



The Global Impact of COVID-19 on Childhood Cancer Outcomes and Care Delivery - A Systematic Review

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Background: Childhood cancer represents a leading cause of death and disease burden in high income countries (HICs) and low-and-middle income countries (LMICs). It is postulated that the current COVID-19 pandemic has hampered global development of pediatric oncology care programs. This systematic review aimed to comprehensively review the global impact of COVID-19 on childhood cancer clinical outcomes and care delivery.

Methods: A systematic search was conducted on PubMed, Embase, Medline, and the African Medical Index from inception to November 3, 2021 following PRISMA guidelines. A manual search was performed to identify additional relevant studies. Articles were selected based on predetermined eligibility criteria.

Findings: The majority of studies reported patients with cancer and COVID-19 presenting as asymptomatic (HICs: 33.7%, LMICs: 22.0%) or with primary manifestations of fever (HICs: 36.1%, LMICs: 51.4%) and respiratory symptoms (HICs: 29.6%, LMICs: 11.7%). LMICs also reported a high frequency of patients presenting with cough (23.6%) and gastrointestinal symptoms (10.6%). The majority of patients were generally noted to have a good prognosis; however the crude mortality rate was higher in LMICs when compared to HICs (8.0% vs 1.8%). Moreover, the pandemic has resulted in delays and interruptions to cancer therapies and delays in childhood cancer diagnoses in both HICs and LMICs. However, these findings were disproportionately reported in LMICs, with significant staff shortages, supply chain disruptions, and limited access to cancer therapies for patients.

Conclusions: The COVID-19 pandemic has resulted in delays and interruptions to childhood cancer therapies and delays in childhood cancer diagnoses, and disproportionately so within LMICs. This review provides lessons learned for future system-wide disruptions to care, as well as provides key points for moving forward better with care through the remainder of this pandemic.

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1 BACKGROUND

With over 400,000 children and adolescents developing cancer each year globally, cancer represents a leading cause of death and disease burden in pediatric populations (1). Moreover, pediatric oncology patients in low- and middle-income countries (LMICs) are five times as likely to die from a diagnosis of cancer compared to those in high-income countries, due to delays in diagnosis, obstacles to accessing care, and higher rates of relapse, amongst other reasons (2). In recognition of these disparities in cancer care delivery and outcomes, in 2018, the World Health Organization (WHO) launched the Global Initiative for Childhood Cancer with the support of St. Jude and other global partners, with the explicit aim to support childhood cancer programs, reduce global suffering, and increase survival including for six common childhood cancers to at least 60% for all by 2030 (3). Progress in this direction is likely to have been hampered by the COVID-19 pandemic, moving us further away from achieving this goal within the next decade (4).

As of January 16, 2022, there have been over 326 million cases and 5.54 million deaths from COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and straining hospitals and healthcare systems worldwide (5). The pandemic has also impacted pediatric oncology patients. In contrast to adults, the disease has been shown to impact children to a milder degree with varying estimates (6). Additionally, with the emergence of new variants, these risk estimates in healthy children and in children with underlying risk factors are constantly changing (6). Indeed, in a large international sample of pediatric oncology patients with COVID-19, the Global Registry of COVID-19 in Childhood Cancer (GRCCC) created by St. Jude Global and the International Society of Pediatric Oncology reported that deaths attributed to the infection were approximately 4% (data collected as of February 2021) (7). This statistic is lower than the 13% of deaths reported in an analogous registry for adults with cancer (i.e., the COVID-19 and Cancer Consortium), but significantly higher than that of the general pediatric population (6–10).

Moreover, how COVID-19 is affecting cancer care delivery in pediatric populations in areas that have been severely impacted by COVID-19 is only starting to be understood. Pediatric oncology care is heavily reliant on prompt evaluation and diagnosis, multidisciplinary subspecialized teams, timely and coordinated therapy, and access to supportive care, amongst other measures (11–14). There exist inadequacies to accessing quality pediatric cancer care in many countries; the pandemic has only served to further exacerbate these disparities (14–16). Indeed, in a global study of 54 countries across six continents, Jazeih et al. (2020) reported challenges to adult cancer care due to COVID-19 (in April/May 2020). These challenges included overwhelmed healthcare systems, lack of personal protective equipment (PPE), staff shortages, and restricted access to medications which affected cancer care (17). These experiences are similar in the pediatric cancer care setting (12). COVID-19 has, and will, impede vital progress made towards the WHO

Global Initiative's goals to improve childhood cancer survival and decrease disease burden and suffering.

There has not yet been a comprehensive systematic review and synthesis of extant literature characterizing the global impact of COVID-19 on pediatric oncology populations with respect to clinical outcomes and care delivery. As such, the primary objectives of this systematic review were to consolidate the literature with respect to these associations. Moreover, the literature was also reviewed to summarize recommendations and highlight priorities needed to remain on track to achieve WHO's outlined goals for childhood cancer within the next decade.

2 METHODOLOGY

2.1 Search Strategy and Study Selection

Following PRISMA guidelines (Preferred Reporting Items for Systematic Review and Meta-Analyses), we systematically searched PubMed, Embase, CINAHL, and the African Medical Index using the following database-adapted search terms: "Pediatrics," "COVID-19" and "Oncology". The search terms were modified according to the specific vocabulary map of each database, and subsequently searched for papers from January 1, 2019 to November 3, 2021 without any restrictions (See **Appendix A**).

The removal of duplicates and initial screening was performed in Endnote (Clarivate Analytics, Philadelphia, PA, USA). After the removal of duplicate studies across all databases, article titles and abstracts were screened for relevance. Two reviewers (AM and ALM) independently reviewed the studies in accordance with pre-determined eligibility criteria. Articles without an abstract, or those which passed initial eligibility screening, were accessed in full-text for final inclusion/exclusion based on eligibility criteria. Consensus was reached in a follow-up discussion for papers whose eligibility was unclear.

We included any studies that reported an association between COVID-19 and cancer outcomes and/or cancer care delivery in pediatric populations (0–21 years). Data submitted as of November 3, 2021 were included in this report. All types of neoplasms and malignant cancers were included for analysis. Cancer care delivery was defined as any aspect of providing and distributing healthcare services to patient populations. All cancer outcomes (e.g., mortality, morbidity) and methods of cancer care delivery were included. Moreover, all age groups, sexes, ethnicities, and nationalities were included without any language restrictions. Articles were excluded if they: 1) were not available in full text and could not be accessed; 2) were mechanistic studies or preclinical studies; and/or 3) were duplicate studies. The systematic review was registered onto the International Prospective Register of Systematic Reviews (PROSPERO) at CRD42021266758.

2.2 Data Extraction

Data was extracted using a standard data extraction form. The following information was obtained: 1) Primary author & year;

2) Study design; 3) Country of Origin; 4) Study population; 4) Methodology; 5) Primary outcomes; and 6) Main findings.

2.3 Quality Assessment

The risk of bias of included studies was assessed using the GRADE Quality Assessment framework, a critical appraisal tool to rate the certainty of available evidence from “high” to “very low” (18).

3 RESULTS

3.1 Search Results

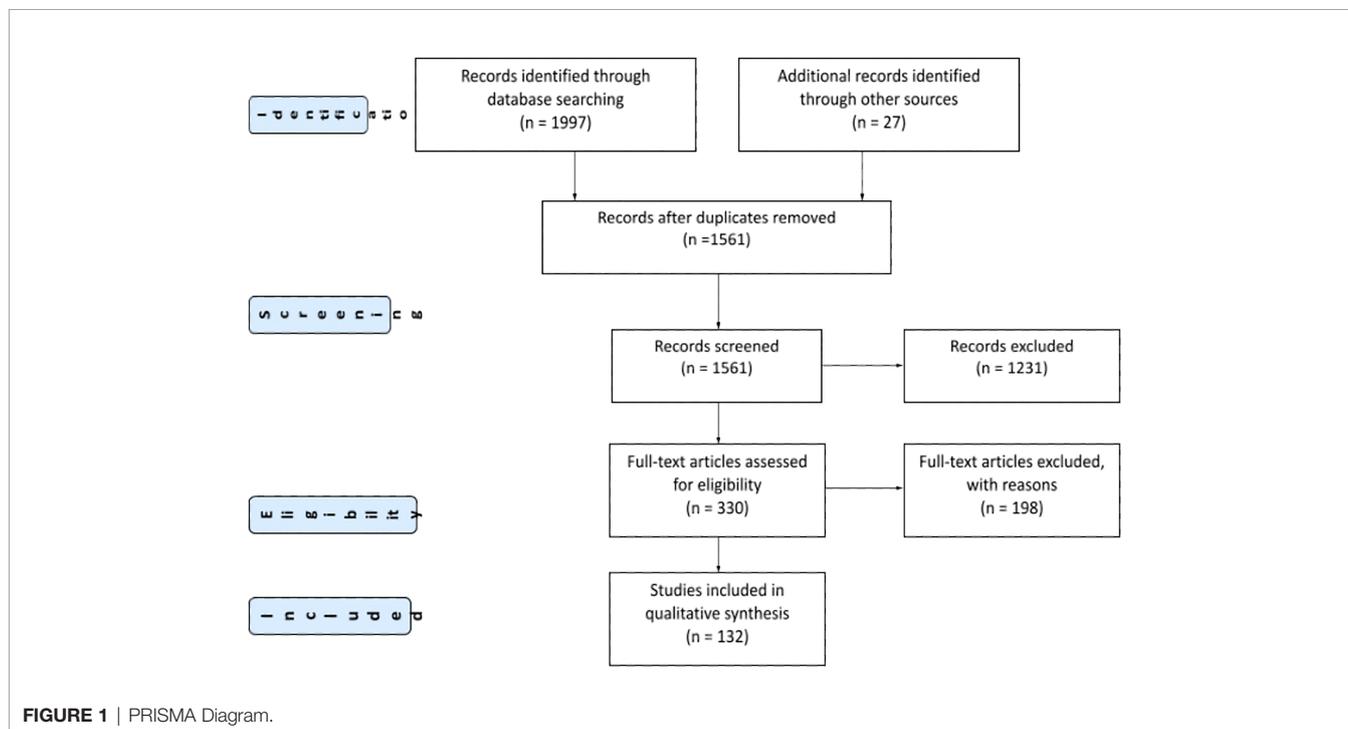
The study selection process is depicted in the PRISMA flowchart (Figure 1). The systematic search from all databases yielded a total of 1561 records. After title and abstract review, 1231 records were excluded, and 330 full-text publications were assessed for eligibility. After full-text review, a further 198 studies were excluded. Additional studies were identified through a subsequent manual search of relevant papers. In total, 132 studies were included with 4398 patients, including 89 articles that examined clinical outcomes of COVID-19 in pediatric patients and 60 studies evaluating cancer care delivery during the pandemic, with some overlap (see Appendix B).

