Profile and Outcomes of Pediatric Hematology and Oncology Patients Diagnosed with COVID-19 in the Philippine General Hospital

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ABSTRACT

Introduction. The coronavirus pandemic has affected millions worldwide. Better understanding of COVID-19 in pediatric hematology-oncology patients in a resource-limited setting is crucial to improve care as the pandemic ensues.

Objectives. This study describes the clinical profile and outcomes of pediatric hematology oncology patients with COVID-19 seen at the Philippine General Hospital (PGH).

Methods. A retrospective, descriptive review of pediatric hematology oncology patients with COVID-19 seen between March 2020 to March 2021 in PGH was done.

Results. Forty patients were identified. Seventeen percent had non-malignant hematologic conditions, 40% had leukemias, and 42.5% had solid tumors. Fever and cough were the most common manifestations. Seventy-six percent were on treatment, 9% were newly diagnosed, and 7% were in relapse or disease progression. Fifty-five percent had mild COVID-19; 5% and 2.5% had severe and critical COVID-19, respectively. Thirty-seven percent were asymptomatic. Cancer-related therapy was placed on hold for most patients. There were two mortalities, none was due to COVID-19.

Conclusion. Results suggest that patients with hematologic and oncologic conditions have a mild course, with majority showing recovery from COVID-19. Delays in cancer-related therapy however, may contribute to disease progression and mortality.

Keywords: COVID-19, pediatric hematology oncology, childhood cancer

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INTRODUCTION

In 2020, the novel coronavirus pandemic (COVID-19, SARS-CoV-2) caused a worldwide health crisis.[1] During the first wave of the pandemic, the Philippines was one of the hardest hit countries in East Asia and Pacific.[2] As of February 2022, it has caused almost four million infections and has claimed 55,094 lives nationwide.[3] The Philippine General Hospital (PGH), one of the referral centers for pediatric hematology and oncology patients, receives around 300 new oncologic and 150 benign hematologic cases annually prior to the pandemic. As a response to the COVID-19 pandemic, PGH was designated as a COVID-19 referral center. Arrangements were made to accommodate COVID-19 positive patients needing medical care.[4]

Table 1 shows COVID-19 disease severity based on the WHO Clinical management guideline.[5]

Table 1. COVID-19 Disease Severity (WHO, 2021)[5]

Mild disease	Symptomatic patients meeting definition of COVID-19 without evidence of viral pneumonia or hypoxia
Moderate disease (Pneumonia)	Child with clinical signs of non-severe pneumonia (cough or difficulty breathing with fast breathing and/or chest indrawing) and no signs of severe pneumonia. Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO_2 greater than or equal to 90% on room air.
Severe disease (severe pneumonia)	Child with clinical signs of pneumonia (cough or difficulty of breathing) and at least one of the following: • Central cyanosis or oxygen saturations less than 90%; severe respiratory distress; general danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions • Fast breathing (in breaths per minute): ○ <2 months: more than or equal to 60 ○ 2-11 months: more than or equal to 50 ○ 1-5 years: More than or equal to 40
Critical disease	Presence of acute respiratory distress syndrome, sepsis, septic shock, acute thrombosis, and multi-inflammatory syndrome in children and adolescents (MIS-C)

Among available data in children with COVID-19, risk factors for hospital admission and subsequent need for critical care include younger age, and presence of pre-existing pulmonary, gastrointestinal, endocrine, and immunocompromised conditions.[6,7] In 2020, St. Jude Children's Research Hospital, together with International Society of Pediatric Oncology (SIOP) launched the Global COVID-19 Observatory and Resource Center, as well as a global registry for COVID-19 in childhood cancer.[8] Early reports on the course of COVID-19 in pediatric cancer patients show that majority of patients manifest with mild symptoms, as in reports from UK, New York-New Jersey, and Italy.[9-11] The burden of COVID-19 in pediatric hematology and oncology is two-fold. Aside from the looming threat of an infection, it has also brought about strain to healthcare delivery and accessibility such as modifications to usual care and delays in cancer-related care.[12]

