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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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ABSTRACT

Upper gastrointestinal acute graft-*versus*-host disease is reported in approximately 30% of hematopoietic stem cell transplant recipients developing acute graft-*versus*-host disease. Currently classified as Grade II in consensus criteria, upper gastrointestinal acute graft-*versus*-host disease is often treated with systemic immunosuppression. We reviewed the Center for International Blood and Marrow Transplant Research database to assess the prognostic implications of upper gastrointestinal acute graft-*versus*-host disease in isolation or with other acute graft-*versus*-host disease manifestations. 8567 adult recipients of myeloablative allogeneic hematopoietic stem cell transplant receiving T-cell replete grafts for acute leukemia, chronic myeloid leukemia or myelodysplastic syndrome between 2000 and 2012 were analyzed. 51% of transplants were from unrelated donors. Reported upper gastrointestinal acute graft-*versus*-host disease incidence was 12.1%; 2.7% of recipients had isolated upper gastrointestinal acute graft-*versus*-host disease, of whom 95% received systemic steroids. Patients with isolated upper gastrointestinal involvement had similar survival, disease-free survival, transplant-related mortality, and relapse as patients with Grades 0, I, or II acute graft-*versus*-host disease. Unrelated donor recipients with isolated upper gastrointestinal acute graft-*versus*-host disease had less subsequent chronic graft-*versus*-host disease than those with Grades I or II disease (P=0.016 and P=0.0004, respectively). Upper gastrointestinal involvement added no significant prognostic information when present in addition to other manifestations of Grades I or II acute graft-*versus*-host disease. If upper gastrointestinal symptoms were reclassified as Grade 0 or I, 425 of 2083

patients (20.4%) with Grade II disease would be downgraded, potentially impacting the interpretation of clinical trial outcomes. Defining upper gastrointestinal acute graft-*versus*-host disease as a Grade II entity, as it is currently diagnosed and treated, is not strongly supported by this analysis. The general approach to diagnosis, treatment and grading of upper gastrointestinal symptoms and their impact on subsequent acute graft-*versus*-host disease therapy warrants reevaluation.

Introduction

Upper gastrointestinal acute graft-*versus*-host disease (UGI aGvHD) is a clinical syndrome of anorexia, food intolerance, nausea and vomiting, first described by Weisdorf *et al.* in 1990.[1] In that cohort of 469 related-donor allogeneic hematopoietic stem cell transplant (HSCT) recipients, UGI symptoms were found in at least 13% of recipients and in almost half of those cases were the only reason for initiating systemic immunosuppression. Of note, all those diagnoses were confirmed by endoscopic biopsy and histological evaluation. In subsequent studies, UGI involvement has been consistently seen in up to 27% of recipients with aGvHD, with perhaps a quarter of those having UGI symptoms in isolation.[2,3] There is a large differential diagnosis for patients presenting with nausea, vomiting and/or anorexia post-allogeneic HSCT including prolonged effects of conditioning treatment and medication side effects. In addition, endoscopic appearance and histological changes such as single cell epithelial necrosis with karyorrhexis, dilation of mucosal crypts or glands, and crypt abscesses or obliteration are not specific.[4-6] Thus, defining and differentiating UGI aGvHD from conditioning toxicity, cytomegalovirus (CMV) or cryptosporidium infection, mycophenolate mofetil (MMF)-related damage/ulceration, and proton-pump inhibitor use can be challenging.[7-9]

In the original series describing this entity, the percentage of those with UGI symptoms (in isolation or plus Grade I skin aGvHD) who developed chronic GvHD (cGvHD) was similar to that seen after non-UGI Grade II aGvHD (74% and 65%) and higher than in those patients with no aGvHD (13%) or Grade I skin aGvHD (50%).[1] Based on this finding, UGI symptoms were incorporated into the "Consensus" or modified Glucksberg grading system as a criterion for Stage 1 GI, overall Grade II aGvHD.[10-12] UGI symptoms are not reflected in the International Bone Marrow Transplant Registry (IBMTR) grading schema. Many subsequent publications used the modified "Consensus" grading report incidence of Grades II-IV aGvHD without delving into the organs involved, while others defined the individual organ systems involved but did not differentiate UGI *versus* lower GI (LGI) symptoms.[13-15] Even when the distribution of GI involvement is specified, only occasionally are aGvHD responses and long-term prognosis differentially followed based on specific involvement; however, certain centers are increasingly focusing on UGI aGvHD.[2,3,16-20]

The prognostic implications and corresponding staging for UGI aGvHD, either in isolation or in combination with other manifestations, have not to our knowledge been validated in a large multi-center population. The need for such evaluation is highlighted by several findings. First, one study involving routine endoscopic evaluation demonstrated that UGI aGvHD, seen in 12 of 26 subjects, uniformly resolved if treated with steroids, did not progress to symptomatic LGI aGvHD, and in almost one-third of patients resolved without alteration in baseline immunosuppression. In that study, the presence of UGI

Table 1. Incidence of acute GvHD in entire cohort.

Maximum grade of aGvHD	Entire cohort (8567) n (%)	MRD (4183) n (%)	URD (4384) n (%)	Biopsy reported as obtained to confirm organ involvement* Organ involved	Total n	Biopsied n (%)	#Biopsies positive	Systemic steroid use^
None	3428 (40.0%)	2038 (48.7%)	1390 (31.7%)					0 (0%)
I	1344 (15.7%)	654 (15.6%)	690 (15.7%)	Skin	1344	218 (16.2%)	212	956 (79.9%)
II	2083 (24.3%)	835(19.9%)	1248 (28.5%)	Skin	1498	295 (19.7%)	263	
				Liver	252	25 (9.9%)	12	
				UGI	872	311 (35.7%)	286	1896 (94.7%)
				LGI	914	327 (35.8%)	301	
III-IV	1712 (20.0%)	656 (15.7%)	1056 (24.1%)	Skin	1316	267 (20.2%)	231	
				Liver	1003	138 (13.8%)	71	
				UGI	167	84 (50.3%)	75	1628 (97.3%)
				LGI	1333	361 (27.1%)	337	
Isolated UGI	229 (2.7%)	81 (1.9%)	148 (3.4%)	UGI	229	49 (21.3%)	42	207 (95.4%)
Any UGI involvement	1039 (12.1%)	430 (10.3%)	609 (13.9%)	UGI	1039	395 (38.0%)	361	966 (95.5%)

*Biopsy was reported as negative, positive, inconclusive, not tested or missing. Total number of biopsies reported excludes those not tested or missing. ^% Systemic steroid use excludes patients missing relevant data. aGvHD: acute graft-*versus*-host disease; MRD: matched related donor; URD: unrelated donor; UGI: upper gastrointestinal; LGI: lower gastrointestinal.