3.2 Clinical Outcomes of COVID-19 in Pediatric Patients With Cancer

We identified 89 studies that evaluated the clinical outcomes of COVID-19 in pediatric patients with cancer (see Appendix B). From all high-income (HICs) and LMICs studied, there was an

overall predominance of male pediatric oncology patients with COVID-19 (60.2% and 60.4%, respectively). Moreover, there was a predominance of pediatric hematological cancer patients with COVID-19 in each of the HICs and LMICs included in our review (63.7% and 61.8%, respectively). Three articles studied the clinical outcomes of COVID-19 in pediatric oncology patients globally (7, 19, 20). In a web survey by Hrusak et al. (2020) early in the pandemic, the authors found that amongst children receiving anticancer treatment globally (including 25 countries in Europe, Asia, Australia, and the Middle East), only 9 cases of COVID-19 infection were identified from over 200 patients tested, with 8/9 of patients presenting with an asymptomatic or mild course of the disease (19). A similar study by the American Society of Hematology noted that of 250 patients with blood cancers and COVID-19 from 74 sites across all continents, 20 (8%) were pediatric patients (<19 years old); 21% of patients had moderate or severe course of disease and the mortality rate was 11.1% (20).

More recently, Mukkada et al. (2021) conducted a global cohort study on pediatric oncology patients with COVID-19 (7). From 1500 submitted reports from 45 countries globally, the authors noted that 19.9% of patients had severe or critical infection and 50 deaths were attributed to COVID-19 infection (3.8%). A higher proportion of severe or critical illness was reported in LMICs when compared to HICs (OR: 5.8, [95% CI: 3.8–8.8]; $p < 0.0001$). Interestingly, in univariate and multivariate logistic regressions, the authors noted that having a hematological malignancy and the presence of comorbidities were among factors significantly associated with severe or critical illness, alongside treatment intensity, older age (age 15–18), and country income group other than HIC (7).



3.2.1 Clinical COVID-19 Outcomes in Children With Cancer Residing in HICs

The majority of studies were conducted in HICs ($n=49$), as defined by the World Bank criteria as of July 2021 (100), including Austria, Canada, France, Japan, Kuwait, Oman, and Poland, Saudi Arabia, Spain, Switzerland, United Arab Emirates, and the United Kingdom. Notably, the majority of studies were conducted in Italy and the United States (**Table 1**). Overall, 1518 patients in HICs were identified to have both a cancer diagnosis and COVID-19.¹ Of 49 studies that stratified cancer types, 928/1470 patients had hematological cancers (63.7%), while 542 patients had solid tumors (36.3%). Clinical symptoms and outcomes of all patients are characterized in **Table 1**. The majority of pediatric oncology patients with COVID-19 from HICs presented as asymptomatic (33.7%) or with primary manifestations of fever (36.1%) or respiratory symptoms (26.6%). One study did not stratify for patient clinical symptoms (**Table 3**) (23).

From 1518 pediatric oncology patients in HICs who were infected with COVID-19, 28 patients died from COVID-19 related complications (crude mortality rate: 1.8%) and were often patients who presented with COVID-19 and refractory or metastatic cancer diagnoses or significant comorbidities. Fifteen of 31 patients were described in an observational study by Johnston et al. (2021) (24). The authors noted that of 917 pediatric oncology patients with COVID-19 in 34 US states, 10.9% of patients required respiratory support, 9.2% were admitted to the hospital, and 1.6% died due to the virus (15 patients, 60% of whom died due to the virus and 40% who died from a combination of cancer and SARS-CoV-2). The presence of comorbidities, such as obesity, hypertension, and asthma, was associated with an increased risk of hospitalization (RR = 1.3, 95% CI: 1.1-1.6) and ICU admission (aRR = 2.3, 9% CI: 1.5-3.6) (24). In another US retrospective cohort study by Kamdar et al. (2021), the authors found that 2/51 patients died from COVID-19; one patient had relapsed T-ALL while another had high-risk neuroblastoma. Both patients developed hypoxia progressive to respiratory failure and shock that was unresponsive to treatment with remdesivir and dextromethorphan (25). In a cross-sectional, cross-national study in Kuwait and Saudi Arabia, Alfraj et al. (2020) also described the case of one COVID-19 related death in a pediatric cancer patient; of 8 medical centers in Kuwait and Saudi Arabia, five pediatric cancer patients required ICU care for COVID-19 and one patient died. In univariate analysis, the presence of a comorbidity was associated with in-ICU mortality (HR=0.0001, 95% 0.0001-0.00016) (23).

The majority of studies, however, described positive outcomes for pediatric cancer patients with COVID-19 with asymptomatic presentations or mild or moderate disease course, and minimal changes to cancer care outcomes. Nine studies described patients who required ICU support due to deterioration but did not die due to the disease (26). Faura et al. (2020), for example, found that of 46 patients in a cohort study in Spain, the majority of patients presented with mild symptoms (51.1%) or were

asymptomatic (25.5%); 11 patients presented with a severe illness course, 4 of whom required PICU care (8%) (27).

Notably, Ding et al. (2020) reported a case series of 5 patients, each of whom required emergency life-saving interventions shortly after presentation, including emergency intubation ($n=4$), resuscitation following cardiac arrest ($n=2$), and pericardiocentesis for tamponade ($n=1$). Two patients died within days of presentation. Interestingly, the authors noted that there was an increase in the percentage of patients requiring prolonged PICU care at cancer diagnosis during the pandemic. In April 2020, the authors noted that 75% of new leukemia/lymphoma patients diagnosed required PICU compared to the monthly average of 12% during 2018-19 (exact number of patients not reported) (28).

3.2.2 Clinical Outcomes of COVID-19 in Children Residing in LMICs

Thirty-six studies ($n=36$) were conducted in low- and middle-income countries (LMICs), of which included Algeria, Brazil, China, Colombia, Egypt, India, Iran, Mexico, Pakistan, Peru, Russia, and Turkey (**Table 2**). A total of 873 patients from LMICs were studied², from which the majority had hematological malignancies (535/865, 61.8%) while a minority were diagnosed with solid tumors (330/865, 38.1%). The majority of pediatric oncology patients were either asymptomatic for COVID-19 (22.0%) or had primary symptoms of fever (51.4%), cough (23.6%), or respiratory symptoms (11.7%). Patient clinical outcomes are characterized in **Table 3**.

From 873 pediatric oncology patients in LMICs, 70 patients died due to COVID-19 related complications (mortality: 8.0%) (see **Appendix B**). Seven of 70 patients were reported in a Mexican retrospective study of patients with acute leukemia (mortality rate: 46.7%, 7/15 patients) (29). The authors noted that the risk of death in children with leukemia and COVID-19 was associated with increased liver enzymes, respiratory distress, and the need for mechanical ventilation, amongst other variables (29). Montoya et al. (2020) also described a report of 7 deaths among 60 patients with COVID-19 and a cancer diagnosis in Peru (mortality rate: 10%; both hematological and solid tumors considered); 4 patients died from complications and progressive disease that the authors noted were not related to COVID-19 while 3 patients had severe pneumonia and deteriorated despite ICU care ($n=1$) or unavailable ICU care (30). The authors noted that patients under non-curative treatment (i.e., palliative care) had a higher risk of death due to COVID-19 than those under curative treatment (30).

Three patients deaths were reported in India wherein all patients had refractory hematological cancers (leukemia, lymphomas) (21). Ganguly et al. (2020) highlighted that of the cases in their care, one patient committed suicide in fear of contracting COVID-19, underlining the excess of fear, stress, and stigma in the community (21). Ten patient deaths were reported in Egypt; Hammad et al. (2021) found that from 76 pediatric

¹Note that this statistic excludes multinational studies, which were mentioned earlier in Section 3.2.

²This statistic excludes multinational studies, which were mentioned earlier in Section 3.2.

TABLE 1 | Baseline characteristics of clinical outcomes for pediatric oncology children with COVID-19 in high-income countries (n = 49 studies).

