTTGCTT	
lncRNA Morrbid	FW	GAGGAAGTGGTGGCTATGAG	56
lncRNA Morrbid	RW	CCTTCATTCTCATTGGAACGAG	
ACTB	FW	TGGAACGGTGAAGGTGACAG	129
ACTB	RW	CTGTAACAACGCATCTCATATTTGG	

2.7 Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics, version 26 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed with the Shapiro–Wilk test. For comparisons of relative expression (ΔΔCt and fold-change values) between COVID-19 patients and healthy controls, independent-samples t-tests were used for normally distributed data; when normality was not met, the nonparametric Mann–Whitney U test was applied. Fold-change values were dichotomized at the cohort median into “high” and “low” expression groups for categorical analyses; associations between expression categories and clinical or demographic variables were evaluated by chi-square test or Fisher’s exact test, as appropriate. Continuous variables were compared between groups using independent-samples t-tests or Mann–Whitney U tests, as warranted by distributional assumptions. A two-tailed p-value < 0.05 was considered statistically significant for all tests.

3. Results

3.1 Elevated Expression of lncRNA Morrbid and lncRNA NeST in COVID-19 Patients

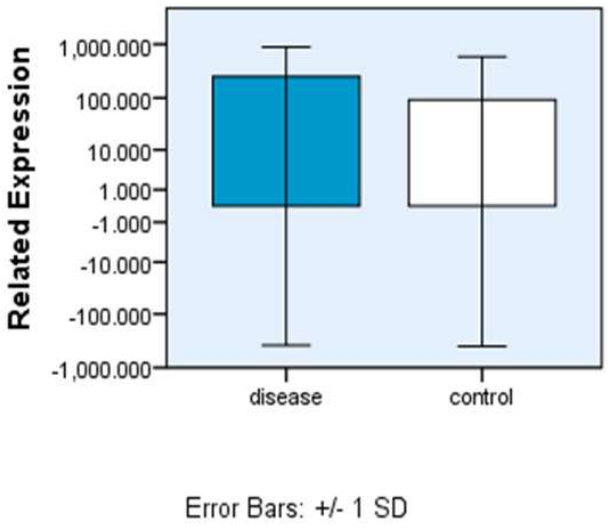
The expression levels of lncRNA Morrbid and lncRNA NeST were significantly upregulated in SARS-CoV-2 patients compared to healthy controls. Quantification by the 2^-ΔΔCt method revealed that the median fold change for lncRNA Morrbid in SARS-CoV-2 positive samples was 34.693, compared to 15.590 in the control group ($p = 0.008$). Likewise, the median fold change for lncRNA NeST was significantly higher in COVID-19 patients (252.172) versus controls (92.272, $p = 0.046$) (Table 2).

Table 2. Expression values and p-values for lncRNA Morrbid and NeST genes in two groups: SARS-CoV-2 patients and controls

lncRNA	Group								P-Value
	Patient				Control				
	No	median	mean	standard deviation	No	median	mean	standard deviation	
Morrbid	46	2.008	34.693	103.496	49	0.326	15.590	78.326	0.008
NeST	46	2.063	252.172	633.887	49	0.730	92.272	492.641	0.046

These findings were further supported by statistical validation using an independent-samples *t*-test. The expression profiles of Morrbid and NeST lncRNAs are shown in Figure 1A and Figure 1B, respectively. Both of which demonstrate a marked elevation in expression levels among SARS-CoV-2–infected individuals compared with the control group. To ensure the accuracy and reliability of the qRT-PCR results, primer specificity and amplification efficiency were thoroughly assessed. Melt curve and standard curve analyses confirmed the absence of nonspecific amplification and established optimal amplification efficiency for all target genes. Additionally, agarose gel electrophoresis verified the expected amplicon sizes for Morrbid, NeST, and ACTB, confirming the precision of the experimental procedure.

