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Clinical Outcomes and Healthcare Resource Utilization for Gastrointestinal Acute Graft-versus-Host Disease after Allogeneic Transplantation for Hematologic Malignancy: A Retrospective US Administrative Claims Database Analysis

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A B S T R A C T

Graft-versus-host disease (GVHD) is the leading cause of nonrelapse mortality among patients who receive allogeneic hematopoietic cell transplantation (allo-HCT). In its acute form (aGVHD), GVHD involves the skin, liver, and gastrointestinal (GI) tract, with GI involvement most strongly associated with poor prognosis. This retrospective cohort study used US healthcare claims data for 2008 to 2015 to identify patients who developed GI aGVHD after allo-HCT performed as curative treatment for hematologic malignancy and compared them with patients who did not develop aGVHD in terms of outcomes related to survival, infections, healthcare resource utilization (HRU), and costs. Whereas the patients without aGVHD saw a 66% improvement in 1-year survival between 2009 and 2015, this effect was not observed in patients with GI aGVHD. Compared with patients without evidence of aGVHD, patients with GI aGVHD were 3.9-fold more likely to develop an infection in the year after allo-HCT. Similarly, patients who developed GI aGVHD were 4.3-fold more likely to have an inpatient admission after allo-HCT discharge, and such an admission cost on average 47% more than an admission for patients without aGVHD. Our findings confirm that GI involvement in aGVHD is associated with higher mortality, risk of infection, HRU, and cost compared with absence of aGVHD.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (allo-HCT) is used to treat a variety of malignant and nonmalignant diseases and remains the sole curative option for many hematologic malignancies [1]. Despite the significant progress made in the field of hematopoietic cell transplantation in recent years, use of this life-saving therapy is limited by the risk of relapse and serious transplantation-related complications, such as infection, major organ dysfunction, and acute and/or chronic graft-versus-host disease (GVHD) [2]. One-year overall survival after allo-HCT can be as low as 45% and may be impacted by various patient- and procedure-related factors, including underlying diagnosis and disease status, conditioning regimen, donor-recipient histocompatibility, donor type, graft source, occurrence of GVHD, and supportive therapies [2-4].

A major contributor to the low success of allo-HCT is the immunologic complication of GVHD, which develops post-transplantation when immunocompetent donor T cells recognize recipient alloantigens as foreign. Despite the development of multiple strategies to prevent or curb GVHD, this complication still occurs in 30% to 80% of allo-HCT recipients [4,5] and has 2 primary clinical manifestations: acute and chronic. Acute GVHD (aGVHD) usually occurs within 100 days post-transplantation and presents with any combination of skin erythema, maculopapular rash, nausea, vomiting, anorexia, profuse watery or bloody diarrhea, ileus, and cholestatic liver disease [6].

aGVHD is graded from I to IV, reflecting clinical severity, and is assessed by the degree of involvement of the 3 principal target organs: the skin, liver and gastrointestinal (GI) tract [7]. Although the skin is the most commonly and often the earliest affected organ, involvement of the GI tract is the second most frequently affected site and portends a poor prognosis [8].

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Clinical features of GI aGVHD include voluminous secretory diarrhea, crampy abdominal pain, and upper GI symptoms such as nausea, vomiting, and anorexia [9,10].

Systemic steroid therapy, occasionally supplemented by oral topical beclomethasone dipropionate, is the generally accepted first line of treatment [11], but approximately 30% to 60% of patients fail to respond and require additional therapies [12-15]. For steroid- refractory patients, the overall survival at 2 years is <20% [12], and currently there are no approved second-line therapies [16]. Multiple treatments have been used off-label in this setting with rather limited success, including anti-T cell antibodies (eg, ATG, alemtuzumab), T cell-suppressive drugs (eg, mycophenolic acid, sirolimus), anticytokine biological agents (eg, TNF-α, IL-6), and a variety of others (eg, pulse cyclophosphamide, PUVA, extracorporeal photopheresis, vedolizumab, Janus-kinase inhibitors) that cause additional progressive immunosuppression, thereby significantly increasing the risk of infection and mortality [16,17].

Identified risk factors for aGVHD-related mortality apart from steroid resistance include older age, overt GI bleeding, low serum albumin, and elevated serum bilirubin [18]. Lower GI involvement (ie, small intestine and colon) has been shown to be an independent predictor of a reduced likelihood of response to steroid therapy, as well as a decreased probability of 1-year survival [19,20]. Even with appropriate treatment, the 1-year nonrelapse mortality for patients with aGVHD ranges from 20% to 37%, depending on severity [21].

Given the limited literature describing the clinical outcomes of GI aGVHD and associated healthcare resource utilization (HRU) and costs in the real world, it is important to review available data in this setting to better understand clinical outcomes and costs of treating this very sick patient population. In this retrospective analysis of US administrative claims data, we investigated real-world clinical outcomes in patients with hematologic cancer undergoing allo-HCT, including those who developed GI aGVHD and those who did not develop GI aGVHD. This analysis also examined the HRU and costs of patients who underwent allo-HCT and subsequently experienced GI aGVHD, including the number of hospitalizations and the average length of inpatient stay.

METHODS

Data Sources

This retrospective, observational, US administrative claims-based study used data from the IBM MarketScan Commercial Claims and Encounters database (Commercial), the MarketScan Medicare Supplemental and Coordination of Benefits database (Medicare Supplemental) and the Social Security Administration Death Master File (SSA DMF) for the period July 1, 2008, to September 30, 2016. Each MarketScan database contains the pharmacy and medical (inpatient and outpatient) claims of its respective populations. Claims data are available for approximately 40 million individuals annually who were covered by a geographically diverse group of self-insured employers and private insurance plans across the United States. The MarketScan databases were further linked to the SSA DMF to obtain data on patient deaths.

All study data were accessed with protocols compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996 regulations. Because all databases used in the study are fully deidentified and compliant with the HIPAA, this study was exempted from Institutional Review Board approval.

