Global characteristics and outcomes of SARS-CoV-2 infection in children and adolescents with cancer (GRCCC): a cohort study

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Summary

Background Previous studies have shown that children and adolescents with COVID-19 generally have mild disease. Children and adolescents with cancer, however, can have severe disease when infected with respiratory viruses. In this study, we aimed to understand the clinical course and outcomes of SARS-CoV-2 infection in children and adolescents with cancer.

Methods We did a cohort study with data from 131 institutions in 45 countries. We created the Global Registry of COVID-19 in Childhood Cancer to capture de-identified data pertaining to laboratory-confirmed SARS-CoV-2 infections in children and adolescents (<19 years) with cancer or having received a haematopoietic stem-cell transplantation. There were no centre-specific exclusion criteria. The registry was disseminated through professional networks through email and conferences and health-care providers were invited to submit all qualifying cases. Data for demographics, oncological diagnosis, clinical course, and cancer therapy details were collected. Primary outcomes were disease severity and modification to cancer-directed therapy. The registry remains open to data collection.

Findings Of 1520 submitted episodes, 1500 patients were included in the study between April 15, 2020, and Feb 1, 2021. 1319 patients had complete 30-day follow-up. 259 (19·9%) of 1301 patients had a severe or critical infection, and 50 (3·8%) of 1319 died with the cause attributed to COVID-19 infection. Modifications to cancer-directed therapy occurred in 609 (55·8%) of 1092 patients receiving active oncological treatment. Multivariable analysis revealed several factors associated with severe or critical illness, including World Bank low-income or lower-middle-income (odds ratio [OR] 5·8 [95% CI 3·8–8·8]; p<0·0001) and upper-middle-income (1·6 [1·2–2·2]; p=0·0024) country status; age 15–18 years (1·6 [1·1–2·2]; p=0·013); absolute lymphocyte count of 300 or less cells per mm³ (2·5 [1·8–3·4]; p<0·0001), absolute neutrophil count of 500 or less cells per mm³ (1·8 [1·3–2·4]; p=0·0001), and intensive treatment (1·8 [1·3–2·3]; p=0·0005). Factors associated with treatment modification included upper-middle-income country status (OR 0·5 [95% CI 0·3–0·7]; p=0·0004), primary diagnosis of other haematological malignancies (0·5 [0·3–0·8]; p=0·0088), the presence of one of more COVID-19 symptoms at the time of presentation (1·8 [1·3–2·4]; p=0·0002), and the presence of one or more comorbidities (1·6 [1·1–2·3]; p=0·020).

Interpretation In this global cohort of children and adolescents with cancer and COVID-19, severe and critical illness occurred in one fifth of patients and deaths occurred in a higher proportion than is reported in the literature in the general paediatric population. Additionally, we found that variables associated with treatment modification were not the same as those associated with greater disease severity. These data could inform clinical practice guidelines and raise awareness globally that children and adolescents with cancer are at high-risk of developing severe COVID-19 illness.

Funding American Lebanese Syrian Associated Charities and the National Cancer Institute.

Introduction

Although the COVID-19 pandemic has left no population unscathed, children overall have had mild disease courses with low mortality.[1–3] Measures of clinical status and service delivery differ between studies; however, severe disease has been reported in 1–6% of paediatric cases, even among hospitalised cohorts, compared with 14% in adults.[1,4,5] Although children appear to do comparatively well, a small proportion still develop respiratory or multiorgan failure. Children and adolescents with cancer or who have received a haematopoietic stem-cell transplantation represent a potentially high-risk population with known risk of morbidity and mortality when infected by other respiratory viruses.[6–8] In paediatric cohorts in the USA, influenza-attributable mortality was calculated to be

Lancet Oncol 2021

Published **Online** August 26, 2021 https://doi.org/10.1016/S1470-2045(21)00454-X

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See Online for appendix

Research in context

Evidence before this study

Healthy children and adolescents infected by SARS-CoV-2 have a milder disease course than adults; however, children with cancer have a higher frequency of severe disease during infection by other respiratory viruses than do healthy children and thus they might be at higher risk for complications due to COVID-19. We searched PubMed from Dec 1, 2019, to Feb 1, 2021, for English language publications using search terms "pediatric", "children", "cancer", "malignancy", "COVID-19", and "SARS-CoV-2". To date, reports in paediatric oncology patients have been limited to case reports and single country observational studies, mostly in high-income countries. Analyses of large cohorts of adult patients with cancer suggest that SARS-CoV-2 could cause severe illness among those receiving treatment for malignancy; however, data suggest that various disease and lifestyle factors could drive these poor outcomes. Several of these factors, such as advanced age, presence of comorbidities, and poor performance status differ in children. None of the previous reports account for global differences in supportive care infrastructure that might affect outcomes.

Added value of this study

This study is the first multinational cohort spanning all World Bank income groups to report COVID-19 outcomes for children and adolescents with cancer. By creating a large, global, hospital-based registry of paediatric oncology patients with laboratory confirmed SARS-CoV-2 infections, we were able to study the effect of the disease across heterogeneous supportive care protocols and demographic backgrounds. Within our cohort, we found that although most children and adolescents with cancer generally had a mild illness during COVID-19 infection, 19·9% developed severe or critical illness. Mortality due to COVID-19 within our cohort was 3·8% (50 of 1319), and although low, this figure is more than four times greater than that reported in published cohorts of general paediatric patients. We were also able to identify several clinical patient factors, including lymphopenia and neutropenia, which were associated with more severe disease. Finally, we documented health disparities across World Bank income groups, with low-income and lower-middle-income countries contributing a greater proportion of cases with severe or critical illness.

Implications of all the available evidence

Children and adolescents with cancer generally recover without incident from COVID-19, but can have a severe course of infection. These findings suggest that, in most cases, cancer-directed therapy can proceed and no antiviral therapy for SARS-CoV-2 is required for COVID-19 disease resolution; however, we did identify several clinical and laboratory factors associated with increased disease severity. The finding of worse outcomes associated with lymphopenia and neutropenia suggests that it might be prudent to delay myelosuppressive and lymphocyte-depleting therapy during active infection if this is feasible in patients with other risk factors for severe disease. Additionally, patients receiving or anticipated to receive intensive cancer-directed therapies should be prioritised for early access to vaccination, when appropriate, and for other supportive care interventions when resources are limited.

