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Pre-transplant marital status and hematopoietic cell transplantation outcomes

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ABSTRACT

Background Evidence about the impact of marital status before hematopoietic cell transplantation (HCT) on outcomes after HCT is conflicting.

Methods We identified patients 40 years of age and older within the Center for International Blood and Marrow Transplant Research registry who underwent HCT between January 2008 and December 2015. Marital status before HCT was declared as one of: married or living with a partner, single (never married), separated or divorced, and widowed. We performed a multivariable analysis to determine the association of marital status with outcomes after HCT.

Results We identified 10,226 allogeneic and 5714 autologous HCT cases with, respectively, a median follow-up of 37 months (range: 1–102 months) and 40 months (range: 1–106 months). No association between marital status and overall survival was observed in either the allogeneic ($p = 0.58$) or autologous ($p = 0.17$) setting. However, marital status was associated with grades 2–4 acute graft-versus-host disease (GvHD), $p < 0.001$, and chronic GvHD, $p = 0.04$. The risk of grades 2–4 acute GvHD was increased in separated compared with married patients [hazard ratio (HR): 1.13; 95% confidence interval (CI): 1.03 to 1.24], and single patients had a reduced risk of grades 2–4 acute GvHD (HR: 0.87; 95% CI: 0.77 to 0.98). The risk of chronic GvHD was lower in widowed compared with married patients (HR: 0.82; 95% CI: 0.67 to 0.99).

Conclusions Overall survival after HCT is not influenced by marital status, but associations were evident between marital status and grades 2–4 acute and chronic GvHD. To better appreciate the effects of marital status and social support, future research should consider using validated scales to measure social support and patient and caregiver reports of caregiver commitment, and to assess health-related quality of life together with health care utilization.

Key Words Hematopoietic cell transplantation, marital status, overall survival, graft-versus-host disease, registries

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INTRODUCTION

The outcomes of patients undergoing hematopoietic cell transplantation (HCT) depend on a multitude of variables such as HCT type, underlying disease, stability of the underlying disease, and patient sociodemographic variables[1,2]. Interest has been increasing in evaluating the potential impact of psychosocial variables—for example, marital status—on HCT outcomes. The results of observational single-centre and registry studies evaluating the association between marital status and outcomes of hematologic malignancies, including HCT outcomes, have been inconsistent[3–10].

Marital status could be considered a surrogate for the presence of a caregiver or social support, where caregivers

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are an important source of both instrumental and emotional support[11]. Moreover, in HCT programs that advocate for outpatient-based programs, reliance on the HCT recipient's social support systems—predominantly a partnered caregiver or spouse—has been increasing[11,12]. Indeed, a systematic review about the influence of social support on HCT demonstrated an association of social support with HCT outcomes, but the conclusions were limited by smaller studies and important covariates variably considered in HCT survival analyses[11]. Additionally, studies in general oncology would further suggest that outcomes are better for married patients, with a larger benefit accruing to male patients[3]. A better understanding of how marital status contributes to HCT outcomes would allow and advocate for a bolstering of supportive resources for the HCT recipient.

We hypothesized that marital status is associated with improved outcomes after HCT, such that patients who are married or living with a partner, compared with those who are not, will experience superior post-HCT overall survival (OS) in the autologous and allogeneic settings alike and superior acute and chronic graft-versus-host disease (GvHD) outcomes in the allogeneic setting. Further, we hypothesized that sex would mediate the foregoing potential associations. Using data from the Center for International Blood and Marrow Transplant Research (CIBMTR), we examined the potential influence of marital status at the time of HCT on OS in the autologous and allogeneic settings, and on acute and chronic GvHD outcomes in the allogeneic setting.

METHODS

Data Source

The CIBMTR is an observational database that captures HCT data from more than 420 HCT centres worldwide. Data are submitted to a statistical centre at the Medical College of Wisconsin, Milwaukee, Wisconsin, U.S.A. Participating centres are required to report all HCTs consecutively; patients are followed longitudinally, and compliance is monitored by on-site audits. Computerized checks for discrepancies, physician review of submitted data, and on-site audits of participating centres ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in CIBMTR's capacity as a public health authority under the U.S. Health Insurance Portability and Accountability Act of 1996 Privacy Rule.

Patient Population and Study Design

We identified patients 40 years of age and older who underwent either autologous or allogeneic HCT for a hematologic malignancy between 1 January 2008 and 31 December 2015 (to best reflect current HCT practices). Given the completeness of the U.S. data within the CIBMTR HCT registry, patients were exclusively from the United States. Additionally, we expected the autologous HCT cohort to be smaller than the allogeneic cohort because CIBMTR data collection for autologous HCT does not necessarily include the marital status variable.

Exposures

Marital status was defined as one of married or living with a partner, single (never married), separated or divorced, and widowed. We selected patients 40 years of age and older to avoid confounding and to ensure balance between the 4 marital strata, given that younger age is associated with being single.

