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ORIGINAL PAPER

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# Hematopoietic Stem Cell Transplantation During the Era of COVID-19 in Queen Rania Children's Hospital

<sup>1</sup>Department of Pediatric Hematology and Medical Oncology, Queen Rania Children's Hospital. Queen Rania AL- Abdullah children Hospital (QRCH), Jordan

<sup>2</sup>Conferences Office, King Hussein Medical City, Jordan

**Corresponding author:** Dr Mousa Qatawneh. Queen Rania AL- Abdullah children's Hospital (QRCH)- Jordan. Mobile number 00962795675938. E-mail: Dr\_m\_qatawneh@yahoo.com. ORCID ID: <http://www.orcid.org/0000-0002-5400-8804>.

Mousa Qatawneh<sup>1</sup>, Mais Aljazazi<sup>1</sup>, Moath Altarawneh<sup>1</sup>, Hadeel Aljamaen<sup>2</sup>, Maher Mustafa<sup>1</sup>, Alaa Alqasem<sup>1</sup>, Amjad Abu Sharar<sup>1</sup>

## ABSTRACT

**Background:** Corona virus disease 2019 (COVID-19) is causing a health crisis nowadays, and all countries are following the recommendations of the WHO to decrease the spread of the disease. Till now, few data are available regarding the clinical course, severity of the disease and the duration of infectivity of COVID-19 in patients received Hematopoietic Stem Cell Transplantation (HSCT). **Objective:** To evaluate the medical protocols and outcome of patients who underwent HSCT during the pandemic of COVID-19. **Methods:** A retrospective review of the medical files of patients who underwent hematopoietic stem cell transplantation during the era of COVID-19. The following data were reviewed for all patients: age, gender, primary disease, viral screening protocols for donors and recipients, COVID-19 status and outcome. The European society for blood and marrow transplantation (EBMT) guidelines were applied strictly on all of our patients, donors and bone marrow transplant unit staff. **Results:** A total of 10 children were transplanted, 8 of them received allogenic transplant from matched donor and two patients received autologous transplant. Regarding allogenic transplants, all of our patients except two were transplanted as an emergency, 2 of them were Aplastic anemia, 2 patients were Fanconi anemia, one patient was Amegakaryocytic thrombocytopenia, and one patient was Acute myeloid leukemia. Only two patients were not an emergency as one of them had Thalassemia major and the other one was Sickle cell anemia. The autologous transplant was done for two patients with Neuroblastoma stage 4 as part of their treatment protocol. At a median

follow up of 5.5 months (range, 2 month-7 months) two patients (20%) developed COVID-19, which was asymptomatic in both of them. One of our patients (10%) died due to cytomegalovirus (CMV) pneumonia. No one of our patient was affected by the emergency regulations applied by the country and hospitals during the pandemic of COVID-19 virus. **Conclusion:** Hematopoietic stem cell transplantation can be performed safely for emergency cases, if we strictly follow the guidelines of EBMT. **Keywords:** Hematopoietic stem cell transplantation, COVID-19.

## 1. BACKGROUND

Corona virus disease 2019 (COVID-19) is causing a health crisis nowadays (1). This virus was noticed by the World health organization (WHO) at the end of 2019 as an extremely contagious virus spreading in Wuhan city in Hubei province, China (2). On 11<sup>th</sup> of March 2020, the WHO declared COVID-19 virus as a pandemic with more than 2 million cases of COVID-19 worldwide (3-5). By February 1, 2021 around 103.925.049 cases of COVID-19 and more than 2.257.793 deaths were reported worldwide (6). In Jordan 328.062 cases of COVID-19 with around 4326 deaths were reported by the Jordanian Ministry of Health till 1<sup>st</sup> February 2021 (6).

The COVID-19 virus has an incubation period ranging between 2 to 14 days with an average of 5 days (7,8,9). The main route for transmission of the virus are droplets and close contact (10). Fortunately, the majority of infected people are asymptomatic, but some patients develop life

threatening complications like acute respiratory distress syndrome, thrombosis and multi organ failure (11-14). The pediatric population presented with less severe disease in comparison to adults (15-18), however children maybe a significant reservoir for COVID-19 in community because they have mild disease and prolonged viral shedding (19).

Nowadays all countries are following the recommendations of the WHO to decrease the spread of the disease, these recommendations include social distancing, hand washing and to have high alert for people with suspicious symptoms (20).