Table 2. Demographics of subgroups with isolated UGI aGvHD or other stages without GI symptoms.

Characteristics of patients	No aGVHD	Grade I (Skin 1/2)	Grade II No UGI	iUGI	Grade III-IV No UGI
Number of patients	3428	1344	1211	229	1545
Number of centers	221	165	165	61	192
Patient-related					
Age at transplant, years, median (range)	42 (18 - 72)	43 (18 - 70)	41 (18 - 71)	43 (18 - 68)	42 (18 - 72)
Sex					
Male	1805 (53)	745 (55)	712 (59)	127 (55)	933 (60)
Female	1623 (47)	599 (45)	499 (41)	102 (45)	612 (40)
Race					
Caucasian	2814 (82)	1179 (88)	1068 (88)	201 (88)	1304 (84)
Karnofsky performance score at HSCT					
≥ 90%	2296 (67)	961 (72)	830 (69)	142 (62)	991 (64)
Disease					
AML	1749 (51)	694 (52)	554 (46)	118 (52)	675 (44)
ALL	736 (21)	282 (21)	276 (23)	49 (21)	338 (22)
CML	600 (18)	242 (18)	220 (18)	35 (15)	343 (22)
MDS	343 (10)	126 (9)	161 (13)	27 (12)	189 (12)
Disease status at transplant					
Early	1836 (54)	750 (56)	699 (58)	115 (50)	777 (50)
Intermediate	772 (23)	288 (21)	248 (20)	66 (29)	331 (21)
Advanced	806 (24)	303 (23)	258 (21)	48 (21)	426 (28)
Donor-related					
Donor type					
HLA-identical sibling	2038 (59)	654 (49)	477 (39)	81 (35)	584 (38)
URD well-matched	1048 (31)	542 (40)	541 (45)	119 (52)	638 (41)
URD partially-matched	342 (10)	148 (11)	193 (16)	29 (13)	323 (21)
HLA-identical sibling donor age, years, median (range)	40 (<1 - 85)	43 (<1 - 68)	41 (<1 - 70)	43 (14 - 70)	42 (3 - 74)
Unrelated donor age, years, median (range)	32 (19 - 61)	33 (19 - 60)	34 (18 - 60)	32 (19 - 59)	35 (19 - 61)
D/R sex match					
M/M	1150 (34)	494 (37)	456 (38)	75 (33)	589 (38)
M/F	909 (27)	361 (27)	291 (24)	55 (24)	346 (22)
F/M	655 (19)	250 (19)	255 (21)	52 (23)	344 (22)
F/F	712 (21)	238 (18)	208 (17)	47 (21)	266 (17)
D/R CMV status					
+/+	1311 (38)	411 (31)	367 (30)	62 (27)	476 (31)
+/-	320 (9)	146 (11)	125 (10)	20 (9)	160 (10)
-/+	794 (23)	363 (27)	306 (25)	84 (37)	390 (25)
-/-	808 (24)	368 (27)	342 (28)	50 (22)	429 (28)
D/R ABO match					
Matched	1936 (56)	719 (53)	636 (53)	120 (52)	777 (50)
Transplant-related					
Time from diagnosis to transplant, months, median (range)	7 (<1 - 310)	7 (<1 - 177)	7 (1 - 279)	6 (1 - 213)	7 (<1 - 309)
Graft type					
Bone marrow	1057 (31)	413 (31)	331 (27)	56 (24)	439 (28)
Peripheral blood	2371 (69)	931 (69)	880 (73)	173 (76)	1106 (72)
TBI used in conditioning regimen	1672 (49)	708 (53)	648 (54)	113 (49)	800 (52)
Steroid-containing GvHD prophylaxis	392 (11)	183 (14)	115 (9)	11 (5)	221 (14)
MMF-containing GvHD prophylaxis	304 (9)	109 (8)	136 (11)	19 (8)	223 (14)
Year of transplant					
2000-2004	1549 (45)	582 (43)	518 (43)	65 (28)	749 (48)

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2005-2008	1192 (35)	478 (36)	478 (39)	106 (46)	575 (37)
2009-2012	687 (20)	284 (21)	215 (18)	58 (25)	221 (14)
cGVHD incidence	1283 (37)	676 (50)	660 (55)	127 (55)	533 (34)
aGvHD Therapy-related steroid use					
Topical steroids +/- other agents	0	216 (16)	46 (4)	7 (3)	15 (1)
Systemic steroids +/- other agents	0	956 (71)	1094 (90)	207 (90)	1476 (96)

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. aGvHD: acute graft-*versus*-host disease; cGvHD: chronic graft-*versus*-host disease D: donor; R: recipient; M: male; F: female; CMV: cytomegalovirus; UGI: upper gastrointestinal; AML: acute myelogenous leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myelogenous leukemia; MDS: myelodysplastic syndrome; HLA: human leukocyte antigen; URD: unrelated donor; TBI: total-body irradiation; MMF: mycophenolate mofetil; HSCT: hematopoietic stem cell transplant.

Table 3A. Clinical outcomes in patients with aGvHD: pairwise comparisons between isolated UGI aGvHD *versus* aGvHD without UGI symptoms.

	Matched Related Donor			Unrelated Donor		
Overall Survival	HR	95% CI	*P*	HR	95% CI	*P*
Isolated UGI (baseline)	1.00			1.00		
Grade I	0.78	0.56-1.10	0.16	0.89	0.68-1.15	0.37
Grade II	0.95	0.67-1.35	0.77	1.12	0.87-1.45	0.38
Grades III/IV	**2.06**	**1.48-2.88**	**<0.0001**	**2.28**	**1.77-2.92**	**<0.0001**
Disease-free Survival						
Isolated UGI (baseline)	1.00			1.00		
Grade I	0.81	0.59-1.11	0.19	0.74	0.57-0.94	0.016
Grade II	0.93	0.67-1.28	0.67	0.94	0.74-1.20	0.63
Grades III/IV	**1.66**	**1.22-2.28**	**0.0015**	**1.66**	**1.31-2.11**	**<0.0001**
Relapse						
Isolated UGI (baseline)	1.00			1.00		
Grade I	0.84	0.58-1.22	0.37	*0.74*	*0.55-0.99*	*0.045*
Grade II	0.89	0.60-1.30	0.54	0.85	0.64-1.14	0.28
Grades III/IV	0.94	0.64-1.39	0.77	0.86	0.64-1.16	0.33
Treatment-related Mortality						
Isolated UGI (baseline)	1.00			1.00		
Grade I	0.83	0.45-1.54	0.55	0.93	0.58-1.52	0.78
Grade II	1.14	0.61-2.13	0.69	1.43	0.90-2.27	0.13
Grades III/IV	**3.39**	**1.87-6.16**	**<0.0001**	**3.91**	**2.5-6.14**	**<0.0001**
Chronic GvHD						
Isolated UGI (baseline)	1.00			1.00		
Grade I	1.16	0.83-1.67	0.38	*1.37*	*1.06-1.79*	*0.016*
Grade II	1.22	0.85-1.72	0.28	**1.59**	**1.22-2.04**	**0.0004**
Grades III/IV	1.09	0.76-1.56	0.65	**1.67**	**1.29-2.17**	**0.0001**

