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Original Article

Association of Innate Immune Responses with SARS-CoV-2 Positivity in Children Under Five Years Old

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ABSTRACT

Introduction: The innate immune system detects viral RNA via *RIG-I* and *MDA5*, triggering type I interferon production. However, the effects of SARS-CoV-2 on these pathways in young children are still unclear. This study compared the expression of *RIG-I*, *MDA5*, *IFN-α*, and *IFN-β* between SARS-CoV-2-positive and SARS-CoV-2-negative children under five years of age with respiratory symptoms.

Materials and methods: This cross-sectional study included 138 children younger than five years who presented with respiratory symptoms, including fever, cough, and/or rhinorrhea, at Khanevadeh Hospital in Tehran, Iran, between April 6 and November 1, 2022. SARS-CoV-2 infection was identified using real-time reverse-transcription polymerase chain reaction (qRT-PCR) targeting the *E* and *RDRP* genes. The relative mRNA levels of *RIG-I*, *MDA5*, *IFN-α*, and *IFN-β* genes were measured using qRT-PCR, with GAPDH serving as the reference gene. The expression levels were then compared between children who tested positive and those who tested negative for SARS-CoV-2.

Results: Children who tested positive for SARS-CoV-2 had significantly higher *IFN-α* expression (0.06 ± 0.02 versus 0.04 ± 0.02) and significantly higher *MDA5* expression (3.03 ± 1.10 versus 1.98 ± 0.56) than those who tested negative. *IFN-β* expression did not differ significantly between the two groups (0.07 ± 0.06 versus 0.07 ± 0.08). The *RIG-I* expression was numerically higher in SARS-CoV-2-positive children, but the difference was not statistically significant.

Conclusion: In children under five years of age with respiratory symptoms, SARS-CoV-2 positivity was linked to higher *MDA5* and *IFN-α* expression, while *RIG-I* and *IFN-β* levels did not significantly differ between infected and uninfected participants. The current findings suggested that *MDA5*-related innate immune signaling may be involved in the early antiviral response to SARS-CoV-2 in young children.

1. Introduction

Coronaviruses are enveloped viruses with a positive-sense, single-stranded RNA genome that cause respiratory infections ranging from mild upper respiratory illness to severe lower respiratory disease[1]. The SARS-CoV-2, the virus that causes COVID-19, emerged in late 2019, spread rapidly worldwide, and led to a global pandemic[1]. Children often have milder illness than adults, but young children infected with SARS-CoV-2 can still develop a range of respiratory and

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systemic symptoms[2-3].

One important early defense against viral infection is the innate immune system. Intracellular pattern-recognition receptors sense viral RNA and activate signaling pathways that produce type I interferons and interferon-stimulated genes[4]. *Retinoic acid-inducible gene I* (*RIG-I*) and *differentiation-associated protein 5* (*MDA5*) are two main cytoplasmic sensors of viral RNA. The *RIG-I* and *MDA5* genes have different but complementary roles in recognizing viral RNA and starting antiviral responses[5]. Both genes belong to the *RIG-I*-like receptor family. Once viral RNA is detected, *RIG-I* and *MDA5* activate downstream signaling that drives production of type I interferons (IFN), including *IFN-α* and *IFN-β*[6]. Interferons then increase expression of interferon-stimulated genes, helping establish an antiviral state in infected cells and nearby tissues[6,7].

SARS-CoV-2 can affect several parts of the host innate immune response. Studies have found changes in IFN responses during SARS-CoV-2 infection, and the strength and timing of these responses may influence the clinical course and disease severity[8,9]. Still, the innate immune response to SARS-CoV-2 in young children remains poorly understood.