At the inception of this study, there was only one report available on adult cancer patients with COVID-19 in the Philippines wherein anticancer treatment, stage IV disease, and lung cancer were seemingly contributory to the development of severe disease.[13] There were no published studies on the outcomes for pediatric hematology and oncology patients afflicted with COVID-19 in the Philippines. This study aims to describe the profile and outcomes of pediatric hematology and oncology patients who were afflicted with COVID-19, including their demographic and clinical profile, clinical presentation and severity of COVID-19 infection, COVID-directed therapy received, outcomes of COVID-19 infection, and cancer-directed therapy modifications. The results of which may strengthen existing data on what we know about COVID-19 in pediatric hematology and oncology patients and provide baseline data for our setting. Data derived from this review may also be used to formulate recommendations to improve healthcare delivery for our patients as the pandemic ensues.

METHODS

This is a retrospective descriptive study conducted at the Division of Pediatric Hematology and Oncology, Department of Pediatrics of the University of the Philippines-Philippine General Hospital through a review of records. This study included all patients, male and female, aged less than 19 years, with an underlying hematologic or oncologic condition, who were diagnosed with COVID-19, regardless of severity, within March 2020 to March 2021. Diagnosis of COVID-19 was based on the presence of a positive reverse transcriptase polymerase chain reaction (RT-PCR) to SARS CoV-2 identified in the patient's respiratory swabs. Excluded were patients who were diagnosed and managed as COVID-19 based on clinical or radiologic parameters but had a negative RT-PCR for SARS-CoV-2.

The principal investigator reviewed and recorded the needed information through review of records using a predesigned data collection form. Only data pertinent to this study were recorded and collected. No identifiers were collected. The patients were given an assigned identification number (AIN) to maintain confidentiality and anonymize their identity. The study used descriptive statistics such as mean, median and standard deviation for continuous variables, and frequency and percentage for categorical data. Outcomes for COVID-19 will include recovery from COVID-19 or mortality (from COVID or other causes). This study protocol was reviewed and approved by the University of the Philippines Manila Research Ethics Board (UPMREB). The study was conducted only upon approval of the UPMREB Panel (UPMREB Code 2021-340-01).

RESULTS

There were 40 cases of COVID-19 among pediatric hematology and oncology patients seen during the study period. COVID-19 infection was documented via the presence of a positive SARS-CoV-2 RT-PCR from their respiratory samples. Patients' clinical characteristics are summarized in Table 2. Mean age was at 9.016 ± 6.0 years; 62.5% were male, and 37.5% were female. Most of the patients were situated at the National Capital region at 65%, five of which were living in a halfway house. Sixteen (40%) had leukemia, 17 (42.5%) had solid tumors, while seven (17.5%) had non-malignant hematologic conditions. The most common underlying hematologic-oncologic condition

Table 2. Profile of Pediatric Hematologic Patients with COVID-19

Characteristic	Frequency or value	Percentage (%)
Age, mean	9.016 ± 6.0	
Sex		
Male	25	62.5
Female	15	37.5
Region		
NCR	26	65.0
Region III	1	2.5
Region IVA	12	30.0
Region V	1	2.5
Living in a halfway house		
Yes	5	12.5
No	35	87.5
Hematologic/Oncologic Diagnosis		
Hematologic malignancy	16	40.0
Acute lymphoblastic leukemia (ALL)	13	
Acute myelogenous leukemia (AML)	1	
Chronic myelogenous leukemia (CML)	2	
Solid tumor	17	42.5
Brain tumor	4	
Retinoblastoma	3	
Osteosarcoma	2	
Lymphoma	2	
Yolk sac tumors, extracranial	4	
Soft tissue sarcoma	1	
Rhabdomyosarcoma	1	
Non-malignant hematologic condition	7	17.5
Aplastic anemia	2	
Immune thrombocytopenia	0	
Hemophilia	2	
MDS	1	
Pure red cell aplasia	1	
Macrocytic anemia	1	
Status of oncologic disease (n=33)		
Newly diagnosed	3	9.0
Remission, on treatment	23	69.0
Relapse or progressive disease	7	21.0
With radiation therapy received prior to COVID-19 diagnosis? (n=33)		
Yes	5	15.0
No	28	85.0

was acute lymphoblastic leukemia (ALL). Majority of the oncologic patients diagnosed with COVID-19 were already receiving interventions during diagnosis (70%).

