

# Hematopoietic Stem Cell Transplantation and Results in Pediatric Patients with Thalassemia Major: Single-Center Study

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## What is already known on this topic?

*Thalassemia major (TM) and sickle cell anemia are the most common single-gene diseases worldwide. Hematopoietic stem cell transplantation (HSCT) is the only curative treatment method for this patient group. The prognosis is much better in transplants from a fully compatible sibling, especially for young patients in the low-risk group.*

## What this study adds on this topic?

*As a result of the examination of the patient files, it was seen that approximately two-thirds of the thalassemia major (TM) patients who were treated and followed up in our center were informed about hematopoietic stem cell transplantation (HSCT) and noted in their files, human leucocyte antigen typing was performed, and HSCT was performed in early childhood in approximately half of them.*

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## ABSTRACT

**Objective:** This study aimed to reveal whether patients with thalassemia major, who were followed up in our clinic, were given information about hematopoietic stem cell transplantation (HSCT) preparations, results, and complications.

**Materials and Methods:** A total of 190 patients diagnosed with thalassemia major between 1991 and 2019 at the Pediatric Hematology-Oncology Clinics of İstanbul Kanuni Sultan Suleyman Education and Research Hospital were retrospectively analyzed.

**Results:** Median age of the patients and follow-up time were 9 years (range 1-5) and 42.9 months (range 1-285), respectively. The IVSI-110 was the most frequently (30.4%) encountered mutation; there was no information about HSCT in 28 patients' files, 36 patients had no human leucocyte antigen-matched donors, and 38 patients had undergone HSCT. Pretransplant median ferritin levels in thalassemia major patients who had undergone HSCT and who had not undergone HSCT were 1751 ng/mL (350-4000) and 1300 ng/mL (396-4000) ( $P = .149$ ), respectively. The median age of HSCT was 6.5 years, and 24 patients were transplanted from human leucocyte antigen-matched sibling donors, 8 from human leucocyte antigen-matched family donors, and 5 patients from human leucocyte antigen-matched unrelated donors with the myeloablative conditioning regimen. Acute and chronic complication rate was higher in patients transplanted from human leucocyte antigen-matched family donors compared to human leucocyte antigen-matched sibling donors (50% vs 28% and 60% vs 8.3%), respectively; complication odd ratio was 6.7 (95% CI 1.4-32).

**Conclusion:** Human leucocyte antigen typing, donor search, and timely information about HSCT were noted to be performed in two-thirds of the thalassemia major patients, and around half of the patients underwent HSCT. Both acute and chronic complications were significantly higher in patients transplanted from matched unrelated donors.

**Keywords:** Children, thalassemia major, hematopoietic stem cell transplantation

## INTRODUCTION

Thalassemia major (TM) is a worldwide hereditary disease mostly seen (>1%) in regions such as Mediterranean countries, the Middle East, Southeast Asia, India, the Far East, and northern Africa.<sup>1</sup> Although the overall carrier frequency in Turkey, as a country in the Mediterranean basin, is reported as 2%-2.5%, it exceeds 10% in certain regions of the country.<sup>2</sup> Patients with TM present with severe anemia that requires regular blood transfusion at an early age, which in one hand maintains normal growth, development, and activities and on the other hand leads to iron overload and thus causes multiple organ dysfunction, such as the heart, liver, pancreas, thyroid, and other endocrine glands.<sup>1,3</sup> Chronic iron overload

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and its toxic effects related to regular red blood cell transfusion can be prevented by regular iron chelation therapy.<sup>4-6</sup> However, poor patient compliance to chelation therapy is a significant challenge in terms of achieving removal of excess iron and decreasing morbidity and mortality associated with cumulative iron toxicity.<sup>3-7</sup> Also, adjunctive treatments have been investigated to prevent damage caused by iron, and they have not been used routinely.<sup>8,9</sup> Hematopoietic stem cell transplantation (HSCT) from a matched family donor is currently considered the only curative standard therapeutic approach for TM.<sup>10,11</sup> Therefore, families should be informed after the diagnosis of TM about HSCT, and human leucocyte antigen (HLA) tissue typing of patients should be performed as soon as possible, and if possible, HSCT from a sibling donor should be considered.<sup>12,13</sup>

This study aimed to reveal whether patients with TM, who were treated with regular erythrocyte suspension transfusion, iron chelation, and followed up at the pediatric hematology and oncology clinic of our hospital, were given information about HSCT, and HSCT preparations, and to document results and complications of TM patients who had undergone HSCT.

