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RESEARCH LETTER

Comorbidities, clinical characteristics and outcomes of COVID-19 in pediatric patients in a tertiary medical center in the Netherlands

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Having pre-existing comorbidities is described as a risk factor for more severe disease in adult corona virus disease 2019 (COVID-19) and in infections with SARS-CoV-1 and MERS-CoV [1]. In adult SARS-CoV-2 infections, patients with pre-existing underlying comorbidities, such as chronic obstructive pulmonary disease, cardiovascular disease, diabetes and obesity, are more likely to have severe disease compared to healthy adults [2]. An inconsistency is seen in current findings on the association with comorbidities and pediatric COVID-19 severity. An important limitation in currently available studies is limited data: severe disease is rare in children compared to adults, and most studies describe COVID-19 severity merely by reporting intensive care unit (ICU) admission or mortality rates instead of detailed data on clinical presentation and outcomes.

A severe manifestation of SARS-CoV-2 infection is multi inflammatory syndrome in children (MIS-C), which usually follows weeks after SARS-CoV-2 infection and is characterized by gastrointestinal symptoms, muco-cutaneous signs and cardiovascular involvement. Several studies describe the association between comorbidities and incidence or mortality of MIS-C [3, 4]. To our knowledge, there are no data on the association between pre-existing comorbidities and the severity of MIS-C.

Thus, the primary aim of this retrospective study was to describe in detail the pre-existing comorbidities and the severity of SARS-CoV-2 infections in pediatric patients in a tertiary medical center in the Netherlands. Second, we aimed to assess the association between comorbidities and disease severity of both acute COVID-19 and MIS-C in pediatric patients. These data will help to determine which groups of children are more vulnerable to severe acute COVID-19 and severe MIS-C, which could aid development of clinical SARS-CoV-2 infection care and management strategies.

This retrospective, observational cohort study was carried out at the tertiary medical center, Amsterdam UMC, the Netherlands. Inclusion criteria were in- and outpatients younger than or equal to 18 years with a positive polymerase chain reaction (PCR) test or serum antibodies (total Ig) against SARS-CoV-2 between March 2020 and April 2021. Patients were excluded when no data on clinical characteristics of the SARS-CoV-2 infection were available.

Data describing pre-existing comorbidities, COVID-19 severity and clinical outcomes were retrieved from medical records. Comorbidities were assessed by extracting data on pre-existing disorders based on ICD-10 codes and body mass index (BMI). A pre-existing disorder was found to be relevant when the disorder could potentially interact with the immune system or other bodily functions which could influence disease severity. The pre-existing comorbidities were classified into comorbidity groups based on the affected organ system. We used the definition of childhood obesity using BMI corrected for age and sex in 2000 by Cole et al., to assess the prevalence of obesity for patients aged 2 years or older [5].

Disease severity of pediatric acute COVID-19 was classified by Dong et al. into five categories: asymptomatic, mild, moderate, severe and critical [6]. For statistical analyses, asymptomatic, mild and moderate cases were combined as non-severe disease, and severe and critical cases were combined as severe disease. Based on the WHO criteria for MIS-C and parallel to the classification mentioned above, the severity of MIS-C was described as moderate, severe or critical [6, 7]. Moderate cases were classified as non-severe, and severe and critical disease were combined as severe disease for the statistical analysis. Clinical outcome described hospitalization, ICU admission and mortality rates in both

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acute COVID-19 and MIS-C. Long-term symptoms after acute COVID-19, known as post-COVID-19 syndrome, were reported based on the clinical definition of post-COVID-19 syndrome according to the NICE guidelines [8]; symptoms that developed during or after acute COVID-19 continuing for more than 12 weeks.

Data analysis was performed with Statistical Package for the Social Sciences (SPSS) using Fisher's or Fisher–Freeman–Halton exact tests. A P value < 0.05 was considered statistically significant. Odds ratios were calculated to describe strengths of associations. In case of contingency tables containing a value of zero, Firth's penalized logistic regression was used to calculate a corresponding odds ratio for the Fisher's exact test to mitigate sparse data bias [9].