Animal models have been essential for elucidating the innate immune response to SARS-CoV-2 and other respiratory viruses. Studies in non-human primates, hamsters, and mice have demonstrated that *RIG-I* and *MDA5* play critical roles in detecting SARS-CoV-2 RNA and initiating IFN responses[10]. For instance, *MDA5*-deficient mice exhibited impaired interferon production and increased viral replication following coronavirus infection, highlighting the nonredundant role of *MDA5* in antiviral defense[11]. Similarly, animal studies have indicated that delayed or dysregulated IFN-α or β signaling correlated with severe disease outcomes, providing mechanistic insights that cannot be fully replicated in human studies[12]. These findings underscored the importance of *RIG-I*-like receptor signaling in controlling SARS-CoV-2 infection and suggested that similar pathways might be relevant in pediatric populations. However, translating these findings to young children requires direct investigation, as age-related differences in immune development may influence antiviral responses. To address this gap, the present study aimed to quantify *RIG-I*, *MDA5*, *IFN-α*, and *IFN-β* expression in symptomatic children under five years of age and to determine whether expression levels differed according to SARS-CoV-2 infection status.

2. Materials and Methods

2.1. Ethical approval

The present study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. The study protocol was reviewed and approved by the Research Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran. Ethical approval was granted under the code IR.TUMS.KHANEHVADEH.REC.1401.397.

2.2. Study design and population

This cross-sectional investigation enrolled 138 children under five years old who attended Khanevadeh Hospital in Tehran, Iran, from April 6 to November 1, 2022. To be included, children needed to have respiratory symptoms such as fever, cough, and/or rhinorrhea. Based on real-time reverse-transcription PCR kit(RT-PCR; GeneovA, Iran) results, participants were divided into two groups, including those who tested positive for SARS-CoV-2 (Group A) and those who tested negative for SARS-CoV-2, which were also considered the control group (Group B). Even though patients tested negative for SARS-CoV-2, they were enrolled because they had respiratory symptoms; thus, they did not represent a healthy, asymptomatic population.

2.3. Clinical specimen collection

Nasopharyngeal and nasal swab specimens were collected from each participant by trained healthcare personnel according to the WHO guidelines for the collection and transport of specimens for SARS-CoV-2 testing and the national COVID-19 specimen collection protocol issued by the Iranian Ministry of Health and Medical Education. Each swab was immediately placed into viral transport medium (VTM; Kiagene, Iran). The specimens were then transported to the Khanevadeh Hospital laboratory, Tehran, Iran, where all molecular testing was performed. Before testing, samples were kept at 2-8°C and processed within 24 hours of collection.

2.4. SARS-CoV-2 RNA extraction and detection

Viral RNA was isolated using the RNAjia extraction kit (Roje, Iran) following the manufacturer's protocol. To identify SARS-CoV-2, RT-PCR was carried out, targeting the *envelope* (*E*) and *RNA-dependent RNA polymerase* (*RdRp*) genes. The RNA was combined with a 25 μL PCR reaction mixture containing 12.5 μL amplification master mix, 0.5 μL (10 pmol) probe, and 1 μL (10 pmol) of each primer. The real-time PCR program included 35 minutes at 38°C and 15 minutes at 90°C, followed by 40 cycles of amplification. For the *E* gene, cycling conditions were 15 seconds at 94°C and 30 seconds at 57°C; for the *RDRP* gene, detection was performed for 30 seconds at 58°C, according to the manufacturer's protocol. The primer sequences were not disclosed owing to the manufacturer's proprietary and commercial confidentiality policy; the primers were used according to the manufacturer's instructions.

2.5. Quantitative RT-PCR

Quantitative real-time PCR (qRT-PCR) was used to quantify the expression of *RIG-I*, *MDA5*, *IFN-α*, and *IFN-β* genes, with *GAPDH* serving as the internal reference gene for normalization. Spearman correlation analysis was performed to examine associations among the expression levels of *RIG-I*, *MDA5*, *IFN-α*, and *IFN-β*.

2.6. Statistical analysis

All statistical analyses were performed using GraphPad Prism version 8 (USA). The normality of the data was assessed using the Shapiro-Wilk test. Because the gene expression data were not normally distributed, between-group comparisons of *RIG-I*, *MDA5*, *IFN-α*, and *IFN-β* expression levels between SARS-CoV-2-positive and SARS-CoV-2-negative children were performed using the Mann-

Whitney U test. Data were presented as mean ± standard deviation (SD). Between-group comparisons of *RIG-I*, *MDA5*, *IFN-α*, and *IFN-β* gene expression levels were performed using the Mann-Whitney U test in GraphPad Prism version 8. A two-sided p-value less than 0.05 was considered statistically significant.

