Correspondence article

Long-term health-related quality of life in patients with β-thalassemia after unrelated hematopoietic stem cell transplantation

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Competing interests statement:
FE: consultancy fees from Amgen, Abbvie, Janssen, and Novartis. Research support (Institution) from Abbvie, Amgen, Novartis, all unrelated to this work.
The other authors have no conflicts of interest to disclose

Running Title: HRQoL in β-thalassemia after unrelated HSCT
Text word count: 1242
Tables: 1
Figures: 1
Number of references: 15
Supplementary information: 1 PDF file

Data availability: The data that support the findings of this study are available from the corresponding author, GC, upon reasonable request

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To the Editor,

in western nations, regular iron chelation therapy and optimization of erythrocyte transfusion support have improved the life expectancy of patients with β-Thalassemia Major (β-TM) born in the last few decades, approaching that of healthy peers (1). Nevertheless, the curative role of hematopoietic stem cell transplantation (HSCT) in β-TM still remains very relevant (2). An international consensus recommends that HSCT be offered as soon as possible before developing iron overload and iron-related tissue damage in patients with an available HLA identical sibling donor (3). However, less than 30% of patients can find a sibling donor within the family, depending on nationality and ethnic group. Lacking a sibling donor, a matched unrelated HSCT represents a valid alternative (4,5). However, this procedure is an option to be performed in centers with appropriate expertise (3,4). Among different parameters used to evaluate the success of the transplant, health-related quality of life (HRQoL) plays a key role. Very little data is available on HRQoL of sibling HSCT and, to our best knowledge, only one study reported HRQoL outcomes in β-TM patients transplanted from unrelated donors (6). Moreover, no direct comparisons on HRQoL are available between patients who underwent siblings or matched unrelated HSCT.

The main objective of our study was to analyze long-term HRQoL in matched unrelated HSCT in β-TM carried out in centers with high expertise in the procedure. The secondary objective was to compare HRQoL between unrelated and sibling HSCT.

Adult patients (age>16 years at survey), eligible for this cross-sectional study were recruited from those who had undergone HSCT in the Hematology Department of Businco and Microcitemico Hospitals in Cagliari, Italy. All patients were initially contacted by telephone or mail to inform them of the study's purposes. Survey instruments and the standardized HRQoL questionnaires Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and Functional Assessment of Cancer Therapy–Bone Marrow Transplant (FACT- BMT) were submitted to patients through a dedicated website. The questionnaires are fully described in supplementary information as well as statistical methods. A separate questionnaire containing sociodemographic and clinical information was also purposed. Enrollment began in July 2020 and ended in July 2021. The study was performed in accordance with the Declaration of Helsinki and it was approved by the Ethics Committee of Cagliari (authorization number: PG/2021/14301). All patients provided written informed consent.

In the time period considered in the research (1995-2016) 127 patients were transplanted (60 matched unrelated and 67 sibling HSCT) with 81% of Overall Survival (OS) and 77% of Thalassemia Free Survival (TFS); 77 available TFS patients were invited to survey and 57 (74%) completed it.

Sociodemographic and clinical features of the cohort are shown in Table 1. HLA identical sibling donor HSCT was received from 23 patients. Thirty-four patients received matched unrelated donor transplant. The median age at the time of transplant was 8 (SD, ±5.49) and 19 years (SD, ±8.1) for sibling and unrelated HSCT, respectively ($p<0.01$). At the survey, the median age was 31 (SD, ±8.2) and 37 years (SD, ±15.1) for siblings and unrelated donors, respectively ($p=0.08$). The median follow-up since transplantation was 18.3 and 22.5 years, respectively. The most frequent conditioning regimen was based on busulfan,

followed by cyclophosphamide. Alternatively, a conditioning regimen based on treosulfan in place of busulfan was administered. The GVHD prophylactic regimen mainly consisted of cyclosporine A, steroids, and/or short-course methotrexate. The incidence of acute and chronic GVHD (grade II-IV) was higher but not statistically different in unrelated compared to sibling HSCT (26% vs. 13% and 24% vs. 17%, respectively, p=0.19 and p=0.40). Venesection was administered in 78% of sibling HSCT patients in comparison with 9% of the unrelated group (p<0.01). At the time of the survey, 62% of unrelated HSCT patients reported the presence of at least one comorbidity such as metabolic or endocrine alterations like osteoporosis, diabetes, and cardiovascular disease. Almost half of them had hepatitis C virus (HCV) infection (p<0.01). Lower percentages of comorbidity were found in sibling HSCT patients (26%). Only one patient reported a secondary malignancy after sibling donor HSCT.

