

Role of Growth Hormone and Insulin-Like Growth Factor-I in Modulating Disease Severity in Children with COVID-19 and Multisystem Inflammatory Syndrome

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Introduction: Multiple factors have been reported to influence both the acute clinical course of SARS-CoV-2 infection (COVID-19) and the risk of developing multisystem inflammatory syndrome in children (MIS-C), including age, sex, ethnicity, comorbidities, and genetic susceptibility. However, additional immunomodulatory influences, including the somatotrophic axis – comprising growth hormone (GH) and insulin-like growth factor-1 (IGF-1) – may also contribute to variations in disease susceptibility and severity. This study aimed to explore the potential role of GH and IGF-1 in the clinical course of COVID-19 and MIS-C.

Patients and Methods: A cohort study was conducted in Ukraine from 2021 to 2023. This study analyzed GH and IGF-1 levels in 90 children aged 1 month to 17 years: 63 with COVID-19, 15 with MIS-C, and 12 healthy non-infected by SARS-CoV-2 peers. Hormone levels were measured using an enzyme-linked immunosorbent assay (ELISA).

Results: GH levels were within the age- and sex-specific reference ranges in all children. However, children in the MIS-C group had significantly lower GH levels than those in the healthy control group. Overall, 27 (30%) patients exhibited reduced IGF-1 levels. The frequency of low IGF-1 increased with disease severity: 12.5% (mild), 25% (moderate), 53.3% (severe COVID-19), and 66.7% (MIS-C). Reduced GH levels correlated with elevated CRP and ferritin levels, neutrophilia, lymphopenia, and increased neutrophil-to-lymphocyte ratio. Low IGF-1 levels were associated with higher levels of CRP, procalcitonin, ferritin, ESR, and IL-6. A GH level <0.54 ng/mL increased the risk of severe COVID-19 by 2.05-fold (AUC = 0.656, 95% CI [0.49–0.83], $p = 0.058$), while a level <0.465 ng/mL was associated with MIS-C (AUC = 0.742, 95% CI [0.64–0.85], $p = 0.003$). An IGF-1 level <52.5 ng/mL showed a trend toward severe COVID-19 (AUC = 0.591, 95% CI [0.44–0.74], $p = 0.270$), whereas <44.1 ng/mL predicted MIS-C (AUC = 0.838, 95% CI [0.72–0.95], $p < 0.001$).

Conclusion: Understanding how GH and IGF-1 influence the pediatric immune system is crucial for anticipating the progression of infectious diseases such as COVID-19 and MIS-C. Their immunomodulatory roles should be considered not only in children with GH deficiency but also in previously healthy patients during clinical monitoring.

Keywords: growth hormone, insulin-like growth factor-1, COVID-19, MIS-C, children

Introduction

Multiple factors have been reported to influence both the acute clinical course of SARS-CoV-2 infection (COVID-19) and the risk of developing multisystem inflammatory syndrome in children (MIS-C), including age, sex, ethnicity, comorbidities, and genetic susceptibility. Collectively, these determinants shape the host immune response to infectious pathogens.^{1–3} Recent multicenter pediatric data have shown that clinical and laboratory parameters, such as shortness of breath, anemia, elevated C-reactive protein, and the presence of comorbidities, are key determinants of COVID-19 severity and mortality in children.⁴ This evidence highlights the importance of exploring additional biological modulators that may further influence the disease course in the pediatric population.

Multisystem inflammatory syndrome in children (MIS-C) is a delayed, post-infectious consequence of SARS-CoV-2 infection and is regarded as a remote immunological phenomenon driven by dysregulated inflammation.^{5,6} It is characterized by persistent fever and multisystem involvement, including mucocutaneous manifestations, cardiovascular dysfunction, gastrointestinal symptoms, coagulopathy, and markedly elevated inflammatory markers in the absence of alternative causes of inflammation.^{7,8} Given the systemic nature of MIS-C and the tropism of SARS-CoV-2 for endocrine tissues, investigating endocrine dysfunction in children with MIS-C is particularly important.

In this context, and in view of the need to identify novel biomarkers of disease severity in both acute SARS-CoV-2 infection and its delayed sequelae, such as MIS-C, the somatotrophic axis, especially growth hormone (GH) and insulin-like growth factor-1 (IGF-1), has attracted growing interest.^{9–13} Given the physiological variability of these hormones during childhood, it is particularly important to investigate their impact as modulators of the immune response and potential regulators of the course of viral infections such as COVID-19. Age-dependent differences also involve adaptive immunity, including both T- and B-cell responses. In children, T-cell immunity is characterised by a more diverse repertoire of $\gamma\delta$ T cells and active mucosal T-cell responses in the pharyngeal lymphoid tissues during SARS-CoV-2 infection. Additionally, B-cell maturation in childhood follows distinct developmental trajectories, resulting in differences in antibody production and mucosal IgA activity.¹⁴ Because GH and IGF-1 significantly influence the functions of immune organs and immune system cells, these hormonal pathways may interact with age-specific immune maturation and contribute to the variability in COVID-19 and MIS-C presentation in children.

Growth hormone exerts its effects through the growth hormone receptor, which belongs to a large family of more than 30 cytokine receptors, including the prolactin (PRLR), erythropoietin (EPOR), thrombopoietin (TPOR), granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor, and notably the interleukin-6 (IL-6) receptor.¹⁵ GH can directly affect target cells or indirectly, in particular through IGF-1. Receptors of these polypeptides are expressed on a wide range of immune cells, including T and B lymphocytes, natural killer (NK) cells, monocytes, neutrophils, and macrophages. They are also present in the bone marrow, thymus, spleen, and lymph nodes, highlighting their crucial role in regulating the immune response to infectious diseases.¹² It has been established that GH plays a vital role in regulating the development of myeloid and lymphoid cells, particularly by promoting the proliferation and functional activation of T cells, B cells, NK cells, and macrophages. This, in turn, influences their antigen response and antibody production.¹² Additionally, through IGF-1, GH stimulates the proliferation of immune cells, reduces apoptosis, and enhances the antiviral immune response.¹⁶ Accordingly, the somatotrophic axis influences immune cell function and cytokine signaling, thereby contributing to the maintenance of immune homeostasis. Deviations in circulating GH and IGF-1 levels may change this balance and modify the host response to pathogens, including SARS-CoV-2. Studies involving adult patients have demonstrated that reduced levels of both IGF-1 and GH are associated with lung injury related to lower respiratory tract involvement in COVID-19, regardless of age and sex.¹⁷ Additionally, decreased IGF-1 has been associated with conditions such as acute respiratory distress syndrome, acute lung injury, and other inflammatory respiratory diseases, highlighting its significance in the development of coronavirus infections.^{18,19}

However, most of the existing studies have primarily focused on adult populations. In children, research on the immunomodulatory role of GH and IGF-1 has been limited to cases with diagnosed GH deficiency. Therefore, our study aimed to investigate the potential immunomodulatory effects of GH and IGF-1 on the course of COVID-19 in children, which is particularly relevant due to the age-related variability of these hormones and the diverse clinical manifestations of SARS-CoV-2 infection. Within this context, our objectives were to: 1) compare serum GH and IGF-1 levels in children with COVID-19, MIS-C, and healthy controls; 2) analyse the associations between GH and IGF-1 levels and markers of systemic inflammation and hematologic profiles; and 3) evaluate the discriminatory performance of GH and IGF-1 for severe COVID-19 and MIS-C using receiver operating characteristic (ROC) analysis.