3. Results

The study enrolled 138 children under five years of age. Real-time RT-PCR confirmed SARS-CoV-2 infection in 22 participants (15.9%); 14 were female, and 8 were male. Five children with SARS-CoV-2 infection were hospitalized, while the remaining 17 received outpatient care. The most commonly reported symptoms were cough, fever, and rhinorrhea. A smaller proportion of children (13.63%) had gastrointestinal symptoms, such as diarrhea and nausea (Table 1).

Table 1. Demographic characteristics of children aged under five years sampled from Khanevadeh Hospital in Iran, in 2022

Symptoms and their population (%)		Gender		Total participants
Cough	n = 5 (22.72%)			
Diarrhea	n = 3 (13.63%)	Male	8 (5.79%)	
Nausea	n = 2 (9.09%)			138
Cough and fever	n = 7 (31.81%)	Female	14 (10.14%)	
Runny nose	n = 5 (22.72%)			

n: number of children that show the symptoms. Symptom percentages were calculated using the number of SARS-CoV-2-positive children (n = 22) as the denominator. Gender percentages were calculated using the total study population (n = 138) as the denominator.

3.1. IFN-α expression

The *IFN-α* expression differed significantly ($p < 0.05$) between participants who tested positive and those who tested negative for SARS-CoV-2, with higher expression in Group A (0.06 ± 0.02) than in Group B (0.04 ± 0.02; $p < 0.05$; Figure 1).

3.2. IFN-β expression

Mean *IFN-β* expression was similar in Group A (0.07 ± 0.06) and Group B (0.07 ± 0.08), and the difference between groups was not statistically significant ($p > 0.05$; Figure 1).

3.3. RIG-I expression

The *RIG-I* expression was 5.14 ± 3.17 among participants who tested negative for SARS-CoV-2 (Group B) and 0.07 ± 0.06 among those who tested positive (Group A). Although the mean values appeared to differ, the difference was not statistically significant ($p > 0.05$; Figure 1).

3.4. MDA5 expression

The *MDA5* expression was higher in participants in Group A (3.03 ± 1.10) than in those in Group B (1.98 ± 0.56); however, the difference was not statistically significant ($p > 0.05$). Among the genes examined, *MDA5* indicated the largest difference between the two groups (Figure 1).