Hematopoietic stem cell transplantation (HSCT) is still considered as a main curative option for many genetic diseases, hematological malignancies, immunodeficiency and hemoglobinopathies (21, 22). Till now, few data are available regarding the clinical course, severity of the disease and the duration of infectivity of COVID-19 in patients received HSCT (23). For doctors working in stem cell transplantation, the stress is extremely high, as HSCT is a high risk procedure. Many challenges face the patients who receive HSCT and their donors, as recipients of HSCT need recurrent unscheduled admissions to the hospital, so they should stay near the hospital temporarily (24,25), also these patients are at high risk for opportunistic infections especially respiratory viral infections as it happened in 50% of patients who received HSCT, while infectious complications happened in 92% of these patients (26-28). Because of this high rate of infectious complications in HSCT, the center of disease control and prevention (CDC) recommendations regarding infection control in HSCT units should be applied strictly.

Hematologic societies, like American society for transplantation and cellular therapy (ASTCT) and the European society for blood and marrow transplantation (EBMT) responded quickly to release guidelines for the physicians to help them during this extraordinary period of viral outbreak. The ASTCT and EBMT recommendations are summarized in table 1 (29, 30).

## 2. OBJECTIVE

To introduce a comprehensive review of the results of the patients underwent HSCT during the pandemic of COVID-19, this retrospective study analyzes the data for the patients who received HSCT in the period from the 1<sup>st</sup> of May 2020 to the 1<sup>st</sup> of February 2021 at Queen Rania Children Hospital (QRCH).

## 3. MATERIAL AND METHODS

This retrospective study was approved by the Ethical committee of the Jordanian Medical Services. The medical records of the patients who underwent HSCT were conducted at QRCH in Amman-Jordan, during the period between May 2020 and February 2021.

A total of ten patients were transplanted in this period, 8 of them (80%) were allogenic transplant and 2 of them (20%) were autologous transplant. The patients and the donors characteristics are summarized in Table 2.

The data reviewed were patient age, gender, patient address, primary disease, date of transplant, type of transplant, complications and COVID-19 status.

EBMT recommendations for HSCT during the pandemic of COVID-19 were strictly applied regarding patients, donors and Bone Marrow Transplant (BMT) unit staff.

Diseases that need HSCT were classified into two groups:

a) High risk diseases: the diseases that need HSCT to be done as soon as possible to decrease morbidity and mortality of these diseases like Aplastic anemia, Congenital amegakaryocytic thrombocytopenia (CAMT) and high risk malignancies.

b) Low risk diseases: the diseases that HSCT can be postponed for a while as HSCT can be substituted temporarily by supportive management like Thalassemia and Sickle cell disease.

During hospitalization, our patients were admitted in a double door positive pressure isolation rooms. The number of the working staff in the BMT unit was reduced to 50% only, each nurse was taking over only one patient during the shift. The residents were not allowed to enter the BMT unit, just the BMT specialists were allowed to enter the BMT unit.

The patients were not allowed to have food from outside the hospital, also no visitors were allowed to enter the BMT unit. The doctors and nurses who have a direct contact with the patients must wear Personal Protective Equipment (PPE) between the two doors of the double door rooms and when they exit they take off the PPE and discard it at the same place where they wear it.

PCR for COVID-19 was done frequently for the staff at QRCH, it was done if any of the staff was symptomatic or if there was a contact with a COVID-19 confirmed case, even if the PCR was negative for the person who has a direct contact with a COVID-19 patient, he was sent home for a week of home isolation, PCR was repeated 1 week after, if still negative he return to work.

Patients and their caregivers were isolated at home for 14 days before admission to the BMT unit, also PCR was done for them 48 hours before the admission to the BMT unit and it must be confirmed as negative. Donors were also isolated at home 14 days before hospital admission, and PCR was done for them just 48 hours before the harvest day.

After discharge from the BMT unit, PCR was done for the patients if they were symptomatic or if they had a contact with a COVID-19 confirmed case. However, PCR was done before any admission to the hospital, as it is applied in QRCH admission protocol. Clinical appointments were reduced as much as possible especially for patients post HSCT, and it was substituted by video and phone calls.

Overall Survival (OS) was calculated from the date of transplant to death or to the date of last follow up. COVID-19 infection was considered if the patient tested positive by PCR.

## 4. RESULTS

The total number of patients underwent HSCT during the period from May 2020 to February 2021 was 10 patients, 5 of them were males (50%) and 5 of them were females (50%). The median age of our patient at time of transplant was (5.5) years. All of our patients were engrafted, median time for engraftment was (13) days. Details about the clinical course during and post HSCT were summarized in Table 3.

