SUPPLEMENTARY APPENDIX

Upper gastrointestinal acute graft-*versus*-host disease adds minimal prognostic value in isolation or with other graft-*versus*-host disease symptoms as currently diagnosed and treated

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Supplemental Methods

The CIBMTR (Center for International Blood and Marrow Transplantation Registry) is a voluntary research organization involving more than 500 transplantation centers collaborating to share patient data and conduct scientific studies. Data management manuals provide instructions on data submission. Quality and compliance are monitored by computerized checks for errors, physician reviews, on-site audits, and annual training.

Patient- and transplant-related variables included recipient age; gender; race; Karnofsky performance score (KPS) at HSCT; graft source (BM or PBSC); donor type (HLA-matched sibling donor vs well-matched URD vs partially matched URD); degree of HLA-matching; donor/ recipient sex match; CMV serology, and ABO status; conditioning regimen (total body irradiation (TBI)-containing versus non-TBI); aGvHD prophylaxis regimen (stratified by use of steroids or MMF); development of cGvHD; and year and center of transplant. Disease-related variables included diagnosis, disease status at transplantation (early, intermediate, or advanced based on CIBMTR definition), and time from induction therapy to transplant.

Supplemental Table 1. Demographic characteristics and outcomes of entire cohort

Supplemental Table 1A. Demographics of entire cohort

Characteristics of patients:	N (%)
Number of patients	**8567**
Number of centers	251
Patient-related	**Median (range or %)**
Age at transplant, years	42 (18 - 72)
Sex	
Male	4736 (55)
Female	3831 (45)
Race	
Caucasian	7273 (85)
Karnofsky performance score at HSCT	
$\geq$ 90%	5737 (67)
Disease	
AML	4181 (49)
ALL	1838 (21)
CML	1571 (18)
MDS	977 (11)
Disease status at transplant	
Early	4631 (54)
Intermediate	1867 (22)
Advanced	2032 (24)
Donor-related	
Donor type	
HLA-identical sibling	4183 (49)
URD well-matched	3243 (38)
URD partially-matched	1141 (13)
HLA-identical sibling donor age, years,	41 (<1 - 85)
Unrelated donor age, years, median (range)	33 (18 - 61)
D/R sex match	

Characteristics of patients:	N (%)
M/M	3001 (35)
M/F	2204 (26)
F/M	1733 (20)
F/F	1625 (19)
D/R CMV status	
+/+	2877 (34)
+/-	856 (10)
-/+	2160 (25)
-/-	2216 (26)
D/R ABO match	
Matched	4618 (54)
Transplant-related	
Time from diagnosis to transplant, months, median (range)	7 (<1 - 310)
Graft type	
Bone marrow	2452 (29)
Peripheral blood	6115 (71)
TBI used in conditioning regimen	4307 (50)
Steroid-containing GvHD prophylaxis	1016 (12)
MMF-containing GvHD prophylaxis	901 (11)
Year of transplant	
2000-2004	3665 (43)
2005-2008	3123 (36)
2009-2012	1779 (21)
Post-transplant-related	
aGvHD grade – Modified Consensus Criteria	
No aGvHD	3428 (40)
I	1344 (16)
II	2083 (24)
III-IV	1712 (20)
cGvHD incidence	3687 (43)
Follow-up of survivors, months, median (range)	71 (1-173)

D – donor; R – recipient; M – male; F – female; CMV – cytomegalovirus;