### MATERIALS AND METHODS

One hundred ninety patients diagnosed with TM between 1991 and 2019 at the Pediatric Hematology-Oncology Clinic of Istanbul Kanuni Sultan Suleyman Education and Research Hospital were included in the study and were retrospectively analyzed. Eighty-eight patients who were lost from follow-up for 1 year or more were excluded from the study. In the remaining 102 patients, hemoglobin electrophoresis, beta-globin mutation, follow-up duration, presence of consanguinity among parents, data of bone marrow transplantation (BMT) preparations including HLA typing and conditioning regimen, data of TM patients who had undergone HSCT, donor-recipient relation, hemoglobin and ferritin levels at the time of diagnosis, chelation therapy use, adherence to chelation therapy status, complications related to HSCT, and overall survive after HSCT were reviewed from the patients' files. Acute complications related to HSCT are defined as hemorrhagic cystitis, engraftment syndrome, renal failure, veno-occlusive disease, acute graft versus host disease (GVHD), while chronic GVHD and presence of chronic infection are defined as chronic complications related to HSCT. The abovementioned acute and chronic complications were used as events in the survival analysis. Complications seen in HSCT TM patients were also compared regarding donor-recipient relation. The current study has been approved by Istanbul Kanuni Sultan Suleyman Education and Research Hospital's ethics committee (approval number 2018-50-11), and informed consent was obtained from the parents of the patients.

### Statistical Analysis

Normality of variance was determined using Kolmogorov-Smirnov test. Pearson chi-square test and Fisher's exact test were used to compare the qualitative data. Mann-Whitney *U* test and *t*-test were used to compare numeric variables between groups. Survival analyses were compared with Kaplan-Meier log-rank analysis. A *P* value of <.05 was

considered statistically significant with 95% CI. Statistical analyses were conducted using the Statistical Package for Social Sciences version 22.0 software (IBM Corp.; Armonk, NY, USA).

### RESULTS

The median age of the 102 patients was 9 years (range 1-25 years) and the median follow-up time was 42.1 months (range 1-285 months). The IVS1-110 beta-thalassemia mutation was the most frequently encountered beta-globin mutation with a frequency of 30.4%, followed by Codon 44 del-C (10.8%), Codon 8 del-AA (6.5%), Codon 39 (C>T) (6.5%), making up the most frequently observed 4 mutations. The consanguinity rate among the parents of patients was 84.4%, and 56.6% of consanguineous marriages were between first cousins. Deferasirox was the most used chelation therapy (82%) in the current study's patients, followed by combination therapy in 10% of patients, deferoxamine in 5% of patients, and deferiprone in 3% of patients. Data about the HSCT procedures including HLA typing, donor search, and whether transplantation was performed or not could be obtained in 74 of 102 patients' files. There was no information about HSCT in 28 patients' file notes. Hematopoietic stem cell transplantation was performed in 38 of 74 patients (51.3%) who had HLA-matched donors, whereas 36 had no suitable donors. Pretransplant mean hemoglobin level and median ferritin level in TM patients who had undergone HSCT and in TM patients who had not undergone HSCT were  $8.3 \pm 0.68$  g/L, and  $8.3 \pm 0.67$  g/L (*P* = .768); and 1751 ng/mL (350-4000), and 1300 ng/mL (396-4000) (*P* = .149), respectively.

Demographic and laboratory characteristics of the patients who had data about HSCT procedures are presented in Table 1. Median age of the HSCT patients at the time of transplantation was 6.5 years. Twenty-four patients were transplanted from HLA-matched sibling donors (MSD), 8 from HLA-matched family donors (MFD), and 5 from HLA-matched unrelated donors (MUD). Myeloablative preparation regimen was used in all cases. When the distribution of transplants by years was examined, approximately 50% of the transplants were noted to be performed in 2017. Acute complication rate was 23.6%, and chronic complication rate was 18.4% in HSCT patients, and 1 patient (3%) died due to acute renal failure.