A



B

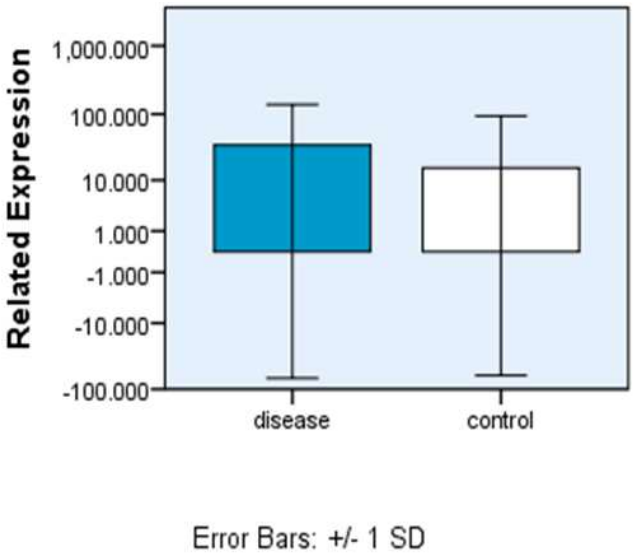


Fig. 1 Comparison of lncRNA expression levels between COVID-19 patients and healthy controls. **(A)** Relative expression of **lncRNA Morrbid** and **(B) lncRNA NeST** PBMCs, as determined by quantitative real-time PCR (qRT-PCR). Data are presented as mean ± standard deviation (SD). Both lncRNAs showed significantly higher expression in COVID-19 patients than in healthy controls.

3.2 Association of lncRNA Expression with Demographic and Clinical Pathological Variables

To determine whether lncRNA expression was influenced by demographic or clinical-pathological characteristics, participants were stratified by age, sex, blood group, and presence of underlying disease. Fold-change values were dichotomized into high- and low-expression groups on the basis of the median, and appropriate association tests were applied. Statistical analyses—including the independent t-test, the Mann-Whitney U test, and the chi-square test—indicated that neither lncRNA *Morrbid* nor lncRNA *NeST* expression was significantly associated with age ($p = 0.540$), sex ($p = 0.443$), or blood group ($p = 0.718$) (Table 3). Moreover, no significant correlation was observed between lncRNA expression and the presence of comorbid conditions such as cardiovascular disease or immunodeficiency.

Table 3. Relationship of gene expression with age, gender, underlying disease, and blood group

		Groups				P-Value
		Patient		**Control**		
		No	Percent	No	Percent	
Gender	M	28	60.9%	26	53.1%	0.443
	F	18	39.1%	23	46.9%	
Blood Group	A+	12	26.1%	13	26.5%	0.718
	A-	4	8.7%	6	12.2%	
	B+	9	19.6%	11	22.4%	
	Don't Know	3	6.5%	0	0.0%	
	O+	12	26.1%	12	24.5%	
	O-	3	6.5%	4	8.2%	
	AB+	3	6.5%	3	6.1%	
	AB-	0	0.0%	0	0.0%	
underlying disease	Doesn't have	41	89.1%	0	0.0%	
	Cardiovascular disease	4	8.7%	0	0.0%	
	immune deficiency	1	2.2%	0	0.0%	
Age		**mean**	**standard deviation**	**mean**	**standard deviation**	0.540

	41.43	13.737	43.31	15.735	

3.3 lncRNA Expression and COVID-19 Symptomatology

To investigate whether lncRNA expression varied according to clinical presentation, patients were classified by the presence or absence of common SARS-CoV-2 symptoms, including pyrexia, cough, dyspnea, fatigue, and gastrointestinal manifestations. Comparative analyses between symptomatic and asymptomatic individuals revealed no statistically significant differences in the expression patterns of either lncRNA under study (Table 4).

Table 4. Signs and information of symptomatic and asymptomatic SARS-CoV-2 patient groups

Signs		**Group**	
		Patients	
		No	**Column N %**
Pyrexia & tremor	no	21	45.7%
	yes	25	54.3%
Tussis	no	17	37.0%
	yes	29	63.0%
Dyspnea	no	20	43.5%
	yes	26	56.5%
Asthenia	no	13	28.3%
	yes	33	71.7%
Myalgia	no	16	34.8%
	yes	30	65.2%
Hyperesthesia	no	33	71.7%
	yes	13	28.3%
Pharyngitis	no	21	45.7%
	yes	25	54.3%
Rhinitis	no	35	76.1%

	yes	11	23.9%
Diarrhea	no	35	76.1%
	yes	11	23.9%
Gastrointestinal discomfort	no	38	82.6%
	yes	8	17.4%
Cephalalgia	no	21	45.7%
	yes	25	54.3%
Precordial Pain	no	24	52.2%
	yes	22	47.8%
Gastritis	no	27	58.7%
	yes	19	41.3%
Arthritis	no	25	54.3%
	yes	21	45.7%
Conjunctivitis	no	43	93.5%
	yes	3	6.5%
Fatigue	no	25	54.3%
	yes	21	45.7%

