Evaluation of Asymptomatic Covid Infection in Children with Pediatric Hemato-Oncologic Disease

Aysenur Bahadir1 · Esra Özkaya2 · Erol Erduran1 · İlknur Tosun2 · Gökçe Pinar Reis2 · Gülay Kaya3

Dear Editor:

The COVID-19 pandemic considerably affects the diagnosis and treatment of pediatric hemato-oncologic patients. For this reason, during the pandemic period, the treatment of patients was mostly tried to be given without hospitalization, dose modifications were made, and they were followed up by phone. COVID-19 infection was excluded by performing a COVID-19 PCR test before receiving treatment and when there is evidence of infection [1, 2]. The present study aimed to examine the incidence of asymptomatic COVID-19 by performing antibody assay in patients who were under follow-up for pediatric hemato-oncologic patients.

This study is a cross-sectional descriptive study. The study included patients aged 2 to 20 years, who were under follow-up for pediatric hemato-oncologic disease between 01.02.2021 and 01.06.2021 in the pediatric hematology-oncology department of Karadeniz Technical University (KTU) Faculty of Medicine. Age, sex, diagnosis, disease state (receiving treatment, completed treatment) of the patients were recorded. The COVID-19 PCR results, family history of COVID-19, and household size were questioned. Patients were compared according to whether they were anti-SARS-CoV-2 positive or negative. In addition, the cases with anti-SARS-CoV-2 positivity were compared between the groups according to their receiving treatment and completed treatment. Assays with an Anti-SARS-CoV-2 spike antibody level of <0.80 U/ml and ≥0.80 U/ml were considered non-reactive and reactive, respectively.

Of 107 study patients, 24 (22.4%) were anti-SARS-CoV-2 positive, and 15 (14.1%) of these cases were male. The mean age of the patients was 8.20 ± 5.28 years. The anti-SARS-CoV-2 total antibodies were detected in 20 of COVID-19 PCR-negative patients (Table 1; Comparison of patients according to the presence of anti-SARS-CoV-2 total antibodies). The anti-SARS-CoV-2 total antibody test was positive in 18 receiving treatment, 6 patients who completed treatment. The most common symptoms presented by PCR-negative COVID-19 patients were cough and fever. We had four PCR-positive COVID-19 patients, all of whom were in the treatment group. One of our patients who was followed up for acute lymphoblastic leukemia (ALL) had a severe COVID-19 infection and was treated as an inpatient. During the last one-year follow-up of our patients who were positive for antibodies, two patients developed acute myeloid leukemia (AML) relapse, three patients died, 13 patients have been on follow-up care, two patients have been continuing their treatment, and four patients have been followed up in another center (Table 2 presents the list of antibody-positive patients).

The COVID-19 pandemic has infected millions of people and caused hundreds of thousands of deaths worldwide. The control of the pandemic could only be achieved after the administration of the developed vaccines. During our study period, vaccination was started for healthcare workers in

---

1 Pediatric Hematology-Oncology, Division of Pediatric Hematology-Oncology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey
2 Division of Clinical Microbiology, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey
3 General Pediatrics, Division of General Pediatrics, Faculty of Medicine, Karadeniz Technical University, Trabzon, Turkey
our country, but families were not vaccinated yet [3]. The present study identified leukemia as the type of cancer with the most common positivity for anti-SARS-CoV-2 total antibodies, which was detected in 22% of these patients. In addition, the positivity for anti-SARS-CoV-2 total antibodies was more common in male patients, with a rate of 62.5%. There were 19 patients (17.7%) with no covid symptoms.

A meta-analysis evaluating 33 studies conducted until November 2020 and 226 pediatric cancer patients with COVID-19 found the type of cancer with the highest number of cases to be hematological cancer. The authors reported that patients who were male and receiving intensive therapy were more affected. In addition, 48% of the patients were asymptomatic or with mild symptoms, while 9.6% had a severe infection. The diagnosis of the patients was established by PCR testing in 80.2% and antibody assay in 13% [2].

