

BMJ Open Impact of the COVID-19 pandemic on patients with paediatric cancer in low-income, middle-income and high-income countries: a multicentre, international, observational cohort study

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To cite: Global Health Research Group on Children's Non-Communicable Diseases Collaborative. Impact of the COVID-19 pandemic on patients with paediatric cancer in low-income, middle-income and high-income countries: a multicentre, international, observational cohort study. *BMJ Open* 2022;**12**:e054690. doi:10.1136/bmjopen-2021-054690

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-054690>).

Received 21 June 2021
Accepted 21 January 2022



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ABSTRACT

Objectives Paediatric cancer is a leading cause of death for children. Children in low-income and middle-income countries (LMICs) were four times more likely to die than children in high-income countries (HICs). This study aimed to test the hypothesis that the COVID-19 pandemic had affected the delivery of healthcare services worldwide, and exacerbated the disparity in paediatric cancer outcomes between LMICs and HICs.

Design A multicentre, international, collaborative cohort study.

Setting 91 hospitals and cancer centres in 39 countries providing cancer treatment to paediatric patients between March and December 2020.

Participants Patients were included if they were under the age of 18 years, and newly diagnosed with or undergoing active cancer treatment for Acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, Hodgkin lymphoma, Wilms' tumour, sarcoma, retinoblastoma, gliomas, medulloblastomas or neuroblastomas, in keeping with the WHO Global Initiative for Childhood Cancer.

Main outcome measure All-cause mortality at 30 days and 90 days.

Results 1660 patients were recruited. 219 children had changes to their treatment due to the pandemic. Patients in LMICs were primarily affected (n=182/219, 83.1%). Relative to patients with paediatric cancer in HICs, patients with paediatric cancer in LMICs had 12.1 (95% CI 2.93 to 50.3) and 7.9 (95% CI 3.2 to 19.7) times the odds of death at 30 days and 90 days, respectively, after presentation during the COVID-19 pandemic ($p<0.001$). After adjusting for confounders, patients with paediatric cancer in LMICs had 15.6 (95% CI 3.7 to 65.8) times the odds of death at 30 days ($p<0.001$).

Conclusions The COVID-19 pandemic has affected paediatric oncology service provision. It has disproportionately affected patients in LMICs, highlighting and compounding existing disparities in healthcare systems globally that need addressing urgently. However, many patients with paediatric cancer continued to

Strengths and limitations of this study

- This is the first large-series, global, multicentre, international cohort study to explore the effect of the COVID-19 pandemic on paediatric oncology care, which includes data from 1660 patients in 39 countries.
- The collaborative approach for this study allowed a large series of high-quality data to be collected in a timely manner without overburdening centres, with 91 centres being involved in this study.
- A single study database was used, which allowed for data-analysis to occur to ascertain the short-term outcome for paediatric oncology patients while the study continued to collect follow-up data.
- This is an interim-report, and many centres involved in the wider study—including all centres in India—have not been able to gain ethical approval to share their data for this report; although approvals will be in place to share data after 12 month follow-up data has been collected in December 2021.
- This study has limited its focus to nine of the the most common paediatric cancers globally as identified by the WHO, and hence does not capture the effects of the pandemic on rarer cancers.

receive their normal standard of care. This speaks to the adaptability and resilience of healthcare systems and healthcare workers globally.

INTRODUCTION

Approximately 200 000–400 000 children are newly diagnosed with cancer annually.^{1–4} Cancers in the paediatric population differ greatly from those in adults, particularly in the diagnoses seen and the availability of suitable healthcare.⁵ Fewer than 20% of all paediatric cancers are found in high-income countries (HICs), where multimodal

care is more accessible.² Despite being ostensibly highly curable diseases, delays in diagnosis and paucity of care for many patients with paediatric cancer has resulted in paediatric cancer being the second leading cause of non-communicable disease deaths for children worldwide.^{1–4} More than 90% of these deaths occur in low-income and middle-income countries (LMICs).⁴ The inordinately high number of person-years of life lost make paediatric cancer care a global health priority.²

The COVID-19 pandemic may have exacerbated the imbalance of paediatric cancer outcomes between LMICs and HICs. There were reports globally on the cancellation of elective health services—including paediatric surgery and radiotherapy, essential outpatient services, shortage of essential medications, delays in diagnosis, hospital inpatient services being overwhelmed and healthcare staffing issues.^{6–8} During the initial phase of the pandemic, the reorganisation of paediatric cancer services worldwide was partly driven by assumptions that patients with paediatric cancer were particularly vulnerable to COVID-19. This assumption has since been refuted⁹ with the largest study to date on this topic identifying only 259 children with cancer suffering from severe COVID-19 infection worldwide.¹⁰ The international paediatric cancer community swiftly adapted their guidance to emphasise the importance of continuing care for patients with paediatric cancer.¹¹ Despite this, three international cross-sectional studies conducted by different research teams at different timepoints reported that the majority of clinicians surveyed believed that their paediatric cancer centre had reduced their usual level of care either as a precaution, or due to a lack of resources or accessibility.^{8 12 13} These reported delays or alterations to treatment—if accurate—could prove extremely detrimental to patients with paediatric cancer in both the short term and the long term.^{8 14}

