

# 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

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

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## Correspondence to

Global Health Research Group on Children's Non-Communicable Diseases Collaborative;  
info@globalchildrenncds.com

## 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.<sup>1–4</sup> Cancers in the paediatric population differ greatly from those in adults, particularly in the diagnoses seen and the availability of suitable healthcare.<sup>5</sup> Fewer than 20% of all paediatric cancers are found in high-income countries (HICs), where multimodal



care is more accessible.<sup>2</sup> 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.<sup>1–4</sup> More than 90% of these deaths occur in low-income and middle-income countries (LMICs).<sup>4</sup> The inordinately high number of person-years of life lost make paediatric cancer care a global health priority.<sup>2</sup>

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.<sup>6–8</sup> 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<sup>9</sup> with the largest study to date on this topic identifying only 259 children with cancer suffering from severe COVID-19 infection worldwide.<sup>10</sup> The international paediatric cancer community swiftly adapted their guidance to emphasise the importance of continuing care for patients with paediatric cancer.<sup>11</sup> 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.<sup>8 12 13</sup> 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.<sup>8 14</sup>

As all international analyses reported thus far have been cross-sectional studies focused on the perceptions of clinicians,<sup>8 12 13</sup> 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.<sup>15</sup> 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.<sup>16</sup> 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<sup>17</sup> (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.<sup>16</sup> The World Bank classification of the fiscal year of 2021 was utilised to categorise centres as HIC or LMIC.<sup>18</sup> 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.<sup>16</sup>

### 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.<sup>16</sup> 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.<sup>19</sup> 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

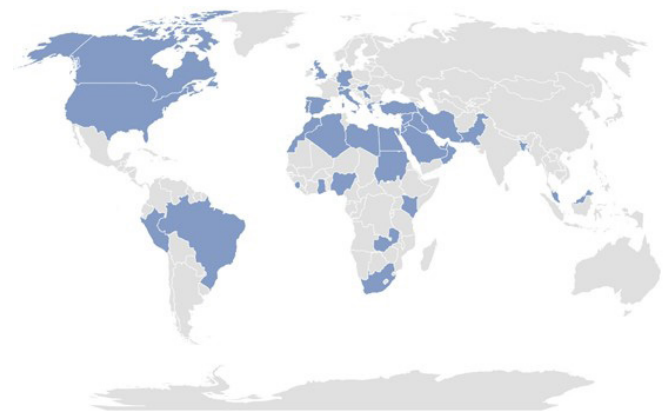
LMIC and HIC countries are presented as proportions or mean (SD) or median (range) and statistical differences were determined using a chi-square test or Fisher's exact test. Statistical differences in 30-day and 90-day mortality between LMICs and HICs were determined using Fisher's exact test due to 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<br>(N=1104)<br>N (%) | HICs<br>(N=556)<br>N (%) | Total<br>(N=1660)<br>N (%) | P value |            |        |
|--------------------------------------|--|----------------------------|--------------------------|----------------------------|---------|------------|--------|
| Age (years),<br>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),<br>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 <sup>th</sup> 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<br>(N=1104)<br>N (%) | HICs<br>(N=556)<br>N (%) | Total<br>(N=1660)<br>N (%) | P value |
|----------|----------------------------|--------------------------|----------------------------|---------|
| Missing  | 40 (3.6)                   | 6 (1.1)                  | 46 (2.8)                   |         |

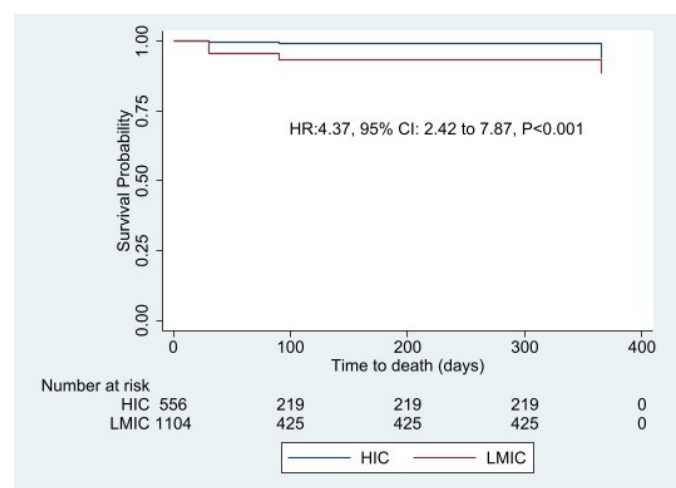
ASA, American Society of Anesthesiologists; HICs, high-income countries; LMICs, low-income and middle-income countries.

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<br>(N=1104)<br>N (%) | HICs<br>(N=556)<br>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

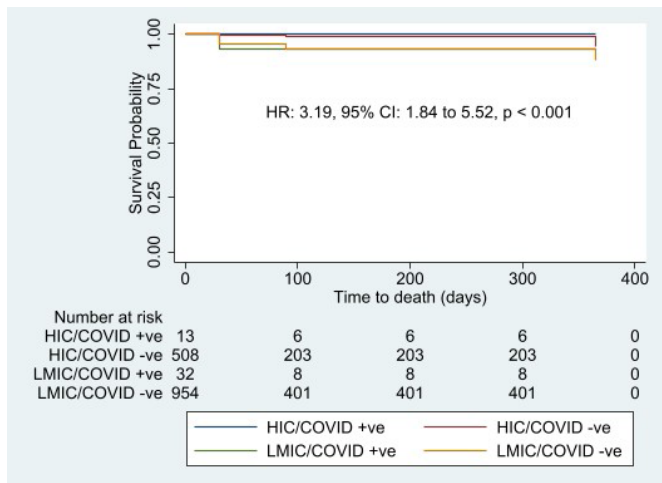
22.8 times the odds of death at 30 days after presentation (table 3 and figure 3).

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<br>(Reference: HIC)         | LMIC   | 15.6  | 3.7 to 65.8     | <0.001  |
|  | Not applicable (No anti-cancer treatment given post March 11 <sup>th</sup> 2020) | 0.62  | 0.08 to 4.73    | 0.642   |
| COVID Status<br>(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<br>(Reference: no anticancer therapy)   | Provide anticancer therapy   | 7.69  | 1.37 to 43.3    | 0.021   |
| Was the first admission planned?<br>(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<sup>1 20</sup> 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,<sup>8 12 13</sup> 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,<sup>21</sup> increasing utilisation of technology,<sup>22</sup> and optimising the allocation of resources<sup>12</sup> 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%,<sup>1 20</sup> whereby children in LMICs had a mean 5-year survival rates of 20%.<sup>1</sup> The discrepancy is due to delays in diagnosis,<sup>23 24</sup> lack of access,<sup>25</sup> poor investment into services<sup>26</sup> and inadequate support for workforce development<sup>27</sup> 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,<sup>28 29</sup> 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.<sup>1 30</sup> 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.<sup>31</sup> 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.<sup>32</sup> 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.<sup>11</sup> 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-19<sup>9</sup> nor is there sufficient evidence that concurrent COVID-19 infection worsens outcomes.<sup>32</sup> 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.<sup>12</sup> 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.<sup>13 24</sup> 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,<sup>1 20</sup> 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.<sup>33</sup> 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.

**Twitter** Global Health Research Group on Children's Non-Communicable Diseases Collaborative @GlobalChildNCDs

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**Collaborators** Steering committee: Soham Bandyopadhyay [UK], Noel Peter [UK] (Asia Lead), Kokila Lakhoo [UK], Simone de Campos Vieira Abib [Brazil] (South America Lead), Hafeez Abdelhafeez [Sudan] (Africa and Middle East Lead), Shaun Wilson [UK] (Australasia Lead), Max Pacht [UK] (Europe and North America Lead), Benjamin Martin [UK] (Europe Lead), Sonal Nagras [Australia] (Australasia Lead), and Mihir Sheth [India] Operational committee: Soham Bandyopadhyay [UK], Catherine Dominic [UK], Suraj Gandhi [UK], Divya Parwani [India], Rhea Raj [UAE], Diella Munezero [Burundi], Rohini Dutta [India], Nsimire Mulanga Roseline [DRC], Kellie McClafferty [UK], Armin Nazari [UK], Smriti Sriram [UK], Sai Pillarisetti [UK], King-David Nweze [UK], Aishwarya Ashwinee [Grenada], Gul Kalra [India], Poorvaprabha Patil [India], Priyansh Nathani [India], Khushman Kaur Bhullar [India], Muhammed Elhadi [Libya], Maryam Khan [Pakistan], Nehal Rahim [Pakistan], Shweta Madhusudan [UK], Joshua Erhabor [UK], Manasi Shirke [UK], Aishah Mughal [UK], Darica Au [UK], Mahan Salehi [UK], Sravani Royyuru [UK], Mohamed Ahmed [Egypt], Syeda Namayah Fatima Hussain [Pakistan], Daniel Robinson [UK],

