CANCER EPIDEMIOLOGY

COVID-19 outcomes in children, adolescents and young adults with cancer

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Abstract

Pediatric oncology patients are at risk for poor outcomes with respiratory viral infections. Outcome data for COVID-19 in children and young adults with cancer are needed; data are sparse for obese/overweight and adolescent and young adult subgroups. We conducted a single center cohort study of COVID-19 outcomes in patients younger than 25 years with cancer. Candidate hospitalization risk factors were analyzed via univariable and multivariable analyses. Eighty-seven patients with cancer and COVID-19 were identified. Most were Hispanic/Latinx (n = 63, 72%). Forty-two (48%) were overweight/obese. Anticancer therapy included chemotherapy only (n = 64, 74%), chimeric antigen receptor T-cells (CAR-T, n = 7), hematopoietic stem cell transplantation (HSCT, n = 12), or CAR-T and HSCT (n = 4). There was no COVID-19 related mortality. Twenty-six patients (30%) required COVID-19 related hospitalization; 4 required multiple hospitalizations. Nine (10%) had severe/critical infection; 6 needed intensive care. COVID-19 resulted in anticancer therapy delays in 22 (34%) of 64 patients on active therapy (median delay = 14 days). Factors associated with hospitalization included steroids within 2 weeks prior to infection, lymphopenia, previous significant non-COVID infection, and low COVID-19 PCR cycle threshold value. CAR-T recipients with B-cell aplasia tended to have severe/critical infection (3 of 7 patients). A COVID-19 antibody response was detected in 14 of 32 patients (44%). A substantial proportion of COVID-19 infected children and young adults with cancer require inpatient management; morbidity may be high in B-cell immunodeficiency. However, a majority of patients can be taken through chemotherapy without prolonged therapy delays. Viral load is a potential outcome predictor in COVID-19 in pediatric cancer.

KEYWORDS

adolescents and young adults, COVID-19, pediatric cancer

What's new?

It is important to understand outcomes of COVID-19 in pediatric patients with cancer, not only to appropriately treat the COVID-19, but also to know how best to modify cancer therapy. Highly immunosuppressive cancer therapy can add to the risk of severe infection, but stopping cancer treatment can allow the cancer to progress. Here, the authors undertook a single-center cohort study of COVID-19 outcomes in 87 patients under age 25 with cancer. None died of COVID-19, but 30% required hospitalization. Risk factors included lymphopenia, recent steroids, CAR T-cell therapy, and high viral load. Most patients could continue chemotherapy without prolonged delays.

1 | INTRODUCTION

Understanding outcomes of COVID-19 in pediatric patients with cancer is essential for the treatment of COVID-19 and the optimal modification of cancer therapy to minimize both the risk of severe infection due to immunosuppressive cancer therapy and the risk of cancer progression due to interruption of cancer therapy. COVID-19 in adults with cancer results in high severe disease (26%) and death (13%) rates.[1] Multicenter registry and several small single center studies have provided valuable insights regarding COVID-19 in pediatric cancer.[2-8] Two multicenter registry studies showed low rates of mortality (0%-1%) and severe infection (6%-8%) in children with cancer in high income countries.[2-4] In contrast, another multinational registry reported substantial morbidity including a 37% hospitalization rate.[5]

Several gaps remain in the knowledge of COVID-19 in pediatric cancer. The rate of hospitalization for COVID-19 has not been well defined. Pediatric oncology patients require hospitalization for anticancer therapy or management of toxicities. In published studies, COVID-19 related and unrelated hospitalizations were not separately reported[4] or the criteria used to distinguish the two were unclear.[2,3,5] Lack of uniform criteria for COVID-19 testing across centers, inherent limitations of multicenter registry studies related to the depth of data, differences in management practices between centers, and the use of an infection severity classification system that did not include oxygen saturation create challenges in the extrapolation of morbidity data from published registry studies[2-5,8] to clinical practice. Furthermore, data regarding details of anticancer therapy modification in the context of specific intensive anticancer therapy regimens remain scarce.

Obesity and Hispanic/Latinx ethnicity are risk factors for adverse outcomes in COVID-19 in adults without cancer.[9-11] There is a paucity of data for COVID-19 outcomes in pediatric cancer patients with obesity, a subgroup that has inferior cancer survival outcomes relative to nonobese patients.[12] One multicenter study reported a similar hospitalization rate but a higher rate of anticancer therapy modification for Hispanic/Latinx pediatric cancer patients relative to their peers.[8] The adolescent/young adult age group (AYA, 15-29 years) has lower cancer cure rates and higher rates of anticancer therapy induced toxicities relative to younger children,[13] raising the possibility of worse COVID-19 outcomes in this age group. However, AYA have either been fully or partly excluded in several pediatric studies of COVID-19 and cancer.[2-5] Chimeric antigen receptor T-cell therapy (CAR-T) recipients have unique immunodeficiencies (B-cell aplasia), and a recent study reported high mortality (33%) in COVID-19 infected adult CAR-T recipients.[14] Little data has been reported for outcomes of COVID-19 in pediatric CAR-T recipients, a group of patients with lower prevalence of organ dysfunction than adults.

In our study, we report COVID-19 morbidity outcomes, risk factors associated with COVID-19 related hospitalization including viral load, and detailed data about anticancer therapy modifications in a cohort of children and AYA with cancer receiving chemotherapy, hematopoietic stem cell transplantation (HSCT), or CAR-T and comprised of substantial proportions of Hispanic/Latinx and overweight/obese patients.

