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Long-COVID symptoms after multisystem inflammatory syndrome in children during different pandemic waves

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ABSTRACT

Introduction: This study aimed to assess and compare the long-term non-cardiac complications of the multisystem inflammatory syndrome in children (MIS-C) triggered by consecutive variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Material and methods: Multisystem inflammatory syndrome in paediatric patients was assessed in the paediatric office at 4–12 and 12–24 weeks and then by a telephone survey at least 24 weeks after hospitalisation. During each follow-up, we obtained information regarding the prevalence of long-COVID symptoms, body mass index, COVID status, need for rehospitalisations, and any consultations with specialists. Additionally, we assessed the participant's quality of life (QoL) using the KIDSCREEN-10 questionnaire over the phone.

Results: A total of 116 patients with MIS-C (74 during Original/Alpha, 27 during Delta, and 15 during Omicron variant surges) admitted to the Children's Hospital of Krakow between 1 November 2020 – 5 May 2023 were included in the analysis. Regardless of the follow-up period, the frequency and variation of most symptoms did not differ significantly between groups. The only difference was a higher frequency of fatiguability/weakness in the Original/Alpha group, during the 4–12-week follow-up (37.9% vs. 10.5% vs. 9.1%; $p = 0.03$). The multivariable regression revealed older age (OR = 1.13, 95% CI: 1.01–1.26, $p = 0.03$), but not the particular variant, as an independent factor for long-COVID. Additionally, the results of long-term follow-up (more than 24 weeks) showed above-average KIDSCREEN-10 scores despite a high incidence of long-COVID symptoms.

Conclusions: The impact of individual SARS-CoV-2 variants appears to be less important on the onset of long-COVID symptoms than other factors, such as age. Long-term follow-up indicated an overdiagnosis of non-specific long-COVID symptoms, in the case that the QoL after MIS-C was non-inferior to the general paediatric population.

KEY WORDS:

quality of life, SARS-CoV-2, multisystem inflammatory syndrome, variants of concern.

INTRODUCTION

Multisystem inflammatory syndrome in children (MIS-C) is a rare but severe condition, occurring approximately 2–6 weeks after severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection [1]. The clinical

picture of the acute phase has been well-defined, with affected patients presenting with fever and mucocutaneous, cardiovascular, neurological, gastrointestinal, and respiratory symptoms [2, 3]. The disease course can be severe, with up to 30–50% of patients developing symptoms of cardiac or respiratory failure requiring hospitaliza-

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tion in the Paediatric Intensive Care Unit (PICU) [3, 4]. The prognosis after MIS-C is uncertain, with some individuals developing long-lasting symptoms that persist for many weeks [5–7]. The aetiology of these symptoms is complex and could be a result of complications from the acute phase of MIS-C or the treatment regime, as well as long coronavirus disease (long-COVID). During the COVID-19 pandemic, multiple variants of SARS-CoV-2 were identified, with Alpha, Delta, and Omicron being considered the most relevant variants of concern (VOC) that modified the course of COVID-19 [8]. There is a lack of data assessing the impact of individual SARS-CoV-2 variants on the long-term complications of MIS-C.

This study's primary aim was to present the symptoms of long-COVID in children after MIS-C depending on the dominant SARS-CoV-2 VOCs. The secondary aim was to assess the quality of life (QoL) using a standardised KIDSCREEN-10 questionnaire, as well as the frequency of rehospitalisation and outpatient specialist consultations in children after MIS-C, during the 3 pandemic waves.

MATERIAL AND METHODS

PATIENT IDENTIFICATION AND SELECTION

This study prospectively enrolled all patients aged 0–18 years of age admitted to the Department of Paediatrics at the University Children's Hospital of Kraków between 1 November 2020 and 5 May 2023, with a diagnosis of MIS-C, who continued their follow-up after discharge. Multisystem inflammatory syndrome in children was diagnosed according to the U.S. Centers for Disease Control and Prevention definition [9]. Patients diagnosed with a bacterial infection were excluded.