Mean scores of SF-36 scales of patients transplanted with sibling donor and patients transplanted with unrelated donor are reported in Supplementary Table 2.

Adjusted mean scores differences between the two groups (sibling donor vs unrelated donor) of the 8 SF-36 scales are graphically displayed in Figure 1.

No statistically significant differences were observed for all the physical and mental health domains. The differences in mean scores and corresponding 95% CIs of the SF-36 physical health-related domains were: general health (GH), Δ=5.1; 95%CI, -6.5 to 16.7, p=0.38; bodily pain (BP), Δ=9.2; 95%CI, -3.3 to 21.7, p=0.14; role limitations as a result of physical functioning (RP), Δ=5.4; 95%CI, -15.5 to 26.3, p=0.60; physical functioning (PF), Δ=7.4; 95%CI, -1.9 to 16.8, p=0.11). Regarding mental health related domains, we observed the following mean score differences: vitality (VT), Δ=3.3; 95%CI, -7.1 to 13.7, p=0.53; social functioning (SF), Δ=7.0; 95%CI, -5.1 to 19.2, p=0.25; role emotional functioning (RE), Δ= 7.2; 95%CI, -13.5 to 28.0, p=0.49; mental health (MH), Δ=2.2; 95%CI, -8.1 to 12.5, p=0.67

Adjusted mean score differences for the physical component score (PCS) and mental component score (MCS) were Δ=2.9; 95%CI, -1.5 to 7.4, p=0.19 and Δ=1.3; 95%CI, -4.0 to 6.5, p=0.63, respectively. Albeit not statistically significant, the magnitude of the difference observed in the PCS may suggest a trend for a better overall physical condition in unrelated HSCT (Figure 1).

HRQoL assessment by the FACT-BMT questionnaire showed no statistically significant difference between sibling and unrelated HSCT in physical well-being (p=0.79), social well-being (p=0.92), emotional well-being (p=0.48), functional well-being (p=0.84), FACT-General (p=0.94), BMTS scores (p=0.73) and BMT total score (p=0.73) (Supplementary Table 3). Additional multivariable linear regression analysis on the BMT subscale revealed no association between this outcome and the following variables: sex, age, education, living arrangements, ferritin level, GVHD and type of HSCT (unrelated or sibling) (Supplementary Table 4).

Despite the curative role of HSCT in β-TM, few data are available on HRQoL (6-15) and the majority of reports are available in the setting of sibling donor HSCT (Supplementary Table 5). Our study represents the first collection of HRQoL in long-term follow-up of unrelated HSCT β-TM patients. Overall, we found a good profile HRQoL in different physical and mental domains. The secondary objective of our study was to compare the HRQoL between sibling and unrelated β-TM HSCT patients. Despite higher age at

transplant in the unrelated group and consequently a higher rate of comorbidity, there were no differences in physical and mental health domains by SF-36 scales. In addition, the more transplant-specific scale FACT-BMT, adjusted by different confounding, did not find significant differences between the two groups. As expected, the rate of acute and chronic GVHD was slightly higher in unrelated transplanted patients.
Despite these innovative results, the present study has several limitations. The relatively low rate of patients responding to the survey may have selected the most motivated or with the best HRQoL. In addition, given the exploratory nature of the study our results should not be interpreted as confirmatory and further studies in this area are needed.
In conclusion, our study supports the role of unrelated HSCT in β-TM and confirms that it represents a feasible and good alternative in patients without a sibling donor. HRQoL remains a critical outcome for physicians and patients in their counseling before HSCT procedure. Given the new developments in gene therapy and new treatment reducing transfusion burden, an alternative option to unrelated HSCT should be also carefully considered.

Acknoledgements:
We thank Dr. Emanuela Morelli abd Dr. Luigi Marras for collecting web data and supporting the analysis of data

Author contributions:
OM, GC conceptualized and designed the study; OM, GC, EP, CT, VF, SB, AP, MGO, AV, GLN treated patients, collected and assembled the data; OM and FE performed the statistical analysis; OM, GC wrote the manuscript; OM, GC, FE, EP, CT, VF, SB, AP, MGO, AV, GLN were responsible for the final approval of the manuscript.

Competing interests statement:
FE: consultancy fees from Amgen, Abbvie, Janssen, and Novartis. Research support (Institution) from Abbvie, Amgen, Novartis, all unrelated to this work.
The other authors have no conflicts of interest to disclose

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Figure and table legend:

Figure 1. Differences in mean scores and corresponding 95% CIs of (A) physical and (B) mental health-related scale, (C) physical and (D) mental component summary scores reported from the SF-36 questionnaire, between thalassemia patients transplanted from unrelated or sibling donors.
Comparisons were adjusted by a multivariable regression model, including sex, age, highest level of education (university degree or higher vs lower), living arrangements (living alone vs living with someone) and ferritin level. Positive differences in all scales indicate a general better profile in patients transplanted from unrelated donors.

