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# Management and Outcome of Coronavirus Disease 2019 (COVID-19) in Pediatric Cancer Patients: A Single Centre Experience from a Developing Country

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## Abstract

**Few cancer centers from developing countries have described the impact of COVID-19 on pediatric cancer patients. Seventy-six pediatric oncology patients with COVID-19 infection were recruited. Most patients had a favorable outcome with sixty-day overall survival of 86.8%. Mortalities occurred only among patients with critical forms of infection. The potential benefits of remdesivir in pediatric oncology patients require further studies.**

**Introduction:** Sufficient data pertaining to the impact of the Coronavirus disease 2019 (COVID-19) on pediatric cancer patients is still lacking. The aim of this prospective study was to describe clinical management and outcomes of COVID-19 in pediatric oncology patients. **Patients and Methods:** Conducted between May 1, 2020 and November 30, 2020, this study included 76 pediatric oncology patients with confirmed COVID-19. Remdesivir (RDV) was the antiviral therapy used. **Results:** The median age of patients was 9 years. Sixty patients were on first line treatment. Hematological malignancies constituted 86.8% of patients. Severe to critical infections were 35.4% of patients. The commonest symptom was fever (93.4%). Chemotherapy was delayed in 59.2% of patients and doses were modified in 30.2%. The 60-day overall survival (OS) stood at 86.8%, with mortalities occurring only among critical patients. Of sixteen acute leukemia patients in the first induction therapy, 13 survived and 10 achieved complete remission. A negative RT-PCR within 2 weeks and improvement of radiological findings were statistically related to disease severity ( $P = .008$  and  $.002$ , respectively). Better OS was associated with regression of radiological findings after 30 days from infection ( $P = .002$ ). Forty-five patients received RDV, 42.1% had severe and critical forms of infection compared to 25.7% in the No-RDV

**Abbreviations:** ALL, Acute lymphoblastic leukaemia; AML, Acute myeloid leukaemia; ARDS, Acute respiratory distress syndrome; COVID-19, Coronavirus disease-2019; CML, Chronic myeloid leukaemia; CR, Complete remission; CRP, C-reactive protein; CRS, Cytokine release syndrome; CT, Computed tomography; DS, Down syndrome; FA, Fanconi anaemia; LL, Lymphoblastic lymphoma; No-RDV, No Remdesivir; OS, overall survival; POCC, Pediatric Oncology COVID Patient; RDV, Remdesivir; RT-PCR, Reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SFCE, French Society of Pediatric Oncology.

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group and yet OS was comparable in both groups. **Conclusion:** Most pediatric cancer patients with COVID-19 should have good clinical outcomes except for patients with critical infections. Cancer patients can tolerate chemotherapy including induction phase, alongside COVID-19 treatment. In severe and critical COVID-19, RDV might have a potential benefit.

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**Keywords:** COVID-19, immunocompromised patients, remdesivir, pediatric cancer, SARS-CoV-2

## Introduction

The Coronavirus disease-2019 (COVID-19) outbreak was declared a pandemic at the start of 2020. Cancer patients are amongst the most vulnerable groups to infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Most healthy children present with asymptomatic or mild form of the disease.<sup>1</sup> Data pertaining to children with cancer are still limited. The general fear is that the course of infection might be more severe compared with healthy children.<sup>2</sup> Of the few published studies so far, most have concluded that pediatric oncology patients experience mild to moderate courses of infection.<sup>3,4</sup> Still mortality rates higher than 3% have been reported.<sup>5,6</sup>

The difficulty in determining the true impact of SARS-CoV-2 infection in cancer patients is that cancer encompasses different tumor subtypes and the lack of a unified approach to patient screening and management across different cancer centers.<sup>3</sup>

Risks of administering chemotherapy to children infected with SARS-CoV-2 is still unclear. A higher risk of severe events was observed among adult patients who had received chemotherapy during the month prior to a COVID-19 diagnosis compared with those who had not.<sup>7</sup> The current situation mandates that chemotherapy be tailored according to the clinical scenario of each patient.<sup>8</sup>

Studies are still ongoing in order to determine the best antiviral therapy for COVID-19.<sup>9</sup> Preliminary studies have touted the potential benefits of remdesivir (RDV) in patients with severe COVID-19.<sup>10,11</sup>

This study aimed to describe the clinical course and management of SARS-CoV-2 infections in 76 pediatric oncology patients, detailing disease severity, duration to achieve a negative RT-PCR test, modifications made to protocols, and survival outcomes in patients who had been treated with RDV and those treated without it.

## Methodology

### Study Population

This prospective study recruited 76 pediatric oncology patients  $\leq 18$  years of age with confirmed COVID-19 infection. Patients were treated at the Children's Cancer Hospital of Egypt, from May to November 2020 and followed up for a minimum of 2 months. Patients were eligible for COVID-19 screening, if they had respiratory symptoms and at least 2 of the following:

- 1) unexplained fever or gastrointestinal symptoms
- 2) abnormal chest imaging
- 3) laboratory test with lymphopenia or elevated C-reactive protein (CRP) or D-dimer
- 4) contact with SARS-CoV-2 confirmed patients

Data included demographics, cancer diagnosis and treatment, COVID-19 severity and management, computed tomography (CT) and laboratory findings, and survival outcome. Approval of the hospital ethical committee and family consents were obtained.

### Detection of SARS-CoV-2

Allplex2019-nCoV Assay (Seegene, Seoul, South Korea) was used for Multiplex real-time PCR detection of SARS-CoV-2 according to manufacturer instructions.