Of the 13 patients with ALL, four were in the intensive phase of chemotherapy. Three were on induction and one was on SIOP PODC Regimen 3 consolidation. Majority were receiving less intensive chemotherapy, with eight on SIOP PODC maintenance phase, and one on interim maintenance. Both AML and CML were in relapse or disease progression at the time of COVID- 19 infection. COVID -19 diagnosis was confirmed with a median of 2 days (range -3 to 16 days) from the time of last chemotherapy for leukemia patients.

Among the 17 solid tumor patients, seven had no recent chemotherapy, while 10 were ongoing chemotherapy. Five patients recently had radiation therapy, with two receiving radiotherapy only, and three on concurrent chemoradiation. A median of 20.5 days (range 0-44 days) passed between last chemotherapy for solid tumors to the time of COVID-19 diagnosis. For those undergoing radiation therapy, COVID-19 was diagnosed between 1-33 days from the last therapy date, with a median of 1.

For the benign hematologic conditions, two cases were on cyclosporine, while five had no immunosuppressive therapy.

Diagnosis and Outcome of COVID-19

Characteristics of COVID-19 infection are summarized in Table 3. Among the 40 cases of COVID-19, fifty-two percent (52%) manifested with symptoms of COVID-19, leading to a test being done. Among the 40 cases, 36 were 1st infections, while there were four cases of reinfections. One of the patients tested positive for COVID-19 thrice. Two patients tested positive for COVID-19 twice. For all three patients, RT-PCR tests were done within three months from the last, with documentation of a negative result in between. Forty percent (40%) did not report any symptoms. Among those with symptoms, the most common are fever (37.5%), cough (30%) and colds (12.5%). Eight patients (20%) had a household member with a documented concomitant COVID-19 infection. Majority of the patients were managed at home, 15 were admitted, while two were already admitted at the time of COVID-19 diagnosis. Only four of the 15 admitted patients were admitted for COVID-19, one for diarrhea, while three were admitted for respiratory distress.

Majority (92.5%) were classified as asymptomatic (37.5%) and mild (55%), while only 7.5% were classified as having severe and critical COVID-19. Most of the patients (75%) did not receive any COVID-related therapy, while the most common COVID-related management was zinc sulfate (25%) and vitamin D (20%). Only two patients were intubated, and six were placed on supplemental oxygen. Among the six patients on supplemental oxygen, four were due to severe anemia (non-COVID related). Recovery from COVID-19 was seen in all patients; however, there were two mortalities in this cohort, with an all-cause mortality of 5%. None of the mortalities were attributable to COVID-19 alone; rather, these were due to disease progression and nosocomial pneumonia.

Only 24 patients had complete blood counts available. Most were non-neutropenic with an overall mean absolute neutrophil count (ANC) of 5,024 ± 4,027. Among those ongoing treatment, median ANC was 4,231 (IQR 2213.5 to 6894). Only three had neutropenia (ANC range 0 to 144), all of which were classified as having mild COVID-19. Two patients had ALL – one on reinduction, another on maintenance. The third was admitted for febrile neutropenia nine days post chemotherapy with cisplatin and doxorubicin. Absolute lymphocyte count (ALC) was at

