

REVIEW

COVID-19 outcomes in paediatric cancer: A large scale pooled meta-analysis of 984 cancer patients

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Abstract

We aimed to study the outcomes of COVID-19 in paediatric cancer patients. On 26 October 2021, we did a systematic search for relevant articles in seven electronic databases followed by manual search. We included cancer patients aged ≤ 18 years. Event rates and the 95% confidence interval (95%CI) were used to report the results. We included 21 papers after screening of 2759 records. The pooled rates of hospitalisation, intensive care unit (ICU) admission and mortality were 44% (95%CI: 30–59), 14% (95%CI: 9–21) and 9% (95%CI: 6–12), respectively. Moreover, subgroup analysis revealed that high income countries had better COVID-19 outcomes compared to upper middle income countries and lower middle income countries in terms of hospitalisation 30% (95%CI: 17–46), 60% (95%CI: 29–84) and 47% (95%CI: 36–58), ICU admission 7% (95%CI: 1–32), 13% (95%CI: 7–23) and 18% (95%CI: 6–41), and mortality 3% (95%CI: 2–5), 12% (95%CI: 8–18) and 13% (95%CI: 8–20), in order. In general, absence of specific pharmacologic intervention to prevent infection with the scarcity of vaccination coverage data among paediatric groups and its impact, high priority caution is required to avoid SARS-CoV-2 infection among paediatric cancer patients. Furthermore, our results highlight the importance of promoting care facilities for this vulnerable population in low and middle income regions to ensure quality care among cancer patients during pandemic crisis.

KEY WORDS

cancer, COVID-19, meta-analysis, paediatric, paediatrics

1 | INTRODUCTION

Since 2019, following the emergence of SARS-CoV-2 virus, approximately 419 million individuals have been affected with the COVID-19 disease leaving more than 5.8 million deaths.¹ The risk of getting infected and disease severity vary according to the presence of risk factors including age, co-morbid conditions, immunosuppressive conditions, and appropriate adoption of non-

pharmaceutical measures.^{2,3} However, children were reported to have mild grade of infection, but severe outcomes including multiple inflammatory syndrome, hospitalisation requiring mechanical ventilation and death may also happen.³ Multitude of risk factors are associated with increased severity in children, particularly in those with immunosuppressive conditions that is cancer, congenital heart disease, pulmonary compromise, obesity and diabetes.^{4–6}

Abbreviations: BMI, Body mass index; CI, Confidence interval; HICs, High income countries; ICU, Intensive care unit; LICs, Low income countries; LMICs, Low middle income countries; NIH, National Institutes of Health; RT-PCR, Reverse transcriptase polymerase chain reaction; UMICs, Upper middle income countries.

COVID-19 disease incidence is higher in children with cancer than in the general paediatric population.⁷ These patients are subjected to an increased likelihood of being infected subsequently progressing to higher risk of morbidity and mortality. Additionally, oncologic treatment and follow-up mandate frequent visits, increased duration of exposure to hospitals and health care providers in an immune-depleted highly susceptible cancer patients may further enhance the risk of infection.⁸ However, researchers also revealed that decreased inflammatory response among blood cancer patients might provide protection from severe COVID-19 morbidity.^{9,10} Yet, few data are available regarding the true impact of COVID-19 on paediatric cancer patients and the emerging evidence is limited to case reports, case series and small cohorts mostly from developed countries.

Several society recommendations and review articles have been released to guide clinicians to manage cancer patients affected with SARS-CoV-2.¹¹⁻¹⁴ All authorities attempted to provide circumstantial evidence to guide the management of paediatric cancer patients during rapidly evolving nature of COVID-19 pandemic with new waves of infections and variant of concerns. A systematic review from the early phase of pandemic reported 4% mortality risk (95%CI 1-9) after pooling the data from nearly 100 paediatric cancer patients.¹⁵ With the limited availability of data arising from immense heterogeneity in sources, the authors acknowledged that the estimate is subjected to undermine the impact of COVID-19 risk in paediatric cancer patients. Another study reported higher survival rate of paediatric cancer patients from COVID-19 and sub-group analysis comparing haematological cancer and solid tumours did not reveal significant differences.¹⁶ Although the review authors included data mostly from developed countries with small study size and follow up duration to report complete outcomes during analysis. Such differences in the literature imply the heterogeneous nature of data and with the concurring new waves of infections across both developed and developing countries, it is crucial to review the plethora of published evidence to investigate the impact of COVID-19 on the outcome of paediatric cancer patients. This systematic review and meta-analysis study was carried out to investigate the outcome of COVID-19 on paediatric cancer patients with particular focus to mortality, hospitalisation and intensive care unit (ICU) admission.

2 | METHOD

2.1 | Search strategy

In 26 October 2021, we performed comprehensive search in accordance with the PRISMA group recommendations for conducting high quality systematic review studies.¹⁷ Many keywords were extracted from pilot searching of relevant articles then a search term was developed '(COVID-19 OR COVID 19 OR novel coronavirus OR

SARS-CoV-2) AND (cancer OR cancers OR oncology) AND (paediatrics OR children)' for identifying the most relevant papers in seven databases (Figure 1). Moreover, at least two authors did manual search for collecting all the available literature meeting our inclusion criteria.

2.1.1 | Inclusion criteria

Any study reporting outcomes of COVID-19 infection in paediatric cancer patients aged 0–18 years were included. Any paper reported with language other than English was also included.

2.1.2 | Exclusion criteria

Cancer patients >18 years old, studies that report a combination of paediatric and adult cancer patients in which paediatric patients information could not be extracted alone, papers that combined benign disorders with cancer data in which cancer data could not be extracted alone, preprint articles that did not undergo peer review, review articles, case reports <5 patients and duplicate studies that included the same patients of already included papers.

2.2 | Screening and data extraction

After searching in seven databases, all results were exported to EndNote Version 8 software and all duplicated records were removed, and then exported the results into Microsoft Excel sheet. At least two authors scanned all the records against the selection criteria and discrepancies were resolved by discussion on two successive stages: one through title and abstract screening and the other through full text screening.

A data extraction template was built by the most experienced member and included the characteristics of each study (Reference ID, type of cancer, diagnostic method of COVID-19, male prevalence, sample size, study design and age; Table 1) and COVID-19 outcomes (hospitalisation, ICU admission and mortality). At least two authors did the extraction from each included paper.