STUDY DESIGN

All enrolled patients, upon admission to the hospital, underwent an analysis of a pre-defined set of data, including demographic characteristics (age, sex, race, ethnicity, body mass index [BMI]), SARS-CoV-2 status (polymerase chain reaction – PCR, or antigen test, serological test, vaccination status), and clinical symptoms (cardiac, neurological, respiratory, gastrointestinal, and mucocutaneous). The BMI of the patients was transformed to age- and gender-adjusted percentiles using World Health Organization growth charts [10]. The association between SARS-CoV-2 variants and MIS-C cohorts was assumed based on the Polish sequencing database [11]. The following groups were defined: Original/Alpha (patients hospitalised between 1 November 2020 and 30 July 2021), Delta (patients hospitalised between 1 August 2021 and 30 January 2022), and Omicron (patients hospitalised between 1 February 2022 and 5 May 2023).

During the hospitalisation, the patient's clinical symptoms were analysed [2, 3]. Treatment recommendations of the patients enrolled in this study were in line with the American College of Rheumatology's recommendations [9].

After discharge, the follow-up was performed and divided into the following periods: 4–12 and 12–24 weeks after hospitalisation, and over 24 weeks after hospitalisation.

In the time of 4–12 and 12–24 weeks after the MIS-C hospitalisation the follow-up was carried out during face-to-face visits to the Paediatric Outpatient Clinic of the University Children's Hospital of Kraków. Information concerning long-COVID symptoms, BMI, SARS-CoV-2 reinfections, vaccination status against COVID-19, visits to outpatient specialty clinics, and rehospitalisations were obtained during the interview with the patients and their caregivers and from the hospital database. According to the CDC, long-COVID symptoms are defined as a wide range of new, returning, or ongoing health problems that continue or develop 4 weeks after a COVID-19 infection [12]. Additionally, the outpatient visits and rehospitalisations were divided into those related and not related to MIS-C. Events related to MIS-C were considered to be those that resulted from the need for continued specialist follow-up and treatment or expand the diagnosis to new disorders found during the MIS-C hospitalisation.

During the follow-up period over 24 weeks after the MIS-C hospitalisation, a telephone questionnaire was conducted with the patient's caregivers. Between 1 July 2023 and 30 September 2023, at least 3 attempts were made to contact the caregivers by phone on different days at different times of the day. The questionnaire was divided into 2 parts. The first part, intended for patients of all ages, was a self-conducted survey containing questions about long-COVID symptoms, weight, height, SARS-CoV-2 reinfection, vaccination status against COVID-19, visits to outpatient specialty clinics, and rehospitalisations. A detailed description of the questionnaire is provided in the supplemental data. The second part included the administration of the KIDSCREEN-10 Index, Health Questionnaire for Children and Young People, Parent Version (The KIDSCREEN Group, 2004; EC Grant Number: QLG-CT-2000- 0075,1 KIDSCREEN-10 Index, Parent, Version in the Polish language), which were standardised for the Polish population. KIDSCREEN-10 is a tool used to assess the subjective health and the psychological, mental, and social well-being of children and adolescents between the ages of 8 and 18 years [13]. The questionnaire includes 10 questions answered using a Likert scale. To score and analyse the KIDSCREEN-10, negatively worded items were recoded so that for all items, higher scores indicated a better QoL. The raw score was calculated as a sum of all items and ranged from 10 to 50. The raw scores were transformed into Rasch person parameter estimates and, subsequently, *T*-values. Higher *T*-values represented a better

QoL. The results of obtained *T*-values were then compared to Poland National Norm Data.

STATISTICAL METHODS

The statistical analysis was performed using Statistica software, version 13.3 (TIBCO Software Inc., Palo Alto, CA, USA). The Shapiro-Wilk test was applied to assess the distribution of continuous data. The results for categorical variables were presented as numbers with percentages, whereas for continuous variables, mean values with standard deviations (SD) or medians with first and third quartiles (Q1, Q3) were used. The χ^2 test, Fisher exact test, Mann-Whitney *U* test, and Kruskal-Wallis test were applied to compare the characteristics of the study groups, differences in the MIS-C course and management, and long-COVID symptoms. Repetitive BMI measurements were analysed with Friedman's rank test. Risk factors for long-COVID at 4–12- and 12–24-week follow-ups were identified using logistic regression. To compare the re-

sults of KIDSCREEN-10 between the study group and the reference population, Student's *t*-test was performed. Statistical significance was set at *p*-values < 0.05.