Three of our patients (30%) had a Cytomegalovirus

	ASTCT	EBMT
HSCT recipient		
COVID-19-positive	HSCT postponed until the patient is asymptomatic and 2 PCR tests are negative at least 1 week apart. Reduce intensity conditioning regimen must be considered	Low risk diseases: postpone for three months  High risk diseases: postpone until patient is asymptomatic and 2 PCR tests are negative at least 24 hours apart
Close contact with COVID-19 positive patient or travel to an area considered as high-risk according to CDC or close contact with a person who traveled to an area considered as high risk	postpone for 14–21 days of last contact, or to obtain at least two negative PCR tests one week apart Close monitoring for symptoms	Low risk of disease: postpone for 14–21 days of last contact.
		High-risk of disease: postpone for 14–21 days of last contact according to clinical judgment
		Confirmation of negative PCR must be done before proceeding
High prevalence of COVID-19 in community	PCR at initial evaluation of the patient and two days before conditioning	
	Consider temporary treatment or postpone as much as possible	
Donor		
COVID-19 positive	Postpone at least for 28 days and donor must be asymptomatic and PCR is negative	Donor must be excluded and the duration is unclear
Close contact with COVID-19 positive patient or travel to an area considered as high-risk according to CDC or close contact with a person who traveled to an area considered as high risk	Donor must be excluded for 28 days	Donor must be excluded for 28 days.
	In high risk situations you may consider the donor if he is asymptomatic and negative PCR. Close follow up must be done .	If bone marrow transplant is urgent, exception maybe done providing that the donor is asymptomatic with a negative PCR and no other available suitable donors. Earlier collection is possible

Table 1. ASTCT and EBMT recommendations for HSCT during the pandemic of COVID-19

(CMV) reactivation in blood which required admission for Intravenous management. OS was (90%), One of our patients (10%) died on day (+90) due to CMV pneumonitis, his primary disease was Thalassemia major. Two patients (20%) developed Graft Versus Host Disease (GVHD), the primary disease for the first patient was CAMT, and she developed skin GVHD on day (+60), she was treated by steroids, on the other hand sickle cell disease was the primary disease for the second patient who developed skin and gastrointestinal GVHD on day (+90) and it was refractory to steroids so she was started on ruxolitinib with an excellent response.

Disease relapse in one of our patients on day (+130), her primary disease was AML, and she is now on palliative management. No any case of COVID-19 was reported for the donors and the caregivers. None of our patients had COVID-19 infection before admission to BMT unit nor during admission in the BMT unit.

Two patients (20%) were diagnosed with COVID-19 infection post-HSCT, the primary disease for both of them was aplastic anemia. The first patient was a 5 3/12 years old male patient; he was diagnosed with COVID-19 infection at days (+166). PCR was done for him because he was planned for a surgery for Hickman line removal and PCR is mandatory before surgery as part of QRCH protocol. The second patient was a 21 months old male patient; he was diagnosed with COVID-19 infection at day (+178). PCR was done for him as he had a contact with a confirmed COVID-19 case. Both of them had a benign course of COVID-19 infection as they were asymptomatic with normal radiological findings. The first patient had a negative PCR for COVID-19 after 25 days while the second patient had a negative PCR after 21 days. Clinical status and lab investigations for these patients are summarized in Table 4.

Patient No.	Age (Years)	Address	Gender	Primary Diagnosis	Type Of HSCT	Donor	Date of transplant	Anti GVHD Prophylaxis
1	10	Amman	male	Thalassemia major	allogenic	Brother HLA 10/10	12/5/2020	cyclosporine
2	6.5	Mafraq	male	Fanconi anemia	allogenic	Father HLA 10/10	13/5/2020	cyclosporine
3	5 3/12	As-Salt	male	Aplastic anemia	allogenic	Brother HLA 9/10	29/6/2020	Mycophenolate
4	1 9/12	Ajloun	male	Aplastic anemia	allogenic	Sister HLA 10/10	29/6/2020	Mycophenolate
5	12 6/12	Irbid	female	SCA	allogenic	Sister HLA 10/10	26/7/2020	Tacrolimus, Ruxolitinib
6	2 5/12	Amman	female	CAMT	allogenic	Mother HLA 10/10	3/8/2020	Tacrolimus Prednisolone
7	6	Amman	female	AML	allogenic	Brother HLA 10/10	31/8/2020	Cyclosporine
8	2 8/12	Amman	female	N.B stage 4	autologous	-	14/9/2020	-
9	5 8/12	Amman	male	Fanconi anemia	allogenic	Mother HLA 10/10	25/10/2020	Cyclosporine
10	4 5/12	Ma'an	female	N.B stage 4	autologous	-	26/10/2020	-