- Anna Casey [UK], Mehdi Khan [UK], Alexandre Dukundane [Rwanda], Kwizera Festus [Rwanda], Vaishnavi Govind [Grenada], Rohan Pancharatnam [UK], Lorraine Ochieng [UK], Elliott H Taylor [UK], Hritik Nautiyal [UK], Marta de Andres Crespo [UK], Somy Charuvila [UK], and Alexandra Valetopoulou [UK] Research Capacity Building Committee: Krithi Ravi [UK], Fatumata Jalloh [UK], Nermin Badwi [Egypt], Shahnur Shah [Kenya], Gul Kalra [India], Rohini Rajpal [India], Masooma Rana [Pakistan], Muskaan Abdul Qadir [Pakistan], Emmanuel Uwiringiyimana [Rwanda], Abdelrahman Azzam [Egypt], Mayara Fanelli [Brazil], Gustavo Mendonça Ataíde Gomes [Brazil], Igor Lima Buarque [Brazil], Isadora Schwaab Guerini [Brazil], Anfel Bouderbala [Algeria], Sarah Alfurais [Turkey], Mohamed Gamal [Egypt], Yara Hijazi [Palestine], Shatha Tailakh [Jordan], Hamza Al-Naggar [Yemen], Zain Douba [Syria], Sewar Elejla [Palestine], Abdullah Eldaly [Egypt], Ekram Sharashi [Libya], Ahmad Mansour [Palestine], Tamara Elyan [Palestine], Aouabed Nesrine [Algeria], Ammar Ayman [Egypt], Aya Zazo [Syria], Mohamed Bonna [Egypt], Safia Lorabi [Algeria], Hassan Alalami [Palestine], Rawan Yasser Emam [Egypt] Writing committee: Soham Bandyopadhyay [UK], Rohini Dutta [India], Shweta Madhusudan [UK], Suraj Gandhi [UK], Mehdi Khan [UK], Rhea Raj [UAE], Muath Alser [Egypt], Mohamad K. Abou Chaar [Jordan], Dennis Mazingi [Zimbabwe], Hira Zuberi [Pakistan], Iyad Sultan [Jordan], Dhruva Nath Ghosh [India], Nitin James Peters [India], Reto M Baertschiger [Canada], Augusto Zani [Canada], Noel Peter [UK], and Kokila Lakhoo [UK] Statistics committee: Lucy Davies [UK] and Soham Bandyopadhyay [UK] Local teams: Abubakar Tafawa Balewa University Teaching Hospital, Nigeria 1. Kefas John Bwala 2. AM Umar 3. Abdurahman Aremu 4. Dauda E. Suleiman 5. Tybat Aliyu Aga Khan University Hospital, Pakistan 1. Ayesha Saleem 2. Muhammad Arshad 3. Kashaf Turk 4. Sadaf Altaf Ahmadu Bello University Teaching Hospital, Nigeria 1. Oluseyi Oyebo Ogunso 2. Tunde Talib Sholadoye 3. Musliu Adetola Tolani 4. Yakubu Alfa 5. Keffi Mubarak Musa AIC Kijabe Hospital, Kenya 1. Eric Mwangi Irungu 2. Ken Muma 3. Sarah Muma 4. Mitchell Obat Ain Shams Hospitals "El-Demerdash", Egypt 1. Youssef Sameh Badran Al-Basheer Hospital, Jordan 1. Abdulrahman Ghassan Qasem 2. Faris Ayastra 3. Reema Alnajjar Al-Hussein University Hospital, Egypt 1. Mohamed Abdel-Maboud 2. Abdelrahman Bahaa 3. Ayat M. Saadeldin 4. Mohamed Adwi 5. Mahmoud Adly 6. Abdallah Elshenawy Alder Hey Children Hospital, UK 1. Amer Harky 2. Leanne Gentle 3. Kirstie Wright 4. Jessica Luyt 5. Olivia White 6. Charlotte Smith 7. Nathan Thompson 8. Thomas Smith 9. Imogen Harrison Bangladesh Shishu Hospital & Institute, Bangladesh 1. Ashrarur Rahman Mitul 2. Sabbir Karim 3. Nazmul Islam Benghazi pediatric hospital, Libya 1. Sara Kader Alsaeti 2. Fatma Saleh Benkhial 3. Mohammed Miftah Faraj Almihashhish 4. Eman Salem Muftah Burzeiza 5. Hend Mohammed Masoud 6. Mabroukah Saeid Alshamikh 7. Raja Mari Mohammed Nasef 8. Fatma Mohammed Masoud Birmingham Children's Hospital, UK 1. William B Lo 2. Nyararai Togarepi 3. Elaine Carrolan 4. Benjamin Martin 5. Max Pachl 6. Benjamin J O'Sullivan Borg El Arab University Hospital, Egypt 1. Mohamed Hassanin 2. Ahmed Saleh 3. Mahmoud Bassyony 4. Mostafa Qatora 5. Mohamed Bahaaeldin 6. Shady Fadel 7. Yasmine El Chazli Centre Anti-Cancer, Batna, Algeria 1. Anfel Bouderbala 2. Kamel Hamizi 3. Safia Lorabi 4. Mehdi Anouar Zekkour 5. Rima Rahmoun 6. Boutheyna Drid 7. Salma Najje Abu Teir Centre hospitalier universitaire de Batna, Algeria 1. Safia Lorabi 2. Mohamed Yazid Kadir 3. Yassine Zerizer 4. Nacer Khernane 5. Brahim Saada Centre Hospitalo-Universitaire Ibn Sina de Rabat (CHIS), Morocco 1. Imane Amouze 2. Yahya Elkaoune 3. Hajar Moujtahid 4. Ghita Chaoui 5. Hajar Benaoud 6. Meryem Gounni 7. Narjiss Aji 8. Laila Hessissen Centro Hospitalar Universitário de São João, Portugal 1. Joana Mafalda Monteiro 2. Susana Nunes 3. Maria do Bom-Sucesso Children's Hospital of Wisconsin, United States of America 1. Dave R. Lal 2. Brian T. Craig 3. Kerri Becktell Chittagong Research Institute For Children Surgery, Bangladesh 1. Tahmina Banu 2. Md Afruzul Alam 3. Orindom Shing Pulock 4. Tasmiah Tahera Aziz Clinic for Neurosurgery, Clinical Center of Serbia, Serbia 1. Rosanda Ilic 2. Danica Grujicic 3. Tijana Nastasovic 4. Igor Ladic 5. Mihailo Milicevic 6. Vladimir Bascarevic 7. Radovan Mijalcic 8. Vuk Scepanovic 9. Aleksandar Stanimirovic 10. Aleksandra Paunovic 11. Ivan Bogdanovic Dhaka Medical College Hospital, Bangladesh 1. Shahnoor Islam 2. AKM Amirul Morshed A. K. M. Khairul Basher 3. Mehnaz Akter 4. S. M. Rezanur Rahman 5. Zannat Ara 6. Mohammed Tanvir Ahammed 7. Tania Akter 8. Kamrun Nahar 9. Fatema Sayed 10. Ashfaque Nabi 11. Md. Asif Iqbal 12. Md. Masud Rana 13. Md. Asaduzzaman 14. Md. Hasanuzzaman Dr. Lutfi Kirdar Kartal Training and Research Hospital, Turkey 1. Kemal Tolga Saracoglu 2. Elif Akova 3. Evren Aydogmus 4. Bekir Can Kendirlioglu 5. Tufan Hicdonmez Dubai Hospital, United Arab Emirates 1. Arshiya Adhnon 2. Asim Noor Rana 3. Hani Humad 4. Anjan Madasu El Safa Hospital, Egypt 1. Ahmed Y Azzam 2. Mohammed A Azab El Sheikh Zayed Specialized Hospital, Egypt 1. Sherief Ghozy 2. Alzhraa Salah Abbas Federal Medical Center, Abeokuta, Nigeria 1. Olanrewaju Moses Federal Medical Center, Lokoja, Nigeria 1. Ibiyeye Taiye Taibat 2. Taiwo Jones 3. Kalu Ukoha 4. Olagundoye Goke 5. Okorie Ikechukwu Federal Teaching Hospital Ido-Ekiti, Nigeria 1. Abiodun Idowu Okunlola Frere Hospital, South Africa 1. Milind Chitnis 2. Helga Nauhaus 3. Danelle Erwee Gloucestershire Hospitals NHS Foundation Trust, United Kingdom 1. Robyn Brown 2. Agata Chylinska 3. Robin Simpson 4. Prasanna Gomes 5. Noel Peter GPACI - Grupo de Pesquisa e Assistência ao Câncer Infantil, Brazil 1. Marco Aurelio Ciriaco Padilha 2. Elvercio Pereira de Oliveira Junior 3. Lucas Garschagen de Carvalho 4. Fabiola Leonelli Diz Helwan University Hospital, Egypt 1. Mohamed El Kassas 2. Usama Eldaly 3. Ahmed Tawheed 4. Mohamed Abdelwahab Hôpital des Spécialités ONO, Morocco 1. Oudrhiri Mohammed Yassaad 2. Bechri Hajar 3. El Ouahabi Abdessamad 4. Arkha Yasser 5. Hessissen Laila Ibn-Al-Atheer Teaching Hospital, Mosul, Iraq 1. Farah Sameer Yahya (Department of Pediatrics, College of Medicine, University of Mosul, Mosul, Iraq) 2. Yasir Al-Agele Instituto Nacional de Enfermedades Neoplásicas, Peru 1. Maria Teresa Peña Gallardo 2. Jacqueline Elizabeth Montoya Vásquez 3. Juan Luis García León 4. Sebastián Shu Yip John Radcliffe Hospital, United Kingdom 1. Mariam Lami 2. Matthew H V Byrne 3. Duha Jasim 4. Harmit Ghattaura 5. Soham Bandyopadhyay 6. Kokila Lakhoo Johns Hopkins Hospital Bloomberg Children's Hospital, United States of America 1. Eric W Etchill 2. Daniel Rhee 3. Stacy Cooper 4. Kevin Crow 5. Morgan Drucker 6. Megan Murphy 7. Benjamin Shou 8. Alan Siegel Kanuni Sultan Süleyman Research and Training Hospital, Turkey 1. Yasin Kara 2. Gül Nihal Özdemir Kasr Al Ainy Hospital, Egypt 1. Mahmoud Efiky 2. Ehab El Refaee Khoula Hospital, Oman 1. John George Massoud King Abdullah University Hospital, Jordan 2. Ayah Bassam Ibrahim 3. Ruaa Bassam Ibrahim 4. Faris Abu Za'nouneh 5. Ranya M. Baddourah 6. Toqa Fahmawee 7. Ayah Al-Shraideh King Fahd Central Hospital, Saudi Arabia 1. Ghazwani Salman 2. Ehab Alameer (Jazan University) 3. Al-Mudeer Ali 4. Ghazwani Yahia 5. Khozairi Waleed King Hussein Cancer Center, Jordan 1. Mohamad K. Abou Chaar 2. Iyad Sultan 3. Khalil Ghandour 4. Shaima' Al-Dabaibeh 5. Ammar Al-Basiti 6. Hazim Ababneh 7. Omaima El-Qurneh King Salman Armed Forces Hospital, Saudi Arabia 1. Yousef Alalawi 2. Ahmad Al Aayed 3. Ehab Hanafy 4. Naif Al Bolowi KK Women's and Children's Hospital, Singapore 1. Amos HP Loh 2. Anette S Jacobsen 3. Heidi Barola 4. Aubrey L Pagaduan 5. Jingdan Fan Lagos University Teaching Hospital, Nigeria 1. Olumide Abiodun Elebute 2. Adesoji O. Ademuyiwa 3. Christopher O. Bode 4. Justina O. Seyi-Olajide 5. Oluwaseun Ladipo-Ajayi 6. Felix M. Alakaloko 7. George C. Iheidiwa 8. Kareem O. Musa 9. Edamisan O. Temiye 10. Olufemi Oni 11. Adeseye M. Akinsete Lahore General Hospital, Pakistan 1. Janita Zarrish 2. Ramsha Saleem 3. Soha Zahid 4. Atiqa Amirali 5. Ahsan Nadeem 6. Sameer Saleem Tebha 7. Zonaira Qayyum 8. Sana Tahir 9. Anneqa Tahir 10. Rabbey Raza Khan 11. Ayesha Mehmood 12. Iqra Effendi Liaquat National Hospital and Medical College, Pakistan 1. Muhammad Arshad 2. Taimur Iftikhar Qureshi 3. Pooja Kumari Mater Dei Hospital, Sir Anthony Mamo Oncology Centre, Malta 1. Victor Calvagna 2. Nathalie Galea 3. Ariana Axiq Mayo Clinic, United States of America 1. Matthew R Schuelke 2. Jake A. Kloeber 3. Robert L. Owen 4. Alexander S. Roth 5. Catherine Yang 6. J. Hudson Barnett 7. Lucien P. Jay 8. Kirk David Wyatt 9. Paul J. Galaray Medical University of Pecs, Department of Paediatrics, Hungary 1. Agnes Vojcek Menoufia University Hospital, Egypt 1. Mahmoud Maher Abdelnaby Alrahawy 2. Seham M Ragab 3. Abdallah R Allam 4. Eman Ibrahim Hager 5. Abdelrahman Azzam 6. Ammar Ayman Ministry of Health Marmara University Pendik Research and Application Hospital, Turkey 1. Kivilcim Karadeniz Cerit 2. Adnan Dağçınar 3. Tümay Umuroğlu 4. Ayten Saraçoğlu 5. Mustafa Sakar 6. Can Kıvrak 7. Gül Çakmak MISR Cancer Centre, Egypt 1. Ibrahim Sallam 2. Gamal Amira 3. Mohamed Sherief 4. Ahmed Sherif National Cancer Institute, Brazil 1. Simone de Oliveira Coelho 2. Arissa Ikeda 3. Licia Portela 4. Marianne Monteiro Garrigo 5. Ricardo Vianna de Carvalho 6. Fernanda Lobo 7. Sima Ester Ferman 8. Fernanda Ferreira da Silva Lima National Cancer Institute, Sudan 1. Moawia Mohammed Ali Elhassan 2. Nada Osman Yousef Elhaj 3. Hytham K. S. Hamid National Hospital, Nigeria 1. Emmanuel A. Ameh 2. Vincent E. Nwatah 3. Adewumi B. Oyesakin Nnamdi Azikiwe University Teaching Hospital, Nigeria 1. Andrew Nwankwo Osuigwe 2. Okechukwu Hyginus Ekwunife 3. Chisom Adaobi Nri-Ezedi 4. Eric Okechukwu Umeh Ola During Children's Hospital, Sierra Leone 1. Nellie Bell Olabisi Onabanjo University Teaching Hospital, Nigeria 1. Ibukunolu Olufemi Ogunde 2. Abiodun Folashade Adekanmbi 3. Olubunmi Motunrayo Fatungase 4. Olubunmi Obafemi Obadinni Ondokuz Mayıs Üniversitesi, Turkey 1. Sarah Al-Furais 2. Humaida Hemlae 3. Sreylis Nay Pantai Jerudong Specialist Centre, Brunei 1. John Mathew 2. R M Jeffri Ismail Pediatric Oncology Institute - GRAACC, Brazil 1. Simone de Campos Vieira Abib 2. Fabianne Altruda de Moraes Costa Carlesse 3. Mayara Caroline Amorim Fanelli 4. Fernanda Kelly Marques de Souza Policlinico Umberto I, Sapienza University of Rome, Italy 1. Pierfrancesco Lapolla 2. Andrea Mingoli 3. Denis Cozzi 4. Anna Maria Testi 5. Paolo Musiu 6. Paolo Sapienza 7. Gioia Brachini 8. Martina Zambon 9. Simona Meneghini 10. Pierfranco Cicerchia 11. Bruno Cirillo Prince Mohammed bin Nasser Hospital, Jazan, Saudi Arabia 1. Ghazwani Salman Raparin Pediatric Teaching Hospital, Iraq 1. Abdulrahman Omar Taha Saadna Mohamed Abdenour, Algeria 1. Aouabed Nesrine 2. Bouaoud Souad 3. Mebarki Malika 4. Bioud Belkacem Sabha Medical Centre, Libya 1. Ayman Meelad 2. Hajier Salim Alrashed Salmaniya Medical Complex, Bahrain 1. Fayza Haider 2. Fatema Naser Al Fayed Shahid Baghaei Hospital, Iran 1.