Materials and Methods

A cohort study was conducted during the COVID-19 pandemic from 2021 to 2023 in pediatric hospitals in Ternopil, Ukraine. An a priori sample size calculation was performed using G*Power (version 3.1.9.7). For a one-way ANOVA (fixed effects, omnibus) comparing three groups (COVID-19, MIS-C, control), assuming a large effect size (Cohen's $f =$

0.40), a two-sided $\alpha = 0.05$, and 80% power, the required total sample size was 66 participants. The planned recruitment target was set to meet or exceed this threshold.

All study participants were included after obtaining written informed consent from their parents or guardians. This research was conducted in accordance with the principles of the Declaration of Helsinki (2024 edition).²⁰ The study was carried out within two consecutive institutional research projects, each approved by the Institutional Ethics Committee: Protocol No. 61 (approved on November 30, 2020) and Protocol No. 71 (approved on October 25, 2022). These approvals covered the respective stages of participant enrolment and data collection conducted between 2021 and 2023.

A total of 102 children were included in the study. The inclusion criteria for each group were as follows: 1) COVID-19 group: laboratory-confirmed SARS-CoV-2 infection by PCR or antigen testing; 2) MIS-C group: MIS-C diagnosed based on the World Health Organisation (WHO) criteria, as described below; and 3) control group. The control group consisted of children attending the same hospitals for routine examinations. These controls had no clinical signs of acute infection at the time of sampling and tested negative for SARS-CoV-2. It is important to note that all children included in the study were unvaccinated against SARS-CoV-2.

Twelve children were excluded from further investigation of the role of GH and IGF-1 due to the presence of exclusion criteria. These criteria included a previously established diagnosis of growth hormone deficiency (documented prior to the current admission), irrespective of ongoing GH replacement therapy, a previously diagnosed endocrine disorder, genetic diseases, chronic systemic diseases, oncological diseases, nutritional status disorders (malnutrition, overweight, or obesity), history of trauma or surgical interventions within the last 3 months before inclusion in the study, and absence of informed consent from the child's parents/guardians.

Ultimately, a total of 90 children, aged 1 month to 17 years, were included in the analysis of GH and IGF-1 levels. This group consisted of 63 infected children with SARS-CoV-2, 15 diagnosed with MIS-C, and 12 in the control group who were not infected with SARS-CoV-2. The demographic characteristics of the children included in the study are presented in Table 1. No statistically significant differences in age distribution were observed among the study groups; however, male sex was significantly more prevalent in the MIS-C group.

The severity of COVID-19 was assessed according to the World Health Organisation (WHO) recommendations.²¹ Mild disease was defined as the presence of clinical symptoms of COVID-19 without signs of pneumonia or hypoxia. Moderate severity was characterised by pneumonia symptoms (fever, cough, dyspnea, tachypnea, and chest indrawing) with a $\text{SpO}_2 \geq 90\%$ on room air. Severe disease was diagnosed in cases of severe pneumonia with the development of respiratory distress syndrome, SpO_2 of $< 90\%$ while breathing room air, or the appearance of danger signs such as impaired consciousness, seizures, and refusal to eat or drink. Pneumonia was defined by clinical features of lower respiratory tract disease and was confirmed by chest imaging (lung ultrasound or chest X-ray). Children without lung

Table 1 Demographic Characteristic of Patients with COVID-19 and MIS-C Involved in the Study

Group		Age, Years	Sex, n (%)	
			Male	Female
COVID-19	Mild n=24	3.50 (1.30; 9.00)	12 (50.00)	12 (50.00)
	Moderate n=24	3.05 (0.80; 9.00)	18 (75.00)	6 (25.00)
	Severe n=15	13.00 (2.00; 16.00)	7 (46.67)	8 (53.33)
MIS-C n=15		9.00 (2.00; 11.80)	13 (86.67)	2 (13.33)
Control group n=12		9.50 (4.00; 14.00)	5 (41.67)	7 (58.33)
		H = 9.40; $p = 0.052$	$\chi^2 = 10.54$; $p = 0.032^*$	

Note 1. * – a statistically significant result ($p < 0.05$).

Abbreviations: MIS-C, multisystem inflammatory syndrome in children; H, Kruskal–Wallis test statistic and p – level of its significance; χ^2 , p , Pearson Chi-square test and its significance level.

involvement were those who did not exhibit clinical signs of lower respiratory tract disease and did not have imaging evidence of pneumonia. Based on these criteria, 24 children had mild COVID-19, 24 had moderate disease, and 15 had severe COVID-19.

The diagnosis of MIS-C was established based on the WHO criteria,⁷ which included: patient age from 0 to 19 years, fever lasting ≥ 3 days, and the presence of at least two of the following: skin rash or bilateral non-purulent conjunctivitis or other signs of skin and mucosal inflammation; arterial hypotension or shock; heart involvement (myocarditis, pericarditis, valvular disease, coronary artery abnormalities, elevated troponin or NT-proBNP); coagulopathy (elevated D-dimer, prothrombin time or APTT); and acute gastrointestinal symptoms (diarrhea, vomiting, abdominal pain). Mandatory conditions included laboratory evidence of systemic inflammation (elevated ESR, C-reactive protein, or procalcitonin), exclusion of other causes of inflammation (including bacterial sepsis, staphylococcal or streptococcal toxic shock syndrome), and confirmation of SARS-CoV-2 infection (positive PCR, antigen test, serological detection of antibodies) or documented close contact with a COVID-19 patient within the preceding 4 weeks.

Fasting morning venous blood sampling was performed within the first 24 hours after the patient's hospitalisation and before the initiation of therapy. The samples were collected in plain red-top venipuncture tubes without anticoagulant, clotted at room temperature up to 1 hour, and then centrifuged at $1,000 \times g$ for 15–20 minutes at 2–8°C to separate the serum. The serum was stored at –20°C up to 1 month in polypropylene tubes, as recommended by the manufacturers. Before each ELISA run, frozen samples were thawed once at 2–8°C, mixed, and centrifuged to remove any precipitates. For each assay run, a calibration (standard) curve was generated on the corresponding microplate, and serum concentrations of all studied parameters (GH, IGF-1, C-reactive protein, ferritin, procalcitonin, and IL-6) were obtained by interpolating sample optical density values from the respective standard curve. According to the manufacturer's documentation, the coefficients of variation for both intra- and inter-assay were within acceptable limits.