1% in patients with acute lymphoblastic leukaemia, whereas attributable case fatality due to any respiratory viral infection was 5·4% in the first year after haematopoietic stem-cell transplantation.[7,8] To support clinical and health policy decision making, appraisal of the clinical manifestations and outcomes of SARS-CoV-2 infection in this unique population is warranted, particularly given global resource constraints and current population-level treatment and vaccination prioritisation efforts.

A multinational registry documented death in 13% of adult patients with cancer and a COVID-19 diagnosis, confirming early concerns that the COVID-19 death rate in adult oncology patients exceeded that in the general population.[9,10] A pooled meta-analysis showed mortality in 25·6% of adult patients with cancer.[11] By contrast, data from a large cohort in the UK and a multinational European cohort showed that poor outcomes in these patients appear to be driven by age, sex, and comorbidities, with the European cohort showing no effect of cancer diagnosis when comparing patients with cancer to control individuals without cancer.[12,13] Data are scarce for children with cancer; small national series using different inclusion criteria, severity classifications, and testing strategies suggest disparities between countries with severe or critical infections ranging from 6·6% to 21% of included patients and mortality between zero and 10%.[14–19] The clinical risk factors associated with COVID-19 disease severity among these patients are not well established.[20] In addition, as 90% of children and adolescents at risk of developing cancer live in low-income and middle-income countries, evaluation of differences in infection-related treatment and outcomes is necessary to address global inequities in COVID-19 management.[21]

Recognising that children and adolescents with cancer would constitute a small proportion of a sampled population within any individual institution, the St Jude Global programme of St Jude Children's Research Hospital and the International Society of Paediatric Oncology created the Global COVID-19 Observatory and Resource Center for Childhood Cancer and promoted centralised, hospital-based data collection from the global community. The primary goal was to facilitate collaboration and inform care decisions using real-time data and provide an interactive visualisation and online discussion community.[22] In this study, we aimed to describe disease severity among a large global cohort of

For the **Global COVID-19 Observatory and Resource Center for Childhood Cancer** see http://covid19childhoodcancer.org/

children and adolescents with cancer or haematopoietic stem-cell transplantation, and identify actionable risk factors associated with disease severity.

Methods

Study design and participants

We did a cohort study with cases reported from 131 institutions in 45 countries (appendix p 2). Launched on April 15, 2020, the St Jude Global and International Society of Paediatric Oncology Global Registry of COVID-19 in Childhood Cancer (GRCCC) is housed in the REDCap application, which was created by Vanderbilt University Medical Center (Nashville, TN, USA) and hosted at St Jude Children's Research Hospital (Memphis, TN, USA). The registry is based on voluntary reporting of laboratory-confirmed cases of SARS-CoV-2 infection in children and adolescents (<19 years) who have a current or past diagnosis of cancer or who have received a haematopoietic stem-cell transplantation. Cases without laboratory confirmation are excluded to reduce confounding by other respiratory infections with similar clinical presentations. The registry has been publicised through conferences and targeted emails through St Jude Global and International Society of Paediatric Oncology networks of providers. There were no centre-specific exclusion criteria.

This study was reviewed by St Jude Children's Research Hospital institutional review board as not involving human participants as no identifiable private information or biospecimens are provided. This study was subject to approvals by local ethics committees according to local policy. Individual investigators were responsible for assuring that participation was compliant with local regulations.

Procedures

De-identified data were requested on a maximum of 80 variables (21 required responses) contained on three forms. No dates were collected beyond the date of data entry; day 0 was defined by the reporter as the day of onset of symptoms or the day of diagnosis of an asymptomatic infection. The reason for SARS-CoV-2 testing was not collected. Data fields include oncological diagnosis, treatment phase, non-oncological comorbid conditions, imaging findings, anatomical location of infection, and COVID-19-directed therapy. Outcomes collected include requirement for higher level of care, respiratory support requirements, laboratory and clinical status of the SARS-CoV-2 infection, vital status, and interruptions in cancer-directed treatment. One form is structured for initial intake, a second for outcomes at 30 days, and an additional form at 60 days for patients without documented clinical or laboratory resolution of infection at the 30-day timepoint. Data collection could be prospective or retrospective, but follow-up is prompted at 30 days after data entry or at intake if the reporter confirms that at least 30 days since symptoms or diagnosis have passed.

Data submitted as of Feb 1, 2021, are included in this report. Each institution that had reported at least a single case as of the time of the data cutoff, was requested to confirm that all institutional cases had been entered in an unbiased fashion as of the time of the final case entry by the institution. All cases corresponding to institutions that did not confirm unbiased data entry were excluded from analysis.

Statistical analysis

Descriptive statistics were used to summarise demographic and clinical characteristics and outcomes. Age in years was categorised as younger than 1 year, 1–9 years, 10–14 years, and 15–18 years based on known associations of age group with the prognosis of children with cancer. Neutropenia (absolute neutrophil count ≤500 cells per mm^3) and lymphopenia (absolute lymphocyte count ≤300 cells per mm^3) definitions were selected to be globally applicable and clinically relevant. World Bank designations for income groups—high-income countries, upper-middle-income countries, lower-middle-income countries, and low-income countries—were used to describe economic context.

Assuming outcomes such as mortality and admission to a higher level of care would be rare, a primary outcome measure of disease severity was defined to evaluate the association of potential risk factors with adverse outcomes. This is a composite measure incorporating anatomical level of respiratory tract involvement (upper versus lower), respiratory support level, requirement for higher level of care for any reason, and death attributed to COVID-19. To distinguish groups of patients with different support requirements, severity was collapsed into three levels: asymptomatic, mild or moderate, and severe or critical. Disease severity was classified as follows. Critical indicated evidence of organ dysfunction, intubation, or death due to COVID-19. Severe indicated requirement for a higher level of care for any reason or any oxygen support needed greater than regular nasal cannula or facemask, but less than intubation. Moderate indicated upper respiratory tract illness requiring nasal cannula or face mask, lower respiratory tract infection with support no greater than conventional nasal cannula or face mask, no need for higher support levels for any organ system, or no need for higher level of care. Mild indicated respiratory disease limited to upper respiratory tract illness on room air, any symptoms without need for higher support levels for any organ system, or no need for higher level of care. Asymptomatic indicated positive test for SARS-CoV-2, and no symptoms of a respiratory or non-respiratory nature. Another primary outcome was treatment modification, defined as one or more of the following: chemotherapy reduction, chemotherapy withheld, surgery delay, or radiotherapy delay; treatment on plan included treatment as planned or unknown treatment modification status.