RESULTS

STUDY GROUP

A total of 120 patients were diagnosed with MIS-C throughout the analysed time period. Four patients were excluded from the analysis because they failed to participate in the follow-ups. Therefore, the study group consisted of 74 patients (63.8%) admitted during the Original/Alpha variants dominance, 27 patients (23.3%) during the Delta variant, and 15 patients (12.9%) during the Omicron variant. The detailed characteristics of the study population and the MIS-C course and management are provided in Table 1.

In the study group, we found a predominance of White ancestry (98.3%). Multisystem inflammatory syndrome in

TABLE 1. The demographic data, selected symptoms and management during acute phase of multisystem inflammatory syndrome in children in studied groups

Group	Total, <i>N</i> = 116	Group 1 Original/Alpha, <i>n</i> = 74	Group 2 Delta, <i>n</i> = 27	Group 3 Omicron, <i>n</i> = 15	<i>p</i> -value
Male, <i>n</i> (%)	71 (61.2)	45 (60.8)	20 (74.1)	6 (40)	0.09*
Age (months) Median (Q1–Q3)	71 (35–117)	75 (34–127)	80 (47–115)	37 (21–58)	0.04**
BMI (%) Median (Q1–Q3)	48 (11–72)	46 (13–70)	37 (8–70)	68 (8–93)	0.58**
Cardiac failure with systolic function impairment or hypotension, <i>n</i> (%)	45 (38.8)	33 (44.6)	10 (37.1)	2 (13.3)	0.08*
NT-proBNP [pg/ml] Median (Q1–Q3)	4554 (1983–11238)	5036 (2026–11656)	4317 (1746–7940)	4965 (2311–8140)	0.83**
CRP [mg/l] Median (Q1–Q3)	164.4 (70.8–220.9)	164.3 (73.9–223.2)	176.2 (71.7–216.2)	132 (63–182.5)	0.58**
IVIG, <i>n</i> (%)	112 (96.6)	71 (95.9)	27 (100)	14 (93.3)	0.44***
Low-to-moderate dose of corticosteroids, <i>n</i> (%)	95 (84.1)	64 (86.5)	20 (74.1)	11 (73.3)	0.19***
High dose of corticosteroids, <i>n</i> (%)	8 (6.9)	5 (6.8)	1 (3.7)	2 (13.3)	0.42***
Milrinone, <i>n</i> (%)	28 (24.1)	23 (31.1)	5 (18.5)	0 (0)	0.03*
Dopamine, <i>n</i> (%)	10 (8.6)	8 (10.8)	2 (7.4)	0 (0)	0.63***
Epinephrine, <i>n</i> (%)	9 (7.7)	6 (8.1)	3 (11.1)	0 (0)	0.52***
PICU admission, <i>n</i> (%)	17 (14.7)	12 (16.2)	4 (14.8)	1 (6.7)	0.8***
LOS (days) Median (Q ₁ –Q ₃)	10 (9–13)	11 (9–14)	9 (8–11)	10 (7–13)	0.06**
LOS in PICU (days) Median (Q ₁ –Q ₃)	7 (5–8)	7 (4–9)	6 (3–12)	–	0.63^

BMI – body mass index, CRP – C-reactive protein, IVIG – intravenous immunoglobulin, LOS – length of stay, MIS-C – multisystem inflammatory syndrome in children, NT-proBNP – N-terminal pro B-type natriuretic peptide/brain natriuretic peptide, PICU – pediatric intensive care unit, Q1 – first quartile, Q3 – third quartile

* χ^2 test

** Kruskal-Wallis test

*** Fisher exact test

^ Mann-Whitney *U* test

children affected boys more frequently than girls during the Original/Alpha and Delta periods (60.8% and 74.1%, respectively), whereas during the Omicron variant, only 40% of MIS-C cases affected males ($p = 0.09$). Patients from the Omicron group tended to be younger than the Delta and Original/Alpha groups, 37 (21–58) months vs. 80 (47–115) months vs. 75 (34–127) months, respectively ($p = 0.04$). All groups were characterised by a similar distribution of BMI percentiles ($p = 0.58$). Most patients (84.5%) had positive antibodies to SARS-CoV-2. A positive nasopharyngeal swab using PCR or antigens occurred only in the Original/alpha group and accounted for 9.5% of all patients. Importantly, among all MIS-C cases, none of the patients were vaccinated against COVID-19 before hospitalisation.

MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN – COURSE AND MANAGEMENT

Patients, irrespective of dominant variant, presented typical symptoms of MIS-C, with a predominance of mucocutaneous ($n = 111$, 95.7%), cardiovascular ($n = 97$, 83.6%), gastrointestinal ($n = 92$, 79.3%), respiratory ($n = 87$, 75%), and neurological ($n = 11$, 9.5%) symptoms. On the other hand, the incidence of severe MIS-C and cardiac failure with systolic function impairment or hypotension decreased with every subsequent VOC (44.6% vs. 37.1% vs. 13.3%, $p = 0.08$). Although some discrepancies in the clinical course between the groups were observed, it was not reflected in significant differences in laboratory markers including the maximum C-reactive protein and NT-proBNP levels ($p = 0.83$, $p = 0.58$).

The use of anti-inflammatory medications was not significantly different between the groups. Over 90%

of patients received intravenous immunoglobulin alone or in combination with low-to-moderate doses of corticosteroids as the first-line treatment. In contrast, a major difference was observed between pandemic waves concerning inotropic agent administration. Milrinone treatment was required in 31.1% of patients in the Original/Alpha group and 18.5% in the Delta group, but it was not administered in the Omicron group ($p = 0.03$).

The hospitalisation was complicated by PICU admission in 16.2%, 14.8%, and 6.7% of MIS-C cases from consecutive pandemic waves ($p = 0.8$), but none of our patients required extracorporeal membrane oxygenation (ECMO) or died. The median time of hospitalisation was not significantly different between the groups ($p = 0.06$) and did not exceed 11 days in any group.

RESULTS FROM THE 4–12-WEEK FOLLOW-UP

Between 4 and 12 weeks after admission, 58 (78.4%) patients from the Original/Alpha group, 19 (70.4%) from the Delta group, and 11 (73.3%) from the Omicron group were followed up in the paediatric outpatient clinic. In the Original/Alpha group, patients most frequently (50%) reported long-COVID symptoms. In comparison to the Delta and Omicron groups, 42.1% and 36.4% of participants reported long-COVID symptoms, respectively ($p = 0.64$). There were no significant differences in the frequency of specific symptoms between patients from the different pandemic waves except for a higher incidence of fatiguability in the Original/Alpha group compared to the Delta and Omicron groups ($p = 0.03$). Remarkably, participants of the Original/Alpha group presented the most complex clusters of symptoms. No patients presented symptoms of cardiac failure during the follow-up period.

TABLE 2. Long-COVID symptoms and body mass index results during 4–12 weeks of follow-up

Group	Total, $N = 88$	Group 1 Original/Alpha, $n = 58$	Group 2 Delta, $n = 19$	Group 3 Omicron, $n = 11$	p -value
Any long-COVID syndrome, n (%)	41 (46.6)	29 (50)	8 (42.1)	4 (36.4)	0.64*
Increased fatiguability/weakness, n (%)	25 (28.4)	22 (37.9)	2 (10.5)	1 (9.1)	0.03*
Peripheral edema, n (%)	4 (4.5)	4 (6.9)	0 (0)	0 (0)	0.75**
Subjective feeling of heart palpitations, n (%)	5 (5.7)	3 (5.2)	2 (10.5)	0 (0)	0.63**
Neurological symptoms ^a , n (%)	8 (9.1)	6 (10.3)	2 (10.5)	0 (0)	0.73**
Aggression, psychomotor agitation, n (%)	8 (9.1)	6 (10.3)	0 (0)	2 (18.2)	0.21**
Nightmares, n (%)	7 (7.9)	5 (8.6)	0 (0)	2 (18.2)	0.13**
Rash, n (%)	1 (1.1)	1 (1.7)	0 (0)	0 (0)	1.0**
Arthralgia, n (%)	1 (1.1)	0 (0)	1 (5.26)	0 (0)	0.34**
Hair loss, n (%)	3 (3.4)	3 (5.2)	0 (0)	0 (0)	0.71**
BMI (%)	62 (32–77)	68 (34–82)	57 (27–73)	36 (17–59)	0.2***
Median (Q_1 – Q_3)					