Growth hormone and IGF-1 were determined using the immunoenzymatic test systems – hGH AccuBind ELISA Kit (Cat. No: 1725–300) (Monobind Inc., USA) and Human IGF-1 (Insulin-like Growth Factor 1) ELISA Kit (Cat. No: E-EL-H0086) (Elabscience, USA). To assess inflammation markers, the following test systems were used: Human CRP (C-Reactive Protein) ELISA Kit (Cat. No: E-EL-H0043) (Elabscience, USA), Human PCT (Procalcitonin) ELISA Kit (Cat. No: E-EL-H1492) (Elabscience, USA), Ferritin AccuBind ELISA Kit (Cat. No: 2825–300A) (Monobind Inc., USA), and Human IL-6 (Interleukin 6) ELISA Kit (Cat. No.: E-EL-H6156) (Elabscience, USA). All children underwent a complete blood count to determine the leukocyte formula parameters and erythrocyte sedimentation rate (ESR) as markers of systemic inflammation.

Statistical analysis was performed using GraphPad Prism 8.4.3 and Statistica 13.0 software (StatSoft Inc., Tulsa, Oklahoma, USA). All quantitative indicators were analysed for normal distribution using the Shapiro–Wilk *W*-test and by constructing distribution histograms. Due to the absence of a normal distribution, quantitative laboratory indicators are presented as the median and interquartile range (the lower and upper quartiles). Quantitative values were compared using the Kruskal–Wallis test. To study the relationships between indicators, correlation analysis was performed using Spearman's coefficient and the calculation of the 95% confidence interval (CI). Prognostic factors were assessed using multivariable logistic regression, with adjustment for age and sex when estimating the associations of GH and IGF-1 with the outcomes of severe COVID-19 and MIS-C. To determine the diagnostically significant threshold values, receiver operating characteristic (ROC) analysis was performed, involving the construction of an ROC curve and the determination of the cut-off value. For each outcome (severe COVID-19 and MIS-C), ROC curves were constructed for serum GH and IGF-1 levels. The following parameters were calculated: area under the ROC curve (AUC), standard error, 95% CI, and *p*-value, as well as the optimal cut-off value with the corresponding sensitivity (Sn), specificity (Sp), 95% CI for sensitivity and specificity, and the likelihood ratio. The level of statistical significance was set at $p < 0.05$.

Results

GH and IGF-I Levels According to Disease Severity

A comparative analysis was conducted to examine the levels of growth hormone and insulin-like growth factor-1 in children with COVID-19, MIS-C, and healthy peers. The study found that the growth hormone levels in all children

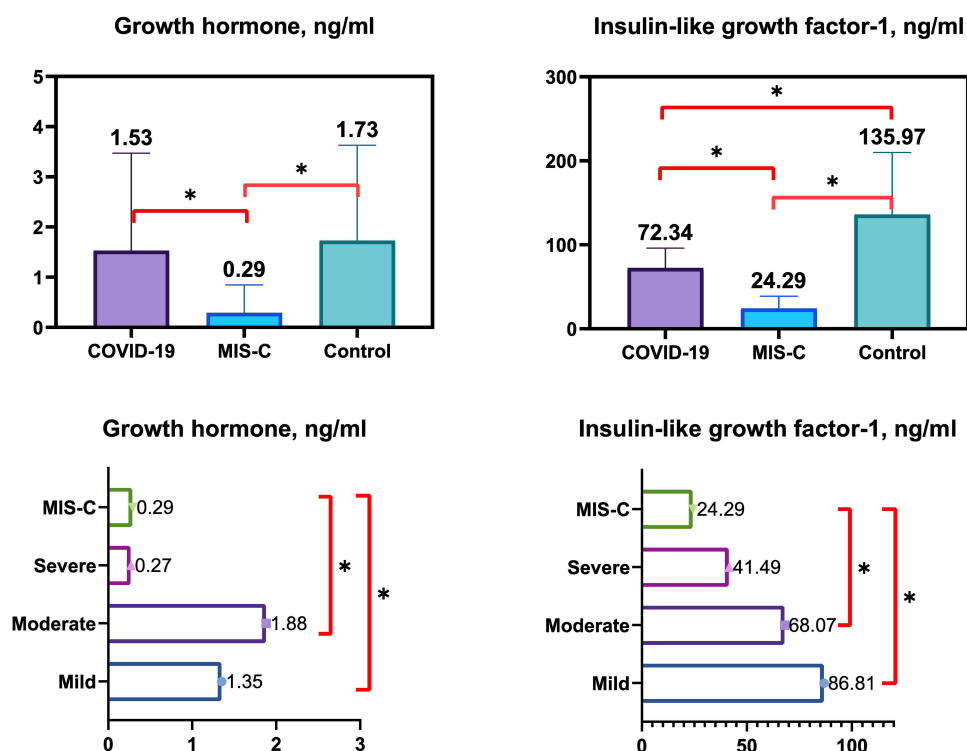


Figure 1 Growth hormone and insulin-like growth factor-I levels in children with COVID-19 and MIS-C.
Note: Red brackets]* indicate statistically significant differences between groups ($p < 0.05$).

included in the study corresponded to the reference values according to age and sex. However, 27 children (30%) had lower levels of IGF-1 compared to the reference values. This decrease in IGF-1 level was not observed in healthy children. The frequency of low IGF-1 levels increased with disease severity: 12.5% in mild cases, 25% in moderate cases, 53.33% in severe cases, and 66.67% in MIS-C ($\chi^2=22.42$, $p < 0.001$).

A comparison of GH levels between the children with COVID-19 and the control group did not show any significant differences. However, in the MIS-C group, GH levels were significantly lower (0.29 [0.10; 0.88] ng/mL) than those in the control group (1.73 [0.64; 3.63] ng/mL) ($p = 0.021$). Additionally, both SARS-CoV-2-infected groups had substantially lower IGF-1 levels than healthy controls (Figure 1).

In children with acute coronavirus infection, regardless of the severity, the growth hormone level was significantly higher than in those with MIS-C – 1.53 (0.26; 3.59) versus 0.29 (0.10; 0.88) ng/mL ($p = 0.014$). It is worth noting that in children with MIS-C, the IGF-1 level was three times lower (24.29 (16.41; 38.83) ng/mL) compared to those with acute COVID-19 infection (72.34 (39.15; 96.01) ng/mL) ($p = 0.002$) (Figure 1). This between-group comparison was unadjusted for age and sex.

Analysis of GH and IGF-1 levels in relation to the severity of COVID-19 did not reveal any significant differences between groups with mild, moderate, and severe disease courses. However, pediatric patients with mild and moderate courses of coronavirus infection had significantly higher levels of both GH and IGF-1 than patients with MIS-C. Although MIS-C represents a distinct clinical entity, GH concentrations in severe acute COVID-19 were similar to those measured in MIS-C (Figure 1).

