



Emergency general surgery procedures in hematopoietic stem cell transplant recipients[☆]



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ABSTRACT

Background: Outcomes of emergency general surgery (EGS) procedures on hematopoietic stem cell transplant (HST) recipients have not been defined in a large, national database. Whether EGS during HST engraftment admission, or in HST patients with graft versus host disease (GVHD) results in worse outcomes is unknown.

Methods: The National Inpatient Sample (NIS) was examined for patients with a history of BMT between 2001 and 2014.

Results: There were 520,000 HST admissions meeting inclusion criteria, of which, 14,143 (2.7%) required EGS. Of those requiring EGS, 378 (2.7%) were during engraftment admission and 13,765 (97.3%) on subsequent admission. For those requiring EGS during subsequent admission, 9,920 (72.1%) had a history of GVHD and 3,845 (27.9%) did not. On multivariate analysis, requirement of EGS was associated with mortality (OR: 1.71, 95%CI: 1.47–1.99, $p < 0.001$). For patients requiring EGS, engraftment admission or GVHD was not associated with mortality.

Conclusions: While EGS results in worse survival for the HST population, patients in their engraftment admission do not appear to be at increased mortality risk. In addition, GVHD does not worsen survival.

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Introduction

Hematopoietic stem cell transplants (HST) have become a viable treatment option for patients with hematologic and lymphoid cancers.¹ According to the Center for International Blood and Marrow Research (CIBM), there are over 8,000 total bone marrow transplants being performed in the United States annually.² HST can result in numerous complications and these patients are at highest risk for morbidity and mortality within two years of their engraftment admission. However, delayed complications can also occur,^{3–6} with the most important being graft

versus host disease (GVHD). GVHD is a known marker for poor outcomes in HST recipients with mortality rates as high as 60%. Patients with GVHD are at risk for devastating surgical emergencies such as gastrointestinal bleeds and bowel perforation.^{1,7,8} While the sequelae of complications that develop from HST have been well-established, the outcomes of emergency general surgery (EGS) procedures in this patient population have yet to be defined.

There is a paucity of data examining EGS procedures in HST patients. In addition, because of these patients' comorbidities, such as cytopenias and active infection, and frequent use of immunosuppression,^{3,9,10} the decisions involving EGS are complicated and often made in the absence of data. The goal of this study is to establish the outcomes of EGS procedures in the BMT population using a large, national database. In addition, we aim to determine if EGS procedures during HST engraftment admission, or in HST patients with GVHD is associated with worse results. We

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hypothesized that HST patients requiring EGS would have worse outcomes during engraftment admission and in the presence of GVHD.

Material and methods

Database

The National Inpatient Sample (NIS) Database from January 2001 to December 2014 was utilized for this study. The NIS database was developed by the Healthcare Cost and Utilization Project (HCUP) and contains data from approximately 8 million hospital stays each year. The database represents a stratified sample of 20% of non-federal hospitals in the United States. The NIS database is the largest publicly available, all payer inpatient health care database in the United States. A self-weighting design decreases the margin of error for estimates and delivers population based estimates. All of our statistical analysis was based on this weighting design as established in previous studies.^{11–13} The Partners Human Research Committee, the institutional review board of Partners Healthcare, approved this study.

Study population

Adult recipients, age 18 or older, who underwent HST were initially identified by the International Classification of Disease, Ninth Revision (ICD-9) diagnosis and procedure code as established in prior studies.⁶ Emergency general surgery procedures were defined as one of seven emergency general surgery operations that account for the majority of admissions, deaths, complications and inpatient costs in the United States as determined in a prior study.^{12,14} These seven procedures include: 1) open and other partial excision of large intestines, 2) other excision of small intestines, 3) cholecystectomy, 4) control of hemorrhage and suture of ulcer of stomach or duodenum, 5) lysis of peritoneal adhesions, 6) appendectomy, and 7) laparotomy. ICD-9-CM procedure codes were used to identify HST patients who underwent EGS procedures. HST patients were separated into those that were in their initial engraftment admission and those that had a subsequent admission. Patients in their initial engraftment admission were divided into those undergoing autologous or allogeneic hematopoietic stem cell transplant. Patients that were admitted to the hospital in a subsequent admission were divided into those with a history of GVHD and those without as shown in Fig. 1.