2 | METHODS

2.1 | Data extraction

Since March 2020, patients with cancer at Children's Hospital Los Angeles (CHLA) have been universally screened using reverse-transcriptase-PCR (RT-PCR) for the detection of SARS-CoV-2 in nasopharyngeal specimens. Patients were screened prior to any sedation, hospitalization, CAR-T, or HSCT. In addition, RT-PCR was performed in patients with symptoms suspicious for COVID-19. CHLA's Children's Center for Cancer and Blood Disease COVID-19 database was used to identify patients with cancer aged 25 years and younger who were treated with chemotherapy, HSCT, or CAR-T, and diagnosed with COVID-19 by RT-PCR. Inclusion and exclusion criteria are shown in Figure S1. In the case of patients who received chemotherapy only, patients who developed COVID-19 while receiving chemotherapy or within 6 months of completion of chemotherapy were included. There were no posttherapy time-based exclusion criteria for HSCT and CAR-T patients. We retrospectively reviewed medical records of patients treated at CHLA for a cancer and diagnosed with COVID-19 between March 1, 2020 and March 1, 2021. In addition, we prospectively enrolled patients with COVID-19 between March 2, 2021 and August 5, 2021. We used a data extraction form consisting of fields covering patient demographics, cancer diagnosis, anticancer therapy, comorbidities, laboratory values, clinical course of COVID-19 infection, anti-COVID-19 therapies, and

COVID-19 related modifications of anticancer therapy. Data was stored in a REDCap database (version 11.3.2). The study was approved by the CHLA Institutional Review Board (IRB). The IRB granted a consent waiver for retrospective data extraction. Informed consent was obtained for prospectively enrolled patients. Following March 1, 2021, patients were enrolled onto a prospective trial that collected clinical data, and obtained blood samples at serial timepoints to assess the immune response to COVID-19 infection. Due to a sharp decline in new cases, accrual for the prospective study was low; thus, these patients are aggregated here with the retrospective patients.

Obesity/overweight status was defined based on CDC criteria.[15,16] Comorbidities were defined as coexisting organ dysfunction, health conditions that required ongoing therapeutic intervention, or developmental delay. Neutropenia and lymphopenia were both defined as <500 based on CTCAE version 5.0 criteria for grade 3 or higher neutropenia and lymphopenia.[17] Metrics used to assess COVID-19 infection severity included WHO severity class (mild, moderate, severe, or critical)[18] and the need for hospitalization for management of COVID-19 related manifestations. All pediatric oncology patients with febrile neutropenia at our center are hospitalized for sepsis work-up regardless of clinical symptoms and remain inpatient until count recovery due to the risk of life-threatening bacterial infection. Hence, COVID-19 related hospitalizations were defined as hospital stays where COVID-19 manifestations necessitated inpatient management (respiratory support, intravenous fluids, or vasopressors) and excluded hospitalizations of COVID-19 infected patients that were solely for febrile neutropenia. While it is possible that fever in patients admitted solely for febrile neutropenia may be due to COVID-19, the need for hospitalization is not reflective of COVID-19 infection severity in these patients. Hospitalizations were classified as COVID-19 related based on a consensus of two reviewers (RP and CP). A hospitalization was deemed to be COVID-19 related if both reviewers determined the hospitalization to be COVID-19 related.

A WHO COVID-19 severity classification-based categorization was used to classify COVID-19 infections into mild, moderate, severe, and critical disease (Table S1). Mild disease was defined as COVID-19 infection without evidence of pneumonia. Moderate disease included infections with evidence of pneumonia that did not meet the definition of severe disease. Severe disease was defined as an oxygen saturation <90% on room air or signs of severe respiratory distress (accessory muscle use or grunting). Critical disease included cases requiring life-sustaining treatment (noninvasive or invasive ventilation or vasopressors) for acute respiratory distress syndrome (ARDS), septic shock, or multisystem inflammatory syndrome of children. We assessed each intensive care admission through a detailed review of the medical records including a search for confounding etiologies (eg, bacterial sepsis or hyperleukocytosis) to determine whether the admission was attributable to the need for intensive care support for COVID-19 manifestations.

The control cohort consisted of all healthy individuals younger than 25 years of age without cancer who were seen at the CHLA emergency room with RT-PCR confirmed COVID-19 between March 1, 2020 and March 15, 2021. In order to identify patients seen with COVID-19 in the emergency room, we searched the CHLA Electronic Medical Records system using the ICD-10 code for COVID-19 (U07.1) as the query. Only those patients with a documented positive COVID-19 RT-PCR result were retained. Patients with a history of hematology/oncology, pulmonology, or rheumatology clinic encounters were excluded to eliminate those with cancer, those on immunosuppressive medications, or those with pulmonary comorbidities. In addition, medical records for individual patients were reviewed to exclude those with cancer, immunodeficiencies, or pulmonary comorbidities. Figure S2 depicts the approach used to generate the control cohort.

2.2 | Antibody assay

Antibody data for retrospective patients were extracted from the results of clinical antibody testing obtained by the treating physician. The anti-COVID-19 IgG antibody assay was done on plasma or serum using the EUROIMMUN Anti-SARS-CoV-2 ELISA kit.[19] In the case of prospective patients, the assay was done on plasma samples using the same kit. The test has been validated for serum and plasma samples. A sample: internal control ratio >1.2 was considered a positive result.

2.3 | COVID-19 PCR

Nasopharyngeal swabs were sent to the Clinical Virology Laboratory at CHLA for testing by RT-PCR. The CDC,[20] Taqpath (Thermo Fisher, Walham, MA),[21] Xpert Xpress (Cepheid, Sunnyvale, CA),[22] or Simplexa (Diasorin Molecular, Cypress, CA)[23] SARS-CoV-2 RT-PCR assays were used. Cycle threshold (C_t values) were extracted from the C_t value data generated during the clinical RT-PCR assay. These C_t values were not available to the treating physician and were not used for clinical decision making.

2.4 | Statistical analysis

Statistical analysis was done using R version 3.6.1 and the R package epitools.[24] Fishers' exact (categorical variables) or t-test (PCR C_t value) were used for univariable analysis. Logistic regression was used for multivariable analysis. Two-sided tests with $P < .05$ were considered significant. The primary endpoints were COVID-19 related hospitalization and WHO severity grade (severe/critical vs nonsevere/critical). To identify risk factors associated with COVID-19 related hospitalization in patients with cancer, we first screened candidate clinical and laboratory predictors in univariable analyses. All categorical variables with Fisher's exact P-value <.05 were considered in a multivariable (MV) analysis. This initial MV model included data from all patients with cancer who had COVID-19 infection. We then built a MV model that included PCR C_t value and all the categorical variables that showed a Wald's test P-values <.05 in the initial MV model. Patients with missing PCR C_t values (8 patients) were excluded in this final MV model. MV analysis was done using the R function glm (family = binomial), which generates Wald's test P-values.