Age- and Sex-Specific Patterns of GH and IGF-I in Pediatric COVID-19 and MIS-C

Further analysis of age-specific characteristics revealed that in older children (12–17 years), the level of growth hormone decreased significantly compared to that in preschool-aged children (2–5 years) infected with SARS-CoV-2. These comparisons reflect absolute measured serum concentrations of GH and IGF-1 within predefined age categories (Table 2) and were not normalised to age-specific reference values, as all GH measurements remained within the corresponding

Table 2 Age and Sex Differences in Growth Hormone and Insulin-Like Growth Factor-I in Children with COVID-19 and MIS-C

Parameter	GH, ng/mL		IGF-I, ng/mL	
Periods of childhood	COVID-19	MIS-C	COVID-19	MIS-C
Infancy (A)	2.25 (1.17; 3.59)	–	56.43 (42.31; 97.02)	–
Toddler (B)	1.60 (0.77; 3.12)	0.24 [#] (0.10; 0.37)	52.58 (17.06; 87.72)	27.70 (14.68; 29.55)
Early childhood (C)	2.51 (0.84; 4.11)	0.10 [#] (0.09; 0.11)	66.59 (36.66; 91.85)	16.41 [#] (13.94; 36.74)
Middle Childhood (D)	0.85 (0.11; 1.89)	0.64 (0.29; 1.09)	87.65 (74.27; 97.94)	23.54 [#] (17.87; 42.72)
Early adolescence (E)	0.55 ^C (0.09; 1.54)	0.74 (0.18; 1.59)	94.02 (40.59; 106.49)	38.83 [#] (24.02; 41.49)
H, p	H = 10.45; p = 0.033	H = 5.06; p = 0.168	H = 6.18; p = 0.186	H = 1.96; p = 0.581
Sex				
Male	1.73 (0.27; 2.81)	0.29 (0.10; 0.88) [#]	69.55 (39.15; 96.01)	24.02 (16.41; 29.55) [#]
Female	1.17 (0.26; 3.91)	0.28 (0.18; 0.39) [#]	78.21 (39.70; 95.36)	76.52 ^M (38.83; 114.20)

Note: [#] – a statistically significant result comparing the COVID-19 group and MIS-C group ($p < 0.05$). ^{A, B, C, D, E} – a statistically significant result between age groups inside one group (COVID-19 or MIS-C) ($p < 0.05$). ^M – a statistically significant result between males and females inside one group (COVID-19 or MIS-C) ($p < 0.05$).

Abbreviations: GH, growth hormone; IGF-I, insulin-like growth factor-I; MIS-C, multisystem inflammatory syndrome in children; H, Kruskal–Wallis test statistic and p, level of its significance.

reference ranges. Notably, this age-related pattern was not observed in the MIS-C group. It is essential to highlight that in the presence of MIS-C, the GH level in children aged 1–5 years was significantly lower than the values obtained during acute SARS-CoV-2 infection. IGF-1 levels were significantly lower in MIS-C than in COVID-19 in children over 2 years of age. However, no age-related differences in IGF-1 levels were observed between the COVID-19 and MIS-C groups (Table 2).

The levels of GH and IGF-1 did not differ significantly between male and female with coronavirus infection. However, in cases of MIS-C, the IGF-1 level in males was significantly lower than that in females, and it also significantly decreased compared with levels observed during acute SARS-CoV-2 infection (Table 2).

Multivariable Analysis of the Predictive Value of GH and IGF-I for Severe COVID-19 and MIS-C

Given the established differences in GH and IGF-1 levels in various courses of COVID-19 and MIS-C, as well as the sex and age-related characteristics of their concentrations, logistic regression analysis was conducted to assess the role of these three predictors in the development of severe COVID-19 and MIS-C in children. The analysis revealed that there was no isolated relationship of growth hormone on the severity of COVID-19 when considering the patient's age and sex. However, male sex (OR = 0.17; 95% CI 0.03–0.87; $p = 0.036$) and lower growth hormone levels (OR = 0.35; 95% CI 0.16–0.76; $p = 0.009$) were found to be independent predictors of MIS-C development in children. Logistic regression models with three independent variables (age, sex, and IGF-1) were used to evaluate the impact of IGF-1 on the severity of COVID-19 and MIS-C. The results were statistically significant: $\chi^2 = 11.28$, $p = 0.010$ for severe COVID-19 and $\chi^2 = 14.29$, $p = 0.003$ for MIS-C. The analysis showed that lower IGF-1 levels and increasing age of the children increased the risk of developing severe COVID-19. For MIS-C, age and sex differences had no statistically significant effect, whereas low IGF-1 levels significantly increased the likelihood of developing the syndrome (Table 3).

Table 3 Results of Multivariable Logistic Regression Analysis of the Combined Effect of Age, Sex, and GH and IGF-I Levels on the Risk of Severe COVID-19 and MIS-C in Children

Dependent Variable	Predictors	Estimate	SE	t	p	OR (unit ch) (95% CI)
Severe COVID-19 ($\chi^2 = 6.24$, $p = 0.101$)	Constant	-2.90	1.05	-2.76	0.007*	0.05 (0.01–0.44)
	Age	0.08	0.05	1.56	0.123	1.09 (0.98–1.21)
	Sex	0.67	0.59	1.14	0.257	1.96 (0.61–6.34)
	GH	-0.23	0.22	-1.06	0.292	0.79 (0.51–1.22)
Severe COVID-19 ($\chi^2 = 11.28$, $p = 0.010^*$)	Constant	-3.11	1.07	-2.90	0.005*	0.04 (0.01–0.38)
	Age	0.14	0.06	2.46	0.016*	1.15 (1.03–1.29)
	Sex	1.11	0.66	1.69	0.095	3.04 (0.82–11.27)
	IGF-I	-0.02	0.01	-2.18	0.032*	0.98 (0.97–1.00)
MIS-C ($\chi^2 = 18.55$, $p < 0.001^*$)	Constant	-1.72	1.15	-1.50	0.138	0.18 (0.02–1.75)
	Age	-0.01	0.06	-0.06	0.954	1.00 (0.89–1.12)
	Sex	-1.77	0.83	-2.13	0.036*	0.17 (0.03–0.87)
	GH	-1.06	0.40	-2.66	0.009*	0.35 (0.16–0.76)
MIS-C ($\chi^2 = 14.29$, $p = 0.003^*$)	Constant	0.59	1.09	0.54	0.589	1.81 (0.21–15.88)
	Age	-0.01	0.06	-0.03	0.975	1.00 (0.89–1.12)
	Sex	1.43	0.84	1.70	0.092	4.18 (0.79–22.17)
	IGF-I	-1.78	0.65	-2.75	0.007*	0.17 (0.05–0.61)

Note 1. χ^2 , p – Chi-square statistics and its significance level. SE – standard error of estimate, t – t-statistics, p – p-value, OR (unit ch) (95% CI) – Odds Ratio for a one-unit change and its 95% confidence interval. * – a statistically significant result ($p < 0.05$).

