BMJ Global Health

Twelve-month observational study of children with cancer in 41 countries during the COVID-19 pandemic

Global Health Research Group on Children's Non-Communicable Diseases Collaborative

To cite: Global Health Research Group on Children's Non-Communicable Diseases Collaborative. Twelve-month observational study of children with cancer in 41 countries during the COVID-19 pandemic. *BMJ Global Health* 2022;**7**:e008797. doi:10.1136/bmjgh-2022-008797

Handling editor Seye Abimbola

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgh-2022-008797).

Received 11 February 2022
Accepted 13 April 2022

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ABSTRACT

Introduction Childhood cancer is a leading cause of death. It is unclear whether the COVID-19 pandemic has impacted childhood cancer mortality. In this study, we aimed to establish all-cause mortality rates for childhood cancers during the COVID-19 pandemic and determine the factors associated with mortality.

Methods Prospective cohort study in 109 institutions in 41 countries. Inclusion criteria: children <18 years who were newly diagnosed with or undergoing active treatment for acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, Hodgkin lymphoma, retinoblastoma, Wilms tumour, glioma, osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, medulloblastoma and neuroblastoma. Of 2327 cases, 2118 patients were included in the study. The primary outcome measure was all-cause mortality at 30 days, 90 days and 12 months.

Results All-cause mortality was 3.4% (n=71/2084) at 30-day follow-up, 5.7% (n=113/1969) at 90-day follow-up and 13.0% (n=206/1581) at 12-month follow-up. The median time from diagnosis to multidisciplinary team (MDT) plan was longest in low-income countries (7 days, IQR 3–11). Multivariable analysis revealed several factors associated with 12-month mortality, including low-income (OR 6.99 (95% CI 2.49 to 19.68); p<0.001), lower middle income (OR 3.32 (95% CI 1.96 to 5.61); p<0.001) and upper middle income (OR 3.49 (95% CI 2.02 to 6.03); p<0.001) country status and chemotherapy (OR 0.55 (95% CI 0.36 to 0.86); p=0.008) and immunotherapy (OR 0.27 (95% CI 0.08 to 0.91); p=0.035) within 30 days from MDT plan. Multivariable analysis revealed laboratory-confirmed SARS-CoV-2 infection (OR 5.33 (95% CI 1.19 to 23.84); p=0.029) was associated with 30-day mortality.

Conclusions Children with cancer are more likely to die within 30 days if infected with SARS-CoV-2. However, timely treatment reduced odds of death. This report provides crucial information to balance the benefits of providing anticancer therapy against the risks of SARS-CoV-2 infection in children with cancer.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cancer is the leading cause of death by disease in children. Preliminary data, mostly in high-income countries, suggested that children with cancer and SARS-CoV-2 infection were not at increased risk of death compared with the general paediatric population.

WHAT THIS STUDY ADDS

⇒ This is the largest international cohort study to date to report COVID-19 and oncological outcomes for childhood cancers; the majority of participants were from lower income countries: a neglected group in existing studies. SARS-CoV-2 infection increased odds of death by 30 days, but not after 30 days. Participants in lower income countries had more overall complications, higher odds of starting palliative care and higher odds of death at all time points.

HOW THUS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given the longer term consequences of delaying treatment, it would be prudent to prioritise timely therapy where feasible. Reducing treatment delays has health and economic benefits and could save countless lives during the pandemic.

INTRODUCTION

In the 1960s, 5-year survival for childhood cancer globally was as low as 20%.[1] The introduction of chemotherapy tripled 5-year survival for childhood cancer in high-income countries (HICs).[2] Further advances in chemotherapy, radiotherapy, immunotherapy and surgery and the personalisation of treatment increased 5-year survival for childhood cancer in HICs to 80%.[3–5] Despite this, cancer remains the leading cause of death by disease in children in HICs.[6] The situation is bleaker in low and middle-income countries (LMICs). The 5-year survival for childhood cancer in LMICs collectively lies between 20% and 30%.[5 7 8] Even when considering LMICs with the highest 5-year survival for childhood cancer, survival is higher in HICs.[7 8] Absence of or inaccessibility to both effective diagnostics[9–11] and optimal care[12–15]

account for this inequity in childhood cancer outcomes and derive primarily from inadequate healthcare infrastructure and service delivery networks.[16–18] In recognition of this, the WHO launched the Global Initiative for Childhood Cancer (GICC) in 2018.[19] The GICC laid out a framework for all countries to reach at least 60% 5-year survival for children with the six most common childhood cancers globally by 2030: acute lymphoblastic leukaemia (ALL), Burkitt lymphoma, Hodgkin lymphoma, retinoblastoma, Wilms tumour and low-grade glioma.[19]

The year after the launch of the GICC, the SARS-CoV-2 responsible for the COVID-19 pandemic was detected.[20 21] Preliminary data from HICs suggested that children with cancer and SARS-CoV-2 infection were not at increased risk of mortality compared with the general paediatric population.[22] However, children from HICs are not representative of the majority of childhood cancers. More than 90% of children at risk of developing childhood cancer each year live in LMICs,[23] and they account for 95% of the mortality from cancer in this age group worldwide.[3 16] In the only global cohort study published to date including children with cancer and SARS-CoV-2 infection, the authors detected increased mortality and morbidity in children residing in LMICs.[24] However, it was unclear whether this increase in morbidity and mortality was related to infection status or changes in the standard of oncological care provided. Several cross-sectional studies have identified that the COVID-19 pandemic has substantially affected childhood cancer diagnosis and management worldwide, with its effect being more prominent in LMICs than HICs.[25 26]

In order to support frontline clinicians and governments in making data-driven decisions about the management of childhood cancers, it is critical to determine whether the increased morbidity and mortality documented in the recent cohort study[24] are due to SARS-CoV-2 infection or changes from normal standards of care. One of the challenges of paediatric cancer research is that it is a relatively small disease population.[2] To overcome this obstacle, multicentre studies are essential to generate statistically significant results. Given global studies published to date on childhood cancers during the COVID-19 pandemic have predominantly collected data from HICs, it is also critical to increase data collection from LMICs. However, given the extra pressures on clinicians currently—especially in LMICs—it is also imperative to reduce data collection burden by focussing on a subset of cancers; principally, those espoused by GICC. This study primarily aims to determine all-cause mortality rates for childhood cancers during the COVID-19 pandemic across LMICs and HICs. The secondary aim of the study is to determine the factors that influenced these outcomes including tumour-specific data, patient-specific demographics and changes to health system frameworks as outlined in the study protocol.[27]