In both steps of screening and extraction, one author was incorporated to check the results of each step for preventing any error that can develop results bias and conclusion accordingly.

2.3 | Quality assessment

We rated the quality of evidence using the National Institutes of Health quality assessment tool.¹⁸ The net results of the quality of each paper were reported using the same score reported in earlier published systematic reviews.^{19,20}

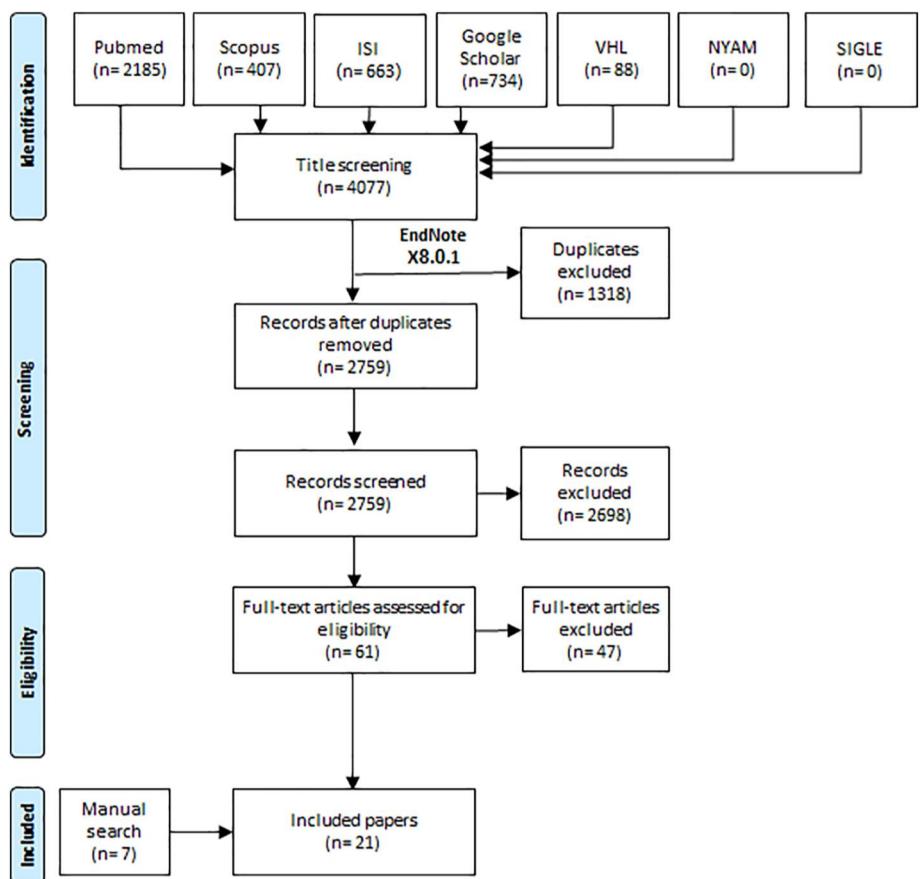


FIGURE 1 Flow diagram showing the process of the study. ISI, Institute of Science Index; NYAM, The New York Academy of Medicine; SIGLE, System for Information on Grey Literature in Europe; VHL, Virtual Health Library

2.4 | Statistical analysis

We conducted the analysis by using the Comprehensive Meta-analysis software version 3. In all outcomes, we reported the results as the pooled prevalence and the associated confidence interval (95%CI). Moreover, we conducted a subgroup analysis for studying the effect of each country income and COVID-19 outcomes in cancer patients. Countries income was categorised into low income countries (LICs), low middle income countries (LMICs), upper middle income countries (UMICs) and high income countries (HICs) that was reported in the World Bank.²¹ We used a random effects model in all the analysis due to presence of heterogeneity estimated by a *p* value of < 0.1 or $I^2 > 50$.²²⁻²⁴ We further assessed publication bias if 10 or more studies were represented in one outcome using the two-tailed Egger's test and publication bias was evident when *p* value < 0.1 .²⁵

3 | RESULTS

We screened a total of 2759 records after transferring the databases results without duplicates. We further assessed 61 full texts for eligibility which ended up with a total of 21 articles including 14

studies and additional seven studies following manual search procedures^{7,26-45} (Figure 1, Table 1).

Two studies were conducted in India, two in Pakistan, two in Brazil, two in Poland, two in Egypt and remaining each one from the following countries: USA, Iran, UK, Colombia, Spain, Peru, Algeria, Greece, Turkey, Mexico and Italy. Diagnosis of COVID-19 was done by reverse transcriptase polymerase chain reaction (RT-PCR) in 14 studies, IgM/IgG and PCR in one study, radiology in one study, radiology and serology in one study and four studies did not report the diagnostic method of COVID-19. Eight, six and seven papers were conducted in LMICs, UMICs and HICs.

3.1 | Hospitalisation

Thirteen studies reported a pooled prevalence 44% patients underwent hospitalisation due to COVID-19 (95%CI: 30–59%; Figure 2a). Subgroup analysis indicated that HICs had lower hospitalisation rate rather than did UMICs and LMICs, 30% (95%CI: 17–46), 60% (95%CI: 29–84) and 47% (95%CI: 36–58), respectively (Figure 2b). We found no evidence of publication bias (*p* = 0.74; Figure 2c).