A total of 83 patients were included in this study, among which 46 patients had pre-existing comorbidities. In Table 1, data on demographics and patient characteristics are summarized. Most common pre-existing comorbidities were obesity ($n = 10$, 21.7%), respiratory disorders ($n = 9$, 19.6%) and neurological disorders ($n = 8$, 17.4%). For a detailed description of pre-existing comorbidities in each comorbidity group (Supplementary table).

From the 58 patients with acute COVID-19, 38 (65.5%) had a pre-existing comorbidity. Most patients had mild COVID-19 disease, in the patient group without comorbidities ($n = 16$, 80.0%) as well as in the patient group with comorbidities ($n = 24$, 63.2%). All the eight patients with severe or critical disease (13.8%), had pre-existing comorbidities. One of these patients died due to the consequences of COVID-19. Table 2 summarizes data on severity and hospital admission per group (comorbidities versus no comorbidities). More severe acute COVID-19 was seen in patients

Table 1 Patient characteristics and key demographics

Patient characteristics	No comorbidities ($n = 37$)	Comorbidities ($n = 46$)
Sex, *n* (%)		
Male	23(62.2)	23 (50.0)
Female	14 (37.8)	23 (50.0)
Age, year, median (IQR)	11.0 (4.5–14.5)	11.5 (4.8–16.0)
Weight, kg, median (IQR)	44.3 (26.6–57.3)	45.7 (19.5–64.0)
Height, cm, median (IQR)	154.0 (122.5–168.0)	145.0 (110.0–168.0)
BMI, median (IQR)	18.6 (16.6–20.7)	18.9 (16.0–23.8)
Pre-existing comorbidities, n (%)		
Obesity		10 (21.7)
Respiratory disorder		9 (19.6)
Systemic auto immune disorder		3 (6.5)
Neurological disorder		8 (17.4)
Cardiovascular disorder		5 (10.9)
Endocrine system disorder		4 (8.7)
Hematological disorder		2 (4.3)
Gastrointestinal disorder		3 (6.5)
Urogenital system disorder		6 (13.0)
Genetic/chromosomal abnormalities		6 (13.0)
Cancer		2 (4.3)
Other comorbidities		4 (8.7)
Pharmacological treatment, *n* (%)		27 (58.7)
Immunosuppressant medication		7 (15.2)
PCR confirmed SARS-CoV-2 infection, *n* (%)	22 (59.5)	37 (80.4)
PCR result negative or unknown, *n* (%)[a]	15 (40.5)	9 (19.6)
Reason for testing, *n* (%)		
Unknown	5 (13.5)	4 (8.7)
Clinical suspicion of SARS-CoV-2 infection	31 (83.8)	39 (84.8)
Symptoms suspicious for COVID-19	31 (83.8)	33 (71.7)
Contact with COVID-19 case	10 (27.0)	15 (32.6)
Routinely (before procedure)	1 (2.7)	2 (4.3)

[a]Patients with negative or unknown PCR results were included only when (IgM and/or IgG) antibodies against SARS-CoV-2 in serum were present. IQR interquartile range.

with pre-existing comorbidities compared to those without comorbidities ($P=0.041$, OR 11.42, 95% CI 1.29–1507.49). Patients with a pre-existing comorbidity also had a higher risk of being admitted to the ICU ($P=0.032$, OR = 11.72, 95% CI 1.31–1547.79) than those without comorbidities.

In particular, the presence of a neurological disorder was found to be associated with acute COVID-19 severity ($P=0.004$, OR 16.11, 95% CI 2.51–103.55). In the group of neurological disorders, 63% had epilepsy or frequent seizures, 50% had cerebral palsy, and other disorders included hydrocephalus and myasthenia gravis. Other main groups of disorders, such as obesity or respiratory disorders, did not show a significant association with disease severity. Table 3 contains the difference in acute COVID-19 severity (non-severe vs severe) between all comorbidity groups.

Twenty-eight patients were diagnosed with MIS-C as a manifestation of SARS-CoV-2 infection. Twenty-five percent of MIS-C patients ($n=7$) had a pre-existing comorbidity. Twelve patients (42.9%) met the criteria for critical disease (Table 2). The majority of MIS-C patients did not have comorbidities, and no significant associations between comorbidities and severity of MIS-C were found. The key findings of this study indicate that, although most pediatric patients have non-severe disease, children with pre-existing comorbidities are more likely to have more severe acute COVID-19 than children without comorbidities. In particular, pediatric neurological disorders were associated with more severe COVID-19.