Outcomes measured

The primary outcome measured was in-hospital mortality after EGS procedures. Secondary outcomes included perioperative complications using ICD-9 codes representing respiratory complications, myocardial infarction, deep vein thrombosis (DVT)/pulmonary embolus (PE), urinary tract infection, cerebrovascular accident, sepsis/septic shock, post-operative hemorrhage, surgical site infection, or any complication as established in prior studies.^{11,13,15} Length of stay and total hospital charges were also examined.

Burden of EGS

Burden of EGS was defined by complications, mortality, and total hospital charges as established in a prior study.¹² To compare burden of EGS in HST patients to non-HST patients, burden of EGS was compared by class of procedure as described above.¹²

Data and statistical analysis

Continuous and categorical variables were compared with Student's t-test and chi square analysis. All continuous variables are presented as mean \pm standard deviation or median as appropriate. Weighted frequencies and multiple variable logistic regression analysis using clinically relevant variables were used to examine post-operative complications. Odds ratio (OR) with 95% confidence intervals were presented for each covariate. A p-value less than 0.05 was considered statistically significant. Data was analyzed using STATA 14.2 software (College Station, TX: StataCorp LP).

Results

Baseline patient characteristics

There were 520,000 total HST admissions during the study period as shown in Fig. 1. Of these, 14,143 (2.7%) had EGS procedures. Of HST admissions requiring EGS, 378 (2.7%) occurred during engraftment admission. A comparison of baseline patient characteristics for HST patients undergoing EGS procedures is shown in Table 1. There was a total of 88 patients in the autologous HST group and 290 in the allogeneic HST group. The autologous HST group was older (55.0 vs. 44.1 years, $p < 0.001$), more likely female (64.7% vs. 60.3%, $p < 0.001$), less likely to be self-pay (5.9% vs. 7.1%, $p = 0.003$),

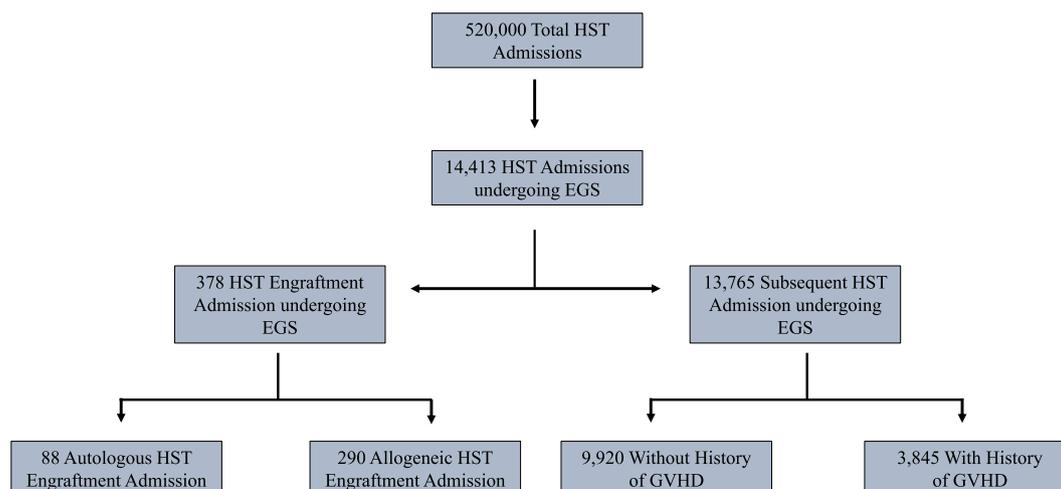


Fig. 1. Data was obtained from the National Inpatient Sample Database. Hematopoietic stem cell transplant recipients (HST) undergoing emergency general surgery (EGS) were identified and separated by engraftment admission and subsequent admission.

Table 1
Baseline patient characteristics for HST admissions with EGS.