TABLE 1 Characteristics of the included studies

Author/year published/ country of patients	Study design	Sample size	Age range	Gender (male)	Diagnostic method	Type of cancer	Quality rating
Palomo-Colli/2021/ Mexico	Retrospective cohort	38	(1–18)	25	NR	Acute lymphoblastic leukaemia (21), acute myeloid leukaemia (3), histiocytosis (3), medulloblastoma (2), Ewing sarcoma (2), osteosarcoma (2), rhabdomyosarcoma (1), synovial sarcoma (1), neuroblastoma (1), Wilms tumour (1), hepatoblastoma (1)	Fair
Totadri/2021/India	Retrospective cohort	37	(1–17)	28	PCR	Acute lymphoblastic leukaemia (16), Ewing sarcoma (7), T-lymphoblastic lymphoma (3), osteosarcoma (3), germ cell tumour (2), rhabdomyosarcoma (2), neuroblastoma (1), pineal brain tumour (1), Hodgkin lymphoma (1), Langerhan cell histiocytosis (1)	Fair
Tyczynski/2020/Poland	Retrospective cohort	8	(4.5–17)	5	PCR	Acute lymphoblastic leukaemia (4), Wilms tumour (2), CNS tumour (1), osteosarcoma (1)	Fair
Ebeid/2020/Egypt	Retrospective cohort	15	8.3 (3.5)*	9	PCR	Acute lymphoblastic leukaemia (8), acute myeloid leukaemia (1), lymphoblastic lymphoma (1), Hodgkin lymphoma (1), other malignancies (2), medulloblastoma (1), Ewing's sarcoma (1)	Fair
Radhakrishnan/2020/ India	Retrospective cohort	15	(1–18)	9	PCR	Acute lymphoblastic leukaemia (8), acute myeloid leukaemia (2), mixed phenotypic acute leukaemia (2), hepatoblastoma (2), Wilms (1)	Fair
Shaheen/2021/Pakistan	Retrospective cohort	17	(1–18)	14	PCR	Acute lymphoblastic leukaemia (6), Burkitt lymphoma (1), Hodgkin lymphoma (2), osteosarcoma (3), Wilms tumour (2), rhabdomyosarcoma (1), hepatoblastoma (1), germ cell tumour (1)	Fair
Fonseca/2021/Colombia	Retrospective cohort	33	(1–17)	21	Radiology/ PCR	Acute lymphoblastic leukaemia (15), medulloblastoma (3), acute myeloid leukaemia (3), Burkitt lymphoma (2), primary mediastinal B-cell lymphoma (1), lymphoblastic lymphoma (1), acute lymphoblastic leukaemia (1), pinealoblastoma (1), osteosarcoma (1), Ewing's sarcoma (1), Wilm's tumour relapse (1), germ cell tumour (1), sacrococcygeal teratoma (1)	Fair
Raza/2021/Pakistan	Retrospective cohort	55	(1–18)	-	NR		Fair
Corso/2021/Brazil	Retrospective cohort	179	(1–18)	103	PCR	Leukaemia (100), lymphoma (15), solid tumours (64)	Fair
Cela/2020/Spain	Retrospective cohort	15	(0–18)	14	NR	Acute lymphoblastic leukaemia (8), non-Hodgkin lymphoma (1), neuroblastoma (1), myelo- dysplastic syndrome (1), melanoma (1), acute myeloblastic leukaemia (1), Ewing sarcoma (1), Wilms tumour (1)	Fair
Montoya/2020/Peru	Retrospective cohort	69	(0–16)	44	IgM/IgG and PCR	Acute lymphoblastic leukaemia (36), non-Hodgkin lymphoma (5), brain tumour (5), Wilms tumour (4), myeloid leukaemia (3), bone tumour (3), soft tissue tumour (3), other (12)	Fair
Arous/2021/Algeria	Case series	7	(1–16)	3	PCR	Leukaemia (5), lymphoma (1), neuroblastoma (1)	Fair
Baka/2021/Greece	Retrospective cohort	15	(5–15)	7	NR	Acute lymphoblastic leukaemia (7), Hodgkin lymphoma (2), non-Hodgkin lymphoma (2), central nervous system tumour (2), osteosarcoma (1), neuroblastoma (1)	Fair

TABLE 1 (Continued)

Author/year published/ country of patients	Study design	Sample size	Age range	Gender (male)	Diagnostic method	Type of cancer	Quality rating
Lima/2021/Brazil	Retrospective cohort	48	6.2 (4.5)*	33	PCR	Leukaemia (31), solid tumours (16), lymphoma (1)	Fair
Bisogno/2021/Italy	Retrospective cohort	29	(0-16)	13	PCR	Leukaemia 16, lymphoma (3), Ewing sarcoma (2), rhabdomyosarcoma (1), hepatoblastoma (2), Wilms tumour (1), central nervous system tumours (1), desmoplastic fibroma (1), rhabdoid tumour (1), Langerhans cells histiocytosis (1)	Fair
Millen/2020/UK	Retrospective cohort	54	(0-16)	29	PCR	Acute lymphoblastic leukaemia (24), acute myeloid leukaemia (4), CNS tumour (5), neuroblastoma (6), sarcomas (4), Wilms tumour (2), hepatoblastoma (2), retinoblastoma (2), Hodgkin lymphoma (1), Burkitt lymphoma (1), others/non-malignant (3)	Fair
Mehrvar-2021-Iran	Retrospective cohort	17	9.1*	10	Radiology and serology	Leukaemia (7), brain tumour (5), lymphoma (3), sarcoma (2)	Fair
Tompson-2021-Poland	Retrospective cohort	155	5.8#	93	PCR	Acute lymphoblastic leukaemia (52), CNS tumour (30), soft tissue sarcoma (16), neuroblastoma (15), Hodgkin lymphoma (10), renal tumour (8), acute myeloid leukaemia (7), non-Hodgkin lymphoma (4), osteosarcoma (4), retinoblastoma (2), other (7)	Fair
Kamdar-2021-USA	Retrospective cohort	51	8.8*	28	PCR	NR	Fair
Hammad-2021-Egypt	Prospective cohort	76	2-10	42	PCR	Leukaemia and lymphoma (66), solid tumours (6), CNS tumours (3), other (1)	Fair
Kebudi-2021-Turkey	Retrospective cohort	51	6#	33	PCR	Leukaemia (26), lymphomas (5), brain tumours (5), neuroblastoma (4), bone tumours (3), soft tissue sarcomas (3) and other solid tumours (5)	Fair

Abbreviations: *, Mean(SD); #, median; NR, not reported.

3.2 | ICU admission

Intensive care unit admission was reported by 10 studies with a prevalence of 14% (95%CI: 9-21; Figure 3a). High income countries had lower ICU admission rate compared to UMICs and LMICs, 7% (95%CI: 1-32), 13% (95%CI: 7-23) and 18% (95%CI: 6-41), respectively (Figure 3b). We found evidence of publication bias ($p < 0.05$; Figure 3c).

3.3 | Mortality

Of total 20 studies, the pooled mortality prevalence was 9% (95%CI: 6-12; Figure 4a). Subgroup analysis demonstrated that mortality was higher in LMICs and UMICs than HICs with the prevalence of 13% (95%CI: 8-20), 12% (95%CI: 8-18) and 3% (95%CI: 2-5), in order (Figure 4b). We found a significant publication bias in mortality outcome ($p = 0.01$; Figure 4c).