Fakher Rahim Tamale Teaching Hospital, Ghana 1. Alhassan Abdul-Mumin 2. Halwani Yanning Fuseini 3. Peter Gyamfi Kwarteng 4. Abubakari Bawa Abdulai 5. Sheba Mary Pognaa Kunfah 6. Gilbert B. Bonsaana 7. Stephanie Ajinkpang 8. Edmund M. Der 9. Francis A. Abantanga 10. Mary Joan Kpiniong 11. Kingsley Aseye Hattor 12. Kingsley Appiah Bimpong Tanta University Hospital, Egypt 1. Mohamed Elbahnasawy 2. Sherief Abdelsalam 3. Ahmed Samir The Hospital for Sick Children, Canada 1. Reto M. Baertschiger 2. Amanpreet Brar 3. Andreea C. Matei 4. Augusto Zani The Indus Hospital, Pakistan 1. Lubna Samad 2. Hira Khalid Zuberi 3. Kishwer Nadeem 4. Naema Khayyam 5. Fatima Ambreen Imran 6. Nida Zia 7. Sadia Muhammad 8. Muhammad Rafie Raza 9. Muhammad Rahil Khan Tishreen University Hospital, Syria 1. Alaa Hamdan 2. Ammar Omran 3. Ahmed Moussa 4. Bardisan Gawrieh 5. Hassan Sallow 6. Alaa Ahmed 7. Abdeljawad Mazloum 8. Ali Abodest 9. Nisreen Ali 10. Munawar Hraib 11. Victor Khoury 12. Abdulrahman Almjersah 13. Mohammad Ali Deeb 14. Mohammad Ahmad Almahmud Alkhalil 15. Akram Ahmed 16. Waseem Shater 17. Ali Farid Alelayan 18. Alaa Guzman Tobruk Medical Centre, Libya 1. Ahmad Bouhuwaish 2. Alqasim Abdulkarim Tripoli University Hospital, Libya 1. Eman Abdulwahed 2. Marwa Biala 3. Reem Ghamgh 4. Amani Alamre 5. Marwa Shelft 6. Asmaa A. M. Albanna 7. Hoda Tawel Unit of Paediatric and Adolescent Haematology and Oncology, 2nd Department of Paediatrics, Aristotle University of Thessaloniki, University General Hospital AHEPA, Greece 1. Emmanuel Hatzipantelis 2. Athanasios Tragiannidis 3. Eleni Tsotridou 4. Assimina Galli-Tsinopoulou Universiti Kebangsaan Malaysia Medical Centre, Malaysia 1. Dayang Anita Abdul Aziz 2. Zarina Abdul Latiff 3. Hamidah Alias 4. C-Khai Loh 5. Doris Lau 6. Azrina Syarizad Khutubul Zaman University Children's Hospital of Basel, Switzerland 1. Raphael N. Vuille-dit-Bille 2. Stefan G. Holland-Cunz 3. Nima Allafi University College Hospital (UCH), Nigeria 1. Taiwo Akeem Lawal 2. Kelvin Ifeanyichukwu Egbuchulem 3. Olakayode Olaolu Ogundoyin 4. Isaac Dare Olulana 5. Biobele J. Brown 6. Oluwasegun Joshua Afolaranmi 7. AbdulBasit Fehintola University Hospital Hamburg-Eppendorf, Germany 1. Annika Heuer 2. Christine Nitschke 3. Michael Boettcher 4. Matthias Priemel 5. Lennart Viezens 6. Martin Stangenberg 7. Marc Dreimann 8. Alonja Reiter 9. Jasmin Meyer 10. Leon Köpke 11. Karl-Heinz Frosch University of Abuja Teaching Hospital, Nigeria 1. Samson Olori 2. Uduak Offiong 3. Philip Mari Mshelbwala 4. Fashie Andrew Patrick 5. Aminu Muhammed Umar 6. Otene ThankGod N. University of Ilorin Teaching Hospital, Nigeria 1. Abdurashheed A Nasir 2. Kazeem O. O. Ibrahim 3. Dupe S. Ademola-Popoola 4. Olayinka T. Sayomi 5. Alege Abdurrrzzaq 6. Ademola A. Adeyeye 7. Khadijah O. Omokanye 8. Lukman O Abdur-Rahman 9. Olubisi Olutosin Bamidele 10. Shakirullah AbdulAzeez 11. Aminat Akinoso 12. Michael O. Adegboye University of Malaya Medical Centre, Malaysia 1. Shireen Anne Nah 2. Yuki Julius Ng 3. Syukri Ahmad Zubaidi University of Texas Medical Branch, United States of America 1. Murad Almasri 2. Sara Ali 3. Rasaq Olaosebikan 4. Akila Muthukumar University Teaching Hospital, Zambia 1. Patricia Shinondo 2. Amon Ngongola 3. Bruce Bvulani 4. Azad Patel Usman Danfodiyo University Teaching Hospital, Nigeria 1. Abdullahi Nuhu-Koko 2. Baba Jibrin 3. Ajiboye L. Olalekan 4. Christopher S. Lukong 5. Ezekiel I. Ajayi Vall d'Hebron University Hospital, Spain 1. Gabriela Guillén 2. Sergio López 3. José Andrés Molino 4. Pablo Velasco Wingat Royal Hospital, Egypt 1. Omar Elmandouh 2. Omar Hamam 3. Rim Elmandouh Yale New Haven Hospital, United States of America 1. Nensi Melissa Ruzgar 2. Rachel Levinson 3. Shashwat Kala 4. Sarah Ullrich 5. Emily Christison-Lagay Zagazig University Hospital, Egypt 1. Aya Sabry Mortada 2. Mahmoud Ahmed Ebada 3. Eman Seif Alnaser Solimam 4. Khaled Abualkher 5. Amr Mohammed Elsayed Yousf 6. Mohamed Mohamed Holail 7. Reem Mohamed Almowafy National/Regional Leads: Algeria: Salah Eddine Oussama Kacimi Bahrain: Fayza Haider Bangladesh: Tahmina Banu, Ashrarur Rahman Mitul Brazil: Simone de Campos Vieira Abib Brunei: Janice Hui Ling Wong Canada: Reto Baertschiger Egypt: Essam Elhalaby, Muath Alser, Mahmoud M. Saad Germany: Guido Seitz, Judith Lindbert Ghana: Francis Abantanga Greece: Georgios Tsoulias, Assimina Galli-Tsinopoulou Hungary: Agnes Vojcek Iran: Maryam Ghavami Adel Iraq: Abdulrahman Omar Taha Italy: Calogero Virgone, Francesco Pata, Gaetano Gallo Jordan: Mohammad K. Abou Chaar, Faris Ayasra Kenya: Eric Mwangi Irungu Libya: Mohammed Elhadi Malaysia: Shireen Anne Nah, Dayang Anita Abdul Aziz Malta: Victor Calvagna Morocco: Outani Oumaima, Zineb Bentounsi, Hajar Moujtahid Nigeria: Adesoji Ademuyiwa Oman: Dhruva Nath Ghosh Pakistan: Muhammad Arshad, Lubna Samad Peru: Lily Saldana Portugal: Jan Godzinsky Saudi Arabia: Abdelbasit Ali, Ehab Alameer Serbia: Dragana Janic Sierra Leone: Mohamed Bella Jalloh, Nellie Bell Singapore: Annette Jacobsen, Chan Hon Chui South Africa: Milind Chitnis Spain: Israel Fernandez Pineda, Lucas Krauel, Maricarmen Olivos Sudan: Waha Rahama, Hazim Eflatih Switzerland: Raphael N. Vuille-dit-Bille Syria: Alaa Hamdan Turkey: Arda Isik United Arab Emirates: Asim Noor Rana United Kingdom: Kokila Lakhoo, Kate Cross, Max Pacht United States of America: Andrea Hayes-Jordan, Roshni Dasgupta Zambia: Patricia Shinondo, Amon Ngongola Middle-East and North Africa: Mohameddraed Elshami

**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 online supplemental appendix S1. KL acts as guarantor for this study.

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## Appendix S1: Global Children's NCDs Collaborative

### Steering committee:

Soham Bandyopadhyay [UK], Noel Peter [UK] (Asia Lead), Kokila Lakhoo [UK], Simone de Campos Vieira Abib [Brazil] (South America Lead), Hafeez Abdelhafeez [Sudan] (Africa and Middle East Lead), Shaun Wilson [UK] (Australasia Lead), Max Pachel [UK] (Europe and North America Lead), Benjamin Martin [UK] (Europe Lead), Sonal Nagras [Australia] (Australasia Lead), and Mihir Sheth [India]

### Operational committee:

Catherine Dominic [UK], Suraj Gandhi [UK], Divya Parwani [India], Rhea Raj [UAE], Diella Munezero [Burundi], Rohini Dutta [India], Nsimire Mulanga Roseline [DRC], Kellie McClafferty [UK], Armin Nazari [UK], Smrithi Sriram [UK], Sai Pillariseti [UK], King-David Nweze [UK], Aishwarya Ashwinee [Grenada], Gul Kalra [India], Poorvaprabha Patil [India], Priyansh Nathani [India], Khushman Kaur Bhullar [India], Muhammed Elhadi [Libya], Maryam Khan [Pakistan], Nehal Rahim [Pakistan], Shweta Madhusudanan [UK], Joshua Erhabor [UK], Manasi Shirke [UK], Aishah Mughal [UK], Darica Au [UK], Mahan Salehi [UK], Sravani Royyuru [UK], Mohamed Ahmed [Egypt], Syeda Namayah Fatima Hussain [Pakistan], Daniel Robinson [UK], Anna Casey [UK], Mehdi Khan [UK], Alexandre Dukundane [Rwanda], Kwizera Festus [Rwanda], Vaishnavi Govind [Grenada], Rohan Pancharatnam [UK], Lorraine Ochieng [UK], Elliott H Taylor [UK], Hritik Nautiyal [UK], Marta de Andres Crespo [UK], Somy Charuvila [UK], and Alexandra Valetopoulou [UK]

### Research Capacity Building Committee:

Krithi Ravi [UK], Fatumata Jalloh [UK], Nermin Badwi [Egypt], Shahnur Shah [Kenya], Gul Kalra [India], Rohini Rajpal [India], Masooma Rana [Pakistan], Muskaan Abdul Qadir [Pakistan], Emmanuel Uwiringiyimana [Rwanda], Abdelrahman Azzam [Egypt], Mayara Fanelli [Brazil], Gustavo Mendonça Ataíde Gomes [Brazil], Igor Lima Buarque [Brazil], Isadora Schwaab Guerini [Brazil], Anfel Bouderbala [Algeria], Sarah Alfurais [Turkey], Mohamed Gamal [Egypt], Yara Hijazi [Palestine], Shatha Tailakh [Jordan], Hamza Al-Naggar [Yemen], Zain Douba [Syria], Sewar Elejla [Palestine], Abdullah Eldaly [Egypt], Ekram Sharashi [Libya], Ahmad Mansour [Palestine], Tamara Elyan [Palestine], Aouabed Nesrine [Algeria], Ammar Ayman [Egypt], Aya Zazo [Syria], Mohamed Bonna [Egypt], Safia Lorabi [Algeria], Hassan Alalami [Palestine], Rawan Yasser Emam [Egypt]

### Writing committee:

Soham Bandyopadhyay [UK], Rohini Dutta [India], Shweta Madhusudanan [UK], Suraj Gandhi [UK], Mehdi Khan [UK], Rhea Raj [UAE], Muath Alser [Egypt], Mohamad K. Abou Char [Jordan], Dennis Mazingi [Zimbabwe], Hira Zuberi [Pakistan], Iyad Sultan [Jordan], Dhruv Nath Ghosh [India], Nitin James Peters [India], Reto M Baertschiger [Canada], Augusto Zani [Canada], Noel Peter [UK], and Kokila Lakhoo [UK]

### Statistics committee:

Lucy Davies [UK] and Soham Bandyopadhyay [UK]

### Local teams:

#### Abubakar Tafawa Balewa University Teaching Hospital, Nigeria

Kefas John Bwala

AM Umar

Abdurahaman Aremu

Dauda E. Suleiman  
Tybat Aliyu  
**Aga Khan University Hospital, Pakistan**  
Ayesha Saleem  
Muhammad Arshad  
Kashaf Turk  
Sadaf Altaf  
**Ahmadu Bello University Teaching Hospital, Nigeria**  
Oluseyi Oyebode Ogunsua  
Tunde Talib Sholadoye  
Musliu Adetola Tolani  
Yakubu Alfa  
Keffi Mubarak Musa  
**AIC Kijabe Hospital, Kenya**  
Eric Mwangi Irungu  
Ken Muma  
Sarah Muma  
Mitchelle Obat  
**Ain Shams Hospitals "El-Demerdash", Egypt**  
Youssef Sameh Badran  
**Al-Basheer Hospital, Jordan**  
Abdulrahman Ghassan Qasem  
Faris Ayasra  
Reema Alnajjar  
**Al-Hussein University Hospital, Egypt**  
Mohamed Abdel-Maboud  
Abdelrahman Bahaa  
Ayat M. Saadeldin  
Mohamed Adwi  
Mahmoud Adly  
Abdallah Elshenawy  
**Alder Hey Children Hospital, UK**  
Amer Harky  
Leanne Gentle  
Kirstie Wright  
Jessica Luyt  
Olivia White  
Charlotte Smith  
Nathan Thompson  
Thomas Smith  
Imogen Harrison  
**Bangladesh Shishu Hospital & Institute, Bangladesh**  
Ashrarur Rahman Mitul  
Sabbir Karim  
Nazmul Islam  
**Benghazi pediatric hospital, Libya**  
Sara Kader Alsaeti  
Fatma Saleh Benkhial  
Mohammed Miftah Faraj Almihashhish  
Eman Salem Muftah Burzeiza

Hend Mohammed Masoud  
Mabroukah Saeid Alshamikh  
Raja Mari Mohammed Nasef  
Fatma Mohammed Masoud  
**Birmingham Children's Hospital, UK**

William B Lo  
Nyararai Togarepi  
Elaine Carrolan  
Benjamin Martin  
Max Pachl  
Benjamin J O'Sullivan  
**Borg El Arab University Hospital, Egypt**

Mohamed Hassanin  
Ahmed Saleh  
Mahmoud Bassiony  
Mostafa Qatora  
Mohamed Bahaaeldin  
Shady Fadel  
Yasmine El Chazli  
**Centre Anti-Cancer, Batna, Algeria**