As all international analyses reported thus far have been cross-sectional studies focused on the perceptions of clinicians,^{8 12 13} there remains a need to corroborate these findings and assess the impact of the pandemic on the outcomes of patients with paediatric cancer. Therefore, we conducted an international, multicentre, cohort study with the primary aim to ascertain the short-term outcome across 16 HICs and 25 LMICs during the COVID-19 pandemic by determining 30-day and 90-day all-cause mortality rates for paediatric oncology patients who underwent treatment. We also examined the factors that influenced these outcomes including tumour specific data, patient-specific demographics, and changes to health system frameworks. Secondary objectives of this study are to evaluate (1) the changes to paediatric cancer management during the COVID-19 pandemic, (2) the factors that influenced these changes from a health systems framework (eg, infrastructure, workforce, redeployment of staff, access to services) and (3) the number of patients with paediatric cancer who were placed under palliative care or who sought abandonment of treatment during the pandemic. The WHO Global Initiative

for Childhood Cancer (GICC) has primarily used six common cancers as a benchmark for assessing global paediatric cancer care: acute lymphoblastic leukaemia (ALL), Burkitt lymphoma, Hodgkin lymphoma, retinoblastoma, Wilms' tumour and low-grade glioma.¹⁵ Therefore, this study focuses on the GICC identified cancer benchmarks and four other paediatric cancer manifestations that had been identified to be common in both LMICs and HICs: sarcoma, high-grade glioma, medulloblastoma and neuroblastomas.

METHODS

Study design

This is a multicentre, international, mixed (retrospective and prospective), collaborative (online supplemental appendix S1) cohort study at 91 hospitals in 39 countries (online supplemental appendix S2). Only routine, anonymised data was collected, and no clinical care pathways were changed for the study as per the study protocol.¹⁶ Participating collaborators gained local approvals in accordance with their institutional ethical regulations (online supplemental appendices S3–S5). Reporting has been conducted in line with the Strengthening the Reporting of Observational Studies in Epidemiology statement for observational studies¹⁷ (online supplemental appendix S6).

Study setting

Hospitals or cancer centres in all continents providing cancer treatment to paediatric patients were eligible to participate in this study.¹⁶ The World Bank classification of the fiscal year of 2021 was utilised to categorise centres as HIC or LMIC.¹⁸ Local collaborators at all study sites were responsible for identifying eligible patients for inclusion and collecting data using the Research Electronic Data Capture (REDCap) web application.

Participants

Patients at participating centres were included if they were under the age of 18 years and newly diagnosed with or undergoing active treatment for an eligible cancer between 12 March 2020—the date that the WHO declared the start of the COVID-19 pandemic—and 12 December 2020. Eligible cancers were: ALL, non-Hodgkin's lymphoma, Hodgkin lymphoma, Wilms' tumour, sarcoma (osteosarcoma, Ewing sarcoma and rhabdomyosarcoma), retinoblastoma, glioma, medulloblastoma and neuroblastoma in keeping with the WHO GICC. Site investigators were provided with a range of written materials setting out possible strategies to capture consecutive eligible patients. In addition, investigators were invited to join social media groups and teleconferences for the purpose of troubleshooting site-specific recruitment issues and shared learning. The importance of working across paediatric oncological specialties was emphasised throughout to minimise bias that could be introduced by certain

patients not being included. Sample size was calculated as per the protocol.¹⁶

Outcome variables

The primary outcomes were all-cause mortality at 30 days and 90 days from initial anti-cancer treatment as of 12th March 2020. The key secondary outcomes were any alterations to paediatric cancer treatment decisions during the COVID-19 pandemic and changes to health system frameworks which led to these alterations, as reported by local collaborators. Additional secondary outcomes were any complications within 30 days of first anti-cancer treatment as of 12th March 2020 and the number of patients who abandoned treatment.

Other variables

Baseline patient variables included age, weight at admission, patient sex and American Society of Anesthesiologists (ASA) grade at the time of presentation. Baseline tumour variables included tumour type, staging and diagnosis date. Definitions for tumour types were provided for reference.¹⁶ Treatment variables included initial multidisciplinary team (MDT) decision, date thereof and treatment type (chemotherapy, radiotherapy, immunological therapy, surgery, palliative treatment and/or no anticancer treatment). For patients receiving radiotherapy, radiation field and type was reported. For patients receiving surgery, hospital COVID-19 designation was reported; a cold hospital was defined as COVID-19-free zone and a hot hospital was defined as a zone with a confirmed COVID-19 case where active treatment for COVID-19 was administered. The National Confidential Enquiry into Patient Outcome and Death (NCEPOD) Classification of Intervention was used to define the urgency of surgery.¹⁹ The reason for surgery—whether diagnostic, curative or palliative—and the time from admission to surgery were also reported. Specific data fields from the proforma can be found in online supplemental appendix S7.