Characteristics of included HIC studies	
Countries	Number of studies, n
Italy	6
United States	19
France	3
Poland	4
Saudi Arabia	2
Spain	5
Kuwait	1
Greece	2
Austria, Canada, Japan, Oman, United Arab Emirates, Switzerland, United Kingdom	7 (one case report or case series conducted in each country)
Gender (applicable in 46/49 studies, 1500 patients)	
Male	904/1500 (60.2%)
Female	596/1500 (39.7%)
Type of malignancy (applicable in 45/49 studies, 1470 patients)	
Hematological	928/1470 (63.7%)
Solid	542/1470 (36.3%)
Required critical care (i.e., ICU, mechanical ventilation)	116/1518(7.6%)
Mortality rate (of 1518 patients)	28/1518 (1.8%)

The bold values are the crude mortality rates.

TABLE 2 | Baseline characteristics of clinical outcomes for pediatric oncology children with COVID-19 in low-and-middle income countries (n = 36 studies).

Characteristics of included LMIC studies	
Characteristics	Number of studies, n
Algeria	1
Brazil	2
China	3
Colombia	1
Egypt	3
India	12
Iran	2
Mexico	4
Pakistan	2
Peru	1
Russia	2
Turkey	3
Gender (applicable in 33/36 studies, 820patients)	
Male	496/820 (60.4%)
Female	324/820 (39.5%)
Type of malignancy (applicable in 35/36 studies, 865 patients)	
Hematological	535/865(61.8%)
Solid	330/865 (38.1%)
Required critical care (i.e., ICU, mechanical ventilation)	98/830(11.8%)
Mortality rate	70/873 (8.0%)

The bold values are the crude mortality rates.

oncology patients admitted to the Children's Cancer Hospital from May-November 2020, 10 patients presented with severe or critical disease and died (31). Corso et al. (2021) also noted that from 179 patients they surveyed, the severity of presentation at diagnosis was significantly associated with fatal outcomes ($p < 0.001$); of 22 deaths, 10 patients had leukemia, 2 had lymphoma, and 8 had solid tumors, while 2 patients had other cancer diagnoses (32).

Several studies found that pediatric oncology patients required intensive care support due to severe or critical disease. Notably, Totadri et al. (2021) noted that of 2115 children under

15 years old tested for COVID-19 in southern India, 37 patients were positive and had cancer diagnoses. The most common underlying malignancies were ALL (n=16) and Ewing sarcoma (n=7) (33). While the majority of patients were asymptomatic or had mild/moderate courses of disease (n=23, 62%), 12 patients presented with severe courses of hypoxia, tachypnea, and shock. Two patients had critical disease and required mechanical ventilation, experiencing shock requiring vasoactive support, and had organ dysfunction, and/or coagulopathy (33). The authors postulated that contributing factors to the illness were oncological emergencies (n=2), dengue co-infection (n=4), and inguinal bacterial abscess (n=1). However, all patients were discharged in a stable condition (33).

3.3 Healthcare Delivery for Pediatric Patients With Cancer During the Pandemic

We identified 60 studies that reported changes to healthcare delivery for pediatric oncology patients during the COVID-19 pandemic (Appendix B).

3.3.1 Healthcare Delivery for Pediatric Oncology Patients With COVID-19 in HICs

Thirty-five articles were conducted in HICs, which included France (n=2), Germany (n=2), Greece (n=1), Israel (n=1), Italy (n=11), Kuwait (n=1), the Netherlands (n=1), Norway (n=1), Saudi Arabia (n=2), Spain (n=1), the United Kingdom (n=2), and the United States (n=10)³. The majority of studies outlining impacts to care delivery were reported in conjunction with clinical outcomes.

In general, many studies reported delaying oncology treatment and chemotherapy for pediatric patients who had concurrent COVID-19 infection; oncological therapies were often recommended after the infection cleared. Ferrari et al. (2020), for example, noted that of 21 patients in treatment in

³These numbers did not include multinational studies.

TABLE 3 | Primary symptoms of COVID-19 in pediatric patients with active cancer in HIC and LMICs.

Symptoms of COVID-19 in pediatric patients with active cancer	HICs (N = 1518 patients)		LMICs (N = 830 patients)	
	Number of patients, N	Percentage of patients	Number of patients, N	Percentage of patients, %
Asymptomatic	511	33.7	149	22.0
Fever	548	36.1	427	51.4
Cough	98	6.4	196	23.6
Respiratory symptoms (e.g., dyspnea, respiratory distress)	450	29.6	97	11.7
Fatigue and malaise	25	1.6	0	0
Flu-like symptoms (e.g., rhinitis, rhinorrhea, sore throat)	27	1.8	98	11.1
GI symptoms (e.g., diarrhea, vomiting, gastroenteritis)	22	1.4	88	10.6

2 studies did not stratify for patient clinical outcomes (21, 22).

onco-hematology centers in Lombardia, Italy, 38% of patients had altered their cancer treatment due to the infection, including delaying chemotherapy, postponing transplant surgeries, or reducing drug dosages. While these patients were not followed-up, the authors noted that due to the aggressive nature of pediatric tumors, postponing therapy may have jeopardized the therapy's efficacy and reduced patient cure rates (34). Similarly, in a retrospective cohort study by Madhusoodan et al. (2020), the researchers noted that of 13 pediatric oncology institutions in the New York/New Jersey region, interruptions to chemotherapy treatment were reported in 67% of all patients (66/98). Delays in cancer-directed surgery or radiation were reported in 6.1% (6/98) of SARS-CoV-2 patients regardless of COVID-19 disease severity (35). Similar interruptions to oncology care were reported in case reports and cohort studies of pediatric oncology patients in other regions of the US (36, 37) Saudi Arabia³⁷ Kuwait (38), Italy (39, 40), and France (41).

Rouger-Gaudichon et al. (2021) noted that per respondents to a questionnaire distributed to 31 pediatric oncology centers in France, 17.9% declared that medical care quality was degraded for all pediatric oncology patients due to the pandemic, regardless of whether they had contracted the virus (42). Twenty centers (71.4%) noted that supportive care quality was also decreased; social and psychological follow-up was conducted virtually in 18 of 20 centers (42). Moreover, many studies did not report fatal outcomes in pediatric oncology patients due to the treatment delay required due to the COVID-19 infection; however, follow-up times were short and thus the impact of these treatment delays on overall survival cannot be definitively determined. Several studies noted that with the clearance of the virus (often, without any COVID-19-specific treatment) and/or for patients who were clinically stable, patients were able to resume chemotherapy treatment as per protocol (34, 37, 43, 44).

Reductions in hospital services due to COVID-19 were not unique to HICs in Europe. In a cross-sectional observational study of 204 children being treated for leukemia/lymphoma (60.4%) or solid tumors (39.6%) in Saudi Arabia, Alshaharni et al. (2020) noted similar treatment delays and reductions in services due to COVID-19. The most common reasons for treatment delays were limited hospital capacity due to social distancing guidelines, hospital cancellations, city lockdown and curfew, and swab requirements prior to admission (45). 30.8% of

patients also reported non-availability of adequate PPE, lack of cancer support, and shortage of medications due to the pandemic (45). The COVID-19 pandemic has added additional burden to families with children being treated for cancer. In a cross-sectional UK study by Darlington et al. (2020), 69.6% of parents of pediatric oncology patients (n=171) reported feelings of anxiety and feeling unsafe in hospital settings due to the pandemic (46). However, these reported worries did not significantly lead to parents stopping or reducing chemotherapy for the child; indeed, only 2% of 171 parents opted for this route (46).

In several instances, hospitals were able to restructure services to better provide care for patients, including guidelines for social distancing (14, 47–50). For example, Vagelli et al. (2020) noted that in a tertiary center in Italy, the hospital team split the hospital into two sections, with one section to manage patients at risk or with suspected/confirmed COVID-19; pediatric oncology patients with COVID-19 were admitted and isolated in the COVID-19 unit if they needed continuous radiotherapy or had complex chemotherapy regimens. Specific routes for patients and healthcare workers were also developed to avoid cross-contamination between patients and potential sources (48). Similar strategies were also employed by the Italian Pediatric Oncology and Hematology Association centers, who noted that in order to control the spread of the virus, 24 centers (67%) redesigned facility common areas and made structural changes to follow social distancing guidelines (49).

Altogether, many HICs reported less pediatric oncology diagnoses when compared to before the pandemic, especially in relation to solid tumour diagnoses (**Appendix B**). Chiaravelli et al. (2020) reported only 16 newly diagnosed cases of pediatric solid tumors from March-May 2020 at the Pediatric Oncology Unit of the Istituto Nazionale Tumori, a referral center for pediatric solid tumors for all of Italy. During the same periods in between 2017-2019, the hospital registered 34, 35, and 36 cases, signifying an absolute decrease of 45.7% cases (p=0.0416). In the eight subsequent weeks following the Italian lockdown (May-June 2020), however, the number of cases registered was in line with previous years, without any rebound (51). Similarly, Offenbacher et al. (2021) noted a statistically significant decrease in solid tumor diagnoses during the pandemic- from an average of 13.6 cases (7.9-19.3) from 2015-2019 to only 4 new cases

during 2020 (52). This delay in diagnosis was not reflected in leukemia patients (mean of 5.2 [3.2-6.8] cases in 2015-2019 and 4 cases during 2020) (52).

Contrarily, Ding et al. (2020) noted that despite a historic mean of 2.96 days between new leukemia patients, the Children's Hospital of Philadelphia did not see any new patients with a leukemia diagnosis for 35 days (March 2-April 6, 2020; the longest gap from 2015-2019 was 18 days) (28). Subsequently, and on consecutive days, two patients presented to the local hospital PICU with an as yet undiagnosed ALL and cardiac arrest. Jarvis et al. (2021) also noted that while the number of solid tumours diagnosed during COVID-19 in the south-eastern region of Norway remained stable from before and during COVID-19, there was a marked reduction in ALL cases (53). During 2017-2019, there was an average of 2.03 cases/month (95% CI 1.63-2.43)- this in stark contrast to the zero diagnoses of new ALL cases made during the first six months of 2020, a probability of which the authors note is less than 0.001 (95% CI 0.00006-0.001) (53).