### Management of Confirmed Patients

According to the guidelines for scoring pediatric patients with COVID-19, disease severity was classified as mild, moderate, severe or critical forms (Table S1).<sup>4</sup> Management according to our institutional policy was as follows:

1. Positive reverse transcription polymerase chain reaction (RT-PCR) tests were repeated weekly.
2. Investigations included a daily complete blood picture, liver and kidney functions, besides weekly ferritin, LDH, CRP and D-dimer tests.
3. All patients underwent baseline chest CTs and repeated every 2 weeks.
4. SARS-CoV-2 treatment approach included:
  - a. All patients received methylprednisolone 1 mg/kg for 7 days and tapered over another week.
  - b. Remdesivir was administered regardless of the disease severity. It was administered as described by Méndez-Echevarría et al.<sup>10</sup> Thirty-one patients did not receive remdesivir as it had not yet been available.
  - c. Anticoagulant Enoxaparin (Clexane) was given to patients with D-dimer levels  $\geq 1$  mcg
  - d. Interleukin-6-receptor inhibitor (Tocilizumab) was administered once cytokine release syndrome (CRS) was suspected. Criteria of CRS and drug doses are described elsewhere.<sup>12,13</sup>
5. Local Children's Cancer Hospital of Egypt guidance for cancer directed therapy
  - a. Newly diagnosed acute lymphoblastic leukemia (ALL) patients were initiated on steroids and antiviral therapy. Induction therapy was given without dose adjustments one-week post-confirmation of a SARS-CoV-2 infection. The initial intrathecal was administered 2 weeks post-confirmation. Other treatment phases (eg, maintenance) were started on time, when possible, with a 25% dose reduction if indicated.
  - b. Newly diagnosed acute myeloid leukemia (AML) patients were initiated on steroids and antiviral therapy. Induction-I should be given without dose adjustment after 1 week from date of

SARS-CoV-2 diagnosis. Induction-II and intensification cycles to be given according to the clinical condition and disease status with a 25% dose reduction, if indicated.

- c. Patients with solid tumors received their chemotherapy without dose adjustment or interruptions alongside with steroids and antiviral therapy.

**Definitions**

Infection with SARS-CoV-2 is considered cleared “viral clearance” after obtaining 2 consecutive negative RT-PCR tests. Radiological improvement was defined as any regression in CT chest findings up to total resolution within 1 month of the baseline CT.

**Statistical Analysis**

The tabulated information was presented using standard descriptive statistics. Chi-square and Fisher’s exact tests were used for categorical variables. Sixty-day overall survival (OS) was estimated using the Kaplan-Meier method with survival duration calculated in days from the date of diagnostic RT-PCR. Log-Rank test was used to compare survival probabilities between subgroups. A 2-sided  $P < .05$  was considered significant. IBM-SPSS Statistics Version-20•0 was used in conducting data analyses.

**Results**

**Demographics, Cancer and Laboratory Characteristics**

Of 420 suspected patients screened, 76 (18%) were laboratory-confirmed as SRAS-COV-2 infection. All except 5 patients were hospitalized, with a median length of hospital stay (LOS) of 14 days (range, 4-55 days).

Table 1 and 2 describe the clinical presentation of patients, cancer and treatment details in relation to COVID-19 severity. The median age of patients was 9 years (range, 1-18 years) and more than 50% were  $\leq 10$  years of age. Sixty-day overall survival (OS) was not significantly influenced by age or gender (Figure S1A and S1B). Sixty patients were on first line treatment, while 7 and 9 patients were on relapsing protocols and under follow up, respectively. The commonest malignancy was acute lymphoblastic leukemia/lymphoma (ALL/LL) (50%). More than 50% of patients had moderate clinical forms of infection.

The median time from onset of symptoms to SARS-COV-2 diagnosis was 4 days (range, 1-14 days), with no statistical difference with respect to survival outcome (Figure S1C). The commonest clinical symptom was fever (93.4%). Eighteen patients (23.6%) had oxygen saturation  $< 95\%$  at time of admission.

Table 3 details laboratory variables and radiological findings. High ferritin ( $> 1000$  ng/mL) and CRP ( $> 100$  mcg/L) levels were found in 50 (65.7%) and 27 (35.4%) patients, respectively. Elevated levels of D-dimer ( $> 1$  mcg/mL) were found in 36 (47.3%) patients. We noticed statistically significant differences in ferritin and D-dimer levels ( $P = .01$  for each) and in absolute lymphocytic counts ( $P = .007$ ) in relation to severity of COVID-19.

Isolated neutropenia ( $< 500/\text{mm}^3$ ), isolated lymphopenia ( $< 500/\text{mm}^3$ ), or a combination of both cytopenias were found in 11 (14.4%), 13 (17.1%), and 28 (36.8%) patients, respectively

(Figure 1). Importantly, 34 (44.7%) patients of the whole cohort were on non-intensive chemotherapy or off therapy and, therefore, most cytopenias were related to a prior intensive chemotherapy before COVID-19 diagnosis.

All patients underwent baseline chest CTs. Six (7.89%) had no radiological findings all through the course of COVID-19. Follow up CT data were not available for 10 of 70 patients. The commonest CT chest finding was ground glass opacities (74.2%). Regression in CT chest findings was noticed in 60% of patients after one month of follow up. Each of the following 4 radiological findings; ground glass opacities, consolidation, nodular lesions and effusion were noted as sole findings or in combinations in some patients (Figure S2). The initial number of CT findings had statistically significant relation with the increased need for supplementary oxygen ( $P = .01$ ) and invasive ventilation ( $P = .04$ ), but no significant impact on OS, (Figure S1D). Regression in CT findings occurred more significantly in patients with moderate and severe illness than in critical patients ( $P = .002$ ) and was associated with better OS ( $P = .001$ ) (Figure 2A).

**Viral Clearance by RT-PCR**

SARS-CoV-2 PCRs remained positive for a median of 14 days (range, 7-68 days). Sixty-five patients had their PCR tests followed up until a negative result was achieved (Figure S3). Thirty-six patients (55.3%) reached a negative PCR within 2 weeks of the initial positive test.

All patients who reached negative PCR survived except for 2 patients. Statistically significant difference in LOS ( $P = .0001$ ) and disease severity ( $P = .008$ ), but not OS, were found between patients who had achieved negative PCRs  $\leq 14$  versus  $> 14$  days postinitial positive test (Figure 2B and Table S2). To be noticed, that only few patients with severe and critical forms of infection (19/65) were followed up until they had reached a negative PCR result, with 8 of 12 critically ill patients died before confirming a negative PCR result. Neutropenia and lymphopenia did not statistically impact the time needed to reach a negative PCR ( $P = .08$  and  $.6$ , respectively). It is worth noting that there were no mortalities among patients with persistently positive PCRs for  $> 30$  days. Repeated positive PCRs may thus not be true indicator of continued infectivity, but rather of inactive virus shedding (Figure S1E).

