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Invasive Pulmonary Aspergillosis in Hospitalized Hematopoietic Stem Cell Transplantation Recipients: Outcomes Based on The United States National Readmission Database

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ORIGINAL RESEARCH REPORT

Invasive Pulmonary Aspergillosis in Hospitalized Hematopoietic Stem Cell Transplantation Recipients: Outcomes Based on the United States National Readmission Database

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Abstract

Background and objective: **Hematopoietic stem cell transplant (HSCT) is a well-established treatment for hematologic malignancies and certain autoimmune and congenital conditions. HSCT is associated with immunocompromise and increased risk of infections. This study assessed whether invasive pulmonary aspergillosis (IPA) affects in-hospital mortality and 30-day readmission among HSCT patients. A secondary objective was to examine potential differences in complications between HSCT with and without IPA.**

Materials and methods: **A retrospective study of a nationally representative cohort of hospital admissions was conducted, with data collected from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project Nationwide Readmissions Database between 2013 and 2019. The International Classification of Diseases, 10th revision (ICD−10), and 9th revision (ICD-9) diagnostic codes were used to identify patients with IPA and HSCT. All adult patients ≥18 years were included in the study.**

Results: **There were 90,451 hospitalizations for HSCT from 2013 to 2019; 89,331 (98.8%) had HSCT without IPA, while 1092 (1.2%) hospitalizations had HSCT with IPA. The in-hospital mortality for HSCT-IPA was higher compared to HSCT without IPA (18.3% vs. 4.2%; $p < 0.001$). HSCT-IPA had a significantly higher 30-day readmission rate (36.2%) than that of HSCT without IPA (24.0%). HSCT-IPA also had a higher mean cost of admission ($303,437) than that of HSCT without IPA ($57,587).**

The HSCT-IPA group had higher multi-organ complications, including respiratory failure (51.3% vs. 13.5%, $p < 0.001$), sepsis (38.2% vs. 18.5%, $p < 0.001$), septic shock (16.1% vs. 5.1%, $p < 0.001$), need for mechanical ventilation (21.1% vs. 5.1% $p < 0.001$), non-invasive positive pressure ventilation (4.9% vs. 2.5%, $p < 0.001$), and intensive-care unit admission (21.8% vs. 6.1% $p < 0.001$).

Conclusion: **IPA is a rare but severe complication associated with HSCT, with higher in-hospital mortality, complications due to multi-organ failure, readmission rates, and cost of hospitalization when compared to HSCT without IPA.**

1. Introduction

Hematopoietic stem cell transplant (HSCT) was developed in the 1950s and is an approach to cancer treatment. It has since become a standard of care in treating various hematological malignant and non-malignant conditions [1]. HSCT can be described as autologous, wherein a patient will be a stem cell

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self-donor, or allogeneic, where a patient receives stem cells from a healthy donor. While HSCT has revolutionized the management of malignant and non-malignant conditions, it is not without complications. HSCT, particularly allogeneic transplant, wherein patients can receive matched or unmatched donor cells, has a high association of morbidity and mortality due to complications related to neutropenia, infection, and graft-vs-host-disease [2–4].

Pulmonary complications account for 40–60% of patients undergoing HSCT and may include infectious and non-infectious etiologies [5,6]. Of the infectious etiologies, bacterial, viral, and fungal pneumonia have been observed in all three engraftment phases: pre-engraftment, early post-engraftment, and late post-engraftment [4]. *Aspergillus* spp is a fungal pathogen that may be associated with a spectrum of pulmonary diseases, including invasive pulmonary aspergillosis (IPA) [6]. IPA is a rare but fatal opportunistic infection that impacts patients who have undergone HSCT [7].