TABLE 1 Baseline patient, cancer, immune status, and anticancer therapy characteristics

		N = 87
Age (years)	Median (range)	12 (0-24)
Sex, n (%)		
	Male	48 (55)
	Female	39 (45)
Ethnicity, n (%)		
	Hispanic	64 (74)
	Non-Hispanic	23 (26)
Weight status		
	Overweight	14 (16)
	Obese	28 (32)
	Lean	45 (52)
Cancer, n (%)		
	Hem, n (%)	63 (72)
	ALL	53
	AML	2
	Hodgkin	2
	NHL	2
	Other	4
	Non-Hem, n (%)	24 (28)
	Brain	3
	Sarcoma	7
	Neuroblastoma	8
	Wilms	3
	Retinoblastoma	1
	Other	2
Therapy, n (%)		
	Chemo	64 (74)
	HSCT	12 (14)
	CAR	7 (8)
	CAR & HSCT	4 (4)
Chemotherapy intensity (n = 64)[a]		
	Intense	29
	Nonintense	35
HSCT type (n = 16)		
	Allogeneic	10
	Autologous	6
Days since therapy, median (range)[b]		
	HSCT	305 (−39 to 3939)
	CAR	629 (21-2142)
Steroids[c], n (%)		18 (21)
Anthracyclines, n (%)		65 (75)
Neutropenia[d], n (%)		14 (16)
Lymphopenia[e], n (%)		35 (40)
Any Comorbidity, n (%)		51 (59)
	Neurological	14
	Cardiac	9

TABLE 1 (Continued)

		N = 87
	Pulmonary	5
	Renal	4
	Endocrine	4
	Infection[f]	8
	Gastrointestinal	10
	Other	19
GVHD		
	Acute	1
	Chronic	2
Immune status (allo-HSCT, n = 9)[g]		
	Lymphopenia	0
	Neutropenia	0
	CD4 < 200	0
Immune status (CAR, n = 8)[g]		
	Lymphopenia	3
	Neutropenia	0
	CD4 < 200	2
	B-cell aplasia	7

[a]Intense: patients in the midst of a highly myelosuppressive phase of chemotherapy at the time of COVID-19 infection.
[b]Days: time interval between the date of last anticancer therapy (HSCT or CAR) and the date of the first positive COVID-19 PCR.
[c]Received systemic steroids (not including steroids given as part of COVID-19 management) within 2 weeks prior to the date of COVID-19 diagnosis.
[d]Absolute neutrophil count <500.
[e]Absolute lymphocyte count <500.
[f]Includes 4 patients with non-COVID viral infection and 4 patients with fungal infection.
[g]Patients who had received both HSCT and CAR were classified as HSCT or CAR based on the last anticancer therapy prior to COVID-19 infection.

3 | RESULTS

3.1 | Baseline characteristics

We identified 87 patients with cancer and RT-PCR confirmed COVID-19 infection. Eighty-four patients were identified through retrospective review while the remaining three were prospectively identified at the time of COVID-19 diagnosis. Tables 1 and S2 (detailed data for individual subjects) list the baseline characteristics for the cohort. The median age was 12 years. A majority of the cohort (74%) was of Hispanic/Latinx ethnicity. Almost half the patients (n = 42, 48%) were either obese (n = 28) or overweight (n = 14). The most common cancer was acute lymphoblastic leukemia (ALL, 61%). Anticancer therapy regimens included chemotherapy alone (74%), HSCT (n = 12), anti CD19 CAR-T (n = 7), and both HSCT and CAR-T (n = 4). Among those who received chemotherapy alone, 29 (45%) had COVID-19 during an intensive phase of chemotherapy (ALL induction, ALL

**TABLE 2**   Clinical presentation and outcomes of COVID-19 infection

			N = 87
Clinical presentation, n (%)			
		Asymptomatic	26 (30)
		Fever	38 (44)
		Myalgia	16 (18)
		URI	47 (54)
		LRI	18 (21)
		GI	25 (29)
		Neurological	9 (10)
		Cardiac	5 (6)
		Skin	6 (7)
Hospitalization, n (%)			
		COVID related	26 (30)
		Multiple hospitalizations	4
		COVID unrelated	14 (16)
		Not hospitalized	47 (54)
Severity[a]			
		Mild	69
		Moderate	10
		Severe	2
		Critical	6
Hypoxia, n (%)			12 (14)
Intensive care, n (%)			6 (7)
		Invasive ventilation[b]	2
		Organ failure	6
Any treatment, n (%)			19 (22)
		Remdesivir	14
		Steroids	11
		Monoclonal	2
		Convalescent Plasma	4
		Hydroxychloroquine	1
		Azithromycin	2
		Other	1
Therapy delay (n = 64 on active therapy)			
		Delayed	22
Duration of delay (days, median (range))			14 (2-39)[c]

Abbreviations: LRI, lower respiratory infection; URI, upper respiratory infection.

[a]Severity was graded using the World Health Organization scale. Mild: no pneumonia or hypoxia. Moderate: clinical signs of pneumonia, chest radiography may help in diagnosis. Severe: oxygen saturation <90% on room air or signs of severe respiratory distress (accessory muscle use, grunting.) Critical: life-sustaining treatment for conditions such as acute respiratory distress syndrome (ARDS), sepsis, or septic shock.

[b]Intubation and ventilation.

[c]Radiotherapy was omitted in one patient due to COVID-19.
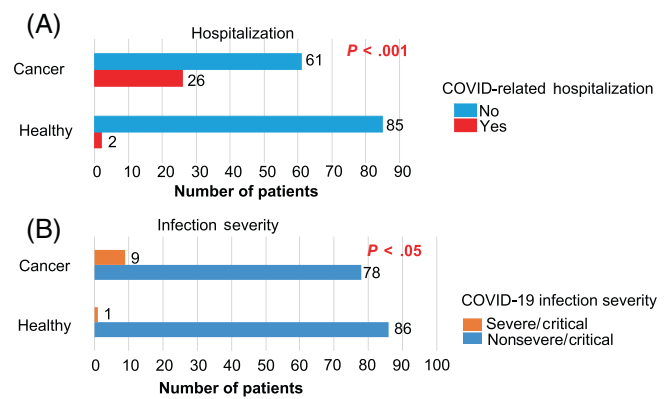
FIGURE 1   Hospitalization (A) and infection severity (B) outcomes in children, adolescents and young adults (AYA) with cancer and COVID-19 infection (cancer, N = 87 patients) and children and AYA without cancer who had COVID-19 infection (healthy, n = 87). Two-sided Fisher exact test P-values for cancer vs healthy shown

delayed intensification, acute myeloid leukemia therapy, and therapy phases that are expected to drop ANC to less than 500 for more than 1 week). Over half the patients (59%) had at least one comorbidity.