Study Design and Population

The study included patients with at least 1 inpatient claim with an allo-HCT procedure code (see Supplementary Table 1) in any position during the identification period of January 1, 2009, to October 1, 2015. The date of the first allo-HCT code was defined as the index date. Patients were included whose qualifying allo-HCT procedure resulted in at least 18 days of inpatient hospitalization. This cutoff value was determined after reviewing the distribution of inpatient hospital stays for allo-HCT recipients.

Eligible patients met the following criteria: (1) preexisting hematologic malignancy; (2) continuous enrollment with medical and pharmacy benefits for 6 months before the index date; (3) eligible for linking with the SSA DMF; and (4) discharged alive from their index allo-HCT hospitalization. Patients were observed for a variable follow-up period starting from the index allo-HCT date and ending at death or censoring. Patients were censored on disenrollment, at the end of the study period (September 30, 2016), or at 1 year after allo-HCT.

Using the codes listed in Supplementary Table 1, eligible patients were first divided into 2 cohorts: patients diagnosed with aGVHD (aGVHD cohort) and those not diagnosed with aGVHD (no-aGVHD cohort). A subset of patients with aGVHD were further classified into those developing GI aGVHD. To identify patients with GI aGVHD, an algorithm was devised that uses diagnostic coding in the following groups of intestinal symptoms: ileus, hematochezia (ie, passage of fresh blood in stools), acute abdomen, abdominal pain, vomiting, diarrhea, anorexia, dyspepsia, nausea, and early satiety. Each symptom was assigned a severity score of 1 to 4. Patients with a total severity score of ≥3 were classified as having intestinal aGVHD. Based on the assigned scores, patients with paralytic ileus, hematochezia, acute abdomen, ileus, and/or bilious or projectile vomiting or vomiting of fecal matter were de facto considered to have intestinal aGVHD (Table 1). Detailed coding can be found in Supplementary Table 2.

Study Variables

Baseline demographic characteristics, including age, sex, US geographic region, insurance type, payer and year of allo-HCT procedure were assessed on the index date. The duration of follow-up from index date until death or date of censoring was also recorded. Baseline clinical characteristics, including indication for allo-HCT, Deyo-Charlson Comorbidity Index (DCCI), and the presence of comorbid conditions of interest (ie, inflammatory bowel diseases, moderate/severe hepatic disease, arrhythmia, and morbid obesity) were assessed over the 6-month pre-index period. The Charlson Comorbidity Index (CCI) was developed to predict the risk of death within 1 year of hospitalization for patients with specific comorbid conditions. This study used the DCCI, a modification of the CCI that has been adapted for use with administrative data [22].

Outcome Measures

Outcome measures assessed included overall mortality, type and proportion of patients with infections (ie, respiratory, nervous system, digestive system, other bacterial, viral, fungal, and parasitic diseases), HRU, and costs.

Table 1
Algorithm to Define GI aGVHD

Description	Category	Severity, 1-4 (high)
Paralytic ileus	PILEUS	4
Blood in stool (hematochezia)	STOOL	4
Melena (hematochezia)	STOOL	4
Acute abdomen	ACUAB	3
Ileus, unspecified	ILEUS	3
Bilious vomiting	SVOMIT	3
Projectile vomiting	SVOMIT	3
Vomiting of fecal matter	SVOMIT	3
Abdominal pain, epigastric	ABPAIN	2
Abdominal pain, generalized	ABPAIN	2
Abdominal pain, left lower quadrant	ABPAIN	2
Abdominal pain, left upper quadrant	ABPAIN	2
Abdominal pain, other specified site	ABPAIN	2
Abdominal pain, periumbilical	ABPAIN	2
Abdominal pain, right lower quadrant	ABPAIN	2
Abdominal pain, right upper quadrant	ABPAIN	2
Abdominal pain, unspecified site	ABPAIN	2
Anorexia	ANORX	2
Diarrhea	DIAR	2
Nausea with vomiting	VOMIT	2
Vomiting alone	VOMIT	1
Vomiting without nausea	VOMIT	1
Vomiting, unspecified	VOMIT	1
Dyspepsia and other specified disorders of stomach function	DYSP	1
Nausea	NAUS	1
Nausea alone	NAUS	1
Early satiety	EARL	1

PILEUS indicates paralytic ileus; *STOOL*, hematochezia; *ACUAB*, acute abdomen; *ILEUS*, ileus; *SVOMIT*, severe vomiting; *ABPAIN*, abdominal pain; *ANORX*, anorexia; *DIAR*, diarrhea; *VOMIT*, vomiting; *DYSP*, dyspepsia. *NAUS*, nausea; *EARL*, early satiety.