**Description of Special Groups of Patients**

Patients with acute leukemia encompassed 76.3% of our cohort (Table S3). Most ALL/LL (88%) were on maintenance therapy, while 55% of AML patients were in the induction phase.

Despite not being statistically significant, AML patients were more likely than ALL patients to present with severe or critical form of disease (40% vs. 27%); to require invasive ventilation; and to have increased need for tocilizumab. Furthermore, only 25% of AML reached a negative PCR within 2 weeks compared to 52.6% of ALL. Improvement of CT chest findings was statistically higher in the ALL group;  $P = .003$ .

Interestingly, all acute leukemia patients  $\leq 2$  years of age ( $n = 5$ ) have survived, and only one patient presented with severe clinical course that required oxygen support and tocilizumab.

# COVID-19 in Pediatric Cancer Patients

**Table 1** Demographic, Cancer and Chemotherapy Details in Relation to COVID-19 Severity Index (n = 76)

Variables	COVID-19 Clinical Severity					P Value
	Mild (n = 6, 7.8%)	Moderate (n = 43, 56.5%)	Severe (n = 15, 19.7%)	Critical (n = 12, 15.7%)	Total (n = 76, 100%)	
<b>Gender</b>						
Female	2 (33.3%)	18 (41.8%)	8 (53.3%)	6 (50.0%)	34 (44.7%)	.82
Male	4 (66.6%)	25 (58.1%)	7 (46.6%)	6 (50.0%)	42 (55.2%)	
<b>Age category</b>						
≤ 2 years	1 (16.6%)	3 (6.9%)	2 (13.3%)	0	6 (7.8%)	.2
>2≤10 years	2 (33.3%)	17 (39.5%)	10 (66.6%)	7 (58.3%)	36 (47.3%)	
>10 years	3 (50.0%)	23 (53.4%)	3 (20.0%)	5 (41.6%)	34 (44.7%)	
<b>Cancer diagnosis</b>						
<b>Hematological malignancies</b>	<b>5 (83.3%)</b>	<b>39 (90.6%)</b>	<b>11 (73.3%)</b>	<b>11 (91.6%)</b>	<b>66 (86.8%)</b>	
ALL/LL	3 (50.0%)	24 (55.8%)	8 (53.3%)	3 (25.0%)	38 (50.0%)	
AML	1 (16.6%)	11 (25.5%)	2 (13.3%)	6 (50.0%)	20 (26.3%)	
Lymphoma	1 (16.6%)	2 (4.6%)	0	2 (16.6%)	5 (6.5%)	
CML	0	2 (4.6%)	1 (6.6%)	0	3 (3.9%)	.15
<b>Solid tumors</b>	<b>0</b>	<b>3 (6.9%)</b>	<b>3 (20.0%)</b>	<b>0</b>	<b>6 (7.8%)</b>	
Neuroblastoma	0	2 (4.6%)	1 (6.6%)	0		
RMS/NRMS	0	1 (2.32%)	2 (13.3%)	0		
<b>CNS tumors</b>	<b>1 (16.6%)</b>	<b>0</b>	<b>1 (6.6%)</b>	<b>1 (8.3%)</b>	<b>3 (3.9%)</b>	
<b>Others<sup>a</sup></b>	<b>0</b>	<b>0</b>	<b>1 (6.6%)</b>	<b>0</b>	<b>1 (1.3%)</b>	
<b>Associated syndromes</b>						
Down Syndrome	0	3 (6.9%)	0	1 (8.3%)	4 (5.2%)	
Fanconi anemia	0	0	0	1 (8.3%)	1 (1.3%)	
<b>Radiotherapy/immune therapy 30 days prior to COVID-19 diagnosis</b>						
Immune therapy	0	3 (6.9%)	1 (6.6%)	2 (16.6%)	6 (7.8%)	
Radiotherapy	1 (16.6%)	0	2 (13.3%)	1 (8.3%)	4 (5.2%)	
<b>Was the last cycle prior to COVID-19 a known intensive chemotherapy?</b>						
Yes	3 (50.0%)	22 (51.1%)	7 (46.6%)	10 (83.3%)	42 (55.2%)	.2
No (incl. non-intensive and off therapy)	3 (50.0%)	21 (48.8%)	8 (53.3%)	2 (16.6%)	34 (44.7%)	
<b>Days from the last chemotherapy given prior to COVID-19 diagnosis</b>						
≤14 days	2 (33.3%)	20 (46.5%)	7 (46.6%)	5 (41.6%)	34 (44.7%)	
>14-≤30 days	1 (16.6%)	11 (25.5%)	2 (13.3%)	4 (33.3%)	18 (23.6%)	.59
>30 days	1 (16.6%)	1 (2.32%)	2 (13.3%)	2 (16.6%)	6 (7.8%)	
>365 days (off therapy)	1 (16.6%)	5 (11.6%)	2 (13.3%)	1 (8.3%)	9 (11.8%)	
Newly diagnosed patients before the start of treatment	1 (16.6%)	6 (13.9%)	2 (13.3%)	0	9 (11.8%)	
<b>Chemotherapy cycles after COVID-19 confirmation</b>						
Cycles delayed without modification	1 (16.6%)	16 (37.2%)	4 (26.6%)	1 (8.3%)	22 (28.9%)	
Cycles delayed and modified	2 (33.3%)	14 (32.5%)	6 (40.0%)	1 (8.3%)	23 (30.2%)	.8
No protocol adjustment (incl. no further cycles)	2 (33.3%)	8 (18.6%)	3 (20.0%)	2 (16.6%)	15 (19.7%)	
NA (under follow up/died before next cycle)	1 (16.6%)	5 (11.6%)	2 (13.3%)	8 (66.6%)	16 (21.0%)	
<b>Duration of delay in chemotherapy cycles (n = 45)</b>	<b>3 (50.0%)</b>	<b>30 (69.7%)</b>	<b>10 (66.6%)</b>	<b>2 (16.6%)</b>	<b>45 (59.2%)</b>	
≤15 days	2 (66.6%)	12 (40.0%)	5 (50.0%)	0	19 (42.2%)	.8
>15≤30 days	1 (33.3%)	11 (36.6%)	3 (30.0%)	1(50.0%)	16 (35.5%)	
>30 days	0	7 (16.2%)	2 (20.0%)	1(50.0%)	10 (22.2%)	