Studies describing the relationship between IPA and HSCT have often been limited due to small patient populations [8–10]. To our knowledge, there are limited data on recent nationwide findings of baseline demographics, complications, and outcomes of patients with IPA who have undergone HSCT [11]. Understanding recent epidemiological data in this patient population can help inform clinicians on risk factors and trends for this rare but fatal fungal infection. This manuscript reports data from the National Readmission Database (NRD) to elucidate the incidence, mortality, readmission, baseline demographics, hospitalization cost, and complications associated with inpatient admissions for HSCT recipients with and without IPA.

2. Methods

2.1. Study population and inclusion criteria

This study is an observational cohort of patients hospitalized with HSCT with and without IPA during 2013–2019 in the NRD. The database was obtained from the Agency for Healthcare Research and the Quality's Healthcare Cost and Utilization Project (HCUP). The NRD is the largest publicly available all-payer inpatient care database in the United States (US) and contains discharge-level data included in the HCUP. The NRD represents 49.1% of total US hospitalizations. There is reliable data on approximately 28 million discharges annually, estimating >50 million discharges from 21 states with verified linkage numbers. Patients can be tracked using these linkage numbers for readmission within the same calendar year. The database provides de-identified information about the patient's demographics and hospital-based information. Furthermore, it provides information about the readmission status and days to readmission. Because a publicly available database was used with de-identified patient information, this study was exempt from obtaining permission from the Institutional Review Board. However, it was performed according to the ethical criteria established by the HCUP.

2.2. Patient and hospital characteristics

Baseline patient demographic characteristics, including sex, age, and insurance payer, were retrieved via the NRD. Further baseline conditions were also extracted using diagnostic codes, including hypertension, dyslipidemia, diabetes mellitus, obesity, smoking status, peripheral vascular disease (PVD), chronic obstructive pulmonary disease (COPD), asthma, Hepatitis B, Hepatitis C, pulmonary hypertension (PH), chronic kidney disease (CKD), and graft versus host disease (GVHD). Complications associated with the hospital encounters were accounted for via diagnostic codes, including acute kidney injury (AKI), AKI requiring dialysis, pulmonary embolism (PE), atrial fibrillation (AF), sepsis, urosepsis, septic shock, acute respiratory failure, pneumonia, ICU admission, need for non-invasive ventilation (NIV), mechanical ventilation (MV), and in-hospital mortality. These baseline demographics, comorbid conditions, and associated complications were obtained via ICD-9 and ICD-10 codes (Supplementary File 1). International Classification of Diseases-9 and -10 (ICD-9 and ICD-10) procedure codes were also used to identify NIV and MV utilization.

2.3. Study definitions

IPA and HSCT were defined by ICD-10 codes "B440," "B441," "B442," and "B447," and ICD-9 codes "4846″ and "1173." Patients younger than 18 years of age (n = 63,016) were excluded from the study. Furthermore, index hospitalizations of December (n = 14,546) were also excluded because 30-day readmission data was unavailable for those patients. After excluding these populations, the database identified 90,451 and 1092 index hospitalizations of HSCT patients and patients with IPA, respectively, between 2013 and 2019.

2.4. Outcomes

The study's primary outcome was in-hospital mortality until hospital discharge in HSCT with and

without IPA. Other outcomes were complications associated with the hospitalization encounter. The absolute yearly mortality and IPA rate among HSCT were calculated for 2013–2019.

2.5. Statistical methods

Categorical variables have been stated as both percentages and weighted values; meanwhile, continuous variables have been denoted as the mean ± standard deviation, wherein the median was within the 25th and 75th percentiles. Descriptive statistics were also implemented for demographics and comorbidities. These descriptive statistics were stratified such that patients with IPA were compared to patients without IPA. Survey statistics were used to calculate weighted analysis and compared with Pearson's chi-square test and t-test for categorical and continuous variables, respectively. We also calculated complications (via Pearson's chi-square test) associated with HSCT encounters with and without IPA were also calculated.