Anfel Bouderbala  
Kamel Hamizi  
Safia Lorabi  
Mehdi Anouar Zekkour  
Rima Rahmoun  
Boutheyna Drid  
Salma Naje Abu Teir  
**Centre hospitalier universitaire de Batna, Algeria**

Safia Lorabi  
Mohamed Yazid Kadir  
Yassine Zerizer  
Nacer Khernane  
Brahim Saada  
**Centre Hospitalo-Universitaire Ibn Sina de Rabat (CHIS), Morocco**

Imane Ammouze  
Yahya Elkaoune  
Hajar Moujtahid  
Ghita Chaoui  
Hajar Benaouda  
Meryem Gounni  
Narjiss Aji  
Laila Hessissen  
**Centro Hospitalar Universitário de São João, Portugal**

Joana Mafalda Monteiro  
Susana Nunes  
Maria do Bom-Sucesso  
**Children's Hospital of Wisconsin, United States of America**  
Dave R. Lal  
Brian T. Craig  
Kerri Beckett

**Chittagong Research Institute For Children Surgery, Bangladesh**

Tahmina Banu

Md Afruzul Alam

Orindom Shing Pulock

Tasmiah Tahera Aziz

**Clinic for Neurosurgery, Clinical Center of Serbia, Serbia**

Rosanda Ilic

Danica Grujicic

Tijana Nastasovic

Igor Lazic

Mihailo Milicevic

Vladimir Bascarevic

Radovan Mijalcic

Vuk Scepanovic

Aleksandar Stanimirovic

Aleksandra Paunovic

Ivan Bogdanovic

**Dhaka Medical College Hospital, Bangladesh**

Shahnoor Islam

AKM Amirul Morshed

A. K. M. Khairul Basher

Mehnaz Akter

S. M. Rezanur Rahman

Zannat Ara

Mohammed Tanvir Ahammed

Tania Akter

Kamrun Nahar

Fatema Sayed

Ashfaque Nabi

Md. Asif Iqbal

Md. Masud Rana

Md. Asaduzzaman

Md. Hasanuzzaman

**Dr. Lutfi Kirdar Kartal Training and Research Hospital, Turkey**

Kemal Tolga Saracoglu

Elif Akova

Evren Aydogmus

Bekir Can Kendirlioglu

Tufan Hicdonmez

**Dubai Hospital, United Arab Emirates**

Arshiya Adhnon

Asim Noor Rana

Hani Humad

Anjan Madasu

**El Safa Hospital, Egypt**

Ahmed Y Azzam

Mohammed A Azab

**El Sheikh Zayed Specialized Hospital, Egypt**

Sherief Ghozy

Alzhraa Salah Abbas



**Federal Medical Center, Abeokuta, Nigeria**

Olanrewaju Moses

**Federal Medical Center, Lokoja, Nigeria**

Ibiyeye Taiye Taibat

Taiwo Jones

Kalu Ukoha

Olagundoye Goke

Okorie Ikechukwu

**Federal Teaching Hospital Ido-Ekiti, Nigeria**

Abiodun Idowu Okunlola

**Frere Hospital, South Africa**

Milind Chitnis

Helga Nauhaus

Danelle Erwee

**Gloucestershire Hospitals NHS Foundation Trust, United Kingdom**

Robyn Brown

Agata Chylinska

Robin Simpson

Prasanna Gomes

Noel Peter

**GPACI - Grupo de Pesquisa e Assistência ao Câncer Infantil, Brazil**

Marco Aurelio Ciriaco Padilha

Elvercio Pereira de Oliveira Junior

Lucas Garschagen de Carvalho

Fabiola Leonelli Diz

**Helwan University Hospital, Egypt**

Mohamed El Kassas

Usama Eldaly

Ahmed Tawheed

Mohamed Abdelwahab

**Hôpital des Spécialités ONO, Morocco**

Oudrhiri Mohammed Yassaad

Bechri Hajar

El Ouahabi Abdessamad

Arkha Yasser

Hessissen Laila

**Ibn-Al-Atheer Teaching Hospital, Mosul, Iraq**

Farah Sameer Yahya (Department of Pediatrics, College of Medicine, University of Mosul, Mosul, Iraq)

Yasir Al-Agele

**Instituto Nacional de Enfermedades Neoplásicas, Peru**

Maria Teresa Peña Gallardo

Jacqueline Elizabeth Montoya Vásquez

Juan Luis García León

Sebastián Shu Yip

**John Radcliffe Hospital, United Kingdom**

Mariam Lami

Matthew H V Byrne

Duha Jasim

Harmit Ghataura

Soham Bandyopadhyay

Kokila Lakhoo

**Johns Hopkins Hospital Bloomberg Children's Hospital, United States of America**

Eric W Etchill

Daniel Rhee

Stacy Cooper

Kevin Crow

Morgan Drucker

Megan Murphy

Benjamin Shou

Alan Siegel

**Kanuni Sultan Süleyman Research and Training Hospital, Turkey**

Yasin Kara

Gül Nihal Özdemir

**Kasr Al Ainy Hospital, Egypt**

Mahmoud Elfiky

Ehab El Refaee

**Khoula Hospital, Oman**

John George Massoud

**King Abdullah University Hospital, Jordan**

Ayah Bassam Ibrahim

Ruaa Bassam Ibrahim

Faris Abu Za'nouneh

Ranya M. Baddourah

Toqa Fahmawee

Ayah Al\_Shraideh

**King Fahd Central Hospital, Saudi Arabia**

Ghazwani Salman

Ehab Alameer

Al-Mudeer Ali

Ghazwani Yahia

Khozairi Waleed

**King Hussein Cancer Center, Jordan**

Mohamad K. Abou Chaar

Iyad Sultan

Khalil Ghandour

Shaima' Al-Dabaibeh

Ammar Al-Basiti

Hazim Ababneh

Omaima El-Qurneh

**King Salman Armed Forces Hospital, Saudi Arabia**

Yousef Alalawi

Ahmad Al Ayed

Ehab Hanafy

Naif Al Bolowi

**KK Women's and Children's Hospital, Singapore**

Amos HP Loh

Anette S Jacobsen

Heidi Barola

Aubrey L Pagaduan

Jingdan Fan

**Lagos University Teaching Hospital, Nigeria**

Olumide Abiodun Elebute

Adesoji O. Ademuyiwa

Christopher O. Bode

Justina O. Seyi-Olajide

Oluwaseun Ladipo-Ajayi

Felix M. Alakaloko

George C. Ihediwa

Kareem O. Musa

Edamisan O. Temiye

Olufemi Oni

Adeseye M. Akinsete

**Lahore General Hospital, Pakistan**

Janita Zarrish

Ramsha Saleem

Soha Zahid

Atiqa Amirali

Ahsan Nadeem

Sameer Saleem Tebha

Zonaira Qayyum

Sana Tahir

Anneqa Tahir

Rabbey Raza Khan

Ayesha Mehmood

**Liaquat National Hospital and Medical College, Pakistan**

Muhammad Arshad

Taimur Iftikhar Qureshi

Pooja Kumari

**Mater Dei Hospital, Sir Anthony Mamo Oncology Centre, Malta**

Victor Calvagna

Nathalie Galea

Ariana Axiaq

**Mayo Clinic, United States of America**

Matthew R Schuelke

Jake A. Kloebe

Robert L. Owen

Alexander S. Roth

Catherine Yang

J. Hudson Barnett

Lucien P. Jay

Kirk David Wyatt

Paul J. Galardy

**Medical University of Pecs, Department of Paediatrics, Hungary**

Agnes Vojcek

**Menoufia University Hospital, Egypt**

Mahmoud Maher Abdelnaby Alrahawy

Seham M Ragab

Abdallah R Allam

Eman Ibrahim Hager

Abdelrahman Azzam

Ammar Ayman

**Ministry of Health Marmara University Pendik Research and Application Hospital,  
Turkey**

Kıvılcım Karadeniz Cerit

Adnan Dağçınar

Tümay Umuroğlu

Ayten Saraçoğlu

Mustafa Sakar

Can Kıvrak

Gül Çakmak

**MISR Cancer Centre, Egypt**

Ibrahim Sallam

Gamal Amira

Mohamed Sherief

Ahmed Sherif

**National Cancer Institute, Brazil**

Simone de Oliveira Coelho

Arissa Ikeda

Licia Portela

Marianne Monteiro Garrigo

Ricardo Vianna de Carvalho

Fernanda Lobo

Sima Ester Ferman

Fernanda Ferreira da Silva Lima

**National Cancer Institute, Sudan**

Moawia Mohammed Ali Elhassan

Nada Osman Yousif Elhaj

Hytham K. S. Hamid

**National Hospital, Nigeria**

Emmanuel A. Ameh

Vincent E. Nwatah

Adewumi B. Oyesakin

**Nnamdi Azikiwe University Teaching Hospital, Nigeria**

Andrew Nwankwo Osuigwe

Okechukwu Hyginus Ekwunife

Chisom Adaobi Nri-Ezedi

Eric Okechukwu Umeh

**Ola Daring Children's Hospital, Sierra Leone**

Nellie Patiala

**Olabisi Onabanjo University Teaching Hospital, Nigeria**

Ibukunolu Olufemi Ogundele

Abiodun Folashade Adekanmbi

Olubunmi Motunrayo Fatungase

Olubunmi Obafemi Obadaini

**Ondokuz Mayıs Üniversitesi, Turkey**

Sarah Al-Furais

Humaida Hemlae

Sreylis Nay

**Pantai Jerudong Specialist Centre, Brunei**

John Mathew

R M Jeffri Ismail

**Pediatric Oncology Institute – GRAACC, Brazil**

Simone de Campos Vieira Abib

Fabianne Altruda de Moraes Costa Carlesse

Mayara Caroline Amorim Fanelli

Fernanda Kelly Marques de Souza

**Policlínico Umberto I, Sapienza University of Rome, Italy**

Pierfrancesco Lapolla

Andrea Mingoli

Denis Cozzi

Anna Maria Testi

Paolo Musiu

Paolo Sapienza

Gioia Brachini

Martina Zambon

Simona Meneghini

Pierfranco Cicerchia

Bruno Cirillo

**Prince Mohammed bin Nasser Hospital, Jazan, Saudi Arabia**

Ghazwani Salman

**Raparin Pediatric Teaching Hospital, Iraq**

Abdulrahman Omar Taha

**Saadna Mohamed Abdenour, Algeria**

Aouabed Nesrine

Bouaoud Souad

Mebarki Malika

Bioud Belkacem

**Sabha Medical Centre, Libya**

Ayman Meelad

Hajier Salim Alrashed

**Salmaniya Medical Complex, Bahrain**

Fayza Haider

Fatema Naser Al Fayezi

**Shahid Baghaei Hospital, Iran**

Fakher Rahim

**Tamale Teaching Hospital, Ghana**

Alhassan Abdul-Mumin

Halwani Yaninga Fuseini

Peter Gyamfi Kwarteng

Abubakari Bawa Abdulai

Sheba Mary Pognaa Kunfah

Gilbert B. Bonsaana

Stephanie Ajinkpang

Edmund M. Der

Francis A. Abantanga

Mary Joan Kpiniong

Kingsley Aseye Hattor

Kingsley Appiah Bimpong

**Tanta University Hospital, Egypt**

Mohamed Elbahnasawy

Sherief Abdelsalam

Ahmed Samir

**The Hospital for Sick Children, Canada**

Reto M. Baertschiger

Amanpreet Brar

Andreea C. Matei

Augusto Zani

**The Indus Hospital, Pakistan**

Lubna Samad

Hira Khalid Zuberi

Kishwer Nadeem

Naema Khayyam

Fatima Ambreen Imran

Nida Zia

Sadia Muhammad

Muhammad Rafie Raza

Muhammad Rahil Khan

**Tishreen University Hospital, Syria**

Alaa Hamdan

Abdeljawad Mazloun

Ali Abodest

Nisreen Ali

Bardisan Gawarieh

Ammar Omran

Almed Moussa

Alaa Ahmed

Munawar Hraib

Victor Khoury

Abdulrahman Almjersah

Mohammad Ali Deeb

Almahmod Alkhalil

Akram Ahmed

Mohammad Ahmad

Ali Alelayan

Ali Hammed

Wassem Shater

**Tobruk Medical Centre, Libya**

Ahmad Bouhuwaish

Alqasim Abdulkarim

**Tripoli University Hospital, Libya**

Eman Abdulwahed

Marwa Biala

Reem Ghamgh

Amani Alamre

Marwa Shelft

Asmaa A. M. Albanna

Hoda Tawel

**Unit of Paediatric and Adolescent Haematology and Oncology, 2nd Department of Paediatrics, Aristotle University of Thessaloniki, University General Hospital AHEPA, Greece**

Emmanuel Hatzipantelis

Athanasios Tragiannidis

Eleni Tsotridou

Assimina Galli-Tsinopoulou

**Universiti Kebangsaan Malaysia Medical Centre, Malaysia**

Dayang Anita Abdul Aziz

Zarina Abdul Latiff

Hamidah Alias

C-Khai Loh

Doris Lau

Azrina Syarizad Khutubul Zaman

**University Children's Hospital of Basel, Switzerland**

Raphael N. Vuille-dit-Bille

Stefan G. Holland-Cunz

Nima Allafi

**University College Hospital (UCH), Nigeria**

Taiwo Akeem Lawal

Kelvin Ifeanyichukwu Egbuchulem

Olakayode Olaolu Ogundoyin

Isaac Dare Olulana

Biobele J. Brown

Oluwasegun Joshua Afolaranmi

AbdulBasit Fehintola

**University Hospital Hamburg-Eppendorf, Germany**

Annika Heuer

Christine Nitschke

Michael Boettcher

Matthias Priemel

Lennart Viezens

Martin Stangenberg

Marc Dreimann

Alonja Reiter

Jasmin Meyer

Leon Köpke

Karl-Heinz Frosch

**University of Abuja Teaching Hospital, Nigeria**

Samson Olori

Uduak Offiong

Philip Mari Mshelbwala

Fashie Andrew Patrick

Aminu Muhammed Umar

Otene ThankGod N.