3.3.2 Healthcare Delivery for Pediatric Oncology Patients With COVID-19 in LMICs

Twenty-four studies were conducted in LMICs, including Armenia (n=1), China (n=1), Mexico (n=1), Turkey (n=2), India (n=10), Iran (n=2), and Pakistan (n=4) (**Appendix B**). Similar to HICs, studies conducted in LMICs reported delays to chemotherapy (33, 54-57), decrease in surgery rates (55, 58), and decline in the number of new diagnoses and supportive care services offered (i.e., palliative care, psychologist, social welfare services, residential supports) (59, 60). One comprehensive retrospective chart review by Kutluk and colleagues (2021) noted that in a major Turkish pediatric oncology department, outpatient and inpatient visits were reduced by 29.6% ($p < 0.0001$) from March-October 2020 as compared to an analogous time period before the pandemic (61). Similarly, the mean number of inpatients were reduced by 25.5% ($p < 0.00001$); from 23.8 patients/day to an average of 17.7 patients/day during the pandemic period (61). The number of chemotherapies (14.19/day vs 17.92; $p < 0.0001$), radiotherapies (6.04/day vs 6.79, $p = 0.035$), surgical procedures (1.59/day vs 2.36, $p = 0.000015$), and imaging studies (12.46/day vs 19.62, $p < 0.0001$) conducted were also reduced as compared to the control period (61).

Case series and surveys conducted in Mexico and Armenia, respectively, noted that the main challenges during the COVID-19 pandemic were staff shortages (reduced to 50% in a single center in Mexico City) due to positive cases and direct contact with infected staff (62, 63). At one hematology center in Armenia, researchers noted supply chain disruptions and delays (e.g., chemotherapy infusions postponed) as well as increases in the price of certain drugs and supplies (e.g., the price of PPE increased by more than 10 times) (62).

The reorganization of hospital services were reported to have mixed results (21, 59, 64). Ganguly et al. (2021), for example, noted that in a tertiary government healthcare center in India, conversion to telemedicine greatly benefitted their patients; in the period between April-July 2020, the number of

teleconsultations rose exponentially (32 in April to 197 in July, 2020). Chemotherapy plans and prescriptions issues were also managed through email and were especially helpful for patients who lived far from the medical center (21). It was not specified, however, how patients who did not have access to internet or electricity fared with these changes. Sajid et al. (2021) also noted a reorganization of pandemic services in a single healthcare institution in Pakistan; however, to more negative results (64). The authors noted that due to shared inpatient space, any child suspected of being exposed to a healthcare provider with suspected COVID-19 would lead to a cascade of exposed children with multiple children requiring isolation and testing (64). Testing every febrile neutropenic patient with COVID-19 led to undue healthcare expenditures for most self-paying families. As well, many families did not have access to smartphones or the internet making teleconsultation and receiving prescriptions challenging, especially for patients who lived in rural areas and did not have other healthcare access or transport services (64). In another study, Bansal et al. (2021) noted that of the 326 children with retinoblastoma seen nationwide in India, distance was a major deterrent for follow-up and receiving care, and which severely impacted follow-up care for families with middle and lower socioeconomic status (43% and 41% respectively). A mean therapy delay of 45.8 ± 24.3 weeks was reported and the authors noted that disease activity worsened in 60% of active cases (65).

Notably, more severe outcomes were reported in LMICs than in studies conducted in HICs. From a study that gathered survey data across 15 African francophone countries, Traore et al. (2021) reported a severe shortage of hospital equipment, including 50% of participants reporting a shortage of blood supplies, lack of PPE in 80% (20/25) of centres interviewed, and lack of COVID-19 care units in the majority of pediatric oncology centres (66). Indeed, only 35% of facilities had adapted their services for COVID-19, including isolation for patients suspected of having COVID-19 (17%) and only 4% of centres had a special hospital circulation route for patients with cancer to protect them from coming into contact with COVID-19 patients. Moreover, 60% of centres reduced their activities because of staff shortages and postponed surveillance consultations (66). In a similar study of 20 Latin American countries by Vasquez et al. (2021), pediatric onco-hematologists noted indefinite postponement of surveillance consultations (89% of participants), cancer surgeries (45%), radiotherapy schedules (33%), and outpatient consultations (26%) (13). A shortage of healthcare supplies was noted by 79% of participants (e.g., blood products, pathology samples, PPE), which was more frequent in countries with a health-care expenditure of less than 7% of GDP, high COVID-19 incidence rates, and with more stringent travel restrictions (13). The Pediatric Oncology East and Mediterranean group found analogous results when surveying 34 centres from the Middle East, North Africa, and West Asian regions (**Appendix B**). In the recent global study by Mukkada et al. (2021), the authors also noted that chemotherapy was withheld or modified in 44.6% and 55.8% of patients receiving active therapy, respectively. Interestingly, in multivariable

analysis, treatment modifications were noted to be most significantly associated with income group, specifically for UMICs [OR=0.5 (95% CI 0.3-0.7)] (7).

Graetz et al. (2021) distributed a survey to 79 countries and 213 institutions from all WHO regions and found that while pediatric cancer care has been affected globally, this effect was more pronounced in LMICs. Thirteen of 15 hospitals that completely closed their pediatric oncology units during the pandemic were located in LMICs, and LMICs were more likely to report decreases in the financial support they received from their respective governments during this time ($p=0.0004$). As a consequence, the long-standing issue of treatment abandonment in LMICs was thus further compounded by the pandemic, and much more so than for HICs ($p<0.0001$). Moreover, LMIC institutions also reported additional barriers to life-saving interventions ($p=0.019$), more severe complications ($p=0.0059$), and deaths ($p<0.0001$) due to COVID-19 (67).

4 DISCUSSION

4.1 Clinical Outcomes

Overall, the majority of studies reported patients with cancer and COVID-19 presenting with symptoms of fever (HICs: 36.1%, LMICs: 51.4%) and/or respiratory symptoms (HICs: 29.6%, LMICs: 11.7%). Interestingly, moderate to large proportions of patients with cancer and COVID-19 were reported as asymptomatic in both HICs (33.7%) and LMICs (22.0%). These findings are similar to those reported in other analyses of COVID-19 in pediatric patients without cancer, further confirming that children infected with COVID-19 have a generally milder disease course and better prognosis than adults, regardless of whether the patient is from a HIC or LMIC (68–73). In a meta-analysis by Dorantes-Acosta et al. (2020), for example, the authors found that amongst eight studies of pediatric oncology patients with COVID-19 in France, Italy, the US, Spain, and Mexico, a 100% survival rate was reported. Most COVID-19 cases in this review were in patients with leukemia, and fever was the most common symptom requiring admission in children, as was also found within our study (74).

These results are interesting insofar as one of the primary consequences of cancer therapies is immunosuppression in both pediatric and adult patient populations. Ruggiero et al. (2020) note that children receiving immunosuppressive chemotherapy have both qualitative and quantitative abnormalities in T cell function and immunoglobulin levels that persist for months after the completion of therapy (75). Indeed, in adult cancer patients, COVID-19 has posed a substantial risk for morbidity and mortality (4, 76, 77). In a recent systematic review, El-Gohary et al. (2020) found that adult cancer patients with COVID-19 had a higher risk of severe and critical disease, ICU admission, mechanical ventilation, and higher mortality rates as compared to noncancer patients, and had higher risk of COVID-19-related complications (77). Our review and analysis thus suggests a different course for COVID-19 in pediatric oncology patients.

Overall, there was predominance of male pediatric oncology patients with COVID-19 (HICs: 60.2%, LMICs: 60.4%). This male

predominance has been observed for COVID-19 severity in adults across multiple studies and aligns with the finding that males have increased susceptibility to infectious diseases of various kinds (78, 79). Moreover, as also described in adults (80, 81), there was a predominance of pediatric hematological cancer patients with COVID-19 in each of the HICs and LMICs included in our review (63.7% and 61.8%, respectively). It is also interesting to note that, in both HICs and LMICs reported in this review, the majority of patients who died from COVID-19 were those patients with progressive or refractory cancers (52, 82) or who had significant comorbidities additional to their cancer diagnosis (23). Altogether, these results and previous findings speak to altered mechanisms for COVID-19 infection in pediatric populations leading to a milder course of the infection (83).

Moreover, while the majority of patients in both HICs and LMICs were generally noted to have a good prognosis (survival of 98.2% and 92.0%, respectively), there was an obvious discrepancy in this data. Indeed, while 28/1518 pediatric patients with cancer died of COVID-19-related causes in HICs, this proportion increased to 70/874 patients in LMICs. This is in alignment with previous research demonstrating higher mortality rates in pediatric patients with COVID-19 in LMICs as compared to HICs. In a recent systematic review, Kitano et al. (2021) reported that pediatric deaths/million children and case fatality rates were significantly higher in LMICs than in HICs (2.77 in LMICs vs 1.32 in HICs, $p<0.001$; and 0.24% vs 0.01%, $p<0.001$, respectively) (84). Higher mortality rates for pediatric patients in LMICs have not only been reported for COVID-19, but also many other infections and illnesses including respiratory infections (85), pertussis (86), and sepsis (87), amongst others.

