

Long-COVID in immunocompromised children

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Abstract

Purpose

Coronavirus disease 2019 (COVID-19) can lead to an illness characterized by persistent symptoms which affect various organs and systems, known as long-COVID. This study aimed to assess the prevalence and clinical characteristics of long-COVID in children with immunodeficiency, in comparison to those without.

Methods

A self-constructed questionnaire was created, which included questions regarding the child's general health, the course of their COVID-19, their symptoms of long-COVID and its impact on their daily functioning, the diagnosis of multisystem inflammatory syndrome (MIS-C), and vaccination status. The questionnaire was completed by parents of 147 children - 70 children with a diagnosis of immunodeficiency (47.6 %) and 77 who were immunocompetent (52.4 %).

Results

Immunocompetent children were more significantly affected by long-COVID than those immunocompromised. Its prevalence in the first 12 weeks post-infection was 60.0 % and 35.7 % in these groups, respectively. Beyond this period, these percentages had dropped to 34.6 % and 11.43 %, respectively. Children who were immunocompetent suffered more often from fatigue, reduced exercise tolerance and difficulty concentrating. Meanwhile, there was a slight increase in complaints of gastrointestinal symptoms in immunocompromised patients. The risk of developing long-COVID increased with age and COVID-19 severity in both groups. Furthermore, the daily activities of immunocompetent children were limited more frequently (41.8 %) than for those who were immunocompromised (25 %).

Conclusions

Although immunocompromised children experienced long-COVID, its prevalence and impact on daily functioning were significantly lower than among immunocompetent children. However, as the pathomechanisms of long-COVID are not yet fully understood, it is not currently possible to fully explain these findings.

What Is Known?

- Long-COVID is characterized by persistent symptoms following COVID-19, which can affect various tissues and organs, as well as mental health.
- Due to the similar course of COVID-19 – mainly mild or asymptomatic - among children with and without immunodeficiency, the question arises, over whether the prevalence and severity of long-COVID is also similar in both groups.

What Is New?

- Immunocompromised children also suffer from long-COVID, but the prevalence is significantly lower than in the immunocompetent group of children.
- The potential causes of less frequent and milder long-COVID in this group may be the milder course of COVID-19 and the state of reduced immunity protecting against neuroinflammation.

Introduction

Our understanding of the course of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children has evolved over the last two and a half years of the current coronavirus pandemic. Initially, children were typically asymptomatic or had mild COVID-19 symptoms, hospitalization rates were low and complications were rare [1]. Following the introduction of universal vaccinations in adults and adolescents, children under the age of five years became the primary victims of the disease, besides unvaccinated people. Indeed, they have been presenting with more severe symptoms and the hospitalization rate became slightly higher. Alongside this, two significant complications of COVID-19 have appeared, namely MIS-C and long-COVID [2]. While the former is a complication that occurs only in children and adolescents, the latter has affected all age groups and has only recently begun to attract the attention of pediatricians.

Long-COVID, otherwise known as post-COVID syndrome, is characterized by persistent symptoms following COVID-19. Such symptoms can affect the sensory, neurological, cardiovascular, and respiratory systems, as well as mental health. Since there are no strictly defined diagnostic criteria, researchers and physicians have attributed more than 200 symptoms to the syndrome. Some of the most common symptoms described are fatigue, dyspnea, cough, chest pain, headache, concentration difficulties and sleep disturbances. According to guidelines published by the National Institute for Health and Care Experience (NICE), long-COVID can be divided into two categories [3]:

1. Ongoing symptomatic COVID-19 - signs and symptoms of COVID-19 from 4 weeks up to 12 weeks post-infection.
2. Post-COVID-19 syndrome - signs and symptoms that continue or develop after SARS-CoV-2 infection persist for more than 12 weeks from the onset of the disease and are not explained by alternative diagnoses. It usually manifests by a group of symptoms, which can fluctuate, change over time, and affect any part of the body.

The course of COVID-19 is mainly asymptomatic or oligosymptomatic in children, and is thought to be similar among those immunocompetent and immunodeficient [4]. Therefore the question arises over whether the prevalence and severity of long-COVID is also similar in both groups, or does immunodeficiency favor the development of the symptoms mentioned above.