	Engraftment Admission		Subsequent Admission		p-value
	Autologous (n = 88)	Allogeneic (n = 290)	No GVHD (n = 9,920)	GVHD (n = 3,845)	
Age (years)	55.0 ± 5.0	44.1 ± 2.7	51.2 ± 0.47	49.2 ± 0.56	<0.001
Female	55 (64.7)	175 (60.3)	5,495 (59.2)	2,030 (52.9)	<0.001
Charlson Comorbidity Index > 1	10 (11.8)	55 (19.0)	2,440 (26.3)	1,185 (30.8)	<0.001
Elective Admission	20 (23.5)	85 (29.3)	2,555 (27.6)	1,055 (27.5)	0.37
Public Insurance	40 (47.1)	130 (46.4)	4600 (50.0)	1820 (47.9)	0.003
Private Insurance	40 (47.1)	125 (44.6)	3,640 (39.5)	1,670 (44.0)	0.003
Self-Pay	5 (5.9)	20 (7.1)	665 (7.2)	215 (5.7)	0.003
Other Insurance	0 (0)	5 (1.8)	300 (3.3)	95 (2.5)	0.003
White	65 (81.3)	165 (61.1)	5,785 (66.6)	2,400 (66.8)	0.71
Black	5 (6.3)	45 (16.7)	945 (10.9)	435 (12.1)	0.71
Hispanic	10 (12.5)	40 (14.8)	1,330 (15.3)	505 (14.1)	0.71
Other Ethnicity	0 (0)	20 (7.4)	630 (7.3)	255 (7.1)	0.71
Any Complication	10 (11.8)	50 (17.2)	2,050 (22.1)	735 (19.1)	<0.001
Mortality	0 (0)	5 (1.7)	300 (3.2)	130 (3.4)	0.01

and less likely to have a Charlson Comorbidity Index >1 (11.8% vs. 19.0%, $p < 0.001$). Number of elective admissions and ethnicity was not different among patients in engraftment admissions.

There were 13,765 HST subsequent admissions after engraftment, during which they had EGS. Of these, 9,920 (72.1%) subsequent admissions for patients without a history of GVHD and 3,845 (27.9%) admissions for patients with GVHD as seen in Table 1. Patients in subsequent admission without GVHD were older (51.2 vs. 49.2 years, $p < 0.001$), more likely to be female (59.2% vs. 52.9%, $p < 0.001$), less likely to have Charlson Comorbidity Index <1 (26.3% vs. 30.8%, $p < 0.001$), and more likely to be self-insured (7.2% vs. 5.7%, $p = 0.003$). There was no difference in elective admission or ethnicity among subsequent admissions.

Morbidity and mortality

As seen in Table 1, mortality was higher in HST patients requiring EGS on subsequent admission as compared to those on engraftment admission. Mortality was higher for patients with GVHD (3.4%) as compared to non-GVHD (3.2%); $p = 0.01$. Patients in subsequent admissions that had EGS procedures also had a higher rate of any complications with non-GVHD (22.1%, $n = 2,050$) being higher than patients with GVHD (19.1%, $n = 735$); $p < 0.001$. Patients on engraftment admissions for autologous HST that had EGS had lower complication rates than those with allogeneic HST (11.8% vs. 17.2%, $p < 0.001$).

When looking at individual complications among engraftment admissions as seen in Table 2, there was no difference in rate of respiratory complications, myocardial infarction, DVT/PE, urinary tract infection, cerebrovascular accident, sepsis/septic shock, or surgical site infection. Risk of post-operative hemorrhage was

highest among the allogeneic, engraftment admission group (0.0% vs. 8.6%, $p = 0.01$). Length of stay was longer in the allogeneic group (10.5 vs. 24.4 days). There was no difference in mortality when comparing the two groups.

A comparison of subsequent admissions without GVHD and GVHD is shown in Table 3. There was no difference in rate of DVT/PE, cerebrovascular accidents, post-operative hemorrhage, sepsis/septic shock, and surgical site infections. Admissions without GVHD had higher rates of respiratory complications (7.5% vs. 5.9%, $p = 0.02$), myocardial infarctions (1.7% vs. 0.7%, $p < 0.001$), urinary tract infections (7.1% vs. 3.3%, $p < 0.001$), and any complication (22.1% vs. 19.1%, $p = 0.04$). Length of stay was higher in non-GVHD admissions (13.1 vs. 7.6 days, $p < 0.001$).