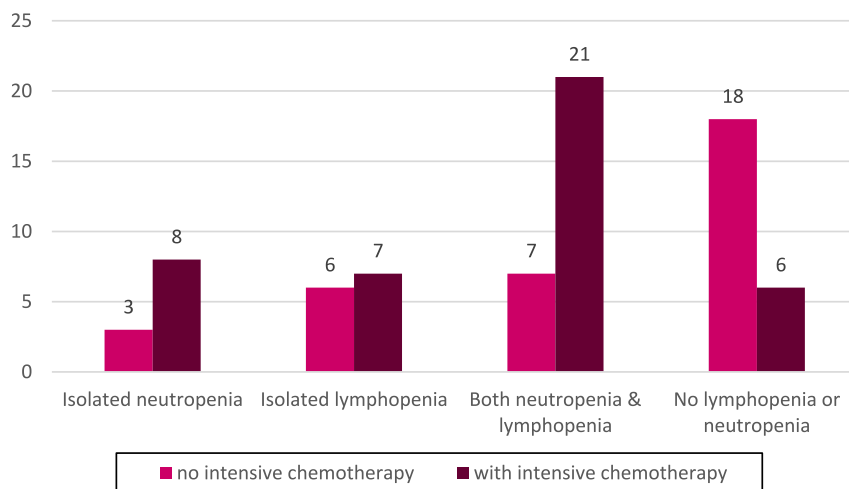
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**Table 1** (continued)

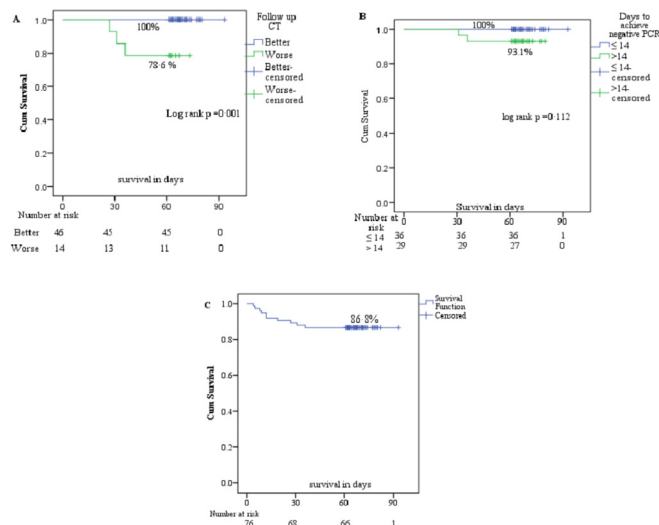
Variables	COVID-19 Clinical Severity					P Value
	Mild (n = 6, 7.8%)	Moderate (n = 43, 56.5%)	Severe (n = 15, 19.7%)	Critical (n = 12, 15.7%)	Total (n = 76, 100%)	
<b>Type of Chemotherapy modifications (n = 23)</b>	<b>2 (33.3%)</b>	<b>14 (32.5%)</b>	<b>6 (40.0%)</b>	<b>1 (8.3%)</b>	<b>23 (30.2%)</b>	
25% dose reduction	2 (100%)	13 (92.8%)	5 (83.3%)	0	20 (26.3%)	
Line of treatment changed	0	1 (7.1%)	1 (16.6%)	1 (100%)	3 (3.94%)	

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; CML = chronic myeloid leukemia; Incl = including; LL, lymphoblastic lymphoma; NA = not applicable; NRMS = nonrhabdomyosarcoma; RMS = rhabdomyosarcoma.  
<sup>a</sup> Others: eosinophilic granuloma.

**Figure 1** Lymphopenia (<500 mm<sup>3</sup>) and neutropenia (<500 mm<sup>3</sup>) in relation to the intensity of chemotherapy.



**Figure 2** (A-C): Sixty-day overall survival (OS) in relation to (A) Computed tomography (CT) follow up response after 1 month from infection (better/worse), (B) Duration (days) to achieve a negative PCR test (≤14 and >14 days), and (C) whole cohort overall survival.





**Table 2** Clinical Characteristics in Relation to COVID-19 Clinical Severity (n = 76)

Variables	COVID-19 Clinical Severity					P Value	
	Mild (n = 6, 7.8%)	Moderate (n = 43, 56.5%)	Severe (n = 15, 19.7%)	Critical (n = 12, 15.7%)	Total (n = 76, 100%)		
<b>Clinical signs of COVID-19</b>							
Fever	6 (100%)	40 (93.0%)	13 (86.6%)	12 (100%)	71 (93.4%)	.6	
Cough	2 (33.3%)	24 (55.8%)	6 (40.0%)	9 (75.0%)	41 (53.9%)	.2	
Tachypnea	0	4 (9.3%)	10 (66.6%)	5 (41.6%)	19 (25.0%)	<b>.001</b>	
Hypoxemia at presentation	0	0	9 (60.0%)	9 (75.0%)	18 (23.6%)	<b>.001</b>	
<b>O2 saturation</b>							
<90%	0	0	4 (26.6%)	4 (33.3%)	8 (86.5%)	<b>.001</b>	
≥90- <95%	0	0	5 (33.3%)	5 (41.6%)	10 (13.1%)		
≥95%	6 (100%)	43 (100%)	6 (40.0%)	3 (25.0%)	58 (76.3%)		
Diarrhea	0	6 (13.9%)	2 (13.3%)	4 (33.3%)	12 (15.7%)	.3	
<b>Loss of smell/taste</b>							
Yes	3 (50.0%)	16 (37.2%)	3 (20.0%)	1 (8.3%)	23 (30.2%)	.1	
Not assessed	2 (33.3%)	20 (46.5%)	6 (40.0%)	9 (75.0%)	37 (48.6%)		
<b>Sore throat</b>							
Yes	2 (33.3%)	14 (32.5%)	3 (20.0%)	1 (8.3%)	20 (26.3%)	.4	
Not assessed	2 (33.3%)	19 (44.1%)	6 (40.0%)	8 (66.6%)	35 (46.0%)		
<b>Other symptoms</b>							
GIT symptoms (abdominal pain and diarrhea)	0	4 (9.3%)	0	0	4 (5.2%)		
Bony pain	0	5 (11.6%)	0	0	5 (6.5%)		
Hyperbilirubinemia	0	0	0	1 (8.3%)	1 (1.3%)		
Vesicular rash	0	0	0	2 (16.6%)	2 (2.6%)		
Disturbed conscious level	0	0	1 (6.6%)	0	1 (1.3%)		
<b>Duration of symptoms before confirming COVID-19</b>							
≤ 7 days	5 (83.3%)	36 (83.7%)	10 (66.6%)	10 (83.3%)	61 (80.2%)	.52	
> 7 days	1 (16.6%)	7 (16.2%)	5 (33.3%)	2 (16.6%)	15 (19.7%)		
<b>Length of hospital stay (d)</b>							
Median, range (14, 4-55)							
≤14 days	1 (16.6%)	25 (58.1)	7 (46.6%)	5 (41.6%)	38 (50.0%)	.34	
>14 days	3 (50.0%)	15 (34.8%)	8 (53.3%)	7 (58.3%)	33 (43.4%)		
Home isolation	2 (33.3%)	3 (6.9%)	0	0	5 (6.5%)		
<b>Associated infections during course of COVID-19</b>							
Tissue infection (gram positive)	0	2 (4.6%)	0	0	2 (2.6%)	<b>.012</b>	
<b>Bacteremia</b>							
Gram positive	0	1 (2.3%)	3 (20.0%)	1 (8.3%)	5 (6.5%)		
Gram negative (multidrug resistance)	0	3 (6.9%)	1 (6.6%)	5 (41.6%)	9 (11.8%)		
<b>Respiratory viral infection</b>							
Human Rhinovirus	0	1 (2.3%)	2 (13.3%)	1 (8.3%)	4 (5.2%)		
Adenovirus	0	0	0	2 (16.6%)	2 (2.6%)		
Radiological fungal chest	0	3 (6.9%)	0	1 (8.3%)	4 (5.2%)		