Outcomes and Definitions

Overall survival was defined as death from any cause. Surviving patients were censored at last follow-up; cases of acute and chronic GvHD were diagnosed and graded according to consensus criteria[13,14].

Marital status is declared at the level of each participating centre at a single time point before HCT (upon enrolment within the CIBMTR database) as one of married or living with a partner, single (never married), separated or divorced, or widowed.

Statistical Analysis

Baseline patient, clinical, and sociodemographic variables were summarized using descriptive statistics. The primary outcome was OS, with grades 2–4 acute GvHD and chronic GvHD being secondary outcomes. The OS probabilities were estimated using Kaplan–Meier curves. To accommodate competing risks, the probabilities of acute and chronic GvHD were calculated using the cumulative incidence estimator. Multivariable analysis using Cox proportional hazards models was performed to determine the association of marital status with the primary and secondary outcomes, while adjusting for patient, clinical, and sociodemographic variables. In addition to marital status, the variables considered in the models included age, sex, race, performance status, education, smoking status, income and insurance status, distance to the HCT centre, employment status, disease type, disease risk and status at HCT, recipient cytomegalovirus serostatus, donor or graft type, donor–recipient sex and ABO match, conditioning regimen intensity, comorbidity index, GvHD prophylaxis for allogeneic HCT recipients, and HCT period. The assumption of proportional hazards was tested for each variable. A stepwise model-building approach was used to develop models for OS and for acute and chronic GvHD. A p value less than 0.05 was considered statistically significant. The analysis was performed using the SAS software application (version 9: SAS Institute, Cary, NC, U.S.A.).

RESULTS

Patient Characteristics

We identified 10,226 allogeneic and 5714 autologous HCT cases; median follow-up of survivors was, respectively, 37 months (range: 1–102 months) and 40 months (range: 1–106 months). Overall, completeness of follow-up was 100%, 99%, 97%, and 93% at 1, 2, 3, and 4 years respectively for patients undergoing allogeneic HCT. Similarly, completeness of follow-up was 99%, 98%, 95%, and 91% at 1, 2, 3, and 4 years respectively for patients undergoing autologous HCT. Table I sets out the baseline patient, clinical, and sociodemographic variables for patients undergoing allogeneic and autologous HCT.

TABLE I Characteristics of adult patients, 40 years of age and older, with hematologic malignant disease before hematopoietic cell transplantation (HCT)

Characteristic	Recipients of allogeneic HCT, by marital status				Recipients of autologous HCT, by marital status			
	Married	Single (never married)	Separated or divorced	Widowed	Married	Single (never married)	Separated or divorced	Widowed
Patients *(n)*	7999	741	1175	311	4308	478	695	233
Centres *(n)*	122	100	110	84	121	90	101	75
Patient-related								
Age at transplantation (years)								
Median	59	53	57	65	60	55	58	66
Range	40–79	40–78	40–76	42–78	40–80	40–77	40–79	44–78
Age group at transplantation [*n* (%)]								
40–49 Years	1557 (19)	293 (40)	285 (24)	11 (4)	616 (14)	160 (33)	120 (17)	5 (2)
50–59 Years	2781 (35)	260 (35)	483 (41)	72 (23)	1489 (35)	175 (37)	311 (45)	56 (24)
60–69 Years	3101 (39)	165 (22)	363 (31)	179 (58)	1821 (42)	126 (26)	237 (34)	127 (55)
70–79 Years	560 (7)	23 (3)	44 (4)	49 (16)	382 (9)	17 (4)	27 (4)	45 (19)
Sex [*n* (%)]								
Men	5027 (63)	391 (53)	541 (46)	88 (28)	2773 (64)	253 (53)	317 (46)	61 (26)
Women	2972 (37)	350 (47)	634 (54)	223 (72)	1535 (36)	225 (47)	378 (54)	172 (74)
Race [*n* (%)]								
White	7177 (90)	581 (78)	994 (85)	277 (89)	3483 (81)	278 (58)	465 (67)	166 (71)
African American	375 (5)	112 (15)	111 (9)	19 (6)	619 (14)	176 (37)	203 (29)	56 (24)
Asian	238 (3)	19 (3)	29 (2)	12 (4)	112 (3)	7 (1)	9 (1)	4 (2)
Other	95 (1)	5 (<1)	14 (1)	3 (<1)	45 (1)	6 (1)	9 (1)	3 (1)
Missing	114 (1)	24 (3)	27 (2)	0	49 (1)	11 (2)	9 (1)	4 (2)
Karnofsky PS before transplantation [*n* (%)]								
<90	3196 (40)	296 (40)	484 (41)	125 (40)	1757 (41)	224 (47)	319 (46)	111 (48)
≥90	4642 (58)	432 (58)	666 (57)	179 (58)	2433 (56)	243 (51)	355 (51)	114 (49)
Missing	161 (2)	13 (2)	25 (2)	7 (2)	118 (3)	11 (2)	21 (3)	8 (3)
HCT comorbidity index [*n* (%)]								
0	2709 (34)	257 (35)	376 (32)	82 (26)	1688 (39)	173 (36)	250 (36)	67 (29)
1–2	2147 (27)	190 (26)	335 (29)	84 (27)	1216 (28)	143 (30)	206 (30)	69 (30)
≥3	3131 (39)	291 (39)	462 (39)	144 (46)	1397 (32)	161 (34)	239 (34)	96 (41)
Missing	12 (<1)	3 (<1)	2 (<1)	1 (<1)	7 (<1)	1 (<1)	0	1 (<1)
Highest education grade [*n* (%)]								
≤High school	2007 (25)	205 (28)	369 (31)	93 (30)	1320 (31)	147 (31)	212 (30)	94 (40)
College	1095 (14)	97 (13)	200 (17)	52 (17)	700 (16)	86 (18)	125 (18)	37 (16)
Graduate school	2426 (30)	198 (27)	280 (24)	72 (23)	1291 (30)	114 (24)	165 (24)	44 (19)
Missing	2471 (31)	241 (33)	326 (28)	94 (30)	997 (23)	131 (27)	193 (28)	58 (25)
Disease-related								
Disease [*n* (%)]								
AML	3296 (41)	324 (44)	509 (43)	136 (44)				
ALL	622 (8)	66 (9)	92 (8)	10 (3)				
Other leukemia	476 (6)	33 (4)	60 (5)	12 (4)				
CML	245 (3)	37 (5)	59 (5)	4 (1)				
MDS	2658 (33)	204 (28)	355 (30)	130 (42)				
HL or NHL	662 (8)	73 (10)	88 (7)	19 (6)				
NHL					1264 (29)	121 (25)	164 (24)	56 (24)
HL					152 (4)	30 (6)	31 (4)	9 (4)
Plasma-cell disorder	40 (<1)	4 (<1)	12 (1)	0	2892 (67)	327 (68)	500 (72)	168 (72)

