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Full Length Article
Allogeneic – Adult

Noninfectious Pulmonary Toxicity after Allogeneic Hematopoietic Cell Transplantation

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A B S T R A C T

Noninfectious pulmonary toxicity (NPT), a significant complication of allogeneic hematopoietic cell transplantation (alloHCT), includes idiopathic pneumonia syndrome (IPS), diffuse alveolar hemorrhage (DAH), and cryptogenic organizing pneumonia (COP), with an overall incidence ranging from 1% to 15% in different case series and a variable mortality rate. A registry study of the epidemiology and outcomes of NPT after alloHCT has not been conducted to date. The primary objective of the present study was to assess the incidence of and risk factors for IPS, DAH, and COP; the secondary objective was to assess overall survival (OS) in patients developing NPT. This

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Idiopathic pneumonia syndrome
Cryptogenic organizing pneumonia

retrospective study included adult patients who underwent alloHCT between 2008 and 2017 and reported to the Center for International Blood and Marrow Transplant Research. Multivariable Cox proportional hazards regression models were developed to identify the risk factors for development of NPT and for OS, by including pretransplantation clinical variables and time-dependent variables of neutrophil and platelet recovery, and acute graft-versus-host disease (GVHD) post-transplantation. This study included 21,574 adult patients, with a median age of 55 years. According to the HCT Comorbidity Index (HCT-CI), 24% of the patients had moderate pulmonary comorbidity and 15% had severe pulmonary comorbidity. The cumulative incidence of NPT at 1 year was 8.1% (95% confidence interval [CI], 7.7% to 8.5%). Individually, the 1-year cumulative incidences of IPS, DAH, and COP were 4.9% (95% CI, 4.7% to 5.2%), 2.1% (95% CI, 1.9% to 2.3%), and .7% (95% CI, .6% to .8%), respectively. Multivariable analysis showed that severe pulmonary comorbidity, grade II-IV acute GVHD, mismatched unrelated donor and cord blood transplantation, and HCT-CI score $\geq$1 significantly increased the risk of NPT. In contrast, alloHCT performed in 2014 or later, non-total body irradiation (TBI)- and TBI-based nonmyeloablative conditioning and platelet recovery were associated with a decreased risk. In a landmark analysis at day+100 post-transplantation, the risk of DAH was significantly lower in patients who had platelet recovery by day +100. Multivariable analysis for OS demonstrated that NPT significantly increased the mortality risk (hazard ratio, 4.2; $P < .0001$).

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INTRODUCTION

Allogeneic hematopoietic cell transplantation (alloHCT) is a potentially curative treatment for a variety of malignant and nonmalignant diseases. However, alloHCT outcomes are limited by significant complications, including pulmonary toxicity, that are major drivers of nonrelapse mortality (NRM) [1]. However, limited data, primarily from single-center retrospective studies, have been reported on the prevention and management of noninfectious pulmonary toxicity (NPT), which is associated with high mortality post-alloHCT [2]. Despite advances in supportive care, pulmonary complications still develop in 30% to 60% of alloHCT recipients, resulting in an NRM as high as 50% in those patients [3,4]. Previously reported risk factors include preexisting pulmonary toxicity of chemotherapies, use of total body irradiation (TBI) in alloHCT conditioning, graft-versus-host disease (GVHD), and such comorbidities as restrictive lung disease and smoking history. Smaller studies have suggested an increased risk of developing NPT with TBI-based myeloablative conditioning (MAC) [5].

NPT occurring early post-alloHCT has traditionally included the following entities: idiopathic pneumonia syndrome (IPS), diffuse alveolar hemorrhage (DAH), and cryptogenic organizing pneumonia (COP) [6]. IPS is defined by widespread alveolar injury with signs and symptoms of pneumonia in the absence of active lower respiratory tract infection [2]. Clinical symptoms can be insidious and nonspecific, and diagnosis may require a high index of suspicion after excluding infectious and alternative pathologies [2,6,7]. IPS can occur as early as 2 to 6 weeks post-transplantation, with an incidence of 2% to 15% [2,4,8,9]. Treatment is empirical, with high-dose systemic corticosteroids as the established standard [10]. The tumor necrosis factor (TNF)-α inhibitor etanercept has been shown to benefit IPS patients in several clinical trials; nonetheless, a high mortality rate has been recorded, even in responders [2,4,8,11,12].

DAH presents with progressively bloodier returns from bronchoalveolar lavage and evidence of widespread alveolar injury and can cause rapidly progressive acute respiratory failure [13,14]. DAH has been shown to develop in the first 4 weeks post-transplantation, with an incidence of 2% to 14%, and is associated with mortality rates ranging from 64% to 100% [15–17].

COP is marked by a restrictive pattern on pulmonary function testing (PFT) with pathology showing patchy granulation tissue invading alveolar ducts with interstitial inflammation [18]. The incidence of COP is 1% to 10% and it usually occurs between 2 and 15 months after alloHCT, but response to corticosteroids is generally favorable [2,17,19,20].