		HSCT Status		P
		Yes (n = 38)	No (n = 36)	
Gender	Male, (n, %)	19 (50)	18 (50)	
	Female, (n, %)	19 (50)	18 (50)	
Age, years, median		6.5 (0.2-16.5)	14 (0.4-30)	
Follow-up time, months, median		108 (9-196)	126 (38-285)	
Pretransplant hemoglobin (g/dL), mean		$8.3 \pm 0.67$	$8.3 \pm 0.68$	.768
Pretransplant ferritin (ng/mL), median		1751	1300	.149
HSCT, hematopoietic stem cell transplantation.				

**Table 2.** Donor Type and Complications in HSCT Patients

Donor information, (n, %)	Matched sibling donor	24 (63)
	Matched family donor	8 (21)
	Matched unrelated donor	5 (13)
	Unknown	1 (3)
	Total	38 (100)
Complications, (n, %)	Acute GVHD	3 (7.8)
	Hemorrhagic cystitis	1 (2.6)
	Veno-occlusive disease	1 (2.6)
	Engraftment syndrome	3 (7.8)
	Acute renal failure	1(2.6)
	Chronic infection	1(2.6)
	Chronic GVHD	6 (15.7)
	Death	1(2.6)

GVHD, graft versus host disease.

**Table 3.** Complications Distribution According to Donor Type

HSCT Type	Complications	N (%)
MSD (n = 24)	Acute complications	
	Hemorrhagic cystitis	1 (4.1%)
	Engraftment syndrome	2 (8.3%)
	Acute renal failure	1 (4.1%)
MFD (n=8)	Veno-occlusive disease	1 (12.5%)
	Acute GVHD	3 (37.5%)
MUD (n = 5)	Engraftment syndrome	1 (20%)
MSD (n = 24)	Chronic complications	
	Chronic GVHD	1 (4.1%)
	Chronic infection	1 (4.1%)
MFD (n = 8)	Chronic GVHD	2 (25%)
MUD (n = 5)	Chronic GVHD	3 (60%)

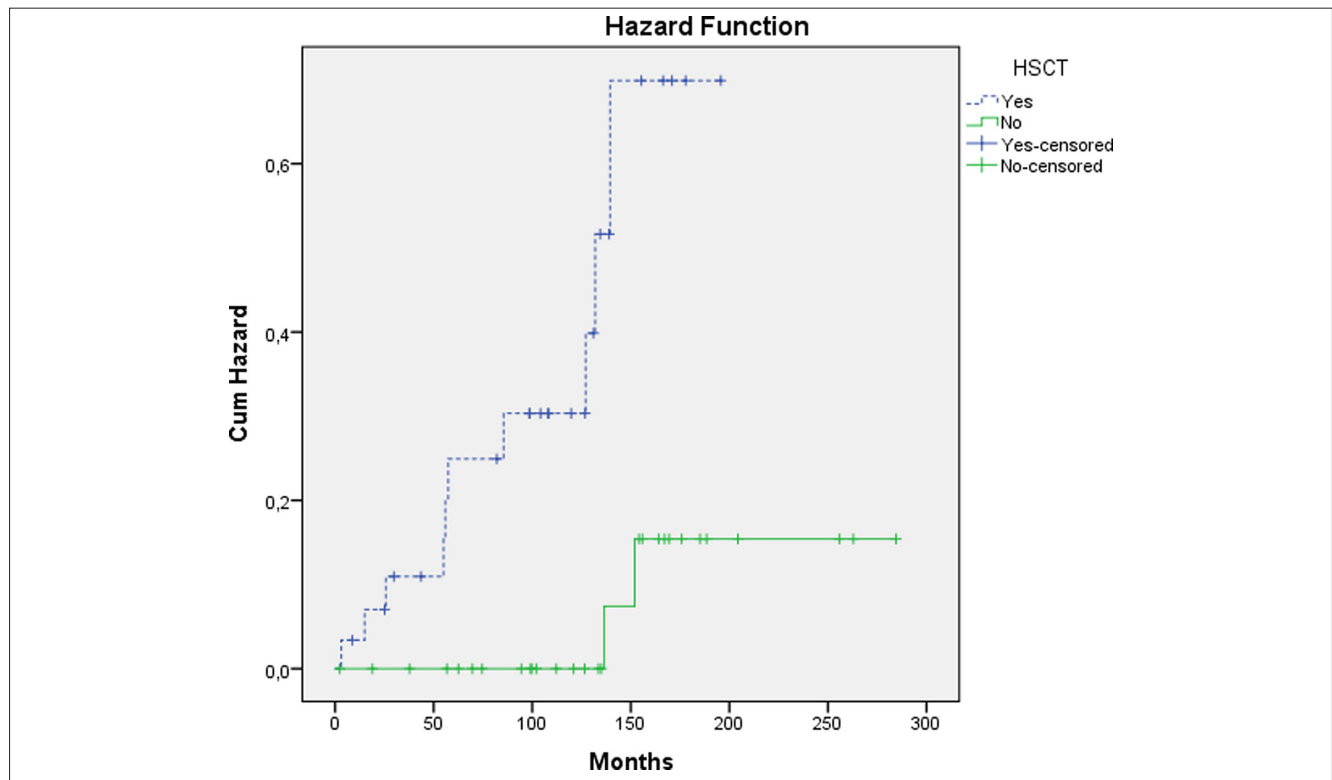
MSD, matched sibling donor; MFD, matched family donor; MUD, matched unrelated donor.