Recognising the difficulty of aggregating data across centres using different treatment protocols, a treatment

	Overall (n=1500)	Low-income or lower-middle-income country (n=318)	Upper-middle-income country (n=824)	High-income country (n=358)	p value
WHO Region					
African Region	41 (2·7%)	8 (2·5%)	33 (4·0%)	0	..
Region of the Americas	847 (56·5%)	11 (3·5%)	675 (81·9%)	161 (45·0%)	..
Eastern Mediterranean	211 (14·1%)	211 (66·4%)	0	0	..
European Region	322 (21·5%)	10 (3·1%)	115 (14·0%)	197 (55·0%)	..
South-East Asian Region	63 (4·2%)	63 (19·8%)	0	0	..
Western Pacific Region	16 (1·1%)	15 (4·7%)	1 (0·1%)	0	..
Age, years					0·041
Median	8 (4–13)	8 (4–13)	7 (4–12)	9 (4–14)	
Age, years (category)					0·022
<1	42 (2·8%)	6 (1·9%)	24 (2·9%)	12 (3·4%)	..
1–9	823 (54·9%)	181 (56·9%)	471 (57·2%)	171 (47·8%)	..
10–14	385 (25·7%)	69 (21·7%)	207 (25·1%)	109 (30·4%)	..
15–18	250 (16·7%)	62 (19·5%)	122 (14·8%)	66 (18·4%)	..
Sex					0·17
Male	891 (59·4%)	199 (62·6%)	494 (60·0%)	198 (55·3%)	..
Female	607 (40·5%)	119 (37·4%)	330 (40·0%)	158 (44·1%)	..
Other	2 (0·1%)	0	0	2 (0·6%)	..
Cancer type					<0·0001
Acute lymphoblastic leukaemia or acute lymphoblastic lymphoma	737 (49·1%)	164 (51·6%)	413 (50·1%)	160 (44·7%)	..
Other haematological malignancies	266 (17·7%)	75 (23·6%)	141 (17·1%)	50 (14·0%)	..
Solid tumours	363 (24·2%)	68 (21·4%)	204 (24·8%)	91 (25·4%)	..
CNS tumours	126 (8·4%)	11 (3·5%)	64 (7·8%)	51 (14·2%)	..
Post-haematopoietic stem-cell transplantation, non-malignancy	8 (0·5%)	0	2 (0·2%)	6 (1·7%)	..
Treatment type					<0·0001
Cancer-directed therapy	1243 (82·9%)	258 (81·1%)	719 (87·3%)	266 (74·3%)	..
Palliative therapy	53 (3·5%)	14 (4·4%)	32 (3·9%)	7 (2·0%)	..
Treatment completed	127 (8·5%)	17 (5·3%)	53 (6·4%)	57 (15·9%)	..
No active treatment	69 (4·6%)	28 (8·8%)	13 (1·6%)	28 (7·8%)	..
Unknown	8 (0·5%)	1 (0·3%)	7 (0·8%)	0	..
Time since last chemotherapy, days					0·58
≤30	1171/1203 (97·3%)	246/255 (96·5%)	690/708 (97·5%)	235/240 (97·9%)	..
>30	32/1203 (2·7%)	9/255 (3·5%)	18/708 (2·5%)	5/240 (2·1%)	..
Received haematopoietic stem-cell transplantation					<0·0001
Yes	81 (5·4%)	9 (2·8%)	31 (3·8%)	41 (11·5%)	..
No	1414 (94·3%)	309 (97·2%)	789 (95·8%)	316 (88·3%)	..
Unknown	5 (0·3%)	0	4 (0·5%)	1 (0·3%)	..
Time since transplantation, days					0·51
<30	6/81 (7·4%)	0	4/31 (12·9%)	2/41 (4·9%)	..
31–99	13/81 (16·0%)	1/9 (11·1%)	4/31 (12·9%)	8/41 (19·5%)	..
100–300	20/81 (24·7%)	1/9 (11·1%)	9/31 (29·0%)	10/41 (24·4%)	..
>300	31/81 (38·3%)	6/9 (66·7%)	9/31 (29·0%)	16/41 (39·0%)	..
Unknown or missing*	11/81 (13·6%)	1/9 (11·1%)	5/31 (16·1%)	5/41 (12·2%)	..
Received radiotherapy					<0·0001
Yes	156/1453 (10·7%)	25/279 (9·0%)	73/819 (8·9%)	58/355 (16·3%)	..
No	1249/1453 (86·0%)	253/279 (90·7%)	730/819 (89·1%)	266/355 (74·9%)	..
Unknown	48/1453 (3·3%)	1/279 (0·4%)	16/819 (2·0%)	31/355 (8·7%)	..

(Table 1 continues on next page)

	Overall (n=1500)	Low-income or lower-middle-income country (n=318)	Upper-middle-income country (n=824)	High-income country (n=358)	p value
(Continued from previous page)					
Absolute neutrophil count, cells per mm³					<0·0001
≤500	375/1212 (30·9%)	109/243 (44·9%)	202/716 (28·2%)	64/253 (25·3%)	..
>500	837/1212 (69·1%)	134/243 (55·1%)	514/716 (71·8%)	189/253 (74·7%)	..
Absolute lymphocyte count, cells per mm³					<0·0001
≤300	273/1188 (23·0%)	82/237 (34·6%)	128/702 (18·2%)	63/249 (25·3%)	..
>300	915/1188 (77·0%)	155/237 (65·4%)	574/702 (81·8%)	186/249 (74·7%)	..
Comorbidities†					0·71
At least one comorbidity	256 (17·1%)	51 (16·0%)	150 (18·2%)	55 (15·4%)	..
None	1173 (78·2%)	259 (81·4%)	659 (80·0%)	255 (71·2%)	..
Unknown	71 (4·7%)	8 (2·5%)	15 (1·8%)	48 (13·4%)	..
Intensive treatment					<0·0001
Yes	478 (31·9%)	104 (32·7%)	301 (36·5%)	73 (20·4%)	..
No	1022 (68·1%)	214 (67·3%)	523 (63·5%)	285 (79·6%)	..

p values were calculated using the χ^2 test, Fisher's exact test, or the Kruskal-Wallis test. *Missing refers to patients who did not answer the question regarding time since transplantation. †Comorbidities included history of high-dose steroid within 14 days before diagnosis or illness, pre-existing pulmonary disease, pre-existing cardiac insufficiency, and a free text option for other conditions (eg, obesity, graft-versus-host disease, trisomy 21, pre-existing renal disease, among others).