Data validation

To validate the data and reduce the potential for bias due to incomplete case ascertainment, a three-stage process was performed at a randomly selected subset (10%) of participating centres. First, key processes used to recruit and follow-up eligible patients were self-reported by local leads. Second, an independent validator from the same centre quantitatively reported case ascertainment. Third, a local independent validator randomly sampled a section of the data for accuracy. The targets for validation were a secure and accurate record of patients entered onto REDCap with no case/data duplication and data accuracy >95%.

Statistical methods

All duplicates were removed post-data validation. Missing data for covariates were analysed to determine if they were related to the outcome and either complete-case analyses or multiple imputation techniques were used for the analyses accordingly. Baseline characteristics for

LMIC and HIC countries are presented as proportions or mean (SD) or median (range) and statistical differences were determined using a chi-square test or Fisher's exact test. Statistical differences in 30-day and 90-day mortality between LMICs and HICs were determined using Fisher's exact test due to low event rates. A discrete time survival model was used to assess time to 30-day mortality adjusting for important prognostic factors and displayed using Kaplan-Meier plots. Multivariate logistic regression analyses were conducted between covariates and the primary outcome of 30-day mortality. The LASSO (Least Absolute Shrinkage and Selection Operator) method was utilised for variable selection, and to determine the final multi-level multivariable logistic model of covariates affecting outcomes. Results are presented as ORs or hazard ratios with corresponding 95% CIs. Data were analysed using Stata V.15.1 and SAS V.9.4.

Patient and public involvement

The steering committee met with the parents of 11 children from across North America, Europe, Asia and Africa during the planning of this study. Their children had a range of neoplasms including leukaemia, rhabdomyosarcoma, osteosarcoma and Wilm's tumour. It was found that 40% of the children represented in the group had been impacted by COVID-19 in one of three key-ways: follow-up clinics had become virtual; delays in treatment; and parents having to receive news from doctors without their partners. All parents agreed on the value and benefit of the study. Two parents (one from the UK and one from Nigeria) agreed to provide their input on the findings and dissemination of the results.

RESULTS

A total of 1660 patients were eligible for the study. They were recruited consecutively across the 91 hospitals (LMICs: 65/91, 71.4%) in 39 countries (figure 1, online supplemental appendices S1 and S2). A total of 1104 patients (66.5%) were from LMICs and 556 were from HICs (table 1 and online supplemental appendix S8). Patients with paediatric cancer in LMICs were typically

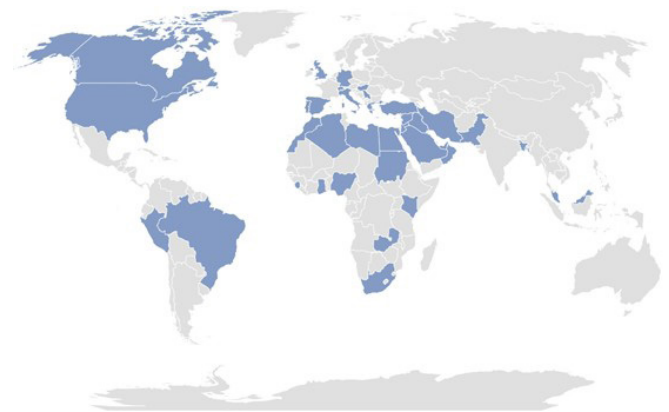


Figure 1 Location of the 39 countries that had centres participating in this study.