Bold values indicate significance at *P*-value <0.01. Italicized values indicate 0.1< *P*-value <0.05. aGvHD: acute graft-*versus*-host disease; UGI: upper gastrointestinal.

aGVHD did not affect development of cGVHD or survival.[21] Second, other studies have found that the vast majority of patients with symptoms prompting a GI evaluation will have diffuse intestinal involvement, suggesting that symptom-directed upper endoscopy may not be necessary.[22-24] Third, the reliance on biopsy confirmation in the diagnosis and reporting of UGI aGvHD varies widely, and currently the diagnosis and reporting is often based on relatively non-specific symptoms. Lastly, GvHD-related mortality and patterns of therapy in general have changed over the past two decades.[25]

We conducted a systematic analysis to determine: 1) the prognostic impact of isolated UGI (iUGI) aGvHD and thus verify the position of this manifestation in the Consensus grading scheme when present alone, and 2) if UGI symptoms add prognostic value when present in addition to skin, LGI or hepatic aGvHD. We hypothesized that as currently diagnosed, reported and treated, the impact of UGI aGvHD on transplant-related outcomes would be less than initially reported.

Methods

All patients provided informed consent to the Center for International Blood and Marrow Transplant Research (CIBMTR) research program. This study was approved by the Institutional Review Board of the National Marrow Donor Program.

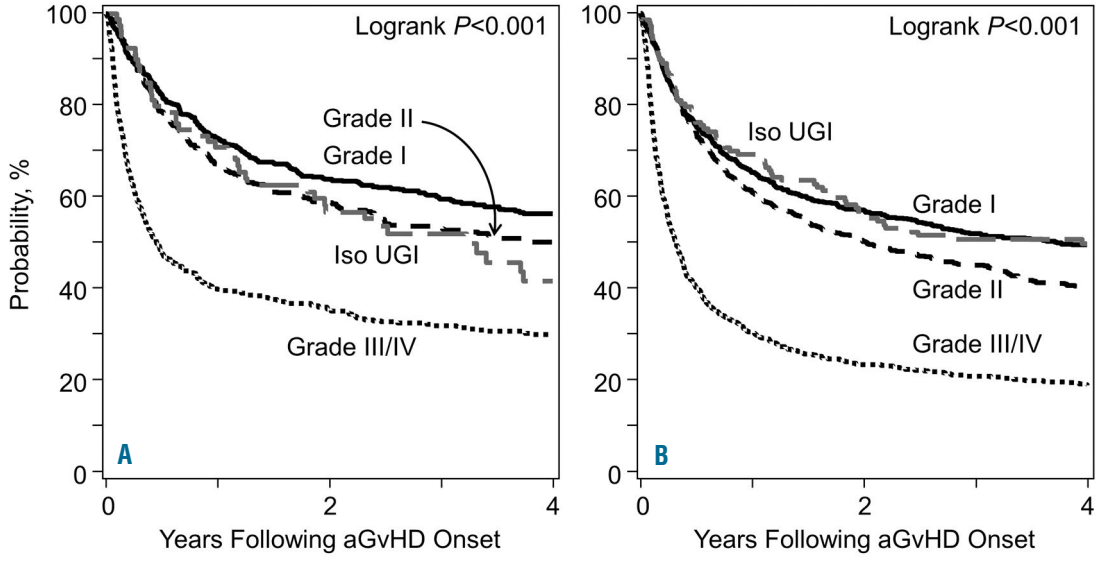

Figure 1. Overall survival for patients with isolated UGI aGvHD *versus* aGvHD without UGI symptoms. Kaplain-Meier probabilities of overall survival from time of aGvHD onset for patients with iUGI symptoms, and subsets of patients with other grades of aGvHD but without any UGI symptoms. Patients who did not develop aGvHD are not represented. A. Transplantation from a matched-related donor. B. Transplantation from a well-matched or partially-matched unrelated donor. UGI: upper gastrointestinal. aGvHD: acute graft-*versus*-host disease.

Patient Selection

The study population included all adult patients > 18 years old who received an allogeneic HSCT from a fully human leukocyte antigen (HLA)-matched related (MRD) or well-matched or partially-matched unrelated donor (URD) following myeloablative conditioning for acute myelogenous leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML), or myelodysplastic syndrome (MDS) between 2000 and 2012.[26,27] Only recipients of peripheral blood stem cell (PBSC) or bone marrow (BM) grafts, without *ex vivo* or *in vivo* T-cell depletion (e.g., without CD34$^+$ cell-selection, anti-thymocyte globulin, or alemtuzumab use), who received calcineurin inhibitor-based aGvHD prophylaxis were analyzed.

Definition/diagnosis of acute GvHD

CIBMTR form 2100 based on modified Glucksberg criteria, was used to collect outcome data.[10] UGI aGvHD is defined as "persistent nausea with histological evidence of GvHD in stomach or duodenum" - Stage 1 GI Grade II aGvHD. However, CIBMTR guidance reads that "organ staging and overall grade of GvHD should be calculated from the clinical picture, not histology". Thus, those with persistent nausea clinically thought to be consistent with GvHD and treated accordingly may be classified as having upper GI aGvHD.

Other data included date of onset of first episode of aGvHD, whether diagnosis was based on biopsy findings, maximum organ involvement and grade of aGvHD, and specific therapy for aGvHD. Histological confirmation of UGI symptoms consisted of endoscopy and biopsy of stomach or duodenum and was reported as "negative, positive, inconclusive, not tested, or missing". Current analyses were based on maximal reported severity and organ involvement (Table 1 and Table 2).