Table 2. Patients and Donors Characteristics

Patient No.	GVHD	CMV Reactivation	Covid-19	Renal impairment	Status
1	No	Yes, day (+70)	No	No	Died, day (+90)
2	No	No	No	No	No chronic complications
3	No	No	Yes, day (+166)	Yes, day (+40) (improved)	No chronic complications
4	No	No	Yes, day (+178)	Yes, day (+35) (improved)	No chronic complications
5	Yes, Day (+90) Skin and GI	No	No	No	Grade 1-2 skin chronic GVHD
6	Yes, Day (+60) Skin	Yes, Day (+90)	No	No	No chronic complications
7	No	Yes, day (+75)	No	No	Relapsed, Day (+130)
8	No	No	No	No	completing Neuroblastoma treatment protocol
9	No	No	No	No	No chronic complications
10	No	No	No	No	completing Neuroblastoma treatment protocol

Table 3. Clinical course and complications during and post-HSCT for the patients

## 5. DISCUSSION

Till now, few data are available regarding clinical course, the severity of the disease and the duration of infectivity of COVID-19 in patients receiving HSCT (23).

Due to the frequent updates for COVID-19, the EBMT and ASTCT are publishing frequent updates regarding the recommendations for HSCT during the pandemic of COVID-19 (29, 30). In our center. As we follow the EBMT recommendations strictly, the number of cases who underwent HSCT during the pandemic of COVID-19 was 40% less than the expected number for the same period, as we transplanted around 16 patients in the same period (9 months) each year before the pandemic of COVID-19. This reduction of the number of HSCT cases was done because we want to spare the resources (ICU beds, personnel and blood products) which we expect to be in very high demands during the COVID-19 era. This was applied by multiple transplant centers worldwide (31).

Seven of our patients (70%) were transplanted before the 4<sup>th</sup> of September 2020, which is the date of the outbreak of COVID-19 in Jordan, the cases were as the following: 2 cases of aplastic anemia, 1 case of CAMT, 1 case of thalassemia major, 1 case of SCA, 1 case of fanconi anemia and 1 case of AML. HSCT for the low risk diseases (Thalassemia and SCA) were done because at the time of their HSCT, Jordan was having very few cases of COVID-19 (6). After the 4<sup>th</sup> of September 2020, HSCT was done for only 3 patients (30%), the cases were high risk diseases: 2 autologous transplants for stage 4 neuroblastoma and one transplant for fanconi anemia. The fanconi anemia patient was blood and platelet transfusion dependent and he had intracranial hemorrhage and lower GI bleeding in the 3 months before his transplant, so his transplant was mandatory to save his life. This decrease in the number of cases transplanted after the 4<sup>th</sup> of September was due to the rapid increase in the number of COVID-19 cases in Jordan (6), so HSCT was

Patient No.	Time Of Covid-19 Infection	WBC's Count	Lymphocyte Count	C-Reactive Protein	IgG Level	Chest CT Scan	Clinical Course	Time for PCR negativity
3	Day (+166)	4400	2100	15	784	Normal	Asymptomatic, Home isolation	25 days
4	Day (+178)	5100	2500	10.6	830	Normal	Asymptomatic, Home Isolation	21 days

Table 4. Clinical status and lab investigations for COVID-19 patients post-HSCT

risky at that time and the ideal action was to postpone all the patients with low risk disease. This action was done because HSCT patients are at higher risk to have COVID-19 related complications especially in the first days after the transplant because of the conditioning they received and the delayed immune reconstitution after transplant (32), as the conditioning the patients received will lead to the loss of their B and T lymphocytes including the loss of memory cells, in addition to the mucocutaneous barriers damage (33). Severe complications of COVID-19 in patients post HSCT were reported in multiple articles, Grace Fisler et al and his colleagues reported a patient who had COVID-19 on day (+8) post-transplant and she developed respiratory failure and intubation for long time (34).

None of our patients, their caregiver and their donors developed COVID-19 before transplant or during hospitalization in the BMT unit, these results were achieved because the EBMT recommendations were applied strictly as we isolate the patients, caregivers and donors at home for 14 days before admission to the hospital, this will help to protect our patients from getting the virus in the critical period of the transplant especially in the period before engraftment. The idea behind the home isolation for the donors despite the that they will not have a direct contact with the patients during BMT admission is that the COVID-19 can be detected in blood of infected people, and most of our patients received raw bone marrow from the donors without any manipulation, so we want the donors to be safe and COVID-19 free at the time of transplant. Virus detection in blood of some COVID-19 patients were reported in multiple international article from China and Singapore (35, 36).