Table 3. Profile of COVID-19 Infection in Pediatric Hematology Oncology Patients

	Frequency; Mean/ Median	Percentage (%)
Reason for COVID-19 testing (n=40)		
Requirement for admission or procedure	16	40.0
Symptoms developed	21	53.0
Exposure	3	7.0
Symptoms for COVID-19		
Fever	15	37.5
Cough	12	30.0
Colds	5	12.5
Diarrhea	3	7.5
Difficulty of breathing	4	10.0
Shock	1	2.5
Body aches/ malaise	4	10.0
Rash	2	5.0
Chest pain	1	2.5
Otorrhea`	1	2.5
Asymptomatic	16	40.0
Number of COVID-19 infections (n=40)		
First infection	36	90.0
Reinfection	4	10.0
Known exposure?		
Yes	8	20.0
No	32	80.0
Need for admission (n=40)		
Admitted	15	37.5
Not admitted	23	57.5
Already admitted	2	5.0
Reasons for admission (n=18)*		
COVID-related	4	22.0
Non-COVID related	14*	78.0
Disease progression	4	
Febrile neutropenia	3	
Active bleeding	2	
Transfusion	5	
Severity of COVID-19 infection		
Asymptomatic	15	37.5
Mild	22	55.0
Moderate	0	0.0
Severe	2	5.0
Critical	1	2.5
COVID-related therapy received		
None	30	75.0
Zinc sulfate	10	25.0
Vitamin D	8	20.0
Azithromycin	2	5.0
Steroids	3	7.5
Convalescent plasma	2	5.0
IVIg	2	5.0
Highest oxygen support needed		
Intubation	2	5.0
Face mask	3**	7.5
Nasal cannula	3**	7.5
Room air/ none	32	80.0

* *2 patients admitted more than once during the duration of COVID infection*
** *2 out of 3 patients were given supplemental oxygen for support, not due to COVID-19*

a median of 932 (IQR 629 to 1748). All severe and critical COVID patients had lymphopenia. Inflammatory markers (ferritin, D-dimer and Interleukin-6 (IL-6)) were done for 12 of the 17 admitted cases. Among those who had ferritin done, 4 out of 10 had elevated ferritin with a median of 197 ng/mL (84.3- 1367). D-dimer was elevated for all patients, with a median of 1.94 (1.025- 3.245). Eight patients had IL-6 done. Half had elevated IL-6. Repeat RT-PCR tests for COVID-19 were done for 35 of the patients. Median time to negative swab was at 15 days (IQR 12.5- 24), with a range of 6 days to 35 days.

Table 4 shows a summary of the patients who had severe and critical COVID-19. Patient A was previously admitted for pneumonia and was treated as probable COVID after testing negative for RT-PCR on two determinations during the said admission. He was improved on discharge; however, was readmitted three days after due to desaturation and recurrence of respiratory distress, now testing positive for COVID-19 via nasopharyngeal RT-PCR. He was given convalescent plasma with note of recovery. Patient B was intubated due to progressing respiratory distress. He had marked lymphopenia and markedly elevated IL-6 (3x) and D-dimer (22x). He received convalescent plasma and was started on IVIg after note of dilated coronaries on workup of cardiomegaly. The third patient developed respiratory distress post-operatively, hence was worked up for COVID-19. He was concomitantly treated for intracranial hemorrhage and was given steroids, azithromycin, and IVIg. None received anticoagulation. All showed improvement and discharged well.

Cancer-related therapy delays

Interruptions and delays for cancer-directed therapy was observed among patients diagnosed with COVID-19. Two patients were continued on therapy as planned (ALL maintenance, cyclosporine for aplastic anemia), while the rest had delays and interruptions in chemotherapy, radiation therapy or surgery. Mean days of interruption was at 29.6 ±13 days (range of 8 to 51 days). Mean number of days of interruption of cancer-related therapy was 35 ± 12 days (range of 19 to 51 days) for leukemias, and 24.42 ± 13 days (range 8 to 27 days) for solid tumors. For patients with solid tumors who had therapy on hold, three were not resumed on cancer-directed therapy due to disease progression. One eventually

Table 4. Summary of Severe and Critical COVID-19 Patients

	Patient A	Patient B	Patient C
Underlying condition	B cell ALL	B cell ALL	Medulloblastoma
Status of therapy	On therapy, maintenance	On therapy, interim maintenance	Newly diagnosed
Severity of COVID-19	Severe	Critical	severe
Days from last chemotherapy	13 days	9 days	n/a
Absolute neutrophil count	10,624	4,316	6,068
Absolute lymphocyte Count	1,152	624	738
Ferritin (17.9- 464 ng/mL)	109	286	1,370
D-dimer (0-0.5ug/mL)	1.85	11.4	2.25
Interleukin-6 (0-50 pg/mL)	956	149	44
Highest oxygen support	Nasal cannula	Mechanical ventilation	Face Mask
COVID-19-related therapy	Steroids Convalescent plasma	Steroids Convalescent plasma IVIg	Steroids Azithromycin IVIg
Outcome of COVID-19	Recovered	Recovered	Recovered

died from disease progression and nosocomial infection. Among the patients with leukemia who had cancer-related therapy on hold, one eventually had disease progression and died, while two were palliative cases at the onset of COVID-19 diagnosis.