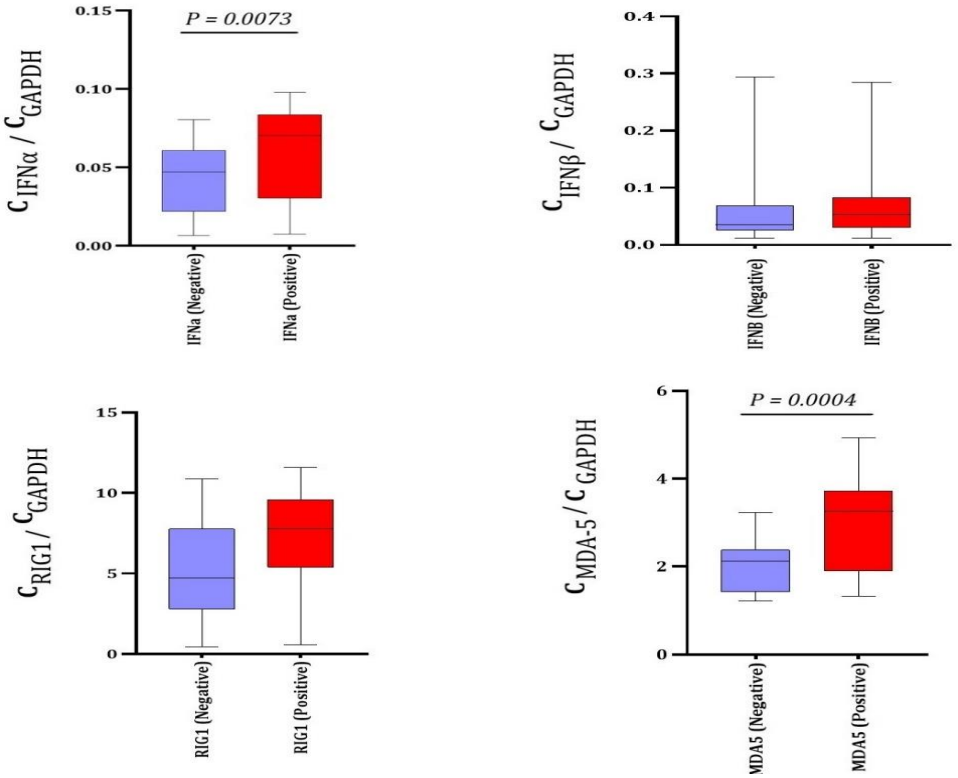


Figure 1. Expression of *RIG-1*, *MDA-5*, *IFN-α*, and *IFN-β* genes in children aged under five years sampled from Khanevadeh Hospital, Tehran, Iran, in 2022

3.5. Correlation analysis

A significant positive correlation was found between *RIG-1* and *IFN-α* expression (Spearman's rho = 0.440, p = 0.046), suggesting that these two markers tend to increase together (Table 2). In contrast, no significant correlations were observed between *IFN-β* and either *RIG-1* (rho = -0.261, p = 0.253) or *MDA5* (rho = 0.268, p = 0.241), nor between *MDA5* and *RIG-1* (rho = -0.142, p = 0.540) or *IFN-α* (rho = -0.044, p = 0.849). The *IFN-α* and *IFN-β* were also uncorrelated (rho = 0.039, p = 0.867).

Table 2. Correlation of *RIG-1*, *MDA-5*, *IFN-α*, and *IFN-β* genes in children aged under five years sampled from Khanevadeh Hospital, Tehran, Iran, in 2022

Parameters	*IFN-α*	*IFN-β*	*RIG-1*	*MDA5*
IFN-α				-0.044
IFN-β			0.440	0.849
		0.039	0.046	0.268
	1.000	0.867	-0.261	0.241
RIG-1		1.000	0.253	-0.142
			1.000	0.540
MDA5				1.000

IFN-α: *Interferon alfa*, *IFN-β*: *Interferon beta*, *RIG-1*: *Retinoic acid-inducible gene 1*, *MDA5*: *Anti-Melanoma Differentiation-Associated gene 5*. Spearman correlation analysis was performed to examine associations among the expression levels of *RIG-I*, *MDA5*, *IFN-α*, *and IFN-β*.

4. Discussion

The present study examined the expression of selected innate immune genes in children under five years of age, grouped by their SARS-CoV-2 infection status. The main results indicated that children who tested positive for SARS-CoV-2 had notably higher *MDA5* and *IFN-α* expression, while *IFN-β* and *RIG-I* demonstrated no significant differences. The higher *MDA5* expression in SARS-CoV-2-positive participants was biologically plausible, since *MDA5* acts as a cytoplasmic detector of viral RNA. After viral RNA is detected, *MDA5* can activate signaling pathways that help trigger antiviral interferon responses[5]. Nahavandi-Parizi et al.[13] reported downregulation of *RIG-I* and *IPS-1* in patients with severe COVID-19. Although disease severity differed, this finding was broadly consistent with *RIG-I*-like receptor signaling and the higher *MDA5* expression observed among SARS-CoV-2-positive children in the present study.

The increased expression of *IFN-α* was consistent with the activation of IFN antiviral responses during viral infection[14]. However, because the present study used a cross-sectional design, the results indicated a link between SARS-CoV-2 positivity and changes in gene expression, rather than proving a direct causal link between SARS-CoV-2 infection and these changes in gene expression. By contrast, *IFN-β* expression was similar in the positive and negative groups, with no notable difference. Thus, the present results should not be taken as evidence that SARS-CoV-2 infection suppresses or lowers *IFN-β* expression in young children[14-17].