Considerable inconsistency is seen in current evidence on the association between comorbidities and pediatric COVID-19 severity. A meta-analysis by Tsankov et al. combined the findings of several heterogeneous articles, concluding an association between comorbidities and acute COVID-19 severity [10]. However, most of the included studies had a small sample size and only described the association between comorbidities and ICU admission or mortality rate instead of severity as a detailed description of clinical characteristics. This could create selection bias because children with comorbidities could be admitted to the ICU as a preventative measure instead of due to clinical deterioration [10]. Our study methods included a detailed clinical evaluation to describe COVID-19 disease severity following a classification system in addition to ICU admission.

Corroborating our findings, two studies, performed in other countries and using a similar classification system, found that children with comorbidities have a higher risk for more severe COVID-19, including a larger cohort of 3837 pediatric patients [11, 12]. The other study also found an association between more severe COVID-19 and neurological disorders, which included mostly epilepsy or severe neuro-disability similar to the patients in our study [11]. Another multicenter observational study in the UK also found that among comorbidities in patients who needed critical care due to COVID-19, neurological disorders (such as neurodisability) were one of the most common [13]. Neurological disabilities, such as cerebral palsy, which influence motor functions, could lead to difficulties in spontaneous breathing and clearing respiratory secretions, which could worsen respiratory infections and thus explain this association with more severe acute COVID-19. Moreover, SARS-CoV-2 can affect the nervous system through damage to neuronal cells, muscle tissues and vascular cells, which are likely to be more vulnerable in children with comorbidities [14].

In contrast, three of the studies that used a similar classification of severity, all with relatively small sample sizes, found that having comorbidities was not associated with disease severity in pediatric patients [15–17]. This inconsistency is possibly due to the missing consensus on definitions of relevant pre-existing comorbidities and to a missing universal classification of disease severity of acute COVID-19. In our results, we particularly did not find an association between obesity and severity of acute COVID-19, which has been seen in some other studies [10, 11]. It is thought that higher visceral adiposity is associated with higher inflammatory cytokine levels correlated with COVID-19 severity, which might explain why more severe acute COVID-19 can be seen in obese patients [10]. We also do not report an association between respiratory disorders, such as asthma, and acute COVID-19 severity, which is in accordance with findings related to SARS-CoV-1 and MERS-CoV infections [18]. It is suggested that human coronaviruses may not have the capacity to enhance asthmatic inflammation, unlike the human rhinovirus or respiratory syncytial virus [18].

Our findings imply that having comorbidities is not a risk factor for having more severe MIS-C compared to having no comorbidities. This is in accordance with previous findings that pre-existing comorbidities among MIS-C patients are rare [3]. Healthcare professionals should be aware of the association between pre-existing comorbidities and severity of COVID-19 to determine adequate management strategies for this specific group. Furthermore, the implications made in this study should be taken into consideration in the debate on SARS-CoV-2 vaccination in children. It is worth noting that the absolute numbers of severe disease due to acute pediatric COVID-19 are low and that the size of the effect comorbidities has on disease severity remains uncertain. However, effects of the COVID-19 pandemic on children in particular, such as social isolation and interruption in education, also should be considered in future management or prevention strategies [19]. This study substantiates the need for large-scale studies with well-defined evaluation and classification

