

# Clinical Characteristics and Outcomes of a Cohort of Pediatric Oncohematologic Patients With COVID-19 Infection in the City of Bogotá, Colombia

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**Background:** In children, the complications of severe acute respiratory syndrome coronavirus 2 infection occur less frequently than in adults but the characteristics of this disease in oncology patients are not well characterized.

**Methods:** This was a retrospective study in patients younger than 18 years of age with coronavirus disease 2019 (COVID-19) and cancer diagnoses between April and September 2020. Demographic variables, laboratory, and radiologic findings and complications of each case were identified. A descriptive analysis was performed.

**Results:** A total of 33 patients were identified; the median age was 10 years. Fifteen patients (42%) were in chemotherapy at the time of the infection diagnosis, in two patients the chemotherapy protocol was permanently suspended. The most common symptom was fever in 20 patients (60%). Seven patients (21.2%) showed mild pneumonia, four patients (12.1%) severe pneumonia, and three cases (9.0%) were classified as critical. In the evaluated cohort, five patients (15.1%) died, and in two of those, death was caused by COVID-19 infection.

**Conclusions:** Children with an oncologic disease, the search for COVID cases should be oriented to patients with fever, including febrile neutropenia, the presence of respiratory symptoms, and the search for epidemiologic contact. A higher frequency of complications and mortality attributed to COVID-19, two in pediatric oncohematologic patients was found. Institutional strategies to detect the infection early and lower institutional infection are indicated.

**Key Words:** COVID-19, COVID-19 drug treatment, child, hematology, oncology service, pediatrics

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The pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has drastically affected Colombia.

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By November 16, 2020, a total of 1,198,746 cases of coronavirus disease (COVID-19) had been reported, with Colombia ranking ninth in infections worldwide with an infection rate of 23,465 per million inhabitants.<sup>1</sup> By the same date, a total of 34,031 deaths were reported, with a mortality rate of 666 per 1,000,000 inhabitants, ranking 16th worldwide in deaths per capita.<sup>2</sup> In the pediatric population, clinical outcomes register a lower frequency of complications, and most cases occur with mild or asymptomatic infections.<sup>3,4</sup> Nevertheless, in patients with a suppressed immune system, such as those treated for cancer, information on clinical features and outcomes of COVID-19 infection is limited.<sup>5</sup>

In adults with cancer, there is three times higher mortality risk associated with COVID-19, and the reported mortality is approximately 20%,<sup>6</sup> which is significantly higher than that of the general population. To date, publications regarding the outcomes of the pediatric population with oncologic and COVID-19 diagnosis have been reported; however, the clinical outcomes in the different studies regarding the severity of the infection differ worldwide.<sup>5,7–9</sup>

This study aimed to evaluate the frequency of COVID-19 infection and clinical aspects of children with an oncologic diagnosis and/or nonmalignant hematologic conditions and COVID-19 in Colombia.

## MATERIALS AND METHODS

This was an observational, descriptive, and retrospective study developed by reviewing all cases with a confirmed COVID-19 diagnosis established by the polymerase chain reaction or antigen test, in patients younger than 18 years of age in a pediatric hospital between April and September 2020. Patients with a confirmed oncologic or benign hematologic diagnosis (cases with confirmed cancer or benign hematologic pathologies, such as congenital or acquired bone marrow failure, sickle cell disease, and thalassemia) and all patients with allogeneic or autologous stem cell transplantation were included in this study. This study was approved by the institution's ethics committee (registration number: 340-20).

Demographic characteristics, clinical data, laboratory parameters, outcomes, medical complications, admission to the pediatric intensive care unit (PICU), and mortality were obtained from clinical records. The cases were classified as mild, severe, or critical according to the Colombian consensus recommendations for diagnosis, management, and treatment of the infection by SARS-CoV-2/COVID-19 in healthcare facilities.<sup>10</sup>

Laboratory variables included leukocyte, neutrophil, lymphocyte, and platelet counts, as well as fibrinogen, ferritin, and D-dimer levels; these parameters were only recorded if they were obtained from serum samples taken within the first 24 hours of symptom onset. Cases with neutropenia, lymphopenia (defined as an absolute cell count <1500/mm<sup>3</sup>), and thrombocytopenia (platelet count <150,000/μL) were quantified.