To assess mortality among patients with IPA, the 95% confidence interval (CI) and odds ratios were calculated in a multivariate logistic regression. These calculations were adjusted for model 1 variables, including demographic values such as age, sex, type of insurance, and location and type of the hospital, as well as comorbid conditions such as obesity, smoking status, diabetes, dyslipidemia, hypertension, cancer history, transplant history, PVD, and CKD. A similar linear regression model was used to calculate mortality associated with NIV and MV amongst patients with IPA.

Lastly, we included calculations to evaluate median inflated costs for index hospitalizations in both study groups. Statistical analyses were completed using STATA version 16.1 (College Station, TX, US). All p values were two-sided with a significance threshold of $p < 0.05$.

3. Results

3.1. Baseline characteristics

During 2013–2019, 90,451 index hospitalizations for HSCT (mean age 55.3 ± 15.0 years, 42.9% females) were recorded in the NRD. Of these hospitalizations, 1092 (1.2%) patients had IPA during the hospital encounter. The HSCT-IPA patient population was more likely to have underlying COPD, asthma, PH, Hepatitis C, GVHD, and a smoking history when compared to HSCT without IPA. Baseline conditions that did not differ between IPA and non-IPA groups were alcohol abuse, obesity, HTN, DM, and CKD. Baseline characteristics of

Table 1. Baseline characteristics for HSCT patients with and without IPA.

	HSCT (n = 90,451)		P-value
	Present IPA	Absent IPA	
I. No. of observations (Weighted) (%)	1092 (1.2%)	89,359 (98.8%)	
II. Demographic characteristics			
Age ±S.D.	50.8 ± 15.2	55.5 ± 15.2	<0.001
Female— No. (%)	469 (42.9%)	38,180 (42.7%)	0.9
Male— No. (%)	623 (57.1%)	51,179 (57.3%)	0.9
III. Comorbidities — No. (%)			
Alcohol abuse	25 (2.3%)	1507 (1.7%)	0.5
Smoke	365 (33.4%)	23,542 (26.3%)	0.03
Obesity	98 (9%)	8951 (10%)	0.5
HTN	572 (52.4%)	42,603 (47.7%)	0.2
DM	273 (25%)	20,191 (22.6%)	0.4
PVD	11 (1%)	2475 (2.8%)	0.03
COPD	168 (15.4%)	8686 (9.7%)	0.003
Asthma	122 (11.2%)	6749 (7.6%)	0.03
CKD	218 (20.1%)	18,840 (21.1%)	0.7
PH	117 (10.7%)	3991 (4.5%)	<0.001
Hepatitis C	30 (2.7%)	1098 (1.2%)	0.01
GVHD	306 (28.1%)	11,118 (12.4%)	<0.001
IV. Hospital Demographics— No. (%)			
Urban Hospital	1092 (100%)	88,713 (99.3%)	<0.001
Teaching Hospital	1026 (94%)	75,376 (84.4%)	<0.001
Insurance Status			
Medicare	369 (33.8%)	40,748 (45.6%)	<0.001
Medicaid	130 (11.9%)	9472 (10.6%)	
Private	584 (53.5%)	37,978 (42.5%)	
Self-pay	10 (0.9%)	1001 (1.1%)	

Table 2. Major complications in HSCT patients with and without IPA.

	HSCT		P-value
	Present IPA	Absent IPA	
No. of observations (Weighted) (%)	1092 (1.2%)	89,359 (98.8%)	
AF	148 (13.6%)	7387 (8.3%)	0.006
Sepsis	415 (38%)	16,560 (18.5%)	<0.001
Septic Shock	174 (15.9%)	4539 (5.1%)	<0.001
Pneumonia	711 (65.1%)	17,350 (19.4%)	<0.001
Urosepsis	170 (15.6%)	6894 (7.7%)	<0.001
Acute Ischemic Stroke	24 (2.2%)	1096 (1.23%)	0.20
AKI	600 (54.8%)	19,696 (22%)	<0.001
AKI Requiring Hemodialysis	91 (8.3%)	952 (1.07%)	<0.001
Acute Respiratory Failure	560 (51.3%)	12,037 (13.5%)	<0.001
PE	112 (10.3%)	3817 (4.3%)	<0.001
MV	231 (21.1%)	4562 (5.1%)	<0.001
NIPPV	54 (4.9%)	2271 (2.5%)	<0.001
ICU	238 (21.8%)	5497 (6.1%)	<0.001

HSCT patients with and without IPA subgroups are provided in Table 1.