BMI – body mass index, long-COVID – long-coronavirus disease, Q_1 – first quartile, Q_3 – third quartile

^a Headaches, hand tremors, increased intensity of tics, palate paralysis, abnormal gait, absence seizures, one-sided muscle weakness, visual disturbances

* χ^2 test

**Fischer exact test

***Kruskal-Wallis test

The detailed characteristics of complaints received between 4–12 weeks after admission are provided in Table 2.

During this period, 65 (87.8%) patients from the Original/Alpha and 25 (92.6%) patients from the Delta group visited at least one specialist outpatient clinic, compared to only 8 (53.3%) in the Omicron group ($p = 0.004$). Cardiac visits occurred in 63 (85.1%) patients from the Original/Alpha, 25 (92.6%) from the Delta, and 6 (40%) from the Omicron group ($p < 0.001$). Non-cardiac outpatient control (including visits to the following clinics: rheumatology, immunology, endocrine, neurology, gastroenterology, nephrology, urology, and dermatology) were required in 12 (16.2%), 4 (14.8%), and 3 (20%) patients from the consecutive pandemic waves, respectively ($p = 0.87$). All, except one, non-cardiac visits (urology) were MIS-C related. Only 3 patients from the Original/Alpha group and one patient each from the Delta and Omicron groups were hospitalised (2 for gastroenteritis and one for allergy diagnostics) during the analysed time period. None of these patients were rehospitalised for MIS-C and none of these events were MIS-C related.

RISK FACTORS FOR LONG-COVID AT 4–12-WEEK FOLLOW-UP

Univariable logistic regression analysis indicated older age (OR = 1.13 per year, 95% CI: 1.02–1.25), history of cardiac failure with systolic function impairment or hypotension (OR = 2.47, 95% CI: 1.04–5.88), and length of hospital stay (OR = 1.2 per 1 day, 95% CI: 1.05–1.37) as risk factors for long-COVID manifestations between 4 and 12 weeks from admission. However, older age and length of hospital stay were the only independent prognostic factors identified in the multivariable model (Table 3). Being one year older increased the probability of long-COVID during the 4–12 week follow-up by 13%, whereas a one day longer hospital stay increased the chance by 20%.

RESULTS FROM THE 12–24-WEEK FOLLOW-UP

Only 16 (21.6%) patients from the Original/Alpha group, none from the Delta group, and 2 (13.3%) from the Omicron group continued follow-up in the paediatric outpatient clinic between 12 and 24 weeks after admission. Among them, symptoms of long-COVID were found exclusively in 5 children from the Original/Alpha group. On the other hand, during a search of the hospital's database, we found that during this period, specialist consultations in outpatient clinics were required in 49 (66.2%) participants from the Original/Alpha, 10 (37.1%) from the Delta, and 10 (66.7%) from the Omicron group ($p = 0.03$). Cardiac visits accounted for 39 (52.7%) of the visits in the Original/Alpha, 5 (18.5%) in the Delta, and 4 (26.7%) in the Omicron group ($p = 0.004$). Non-cardiac follow-up (including visits to the following clinics: rheumatology, immunology, en-

TABLE 3. Multivariable logistic regression analysis of factors associated with long-COVID manifestation between 4–12 weeks from admission

Factor	OR	+ 95% CI	– 95% CI	p-value
Older age	1.13	1.01	1.26	0.03
LOS	1.2	1.05	1.37	0.01

BMI – body mass index, CI – confidence interval, CRP – C-reactive protein, ICU – intensive care unit, LOS – length of stay