The radiologic report recorded in the medical chart was used to describe the radiologic patterns related to COVID-19 infection.

All treatments administered to patients such as low molecular weight heparin, antivirals, and plasma transfusion, were evaluated and the status of oncologic treatment was registered.

The epidemiologic analysis was performed using the IBM Statistical Package for the Social Sciences 22 system (IBM Corp., Armonk, NY).<sup>11</sup> A descriptive analysis was conducted for all variables in their measures of central tendency and dispersion for the continuous variables and absolute and relative frequencies for nominal variables.

## RESULTS

A total of 1669 suspected, and 289 confirmed cases were analyzed and registered in the institution. Of the confirmed cases, 33 (11.4%) patients had an oncohematologic diagnosis and were included in this research. Confirmation of the infection was obtained in all the cases by the polymerase chain reaction test for SARS-CoV-2/COVID-19.

The median age of the 33 patients was 10 years (range, 1–17 years), and 21 male patients (63.6%) were included in this study. Four patients (12.1%) reported an epidemiologic contact for COVID-19. A confirmed diagnosis of cancer was established in 32 cases (96.9%), and only one patient had a nononcologic diagnosis of acquired bone marrow failure.

Eight patients (24.2%) were asymptomatic at the time of the test and in these cases, the test was conducted for the following reasons: in four cases (12.1%) owing to an epidemiologic link, in two cases (6.0%) as screening before other procedures (hematopoietic stem cell transplantation and radiotherapy), in one case (3.0%) owing to radiologic findings not explained by the underlying pathology, and in the one case (3.0%) because of unexplained oxygen requirements.

The most common symptom was fever (20 cases, 60%), followed by rhinorrhea in 14 cases (42%), 10 cases presented with coughing (30%), 4 cases had chest pain (12.1%), 1 had dyspnea (3.0%), and 1 case (3.0%) presented with hypoxemia (oxygen requirement without underlying associated symptoms). Gastrointestinal symptoms occurred in four patients (12.1%), two patients had diarrhea (6.0%) and two had abdominal pain (6.0%). There were no cases of simultaneous respiratory and gastrointestinal symptoms. Other reported symptoms included a patient with low back pain and case of dysgeusia. Eight patients (24.2%) had febrile neutropenia at the time of suspected COVID-19 infection.

Fifteen patients (42%) were undergoing active chemotherapy at the time of infection. Seven of these patients (21.2%) had no changes in their established protocol (most of them corresponded to acute leukemias in the induction phase) and for six patients (18.1%), it was necessary to delay the administration of chemotherapy once COVID-19 diagnosis was confirmed. In only two cases (6.06%), the chemotherapy protocol was permanently suspended owing to complications inherent to the infection.

Regarding laboratory parameters, at least one case of cytopenia was identified in 21 cases (63.6%), and all the cases were related to a history of recent chemotherapy and were attributed to this cause. Table 1 summarizes the laboratory findings.

The cases included in this study were also classified according to severity: seven cases (21.2%) had mild pneumonia, four cases (12.1%) had severe pneumonia, and three cases (9.0%) were critically ill with pneumonia. Seven children (21.2%) were admitted to the PICU. Concerning complications of severe and critical cases, four patients (12.2%) had ventilatory failure associated with the infection, three (9.0%) were managed with invasive mechanical ventilation, and one case (3.0%) was managed with noninvasive ventilation. Other registered complications included three cases (9.0%) of shock that required vasopressor medications; pleural

effusion was reported in two patients (6.0%); one case (3.0%) required close monitoring owing to the risk of ventilatory failure; and one case (3.0%) had disseminated intravascular coagulation and received management with low molecular weight heparin. One case (3.0%) was diagnosed as multisystem inflammatory syndrome and received additional management with immunoglobulin G. Finally, 16 patients (48%) required supplementary oxygen through a nasal cannula.