Table 1: **Baseline characteristics by World Bank income group**

intensity variable was created to summarise anticipated effects of therapy on haematological parameters and organ systems. Treatment was categorised as intense if it would be expected to result in long-lasting myelosuppression and immunosuppression, including treatment for acute myeloid leukaemia, induction or re-induction therapy for acute lymphoblastic leukaemia, acute lymphoblastic lymphoma, or any other lymphoma except for Hodgkin lymphoma, as well as if the patient was less than 30 days from autologous or less than 100 days from allogeneic haematopoietic stem-cell transplantation.

Comparison of proportions between groups was made with χ^2 or Fisher's exact tests. The Kruskal-Wallis test was used to compare medians between groups. Univariate logistic regression was used to examine the association between each outcome and patient characteristics. Multivariable logistic regression was used to explore the effect of factors that were significant ($p<0·05$) in univariate analyses for each outcome. All data analyses were done using SAS software, version 9.4 and R, version 4.0.4.

Role of the funding source

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

Results

Between April 15, 2020, and Feb 1, 2021, 1520 cases of SARS-CoV-2 infection were submitted to the GRCCC. Of the 1520 cases submitted, 20 were excluded from analyses. 12 were ineligible due to non-malignancy or no haematopoietic stem-cell transplantation, and eight due to inadequate data submission. There were 1500 qualifying episodes entered as of Feb 1, 2021 (appendix p 1), with 1319 having complete 30-day follow-up. Clinical characteristics of the included patients by World Bank country income level are summarised in table 1. The median age of patients included was 8 years (IQR 4–13), with 42 (2·8%) of 1500 aged younger than 1 year and 250 (16·7%) aged 15–18 years. Most cases of SARS-CoV-2 infection occurred in patients with a diagnosis of acute lymphoblastic lymphoma or acute lymphoblastic leukaemia (737 [49·1%]), followed by extracranial solid tumours (363 [24·2%]). Comorbidities were documented in 256 (17·1%) patients, with receipt of high-dose steroids within the previous 14 days being the most common comorbidity (101 [6·7%]; appendix p 3). Most patients (824 [54·9%]) were reported from upper middle-income countries, with few (five [0·3%]) reported from low-income countries. Low-income countries and lower-middle income countries were pooled together for analyses due to the small amount of data.

Most patients (1243 [82·9%] of 1500) were receiving cancer-directed therapy at the time of SARS-CoV-2 infection. Of the 1203 respondents providing a response, most patients (1171 [97·3%]) had received chemotherapy within 30 days of the episode. 81 (5·4%) patients were haematopoietic stem-cell transplantation recipients; in these patients, most infections (31 [42·5%] of 73) occurred more than 300 days post-transplant (table 1). Age, primary diagnosis, treatment type, haematopoietic stem-cell transplantation receipt, radiotherapy, absolute lymphocyte count at SARS-CoV-2 diagnosis (≤300 cells per mm³ *vs* >300 cells per mm³) absolute neutrophil count at SARS-CoV-2 diagnosis (≤500 cells per mm³ *vs* >500 cells per mm³), and treatment intensity were all

	Overall (n=1319)	Low-income or lower-middle-income country (n=296)	Upper-middle-income country (n=709)	High-income country (n=314)
Disease severity				
Asymptomatic	456/1301 (35·0%)	87/288 (30·2%)	233/702 (33·2%)	136/311 (43·7%)
Mild or moderate	586/1301 (45·0%)	81/288 (28·1%)	353/702 (50·3%)	152/311 (48·9%)
Severe or critical	259/1301 (19·9%)	120/288 (41·7%)	116/702 (16·5%)	23/311 (7·4%)
Treatment modification*				
Treatment modified	609/1092 (55·8%)	163/240 (67·9%)	299/622 (48·1%)	147/230 (63·9%)
Chemotherapy reduced	80/609 (13·1%)	34/163 (20·9%)	41/299 (13·7%)	5/147 (3·4%)
Chemotherapy withheld	487/609 (80·0%)	125/163 (76·7%)	234/299 (78·3%)	128/147 (87·1%)
Radiotherapy delayed	25/609 (4·1%)	3/163 (1·8%)	14/299 (4·7%)	8/147 (5·4%)
Surgery delayed	41/609 (6·7%)	10/163 (6·1%)	20/299 (6·7%)	11/147 (7·5%)
Treatment on plan (includes unknown)	483/1092 (44·2%)	77/240 (32·1%)	323/622 (51·9%)	83/230 (36·1%)
Death				
Due to COVID-19	50/83 (60·2%)	20/33 (60·6%)	26/43 (60·5%)	4/7 (57·1%)
Median time to death, days	8 (3–14)	9 (4–13)	7 (3–13)	20 (11–25)
Due to other causes	33/83 (39·8%)	13/33 (39·4%)	17/43 (39·5%)	3/7 (42·9%)
Median time to death, days	16 (8–29)	16 (8–29)	10 (4–21)	26 (24–32)
Hospitalisation				
Hospitalised, ward status	658 (49·9%)	61 (20·6%)	472 (66·6%)	125 (39·8%)
Hospitalised, higher level of care†	231 (17·5%)	117 (39·5%)	95 (13·4%)	19 (6·1%)
Not hospitalised	430 (32·6%)	118 (39·9%)	142 (20·0%)	170 (54·1%)

Data are n, n/N (%), n (%), or median (IQR). *Treatment modification corresponds to a "select all that apply" question in the survey, thus sum of count numbers could exceed total number. †Higher level of care included intensive care unit, intermediate care unit, high dependency unit, and emergency room.

Table 2: **Patient outcomes by World Bank income group**

significantly associated with World Bank income group, whereas sex, time since last chemotherapy, time since transplant, and having at least one comorbidity were not (table 1).