It appears highly likely that these discrepancies in mortality data are due to differences in COVID-19 testing, presentation, and level of care influencing symptom profile and prognosis depending on the income level of the country. Moreover, underlying socioeconomic disparities likely add data discrepancies, with decreased access to healthcare facilities in the case of COVID-19 infection and decreased supportive care mechanisms, amongst other barriers (64, 65). In a review conducted in September 2020, Zar et al. (2020) also noted that while the direct effects of COVID-19 in LMICs are less of a concern in children who remain largely asymptomatic or develop mild illness as in HICs, indirect effects in LMICs may be more worrisome, and impact prognosis (88). These include difficulties of maintaining regular childhood preventive and curative services as healthcare resources are constrained, diversion of resources from child health to address pandemic health in adults, and the timely identification of affected individuals with subsequent self-isolation (88).

4.2 Healthcare Delivery

From the 60 studies that reported upon the impact of COVID-19 on healthcare delivery in HICs and LMICs, there were delays and interruptions in cancer therapies as well as delays in diagnosis. Ferrari et al. (2020), for example, noted the postponement of transplant surgeries, delays in chemotherapy, and reductions in drug dosages in a tertiary center in Italy (34). In a French study by Rouger-Gaudichon et al. (2020), the authors noted that, from

a survey of medical centers that took care of COVID-19 patients, many centers noted a degradation of medical care quality in pediatric oncology including a decrease in supportive care quality, regardless of whether patients had contracted the virus (41).

There is a mixed picture regarding how COVID-19 has impacted delays to diagnosis for cancer. While some studies reported that delays in diagnosis were potentially occurring for some cancers, there is insufficient data to indicate what impact COVID-19 has on delayed diagnoses or data to report on which particular category of cancers are experiencing greater diagnostic delays. This is in line with previous research demonstrating national and international variability regarding diagnostic delays for childhood cancers, often dependent on type or ways of measuring these delays. These delays are postulated to be due to increased fear of catching COVID-19 in the healthcare system, lockdowns, restricted public transportation and access to the healthcare centers, and hospital prioritization for patients with COVID-19 (34, 51, 52, 89, 90).

Healthcare delays and disruptions have been particularly increased for pediatric oncology patients in LMICs. Staff shortages were described primarily in LMICs, with supply chain disruptions, and increase in prices of chemotherapeutic drugs and PPE (62). These results are well captured by Graetz et al. (2021) who described pronounced health service disruptions to childhood cancer care in LMICs, with a greater number of hospital closures, decrease in financial support from the government, and limited access to cancer therapies (67). Overall, these results indicate that care delivery in COVID-19 is reflective of healthcare systems around the world. Before the pandemic, many LMIC healthcare systems had already been strained with decreased resources and access for care for children with cancer (91, 92). In the time of COVID-19, these institutions have noted greater staff and supply shortages, treatment modification, and lack of supportive care (58, 64, 67).

4.3 Limitations

There are several limitations of this study. First, while this study is a systematic review on the impact of COVID-19 on global pediatric cancer outcomes and care delivery, it is not a meta-analysis. Indeed, the methodological heterogeneity amongst reported studies (e.g., due to patient population, types of tumors studied, clinical outcomes measured) limited our ability to quantitatively assess data between cancer diagnoses and between HICs/LMICs. Moreover, the limited follow-up time for many of the reported studies rendered us unable to make concrete conclusions about mortality rates for pediatric oncology patients affected by COVID-19. It is also important to note that, while the majority of studies confirmed COVID-19 diagnosis in children through RT-PCR, a small subset of studies did not specifically report how the diagnosis of COVID-19 was made (i.e., 7 studies) (21, 24, 38, 93–96); we have included these articles for completeness. Further, several studies included in this review were case reports or cohort/cross-sectional studies written up as letters to the editor. As such, our ability to complete a risk of bias assessment for studies varied (see **Appendix B** for risk of bias assessment).

Additionally, while we aimed to consolidate information from all countries, there was a discrepancy between the number of studies reported in HICs and LMICs. For example, there were only 36 (n=873 patients) studies that reported clinical outcomes in LMICs while 49 studies (n=1518 patients) were reported in HICs. As well, some countries had a preponderance of studies; in HICs, for example, the majority of studies were conducted in the United States (19/49). In LMICs, the majority of studies were reported in India (12/36). These discrepancies skewed data and impacted the analyses that we are able to make between countries. As well, while this paper presents an overview of the similarities and differences in clinical outcomes and care delivery between World Bank economies, it is difficult to compare outcomes between countries without also addressing the politics, economics, and health policies of each specific country. Future reviews should aim to incorporate these factors to make contextual conclusions and COVID-19 recommendations.

4.4 Conclusions and Avenues for Future Research

In the early months of the pandemic, Sullivan et al. (2020) created rapid response recommendations for children with cancer globally, including recommendations for patients with ALL, Burkitt's lymphoma, and retinoblastoma, amongst others, as well as recommendations on how to effectively adopt and distribute treatment modalities including radiotherapy, surgery, nursing, and palliative care (44). Pritchard-Jones et al. (2021) also recommended ongoing psychosocial support for families, maintaining consistent and timely cancer services, using collaborative data registries such as the Global COVID-19 Registry to gain knowledge regarding COVID-19 in child cancer patients, and an early return to surgery and radiotherapy treatment (97). Recently, in a large US cohort study, Martin et al. (2021) observed that there were differences in demographic characteristics and pre-existing comorbidities between severity subgroups wherein marginalized populations (e.g., Black/African American race), being younger than 12 years, and having a pediatric complex chronic condition were predictive of peak disease severity (98). These results may suggest that early identification of children likely to progress to severe disease could be achieved using key data elements, and may help in the treatment of pediatric populations. As also noted by Graetz et al. (2021), teamwork, flexible and coordinated approaches to care, among-institution collaboration, partnerships with government, private, and non-profit organizations are key to fostering healthcare resilience (67), and should be prioritized as we remain in the depths of this pandemic and as we move beyond it.

This was the first study that aimed to comprehensively describe all published studies globally on the clinical outcomes and impacts to healthcare delivery in pediatric oncology patients with COVID-19, while stratifying for economies. Future studies should aim to assess the clinical impacts of COVID-19 in pediatric oncology amongst larger patient cohorts, and take into account vaccination and COVID-19 variants. Further, there need to be consolidated outcome measures that allow for evaluation of cancer care between patient cohorts both intra- and inter-nationally (98). With the delta and omicron variants, and

future potential variants of COVID-19, it will also be imperative to determine how new strains of the virus impact clinical outcomes and access to healthcare for pediatric cancer patients globally.

In conclusion, COVID-19 has impacted pediatric oncology patients around the world, both in terms of clinical outcomes and care delivery. In order to meet the WHO Global Initiative for Childhood Cancer goals by 2030, it will be imperative to apply consolidated recommendations to diagnose, treat, and accommodate children with cancer during the pandemic and beyond.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**. Further inquiries can be directed to the corresponding author.

REFERENCES

- Ward ZJ, Yeh JM, Bhakta N, Frazier AL, Atun R. Estimating the Total Incidence of Global Childhood Cancer: A Simulation-Based Analysis. *Lancet Oncol* (2019) 20:483–93. doi: 10.1016/S1470-2045(18)30909-4
- Lam CG, Howard SC, Bouffet E, Pritchard-Jones K. Science and Health for All Children With Cancer. *Science* (2019) 363:1182–6. doi: 10.1126/science.aaw4892
- World Health Organization. *WHO Global Initiative for Childhood Cancer: An Overview* (2021). Available at: <https://www.who.int/docs/default-source/documents/health-topics/cancer/who-childhood-cancer-overview-booklet.pdf>.
- Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer Patients in SARS-CoV-2 Infection: A Nationwide Analysis in China. *Lancet Oncol* (2020) 21:335–7. doi: 10.1016/S1470-2045(20)30096-6
- Dong E, Du H, Gardner L. An Interactive Web-Based Dashboard to Track COVID-19 in Real Time. *Lancet Infect Dis* (2020) 20:533–4. doi: 10.1016/S1473-3099(20)30120-1
- Boulad F, Kamboj M, Bouvier N, Mauguen A, Kung AL. COVID-19 in Children With Cancer in New York City. *JAMA Oncol* (2020) 6:1459–60. doi: 10.1001/jamaoncol.2020.2028
- Mukkada S, Bhakta N, Chantada GL, Chen Y, Vedaraju Y, Faughnan L, et al. Global Characteristics and Outcomes of SARS-CoV-2 Infection in Children and Adolescents With Cancer (GRCC): A Cohort Study. *Lancet Oncol* (2021) 22:1416–26. doi: 10.1016/S1470-2045(21)00454-X
- COVID-19 and Childhood Cancer Registry. Available at: <https://global.stjude.org/en-us/global-covid-19-observatory-and-resource-center-for-childhood-cancer/registry.html> (Accessed Nov 3, 2021).
- Göttinger F, Santiago-García B, Noguera-Julian A, Lanaspá M, Lancella L, Calò Carducci FI, et al. COVID-19 in Children and Adolescents in Europe: A Multinational, Multicentre Cohort Study. *Lancet Child Adolesc Health* (2020) 4:653–61. doi: 10.1016/S2352-4642(20)30177-2
- Kuderer NM, Choueiri TK, Shah DP, Shyr Y, Rubinstein SM, Rivera DR, et al. Clinical Impact of COVID-19 on Patients With Cancer (CCC19): A Cohort Study. *Lancet* (2020) 395:1907–18. doi: 10.1016/S0140-6736(20)31187-9
- Rubio-San-Simón A, Verdú-Amorós J, Hladun R, Juan-Ribelles A, Molero M, Guerra-García P, et al. Challenges in Early Phase Clinical Trials for Childhood Cancer During the COVID-19 Pandemic: A Report From the New Agents Group of the Spanish Society of Paediatric Haematology and Oncology (SEHOP). *Clin Transl Oncol* (2021) 23:183–9. doi: 10.1007/s12094-020-02399-3
- Saab R, Obeid A, Gachi F, Boudiaf H, Sargsyan L, Al-Saad K, et al. Impact of the Coronavirus Disease 2019 (COVID-19) Pandemic on Pediatric Oncology