TABLE I Continued

Characteristic	Recipients of allogeneic HCT, by marital status				Recipients of autologous HCT, by marital status			
	Married	Single (never married)	Separated or divorced	Widowed	Married	Single (never married)	Separated or divorced	Widowed
Disease risk index [*n* (%)]								
Low	752 (9)	82 (11)	116 (10)	20 (6)				
Intermediate	4041 (51)	354 (48)	587 (50)	148 (48)				
High	2393 (30)	213 (29)	344 (29)	109 (35)				
Very high	231 (3)	30 (4)	35 (3)	10 (3)				
Missing	582 (7)	62 (8)	93 (8)	24 (8)				
Disease status [*n* (%)]								
Early					807 (19)	80 (17)	122 (18)	42 (18)
Intermediate					2926 (68)	348 (73)	494 (71)	163 (70)
Advanced					212 (5)	20 (4)	21 (3)	5 (2)
Other plasma disorder (not MM)					355 (8)	30 (6)	57 (8)	23 (10)
Missing					8 (<1)	0	1 (<1)	0
Recipient CMV serology [*n* (%)]								
Negative	2997 (37)	296 (40)	394 (34)	89 (29)				
Positive	4941 (62)	443 (60)	770 (66)	221 (71)				
Missing	61 (<1)	2 (<1)	11 (<1)	1 (<1)				
Donor-related								
Donor or graft type [*n* (%)]								
Cord blood	946 (12)	112 (15)	155 (13)	44 (14)				
HLA-identical sibling BM	87 (1)	9 (1)	23 (2)	2 (<1)				
HLA-identical sibling PB	2149 (27)	217 (29)	284 (24)	72 (23)				
Other related BM	235 (3)	13 (2)	31 (3)	7 (2)				
Other related PB	388 (5)	48 (6)	63 (5)	23 (7)				
Well-matched unrelated BM	457 (6)	41 (6)	71 (6)	15 (5)				
Well-matched unrelated PB	2986 (37)	228 (31)	424 (36)	121 (39)				
Partially-matched unrelated BM	98 (1)	12 (2)	10 (<1)	2 (<1)				
Partially-matched unrelated PB	609 (8)	55 (7)	103 (9)	24 (8)				
Mismatched unrelated PB	26 (<1)	4 (<1)	7 (<1)	0				
PB					4308	478	696	233
Unknown	18 (<1)	2 (<1)	4 (<1)	1 (<1)				
Donor age, unrelated only (years)								
Median	29	30	29	29				
Range	18–69	19–60	18–59	18–59				
Donor–recipient sex match [*n* (%)]								
Male–Male	3041 (38)	203 (27)	308 (26)	43 (14)				
Male–Female	1542 (19)	170 (23)	308 (26)	109 (35)				
Female–Male	1427 (18)	135 (18)	167 (14)	36 (12)				
Female–Female	1028 (13)	120 (16)	234 (20)	79 (25)				
CB recipient, male	550 (7)	52 (7)	66 (6)	9 (3)				
CB recipient, female	396 (5)	60 (8)	89 (8)	35 (11)				
Missing	15 (<1)	1 (<1)	3 (<1)	0				
Donor-recipient ABO match [*n* (%)]								
Matched	2248 (28)	180 (24)	310 (26)	63 (20)				
Minor mismatch	917 (11)	86 (12)	137 (12)	24 (8)				
Major mismatch	816 (10)	83 (11)	126 (11)	33 (11)				
Bidirectional	245 (3)	24 (3)	36 (3)	12 (4)				
Cord blood	946 (12)	112 (15)	155 (13)	44 (14)				
Missing	2827 (35)	256 (35)	411 (35)	135 (43)				