4 | DISCUSSION

We found that the rates of hospitalisation, ICU admission and mortality of paediatric cancer patients were 44%, 14% and 9%, in order. Moreover, MICs had worse COVID-19 outcomes compared to HICs.

The previous systematic review of 15 studies that included case reports and observational studies indicated a survival rate of 99% for paediatric cancer patients with COVID-19.¹⁶ However, our prevalence of COVID-19 mortality (9%) was higher than the previous systematic review (1%) as we included only observational studies in addition to the large number of the included studies in our meta-analysis with a sample size of 984 patients compared to 191 patients in the previous meta-analysis.

In comparison with adults, children usually develop less severe SARS-CoV-2 infections. Many factors have been suggested to elucidate this finding. One of these explanations is that the incomplete maturity of adaptive immunity may protect children from hyper-

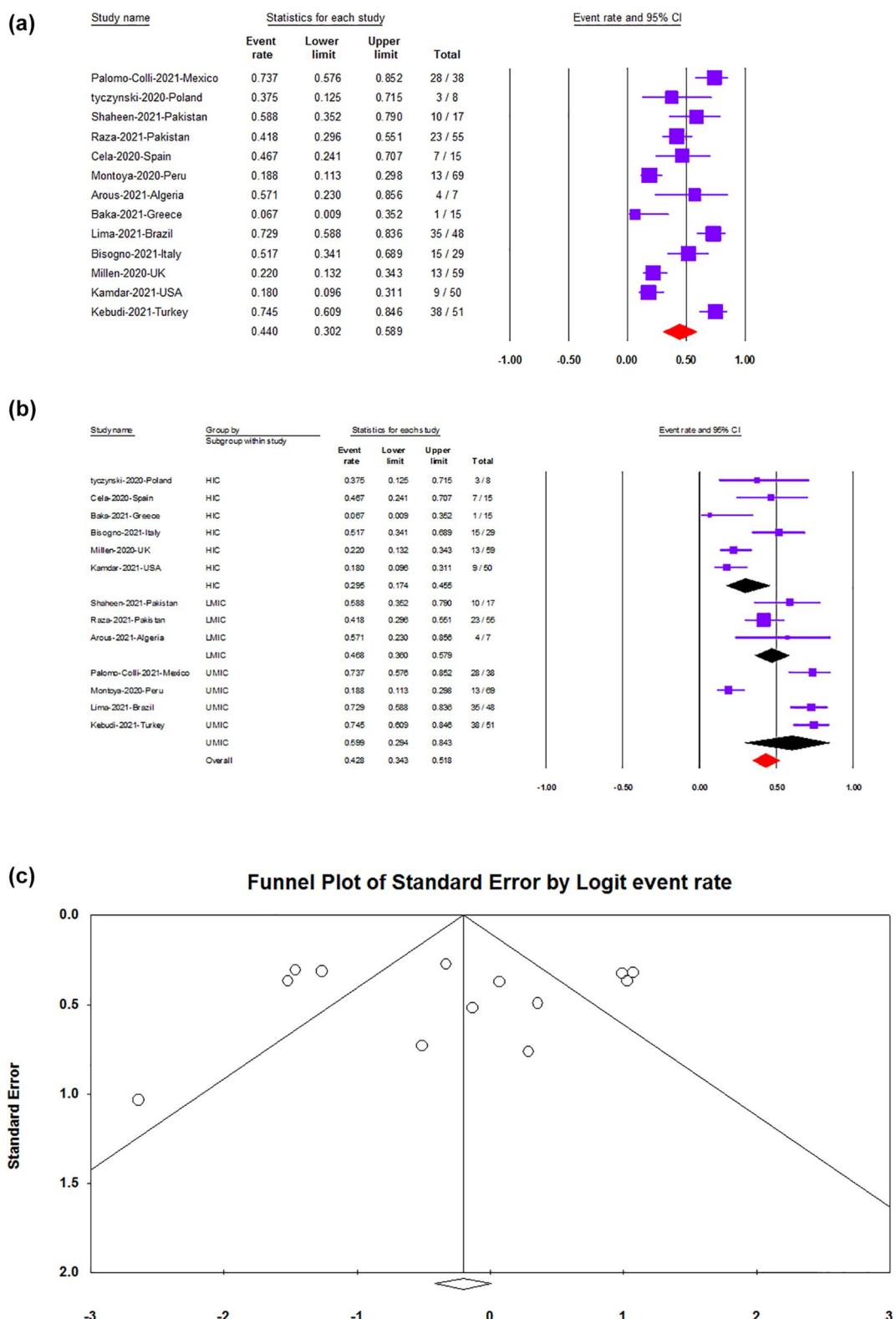


FIGURE 2 (a) The prevalence of hospitalisation in paediatric cancer patients represented with the event rate and 95% confidence interval (95%CI). (b) Subgroup analysis of the prevalence of hospitalisation in paediatric cancer patients according the income of countries represented with the event rate and 95% confidence interval (95%CI). (c) Funnel plot of the publication bias of hospitalisation outcome

inflammation observed in adults.⁴⁶ However, immunocompromised paediatric patients, especially cancer patients, represent a vulnerable population that should have a close follow up.⁴⁷ Unfortunately, there

is no specific treatment for paediatric cancer patients with COVID-19 infection. A global report from many cancer societies consolidated essential information for clinicians regarding the diagnosis and