Most diagnostic tests were nasopharyngeal swabs (1212 [80·8%] of 1500), followed by nasal swabs (262 [17·5%]) and oropharyngeal swabs (126 [8·4%]; appendix p 4). 854 (56·9%) of 1500 patients were symptomatic at the time of COVID-19 testing; median time from onset of symptoms to testing was 2 days (IQR 1–4) in patients for whom this information was available (n=703). The most commonly reported symptoms at presentation were fever (619 [41·3%]) and cough (356 [23·7%]; appendix p 5).

Of 1319 patients with 30-day follow-up data, 889 (67·4%) were hospitalised, and 231 (17·5%) required admission or transfer to a higher level of care (table 2). When considering non-respiratory pathology, the most common single organ system with documented dysfunction was cardiac (33 [2·5%]), and 43 (3·3%) patients had multiorgan dysfunction (appendix p 7). 386 (29·3%) patients received COVID-19 directed therapy, with 275 (71·2%) of those receiving azithromycin and 197 (51·0%) steroids. Antivirals were rarely used, and remdesivir was administered in 65 (16·8%) patients receiving therapy (appendix p 6). There were 83 (6·3%) deaths in this cohort and 60·2% (50 of 83) of those deaths (3·8% of cohort) were attributed to COVID-19. Median time to death attributed to COVID-19 was 8 days (IQR 3–14; table 2).

Most patients with follow-up data either remained asymptomatic (456 [35·0%] of 1301) or had mild or moderate infection (586 [45·0%] of 1301); however, a substantial percentage (259 [19·9%] of 1301) developed either severe or critical COVID-19-related illness (table 2). Chemotherapy was withheld in 44·6% (487 of 1092) of patients receiving active therapy and some modification to therapy occurred in 609 (55·8%) patients on active therapy. Treatment modifications were least common in patients from upper-middle-income countries compared with other income groups (p<0·0001), where treatment according to plan was more common than for other income groups (table 2). A higher proportion of severe or critical outcomes was seen in patients in low-income and lower-middle-income countries (120 [41·7%] of 288) relative to patients in other income groups. 330 (31·3%) of 1055 (the number of patients for whom data were available) infections were in patients with an absolute neutrophil count of 500 or less cells per mm³, who then made up 124 (50·2%) of 247 of those with severe or critical illness. Similarly, although patients with an absolute lymphocyte count of 300 or less cells per mm³ contributed only 240 (23·1%) of 1040 (the number of patients for whom data were available) infections in the total sample, this group contributed 103 (42·7%) of 241 infections in the severe or critical group (table 3). Patients with haematological malignancies contributed the largest proportion (208 [80·3%] of 259) of either severe or critical disease by diagnosis type (figure). In patients with acute lymphoblastic leukaemia or acute lymphoblastic lymphoma, severe or critical disease was most common in those receiving induction therapy, relapse or refractory therapy, and the maintenance or continuation phase of therapy (table 3).

Income group, cancer type, age, absolute lymphocyte count, absolute neutrophil count, presence of comorbidities, and treatment intensity were significantly associated with severe or critical illness in univariate logistic regression analyses, whereas sex was not. In multivariable analysis, low-income or lower-middle-income (OR 5·8 [95% CI 3·8–8·8]; p<0·0001) and upper-middle-income group (1·6 [1·2–2·2]; p=0·0024), age 15–18 years (1·6 [1·1–2·2]; p=0·013), absolute lymphocyte count of 300 or less cells per mm³ (2·5 [1·8–3·4]; p<0·0001), absolute neutrophil count of 500 or less cells per mm³ (1·8 [1·3–2·4]; p=0·0001), and intensive treatment (1·8 [1·3–2·3]; p=0·0005) were associated with

increased severity of infection, whereas other variables were not (table 4).

To investigate the effect of COVID-19 diagnosis on cancer treatment, univariate and multivariable logistic regression analyses were done. Income group, cancer type, absolute lymphocyte count, presence of comorbidities, and presence of COVID-19 symptoms at presentation, were significantly associated with treatment modification in univariate logistic regression analyses, whereas other variables were not (table 5). In multivariable analysis, treatment modification was associated with the upper-middle income group (OR 0·5 [95% CI 0·3–0·7]; p=0·0004), other haematological malignancies (0·5 [0·3–0·8]; p=0·0088), the presence of COVID-19 symptoms (1·8 [1·3–2·4]; p=0·0002), and the presence of comorbidities (1·6 [1·1–2·3]; p=0·020; table 5).

Discussion

To our knowledge, this is the first international study and largest cohort to date to report COVID-19 outcomes for children and adolescents with cancer and those who have received a haematopoietic stem-cell transplantation. We have shown that although infection outcomes are generally favourable, severe disease can occur, particularly