Earlier studies have reported wide variation in interferon responses during SARS-CoV-2 infection[18,19]. The differences may be due to several factors, including age, how severe the disease was, viral load, when samples were collected, where samples were taken, host features, and differences in study methods[19]. The present study provided further insight into the innate immune response in young children with symptoms. However, the relatively small number of SARS-CoV-2-positive participants limited the strength and generalizability of the conclusions.

The increased *MDA5* and *IFN-α* expression observed in SARS-CoV-2-positive children in the present study aligned with findings from laboratory animal models that have established the importance of *RIG-I*-like receptor signaling in coronavirus recognition[20]. In the context of SARS-CoV-2 specifically, Huang et al.[21] have demonstrated that the *RIG-I*-like receptor signaling pathway is broadly upregulated in the lungs of infected mouse models. Furthermore, research using K18-hACE2 mice has demonstrated that synthetic *RIG-I* agonists drastically reduce viral replication in both the upper and lower airways, and prophylactic treatment substantially decreases morbidity and mortality[22]. The finding that *RIG-I* ligands confer greater protection than recombinant IFN alone suggested that direct activation of innate immune sensing receptors may induce a broader antiviral effector profile[22]. These findings in children, elevated *MDA5* and *IFN-α* in those with SARS-CoV-2, were consistent with animal data and support the translational relevance of these pathways in the pediatric antiviral response. Syrian golden hamster models have further contributed to this understanding, reporting remarkable induction of interferon-stimulated genes upon SARS-CoV-2 infection, while interferon administration has been shown to restrict viral replication and improve lung pathology[23]. Studies using murine coronavirus models, such as mouse hepatitis virus (MHV), have demonstrated that *MDA5* was critical for inducing IFN transcription in infected cells[24]. Notably, *MDA5*-deficient mice demonstrated more severe disease, reduced survival, and increased viral spread after coronavirus infection, despite similar viral replication in target organs, suggesting that *MDA5* signaling helps regulate pathological inflammatory responses[20].

5. Conclusion

The SARS-CoV-2 positivity was associated with higher expression of *MDA5* and *IFN-α* in symptomatic children younger than five years of age, while no significant differences were observed in *IFN-β* or *RIG-I* gene expression. The current findings suggested that *MDA5*-mediated innate immune signaling may play an important role in the host response to SARS-CoV-2 in young children. Nevertheless, given the cross-sectional nature of the study, the observed relationships should be iFinalnterpreted as associations rather than as evidence of a direct causal effect of SARS-CoV-2 infection on host gene expression. Limitations of the present study included using a symptomatic rather than healthy control group, lacking viral load or Ct data, and measuring mRNA only, without protein or functional assessment. Further studies with larger cohorts and longitudinal sampling are needed to investigate respiratory co-infections, measure viral loads, and assess protein-level and functional immune responses. These studies can clarify how *MDA5* and interferon pathways contribute to SARS-CoV-2 infection.

Declarations

Authors' contributions

Samira Asli and Nafiseh Taheri contributed to study conception and design, sample collection, and molecular analysis. Maryam Dehghani Firoozabadi contributed to data analysis and interpretation. Hannaneh Askari contributed to sample collection and laboratory processing. Arastoo Vojdani contributed to RNA extraction and qRT-PCR experiments. Elham Babaei contributed to statistical analysis and preparation of tables and figures. Sajjad Asli contributed to literature review and drafting of the manuscript. Mohammad Reza Shahami contributed to clinical data collection and patient recruitment. Saeid Amel Jamehdar contributed to study supervision, project administration, and critical revision of the manuscript. All authors read and approved the final edition of the manuscript.

Availability of data and materials

All data synthesized in the present study are derived from the cited publications and sources listed in the manuscript.

Competing interests

The authors declared no conflicts of interest.

Ethical considerations

The present study has not been submitted elsewhere; also, plagiarism and data integrity were checked by the authors. No AI tool was used during the writing of the present manuscript. The authors take full responsibility for the accuracy, originality, and integrity of the final manuscript before submission, after primary acceptance, and publication.

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