4. Discussion

In the present study, we investigated the expression levels of the immune-related long non-coding RNAs (lncRNAs) Morrbid and NeST in PBMCs from COVID-19 patients and healthy controls. Both lncRNAs were significantly upregulated in the COVID-19 group, demonstrating an association between their altered expression and SARS-CoV-2 infection. No significant associations were observed between the expression levels of either lncRNA and demographic or clinical characteristics, including age, sex, blood group, and underlying diseases. Although the functional significance of these expression changes remains to be established, our findings are consistent with accumulating evidence that immune-related lncRNAs are differentially expressed during viral infections. Therefore, Morrbid and NeST may represent candidate biomarkers associated with the host immune response to SARS-CoV-2 infection. However, given the observed

variability in gene expression, further validation in larger independent cohorts and complementary functional studies is required to confirm their biological and potential clinical significance.

The observed elevation in Morrbid expression may reflect its immunomodulatory role in regulating the lifespan and apoptosis of myeloid and T cells during viral infection. Earlier investigations have demonstrated that Morrbid expression is induced in $CD8^+$ T cells following viral challenge and type I interferon (IFN) signaling, thereby modulating cytotoxic T-cell activity and preventing excessive immune activation (14). In line with these observations, our results suggest that SARS-CoV-2 infection may trigger Morrbid expression as part of an antiviral mechanism aimed at balancing cytotoxic activity and cell survival throughout the course of infection. Similarly, the upregulation of the lncRNA NeST (IFNG-AS1) in COVID-19 patients is consistent with its established function in enhancing interferon-γ (IFN-γ) transcription and promoting antiviral cytokine production. NeST is predominantly expressed in $CD4^+$, $CD8^+$, and NK cells, where it facilitates immune activation by modulating chromatin structure at the IFNG locus (16). The increased NeST expression detected in this study may contribute to the hyperinflammatory state characteristic of severe COVID-19 by amplifying IFN-γ and other pro-inflammatory cytokines, including TNF-α and IL-8. This interpretation aligns with prior reports indicating that dysregulated lncRNA expression can exacerbate cytokine signaling and promote immune-mediated tissue injury in viral infections (17). Taken together, our findings highlight that both Morrbid and NeST are upregulated in the immune cells of COVID-19 patients and may serve as potential biomarkers for disease detection or for assessing immune activation status. Their consistent overexpression suggests an active involvement in the fine-tuning of immune cell function during SARS-CoV-2 infection, possibly through pathways associated with interferon signaling and T-cell regulation (18). Despite the valuable findings of this study, several limitations should be acknowledged. The relatively small sample size and the considerable inter-individual variability in the expression levels of Morrbid and NeST limit the generalizability of our findings and preclude definitive conclusions regarding their clinical utility. In addition, although differential expression was demonstrated by qRT-PCR, no complementary molecular or functional assays were performed to investigate the biological roles of these lncRNAs or to validate their regulatory effects on immune responses. Therefore, the present findings should be considered preliminary. Future studies involving larger, independent patient cohorts together with complementary experimental approaches are required to validate these observations, elucidate the

molecular mechanisms underlying Morrbid and NeST dysregulation, and determine their potential clinical significance.Overall, our findings demonstrate that lncRNA Morrbid and lncRNA NeST are significantly upregulated in the PBMCs of COVID-19 patients compared with healthy controls, indicating an association between their altered expression and SARS-CoV-2 infection. These results support the growing evidence that immune-related lncRNAs are dysregulated during viral infections and suggest that Morrbid and NeST may represent candidate biomarkers associated with the host immune response to COVID-19. Further validation in larger cohorts and functional studies will be essential to establish their biological relevance and potential clinical applicability.

5. Conclusion

In conclusion, the present study demonstrated that the expression levels of the immune-related long non-coding RNAs Morrbid and NeST were significantly elevated in peripheral blood mononuclear cells (PBMCs) from COVID-19 patients compared with healthy controls. These findings indicate that altered expression of these lncRNAs is associated with SARS-CoV-2 infection and further support the growing evidence that immune-related lncRNAs are dysregulated during viral diseases. Accordingly, Morrbid and NeST may represent candidate biomarkers associated with the host immune response to COVID-19. However, considering the observed variability in gene expression and the exploratory nature of this study, larger independent patient cohorts and complementary functional investigations are required to validate these findings, clarify the biological roles of these lncRNAs, and determine their potential clinical utility.

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