METHODS

Study design and participants

This is a prospective cohort study with cases reported from 109 institutions in 41 countries (online supplemental appendix S2). Data was collected in the REDCap application hosted at the University of Oxford (Oxford, UK). Data were voluntarily reported for all children under the age of 18 years who were 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 inclusive. Eligible cancers were those identified by the GICC[19] and those deemed significant by LMIC collaborators: ALL, non-Hodgkin's lymphoma (including Burkitt lymphoma), Hodgkin lymphoma, retinoblastoma, Wilms tumour, glioma, sarcoma (osteosarcoma, Ewing sarcoma and rhabdomyosarcoma), medulloblastoma and neuroblastoma.[28] Participants who were 18 years or older were excluded to reduce confounding by care provided by adult cancer services. There were no centre-specific exclusion criteria. This study was reviewed by the University of Oxford institutional review board as not involving human participants, and no identifiable private information or biospecimens being provided. This study was subjected to approvals by local ethics committees according to local policy. Individual investigators (listed in online supplemental appendix S1) were responsible for assuring that participation was compliant with local regulations.

Procedures

Deidentified data were requested on a maximum of 112 variables (10 required responses) contained on eight forms. Baseline information was collected regarding the patient's age, weight, sex, American Society of Anaesthesiologists (ASA) grade and whether the patient was newly diagnosed with or undergoing active treatment for an eligible cancer between 12 March 2020 and 12 December 2020 inclusive. Participants 18 years or older and participant data outside of this data range were excluded. Where date of birth was unknown, the contributor of that data set was contacted to verify the patient was born in 2003 or later. Tumour-specific data were collected regarding diagnosis,[28] date of diagnosis, staging,[29] multidisciplinary team (MDT) decision date, what the MDT management plan was during the pandemic, and what the MDT plan would have been prior to the pandemic. The time from diagnosis to MDT decision date was calculated for each patient. Data were collected regarding the chemotherapy, radiotherapy, immunotherapy, surgery, and palliative care that patients received, any deviations from the MDT plan made during the pandemic, and any specific factors related to the COVID-19 pandemic that had driven these deviations. Outcomes collected included laboratory and clinical status of SARS-CoV-2 infection, complications within 30 days from anticancer treatment, interruptions in cancer-directed treatment and vital status. All terminology used were selected to be globally applicable and clinically relevant. Participant data could be collected

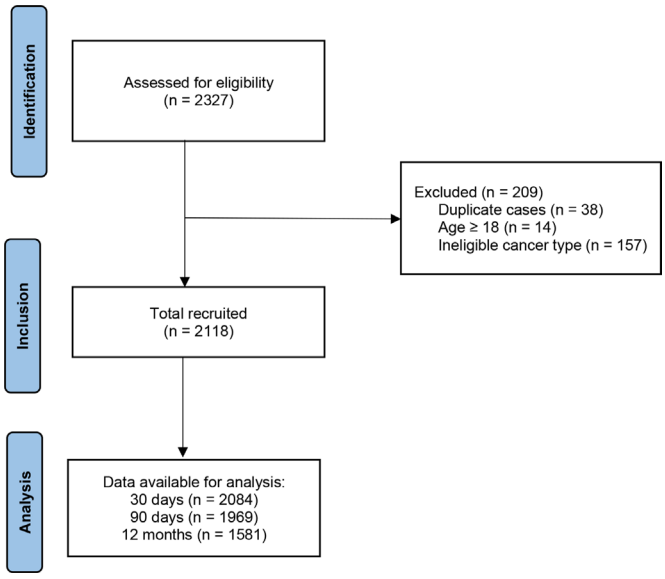

Figure 1 STROBE flowchart of participants in this study. STROBE, STrengthening the Reporting of OBservational studies in Epidemiology.

prospectively or retrospectively provided 30-day, 90-day and 12-month follow-up data were collected prospectively. Each institution that had reported at least a single case was requested to confirm that all institutional cases had been entered in an unbiased fashion as of the time of the final case entry by the institution. All cases corresponding to institutions that did not confirm unbiased data entry were excluded from analysis. Data validation was performed on a randomly selected subset (10%) of participating centres. A research checklist has been used to report the study (online supplemental appendix S3).

Statistical analysis

Descriptive statistics were used to summarise demographic and clinical characteristics and outcomes. 2021 World Bank designations for income groups—HICs, upper middle-income countries (UMICs), lower middle-income countries (LoMICs) and low-income countries (LICs)—were used to describe economic context.[30] The primary outcome measures were all-cause mortality at 30 days, 90 days and 12 months from MDT plan. Secondary outcomes were treatment modification, complications within 30 days of first anticancer treatment and SARS-CoV-2 infection status: cases were those confirmed by laboratory testing; cases without laboratory confirmation were classified as 'probably SARS-CoV-2'. Another secondary outcome was the health system framework factors affected by the COVID-19 pandemic, defined as one or more of the following: decision-making, infrastructure, workforce, service delivery, financing and patient factors. Comparison of proportions between groups was made with χ^2. The Kruskal-Wallis test and Dunn's post hoc test were used to compare medians between groups. Univariate logistic regression was used to examine the association between each outcome and patient characteristics. Multivariable logistic regression was used to explore the effect of factors that were significant (p<0·05) in univariate analyses for each outcome. All data analyses were done using STATA/IC V.16.1.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report.

RESULTS

Between 12 March 2020 and 12 December 2020, 2327 cases were identified. Of these 2327 cases, 209 were excluded from analyses (figure 1). Thirty-eight were duplicates of cases that had already been included into the study, 14 were 18 years or older and 157 were excluded based on cancer diagnosis eligibility. Of the remaining 2118 qualifying cases, 2084 (98.4%) completed 30-day follow-up, 1969 (93.0%) completed 90-day follow-up and 1581 (74.6%) completed 12-month follow-up. Clinical characteristics of the included patients by World Bank country income level are summarised in table 1. Most patients (n=1450/2118, 68.5%) were from LMICs, principally LoMICs (n=766/2118, 36.2%) (online supplemental appendix S4). The median age of patients included was 6 years (IQR 3–11), with 7.6% (n=161/2107) younger than 1 year and 8.7% (n=183/2107) aged 15–17 years, with age missing for 11 patients. 1244 (59.0%) of 2108 patients were men, with sex missing for 10 patients and one participant being inter-sex.