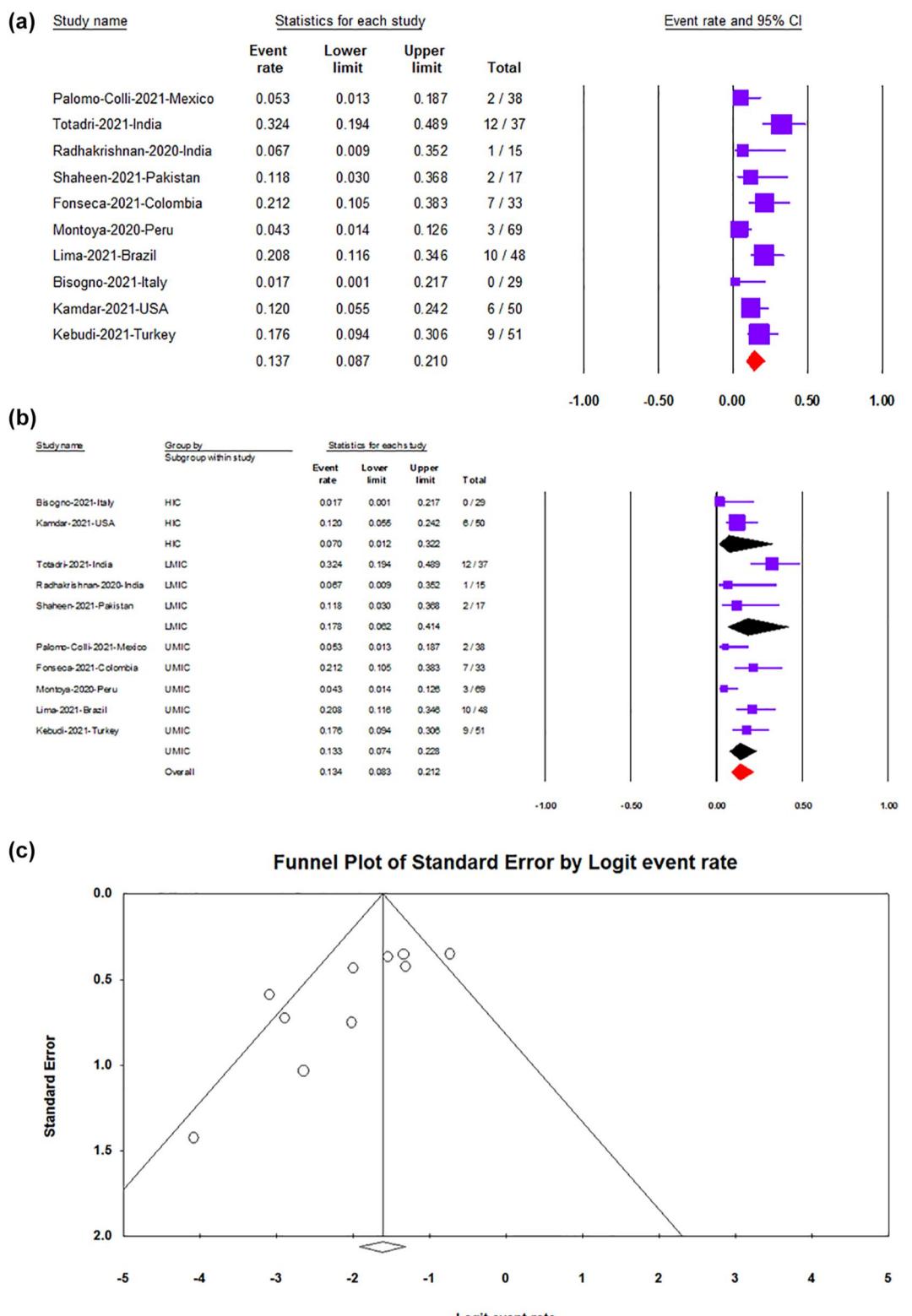


FIGURE 3 (a) The prevalence of intensive care unit (ICU) admission in paediatric cancer patients represented with the event rate and 95% confidence interval (95%CI). (b) Subgroup analysis of the prevalence of ICU admission in paediatric cancer patients according the income of countries represented with the event rate and 95% confidence interval (95%CI). (c) Funnel plot of the publication bias of ICU admission outcome

treatment of COVID-19 in cancer patients.⁴⁸ The report recommended wearing efficient personnel protective equipment for both the children and the care team for preventing COVID-19

transmission. Moreover, children who are undergoing surgical procedure to treat cancer were encouraged not to delay their surgery during the COVID-19 era for provoking better disease outcomes.

