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

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March 08, 2024

Abstract

The EPICO-SEHOP 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. 15%), 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.

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 previously 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.

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 diagnosed in a hospital with 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, categorizing them 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.

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

Categorical variables were compared using the Chi-squared 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)

RESULTS

A total of 1,017 children without cancer or any comorbidities and 257 pediatric patients with cancer or treated with alloHSCT (including 3 patients who received alloHSCT for non-oncological diseases), and infected with SARS-CoV-2 between March 1st, 2020 and March 1st, 2022, were reported.

There were 109 reported patients diagnosed with solid tumors, 34 with lymphoma, 9 with acute myeloid leukemia, 81 with ALL (38 of them in maintenance), 20 alloHSCT recipients (14 of whom were less than 300 days post-transplantation).

Table 1 represents 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 , neither in contagion at school between children with and without cancer (0,5% vs 2,9%, p 0,062)

Within the group of patients with cancer/alloHSCT, vaccinated patients did not require oxygen while 5.9% of the unvaccinated patients did. However, these differences were not statistically significant ($p = 0.338$). Patients who had received chemotherapy(CT) or radiotherapy(RT) in the last 30 days before infection did not require more oxygen support (5% and 0% respectively) than patients who had not received CT/RT (6.7% and 6.7%) or received it later (7.7% and 6.2%).

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

Of the 4 patients with cancer/alloHSCT who died from COVID-19, none were vaccinated, 3 of them had received recent alloHSCT, 1 with primary immunodeficiency and 2 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, 9.9% of children with both cancer and other comorbidities required oxygen, compared to 2.2% for those with cancer and without comorbidities (p0.043). When comparing patients with cancer and any other comorbidities to those with neither cancer nor other comorbidities, the former had lower oxygen need (9.6% vs 30.8%, $p<0.001$).

During the period of the *Omicron* variant, the number of cancer patients registered was higher but milder than those from previous waves (p 0.181).

DISCUSSION

A common national registry of children with SARS-CoV-2 aims to assess more accurately whether cancer leads to more severe COVID-19. In our analysis, severe COVID-19 was more frequently detected in children without comorbidities (15%) than in children with cancer (7,1%), except in the case of recent alloHSCT (35.7%), as other studies reflected (8,12), 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. These rate is similar to the global GRCCC study (2), although with lower mortality (3.8%), probably because our patient's data are located in a high-income country and during periods where less severe variants were included (13). Indeed, we found a milder infection, although not statistically significant, in the later phases of the pandemic and in vaccinated patients (14–16), 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 (17).

Nosocomial transmission was higher among children with cancer (11,2% vs 0,8%, p<0,001) , 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, since 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 (18,19).

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.

CONFLICT OF INTEREST STATEMENT

None of the authors have a conflict of interest to disclose

ACKNOWLEDGEMENTS

We thank the COVID-19 working group for children with cancer from SEHOP (Ana Fernández-Teijeiro, Lucas Moreno, Andres Morales, Anna Faura, Elena Cela, Itziar Astigarraga, Pablo Velasco), who have guided this study and other related projects within the society.

We thank the EPICO-AEP registrars who have registered and corrected data for children with COVID-19 in Spain. The EPICO-AEP project has received funding from the Carlos III Health Institute (ISCIII) through project PI20/00995 and co-financed by the European Union; and Asociación Española de Pediatria (2020 Reseach grant).

Statistical analysis has been carried out in the Statistics and Bioinformatics Unit (UEB) Vall d'Hebron Hospital Research Institute (VHIR) and Biocruces Bizkaia Research Institute.

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TABLE 1. - Characteristics of SARS-CoV-2 infection in children without comorbidities and children with cancer. Descriptive analysis (mean (SD); N (%)) and p values obtained by Chi-Squared, Fisher, Mann-Whitney test or logistic regression. Only significant variables are shown.

	No cancer, no comorbidities (n=1017)	**Cancer (n=257)**	**All (n=1274)**	**p**	**ν$^{\alpha}$**
Age (years)	5.1 (5,3)	9.2 (5,2)	5.8 (5.5)	<0.001	1230
Health care exposure associated with infection	8 (0.8%)	24 (11.2%)	32 (2.6%)	<0.001	123
Household exposure associated with infection	428 (42.1%)	37 (17.3%)	465 (37.8%)	<0.001	1231
COVID-19 vaccine	10 (6.5%)	35 (25.4%)	45 (15.4%)	<0.001	292
Waves* 1 2 3 4 5 6	212 (21%) 390 (38.6%) 126 (12.5%) 38 (3.8%) 60 (5.9%) 185 (18.3%)	33 (29.2%) 25 (22.1%) 9 (8%) 2 (1.8%) 3 (2.7%) 41 (36.9%)	245 (21.8%) 415 (36.9%) 135 (12%) 40 (3.6%) 63 (5.6%) 226 (20.1%)	<0,001	1124
COVID-19 symptoms					

	No cancer, no comorbidities (n=1017)	**Cancer (n=257)**	**All (n=1274)**	**p**	**ν$^{\alpha}$**
Fever	772 (76.4%)	67 (53.6%)	839 (73.9%)	<0.001	1135
Cough	408 (40.5%)	37 (30.1%)	445 (39.3%)	0.033	1131
Rhinorrhoea	387 (38,4%)	35 (28,5%)	422 (37,5%)	0,036	1125
Abdominal pain	235 (26,9%)	13 (10,8%)	248 (24,9%)	<0,001	995
Vomiting/nausea	280 (27,9%)	20 (16,4%)	300 (26,6%)	0,009	1127
Diarrhoea	208 (20,7%)	13 (10,6%)	221 (19,6%)	0,011	1130
Codetection^{+}	83 (18,3%)	14 (8,6%)	97 (15,7%)	0,005	616
Radiological image Normal	208 (57,8%) 50 (13,9%) 102 (28,3%)	52 (74,3%) 7 (10%) 11 (15,7%)	260 (60,5%) 57 (13,3%) 113 (26,3%)	0,032	430
Parenchymatous condensation					
Other infiltrates					
Oxygen support	139 (15%)	18 (7,1%)	157 (13,3%)	0,002	1179
Hospital admission Not hospitalized	458 (45,9%) 539 (54,1%)	69 (53,1%) 61 (46,9%)	527 (46,8%) 600 (53,2%)	0,125	1127
Hospitalized					
Death related to COVID-19	0 (0%)	4 (1,6%)	4 (0,31%)	0.002	1274

$^{\alpha}$Available data

*Waves as incidence of SARS-CoV-2 variants in Spain(3)

$^{+}$The codetection identified was virus-virus in 45.8% of the cases detected and virus-bacteria in 54.2%

TABLE 2. - Comparative outcomes of SARS-CoV-2 infected patients within each cancer group and those without cancer or comorbidities. Descriptive analysis (mean (SD); N (%)) and p values obtained by Chi-Squared, Fisher, Mann-Whitney test or logistic regression. Only significant variables are shown.

$^{\alpha}$Available data. Allo-HSCT : allogeneic stem cell transplantation;HSCT : hematopoietic stem cell transplantation . PICU: Pediatric Intensive Care Unit

Abbreviations: AlloHSCT - Allogeneic Hematopoietic Stem Cell Transplantation; HSCT - Hematopoietic Stem Cell Transplantation; ALL - Acute Lymphoblastic Leukemia; PICU - Pediatric Intensive Care Unit.