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**Table 2** (continued)

Variables	COVID-19 Clinical Severity					P Value
	Mild (n = 6, 7.8%)	Moderate (n = 43, 56.5%)	Severe (n = 15, 19.7%)	Critical (n = 12, 15.7%)	Total (n = 76, 100%)	
<b>Post COVID-19 complications<sup>a</sup> (12 patients)</b>						
Bilateral femoral vein thrombosis	0	0	1 (6.6%)	0	1 (1.3%)	
Elevated serum creatinine (RDV related)	0	1 (2.3%)	0	0	1 (1.3%)	
<b>Chest complications</b>						<b>.001</b>
Diffuse alveolar hemorrhage	0	0	0	2 (16.6%)	2 (2.6%)	
Lung fibrosis	0	1 (2.3%)	0	0	1 (1.3%)	
ARDS	0	0	0	6 (50.0%)	6 (7.8%)	
Pneumothorax	0	0	1 (6.6%)	3 (25.0%)	4 (5.2%)	
<b>Survival status</b>						<b>.001</b>
Alive	6 (100%)	43 (100%)	15 (100%)	2 (16.6%)	66 (86.8%)	
Dead	0	0	0	10 (83.3%)	10 (13.1%)	

Abbreviations: ARDS = acute respiratory distress syndrome; GIT = gastrointestinal tract; O2 = oxygen; RDV = remdesivir  
<sup>a</sup> Same patient can have ≥1 complication

Twenty newly diagnosed acute leukemia patients were confirmed as SARS-COV-2 infected during or at the start of their first induction cycle. There were seven new ALL patients with no dose adjustment needed except for one patient who completed induction without 6-mercaptopurine. Interruption of chemotherapy (range, 7-21 days) occurred in 5 patients. Four patients achieved complete remission (CR) at end of induction, 2 patients were not in remission, and one patient died before evaluation. At end of the study, 5 of 7 patients had survived and one had died from acute respiratory distress syndrome (ARDS) and one from malignant disease progression. Nine new AML patients were in first induction and no dose adjustments were done to their protocols. At end of the study 7 of 9 patients had survived and 6 of 7 had achieved CR. The remaining 4 new patients had Hodgkin’s disease, glioblastoma and rhabdomyosarcoma (n = 2) and, with the exception of the glioblastoma patient, all survived.

Five leukemia patients were associated with known syndromes: 4 down syndrome (DS) patients (3 AML and 1 ALL) and one AML patient with Fanconi anemia (FA). All of them were on active treatment. Two patients became critical and died. The cause of death was ARDS in the AML-FA and gram-negative septicemia in the AML-DS patient. The 3 surviving patients achieved a negative PCR within 2 weeks of infection.

Three patients had undergone allogeneic transplants for more than 1 year (AML [n = 2] and chronic myeloid leukemia [n = 1]) prior to infection and were on immunotherapy for chronic graft versus host disease. Two of them presented with moderate severity and one was critically ill and died.

**Description of Cancer Directed Therapy**

More than half (n = 40) of our patients were on intensive chemotherapy and 44.7% (n = 34) had received chemotherapy within 2 weeks prior to their COVID-19 diagnosis (Table 1).

The duration from last chemotherapy did not have statistically significant impact on COVID-19 severity (P = .59), however more severe and critical patients (n = 18/27) were noted among the group that had received chemotherapy within a month prior to the infection. Chemotherapy was delayed in 59.2% of patients with median of 21 days (range, 5-71 days). Of these 42.5% were delayed for ≤ 2 weeks, and doses were modified in 30.2%.

**COVID-19 Directed Treatment, Complications and Outcome**

Table 4 describes patients who were assigned to receive remdesivir (RDV) and those who were not (No-RDV). Coincidentally, more severe to critical patients were in the RDV group (42.1%) compared to the No-RDV group (25.7%) and yet OS was still comparable between both groups (84.4% vs. 90.3%, P = .5) (Figure S1F). There were no reported remdesivir-related adverse events except for a 16-year-old patient who developed a 2 folds elevation in serum creatinine above the baseline.

Based on remdesivir administration, the time needed to reach a negative PCR between both groups (≤14 and >14 days) did show statistical difference. Similarly, there were no statistically significant difference in the duration of delay of chemotherapy, the need for tocilizumab, improvement of CT findings and LOS between both groups.

At the end of the study 10 patients had died with 60-day OS of 86.8% (Figure 2C). All deceased patients had hematological malignancies except for one with a CNS tumor.