TABLE I Continued

Characteristic	Recipients of allogeneic HCT, by marital status				Recipients of autologous HCT, by marital status			
	Married	Single (never married)	Separated or divorced	Widowed	Married	Single (never married)	Separated or divorced	Widowed
Treatment related								
Conditioning intensity [*n* (%)]								
MAC–TBI	1165 (15)	159 (21)	176 (15)	20 (6)				
MAC–CTx	2658 (33)	260 (35)	459 (39)	77 (25)				
RIC/NST	4156 (52)	321 (43)	537 (46)	213 (68)				
Missing	20 (<1)	1 (<1)	3 (<1)	1 (<1)				
Conditioning regimen [*n* (%)]								
BEAM or BEAM-like					1060 (25)	114 (24)	157 (23)	55 (24)
Busulfan-based					232 (5)	24 (5)	27 (4)	9 (4)
TBI ± cytarabine ± others					121 (3)	11 (2)	15 (2)	1 (<1)
Melphalan-based (MM only)					2817 (65)	319 (67)	494 (71)	166 (71)
Other					78 (2)	10 (2)	2 (<1)	2 (<1)
GvHD prophylaxis [*n* (%)]								
Ex vivo T cell depletion, CD34 selection	197 (2)	21 (3)	31 (3)	10 (3)				
Post-cyclophosphamide + others	420 (5)	39 (5)	54 (5)	18 (6)				
Tacrolimus-based	5954 (74)	543 (73)	885 (75)	227 (73)				
Cyclosporine-based	1189 (15)	126 (17)	182 (15)	43 (14)				
Others	129 (2)	2 (<1)	9 (<1)	7 (2)				
Missing	110 (1)	10 (1)	14 (1)	6 (2)				
Sociodemographic								
Smoking history [*n* (%)]								
Nonsmoker	4263 (53)	405 (55)	533 (45)	153 (49)	2429 (56)	263 (55)	335 (48)	136 (58)
Former smoker	2527 (32)	182 (25)	355 (30)	109 (35)	1246 (29)	110 (23)	182 (26)	62 (27)
Current smoker	883 (11)	122 (16)	244 (21)	36 (12)	449 (10)	82 (17)	156 (22)	26 (11)
Missing	326 (4)	32 (4)	43 (4)	13 (4)	184 (4)	23 (5)	22 (3)	9 (4)
Employment status [*n* (%)]								
Full time	2210 (28)	203 (27)	297 (25)	52 (17)	1335 (31)	179 (37)	203 (29)	28 (12)
Part time	405 (5)	37 (5)	56 (5)	15 (5)	244 (6)	15 (3)	40 (6)	5 (2)
Unemployed	754 (9)	81 (11)	149 (13)	19 (6)	309 (7)	57 (12)	68 (10)	19 (8)
Medical disability	1509 (19)	211 (28)	330 (28)	53 (17)	582 (14)	100 (21)	171 (25)	36 (15)
Retired	2250 (28)	114 (15)	216 (18)	148 (48)	1503 (35)	83 (17)	150 (22)	124 (53)
Missing	871 (11)	95 (13)	127 (11)	24 (8)	335 (8)	44 (9)	63 (9)	21 (9)
Insurance type [*n* (%)]								
None	38 (<1)	4 (<1)	11 (<1)	2 (<1)	36 (<1)	4 (<1)	17 (2)	0
Disability insurance ± others	209 (3)	25 (3)	29 (2)	5 (2)	116 (3)	10 (2)	21 (3)	4 (2)
Private health insurance ± others	5148 (64)	419 (57)	618 (53)	112 (36)	2710 (63)	276 (58)	389 (56)	89 (38)
Medicaid ± others	480 (6)	144 (19)	243 (21)	37 (12)	245 (6)	113 (24)	127 (18)	25 (11)
Medicare ± others	1879 (23)	115 (16)	242 (21)	146 (47)	1089 (25)	64 (13)	126 (18)	109 (47)
Others	218 (3)	31 (4)	29 (2)	8 (3)	99 (2)	11 (2)	15 (2)	5 (2)
Missing	27 (<1)	3 (<1)	3 (<1)	1 (<1)	13 (<1)	0	0	1 (<1)
Median income level [*n* (%)]								
<$90,000	6345 (79)	620 (84)	955 (81)	259 (83)	3695 (86)	425 (89)	618 (89)	221 (95)
≥$90,000	1275 (16)	79 (11)	160 (14)	35 (11)	491 (11)	35 (7)	52 (7)	9 (4)
Missing	379 (5)	42 (6)	60 (5)	17 (5)	122 (3)	18 (4)	25 (4)	3 (1)

