Do Pre-existing Comorbid Conditions Influence the Clinical Course of COVID-19 Infection in Childhood?

Gulsum Iclal Bayhan (✉ gibayhan@gmail.com)
Yildirim Beyazit University, Faculty of Medicine  https://orcid.org/0000-0002-1423-4348

Tugba Bedir Demirdag
Gazi University, Faculty of Medicine

Saliha Kanik Yuksek
Children's Hospital of Ankara City Hospital

Aslinur Ozkaya Parlakay
Yildirim Beyazit University, Faculty of Medicine

Belgin Gulhan
Children's Hospital of Ankara City Hospital

Bedia Dinc
Ankara City Hospital

Busra Bulut
Yildirim Beyazit University, Faculty of Medicine

Emrah Senel
Yildirim Beyazit University, Faculty of Medicine

Research

Keywords: Children, co-morbidity, COVID-19, lower respiratory tract infection, upper respiratory tract infection

DOI: https://doi.org/10.21203/rs.3.rs-95072/v1

License: ☒ ☀ This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Background

COVID-19 has a milder clinical course in childhood with significantly lower mortality than in adulthood. The presence of comorbid conditions such as cardiovascular disease and respiratory disease is thought to be associated with increased mortality in adults. There is very little information on the clinical course of COVID-19 in children with pre-existing comorbid conditions.

Methods

We retrospectively evaluated laboratory-confirmed pediatric COVID-19 at the Children's Hospital of Ankara City Hospital. The patients were classified as those with and without pre-existing comorbid conditions and the two groups were compared for age, gender, clinical picture at presentation, the presence of severe disease, and pediatric intensive care unit (PICU) requirement.

Results

A total of 317 children were confirmed to have COVID-19 infection. A pre-existing comorbid condition was present in 59 (18.6%) and absent in 258 (81.4%). The rate of lower respiratory tract infection was significantly higher in the patients with comorbidities (p=0.012). None of our patients had severe disease on admission and severe disease did not develop during follow-up.

Conclusions

Our results indicate that the clinical course of COVID-19 in children with pre-existing comorbid conditions may not be as severe as in adults, and lower respiratory infection may be more common in children with pre-existing comorbidities.

Introduction

COVID-19 infection only results in mild symptoms and signs in 80% of the patients and mortality mostly occurs in patients aged 60 years or more or those who have pre-existing comorbid conditions. COVID-19 can affect every pediatric age group. It generally has a milder clinical course in children than in adults. Children make up 2% of all COVID-19 cases in China, 1.2% in Italy, and 5% in the USA. In Turkey, the total number of COVID-19 cases was 198,284 on 2 July 2020, and 2% of all COVID-19 cases were in the 15 years or younger age group and 13.7% in the 15–24 years age group. The presence of comorbid conditions such as cardiovascular disease and respiratory disease is thought to be associated with increased mortality in adults. There is very little information on the clinical course of COVID-19 in children with pre-existing comorbid conditions. The impact of preexisting comorbid conditions on the prognosis of COVID-19 in children is therefore not clear yet.
This study was conducted at the Ankara City Hospital, which is one of the hospitals designated as pandemic hospital in Ankara, Turkey. The Children's Hospital section of the Ankara City Hospital was the only hospital designated as a pandemic hospital for children in Ankara at the beginning of the pandemic. Filiation procedures were strictly observed in Turkey from the time the first COVID-19 case was diagnosed in the country. Every person with exposure to a COVID-19 case was found and a nasopharyngeal swab sample was obtained for a polymerase chain reaction (PCR) assay, together with an exposure history. Every PCR-positive child who presented at the Ankara City Hospital during the study period was hospitalized. Following discharge, every patient was followed-up by telephone for 14 days. We retrospectively evaluated our pediatric COVID-19 patients and investigated whether accompanying comorbid conditions influence the clinical presentation and prognosis of COVID-19 in children in the current study.