The direct cause of death was difficult to be linked solely to COVID-19, but 5, 2, and 3 patients died from ARDS, malignant disease progression and gram-negative septicemia, respectively.



**Table 3** Laboratory and Radiological Findings for the Whole Cohort

Laboratory and Radiological Variables	COVID-19 Clinical Severity					P Value
	Mild (n = 6, 7.8%)	Moderate (n = 43, 56.5%)	Severe (n = 15, 19.7%)	Critical (n = 12, 15.7%)	Total (n = 76, 100%)	
<b>Absolute neutrophilic count (cells/mm<sup>3</sup>)</b>						
≤500	3 (50.0%)	22 (51.1%)	5 (33.3%)	9 (75.0%)	39 (51.3%)	.1
>500 ≤1000	2 (33.3%)	6 (13.9%)	1 (6.6%)	1 (8.3%)	10 (13.1%)	
>1000	1 (16.6%)	15 (34.8%)	9 (60.0%)	2 (16.6%)	27 (35.5%)	
<b>Absolute lymphocytic count (cells/mm<sup>3</sup>)</b>						
≤500	1 (16.6%)	21 (48.8%)	7 (46.6%)	12 (100%)	41 (53.9%)	<b>.007</b>
>500 ≤1000	1 (16.6%)	10 (23.2%)	4 (26.6%)	0	15 (19.7%)	
>1000	4 (66.6%)	12 (27.9%)	4 (26.6%)	0	20 (26.3%)	
<b>Initial D-dimer level (mcg/mL)</b>						
Median 1 mcg (range, 0.27-20 mcg/mL)						
≤0.5	5 (83.3%)	11 (25.5%)	1 (6.6%)	2 (16.6%)	19 (25.0%)	<b>.01</b>
>0.5 ≤1	0	11 (25.5%)	4 (26.6%)	1 (8.3%)	16 (21.0%)	
>1	1 (16.6%)	16 (37.2%)	10 (66.6%)	9 (75.0%)	36 (47.3%)	
Missed	0	5 (11.6%)	0	0	5 (6.5%)	
<b>LDH level</b>						
High (> 745 U/L)	1 (16.6%)	12 (27.9%)	8 (53.3%)	5 (41.6%)	26 (34.2%)	.2
Normal (≤ 745 U/L)	5 (83.3%)	31 (72.0%)	7 (46.6%)	7 (58.3%)	50 (65.5%)	
<b>CRP level (mg/ L)</b>						
≤50	6 (100%)	20 (46.5%)	7 (46.6%)	6 (50.0%)	39 (51.3%)	.2
>50 ≤100	0	8 (18.6%)	1 (6.6%)	0	9 (11.8%)	
>100 ≤200	0	7 (16.2%)	4 (26.6%)	1 (8.3%)	12 (15.7%)	
>200	0	8 (18.6%)	2 (13.3%)	5 (41.6%)	15 (19.7%)	
Not available	0	0	1 (6.6%)	0	1 (1.31%)	
<b>Ferritin level (ng/mL)</b>						
≤500	4 (66.6%)	7 (16.2%)	5 (33.3%)	0	16 (21.0%)	<b>.01</b>
>500 ≤1000	0	5 (11.6%)	2 (13.3%)	1 (8.3%)	8 (10.5%)	
>1000	1 (16.6%)	30 (69.7%)	8 (53.3%)	11 (91.6%)	50 (65.7%)	
Not available	1 (16.6%)	1 (2.3%)	0	0	2 (2.6%)	
<b>IgG level</b>						
Low (<600 mg/dL)	1 (16.6%)	10 (23.2%)	6 (40.0%)	4 (33.3%)	21 (27.6%)	.7
Normal (≥600 mg/dL)	3 (50.0%)	23 (53.4%)	7 (46.6%)	6 (50.0%)	39 (51.3%)	
Not available	2 (33.3%)	10 (23.2%)	2 (13.3%)	2 (16.6%)	16 (21.0%)	
<b>Interval between positive and 1st negative PCRs (d)</b>						
Median of 14 d (range, 7-68)						
≤14	0	26 (60.0%)	10 (66.6%)	0	36 (47.3%)	<b>.008</b>
>14	4 (66.6%)	16 (37.2%)	5 (33.3%)	4 (33.3%)	29 (38.2%)	
Not repeated (died/home isolation)	2 (33.3%)	1 (2.3%)	0	8 (66.6%)	11 (14.4%)	
<b>Description of initial CT chest findings (n = 70)<sup>a</sup></b>	<b>0</b>	<b>43 (100%)</b>	<b>15 (100%)</b>	<b>12 (100%)</b>	<b>70 (92.1%)</b>	

(continued on next page)

**Table 3** (continued)

Laboratory and Radiological Variables	COVID-19 Clinical Severity					P Value
	Mild (n = 6, 7.8%)	Moderate (n = 43, 56.5%)	Severe (n = 15, 19.7%)	Critical (n = 12, 15.7%)	Total (n = 76, 100%)	
<b>Laterality</b>						
Unilateral	0	9 (20.9%)	1 (6.6%)	1 (8.3%)	11/70 (15.7%)	.4
Bilateral	0	34 (79.0%)	14 (93.3%)	11 (91.6%)	59/70 (84.2%)	
<b>Description of radiological findings</b>						
Ground glass opacities	0	31 (72.0%)	12 (80.0%)	9 (75.0%)	52/70 (74.2%)	
Consolidation	0	23 (53.4%)	10 (66.6%)	11 (91.6%)	44/70 (62.8%)	
Nodules (pulmonary or subpleural)	0	14 (32.5%)	5 (33.3%)	4 (33.3%)	23/70 (32.8%)	
Effusion	0	4 (9.3%)	4 (26.6%)	5 (41.6%)	13/70 (18.5%)	
<b>Radiological findings per patient</b>						
Single finding	0	20 (46.5%)	3 (20.0%)	2 (16.6%)	25/70 (35.7%)	<b>.06</b>
Multiple findings	0	23 (53.4%)	12 (80.0%)	10 (83.3%)	45/70 (64.2%)	
<b>Chest CT follow up after 30 d</b>						
Better (regressive/ near resolution / total resolution)	0	34 (79.0%)	12 (80.0%)	0	46 (65.7%)	<b>.002</b>
Worse (progressive)	0	6 (13.9%)	3 (20.0%)	5 (41.6%)	14 (20.0%)	
Not repeated (died/home isolation)	0	3 (6.9%)	0	7 (58.3%)	10 (14.2%)	

Abbreviations: CRP = C-reactive protein; CT = computed tomography; LDH = lactate dehydrogenase; IgG = Immunoglobulin G.  
<sup>a</sup> Excluding patients without radiological findings in their baseline chest computed tomography.