Data were available for 1215 patients who were newly diagnosed with cancer during the COVID-19 pandemic concerning the time from diagnosis to the time the initial MDT management plan was made. The median time from diagnosis to MDT plan varied across LICs (7 days, IQR 3–11; n=23), LoMICs (2 days, IQR 0–8; n=524), UMICs (1 day, IQR 0–9; n=348) and HICs (2 days, IQR 0–7; n=320). The Kruskal-Wallist test revealed a statistically significant difference in median time from diagnosis to MDT plan (χ^2=10.688, p=0.0135) between two or more of the income groups. Pairwise comparisons using Dunn's test indicated that the median time from diagnosis to MDT plan among LIC patients was significantly different from those of LoMIC (p=0.009), UMIC (p=0.002) and HIC (p=0.003) patients. Dunn's test also indicated that the median time from diagnosis to MDT plan among LoMIC patients was significantly different from those of UMIC (p=0.030) patients. No other differences were statistically significant at a significance level of 0.05.

The MDT plans made for all the participants are summarised in table 2. MDTs in HICs were observed to be significantly more likely to opt for chemotherapy (χ^2=7.462, p=0.006) and immunotherapy (χ^2=32.019, p<0.001) over no treatment compared with MDTs in LMICs. No other differences between HICs and LMICs were statistically significant at a significance level of 0.05. Among patients planned for chemotherapy

Table 1 Baseline characteristics by World Bank income group

	Low-income countries (N=36), n (%)	Lower-middle income countries (N=766), n (%)	Upper-middle income countries (N=648), n (%)	High-income countries (N=668), n (%)
Age (years), median (IQR)	4 (2.5, 7), 36 (100)	5 (3, 10), 761 (99.3)	6 (2, 11), 647 (99.8)	7 (3, 12), 663 (99.3)
Sex				
Female	15 (41.7)	277 (36.2)	296 (45.7)	275 (41.2)
Male	21 (58.3)	485 (63.3)	351 (54.2)	387 (57.9)
Intersex	0 (0)	0 (0)	0 (0)	1 (0.1)
Missing	0 (0)	4 (0.5)	1 (0.1)	5 (0.7)
Weight (kg), median (range)	17.7 (15.0, 27.75), 36 (100)	17.7 (12.0, 26.0), 741 (96.7)	20.3 (14.1, 35), 632 (97.5)	25 (16, 46.4), 648 (97.0)
American Society of Anesthesiologists (ASA) grade				
1—A normal healthy patient	2 (5.6)	198 (25.8)	169 (26.1)	107 (16.0)
2—A patient with mild systemic disease	21 (58.3)	218 (28.5)	377 (58.2)	259 (38.8)
3—A patient with severe systemic disease	8 (22.2)	132 (17.2)	90 (13.9)	267 (40.0)
4—A patient with severe systemic disease that is a constant threat to life	3 (8.3)	39 (5.1)	9 (1.4)	25 (3.7)
5—A moribund patient who is not expected to survive without an operation	2 (5.6)	6 (0.8)	2 (0.3)	1 (0.1)
Missing	0 (0)	173 (22.6)	1 (0.2)	9 (1.3)
Tumour type				
Acute lymphoblastic leukaemia	11 (30.6)	292 (38.1)	251 (38.7)	291 (43.6)
Ewing sarcoma	0 (0)	30 (3.9)	21 (3.2)	33 (4.9)
Glioma	1 (2.8)	30 (3.9)	57 (8.8)	79 (11.8)
Hodgkin lymphoma	3 (8.3)	48 (6.3)	30 (4.6)	43 (6.4)
Medulloblastoma	4 (11.1)	29 (3.8)	47 (7.3)	33 (4.9)
Neuroblastoma	4 (11.1)	48 (6.3)	45 (6.9)	61 (9.1)
Non-Hodgkin lymphoma	4 (11.1)	53 (6.9)	45 (6.9)	36 (5.4)
Osteosarcoma	0 (0.0)	24 (3.1)	37 (5.7)	28 (4.2)
Retinoblastoma	6 (16.7)	47 (6.1)	40 (6.2)	6 (0.9)
Rhabdomyosarcoma	1 (2.8)	47 (6.1)	25 (3.9)	30 (4.5)
Wilms tumour	2 (5.6)	118 (15.4)	50 (7.7)	28 (4.2)

by the MDT, there was a significant difference between the proportion of patients who had a central venous catheter inserted in two or more of the income groups (χ^2=479.287, p<0.001): 84.0% (n=489/582) in HICs, 61.1% (n=275/450) in UMICs, 24.9% (n=163/654) in LoMICs and 0.0% (n=0/31) in LICs. Of the 2118 participants, 20 (0.9%) would reportedly have had a different management plan if the MDT meeting had been held prior to the pandemic: 17 (85.0%) were based in LoMICs and 3 (15.0%) in UMICs.

There was a significant difference in laboratory testing for SARS-CoV-2 infection (χ^2=213.606, p<0.001) between HICs (n=362/635, 57.0%) and LMICs (n=318/1347, 23.6%). In LMICs, most patients were not screened for SARS-CoV-2 infection (n=719/1347, 53.4%). A minority of participants in LMICs underwent symptomatic screening (n=300/1347, 22.3%) or CT testing (n=10/1347, 0.7%). In HICs, 192 patients (30.2%) were not screened for SARS-CoV-2 infection. The remaining 81 patients in HICs (12.8%) underwent symptomatic screening only. Thirty-five patients were confirmed to be infected with SARS-CoV-2 following laboratory testing (HICs: 7; LMICS: 28), and 27 patients were suspected to probably have SARS-CoV-2 infection (HICs: 2; LMICs: 25).