**Table 1** Baseline characteristics

Variable		LMICs (N=1104) N (%)	HICs (N=556) N (%)	Total (N=1660) N (%)	P value		
Age (years), median (range)		5.00 (2.0–10.0)	7.00 (3.0–13.0)	6.00 (3.0–11.0)	<0.001		
Sex	Female	469 (42.5)	230 (41.4)	699 (42.1)	0.66		
	Male	631 (57.2)	324 (58.3)	955 (57.5)			
	Missing	4 (0.4)	2 (0.4)	6 (0.4)			
Weight (kg), median (range)		18.0 (13.0–29.0)	27.1 (16.8–49.1)	20.0 (14.0–35.0)	<0.001		
ASA grade	(1a) Normal healthy patient	344 (31.2)	101 (18.2)	445 (26.8)	<0.001		
	(2a) Patient with mild systemic disease	423 (38.3)	206 (37.1)	629 (37.9)			
	(3a) Patient with severe systemic disease	149 (13.5)	220 (39.6)	369 (22.2)			
	(4a) Patient with severe systemic disease that is a constant threat to life	34 (3.1)	25 (4.5)	59 (3.6)			
	(5a) Moribund patient who is not expected to survive without the operation	8 (0.7)	0 (0.0)	8 (0.5)			
	Missing	146 (13.2)	4 (0.7)	150 (9.0)			
Tumour type	Non-Hodgkin's lymphoma	89 (8.1)	29 (5.2)	118 (7.1)	<0.001		
	Acute lymphoblastic leukaemia	380 (34.4)	234 (42.1)	614 (37.0)			
	Ewing sarcoma	32 (2.9)	31 (5.6)	63 (3.8)			
	Glioma	73 (6.6)	69 (12.4)	142 (8.6)			
	Hodgkin lymphoma	63 (5.7)	38 (6.8)	101 (6.1)			
	Medulloblastoma	57 (5.2)	31 (5.6)	88 (5.3)			
	Neuroblastoma	80 (7.2)	48 (8.6)	128 (7.7)			
	Osteosarcoma	45 (4.1)	25 (4.5)	70 (4.2)			
	Retinoblastoma	87 (7.9)	4 (0.7)	91 (5.5)			
	Rhabdomyosarcoma	61 (5.5)	25 (4.5)	86 (5.2)			
	Wilms tumour	137 (12.4)	22 (4.0)	159 (9.6)			
	Was patient tested for COVID-19?	No	631 (57.2)	148 (26.6)		779 (46.9)	<0.001
		Yes	367 (33.2)	366 (65.8)		733 (44.2)	
Missing		106 (9.6)	42 (7.6)	148 (8.9)			
Was patient diagnosed with COVID-19?	No	943 (85.4)	519 (93.3)	1462 (88.1)	0.004		
	Not applicable (no anti-cancer treatment given post March 11 th 2020)	11 (1.0)	3 (0.)	14 (0.8)			
	Proven with laboratory test or CT Thorax	31 (2.8)	6 (1.1)	38 (2.2)			
	Probable—clinically suspected	5 (0.54)	3 (0.5)	8 (0.5)			
	Unknown	74 (6.7)	19 (3.4)	93 (5.6)			

Continued

Table 1 Continued

Variable	LMICs (N=1104) N (%)	HICs (N=556) N (%)	Total (N=1660) N (%)	P value
Missing	40 (3.6)	6 (1.1)	46 (2.8)	

ASA, American Society of Anesthesiologists; HICs, high-income countries; LMICs, low-income and middle-income countries.

younger, lighter in weight and had a lower ASA grade at presentation than the patients recruited in HICs (table 1). The most common paediatric cancer in both HICs and LMICs included in this study was ALL (n=614/1660, 37.0%). Retinoblastomas were more common among LMIC patients (n=87/1104, 7.9%) than HIC patients (n=4/556, 0.7%). A minority of patients with paediatric cancer in both LMICs and HICs were diagnosed with COVID-19.

Central nervous system (CNS) involvement data were available for 557 patients with ALL (LMICs: n=337/380, 88.7%; HICs: n=220/234, 94.0%). Most of these patients were negative for CNS involvement (LMICs: n=312/337, 92.6%; HICs: n=179/220, 81.4%). Ann Arbor staging data was available for most patients with Hodgkin lymphoma (LMICs: n=52/63, 82.5%; HICs: n=33/38, 86.8%). Among HIC patients, 17 were stage II (51.5%), 5 were stage III (15.2%), and 11 were stage IV (33.3%). Among LMIC patients, 5 were stage I (9.6%), 14 were stage II (26.9%), 14 were stage III (26.9%) and 19 were stage IV (36.5%). Similarly, Ann Arbor staging data were available for most patients with non-Hodgkin's lymphoma (LMICs: n=61/89, 68.5%; HICs: n=23/29, 79.3%). Among HIC patients, five were stage I (21.7%), five were stage II (21.7%), seven were stage III (30.4%) and six were stage IV (26.1%). Among LMIC patients, 7 were stage I (11.5%), 8 were stage II (13.1%), 31 were stage III (50.8%) and 15 were stage IV (24.6%). Staging data were available for 131 patients with glioma (LMICs: n=65/73, 89.0%; HICs: n=66/69, 95.7%). Most of these patients had a low-grade glioma (LMICs: n=40/65, 61.5%; HICs: n=53/66, 80.3%). For the remaining 499 patients in LMICs with a paediatric cancer, staging was known for 400 patients (80.2%): 208 had localised cancer (52.0%), 75 had regional cancer (18.8%), and 117 had metastatic cancer (29.3%). Similarly, for the remaining 186 patients in HICs with a paediatric cancer, 68 had localised cancer (36.6%), 21 had regional cancer (11.3%) and 64 had metastatic cancer (34.4%).