Table 1. Sociodemographic and clinical characteristic of 23 thalassemia patients transplanted from sibling donor compared with 34 unrelated transplanted patients. Abbreviations: SD, standard deviation; CV, cardiovascular; DMD, mellitus diabetes; TX, transfusion; RBC, reed blood cells; IC, iron chelation; SubC, subcutaneous; GVHD, graft versus host disease.

	Sibling HSCT N=23	Unrelated HSCT N=34	P-Value
Median age at survey (SD)	31 (8.2)	37 (15.1)	0.08
Median age at transplant (SD)	8 (5.49)	19 (8.1)	<0.01
Gender, n (%)			
Female	9 (39)	22 (65)	0.06
Male	14(61)	12 (35)	
Level of education, n (%)			
Compulsory School	6 (26)	13 (38)	0.56
High school	11 (48)	12 (35)	
University degree or higher	4 (17)	6 (18)	
Employment status, n (%)			
Employed	11 (48)	19 (56)	0.24
Temporarily abandoned	1 (4)	2 (6)	
Definitely abandoned	2 (9)	2 (6)	
In search of	5 (22)	2 (6)	
Retiree	4 (17)	1 (3)	
Student	5 (22)	4 (12)	
Living arrangements, n (%)			
Living alone	2 (9)	5 (15)	0.09
Living with partner	10 (43)	19 (56)	
Living with my family	10 (43)	5 (15)	
Marital Status, n (%)			
Single	12 (52)	12 (35)	ns
Married/with partner	10(43)	18(53)	
Divorced	0 (0)	0 (0)	
Widowed	0 (0)	0 (0)	
Number of sons, n (%)			
0	16 (70)	24 (71)	0.80
1	4(17)	5 (15)	
2	2 (9)	1 (3)	
3	0 (0)	0 (0)	
Comorbidities, n (%)			
No	17 (74)	6 (18)	<0.01
Yes	6 (26)	21 (62)	
Comorbidities ≥3, n (%)			
No	21 (91)	9 (26)	<0.01
Yes	2 (9)	18 (53)	
CV diseases, n (%)			
No	21 (91)	14 (41)	<0.01
Yes	2 (9)	12 (6)	
Osteoporosis, n (%)			
No	22 (96)	14 (41)	<0.01
Yes	1 (4)	13 (38)	

	Sibling HSCT N=23	Unrelated Donor N=34	P-Value
DMD, n (%)			
No	3 (13)	21 (62)	0.43
Yes	1 (4)	3 (9)	
HBV, n (%)			
No	23 (100)	34 (100)	0.84
Yes	0 (0)	0 (0)	
HCV, n (%)			
No	20 (87)	17 (50)	<0.01
Yes	3 (13)	16 (47)	
TX need, n (%)			
No	22 (96)	33 (97)	0.77
Yes	1 (4)	1 (3)	
RBC unit*, n (%)			
none	22 (96)	33 (97)	0.77
0-3 RBC units	1 (4)	1 (3)	
Ferritin level (mcg/L), mean (SD)	1581 (996.1)	1673 (1260)	0.77
IC, n (%)			
No	22 (96)	33 (97)	0.77
Yes	1 (4)	1 (3)	
Oral IC, n (%)			
No	22 (96)	33 (97)	0.77
Yes	1 (4)	1 (3)	
SubC IC, n (%)			
No	0 (0)	0 (0)	
Yes	0 (0)	0 (0)	
Splenectomy, n (%)			
No	23 (100)	31 (91)	0.51
Yes	0 (0)	3 (9)	
Tumors, n (%)			
No	22 (96)	34 (100)	0.65
Yes	1 (4)	0 (0)	
Venesection, n (%)			
No	5 (22)	31(91)	<0.01
Yes	18 (78)	3(9)	
Acute GVHD, n (%)			
No	21 (91)	25(74)	0.19
Yes	3 (13)	9(26)	
Chronic GVHD, n (%)			
No	20 (87)	26 (76)	0.40
Yes	4 (17)	8 (24)	