A total of 212 patients (10.0%), 42 patients (2.0%), 5 patients (0.2%) and 98 patients (4.6%) were, respectively, reported to have had their chemotherapy, radiotherapy, immunotherapy and surgery care affected by the COVID-19 pandemic. In multivariable analysis, residing in an LMIC (OR 3.72 (95% CI 2.52 to 5.50)) was associated with increased odds of oncological care being affected by the COVID-19 pandemic. Online supplemental appendix S5 summarises the specific factors related to the COVID-19 pandemic that were reported to have affected cancer care. Of 2075 patients, 238 patients

Table 2 Treatments planned and received during the COVID-19 pandemic by World Bank income group

	Low-income countries % (n/N)	Lower-middle income countries % (n/N)	Upper-middle income countries % (n/N)	High-income countries % (n/N)
Multi-disciplinary team (MDT) management plan during the pandemic				
Chemotherapy	86.1 (31/36)	89.4 (685/766)	84.0 (544/648)	91.0 (608/668)
Radiotherapy	16.7 (6/36)	16.7 (128/766)	12.7 (82/648)	16.8 (112/668)
Immunotherapy	0.0 (0/36)	0.3 (2/766)	2.9 (19/648)	5.8 (39/668)
Surgery	30.6 (11/36)	31.9 (244/766)	33.0 (214/648)	28.6 (191/668)
Palliative care	8.3 (3/36)	0.8 (6/766)	0.5 (3/648)	0.6 (4/668)
MDT plan that would have been proposed prior to the pandemic				
Chemotherapy	86.1 (31/36)	90.2 (691/766)	83.8 (543/648)	91.0 (608/668)
Radiotherapy	16.7 (6/36)	17.1 (131/766)	12.8 (83/648)	16.8 (112/668)
Immunotherapy	0.0 (0/36)	0.5 (4/766)	2.9 (19/648)	5.8 (39/668)
Surgery	30.6 (11/36)	31.1 (238/766)	32.9 (213/648)	28.6 (191/668)
Palliative care	8.3 (3/36)	0.5 (4/766)	0.5 (3/648)	0.6 (4/668)
Treatment provided within 30 days for patients planned to have that treatment at MDT				
Chemotherapy	80.6 (25/31)	84.7 (559/660)	86.4 (389/450)	87.8 (496/565)
Radiotherapy	0.0 (0/6)	22.0 (28/127)	44.4 (20/45)	42.2 (43/102)
Immunotherapy	–	100.0 (2/2)	75.0 (12/16)	55.9 (19/34)
Surgery	18.2 (2/11)	27.6 (62/225)	36.4 (60/165)	36.4 (63/173)
Treatment provided within 90 days for patients planned to have that treatment at MDT				
Chemotherapy	80.6 (25/31)	88.9 (601/676)	88.7 (481/542)	91.3 (553/606)
Radiotherapy	0.0 (0/6)	48.0 (60/125)	39.0 (32/82)	46.8 (52/111)
Immunotherapy	–	100.0 (2/2)	89.5 (17/19)	69.2 (27/39)
Surgery	18.2 (2/11)	84.0 (110/131)	38.8 (83/214)	47.1 (89/189)
Treatment provided within 12 months for patients planned to have that treatment at MDT				
Chemotherapy	90.0 (27/30)	96.6 (625/647)	95.1 (504/530)	93.7 (562/600)
Radiotherapy	0.0 (0/6)	62.7 (69/110)	49.4 (40/81)	54.7 (58/106)
Immunotherapy	–	100.0 (2/2)	89.5 (17/19)	83.3 (30/36)
Surgery	45.5 (5/11)	75.7 (159/210)	66.0 (132/200)	64.0 (119/186)
Treatment provided within 12 months for all patients				
Chemotherapy	84.9 (28/33)	92.5 (649/702)	88.9 (552/621)	88.4 (577/653)
Radiotherapy	0.0 (0/30)	16.6 (93/560)	20.8 (119/571)	12.7 (76/599)
Immunotherapy	0.0 (0/30)	1.5 (8/547)	9.8 (54/551)	10.7 (64/597)
Surgery	22.6 (7/31)	37.2 (226/607)	34.6 (202/584)	33.7 (207/615)

(11.5%) were started on palliative care. 232 of these patients originally had treatment plans made at the initial MDT: 206 (14.6%) of 1413 participants in LMICs and 26 (3.9%) of 662 participants in HICs (χ2=51.502, p<0.001) (online supplemental appendix S6). Income group, age, sex, ASA grade, chemotherapy and radiotherapy within 30 days of the MDT, change in radiotherapy and surgery treatment due to the COVID-19 pandemic and tumour type were significantly associated with palliative treatment in univariate logistic regression analyses, whereas immunotherapy within 30 days of the MDT, surgery within 30 days of the MDT and SARS-CoV-2 infection status were not. In multivariable analysis, residing in an LIC (OR 27.13 (95% CI 12.7 to 58.6); p<0.001), an LoMIC (OR 3.29 (95% CI 2.10 to 5.17); p<0.001), and an UMIC (OR 4.82 (95% CI 3.09 to 7.51); p<0.001) were associated with increased odds of palliative care. Increasing age, male sex, ASA grade, radiotherapy within 30 days of the MDT and tumour type were also associated with increased odds of palliative care (table 3).

At 30 days, there were 71 (3.4%) deaths in this cohort with 66 deaths (4.6%) among 1427 participants in LMICs, and five deaths (0.8%) among 657 participants in HICs (χ^2=20.411, p<0.001). Income group, ASA grade, chemotherapy within 30 days of the MDT, SARS-CoV-2 infection status and tumour type were significantly associated with