After 30 days postpresentation, 64 patients (3.9%) were lost to follow-up (figure 2 and table 2). Where data were available, the risk of death among patients with paediatric cancer in LMICs at 30 days after presentation was 4.3% (95% CI 3.1 to 5.5). The tumour types of the patients in LMICs that died at 30 days were ALL (n=8), non-Hodgkin's lymphoma (n=7), medulloblastoma (n=7), glioma (n=6), neuroblastoma (n=6), rhabdomyosarcoma (n=4), retinoblastoma (n=3), Wilms' tumour (n=3) and osteosarcoma (n=1). Of these deaths, 2 were

in low-income countries (n=2/35, 5.7%), 16 were in lower-middle-income countries (n=16/488, 3.3%) and 27 were in upper-middle-income countries (n=27/528, 5.1%). The risk of death among patients with paediatric cancer in HICs at 30 days after presentation was 0.4% (95% CI 0.0 to 0.9). The tumour types of the patients in HICs that died at 30 days were ALL (n=1) and rhabdomyosarcoma (n=1). Relative to patients with paediatric cancer in HICs, patients with paediatric cancer in LMICs had 12.1 (95% CI 2.9 to 50.3) times the odds of death at 30 days after presentation during the COVID-19 pandemic (p<0.001). At 90 days, 187 patients (11.3%) overall had been lost to follow-up (figure 2 and table 2). The risk of death among patients with paediatric cancer in LMICs at 90 days after presentation was 7.0% (95% CI 5.4 to 8.6). The risk of death among patients with paediatric cancer in HICs at 90 days after presentation was 0.9% (95% CI 0.1 to 1.8). Relative to patients with paediatric cancer in HICs, patients with paediatric cancer in LMICs had 7.9 (95% CI 3.2 to 19.7) times the odds of death at 90 days after presentation during the COVID-19 pandemic (p<0.001). Among paediatric patients who survived to 30 days, relative to patients with paediatric cancer in HICs (0.6%), patients with paediatric cancer in LMICs (2.3%) had 4.2 (95% CI 1.2 to 14.1) times the odds of death at 90 days after presentation during the COVID-19 pandemic

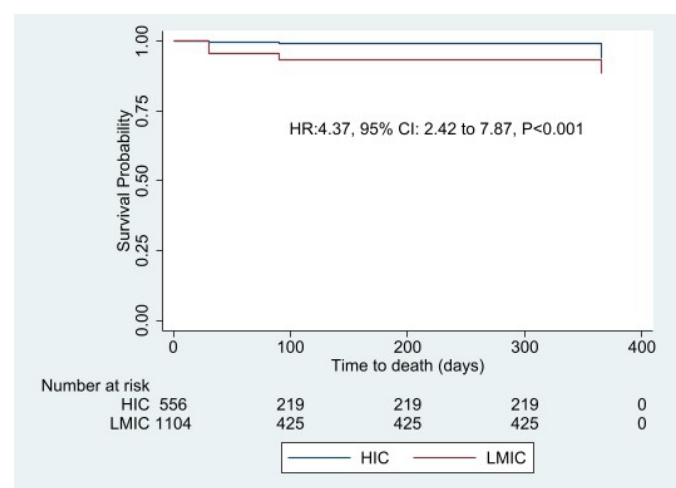


Figure 2 Kaplan-Meier survival curve of patients with paediatric cancer in high-income countries (HICs) and low-income and middle-income countries (LMICs) adjusted for COVID-19 test outcome, MDT decision: anti-cancer therapy and whether the first admission was planned. MDT, multidisciplinary team.

Table 2 Thirty-day and 90-day mortality

		LMICs (N=1104) N (%)	HICs (N=556) N (%)	P value
30-day mortality	Alive	1006 (91.1)	543 (97.7)	<0.0001
	Dead	45 (4.1)	2 (0.4)	
	Unknown	53 (4.8)	11 (2.0)	
90-day mortality	Alive	878 (79.5)	524 (94.2)	<0.0001
	Dead	66 (6.0)	5 (0.9)	
	Unknown	160 (14.5%)	27 (4.9%)	

HICs, high-income countries; LMICs, low-income and middle-income countries.

($p=0.0104$). The tumour types of the patients in LMICs that died between 30 and 90 days were ALL ($n=7$), non-Hodgkin's lymphoma ($n=1$), medulloblastoma ($n=2$), glioma ($n=1$), neuroblastoma ($n=5$), rhabdomyosarcoma ($n=1$), Wilms' tumour ($n=2$), Ewing's sarcoma ($n=1$) and osteosarcoma ($n=1$). The tumour types of the patients in HICs that died between 30 and 90 days were ALL ($n=2$) and non-Hodgkin's lymphoma ($n=1$). All these deaths occurred in middle-income countries: 18 in lower-middle-income countries ($n=18/427$, 4.2%), and 3 were in upper-middle-income countries ($n=3/442$, 0.7%).

After adjusting for confounders, relative to patients with paediatric cancer in HICs, patients with paediatric cancer in LMICs had 15.6 times the odds of death at 30 days after presentation during the COVID-19 pandemic ($p<0.001$) (table 3). After adjusting for confounders, relative to patients with paediatric cancer who were not proven to be COVID-19 positive, patients with paediatric cancer who were COVID-19 positive postpresentation had

22.8 times the odds of death at 30 days after presentation (table 3 and figure 3).