In this regard, this study aimed to evaluate and compare the prevalence and clinical characteristics of long-COVID in immunocompetent and immunodeficient children, who were admitted to the COVID-19 Subunit of the tertiary referral hospital in Warsaw, Poland.

Materials And Methods

Procedure

A self-constructed questionnaire was used to conduct this study. This included questions about general health condition, diagnosis of MIS-C, COVID-19 vaccination status, the course of COVID-19, the presence of long-COVID symptoms, and how this impacted on the child's daily functioning.

Study group

The questionnaire was completed by parents of 147 children who had been admitted, at least three months prior, to the COVID-19 Subunit in the Department of Pediatrics, Nutrition, and Metabolic Disorders, Children's Memorial Health Institute in Warsaw, Poland. Participants were admitted at some point between the 1st of November 2020 and the 31st of January 2022. All participants had SARS-CoV-2 infection confirmed by nasopharyngeal swab, followed by reverse transcription polymerase chain reaction (RT-PCR) or rapid antigen test.

Division of the study group

Study participants were stratified into two separate cohorts, depending on whether or not they had an immunodeficiency. Children with immunodeficiency (n = 70) comprised 47.6 % of the participants, whilst the control group (n = 77) comprised 52.4 %. Inclusion in the immunodeficient cohort was dependent on the presence of tumors, liver or kidney transplantation, demyelinating diseases, ulcerative colitis treated with immunosuppressant's, end-stage renal disease, asplenia or primary immunodeficiency. Some of the participants displayed multiple of the inclusion criteria.

Statistical analysis

All data were analyzed using Microsoft Excel and Statistica 13 software. Quantitative data was evaluated using the Mann-Whitney U test when the distribution was significantly different from Gaussian distribution, which was determined in the Shapiro–Wilk test. Meanwhile, qualitative data was compared using the chi-square test. The probability value of $p < 0.05$ was considered to be statistically significant.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional Ethics Committee of the Children's Memorial Health Institute in Warsaw, Poland (No. 41/KBE/2021).

Results

Characteristics of the group

Among immunocompromised children (37 males and 33 females), age ranged from 8 months to 17 years (median 7.0; Q1 = 4.0; Q3 = 13.0). This distribution was similar in the immunocompetent children (41 males and 36 females), ranging in age from 4 months to 17 years (median 9.0; Q1 = 4.0; Q3 = 13.0).

Within the immunodeficient cohort, the most common immunosuppressive factors were tumors during treatment (n = 46; 65.7 %), liver or kidney transplantation (n = 17; 24.3 %), ulcerative colitis (n = 4; 5.7 %), demyelinating diseases (n = 3; 4.3 %), then primary immunodeficiency (n = 2; 2.9 %).

None of the immunocompromised children suffered from allergic diseases, whereas the prevalence of these diseases in the control group was 28.6 % (n = 22). Immunization against COVID-19 was also significantly higher in immunocompetent children (26.0 % vs 4.3 %; $p < 0.01$). Only one participant was diagnosed with MIS-C, though this was not characterized by an immunosuppressive factor.

The course of SARS-CoV-2 infection

The course of SARS-CoV-2 infection among the immunocompromised cohort was mainly asymptomatic (45.7 %) or mild (38.6 %), with fever, cough, rhinitis and fatigue, the most common symptoms. On the other hand, the immunocompetent cohort were more often symptomatic (87.0 %) with a mild (48.1 %) or moderate (31.2 %) illness. The range of symptoms reported in both groups are presented in Table 1.

Table 1. The range of symptoms of SARS-CoV-2 infection in the group of children with and without immunodeficiency.

	ID (+) n=70		ID (-) n=77		<i>P</i>
Lack of symptoms	32	45.7%	10	13.0%	0.01
Fever	28	40.0%	47	61.0%	0.01
Cough	19	27.1%	30	39.0%	0.13
Rhinitis	18	25.7%	35	45.5%	0.01
Dyspnea	3	4.3%	6	7.8%	0.38
Diarrhea	3	4.3%	10	13.0%	0.06
Vomiting	6	8.6%	10	13.0%	0.38
Fatigue	13	18.6%	33	42.9%	0.01
Headache	6	8.6%	24	31.2%	0.01
Muscle pain	8	11.4%	19	24.7%	0.04
Rash	0	0.0%	4	5.2%	0.05
Chest pain	2	2.9%	3	3.9%	0.73
Sore throat	1	1.4%	5	6.5%	0.13
Loss of taste and smell	3	4.3%	10	13.0%	0.95

Abbreviations: ID (+) – children with immunodeficiency; ID (-) – children without immunodeficiency

Long-COVID

The prevalence of a range of long-COVID symptoms in both cohorts, divided into the period of time up to 12 weeks from the diagnosis of the infection and greater than 12 weeks, is presented in Figure 1.