3.2 | COVID-19 outcomes

Clinical presentation: 61 patients (70%) had symptomatic infection. The most common clinical presentations were fever and upper respiratory infection symptoms (Table 2).

Mortality and morbidity outcomes: There were no COVID-19 related deaths; two patients died from progression of cancer. Twenty-six (30%) patients required hospitalization for the management (respiratory support, intravenous fluids, or vasopressors) of COVID-19 manifestations (COVID-19 related hospitalizations). Four patients (Table S3) needed multiple hospitalizations due to recurrent fever and respiratory symptoms (data for three of these four have been previously reported[25]). COVID-19 PCR positivity was seen at all these recurrent hospitalizations. Nine patients (10%) had severe or critical infection (as defined by the WHO COVID-19 severity classification); 6 (7%) needed intensive care management. The median duration following COVID-19 for which data was available was 98 days (19-351 days). COVID-19 outcomes are described in Tables 2 and S2 (detailed data for individual subjects).

COVID-19 directed therapy: 19 (22%) patients required treatment for COVID-19; the most common treatments were Remdesivir and steroids (Table 2).

COVID-19 related complications: Two patients (one CAR-T recipient and one autologous HSCT recipient) developed multisystem inflammatory syndrome of children (treated with IVIG and Anakinra in the CAR-T recipient). One patient developed a new thrombus. Two patients experienced COVID-19 symptoms of intermittent fever and respiratory symptoms for greater than 2 months.

Changes to anticancer therapy: Among the 64 patients who were in the midst of anticancer therapy, 22 (34%) experienced modifications or delay in anticancer therapy as a result of COVID-19 infection (median delay = 14 days, range = 2-39 days, radiation therapy discontinued for one patient). Anticancer therapy was delayed or modified in 13 of 31 patients and 9 of 33 patients in the midst of intensive and nonintensive anticancer therapy respectively. Among the eight patients who presented with COVID-19 at the time of cancer diagnosis, chemotherapy was delayed or modified up to 2 weeks in two (both with acute leukemia), and there was no worsening of COVID-19 with intensive chemotherapy in the seven patients who required an intensive regimen (Table S4). The three patients with COVID-19 at the time of leukemia diagnosis showed absence of minimal residual disease at the end of induction.

Duration of PCR positivity: Repeat RT-PCR data were available for 50 patients. In 14 patients, a positive PCR result was seen in at least two successive tests. The time interval between the first and last positive tests was >3 weeks for 12 of these patients and >6 weeks for four of these patients. Two patients (one CAR-T recipient with B-cell aplasia, one with ALL) showed PCR positivity for >150 days.[25]

Comparison to healthy cohort: Children and AYA with cancer and COVID-19 showed a significantly higher rate of hospitalization and severe/critical infection relative to a cohort of COVID-19 infected patients without cancer that were seen at our center (Figure 1). The two cohorts did not significantly differ in gender, ethnicity, proportion of AYA, or time period of COVID-19 diagnosis (Table S5).

3.3 | Risk factors associated with COVID-19 outcomes

Risk factors significantly associated with COVID-related hospitalization in a univariable analysis included neutropenia (<500 cells per mm^3), lymphopenia (<500 cells per mm^3), steroid exposure within 2 weeks prior to the diagnosis of COVID-19, and history of a prior significant non-COVID infection (defined as past infections for which patients were receiving ongoing secondary prophylaxis medications at the time of COVID-19 infection). Four patients had a past history of invasive fungal infection, and four patients had a past history of viral infection (CMV, HHV-6, and HSV). Conversely, age in the AYA range (age ≥15), body mass index (BMI) in the obese/overweight range (BMI >25), and Hispanic/Latinx ethnicity were not significantly associated with hospitalization. The RT-PCR cycle threshold value (C_t) for virus detection is an inverse measure of viral load. Patients who required hospitalization had a significantly lower C_t (C_t data available for 79 patients, mean C_t = 20.2 vs 27.2, hospitalized (n = 24) vs not hospitalized (n = 55), P < .05, Figure 2A). The low number of patients with severe/critical COVID-19 infection limited the ability to analyze associations with disease severity. However, CAR-T (as the last therapy prior to COVID-19) tended to be associated with severe/critical infection (P = .04, Figure 2B); three of eight CAR-T recipients developed severe/critical infection; all three had B-cell aplasia.

In a multivariable analysis of categorical variables that were significant in the univariable analysis (Table 3), only lymphopenia, prior steroids, and a history of non-COVID infection retained a significant association with hospitalization. The multivariable analysis was then repeated with the above mentioned three variables along with the continuous variable, C_t. Lymphopenia, prior steroids, a history of non-COVID infection, and lower C_t retained a significant association with hospitalization in the multivariable model (Table 3), indicating that these factors are independent potential risk factors for COVID-19 related hospitalization in children and AYA with cancer.