Supplemental Table 1B. Clinical outcomes of entire cohort

	Entire Study Population (n = 8567)		MRD Recipients (n = 4183)		URD Recipients (n = 4384)		p-value
Outcomes	n Eval	Prob (95% CI)	n Eval	Prob (95% CI)	n Eval	Prob (95% CI)	
Overall survival	8567		4183		4384		
100-day		84 (83-85)%		88 (87-89)%		81 (79-82)%	**<0.001**
6-month		74 (73-75)%		79 (78-81)%		70 (68-71)%	**<0.001**
1-year		62 (61-63)%		67 (66-69)%		57 (55-58)%	**<0.001**
2-year		52 (51-53)%		57 (56-59)%		47 (46-49)%	**<0.001**
Transplant-related mortality	8296		4125		4291		
100-day		11 (10-11)%		8 (7-9)%		13 (12-14)%	**<0.001**
6-month		14 (14-15)%		11 (10-12)%		18 (17-19)%	**<0.001**
1-year		19 (18-20)%		15 (14-16)%		23 (22-24)%	**<0.001**
2-year		22 (21-23)%		18 (17-20)%		27 (25-28)%	**<0.001**
Relapse	8416		4125		4291		
100-day		14 (13-14)%		13 (12-14)%		15 (14-16)%	*0.03*
6-month		22 (21-23)%		21 (20-23)%		23 (22-24)%	0.12
1-year		29 (28-29)%		28 (27-30)%		29 (27-30)%	0.64
2-year		33 (32-34)%		34 (32-35)%		33 (32-34)%	0.45
Disease-free survival	8158		4125		4291		
100-day		75 (74-76)%		79 (78-80)%		72 (71-73)%	**<0.001**
6-month		63 (62-64)%		67 (66-69)%		60 (58-61)%	**<0.001**
1-year		52 (51-53)%		56 (55-58)%		48 (47-50)%	**<0.001**
2-year		44 (43-45)%		48 (46-49)%		40 (39-42)%	**<0.001**
Chronic GVHD	8375		4046		4329		
6-month		28 (27-29)%		24 (23-25)%		30 (28-31)%	**<0.001**
1-year		43 (42-44)%		39 (37-40)%		44 (42-45)%	**<0.001**
2-year		47 (46-48)%		42 (41-44)%		48 (46-49)%	**<0.001**

Bold values indicate significance at p-value <0.01. Italicized values indicate 0.1≤ p-value <0.05.

Supplemental Table 2. Significant covariables for clinical outcomes when analyzed by grades of aGvHD with and without UGI symptoms (p-values reported)

Factor	Survival		DFS		Relapse		TRM		Chronic GvHD	
	MRD[a]	URD[b]	MRD[c]	URD[d]	MRD[e]	URD[f]	MRD[g]	URD[h]	MRD[i]	URD[j]
Recipient age	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**			**<0.0001**	**<0.0001**		
Graft source	0.080						*0.021*			
CMV serology		**0.0012**					*0.042*	**0.0027**		
ABO matching								**0.0025**		
GvHD ppx incl steroids	**0.0020**	**0.0021**	*0.030*	*0.031*			**0.0003**	*0.013*	*0.033*	
GvHD ppx incl MMF	*0.043*	**0.0002**		*0.018*				**<0.0001**		
Time to tx, AML	**0.0060**	**0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**				**<0.0001**
Time to tx, ALL	**0.0004**	**0.0014**	**0.0001**	**0.0131**			**0.0016**			*0.017*
KPS	**<0.0001**		**<0.0001**		**<0.0001**	**0.0011**	**0.0020**	**<0.0001**		
Disease type							*0.026*			
Disease stage		**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**0.0001**	**<0.0001**		**0.0002**
Race	**0.0030**		**0.025**				**0.0011**			
URD HLA-matching		**0.0075**		0.14				*0.011*		**0.0036**
Sex match	**0.0061**					*0.010*			**<0.0001**	**0.0009**
Conditioning regimen					0.061			**0.0037**		
Year of HSCT					**0.0001**					**<0.0001**