**University of Ilorin Teaching Hospital, Nigeria**

Abdulrasheed A Nasir

Kazeem O. O. Ibrahim

Dupe S. Ademola-Popoola

Olayinka T. Sayomi

Alege Abdurrzzaq  
Ademola A. Adeyeye  
Khadijah O. Omokanye  
Lukman O Abdur-Rahman  
Olubisi Olutosin Bamidele  
Shakirullah AbdulAzeez  
Aminat Akinoso  
Michael O. Adegboye  
**University of Malaya Medical Centre, Malaysia**  
Shireen Anne Nah  
Yuki Julius Ng  
Syukri Ahmad Zubaidi  
**University of Texas Medical Branch, United States of America**  
Murad Almasri  
Sara Ali  
Rasaq Olaosebikan  
Akila Muthukumar  
**University Teaching Hospital, Zambia**  
Patricia Shinondo  
Amon Ngongola  
Bruce Bvulani  
Azad Patel  
**Usman Danfodiyo University Teaching Hospital, Nigeria**  
Abdullahi Nuhu-Koko  
Baba Jibrin  
Ajiboye L. Olalekan  
Christopher S. Lukong  
Ezekiel I. Ajayi  
**Vall d'Hebron University Hospital, Spain**  
Gabriela Guillén  
Sergio López  
José Andrés Molino  
Pablo Velasco  
**Wingat Royal Hospital, Egypt**  
Omar Elmandouh  
Omar Hamam  
Rim Elmandouh  
**Yale New Haven Hospital, United States of America**  
Nensi Melissa Ruzgar  
Rachel Levinson  
Shashwat Kala  
Sarah Ullrich  
Emily Christison-Lagay  
**Zagazig University Hospital, Egypt**  
Aya Sabry Mortada  
Mahmoud Ahmed Ebada  
Eman Seif Alnaser Solimam  
Khaled Abualkher  
Amr Mohammed Elsayed Yousf  
Mohamed Mohamed Holail



Reem Mohamed Almowafy

**National/Regional Leads:**

Algeria: Salah Eddine Oussama Kacimi  
Bahrain: Fayza Haider  
Bangladesh: Tahmina Banu, Ashrarur Rahman Mitul  
Brazil: Simone de Campos Vieira Abib  
Brunei: Janice Hui Ling Wong  
Canada: Reto Baertschiger  
Egypt: Essam Elhalaby, Muath Alser, Mahmoud M. Saad  
Germany: Guido Seitz, Judith Lindbert  
Ghana: Francis Abantanga  
Greece: Georgios Tsoulfas, Asimina Galli-Tsinopoulou  
Hungary: Agnes Vojcek  
Iran: Maryam Ghavami Adel  
Iraq: Abdulrahman Omar Taha  
Italy: Calogero Virgone, Francesco Pata, Gaetano Gallo  
Jordan: Mohammad K. Abou Chaar, Faris Ayasra  
Kenya: Eric Mwangi Irungu  
Libya: Muhammed Elhadi  
Malaysia: Shireen Anne Nah, Dayang Anita Abdul Aziz  
Malta: Victor Calvagna  
Morocco: Outani Oumaima, Zineb Bentounsi  
Nigeria: Adesoji Ademuyiwa  
Oman: Dhruv Nath Ghosh  
Pakistan: Muhammad Arshad, Lubna Samad  
Peru: Lily Saldana  
Portugal: Jan Godzinsky  
Saudi Arabia: Abdelbasit Ali, Ehab Alameer  
Serbia: Dragana Janic  
Sierra Leone: Mohamed Bella Jalloh, Nellie Bell  
Singapore: Annette Jacobsen, Chan Hon Chui  
South Africa: Milind Chitnis  
Spain: Israel Fernandez Pineda, Lucas Krauel, Maricarmen Olivos  
Sudan: Waha Rahama, Hazim Elfatih  
Switzerland: Raphael N. Vuille-dit-Bille  
Syria: Alaa Hamdan  
Turkey: Arda Isik  
United Arab Emirates: Asim Noor Rana  
United Kingdom: Kokila Lakhoo, Kate Cross, Max Pacht  
United States of America: Andrea Hayes-Jordan, Roshni Dasgupta  
Zambia: Patricia Shinondo, Amon Ngongola  
Middle-East and North Africa: Mohamedraed Elshami

**Appendix S2: Participating Centres****LMIC**

Centre Anti-Cancer, Algeria  
Centre hospitalier universitaire de Batna, Algeria  
CHU Saâdna Abdenour de Sétif, Algeria  
Chittagong Medical College Hospital, Bangladesh  
Dhaka Medical College Hospital, Bangladesh  
Dhaka Shishu (Children) Hospital, Bangladesh  
Brazilian National Cancer Institute (INCA), Brazil  
GPACI - Grupo de Pesquisa e Assistência ao Câncer Infantil, Brazil  
Pediatric Oncology Institute – GRAACC, Brazil  
Ain Shams University Hospital, Egypt  
Al-Hussein University Hospital, Egypt  
Borg El-Arab University Hospital, Egypt  
El Safa Hospital, Egypt  
El Sheikh Zayed Specialized Hospital, Egypt  
Helwan University Hospital, Egypt  
Kasr Al Ainy Hospital, Egypt  
Menoufia University Hospital, Egypt  
MISR Cancer Centre, Egypt  
Tanta University Hospital, Egypt  
Wingat Royal Hospital, Egypt  
Zagazig University Hospital, Egypt  
Tamale Teaching Hospital, Ghana  
Shahid Baghaei Hospital, Iran  
Ibn Al-Atheer Hospital, Iraq  
Raparin Pediatric Teaching Hospital, Iraq  
Al Bashir Hospital, Jordan  
King Abdullah University Hospital, Jordan  
King Hussein Cancer Center, Jordan  
AIC Kijabe Hospital, Kenya  
Benghazi Pediatric Hospital, Libya  
Sabha Medical Centre, Libya  
Tobruk Medical Centre, Libya  
Tripoli University Hospital, Libya  
Universiti Kebangsaan Malaysia Medical Centre, Malaysia  
University of Malaya Medical Centre, Malaysia  
Centre Hospitalo-Universitaire Ibn Sina de Rabat (CHIS), Morocco  
Hôpital des Spécialités ONO, Morocco  
Abubakar Tafawa Balewa University Teaching Hospital, Nigeria  
Ahmadu Bello University Teaching Hospital, Nigeria  
Federal Medical Center, Abeokuta, Nigeria  
Federal Medical Center, Lokoja, Nigeria  
Federal Teaching Hospital Ido-Ekiti, Nigeria  
Lagos University Teaching Hospital, Nigeria  
National Hospital, Nigeria  
Nnamdi Azikiwe University Teaching Hospital, Nigeria  
Olabisi Onabanjo University Teaching Hospital, Nigeria  
University College Hospital (UCH), Nigeria  
University of Abuja Teaching Hospital, Nigeria  
University of Ilorin Teaching Hospital, Nigeria  
Usman Danfodiyo University Teaching Hospital, Nigeria  
Aga Khan University Hospital, Pakistan  
Lahore General Hospital, Pakistan  
Liaquat National Hospital and Medical College, Pakistan  
The Indus Hospital, Pakistan  
Instituto Nacional de Enfermedades Neoplásicas, Peru  
Clinic for Neurosurgery, Clinical Center of Serbia, Serbia

Ola Daring Children's Hospital, Sierra Leone  
Frere Hospital, South Africa  
National Cancer Institute, Sudan  
Tishreen University Hospital, Syria  
Dr. Lutfi Kirdar Kartal Training and Research Hospital, Turkey  
Kanuni Sultan Süleyman Research and Training Hospital, Turkey  
Ministry of Health Marmara University Pendik Research and Application Hospital, Turkey  
Ondokuz Mayıs Üniversitesi, Turkey  
University Teaching Hospital, Zambia

### **HIC**

Salmaniya Medical Complex, Bahrain  
Pantai Jerudong Specialist Centre, Brunei  
The Hospital for Sick Children, Canada  
University Medical Center Hamburg-Eppendorf, Germany  
AHEPA University General Hospital, Greece  
Medical University of Pecs, Department of Paediatrics, Hungary  
Policlinico Umberto I, Sapienza University of Rome, Italy  
Mater Dei Hospital, Sir Anthony Mamo Oncology Centre, Malta  
Khoula Hospital, Oman  
Centro Hospitalar Universitário de São João, Portugal  
King Fahd Central Hospital, Saudi Arabia  
King Salman Armed Forces Hospital, Saudi Arabia  
Prince Mohammed bin Nasser Hospital, Jazan, Saudi Arabia  
KK Women's and Children's Hospital, Singapore  
Vall d'Hebron University Hospital, Spain  
University Children's Hospital of Basel, Switzerland  
Dubai Hospital, United Arab Emirates  
Alder Hay Children's Hospital, United Kingdom  
Birmingham Children's Hospital, United Kingdom  
Gloucestershire Hospitals NHS Foundation Trust, United Kingdom  
John Radcliffe Hospital, United Kingdom  
Children's Hospital of Wisconsin, United States of America  
Johns Hopkins Hospital Bloomberg Children's Hospital, United States of America  
Mayo Clinic, United States of America  
University of Texas Medical Branch, United States of America  
Yale New Haven Hospital, United States of America



Human Research Protection Program  
Institutional Review Boards  
FWA00002571  
25 Science Park – 3rd Fl., 150 Munson St.  
New Haven CT 06520-8327

Telephone: 203-785-4688  
<http://www.yale.edu/hrpp>

September 1, 2020

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## APPROVAL OF SUBMISSION VIA EXPEDITED REVIEW

**Approval Date:** 9/1/2020

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|                         |   |
|-------------------------|---|
| <b>Investigator:</b>    | Emily Christison-Lagay  |
| <b>Type of Review:</b>  | Initial Study   |
| <b>Title of Study:</b>  | Pediatric tumor surgery during the COVID-19 pandemic: an international, multicenter observational cohort study (COVIDPaedCancerSurg) – Yale New Haven Hospital branch |
| <b>IRB Protocol ID:</b> | 2000028852  |
| <b>Submission ID:</b>   | 2000028852  |

---

Research activities associated with this submission are approved and may begin consistent with the terms of IRB approval.

The IRB has determined that this protocol presents minimal risk to subjects.

This approval is for medical record review only. This approval does not authorize patient contact.

Please be advised that Yale-New Haven Hospital and Yale Medical Group have implemented a new reporting request process. Requests for medical records should be made through JDAT as described at <http://medicine.yale.edu/ycci/oncore/availableservices/datarequests/datarequests.aspx>.

YNHH and Yale University consider it a violation of patient privacy for research personnel to review medical records of patients who have opted out of research use of their records. All record review requests should therefore be through JDAT.

The IRB has determined that informed consent can be waived for this medical record review.

The IRB has granted a waiver of HIPAA authorization for access to and use of protected health information (PHI) as described in the approved protocol for this medical record review. This waiver does not authorize subject contact.



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HIPAA regulations require that accounting logs be maintained when researchers access patient records under a waiver of authorization including those approved for recruitment purposes. You are thereby reminded of your obligation to create the log. For further information on maintaining logs and on the accounting of disclosures, please see [hipaa.yale.edu](http://hipaa.yale.edu).

IRB approval of research or proposed changes to previously approved research does NOT constitute institutional approval for initiating or resuming in-person research during a pandemic. It is your responsibility to comply with institutional, federal, state, and local requirements (including Centers for Disease Control (CDC) and State of Connecticut guidelines), and other applicable policies. Please review the Yale requirements for research reactivation on the Yale website: <https://research.yale.edu/phase-2-research-reactivation>.

---

See the next pages for important reminders and the list of IRB approved documents.