As the data demonstrate, there is significant heterogeneity in the published literature on the incidence and variability in outcomes of early NPT. Historically, this has stemmed from a lack of consensus on evaluation, treatment, and response; the evolution of cancer treatment and transplantation regimens, including supportive care over time; the lack of prospective clinical trials data; and the limitations of retrospective, single-center studies, reflecting the associated geographical biases when approaching and managing NPT. We conducted the present retrospective registry study to better understand the epidemiology of NPT developing early on after alloHCT, confirm the risk factors for NPT, and examine the impact of NPT on transplantation outcomes [2].

METHODS

Data Sources

The Center for International Blood and Marrow Transplant Research (CIBMTR) is a nonprofit research collaboration between the National Marrow Donor Program/Be The Match and the Medical College of Wisconsin. More than 330 medical centers worldwide submit clinical data to the CIBMTR on HCT and other cellular therapies; the CIBMTR's Research Database currently includes long-term clinical data for more than 585,000 patients. Participating centers are required to report all transplantations consecutively; compliance is monitored by onsite audits, and patients are followed longitudinally. Computerized checks for discrepancies, physicians' reviews of submitted data, and onsite audits of participating centers ensure data quality. Studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

Patients

This analysis included adult patients (age $\geq$18 years) undergoing a first alloHCT as reported to the CIBMTR between 2008 and 2017. Patients with any disease indication, graft source, and donor source were included. AlloHCT recipients with <100 days of follow-up were excluded.

Objectives, Endpoints, and Definitions

The primary objective of this study was to evaluate the incidence of and risk factors for the development of IPS, DAH, COP, and the composite NPT. Other transplantation complications involving the lungs, including periengraftment respiratory distress syndrome, pulmonary veno-occlusive disease, and late-onset post-transplantation pulmonary entities of interstitial lung disease and bronchiolitis obliterans syndrome were not included in this analysis. The secondary objective was to evaluate the impact of NPT on overall survival (OS) after alloHCT. IPS, DAH, and COP were diagnosed and reported by the contributing transplantation centers based on the clinical, histopathologic, and imaging data obtained. OS was defined as the time from alloHCT to death from any cause, with surviving patients censored at last follow-up.

Statistical Analysis

NPT as a composite endpoint was reached if the patient developed any one of IPS, DAH, or COP. Death from any cause was a competing risk. Multivariable proportional cause-specific hazards models and Cox models with forward stepwise selection and a significance level of .01 were developed to identify the risk factors for NPT and OS. Covariates included indication for transplantation (ie, underlying disease), Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) score (minus the pulmonary component), presence and severity of a pulmonary comorbidity (moderate or severe, as defined in the HCT-CI), graft source, donor type, conditioning intensity and use of TBI, neutrophil recovery (defined as achievement of an absolute neutrophil count >500/μL for 3 consecutive days), platelet recovery (defined as a platelet count >20,000/μL for 3 consecutive days, without transfusion in the previous 7 days), grade II-IV acute GVHD, and year of transplantation. Conditioning intensities were defined by the CIBMTR consensus criteria [21]. Pretransplantation pulmonary comorbidity severity was defined according to the HCT-CI as moderate characterized by forced expiratory volume in 1 second and/or diffusing capacity of the lungs for carbon monoxide of 66% to 80% and dyspnea on slight activity, or severe, marked by forced expiratory volume in 1 second and/or diffusing capacity of the lungs for carbon monoxide ≤65%, dyspnea at rest, and the need for supplemental oxygen [22]. Neutrophil and platelet recovery, as well as acute GVHD, were added as time-dependent covariates in the regression model. The assumption of proportional hazards for each factor was tested by examining time-varying effects. Potential interactions between the main effect and significant covariates were tested as well. In addition, landmark analyses at day +100 were conducted to examine the impact of NPT on OS after alloHCT. For the landmark survival analysis, covariates included disease indication for alloHCT, age, HCT-CI score (minus the pulmonary component), Karnofsky Performance Scale, smoking history, pulmonary comorbidity severity, prior autoHCT, year of transplantation, and donor source. Adjusted OS and cumulative incidence of NPT, IPS, DAH, and COP were calculated based on the final regression model. A center effect was tested using the score test of homogeneity. When there was a significant center effect, the marginal regression model was fit to account for it. All analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients, Disease, and Transplantation Characteristics

A total of 21,574 adult alloHCT recipients were included in the study (Table 1). The median age at alloHCT was 55 years (range, 18 to 88 years), 59% were male, and 74% were Caucasian. Fifty-nine percent of patients had a Karnofsky Performance Scale score ≥90. Based on the HCT-CI score, 24% of the patients had moderate pulmonary impairment and 15% had severe pulmonary impairment. Before transplantation, 3% of the patients had a history of mechanical ventilation, 5% had a history of invasive fungal infection, and 40% had a smoking history. Most patients (64%) had a matched sibling or matched unrelated donor. Peripheral blood stem cells were the most frequent graft source (71%). MAC, reduced-intensity conditioning, and nonmyeloablative (NMA) conditioning regimens were used in 49%, 34%, and 17% of patients, respectively. Twenty percent of the patients received TBI-based MAC, and 19% had TBI-based NMA conditioning. The median duration of follow-up of survivors was 49 months (range, 3 to 131 months).