DISCUSSION

Data on the effect of COVID-19 infection among pediatric hematology and oncology patients can help us formulate guidelines for the care of this population as the COVID-19 pandemic continues to plague us worldwide. The result of this study builds to what we currently know about COVID-19 infection in this population. In this study, we find out that more than 90% of patients with an underlying hematologic or oncologic condition develop asymptomatic or mild infections, with only 7.5% developing severe disease. Similar findings were seen in other reports, wherein the majority of patients have asymptomatic-mild illnesses not requiring hospitalization. Fever and cough were also the most common symptoms, similar to reported studies.[9-11,14] Similarly, ALL was also the most common underlying condition among patients who tested positive for COVID-19.[9-11] Data from the Global Registry of COVID-19 in Childhood Cancer (GRCCC) also shows that majority of patients had mild to moderate disease. Asymptomatic disease was found in 35% of patients, while 45% had mild to moderate disease, and 19.9% had severe or critical COVID-19. Mortality was at 3.8%. While this may seem low, this is 4x higher compared with published general pediatric populations. Furthermore, looking at the subset of low-middle income countries similar to our country, severe or critical COVID occurred in 41.7% of this subset, with 6.7% deaths attributable to COVID-19.[15] A review on immunocompromised children (children with rheumatologic conditions, chronic renal disease, chronic gastrointestinal conditions, and hematologic, oncologic conditions) show that these children mostly have mild COVID-19, comparable with the general pediatric population. Reasons for a milder course of COVID-19 in children are postulated to be multifactorial. Mechanisms involving decreased viral entry through the nasal epithelium because of lower angiotensin converting enzyme 2 receptor expression, and viral interference; as well as the lower interferon antiviral response compared to adults, are some of the theories for a milder course of COVID-19 in children. Decreased neutrophil and monocyte/ macrophage activation, better phagocytosis, and a more efficient humoral T and B cell response in children causing a more favorable inflammatory outcome are other theories that contribute to an overall better prognosis for children. Reduced exposures, since children have more limited movements during the pandemic compared to adults, also contribute to an overall lower incidence and severity in children.[16,17] Compared to adults, pediatric hematology and oncology patients seem to fare better.[18,19] The COVID-19 and Cancer Consortium recently showed that adult cancer patients with older age, recent chemotherapy, and hematologic malignancy, tend to have poorer outcomes compared to other cancer patients. Patients on R-CHOP, platinum and etoposide combinations, and DNA methyltransferase inhibitors had a higher all-cause mortality.[20] The GRCCC data also reported significant association for severe or critical COVID-19 with the lower income group, age 15-18 years, ALC of less than 300, ANC of less than 500, and intensive treatment.[15]

Perhaps a more pressing concern is whether treatment for the primary condition should be delayed or modified for patients with COVID-19. In our cohort of patients, only one patient was continued on maintenance therapy with no noted problems. The rest of cancer patients had cancer-related therapy on hold. Experience in other centers report interruptions with chemotherapy, especially among reports during the initial months of the pandemic. In New York