3.4 | Antibody response to COVID-19 infection

Anti-COVID-19 IgG antibody data were available for 32 patients (Table 4). Antibodies were detected in 18 patients. Among these
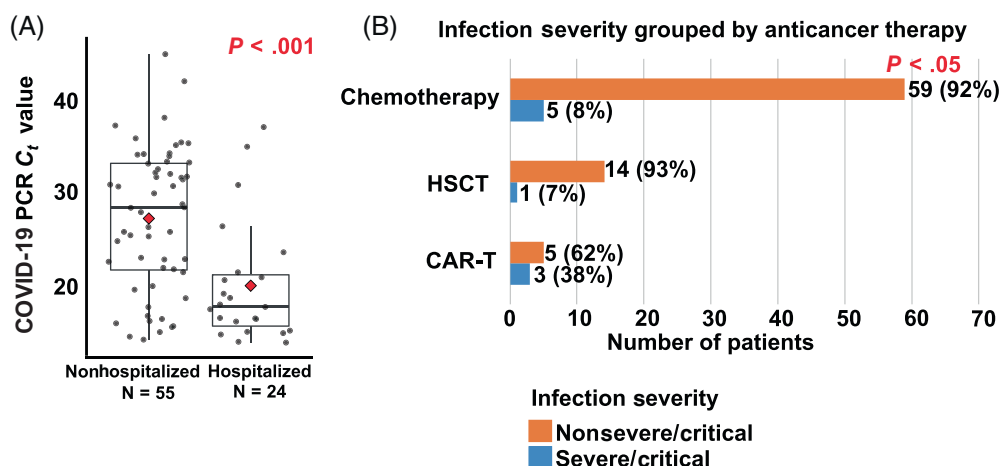
FIGURE 2 Associations between COVID-19 outcomes and COVID-19 PCR cycle threshold value or type of anticancer therapy. (A) Cycle threshold value for diagnostic COVID-19 PCR in children, adolescents and young adults (AYA) with cancer and COVID-19 infection grouped by need for COVID-19 related hospitalization (PCR cycle threshold value data available for 79 patients). Red diamond: mean. Two-sided *t* test *P* value shown. Each data-point represents an individual patient (B) COVID-19 infection severity grouped by type of anticancer therapy. *P* value: Two-sided Fisher exact test *P* value for a comparison of the three groups testing for a difference between at least two of the three groups

TABLE 3 Associations between risk factors and COVID related hospitalization

Variables		Hospitalized N = 26	Not hospitalized N = 61	Univariable OR	P value	Multivariable[a] (n = 79; 24 hospitalized and 55 not hospitalized) OR	P value
Age (years)							
	≥15 years	11	18	1.8 (0.7-4.5)	.31	ND	ND
	<15 years	15	43				
Sex							
	Male	17	31	1.8 (0.7-4.7)	·25	ND	ND
	Female	9	30				
Ethnicity							
	Hispanic	22	42	2.5 (0.8-8.2)	·18	ND	ND
	Non-Hispanic	4	19				
Weight status[b]							
	Obese/OW	14	28	1.4 (0.5-3.5)	.64	ND	ND
	Lean	12	33				
Cancer							
	Hem	22	41	2.7 (0.8-8.8)	.12	ND	ND
	Non-hem	4	20				
Comorbidities							
	Yes	18	33	1.9 (0.7-5.1)	.24	ND	ND
	No	8	28				
Co_pulm							
	Yes	3	2	3.9 (0.6-24.5)	.16	ND	ND
	No	23	59				
Co_cardiac							
	Yes	4	5	2 (0.5-8.3)	·44	ND	ND
	No	22	56				
Co_renal							
	Yes	1	3	0.8 (0.1-7.8)	1	ND	ND
	No	25	58				
Co_neuro							
	Yes	4	10	0.9 (0.3-3.3)	1	ND	ND
	No	22	51				
Co_GI							
	Yes	4	6	1.7 (0.4-6.5)	·48	ND	ND
	No	22	55				
Co_endocrine							
	Yes	1	3	0.8 (0.1–7.8)	1	ND	ND
	No	25	58				
Co_infection							
	Yes	5	3	4.6 (1–21)	.048	6.6 (1.02-42.7)	.046
	No	21	58				
Co_other							
	Yes	9	10	2.7 (0.9-7.8)	.15	ND	ND
	No	17	51				

(Continues)

TABLE 3 (Continued)

Variables		Hospitalized N = 26	Not hospitalized N = 61	Univariable OR	P value	Multivariable[a] (n = 79; 24 hospitalized and 55 not hospitalized) OR	P value
Therapy							
	Chemo	21	43		.37	ND	ND
	HSCT	2	13	0.3 (0.1-1.5)	.21		
	CAR	3	5	1.2 (0.3-5.6)	1		
Steroids							
	Yes	12	6	7.9 (2.5-24.6)	.003	5.1 (1.3-20.1)	.02
	No	14	55				
Anthracycline							
	Yes	22	43	2.3 (0.7-7.6)	.19	ND	ND
	No	4	18				
Neutropenia							
	Yes	9	5	5.9 (1.7-20.1)	.004		NS
	No	17	56				
Lymphopenia							
	Yes	17	18	4.5 (1.7-12)	.004	7.1 (1.8-28)	.006
	No	9	43				
PCR C_t (mean)		20.2 (n = 24)	27.2 (n = 55)		.0002	0.9 (0.83-0.97)	.01

Note: All P values are two sided. Univariable P values (Fisher exact test for all categorial variables and t-test for C_t) were not adjusted for multiple comparisons and should be interpreted with caution. Multivariable analysis was done using logistic regression. Steroids: exposure to steroids within 14 days prior to COVID-19 diagnosis (does not include steroids administered for COVID-19 management). Neutropenia: ANC <500. Lymphopenia: ALC <500.
Abbreviations: Co, comorbidity; GI, gastrointestinal; ND, not done; Neur: neurological; NS, not significant; Pulm: pulmonary.
[a]Multivariable analysis P values and odds ratios shown are from a logistic regression analysis of data from the 79 patients for whom PCR C_t data were available. Lymphopenia, Steroids, and Coinfection were significantly associated with hospitalization, and neutropenia was not significantly associated with hospitalization in a separate multivariable logistic regression analysis of data from all 87 patients that did not include PCR C_t as a variable.
[b]Obesity/overweight (OW) status was defined based on CDC criteria.[15,16]

18, two were CAR-T recipients receiving IVIG for B-cell aplasia (one had received monoclonal antibody), one was a patient in the midst of ALL chemotherapy who had received monoclonal COVID-19 antibody therapy, and one was undergoing AML chemotherapy and had received convalescent plasma. Antibody positivity in these four patients was most likely from the IVIG, monoclonal antibody or convalescent plasma. One of the patients who received monoclonal COVID-19 antibody therapy showed high antibody levels >90 days following monoclonal antibody therapy. Among the remaining 14 patients who showed antibodies, 5 were HSCT recipients (all >150 days post-HSCT), and four other patients were diagnosed with COVID-19 at the time of cancer diagnosis or within 2 weeks of initiation of chemotherapy for a new diagnosis of cancer or relapsed cancer. Two of these 14 patients showed antibodies for >90 days.