Table 2
Demographics

Variable	All Patients (N = 1215)		All aGVHD Cohort (N = 542)		GI aGVHD Cohort (N = 327)		No-aGVHD Cohort (N = 673)	
Age, yr, mean ± SD	50.4 ± 14.6		50.3 ± 14.5		50.1 ± 15.0		50.5 ± 14.6	
Age category, n (%)								
<18 yr	52	(4.2)	22	(4.1)	15	(4.6)	30	(4.5)
18-39 yr	181	(14.9)	86	(15.9)	55	(16.8)	95	(14.1)
40-59 yr	617	(50.8)	275	(50.7)	162	(49.5)	342	(50.8)
≥60 yr	365	(30.1)	159	(29.3)	95	(29.1)	206	(30.6)
Male sex, n (%)	694	(57.1)	309	(57.0)	186	(56.9)	385	(57.2)
US geographic region, n (%)								
Northeast	263	(21.6)	102	(18.8)	67	(20.5)	161	(23.9)
North Central	339	(27.9)	148	(27.3)	85	(26.0)	191	(28.4)
South	429	(35.3)	187	(34.5)	115	(35.2)	242	(36.0)
West	184	(15.1)	105	(19.4)	60	(18.3)	79	(11.7)
Payer, n (%)								
Commercial	1086	(89.4)	483	(89.1)	285	(87.2)	603	(89.6)
Medicare	129	(10.6)	59	(10.9)	42	(12.8)	70	(10.4)
Year of allo-HCT, n (%)								
2009	143	(11.8)	55	(10.1)	31	(9.5)	88	(13.1)
2010	161	(13.3)	56	(10.3)	35	(10.7)	105	(15.6)
2011	165	(13.6)	68	(12.5)	40	(12.2)	97	(14.4)
2012	189	(15.6)	83	(15.3)	40	(12.2)	106	(15.8)
2013	211	(17.4)	104	(19.2)	63	(19.3)	107	(15.9)
2014	195	(16.0)	93	(17.2)	66	(20.2)	102	(15.2)
2015	151	(12.4)	83	(15.3)	52	(15.9)	68	(10.1)
Length of follow-up, mo, mean ± SD	9.48 ± 3.66		9.66 ± 3.45		9.57 ± 3.34		9.33 ± 3.83	
Indication for allo-HCT procedure, n (%)								
Acute myelogenous leukemia	767	(63.1)	346	(63.8)	213	(65.1)	421	(62.6)
Acute lymphoblastic leukemia	345	(28.4)	161	(29.7)	106	(32.4)	184	(27.3)
Myelodysplastic syndrome	373	(30.7)	170	(31.4)	100	(30.6)	203	(30.2)
Multiple myeloma and plasma cell neoplasms	148	(12.2)	64	(11.8)	34	(10.4)	84	(12.5)
Chronic lymphocytic leukemia	139	(11.4)	60	(11.1)	39	(11.9)	79	(11.7)
Other*	15	(1.2)	8	(1.5)	7	(2.1)	7	(1.0)
DCCI, n (%)								
0	72	(5.9)	32	(5.9)	15	(4.6)	40	(5.9)
1	26	(2.1)	11	(2.0)	5	(1.5)	15	(2.2)
2	639	(52.6)	265	(48.9)	154	(47.1)	374	(55.6)
3+	478	(39.3)	234	(43.2)	153	(46.8)	244	(36.3)

* Includes lymphosarcomas and other connective tissue and soft tissue neoplasms.

To align with the definition of acute GVHD developing within 100 days of allo-HCT, HRU and costs were measured in the first 100 days after allo-HCT and reported across the following: inpatient hospitalizations, emergency room (ER) visits, ambulatory visits, hospital outpatient visits, and GI-specific diagnostic procedures. Healthcare costs were also assessed for outpatient pharmacy costs. All costs were adjusted to 2016 US dollars using the medical care component of the Consumer Price Index [23].

Statistical Analysis

Descriptive statistics were calculated for demographic characteristics, clinical characteristics, and all outcome measures. Categorical variables are presented as count and percentage; continuous variables, mean ± SD. Statistical tests of significance were conducted between the GI aGVHD cohort and the no-aGVHD cohort, using the chi-square test for categorical variables and the dependent *t* test for continuous variables.

Individual multivariate models were built to assess overall survival, length of stay (LOS) if hospitalized, and the probabilities of bacterial infection, cytomegalovirus (CMV) infection, aspergillus infection, GI aGVHD, inpatient admission, and emergency department visit. In addition, models were built to assess costs in the first 100 days for total healthcare, index inpatient admission, and subsequent inpatient admission(s). The main explanatory item of interest was patient cohort (ie, GI aGVHD versus no aGVHD, except when GI aGVHD was the outcome modeled). Additional explanatory items in each model included patient baseline demographic factors and clinical characteristics. Survival was analyzed with Cox proportional hazards regression (with the proportionality assumption upheld). All other outcomes were analyzed with generalized linear regression. The error distribution was a negative binomial with log link for the LOS outcome and a binomial with logit link for all other outcomes. The α level for all statistical tests was .05.

RESULTS

Baseline Demographic and Clinical Characteristics

A total of 1215 patients with a hematologic malignancy were identified as eligible for linking with the SSA death file and discharged alive from allo-HCT. Among them 542 (44.6%) developed aGVHD and 673 (55.4%) had no evidence of aGVHD (Figure 1). Of the 542 patients with aGVHD, approximately 60% had GI involvement (n = 327) according to the algorithm for GI involvement outlined in Table 1.

The mean age of patients included in the analysis was 50 ± 15 years irrespective of aGVHD status. On average, across all cohorts, 57% of the patients were male and had commercial insurance (87.2% to 89.6%). Mean duration of follow-up for all patients was 9.48 ± 3.66 months (Table 2).

There was a similar distribution in most common underlying malignancies between patients who went on to develop GI aGVHD compared with those who did not develop aGVHD: acute myelogenous leukemia (65.1% versus 62.6%), acute lymphoblastic leukemia (32.4% versus 27.3%), myelodysplastic syndrome (30.6% versus 30.2%), chronic lymphocytic leukemia (11.9% versus 11.7%), multiple myeloma and plasma cell neoplasms (10.4% versus 12.5%), and other (including lymphosarcomas and other connective tissue and soft tissue neoplasms; 2.1% versus 1.0%) (Table 2).