Mortality risk

Results of logistic regression for in-hospital survival among HST patients undergoing EGS is shown in Table 4. Female gender was associated with survival (OR: 0.60, 95%CI: 0.44–0.82, $p = 0.001$). Increasing Charlson Comorbidity Index was associated with mortality (OR: 1.76, 95%CI: 1.47–2.11, $p < 0.001$). Patients requiring EGS during their allogeneic, engraftment admission were not at increased risk for mortality (OR: 1.26, 95%CI: 0.13–11.80, $p = 0.84$) when compared to those having autologous, engraftment admission. Patients requiring EGS on subsequent admission did not have worse survival, either in the presence of GVHD (OR: 0.93, 95%CI: 0.12–7.18, $p = 0.94$) or without a history of GVHD (OR: 0.47, 95%CI: 0.06–3.67, $p = 0.47$).

Logistic regression for all HST patients is shown in Table 5. Patients that had EGS were at increased risk of inpatient mortality (OR: 1.71, 95%CI: 1.47–1.99, $p < 0.001$). Of note, patients on their

Table 2
Comparison of morbidity and mortality in HST engraftment admissions.

	Autologous (n = 88)	Allogeneic (n = 290)	p-value
Respiratory Complications	5 (5.9)	25 (8.6)	0.50
Myocardial Infarction	0 (0)	0 (0)	0.99
Deep Vein Thrombosis/Pulmonary Embolus	0 (0)	0 (0)	0.99
Urinary Tract Infection	0 (0)	5 (1.7)	0.35
Cerebrovascular Accident	0 (0)	0 (0)	0.99
Sepsis/Septic Shock	5 (5.9)	15 (5.2)	0.99
Post-Operative Hemorrhage	0 (0)	25 (8.6)	0.01
Surgical Site Infection	0 (0)	10 (3.5)	0.13
Any Complication	10 (11.8)	50 (17.2)	0.25
Length of Stay, mean	10.5 ± 3.6	24.4 ± 4.1	<0.001
Mortality	0 (0)	5 (1.7)	0.35

Table 3
Comparison of morbidity and mortality in subsequent admissions with EGS.

	No GVHD (n = 9,920)	GVHD (n = 3,845)	p-value
Respiratory Complications	695 (7.5)	225 (5.9)	0.02
Myocardial Infarction	155 (1.7)	25 (0.7)	<0.001
Deep Vein Thrombosis/Pulmonary Embolus	55 (0.6)	15 (0.4)	0.28
Urinary Tract Infection	655 (7.1)	125 (3.3)	<0.001
Cerebrovascular Accident	35 (0.4)	10 (0.3)	0.49
Sepsis/Septic Shock	645 (6.9)	275 (7.2)	0.052
Post-Operative Hemorrhage	450 (4.8)	155 (4.0)	0.18
Surgical Site Infection	255 (2.7)	105 (2.7)	0.64
Any Complication	2,050 (22.1)	735 (19.1)	0.04
Length of Stay, mean	13.1 ± 0.5	7.6 ± 0.3	<0.001
Mortality	300 (3.2)	130 (3.4)	0.31

engraftment admission for allogeneic HST were at increased risk for mortality (OR: 5.72, 95%CI: 3.91–8.37, $p < 0.001$) when compared to those on autologous, engraftment admission. Patients with GVHD on subsequent admission (OR: 2.21, 95%CI: 1.54–3.18, $p < 0.001$) had higher risk of mortality as compared to those without GVHD (OR: 1.94, 95%CI: 1.35–2.79, $p < 0.001$).

Burden of EGS in HST

To determine if morbidity and mortality of EGS is higher in HST patients compared to non-HST patients, burden of EGS for HST and non-HST patients was compared by class of procedure in Table 5. HST patients had higher mortality for open and other partial excision of large intestines (6.10% vs. 5.10%, $p = 0.049$), cholecystectomy (1.30% vs. 0.90%, $p < 0.001$), appendectomy (0.53% vs. 0.17%, $p = 0.001$), and laparotomy (15.60% vs. 12.60%, $p < 0.001$). Mortality was not significantly different for control of hemorrhage and suture of ulcer of stomach or duodenum or for lysis of peritoneal adhesions.

HST admissions had higher complication rates in open and other partial excision of large intestines (41.30% vs. 27.50%, $p < 0.001$), cholecystectomy (18.50% vs. 13.00%, $p < 0.001$), control of hemorrhage and suture of ulcer of stomach or duodenum (63.80% vs. 57.70%, $p < 0.001$), lysis of peritoneal adhesions (18.90% vs. 12.90%, $p < 0.001$), and laparotomy (45.50% vs. 37.80%, $p = 0.002$). Median hospital charges were higher for HST admissions as compared to non-HST admissions in all seven EGS procedures as seen in Table 6.