Statistical approach

The primary endpoint of this study, when analyzed by aGvHD occurrence, was overall survival (OS), encompassing death from any cause. Secondary endpoints included treatment-related mortality (TRM) defined as death while in continuous remission; relapse, defined as a clinical recurrence, progression or persistent disease following transplantation; disease-free survival (DFS), defined as absence of death or relapse; and cGvHD.[28]

Variables related to patient, disease, and transplantation characteristics were reported using descriptive statistics. Patient-, disease-, and treatment-related factors were compared between related and URD groups, using the χ^2 test for categorical variables and the Mann-Whitney test for continuous variables. Probabilities of OS and DFS were calculated using the Kaplan-Meier estimator, with variance estimated by Greenwood's formula. Cumulative incidence estimates for relapse, TRM and cGvHD were calculated by treating TRM and relapse as competing risks, respectively.[29]

Cox proportional hazard testing models were applied in multivariable analyses. Patient-, disease-, transplant-, and aGvHD-related variables were tested *via* a stepwise forward-selection procedure. Patient-, disease-, and transplant-related variables are detailed in the *Online Supplementary Methods*. In all multivariable analyses, transplantation time was treated as the starting time point, and all GvHD-related variables were treated as time-dependent variables. Multiple time-dependent variables were defined separately at the onset of aGvHD, based on the highest aGvHD grade that a patient developed. For each patient, only a single time-dependent variable was triggered. Our primary results, as shown in Table 3A, highlighted comparisons between patients with various aGvHD manifestations +/- UGI symptoms and excluded recipients without aGvHD. The Kaplan-Meier and cumulative incidence curves were also plotted from time of aGvHD onset. In our secondary results, as shown in Table 3B, recipients without aGvHD were highlighted as the baseline comparator.

Results shown in Tables 3A, 3B, and 4 and *P*-values referred to in the text were derived from the same multivariable models involving all patient GvHD-related groupings, although only particular comparisons are cited in each table. For each set of comparisons, demographics were compared, and significant differences that affected a particular outcome were addressed *via* the respective statistical models. To adjust for multiple comparisons, a 2-sided *P*-value of <0.01 was used as the significance threshold.

Table 3B. Clinical outcomes in patients with and without aGvHD: pairwise comparisons between no aGvHD *versus* isolated UGI or aGvHD without UGI symptoms.

	Matched Related Donor			Unrelated Donor		
Overall Survival	HR	95% CI	*P*	HR	95% CI	*P*
No aGvHD (Baseline)	1.00			1.00		
Isolated UGI	1.18	0.85-1.63	0.33	1.01	0.79-1.29	0.94
Grade I	0.92	0.80-1.06	0.25	0.89	0.79-1.02	0.088
Grade II	1.12	0.96-1.31	0.16	*1.13*	*1.00-1.27*	*0.046*
Grades III/IV	**2.43**	**2.14-2.76**	**<0.0001**	**2.30**	**2.07-2.55**	**<0.0001**
Disease-free Survival						
No aGvHD (Baseline)	1.00			1.00		
Isolated UGI	1.04	0.77-1.41	0.78	1.09	0.86-1.38	0.48
Grade I	*0.84*	*0.74-0.96*	*0.011*	**0.80**	**0.71-0.91**	**0.0006**
Grade II	0.97	0.84-1.13	0.71	1.03	0.91-1.15	0.68
Grades III/IV	**1.74**	**1.54-1.96**	**<0.0001**	**1.81**	**1.63-2.01**	**<0.0001**
Relapse						
No aGvHD (Baseline)	1.00			1.00		
Isolated UGI	0.93	0.66-1.33	0.70	1.04	0.79-1.37	0.78
Grade I	**0.79**	**0.67-0.92**	**0.0032**	**0.77**	**0.66-0.90**	**0.0011**
Grade II	*0.83*	*0.68-1.00*	*0.048*	0.89	0.76-1.03	0.12
Grades III/IV	0.88	0.73-1.06	0.18	0.90	0.77-1.05	0.19
Treatment-related Mortality						
No aGvHD (Baseline)	1.00			1.00		
Isolated UGI	1.24	0.69-2.24	0.48	0.85	0.54-1.34	0.49
Grade I	1.03	0.81-1.31	0.81	*0.80*	*0.65-0.98*	*0.033*
Grade II	**1.41**	**1.10-1.81**	**0.0074**	*1.21*	*1.01-1.46*	*0.038*
Grades III/IV	**4.21**	**3.51-5.05**	**<0.0001**	**3.33**	**2.87-3.86**	**<0.0001**
Chronic GvHD						
No aGvHD (Baseline)	1.00			1.00		
Isolated UGI	1.36	0.97-1.9	0.08	0.95		0.69
Grade I	**1.58**	**1.37-1.83**	**<0.0001**	**1.31**	**1.14-1.51**	**0.0002**
Grade II	**1.65**	**1.41-1.93**	**<0.0001**	**1.5**	**1.30-1.72**	**<0.0001**
Grades III/IV	**1.47**	**1.25-1.75**	**<0.0001**	**1.59**	**1.37-1.84**	**<0.0001**

Bold values indicate significance at *P*-value <0.01. Italicized values indicate 0.1< *P*-value <0.05. N.B., Tables 3A, 3B, and 4 were derived from the same multivariable model treating time of transplantation as the starting point and each GvHD-related group as a time-dependent variable, although only particular comparisons are cited in each table. In Table 3A, patients with isolated UGI GvHD were set as the baseline comparator (HR =1.00). In Table 3B, patients without aGvHD were set as the baseline comparator (HR =1.00). Covariates, including those with significant impacts on transplant-related outcomes can be found in *Online Supplementary Table S2*. UGI: upper gastrointestinal. aGvHD: acute graft-*versus*-host disease.

Results

Patient characteristics and outcomes – entire cohort

A total of 8567 adult recipients of myeloablative allogeneic transplant with a T cell-replete PBSC or BM graft for AML, ALL, CML or MDS from 251 transplant centers were analyzed (*Online Supplementary Table S1A*). The median age of recipients was 42 years (range, 18-72). Indications for HSCT were AML/MDS (60%), ALL (21%), and CML (18%). Stem cells were from 6/6 HLA-matched siblings (49%), "well-matched" (38%), and "partially-matched" URDs (13%).[26] Donor/recipient pairings were female/male in 20%, and 71% of patients received PBSCs. All patients received a calcineurin inhibitor-based aGvHD prophylaxis regimen. Eleven and 12% received MMF or steroids for aGvHD prophylaxis, respectively.

For the entire population, 1-year survival was estimated at 62%, 1-year DFS at 52%, 1-year relapse at 29%, 100-day TRM at 11%, and incidence of cGvHD at 1 year at 43% (*Online Supplementary Table S1B*). Median follow-up of survivors was 71 months (range, 1-173). Given significant differences in rates of OS, DFS, TRM and cGvHD seen between MRD and URD recipients, these groups were analyzed separately.