TABLE I Continued

Characteristic	Recipients of allogeneic HCT, by marital status				Recipients of autologous HCT, by marital status			
	Married	Single (never married)	Separated or divorced	Widowed	Married	Single (never married)	Separated or divorced	Widowed
Distance from HCT centre [*n* (%)]								
0–99 Miles	5600 (70)	569 (77)	864 (74)	234 (75)	3160 (73)	382 (80)	561 (81)	187 (80)
100–499 Miles	1762 (22)	118 (16)	220 (19)	55 (18)	928 (22)	75 (16)	107 (15)	39 (17)
500–999 Miles	176 (2)	9 (1)	22 (2)	6 (2)	98 (2)	6 (1)	10 (1)	4 (2)
≥1000 Miles	188 (2)	20 (3)	32 (3)	4 (1)	42 (<1)	5 (1)	8 (1)	2 (<1)
Missing	273 (3)	25 (3)	37 (3)	12 (4)	80 (2)	10 (2)	9 (1)	1 (<1)
Year of transplantation [*n* (%)]								
2008–2010	2985 (37)	276 (37)	463 (39)	81 (26)	1836 (43)	167 (35)	276 (40)	104 (45)
2011–2013	2300 (29)	209 (28)	304 (26)	97 (31)	1172 (27)	144 (30)	185 (27)	48 (21)
2014–2015	2714 (34)	256 (35)	408 (35)	133 (43)	1300 (30)	167 (35)	234 (34)	81 (35)
Time from Dx to HCT (years)								
Median	8	9	9	8	9	10	9	10
Range	<1 to 409	2 to 357	<1 to 350	2 to 293	<1 to 291	1 to 192	1 to 295	1 to 179
Follow-up of survivors (months)								
Median	37	37	37	36	43	37	37	41
Range	3–102	1–102	3–101	3–97	1–104	1–101	1–106	2–98

PS = performance status; AML = acute myelogenous leukemia; ALL = acute lymphoblastic leukemia; CML = chronic myelogenous leukemia; MDS = myelodysplastic syndrome; HL = Hodgkin lymphoma; NHL = non-Hodgkin lymphoma; MM = multiple myeloma; CMV = cytomegalovirus; HLA = human leucocyte antigen; BM = bone marrow; PB = peripheral blood; MAC = myeloablative conditioning; TBI = total body irradiation; CTx = chemotherapy; RIC = reduced intensity conditioning; NST = non-myeloablative stem-cell transplantation; BEAM = carmustine–etoposide–cytarabine–melphalan; Dx = diagnosis.

Of the patients undergoing allogeneic HCT, 7999 (78%), 741 (7%), 1175 (11%), and 311 (3%) identified, respectively, as married or living with a partner, single (never married), separated or divorced, and widowed. Similarly, of the patients undergoing autologous HCT, 4308 (75%), 478 (8%), 695 (12%), and 233 (4%) identified, respectively, as married or living with a partner, single (never married), separated or divorced, and widowed.

In general, we observed no appreciable differences in baseline patient, clinical, or sociodemographic variables for the patients in the 4 marital status categories. However, a few notable minor imbalances were evident, with widowed patients being more likely than non-married patients to be female, older, and retired.

Marital Status and Allogeneic HCT Outcomes

Based on the results of the multivariable analysis, OS was not statistically different in the 4 marital status categories for patients receiving allogeneic HCT ($p = 0.58$). Table II summarizes the results of the regression analyses. When compared with patients who were married or living with a partner, those who were single (never married), separated or divorced, and widowed were not at increased risk of death (respectively, HR: 1.06; 95% CI: 0.95 to 1.17; HR: 0.99; 95% CI: 0.91 to 1.08; HR: 1.07; 95% CI: 0.92 to 1.24). Figure 1 shows the probabilities of OS by marital status adjusted for age, performance status, HCT comorbidity index, disease risk index, and other factors associated with mortality risk. The 5-year adjusted OS probabilities were 37% (95% CI: 36% to 39%) for patients who were married or living with a partner and 39% (95% CI: 35% to 43%) for those who were single (never married), 39% (95% CI: 35% to 42%) for those who were separated or divorced, and 35% (95% CI: 29% to 42%) for those who were widowed.

In contrast, marital status was associated with grades 2–4 acute ($p < 0.001$) and chronic GvHD ($p = 0.04$). The risk of grades 2–4 acute GvHD was greater in patients who were separated or divorced compared with those who were married or living with a partner (HR: 1.13; 95% CI: 1.03 to 1.24; $p = 0.01$). However, the risk of grades 2–4 acute GvHD appeared to be lower for patients who were single (never married) than for those who were married or partnered (HR: 0.87; 95% CI: 0.77 to 0.98; $p = 0.03$). The risk of chronic GvHD was lower in patients who were widowed than in those who were married or living with a partner (HR: 0.82; 95% CI: 0.67 to 0.99; $p = 0.03$).