It is clear from the graph in Figure 1 that immunocompetent children were more significantly affected by prolonged COVID-19 symptoms when compared to the immunocompromised cohort. This was evident within the first 12 weeks post-infection, but also in the period after 12 weeks. The prevalence of ongoing symptomatic COVID-19 in the first 12 weeks post-infection, defined as the presence of at least one symptom, was 60.0 % and 35.7 % in these groups, respectively ($p = 0.02$). In the period beyond 12 weeks post-infection, the percentages dropped to 34.6 % and 11.43 %, respectively ($p = 0.01$).

During the first 12 weeks post-infection, the immunocompetent cohort suffered more often from fatigue, reduced exercise tolerance, difficulty in concentrating, sleep disorders, and chronic coughing. In contrast, children in the immunocompromised cohort experienced gastrointestinal symptoms more often. Beyond the 12 week post-infection period, the prevalence of almost all symptoms had significantly decreased. However, children in the immunocompetent cohort continued to display post-COVID-19 symptoms, including difficulty in concentrating, reduced exercise tolerance, fatigue, headache and frequent

infections. In turn, the children in the immunocompromised cohort continued to suffer from fatigue, irritation and gastrointestinal symptoms. Additionally, the parents of four immunocompromised children reported the persistence of SARS-CoV-2 in nasopharyngeal swabs, beyond 12 weeks post-infection.

During the first 12 weeks post-infection, the presence of long-COVID symptoms correlated with age. Indeed, the older the child, the greater the likelihood of developing symptoms. This was observed in all participants when considered as a whole and within the individual cohorts of immunocompromised and immunocompetent children. In the period beyond 12 weeks, there was no such relationship in any of the cohorts. Nonetheless, the relationship between the severity of COVID-19 symptoms and the presence of long-COVID, both up to 12 weeks and beyond 12 weeks, was significant. This was true for the study population as a whole, as well as for the immunodeficient cohort and the immunocompetent cohort (Table 2).

Table 2. Influence of age and the severity of COVID-19 on the development of long-COVID symptoms in the whole study group and within the individual cohorts of immunocompromised and immunocompetent children.

Impact of age on the development of long-COVID						
	whole study group		ID (+)		ID (-)	
	Association	<i>p</i>	Association	<i>p</i>	Association	<i>p</i>
symptoms <12 weeks post-infection	3.21	<i>0.01</i>	2.62	<i>0.01</i>	1.64	<i>0.04</i>
symptoms >12 weeks post-infection	1.19	0.24	0.25	0.80	1.34	0.18
Impact of the severity of COVID-19 on the development of long-COVID						
	whole study group		ID (+)		ID (-)	
	Association	<i>p</i>	Association	<i>p</i>	Association	<i>p</i>
symptoms <12 weeks post-infection	4.45	<i><0.01</i>	3.25	<i><0.01</i>	2.30	<i>0.02</i>
symptoms >12 weeks post-infection	4.18	<i><0.01</i>	2.27	<i>0.02</i>	2.45	<i>0.01</i>

Abbreviations: ID (+) – children with immunodeficiency; ID (-) – children without immunodeficiency

However, no correlation was found between allergic diseases and the symptoms of long-COVID in the control group, which was the only one presenting allergies, either up to 12 weeks or beyond 12 weeks post-infection (Fig. 2).

According to the parents' of the participants, the presence of long-COVID symptoms limited the daily activities of immunocompetent children more frequently (41.8 %) than it did for the immunocompromised

children (25 %; $p = 0.03$).