3.2. Complications

The HSCT-IPA group had higher multi-organ complications, including AF (13.6% vs. 8.3%; $p < 0.007$), sepsis (38% vs. 18.5%, $p < 0.001$), septic shock (15.9% vs. 5.1%, $p < 0.001$), pneumonia (65.1% vs. 19.4%, $p < 0.001$), urosepsis (15.6% vs. 7.7, $p < 0.001$), AKI (54.8% vs. 22%; $p < 0.001$), AKI requiring dialysis (8.3% vs. 1.1%, $p < 0.001$), acute respiratory failure (51.3% vs. 13.5%, $p < 0.001$), and PE (10.3% vs. 4.3%; $p < 0.001$). Furthermore, the HSCT-IPA group had a higher need for ICU-level care (21.8% vs. 6.1%, $p < 0.001$), requirement for non-invasive positive pressure ventilation (NIPPV) (4.9% vs. 2.5%, $p < 0.001$), and requirement for MV (21.1% vs. 5.1%, $p < 0.001$). The comparison of multi-organ manifestations in HSCT patients with and without IPA is provided in Table 2.

3.3. In-hospital mortality and readmission outcomes

Among the 89,331 index hospitalizations for HSCT without IPA, 3785 (4.2%) died during hospitalization. Meanwhile, among the 1092 index hospitalizations for HSCT-IPA, 200 (18.3%) died during hospitalization ($p < 0.001$; Table 3).

Of the remaining 892 HSCT-IPA patients discharged, 200 (36.2%) were readmitted within 30 days. Meanwhile, among the 85,546 HSCT without IPA patients who were discharged, 20,523 (24.0%) were readmitted within 30 days. The primary system-based cause for readmission in the HSCT-IPA group was infectious (47.1%), followed by hematological (25.8%). The primary system-based causes for readmission in the HSCT without IPA group were hematological (34.3%) and infectious (17.1%). The results are shown in (Fig. 1). The in-hospital readmission mortality was greater in the HSCT-IPA group than in the HSCT without IPA group (22.0% vs. 7.1%, $p < 0.001$; Table 3).

Table 3. Outcomes of hospitalized HSCT patients with and without IPA.

	HSCT		P-value
	Present IPA	Absent IPA	
I. No. of observations (Weighted) (%)	1092 (1.2%)	89,359 (98.8%)	
II. Dispositions			
Discharged Home	536 (49.1%)	61,210 (68.5%)	<0.001
Home Health Care	272 (25%)	16,117 (18%)	<0.001
Skilled Nursing Facility	57 (5.2%)	6472 (7.2%)	<0.001
Inpatient Rehab Facility	23 (2.1%)	1232 (1.4%)	<0.001
Against Medical Advice	3 (0.3%)	660 (0.7%)	<0.001
In-hospital Mortality	200 (18.3%)	3785 (4.2%)	<0.001
III. Readmissions			
No of observations (Weighted) (%)	892 (1.0%)	85,546 (98.9%)	
30-day all-cause readmission	200 (36.2%)	20,523 (24.0%)	
In-hospital Mortality amongst readmissions	44 (22.0%)	6074 (7.1%)	<0.001