Factors included in the analysis: sex, age, COVID-19 variant, BMI pc, NT-proBNP max, CRP max, cardiac failure, high dose of corticosteroids, ICU admission, LOS

Hosmer-Lemeshow statistic = 7.13, $p = 0.52$

docrinology, neurology, haematology, gastroenterology, nephrology, urology, and dermatology) was obtained in 20 (27.1%) patients from the Original/Alpha, 6 (22.2%) from the Delta, and 9 (60%) from the Omicron groups ($p = 0.02$). All, except one, of the non-cardiac visits (urologic) were MIS-C related. Three hospitalisations (inguinal hernia and cryptorchidism surgery, complicated sinusitis, and the diagnosis of PFAPA – periodic fever, aphthous stomatitis, pharyngitis, and adenitis) were observed during the analysed period. One in the Original/Alpha and 2 in the Omicron groups, none were linked to MIS-C.

RESULTS FROM THE OVER-24-WEEK FOLLOW-UP (TELEPHONE SURVEY)

The response rate for the telephone survey was 81.1%. The questionnaire was completed by 63 (85.1%) legal guardians from the Original/Alpha, 19 (70.4%) from the Delta, and 12 (80%) from the Omicron group. The median time for follow-up calls based on the groups was 945 days (890–964), 575 days (550–593), and 306 (251–345) days ($p < 0.001$), respectively. The frequency of long-COVID symptoms was high, exceeding 50% in all groups. The occurrence of long-COVID symptoms between 4 and 12 weeks after admission was the only risk factor for prolonged symptoms (OR 3.22, 95% CI: 1.32–7.87). Sex, age, COVID-19 variant, history of cardiac failure, high doses of corticosteroids, PICU admission, length of stay, and time from admission to the survey were not related to long-COVID risk. Among individual symptoms, sleep disturbances were the most commonly reported symptom for the Original/Alpha and Omicron variants (28.6% and 41.8%, respectively), and headaches for the Delta variant (21.1%). The detailed characteristics of long-COVID presentations obtained by telephone survey are provided in Table 4. About 10% of children from the first 2 pandemic waves required rehabilitation after discharge, whereas it was not necessary for anyone from the Omicron group ($p = 0.73$). No major differences were observed in the proportion of patients requiring psychological care during follow-up (9.52% vs. 5.26% vs. 16.67%, $p = 0.66$).

Only patients from the Original/Alpha group were vaccinated against COVID-19 at discharge from the hospital.

TABLE 4. Long-COVID symptoms and body mass index results reported in telephone survey

Group	Total, N = 94	Group 1 Original/Alpha, n = 63	Group 2 Delta, n = 19	Group 3 Omicron, n = 12	p-value
Any long-COVID syndrome, n (%)	53 (56.4)	35 (55.6)	10 (52.6)	8 (66.7)	0.73*
Increased fatiguability/weakness, n (%)	22 (23.4)	17 (27)	3 (15.8)	2 (16.7)	0.62**
Subjective feeling of heart palpitations, n (%)	6 (6.4)	5 (7.9)	0 (0)	1 (8.3)	0.54**
Headaches, n (%)	21 (22.3)	14 (22.9)	4 (21.1)	3 (25)	1.0**
Sleep disturbances, n (%)	25 (26.6)	18 (28.6)	2 (10.5)	5 (41.7)	0.13*
Arthralgia, n (%)	12 (12.7)	7 (11.1)	3 (15.8)	2 (16.7)	0.71**
Stomachache, n (%)	4 (4.3%)	4 (6.4)	0 (0)	0 (0)	0.75**
Other ^a , n (%)	10 (10.6)	6 (9.5)	4 (21.1)	0 (0)	0.17**
BMI (%) Median (Q ₁ –Q ₃)	41 (17–79)	40 (19–53)	41 (12–72)	80 (1–89)	0.83***

BMI – body mass index, long-COVID- long-coronavirus disease, Q1 – first quartile, Q3 – third quartile

^a Depression, sleepiness, psychomotor agitation, anxiety, concentration disorder, excessive sweating

* χ^2 test

** Fischer exact test

*** Kruskal-Wallis test

However, even in this group, the number of vaccinated patients was small (9, 14.29%). Similarly, COVID-19 reinfections were observed exclusively in this group (17.46% vs. 0% vs. 0%, $p = 0.05$).

