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BRIEF REPORT

Cancer is not a risk factor for severe COVID-19 in children, except in patients with recent allogeneic hematopoietic stem cell transplantation or comorbidities

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Abstract

The EPICO (Spanish general registry of COVID-19 in children)-SEHOP (Spanish Society of Pediatric Hematology and Oncology) platform gathers data from children with SARS-CoV-2 in Spain, allowing comparison between children with cancer or allogeneic hematopoietic stem cell transplantation (alloHSCT) and those without. The infection is milder in the cancer/alloHSCT group than in children without comorbidities (7.1% vs. 14.7%), except in children with recent alloHSCT (less than 300 days), of which 35.7% experienced severe COVID-19. These data have been shared with the SEHOP members to support treatment and isolation policies akin to those for children without cancer, except for those with recent alloHSCT or additional comorbidities. This highlights the collaborative registries potential in managing pandemic emergencies.

KEYWORDS
allogenic HSCT, cancer, children, comorbidities, COVID-19, Registry

Abbreviations: ALL, acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplantation; EPICO-AEP, Spanish general registry of COVID-19 in children; SEHOP, Spanish Society of Pediatric Hematology and Oncology.

1 | INTRODUCTION

Previous studies have shown that pediatric patients with cancer and SARS-CoV-2 infection generally have a mild course, but with a mortality rate of 3.8%, higher than in the general pediatric population according to previous reports.[1–4] This severity is higher in allogeneic hematopoietic stem cell transplantation (alloHSCT) recipients, registering a mortality of 5%–6%.[5–8]

A recent meta-analysis has shown that the severity and mortality of COVID-19 in this population is higher in low middle-income countries, suggesting that the inclusion of countries with different health resources may influence the analysis of the severity of COVID-19.[2,9]

The comparison of the morbidity and mortality of COVID-19 between pediatric patients with cancer or HSCT and children without comorbidities has been made from registries and publications that did not include both populations, making it difficult to thoroughly analyze it.[7]

The registration and analysis of a population attended with the same health resources and including the same variables in the pediatric population without comorbidities and with cancer could help to define more accurately the clinical characteristics and outcome differences of this infection between both populations, and guide its management in pediatric oncology units. Therefore, in November 2020, a specific form designed by the Spanish Society of Pediatric Hematology and Oncology (SEHOP) for pediatric patients managed in oncological units (with cancer or alloHSCT) was added to the Spanish general registry of COVID-19 in children (EPICO-AEP). The aim of this study was to keep treating physicians updated on the course and management of COVID-19 in children with cancer in Spain, during the early phases of the pandemic when there was no literature on this subject. For this purpose, internal analyses were presented during the national SEHOP congresses in 2021[10] and 2022.[11] Here, we analyze these harmonized data.

2 | METHODS

EPICO-AEP is a Spanish multicenter cohort study, approved by the Ethics Committee of Hospital 12 de Octubre (code 20/101). Eligible participants were children (0–18 years) diagnosed in a hospital with acute SARS-CoV-2 infection.

Researchers from each participating hospital collected anonymized data using the electronic system REDCap, including epidemiological, demographic, clinical, and laboratory variables.

To assess whether there may be differences in the impact of COVID-19 depending on the type of cancer or the treatment received, they were categorized into five groups: solid tumors, lymphoma and acute lymphoblastic leukemia (ALL), ALL in maintenance, alloHSCT recipients within 300 days, and alloHSCT recipients beyond 300 days.

To assess risk factors for severe COVID-19, we stratified patient severity based on oxygen therapy requirements, a more specific and uniform indicator of severity compared to hospitalization status, as admission policies varied by hospital and pandemic phase, and Spanish pediatric hospitals follow the guidelines for the care of the critically ill child that indicate the administration of oxygen only if the hemoglobin saturation is below 94%.[12]

Qualitative variables were described as number and percentage. Quantitative variables were described as median and interquartile range (IQR).

Categorical variables were compared using chi-square test. The comparison of continuous variables between two groups was assessed with the Student's *t*-test or Mann–Whitney *U* test, as appropriate. More than two groups were analyzed with either ANOVA or Kruskal–Wallis. Confidence intervals for all analyses were considered at 95%.

All statistical analyses were performed with R software, version 4.2.2 (2015 The R Foundation for Statistical Computing).

3 | RESULTS

A total of 990 children without cancer or any comorbidities and 256 pediatric patients with cancer or treated with alloHSCT (including three patients who received alloHSCT for non-oncological diseases), and infected with SARS-CoV-2 between March 1, 2020 and March 1, 2022, were reported.

There were 109 reported patients diagnosed with solid tumors, 34 with lymphoma, eight with acute myeloid leukemia, 85 with ALL (38 of them in maintenance and 20 without data on the current treatment cycle), and 20 alloHSCT recipients (14 of whom were less than 300 days post transplantation).

Table 1 presents the characteristics of the infection in which significant differences were found between children without comorbidities and children with cancer/alloHSCT.