Changes were observed in the count and morphology of blood cells due to the COVID-19 infection. The most common finding was lymphopenia. In addition, depending on the severity of the COVID-19 infection, other findings in neutrophils included dysplastic anomalies [4]. Dysplastic myelocytes and giant platelets were observed in the peripheral smear of our ALL patient, who had severe COVID-19 infection, and the findings remained unchanged at follow-up. The patient was diagnosed with AML approximately six months later. The coexistence of LBL and AML is also a rare condition, and the presence of antibody positivity in this patient suggested a previous COVID-19 infection. Viral respiratory infections are the most common type of infection in children. As COVID-19 is highly transmissible, most children and adults will contract this virus during the pandemic. It is not possible to say that SARS-CoV-2 is an oncogenic virus based on available research. However, chronic inflammation and certain viral pathogens can promote oncogenesis. Therefore, we believe that long-term immunological and oncological studies are needed.

We believe that cancer patients who have COVID-19 infection, should be monitored closely for potential effects. There is a need for several randomized controlled studies regarding the effects of this virus on hemato-oncological patients.

**Acknowledgements** The study was approved the ethics committee at Karadeniz Technical University (2021/45). The study has been supported by a research grant of Karadeniz Technical University Pediatric Association (12.04.2021/59).

**Declarations** The authors have no relevant financial or non-financial interests to disclose.

The authors have no competing interests to declare that are relevant to the content of this article. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. The authors have no financial or proprietary interests in any material discussed in this article.

All procedures performed in studies involving human participants

| Table 1 Comparison of patients according to the presence of anti-SARS-CoV-2 total antibodies |
|------------------------------------------------|
| anti-SARS CoV-2 | Negative | Positive | p         |
| Age (year)      | n = 83(%) | n = 24(%) |           |
| Gender          |           |           |           |
| Female          | 10.12 ± 4.74 | 8.21 ± 5.28 | 0.089     |
| Male            | 34 (41%)   | 9 (37.5%)  | 0.945     |
| COVID-19 PCR    |           |           |           |
| Negative        | 83 (100%)  | 20 (83.3%) | 0.002     |
| Positive        | 0 (0%)     | 4 (16.7%)  |           |
| Cancer type     |           |           |           |
| Leukemia        | 49 (59.1%) | 14 (58.3%) |           |
| Lymphoma        | 17 (20.5%) | 3 (12.5%)  |           |
| Solid Tumors    | 9 (10.8%)  | 3 (12.5.0%)|           |
| Brain Tumors    | 8 (9.6%)   | 2 (8.3%)   |           |
| Aplastic Anemia | 0 (0%)     | 2 (8.3%)   |           |
| Treatment       |           |           |           |
| Receiving Treatment | 58 (70%) | 18 (75%) |           |
| Completed Treatment | 25 (30%) | 6 (25%) |           |
| Intrafamilial COVID-19 | No | 80 (96.4%) | 16(66.7%) | <0.001 |
|                  | Yes       | 3 (3.6%)  | 8(33.3%)  |           |
| Household size  |           |           |           |
| <5              | 43 (51.8%) | 8(33.3%) | 0.173     |
| >5              | 40 (48.2%) | 16(66.7%) |           |
Table 2 Presents the list of antibody-positive patients