AUTHOR CONTRIBUTIONS

AM and ALM contributed to the overall design, article selection, review, and manuscript preparation. TW contributed to data extraction and review. BG contributed to data extraction and review. CL contributed to article identification, analysis and interpretation of data, critical revisions and manuscript review. RA contributed to article identification, analysis and interpretation of data, critical revisions and manuscript review. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fonc.2022.869752/full#supplementary-material>

- Care in the Middle East, North Africa, and West Asia Region: A Report From the Pediatric Oncology East and Mediterranean (POEM) Group. *Cancer* (2020) 126:4235–45. doi: 10.1002/cncr.33075
- Vasquez L, Sampor C, Villanueva G, Maradiegue E, Garcia-Lombardi M, Gomez-García W, et al. Early Impact of the COVID-19 Pandemic on Paediatric Cancer Care in Latin America. *Lancet Oncol* (2020) 21:753–5. doi: 10.1016/S1470-2045(20)30280-1
- Kaspers GJL. COVID-19: How Will This Impact Children With Cancer, Now and in the Future? *Expert Rev Anticancer Ther* (2020) 20:527–9. doi: 10.1080/14737140.2020.1781621
- Riera R, Bagattini AM, Pacheco RL, Pachito DV, Roitberg F, Ilbawi A. Delays and Disruptions in Cancer Health Care Due to COVID-19 Pandemic: Systematic Review. *JCO Glob Oncol* (2021) 7:311–23. doi: 10.1200/GO.20.00639
- The Impact of the COVID-19 Pandemic on Noncommunicable Disease Resources and Services: Results of a Rapid Assessment*. Geneva: World Health Organization (2020). Available at: <https://play.google.com/store/books/details?id=7sYPzgEACAAJ>.
- Jazieh AR, Akbulut H, Curigliano G, Rogado A, Alsharm AA, Razis ED, et al. Impact of the COVID-19 Pandemic on Cancer Care: A Global Collaborative Study. *JCO Glob Oncol* (2020) 6:1428–38. doi: 10.1200/GO.20.00351
- Sanderson S, Tatt ID, Higgins JPT. Tools for Assessing Quality and Susceptibility to Bias in Observational Studies in Epidemiology: A Systematic Review and Annotated Bibliography. *Int J Epidemiol* (2007) 36:666–76. doi: 10.1093/ije/dym018
- Hrusak O, Kalina T, Wolf J, Balduzzi A, Provenzi M, Rizzari C, et al. Flash Survey on Severe Acute Respiratory Syndrome Coronavirus-2 Infections in Paediatric Patients on Anticancer Treatment. *Eur J Cancer* (2020) 132:11–6. doi: 10.1016/j.ejca.2020.03.021
- Wood WA, Neuberger DS, Thompson JC, Tallman MS, Sekeres MA, Sehn LH, et al. Outcomes of Patients With Hematologic Malignancies and COVID-19: A Report From the ASH Research Collaborative Data Hub. *Blood Adv* (2020) 4:5966–75. doi: 10.1182/bloodadvances.2020003170
- Ganguly S, Bakhshi S. Teleconsultations and Shared Care in Pediatric Oncology During COVID-19. *Indian J Pediatr* (2021) 88:1–2. doi: 10.1007/s12098-020-03499-2
- Ramaswamy A, Nayak L, Roy Moulik N, Sengar M, Chinnaswamy G, Jobanputra K, et al. COVID-19 in Cancer Patients on Active Systemic Therapy - Outcomes from LMIC Scenario With an Emphasis on Need for Active Treatment. *Cancer Med* (2020) 9:8747–53. doi: 10.1002/cam4.3423
- Alfraj A, Bin Alamir AA, Al-Otaibi AM, Alsharrah D, Aldaithan A, Kamel AM, et al. Characteristics and Outcomes of Coronavirus Disease 2019 (COVID-19) in Critically Ill Pediatric Patients Admitted to the Intensive