Within the entire cohort, 2.7% of recipients had iUGI aGvHD (n=229). Overall 12.1% of recipients were documented as having any UGI aGvHD symptoms (Table 1). Rates of Grades II-IV aGvHD were 35.6% for MRD and 52.6% for URD recipients. Only 21.3% of patients recorded as having iUGI aGvHD had confirmation with a gastrointestinal biopsy; 42 of the 49 biopsies were consistent with aGvHD. Of patients with any UGI involvement, 38.0% were recorded as undergoing a GI biopsy, either upper or lower. Overall, rates of biopsies in those with UGI symptoms were higher than rates of skin, liver, or LGI biopsies. Only 11% of the 1904 patients biopsied had

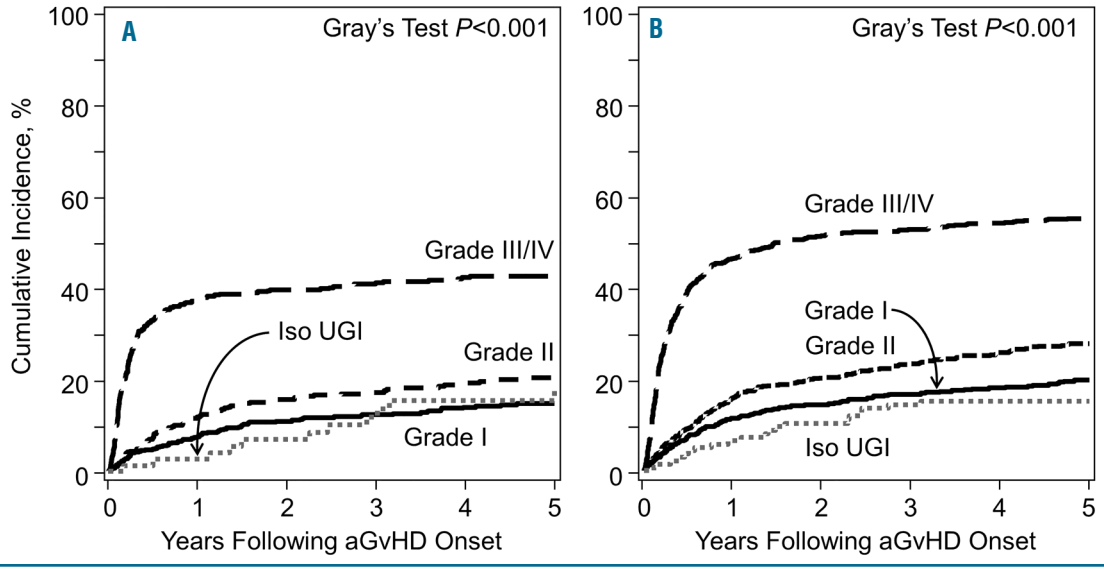

Figure 2. Treatment-related mortality for patients with isolated UGI aGvHD *versus* aGvHD without UGI symptoms. Cumulative incidence curves of TRM from time of aGvHD onset for patients with isolated UGI symptoms and subsets of patients with other grades of aGvHD without any UGI symptoms. A. Transplantation from a matched-related donor. B. Transplantation from a well-matched or partially-matched unrelated donor. UGI: upper gastrointestinal. aGvHD: acute graft-*versus*-host disease.

pathology reports submitted to the CIBMTR. Given the limiting numbers and reliability of biopsy-confirmed results, all subsequent analyses were conducted on the clinical grades reported. The timing of onset of UGI or any individual organ involvement was not captured in the CIBMTR database.

A notable feature of this cohort was the use of systemic steroids recorded in 79.8% of patients with maximum Grade I (skin-only) disease. In patients with iUGI or UGI symptoms plus Stage I or II skin disease (both Grade II) systemic steroids were received in 95.4% and 91.6% of cases, respectively (Table 1). Further data on timing and doses of therapeutic modalities/doses and response to therapy were not available.

Prognostic impact of isolated upper GI acute GvHD

Acute GvHD populations analyzed. In order to determine the optimal placement of iUGI aGvHD within the aGvHD grading system, we performed pairwise comparisons between patients with aGvHD starting from the time of transplantation: specifically, those with iUGI aGvHD *versus* those with Grades I, II (Stage 3 skin, Stage 1 liver or Stage 1 LGI), or III/IV aGvHD without UGI manifestations (*Online Supplementary Figure S1*). Notable differences in baseline characteristics included a higher percentage of patients without aGvHD receiving MRD grafts (59%) and a higher prevalence of partially-matched URD grafts among patients with Grades III/IV aGvHD (20%) *versus* those without aGvHD (10%), although significant differences in demographics were addressed *via* the respective statistical models (Table 2).

Overall Survival. There were no significant differences in survival between patients with iUGI aGvHD and those with Grades I or II aGvHD without UGI symptoms in univariate or multivariable analyses (Table 3A, Figure 1). As anticipated, patients with iUGI aGvHD had better survival than those with Grade III/IV aGvHD (MRD Hazard ratio (HR) 2.06, $P<0.0001$; URD HR 2.28, $P<0.0001$). Covariates with significant impacts on survival and other transplant-related outcomes in these analyses are reported in *Online Supplementary Table S2*.

Disease-free survival and relapse. There were no significant differences in DFS between patients with iUGI aGvHD and those with Grades I or II aGvHD, although there was a trend towards improved DFS in those with Grade I aGvHD after URD HSCT ($P=0.016$) (Table 3A). Patients experiencing Grade III/IV aGvHD demonstrated worse DFS (MRD HR 1.66, $P=0.0015$; URD HR 1.66, $P<0.0001$). There was no significant difference in relapse incidence between patients with iUGI aGvHD and those with other grades of aGvHD.

Treatment-related mortality and chronic GvHD. TRM was similar for patients with iUGI aGvHD, and those with Grades I or II aGvHD. Patients with Grade III/IV aGvHD had more TRM (MRD HR 3.39, $P<0.0001$; URD HR 3.91, $P<0.0001$) (Table 3A, Figure 2). The incidence of cGvHD after iUGI symptoms was similar to the incidence with Grades I or II aGvHD in MRD recipients. After URD HSCT, those with iUGI aGvHD had less frequent cGvHD than patients with Grade I (HR 1.38, $P=0.016$) and Grade II aGvHD (HR 1.59, $P=0.0004$).