	Asymptomatic (n=456)	Mild or moderate (n=586)	Severe or critical (n=259)	Total (n=1301)	p value
Income group*					<0·0001
Low-income or lower-middle-income country	87/288 (30·2%)	81/288 (28·1%)	120/288 (41·7%)	288	..
Upper-middle-income country	233/702 (33·2%)	353/702 (50·3%)	116/702 (16·5%)	702	..
High-income country	136/311 (43·7%)	152/311 (48·9%)	23/311 (7·4%)	311	..
Age, years*					0·013
<1	13/31 (41·9%)	15/31 (48·4%)	3/31 (9·7%)	31	..
1–9	264/707 (37·3%)	315/707 (44·6%)	128/707 (18·1%)	707	..
10–14	120/336 (35·7%)	150/336 (44·6%)	66/336 (19·6%)	336	..
15–18	59/227 (26·0%)	106/227 (46·7%)	62/227 (27·3%)	227	..
Sex*					0·32
Male	285/778 (36·6%)	345/778 (44·3%)	148/778 (19·0%)	778	..
Female	171/521 (32·8%)	239/521 (45·9%)	111/521 (21·3%)	521	..
Other†	0	2/2 (100·0%)	0	2	..
Cancer type					<0·0001
Acute lymphoblastic leukaemia or acute lymphoblastic lymphoma	184 (40·4%)	309 (52·7%)	145 (56·0%)	638 (49·0%)	..
Other haematological malignancies	68 (14·9%)	106 (18·1%)	63 (24·3%)	237 (18·2%)	..
Solid tumours	143 (31·4%)	128 (21·8%)	41 (15·8%)	312 (24·0%)	..
CNS tumours	57 (12·5%)	42 (7·2%)	7 (2·7%)	106 (8·1%)	..
Post-haematopoietic stem-cell transplantation, non-malignancy†	4 (0·9%)	1 (0·2%)	3 (1·2%)	8 (0·6%)	..
Phase of treatment*‡					0·0001
Induction	37/168 (22·0%)	80/168 (47·6%)	51/168 (30·4%)	168	..
Consolidation	48/106 (45·3%)	46/106 (43·4%)	12/106 (11·3%)	106	..
Reinduction or interim maintenance	24/62 (38·7%)	27/62 (43·5%)	11/62 (17·7%)	62	..
Maintenance or continuation	44/172 (25·6%)	95/172 (55·2%)	33/172 (19·2%)	172	..
Relapse or refractory therapy	15/57 (26·3%)	25/57 (43·9%)	17/57 (29·8%)	57	..
Immunotherapy or cell therapy†	2/3 (66·7%)	1/3 (33·3%)	0	3	..
Received haematopoietic stem-cell transplantation*					0·58
Yes	30/76 (39·5%)	30/76 (39·5%)	16/76 (21·1%)	76	..
No	425/1224 (34·7%)	556/1224 (45·4%)	243/1224 (19·9%)	1224	..
Unknown†	1/1 (100·0%)	0	0	1	..
Time since transplant, days*					0·61
<30	1/6 (16·7%)	3/6 (50·0%)	2/6 (33·3%)	6	..
31–99	5/13 (38·5%)	3/13 (23·1%)	5/13 (38·5%)	13	..
100–300	5/17 (29·4%)	9/17 (52·9%)	3/17 (17·6%)	17	..
>300	12/30 (40·0%)	12/30 (40·0%)	6/30 (20·0%)	30	..
Unknown†	1/3 (33·3%)	2/3 (66·7%)	0	3	..

(Table 3 continues on next page)

	Asymptomatic (n=456)	Mild or moderate (n=586)	Severe or critical (n=259)	Total (n=1301)	p value
(Continued from previous page)					
Absolute neutrophil count, cells per mm³					<0·0001
≤500	42/299 (14·0%)	164/509 (32·2%)	124/247 (50·2%)	330/1055 (31·3%)	..
>500	257/299 (86·0%)	345/509 (67·8%)	123/247 (49·8%)	725/1055 (68·7%)	..
Absolute lymphocyte count, cells per mm³					<0·0001
≤300	30/297 (10·1%)	107/502 (21·3%)	103/241 (42·7%)	240/1040 (23·1%)	..
>300	267/297 (89·9%)	395/502 (78·7%)	138/241 (57·3%)	800/1040 (76·9%)	..
Comorbidities*					0·0007
At least one comorbidity	376/1016 (37·0%)	449/1016 (44·2%)	191/1016 (18·8%)	1016	..
None	55/223 (24·7%)	108/223 (48·4%)	60/223 (26·9%)	223	..
Unknown†	25/62 (40·3%)	29/62 (46·8%)	8/62 (12·9%)	62	..
Intensive treatment*					<0·0001
Yes	105/422 (24·9%)	183/422 (43·4%)	134/422 (31·8%)	422	..
No	351/879 (39·9%)	403/879 (45·8%)	125/879 (14·2%)	879	..

p values were calculated using the X^2 test or Fisher's exact test. *Data based on row totals rather than column totals. †Excluded from significance testing. ‡Phase of treatment refers to acute lymphoblastic leukaemia or acute lymphoblastic lymphoma.

Table 3: **Baseline characteristics by disease severity**

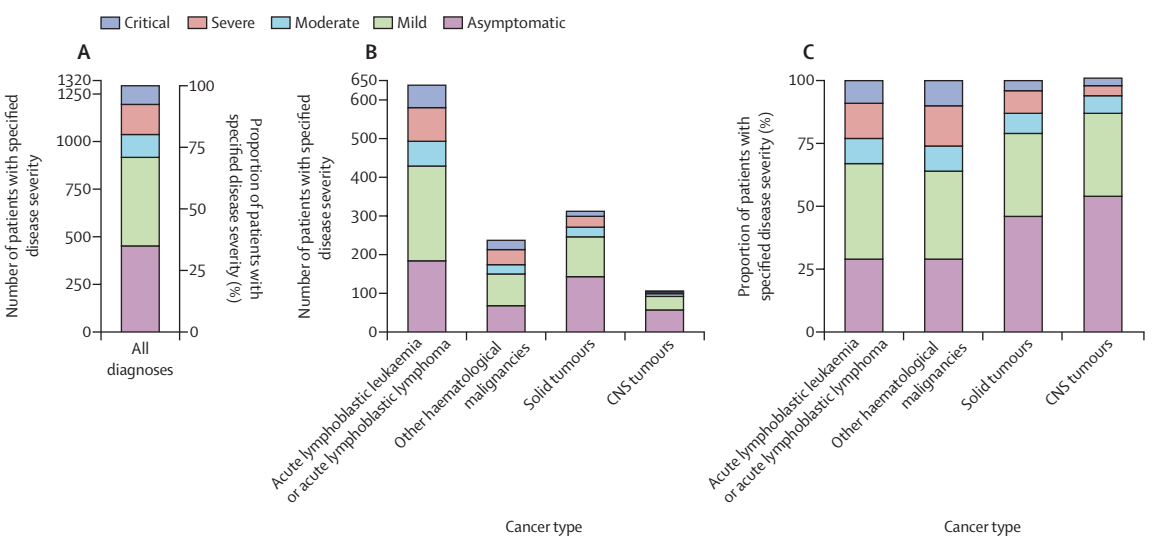

Figure: **Disease severity by cancer type**
(A) Number and proportion of patients with specified disease severity in all diagnoses. (B) Number of patients with specified disease severity by cancer type. (C) Proportion of patients with specified disease severity by cancer type.

in patients receiving intensive chemotherapy, and patients with lymphopenia and neutropenia. Mortality is lower than reported in adults with cancer and SARS-CoV-2 infection; however, the proportion within our cohort is still more than four times that reported in the general paediatric population. This report provides important data to support frontline clinicians making data-driven decisions about COVID-19 management, governments making prioritisation decisions, and health-care societies and organisations developing evidence-based guidelines.