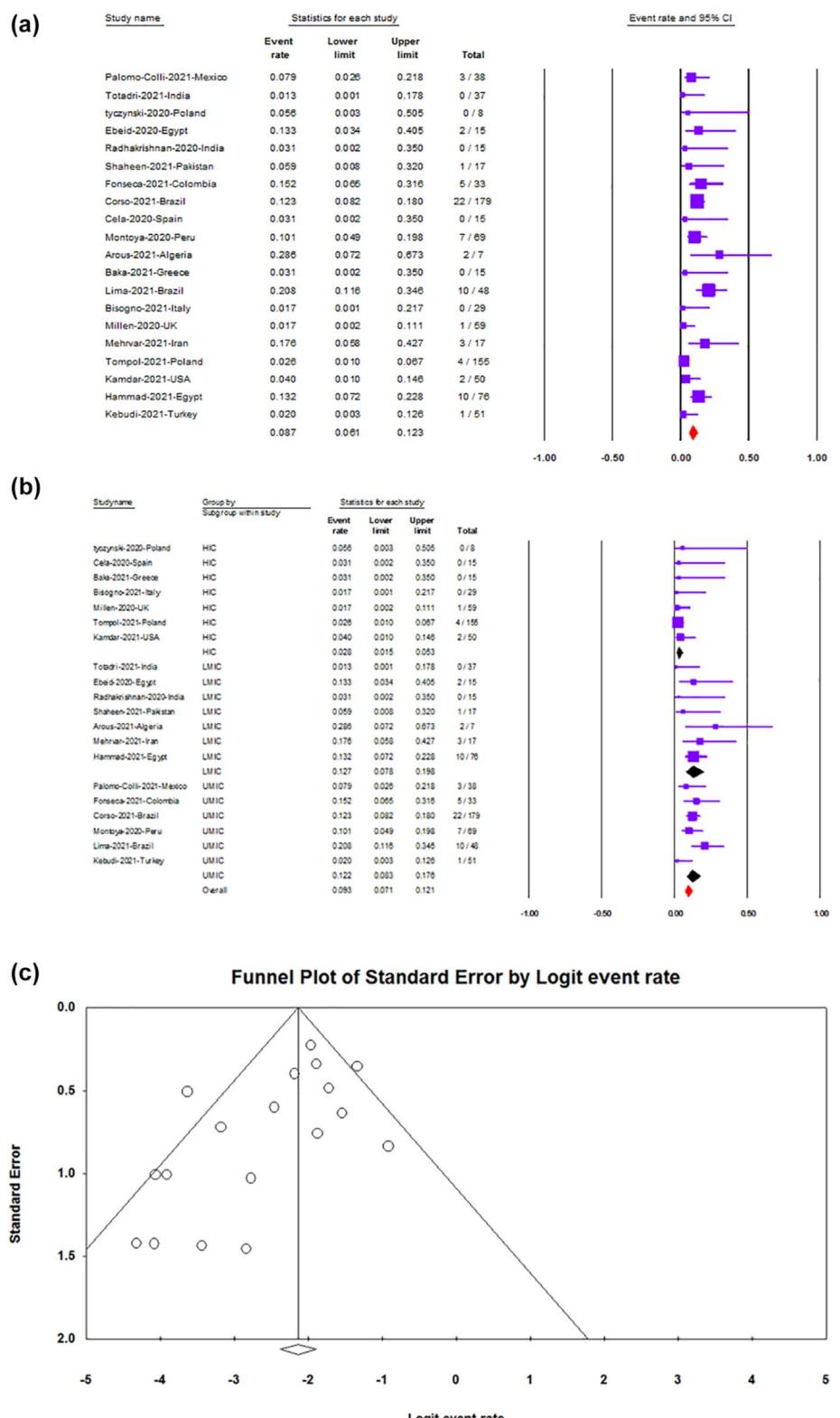


FIGURE 4 (a) The prevalence of mortality in paediatric cancer patients represented with the event rate and 95% confidence interval (95% CI). (b) Subgroup analysis of the prevalence of mortality in paediatric cancer patients according the income of countries represented with the event rate and 95% confidence interval (95%CI). (c) Funnel plot of the publication bias of mortality outcome

Furthermore, identifying the source of infection and transmission dynamics in each oncology centre whether being a patient or a medical staff is essential for the prevention of new COVID-19

cases.⁴⁸ In addition, it was recommended that paediatric cancer patients with SARS-CoV-2 infections should not have major modifications in their underlying therapy.⁴⁷

It was suggested that paediatric oncology patients have a better COVID-19 outcomes compared with adults but they may have a worse COVID-19 outcomes than that of the general paediatric population.⁴⁷ This observation was supported by the fact that the various modalities for cancer treatment which include chemotherapy, immunotherapy, radiotherapy or bone marrow transplantation tend to suppress the immune system for cancer patients. This weakened immune system is liable for an attack of many opportunistic infections.⁴⁹

Our analysis revealed that MICs countries had higher prevalence of COVID-19 hospitalisation, ICU admission and mortality compared to HICs. In a recent large cohort studies that included 1500 paediatric patients diagnosed with cancer or referred to the oncologic centres for undergoing haematopoietic stem-cell transplantation, COVID-19 severity and COVID-19 mortality were higher in the LICs and LMICs than UMICs and HICs.⁵⁰ However, we did not extract data from this cohort as it included non-cancer patients which we settled previously as one of our exclusion criteria.

Recent research papers have identified many factors that can impact the progression of the infection including age, body mass index, co-infection, neutropenia, initial presentation and the existence of comorbidities.^{34,51,52} Paediatric patients with cancer having low socio-economic facilities are at greater risk of developing severe COVID-19 outcomes like hospitalisation and death. This may be related to the precarious nutritional status of children in these countries.³⁴ Sociocultural behaviours of people living in these regions and lack of adequate hygiene maintenance may also contribute to infection risk in paediatric cancer patients.³⁵ Moreover, the inequalities in country income may also have an impact on patients' access to health care facilities, especially during the lockdown period, which possibly explain the higher mortality in MICs in our results.³⁵ Furthermore, the delay in COVID-19 diagnosis is a significant predictor of COVID-19 severity that reflects in turn for COVID-19 adverse outcomes.⁵³ In the cohort study of Kebudi et al, nearly two thirds of paediatric cancer patients with COVID-19 infection had a delay/interrupted chemotherapy schedule.⁴⁵ The interruption or delaying of cancer treatment on paediatric patients during the pandemic involves multiple factors including understaffing of health care providers (either infected by COVID-19 or serving as front line for the COVID-19 cases) and the shortage of personnel protective equipment. The long lockdown periods had adverse economic effect among families in LMICs reflected by the reduction in the hospital visits from affected patients during COVID-19 era.^{54,55}

PCR is the most specific and sensitive diagnostic test for COVID-19; in LICs and MICs, PCR testing is expensive and most patients cannot afford it is cost.⁵³ In addition, infection from healthcare professional is not uncommon in LICs and MICs due to the shortage in the personal protective equipment.^{56,57} Vaccination can be a potential tool for preventing risk of COVID-19 severity. Currently, there is no evidence on vaccine efficacy and safety in paediatric oncology patients.⁵¹ Adults data showed that oncological patients

may have a decreased response to vaccine and they might develop infection after immunisation.⁵⁸ Caregivers and family members vaccination against COVID-19 may play a pivotal role in this situation.⁵¹ Additional research to find out the risk/benefit ratio of vaccination in paediatric cancer patients is urgently is needed to mitigate the disease burden.

Although the number of the included patients is high, most of the studies of this systematic review did not distinguish between solid tumours and other malignancies. This may be a source of bias since some haematological malignancies can have worse outcomes at short time-frame and this might overestimate the burden with the course of the infection. Furthermore, the retrospective nature of the included studies is a limitation in our report. More prospective studies are needed to provide evidence about each variety of cancer. Although, the prevalence of ICU admission in our study was of 14% but, in some countries, the establishment of clinical facilities providing high-level care interventions minimised admissions to ICU.¹³ Besides, different clinical categorisation in treating hospitalised patients across countries guidelines might resulted differential ICU admission rate. In addition, significant heterogeneity was prevalent across data sources and variables that is the ethnicity, age, gender, COVID-19 diagnostic method, cancer type and the treatment of both cancer and COVID-19 infection. Moreover, we did not find any paper that discussed the outcomes of COVID-19 in cancer patients in LICs which indicates a necessity for more data for finding the survival outcome from this group of patients.