An IgG antibody response was not detected in 14 of the 32 patients with available Anti-COVID-19 IgG antibody data. Two of the patients with undetectable antibodies were tested within 7 days of diagnosis of COVID-19, a timepoint that may have been too early for the detection of an antibody response. Ten of the remaining 12 negative patients were tested at ≥27 days after the diagnosis of COVID-19. Among these 10, 4 were CAR-T recipients with B-cell aplasia, and 4 were diagnosed with COVID-19 during an intensive

phase of chemotherapy. Overall, these data suggest that at least some patients among those with active leukemia who have not yet or just initiated chemotherapy or those with a history of allogeneic HSCT >6 months prior to COVID-19 can mount an immune response to COVID-19. Furthermore, the antibody response is sustained for several months in some patients.

4 | DISCUSSION

Our study provides comprehensive data for COVID-19 outcomes as well as the underlying cancer for a pediatric cohort with robust representation of Hispanic/Latinx and AYA individuals. Consistent with the low to no mortality reported in other studies of COVID-19 in pediatric cancer, there were no COVID-19 related deaths in our cohort. However, we observed a substantial rate of COVID-19 related hospitalization in our study; over one in four patients and over one in three symptomatic patients required hospitalization. A small minority required recurrent hospitalization, a finding not reported in other cohorts. Consistent with other studies,[2-4] the overall rate of severe/critical infection and need for intensive care were low. While the rate of severe/critical infection for the whole cohort was low, CAR-T recipients with COVID-19

TABLE 4 Data for anti-COVID-19 IgG antibodies

Subject ID	Diagnosis	Therapy	Antibody ratio[a]	Phase of therapy at COVID-19 diagnosis	Antibody testing timepoint (days)[b]	Comment
2	ALL	HSCT	6.7	305 days post-HSCT	38	
3	ALL	CAR	Negative		110	B-cell aplasia
4	ALL	HSCT	7.5	165 days post-HSCT	17	
5	ALL	CAR	6.9		27	On IVIG, received monoclonal, B-cell aplasia
7	ALL	HSCT	4.9	923 days post-HSCT	41	
8	ALL	CAR	7.7		28	On IVIG, was negative at 16 days, B-cell aplasia
9	ALL	HSCT	4.8	258 days post-HSCT	50	
10	ALL	HSCT	6.9	1075 days post-HSCT	26	
12	Neuroblastoma	HSCT	1.5		17	
13	ALL	CAR	Negative		52	B-cell aplasia
16	NHL	CAR	Negative		39	B-cell aplasia
18	Soft tissue sarcoma	HSCT	Negative		14	
20	ALL	Chemo	2.3	Delayed intensification	83	
22	ALL	Chemo	Negative	Maintenance	27	
23	Bone sarcoma	Chemo	7.5	Induction week 1	4	
25	Neuroblastoma	Chemo	Negative	Induction cycle 2	31	
37	AML	Chemo	1.4	At cancer diagnosis	39	Was negative at 21 days
40	ALL	Chemo	Negative	Consolidation	86	
42	ALL	Chemo	Negative	Induction Day 27	3	
52	Sarcoma	Chemo	Negative	Cycle 5	19	
53	AML	Chemo	2	At cancer diagnosis	2	Received convalescent plasma
58	ALL	Chemo	11.2	Induction Day 5	46	Antibody ratio = 8.2 at Day 117
59	ALL	Chemo	Negative	Maintenance	31	
60	NHL	Chemo	Negative	COP-R prophase (week 1 of induction chemotherapy)	149	
64	Relapsed ALL	Chemo	9.3	Reinduction Day 10	38	
75	ALL	Chemo	Negative	Delayed intensification	31	
78	ALL	Chemo	4.4	Maintenance	23	
79	Neuroblastoma	HSCT	Negative	161 days post-HSCT, cycle 3 of post-HSCT anti-GD2 immunotherapy	7	
84	ALL	CAR	Negative	2142 days post-CAR	148	B-cell aplasia
85	ALL	Chemo	2.9	Induction Day 27	2	Antibody titer 1.2 at Day 92
86	ALL	Chemo	2.2	Maintenance	19	
87	ALL	Chemo	8.3	Interim maintenance	2	received monoclonal, antibody titer 8.3 at Day 98

Abbreviation: COP-R, cyclophosphamide, vincristine, prednisone, and rituxumab.
[a]Antibody ratio: ratio of sample to internal control.[17] Negative: antibody ratio < 1.2. Days postinfection: Day 0 = day of PCR diagnosis of COVID-19.
[b]Time interval between the date of the first positive COVID-19 RT-PCR and the date when the sample was obtained for antibody testing.

tended to have severe/critical infection, results consistent with a high risk for adverse outcomes in COVID-19 in the setting of CAR-T induced B-cell immunodeficiency.[14] The need for inpatient management for several nonsevere infections observed in both our cohort and a multinational registry study[5] suggests that severity scales based largely on respiratory criteria do not fully capture the extent of morbidity in COVID-19 in pediatric cancer. Several aspects of our findings differ from those reported in studies of adults with COVID-19. In contrast to studies of the general adult population,[9-11] our data suggests that children and AYA with cancer who are overweight/obese or

are of Hispanic/Latinx ethnicity do not seem to be at higher risk for adverse COVID-19 outcomes relative to other pediatric oncology patients. Up to a fifth of adults with COVID-19 infection have been reported to experience symptoms for months, a syndrome that has been termed long or post-COVID-19 condition.[26] However, prolonged COVID-19 symptoms were rarely observed in our cohort during a median observation time period of >3 months. A multicenter study of 30 adult CAR-T recipients with COVID-19 reported a COVID-19 related mortality rate of 33%.[14] In comparison, we observed no deaths among eight CAR-T recipients.