Five of the cohort patients (15.1%) died. In the first three cases, death was considered not attributable to COVID-19. These deaths were caused by the following underlying diseases: one patient died because of an acute myeloid leukemia relapse; the second patient died as a complication of neutropenic colitis in acute lymphoblastic leukemia (neutropenic colitis and intestinal perforation with progression to multiple organ failure); and the third patient died because of medulloblastoma. Initially, this patient had COVID-19 infection; however, 1 month later, the patient presented with new bacterial pneumonia with respiratory deterioration and death.

After analyzing the causes of death, the mortality attributable to infection was 6%. The diagnosis of acute lymphoblastic leukemia was established in the first case and this case was in the induction phase of chemotherapy. The test was performed owing to a positive epidemiologic link, and the patient was initially asymptomatic. In the second case, the diagnosis was relapsed acute lymphoblastic leukemia, and the patient was receiving the induction phase of chemotherapy. The test was performed because of persistent hypoxemia without associated respiratory symptoms. Both the patients presented with progressive respiratory deterioration owing to multilobar pneumonia that progressed into acute respiratory distress syndrome and evolved into multiple organ failure.

## DISCUSSION

The COVID-19 pandemic has led to unprecedented changes in society and health systems, to which healthcare workers had to adapt. Currently, there is limited data on COVID-19 infection in pediatric patients with cancer. Since mortality is higher in adults, further studies in children are urgently needed; therefore, several strategies have been developed to counteract the impact of the pandemic in these cases.

In our study, 33 oncohematologic patients were identified representing 11.4% of the pediatric patients with COVID-19 treated at our institution, which is higher than the number of cases reported in other studies.<sup>7</sup> This may be related to the moment at which this study was concluded, encompassing the epidemiologic peak of the pandemic in Colombia. The implemented measures allowed the identification of cases with and without respiratory symptoms, and asymptomatic patients who needed measures to avoid possible adverse outcomes related to the infection.

A collateral effect of the pandemic on these patients may lead to an increased chance of reduction in cancer treatment, affecting the prognosis and outcome of the underlying disease.<sup>12,13</sup> In this study, 42% of the patients were receiving chemotherapy when infection was detected, making it necessary to postpone treatment in 18.1% of the patients and suspending it in 6.1% of the cases. There are no data regarding what has happened in other cohorts, and as of now, we do not know the impact of the pandemic on the oncologic outcome of these patients. However, it is crucial to select suitable patients for a prompt resumption of oncologic treatment, seeking to keep the treatment protocols and treatment related to the underlying disease unchanged.

As other studies have described, the most frequent symptom in our cohort was fever,<sup>8,9</sup> followed by respiratory symptoms, and then gastrointestinal symptoms. No other symptoms, such as

**TABLE 1.** Summary of Laboratory Parameters and Radiologic Findings According to Admission to the Pediatric Intensive Care Unit

Variables	Not Admitted to PICU (n = 26)	Admission to PICU Related to COVID-19 (n = 7)
Acute lymphoblastic leukemia B	10	5
Medulloblastoma	2	1
Acute myeloid leukemia	3	-
Burkitt lymphoma	2	-
Primary mediastinal B-cell lymphoma	1	-
Lymphoblastic lymphoma	-	1
Acute lymphoblastic leukemia T	1	-
Pinealoblastoma	1	-
Osteosarcoma	1	-
Ewing's sarcoma	1	-
Wilm's tumor relapse	1	-
Germ cell tumor	1	-
Sacroccygeal teratoma	1	-
Bone marrow failure	1	-
Laboratory		
Leukocytes	2930 (range 60–18,252)	600 (140–4750)
Lymphocytes	1100 (60–1,80,070)	110 (10–510)
Neutrophils	580 (0–15,750)	400 (0–3930)
Platelets	86,000 (5000–42,4000)	7,00,000 (21,000–30,5000)
D-dimer	1967 (1486–3033)*	1784 (1054–2515)†
Fibrinogen	672 (561–1635)‡	486§
Ferritin	724 (138–230)¶	1890 (1450–2330)¶
Radiology		
Cases with thorax radiogram at the time of diagnosis	19 (73.1%)	5 (71.4%)
Findings		
Normal	11 (42.3%)	1 (14.3%)
Ground glass	2 (7.7%)	1 (14.3%)
Unique consolidation	2 (7.7%)	1 (14.3%)
Perihilar interstitial compromise	2 (7.7%)	1 (14.3%)
Costophrenic recess blunting	1 (3.8%)	-
Atelectasis	1 (3.8%)	-
Multi-lobe opacity	-	1 (14.3%)

COVID-19 indicates coronavirus disease 2019; PICU, pediatric intensive care unit.