Discussion

The number of hematopoietic stem cell transplants carried out per year is on the rise, while survival for these patients continues to improve.^{9,16} As a result, the number of HST patients presenting to acute care surgeons with surgical emergencies will increase. No studies to date have examined the burden of EGS procedures in the

HST population. While HST patients are known to have increased morbidity and mortality early after HST, whether these patients requiring EGS during their engraftment admission have worse outcomes has yet to be determined. Our study demonstrated that overall, complications are higher among HST patients undergoing EGS on subsequent admission. Furthermore, while previous studies show that HST patients with GVHD have higher morbidity,¹⁷ the present study found that those *without* GVHD on subsequent admissions that were undergoing EGS had the highest number of complications.

Interestingly, we found that patients on allogeneic engraftment admission undergoing EGS had a higher degree of post-operative hemorrhage. While there is some data to suggest that allogeneic HST patients may have a greater number of bleeding complications,^{18,19} further studies are needed to investigate this finding. Acute care surgeons must take all of these factors into account when counseling allogeneic HST patients seen in consultation for possible EGS procedures.

Mortality risk in HST patients is highest in the first year post-transplantation, with the highest risk thought to be in the first 100–200 days.⁹ While the NIS database does not allow us to determine risk of mortality in temporal relationship to HST, we set out to determine if patients receiving EGS during the same admission as HST were at increased risk for death. Overall mortality rate in patients undergoing EGS was lower in engraftment admissions as compared to subsequent admissions, with a higher mortality rate in allogeneic HST. Among *all* HST admissions, allogeneic engraftment admission was associated with worse survival as seen in this study (Table 4) and in prior studies.^{20,21} However, on multivariate analysis, for HST patients undergoing EGS, allogeneic engraftment admission was not associated with increased mortality. Allogeneic HST patients appear to be at risk for worse outcomes during their engraftment admission, however, why this increased risk of mortality is not conveyed when allogeneic HST patients undergo EGS needs further exploration.

Table 4
Multivariate logistic regression for HST admissions with EGS.

	Odds Ratio	95% Confidence Interval	p Value
Age	1.00	0.99–1.01	0.34
Female	0.60	0.44–0.82	0.001
Charlson Comorbidity Index	1.76	1.47–2.11	<0.001
White	Reference	Reference	Reference
African American	0.63	0.36–1.12	0.12
Hispanic	0.84	0.51–2.35	0.48
Other Race	1.38	0.81–2.35	0.24
Engraftment Admission Autologous HST	Reference	Reference	Reference
Engraftment Admission Allogeneic HST	1.26	0.13–11.80	0.84
Subsequent Admission with GVHD	0.93	0.12–7.18	0.94
Subsequent Admission, no GVHD	0.47	0.06–3.67	0.47

Table 5
Logistic regression examining variables associated with mortality for HST admissions.

	Odds Ratio	95% Confidence Interval	p Value
EGS	1.71	1.47–1.99	<0.001
Age	1.00	1.00–1.00	<0.001
Female	0.72	0.69–0.76	<0.001
Charlson Comorbidity Index	1.84	1.78–1.90	<0.001
White	Reference	Reference	Reference
African American	0.76	0.70–0.84	<0.001
Hispanic	1.08	0.99–1.17	0.09
Other Race	1.20	1.08–1.33	<0.001
Engraftment Admission Autologous HST	Reference	Reference	Reference
Engraftment Admission Allogeneic HST	5.72	3.91–8.37	<0.001
Subsequent Admission with GVHD	2.21	1.54–3.18	<0.001
Subsequent Admission, no GVHD	1.94	1.35–2.79	<0.001

Table 6
Comparison of Burden of EGS in HST and non-HST Admissions.