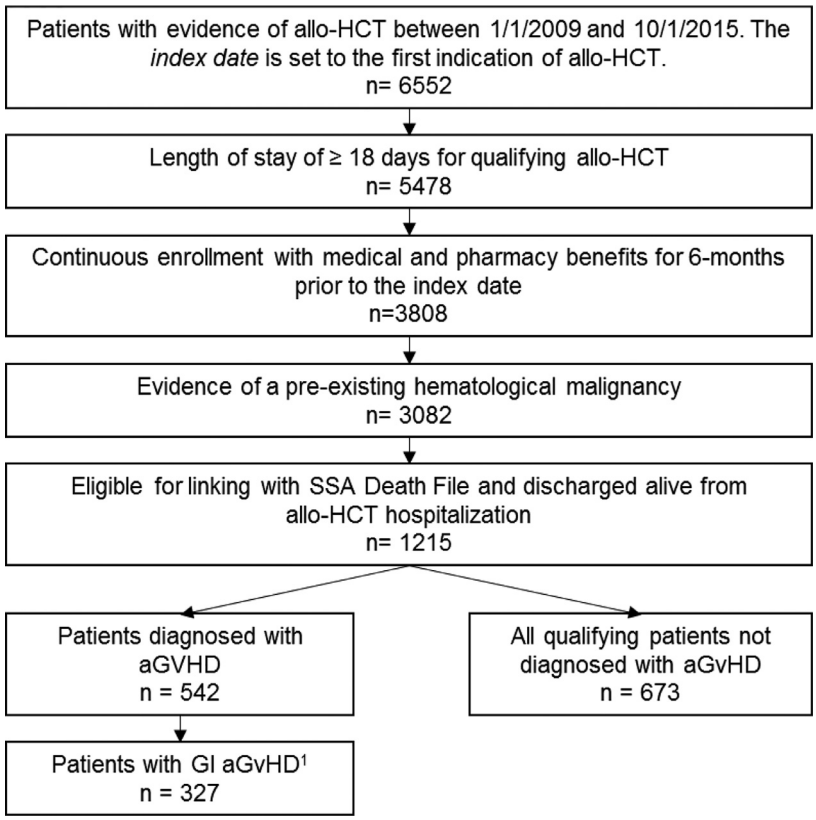

Figure 1. Patient selection. [1]Patients scoring ≥3 using the GI aGVHD symptom severity algorithm.

Risk of Developing GI aGVHD and Probability of Overall Survival

The proportion of patients who developed GI aGVHD increased from 22% in 2009 to 34% in 2015 (Table 2). After controlling for patient baseline demographic factors and clinical characteristics, in the pairwise comparison to 2009, the risk of developing GI aGVHD versus no aGVHD was 1.65 (95% CI, 0.93 to 2.93). Age, sex, and underlying malignancy were also not statistically associated with an increased risk of developing GI aGVHD (Table 3). The results for the full risk model and all other models developed for this study are provided in Supplementary Table 3.

Mortality was higher in the aGVHD cohort compared with the no-aGVHD cohort during study follow-up (27.8% versus 19.6%; P = .003) (Figure 2A). Multivariate analysis showed a 66% decrease in the likelihood of dying within 1 year of allo-HCT procedure between 2009 and 2015 for the no-aGVHD cohort (hazard ratio [HR], .34; 95% CI, .19 to .62; $P < .001$), but not for the GI aGVHD cohort (HR, .63; 95% CI, .36 to 1.10; $P = .10$) (Figure 2B).

Table 3
Probability of Developing GI aGVHD

Variable	OR	Lower 95% CL	Upper 95% CL	*P* Value
Age (10-yr increase)	0.94	0.84	1.05	.3061
Female (versus male)	0.98	0.74	1.29	.8733
Indication for allo-HCT procedure*				
Acute myelogenous leukemia	1.09	0.80	1.49	.5783
Acute lymphoblastic syndrome	1.28	0.92	1.79	.1366
Myelodysplastic syndrome	1.20	0.86	1.69	.2800
Multiple myeloma/plasma cell neoplasms	0.98	0.62	1.55	.9365
Chronic lymphocytic leukemia	1.20	0.76	1.89	.4294
Other hematologic malignancy	2.93	0.95	8.99	.0608
Year of transplantation (versus 2009)				
2015	1.65	0.93	2.93	.0845
2014	1.66	0.98	2.82	.0616
2013	1.41	0.83	2.40	.1997
2012	0.93	0.53	1.65	.8087
2011	1.08	0.61	1.91	.7815
2010	0.82	0.46	1.46	.4986

* Reference is the subset of patients who did not have the condition indicated.
CL indicates confidence level.

Infection Outcomes

During the follow-up period, the rate of infections were higher in patients who developed GI aGVHD compared with those who did not develop aGVHD (Table 4). More than twice as many patients in the GI aGVHD cohort were diagnosed with a viral infection than those in the no aGVHD cohort (47.7% versus 22.0%; $P < .001$); in particular, the incidence of CMV infections was 22.5% higher in the GI aGVHD cohort (38.8% versus 16.3%; $P < .001$). Likewise, the incidence of fungal infections in general was higher in the GI aGVHD cohort (35.8% versus 20.8%; $P < .001$) and aspergillosis in particular (7.0% versus 3.9%; $P = .03$).

In multivariate analysis, patients in the GI aGVHD cohort were 2.4 times more likely than the no-aGVHD cohort to have any type of bacterial infection ($P < .001$) and 3.2 times more likely to have a CMV infection ($P < .001$) within 1 year of the allo-HCT procedure (Figure 3). After adjusting for potential confounders, there was no statistically significant difference in the likelihood of aspergillosis between the 2 cohorts ($P = .10$) (Supplementary Table 3).

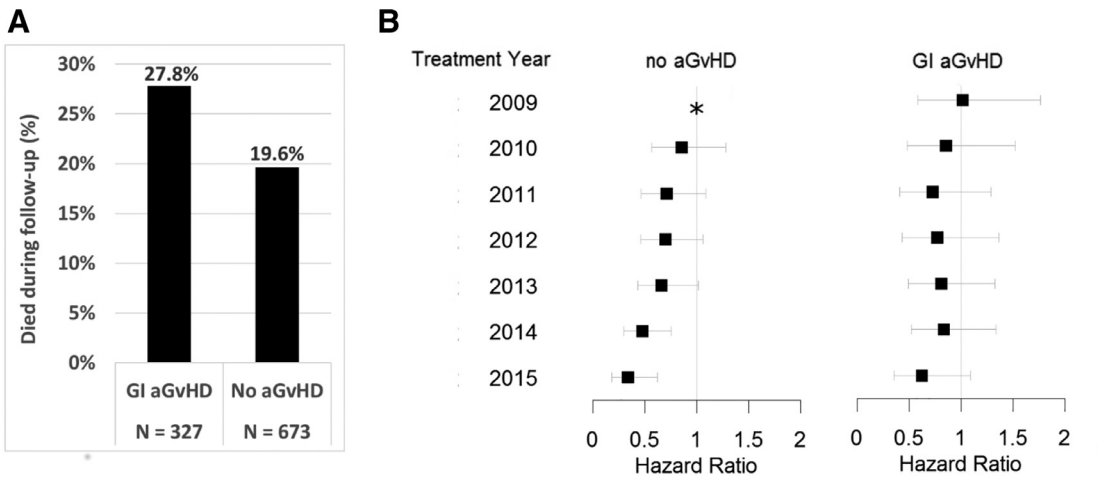

Figure 2. (A) Unadjusted percentage of patients in each cohort who died during follow-up. (B) HRs for survival (time to death) by cohort and index year. *Indicates the reference group.