Secondary analysis including patients without acute GvHD. In secondary analyses starting at the time of transplantation, pairwise comparisons were performed between patients without aGvHD and those with iUGI and Grades I, II and III/IV, recognizing that some patients in the "No aGvHD" group experienced early deaths related to TRM before the possible onset of aGVHD. In analyses for OS, DFS, TRM, and cGvHD incidence, outcomes after iUGI aGvHD were not significantly different from those of patients with no aGvHD (Table 3B). In comparison, patients with Grade II aGvHD without UGI symptoms trended towards worse TRM (MRD $P=0.0074$, URD $P=0.038$), and those with Grade I or II aGvHD had increased cGvHD than those without aGvHD (MRD and URD, all P-values ≤ 0.0002). Additionally, patients with

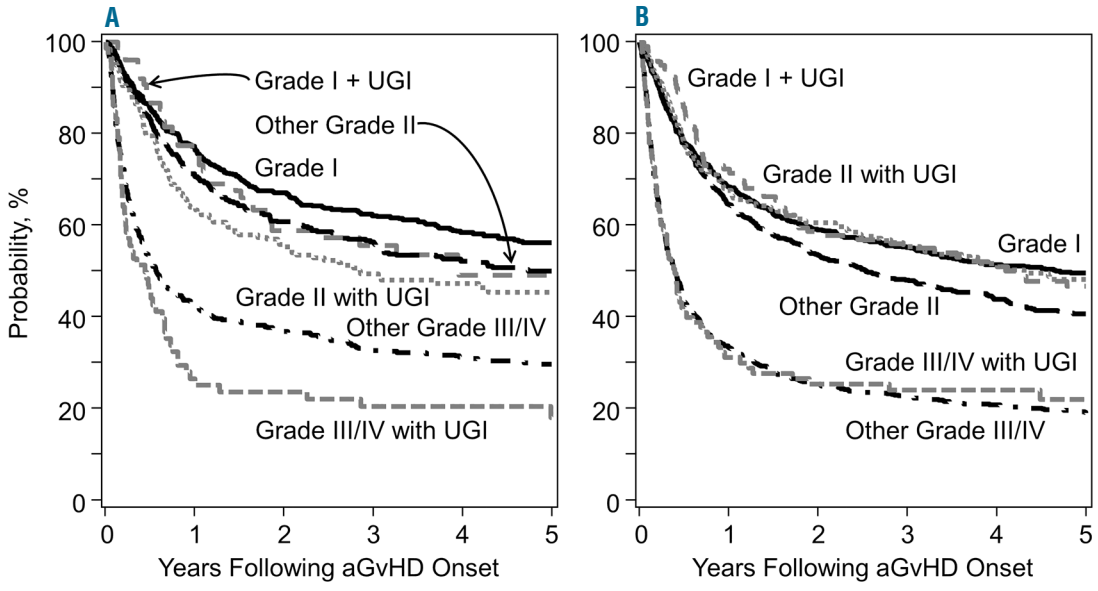

Figure 3. Overall survival for patients with aGvHD with or without UGI symptoms. Kaplan-Meier probabilities of overall survival from time of aGvHD onset for patients with various grades of aGvHD with or without any UGI symptoms. A. Transplantation from a matched-related donor. B. Transplantation from a well-matched or partially-matched unrelated donor. UGI: upper gastrointestinal. aGvHD: acute graft-*versus*-host disease.

Grade II aGvHD (non-UGI) symptoms tended to have inferior OS and DFS and higher TRM compared to those with Grade I aGvHD, particularly after URD HSCT (*data not shown*).

Prognostic impact of upper GI acute GvHD with additional GvHD involvement

Populations Analyzed. To investigate the prognostic impact of UGI aGvHD symptoms when present in addition to other manifestations, we performed pairwise comparisons between patients with aGvHD involving various organs without UGI involvement and those with similar organ involvement plus UGI symptoms. Significant differences in demographics between those who did and did not experience UGI symptoms at a given aGvHD grade, such as year of transplantation, were addressed in the statistical models (*Online Supplementary Table S3*).

Overall survival, disease-free survival, and relapse. There was no significant difference in OS, DFS or relapse between patients with aGvHD either with or without UGI symptoms within each aGvHD grade (Table 4, Figure 3). Inferior OS and DFS were seen after MRD HSCT when UGI symptoms were noted in addition to Grades III/IV disease, but this did not attain statistical significance (HR 1.39, *P*=0.027; HR 1.38, *P*=0.027, respectively). Of note, patients with Grade I skin-only aGvHD had similar outcomes to those with Stage 1-2 skin aGvHD plus UGI involvement (currently Grade II).

Treatment-related mortality and chronic GvHD. There was no difference in TRM between patients with aGvHD with or without UGI symptoms, with the exception that more severe TRM was seen for MRD recipients when UGI symptoms occurred in addition to Grades III/IV manifestations (HR 1.78, *P*=0.0028). Unlike what was observed during the initial description of UGI aGvHD, there was no consistent effect of additional symptoms of UGI aGvHD on the subsequent development of cGvHD, including in patients with otherwise skin-only Grade I aGvHD (MRD HR 1.00, *P*=1.00; URD HR 1.15, *P*=0.32) (Figure 4).

Prognosis of isolated UGI acute GvHD compared to Other Grade II organ involvement

In a secondary subset analysis, we analyzed patients who had Grade II manifestations other than UGI involvement, namely those who had skin-only Stage 3 disease (n=505), those who had liver involvement +/- any other non-UGI Grade II involvement (n=185), and those who had only LGI +/- skin disease (n=185). Those with liver disease tended to have been transplanted earlier, between 2000-2004; otherwise, the demographics were similar.

Compared to patients with iUGI aGvHD, only URD recipients with Grade II liver involvement had inferior OS (HR 1.68, *P*=0.0027) and TRM (HR 2.08, *P*=0.011) (*Online Supplementary Table S4*). No differences were seen between iUGI and other Grade II subgroups for any outcomes after MRD transplant. However, URD recipients from the groups with liver, LGI or skin involvement all showed increased rates of cGvHD over those with iUGI (all *P*-values <0.004).