In terms of outcomes observed, although a fifth of children with cancer developed severe or critical disease after SARS-CoV-2 infection, most patients recovered without advanced support needs. The large proportion of asymptomatic patients underscores the need for aggressive infection control measures as these patients can pose infection risks to other patients and health-care providers. The GRCCC is restricted to laboratory-confirmed cases, so deaths could have been underestimated, particularly in low-income countries and lower-middle-income countries where testing capacity is limited by availability of testing supplies and infrastructure. Death related to COVID-19 was reported in 3·8% (50 of 1319) of all patients with registry follow-up data. This result is considerably lower

than the 13–28% reported in adults with cancer; however, it is disproportionately high compared with 0·01–0·70% mortality in cohorts of general paediatric patients.[9,13,23,24]

Given the urgency of a new infectious threat, we also developed an innovative dissemination mechanism for global data processing and reporting in a rare disease population. Quantifying the disease burden associated with SARS-CoV-2 in childhood cancer would take years using a standard population-based cancer registry approach. Additionally, with limited clinical information available in most population-based registries, key risk factors would be missed. Using a hospital-based approach, backed by strong leadership within the paediatric cancer community, we were able to coordinate a multi-institutional collaboration and provide detailed, near real-time data summaries within 6 months from the start of the pandemic as a free and interactive data visualisation.

To identify outcome differences, we developed an objective measure of disease severity. Previously proposed schema included subjective data measurements, such as shortness of breath combined with findings from imaging, which might not always be assessed.[1] Additionally, other criteria might require measures such as oxygen saturation, which are not reliably available globally. Our clinical GRCCC classification system closely resembles the WHO Clinical Progression Scale, and was designed to be feasible across multiple institutions and health-care delivery settings, as it relied on a large and heterogeneous group of voluntary reporters who received no training in data preparation.[25] Using this measure, we observed a larger proportion of severe or critical illness compared with case series from high-income countries and cohorts of paediatric oncology patients.[18,26] This result might be due to the larger contribution of patients from low-income countries and lower-middle-income countries to our registry, as we observed an association between the two income groups combined and severe or critical illness.

Using the GRCCC severity score classification, we identified risk factors associated with the development of severe or critical disease. In particular, being aged 15–18 years, lymphopenia (absolute lymphocyte count ≤300 cells per mm³), neutropenia (absolute neutrophil count ≤500 cells per mm³), and intensive treatment were identified as significant on multivariable analyses. However, the effect of older age on outcomes needs further study due to the study limitations discussed below. Several variables associated with immune status were also independently associated with severe disease in our model. Our finding that lymphopenia was associated with more severe disease replicates findings for respiratory syncytial virus infections in paediatric patients with cancer, even though lymphopenia has not been associated with more severe disease in non-SARS-CoV-2 coronaviruses.[27,28] Neutropenia showed a weaker association but remains a clinically relevant marker for immunocompromise associated with infection risk. Treatment intensity, a modifiable non-patient associated variable, was also independently associated with disease severity and could inform practice. The observed relationship of severe illness with low-income and lower-middle income countries could be related to differences in supportive care infrastructure and delays in presentation. In addition, health-care system disruptions that affect all aspects of care delivery might be more pronounced in low-income and lower-middle-income countries. Lastly, although male sex is associated with more severe COVID-19 disease in adults, there was no effect of sex upon disease severity in our cohort.

From a clinical perspective, we have also identified how treatment practices appear to differ globally and do not correlate with the risk factors associated with severe illness. In our cohort, 55·8% (609 of 1092) of patients were reported to have an interruption in cancer-directed therapy. Our finding of frequent interruption to intended

	Univariate analysis		Multivariable analysis	
	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)
Income group	<0·0001	..	<0·0001	..
Low-income or lower-middle-income country	..	3·5 (2·5–4·9)	<0·0001	5·8 (3·8–8·8)
Upper-middle-income country	..	1·6 (1·3–2·1)	0·0024	1·6 (1·2–2·2)
High-income country	..	1 (ref)	..	1 (ref)
Cancer type	<0·0001	..	0·14	..
Acute lymphoblastic leukaemia or acute lymphoblastic lymphoma	..	2·0 (1·6–2·6)	0·086	1·4 (1·0–2·0)
Other haematological malignancies	..	2·3 (1·6–3·1)	0·55	1·2 (0·8–1·9)
Solid tumours	..	1 (ref)	..	1 (ref)
CNS tumours	..	0·7 (0·5–1·0)	0·53	0·9 (0·5–1·5)
Age, years	0·0015	..	0·046	..
<1	..	0·7 (0·4–1·4)	0·99	1·0 (0·5–2·4)
1–9	..	1 (ref)	..	1 (ref)
10–14	..	1·1 (0·8–1·4)	0·53	0·9 (0·7–1·3)
15–18	..	1·7 (1·3–2·3)	0·013	1·6 (1·1–2·2)
Sex	0·14	..	..	..
Male	..	1 (ref)	..	..
Female	..	1·2 (1·0–1·4)	..	..
Absolute lymphocyte count, cells per mm³	<0·0001	..	<0·0001	..
≤300	..	3·6 (2·7–4·8)	<0·0001	2·5 (1·8–3·4)
>300	..	1 (ref)	..	1 (ref)
Absolute neutrophil count, cells per mm³	<0·0001	..	0·0001	..
≤500	..	3·2 (2·5–4·2)	0·0001	1·8 (1·3–2·4)
>500	..	1 (ref)	..	1 (ref)
Comorbidities	0·0001	..	0·074	..
Yes (one or more)	..	1·7 (1·3–2·2)	0·074	1·4 (1·0–1·9)
None	..	1 (ref)	..	1 (ref)
Intensive treatment	<0·0001	..	0·0005	..
Yes	..	2·3 (1·9–2·9)	0·0005	1·8 (1·3–2·3)
No	..	1 (ref)	..	1 (ref)

Data shown for 1301 participants.