No differences were found in the distribution by sex, or in school-based transmission rates between children with and without cancer (0.5% vs. 2.8%, $p = .073$).

Although the vaccination status record was insufficient ($n = 291$) to compare vaccine coverage among different groups, we did identify that within the group of patients with cancer/alloHSCT, vaccinated patients did not require oxygen whereas 5.9% of the unvaccinated patients did. However, these differences were not statistically significant ($p = .338$). Patients who had received chemotherapy (CT) or radiotherapy (RT) in the last 30 days before infection did not require more oxygen support (5.8% and 0%, respectively) than patients who had not received CT/RT (6.8% and 6.8%) or received it later (7.7% and 6.2%).

Table 2 summarizes the outcomes comparing cancer/alloHSCT subgroups and children without comorbidities.

Admission to the PICU or the need for vasopressors was more frequently associated with the requirement for oxygen therapy, which was necessary in 68% of PICU cases and 78% of those receiving vasopressors ($p < .01$).

Of the four patients with cancer/alloHSCT who died from COVID-19, none were vaccinated, three of them had received recent alloHSCT,

TABLE 1 Characteristics of SARS-CoV-2 infection in children without comorbidities and children with cancer.

	No cancer, no comorbidities ($n = 990$)	Cancer ($n = 256$)	All ($n = 1246$)	p	n[a]
Age (years)	5 (5.3)	9.2 (5.2)	5.8 (5.5)	<.001	1202
Healthcare exposure associated with infection	8 (0.8%)	24 (11.3%)	32 (2.7%)	<.001	1203
Household exposure associated with infection	420 (42.4%)	37 (17.4%)	457 (38%)	<.001	1203
COVID-19 vaccine	10 (6.5%)	35 (25.5%)	45 (15.5%)	<.001	291
Waves[b]					
1	198 (20.1%)	33 (29.2%)	231 (21.1%)	<.001	1097
2	387 (39.3%)	25 (22.1%)	412 (37.6%)		
3	120 (12.2%)	9 (8%)	129 (11.8%)		
4	35 (3.6%)	2 (1.8%)	37 (3.4%)		
5	59 (5.9%)	3 (2.7%)	62 (5.7%)		
6	185 (18.8%)	41 (36.3%)	226 (20.6%)		
COVID-19 symptoms					
Fever	746 (75.9%)	67 (53.6%)	813 (73.4%)	<.001	1108
Cough	400 (40.8%)	37 (30.1%)	437 (39.6%)	.029	1104
Rhinorrhoea	383 (39.3%)	35 (28.5%)	418 (38.1%)	.026	1098
Abdominal pain	213 (25.1%)	13 (10.8%)	226 (23.3%)	<.001	968
Vomiting/nausea	262 (26.8%)	20 (16.4%)	282 (25.6%)	.018	1100
Diarrhoea	193 (19.7%)	13 (10.6%)	206 (18.7%)	.02	1103
Codetection[c]	80 (18.4%)	14 (8.6%)	94 (15.7%)	.005	598
Radiological image					
Normal	192 (57%)	52 (74.3%)	244 (60%)	.026	407
Parenchymatous condensation	50 (14.8%)	7 (10%)	57 (14%)		
Other infiltrates	95 (28.2%)	11 (15.7%)	106 (26%)		
Oxygen support	132 (14.7%)	18 (7.1%)	150 (13%)	.002	1151
Hospital admission					
Not hospitalized	458 (45.9%)	69 (53.1%)	527 (46.8%)	.125	1127
Hospitalized	539 (54.1%)	61 (46.9%)	600 (53.2%)		
Death related to COVID-19	0 (0%)	4 (1.6%)	4 (0.32%)	.002	1246

Note: Descriptive analysis [mean (SD); *N* (%)] and *p*-values obtained by chi-square, Fisher, Mann–Whitney test, or logistic regression. Only significant variables are shown.

[a]Available data.

[b]Waves as incidence of SARS-CoV-2 variants in Spain.[3]

[c]The codetection identified was virus–virus in 45.8% of the cases detected and virus–bacteria in 54.2%.

one with primary immunodeficiency and two with ALL, and one patient had a progressive diffuse midline glioma, with a severe neurological deficit, obesity, and palliative care. Therefore, we analyzed the impact of other comorbidities in children with cancer, 9% of children with both cancer and other comorbidities required oxygen, compared to 2.2% for those with cancer and without comorbidities ($p = .045$). When comparing patients with cancer and any other comorbidities to those without cancer but with other comorbidities, the former had lower oxygen need (9.6% vs. 30.8%, $p < .001$).

During the period of the *Omicron* variant, the number of cancer patients registered was higher, but disease severity was milder than those from previous waves ($p = .178$) (Figure 1).

4 | DISCUSSION

A common national registry of children with SARS-CoV-2 aims to assess more accurately whether cancer leads to more severe

TABLE 2 Comparative outcomes of SARS-CoV-2-infected patients within each cancer group and those without cancer or comorbidities.