Table II summarizes the multivariable analyses. Figures 2 and 3 show the probabilities of grades 2–4 acute GvHD and chronic GvHD by marital status, adjusted for disease, conditioning, employment, distance to the HCT center, GvHD prophylaxis, and other factors associated with the development of GvHD. There was no interaction between marital status and sex.

Marital Status and Autologous HCT Outcomes

We observed no statistical difference in OS between the 4 marital status categories for patients receiving autologous HCT (Figure 4, $p = 0.17$). Table II summarizes the analyses.

Compared with patients who were married or living with a partner, single (never married), separated or divorced, and widowed patients were not at an increased risk of death (respectively, HR: 1.10; 95% CI: 0.92 to 1.33; HR: 1.17;

TABLE II Multivariable analyses of hematopoietic cell transplantation (HCT) outcomes

Variable	Pts (*n*)	Outcome							
		Overall survival			Graft-versus-host disease				
					Acute, grades 2–4			Chronic	
		HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Allogeneic HCT										
Marital status, overall *p* value	10,226			0.58			<0.001			0.04
Marital status category										
Married	7,999			1.00			1.00			1.00
Single (never married)	741	1.06	0.95 to 1.17	0.29	0.87	0.77 to 0.98	0.03	0.90	0.80 to 1.01	0.07
Separated or divorced	1,175	0.99	0.91 to 1.08	0.79	1.13	1.03 to 1.24	0.01	0.94	0.86 to 1.04	0.23
Widowed	311	1.07	0.92 to 1.24	0.41	1.17	0.99 to 1.38	0.07	0.82	0.67 to 0.99	0.03
Autologous HCT										
Marital status, overall *p* value	5,714			0.17						
Marital status category										
Married	4,308			1.00						
Single (never married)	478	1.10	0.92 to 1.33	0.3						
Separated or divorced	695	1.17	1.01 to 1.36	0.04						
Widowed	233	1.08	0.86 to 1.37	0.51						

Pts = patients; HR = hazard ratio; CI = confidence interval.

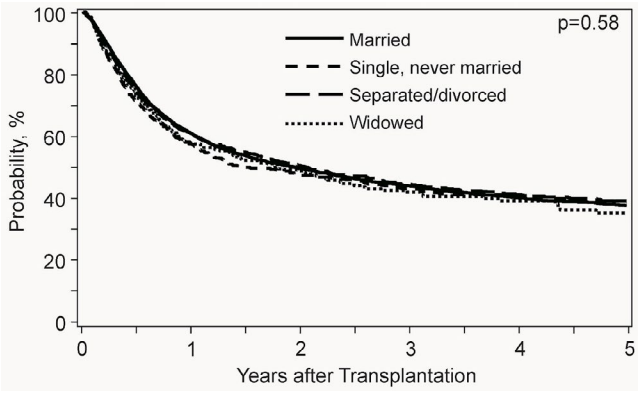

FIGURE 1 Adjusted overall survival in allogeneic hematopoietic cell transplantation, by marital status.

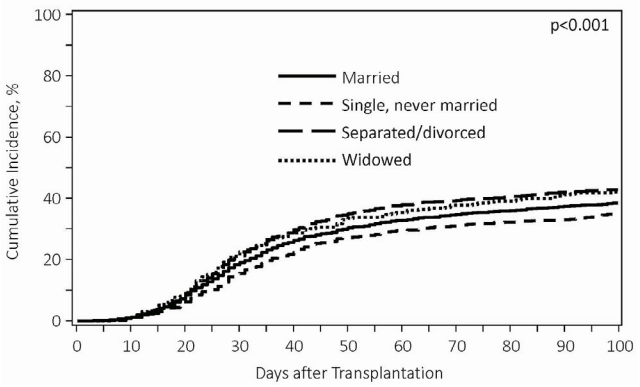

FIGURE 2 Adjusted cumulative incidence of grades 2–4 acute graft-versus-host disease after allogeneic hematopoietic cell transplantation, by marital status.

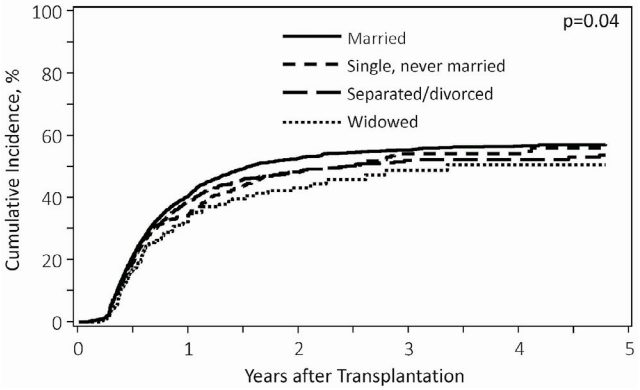

FIGURE 3 Adjusted cumulative incidence of chronic graft-versus-host disease after allogeneic hematopoietic cell transplantation, by marital status.

