

## LETTER TO THE EDITOR

# COVID-19 in pediatric hematopoietic stem cell transplantation: The experience of Spanish Group of Transplant (GETMON/GETH)

To the Editor:

COVID-19 mortality risk factors have been defined, including comorbidities such as cardiovascular disease, hypertension, and diabetes.<sup>1</sup> Cancer also appears to increase both incidence and risk of adverse events. So, the incidence of COVID-19 in children with cancer in Madrid has recently been reported and is 1.3% higher than in the general pediatric population.<sup>2</sup> However, there is no published experience on the impact of COVID-19 on pediatric hematopoietic stem cell transplantation (HSCT). We have collected all posttransplant cases of COVID-19 within the Grupo Español de Trasplante Hematopoyético Pediátrico (GETMON/GETH).

This case series includes children with confirmed COVID-19 by PCR that underwent HSCT in Spain until May 15, 2020. The main characteristics of patients are included in Table 1. We identified eight children with a median age of 10 years old (range 1-12), which is an incidence of 3% of the pediatric HSCT performed annually in Spain. A total of seven recipients (87%) were male. Median Lansky score was 80% and ECOG scale of 1. The underlying disease was immunodeficiency in three cases (37.5%) and leukemia/myelodysplasia in the other five (62.5%). Graft type of donor was a human leukocyte antigen (HLA)-identical unrelated donor in three cases (37.5%), a haploidentical donor in three (37.5%), and a HLA-identical sibling donor in the other two cases (25%). Median presentation time of COVID-19 was 18 months (range 1 month-2 years) after HSCT.

The most common symptoms were fever in five patients (62.5%), respiratory symptoms in four (50%), and diarrhea in the other two (25%). None of the patients were asymptomatic. Five patients (62%) had abnormal radiographic findings, mainly bilateral multifocal opacities and one of them developed alveolar hemorrhage. Three patients (37.5%) had viral coinfections: coronavirus NL63, rhinovirus + parainfluenza 4, and influenza B + rhinovirus + parainfluenza 1.

Two patients (25%) were hospitalized due to the COVID-19 infection, three patients (37.5%) were already hospitalized, and three patients (37.5%) were managed in the outpatient clinic.

One patient had acute graft-versus-host disease (GvHD) grade II, one had chronic GvHD, and one had engraftment syndrome during COVID-19 infection. These three patients were taking steroids.

The laboratory results are detailed in Supplemental Table S1. Median neutrophil and lymphocyte cell count at diagnosis were 2585/ $\mu$ L (range 920-4600) and 1025/ $\mu$ L (range 90-6310), respectively. T lymphocyte count was 918/ $\mu$ L (range 15-960) and B lymphocyte

85/ $\mu$ L (range 0-230). Patients severely ill were more lymphopenic and had the lowest ratio CD4/CD8. The measure of inflammatory markers showed median ferritin levels of 2464 ng/mL (range 900-5832), median C-reactive protein levels of 12 mg/dL (range 0.35-53.8), and median D-dimer levels of 1  $\mu$ g/mL (range 0.5-2.87).

Immunodeficiency scoring index (ISI score) developed for respiratory viral infections was used to categorize severity.<sup>3</sup> There was a correlation between the virus clearance time and the ISI score. Furthermore, patients with the highest ISI score (moderate-severe risk) required admission to the intensive care unit (ICU).

Regarding treatment, most patients (75%) received hydroxychloroquine. The two more severe patients received hydroxychloroquine combined with different drugs such as azithromycin, remdesivir, lopinavir/ritonavir, tocilizumab, siltuximab, and anakinra. In a severely ill child, coronavirus PCR was negative after memory T cell adoptive therapy obtained from his HLA identical donor. Two patients did not receive any treatment. Treatment details are shown in Table S2.

Two patients required admission to the ICU for mechanical ventilation. One of them is now on extracorporeal membrane oxygenation (ECMO) due to adult respiratory distress syndrome. The other patient died from alveolar hemorrhage.

Coronavirus PCR became negative in a mean time of 20 days in six patients (75%), one patient with immunodeficiency remains positive, and the other patient died with positive PCR.

Seven of the eight patients are alive with a median follow up of 52 days (range 25-60), and only one patient has died, which means a mortality rate of 12.5%.

Although this study has the limitations of being a short case series, there are several conclusions from the results.

Firstly, the incidence of COVID-19 is also lower after HSCT in children than in adults,<sup>4</sup> as it has been published in the general population. This is probably because angiotensin enzyme converting 2 (ACE2) expression may be lower in pediatric population and because of the presence of other common respiratory viruses in children that compete with it.<sup>5</sup>

Secondly, most cases in our series also occur in boys, similar to studies showing that males are more susceptible to SARS-CoV infection than females because of a protective effect for estrogen receptor.<sup>1</sup>

Thirdly, immunodeficiencies have a higher risk of COVID-19 since they account for more than a third of cases, when they only account for 10% of the indication for pediatric HSCT. This may be due to the lack of

**TABLE 1** Patients' clinical characteristics

No	Age (years)	Gender	Diagnosis	Type of HSCT	GvHD (acute or chronic)	Time after HSCT	Symptoms	Radiology	ISI score	Status
1	8	M	PID	MSD	Yes	1 month	Fever, dyspnea	Bilateral opacities	6	Alive
2	1	F	PID	HAPLO	No	2 months	Rhinitis, diarrhea	Normal	2	Alive
3	12	M	PID	MUD	No	2 years	Dyspnea	Bilateral opacities	1	Alive
4	11	M	MDS	MUD	No	2 years	Faringitis	Peribronchial thickenings	1	Alive
5	12	M	ALL	HAPLO	No	4 months	Fever	Bilateral opacities	2	Alive
6	10	M	AML	HAPLO	Yes	4 months	Fever	Normal	4	Alive
7	11	M	ALL	MUD	Yes	1 year	Fever, rhinitis, cough, diarrhea	Alveolar hemorrhage	7	Dead
8	9	M	ALL	MSD	No	2 years	Fever	Normal	1	Alive

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; F, female; GvHD, graft-versus-host disease; HAPLO, haploidentical donor; HSCT, hematopoietic stem cell transplantation; ISI score, immunodeficiency scoring index (low risk 0-2, moderate risk 3-6, high risk 7-12); M, male; MDS, myelodysplastic syndrome; MSD, matched sibling donor; MUD, matched unrelated donor; PID, primary immunodeficiency.

development of thymus in these patients, with significant alteration of cellular immunity.<sup>6</sup> So, the quantity and type of affected T lymphocytes seems to be more decisive for COVID-19, with lowest ratio CD4/CD8 in our severely ill patients.

And finally, the ISI score is very useful to assess the need for treatment and the prognosis of patients with COVID-19.

#### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.