A total of 219 children had delays or alterations to treatment. An initial MDT decision was made for 1435 of the included children (86.4%) to receive chemotherapy: 931 in LMICs and 504 in HICs. Secondary to the effects of the COVID-19 pandemic, 7 children in LMICs had their planned chemotherapy cancelled, 84 and 17 children in LMICs and HICs, respectively, had delayed delivery of their chemotherapy, 8 children in LMICs were given a reduced dose from the normal regimen that would have been given prior to the pandemic, 2 children in LMICs were given an increased dose compared with the normal regimen, 7 children in LMICs had fewer cycles of chemotherapy relative to the normal regimen, 6 children in LMICs and one child in an HIC had more cycles of chemotherapy relative to the normal regimen, 5 children in LMICs and 1 child in an HIC had a shorter duration of total treatment than would normally be given, 18 children

Table 3 Multivariable Generalised Linear Model analysis using Least Absolute Shrinkage and Selection Operator method for variable selection: 30-day mortality

		OR	95% CI	P value
World Bank Income Status (Reference: HIC)	LMIC	15.6	3.7 to 65.8	<0.001
	Not applicable (No anti-cancer treatment given post March 11 th 2020)	0.62	0.08 to 4.73	0.642
COVID Status (Reference: COVID negative)	Proven with laboratory test or CT Thorax	22.8	3.75 to 4.73	0.013
	Probable – clinically suspected	0.001	0.001 to 999.99	–
	Unknown	0.30	0.04 to 2.31	0.250
MDT decision (Reference: no anticancer therapy)	Provide anticancer therapy	7.69	1.37 to 43.3	0.021
Was the first admission planned? (reference: Yes)	No	0.23	0.12 to 0.44	<0.001

HIC, high-income country; LMIC, low-income and middle-income country; MDT, multidisciplinary team.

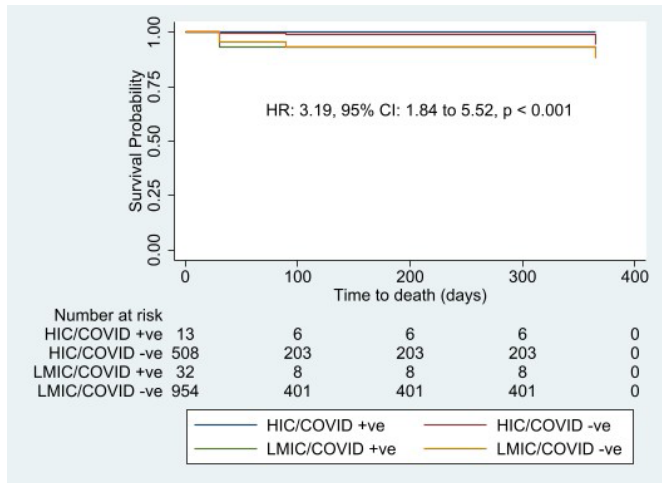


Figure 3 Kaplan-Meier survival curve of patients with paediatric cancer in high-income countries (HICs) and low-income and middle-income countries (LMICs) stratified by COVID-19 positivity.

in LMICs had a longer duration of treatment than would normally be given, 21 children in LMICs and one child in an HIC were given a different chemotherapy agent compared with the normal regimen, and 8 children in LMICs were given chemotherapy through an alternative route of administration. In addition, the families of 17 children in LMICs and 1 child in an HIC abandoned this treatment. The drivers behind these changes are listed in [table 4](#).

Similarly, an initial MDT decision was made for 226 of the included children (13.6%) to receive radiotherapy: 131 in LMICs and 95 in HICs. Secondary to the effects of the COVID-19 pandemic, one child in an LMIC had their planned radiotherapy cancelled, eight and eight children in LMICs and HICs, respectively, had delayed delivery of their radiotherapy, and three children were given radiotherapy through a different modality than would normally be given. In addition, the family of one child in an HIC abandoned their treatment. An initial MDT decision was made for 48 of the included children (2.9%) to receive immunotherapy: 18 in LMICs and 30 in HICs. Secondary to the effects of the COVID-19 pandemic, 1 child in an LMIC had their planned immunotherapy cancelled, 2 and 3 children in LMICs and HICs, respectively, had delayed delivery of their immunotherapy. In addition, the family of one child in an HIC abandoned this treatment. An initial MDT decision was made for 518 patients (31.2%) to undergo surgery: 364 in LMICs and 154 in HICs. Secondary to the effects of the COVID-19 pandemic, one child in an LMIC had their planned surgery cancelled, 47 and 10 children in LMICs and HICs, respectively, had delayed surgery, 8 children in LMICs and one child in an HIC had a change in the choice of their operation, 8 children in LMICs and one child in an HIC had their operation performed in an alternative hospital (reported to have prevented a delay in surgery), once child in an LMIC underwent neoadjuvant therapy where this would

not typically have been indicated, 3 children in LMICs and one child in an HIC underwent a longer course of neoadjuvant therapy, 1 child in an LMIC did not undergo a neoadjuvant therapy that would normally be indicated and 1 child was switch to palliative care. An additional 10 children in LMICs and 4 children in HICs were deemed to be for palliative care at the initial MDT. In addition, the families of three children in LMICs and one child in an HIC abandoned this treatment. The drivers behind these changes are listed in [table 4](#).