The analysis of repeated measurements revealed that BMI percentiles were significantly higher at 4–12-week follow-ups compared to the values from admission or declared by caregivers during the telephone survey (over 24 weeks after MIS-C) in the Original/Alpha group (46 [13–70] vs. 68 [34–82] vs. 40 [19–53], $p = 0.002$). A similar trend was observed in the Delta group (37 [8–70] vs. 57 [27–73] vs. 41 [12–72], $p = 0.07$), but not in the Omicron variant group (68 [8–93] vs. 36 [17–59] vs. 80 [1–89], $p = 0.22$).

KIDSCREEN-10

KIDSCREEN-10 was completed by 45 (73.7%) parents whose children were between 8 and 18 years of age. Among them, 32 (71.1%) belonged to the Original/Alpha group, 10 (22.2%) to the Delta group, and 3 (6.7%) to the Omicron group. There were no missing answers. The mean T -value was not significantly different between consecutive pandemic waves (56.72 ± 8.65 vs. 64.71 ± 8.5 vs. 59.79 ± 18.25 , $p = 0.07$). In comparison with the reference population, the whole group obtained significantly higher T -values, revealing a better QoL ($p < 0.001$).

DISCUSSION

The long-term complications of MIS-C have been a research topic, particularly in the context of the occurrence of long-COVID symptoms [6, 14, 15]. There is no uniform definition for paediatric long-COVID, and the available studies are characterised by a great diversity of methodologies, resulting in incidence ranging 4–66% depending on the criteria adopted [16, 17]. There is also a lack of data comparing long-COVID symptoms

after MIS-C in successive waves of the pandemic, despite the course of COVID-19 varying depending on the causative variant [8]. In our study, regardless of the length of the observation period, most of the reported symptoms of long-COVID did not differ significantly between the groups. The only statistically significant differences were observed during the 4–12-week follow-up, where fatiguability/weakness was more frequently found in the Original/Alpha group. It is unclear whether the outcome of this observation is due to the effect of the variant itself or other factors, primarily the age of the patients. Patients in the Original/Alpha and Delta groups were significantly older than in the Omicron group, and during multivariable analysis, older age was identified as an independent risk factor for long-COVID symptoms. Similar results were obtained in studies by other authors where long-COVID symptoms were more common in older children [18, 19]. Another factor that may affect the outcome of this observation is the higher incidence of cardiac failure with systolic function impairment in the Original/Alpha group. However, it is worth noting that we did not observe symptoms of cardiac failure in any patient after discharge. On the other hand, patients in the Delta group had similar demographics and a clinical course of MIS-C to the Original/Alpha group but differed in the incidence of fatiguability/weakness. The high incidence of fatiguability/weakness seen in the Original/Alpha group may, therefore, have been influenced by the psychological burden on young people related to the first period of the pandemic and the resulting restrictions [20, 21].

The frequency and diversity of all long-COVID symptoms during the 4–12-week follow-up were comparable to observations by other authors, with a predominance of fatiguability, headaches, and cognitive function impairment, except for hair loss, which was found only in our cohort [7, 15]. However, since there is a scarcity of clinical studies

in children, research in adult patients observed an incidence of telogen effluvium of up to 20% after COVID-19 [22, 23]. Also, in this follow-up period, an increase in mean BMI values was observed in the Original/Alpha and Delta groups, but not in the Omicron group, and this probably resulted from the recommendation to limit physical activity in patients after cardiac failure. Later, in the follow-up period, a normalisation of BMIs was observed. A temporary increase in BMI after MIS-C was also observed in studies by other authors [7].