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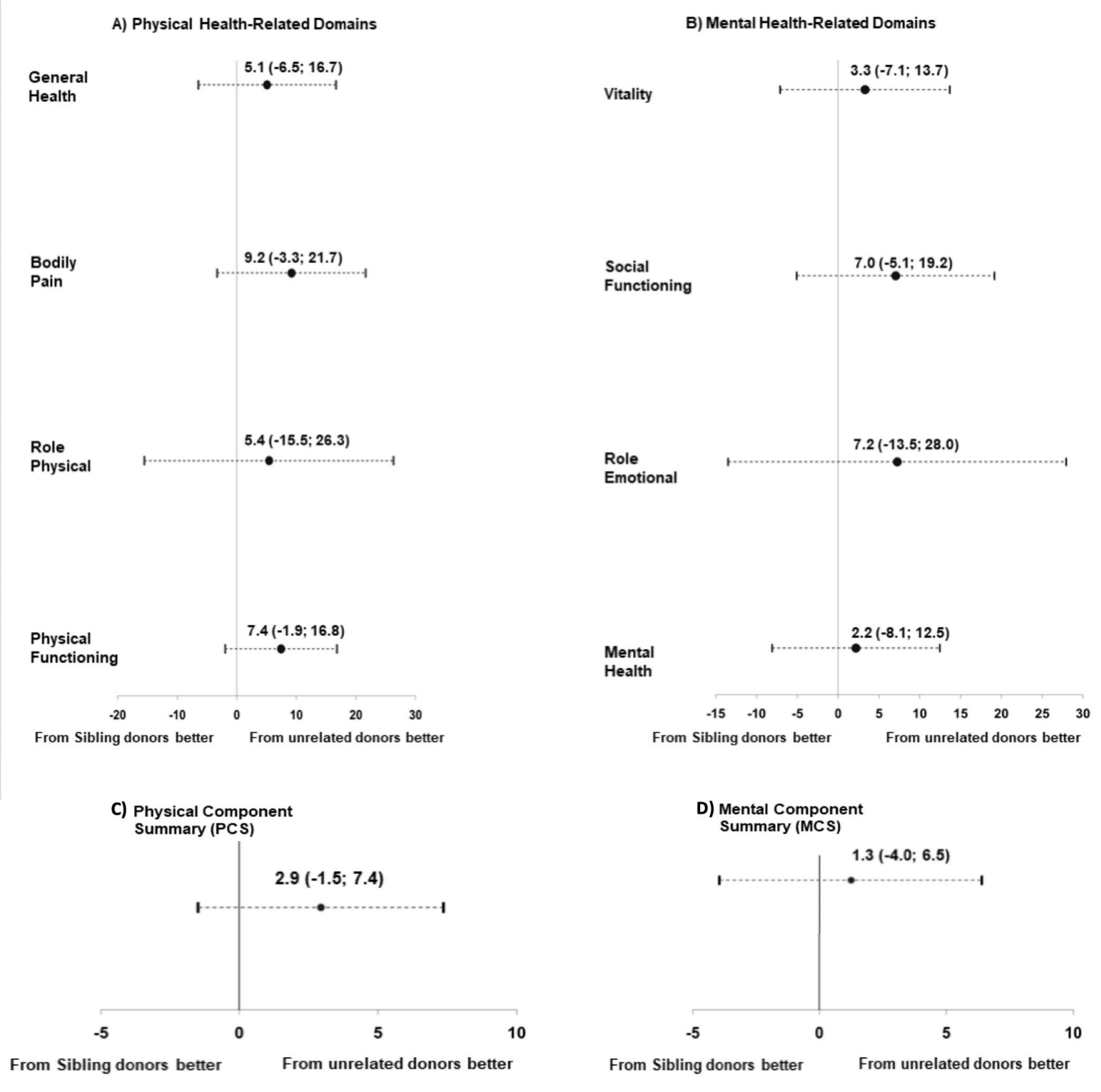
A) Physical Health-Related Domains
General Health
5.1 (-6.5; 16.7)
Bodily Pain
9.2 (-3.3; 21.7)
Role Physical
5.4 (-15.5; 26.3)
Physical Functioning
7.4 (-1.9; 16.8)
-20 -10 0 10 20 30
From Sibling donors better
From unrelated donors better
B) Mental Health-Related Domains
Vitality
3.3 (-7.1; 13.7)
Social Functioning
7.0 (-5.1; 19.2)
Role Emotional
7.2 (-13.5; 28.0)
Mental Health
2.2 (-8.1; 12.5)
-15 -10 -5 0 5 10 15 20 25 30
From Sibling donors better
From unrelated donors better
C) Physical Component Summary (PCS)
2.9 (-1.5; 7.4)
-5 0 5 10
From Sibling donors better
From unrelated donors better
D) Mental Component Summary (MCS)
1.3 (-4.0; 6.5)
-5 0 5 10
From Sibling donors better
From unrelated donors better