Abbreviations: GH, growth hormone; IGF-I, insulin growth factor I; MIS-C, multisystem inflammatory syndrome in children.

Association of GH and IGF-I with Pneumonia in Children with COVID-19 and MIS-C

GH and IGF-1 levels were evaluated according to the primary clinical determinant of COVID-19 severity used in this study: the presence of imaging-confirmed pneumonia (lung involvement). The results suggest that lung involvement in children is associated with changes in the levels of both hormones. Children with pneumonia infected with SARS-CoV-2 had lower growth hormone levels (0.99 (0.11; 2.25) ng/mL) compared to patients without lung involvement (1.35 (0.66; 4.22) ng/mL), although this difference did not reach statistical significance ($p = 0.053$). The IGF-1 level in the pneumonia group was half as low (41.90 (24.02; 92.74) ng/mL) compared to patients without lung involvement (86.81 (54.47; 96.46) ng/mL), and this difference was statistically significant ($p = 0.011$).

Associations Between GH/IGF-I and Inflammatory Markers

Following observations of changes in GH and IGF-1 levels in children with COVID-19 and MIS-C, a study was conducted to investigate their relationship with the intensity of the inflammatory process. Specifically, this study examined pro-inflammatory markers, including C-reactive protein (CRP), ferritin, procalcitonin, IL-6, leukocytes, neutrophils, lymphocytes, the neutrophil-to-lymphocyte ratio (NLR), and erythrocyte sedimentation rate (ESR), which are known to be associated with disease severity. As shown in Table 4, children with MIS-C exhibited significantly higher levels of all evaluated inflammatory markers compared to the control group. Additionally, the COVID-19 group

Table 4 Inflammatory Markers in Children with COVID-19, MIS-C, and Healthy Controls

Parameter	Group			H, p	p
	COVID-19	MIS-C	Control		
CRP, mg/L	11.77 (6.00; 22.00)	48.00 (31.20; 96.00)	1.09 (0.58; 1.85)	H = 46.67; p < 0.001*	p _{COVID-19-MIS-C} =0.002* p _{COVID-19-Control} <0.001* p _{MIS-C-Control} <0.001*
PCT, ng/mL	0.20 (0.10; 0.51)	0.93 (0.63; 3.65)	0.03 (0.02; 0.06)	H = 40.23; p < 0.001*	p _{COVID-19-MIS-C} <0.001* p _{COVID-19-Control} <0.001* p _{MIS-C-Control} <0.001*
Ferritin, ng/mL	82.73 (39.33; 141.60)	261.50 (134.90; 390.10)	43.60 (31.35; 97.88)	H = 22.29; p < 0.001*	p _{COVID-19-MIS-C} <0.001* p _{COVID-19-Control} =0.323 p _{MIS-C-Control} <0.001*
IL-6, ng/L	84.44 (40.91; 208.20)	295.40 (106.10; 608.88)	3.79 (2.81; 6.83)	H = 36.53; p < 0.001*	p _{COVID-19-MIS-C} =0.029* p _{COVID-19-Control} <0.001* p _{MIS-C-Control} <0.001*
ESR, mm/hour	16.00 (9.00; 24.00)	26.60 (16.00; 47.00)	6.50 (5.00; 9.00)	H = 21.59; p < 0.001*	p _{COVID-19-MIS-C} =0.023* p _{COVID-19-Control} =0.003* p _{MIS-C-Control} <0.001*
WBC, ×10 ⁹ /L	7.67 (4.39; 10.71)	16.06 (12.64; 20.90)	6.76 (5.90; 7.75)	H = 25.56; p < 0.001*	p _{COVID-19-MIS-C} <0.001* p _{COVID-19-Control} =0.737 p _{MIS-C-Control} <0.001*
NEU, %	54.00 (35.00; 69.00)	73.00 (63.00; 90.00)	53.00 (42.00; 57.50)	H = 8.21; p = 0.017*	p _{COVID-19-MIS-C} =0.022* p _{COVID-19-Control} =1.000 p _{MIS-C-Control} =0.047*
LYM, %	37.00 (20.70; 50.00)	15.00 (7.00; 25.00)	40.50 (36.00; 47.00)	H = 10.73; p = 0.005*	p _{COVID-19-MIS-C} =0.015* p _{COVID-19-Control} =0.707 p _{MIS-C-Control} =0.007*
NLR	1.46 (0.74; 3.00)	5.33 (2.80; 13.00)	1.36 (0.87; 1.60)	H = 10.10; p = 0.006*	p _{COVID-19-MIS-C} =0.014* p _{COVID-19-Control} =1.000 p _{MIS-C-Control} =0.012*

Note. * – a statistically significant result (p < 0.05).

Abbreviations: H, Kruskal–Wallis test, p, level of significance, CRP, C-reactive protein, PCT, procalcitonin, IL-6, interleukin-6, WBC, white blood cells, NEU, neutrophils, LYM, lymphocytes, NLR, neutrophil-to-lymphocyte ratio.

demonstrated elevated concentrations of CRP, procalcitonin, IL-6, and ESR compared to their healthy peers without infection.

Based on these findings, we further investigated whether changes in GH and IGF-1 levels were linked to the inflammatory burden in SARS-CoV-2 infection. The results indicated that a decrease in GH levels was accompanied by increases in CRP, ferritin, and the development of neutrophilia, lymphopenia, and an elevated NLR. Similarly, a decrease in IGF-1 levels in COVID-19 and MIS-C correlated with higher concentrations of pro-inflammatory markers such as CRP, procalcitonin, ferritin, and ESR (Table 5).

ROC Analysis: Cut-off Values of GH and IGF-I for Severe Pediatric COVID-19 and MIS-C

After considering the impact of both GH and IGF-1 on the intensity of the pro-inflammatory component and the clinical course of SARS-CoV-2 infection, we determined the threshold levels of both hormones for diagnosing severe COVID-19

Table 5 Association Between GH and IGF-I Levels and Inflammatory Markers in Children Infected with SARS-CoV-2

Parameter	GH			IGF-I		
	r_s	95% CI	p-value	r_s	95% CI	p-value
CRP	-0.21	-0.42 to 0.02	0.033*	-0.36	-0.54 to -0.14	0.001*
PCT	-0.10	-0.32 to 0.14	0.200	-0.27	-0.47 to -0.04	0.010*
Ferritin	-0.24	-0.44 to -0.01	0.019*	-0.24	-0.44 to -0.01	0.020*
IL-6	-0.10	-0.32 to 0.13	0.387	-0.28	-0.48 to -0.06	0.009*
ESR	-0.06	-0.28 to 0.17	0.303	-0.22	-0.42 to 0.02	0.030*
WBC	-0.18	-0.39 to 0.05	0.058	-0.18	-0.40 to 0.05	0.053
NEU	-0.23	-0.43 to 0.01	0.025*	-0.03	-0.25 to 0.20	0.411
LYM	0.24	0.01 to 0.44	0.017*	0.05	-0.18 to 0.27	0.343
NLR	-0.23	-0.44 to -0.01	0.021*	-0.05	-0.28 to 0.18	0.331

Note 1. * – a statistically significant result ($p < 0.05$). r_s – Spearman correlation coefficient, 95% CI – 95% confidence interval.