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**IMPORTANT REMINDERS:**

- This research does not require IRB continuing review.
  - You are obligated to submit the following to the IRB:
    - **Modifications:** Changes must be submitted with a modification and approved by the IRB prior to implementation except to eliminate immediate hazards to participants. This includes changes to study procedures, informed consent documents, recruitment activities or study personnel.
    - **Reportable New Information:** Information that requires prompt reporting to the IRB must be done so within 5 days of the PI becoming aware of the event (see Policy 710: Reporting Unanticipated Problems Involving Risks to Subjects or Others, including Adverse Events). This includes potential serious noncompliance, continuing noncompliance, and unanticipated problems to subjects or others.
    - **Closure request** (to end the IRB's oversight) when:
      - i. The protocol is permanently closed to enrollment,
      - ii. All subjects have completed all protocol related interventions and interactions, and
      - iii. Analysis of private identifiable information is completed.
  - In conducting this activity, you should refer to and follow the Investigator Manual (HRP-103) as applicable, which can be found in the IRB Library within the IRB system.
-



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**IRB APPROVED DOCUMENTATION:**

- Main Data Collection Form, Category: Study questionnaires, measures, focus groups/interview questions;
- YNHH Specific Data Collection Form, Category: Study questionnaires, measures, focus groups/interview questions;
- Concept Approval, Category: Ancillary Committee Approval;
- Medical Record Review Protocol, Category: IRB Protocol;

---

Please keep this letter with your copy of the approved protocol documents.

E-mail: [mhrec@moh.gov.bn](mailto:mhrec@moh.gov.bn)



MHREC Executive Screening Suite  
Basement Carpark Level 1  
Raja Isteri Pengiran Anak Saleha Hospital  
Bandar Seri Begawan BA1710  
Negara Brunei Darussalam

Our Ref : MHREC/MOH/2020/14(2)

25<sup>th</sup> November 2020  
9 Rabiulakhir 1442

To:  
Miss Janice Wong  
Consultant Paediatric Surgeon  
Department of General Surgery  
RIPAS Hospital

Dear Miss Janice,

**Re: "A global study looking at the Impact of the Coronavirus disease (COVID-19) on the care of childhood cancers (COVIDPaedsCancer)"**

We are pleased to inform you that Medical and Health Research & Ethic Committee has given **full approval** to your research proposal entitled above.

Please also adhere to the conditions stated below:

- The study should comply to the Guidelines for Good Clinical Practice
- Any deviation to the study should have MHREC's written approval
- Please provide us a report of your research findings

This approval is valid for one year from the date of this letter or the proposed duration that you have applied for your study, whichever is shorter. If you wish to extend your research beyond this period, you are required to apply to MHREC at least one month before the end of your approval including a preliminary report of your research findings.

All the best with your research.

**"BERSAMA KE ARAH WARGA SIHAT"**  
"Warga Sihat Negara Sejahtera"

Yours Sincerely,

[Dr Alice Yong Moi Ling]

**Chairperson of Medical and Health Research & Ethics Committee**

Hspkh  
Cc 1. Deputy Permanent Secretary (Professional), MOH  
2. Director General of Medical and Health Services, MOH.

---

A global study looking at the Impact of the Coronavirus disease (COVID-19) on the care of childhood cancers (COVIDPaedsCancer)





MINIT

Yang Mulia  
Miss Janice Wong  
*MBChB(Edin) MRCSEd FAMS(Paed Surgery)*  
Konsultan Pembedahan Pediatrik  
Jabatan Pembedahan Umum  
Hospital Raja Isteri Pengiran Anak Saleha

**MEMOHON KEBENARAN MENJALANKAN AUDIT "A GLOBAL STUDY LOOKING AT THE IMPACT OF THE CORONAVIRUS DISEASE (COVID-19) ON THE CARE OF CHILDHOOD CANCERS (COVIDPAEDSCANCER)"**

Dengan hormatnya merujuk permohonan Doktor bertarikh 20 Muharram 1442 bersamaan 10 Ogos 2020 mengenai perkara tersebut di atas.

Sehubungan dengan itu, Pejabat ini **tidak ada halangan** bagi Doktor menjalankan penyelidikan yang tersebut di atas. Walaubagaimanapun persetujuan atau keizinan dari *Medical and Research and Ethics Committe MHREC* perlu dipastikan dahulu sebelum membuat kajian.

Sekian disampaikan untuk makluman Doktor mengenainya.

'Bersama Ke Arah Warga Sihat'  
'Sentiasa Berkhidmat Dengan Petunjuk Allah'

**[ABDOL HAZIS BIN HAJI AHAD]**  
Pemangku Ketua Pegawai Eksekutif Tingkat Khas  
Hospital Raja Isteri Pengiran Anak Saleha

Rujukan Kami: 11/CEO/HRIPAS/4049/2002 Pt.2  
Tarikh: 29 Muharram 1442H/ 17 September 2020

cc. Pejabat Ketua Pengarah Perkhidmatan dan Perubatan.  
*Medical and Health Research and Committee MHREC*  
Penguasa Perubatan, Hospital Raja Isteri Pengiran Anak Saleha.

Dkn2012 / HA2

Tanta University  
Faculty of Medicine  
Research Ethics Committee  
Federal Wide Assurance ( FWA)  
FWA00022834  
IRB0010038



جامعة طنطا  
كلية الطب  
لجنة أخلاقيات البحث العلمي

## Research Ethics Committee Review Report

Approval Code: 33965/7/20

Name of the PI: محمد جمال البهنساوي

Position : مدرس

Name of the Department : طب الطوارئ و الاصابات

Type of the research: MSc  MD  Promotion research

Project

Paediatric tumour during the COVID-19 pandemic: an international, multicentre, observational cohort study

اورام الاطفال أثناء جائحة الكورونا المستجد: دراسة ملاحظة. جمعية من عدة مراكز دولية

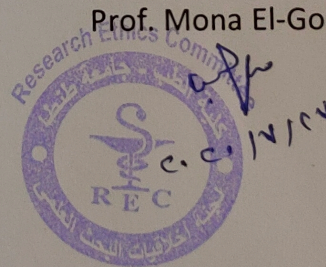
Approved  Disapproved  Approved after modification

This Research proposal conforms to the accepted ethical standard

Date: 19/7/2020

Chief of Ethics committee

Prof. Mona El-Gohary



STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

|                              | Item No | Recommendation   | Page No |
|------------------------------|---------|--|---------|
| <b>Title and abstract</b>    | 1       | (a) Indicate the study's design with a commonly used term in the title or the abstract   | 1       |
|                              |         | (b) Provide in the abstract an informative and balanced summary of what was done and what was found  | 2       |
| <b>Introduction</b>          |         |  |         |
| Background/rationale         | 2       | Explain the scientific background and rationale for the investigation being reported   | 3       |
| Objectives                   | 3       | State specific objectives, including any prespecified hypotheses   | 3       |
| <b>Methods</b>               |         |  |         |
| Study design                 | 4       | Present key elements of study design early in the paper  | 3       |
| Setting                      | 5       | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection  | 4       |
| Participants                 | 6       | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up<br>(b) For matched studies, give matching criteria and number of exposed and unexposed  | 4       |
| Variables                    | 7       | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable   | 4-5     |
| Data sources/<br>measurement | 8*      | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group   | 4-5     |
| Bias                         | 9       | Describe any efforts to address potential sources of bias  | 4       |
| Study size                   | 10      | Explain how the study size was arrived at  | 4-5     |
| Quantitative variables       | 11      | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why   | 5       |
| Statistical methods          | 12      | (a) Describe all statistical methods, including those used to control for confounding<br>(b) Describe any methods used to examine subgroups and interactions<br>(c) Explain how missing data were addressed<br>(d) If applicable, explain how loss to follow-up was addressed<br>(e) Describe any sensitivity analyses | 4-5     |
| <b>Results</b>               |         |  |         |
| Participants                 | 13*     | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed<br>(b) Give reasons for non-participation at each stage<br>(c) Consider use of a flow diagram                        | 5       |
| Descriptive data             | 14*     | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders<br>(b) Indicate number of participants with missing data for each variable of interest<br>(c) Summarise follow-up time (eg, average and total amount)                         | 5-6     |
| Outcome data                 | 15*     | Report numbers of outcome events or summary measures over time   | 6-10    |

|                          |    |   |       |
|--------------------------|----|---|-------|
| Main results             | 16 | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(b) Report category boundaries when continuous variables were categorized<br>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 6-7   |
| Other analyses           | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses  | 8-10  |
| <b>Discussion</b>        |    |   |       |
| Key results              | 18 | Summarise key results with reference to study objectives  | 10    |
| Limitations              | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias  | 11    |
| Interpretation           | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence  | 10-11 |
| Generalisability         | 21 | Discuss the generalisability (external validity) of the study results   | 11    |
| <b>Other information</b> |    |   |       |
| Funding                  | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based   | 12    |

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

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## Baseline Information

Record ID \_\_\_\_\_

**The Global Health Research Group for Children's Non-Communicable Diseases (Global Children's NCDs ) wishes to thank you for being a collaborator on our international multi-center study looking at the impact of the Coronavirus disease (COVID-19) on the care of childhood cancers: COVIDPaedsCancer**

Are you able to provide a patient's date of birth?  Yes  
 No

In order to contribute to COVIDPaedsCancer you should first secure local study approval.  Yes  
 No

Has local study approval been secured?

Please secure local study approval before adding any patient data onto REDCap

Please select the option that is true for this patient  Patient was undergoing active anti-cancer treatment on 12th March 2020  
 Patient newly presented post 11th March 2020  
 Neither of the above

Date of birth

\_\_\_\_\_  
(Day-Month-Year)

Age of patient (in years)

Does this patient have a tumour?  Yes  
 No

This patient does not meet the inclusion criteria for COVIDPaedsCancer

Sex  Female  
 Male  
 Ambiguous

Weight (kg)

\_\_\_\_\_  
(First weight undertaken during admission)

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ASA Grade

- 1 - a normal healthy patient
  - 2 - a patient with mild systemic disease
  - 3 - a patient with severe systemic disease
  - 4 - a patient with severe systemic disease that is a constant threat to life
  - 5 - a moribund patient who is not expected to survive without the operation
- (ASA (American Society of Anesthesiologists) grade at the time of surgery)
- 

Did this patient present to the hospital before July 12th 2020?

- Yes
- No

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## Tumour Details

|  |   |
|--|---|
| Diagnostic group/subgroup of tumour  | <input type="radio"/> Acute lymphoblastic leukaemia<br><input type="radio"/> Hodgkin lymphoma<br><input type="radio"/> Non-Hodgkin lymphoma<br><input type="radio"/> Neuroblastoma<br><input type="radio"/> Wilms Tumour<br><input type="radio"/> Rhabdomyosarcoma<br><input type="radio"/> Osteosarcoma<br><input type="radio"/> Ewings sarcoma<br><input type="radio"/> Retinoblastoma<br><input type="radio"/> Glioma<br><input type="radio"/> Medulloblastoma |
| Grade of glioma  | <input type="radio"/> Low grade (WHO grade I/II)<br><input type="radio"/> High grade (WHO grade III/IV)<br><input type="radio"/> Unknown  |
| Staging  | <input type="radio"/> CNS negative (CNS 1)<br><input type="radio"/> CNS positive (CNS 2/3)<br><input type="radio"/> Unknown<br>(Central nervous system (CNS) disease: the presence of leukemia cells in the cerebral spinal fluid)  |
| Staging  | <input type="radio"/> Ann Arbor-stage IA/B<br><input type="radio"/> Ann Arbor-stage IIA/B<br><input type="radio"/> Ann Arbor-stage IIIA/B<br><input type="radio"/> Ann Arbor-stage IVA/B<br><input type="radio"/> Unknown   |
| Staging  | <input type="radio"/> Localised<br><input type="radio"/> Regional<br><input type="radio"/> Metastatic<br><input type="radio"/> Unknown  |
| Date of diagnosis  | _____   |
|  | (Day-Month-Year)  |
| What was the initial MDT (tumour board) decision for managing this tumour? (select all that apply) | <input type="checkbox"/> Chemotherapy<br><input type="checkbox"/> Radiotherapy<br><input type="checkbox"/> Immunological therapy<br><input type="checkbox"/> Surgery<br><input type="checkbox"/> No anticancer therapy  |
| Was a central venous catheter inserted in the patient?   | <input type="radio"/> Yes<br><input type="radio"/> No<br>(Insertion of a central venous catheter does not count as surgery)   |
| What type of central venous catheter was inserted?   | <input type="radio"/> Peripherally inserted central catheter (PICC line)<br><input type="radio"/> Portacaths<br><input type="radio"/> Other   |
| What type of central venous catheter was inserted? (other selected)                                | _____   |

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Date of treatment decision by the tumour board

---

(Day-Month-Year)

---

Would this decision have been different prior to the COVID-19 pandemic?

- Yes  
 No

---

What would the pre-COVID 19 decision for managing this tumour be?

- Chemotherapy  
 Radiotherapy  
 Immunological therapy  
 Surgery  
 No anticancer therapy



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## Chemotherapy

---

|   |   |
|---|---|
| Did the patient have chemotherapy post March 11th 2020?                 | <input type="radio"/> Yes<br><input type="radio"/> No |
| Did the patient have chemotherapy during their 30-day follow up period? | <input type="radio"/> Yes<br><input type="radio"/> No |
| Did the patient have chemotherapy during their 90-day follow up period? | <input type="radio"/> Yes<br><input type="radio"/> No |
| Is there still a plan for chemotherapy treatment?                       | <input type="radio"/> Yes<br><input type="radio"/> No |

---

|  |   |
|--|---|
| Were there any changes to the chemotherapy treatment due to the COVID-19 pandemic? | <input type="checkbox"/> No change to chemotherapy care because of COVID-19<br><input type="checkbox"/> Chemotherapy treatment cancelled because of COVID-19<br><input type="checkbox"/> Chemotherapy treatment delayed because of COVID-19<br><input type="checkbox"/> Reduction from typical chemotherapy dose because of COVID-19<br><input type="checkbox"/> Increase from typical chemotherapy dose because of COVID-19<br><input type="checkbox"/> Reduction in the number of cycles of chemotherapy because of COVID-19<br><input type="checkbox"/> Increase in the number of cycles of chemotherapy because of COVID-19<br><input type="checkbox"/> Shorter duration of treatment because of COVID-19<br><input type="checkbox"/> Longer duration of treatment because of COVID-19<br><input type="checkbox"/> Change in choice of chemotherapy agent<br><input type="checkbox"/> Change in route of administration of chemotherapy agent<br><input type="checkbox"/> Change to/addition of an alternative anti-cancer treatment modality because of COVID-19 |
|--|---|

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---

What were the reasons for the change(s) to the treatment?