95% CI: 1.01 to 1.36; HR: 1.08; 95% CI: 0.86 to 1.37). Figure 4 shows the probabilities of OS by marital status adjusted for age, performance status, HCT comorbidity index, and disease risk index—the other factors associated with mortality risk. The 5-year adjusted survival probabilities were

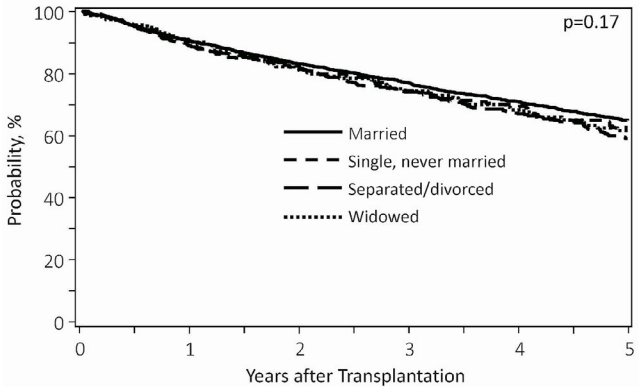

FIGURE 4 Adjusted overall survival after autologous hematopoietic cell transplantation, by marital status.

65% (95% CI: 62% to 67%) for patients who were married or living with a partner and 62% (95% CI: 56% to 68%) for those who were single (never married), 59% (95% CI: 54% to 64%) for those who were separated or divorced, and 61% (95% CI: 53% to 69%) for those who were widowed. As for the allogeneic population, no interaction of marital status and sex with survival was evident.

DISCUSSION

Our study suggests that marital status is not associated with OS after HCT in either the allogeneic or autologous setting. However, marital status appears to influence the post-HCT outcomes of grades 2–4 acute GvHD and chronic GvHD alike. In particular, the evidence demonstrates that, compared with patients undergoing allogeneic HCT who are married or living with a partner, those who are separated or divorced are at a higher risk of acute GvHD (HR: 1.13; p = 0.008), and those who are single appears to be protected (HR: 0.87; p = 0.03). Likewise, being widowed appears to be protective against chronic GvHD (HR: 0.82; p = 0.03). We believe that those results are compelling given our multicentre data, the large sample size, and the inclusion of a comprehensive set of patient, disease, and psychosocial variables as covariates (Table I). Taken together, the evidence demonstrates a relationship between marital status and post-HCT GvHD outcomes.

It is difficult to reconcile the counterintuitive results in the allogeneic setting, where, compared with being married or living with a partner, being single is associated with less acute GvHD and being widowed is associated with less chronic GvHD. Given our large sample size of more than 10,000 recipients of allogeneic HCT and the observed HRs close to 1, it is possible that some associations are statistically significant, but possibly not clinically meaningful. Moreover, it remains unclear how marital status might exert its effects. Marital status might influence HCT outcomes through some combination of instrumental, emotional, or informational social support frameworks, where a partnered caregiver or the married state might be considered to be the optimal "intervention" that embraces all of those framework aspects[11]. Further, Foster *et al.*[15] suggest that "general" social support lacks "the interpersonal resonance and the interactive empathy characteristic of partnered relationships." Indeed, the quality of social support is associated with post-HCT outcomes: Frick *et al.*[16] suggested that positive social support does not affect HCT survival, but that the presence of problematic social support is associated with inferior survival. In contrast, Ehrlich *et al.*[17] recently suggested that pre-HCT emotional support was significantly associated with better outcomes after allogeneic HCT. Additionally, socioeconomic support has also been associated with superior HCT outcomes[18,19]. Taking those data together, marital status might be an imperfect surrogate for social support, given that the persistence, quality, and strength of the marital relationship is not assessed, potentially explaining our incongruent results.

Is there a biologic basis or biomarker that might help in gaining insights? It has been suggested that behaviour within social relationships can modulate the responsivity of the immune system to stress and the depressive–reactive pathways, with depression potentially being a central pathway to immune dysfunction, leading to poor biophysical outcomes[20,21]. Further, spousal similarities noted in gene expression, immune profiles, and gut microbiota might offer additional insight into potential biologic or biomarker understandings within the larger construct of social support[20,22]. In the HCT setting, the "conserved transcriptional response to adversity" (CTRA) gene expression profile of cytokines in recipients of HCT might be a potential stress biomarker that links socioeconomic status with post-HCT biophysical outcomes[23,24]. Meaningful differences in CTRA expression profiles between HCT recipients of low and high socioeconomic groups has been demonstrated, with CTRA expression being associated with upregulation of CREB activity, inhibition of interferon response factor signalling, and desensitization of glucocorticoid receptor activity[25]. Untangling various aspects of socioeconomics (including social support and marital status) and its relative influence on CTRA undoubtedly remains to be elucidated. However, is intriguing to ponder that both the quantity and quality of social support might lead to changes of the stress biomarker CTRA in HCT recipients, which might in turn influence the development of GvHD and disease relapse. Still, it is unclear how such potential biomarkers or surrogate markers for social support might influence post-HCT outcomes or whether they are modifiable.