Table 4: **Results of univariate and multivariable analysis for disease severity**

	Univariate analysis		Multivariable analysis	
	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)
Income group	<0·0001	..	<0·0001	..
Low-income or lower-middle-income country	..	1·2 (0·8–1·8)	0·80	1·0 (0·6–1·6)
Upper-middle-income country	..	0·5 (0·4–0·7)	0·0004	0·5 (0·3–0·7)
High-income country	..	1 (ref)	..	1 (ref)
Cancer type	<0·0001	..	<0·0001	..
Acute lymphoblastic leukaemia or acute lymphoblastic lymphoma	..	1·4 (1·1–1·9)	0·089	1·3 (0·9–1·9)
Other haematological malignancies	..	0·7 (0·5–1·0)	0·0088	0·5 (0·3–0·8)
Solid tumours	..	1 (ref)	..	1 (ref)
CNS tumours	..	0·9 (0·5–1·5)	0·069	0·5 (0·3–1·0)
Age, years	0·85	..	..	..
<1	..	1·0 (0·4–2·1)	..	..
1–9	..	1 (ref)	..	..
10–14	..	1·0 (0·8–1·4)	..	..
15–18	..	1·2 (0·8–1·6)	..	..
Sex	0·86	..	..	..
Male	..	1 (ref)	..	..
Female	..	1·0 (0·8–1·2)	..	..
Absolute lymphocyte count, cells per mm³	0·049	..	0·58	..
≤300	..	1·4 (1·0–1·9)	0·58	1·1 (0·8–1·6)
>300	..	1 (ref)	..	1 (ref)
Absolute neutrophil count, cells per mm³	0·23	..	..	..
≤500	..	1·2 (0·9–1·6)	..	..
>500	..	1 (ref)	..	..
Comorbidities	0·016	..	0·020	..
Yes (one or more)	..	1·5 (1·1–2·1)	0·020	1·6 (1·1–2·3)
None	..	1 (ref)	..	1 (ref)
Intensive treatment	0·18	..	..	..
Yes	..	0·8 (0·7–1·1)	..	..
No	..	1 (ref)	..	..
COVID-19 symptoms	0·0007	..	0·0002	..
Yes (one or more)	..	1·5 (1·2–1·9)	0·0002	1·8 (1·3–2·4)
No symptoms	..	1 (ref)	..	1 (ref)

Data shown for 1092 participants.

Table 5: **Results of univariate and multivariable analysis for treatment modification**

therapy agrees with a large multinational survey; however, the finding that treatment modifications are less frequent in upper-middle-income countries differs from that report.[29] Instead, we observed that disruption in care was bimodal, occurring more frequently in high-income countries and low-income countries and lower-middle-income countries. Treatment modifications could occur for various reasons; a Latin American survey showed interruptions in supply of blood products and chemotherapy during the pandemic, which would result in treatment modification.[30] Our study design did not allow us to assess the drivers of interruption or its effect on overall survival or other important metrics, which merit further study. However, as absolute lymphocyte count, absolute neutrophil count, and age are not significantly associated with treatment disruption in our models, our data suggest there might be opportunity to improve outcomes by tailoring treatment decisions to identified risk factors when provider decision making, rather than health system limitations, are driving disruptions.

Finally, there are several potential limitations to consider when interpreting our results. First, our findings used a hospital-based registry approach, which prohibits us from making population-level conclusions. It is possible that recall bias might have led to the inclusion of more severe cases. To mitigate this bias, we requested that all reporters attest that they submitted all institutional cases meeting inclusion criteria. Although we are not aware of a bias towards sicker patients or more advanced disease, we cannot confirm that contributing institutions are representative. Reporting cases to the GRCCC was an additional task for an overwhelmed workforce, so reporting institutions might have been ones with greater human resources and support. Second, our requirement for laboratory confirmation of SARS-CoV-2 infection probably contributed to under-representation by lower-income settings where there might have been poorer availability of diagnostic tests. Specifically, participation was rare from the African, South-East Asian, and Western Pacific Regions, and low-income countries in general. Third, our severity scores might include some misclassifications. However, as the severe and critical categories rely on service delivery interventions only, our aggregate analyses should not be affected. Fourth, due to global data privacy rules, we were unable to collect protected health information, including all elements relating to dates. As a result, we cannot comment on time trends in disease severity or treatments delivered. Fifth, due to the inability to capture race or ethnicity consistently across a global cohort, we were unable to ascertain the effects of these factors on infection severity. Race and ethnicity represent an important area for continued investigation as such factors are associated with disease severity in other cohorts. Finally, the data fields we used at the onset of the pandemic did not adequately capture multisystem inflammatory syndrome in children. These data fields were updated on Nov 23, 2020, to incorporate multisystem inflammatory syndrome in children and we expect that continued data field updates will yield additional information in subsequent analyses.

Although vaccination and treatment options are developing, disparities in vaccine access, vaccine hesitancy, and the evolution of viral variants mean that the pandemic will continue to affect health care for the foreseeable future. Several of these factors will also increase the burden in countries with limited resources, in which disease severity is already the most concerning. For these reasons, we plan to continue the GRCCC programme to inform global treatment and resource allocation decision making with current and relevant data.

Contributors

SM provided an overall lead to the registry development, implementation, and analysis, with the operational support of MRH. SM, NB, GLC, VMS, MAC, MD, and CRG designed the study, with additional input from DCM, MS, EB, and KPJ. KPJ, GLC, EB, MS, RD, and LH supported and oversaw the dissemination of the registry through the International Society of Paediatric Oncology. NB, PF, SJ, MM, CL, and AA supported and oversaw the dissemination of the registry through the St Jude Global Alliance. LF, HMT, YC, YV, and MD oversaw data collection. YC, YV, MD, and RR were responsible for all the data summaries and analyses, and data visualisations, with input from SM and NB. SM wrote the first draft of the manuscript with input from NB and CRG. All authors reviewed and approved the final manuscript. YC and YV verified the raw data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

EB participates on the data safety monitoring board or advisory board for Novartis and Bayer and reports institutional clinical trial support from Roche and Bristol Myers Squibb. All other authors declare no competing interests.

Data sharing

Aggregate de-identified data are available as part of a public data visualisation in the Global COVID-19 Observatory and Resource Center for Childhood Cancer. Individual de-identified patient data with site identifiers removed and geographical region of patient residence limited to country will be made available upon request beginning 6 months after Article publication. Individuals can email the corresponding author with enquiries regarding the dataset.

Acknowledgments

This work has been supported in part by the American Lebanese Syrian Associated Charities and Cancer Center Support grant (number CA21765) from the National Cancer Institute through the National Institutes of Health. We thank Whitney Foster, Meghana Avula, Janet Middlekauff, Paula Naidu, Susanne Wollaert, Olga Kozhaeva, Tessie Laub, and Andrew Pappas for their technical support.

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