[a] Stratification for multivariable analysis for Overall Survival (MRD): for year of HSCT - 2000-2004, 2005-2008, and 2009-2012; for disease type - AML, MDS, CML and ALL; for disease stage - early, intermediate, advanced and unknown.
[b] Stratification for multivariable analysis for Overall Survival (MUD): for year of HSCT - 2000-2004, 2005-2008, and 2009-2012; for graft source - bone marrow and peripheral blood; for Karnofsky group status (KPS) - <90% or $\geq$ 90% at HSCT.
[c] Stratification for multivariable analysis for Disease-Free Survival (MRD): for disease type - AML, MDS, CML and ALL; for graft source - bone marrow and peripheral blood.
[d] Stratification for multivariable analysis for Disease-Free Survival (MUD): for year of HSCT - 2000-2004, 2005-2008, and 2009-2012; for graft source - bone marrow and peripheral blood; for disease type - AML, MDS, CML and ALL; for KPS - <90% or $\geq$ 90% at HSCT.
[e] Stratification for multivariable analysis for Relapse (MRD): for disease type - AML, MDS, CML and ALL; for graft source - bone marrow and peripheral blood.
[f] Stratification for multivariable analysis for Relapse (MUD): for year of HSCT - 2000-2004, 2005-2008, and 2009-2012; for graft source - bone marrow and peripheral blood; for disease type - AML, MDS, CML and ALL.
[g] Stratification for multivariable analysis for TRM (MRD): for year of HSCT - 2000-2004, 2005-2008, and 2009-2012; for sex match - M/M, M/F, F/M, F/F based on donor/recipient sex.
[h] Stratification for multivariable analysis for TRM (MUD): for year of HSCT - 2000-2004, 2005-2008, and 2009-2012; for graft source - bone marrow and peripheral blood; for disease type - AML, MDS, CML and ALL; for sex match - M/M, M/F, F/M, F/F based on donor/recipient sex.
[I] Stratification for multivariable analysis for Chronic GvHD (MRD): for year of HSCT - 2000-2004, 2005-2008, and 2009-2012; for graft source - bone marrow and peripheral blood; for conditioning regimen - cyclophosphamide + TBI +/- others, TBI+/- others, busulfan + cyclophosphamide +/- others, busulfan + fludarabine, and others.
[j] Stratification for multivariable analysis for Chronic GvHD (MUD): for graft source - bone marrow and peripheral blood; for disease type - AML, MDS, CML and ALL; for conditioning regimen - cyclophosphamide + TBI +/- others, TBI+/- others, busulfan + cyclophosphamide +/- others, busulfan + fludarabine, and others; for recipient age - 18-29, 30-39, 40-,49 and 50+; for GVHD ppx – MMF, not MMF.
Ppx – prophylaxis
Bold values indicate significance at p-value <0.01. Italicized values indicate 0.1$\leq$ p-value <0.05.

Supplemental Table 3. Demographics of subgroups without or with UGI symptoms within each stage of acute GvHD

Characteristics of patients:	Grade I (Skin 1/2)	Grade II UGI+Skin 1/2	Grade II no UGI	Grade II UGI+other II	Grade III-IV No UGI	Grade III-IV +UGI
Number of patients	**1344**	**196**	**1211**	**447**	**1545**	**167**
Number of centers	165	78	165	93	192	74
Patient-related						
Age at transplant, years, median (range)	43 (18 - 70)	43 (18 - 66)	41 (18 - 71)	43 (19 - 70)	42 (18 - 72)	42 (19 - 68)
Sex						
Male	745 (55)	91 (46)	712 (59)	242 (54)	933 (60)	81 (49)
Race						
Caucasian	1179 (88)	171 (87)	1068 (88)	391 (87)	1304 (84)	145 (87)
Karnofsky performance score at HSCT						
≥ 90%	961 (72)	127 (65)	830 (69)	290 (65)	991 (64)	100 (60)
Disease						
AML	694 (52)	103 (53)	554 (46)	215 (48)	675 (44)	73 (44)
ALL	282 (21)	46 (23)	276 (23)	89 (20)	338 (22)	22 (13)
CML	242 (18)	20 (10)	220 (18)	73 (16)	343 (22)	38 (23)
MDS	126 (9)	27 (14)	161 (13)	70 (16)	189 (12)	34 (20)
Disease status at transplant						
Early	750 (56)	111 (57)	699 (58)	257 (57)	777 (50)	86 (51)
Intermediate	288 (21)	35 (18)	248 (20)	93 (21)	331 (21)	34 (20)
Advanced	303 (23)	50 (26)	258 (21)	95 (21)	426 (28)	46 (28)
Missing	3 (<1)	0	6 (<1)	2 (<1)	11 (<1)	1 (<1)