Discussion

We embarked upon this analysis to expand on the observations of Weisdorf *et al*. derived from a single institution in 1990 regarding the incidence and prognostic impact of UGI aGvHD on clinical outcomes. Our population included adult recipients of MRD and well- or partially-matched URD T-cell replete HSCTs following myeloablative conditioning for AML, ALL, CML and MDS from the CIBMTR database. Rates of Grades II-IV aGvHD seen were 44.3%, consistent with historical experience.[30-32] Of the entire cohort, 2.7% experienced iUGI aGvHD (n=229) and 12.1% had UGI involvement. This

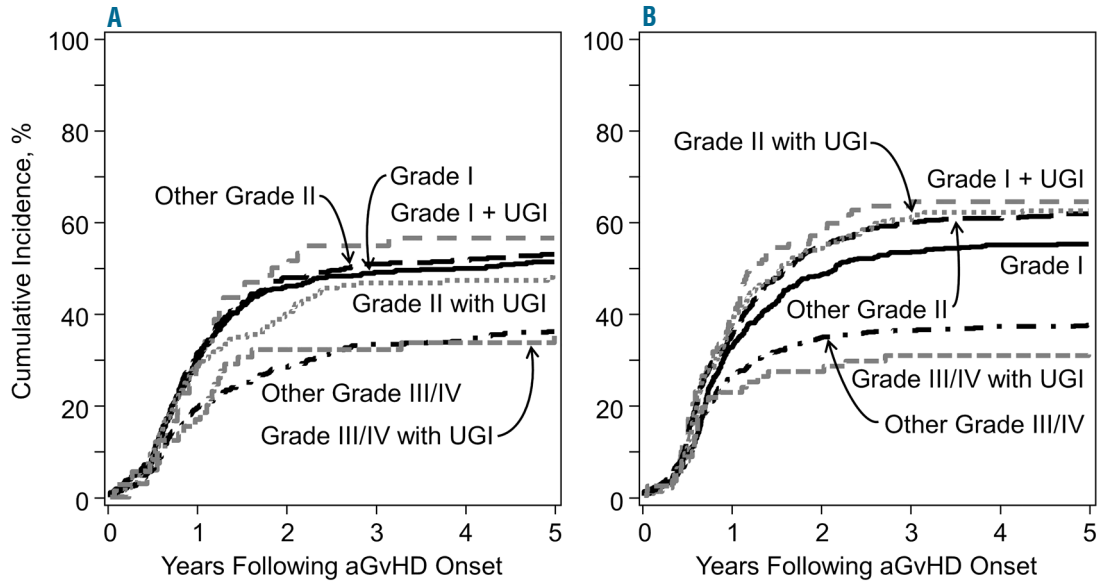

Figure 4. Cumulative incidence of cGvHD according to aGvHD grades and UGI symptoms. Cumulative incidence curves for cGvHD from time of aGvHD onset for patients with various grades of aGvHD with or without any UGI symptoms, as labeled. A. Transplantation from a matched-related donor. B. Transplantation from a well-matched or partially-matched unrelated donor. UGI: upper gastrointestinal. aGvHD: acute graft-*versus*-host disease.

incidence was similar to the 13% described after myeloablative MRD HSCT in 1990.[1] Among those who developed aGvHD, 20% had UGI involvement similar to the rates of 24-39% observed by others. The rate of isolated UGI symptoms among those with aGvHD was 4.4% compared with 6.7%, historically.[2,3,19,20,33]

Using this CIBMTR cohort, we sought to address two major questions. First, we sought to determine the correct placement of iUGI aGvHD, currently defined as Stage 1 GI and overall Grade II aGvHD. We found no differences in OS, DFS, relapse, TRM or cGvHD incidence between patients with iUGI and those with Grade I or Grade II aGvHD without UGI symptoms, and noted a reduced incidence of cGvHD after iUGI among URD recipients. Furthermore, in a limited secondary analysis, we noted no difference in outcomes comparing patients with iUGI aGvHD to those without aGvHD. Thus, we did not reproduce the initial findings by Weisdorf *et al.* that rates of cGvHD after iUGI were above those in Grades 0 and I aGvHD but similar to those after Grade II non-UGI GvHD.[1]

Next, we asked whether the presence of UGI when found in conjunction with other aGvHD manifestations impacted outcomes, specifically focusing on whether UGI symptoms in addition to Grade I skin-only disease yielded outcomes similar to Stage II disease (i.e., Skin Stage 3, Liver Stage 1, and LGI Stage 1). We found no impact on outcomes in early Grades I or II aGvHD, whereas documentation of UGI symptoms in addition to Grades III/IV aGvHD correlated with worse outcomes, particularly TRM, after MRD HSCT. Whether UGI symptoms severe enough to be diagnosed in the setting of Grade III/IV manifestations comprise the same entity and share the same pathology as iUGI cannot be ascertained, and the biologic rationale for this finding is unclear. However, these findings are unlikely to change the management of this patient group. Based on these analyses, our study does not show a significant prognostic impact of UGI aGvHD, in isolation or combination, on transplant-related outcomes and suggests that the classifying of UGI as a Grade II entity as it is currently diagnosed and reported might be incorrect.

The major limitations of this analysis, and any investigation of UGI aGvHD, are the difficulties surrounding diagnosis, lack of specificity of symptoms, unclear time of onset, and a seeming reluctance among transplant physicians to pursue or document biopsy confirmation of UGI involvement.[34] Anecdotally, individual transplant centers vary in UGI biopsy performance and reporting, especially when LGI symptoms are present.[35,36] In the study herein, only 61 of 251 participating centers reported a case of iUGI aGvHD. Among the 8567 patients included, only 1737 biopsies (20.3%) were documented. In patients with iUGI aGvHD specifically, 69% did not have a biopsy recorded. Therefore, the incidence may be under-reported in our database or confused with non-specific GI inflammation.

Perhaps most importantly, the above results are in the context of systemic steroid administration to 90% of patients with UGI aGvHD, with dose, duration of, and response to therapy not specified in this data set. It is highly possible that widespread use of systemic steroids is impacting outcomes in this group, especially as many have demonstrated that UGI aGvHD has higher response rates than other Grade II manifestations.[1,2,33] Therefore, we can only state that UGI aGvHD, when diagnosed, reported to the CIBMTR, and treated according to current standards of care across multiple institutions, does not impact prognosis. This is in contrast to all other manifestations of aGvHD, particularly Grades II-IV for which, despite treatment with systemic corticosteroids, occurrence is historically associated with worse outcomes.[10-12,33,37]

In our primary analyses, utilizing a multivariate model including all patient groups and starting from the time of

Table 4. Comparison of clinical outcomes in patients with aGvHD: pairwise comparisons between those without or with UGI symptoms.