An interesting observation is the higher incidence of long-COVID symptoms reported in all groups, especially in the Omicron group, during the telephone survey (at least 24 weeks after the onset of the disease). This observation contrasts with results from a systematic review involving adult patients, which suggest that patients after the Omicron variant have a lower risk of developing long-COVID symptoms [24]. Unfortunately, there is a lack of studies on the long-term complications of SARS-CoV-2 infections in children based on the variants. In our study, the follow-up period for the Original/Alpha and Delta patients was significantly longer compared to Omicron patients, the extension of this observation period could reveal differences in the duration of symptoms between the groups. The most common symptom, reported during the telephone survey, as in previous follow-up periods, was fatiguability/weakness, which was observed in 23.4% of patients. In the results of studies by other authors, the prevalence of long-COVID symptoms, connected with fatiguability/weakness or tiredness, during a 6-month observation period was characterised by a broad range. Our results were higher compared to a study by Roge *et al.* [15], in which decreases in physical activity, increased tiredness, and difficulty concentrating were observed in 9.5% of patients. On the other hand, our results were comparable to the results found in the Rollins *et al.* [25] study, in which parents reported fatigue in 22.3% of patients, and was even lower than in Penner *et al.* [7], which had a worse 6-min walk test score, and the incidence of abnormalities on neurological examination was found in 45% of patients.

Such a discrepancy in these results may be due to the fact that the symptoms of long-COVID are non-specific and may overlap with post-intensive care syndrome [26] or critical illness myopathy [27]. In our study, the incidence of PICU admissions was lower than in the other observational studies, probably because patients with cardiac failure, who only required an infusion of milrinone, were not transferred to the PICU at our institution. Steroid use was comparable with the reports of other authors [7, 15, 25]. The high percentage of long-COVID symptoms reported in our telephone survey contrasts with the above-average results of QoL assessment using a more objective tool like the standardised KIDSCREEN-10 questionnaire. Therefore, we cannot exclude the overdiagnosis of long-COVID

during a telephone survey compared to a direct visit to the paediatric office. The symptoms of long-COVID are non-specific, and the diagnosis is made after ruling out other causes of the presented symptoms, which is much more difficult in the case of a telephone survey. Thus, results should be interpreted with caution.

It is worth noting that, despite having recovered from a serious illness, only a small percentage (9.6%) of our patients were vaccinated against COVID-19 after undergoing MIS-C. A similar trend has been described in the studies of other authors, where vaccination status was even lower and amounted to only 3.2% of participants [28]. Although the recurrence of MIS-C after reinfection with SARS-CoV-2 seems unlikely [29], there are isolated reports of this phenomenon [30]. In our cohort, COVID-19 reinfections were found only in the Original/Alpha group, and none of these patients developed MIS-C. Taking into account the protective effect of the vaccination against COVID-19 and the occurrence of MIS-C [31], the decision about vaccinations should be made individually.

Our study has some limitations. We did not include patients after COVID-19 without MIS-C, which would have allowed for a more accurate distinction of complications associated with MIS-C alone. However, this study aimed to compare the long-term complications of MIS-C caused by the different variants of SARS-CoV-2. The assessment of long-COVID symptoms during the 12–24-week period in our study was limited by the small number of patients who presented in the paediatric office. On the other hand, during the 12–24-week follow-up, more than half of patients needed specialist consultation, which was MIS-C related. It is possible that frequent check-ups in outpatient specialty clinics during pandemic restrictions may have influenced the decision not to attend an appointment at the paediatric office. However, most of the participants continued with at least one form of follow-up. In our study, we relied on self-reported neurological symptoms by patients or their caregivers. Scheduling visits to the neurological outpatient clinic, in all patients, could improve the detection of minor neurological deficits.

CONCLUSIONS

During short-term (4–12 weeks) follow-up, the older age of patients significantly increased the risk of long-COVID symptoms in children after MIS-C. Patients who report symptoms up to 12 weeks after MIS-C continued to present with symptoms beyond 24 weeks, which could help plan care after hospital discharge.

During long-term (over 24 weeks) follow-up, the QoL after MIS-C seems to be non-inferior to the overall paediatric population. Long-COVID symptoms are non-specific, which can lead to overdiagnosis. Systematic long-term follow-up in children after MIS-C, with effective exclusion

of other causes, could allow for a better differentiation of the real consequences of MIS-C and SARS-CoV-2 on QoL.

DISCLOSURE

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