Acute complication rate was higher in patients transplanted from HLA-MFDs compared to patients transplanted from HLA-MSDs (50% vs 28%). Chronic complications related to HSCT were also higher in patients transplanted from MUDs compared to patients transplanted from MSDs (60% vs 8.3%) (Table 2, Table 3).

Complications were seen at the rate of 53% in our patients who underwent BMT at the end of 24 months and 15% at the end of 18 months in patients who did not undergo BIT, and the difference was statistically significant ( $P = .002$ ) (Figure 1). It was significantly higher in transplant recipients than in non-transplant ( $P = .002$ ), and complication odds increased 6.7 times (95% CI: 1.4-32) in non-sibling transplants.

**DISCUSSION**

Life-long erythrocyte transfusion to maintain normal growth and development and iron chelation treatment to avoid complications associated with chronic transfusions are the current therapeutic approaches for TM.<sup>12,13</sup> Life expectancy for TM patients exceeds 40 years in regularly transfused and chelated patients.<sup>14</sup> Hematopoietic stem cell transplantation is the only available curative therapy for TM despite the transplant-associated toxicities and mortality even in the presence of suitable donor including siblings born via *in vitro* fertilization and young thalassemia patient with no comorbidity, which could release the patient from life-long treatments and possible iron



**Figure 1.** Kaplan-Meier curves of cumulative complications in patients with and without HSCT by month at follow-up. HSCT, hematopoietic stem cell transplantation.

accumulation.<sup>15–17</sup> Clinical trials with gene therapy are ongoing for transfusion-dependent thalassemia patients and may be an alternative to HSCT in the future.<sup>18</sup>

In the current study, 74 of 102 (72.5%) patients were informed about HSCT procedures, and after patient and donor HLA typing, HSCT was performed in 38 of 74 patients (51.3%). The optimal outcome in MFD HSCT for TM patients has been identified at the age of  $\leq 14$  years by The European Society for Blood and Marrow Transplantation.<sup>12,19</sup> The most successful outcomes in HSCT are reported to be obtained when it is performed from an MSD at the age of  $< 9$  years. As age progresses, apart from stem cell rejection, acute and chronic complications and related morbidity and mortality increase significantly and the success of HSCT decreases. In this regard, timely HSCT information and donor HLA typing are very important in order to perform HSCT before major organ dysfunction and complications.<sup>11,17</sup> The mean age at the time of HSCT in patients with TM was reported as 6.6 years by Yeşilipek et al<sup>15</sup> from Turkey. In a study by Li et al<sup>20</sup> they compared 52 TM patients who underwent HSCT from MUDs and 30 TM patients who underwent HSCT from MSDs and the median age of the patients at the time of transplantation was 6 years. In a report of 48 TM patients, who underwent MUD HSCT, by Sun et al<sup>21</sup> the median age of the patients was 4 years (range 2–11). The median age of the patients at the time of HSCT in the current study was 6.5 years (0.2–16.5), and no significant difference was found in the present study's results compared to above-mentioned studies. We concluded that TM patients, who were followed up at our pediatric hematology-oncology clinic, were timely referred to HSCT centers for transplantation.