Defining clinical and biomarker predictors of hospitalization in COVID-19 in pediatric oncology is critical for informing decisions regarding early administration of monoclonal antibodies or antivirals. Consistent with other studies, lymphopenia and prior steroids were associated with higher COVID-19 morbidity. Of note, unlike other studies,[4,5] neutropenia was not associated with higher morbidity in our cohort when adjusted for other risk factors. Inclusion of CAR-T recipients, a subgroup that tended to have severe infection despite the absence of neutropenia, could account for this lack of association. The association between lymphopenia and morbidity seen in our study is consistent with the essential role of lymphocytes in mediating an effective anti-COVID-19 immune response.[27,28] Given the need for prognostic biomarkers in COVID-19, several studies have investigated the value of PCR C_t, a surrogate measure of viral load, as an outcome predictor in COVID-19 in the general population. However, varying data ranging from no prognostic value to being a risk factor for mortality have been reported for PCR C_t in adults with COVID-19;[29–31] C_t value criteria for demarcation between low and high viral loads remain to be defined.[29] To our knowledge, our study represents the first report of an association between low C_t and hospitalization in COVID-19 in pediatric cancer. Our results raise the need for further prospective studies investigating C_t as a potential biomarker for predicting outcomes in COVID-19 in pediatric cancer.

Given the risk of worsening of COVID-19 infection with immunosuppressive anticancer therapy, COVID-19 in patients with cancer can have significant ramifications for the delivery of effective anticancer therapy. Balancing interruption of anticancer therapy against the risk for malignancy progression can be challenging, especially in patients with newly diagnosed cancers. Chemotherapy was delayed or modified in a third of patients in our cohort, a proportion lower than the 63% rate reported in an international registry study.[4] The averaged nature of the rate across chemotherapy regimens that likely varied between different countries may account for the discrepancy. Our study also describes patients with COVID-19 at the time of the diagnosis of cancer. Two of five patients with newly diagnosed hematologic malignancies experienced delays and/or modifications in induction therapy. However, several patients with mild COVID-19 were able to tolerate intensive induction regimens without worsening of COVID-19. Overall, these results suggest that most children with cancer and COVID-19, including those who are newly diagnosed, can be taken through chemotherapy without prolonged delays.

Characterization of the immune response to COVID-19 in patients receiving anticancer therapy is needed to inform COVID-19 therapy and prophylaxis approaches in pediatric cancer. Antibody responses were detected in over a third of patients in our study for whom anti-COVID-19 IgG data were available, a result consistent with the notion that some subgroups of pediatric oncology patients including HSCT recipients could benefit from COVID-19 vaccination. In a few patients, we found antibodies that were most likely from monoclonal antibody therapy or IVIG including one patient who showed antibodies for >90 days. These results suggest a single dose of monoclonal antibody may provide immunity in pediatric cancer patients for several months, and that in some instances IVIG could provide antibodies.

A key strength of our study is the detailed nature of clinical, laboratory, and outcome data provided for the entire cohort, valuable data for informing management decisions in clinical practice. Our study has several limitations. The data were from a single center and largely retrospective. The number of HSCT and CAR-T-cell recipients was low, limiting the ability to make conclusions about outcomes in these patients. The number of patients with severe/critical infection was low, limiting the ability to analyze predictors of severe/critical infection. The relatively small size of the study cohort limited the ability to analyze associations in the multivariable analysis especially for variables with a sparse distribution. Antibody data were available for just a third of the patients, and the timepoints for these data varied between patients. The timepoint in the infection course at which RT-PCR was obtained would have inevitably varied between patients, a caveat to the association between C_t and hospitalization. However, we observed lower C_t in patients who required hospitalization. Since these patients would be expected to have undergone PCR later in the course of infection relative to those who did not require hospitalization, it is unlikely that the temporal decline in viral load after the onset of symptoms that typically occurs in COVID-19[32] majorly confounded our analysis. The comparison of hospitalization rates between COVID-19 infected children with or without cancer could be confounded by physician bias toward admitting children with cancer given their immunodeficiencies. Nevertheless, we also found a higher rate of severe/critical infection defined by objective WHO criteria in children with cancer relative to those without cancer, an outcome analysis unlikely to be confounded by such biases. Lastly, 18 of the HSCT or CAR-T recipients in our cohort were also included in the recently reported Pediatric Oncology COVID-19 Case (POCC) registry study.[8] Here, we include previously unreported data for these 18 patients including outcomes specifically in the CAR-T subgroup, immune responses, and RT-PCR C_t data.

Our study provides data that could inform the management of the infection and the anticancer therapy in COVID-19 in children and AYA receiving intensive cancer therapy regimens. Prospective multi-center studies are needed to define clinical as well as immune and viral biomarker prognostic factors in COVID-19 in pediatric cancer.

AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors, unless clearly specified in the text. **Rebecca S. Parker**: collection of data, data analysis and interpretation, and manuscript writing. **Justin Le**: processed blood samples and manuscript writing. **Andrew Doan,**

CONFLICT OF INTEREST

The authors have no competing financial interests. Pia S. Pannaraj has received consultant fees from Sanofi-Pasteur and Seqirus and receives funding from Pfizer and AstraZeneca for studies unrelated to this manuscript.

DATA AVAILABILITY STATEMENT

Detailed data for individual subjects are provided in Table S2. Further data that support the findings of our study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Our study was approved by the Children's Hospital Los Angeles (CHLA) Institutional Review Board (IRB). The IRB granted a consent waiver for retrospective data extraction. Informed consent was obtained for prospectively enrolled patients.