**Discussion**

Few cancer centers from Egypt have described the management and course of SARS-CoV-2 infection in pediatric cancer patients.<sup>14,15</sup> The percentage of patients that were included in this study stood at 18% of all suspected patients; higher than other single and multicenter studies.<sup>16,17</sup> This could be due to our policy of screening highly suspicious patients. Similar to others, we admitted most patients irrespective of COVID-19 severity to exclude other associated serious bacterial infections.<sup>8</sup> Our decision to admit patients was influenced by the low socioeconomic status of families and the need to monitor for clinical deterioration. Madhusoodhan et al. stated that 75% of COVID-19 patients were admitted despite only 38.4% required inpatient care for COVID-19-related symptoms.<sup>18</sup>

The slightly higher percentage of male patients in this study was comparable to another study on healthy children that reported a 56.6% of males.<sup>19</sup> The median age for our patients was lower than the New York-New Jersey report, where most of their patients were older than 10 years with a median age of 12 years.<sup>18</sup>

In this study, most severe to critical patients belonged to >2 - ≤ 10 age group. Madhusoodhan et al. reported, that severe disease forms were more common in age >10 years.<sup>18</sup> Importantly, our patients ≤ 2 years of age survived with no serious complications. Conversely, Dong et al. reported that infants were more likely to

develop life-threatening course of disease than older children.<sup>19</sup> Despite that >50% of our patients presented with mild to moderate forms of COVID-19 infection, severe and critical forms were higher than other reports.<sup>3,16</sup> Supplementary oxygen and invasive ventilation were required in 18.4% and 15.7% of our patients, respectively. The French Society of Pediatric Oncology (SFCE) and others reported that 12% to 20% of their patients had presented with severe form of infection that required intensive care admission.<sup>7,8</sup>

Preliminary reports suggested that cancer patients were at risk of increased mortality from SARS-COV-2 infection compared to the general population.<sup>2,20</sup> Singling out COVID-19 as the cause of mortality in oncology patients is difficult as other factors may contribute to mortality risk in cancer patients. The percentage of COVID-19 related deaths in our cohort, after the exclusion of septicemia and cancer progression was estimated at 6.5%, yet we cannot rule out the true incidence of infection associated with SARS-COV-2 infection. The St. Jude and the Pediatric Oncology COVID Patient (POCC) registries reported a mortality rate of 4.6% and 3.4%, respectively.<sup>5,6</sup>

Lee et al. observed that patients with hematological malignancies were at increased risk of COVID-19 infection compared to solid tumors and to present with more critical clinical form (OR 1.57, 95% CI 1.15-2.15; P < .0043), requiring invasive ventilation.<sup>21</sup> In this cohort, 11 of 12 patients who had deteriorated and

# COVID-19 in Pediatric Cancer Patients

**Table 4** Patients Characteristics in Relation to Antiviral Therapy (Remdesivir vs. no Remdesivir)

Variables	Remdesivir (RDV) (n = 45)	No Remdesivir (No-RDV) (n = 31)	P Value
<b>Gender</b>			
Female	20 (44.4%)	14 (45.1%)	.95
Male	25 (55.5%)	17 (54.8%)	
<b>Diagnosis</b>			
Hematological malignancies	39 (86.6%)	27 (87.0%)	.62
Solid and CNS tumors	6 (13.3%)	3 (9.6%)	
Others <sup>a</sup>	0	1 (3.2%)	
<b>Age category</b>			
Median, range (y)	9 (2-18)	10 (1-18)	.62
≤10 y	26 (57.7%)	16 (51.6%)	
>10 y	19 (42.2%)	15 (48.3%)	
<b>COVID-19 clinical severity</b>			
Mild	4 (8.8%)	2 (6.4%)	.43
Moderate	22 (48.8%)	21 (67.7%)	
Severe	10 (22.1%)	5 (16.1%)	
Critical	9 (20%)	3 (9.6%)	
<b>Type of oxygen support</b>			
Room air	27 (60.0%)	23 (74.1%)	.22
SOM/Nasal cannula/NRM	9 (20.0%)	5 (16.1%)	
Ventilator	9 (20.0%)	3 (9.6%)	
Anti-IL6 (number of patients)	6 (13.3%)	4 (12.9%)	.95
Follow up Chest CT response after 30 d <sup>b</sup>	41 (91.1%)	29 (93.5%)	.23
Better (regressive/ near resolution / total resolution)	25 (60.9%)	21 (72.4%)	
Worse (progressive)	10 (24.3%)	4 (13.7%)	
Not repeated (died/home isolation)	6 (14.6%)	4 (13.7%)	
Number of patients with delayed chemotherapy cycles during infection course	28 (62.0%)	17 (54.8%)	.32
<b>Length of hospital stay (d)</b>			
Median, range (d)	15 (7-53)	13 (4-55)	.051
≤14	21 (46.6%)	17 (54.8%)	
>14	24 (53.3%)	9 (29.0%)	
Home Isolation	0	5 (16.1%)	
<b>Interval between positive and 1st negative PCRs (days)</b>			
Median, range (d)	15 (4-67)	14 (6-50)	.62
≤14	21 (46.6%)	15 (48.3%)	
>14	19 (42.2%)	10 (32.2%)	
Not available (died/home isolation)	5 (11.1%)	6 (19.3%)	
<b>Survival status</b>			
Alive	38 (84.0%)	28 (90.3%)	.58
Dead	7 (15.5%)	3 (9.6%)	
<b>Cause of death</b>			
ARDS	2 (4.4%)	3 (9.6%)	P = .5
Disease progression	2 (4.4%)	0	
Bacterial sepsis	3 (6.6%)	0	
60-day overall survival	84.4%	90.3%	

Abbreviations: Anti-IL6 = anti-interleukin-6; ARDS = acute respiratory distress syndrome; CNS = central nervous system; CT = computed tomography; NRM = non-rebreather mask; SOM = Simple oxygen mask.