Table 3 Results of univariate and multivariable analysis for palliative care

	Univariate analysis		Multivariable analysis (N=1706)	
	P value	Odds ratio (95% CI)	P value	Odds ratio (95% CI)
Income group				
High-income countries	Reference	1.0	Reference	1.0
Upper-middle income countries	<0.001	4.82 (3.09 to 7.51)	<0.001	7.52 (4.45 to 12.69)
Lower-middle income countries	<0.001	3.29 (2.10 to 5.17)	<0.001	5.09 (3.03 to 8.56)
Low-income countries	<0.001	27.3 (12.7 to 58.6)	<0.001	44.46 (19.15 to 103.23)
Age (for every year older)	0.004	1.04 (1.01 to 1.07)	0.001	1.06 (1.02 to 1.10)
Sex				
Female	Reference	1.0	Reference	1.0
Male	0.046	1.34 (1.01 to 1.77)	0.026	1.45 (1.04 to 2.00)
American Society of Anaesthesiologists (ASA) grade				
1	Reference	1.0	Reference	1.0
2	0.005	1.73 (1.18 to 2.55)	0.001	2.09 (1.34 to 3.26)
3	0.307	1.26 (0.81 to 1.96)	0.001	2.54 (1.48 to 4.36)
4	<0.001	4.27 (2.34 to 7.80)	<0.001	4.95 (2.43 to 10.09)
5	<0.001	9.32 (2.72 to 31.96)	0.011	5.99 (1.50 to 23.99)
Treatment provided within 30 days				
Chemotherapy	<0.001	0.43 (0.31 to 0.57)	0.119	0.74 (0.51 to 1.08)
Radiotherapy	<0.001	2.87 (1.93 to 4.28)	0.013	1.83 (1.14 to 2.96)
Immunotherapy	0.083	0.45 (0.18 to 1.11)	NA	NA
Surgery	0.683	1.09 (0.73 to 1.61)	NA	NA
Changes to treatment due to the COVID-19 pandemic				
Change to chemotherapy	0.123	1.38 (0.92 to 2.07)	NA	NA
Change to radiotherapy	0.038	2.22 (1.04 to 4.70)	0.808	0.90 (0.37 to 2.17)
Change to immunotherapy	NA	NA	NA	NA
Change to surgery	0.009	2.01 (1.19 to 3.39)	0.092	1.82 (0.91 to 3.66)
Tumour type				
Acute lymphoblastic leukaemia	Reference	1.0	Reference	1.0
Ewing sarcoma	0.473	1.35 (0.59 to 3.07)	0.559	1.31 (0.53 to 3.19)
Glioma	<0.001	3.97 (2.55 to 6.20)	<0.001	4.28 (2.40 to 7.62)
Hodgkin lymphoma	0.839	0.92 (0.43 to 1.98)	0.435	0.70 (0.29 to 1.70)
Medulloblastoma	<0.001	4.42 (2.67 to 7.30)	0.002	2.59 (1.40 to 4.79)
Neuroblastoma	0.010	2.00 (1.18 to 3.39)	0.013	2.22 (1.18 to 4.17)
Non-Hodgkin lymphoma	0.482	1.26 (0.66 to 2.41)	0.910	0.96 (0.46 to 2.00)
Osteosarcoma	<0.001	3.47 (1.94 to 6.22)	0.008	2.57 (1.28 to 5.13)
Retinoblastoma	0.474	1.31 (0.63 to 2.73)	0.933	0.96 (0.41 to 2.26)
Rhabdomyosarcoma	<0.001	2.77 (1.56 to 4.91)	0.002	2.84 (1.46 to 5.51)
Wilms tumour	0.301	1.34 (0.77 to 2.32)	0.237	1.48 (0.77 to 2.85)
SARS-CoV-2 infection status				
Not suspected or detected	Reference	1.0	NA	NA
Probable SARS-CoV-2 infection	0.534	1.40 (0.48 to 4.10)	NA	NA
Laboratory confirmed SARS-CoV-2 infection	0.938	1.04 (0.36 to 2.98)	NA	NA

death at 30 days (table 4). No other factors were statistically significant at a significance level of 0.05. Thirty-day complications from the various anticancer therapies are described in online supplemental appendix S7. At 90 days, there were 113 (5.7%) deaths in this cohort with 105 deaths (7.9%) among 1321 participants in LMICs,

Table 4 Univariate analysis and multivariable analysis of patient vital status at 30 days, 90 days and 12 months

	Univariate analysis		Multivariable analysis	
	P value	OR (95% CI)	P value	OR (95% CI)
Factors associated with death at 30 days				
Income group				
High-income countries	Reference	1.0	Reference	1.0
Upper-middle income countries	0.090	2.48 (0.87 to 7.07)	0.150	2.43 (0.72 to 8.15)
Lower-middle income countries	<0.001	8.36 (3.30 to 21.19)	<0.001	9.52 (3.46 to 26.20)
Low-income countries	<0.001	43.47 (13.64 to 138.52)	<0.001	39.79 (9.65 to 164.16)
Age (for every year older)	0.858	1.00 (0.95 to 1.05)	NA	NA
Sex				
Female	Reference	1.0	NA	NA
Male	0.961	0.99 (0.61 to 1.60)	NA	NA
Weight (for every kg heavier)	0.247	0.99 (0.98 to 1.01)	NA	NA
American Society of Anaesthesiologists (ASA) grade				
1	Reference	1.0	Reference	1.0
2	0.722	0.87 (0.39 to 1.92)	0.471	0.72 (0.29 to 1.77)
3	0.125	1.84 0.84 to 3.99)	0.077	2.27 (0.91 to 5.64)
4	<0.001	13.69 (5.98 to 31.34)	<0.001	8.93 (3.34 to 23.85)
5	<0.001	55.08 (14.39 to 210.78)	<0.001	30.75 (4.70 to 200.98)
Tumour type				
Acute lymphoblastic leukaemia	Reference	1.0	Reference	1.0
Ewing sarcoma	0.708	0.68 (0.09 to 5.19)	0.791	1.34 (0.15 to 11.65)
Glioma	0.003	3.52 (1.56 to 7.97)	0.106	2.55 (0.82 to 7.92)
Hodgkin lymphoma	NA (no deaths)	NA (no deaths)	NA (no deaths)	NA (no deaths)
Medulloblastoma	<0.001	7.92 (3.71 to 16.90)	0.001	6.33 (2.22 to 18.04)
Neuroblastoma	0.044	2.56 (1.03 to 6.39)	0.560	1.43 (0.43 to 4.81)
Non-Hodgkin lymphoma	0.001	3.95 (1.69 to 9.22)	0.047	3.12 (1.01 to 9.62)
Osteosarcoma	0.657	0.63 (0.08 to 4.83)	0.703	1.51 (0.18 to 12.80)
Retinoblastoma	0.040	2.95 (1.05 to 8.30)	0.563	1.54 (0.36 to 6.69)
Rhabdomyosarcoma	0.044	2.89 (1.03 to 8.12)	0.069	3.01 (0.92 to 9.89)
Wilms tumour	0.764	1.19 (0.39 to 3.62)	0.807	0.85 (0.24 to 3.07)
Treatment provided within 30 days				
Chemotherapy	<0.001	0.20 (0.12 to 0.32)	0.002	0.35 (0.18 to 0.69)
Radiotherapy	0.466	1.35 (0.60 to 3.00)	NA	NA
Immunotherapy	NA (no deaths)	NA (no deaths)	NA (no deaths)	NA (no deaths)
Surgery	0.644	0.84 (0.40 to 1.77)	NA	NA
Changes to treatment due to the COVID-19 pandemic				
Change to chemotherapy	0.961	0.98 (0.44 to 2.17)	NA	NA
Change to radiotherapy	0.149	2.42 (0.73 to 8.06)	NA	NA
Change to immunotherapy	NA (no deaths)	NA (no deaths)	NA (no deaths)	NA (no deaths)
Change to surgery	0.278	1.68 (0.66 to 4.27)	NA	NA
SARS-CoV-2 infection status				
Not suspected or detected	Reference	1.0	Reference	1.0
Probable SARS-CoV-2 infection	<0.001	7.40 (2.70 to 20.25)	0.002	8.40 (2.23 to 31.58)
Laboratory confirmed SARS-CoV-2 infection	0.071	3.05 (0.91 to 10.26)	0.029	5.33 (1.19 to 23.84)
Factors associated with death at 90 days				
Income group				
High-income countries	Reference	1.0	Reference	1.0
Upper-middle income countries	<0.001	5.43 (2.52 to 11.70)	<0.001	6.12 (2.71 to 13.81)
Lower-middle income countries	<0.001	7.42 (3.51 to 15.69)	<0.001	10.19 (4.52 to 22.97)