Unadjusted HRU and Costs

Although HRU was high for all the allo-HCT recipients, patients in the GI aGVHD cohort were more likely than those in the no-aGVHD cohort to have a subsequent hospitalization, ER visit, ambulatory visit and other outpatient visit following discharge from their allo-HCT and had more frequent utilization than patients (Table 5). The average LOS for index allo-HCT hospitalization was 4 days longer for the GI aGVHD cohort compared with the no aGVHD cohort ($P < .003$). Within the first 100 days, patients who developed GI aGVHD were more likely to be readmitted to the hospital (59.9% versus 32.5%; $P < .001$) and had more frequent ambulatory visits (33.5 ± 20.9 visits versus 27.8 ± 18.2 visits; $P < .001$) than patients who did not develop aGVHD.

The unadjusted total healthcare cost was significantly higher in the first 100 days post- index for GI aGVHD patients ($384,607 ± $296,210) compared to the patients who did not develop aGVHD: ($295,529 ± $202,206) ($P = .003$) (Table 5). The cost of index allo-HCT hospitalization was $30,871 higher per patient in the GI aGVHD cohort ($P < .001$). In the first 100 days post-index, patients in the GI aGVHD cohort spent on average $43,790 more on subsequent inpatient hospitalizations, $8,533 more on ambulatory visits, and $1,607 more on outpatient pharmacy purchases.

Adjusted HRU and Costs

The adjusted odds of inpatient admission, ER visit, and inpatient LOS (in days) for the GI aGVHD cohort versus the no aGVHD cohort were estimated with multivariate modeling (Figure 4). Compared with the no-aGVHD, patients in the GI aGVHD cohort were 4.3 times more likely to have a subsequent inpatient hospitalization following allo-HCT procedure ($P < .001$) and 1.78 times more likely to have an ER visit after discharge ($P < .001$). Among those who had a subsequent inpatient admission, patients in the GI aGVHD cohort were hospitalized 82% longer than those in the no aGVHD cohort ($P < .001$).

After adjusting for baseline demographic and clinical characteristics, patients who developed GI aGVHD spent on average 28% more on total healthcare costs in the first 100 days ($P < .001$) than patients who did not develop aGVHD (Figure 4).

Table 4
Incidence of Infections During the Follow-Up Period after Allo-HCT (N = 327)

Infection	aGVHD Cohort (N = 375), n (%)	No-aGVHD Cohort (N = 673), n (%)	*P* Value
Any infection	301 (92.1)	495 (73.6)	<.001
Respiratory infections	190 (58.1)	303 (45.0)	<.001
Nervous system infections	12 (3.7)	16 (2.4)	.245
Digestive system infections	23 (7.0)	18 (2.7)	.001
Intestinal infectious diseases	102 (31.2)	106 (15.8)	<.001
Other bacterial diseases	178 (54.4)	225 (33.4)	<.001
Viral infections of interest	156 (47.7)	148 (22.0)	<.001
CMV infection	127 (38.8)	110 (16.3)	<.001
Fungal infections	117 (35.8)	140 (20.8)	<.001
Aspergillosis	23 (7.0)	26 (3.9)	.029
Other infectious and parasitic diseases	8 (2.5)	19 (2.8)	.730

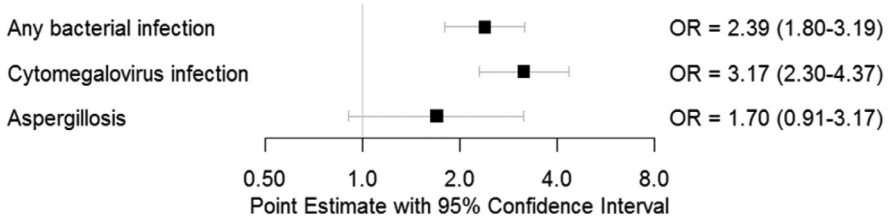

Figure 3. Adjusted odds of developing any bacterial infection, CMV infection, or aspergillosis for patients who developed GI aGVHD compared with those who did not develop aGVHD.

The index hospital admission cost on average 13% more (P = .002) for the GI aGVHD cohort, and they spent 47% more on subsequent admissions within the first 100 days (P = .001).

DISCUSSION

The results presented here confirm and extend the existing literature linking the occurrence of acute GVHD with higher mortality and risk of infections (bacterial, viral, and fungal) and provide unique insight into HRU and costs from a real-world claims database [24-27].

The GI tract is a major target organ in aGVHD, and inflammation and damage to the GI tract is a major mechanism for the development and amplification of systemic aGVHD [8]. Most of the fatal cases of aGVHD involve severe lower GI GVHD [2]. Patients with acute lower intestinal GVHD experience substantial symptoms, often voluminous secretory watery or bloody diarrhea, abdominal pain, and GI bleeding [28]. The true proportion of patients who develop acute GI GVHD is difficult to determine from the published literature. Martin et al [10] reported an overall proportion of approximately 60% to 70% of patients with grade II-IV aGVHD in a study of allo-HCT recipients with sibling donors diagnosed between 1985 and 2001. In a study of patients diagnosed between 2005 and 2011, Bhutani et al [29] reported GI aGVHD in 32% of allo-HCT recipients.

In this US claims analysis of 1215 allo-HCT recipients with an underlying hematologic malignancy undergoing transplantation between 2009 and 2015, 44.6% of patients developed aGVHD. The GI tract was involved in 60% of patients with aGVHD, which equates to approximately 27% of the total study cohort. Although grading is not available in claims data, it is reasonable to assume patients in the GI aGVHD cohort in this study have grade II-IV aGVHD based on the algorithm that we used. However, we are not able to determine the proportions by grade or by stage. There was a trend toward an increasing risk of developing GI aGVHD during the years of the study; however, survival did not improve for this cohort. It can be speculated that this is related to the increasing number of alternative donor transplants and in the experimental procedures in the current era.