Two of our patients (20%) had COVID-19 post-HSCT, they had the infection after day (+100), and both of them were males (100%). This high Cumulative Incidence (CI) of COVID-19 cases in our patients may be explained by the frequent hospital visits and admissions, as they must have close follow up at the BMT clinic because they need frequent drugs level monitoring, CMV status monitoring, Intravenous Immunoglobulin (IVIG) administration every two weeks until The IgG level reaches more than 700 mg/dl and for management of any complications might happen post-HSCT like CMV reactivation and GVHD, so these patients have more contact with population including people who are COVID-19 positive, keeping in mind that 4 of our patients (40%) are using public transportation to reach the hospital which is located in Amman, Jordan. On the other hand, 5 of our patients (50%) live outside Amman. However, because of the limited number of the cases in this study, the statistical analysis may be inadequate and a more

prospective multi institutional study is needed, and this is considered a limitation for this study.

The male predominance reported by our study also was reported by Vicent et al, as (87%) of their patients who had COVID-19 post-HSCT were males (37), This can be explained by the protective effect for estrogen receptors in females (38).

Both of our patients who had COVID-19 post-HSCT were asymptomatic, and they didn't have any abnormal radiological findings on high resolution chest CT scan at the time when they tested positive by PCR. This benign course of COVID-19 infection post-HSCT was noted also by multiple international articles, Gabriele et al described COVID-19 in two of their patients post-HSCT, one of them was a case of AML who had the infection on day (+180) and the other one was severe combined immunodeficiency who had the infection on day (+167), both of them were reported to have a benign course of COVID-19 post-HSCT (37). Also Al Yazidi et al described a benign course of COVID-19 in three patients, 2 of them were leukemia cases on chemotherapy and one of them was a two-year old child who had COVID-19 post-HSCT (38), Rossoff et al also reported six children with malignancy and post-HSCT who had a benign course of COVID-19 without any complications (41).

At the same time, the Spanish group of transplant reported that 5 out of 8 children with COVID-19 post-HSCT required an inpatient management with 2 of them required PICU management (37).

Our results regarding the benign course of COVID-19 in our patients may be explained by the fact that our patients had the COVID-19 after long duration post-HSCT (day +166 and day +178), so at the time of infection they had normal WBC count, lymphocyte count and normal immunoglobulins level. Also our patients didn't have any sign of GVHD which is a risk factor for viral infections (42,43). On the other hand our patients were very young, and all the data described mild and self-limited course of COVID-19 in children (44,45), This may be explained by the fact that Angiotensin Converting Enzyme 2 (ACE2) is the most important receptor for SARS-CoV-2 to enter into human cells, and the expression of the ACE2 in lung and nasal epithelium increases with age, and children have ACE2 receptors with a lower affinity for COVID-19 and a different distribution across body sites, these factors in children make the entry of the virus into cells of the young patients more difficult (46, 47).

Our two patients were isolated at home for 14 days and follow up for them was done by phone and video calls. Fortunately, these two patients were receiving Mycophenolate as GVHD prophylaxis which doesn't need blood level moni-

toring, unlike cyclosporine which needs frequent blood monitoring. Mycophenolate was started for them instead of cyclosporine because both of them developed mild renal impairment while on cyclosporine at the first days post-HSCT, and the renal impairment improved after stopping cyclosporine. PCR negativity for COVID-19 was achieved after 25 days in the first patient, while the second patient had a negative PCR after 21 days. This may be explained by the good immune response for our patients. Now our patients are doing well and free of COVID-19 chronic complications.

## 6. CONCLUSION

HSCT can be done during the pandemic of COVID-19 if the EBMT and ASTCT recommendations are strictly applied. COVID-19 infection had a benign course in patients post-HSCT especially after day (+100) as there will be a good immune recovery.

- **Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms.
- **Author's contribution:** M.Q. M.A. H. A. and A.A. gave a substantial contribution to the conception and design of the work. M.M., A.A. sharar gave a substantial contribution of data. M. Q., M.J. gave a substantial contribution to the acquisition, analysis, or interpretation of data for the work. M.Q., M.A., M.M. had a part in article preparing for drafting or revising it critically for important intellectual content. M. Q., M.A., M. Mustafa gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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