DISCUSSION

Children with cancer have had their treatments delayed, interrupted, or modified due to the direct effects of COVID-19 and the measures imposed to minimise COVID-19 mortality and morbidity. These delays and alterations only affected a minority of patients with paediatric cancer. They primarily affected patients with paediatric cancer in LMICs. Relative to patients with paediatric cancer in HICs, patients with paediatric cancer in LMICs had 12.1 and 7.9 times the risk of death at 30 days and 90 days, respectively, after presentation during the COVID-19 pandemic. After adjusting for confounders—such as age, sex, weight, ASA grade, tumour type and tumour staging, relative to patients with paediatric cancer in HICs, patients with paediatric cancer in LMICs had 15.6 times the odds of all-cause mortality during the COVID-19 pandemic. This is substantially higher than prepandemic figures of children in LMICs being four times more likely to die.^{1 20} A minority of patients with paediatric cancer in both LMICs and HICs were diagnosed with COVID-19, with most of these cases being in LMICs. Being diagnosed with COVID-19 was associated with greater odds of death at 30 days after presentation. It should be noted that being diagnosed with COVID-19 was a reason for delays in seeking care and providing treatment as well as alterations to treatment.

While our analyses do corroborate the perceptions of clinicians globally,^{8 12 13} the provision of paediatric oncology services have been adversely impacted by the COVID-19 pandemic, this has only affected a minority of patients receiving treatment. Most patients with paediatric cancer have continued to receive the standard of care that they would have received prior to the pandemic. This speaks to the adaptability and resilience of health-care systems and healthcare workers globally. Creation of new legislation,²¹ increasing utilisation of technology,²² and optimising the allocation of resources¹² are some of the commendable efforts that have mitigated the impact of the pandemic on patients with paediatric cancer. The benefits of these interventions could persist beyond the pandemic. The probability of this occurring is dependent on individuals, organisations dedicated to paediatric cancer care, and governments continuing to work collectively, interprofessionally and globally.

It should be noted that the impact of the COVID-19 pandemic on paediatric oncology services highlights

**Table 4** Reasons for the changes to the treatments

Reason for the change	Chemotherapy (N)	Radiotherapy (N)	Immunotherapy (N)	Surgery (N)
Decision making	85	10	3	35
Change in policy	47	5	2	26
Change in treatment plan by lead clinician	38	5	1	9
Infrastructure	78	9	2	53
Lockdown/travel restrictions	48	3	0	36
Lack of hospital beds	12	2	0	10
Lack of outpatient facilities for support	3	2	2	0
Lack of blood products	1	0	0	1
Lack of personal protective equipment	6	1	0	3
Lack of equipment to deliver the therapy	4	1	0	2
Lack of drugs	4	0	0	1
Workforce	13	1	0	5
Insufficient staff due to redeployment/restructuring	9	1	0	5
Insufficient staff due to sickness	4	0	0	0
Service delivery	12	3	0	15
Restructuring of services	3	1	0	4
Transfer to a different institution	9	2	0	11
Financing	3	3	0	3
Inability to pay	3	3	0	3
Patient factors	20	1	1	5
Patient/patient's family choose to avoid treatment due to the pandemic	18	1	1	4
Caregiver infected with COVID-19	2	0	0	1
Other	14	4	0	5
Patient has COVID-19	6	3	0	0

existing inequities in healthcare systems. Prior to the pandemic, children diagnosed with cancer in an HIC had a mean 5-year survival rate of 80%,^{1 20} whereby children in LMICs had a mean 5-year survival rates of 20%.¹ The discrepancy is due to delays in diagnosis,^{23 24} lack of access,²⁵ poor investment into services²⁶ and inadequate support for workforce development²⁷ in LMICs. Our results indicate the pandemic has exacerbated these issues: increasing delays, reducing access and diverting resources to other areas. While single centre studies have reported that the pandemic has caused delays to care in HICs,^{28 29} our results show these issues are principally affecting children in LMICs. These delays could adversely impact short-term outcomes with children in LMICs at

approximately 15 times the odds of dying, which is higher than figures reported prior to the pandemic.^{1 30} This disparity in mortality needs urgent attention from policy-makers and health advocates globally, especially given the lack of funding for childhood cancers in LMICs. In addition, our results suggest that the COVID-19 pandemic is contributing to the existing issue of treatment abandonment in LMICs.³¹ All in all, the pandemic has exacerbated pre-existing disparities, and clearly demonstrated that children in the poorest nations are once again being disproportionately affected.