Irregular chelation is one of the identified independent prognostic factors in children with TM undergoing HSCT.<sup>12</sup> In this regard, serum ferritin level can be used as a noninvasive method to predict iron overload before proceeding to transplant. The pre-transplant median ferritin levels were reported to be 3252 ng/mL (233–8250 ng/mL) by Li et al<sup>20</sup> and 1829 ng/mL (409–4960) by Sun et al<sup>21</sup> in thalassemia patients undergoing HSCT. In the present study, the median pre-transplant ferritin level was 1796 ng/mL (350–4000) in TM patients who had HSCT.

La Nasa et al<sup>22</sup> reported a 41% rate of acute GVHD in 32 TM patients transplanted from MUDs in Italy between 1992 and 2001. Locatelli et al<sup>23</sup> cited this study in terms of alternative donor use in TM patients. Acute GVHD rate was 9.6% and 3.6% in TM patients transplanted from MUDs and MSDs, respectively, in the study reported by Lie et al.<sup>20</sup> and in a recent single-center study by John et al.<sup>24</sup> acute GVHD rate was 14% in 57 TM patients transplanted from MSDs. Data about the acute complications in the present study were only available for 21 TM patients, and there were 3 patients who developed acute GVHD transplanted from MFDs.

Acute renal failure rate after HSCT was reported to be 15%–66% by Carreras et al.<sup>12</sup> and in the study by Mima et al.<sup>25</sup> the rate of renal injury after HSCT was 15.7%. In our study, the rate of hemorrhagic cystitis developing after HSCT was 7.1%, and 1 patient developed HSCT-related acute renal failure. Our results were consistent with the data in the literature.<sup>12,24,26</sup>

In a single-center study by John et al.<sup>24</sup> they reported the rate of 14% of VOD in TM patients transplanted from MSDs and the rate of 21% of VOD in TM patients transplanted from MUDs. In the study by Li et al.<sup>20</sup> VOD rate was 3.8% in TM patients transplanted from MUDs and 10.7% in TM patients transplanted from MSDs and mismatched donors. In our study, there was only 1 patient (2.7%) with VOD complications. The rate of VOD in the current study's patients was lower, which was attributed to the lack of information in the patients' medical files, and the fact that the patients were not followed up in our center after the HSCT period as all patients underwent HSCT in another medical center with HSCT Unit.

In a study from Italy by La Nasa et al.<sup>22</sup> chronic GVHD rate was 25% in TM patients transplanted from MUDs. John et al<sup>24</sup> reported a rate of chronic GVHD of 15% and 53% in 57 TM patients transplanted from MSDs and MUDs, respectively. In the present study, the rate of chronic GVHD was 4.1% in TM patients transplanted from MSDs, 25% in TM cases transplanted from MFDs, and 60% in TM children transplanted from MUDs.

In a study by John et al.<sup>24</sup> they reported 5 deaths, 3 due to sepsis and 2 due to alveolar hemorrhage, in 56 children with TM who underwent HSCT. In our study, 1 patient died due to renal failure. The death rate in the current study was lower than in the literature, probably due to the lack of patients' medical records after the HSCT period considering the fact that the patients were followed up in the center where HSCT was performed. Complications increased significantly in our patients who underwent BMT compared to those who did not ( $P = .002$ ).

There are limitations in the present study. The study had retrospective design, and patients' data were obtained from their medical files. Some information was missing in the patients' files, and in some thalassemia patients who had HSCT, episcrisis was not available. Because HSCT Unit was not available in our pediatric hematology-oncology clinic, all HSCTs were performed in other centers with HSCT Unit in Istanbul. Thus, patients could not be followed up after the HSCT period, and acute complications associated with HSCT and chimerism status could not be obtained in detail. Despite all these limitations, we think the present study is important as it is the first study conducted in our center.

## CONCLUSION

Examination of the patient's files revealed that approximately two-thirds of the TM patients, who had been treated and followed up in our center, were noted to be informed about HSCT, and after donor HLA typing, around half of the thalassemia patients who had a suitable donor undergone HSCT. Transplant-associated complications were significantly higher in thalassemia patients transplanted from MUDs compared to those transplanted from MSDs.

**Ethics Committee Approval:** This study was approved by Ethics committee of Istanbul Kanuni Sultan Suleyman Education and Research Hospital, Health Sciences University, (Approval No: 2018-50-11).

**Informed Consent:** Verbal informed consent was obtained from the patients who agreed to take part in the study.

**Peer-review:** Externally peer-reviewed.

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