Discussion

Initial reports of long-COVID were described in Italian adults during August of 2020 [5], with the first five children suffering from this syndrome identified by Ludvigsson in Sweden in November of 2020 [6]. According to his observations of these five children, the most common symptoms were fatigue, dyspnea, palpitations, chest pain, headache, concentration difficulties, and muscle weakness. Following the publication of this information, Ludvigsson was contacted by parents of a further 35 Swedish children with similar complications [7], and similar reports began to quickly emerge from other parts of the world. The second such report of these symptoms in children were described by Buensenso et al., from Rome. This report described 123 children whose parents had been surveyed around five months after diagnosis of COVID-19. Symptoms were reported to persist in 58 % of the children, the most common of which were insomnia, fatigue, nasal congestion, headache, muscle pain and difficulty concentrating [8]. Subsequent studies reported similar symptoms, although the prevalence of long-COVID varied widely (4 – 66 %) [9]. A larger prospective controlled study, which included a cohort of 1734 children who had tested positive for SARS-CoV-2, was published in August of 2021. The authors, Molteni et al., observed that children most often displayed symptoms of fatigue, headache and anosmia. However, they did not report impaired concentration, anxiety, or memory disturbances. Moreover, they estimated the prevalence of post-COVID symptoms to be only 4.4 % on day 28 following a positive test and 1.8 % on day 56. Nonetheless, this percentage was significantly higher than in the control group, whilst the authors also suggested that older children (> 12 years of age) experienced a higher incidence of symptoms than younger [10].

Unfortunately, the prevalence of symptoms in the immunodeficient children cannot be compared as no similar studies have been conducted yet, to our knowledge. Therefore, we can only compare our control group, in which the prevalence of long-COVID was relatively high (60.0 %) and increased with age. Moreover, the most frequently reported symptoms described by us were consistent with those obtained by previous researcher. Like others, we did not find a relationship between long-COVID and the presence of allergic diseases. However, we have demonstrated that the syndrome affects immunocompromised children less often. Why immunodeficient children are spared from the development of long-COVID is unclear, though mechanisms underlying this complication can be investigated. Although the underlying cause of long-COVID has yet to be established, there are several possible theories that do not exclude one another [11,12].

One of the possible causes may be the higher frequency of asymptomatic SARS-CoV-2 infection in this group. Although it has been suggested that the severity of COVID-19 does not correlate with the presence or severity of long-COVID [13,14], it is currently postulated that this relationship is dependent on the type of symptoms. Organ or tissue damage caused by SARS-CoV-2, such as fibrosis and scarring, as well as inflammation, may lead to long-term consequences [11], such as severe pneumonia, chronic cough or breathing difficulties. [15]. This would explain the presence of chronic respiratory symptoms and persistent declines in blood oxygen saturation in several of our patients after severe COVID pneumonia

requiring intensive treatment. However, this pathomechanism does not explain the presence of the general and neurocognitive symptoms of long-COVID.

As for the symptoms that affect the central nervous system, such as concentration and sleep disorders, fatigue, and irritability, the pathomechanisms seem to be at least partially understood. Recent reports have suggested that the spike protein of the virus can cross the blood-brain barrier and cause perivascular inflammation [16,17]. Moreover, molecular mimicry between the spike protein and human proteins contributes to autoimmunity and activates toll-like receptors (TLRs), leading to the release of inflammatory cytokines [18]. Various researchers have linked this phenomena to neuroinflammation that may damage brain blood vessels and brain cells, contributing to long-COVID [19,19-21]. Additionally, mast cells may also contribute, as they have been shown to be activated by SARS-CoV-2 and release numerous chemokines and cytokines that may promote inflammatory symptoms [11,22]. Therefore, we propose that the state of reduced immunity may constitute a protective factor against this inflammatory reaction and, thus, protect against the symptoms of long-COVID.

Another possible pathomechanism of long-COVID is the persistence of SARS-CoV-2 reservoirs in specific tissues, with some patients infected with the virus not able to clear it for a long period. Therefore, they are characterized by viral ribonucleic acid (RNA) and proteins in nasopharyngeal swabs and samples of feces [23,24]. Moreover, immunosuppression seems to facilitate SARS-CoV-2 persistence [11,25,26], which leads to mutations in the virus that confer resistance to a typical class of neutralizing antibodies. It is possible that SARS-CoV-2 evades the immune response and thus causes persistent symptoms [26]. Among several of our immunocompromised patients, we observed the persistence of SARS-CoV-2 for up to 3 months, however, this did not lead to the symptoms of long-COVID. Nevertheless, it was a significant inconvenience, as parents reported that it hindered the treatment of underlying diseases.