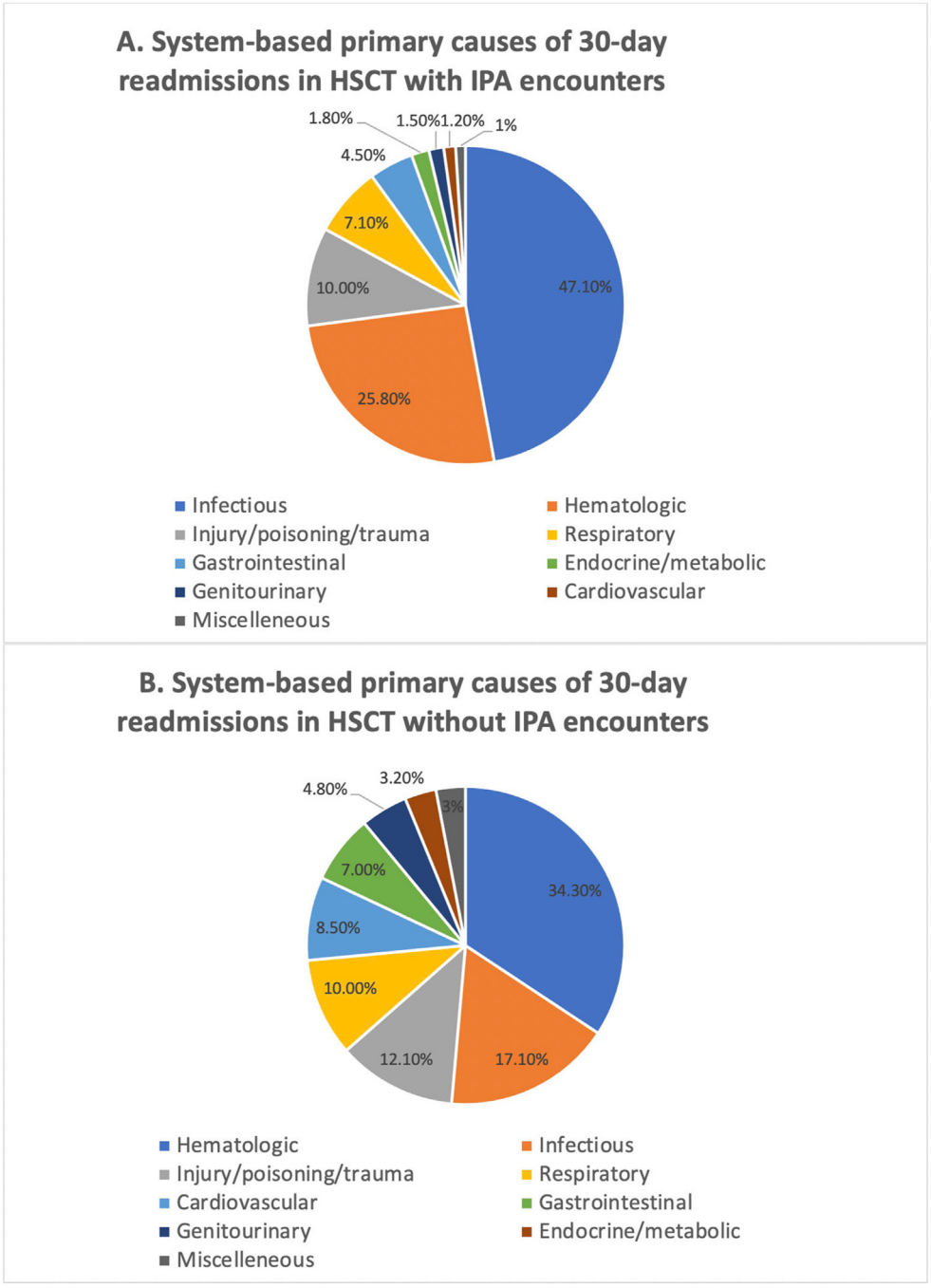

Fig. 1. Causes of 30-day readmission amongst Hematopoietic Stem-Cell Transplantation (HSCT) encounters, stratified by presence or absence of Invasive Pulmonary Aspergillosis (IPA).

3.4. Disposition

Among the 8209 patients who were hospitalized for HSCT-IPA, 78 (7.3%) were discharged to a skilled care or inpatient rehabilitation facility, 273 (25.0%) were discharged with home care, and 534 (49.0%) were discharged home.