5 | CONCLUSION

In front of the absence of specific treatments and the lack of data on vaccine, caution should be taken to avoid COVID-19 infection among paediatric cancer patients. Hospitals in LICs and MICs should improve their services and management protocols to mitigate the burden of SARS-CoV-2 infection in paediatric cancer patients.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Amr Ehab El-Qushayri was responsible for the idea and the study design. All authors shared in the data extraction. Amr Ehab El-Qushayri analysed the data and interpreted it. All authors shared in the writing of the full text and approval of final version before submission.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. <https://www.worldometers.info/coronavirus/>
2. Zhang J, Wang X, Jia X, et al. Risk factors for disease severity, unimprovement, and mortality in COVID-19 patients in Wuhan, China. *Clin Microbiol Infect.* 2020;26(6):767-772.
3. Bailey LC, Razzaghi H, Burrows EK, et al. Assessment of 135 794 pediatric patients tested for severe acute respiratory syndrome coronavirus 2 across the United States. *JAMA Pediatr.* 2021;175(2):176-184.
4. Yasuhara J, Kuno T, Takagi H, Sumitomo N. Clinical characteristics of COVID-19 in children: a systematic review. *Pediatr Pulmonol.* 2020;55(10):2565-2575.
5. Lingappan K, Karmouty-Quintana H, Davies J, Akkanti B, Harting MT. Understanding the age divide in COVID-19: why are children overwhelmingly spared? *Am J Physiol Lung Cell Mol Physiol.* 2020;319(1):L39-L44.
6. Shekerdeman LS, Mahmood NR, Wolfe KK, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. *JAMA Pediatr.* 2020;174(9):868-873.
7. de Rojas T, Pérez-Martínez A, Cela E, et al. COVID-19 infection in children and adolescents with cancer in Madrid. *Pediatr blood cancer.* 2020.
8. Venkatesulu BP, Mallick S, Lin SH, Krishnan S. A systematic review of the influence of radiation-induced lymphopenia on survival outcomes in solid tumors. *Crit Rev Oncol/Hematol.* 2018;123:42-51.
9. Thibaud S, Tremblay D, Bhalla S, Zimmerman B, Sigel K, Gabrilove J. Protective role of Bruton tyrosine kinase inhibitors in patients with chronic lymphocytic leukaemia and COVID-19. *Br J Haematol.* 2020.
10. Treon SP, Castillo JJ, Skarbnik AP, et al. The BTK inhibitor ibrutinib may protect against pulmonary injury in COVID-19-infected patients. *Blood.* 2020;135(21):1912-1915.
11. Brissot E, Labopin M, Baron F, et al. Management of patients with acute leukemia during the COVID-19 outbreak: practical guidelines from the acute leukemia working party of the European Society for Blood and Marrow Transplantation. *Bone Marrow Transplant.* 2021;56(3):532-535.
12. ESMO E. *Cancer patient management during the COVID-19 pandemic.* 2020.
13. Giannakoulis VG, Papoutsi E, Siempos, II. Effect of cancer on clinical outcomes of patients with COVID-19: a meta-analysis of patient data. *JCO Glob Oncol.* 2020;6:799-808.
14. Salunke AA, Nandy K, Pathak SK, et al. Impact of COVID-19 in cancer patients on severity of disease and fatal outcomes: a systematic review and meta-analysis. *Diabetes Metab Syndr Clin Res Rev.* 2020.
15. Vijenthira A, Gong IY, Fox TA, et al. Outcomes of patients with hematologic malignancies and COVID-19: a systematic review and meta-analysis of 3377 patients. *Blood.* 2020;136(25):2881-2892.
16. Dorantes-Acosta E, Ávila-Montiel D, Klunder-Klunder M, Juárez-Villegas L, Márquez-González H. Survival and complications in pediatric patients with cancer and COVID-19: a meta-analysis. *Front Oncol.* 2021;3103.
17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009;6(7):e1000100.
18. Health Nlo. Quality assessment tool for observational cohort and cross-sectional studies. *National Heart, Lung, and Blood Institute.* 2014. Accessed November 5, 2015. www.nhlbi.nih.gov/health-pro/guidelines/indevelop/cardiovascular-risk-reduction/tools/cohort
19. Benmelouka AY, Abdelaal A, Mohamed ASE, et al. Association between sarcoidosis and diabetes mellitus: a systematic review and meta-analysis. *Expet Rev Respir Med.* 2021;1:1-7.
20. El-Qushayri AE, Dahy A, Reda A, et al. A closer look at the high burden of psychiatric disorders among healthcare workers in Egypt during the COVID-19 pandemic. *Epidemiology Health.* 2021;43:e2021045.
21. <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>
22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Contr Clin Trials.* 1986;7(3):177-188.
23. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ (Clin Res ed).* 2003;327(7414):557-560.
24. El-Qushayri AE, Ghozy S, Reda A, Kamel AMA, Abbas AS, Dmytriw AA. The impact of Parkinson's disease on manifestations and outcomes of Covid-19 patients: a systematic review and meta-analysis. *Rev Med Virol.* e2278.
25. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315(7109):629-634.
26. Palomo-Collí MÁ, Fuentes-Lugo AD, Cobo-Ovando SR, Juárez-Villegas L. COVID-19 in children and adolescents with cancer from a single center in Mexico city. *J Pediatr Hematol Oncol.* 2021;43(7):e1047-e1048.
27. Totadri S, Srinivasan HN, Joseph LL, et al. The unique balancing act of managing children with cancer and COVID-19 infection: a single center experience from South India. *J Pediatr Hematol Oncol.* 2021.
28. Styczyński J, Balwierz W, Wachowiak J, et al. Epidemiology and prevention strategies of SARS-CoV-2 infection in pediatric hematology and oncology centers in Poland. *Acta Haematol Pol.* 2020;51(4):253-257.
29. Ebeid F, Makkeyah S, Mostafa S, et al. COVID-19 in children with cancer: a single low-middle income center experience. *Authorea Prepr.* 2020.
30. Radhakrishnan V, Ogett J, Rajendran A, et al. COVID19 in children with cancer in low-and middle-income countries: experience from a cancer center in Chennai, India. *Pediatr Hematol Oncol.* 2020;38(2):161-167.
31. Shaheen N, Wali RM, Saeed H, Sandhu II, Qaisar M, Qazi R. Acute morbidity and mortality analysis of COVID-19 in children receiving cancer treatment. *Chemotherapy.* 2021;4:23-25.
32. Fonseca EV, Pardo CA, Linares A, et al. Clinical characteristics and outcomes of a cohort of pediatric oncohematologic patients with COVID-19 infection in the city of Bogotá, Colombia. *Pediatr Infect Dis J.* 2021;40(6):499-502.
33. Raza MR, Maqsood S, Rana ZA, et al. Impact of COVID-19 on the children with cancer in 6 pediatric oncology units (POU's) of Pakistan-a multi-center study. *Cancer Invest.* 2021;(just-accepted).1-11.
34. Corso MCM, Soares VJ, Amorim AMP, et al. SARS-CoV-2 in children with cancer in Brazil: results of a multicenter national registry. *Pediatr Blood Cancer.* 2021;68(12):e29223.
35. Montoya J, Ugaz C, Alarcon S, et al. COVID-19 in pediatric cancer patients in a resource-limited setting: national data from Peru. *Pediatr blood cancer.* 2021.
36. Arous R, Djillali IS, Rouis NO, et al. High mortality of COVID-19 in children with cancer in a single center in Algiers, Algeria. *Pediatr Blood Cancer.* 2021.