- Change in treatment as per local MDT / hospital policy (decision making)
- Change in treatment as per regional policy (decision making)
- Change in treatment as per national policy (decision making)
- Change in treatment plan by lead clinician (decision making)
- Lockdown/Travel restrictions prevent access to treatment (infrastructure)
- Lack of hospital inpatient beds (infrastructure)
- Lack of hospital intensive care beds (infrastructure)
- Lack of outpatient facilities for support post-discharge (infrastructure)
- Lack of blood products (infrastructure)
- Lack of personal protective equipment (infrastructure)
- Lack of equipment (infrastructure)
- Lack of drugs (infrastructure)
- Insufficient staff due to redeployment/restructuring (workforce)
- Insufficient staff due to sickness (workforce)
- No treatment available due to restructuring of services (service delivery)
- Transfer to a different institution for treatment (service delivery)
- Inability to pay for treatment (financing)
- Loss of employment by caregiver (financing)
- Patient/patient's family chooses to avoid treatment during the pandemic (patient factors)
- Treatment not possible as caregiver infected with Coronavirus and under mandatory isolation (patient factors)
- Other

---

What were the reasons for the change(s) to the treatment: other

---

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## Radiotherapy

---

Did the patient have radiotherapy post March 11th 2020?

Yes  
 No

---

Did the patient have radiotherapy during the 30-day follow up period?

Yes  
 No

---

Did the patient have radiotherapy during the 90-day follow up period?

Yes  
 No

---

Is there still a plan for radiotherapy treatment?

Yes  
 No

---

Were there any changes to the radiotherapy treatment due to the COVID-19 pandemic?

- No change to radiotherapy care because of COVID-19
- Radiotherapy treatment cancelled because of COVID-19
- Radiotherapy treatment delayed because of COVID-19
- Decrease in typical radiotherapy dose per fraction because of COVID-19
- Increase in typical radiotherapy dose per fraction because of COVID-19
- Reduction in duration from typical radiotherapy length of treatment because of COVID-19
- Increase in duration from typical radiotherapy length of treatment because of COVID-19
- Change in radiotherapy modality because of COVID-19
- Change to/addition of an alternative anti-cancer treatment modality because of COVID-19

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What were the reasons for the change(s) to the treatment?

- Change in treatment as per local MDT / hospital policy (decision making)
- Change in treatment as per regional policy (decision making)
- Change in treatment as per national policy (decision making)
- Change in treatment plan by lead clinician (decision making)
- Lockdown/Travel restrictions prevent access to treatment (infrastructure)
- Lack of hospital inpatient beds (infrastructure)
- Lack of hospital intensive care beds (infrastructure)
- Lack of outpatient facilities for support post-discharge (infrastructure)
- Lack of blood products (infrastructure)
- Lack of personal protective equipment (infrastructure)
- Lack of equipment (infrastructure)
- Lack of drugs (infrastructure)
- Insufficient staff due to redeployment/restructuring (workforce)
- Insufficient staff due to sickness (workforce)
- No treatment available due to restructuring of services (service delivery)
- Transfer to a different institution for treatment (service delivery)
- Inability to pay for treatment (financing)
- Loss of employment by caregiver (financing)
- Patient/patient's family chooses to avoid treatment during the pandemic (patient factors)
- Treatment not possible as caregiver infected with Coronavirus and under mandatory isolation (patient factors)
- Other

What were the reasons for the change(s) to the treatment: other

---

What was the radiation field?

- Craniospinal
- Focal (brain)

What was the radiation field?

- Local
- Wide field

Radiotherapy approach

- Photon
- Proton beam

Did this represent a change to your typical radiotherapy approach in the pre-COVID-19 era?

- No change to radiotherapy approach
- Yes, chose to avoid photon radiotherapy related to COVID-19
- Yes, chose to avoid proton beam radiotherapy related to COVID-19

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## Immunological Therapy

---

Did the patient have immunotherapy post March 11th 2020?

Yes  
 No

---

Did the patient have immunotherapy during the 30-day follow up period?

Yes  
 No

---

Did the patient have immunotherapy during the 90-day follow up period?

Yes  
 No

---

Is there still a plan for immunotherapy treatment?

Yes  
 No

---

Were there any changes to the immunotherapy treatment due to the COVID-19 pandemic?

- No change to immunotherapy care because of COVID-19  
 Immunotherapy treatment cancelled because of COVID-19  
 Immunotherapy treatment delayed because of COVID-19  
 Change in typical immunotherapy dose because of COVID-19  
 Change in typical immunotherapy length of treatment because of COVID-19  
 Change to/addition of an alternative anti-cancer treatment modality because of COVID-19

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What were the reasons for the change(s) to the treatment?

- Change in treatment as per local MDT / hospital policy (decision making)
- Change in treatment as per regional policy (decision making)
- Change in treatment as per national policy (decision making)
- Change in treatment plan by lead clinician (decision making)
- Lockdown/Travel restrictions prevent access to treatment (infrastructure)
- Lack of hospital inpatient beds (infrastructure)
- Lack of hospital intensive care beds (infrastructure)
- Lack of outpatient facilities for support post-discharge (infrastructure)
- Lack of blood products (infrastructure)
- Lack of personal protective equipment (infrastructure)
- Lack of equipment (infrastructure)
- Lack of drugs (infrastructure)
- Insufficient staff due to redeployment/restructuring (workforce)
- Insufficient staff due to sickness (workforce)
- No treatment available due to restructuring of services (service delivery)
- Transfer to a different institution for treatment (service delivery)
- Inability to pay for treatment (financing)
- Loss of employment by caregiver (financing)
- Patient/patient's family chooses to avoid treatment during the pandemic (patient factors)
- Treatment not possible as caregiver infected with Coronavirus and under mandatory isolation (patient factors)
- Other

---

What were the reasons for the change(s) to the treatment: other

---

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## Surgery

Did the patient have surgery post March 11th 2020?  Yes  
 No

Did the patient have surgery during the 30-day follow up period?  Yes  
 No

Did the patient have surgery during the 90-day follow up period?  Yes  
 No

Date of first surgery post March 11th 2020

\_\_\_\_\_  
(Day-Month-Year)

Is there still a plan for surgical treatment?  Yes  
 No

Were there any changes to the surgical treatment due to the COVID-19 pandemic?

- No change to operative care because of COVID-19
- Operation not offered because of COVID-19
- Operation abandoned because of COVID-19
- Operation delayed because of COVID-19
- Change in choice of operation
- Operation performed in an alternative hospital (e.g. designated COVID-free)
- Interventional radiology procedure performed before surgery where this would not typically have been indicated
- Underwent neoadjuvant therapy where this would not typically have been indicated
- No neoadjuvant therapy given, where this would typically have been indicated
- Underwent a longer or more intensive course of neoadjuvant therapy that would have typically been indicated
- Underwent a shorter or less intensive course of neoadjuvant therapy that would have typically been indicated
- Underwent adjuvant therapy where this would not typically have been indicated
- No adjuvant therapy, where this would typically have been indicated
- Not recruited to a clinical trial, where this would typically have been offered
- Recruited to a clinical trial, where this would not have previously been offered
- Changed to active palliative care instead of operative care

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What were the reasons for the change(s) to the treatment?

- Change in treatment as per local MDT / hospital policy (decision making)
- Change in treatment as per regional policy (decision making)
- Change in treatment as per national policy (decision making)
- Change in treatment plan by lead clinician (decision making)
- Lockdown/Travel restrictions prevent access to treatment (infrastructure)
- Lack of hospital inpatient beds (infrastructure)
- Lack of hospital intensive care beds (infrastructure)
- Lack of outpatient facilities for support post-discharge (infrastructure)
- Lack of blood products (infrastructure)
- Lack of personal protective equipment (infrastructure)
- Lack of equipment (infrastructure)
- Lack of drugs (infrastructure)
- Insufficient staff due to redeployment/restructuring (workforce)
- Insufficient staff due to sickness (workforce)
- No treatment available due to restructuring of services (service delivery)
- Transfer to a different institution for treatment (service delivery)
- Inability to pay for treatment (financing)
- Loss of employment by caregiver (financing)
- Patient/patient's family chooses to avoid treatment during the pandemic (patient factors)
- Treatment not possible as caregiver infected with Coronavirus and under mandatory isolation (patient factors)
- Other

What were the reasons for the change(s) to the treatment: other

---

What type of hospital was the operation performed in?

- Designated COVID-free 'cold' hospital
- Designated COVID-treatment 'hot' hospital
- Undesignated hospital type with emergency department
- Undesignated hospital type without emergency department

Time from admission to operation (preoperative delay)

- < 6 hours
- 6-23 hours
- 24-47 hours
- 48-71 hours
- 72+ hours



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|   |  |
|---|--|
| Urgency of surgery  | <input type="radio"/> IMMEDIATE - life, limb or organ-saving intervention - within minutes of decision to operate<br><input type="radio"/> URGENT - within hours of decision to operate<br><input type="radio"/> EXPEDITED - patient requiring early treatment but no immediate threat to life, limb or organ - within days of decision to operate<br><input type="radio"/> ELECTIVE - Intervention planned or booked in advance of routine admission to hospital<br>(Full definitions available at: <a href="https://www.ncepod.org.uk/classification.html">https://www.ncepod.org.uk/classification.html</a> ) |
| What was the reason urgent or emergency cancer surgery was required?            | <input type="radio"/> Gastro-intestinal obstruction<br><input type="radio"/> Bleeding<br><input type="radio"/> Sepsis<br><input type="radio"/> Tumour progression<br><input type="radio"/> Organ perforation<br><input type="radio"/> Functional compromise<br><input type="radio"/> Other   |
| Other reason for why urgent or emergency cancer surgery was required            | _____  |
| Did the patient have a mandatory self-isolation period before elective surgery? | <input type="radio"/> Yes, two weeks or more<br><input type="radio"/> Yes, less than two weeks<br><input type="radio"/> No   |
| Was screening for COVID-19 performed within the 72 hours before surgery?        | <input type="radio"/> No<br><input type="radio"/> Yes - Laboratory test<br><input type="radio"/> Yes - CT thorax<br><input type="radio"/> Yes - Symptomatic screening or questionnaire only<br><input type="radio"/> Yes - Other   |
| Screening: Other  | _____  |
| Was the patient known to have COVID-19 infection before the time of surgery?    | <input type="radio"/> Yes - proven with laboratory test or CT Thorax<br><input type="radio"/> Probable - clinically suspected<br><input type="radio"/> No<br><input type="radio"/> Unknown   |
| Had the COVID-19 infection resolved?  | <input type="radio"/> Yes<br><input type="radio"/> No  |
| How long before the date of surgery was COVID-19 diagnosed?                     | <input type="radio"/> Less than 1 week<br><input type="radio"/> 2 to 4 weeks<br><input type="radio"/> 5 to 8 weeks<br><input type="radio"/> Greater than 8 weeks   |
| What was the primary purpose of the surgery?                                    | <input type="radio"/> Diagnostic<br><input type="radio"/> Curative<br><input type="radio"/> Palliative   |
| Type of anaesthesia used?   | <input type="radio"/> Local<br><input type="radio"/> Regional<br><input type="radio"/> General   |

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|  |  |
|--|--|
| Operative approach   | <input type="radio"/> Open<br><input type="radio"/> Minimally-invasive<br><input type="radio"/> Minimally-invasive converted to open   |
| Did this represent a change to your typical operative approach in the pre-COVID-19 era?    | <input type="radio"/> No change to operative approach<br><input type="radio"/> Yes, chose to avoid minimally invasive surgery related to COVID-19<br><input type="radio"/> Yes, chose to avoid open surgery related to COVID-19  |
| Designation of the operating theatre   | <input type="radio"/> Designated COVID treatment area (only COVID patients treated there)<br><input type="radio"/> Designated non-COVID treatment area (only non-COVID patients treated there)<br><input type="radio"/> No designation for this area (either COVID or non-COVID patients can be treated there)<br><input type="radio"/> Not applicable |
| Designation of the intensive care unit   | <input type="radio"/> Designated COVID treatment area (only COVID patients treated there)<br><input type="radio"/> Designated non-COVID treatment area (only non-COVID patients treated there)<br><input type="radio"/> No designation for this area (either COVID or non-COVID patients can be treated there)<br><input type="radio"/> Not applicable |
| Would a post-operative intensive care unit stay have been planned in a pre-COVID-19 era?   | <input type="radio"/> Yes<br><input type="radio"/> No  |
| Designation of the postoperative ward  | <input type="radio"/> Designated COVID treatment area (only COVID patients treated there)<br><input type="radio"/> Designated non-COVID treatment area (only non-COVID patients treated there)<br><input type="radio"/> No designation for this area (either COVID or non-COVID patients can be treated there)<br><input type="radio"/> Not applicable |
| Was a post-operative CT head performed?  | <input type="radio"/> Yes<br><input type="radio"/> No  |
| Did any of the operating surgeons contract COVID-19 within 30-days of the date of surgery? | <input type="radio"/> Yes<br><input type="radio"/> No  |
| Did the patient undergo more than one surgery post March 11th 2020?                        | <input type="radio"/> Yes<br><input type="radio"/> No  |

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## No Anticancer Treatment

Did the patient or their family choose to avoid treatment during the pandemic before the initial MDT (tumour board) meeting?  Yes  
 No

Was the patient given palliative treatment post March 11th 2020??  Yes  
 No

Were there any changes to the palliative care treatment due to the COVID-19 pandemic?