It is also important to critically appraise our finding that patients with paediatric cancer who were COVID-19 positive postpresentation had an increased risk of death

at 30 days after presentation. A recent systematic review reported that children with cancer and COVID-19 do not have significantly different outcomes from children with cancer given the same standard of care.³² However, in this cohort study, the patients infected with COVID-19 were not provided the same standard of care as those who did not have the infection, as it was a reason for delaying treatment or changing treatment modalities. This was especially the case for surgical treatment, which may reflect the fact that guidance suggested delaying surgery if needed.¹¹ This underscores a problem unearthed by this study. The most common reason for children with cancer not being given their usual standard of care were changes in policy, lead clinician decision, and lockdown or travel restrictions. Changes may have been driven by the desire to reduce transmission of COVID-19 among patients with paediatric cancer, despite the fact that patients with paediatric cancer are not particularly vulnerable to COVID-19⁹ nor is there sufficient evidence that concurrent COVID-19 infection worsens outcomes.³² Given the response to the pandemic appears to have had a larger effect on care than direct effects of the pandemic itself, the impact of the pandemic on patients with paediatric cancer can be mitigated through policy changes occurring now.

This study did have limitations. As a cohort study, it only followed children through time who were diagnosed with cancer. However, there have been frequent reports that the pandemic has decreased the number of children being identified to have cancer.¹² Therefore, the impact of the COVID-19 pandemic may be greater than that outlined here, especially as the underdiagnosis of cancer is an established reason for the increased mortality of patients with paediatric cancer in LMICs.^{13 24} Furthermore, given existing difficulties in providing care for patients with paediatric cancer in LMICs, there is the possibility that patients who had alterations to their treatment during the COVID-19 pandemic may have had similar alterations if the pandemic had not occurred. To mitigate against this bias, we requested that all data collectors attest they have only submitted new issues brought about by the pandemic. Therefore, although we are not aware of a bias towards baseline gaps in service delivery, we cannot confirm that pre-existing issues with service provision and supply chains did not contribute to the disparity in care showcased by this study. Similarly, although we are aware that children with cancer are four times more likely to die in LMICs than in HICs,^{1 20} we do not have specific baseline data for the centres involved in our study as this is the first study of its kind for most participating LMIC centres. Furthermore, there was a disparity in the type of hospitals participating in this study between LMICs and HICs. Participating LMIC sites tended to be tertiary hospitals, while HIC sites included a larger mix of general hospitals, paediatric hospitals and paediatric oncology hospitals (online supplemental appendix S2). There is an inherent variability in capacity for cancer care between these hospital types.³³ The inclusion of hospitals in HICs

that were not specialised for the care of children with cancer may have resulted in an underestimation of the effect of the COVID-19 pandemic on this population in LMICs relative to HICs. In addition, there was an 18% lost to follow-up at 90 days, and those individuals may have been different from those who were included. Ultimately, over 1400 patients across 39 countries were followed up over 90 days, suggesting we are able to provide a comprehensive report of the global effect of this pandemic on paediatric oncology care. It should be noted, however, that there was an inequitable distribution of participants from HICs and LMICs. Approximately two-thirds of all participants were based in LMICs. However, given the historical lack of presence of individuals from LMICs in international studies, these data points provide a novel opportunity to assess global surgery related knowledge and the quality of global surgery care being offered.

This is the first large-series, geographically comprehensive, multicentre, international cohort study to explore the management of childhood cancers in low, middle and HICs across the globe during the COVID-19 pandemic. It illustrates the stark disparities that continue to exist in children's cancer care, and the multiple impacts that COVID-19 pandemic has had on healthcare systems across the globe. Our results underscore the need for a renewed assessment of resource requirements during this pandemic and the sharing of approaches that have minimised the negative effects on paediatric cancer care. This pandemic has become the defining crisis of our generation, and its ramifications may stretch beyond the acute crisis and have far reaching consequences for the future. Understanding its true impact, taking on key lessons and identifying vulnerabilities within health systems helps us develop solutions, which will also prove critical on our path towards equitable global paediatric oncology care.

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Acknowledgements Thank you to the University of Oxford Medical Sciences Division IT Services Systems Team (MSDIT Systems Team) for the REDCap administration and management. Thank you to the representatives from the College of Surgeons of Southern, East and Central Africa (COSECSA), the Global Children's Initiative for Surgery (GICS), the Pan-African Paediatric Surgical Association (PAPSA), the International Society of Paediatric Oncology (SIOP), and the International Society of Paediatric Surgical Oncology (IPSO) who made this study possible. Thank you to all our collaborators from our country leads to the members of our local mini-teams for driving this study forward.

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Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Map disclaimer The inclusion of any map (including the depiction of any boundaries therein), or of any geographic or locational reference, does not imply the expression of any opinion whatsoever on the part of BMJ concerning the legal status of any country, territory, jurisdiction or area or of its authorities. Any such expression remains solely that of the relevant source and is not endorsed by BMJ. Maps are provided without any warranty of any kind, either express or implied.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. Deidentified data will be shared on request.

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