Among the 89,331 patients who were hospitalized for HSCT without IPA, 660 (0.7%) left against medical advice, 6472 (8.6%) were discharged to a skilled care or inpatient rehabilitation facility, 16,117 (18.0%) were discharged with home care, and 61,035 (68.3%) were discharged home. The results are shown in (Table 3).

3.5. Cost analysis

The median cost per hospitalization was extracted for both HSCT-IPA and HSCT without IPA populations. The median costs per hospitalization for HSCT-IPA and HSCT without IPA were $303,437 ($99,904–$730,397; CI 95%) and $57,587 ($27,250–$165,484; CI 95%), respectively ($303,437 vs. $57,587, $p < 0.001$).

4. Discussion

This study is the first to utilize the NRD to explore baseline demographics, complications, outcomes, cost, and readmission statistics of hospitalized HSCT patients with IPA. The IPA group demonstrated a four times higher likelihood of in-hospital mortality than that of the non-IPA group. The IPA group also had a three times greater chance of admission to the ICU and greater dependence on MV or NIPPV. Complications involving multi-organ dysfunction and sepsis were demonstrated more frequently in the IPA group.

IPA has been linked to a higher mortality rate. The TRANSNET study, a prospective study evaluating outcomes of fungal infections in HSCT patients, demonstrated a one-year survival of 25.4% in patients who developed IPA [11]. An 11-year prospective study by Sun et al. found IPA to have a high in-hospital mortality rate of 30.2% [12]. A literature review by Lin et al. found an inpatient case fatality rate of 58%, with the highest percentage of 86.7% found among patients with HSCT [13]. Another study evaluating outcomes in IPA among ICU admissions found patients with putative IPA to have a mortality rate of 67% and biopsy-proven IPA to have a mortality rate of 79% [14]. Our study found a mortality rate of 18.3% for all patients admitted with HSCT-IPA from 2013 to 2019. A possible explanation for the relatively lower mortality rate in our study is that our method of identifying the IPA group via ICD-codes may not distinguish it from colonization rather than a biopsy-proven infection; second, our study includes all hospitalizations rather than just ICU admission. Third, the database did not differentiate between allogeneic and autologous HSCT, which may have different severity of infection and outcome.

HSCT has been recognized as a risk factor for the development of opportunistic fungal infections, including IPA [5–9,15]. IPA has generally been associated with neutropenia; however, in non-neutropenic hosts, IPA has been associated with glucocorticoid use, COPD, and solid organ transplantation [16,17]. HSCT has been divided into multiple post-transplant phases: neutropenic, early post-engraftment, and late post-engraftment [1]. One study demonstrated that approximately 25% of infections that develop in the neutropenic phase are fungal, and the majority are due to IPA [4]. IPA has been associated with acute and chronic GVHD In the early and late post-engraftment phases. Studies have also demonstrated that GVHD is a greater risk factor than neutropenia for the development of IPA due to the chronic immunosuppressive therapy utilized in the management of GVHD [12,18]. Our study found that GVHD was over two times more prevalent in HSCT patients who developed IPA than in the non-IPA group.

Our study found that HSCT recipients who develop IPA have more multi-organ dysfunction and death than that of the non-IPA group but a significantly greater cost of hospitalization and utilization of long-term, intermediate, and acute care facilities. Many studies have found a similar association between fungal diseases, including *Aspergillus,* and a greater economic burden on the US healthcare system [19,20].

4.1. Study limitations

study has several limitations. First, it is a retrospective observational study and cannot establish causation. Second, we relied on ICD-9 and ICD-10 codes to identify diagnoses. Furthermore, the NRD is subject to inaccurate coding and underreporting of comorbid diagnoses. Due to these limitations with the NRD and utilization of ICD, there was an inability to differentiate between autologous and allogeneic HSCT. There is also a possible inability to differentiate comorbidities from complications due to the nature of the database. Moreover, certain findings are absent, such as those of physical exams, treatment, management, and radiographic and investigational studies. These findings apply to the US population and may not generalize to other demographics. Despite this, the NRD and ICD codes have been utilized in countless clinical studies and are considered highly reliable. Furthermore, the large cohort size confers considerable power in our study and minimizes these limitations.