Abbreviations: GH, growth hormone; IGF-I, insulin-like growth factor I, CRP, C-reactive protein, PCT, procalcitonin, WBC, white blood cells, NEU, neutrophils, LYM, lymphocytes, NLR, neutrophil-to-lymphocyte ratio.

and MIS-C in children. Our findings showed that GH levels < 0.54 ng/mL were associated with a 2.05-fold higher likelihood of severe COVID-19; however, this association did not reach statistical significance (Sn = 60.0%, Sp = 70.7%; AUC = 0.656, 95% CI [0.49–0.83]; $p = 0.058$). Furthermore, a decrease below 0.465 ng/mL was associated with the onset of MIS-C (Sn = 66.7%, Sp = 73.3%; AUC = 0.742, 95% CI [0.64–0.85], $p = 0.003$). In terms of IGF-1 levels, a reduction below 52.5 ng/mL increases the risk of severe COVID-19 by 1.72 times, although this association did not reach statistical significance (Sn = 66.7%, Sp = 61.3%; AUC = 0.591, 95% CI [0.44–0.74], $p = 0.270$). However, for MIS-C, the threshold value of IGF-1 below 44.1 ng/mL was statistically significant and was associated with a 3.5-fold increase in the likelihood of the syndrome (Sn = 93.3%, Sp = 73.3%; AUC = 0.838, 95% CI [0.72–0.95], $p < 0.001$) (Figure 2).

Discussion

The presence of lung involvement determines the severity of coronavirus infection, the development of respiratory distress syndrome, and the intensity of the inflammatory response to the infectious agent. Therefore, it is crucial to identify the factors that determine the effectiveness of anti-infective defence. Several studies have confirmed the immunomodulatory roles of both growth hormone and IGF-1.^{10,17,22} Immune cells express high levels of receptors for these polypeptides, highlighting their significant role in shaping the immune response.²²

Growth hormone is highly sensitive to ischemia and hypovolemia within the hypothalamic-pituitary system. GH deficiency is the most common form of pituitary dysfunction, regardless of the severity of COVID-19. These findings suggest that the SARS-CoV-2 virus may directly affect the central nervous system and/or disrupt cerebrovascular hemodynamics.^{23,24}

When evaluating GH deficiency, it is essential to consider the impact of hypo- or hypercorticism on GH secretion. It has been demonstrated that glucocorticoids are among the primary hormones regulating GH secretion through various mechanisms that affect the hypothalamus, pituitary gland, and liver. Glucocorticoids can either stimulate or suppress GH secretion, depending on the concentration and duration of exposure.²³ Therefore, in our study, we did not analyze administering exogenous glucocorticoids to patients with MIS-C to avoid the influence of this cofactor. However, some studies have shown that a critical course of acute illness can lead to an increase in GH levels, which may be associated

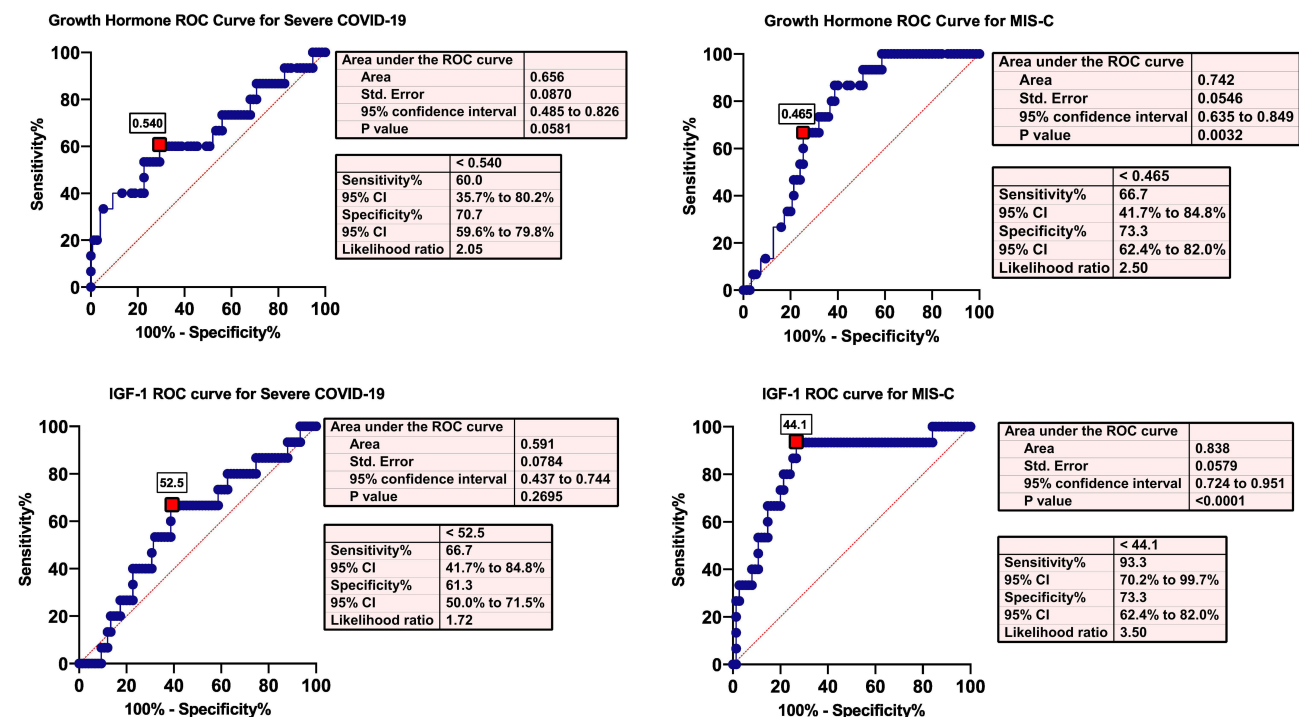


Figure 2 Receiver operating characteristic (ROC) curves of growth hormone and insulin-like growth factor-I for the prediction of severe COVID-19 and MIS-C in pediatric patients.

with the development of resistance to it.^{25,26} This increase in GH levels is typically transient, as the GH secretion has been shown to decline during the later stages of severe systemic inflammation.²⁶