In this study, among allo-HCT recipients with a hematologic malignancy who were discharged alive from the hospital, the survival rate was 72.7% in those who developed GI aGVHD, compared with 80.4% in those who did not develop aGVHD. This finding is consistent with a recent study using data from the Center for International Blood and Marrow Transplant Research that found a 40% to 70% 1-year survival rate in patients (N = 1446) who developed grade II-IV aGVHD treated between 2006 and 2012 [30].

The proportion of patients who did not develop aGVHD among the total group of 1215 patients remained steady across the study period, and their survival improved significantly, by 66%, consistent with improvement in supportive care measures for transplant recipients. In contrast to our findings, Khoury et al [30] examined outcomes following a diagnosis of grade II-IV aGVHD by time period and explored effects according to original prophylactic regimen and grade. There was a decrease in the proportion of grade III-IV aGVHD over time (from 56% for 1999 to 2001 to 47% for 2002 to 2005 and 37% for 2006 to 2012), which is reflective of the longer time period analyzed compared with our study which is a more contemporary analysis.

In this study, we observed a higher proportion of infections in the GI aGVHD cohort compared with the no-aGVHD

Table 5
Unadjusted HRU and Costs in the First 100 Days

Variable	GI aGVHD Cohort (N = 327)		No-aGVHD Cohort (N = 673)		*P* Value
LOS for index allo-HCT hospitalization, d, mean ± SD	36.0 ± 23.4		32.1 ± 17.3		.003
Healthcare utilization in the first 100 days					
Patients with ≥1 subsequent inpatient hospitalization, n (%)	196	(59.9)	219	(32.5)	<.001
Number of subsequent inpatient hospitalizations, mean ± SD	0.9 ±	1.0	0.5 ±	0.8	<.001
Subsequent inpatient hospitalization LOS, d, mean ± SD	15.2 ±	20.9	7.9 ±	15.0	<.001
Patients with ≥1 ER visit resulting in inpatient admission, n (%)	79	(24.2)	111	(16.5)	.004
Number of ER visits, mean ± SD	0.4 ±	0.8	0.3 ±	0.7	.011
Patients with at least 1 ambulatory visit, n (%)	326	(99.7)	654	(97.2)	.008
Number of ambulatory visits, mean ± SD	33.5 ±	20.9	27.8 ±	18.2	<.001
Patients with ≥ 1 hospital outpatient visit, n (%)	322	(98.5)	644	(95.7)	.023
Number of hospital outpatient visits, mean ± SD	18.7 ±	12.1	15.2 ±	11.3	<.001
Patients with ≥ 1 endoscopy or colonoscopy, n (%)	189	(57.8)	123	(18.3)	<.001
Total healthcare costs in the first 100, $, mean ± SD	384,607 ±	296,201	295,520 ±	202,261	<.001
Inpatient costs for index allo-HCT, $, mean ± SD	261,659 ±	230,788	226,482 ±	177,222	.008
Inpatient costs for subsequent hospitalizations, $, mean ± SD	70,282 ±	163,800	26,492 ±	84,521	<.001
ER costs, $, mean ± SD	183 ±	707	257 ±	1091	.261
Ambulatory visit costs, $, mean ± SD	36,530 ±	42,869	27,997 ±	31,987	<.001
Costs for any hospital-based outpatient visit, $, mean ± SD	34,292 ±	41,605	26,089 ±	30,988	<.001
Other outpatient costs, $, mean ± SD	6726 ±	10,667	6673 ±	10,413	.94
Outpatient pharmacy costs, $, mean ± SD	9226 ±	7684	7619 ±	7259	.001

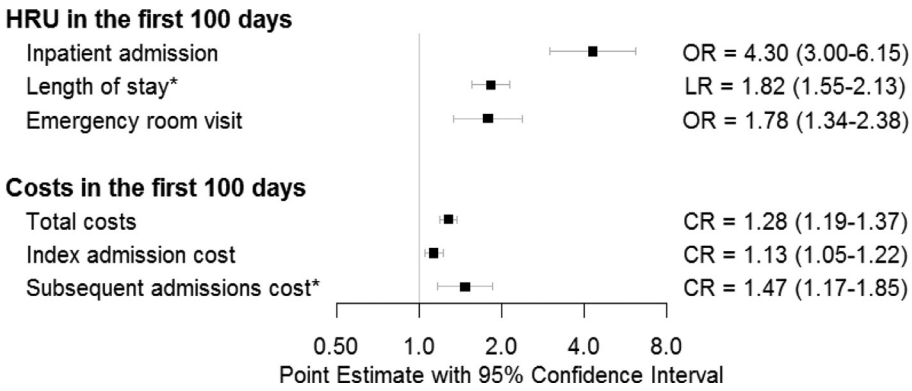

Figure 4. Adjusted HRU and costs for patients who develop GI aGVHD and those who do not develop GVHD. *Compared only among patients with at least 1 subsequent admission. *LR*, length of stay ratio.

cohort (92% versus 74%), consistent for bacterial, viral, and fungal infections. Compared with patients in the no-aGVHD cohort, patients in the GI aGVHD cohort were 2.4 times more likely to develop any bacterial infection and 3.2 times more likely to develop CMV infection. Although the difference was not statistically significant, patients in the GI aGVHD cohort were 1.7 times more likely to develop aspergillosis. Other studies have similarly demonstrated an increased risk of opportunistic infections associated with GI aGVHD [31-34]. This increased risk of infection in patients with GI aGVHD is likely multifactorial and is linked to the use of corticosteroids and other forms of immunosuppressive interventions and a consequence of underlying breakdown of mucosal integrity of the intestinal tract, eventually leading to significant morbidity and mortality.