Materials And Methods

We retrospectively evaluated all laboratory-confirmed pediatric COVID-19 cases between 22 March 2020 and 28 May 2020 at the Children's Hospital of Ankara City Hospital. The COVID-19 diagnosis was confirmed by PCR assay on nasopharyngeal and oropharyngeal swabs. Demographic characteristics, pre-existing comorbidities, and laboratory parameters on admission were collected from the electronic database of the hospital. The patients were classified as those with and without pre-existing comorbid conditions and the two groups were compared for age, gender, clinical picture at presentation, the presence of severe disease, and pediatric intensive care unit (PICU) requirement. We also compared the two groups as regards the laboratory parameters.

We categorized the patients' clinical pictures at presentation according to our observations. The COVID-19 infections were divided into four final diagnoses as asymptomatic infection, upper respiratory tract infection, lower respiratory tract infection, and acute gastroenteritis. Asymptomatic infection was defined as a positive COVID-19 PCR test result without signs or symptoms. Upper respiratory tract infection was defined as clinical signs and symptoms including fever, cough, rhinorrhea, myalgia, sore throat, and pharyngitis. Lower respiratory tract infection was diagnosed based on the clinical signs and auscultation findings. Gastroenteritis was defined as the presence of abdominal pain, vomiting, and diarrhea. The patients were categorized as severe disease in the presence of dyspnea (chest retractions, tachypnea, low saturation defined as 92% in ambient air), and high-flow nasal oxygen or mechanical ventilation requirement.

Statistical analysis

The IBM SPSS Statistics for Windows, version 22.0 software was used for statistical analyses. Categorical variables are presented as numbers and percentages. Continuous variables are presented as mean ± standard deviation or median, minimum-maximum, as appropriate. The chi-square test was used for comparative analyses of the categorical variables between independent groups. Continuous variables were compared with the Mann-Whitney U test or unpaired Student t test as appropriate.
Results

A total of 317 children were confirmed to have COVID-19 infection by 28 May 2020. A pre-existing comorbid condition was present in 59 (18.6%) and absent in 258 (81.4%). The underlying comorbid conditions are listed in Table 1. Four patients had multiple underlying comorbid conditions. Chronic respiratory conditions including asthma, wheezy infant, allergic rhinitis, congenital cystic adenomatoid malformation, broncopulmonary dysplasia, and tracheostomy were present in 19 patients. Three patients had selective Ig A deficiency and 2 had hematologic disease, consisting of one with Fanconi aplastic anemia and one with leukemia undergoing maintenance chemotherapy.

| Underlying comorbid conditions of 317 children with COVID-19 infection |
|-------------------------------------------------|
| N (%)                                           |
| Cardiac                                         | 6 (1.6) |
| Neurologic                                      | 12 (3.7) |
| Respiratory disease                             | 19 (6) |
| Psychiatric                                     | 8 (2.5) |
| Renal disease                                   | 6 (1.6) |
| Immune deficiency                               | 3 (0.9) |
| Hematologic                                     | 2 (0.6) |
| Skin                                            | 2 (0.6) |
| Obesity                                         | 1 (0.3) |
| Hypertension                                    | 1 (0.3) |
| Hyperlipidemia                                  | 1 (0.3) |
| Metabolic disease                               | 1 (0.3) |
| Inflammatory bowel disease                      | 1 (0.3) |
| Familial Mediterranean fever                    | 1 (0.3) |
| Allergic disease                                | 1 (0.3) |

The age and gender distribution were similar in the two patient groups. Table 2 presents the age, gender and final diagnosis values of the patients. The rate of lower respiratory tract infection was significantly higher in the patients with comorbidities (p = 0.012). There were four patients with lower respiratory tract infection and comorbidities, consisting of bronchopulmonary dysplasia, Joubert syndrome (hypotonia, distinctive facial features, eye abnormalities, kidney disease, skeletal abnormalities) complicated with
chronic renal failure and peritoneal dialysis, aortic stenosis, and hydrocephaly with ventriculoperitoneal shunt.