Continued

Table 4 Continued

	Univariate analysis		Multivariable analysis	
	P value	OR (95% CI)	P value	OR (95% CI)
Low-income countries	<0.001	31.30 (11.07 to 88.50)	<0.001	23.94 (7.06 to 81.21)
Age (for every year older)	0.870	1.00 (0.97 to 1.04)	NA	NA
Sex				
Female	Reference	1.0	Reference	1.0
Male	0.595	0.90 (0.61 to 1.32)	NA	NA
Weight (for every kg heavier)	0.284	0.99 (0.98 to 1.01)	NA	NA
American Society of Anaesthesiologists (ASA) grade				
1	Reference	1.0	Reference	1.0
2	0.013	2.34 (1.20 to 4.55)	0.021	2.32 (1.14 to 4.73)
3	0.023	2.29 (1.12 to 4.67)	0.002	3.36 (1.56 to 7.21)
4	<0.001	12.61 (5.60 to 28.40)	<0.001	9.59 (3.78 to 24.32)
5	<0.001	75.64 (16.71 to 342.28)	<0.001	29.39 (5.02 to 172.07)
Tumour type				
Acute lymphoblastic leukaemia	Reference	1.0	Reference	1.0
Ewing sarcoma	0.580	0.66 (0.16 to 2.83)	0.519	1.65 (0.36 to 7.47)
Glioma	0.015	2.31 (1.17 to 4.53)	0.029	2.76 (1.11 to 6.86)
Hodgkin lymphoma	NA (no deaths)	NA (no deaths)	NA (no deaths)	NA (no deaths)
Medulloblastoma	<0.001	5.30 (2.84 to 9.89)	<0.001	4.30 (1.92 to 9.65)
Neuroblastoma	0.003	2.77 (1.43 to 5.36)	0.002	3.37 (1.57 to 7.23)
Non-Hodgkin lymphoma	0.013	2.48 (1.21 to 5.08)	0.091	2.11 (0.89 to 5.02)
Osteosarcoma	0.320	1.64 (0.62 to 4.34)	0.042	3.04 (1.04 to 8.87)
Retinoblastoma	0.183	1.85 (0.75 to 4.57)	0.988	1.01 (0.32 to 3.13)
Rhabdomyosarcoma	0.053	2.32 (0.99 to 5.47)	0.087	2.30 (0.89 to 5.95)
Wilms tumour	0.837	1.09 (0.47 to 2.53)	0.911	1.05 (0.42 to 2.61)
Treatment provided within 90 days				
Chemotherapy	<0.001	0.26 (0.17 to 0.39)	0.002	0.42 (0.24 to 0.73)
Radiotherapy	0.642	0.86 (0.47 to 1.60)	NA	NA
Immunotherapy	NA (no deaths)	NA (no deaths)	NA (no deaths)	NA (no deaths)
Surgery	0.015	0.48 (0.27 to 0.87)	0.001	0.32 (0.16 to 0.65)
Changes to treatment due to the COVID-19 pandemic				
Change to chemotherapy	0.467	1.25 (0.69 to 2.27)	NA	NA
Change to radiotherapy	0.026	3.02 (1.14 to 7.98)	0.728	1.23 (0.39 to 3.90)
Change to immunotherapy	NA (no deaths)	NA (no deaths)	NA (no deaths)	NA (no deaths)
Change to surgery	0.059	2.00 (0.97 to 4.10)	NA	NA
SARS-CoV-2 infection status				
Not suspected or detected	Reference	1.0	Reference	1.0
Probable SARS-CoV-2 infection	0.002	4.95 (1.80 to 13.60)	0.018	3.90 (1.26 to 12.09)
Laboratory confirmed SARS-CoV-2 infection	0.403	1.67 (0.50 to 5.55)	0.467	1.64 (0.43 to 6.28)
Factors associated with death at 12 months				
Income group				
High-income countries	Reference	1.0	Reference	1.0
Upper-middle income countries	<0.001	2.22 (1.44 to 3.41)	<0.001	3.49 (2.02 to 6.03)
Lower-middle income countries	<0.001	2.78 (1.82 to 4.26)	<0.001	3.32(1.96 to 5.61)
Low-income countries	<0.001	6.58 (2.86 to 15.15)	<0.001	6.99 (2.49 to 19.68)
Age (for every year older)	0.226	1.02 (0.99 to 1.05)	NA	NA
Sex				
Female	Reference	1.0	Reference	1.0
Male	0.694	1.06 (0.79 to 1.43)	NA	NA