and Italy, interruptions in cancer-directed therapy were at 67% and 55% of patients, respectively.[10,11] In our institution, cancer-related therapies were placed on hold upon the diagnosis of COVID-19 and resumed once negative; similar to Peru, another LMIC, wherein all patients had interruptions in cancer-related therapy.[21] While no repeat testing is recommended for immunocompetent individuals after completion of isolation; for immunocompromised individuals such as patients with cancer, local guidelines currently recommend isolation for at least 21 days as well a negative RT-PCR before discontinuation of isolation.[22] Prolonged shedding of infectious SARS-CoV-2 in asymptomatic immunocompromised patients has been reported and can last to as long as more than 70 days.[23] In our cohort, median time to a negative swab was at 15 days, with some persisting to 35 days. Corresponding interruption in cancer-related therapy was at a median of 29 days. As the pandemic evolved, changes in the practice on therapy interruption also came about. In Texas, wherein observation period was until September 2020, interruptions were noted in around 32% of patients on therapy. Delays decreased as the pandemic continued. Among those who continued therapy, no detrimental effects were noted.[14] Recognizing the effect of the pandemic on pediatric cancer, leadership from various societies came together for an international consensus for children with cancer during this global crisis, wherein recommendations for continued timely diagnosis and therapy of childhood cancers as much as possible be done, while ensuring patient safety and service constrains.[24] Anecdotally, in other LMICs (Guatemala, India, and Costa Rica), COVID confirmed children are continued on chemotherapy with no modifications as long as asymptomatic. If symptomatic, chemotherapy is placed on hold and resumed when the patient is well and blood counts are acceptable.[25] Unfortunately, in our setting, limitations preclude continuation of therapy even among patients with asymptomatic or mild disease due to the insufficient infrastructure and manpower to accommodate COVID positive patients for chemotherapy continuation. This is because COVID beds are allotted for all pediatric patients who will be admitted for moderate- severe COVID-19. Furthermore, because of the limited number of beds, there would be difficulty in accommodating these patients in the event they develop any complications related to chemotherapy. Unfortunately, among our patients who had therapy interruptions due to COVID-19, four had disease progression, with two eventually leading to mortality. While three of these patients have progressive or relapsed cancers at the diagnosis of COVID, two were clinically responding well to their treatment regimen at the time of COVID diagnosis, but eventually had disease progression shortly after interruption of therapy. One patient was never started on salvage regimen due to the unstable clinical course from concomitant tuberculosis and nosocomial infection. While this comprises only a small number of patients in our cohort, institutional practices may need to be reviewed to mitigate delays in cancer-related therapy for this subset of patients while at the same time ensuring a safe environment for our patients, their families as well as the healthcare team.

An exciting development for the control of the global pandemic is the development of vaccines. While our data reveals that only 20% had a documented household contact, it is still recommended that household members and caregivers of children with cancer with blood disorders be fully immunized against COVID-19; along with advocating for vaccination of our eligible patients, which was initiated in October 2021 in the Philippines for 12-17-year-old children with co-morbidities.[26] This has since expanded to include children 5 to 11 years of age in February 2022.[27] Vaccination of our patients and their household members is an important strategy to afford protection for our patients.

Limitations of the study

The findings of our study may be limited by its retrospective nature. While we reviewed all cases of COVID-19 among the population of interest, data is limited to conclude associations between clinical characteristics and outcomes. Furthermore, with the rapid evolution of the pandemic and its treatment recommendations, our findings may be limited to the experience during the study period and may not be generalizable especially for emerging variants.

Recommendations for further study

In line with the limitations, a multi-center review study in our local setting is recommended to better understand the individual effect of COVID-19 to our patients. Additional studies are also recommended to further shed light on the effects of SARS-CoV-2 variants and vaccination on COVID-19 infection in this population, as well as its effect on pediatric cancer care and service delivery. Long-term follow-up of these patients who had COVID-19 infection is also recommended to determine the impact of delays in cancer-related therapy to patient outcomes.

CONCLUSION

Overall, findings from this study suggest that patients with hematologic and oncologic diseases show a mild disease course of COVID-19, with fever and cough as the most common manifestations of COVID-19 among pediatric hematology and oncology patients. Majority also show recovery from COVID-19. Delays in cancer-related therapy however may contribute to disease progression, especially among relapsed cases; hence, strategies in a resource-limited setting should be explored to mitigate interruptions and improve overall care for pediatric hematology and oncology patients. Furthermore, continued studies in our population are recommended as new SARS-CoV-2 variants and practices emerge in order to determine their impact and effect on patients with blood disorders and cancer.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

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