Table 2
Demographic and clinical characteristics of the patients.

| Comorbid condition present | Comorbid condition absent | p   |
|----------------------------|---------------------------|-----|
| Gender (male/female)       | 32/27                     | 137/121 | 0.87    |
| Age (months) (mean ± SD)   | 123.2 ± 63.4              | 107.7 ± 66.7 | 0.107   |
| Clinical picture at presentation |                       |       |
| -Asymptomatic infection    | 21 (35.6)                 | 85 (32.9) | 0.01    |
| -Upper respiratory tract infection | 33 (55.9) | 163 (63.2) |
| -Lower respiratory tract infection | 4 (6.8)    | 2 (0.8)   |
| -Acute gastroenteritis     | 1 (1.7)                   | 8 (3.1)   |

None of our patients had severe disease on admission and severe disease did not develop during follow-up. There was no intensive care requirement or death in either group. Table 3 presents the laboratory values of the patients with and without comorbidities, with no statistically significant difference between the two groups.
Table 3  
The laboratory results of the patients

|                  | Comorbid condition present | Comorbid condition absent | p    |
|------------------|----------------------------|----------------------------|------|
|                  | N: 59                      | N:258                      |      |
| CRP g/dL         | 0.01 (0.001-21)            | 0.008 (0.001-22)           | 0.68 |
| PCT µg/L         | 0.03 (0–30)                | 0.03 (6.8)                 | 0.14 |
| WBC              | 6140 (1700–13680)          | 6100 (2430–18400)          | 0.51 |
| ALC              | 2080 (450–6650)            | 1965 (320–11370)           | 0.74 |
| ALC < 1500       | 19 (32.8%)                 | 73 (29%)                   | 0.56 |
| ALC < 1000       | 6 (10.3)                   | 14 (5.6)                   | 0.18 |
| ANC              | 1933 (190–8790)            | 2042 (460–13170)           | 0.15 |
| Hb               | 12.9 ± 1.7                 | 13.2 ± 1.3                 | 0.11 |
| PLT              | 278000 (12000–447000)      | 272000 (80000–264000)      | 0.77 |
| D-dimer µg/mL    | 0.43 (0.19–2.97)           | 0.43 (0–35)                | 0.82 |
| < 1              | 41 (89.1%)                 | 175 (86.2%)                | 0.59 |
| ≥ 1              | 5 (10.9%)                  | 28 (13.8%)                 |      |
| AST              | 26 (9–182)                 | 24 (9–98)                  | 0.50 |
| ALT              | 18 (9–199)                 | 20 (8–263)                 | 0.22 |
| LDH              | 257 ± 66                   | 248 ± 64                   | 0.33 |
| CK               | 92 (41–404)                | 89 (35-1091)               | 0.88 |
| Ferritin         | 31.5 (4-151)               | 31 (3-300)                 | 0.32 |

Discussion

COVID-19 has a milder clinical course in childhood with significantly lower mortality than in adulthood. The COVID-19 infection is asymptomatic or has a mild to moderate clinical course in 90% of pediatric cases.\textsuperscript{5} The mortality in children is also lower than that of adults. The mortality rate has been reported as 2.2% a study involving 44672 confirmed COVID-19 infected patients. The same study reported that 1 child died in the 10–19 years age group, and there was no death in the 0–9 years age group.\textsuperscript{6} The mortality
rate among pediatric cases has been reported as 1% across the European region.⁷ High flow nasal oxygen therapy or PICU admission is rarely required in this group.⁸ The reported rates for laboratory-confirmed pediatric COVID-19 cases was 5% for hypoxemia and dyspnea, 0.4–0.6% for acute respiratory distress syndrome, respiratory failure or multiorgan failure, 4% for mechanical ventilation requirement, 3% for inotrope requirement, and 8-9.7% for PICU admission in various studies.⁵,⁷,⁸,⁹ The risk factors related to a severe and complicated clinical COVID-19 infection course in children have not been clearly determined yet.