Continued

Table 4 Continued

	Univariate analysis		Multivariable analysis	
	P value	OR (95% CI)	P value	OR (95% CI)
Weight (for every kg heavier)	0.874	1.00 (0.99 to 1.01)	NA	NA
American Society of Anaesthesiologists (ASA) grade				
1	Reference	1.0	Reference	1.0
2	0.632	1.11 (0.72 to 1.71)	0.211	1.37 (0.83 to 2.26)
3	0.044	1.62 (1.01 to 2.59)	<0.001	3.24 (1.81 to 5.79)
4	<0.001	5.34 (2.78 to 10.27)	<0.001	6.58 (3.03 to 14.26)
5	<0.001	26.72 (5.18 to 137.95)	0.002	17.51 (2.87 to 106.80)
Tumour type				
Acute lymphoblastic leukaemia	Reference	1.0	Reference	1.0
Ewing sarcoma	0.106	1.93 (0.87 to 4.28)	0.133	2.01 (0.81 to 4.99)
Glioma	<0.001	3.71 (2.21 to 6.24)	0.003	2.87 (1.45 to 5.70)
Hodgkin lymphoma	0.067	0.26 (0.06 to 1.10)	–	–
Medulloblastoma	<0.001	3.97 (2.30 to 6.86)	0.040	2.12 (1.03 to 4.33)
Neuroblastoma	<0.001	3.42 (2.04 to 5.73)	<0.001	3.26 (1.80 to 5.90)
Non-Hodgkin lymphoma	0.015	2.10 (1.16 to 3.83)	0.224	1.58 (0.76 to 3.32)
Osteosarcoma	<0.001	3.69 (1.94 to 7.02)	<0.001	4.54 (2.18 to 9.47)
Retinoblastoma	0.356	1.45 (0.66 to 3.17)	0.724	0.84 (0.31 to 2.25)
Rhabdomyosarcoma	<0.001	3.38 (1.75 to 6.50)	0.054	2.18 (0.99 to 4.80)
Wilms tumour	0.453	1.29 (0.67 to 2.48)	0.942	1.03 (0.47 to 2.25)
Treatment provided within 30 days				
Chemotherapy	<0.001	0.36 (0.25 to 0.49)	0.008	0.55 (0.36 to 0.86)
Radiotherapy	0.002	2.03 (1.29 to 3.21)	0.069	1.68 (0.96 to 2.94)
Immunotherapy	0.036	0.29 (0.09 to 0.92)	0.035	0.27 (0.08 to 0.91)
Surgery	0.589	0.88 (0.55 to 1.40)	NA	NA
Treatment provided within 90 days				
Chemotherapy	<0.001	0.32 (0.23 to 0.45)	NA	NA (co-linearity)
Radiotherapy	0.020	1.60 (1.08 to 2.37)	NA	NA (co-linearity)
Immunotherapy	0.082	0.47 (0.20 to 1.10)	NA	NA
Surgery	0.777	0.95 (0.65 to 1.38)	NA	NA
Changes to treatment due to the COVID-19 pandemic				
Change to chemotherapy	0.555	1.15 (0.72 to 1.86)	NA	NA
Change to radiotherapy	0.001	4.08 (1.84 to 9.03)	0.403	1.50 (0.58 to 3.92)
Change to immunotherapy	NA (no deaths)	NA (no deaths)	NA (no deaths)	NA (no deaths)
Change to surgery	0.343	1.38 (0.71 to 2.68)	NA	NA
SARS-CoV-2 infection status				
Not suspected or detected	Reference	1.0	Reference	1.0
Probable SARS-CoV-2 infection	0.033	2.84 (1.09 to 7.42)	0.110	2.35 (0.82 to 6.72)
Laboratory confirmed SARS-CoV-2 infection	0.248	1.71 (0.69 to 4.21)	0.449	1.51 (0.52 to 4.36)

and 8 deaths (1.2%) among 648 participants in HICs (χ^2=36.226, p<0.001). Income group, ASA grade, chemotherapy within 90 days of the MDT, surgery within 90 days of the MDT, and tumour type were significantly associated with death at 90 days. At 12 months, there were 206 (13.0%) deaths in this cohort with 174 deaths (15.7%) among 1107 participants in LMICs, and 32 deaths (6.8%) among 474 participants in HICs (χ2=23.550, p<0.001). Income group, ASA grade, chemotherapy within 30 days of the MDT, immunotherapy within 30 days of the MDT and tumour type were significantly associated with death at 12 months.

DISCUSSION

This is the largest international cohort study to date to report COVID-19 outcomes for childhood cancers. We have shown that during the COVID-19 pandemic, children with cancer are more likely to die within 30 days if infected with SARS-CoV-2, even when adjusting for changes from normal

standards of oncological care. However, the timely administration of chemotherapy is significantly associated with reduced odds of death at 30 days, 90 days and 12 months. Similar significant associations exist between timely surgery and reduced odds of death at 90 days, and timely administration of immunotherapy and reduced odds of death at 12 months. This report provides crucial information for public health policymakers to balance the benefits of providing anticancer therapy against the risks of SARS-CoV-2 infection in children with cancer.

During the COVID-19 pandemic, studies investigating COVID-19 outcomes for cancer patients have typically used 30-day mortality.[24 31–34] The 30-day mortality from our study was 3.4% (n=71/2084). This is similar to the 30-day mortality reported by the Mukkada *et al* study: 3.8%. Their population of interest was children with cancer and SARS-CoV-2 infection. Their marginally higher death rate may reflect the impact of SARS-CoV-2 infection. Equally the high death rate observed in our study may be due to the impact of having a majority of participants from LMICs: to our knowledge, a first for global cohort studies on childhood cancers. Children with cancer in LMICs have historically had lower 5-year survival compared with their HIC counterparts.,[5 7 8] and residence in LMICs is a factor that has been shown in our study to be associated with an increased odds of death at 30 days (4.6%), 90 days (7.9%) and 12 months (15.7%).