- Care Unit: A Multicenter Retrospective Cohort Study. *J Infect Public Health* (2021) 14:193–200. doi: 10.1016/j.jiph.2020.12.010
24. Johnston EE, Martinez I, Davis ES, Caudill C, Richman J, Brackett J, et al. SARS-CoV-2 in Childhood Cancer in 2020: A Disease of Disparities. *J Clin Oncol* (2021) 39:3778–88. doi: 10.1200/JCO.21.00702
 25. Kamdar KY, Kim TO, Doherty EE, Pfeiffer TM, Qasim SL, Suell MN, et al. COVID-19 Outcomes in a Large Pediatric Hematology-Oncology Center in Houston, Texas. *Pediatr Hematol Oncol* (2021) 38(8):695–70. doi: 10.1080/08880018.2021.1924327
 26. André N, Rouger-Gaudichon J, Brethon B, Phulpin A, Thébault É, Pertuisel S, et al. COVID-19 in Pediatric Oncology From French Pediatric Oncology and Hematology Centers: High Risk of Severe Forms? *Pediatr Blood Cancer* (2020) 67:e28392. doi: 10.1002/psc.28392
 27. Faura A, Rives S, Lassaletta Á, Sebastián E, Madero L, Huerta J, et al. Initial Report on Spanish Pediatric Oncologic, Hematologic, and Post Stem Cell Transplantation Patients During SARS-CoV-2 Pandemic. *Pediatr Blood Cancer* (2020) 67:e28557. doi: 10.1002/psc.28557
 28. Ding Y-Y, Ramakrishna S, Long AH, Phillips CA, Montiel-Esparza R, Diorio CJ, et al. Delayed Cancer Diagnoses and High Mortality in Children During the COVID-19 Pandemic. *Pediatr Blood Cancer* (2020) 67:e28427. doi: 10.1002/psc.28427
 29. Sánchez-Jara B, Torres-Jiménez AR, Del Campo-Martínez M de LA, Ortiz-Torres MG, García-Soto A, del Loza-Santiago PR, et al. Clinical Characteristics and Evolution of Pediatric Patients With Acute Leukemia and SARS-CoV2 Virus Infection in a Third Level Hospital in Mexico. *Pediatr Hematol Oncol J* (2021) 6:42–8. doi: 10.1016/j.phoj.2020.11.001
 30. Montoya J, Ugaz C, Alarcon S, Maradiegue E, García J, Díaz R, et al. COVID-19 in Pediatric Cancer Patients in a Resource-Limited Setting: National Data From Peru. *Pediatr Blood Cancer* (2021) 68:e28610. doi: 10.1002/psc.28610
 31. Hammad M, Shalaby L, Sidhom I, Sherief N, Abdo I, Soliman S, et al. Management and Outcome of Coronavirus Disease 2019 (COVID-19) in Pediatric Cancer Patients: A Single Centre Experience From a Developing Country. *Clin Lymphoma Myeloma Leuk* (2021) 21:e853–64. doi: 10.1016/j.clml.2021.07.025
 32. Corso MCM, Soares VJ, Amorim AMP, Cipolotti R, Magalhães IMQ, Lins MM, et al. SARS-CoV-2 in Children With Cancer in Brazil: Results of a Multicenter National Registry. *Pediatr Blood Cancer* (2021) 68:e29223. doi: 10.1002/psc.29223
 33. Totadri S, Srinivasan HN, Joseph LL, Boddu D, Suresh Kochath P, Moorthy M, et al. The Unique Balancing Act of Managing Children With Cancer and COVID-19 Infection: A Single Center Experience From South India. *J Pediatr Hematol Oncol* (2021) 44:e287–92. doi: 10.1097/MPH.0000000000002148
 34. Ferrari A, Zecca M, Rizzari C, Porta F, Provenzi M, Marinoni M, et al. Children With Cancer in the Time of COVID-19: An 8-Week Report From the Six Pediatric Onco-Hematology Centers in Lombardia, Italy. *Pediatr Blood Cancer* (2020) 67:e28410. doi: 10.1002/psc.28410
 35. Madhusoodhan PP, Pierro J, Musante J, Kothari P, Gampel B, Appel B, et al. Characterization of COVID-19 Disease in Pediatric Oncology Patients: The New York-New Jersey Regional Experience. *Pediatr Blood Cancer* (2021) 68:e28843. doi: 10.1002/psc.28843
 36. Gampel B, Lucas AT, Broglie L, et al. COVID-19 in Pediatric Hematology and Oncology Patients in New York City. *Pediatr Blood Cancer* (2020), S36–6. doi: 10.1002/psc.28420
 37. Schied A, Trovillion E, Moodley A. SARS-CoV-2 Infection in a Neutropenic Pediatric Patient With Leukemia: Addressing the Need for Universal Guidelines for Treatment of SARS-CoV-2-Positive, Immunocompromised Patients. *Pediatr Blood Cancer* (2020) 67:e28546. doi: 10.1002/psc.28546
 38. Al-Haddad F, Ali A, Al-Sharrah D, Atyani S, Saleh H, Mullah-Ali AMA. Newly Diagnosed Acute Lymphoblastic Leukemia in a Child With COVID-19 Complicated by MIS-C: A Case Report From Kuwait. *Blood* (2020) 136:24–5. doi: 10.1182/blood-2020-139548
 39. Bisogno G, Provenzi M, Zama D, Tondo A, Meazza C, Colombini A, et al. Clinical Characteristics and Outcome of Severe Acute Respiratory Syndrome Coronavirus 2 Infection in Italian Pediatric Oncology Patients: A Study From the Infectious Diseases Working Group of the Associazione Italiana Di Oncologia E Ematologia Pediatrica. *J Pediatr Infect Dis Soc* (2020) 9:530–4. doi: 10.1093/jpids/piaa088
 40. Marcia M, Vania B, Pruccoli G, Vallero SG, Barisone E, Scolfaro C, et al. Acute Lymphoblastic Leukemia Onset in a 3-Year-Old Child With COVID-19. *Pediatr Blood Cancer* (2020) 67:e28423. doi: 10.1002/psc.28423
 41. Rouger-Gaudichon J, Thébault E, Félix A, Phulpin A, Paillard C, Alimi A, et al. Impact of the First Wave of COVID-19 on Pediatric Oncology and Hematology: A Report From the French Society of Pediatric Oncology. *Cancers* (2020) 12. doi: 10.3390/cancers12113398
 42. Rouger-Gaudichon J, Gariazzo L, Thébault E, et al. Impact of COVID-19 on Cancer Care: A Survey From the French Society of Pediatric Oncology (SFCE). *Pediatr Blood Cancer* (2021) 68:e28554. doi: 10.1002/psc.28554
 43. Ahmad N, Eltawel M, Khan WM, Essa MF, Alharbi T, Al-Sudairy R. COVID-19 in Pediatric Cancer Patients: How Concerned We Should Be? Lessons Learned From a Single Center in Middle East. *J Pediatr Hematol Oncol* (2021) 43:279–80. doi: 10.1097/MPH.0000000000002013
 44. Sullivan M, Bouffé E, Rodriguez-Galindo C, Luna-Fineman S, Khan MS, Kearns P, et al. The COVID-19 Pandemic: A Rapid Global Response for Children With Cancer From SIOP, COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI, and St Jude Global. *Pediatr Blood Cancer* (2020) 67:e28409. doi: 10.1002/psc.28409
 45. Alshahrani M, Elyamany G, Sedick Q, Ibrahim W, Mohamed A, Othman M, et al. The Impact of COVID-19 Pandemic in Children With Cancer: A Report From Saudi Arabia. *Health Serv Insights* (2020) 13:1178632920984161. doi: 10.1177/1178632920984161
 46. Darlington A-SE, Morgan JE, Wagland R, Sodergren SC, Culliford D, Gamble A, et al. COVID-19 and Children With Cancer: Parents' Experiences, Anxieties and Support Needs. *Pediatr Blood Cancer* (2021) 68:e28790. doi: 10.1002/psc.28790
 47. Balduzzi A, Brivio E, Rovelli A, Rizzari C, Gasperini S, Melzi ML, et al. Lessons After the Early Management of the COVID-19 Outbreak in a Pediatric Transplant and Hemato-Oncology Center Embedded Within a COVID-19 Dedicated Hospital in Lombardia, Italy. *Estote Parati. Bone Marrow Transplant* (2020) 55:1900–5. doi: 10.1038/s41409-020-0895-4
 48. Vagelli G, Garrè ML, Garaventa A, Dufour C, Dallorso S, Mesini A, et al. Specific Pathways to Prevent SARS-CoV-2 Infection in Case of Repeated Hospital Admissions for Radiotherapy. *Pediatr Blood Cancer* (2020) 67:e28463. doi: 10.1002/psc.28463
 49. Amicucci M, Canesi M, Rostagno E, Bergadano A, Badino C, Botta D, et al. How We Have Protected Our Patients: The Italian Pediatric Onco-Hematology Units' Response to the COVID-19 Pandemic. *Pediatr Blood Cancer* (2020) 67:e28505. doi: 10.1002/psc.28505
 50. Amicucci M, Canesi M, Rostagno E, Bergadano A, Badino C, Botta D, et al. Management of the Covid-19 Epidemic in Italian Pediatric Hematology and Oncology Centers: A Nurse-Led AIEOP National Survey. *Prof Inferm* (2020) 73:270–7. doi: 10.7429/pi.2020.734270
 51. Chiaravalli S, Ferrari A, Sironi G, Gattuso G, Bergamaschi L, Puma N, et al. Collateral Effect of the COVID-19 Pandemic: Delayed Diagnosis in Pediatric Solid Tumors. *Pediatr Blood Cancer* (2020) 67:e28640. doi: 10.1002/psc.28640
 52. Offenbacher R, Fabish L, Baker A, Chou AJ, Loeb DM. Respiratory Failure in a Child With Pulmonary Metastatic Osteosarcoma and COVID-19. *J Pediatr Hematol Oncol* (2021) 43:e859–60. doi: 10.1097/MPH.0000000000001897
 53. Jarvis KB, Lind A, LeBlanc M, Ruud E. Observed Reduction in the Diagnosis of Acute Lymphoblastic Leukaemia in Children During the COVID-19 Pandemic. *Acta Paediatr* (2021) 110:596–7. doi: 10.1111/apa.15576
 54. Nerli RB, Sanikop AC, Sharma M, Ghagane SC. COVID-19 Pandemic: A Challenge to a Child With Cancer. *Pediatr Blood Cancer* (2020) 67:e28512. doi: 10.1002/psc.28512
 55. Parambil BC, Moulik NR, Dhamne C, et al. COVID-19 in Children With Cancer and Continuation of Cancer-Directed Therapy During the Infection. *Indian J Pediatr* (2021), 1–7. doi: 10.1007/s12098-021-03894-3
 56. Sharma J, Mahajan A, Bakhshi S, Patil V, Verma N. The Impact of COVID-19 Pandemic on Access to Treatment for Children With Cancer in India and Treating Center Practices. *Cancer* (2021) 128:579–86. doi: 10.1002/cncr.33945?casa_token=oG2lom1LPtMAAAAA:K1u_oqYTlZShYc6zFXFCBKU1kpHO8dpjodRrr7I5efpAJkaGavKb0_Yxfg5tKJhzfRAoUuCMefBTMgY
 57. Sindhu II, Sarfraz S, Shaheen N, Khan A, Saeed H. Impact of COVID-19 Pandemic on Treatment of Pediatric Oncology Patients: Report From