Another reason for the persistence of post-COVID symptoms is the reactivation of previously harbored pathogens, due to dysregulation of the host immune response by SARS-CoV-2. It is well known that during their lifetime people accumulate persistent viruses in their bodies, mainly herpesviruses. When the host is in a state of good health these pathogens do not cause any symptoms, however they can reactivate under conditions of reduced immunity or stress. It has been shown that SARS-CoV-2 can dysregulate the immune response that keeps these viruses latent, a process regulated by host interferons, leading to a change in their gene expression or protein production that generate persistent symptoms [11,27]. Various researchers have reported the reactivation of Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and human herpesviruses 6 and 7, during COVID-19 [28-30]. These viruses can infect new organs or tissues, generate new symptoms, or induce neuroinflammatory processes in the central nervous system [11]. It appears that this reactivation should be better promoted in children with immunodeficiency. However, we observe a more intense immune response to the viral infection among immunocompetent children, which may play a significant role in its interaction with herpesviruses. Further research is needed to clarify this issue.

Conclusion

Immunocompromised children suffer from prolonged COVID-19 symptoms, but the prevalence was significantly lower than in the immunocompetent group of children. Indeed, they often presented with fatigue, chronic cough, and gastrointestinal symptoms, yet most of the symptoms subsided within three months and rarely affected the daily functioning of immunocompromised patients. The risk of developing long-COVID in this group increased with age and with the severity of symptoms of SARS-CoV-2 infection.

The potential causes of less frequent and milder long-COVID among immunocompromised children may be the milder course of COVID-19, which does not lead to tissue damage, and the state of reduced immunity protecting against neuroinflammation. Nevertheless, a tendency for the persistence of SARS-CoV-2 reservoirs in this group, and reactivation of the latent herpesviruses should promote the development of post-COVID symptoms.

Based on current scientific data, and due to the fact that the pathomechanism of long-COVID is not fully understood, it is impossible to fully explain the lower prevalence and milder course of this complication among immunocompromised children. Therefore, this issue requires further research.

Declarations

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

Author Contributions: Karolina Kuczborska conceptualized and designed this study, collected the data, performed the initial analyses, and drafted the initial manuscript. Piotr Buda and Janusz Książyk conceptualized and designed this study, reviewed and revised the manuscript. All authors had full access to all the data in this study, and they accept responsibility to submit it for publication.

Ethics approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional Ethics Committee of the Children's Memorial Health Institute in Warsaw, Poland (No. 41/KBE/2021).

Consent to participate: Informed consent was obtained from the parents of all participants included in the study.