Characteristics of patients:	Grade I (Skin 1/2)	Grade II UGI+Skin 1/2	Grade II no UGI	Grade II UGI+other II	Grade III-IV No UGI	Grade III-IV +UGI
Donor-related						
Donor type						
HLA-identical sibling	654 (49)	77 (39)	477 (39)	200 (45)	584 (38)	72 (43)
URD well-matched	542 (40)	92 (47)	541 (45)	200 (45)	638 (41)	63 (38)
URD partially-matched	148 (11)	27 (14)	193 (16)	47 (11)	323 (21)	32 (19)
HLA-identical sibling donor age, years, median (range)	43 (<1 - 68)	44 (17 - 68)	41 (<1 - 70)	44 (15 - 75)	42 (3 - 74)	43 (18 - 66)
Unrelated donor age, years, median (range)	33 (19 - 60)	33 (19 - 57)	34 (18 - 60)	30 (18 - 60)	35 (19 - 61)	33 (20 - 54)
D/R sex match						
M/M	494 (37)	53 (27)	456 (38)	133 (30)	589 (38)	51 (31)
M/F	361 (27)	62 (32)	291 (24)	127 (28)	346 (22)	53 (32)
F/M	250 (19)	38 (19)	255 (21)	109 (24)	344 (22)	30 (18)
F/F	238 (18)	43 (22)	208 (17)	78 (17)	266 (17)	33 (20)
D/R CMV status						
+/+	411 (31)	55 (28)	367 (30)	145 (32)	476 (31)	50 (30)
+/-	146 (11)	20 (10)	125 (10)	44 (10)	160 (10)	21 (13)
-/+	363 (27)	61 (31)	306 (25)	129 (29)	390 (25)	33 (20)
-/-	368 (27)	55 (28)	342 (28)	109 (24)	429 (28)	55 (33)
D/R ABO match						
Matched	719 (53)	102 (52)	636 (53)	238 (53)	777 (50)	90 (54)
Transplant-related						
Time from diagnosis to transplant, months, median (range)	7 (<1 - 177)	6 (1 - 143)	7 (1 - 279)	6 (1 - 210)	7 (<1 - 309)	7 (<1 - 127)

Characteristics of patients:	Grade I (Skin 1/2)	Grade II UGI+Skin 1/2	Grade II no UGI	Grade II UGI+other II	Grade III-IV No UGI	Grade III-IV +UGI
Graft type						
Bone marrow	413 (31)	41 (21)	331 (27)	82 (18)	439 (28)	33 (20)
Peripheral blood	931 (69)	155 (79)	880 (73)	365 (82)	1106 (72)	134 (80)
TBI used in conditioning regimen	708 (53)	90 (46)	648 (54)	201 (45)	800 (52)	75 (45)
Steroid-containing GVHD prophylaxis	183 (14)	22 (11)	115 (9)	51 (11)	221 (14)	21(13)
MMF-containing GVHD prophylaxis	109(8)	23 (12)	136 (11)	65 (15)	223 (14)	22 (13)
Year of transplant						
2000-2004	582 (43)	56 (29)	518 (43)	92 (21)	749 (48)	54 (32)
2005-2008	478 (36)	86 (44)	478 (39)	163 (36)	575 (37)	45 (27)
2009-2012	284 (21)	54 (28)	215 (18)	192 (43)	221 (14)	68 (41)
Post-transplant-related						
cGVHD incidence						
Yes	676 (50)	111 (57)	660 (55)	244 (55)	533 (34)	53 (32)
aGvHD Therapy-related steroid use						
Topical steroids +/- other agents	216 (16)	13 (7)	46 (4)	10 (2)	15 (1)	0
Systemic steroids +/- other agents	956 (71)	175 (89)	1094 (90)	421 (94)	1476 (96)	163 (98)

N.B., for each set of comparisons, demographics were compared, and significant differences that affected a particular outcome were addressed via the respective statistical models.

Supplemental Table 4. Clinical outcomes in HSCT recipients with Grade II aGvHD distinguished by involvement of specific organs

	Matched Related Donor		Unrelated Donor	
Overall Survival	HR	p-value	HR	p-value
Isolated UGI (baseline, n=229)	1.00		1.00	
Grade II with Liver +/- others (n=185)	1.05	0.82	1.68	**0.0027**
Grade II with LGI +/- skin (no liver) (n=521)	0.87	0.46	1.00	0.98
Grade II skin only (n=505)	0.99	0.97	1.11	0.45
Disease-free Survival				
Isolated UGI (baseline)	1.00		1.00	
Grade II with Liver +/- others	0.99	0.97	1.37	0.066
Grade II with LGI +/- skin (no liver)	0.84	0.34	0.84	0.22
Grade II skin only	1.03	0.88	0.94	0.63
Relapse				
Isolated UGI (baseline)	1.00		1.00	
Grade II with Liver +/- others	0.95	0.84	1.17	0.47
Grade II with LGI +/- skin (no liver)	0.80	0.32	0.75	0.10
Grade II skin only	0.97	0.88	0.87	0.40
Treatment-related Mortality				
Isolated UGI (baseline)	1.00		1.00	
Grade II with Liver +/- others	1.23	0.58	2.08	*0.011*
Grade II with LGI +/- skin (no liver)	1.01	0.98	1.35	0.24
Grade II skin only	1.26	0.51	1.34	0.24
Chronic GvHD				
Isolated UGI (baseline)	1.00		1.00	
Grade II with Liver +/- others	1.02	0.94	2.18	**<0.0001**
Grade II with LGI +/- skin (no liver)	1.13	0.54	1.52	**0.0037**
Grade II skin only	1.49	*0.049*	1.53	**0.0027**