| Patient no: | Age (years) | Gender | Diagnosis       | Treatment | COVID-19 PCR (Pandemic during) | anti-SARS CoV-2 (U/ml) | COVID-19 specific symptoms | Intrafamilial COVID-19 (time) | Hospitalization (Chemotherapy, neutropenic fever) | Patient Current Status |
|------------|------------|--------|-----------------|-----------|-------------------------------|------------------------|---------------------------|----------------------------|---------------------------------|----------------------|
| 1          | 4          | Male   | ALL             | Yes       | Negative                       | 1.68                   | No                        | No                         | Yes                              | Remission            |
| 2          | 11         | Male   | ALL             | Yes       | Negative                       | 266.3                  | No                        | No                         | No                               | Another center         |
| 3          | 5          | Male   | ALL             | Yes       | Negative                       | 130.9                  | No                        | No                         | Yes                              | Died                 |
| 4          | 9          | Female | ALL             | Yes       | Negative                       | 4.26                   | No                        | No                         | Yes                              | Remission            |
| 5          | 5          | Male   | ALL             | Yes       | Negative                       | 49.85                  | No                        | No                         | No                               | Receiving treatment     |
| 6          | 6          | Female | ALL             | Yes       | Negative                       | 1.22                   | No                        | No                         | Yes                              | Receiving treatment     |
| 7          | 11         | Female | ALL             | Yes       | Positive                       | 19                     | Fever, Cough, Dyspnea, vomiting (3 months ago) | No                         | Yes                              | AML relapse, Receiving treatment |
| 8          | 18         | Male   | ALL             | Yes       | Positive                       | 345.2                  | Cough (3 months ago)     | Yes (3 months ago)           | No                               | Remission             |
| 9          | 2          | Male   | AML             | Yes       | Negative                       | 1362                   | Fever, diarhea (9 months ago) Cough (1 month ago) | Yes (9 months ago)           | Yes                              | Another center         |
| 10         | 2          | Male   | NHL             | Yes       | Negative                       | 21.7                   | Cough, fever (4 months ago) | No                         | Yes                              | AML relapse HSCT, Remission |
| 11         | 18         | Female | NHL             | Yes       | Negative                       | 248.0                  | No                        | Yes (5 months ago)           | No                               | Remission             |
| 12         | 2          | Male   | Neuroblastoma   | Yes       | Positive                       | 1121                   | No                        | No                         | Yes                              | Another center         |
| 13         | 2          | Female | Wilms Tumor     | Yes       | Negative                       | 86.15                  | No                        | Yes (3 months ago)           | Yok                              | Remission             |
| 14         | 8          | Female | Wilms Tumor     | Yes       | Negative                       | 1.05                   | No                        | No                         | Yes                              | Died                 |
| 15         | 10         | Male   | Brain Tumors    | Yes       | Positive                       | 302.3                  | Cough (6 months ago)     | Yes (6 months ago)           | No                               | Remission             |
| 16         | 2          | Male   | Brain Tumors    | Yes       | Negative                       | 37.47                  | No                        | No                         | Yes                              | Remission             |
| 17         | 7          | Female | Aplastic Anemia | Yes       | Negative                       | 6.28                   | Fever (6 months ago)     | No                         | Yes                              | Died                 |
| 18         | 4          | Female | Aplastic Anemia | Yes       | Negative                       | 18.7                   | No                        | No                         | Yes                              | Another center         |
| 19         | 10         | Male   | ALL             | No        | Negative                       | 397.7                  | No                        | Yes (3 months ago)           | No                               | Remission             |
| 20         | 9          | Male   | ALL             | No        | Negative                       | 2500                   | No                        | Yes (3 months ago)           | No                               | Remission             |
| 21         | 13         | Male   | ALL             | No        | Negative                       | 452.3                  | No                        | Yes (2 months ago)           | No                               | Remission             |
| 22         | 13         | Male   | ALL             | No        | Negative                       | 669.1                  | No                        | No                         | No                               | Remission             |
| 23         | 15         | Male   | ALL             | No        | Negative                       | 777.5                  | No                        | Yes (3 months ago)           | No                               | Remission             |
| 24         | 18         | Female | NHL             | No        | Negative                       | 562.2                  | No                        | No                         | No                               | Remission             |

ALL: Acute Lymphoblastic leukemia, AML: Acute Myeloblastic Leukemia, NHL: Non Hodkin Lymphoma, HSCT: hematopoietic stem cell transplantation
were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Karadeniz Technical University of the Medical School of A (No. 2021/45).

References

1. Kahn AR, Schwalm CM, Wolfson JA et al (2022) COVID19 in Children with Cancer. Curr Oncol Rep 24:295–302
2. Auletta JJ, Adamson PC, Agin JE et al (2020) Pediatric cancer research: Surviving COVID-19, Pediatr Blood Cancer 67(9):e28435. doi: https://doi.org/10.1002/pbc.28435. Epub 2020 Jun 18
3. Millen GC, Arnold R, Cazier JB et al (2021) Severity of COVID-19 in children with cancer: Report from the United Kingdom Paediatric Coronavirus Cancer Monitoring Project. Br J Cancer 124(4):754–759. doi: https://doi.org/10.1038/s41416-020-01181-0. Epub 2020 Dec 10
4. Horiuchi Y, Hayashi F, Yosuke Iwasaki Y et al (2021) Peripheral granular lymphocytopenia and dysmorphic leukocytosis as simple prognostic markers in COVID-19. Int J Lab Hematol 43:1309–1318

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Ayşenur Bahadır], [Esra Özkaya], [Erol Erduran], [İlknur Tosun], [Gökçe Pınar Reis] and [Gülay Kaya]. The first draft of the manuscript was written by [Ayşenur Bahadır] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.