Consent to publish: Not applicable

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Figures

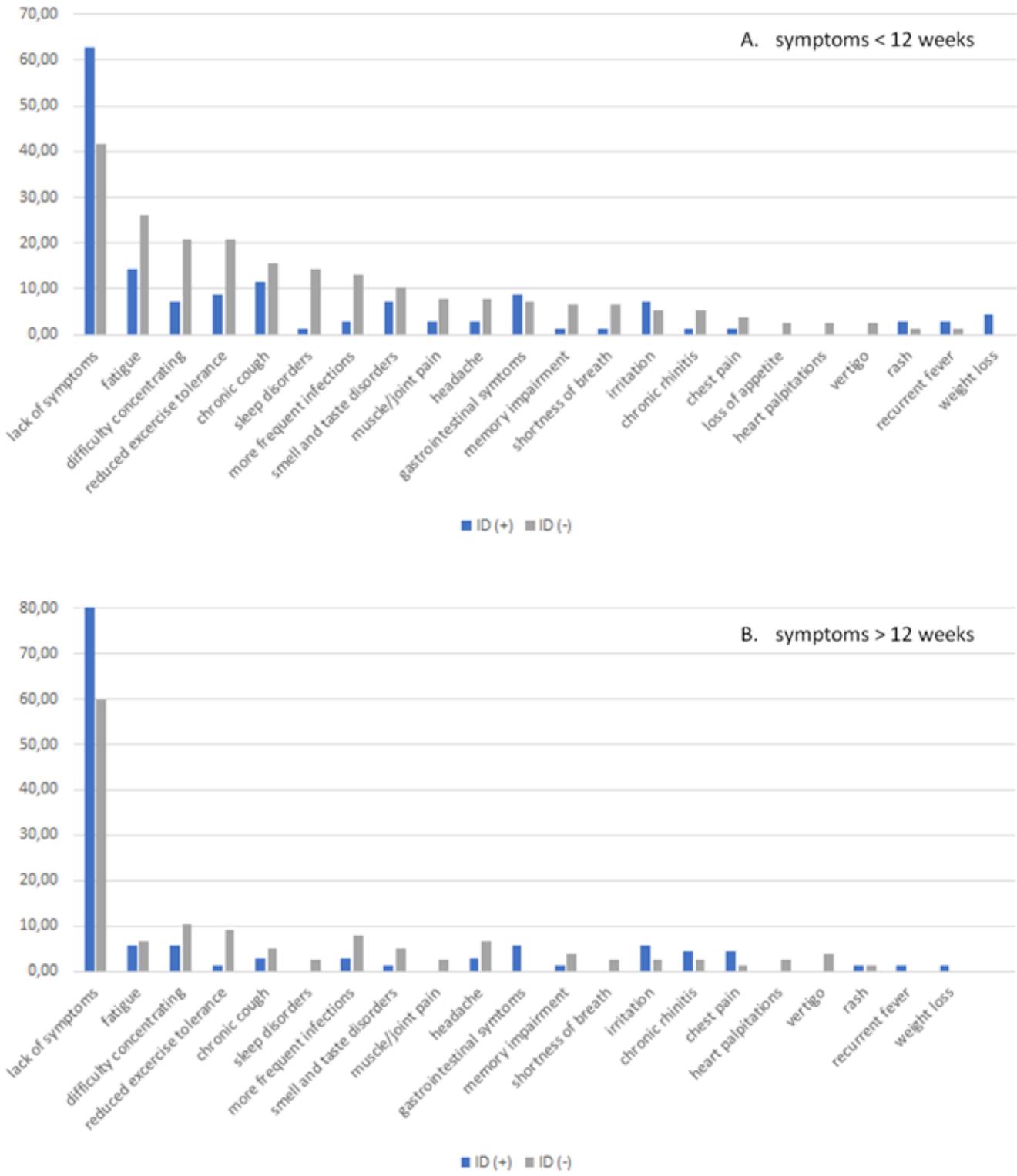


Figure 1

Prevalence of particular symptoms of long-COVID in a group of children with and without immunodeficiency, with a division into the periods of time up to (A) and over 12 weeks (B) from the diagnosis of the infection.

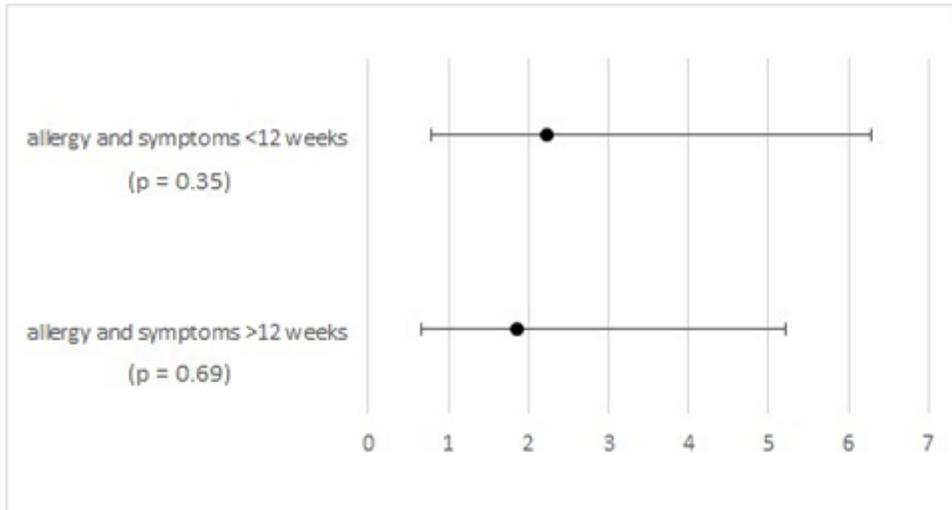


Figure 2

Odds ratios and associated 95% confidence intervals for the impact of allergic diseases on the development of long-COVID symptoms in the immunocompetent cohort, both up to 12 weeks and beyond 12 weeks post-infection.