- Resource-Limited Setting. *J Coll Physicians Surg Pak* (2021) 31:1372–4. doi: 10.29271/jcpsp.2021.11.1372
58. Meybodi KT, Habibi Z, Nejat F. The Effects of COVID-19 Pandemic on Pediatric Neurosurgery Practice and Training in a Developing Country. *Childs Nerv Syst* (2021) 37:1313–7. doi: 10.1007/s00381-020-04953-4
59. Rahat U-A, Faizan M. Challenges for Pediatric Hematology Oncology in Pakistan During Coronavirus Pandemic. *Pediatr Blood Cancer* (2021) 68:e28600. doi: 10.1002/pbc.28600
60. Raza MR, Maqsood S, Rana ZA, et al. Impact of COVID-19 on the Children With Cancer in 6 Pediatric Oncology Units (Pou's) of Pakistan-A Multi-Center Study. *Cancer Invest* (2021), 1–11. doi: 10.1080/07357907.2021.1916027
61. Kutluk MT, Ahmed F, Kirazli M, Bajin İY, Müngen E, Ekinçi S, et al. The Effect of the COVID-19 Pandemic on Paediatric Cancer Care: Lessons Learnt From a Major Paediatric Oncology Department in Turkey. *Ecancermedicalscience* (2021) 15:1172. doi: 10.3332/ecancer.2021.1172
62. Hambardzumyan L, Badikyan M, Grigoryan H, Tadevosyan A, Grigoryan T, Martirosyan N, et al. AML-335: Treating Hematologic Oncology Patients in the Developing World During the COVID-19 Pandemic. *Clin Lymph Myeloma Leuk* (2020) 20:S204–5. doi: 10.1016/S2152-2650(20)30759-X
63. Palomo-Collí MÁ, Fuentes-Lugo AD, Cobo-Ovando SR, Juárez-Villegas L. COVID-19 in Children and Adolescents With Cancer From a Single Center in Mexico City. *J Pediatr Hematol Oncol* (2021) 43:e1047–8. doi: 10.1097/MPH.0000000000002040
64. Sajid MI, Altaf S, Mushtaq N, Belgaumi A, Fadoo Z. Pediatric Hematology Oncology During SARS-CoV-2: A Brief Communication of 28 Patients and Changes in Clinical Practice From a Single Institute in Pakistan. *Pediatr Blood Cancer* (2021) 68:e28527. doi: 10.1002/pbc.28527
65. Bansal R, Aishwarya A, Rao R, Christy MC, Sen M, Regani H, et al. Impact of COVID-19 Nationwide Lockdown on Retinoblastoma Treatment and Outcome: A Study of 476 Eyes of 326 Children. *Indian J Ophthalmol* (2021) 69:2617–24. doi: 10.4103/ijo.IJO_2243_21
66. Traoré F, Couitchere L, Michon J, Hessissen L. Patient Management in Pediatric Oncology During the COVID-19 Pandemic: Report From Francophone Africa. *Pediatr Blood Cancer* (2021) 68:e28571. doi: 10.1002/pbc.28571
67. Graetz D, Agulnik A, Ranadive R, Vedaraju Y, Chen Y, Chantada G, et al. Global Effect of the COVID-19 Pandemic on Paediatric Cancer Care: A Cross-Sectional Study. *Lancet Child Adolesc Health* (2021) 5:332–40. doi: 10.1016/S2352-4642(21)00031-6
68. Ruggiero A, Romano A, Attinà G. Facing the COVID-19 Outbreak in Children With Cancer. *Drugs Context* (2020) 9. doi: 10.7573/dic.2020-4-12
69. Dorantes-Acosta E, Ávila-Montiel D, Klünder-Klünder M, Juárez-Villegas L, Márquez-González H. Survival and Complications in Pediatric Patients With Cancer and COVID-19: A Meta-Analysis. *Front Oncol* (2020) 10:608282. doi: 10.3389/fonc.2020.608282
70. Meena JP, Kumar Gupta A, Tanwar P, Ram Jat K, Mohan Pandey R, Seth R. Clinical Presentations and Outcomes of Children With Cancer and COVID-19: A Systematic Review. *Pediatr Blood Cancer* (2021) 68:e29005. doi: 10.1002/pbc.29005
71. Castagnoli R, Votto M, Licari A, Brambilla I, Bruno R, Perlini S, et al. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection in Children and Adolescents: A Systematic Review. *JAMA Pediatr* (2020) 174:882–9. doi: 10.1001/jamapediatrics.2020.1467
72. Ludvigsson JF. Systematic Review of COVID-19 in Children Shows Milder Cases and a Better Prognosis Than Adults. *Acta Paediatr* (2020) 109:1088–95. doi: 10.1111/apa.15270
73. Jackson WM, Price JC, Eisler L, Sun LS, Lee JJ. COVID-19 in Pediatric Patients: A Systematic Review. *J Neurosurg Anesthesiol* (2022) 34:141–7. doi: 10.1097/ANA.0000000000000803
74. Dorantes-Acosta E, Ávila-Montiel D, Klünder-Klünder M, Juárez-Villegas L, Márquez-González H. Survival in Pediatric Patients With Cancer During the COVID-19 Pandemic: Scoping Systematic Review. *Bol Med Hosp Infant Mex* (2020) 77:234–41. doi: 10.24875/BMHIM.20000174
75. Ruggiero A, Romano A, Attinà G. Covid-19 and Children With Cancer: Are They at Increased Risk of Infection? *Pediatr Res* (2020) 89:398–8. doi: 10.1038/s41390-020-0919-1
76. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA* (2020) 323:1775–6. doi: 10.1001/jama.2020.4683
77. ElGohary GM, Hashmi S, Styczynski J, et al. The Risk and Prognosis of COVID-19 Infection in Cancer Patients: A Systematic Review and Meta-Analysis. *Hematol Oncol Stem Cell Ther* (2020). doi: 10.1016/j.hemonc.2020.07.005
78. newsGP. *Severe COVID Much More Common in Males, Research Shows*. Available at: <https://www1.racgp.org.au/news/clinical/severe-covid-much-more-common-in-males-research-sh> (Accessed Nov 7, 2021).
79. Peckham H, de Groot NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male Sex Identified by Global COVID-19 Meta-Analysis as a Risk Factor for Death and ICU Admission. *Nat Commun* (2020) 11:6317. doi: 10.1038/s41467-020-19741-6
80. Sun C, Pleyer C, Wiestner A. COVID-19 Vaccines for Patients With Haematological Conditions. *Lancet Haematol* (2021) 8:e312–4. doi: 10.1016/S2352-3026(21)00073-9
81. Vijenthira A, Gong IY, Fox TA, Booth S, Cook G, Fattizzo B, et al. Outcomes of Patients With Hematologic Malignancies and COVID-19: A Systematic Review and Meta-Analysis of 3377 Patients. *Blood* (2020) 136:2881–92. doi: 10.1182/blood.2020008824
82. Smith VR, Whittle SB, Coleman RD, Munoz FM, De Guzman MM, Foster JH, et al. Severe COVID-19 Infection in a Child Receiving Immunotherapy for Cancer. *Pediatr Blood Cancer* (2021) 68:e28710. doi: 10.1002/pbc.28710
83. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K, et al. Multisystem Inflammatory Syndrome in Children: A Systematic Review. *EclinicalMedicine* (2020) 26:100527. doi: 10.1016/j.eclinm.2020.100527
84. Kitano T, Kitano M, Krueger C, Jamal H, Al Rawahi H, Lee-Krueger R, et al. The Differential Impact of Pediatric COVID-19 Between High-Income Countries and Low- and Middle-Income Countries: A Systematic Review of Fatality and ICU Admission in Children Worldwide. *PLoS One* (2021) 16:e0246326. doi: 10.1371/journal.pone.0246326
85. Wang X, Li Y, O'Brien KL, Madhi SA, Widdowson M-A, Byass P, et al. Global Burden of Respiratory Infections Associated With Seasonal Influenza in Children Under 5 Years in 2018: A Systematic Review and Modelling Study. *Lancet Glob Health* (2020) 8:e497–510. doi: 10.1016/S2214-109X(19)30545-5
86. Muloiva R, Kagina BM, Engel ME, Hussey GD. The Burden of Laboratory-Confirmed Pertussis in Low- and Middle-Income Countries Since the Inception of the Expanded Programme on Immunisation (EPI) in 1974: A Systematic Review and Meta-Analysis. *BMC Med* (2020) 18:233. doi: 10.1186/s12916-020-01699-3
87. Popescu CR, Cavanagh MMM, Tembo B, Chieme M, Lufesi N, Goldfarb DM, et al. Neonatal Sepsis in Low-Income Countries: Epidemiology, Diagnosis and Prevention. *Expert Rev Anti Infect Ther* (2020) 18:443–52. doi: 10.1080/14787210.2020.1732818
88. Zar HJ, Dawa J, Fischer GB, Castro-Rodriguez JA. Challenges of COVID-19 in Children in Low- and Middle-Income Countries. *Paediatr Respir Rev* (2020) 35:70–4. doi: 10.1016/j.prrv.2020.06.016
89. Carai A, Locatelli F, Mastronuzzi A. Delayed Referral of Pediatric Brain Tumors During COVID-19 Pandemic. *Neuro Oncol* (2020) 22:1884–6. doi: 10.1093/neuonc/noaa159
90. Molica M, Mazzone C, Cordone I, Pasquale A, Niscola P, de Fabritiis P. SARS-CoV-2 Infection Anxieties and General Population Restrictions Delay Diagnosis and Treatment of Acute Haematological Malignancies. *Br J Haematol* (2020) 190:e5–8. doi: 10.1111/bjh.16785
91. Farmer P, Frenk J, Knaul FM, Shulman LN, Alleyne G, Armstrong L, et al. Expansion of Cancer Care and Control in Countries of Low and Middle Income: A Call to Action. *Lancet* (2010) 376:1186–93. doi: 10.1016/S0140-6736(10)61152-X
92. Howard SC, Metzger ML, Wilimas JA, Quintana Y, Pui C-H, Robison LL, et al. Childhood Cancer Epidemiology in Low-Income Countries. *Cancer* (2008) 112:461–72. doi: 10.1002/cncr.23205
93. Rathore P, Kumar S, Shweta, Singh N, Krishnapriya V, Thankachan A, et al. A Child With Acute Lymphoblastic Leukemia in Institutional Isolation During the COVID Pandemic: A Multifaceted Responsibility. *Indian J Palliat Care* (2020) 26:S170–2. doi: 10.4103/IJPC.IJPC_167_20
94. Jarmoliński T, Matkowska-Kocjan A, Rosa M, Olejnik I, Gorczyńska E, Kałwak K, et al. SARS-CoV-2 Viral Clearance During Bone Marrow Aplasia After Allogeneic Hematopoietic Stem Cell Transplantation-A Case Report. *Pediatr Transplant* (2021) 25:e13875. doi: 10.1111/petr.13875

95. de Rojas T, Pérez-Martínez A, Cela E, Baragaño M, Galán V, Mata C, et al. COVID-19 Infection in Children and Adolescents With Cancer in Madrid. *Pediatr Blood Cancer* (2020) 67:e28397. doi: 10.1002/pbc.28397
96. Baka M, Michos A, Alexopoulou A, Bouka P, Bouka E, Dana E, et al. COVID-19 Among Children With Cancer in Greece (2020): Results From the Nationwide Registry of Childhood Hematological Malignancies and Solid Tumors (NARECHEM-St). *Pediatr Blood Cancer* (2021) 68:e29079.
97. Pritchard-Jones K, de CV, Abib S, Esiashevili N, Kaspers GJL, Rosser J, et al. *The Threat of the COVID-19 Pandemic on Reversing Global Life-Saving Gains in the Survival of Childhood Cancer: A Call for Collaborative Action From SIOP, IPSO, PROS, WCC, CCI, St Jude Global, UICC and WHPCA. Ecancermedicalscience*, Vol. 15. (2021). doi: 10.3332/ecancer.2021.1187.
98. Martin B, DeWitt PE, Russell S, Anand A, Bradwell KR, Bremer C, et al. Characteristics, Outcomes, and Severity Risk Factors Associated With SARS-CoV-2 Infection Among Children in the US National COVID Cohort Collaborative. *JAMA Netw Open* (2022) 5:e2143151. doi: 10.1001/jamanetworkopen.2021.43151

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