<sup>a</sup> Others: eosinophilic granuloma.

<sup>b</sup> Excluding patients without radiological findings in their baseline chest computed tomography.

required ventilation had hematological malignancies. Furthermore, AML patients tended to suffer more aggressive clinical course with higher mortalities compared with ALL patients. A pediatric study reported that 55% of AML patients had required intensive care level of care, which was higher compared to other malignancies.<sup>18</sup> This could be due to the higher intensity of chemotherapy and the higher risk of infection in patients of AML, rather than a true impact of COVID-19. In contrast, Kuderer et al. did not observe an increased mortality in hematological malignancies.<sup>22</sup>

Chemotherapy exposes patients to an added risk of immunosuppression and infection. Our results were similar to the SFCE results,<sup>8</sup> where 1 of 3 of our patients had combined neutropenia and lymphopenia, of whom 2 of 3 could be related to prior intensive chemotherapy. Lymphopenia in some adult studies have been linked to disease severity,<sup>23</sup> but our study and Anil et al. could not link any cytopenias to COVID-19 severity.<sup>24</sup>

In this study 68.3% of patients had received chemotherapy within 30 days prior to COVID-19. All our deceased patients were on active treatment, but direct risk of recent chemotherapy on survival could not be assessed. Lee et al. identified that recent chemotherapy leads to higher mortalities during COVID-19 course of infection (OR 2.09, 95% CI 1.09-4.08;  $P = .028$ ).<sup>21</sup> Nevertheless, a study on solid malignancies did not find a significant increase in mortality associated with recent chemotherapy.<sup>22</sup>

Avoiding interruptions in chemotherapy is a challenge during a pandemic. A multicenter survey reported that chemotherapy administration was adversely affected in 29% to 54% of participating centers.<sup>25</sup> Another study reported that 67% of patients needed delays of 2 to 78 days in their cycles, compared to 59% in our patients.<sup>18</sup> Notably, 42.5% of delays in this study lasted  $\leq 15$  days. Others reported that 40% to 54% experienced delays in their treatment.<sup>8,16</sup> It should be noted that 84% of our ALL patients were on weekly maintenance therapy and skipping one week was labelled as “a delay.” Although no definitive recommendations can be given based on this study, our whole cohort survival and remission rates in new patients suggest for that treatment should start without delay or dose adjustment, as also stipulated by Ding et al.<sup>26</sup>

The use of remdesivir was based on preliminary recommendations of studies conducted on severe patients.<sup>11,27</sup> Fifty-nine percent of patients received RDV with a median of 4 days (range, 1-14 days) from onset of symptoms. The lack of parent and/or guardian awareness to the importance of seeking early hospital care and the similarity of symptoms to those of chemotherapy related complications resulted in a delay of antiviral therapy in some patients. The insignificant difference in OS between RDV group, which included more aggressive COVID-19 forms, and No-RDV group could be related to the RDV they had received. Similar results were observed in young adults and pediatric cohorts.<sup>10,16</sup> To date, there is insufficient data regarding the safety of RDV below the age of 12, but we did not observe serious adverse events even in younger patients.<sup>28</sup> Frauenfelder et al. and Orf et al. reported good outcome and tolerance of RDV in pediatric patients.<sup>29,30</sup>

Zheng et al. discussed disease severity as a factor that correlates with the duration to viral clearance, with a median of 21 days in severe disease compared to 14 days in mild disease;  $P = .04$ .<sup>31</sup> Similarly, all our critical patients either had not reached

viral clearance within 2 weeks or had died before clearing the virus.

The importance of this prospective study lies in the fact that it describes the clinical course of SARS-COV-2 in a considerable number of pediatric oncology patients with more than half of them have received the same antiviral therapy. In addition, we managed to achieve good outcome and to conduct well-timed follow up PCR tests and CT scans despite our limited resources. However, one main limitation of this study is that it is based on data from a single center. In addition, some logistic problems related to the availability of PCR kits at the start of the crisis might have led to selection bias as only symptomatic patients being screened. Criteria for hospital admission and treatment were not properly tailored according to the clinical severity and radiological findings of each patient.

## Conclusion

More research should focus on SARS-CoV-2 infection in pediatric cancer patients. While most patients of COVID-19 in this vulnerable group show favorable clinical outcome, severe course of disease do still occur. Cancer patients can tolerate chemotherapy including induction phase, alongside COVID-19 treatment. Delays in chemotherapy and dose adjustments were to a great extent based on fears of the adverse impact of therapy rather than a true need. Further studies are needed to determine the potential benefits of RDV in pediatric oncology patients.

The RDV group included more severe and critical patients compared to the No-RDV group, yet OS was comparable in both groups with no serious adverse events observed in all age groups.

## Clinical Practice Points

Pediatric cancer patients are amongst the most vulnerable groups to infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Most healthy children present with asymptomatic or mild form of the disease. Sufficient data pertaining to the impact of the Coronavirus disease 2019 (COVID-19) on pediatric cancer patients is still lacking.

Hematological malignancies constituted 86.8% of the whole cohort. While most patients infected with SARS-CoV-2 show favorable clinical outcome with 60-day overall survival (OS) of 86.8%, severe course of disease do still occur. Severe to critical form of infections were 35.4% of patients. Better OS was associated with regression of radiological CT chest findings after 30 days from infection ( $P = .002$ ). Of 16 acute leukemia patients in the first induction phase of treatment, 13 survived and 10 achieved complete remission. Chemotherapy was delayed in 59.2% of patients with median of 21 days (range, 5-71 days) and doses were modified in 30.2%. Cancer patients can tolerate chemotherapy including induction phase, alongside COVID-19 treatment and delays in chemotherapy and dose adjustments were to a great extent based on fears of the adverse impact of therapy rather than a true need. Forty-five patients received remdesivir (RDV), 42.1% had severe and critical forms of infection compared to 25.7% in the No-RDV group and yet OS was comparable in both groups. No serious adverse events were observed in all age groups with the administration of RDV but still further studies are needed to determine the potential benefits of RDV in pediatric oncology patients.

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## Disclosure

All Authors have no competing conflict of interest to declare either financial or personal relationships with other organizations.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.cml.2021.07.025](https://doi.org/10.1016/j.cml.2021.07.025).

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