Other studies have examined marital status in the general oncology setting. For instance, data from the U.S. Surveillance, Epidemiology, and End Results program evaluating more than 1.2 million cases of cancer between 2004 and 2008 suggest that "married patients were less likely to present with metastatic disease (adjusted odds ratio [OR], 0.83; 95% CI, 0.82 to 0.84; p < .001), more likely to receive definitive therapy (adjusted OR, 1.53; 95% CI, 1.51 to 1.56; p < .001), and less likely to die as a result of their cancer after adjusting for demographics, stage, and treatment (adjusted hazard ratio, 0.80; 95% CI, 0.79 to 0.81; p < .001) than unmarried patients," where married men benefitted more than married women[3]. In contrast, data from studies evaluating individual malignancies have mixed results, with positive associations being found in patients with myeloma[9], Hodgkin lymphoma[10], and hematologic malignancies in general[8], and no associations being noted in

acute lymphoblastic leukemia[26] and historical studies[6,27]. Interestingly, a systematic review of eighteen studies assessing the influence of marital status and stage of cancer at diagnosis suggests that being unmarried increases the odds of having a later stage of breast cancer (odds ratio: 1.297; 95% CI: 1.035 to 1.627) or melanoma (odds ratio: 1.35; 95% CI: 1.16 to 1.57) at diagnosis[7]. To our knowledge, all reported studies in general oncology and specific malignancies have been based on U.S. Surveillance, Epidemiology, and End Results or state cancer registry data, with methodologic differences between the studies in how the data are analyzed and in the covariates considered or available for analysis.

In contrast to studies in general oncology and specific malignancies, two published studies have assessed marital status with respect to HCT outcomes, and both demonstrated the lack of an association. Gerull *et al.*[5] examined 715 patients who received allogeneic HCT between 2009 and February 2015 in the Swiss Transplant Cohort Study. The authors classified marital status as either single (encompassing single, divorced or separated, and widowed) or in a stable partnership. No differences in OS, progression-free survival, non-relapse mortality, relapse, acute GvHD, or chronic GvHD were observed for the groups with and without a stable partnership. However, patients with missing information about their relationship status experienced significantly worse OS and progression-free survival than did their counterparts whose records had that information. Similarly, Sato *et al.*[4] evaluated 309 Japanese patients who, between January 2000 and January 2017, underwent allogeneic HCT and were classified as either married or unmarried. No differences in 5-year OS, relapse, transplantation-related mortality, and acute or chronic GvHD were observed between the married and unmarried recipients of allogeneic HCT. Limited by small numbers, both studies variably considered important allogeneic HCT covariates that might have influenced the results of their study. However, both studies suggest that, in the HCT setting, other disease and HCT factors remain highly integral to predicting post-HCT outcomes, with marital status having unclear effects. In contrast, an abstract by Foley *et al.*[28], reporting on data for 269 recipients of allogeneic HCT from the University of California–San Francisco between January 2012 and January 2016, suggests that decreased OS is associated with being divorced compared with being single or married ($p = 0.025$). Interestingly, a recent systematic review of recipients of solid-organ grafts suggested that neither social support nor marital status is predictive of medication adherence or post-transplantation outcomes[29].

Limitations

Our study has limitations beyond the traditional biases associated with registry studies. First, it is possible that same-sex unions might not have been considered as married or living with a partner. Additionally, patients might be single (never married) but might still have children who act as caregivers and provide social support. Further, marital status was declared before the HCT without further ascertainment of possible changes in marital status over the longer HCT trajectory. Second, our data from the CIBMTR reflects the U.S. environment, and it might not reflect circumstances in other geographic locations and cultures. However, our results would mirror the experience of both the Swiss and the Japanese cohorts of patients who received allogeneic HCT, whose data suggested the lack of an association between marital status and HCT survival outcomes. Third, an inherent selection bias might be present, given that HCT centres might allow HCT to proceed only in the presence of adequate social support, negating the potential influence of marital status. For instance, HCT centres might assume that married patients have good social support, but might conduct a more rigorous assessment of social support for unmarried patients before proceeding with HCT. Finally, caregiver burden has been recognized to potentially indirectly affect patient care and outcomes[30,31]. Unfortunately, data concerning caregiver or spousal burden, where the quality of caregiving might be affected by competing life circumstances such as work and young children, are unavailable. In the absence of additional data concerning social support, it is impossible to disentangle the overlapping concepts of marital status and social support.

CONCLUSIONS

We suggest that the influence of marital status on the outcomes of OS (in both the autologous and allogeneic HCT settings) and GvHD (in the allogeneic setting) are clinically negligible. Future research should consider measuring social support using validated scales such as those proposed by PROMIS[32] or the patient and caregiver report of caregiver commitment, and should assess health-related quality of life together with health care utilization outcomes to better appreciate the potential effect of marital status and social support.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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