This is particularly true for transplant recipients who do not respond to first-line treatment for aGVHD with steroids. aGVHD that is nonresponsive to steroids is associated with high rates of morbidity and mortality, including overall survival and nonrelapse mortality, primarily from infections and/or multiorgan failure [35,36]. The design of the present study of US claims did not allow the determination of steroid-resistant cases; however, it is likely that most of the deaths and serious infections occurred in patients who failed to respond to steroids.

Finally, our study is unique in that with a claims database, we can analyze hospital resources, unlike other registry studies. After adjusting for baseline demographic and clinical characteristics, compared with patients who did not develop aGVHD, those who developed GI aGVHD were 4 times more likely to be readmitted to the hospital within the first 100 days after allo-HCT. Patients in the GI aGVHD cohort were also significantly more likely to have an ER visit, and had an LOS almost double that seen in the no-aGVHD cohort. Total costs for the first 100 days after allo-HCT were significantly higher for the GI aGVHD cohort (cost ratio, 1.28). Similar findings were seen in a 2012 Swedish study of 1-year costs after allo-HCT, which reported that costs for patients with grade III-IV aGVHD were roughly double those of patients who did not develop aGVHD [25]. In a single-site UK study, the post-transplantation cost of care for patients with aGVHD was driven by the number and duration of inpatient hospitalizations [37]. In a recent study using the US MarketScan databases, Grubb et al [38] reported significantly greater 100-day costs ($73,622; $P < .001$) in patients who developed aGVHD after allo-HCT compared with those who did not develop aGVHD. Those results are similar to our present findings of $83,196 higher 100-day costs in our GI aGVHD cohort compared with our no-aGVHD cohort ($P < .001$). The economic burden associated with aGVHD in general is significant and is even worse with GI aGVHD, which costs nearly $400,000 in the first 100 days after allo-HCT [38]. The considerable financial and healthcare resource utilization burden associated with GI aGVHD highlights the need for better therapies to treat this very sick patient population.

The limitations of this study are similar to the limitations of other claims-based retrospective database analyses. The cost distributions in the current study have a large tail that can be accentuated by the presence of outliers. The functional form of our multivariate analysis accounts for this skewed distribution. The definition of GI aGVHD relies on medical billing, which does not capture the severity of the condition; therefore, symptoms coded on these medical claims were used to identify GI aGVHD and might not have captured all such patients. The use of an algorithm to identify GI GVHD certainly will not be completely accurate; however, our results are similar to those of other published studies,. In addition, there was no information on treatment, grading, or stage of GVHD. To provide a fair comparison among patients who survived long enough to develop aGVHD, this analysis was limited to patients who were discharged alive after allo-HCT and who had an LOS of at least 18 days. Minor infections and complications might not result in medical billing data and thus may be underreported in this study. However, most minor infections and complications are not reported in the published literature on aGVHD, so it not possible to compare other studies if these factors are captured. We were not able to determine the proportions of patients in GVHD treatment trials or to evaluate the proportion of patients receiving GVHD prophylaxis, which could be a reason for the longer LOS and higher number of outpatient visits in the GI aGVHD cohort. This study was limited to those individuals with commercial health coverage or private Medicare supplemental coverage who could be linked to the SSA DMF; therefore, results might not be generalizable to patients with other insurance, without health insurance coverage, or lacking a social security number. Claims data are collected for administrative purposes and are not subject to the same rigor as data collected for clinical trial purposes; thus, the data are subject to data entry errors that create the potential for misclassification errors and bias. Finally, this study combined patients who were identified using International Classification of Diseases (ICD), Ninth Revision, Clinical Modification coding, and those identified using ICD-10 CM coding, which may have introduced a degree of bias. Multivariate regression analysis was conducted to control for this to the extent possible.

CONCLUSION

In this real-world claims retrospective database analysis of patients with a hematologic malignancy who were discharged alive after an allo-HCT, those who developed GI aGVHD had higher mortality, infection rate, HRU, and costs compared with patients without aGVHD. This study highlights the continued unmet need in this patient population for whom there is no established standard of care beyond the first-line treatment with steroids. Therapies aiming to prevent the development GI aGVHD would be ideal to decrease mortality and reduced HRU associated with allo-HCT. Further and continued research is needed in this area to demonstrate the severity of disease and improve both the prevention and treatment of GI aGVHD.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at doi:10.1016/j.bbmt.2018.12.839.