	Matched Related Donor			Unrelated Donor		
Overall Survival	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
UGI + Skin Grade I (currently Grade II) *vs.* Skin Grade I only	1.10	0.77-1.58	0.58	1.04	0.80-1.37	0.76
Grade II plus UGI symptoms *vs.* Grade II without UGI	1.13	0.89-1.44	0.33	0.88	0.72-1.07	0.20
Grades III/IV plus UGI symptoms *vs.* Grades III/IV without UGI	*1.39*	*1.04-1.86*	*0.027*	1.13	0.88-1.45	0.33
Disease-free Survival						
UGI + Skin Grade I (currently Grade II) *vs.* Skin Grade I only	1.02	0.73-1.44	0.90	1.24	0.95-1.62	0.11
Grade II plus UGI symptoms *vs.* Grade II without UGI	1.25	0.99-1.58	0.056	0.92	0.76-1.12	0.40
Grades III/IV plus UGI symptoms *vs.* Grades III/IV without UGI	*1.38*	*1.04-1.84*	*0.027*	1.12	0.86-1.47	0.39
Relapse						
UGI + Skin Grade I (currently Grade II) *vs.* Skin Grade I only	1.01	0.68-1.52	0.94	1.30	0.95-1.78	0.11
Grade II plus UGI symptoms *vs.* Grade II without UGI	1.07	0.79-1.45	0.64	0.87	0.67-1.12	0.27
Grades III/IV plus UGI symptoms *vs.* Grades III/IV without UGI	1.22	0.77-1.94	0.39	0.86	0.53-1.38	0.53
Treatment-related Mortality						
UGI + Skin Grade I (currently Grade II) *vs.* Skin Grade I only	1.05	0.56-1.98	0.87	1.05	0.65-1.71	0.84
Grade II plus UGI symptoms *vs.* Grade II without UGI	1.43	0.99-2.07	0.059	1.06	0.78-1.44	0.72
Grades III/IV plus UGI symptoms *vs.* Grades III/IV without UGI	**1.78**	**1.22-2.60**	**0.0028**	1.38	0.99-1.93	0.058
Chronic GvHD						
UGI + Skin Grade I (currently Grade II) *vs.* Skin Grade I only	1.00	0.70-1.43	1.00	1.15	0.87-1.51	0.32
Grade II plus UGI symptoms *vs.* Grade II without UGI	0.79	0.67-1.01	0.064	0.86	0.70-1.07	0.17
Grades III/IV plus UGI symptoms *vs.* Grades III/IV without UGI	1.20	0.77-1.86	0.43	0.93	0.61-1.43	0.75

Bold values indicate significance at *P*-value <0.01. Italicized values indicate 0.01< *P*-value <0.05. N.B., Tables 3A, 3B, and 4 were derived from the same multivariable model treating time of transplantation as the starting point and each GvHD-related group as a time dependent variable, although only particular comparisons are cited in each table. UGI: upper gastrointestinal. GvHD: graft-*versus*-host disease.

HSCT, we did not cite patients who had no aGvHD as our primary baseline comparator, since that group included individuals who died of early TRM and were never at risk of aGvHD. Instead, all GvHD-related variables were treated as time-dependent variables. Kaplan-Meier and incidence curves for these groups were plotted from time of aGvHD onset. However, in a secondary analysis (Table 3B) we did show outcomes compared to patients without aGvHD. A landmark analysis to eliminate the confounder/competing risk of early death performed at 30 or 60 days from transplantation could have addressed this issue; however, many cases of aGvHD would have been excluded by doing so. Given the incidence of <3% for iUGI and multiple comparisons required, our cohort would not have had enough power to demonstrate statistically significant differences if we chose this statistical approach. While one might argue that the current analyses involving the iUGI group are underpowered, there is unlikely to be a larger dataset in which to perform such comparisons.

Additional limitations of this dataset and analysis include the exclusion of pediatric HSCT recipients,

patients with lymphoma and multiple myeloma, recipients of umbilical cord or haploidentical graft sources, and those undergoing reduced-intensity conditioning. These populations have different rates and potentially different manifestations of aGvHD and merit separate analyses.

Our data can lead in two directions. One, given current non-standardized reporting and treatment patterns, reclassification of patients with UGI GvHD as Grade I could be considered, with Grade I aGvHD generally considered to have few prognostic implications. In our cohort, that reclassification would impact 425 (20.4%) of the 2083 patients currently graded as Grade II. While this would not impact cases of "severe" aGvHD (Grades III-IV), patients with Grades II-IV aGvHD would decrease from 44.3% to 39.9%. Whether such a shift would significantly impact perceived incidence or outcomes of patients Grades II-IV aGvHD, for example, could be investigated by retrospective reanalysis of multicenter studies with GvHD as a major outcome, such as the BMT CTN trials 0201 or 0402 (*clinicaltrials.gov Identifiers: 00075816* and *00406393*).[31,38] Alternatively, an approach which downgrades UGI symptoms could be included in secondary analyses in the prospective PROGRESS 1 and 2 trials currently testing novel aGvHD prophylaxis strategies (*clinicaltrials.gov Identifiers: 02208037* and *02345850*), to assess impact. The implications of a change in grading include powering of future studies as well as interpretation of efficacy, given that major endpoints currently include seemingly non-informative events. Even just relabeling Stage 1 into, for example, 1a for UGI and 1b for LGI, might facilitate the tracking of UGI and LGI symptoms in future analyses.

Alternatively, the general HSCT field could move to a more standardized approach to diagnosis using regular endoscopy biopsies and more consistent pathologic reporting, with or without more detailed organ system reporting, such as in the Minnesota risk-adapted acute GvHD risk score.[2,39] Mehta *et al*. recently published a retrospective single center study in which all UGI aGvHD was confirmed by biopsy and treated in a similar manner with systemic steroids.[40] Patients with Grade II aGvHD consisted of 10% with iUGI, 33% with UGI + other organ involvement, and 57% with no UGI symptoms. In this study, although comparisons with Grade I aGvHD were not performed, all subsets of Grade II aGvHD had similar outcomes in terms of OS, DFS, non-relapse mortality (NRM), relapse and cGvHD. In contrast to our more "real-world" data set, this highly controlled analysis supports maintaining UGI aGvHD as a Grade 2 event. Analysis of this type of controlled data set which includes details on kinetics of individual manifestations, response to therapy, and infectious complications of therapy would be enlightening.

In summary, we challenge the field to revisit how UGI aGvHD is diagnosed, reported, graded and treated given that its current prognostic utility within the Consensus criteria is extremely limited. We would recommend highly standardized prospective trials involving endoscopic biopsies to explore whether system steroid therapy is required for these symptoms in isolation or with Grade I skin-only aGvHD. However, redefining UGI manifestations, especially as currently reported across multiple institutions, to a Grade I-defining entity and evaluating the impact on outcomes of large therapeutic trials of aGvHD prophylaxis and therapy should be considered.

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