ICD-9-CM Code	Procedure Group	Total Number HST	Total Number Non-HST	Mortality Rate for HST	Mortality Rate for Non-HST	p-value	Complication Rate for HST	Complication Rate for Non-HST	p-value	Median Cost (dollars) for HST	Median Charges (dollars) for non-HST	p-Value
45.7x	Open and other partial excision of large intestines	2,055	3,110,042	6.10%	5.10%	0.049	41.30%	27.50%	<0.001	67,547 (36,859–132,673)	43,342 (25,694–81,220)	<0.001
45.6x	Other excision of small intestines	1,080	1,004,668	7.00%	7.20%	0.89	34.70%	37.00%	0.13	69,758 (35,846–128,449)	56,861 (32,458–108,812)	<0.001
51.2x	Cholecystectomy	4,730	5,886,685	1.30%	0.90%	<0.001	18.50%	13.00%	<0.001	39,913 (22,431–70,780)	27,196 (16,655–46,210)	<0.001
44.4x	Control of hemorrhage and suture of ulcer of stomach or duodenum	1,300	1,282,701	6.50%	5.40%	0.08	63.80%	57.70%	<0.001	37,658 (22,077–82,429)	29,993 (16,713–60,692)	<0.001
54.5x	Lysis of peritoneal adhesions	2,720	3,771,905	1.50%	1.40%	0.99	18.90%	12.90%	<0.001	42,485 (22,218–79,324)	25,624 (14,455–48,452)	<0.001
47.0x	Appendectomy	1,915	2,892,145	0.53%	0.17%	0.001	5.40%	5.60%	0.71	31,250 (19,447–48,822)	20,049 (12,939–31,550)	<0.001
54.1x	Laparotomy	385	601,484	15.60%	12.60%	<0.001	45.50%	37.80%	0.002	66,570 (29,217–161,135)	44,377 (21,807–105,644)	<0.001

The presence of GVHD in HST patients is known to convey worse outcomes.^{7,9} In addition, GVHD patients can present with catastrophic surgical emergencies.⁸ In this study, amongst all HST patients, the presence of GVHD in subsequent admission was associated with worse mortality relative to those without GVHD on subsequent admission (Table 4). Yet for HST patients undergoing EGS, GVHD was not associated with worse mortality (Table 3). Acute care surgeons should keep this in mind as patients with GVHD will undoubtedly be seen in consultation for potential abdominal complications.

Unsurprisingly, burden of EGS is higher for HST patients as compared to non-HST patients undergoing EGS. Mortality was higher for HST patients in four of the seven EGS procedures and complication rates were higher in five of seven procedures. The only EGS procedure where morbidity and/or mortality was not higher in the HST population was other excision of small intestines. Acute care surgeons must consider this higher morbidity and mortality burden when determining the risks and benefits of EGS in HST patients. In addition, patients must be counseled about this higher risk of morbidity and mortality. EGS also comes at a significantly higher cost for HST patients, adding to the increased burden. Finally, amongst all HST patients, the requirement for EGS adds a significant mortality risk (OR: 1.71, 95%CI: 1.47–1.99, $p < 0.001$) when compared to HST patients not requiring EGS.

There are several limitations to this study. As with all

administrative databases, there is an inherent selection bias. It is difficult to account for patients that did not undergo EGS because they are simply too sick to be even offered surgery. In addition, the NIS database is limited to inpatient outcomes from a single hospital admission. Therefore, we could not examine long-term survival, complications that occur after discharge, readmissions, or need for further procedures. For this reason, we are also unable to separate patients that have multiple subsequent admissions. Therefore, the same patient that underwent EGS during engraftment admission may have also be counted among subsequent admissions and the same patient could be counted multiple times during subsequent admissions. This introduces a confounder as patients that have had multiple readmissions for EGS will have worse outcomes than those having engraftment admission. Finally, the temporal relationship of HST to subsequent admission could not be evaluated. Therefore, we could not determine how long after HST patients were presenting for EGS and whether they are truly at highest risk for mortality in the first 100–200 days post-transplantation.

Conclusions

EGS during HST engraftment admission does not result in worse survival. Patients with GVHD that undergo EGS do not have higher mortality than those without GVHD. HST patients undergoing EGS during subsequent hospital admission actually have a higher

complication rate than those having EGS during engraftment admission. In addition, overall burden of EGS is higher in HST patients as compared to non-HST patients.

Summary

EGS during HST engraftment admission does not result in worse survival. Patients with GVHD that undergo EGS do not have higher mortality than those without GVHD. HST patients undergoing EGS during subsequent hospital admission actually have a higher complication rate than those having EGS during engraftment admission. In addition, overall burden of EGS is higher in HST patients as compared to non-HST patients.

Conflicts of interests

The authors have no conflicts of interest to report.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.amjsurg.2019.02.030>.

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