The role of GH in thymus function is particularly important in childhood.⁹ It promotes the proliferation of T and B lymphocytes, enhances T cell adhesion to matrix proteins and migration of T cells, and is involved in the regulation of immunoglobulin production.²⁷ Additionally, when combined with IGF-1, GH stimulates the development of myeloid and erythroid cell lines, activates phagocytic activity, enhances the function of natural killer cells and macrophages, and stimulates the production of superoxide anions and cytokines by phagocytes.^{17,27} One of the unique characteristics of GH is its ability to program the macrophage transcriptome by activating signalling cascades similar to those of interferon- γ , specifically the JAK-STAT pathway. This leads to an increase in reactive oxygen species production and a decrease in phagosomal proteolysis, which are crucial for antigenic response and antimicrobial activity, ultimately determining the quality and effectiveness of the immune reaction.²⁸ The literature also suggests that GH can suppress the production of pro-inflammatory cytokines (TNF- α and IL-6) and stimulate the secretion of anti-inflammatory mediators, which could potentially play a significant role in controlling the “cytokine storm” observed in severe cases of COVID-19.^{13,16,17} In children with GH deficiency, disorders of phagocytic activity of neutrophils and monocytes have been described. These disorders were restored after six months of replacement therapy with recombinant GH.²⁹ Studies involving the pediatric population, particularly children with short stature, emphasise the potential immunomodulatory role of GH in the context of the risk of developing COVID-19, with a special focus on disease management in patients requiring GH replacement therapy.³⁰ The immunomodulatory effect of this hormone has also been confirmed in experimental models: after hypophysectomy in rats, pronounced immunodeficiency with impairment of thymus-dependent and antigen-stimulated responses was observed.²⁷ Recent studies suggest that GH replacement therapy may be considered as a supplementary approach in the context of COVID-19 progression. This includes both the acute phase of infection and the recovery period, to support the immune system’s function and ensure adequate lung function.¹³

IGF-1 performs several key functions that are crucial in the course of viral infections, including COVID-19. Its impact on the immune system is achieved through the phosphatidylinositol 3-kinase/protein kinase B and mitogen-activated protein kinase signaling pathways.¹⁸ Insulin-like growth factor 1, which is composed of 70 amino acids, is

primarily produced in the liver.¹⁸ As a major regulator of GH activity, IGF-1 is essential in processes such as cell differentiation, proliferation, and apoptosis, and significantly influences tissue growth and organ function.³¹ Similar to GH, IGF-1 is involved in the development of T- and B-cell clones that play an active role in the antigen response system.¹³ Additionally, IGF-1 also has antioxidant and neuroprotective effects.¹⁸

IGF-1 has a longer half-life than GH, making it less susceptible to changes in GH levels caused by factors such as circadian rhythms, physical activity, nutritional status, and blood glucose levels.³¹ At the same time, it should be noted that other physiological regulators of IGF-1 secretion include thyroxine, estrogen, and cortisol; however, their influence was not considered in our study. Because the liver is responsible for synthesising IGF-1, any impairment in liver function can result in changes in the hormone's levels. Therefore, children with organic liver lesions at the time of examination were excluded from the study to ensure the accuracy of our findings. To control for the potential influence of body weight on IGF-1 levels, the study only included children whose anthropometric status, as determined by WHO growth charts, corresponded to normal body weight.^{32,33}

Among the critical determinants of IGF-1 and GH levels, age and sex of the patients should also be considered. For this reason, when examining fluctuations in their levels in relation to the severity of SARS-CoV-2 infection, these factors were taken into account in the analysis. The research has shown that older children are more prone to severe COVID-19 courses when concurrent IGF-1 levels are reduced. At the same time, no age-related differences in IGF-1 levels were found within the COVID-19 and MIS-C groups. Despite the observed decline in GH levels with age, consideration of patient sex neutralises the role of GH in the pathogenesis of severe COVID-19.

Studies in adults have shown an age-related decline in GH secretion, that is more pronounced in men compared to women. This reduction has been linked to immune dysregulation, chronic low-grade inflammation (inflammaging), metabolic disorders, and an increased risk of severe COVID-19 progression.^{16,17} In contrast, pediatric data indicate that GH levels peak during adolescence, which may contribute to the lower susceptibility to severe SARS-CoV-2 infection observed in this age group.³⁰ This aligns with pubertal physiology: during puberty, 24-hour GH secretion increases approximately 1.5–3-fold, primarily due to greater pulse amplitude and secretory burst mass rather than an increased pulse frequency.³⁴ However, in our cohort, adolescents had lower GH levels compared to children in early childhood. This finding may reflect the pulsatile and episodic nature of GH secretion; therefore, a single blood sample, particularly in adolescents, may not reflect the peak GH concentrations.³⁵ By comparison, circulating IGF-1 levels are more stable over time because IGF-1 is continuously produced and exhibits less short-term fluctuation.³⁶ As a result, IGF-1 may be a more reliable biomarker of integrated daily GH axis activity when only single-timepoint sampling is available. However, in our study, we did not observe significant age-related differences in IGF-1 levels within the COVID-19 and MIS-C groups.

In addition, stress-related hypercorticism, driven by both the disease itself and hospitalization, may be more pronounced during adolescence, further distinguishing this age group from infants and preschool children and potentially contributing to suppression of the somatotrophic axis.³⁷

In summary, the lower GH levels observed in adolescents during SARS-CoV-2 infection appear atypical for pubertal physiology and may indicate transient suppression or dysregulation of the somatotrophic axis in this setting.

The sex distribution of the study cohort was not homogeneous: males were significantly more prevalent in the MIS-C group than in the non-infected control group (86.67% vs 41.67%, $p < 0.05$). This male predominance in the MIS-C group is consistent with prior reports describing a higher frequency of SARS-CoV-2–related severe inflammatory phenotypes among males.^{38–41} Because sex can influence somatotrophic axis activity, sex, particularly male sex, should be taken into consideration when predicting the development of MIS-C in individuals with concurrent GH reduction. Studies have shown that women typically have higher levels of both GH and IGF-1 than men, due to the stimulating effect of estrogen on GH synthesis and local production of IGF-1 in target cells.¹⁷ Additionally, estrogen has been found to increase the expression of GH receptors in target cells.¹⁶ It is worth noting that the concentration of the protein that binds to growth hormone is higher in women than in men, which can affect GH activity. However, it is essential to note that these findings are based on studies conducted in the adult populations.¹⁶

Analysis of the literature has revealed that changes in IGF-1 and GH levels occur not only in endocrine disorders but are also observed in metabolic disturbances and inflammatory diseases. These changes have also been linked to the

development of acute lung injury and acute respiratory distress syndrome.^{10,13} Our study further supports the association between IGF-1 levels and the severity of coronavirus infection. It is important to note that lung involvement and systemic manifestations are key factors in determining the severity of SARS-CoV-2 infection. Our results align with this, as we found that the presence of lung involvement in COVID-19 was associated with lower IGF-1 levels.