Pre-existing comorbidities are more common in adults who need hospitalization or intensive care unit (ICU) admission. Such pre-existing comorbidities have been found in 71% of the hospitalized adult patients, 78% of those admitted to the ICU, and 94% of those who died due to COVID-19.¹⁰ Comorbid conditions related to severe disease in adulthood have been reported as hypertension, diabetes, coronary heart disease, chronic obstructive lung disease, and chronic kidney disease.¹¹,¹²,¹³ Another series has reported cardiovascular or cerebrovascular disease to be related with increased fatality, whereas there was no difference as regards the frequency of diabetes, chronic digestive disorders, tuberculosis, chronic hepatic and renal insufficiency, peripheral vascular disease, or malignancy.¹⁴ There is little data on the clinical course of COVID-19 infection in children with pre-existing comorbid conditions. A study evaluating 48 children treated in the PICU has reported that pre-existing comorbidities were present in more than 80% of the children with COVID-19 admitted to the PICU and the most common of these were developmental delay and/or genetic anomalies. The authors mentioned that prehospitalization comorbidities appear to be an important risk factor for PICU admission.¹⁵ A pediatric series including 171 COVID-19 cases has reported that three patients needed PICU admission and all three had pre-existing comorbidities consisting of hydronephrosis, leukemia, and intussusception.¹⁶ In a multicenter study from Europe including 582 children with confirmed COVID-19 infection, pre-existing medical conditions were found to create a risk for PICU admission requirement.⁷ Four patients died and all were aged older than 10 years. Two had a pre-existing comorbid condition: one had undergone human stem cell transplantation and the other one was receiving chronic palliative care.⁷ The other two fatal cases did not have comorbidities. These data suggest that preexisting comorbid conditions may be a risk factor for PICU admission and also for fatality.

There was no severe disease and no PICU admission in either group in this study. However, lower respiratory tract infection was more common among patients with pre-existing comorbidities.

We did not come across severe disease or PICU admission requirement in our patients, even in those with pre-existing conditions. Viral co-infection with COVID-19 has been reported as an important risk factor for PICU admission requirement.²,⁷ Viral co-infection was not evaluated in the current study. However, the first COVID-19 case in Turkey was seen on 11 March 2020. The fact that the COVID-19 epidemic was seen in Turkey after the winter period when other viral respiratory tract infections, especially RSV and influenza virus, show their peak incidence rate, could indicate a low co-infection rate in our cohort. The strict filiation procedures, early closure of schools, and the curfew imposed on children may also have reduced
the circulation of other viruses as well as COVID-19. Our patients’ good clinical data may result from the absence of other viral co-infections. It has been reported that 15.8–16% of children and adolescents with COVID-19 infection are asymptomatic.\textsuperscript{7,16} In our cohort, the asymptomatic patient ratio was higher in patients, both with and without preexisting comorbid conditions, than reported previously (35.6% vs. 32.9%). Our rate of asymptomatic cases could be high because PCR assays were performed on any person who had contact with an index case during this study period.

Some laboratory parameter changes have been reported as prognostic factors in COVID-19 infection. A high level of procalcitonin (PCT) and lymphopenia have been reported to be associated with a severe clinical course in adults. Serum C-reactive protein (CRP) and PCT levels have been reported to be significantly higher in patients who develop severe disease and are correlated with the severity of COVID-19 in adults. Higher ferritin levels and a d-dimer level >1 µg/mL have been found to be associated with severe pneumonia in adults. Another study found that patients with a d-dimer level ≥ 2 µg/mL had a higher mortality rate. A Troponin I level >.05 ng/mL has also been found to be associated with increased mortality.\textsuperscript{2,3,11,12,13,14,17,18} We did not find any difference between the patients with and without comorbidities as regards the laboratory parameters in this study.

Although COVID-19 infection is mostly benign in the acute period in children, a new inflammatory syndrome developing in association with COVID-19 in some healthy children and adolescents has recently been noted and named the multisystem inflammatory syndrome in children (MIS-C).\textsuperscript{19,20} None of the patients in our study cohort developed this syndrome during follow-up.

**Conclusion**

The number of patients with a comorbid condition was low in this study and the comorbid condition groups did not contain enough patients to demonstrate how they individually influenced the clinical picture in children. We believe our study reflects some aspects of the clinical picture of COVID-19 in children with comorbid conditions as our hospital is a reference hospital for pediatric COVID-19 infection cases and our cohort included all pediatric COVID-19 cases in our hospital between the dates specified. Our results indicate that the clinical course of COVID-19 in children with pre-existing comorbid conditions may not be as severe as in adults, and lower respiratory infection may be more common in children with pre-existing comorbidities.

**Abbreviations**

ALC: absolute lymphocyte count ANC: absolute neutrophil count AST: aspartate aminotransferase, ALT: alanine aminotransferase, CK: *creatine kinase* CRP: C-reactive protein Hb: hemoglobin, , LDH: lactate dehydrogenase

PCR: polymerase chain reaction, PCT: procalcitonin PICU: pediatric intensive care unit PLT: platelets count WBC: white blood cells
Declarations

Ethics approval and consent to participate: An ethical approval was obtained from the Ethics Committees of Ankara City Hospital, Turkey

Consent for publication: Not applicable.