5. Conclusions

IPA in hospitalized HSCT recipients is associated with high mortality compared to HSCT without IPA. These patients also had more multi-organ

dysfunction, higher readmission rates, and a greater cost of admission. Our study implies a need for further study into interventions that prevent and improve outcomes in HSCT patients with IPA.

Conflict of Interest

The authors whose names are listed immediately below certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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Appendix.

Supplementary Table 1. Baseline Characteristics of Allogenic Hematopoietic Stem-Cell Transplantation (Allo-HSCT) encounters, stratified by Presence or Absence of Invasive Pulmonary Aspergillosis (IPA).

	Allo-HSCT (n = 90,451)		P-value
	Present IPA	Absent IPA	
I. No. of observations (Weighted) (%)	114 (1.4%)	7883 (98.6%)	
III. Risk Factors and Comorbidities — No. (%)			
Smoker	35 (30.7%)	2128 (27.0%)	0.8
Obesity	7 (6.0%)	765 (9.7%)	0.6
HTN	62 (54.5%)	3003 (38.1%)	0.4
DLD	30 (26.1%)	1900 (24.7%)	0.9
DM	41 (35.7%)	1230 (15.6%)	0.2
PVD	0 (0%)	49 (0.6%)	0.9
COPD	26 (22.6%)	310 (3.9%)	0.01
Asthma	29 (25.1%)	426 (5.4%)	0.01
CKD	65 (56.7%)	985 (12.5%)	<0.001
CHF	3 (2.9%)	181 (2.3%)	0.7
PAH	33 (29.1%)	118 (1.5%)	<0.001
Malignancy	114 (100%)	7536 (95.6%)	<0.001
GVHD	9 (8.3%)	63 (0.8%)	<0.001
IV. Hospital Demographics— No. (%)			
Teaching Hospital	114 (100%)	7741 (98.2%)	
Insurance Status			
Medicare	4 (3.4%)	741 (9.4%)	
Medicaid	32 (27.4%)	2368 (30.0%)	
Private	79 (69.2%)	4688 (59.5%)	
Self-pay	0 (0%)	76 (1.0%)	

Supplementary Table 2. Outcomes associated with Allogenic Hematopoietic Stem-Cell Transplantation (Allo-HSCT) encounters, stratified by Presence or Absence of invasive pulmonary aspergillosis (IPA).

	HSCT		P-value
	Present IPA	Absent IPA	
I. No. of observations (Weighted) (%)	114 (1.4%)	7883 (98.6%)	
II. Mortality Outcomes			
In-hospital Mortality	200 (18.3%)	3785 (4.24%)	<0.001
III. Putative complications — No. (%)			
AF	45 (39.6%)	836 (10.6%)	0.005
Syncope	22 (19.4%)	71 (0.9%)	<0.001
Sepsis	31 (27.1%)	1096 (13.9%)	0.3
Urosepsis	43 (37.5%)	386 (4.9%)	<0.001
Septic Shock	9 (8.1%)	173 (2.2%)	0.2
Pneumonia	111 (97.5%)	449 (5.7%)	<0.001
Cellulitis	29 (25.4%)	150 (1.9%)	<0.001
PE	0 (0%)	47 (0.6%)	0.9
MV	2 (1.4%)	347 (4.4%)	0.07
NIPPV	0 (0%)	110 (1.4%)	0.7
ICU	3 (2.1%)	489 (6.2%)	0.04

The following complications were excluded due to the number of observations being too low in both IPA and non-IPA groups: VT/VF, heart block, cardiogenic shock, stroke, TIA, acute COPD exacerbation.

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