	No cancer, no comorbidities	Solid tumors	Lymphoma, leukemia, no HSCT, no maintenance	ALL in maintenance, no HSCT	AlloHSCT recipient, <300 days from infusion	AlloHSCT recipient, >300 days from infusion	All	*p*	*n*[a]
PICU admission	90 (10%)	5 (8.8%)	3 (8.6%)	0 (0%)	3 (50%)	0 (0%)	101	.086	1014
Vasopressor support	48 (6.2%)	0 (0%)	0 (0%)	0 (0%)	2 (40%)	0 (0%)	50	.003	882
Oxygen support	132 (14,7%)	6 (5.6%)	5 (7.5%)	0 (0%)	5 (35.7%)	0 (0%)	148	<.001	1131
Death related to COVID-19	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	3 (21.4%)	0 (0%)	4	<.001	1226

Note: Descriptive analysis [mean (SD); *N* (%)] and *p*-values obtained by chi-square, Fisher, Mann–Whitney test, or logistic regression. Only significant variables are shown.

Abbreviations: ALL, acute lymphoblastic leukemia; AlloHSCT, allogeneic hematopoietic stem cell transplantation; HSCT, hematopoietic stem cell transplantation; PICU, pediatric intensive care unit.

[a]Available data.

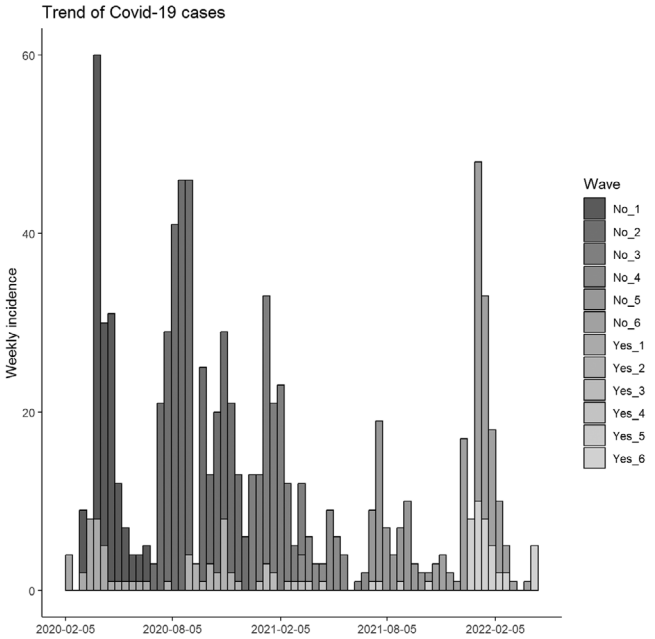

FIGURE 1 Weekly incidence of registered SARS-CoV-2 infection cases. The figure illustrates the annual incidence of SARS-CoV-2 infection by diagnosis date, where the cohort of patients without cancer or other comorbidities (Wave No) is co-located with the cohort of patients with cancer (Wave Yes). The waves are described following the periods outlined by the Spanish Ministry of Health (https://www.sanidad.gob.es/) as Waves (No or Yes) from 1 to 6, with the sixth wave corresponding to the omicron variant.

COVID-19. In our analysis, severe COVID-19 was more frequently detected in children without comorbidities (14.7%) than in children with cancer (7.1%), except in the case of recent alloHSCT (35.7%), as other studies reflected,[8,13] but unrelated to the date of HSCT.

Despite a mild cancer course in children, the mortality rate is 1.6%, which, in our records, is associated with recent alloHSCT or other comorbidities. This rate is similar to the global GRCCC study,[2] although with lower mortality (3.8%), probably because our patients' data are located in a high-income country and during periods where less severe variants were included.[14] Indeed, we found a milder infection, although not statistically significant, in the later phases of the pandemic and in vaccinated patients,[15–17] and no deaths were recorded among them. Additionally, other comorbidities increased the severity in patients with cancer, although their impact was less than in patients without oncological diseases. Chemotherapy and radiation therapy did not seem to be related to clinical severity.[18]

Nosocomial transmission was higher among children with cancer (11.3% vs. 0.8%, $p < .001$), probably due to more frequent hospital visits. However, school transmission rates were similar between children with and without cancer, which may be useful to avoid changing the schooling plan of patients.

Study limitations of selection bias need to be acknowledged, as the initial screening policies in pediatric oncology units could result in a higher registration of mild cases. However, there were no reported cases requiring oxygen or admission to intensive care units in patients with ALL in maintenance, which highlights the mildness of COVID-19 in this population.[19,20]

In conclusion, our data show that the infection is not more severe in patients with cancer/alloHSCT, except in patients with recent alloHSCT or additional comorbidities. These data support, in high-income countries, a policy of infection management similar to that with other respiratory viral infections in cancer pediatric patients, directed by the patient's clinical status or other comorbidities rather than by isolation of SARS-CoV-2.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

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

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