- No change to palliative care because of COVID-19
- Palliative treatment \*not\* provided because of COVID-19
- Palliative treatment provided because of COVID-19
- Palliative treatment delayed because of COVID-19
- Change from typical palliative care plan because of COVID-19

What were the reasons for the change to palliative care treatment?

- Change in treatment as per local MDT / hospital policy (decision making)
- Change in treatment as per regional policy (decision making)
- Change in treatment as per national policy (decision making)
- Change in treatment plan by lead clinician (decision making)
- Lockdown/Travel restrictions prevent access to treatment (infrastructure)
- Lack of hospital inpatient beds (infrastructure)
- Lack of hospital intensive care beds (infrastructure)
- Lack of outpatient facilities for support post-discharge (infrastructure)
- Lack of blood products (infrastructure)
- Lack of personal protective equipment (infrastructure)
- Lack of equipment (infrastructure)
- Lack of drugs (infrastructure)
- Insufficient staff due to redeployment/restructuring (workforce)
- Insufficient staff due to sickness (workforce)
- No treatment available due to restructuring of services (service delivery)
- Transfer to a different institution for treatment (service delivery)
- Inability to pay for treatment (financing)
- Loss of employment by caregiver (financing)
- Patient/patient's family chooses to avoid treatment during the pandemic (patient factors)
- Treatment not possible as caregiver infected with Coronavirus and under mandatory isolation (patient factors)
- Other

What were the reasons for the change to palliative care treatment: other \_\_\_\_\_

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## Outcomes

Was screening for COVID-19 performed within 30 days from their first anti-cancer treatment post March 11th 2020?

- No  
 Yes - Laboratory test  
 Yes - CT thorax  
 Yes - Symptomatic screening or questionnaire only  
 Yes - Other  
 Not applicable (no anti-cancer treatment given post March 11th 2020)

Was screening for COVID-19 performed within 30 days from their first anti-cancer treatment post March 11th 2020: other

Was the patient diagnosed with COVID-19 within 30 days from their first anti-cancer treatment post March 11th 2020?

- Yes - proven with laboratory test or CT Thorax  
 Probable - clinically suspected  
 No  
 Unknown  
 Not applicable (no anti-cancer treatment given post March 11th 2020)

Complications within 30 days from their first surgical treatment post March 11th 2020?

- Anaesthetic complications  
 Anastomotic leak  
 Blood transfusion  
 Cardiac arrest  
 Pneumonia  
 Sepsis  
 Wound dehiscence  
 Line Infection  
 Neurological injury  
 Vascular injury  
 Altered bowel and bladder function  
 Hepatic injury  
 Other loss of function  
 Early recurrence / Incomplete clearance  
 No complications  
 Not applicable (no anti-cancer treatment given post March 11th 2020)

Complications within 30 days from their first chemotherapy treatment post March 11th 2020?

- Anaesthetic complications  
 Anastomotic leak  
 Blood transfusion  
 Cardiac arrest  
 Pneumonia  
 Sepsis  
 Wound dehiscence  
 Line Infection  
 Neurological injury  
 Vascular injury  
 Altered bowel and bladder function  
 Hepatic injury  
 Other loss of function  
 Early recurrence / Incomplete clearance  
 No complications  
 Not applicable (no anti-cancer treatment given post March 11th 2020)

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Complications within 30 days from their first radiotherapy treatment post March 11th 2020?

- Anaesthetic complications
- Anastomotic leak
- Blood transfusion
- Cardiac arrest
- Pneumonia
- Sepsis
- Wound dehiscence
- Line Infection
- Neurological injury
- Vascular injury
- Altered bowel and bladder function
- Hepatic injury
- Other loss of function
- Early recurrence / Incomplete clearance
- No complications
- Not applicable (no anti-cancer treatment given post March 11th 2020)

Complications within 30 days from their first immunotherapy treatment post March 11th 2020?

- Anaesthetic complications
- Anastomotic leak
- Blood transfusion
- Cardiac arrest
- Pneumonia
- Sepsis
- Wound dehiscence
- Line Infection
- Neurological injury
- Vascular injury
- Altered bowel and bladder function
- Hepatic injury
- Other loss of function
- Early recurrence / Incomplete clearance
- No complications
- Not applicable (no anti-cancer treatment given post March 11th 2020)

Outcomes at 30-day follow up?

- Died - did not receive anti-cancer treatment
- Died - during anti-cancer treatment
- Died - on days 0-7 after anti-cancer treatment
- Died - on days 8-30 after anti-cancer treatment
- Alive - remains admitted in hospital
- Alive - transferred to another hospital
- Alive - discharged to a rehabilitation centre
- Alive - discharged home

Mortality at 90-day follow up?

- Alive
- Dead
- Unknown

Total length of hospital stay (days) within the 90-day follow up period

---

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How many admissions did the patient have within their 90-day follow up period?

- 1  
 2  
 3  
 4  
 5  
 6  
 7  
 8  
 9  
 10  
 > 10

---

Was the 1st admission a planned admission?

- Yes  
 No

---

Length of stay during 1st admission

---

---

What treatments were provided during the 1st admission?

- Chemotherapy  
 Radiotherapy  
 Immunological therapy  
 Surgery  
 Complication management  
 None of the above

---

Was the 2nd admission a planned admission?

- Yes  
 No

---

Length of stay during 2nd admission

---

---

What treatments were provided during the 2nd admission?

- Chemotherapy  
 Radiotherapy  
 Immunological therapy  
 Surgery  
 Complication management  
 None of the above

---

Was the 3rd admission a planned admission?

- Yes  
 No

---

Length of stay during 3rd admission

---

---

What treatments were provided during the 3rd admission?

- Chemotherapy  
 Radiotherapy  
 Immunological therapy  
 Surgery  
 Complication management  
 None of the above

---

Was the 4th admission a planned admission?

- Yes  
 No

---

Length of stay during 4th admission

---

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What treatments were provided during the 4th admission?

- Chemotherapy
- Radiotherapy
- Immunological therapy
- Surgery
- Complication management
- None of the above

---

Was the 5th admission a planned admission?

- Yes
- No

---

Length of stay during 5th admission

---

---

What treatments were provided during the 5th admission?

- Chemotherapy
- Radiotherapy
- Immunological therapy
- Surgery
- Complication management
- None of the above

---

Was the 6th admission a planned admission?

- Yes
- No

---

Length of stay during 6th admission

---

---

What treatments were provided during the 6th admission?

- Chemotherapy
- Radiotherapy
- Immunological therapy
- Surgery
- Complication management
- None of the above

---

Was the 7th admission a planned admission?

- Yes
- No

---

Length of stay during 7th admission

---

---

What treatments were provided during the 7th admission?

- Chemotherapy
- Radiotherapy
- Immunological therapy
- Surgery
- Complication management
- None of the above

---

Was the 8th admission a planned admission?

- Yes
- No

---

Length of stay during 8th admission

---

---

What treatments were provided during the 8th admission?

- Chemotherapy
- Radiotherapy
- Immunological therapy
- Surgery
- Complication management
- None of the above

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Was the 9th admission a planned admission?  Yes  
 No

---

Length of stay during 9th admission

---

---

What treatments were provided during the 9th admission?

- Chemotherapy
- Radiotherapy
- Immunological therapy
- Surgery
- Complication management
- None of the above

---

Was the 10th admission a planned admission?  Yes  
 No

---

Length of stay during 10th admission

---

---

What treatments were provided during the 10th admission?

- Chemotherapy
- Radiotherapy
- Immunological therapy
- Surgery
- Complication management
- None of the above

---

Mortality at 12-month follow-up?  Alive  
 Dead  
 Unknown



**Appendix S8 – Baseline Characteristics of low-and-middle-income countries sub-divided into low and middle income countries.**

| Variable   |  | Low-income countries<br>(N=36)<br>N (%) | Lower-middle income countries<br>(N=520)<br>N (%) | Upper-middle income countries<br>(N=548)<br>N (%) |
|--|--|---|---|---|
| <b>Age (years), median (range)</b>   |  | 5.0 (3.5, 9)                            | 5.0 (2, 10)                                       | 5.0 (3, 10)                                       |
| <b>Sex</b>   | Female   | 16 (44.4)                               | 226 (43.5%)                                       | 227 (41.4)  |
|  | Male   | 20 (55.6)                               | 290 (55.8%)                                       | 321 (58.6)  |
|  | Missing  | 0 (0.0)                                 | 4 (0.8%)  | 0 (0.0)   |
| <b>Weight (kg), median (range)</b>   |  | -                                       | 19 (14, 31)                                       | 18 (13, 27)                                       |
| <b>ASA grade</b>   | 1 - a normal healthy patient   | 24 (66.7)                               | 158 (30.4)  | 162 (29.6)  |
|  | 2 - a patient with mild systemic disease                                     | 1 (2.8)                                 | 316 (60.8)  | 106 (19.3)  |
|  | 3 - a patient with severe systemic disease                                   | 0 (0.0)                                 | 28 (5.4)  | 121 (22.1)  |
|  | 4 - a patient with severe systemic disease that is a constant threat to life | 0 (0.0)                                 | 9 (1.7)   | 25 (4.6)  |
|  | 5 - a moribund patient who is not expected to survive without the operation  | 0 (0.0)                                 | 5 (1.0)   | 3 (0.5)   |
|  | Missing  | 11 (30.6)                               | 4 (0.8)   | 131 (23.9)  |
| <b>Tumour Type</b>   | Non-Hodgkin lymphoma   | 6 (16.7)                                | 46 (8.9)  | 37 (6.8)  |
|  | Acute lymphoblastic leukaemia  | 10 (27.8)                               | 192 (36.9)  | 178 (32.5)  |
|  | Ewing sarcoma  | 5 (13.9)                                | 19 (3.7)  | 8 (40.7)  |
|  | Glioma   | 0 (0.0)                                 | 21 (4.0)  | 52 (50.2)   |
|  | Hodgkin lymphoma   | 5 (13.9)                                | 19 (3.7)  | 39 (57.3)   |
|  | Medulloblastoma  | 1 (2.8)                                 | 36 (6.9)  | 20 (61.0)   |
|  | Neuroblastoma  | 3 (8.3)                                 | 43 (8.3)  | 34 (67.2)   |
|  | Osteosarcoma   | 2 (5.6)                                 | 29 (5.6)  | 14 (69.7)   |
|  | Retinoblastoma   | 0 (0.0)                                 | 39 (7.5)  | 48 (78.5)   |
|  | Rhabdomyosarcoma   | 0 (0.0)                                 | 22 (4.2)  | 39 (7.1)  |
|  | Wilms Tumour   | 4 (11.1)                                | 54 (10.3)   | 79 (14.4)   |
| <b>Was patient tested for covid within 30 days from their first anti-cancer treatment?</b> | No   | 32 (91.4)                               | 242 (46.5)  | 355 (64.8)  |
|  | Symptomatic screening only   | 3 (8.6)                                 | 113 (21.7)  | 69 (12.6)   |
|  | Yes – by CT Thorax   | 0 (0.0)                                 | 6 (1.2)   | 1 (0.2)   |
|  | Yes – by laboratory test   | 0 (0.0)                                 | 113 (21.7)  | 49 (8.9)  |
|  | Not applicable (No anti-cancer treatment given post March 11th 2020)         | 0 (0.0)                                 | 8 (1.5)   | 5 (0.9)   |
|  | Missing  | 0 (0.0)                                 | 38 (0.7)  | 68 (12.4)   |

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|  |  |           |            |            |
|--|--|-----------|------------|------------|
| <b>Was patient diagnosed with covid?</b> | No   | 10 (28.6) | 452 (86.9) | 452 (82.5) |
|  | Not applicable (no anti-cancer treatment given post March 11 <sup>th</sup> 2020) | 0 (0.0)   | 7 (1.3)    | 7 (1.3)    |
|  | Proven with laboratory test or CT Thorax   | 0 (0.0)   | 21 (4.0)   | 21 (3.8)   |
|  | Probable - clinically suspected  | 0 (0.0)   | 5 (1.0)    | 5 (0.9)    |
|  | Unknown  | 25 (71.4) | 8 (1.5)    | 8 (1.5)    |
|  | Missing  | 0 (0.0)   | 27 (5.2)   | 55 (10.0)  |

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