Of note, the 30-day mortality figure in our study is substantially lower than the 24% to 30.6% 30-day mortality reported among adult cancer patients during the COVID-19 pandemic.[31–34] This may reflect the lower risk of death in children compared with adults infected with SARS-CoV-2.[35] However, 30-day mortality figures for adults with cancer prior to the pandemic ranged from 3% to 10.6%.[36–38] Therefore, there may have been a higher mortality rate at baseline in adults compared with children; comparable 30-day mortality figures for childhood cancers prior to the pandemic have not—to our knowledge—been published. A high 30-day mortality rate may reflect the aggressiveness of certain adult cancers; however, studies to date have highlighted lack of timely anticancer treatment to be a significant causative factor in driving the high rate of mortality in adult cancers.[36–38] The use of 30-day mortality is increasingly recognised as a novel indicator to monitor quality of care in adult cancer treatment.[36 37 39 40] However, this transition has yet to be made for childhood cancers, where there is a focus on using 5-year survival data.[2] Gathering a sufficient sample from one centre or even one country can take up to 5 years,[2] with an estimated additional 6 years required to formally publish mature 5-year survival data,[41–43] and an average delay of 17 years before the findings is translated into clinical practice.[44] Utilising 30-day mortality may reduce the time taken to recruit, conduct and disseminate the findings from a study. Our study shows that 30-day mortality is significantly different between LMICs and HICs, and this metric can identify patient-specific and system-specific factors associated with mortality. Therefore, the utility of 30-day mortality may extend beyond that of the pandemic as a useful indicator of quality of care in childhood cancer treatment internationally. This comes with a caveat, however, that using 30-day mortality figures that are focused on only one setting may not give a true reflection of the quality of childhood cancer treatment, for example, a hospital-focused 30-day mortality figure may increase if children who would otherwise die at home (with no palliative care) start to be brought in to hospital.

In addition, our study showed that 90-day mortality and 12-month mortality are also significantly different between LMICs and HICs. Therefore, they may prove to be other useful indicators of quality of care for WHO and GICC to monitor the progress of cancer care in LMICs. Of note, SARS-CoV-2 infection was not significantly associated with mortality at 90 days or 12 months. Given the association with 30-day mortality, this could suggest that SARS-CoV-2 infection accelerates mortality among vulnerable children with cancer, but ultimately does not change long-term mortality trends in childhood cancers. However, it is important to note that only a minority of patients underwent laboratory testing for SARS-CoV-2 infection, especially in LMICs, and, therefore, there may be an under-reporting of SARS-CoV-2 infection in our cohort, which could be leading to a misclassification bias affecting the results. Since laboratory testing only occurred for a minority of participants in LMICs, the higher odds of death among patients designated to have 'Probable SARS-CoV-2 infection' may be both a reflection of the impact of SARS-CoV-2 infection and infrastructural issues. Furthermore, SARS-CoV-2 infection was only recorded if it occurred within 30 days of starting anticancer therapy. Patients may have gone onto become infected with SARS-CoV-2 after 30 days, which may account in part for the increase in mortality seen in 90 days and 12 months. The absence of published 90-day and 12-month mortality figures for childhood cancers prior to the pandemic renders this difficult to ascertain. With increasing international attention on scaling-up testing for SARS-CoV-2 infection,[45] future studies can address these uncertainties.

A significant strength of this study is that it is the first international study that has been designed and powered to detect if changes from normal standards of care due to the COVID-19 pandemic have impacted outcomes in childhood cancers. A total of 201 patients (9.5%) reportedly had their care affected because of the COVID-19 pandemic. However, changes to treatment due to the COVID-19 pandemic were not significantly associated with mortality at 30 days, 90 days or 12 months. Yet, delays in treatment—regardless of the underlying reason behind them—were associated with an increased odd of death. Patients in HICs had the fastest average time from diagnosis to initial MDT management plan being made, were more likely to have a central venous catheter inserted on a chemotherapy plan being made and were more likely to have planned anticancer therapy treatment within 30 days and 90 days. These factors may be playing a role in patients in HICs having lower odds of mortality at 30 days, 90 days and 12 months. Tackling the time-lags between diagnosis and treatment are cost-effective interventions for childhood cancers.[18] It is critical that interventions here focus on the unique challenges posed by each

LMIC, as extrapolation of cancer control programme experiences in HICs to LMICs is inappropriate without considering local resources and cultures.[46 47]

There are several potential limitations to consider when interpreting our results. First, clinicians were tasked with determining whether a change to treatment was due to the COVID-19 pandemic. It is possible that response bias might have led to clinicians accounting any change to the COVID-19 pandemic. 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. Second, 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.[48] 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—including the disruptions to care—on this population in LMICs relative to HICs. Third, due to the inability to capture socioeconomic status and ethnicity consistently across a global cohort, we were unable to ascertain the effects of these factors on outcomes. Fourth, due to global data privacy rules and the need to collect this data urgently due to a new infectious threat, no patient reported outcome measures were collected. Fifth, there may have been selection bias from the type of participants lost to follow-up. Sixth, given the small number of children in the study who had laboratory-confirmed SARS-CoV-2 infection or who were started on immunotherapy, the effect sizes for these variables may not reflect a true effect (ie, the findings may be false positives). Finally, this study was unable to collect data from patients who failed to reach a healthcare service provider, and, therefore, it might not reflect the true impact of the pandemic on oncological outcomes.

Childhood cancer is a highly curable disease when healthcare systems provide timely, accurate diagnoses and appropriate therapy. In our study, we have shown for the first time that paediatric cancer survival rate is significantly lower in the short term in LMICs than in HICs. This disparity may be due to health system challenges such as limited access to early detection and lack of effective treatment and care.

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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Contributors This is a paper produced under a collaborative authorship model: Global Health Research Group on Children's Non-Communicable Diseases Collaborative. All authors are solely listed under the collaborative authorship. A full authorship list can be found in Appendix S2. KL is the author acting as gurantor.

Funding Donation from the Kids Operating Room Research Fund.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval All participating centres have gained study approval to participate according to their local institutional ethical regulations. Examples of ethical approval: Brunei Medical and Health Research & Ethics Committee (MHREC/MOH/2020/14(2); Yale Human Research Protection Program Institutional Review Board (2000028852); and Tanta University Research Ethics Committee (33965/7/20).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

Author note The reflexivity statement for this paper is linked as an online supplemental file 1.

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