37. Baka M, Michos A, Alexopoulou A, et al. COVID-19 among children with cancer in Greece (2020): results from the Nationwide Registry of Childhood Hematological Malignancies and Solid Tumors (NARECHEM-ST). *Pediatr blood cancer*. 2021.
38. Lima ALMdA, Borborema MdCD, Matos APR, Oliveira KMMD, Mello MJG, Lins MM. COVID-19 cohort on children with cancer: delay in treatment and increased frequency of deaths. *Rev Bras Saúde Materno Infant*. 2021;21:299-304.
39. Bisogno G, Provenzi M, Zama D, et al. Clinical characteristics and outcome of severe acute respiratory syndrome coronavirus 2 infection in Italian pediatric oncology patients: a study from the Infectious Diseases Working Group of the Associazione Italiana di Oncologia e Ematologia Pediatrica. *J Pediatric Infect Dis Soc*. 2020; 9(5):530-534.
40. Millen GC, Arnold R, Cazier J-B, et al. Severity of COVID-19 in children with cancer: report from the United Kingdom paediatric coronavirus cancer monitoring project. *Br J Cancer*. 2021;124(4): 754-759.
41. Mehrvar A, Qaddoumi I, Tashvighi M, et al. Treatment and outcomes of pediatric patients with cancer and COVID-19 at MAHAK pediatric cancer treatment and research center, Tehran, Iran. Paper presented at: *Seminars in Oncology*. 2021.
42. Węcławek-Tompson J, Zakrzewska Z, Grynewicz-Kwiatkowska O, et al. COVID-19 in pediatric cancer patients is associated with treatment interruptions but not with short-term mortality: a Polish national study. *J Hematol Oncol*. 2021;14(1):1-10.
43. Kamdar KY, Kim TO, Doherty EE, et al. COVID-19 outcomes in a large pediatric hematology-oncology center in Houston, Texas. *Pediatr Hematol Oncol*. 2021;1:1-14.
44. Hammad M, Shalaby L, Sidhom I, et al. Management and outcome of coronavirus disease 2019 (COVID-19) in pediatric cancer patients: a single centre experience from a developing country. *Clin Lymphoma Myeloma Leukemia*. 2021;21(11):e853-e864.
45. Kebudi R, Kurucu N, Tuğcu D, et al. COVID-19 infection in children with cancer and stem cell transplant recipients in Turkey: a nationwide study. *Pediatr blood cancer*. 2021.
46. Zimmermann P, Curtis N. Why is COVID-19 less severe in children? A review of the proposed mechanisms underlying the age-related difference in severity of SARS-CoV-2 infections. *Arch Dis Child*. 2021;106(5):429-439.
47. Connelly JA, Chong H, Esbenshade AJ, et al. Impact of COVID-19 on pediatric immunocompromised patients. *Pediatr Clin*. 2021.
48. Sullivan M, Bouffet E, Rodriguez-Galindo C, et al. The COVID-19 pandemic: a rapid global response for children with cancer from SIOP, COG, SIOP-E, SIOP-PODC, IPSO, PROS, CCI, and St Jude Global. *Pediatr Blood Cancer*. 2020;67(7):e28409.
49. Oh J-K, Weiderpass E. Infection and cancer: global distribution and burden of diseases. *Ann Glob Health*. 2014;80(5):384-392.
50. Mukkada S, Bhakta N, Chantada GL, et al. Global characteristics and outcomes of SARS-CoV-2 infection in children and adolescents with cancer (GRCCC): a cohort study. *Lancet Oncol*. 2021;22(10): 1416-1426.
51. Haesler GM, Ammann RA, Carlesse F, et al. SARS-CoV-2 in children with cancer or after haematopoietic stem cell transplant: an analysis of 131 patients. *Eur J Cancer*. 2021;159:78-86.
52. Jee J, Foote MB, Lumish M, et al. Chemotherapy and COVID-19 outcomes in patients with cancer. *J Clin Oncol*. 2020;38(30): 3538-3546.
53. Faust L, Zimmer AJ, Kohli M, et al. SARS-CoV-2 testing in low- and middle-income countries: availability and affordability in the private health sector. *Microb Infect*. 2020;22(10):511-514.
54. Kebudi R, Chantada G, Kurucu N, Tuğcu D, Mukkada S, Moreira DC. COVID-19: consequences for children with cancer in Turkey and globally. *Turk Arch Pediatr*. 2021;56(4):295-299.
55. Graetz D, Agulnik A, Ranadive R, et al. Global effect of the COVID-19 pandemic on paediatric cancer care: a cross-sectional study. *Lancet Child Adolesc Health*. 2021;5(5):332-340.
56. López-Aguilar J, Cárdenas-Navarrete R, Toba AS, et al. Children with cancer during COVID-19 pandemic. Early experience in Mexico. *Authorea Prepr*. 2020.
57. Bhattacharya S, Hossain MM, Singh A. Addressing the shortage of personal protective equipment during the COVID-19 pandemic in India—a public health perspective. *AIMS Public Health*. 2020;7(2): 223-227.
58. Becerril-Gaitan A, Vaca-Cartagena BF, Ferrigno AS, et al. Immunogenicity and risk of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection after Coronavirus Disease 2019 (COVID-19) vaccination in patients with cancer: a systematic review and meta-analysis. *Eur J Cancer*. 2021.

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