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REFERENCES

1. Kuderer NM, Choueiri TK, Shah DP, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study. *Lancet*. 2020;395(10241):1907-1918. doi:10.1016/S0140-6736(20)31187-9
2. Millen GC, Arnold R, Cazier JB, et al. Severity of COVID-19 in children with cancer: report from the United Kingdom paediatric coronavirus cancer monitoring project. *Br J Cancer*. 2021;124(4):754-759. doi:10.1038/s41416-020-01181-0
3. Mukkada S, Bhakta N, Chantada GL, et al. Global characteristics and outcomes of SARS-CoV-2 infection in children and adolescents with cancer (GRCCC): a cohort study. *Lancet Oncol*. 2021;22(10):1416-1426. doi:10.1016/S1470-2045(21)00454-X
4. Millen GC, Arnold R, Cazier JB, et al. COVID-19 in children with haematological malignancies. *Arch Dis Child*. 2022;107:186-188. doi:10.1136/archdischild-2021-322062
5. Haeusler GM, Ammann RA, Carlesse F, et al. SARS-CoV-2 in children with cancer or after haematopoietic stem cell transplant: an analysis of 131 patients. *Eur J Cancer*. 2021;159:78-86. doi:10.1016/j.ejca.2021.09.027
6. Kamdar KY, Kim TO, Doherty EE, et al. COVID-19 outcomes in a large pediatric hematology-oncology center in Houston, Texas. *Pediatr Hematol Oncol*. 2021;38(8):695-706. doi:10.1080/08880018.2021.1924327
7. Gampel B, Troullioud Lucas AG, Broglie L, et al. COVID-19 disease in New York City pediatric hematology and oncology patients. *Pediatr Blood Cancer*. 2020;67(9):e28420. doi:10.1002/pbc.28420
8. Johnston EE, Martinez I, Davis ES, et al. SARS-CoV-2 in childhood cancer in 2020: a disease of disparities. *J Clin Oncol*. 2021;39(34):3778-3788. doi:10.1200/JCO.21.00702
9. Gao M, Piernas C, Astbury NM, et al. Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study. *Lancet*. 2021;9:350-359. 10.1016/S2213-8587(21)00089-9
10. Foldi M, Farkas N, Kiss S, et al. Obesity is a risk factor for developing critical condition in COVID-19 patients: a systematic review and meta-analysis. *Obes Rev*. 2020;21(10):e13095. doi:10.1111/obr.13095
11. Nanchal R, Patel D, Guddati AK, et al. Outcomes of Covid 19 patients—are Hispanics at greater risk? *J Med Virol*. 2022;94:945-950. doi:10.1002/jmv.27384
12. Orgel E, Sposto R, Malvar J, et al. Impact on survival and toxicity by duration of weight extremes during treatment for pediatric acute lymphoblastic leukemia: a report from the Children's Oncology Group. *J Clin Oncol*. 2014;32(13):1331-1337. doi:10.1200/JCO.2013.52.6962
13. Miller KD, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescents and young adults, 2020. *CA Cancer J Clin*. 2020;70(6):443-459. doi:10.3322/caac.21637
14. Busca A, Salmanton-Garcia J, Corradini P, et al. COVID-19 and CAR-T cells: current challenges and future directions—a report from the EPICOVIDEHA survey by EHA-IDWP. *Blood Adv*. 2022;6:2427-2433. doi:10.1182/bloodadvances.2021005616
15. Force USPST, Barton M. Screening for obesity in children and adolescents: US Preventive Services Task Force recommendation statement. *Pediatrics*. 2010;125(2):361-367. doi:10.1542/peds.2009-2037
16. Fryar CD, Carroll MD, Afful J. *Prevalence of Overweight, Obesity, and Severe Obesity among Adults Aged 20 and over: United States, 1960-1962 through 2017-2018 (2020)*. Hyattsville, MD: National Center for Health Statistics; 2020.
17. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. National Institutes of Health, National Cancer Institute; November 2017. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed April 25, 2020.
18. World Health Organization. *Country & Technical Guidance—Coronavirus Disease (COVID-19)*. World Health Organization. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance-publications. Accessed December 11, 2021.
19. Tilley K, Ayvazyan V, Martinez L, et al. A cross-sectional study examining the seroprevalence of severe acute respiratory syndrome coronavirus 2 antibodies in a university student population. *J Adolesc Health*. 2020;67(6):763-768. doi:10.1016/j.jadohealth.2020.09.001
20. Pandey U, Yee R, Shen L, et al. High prevalence of SARS-CoV-2 genetic variation and D614G mutation in pediatric patients with COVID-19. *Open Forum Infect Dis*. 2021;8(6):ofaa551. doi:10.1093/ofid/ofaa551
21. Appliedbiosystems TaqPath COVID-19 Combi Kit and TaqPath COVID-19 Combo Kit Advanced Instructions for Use. https://www.fda.gov/media/136112/download. Accessed December 13, 2020.
22. Cepheid. Xpert Xpress SARS-CoV-2 Instructions for Use. https://www.fda.gov/media/136314/download. Accessed December 13, 2020.

23. DiaSorin Molecular. Simplexa COVID-19 Direct. https://www.fda.gov/media/136286/download. Accessed December 13, 2020.

24. Aragon TJ, Fay MP, Daniel W, Omidpanah A. epitools. https://cran.r-project.org/web/packages/epitools/epitools.pdf. Accessed May 10, 2022.

25. Truong TT, Ryutov A, Pandey U, et al. Increased viral variants in children and young adults with impaired humoral immunity and persistent SARS-CoV-2 infection: a consecutive case series. *EBioMedicine*. 2021;67:103355. doi:10.1016/j.ebiom.2021.103355

26. World Health Organization. *A Clinical Case Definition of Post COVID-19 Condition by a Delphi Consensus*. World Health Organization; October 6, 2021. https://apps.who.int/iris/bitstream/handle/10665/345824/WHO-2019-nCoV-Post-COVID-19-condition-Clinical-case-definition-2021.1-eng.pdf. Accessed May 10, 2022.

27. Scheid JF, Barnes CO, Eraslan B, et al. B cell genomics behind cross-neutralization of SARS-CoV-2 variants and SARS-CoV. *Cell*. 2021;184(12):3205-3221.e24. doi:10.1016/j.cell.2021.04.032

28. Grifoni A, Weiskopf D, Ramirez SI, et al. Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell*. 2020;181(7):1489-1501.e15. doi:10.1016/j.cell.2020.05.015

29. Salto-Alejandre S, Berastegui-Cabrera J, Camacho-Martinez P, et al. SARS-CoV-2 viral load in nasopharyngeal swabs is not an independent predictor of unfavorable outcome. *Sci Rep*. 2021;11(1):12931. doi:10.1038/s41598-021-92400-y

30. Fajnzylber J, Regan J, Coxen K, et al. SARS-CoV-2 viral load is associated with increased disease severity and mortality. *Nat Commun*. 2020;11(1):5493. doi:10.1038/s41467-020-19057-5

31. El Zein S, Chehab O, Kanj A, et al. SARS-CoV-2 infection: initial viral load (iVL) predicts severity of illness/outcome, and declining trend of iVL in hospitalized patients corresponds with slowing of the pandemic. *PLoS One*. 2021;16(9):e0255981. 10.1371/journal.pone.0255981

32. To KK, Tsang OT, Leung WS, et al. Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study. *Lancet Infect Dis*. 2020;20(5):565-574. doi:10.1016/S1473-3099(20)30196

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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