Table 2 Severity of disease and outcomes

Outcomes	No comorbidities	Comorbidities
Acute COVID-19 ($n=58$)	$n=20$	$n=38$
Severity, *n* (%)		
Asymptomatic	0 (0)	2 (5.3)
Mild	16 (80.0)	24 (63.2)
Moderate	4 (20.0)	25 (10.5)
Severe	0 (0)	4 (13.2)
Critical	0 (0)	3 (7.9)
Hospital admission, *n* (%)	7 (35.0)	12 (31.6)
ICU admission, *n* (%)	0 (0)	6 (15.8)
Hospitalization duration, d, median (IQR)		
Hospital admission	3.0 (0.0–6.0)	4.0 (2.0–11.0)
ICU admission	0 (0)	2.5 (1.8–10.3)
Mortality, *n* (%)	0 (0)	1 (2.6)
Post COVID syndrome, *n* (%)	6 (30.0)	2 (5.3)
Fatigue	4 (20.0)	2 (5.3)
Dyspnea	2 (10.0)	
Concentration problems	2 (10.0)	
Dizzines	1	
MIS-C, $n=28$	$n=21$	$n=7$
Severity, *n* (%)		
Moderate	7 (33.3)	1 (14.3)
Severe	6 (28.6)	2 (28.6)
Critical	8 (38.1)	4 (57.1)
Hospital admission, *n* (%)	21 (100.0)	7 (100.0)
ICU admission, *n* (%)	11 (52.4)	5 (71.4)
Hospitalization duration, d, median (IQR)		
Hospital admission	7.0 (5.0–8.0)	7 (7.0–10.0)
ICU admission	5.0 (3.0–6.0)	3.0 (2.5–6.5)
Mortality, *n* (%)	0 (0)	1 (0)
Long term complaints, *n* (%)	3 (14.3)	1 (14.3)

of disease severity to determine the true strength of the association.

The strengths of this study include the detailed information on clinical characteristics and outcomes to carefully assess the severity of COVID-19 infection and the association between the severity of MIS-C and pre-existing comorbidities.

Our study has a few limitations. First, the retrospective observational study design may cause residual confounding. Second, because severe COVID-19 and hospital admission is rare in children, our study consisted of a small sample size. Selection bias may have affected the results, because asymptomatic or mild children are not always PCR-confirmed and, therefore, are under-represented. Owing to the small sample, there was sparsity in numbers included for statistical analyses, which contributes to the broad confidence intervals. Various international databases have been set up to prospectively study COVID-19 severity in patients with comorbidities, a promising development [10]. Third, the study was carried out at a tertiary center where mostly severely ill children or children with complex comorbidities are treated, which can cause selection bias.

In conclusion, our findings show that pediatric acute COVID-19 is mostly non-severe, but children with pre-existing comorbidities are at risk for developing more severe acute COVID-19 compared to patients without comorbidities. MIS-C is generally more severe than acute COVID-19. However, no association was found between comorbidities and severity of MIS-C. More prospective large-scale data on the susceptibility of children with comorbidities for severe acute COVID-19 are needed, as well as more data on

Table 3 Difference in COVID-19 severity between patients with different comorbid disorders

Variables	Non-severe ($n=50$)	Severe ($n=8$)	P value
Sex, n (%)			
Male	29 (58.0)	4 (50.0)	0.715[a]
Female	21 (42.0)	4 (50.0)	
Comorbidities (total), n (%)	30 (60.0)	8 (100.0)	0.041[a,b]
Main groups of pre-existing disorders, n (%)			
Obesity	3 (6.0)	2 (25.0)	0.136[a]
Respiratory system	4 (8.0)	3 (37.5)	0.128[a]
Systemic autoimmune disorders	2 (4.0)	–	1.000[a]
Neurological system	3 (6.0)	5 (62.5)	0.004[a,b]
Cardiovascular system	5 (10.0)	–	0.563[a]
Endocrine system	4 (8.0)	–	0.566[a]
Hematological system	2 (4.0)	–	1.000[a]
Gastrointestinal system	2 (4.0)	1 (12.5)	0.498[a]
Urogenital system	6 (12.0)	–	0.318[a]
Genetic/chromosomal abnormalities	5 (10.0)	1 (12.5)	1.000[a]
Cancer	2 (4.0)	–	1.000[a]
Immunosuppressive treatment	5 (10.0)	1 (12.5)	1.000[a]

[a]Fisher's exact test. [b]Significant value, $P<0.05$

risk factors for developing severe MIS-C to establish management strategies for SARS-CoV-2 infections in specific groups of pediatric patients.

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Data availability The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethical approval Approval and a waiver for the Medical Research Involving Human Subjects Act was provided by the local medical ethics review committee of Amsterdam UMC (Reference number W21_273#21.300).

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