\*Measured in five cases.

†Measured in two cases.

‡Measured in five patients.

§Only measured in one patient.

¶Measured in four cases.

||Measured in two cases.

anosmia or dysgeusia, were identified in this population. In 24.2% of cases, COVID-19 infection was identified during a febrile neutropenia event, an essential and common finding in other publications.<sup>14,15</sup> There is also a higher risk attributable to complications and admission to the PICU associated with this subgroup.<sup>15</sup> The polymerase chain reaction test in the presence of febrile neutropenia is a suitable screening measure, and it is expected to help with early and appropriate management.

Cytopenia is an adverse effect attributable to chemotherapy, and it is difficult to evaluate this parameter as a prognostic marker. When discriminating the findings according to admission to the PICU, the presence of more severe lymphopenia in the group that required PICU is suggested. However, given the cohort's size, it is not possible to derive direct conclusions regarding the influence on the severity of the infection. Ferritin, D-dimer, and fibrinogen levels were not regularly screened in this cohort, so it was not possible to conclude regarding their usefulness. However, based on the results in other cohorts in adults,<sup>16,17</sup> they can be indicated as parameters for initial systematic evaluation.

Radiologic findings at the time of the suspected diagnosis of the infection were nonspecific, even in the group that required PICU. Conversely, a study<sup>18</sup> that evaluated the chest radiographs in a pediatric cohort documented alteration in 90% of the cases; however, comorbidities of each included case were not detailed, and

the secondary immunodeficiency status of cancer patients may generate discrepancies between the initial clinical manifestations and radiologic findings.

In this cohort, the incidence of critical illness was 21%, with progression to respiratory failure in 12% of the patients, showing a greater progression to critical condition in this group of patients. These results are consistent with those of other studies in which the progression to critical condition fluctuated between 8% and 26%. However, the need for mechanical ventilation was slightly higher in our study, compared with between 4% and 11% in other reports.<sup>8,9,19</sup> Conversely, in other cohorts,<sup>5,20</sup> no mortality or complications associated with infection were reported in patients with cancer, even with low hospitalization rates. This significant behavior variability indicates that the impact of the infection in this population is multifactorial, influenced by the degree of immunosuppression by the underlying disease, the time of chemotherapy protocol and its intensity, and the individual genetic variability and susceptibility, all these factors modify the infection's behavior and influence the diversity of outcomes.<sup>8,9,19,21</sup>

The data showed a 6% mortality rate attributable to COVID-19 in patients with pediatric oncologic diseases, close to what has been reported in cohorts with similar patients, as is the case in New York City with a reported mortality of 5.2%<sup>8</sup> and in Peru, approximately 10% mortality has been reported.<sup>9</sup> These data indicate higher

mortality in patients with cancer compared with that reported in the general pediatric population, in which mortality rate between 0.09% and 0.2% have been described.<sup>4,22</sup>

In conclusion, infection caused by the SARS-CoV-2 in pediatric oncohematologic patients has shown a diverse behavior in different published studies. With respect to children with an oncologic disease, the search for cases should be oriented to patients with fever, including febrile neutropenia, the presence of respiratory symptoms, and the search for epidemiologic contact. These patients require special surveillance for the prompt detection of complications given the limited prognostic information initially provided by diagnostic tools, such as radiology and blood counts, in the light of current knowledge. It is essential to follow more extensive inter-institutional studies in which the impact of conditions, such as hematologic abnormalities, in these patients can be evaluated. This should further generate more strict control and support strategies.

Each case must be carefully considered before postponing chemotherapy regimens. Establishing isolation protocols to mitigate the effects of COVID-19 infection and creating multidisciplinary teams to evaluate each patient and define the continuity of the oncologic treatment individually is indicated.

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