REFERENCES

1. Horowitz MM. Uses and growth of hematopoietic cell transplantation. In: Forman SJ, Negrin RS, Antin JH, Appelbaum FR, eds. *Thomas' Hematopoietic Cell Transplantation*. West Sussex, UK: Wiley; 2004:15–21.
2. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *New Engl J Med*. 2010;363:2091–2101.
3. Gratwohl A, Brand R, Frassoni F, et al. Cause of death after allogeneic haematopoietic stem cell transplantation (HSCT) in early leukaemias: an EBMT analysis of lethal infectious complications and changes over calendar time. *Bone Marrow Transplant*. 2005;36:757–769.
4. Jagasia M, Arora M, Flowers ME, et al. Risk factors for acute GVHD and survival after hematopoietic cell transplantation. *Blood*. 2012;119:296–307.
5. Flowers ME, Inamoto Y, Carpenter PA, et al. Comparative analysis of risk factors for acute graft-versus-host disease and for chronic graft-versus-host disease according to National Institutes of Health consensus criteria. *Blood*. 2011;117:3214–3219.
6. Jagasia MH, Greinix HT, Arora M, et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease, I: the 2014 Diagnosis and Staging Working Group report. *Biol Blood Marrow Transplant*. 2015;21:389–401. e1.
7. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant*. 1995;15:825–828.
8. Hill GR, Ferrara JL. The primacy of the gastrointestinal tract as a target organ of acute graft-versus-host disease: rationale for the use of cytokine shields in allogeneic bone marrow transplantation. *Blood*. 2000;95:2754–2759.
9. Weisdorf DJ, Snover DC, Haake R, et al. Acute upper gastrointestinal graft-versus-host disease: clinical significance and response to immunosuppressive therapy. *Blood*. 1990;76:624–629.
10. Martin PJ, McDonald GB, Sanders JE, et al. Increasingly frequent diagnosis of acute gastrointestinal graft-versus-host disease after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2004;10:320–327.
11. Dignan FL, Clark A, Amrolia P, et al. Diagnosis and management of acute graft-versus-host disease. *Br J Haematol*. 2012;158:30–45.
12. Levine JE, Logan B, Wu J, et al. Graft-versus-host disease treatment: predictors of survival. *Biol Blood Marrow Transplant*. 2010;16:1693–1699.
13. Martin PJ, Schoch G, Fisher L, et al. A retrospective analysis of therapy for acute graft-versus-host disease: secondary treatment. *Blood*. 1991;77:1821–1828.
14. Weisdorf D, Haake R, Blazar B, et al. Treatment of moderate/severe acute graft-versus-host disease after allogeneic bone marrow transplantation: an analysis of clinical risk features and outcome. *Blood*. 1990;75:1024–1030.
15. Van Lint MT, Uderzo C, Locasciulli A, et al. Early treatment of acute graft-versus-host disease with high- or low-dose 6-methylprednisolone: a multicenter randomized trial from the Italian Group for Bone Marrow Transplantation. *Blood*. 1998;92:2288–2293.
16. Martin PJ, Rizzo JD, Wingard JR, et al. First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant*. 2012;18:1150–1163.
17. Fløisand Y, Lundin KEA, Lazarevic V, et al. Targeting integrin $\alpha 4\beta 7$ in steroid-refractory intestinal graft-versus-host disease. *Biol Blood Marrow Transplant*. 2017;23:172–175.
18. Castilla-Llorente C, Martin PJ, McDonald GB, et al. Prognostic factors and outcomes of severe gastrointestinal GVHD after allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2014;49:966–971.
19. MacMillan ML, Weisdorf DJ, Wagner JE, et al. Response of 443 patients to steroids as primary therapy for acute graft-versus-host disease: comparison of grading systems. *Biol Blood Marrow Transplant*. 2002;8:387–394.
20. Harris AC, Ferrara JL, Braun TM, et al. Plasma biomarkers of lower gastrointestinal and liver acute GVHD. *Blood*. 2012;119:2960–2963.
21. Levine JE, Braun TM, Harris AC, et al. A prognostic score for acute graft-versus-host disease based on biomarkers: a multicentre study. *Lancet Haematol*. 2015;2:e21–e29.
22. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45:613–619.
23. United States Department of Labor, Bureau of Labor Statistics. Consumer Price Index: details, report, tables, annual average 2016. Available at: https://www.bls.gov/cpi/data.htm. Accessed 25 January 2018.
24. Griffiths RI, Bass EB, Powe NR, Anderson GF, Goodman S, Wingard JR. Factors influencing third-party payer costs for allogeneic BMT. *Bone Marrow Transplant*. 1993;12:43–48.
25. Svahn BM, Remberger M, Alvin O, Karlsson H, Ringdén O. Increased costs after allogeneic haematopoietic SCT are associated with major complications and re-transplantation. *Bone Marrow Transplant*. 2012;47:706–715.
26. Espérou H, Brunot A, Roudot-Thoraval F, et al. Predicting the costs of allogeneic sibling stem-cell transplantation: results from a prospective, multicenter, French study. *Transplantation*. 2004;77:1854–1858.
27. Svahn BM, Ringdén O, Remberger M. Treatment costs and survival in patients with grades III-IV acute graft-versus-host disease after allogenic hematopoietic stem cell transplantation during three decades. *Transplantation*. 2006;81:1600–1603.
28. Naymagon S, Naymagon L, Wong SY, et al. Acute graft-versus-host disease of the gut: considerations for the gastroenterologist. *Nat Rev Gastroenterol Hepatol*. 2017;14:711–726.
29. Bhutani D, Dyson G, Manasa R, et al. Incidence, risk factors, and outcome of cytomegalovirus viremia and gastroenteritis in patients with gastrointestinal graft-versus-host disease. *Biol Blood Marrow Transplant*. 2015;21:159–164.
30. Khoury HJ, Wang T, Hemmer MT, et al. Improved survival after acute graft-versus-host disease diagnosis in the modern era. *Haematologica*. 2017;102:958–966.
31. Miller W, Flynn P, McCullough J, et al. Cytomegalovirus infection after bone marrow transplantation: an association with acute graft-v-host disease. *Blood*. 1986;67:1162–1167.
32. van Burik JA, Carter SL, Freifeld AG, et al. Higher risk of cytomegalovirus and aspergillus infections in recipients of T cell-depleted unrelated bone marrow: analysis of infectious complications in patients treated with T cell depletion versus immunosuppressive therapy to prevent graft-versus-host disease. *Biol Blood Marrow Transplant*. 2007;13:1487–1498.
33. Hou CY, Xu LL, Chen H, et al. Intestinal aGVHD and infection after hematopoietic stem cell transplantation. *Med Sci Monit*. 2013;19:802–806.
34. Labbé AC, Su SH, Laverdière, et al. High incidence of invasive aspergillosis associated with intestinal graft-versus-host disease following nonmyeloablative transplantation. *Biol Blood Marrow Transplant*. 2007;13:1192–1200.
35. Xhaard A, Rocha V, Bueno B, et al. Steroid-refractory acute GVHD: lack of long-term improved survival using new generation anticytokine treatment. *Biol Blood Marrow Transplant*. 2012;18:406–413.
36. Martin PJ, Bachier CR, Klingemann HG, et al. Endpoints for clinical trials testing treatment of acute graft-versus-host disease: a joint statement. *Biol Blood Marrow Transplant*. 2009;15:777–784.
37. Dignan FL, Potter MN, Ethell ME, et al. High readmission rates are associated with a significant economic burden and poor outcome in patients with grade III/IV acute GVHD. *Clin Transplant*. 2013;27:E56–E63.
38. Grubb WW, Huse S, Alam N, et al. Economic burden of acute graft-versus-host disease (GVHD) following allogeneic hematopoietic cell transplant (HCT) for hematologic malignancies. *Blood*. 2016;128:1187.