Availability of data and material: The dataset supporting the conclusions of this article is included within the article.

Competing interests: The authors declare that they have no competing interests

Funding: The authors received no funding for this work.

Authors' contributions:

Design: Gulsum Iclal BAYHAN, Saliha KANIK YUKSEK, Emrah SENEL

Data collection and processing: Gulsum Iclal BAYHAN, Tugba BEDİR DEMİRDAG, Saliha KANIK YUKSEK, Aslıınur OZKAYA PARLAKAY, Belgin GULHAN

Analysis: Gulsum Iclal BAYHAN, Tugba BEDİR DEMİRDAG

Literature review: Gulsum Iclal BAYHAN, Aslıınur OZKAYA PARLAKAY, Belgin GULHAN

Writer: Gulsum Iclal BAYHAN, Aslıınur OZKAYA PARLAKAY

Critical review: Emrah SENEL

References

1. CDC COVID-19 Response Team (2020). Severe Outcomes Among Patients With Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. MMWR Morb Mortal Wkly Rep. 69(12):343-346. doi: 10.15585/mmwr.mm6912e2.

2. Ludvigsson Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatrica. 2020;109:1088-1095.

3. Sinha IP, Harwood R, Semple MG et al. COVID-19 infection in children. Lancet Respir Med 2020;8:446-447.

4. COVID-19 Stiation Report Turkey 30 June 2020. Available at: https://dosyamerkez.saglik.gov.tr/Eklenti/37778,covid-19-durum-raporupdf.pdf?0 Accessed July 2, 2020

5. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 Among Children in China. Pediatrics 2020;145:e20200702.

6. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41:145-151.
7. Götzinger F, Santiago-García B, Noguera-Julián A, et al. COVID-19 in Children and Adolescents in Europe: A Multinational, Multicentre Cohort Study. Lancet Child Adolesc Health 2020;25:S2352-4642(20)30177-2.

8. Tagarro A, Epalza C, Santos M, et al. Screening and Severity of Coronavirus Disease 2019 (COVID-19) in Children in Madrid, Spain. JAMA Pediatr. 2020 Apr 8:e201346.

9. Cruz AT, Zeichner SL. COVID-19 in Children: Initial Characterization of the Pediatric Disease. Pediatrics 2020;145:e20200834

10. Chow N et al. Preliminary Estimates of the Prevalence of Selected Underlying Health Conditions Among Patients with Coronavirus Disease 2019 - United States, February 12-March 28, 2020. MMWR Morb Mortal Wkly Rep. 2020;69:382-386.

11. Liu F, Li L, Xu M, et al. Prognostic Value of interleukin-6, C-reactive Protein, and Procalcitonin in Patients With COVID-19. J Clin Virol 2020;127:104370

12. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet 2020;395:1054-1062

13. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054-1062.

14. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J 2020;55:2000524.

15. Shekerdemian LS, Mahmood NR, Wolfe KK, et al. International COVID-19 PICU Collaborative. Characteristics and Outcomes of Children With Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units. JAMA Pediatr 2020 May 11. doi: 10.1001/jamapediatrics.2020.1948.

16. Lu X, Zhang L, Du H, et al. SARS-CoV-2 Infection in Children. Chinese Pediatric Novel Coronavirus Study Team. N Engl J Med. 2020;382:1663-1665.

17. Zhang L, Yan X, Fan Q, et al. D-dimer levels on admission to predict in-hospital mortality in patients with Covid-19. J Thromb Haemost 2020;18:1324-1329

18. Weiss P, Murdoch DR. Clinical course and mortality risk of severe COVID-19. Lancet 2020;395:1014-1015.

19. Dufort EM, Koumans EH, Chow EJ, et al. Multisystem Inflammatory Syndrome in Children in New York State. N Engl J Med 2020 Jun 29:NEJMoa2021756

20. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem Inflammatory Syndrome in U.S. Children and Adolescents. N Engl J Med 2020 Jun 29:NEJMoa2021680