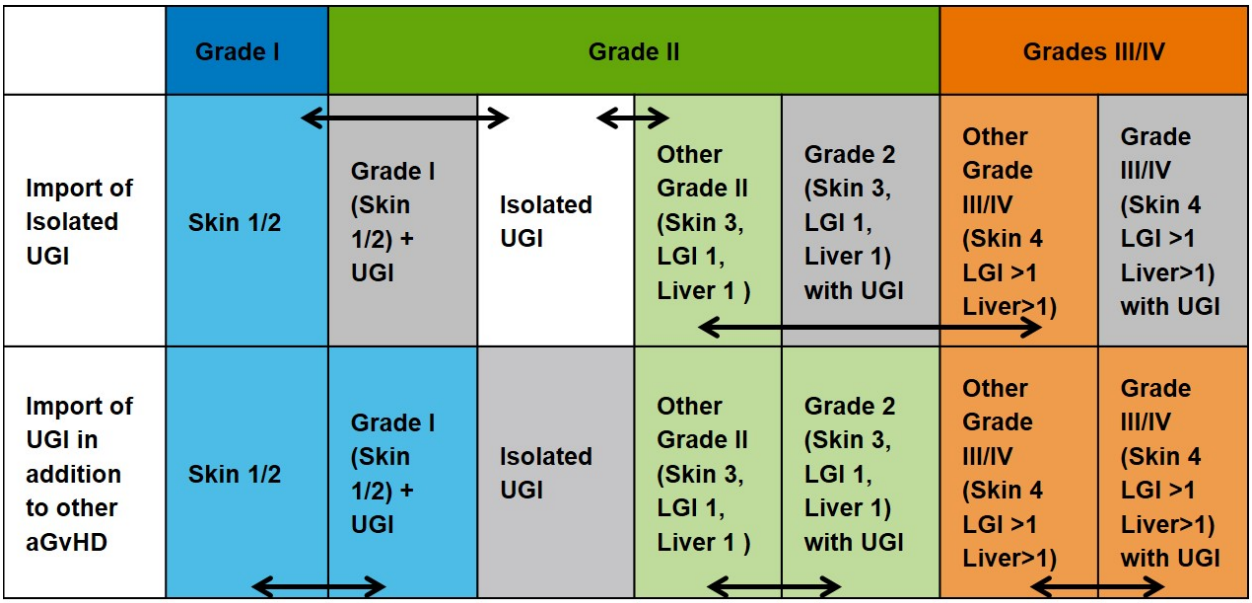
Bold values indicate significance at p-value <0.01. Italicized values indicate at 0.1≤ p-value <0.05.

N.B., Supplemental Table 2 and Primary Manuscript Tables 3A, 3B, and 4 were derived from the same multivariable treating time of transplantation as the starting point and involving all patient GvHD-related groupings, although only particular comparisons are cited in each tableIn this analysis, patients with isolated UGI GvHD were set as the baseline comparator (HR =1.0).

Supplemental Figure Legends

Supplemental Figure 1. Subgroups of subjects with acute GvHD analyzed. Top row: Pairwise comparisons were performed between clinical outcomes in subjects with isolated upper GI acute GvHD (iUGI aGvHD) and patients with Grade I, Grade II, or Grades III/IV aGvHD without UGI manifestations as demonstrated by arrows, with arrow heads in the respective subsets being compared. Bottom row: Pairwise comparisons between subjects with aGvHD involving various organs without any UGI involvement and those with similar organ involvement with concomitant UGI involvement were performed as demonstrated by arrows, with arrow heads in the respective subsets being compared. To accomplish this, subjects with Grade II aGvHD were separated into 4 categories: iUGI, Stage 1/2 Skin plus UGI disease; and Hepatic/Lower GI Stage 1 and/or Skin Stage 3 disease, either with or without UGI involvement.

Supplemental Figure 1. Subgroups of subjects with acute GvHD analyzed



Numerals indicate organ-specific stage