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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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 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.\textsuperscript{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.\textsuperscript{1,4} More than 90\% of these deaths occur in low-income and middle-income countries (LMICs).\textsuperscript{4} The inordinately high number of person-years of life lost make paediatric cancer care a global health priority.\textsuperscript{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.\textsuperscript{5-8} 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 refuted\textsuperscript{9} with the largest study to date on this topic identifying only 259 children with cancer suffering from severe COVID-19 infection worldwide.\textsuperscript{10} The international paediatric cancer community swiftly adapted their guidance to emphasise the importance of continuing care for patients with paediatric cancer.\textsuperscript{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.\textsuperscript{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.\textsuperscript{8,14}

As all international analyses reported thus far have been cross-sectional studies focused on the perceptions of clinicians,\textsuperscript{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.\textsuperscript{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.

\section*{METHODS}

\subsection*{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.\textsuperscript{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 studies\textsuperscript{17} (online supplemental appendix S6).

\subsection*{Study setting}

Hospitals or cancer centres in all continents providing cancer treatment to paediatric patients were eligible to participate in this study.\textsuperscript{16} The World Bank classification of the fiscal year of 2021 was utilised to categorise centres as HIC or LMIC.\textsuperscript{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.

\subsection*{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 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 Wilms’ 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
Table 1  Baseline characteristics

| Variable                                      | LMICs (N=1104) | HICs (N=556) | Total (N=1660) | 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)**               |                |              |                | <0.001  |
|                                               | 18.0 (13.0–29.0) | 27.1 (16.8–49.1) | 20.0 (14.0–35.0) |         |
| **ASA grade**                                 |                |              |                | <0.001  |
| (1a) Normal healthy patient                   | 344 (31.2)     | 101 (18.2)   | 445 (26.8)     |         |
| (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**                               |                |              |                | <0.001  |
| Non-Hodgkin's lymphoma                        | 89 (8.1)       | 29 (5.2)     | 118 (7.1)      |         |
| 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?**           |                |              |                | <0.001  |
| No                                           | 631 (57.2)     | 148 (26.6)   | 779 (46.9)     |         |
| 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?**      |                |              |                | 0.004   |
| No                                           | 943 (85.4)     | 519 (93.3)   | 1462 (88.1)    |         |
| Yes                                          | 167 (14.6)     | 107 (16.7)   | 274 (16.9)     |         |
| Missing                                       | 106 (9.6)      | 42 (7.6)     | 148 (8.9)      |         |
| **Was patient tested for COVID-19?**           |                |              |                | <0.001  |
| No                                           | 631 (57.2)     | 148 (26.6)   | 779 (46.9)     |         |
| Yes                                          | 367 (33.2)     | 366 (65.8)   | 733 (44.2)     |         |
| Missing                                       | 106 (9.6)      | 42 (7.6)     | 148 (8.9)      |         |

Continued
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 positive 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), rhabdosarcoma (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 rhabdosarcoma (n=1). Relative to patients with paediatric cancer in LMICs, 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.

**Table 1** Continued

| Variable | LMICs (N=1104) | HICs (N=556) | Total (N=1660) | 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.
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), rhabdosarcoma (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 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 2  Thirty-day and 90-day mortality

|                     | LMICs (N=1104) | HICs (N=556) | P value |
|---------------------|----------------|--------------|---------|
|                     | Alive          | Dead         | Unknown |
| 30-day mortality    | 1006 (91.1%)   | 45 (4.1%)    | 53 (4.8%) |
|                     |                | 2 (0.4%)     |          |
| 90-day mortality    | 878 (79.5%)    | 66 (6.0%)    | 160 (14.5%) |
|                     | 524 (94.2%)    | 5 (0.9%)     | 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), rhabdosarcoma (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 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  |
| COVID Status (Reference: COVID negative) |       |           |         |
| Not applicable (No anti-cancer treatment given post March 11th 2020) | 0.62  | 0.08 to 4.73 | 0.642   |
| 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.
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 (15.6%) 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, and 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, one child in an LMIC had their planned immunotherapy cancelled, and two and five 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, and 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 been 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 pre-pandemic figures of children in LMICs being four times more likely to die. 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, 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 healthcare systems and healthcare workers globally. Creation of new legislation, increasing utilisation of technology, and optimising the allocation of resources 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...
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 policymakers 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.

| 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          |
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% loss 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 comprehensively, multicentre, international cohort study to explore the management of childhood cancers in low, middle and high-income countries 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 requirement resources 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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