Our study also confirmed the immunomodulatory roles of GH and IGF-1 in children with coronavirus infection. We observed that decreased GH levels were associated with changes in the leukogram, resulting in pro-inflammatory changes, such as increased levels of CRP and ferritin. Significantly, this reduction in GH was also associated with neutrophilia, lymphopenia, and an elevated NLR, reflecting a shift toward a more pro-inflammatory leukocyte profile. Additionally, decreased IGF-1 levels were associated not only with increased CRP, procalcitonin, ferritin, and ESR, but also with higher IL-6 concentrations.

These features of inflammatory regulation have a pathogenetic basis. The growth hormone receptor belongs to the class I cytokine receptor superfamily, which also includes the IL-6 receptor complex.¹⁵ It is important to note that GH and IGF-1 play a role in modulating JAK-STAT activity, a central pathway in cytokine signalling. Their effects are not limited to STAT5 activation, but also involve the induction of key negative regulatory mechanisms such as Suppressor of Cytokine Signaling (SOCS) proteins, Protein Tyrosine Phosphatases (PTP), and Protein Inhibitors of Activated STAT (PIAS).^{15,42} These mechanisms work together to prevent excessive cytokine responses.¹⁵ However, in cases where GH and IGF-1 levels are reduced, dysregulation of these inhibitory systems may occur, leading to inadequate control of the JAK-STAT cascade and increased IL-6-mediated inflammatory activation.^{15,43} This may help explain the observed correlation between lower IGF-1 levels and higher IL-6 levels. At the same time, the bidirectional nature of the interaction between the somatotrophic axis and inflammation is emphasised.^{44,45} Pro-inflammatory cytokines, including IL-6, can suppress GH receptor expression, inhibit downstream signaling, reduce hepatic IGF-1 production, and alter the balance of IGF-binding proteins, collectively contributing to GH resistance and IGF-1 dysregulation.⁴⁴

Although GH is known to stimulate thymopoiesis and regulate neutrophil function, these effects are disrupted in cases of systemic inflammation, such as severe COVID-19 and MIS-C. This is mainly due to the activation of pro-inflammatory cytokines, specifically IL-6. Elevated levels of IL-6 can trigger the release of neutrophils from the bone marrow and induce emergency granulopoiesis through gp130-STAT3 signalling, leading to a significant increase in neutrophil count.^{46–48} At the same time, high levels of IL-6 can also lead to T-cell apoptosis and a decrease in circulating T-lymphocytes, causing lymphopenia.⁴⁹ As a result, these changes in blood cell counts can lead to an elevated neutrophil-to-lymphocyte ratio (NLR), which was also observed in our study.^{50,51}

Given the immunomodulatory role of the somatotrophic axis, it is important to further evaluate GH/IGF-1 levels in children with severe COVID-19 and MIS-C. As GH secretion is pulsatile, IGF-1 may be a more reliable marker of overall GH axis activity. IGF-1 may be explored as an adjunct marker of disease severity alongside standard inflammatory biomarkers, potentially as part of a multimarker risk-stratification approach. It is also important to monitor children who receive systemic glucocorticosteroids, which are commonly included in MIS-C treatment protocols, because exogenous glucocorticoids may affect the somatotrophic axis. However, in our study, hormonal assessments were performed before initiation of therapy; therefore, we were unable to evaluate the impact of glucocorticosteroid treatment on GH/IGF-1 dynamics. Importantly, somatotrophic axis function in adolescents should be monitored not only during acute illness but also longitudinally after recovery to assess potential effects on growth and pubertal development.

Limitations

This study has several limitations that should be considered when interpreting the results. First, the sample size was small ($n = 90$), especially in the MIS-C ($n = 15$) and control groups ($n = 12$). Post hoc sensitivity analyses (G*Power; two-sided $\alpha = 0.05$; power = 0.80) indicated that the MIS-C versus control comparison was powered to detect only large effects (Cohen's $d \geq 1.13$). Second, although we concentrated on GH and IGF-1 as key components of the somatotrophic axis, other physiological regulators of their secretion (thyroid hormones, estrogen, and cortisol), were not assessed in this study and their potential influence on circulating GH/IGF-1 levels and inflammatory associations cannot be excluded. Third, this was a two-centre study conducted in Ternopil, Ukraine, which might limit the applicability of our findings to other settings and populations. Fourth, due to limited serum volume, patient samples were measured in single wells,

which may increase analytical variability. Future research with larger cohorts, a multicentre approach, and more comprehensive endocrine profiling is necessary to corroborate and build upon our results.

Conclusion

This study provides evidence that alterations in the somatotrophic axis, specifically reduced GH and IGF-1 levels, are associated with greater disease severity in children with COVID-19 and MIS-C. Our research demonstrates that lower concentrations of both hormones are linked to inflammatory markers (such as high CRP, procalcitonin, ferritin, and IL-6) and hematologic changes (including increased ESR, neutrophil-to-lymphocyte ratio, neutrophilia, and lymphopenia), all of which are also related to the disease severity. These findings suggest a potential immunomodulatory role of the somatotrophic axis during pediatric SARS-CoV-2 infection, indicating that reduced GH/IGF-1 activity may contribute to immune dysregulation in severe COVID-19 and MIS-C.

Even after adjusting for age and sex, GH and IGF-1 remained associated with severe COVID-19 and MIS-C. Therefore, the immunomodulatory functions of GH and IGF-1 should be considered not only in children with known endocrine disorders, but also in previously healthy pediatric patients with COVID-19 or MIS-C. The identified GH and IGF-1 cut-off values may aid in determining disease severity and clinical decision-making, particularly in children with significant systemic inflammation or pulmonary involvement.

However, it is essential to acknowledge several limitations, including the modest sample size, particularly in the MIS-C and control groups, and the single-time-point measurement of hormones. Larger, multicenter longitudinal studies are necessary to define the dynamics of GH and IGF-1 levels not only during acute COVID-19 and MIS-C, but also in the recovery phase, and determine whether hormonal alterations can contribute to delayed recovery or post-infectious complications. Future research should also investigate whether endocrine or immunomodulatory approaches could be beneficial in personalized treatment strategies for children with acute COVID-19, MIS-C, or post-infectious complications.

Abbreviations

AUC, area under the curve; CI, confidence interval; COVID-19, Coronavirus disease 2019; ESR, erythrocyte sedimentation rate; GH, growth hormone; IGF-1, insulin-like growth factor-1; MIS-C, multisystem inflammatory syndrome in children; Sn, sensitivity; Sp, specificity; WHO, World Health Organisation; 95% CI AUC, 95% confidence interval for the area under the curve.

Disclosure

The authors report no conflicts of interest in this work.

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