Incidence of NPT

The cumulative incidence of NPT as a composite endpoint at 1-year post-alloHCT was 8.1% (95% confidence interval [CI], 7.7% to 8.5%). The cumulative incidences of IPS, DAH, and COP were 4.9% (95% CI, 4.7% to 5.2%), 2.1% (95% CI, 1.9% to 2.3%), and .7% (95% CI, .6% to .8%), respectively (Table 2, Figure 1). Individually, the median time to onset was 3.7 months for IPS, 1.7 months for DAH, and 8.2 months for COP. Among the 1802 patients in the database with reported NPT, 708 (39%) received an interventional diagnostic procedure and 518 (29%) had no invasive testing/diagnostic intervention performed. Data on the remaining 576 patients (32%) were not reported by the respective centers. Of the 708 patients who underwent testing, 596 (84%) had bronchoalveolar lavage or other diagnostic testing, 67 (9%) had a transbronchial biopsy, and 44 (6%) had

Table 1
Baseline Characteristics of Patients Undergoing First AlloHCT between 2008 and 2017

Characteristic	Value
Number of patients	21,574
Number of centers	255
Age, yr, median (range)	55 (18-88)
Male sex, n (%)	12,672 (59)
Caucasian race, n (%)	15,993 (74)
Ethnicity not Hispanic or Latino, n (%)	17,962 (83)
KPS 90-100, n (%)	12,833 (59)
HCT-CI (minus pulmonary comorbidity), n (%)	
0	6018 (28)
1	3001 (14)
2	2884 (13)
3	3712 (17)
4	2262 (10)
5+	3231 (15)
Pulmonary comorbidity (based on the HCT-CI), n (%)	
Moderate	5163 (24)
Severe	3242 (15)
History of mechanical ventilation, n (%)	646 (3)
History of cigarette smoking, n (%)	8541 (40)
Disease indication, n (%)	
AML	8003 (37)
MDS/MPN	6044 (28)
ALL	2362 (11)
Lymphoma	2081 (10)
Nonmalignant disease	1107 (5)
CML	722 (3)
CLL	696 (3)
MM/PCD	300 (1)
Other malignant disease	259 (1)
Refined Disease Risk Index group, n (%)	
Low	2061 (10)
Intermediate	10,846 (50)
High	5955 (28)
Very high	745 (3)
Prior autologous HCT, n (%)	1277 (6)
Donor type, n (%)	
Matched unrelated	8270 (38)
HLA-identical sibling	5576 (26)
Cord blood	2911 (13)
Haploidentical	1978 (9)
Mismatched unrelated	1891 (9)
Other	900 (5)
Graft source, n (%)	
PBSCs	15,335 (71)
BM	3328 (15)
Umbilical cord blood	2911 (13)
Conditioning regimen intensity, n (%)	
MAC	10,665 (49)
RIC	7242 (34)
NMA	3667 (17)
TBI and intensity, n (%)	
Myeloablative TBI	4285 (20)
Nonmyeloablative TBI	4109 (19)
GVHD prophylaxis, n (%)	
Tacrolimus + MMF or MTX or other	13,256 (61)
CSA + MMF or MTX	3837 (18)
PTCy	2246 (10)

(*continued*)

Table 1 (*Continued*)

Characteristic	Value
Ex vivo T cell depletion or CD34 selection, n (%)	694 (3)
ATG/alemtuzumab, n (%)	
ATG alone	5885 (27)
Alemtuzumab alone	656 (3)
Year of alloHCT, n (%)	
2008-2013	10,888 (51)
2014-2017	10,686 (49)
Follow-up of survivors, mo, median (range)	49 (3-131)

KPS indicates Karnofsky Performance Scale; AML, acute myelogenous leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myelogenous leukemia; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; PCD, plasma cell disorder; BM, bone marrow; PBSCs, peripheral blood stem cells; RIC, reduced-intensity conditioning; MMF, mycophenolate mofetil; MTX, methotrexate; CSA, cyclosporine A; PTCy, post-transplantation cyclophosphamide; ATG, antithymocyte globulin

*Other donors included any matched related (not siblings), 1 locus-mismatched related donors, and cases with related donors who do not have HLA-matching information.

open/thoracoscopic (video-assisted) lung biopsy. Of the patients with IPS, 168 (13.2%) had diagnostic testing performed, 514 (40.3%) did not have diagnostic testing, and testing was not reported for 593 (46.5%) (Supplementary Table S1). Of the patients with DAH, 402 (82.4%) completed diagnostic testing, whereas 67 (13.7%) had no diagnostic testing and 19 (3.9%) did not have testing status reported. Of the patients diagnosed with COP, 168 patients (82.8%) underwent testing and 35 (17.2%) did not.

Risk Factors for NPT

Multivariable analysis showed that severe pulmonary comorbidity based on pretransplantation PFT (hazard ratio [HR], 1.35; *P*=.0009), grade II-IV acute GVHD (HR, 1.43; $P < .0001$), receipt of a mismatched unrelated donor transplant (HR, 1.33; *P*=.005) or cord blood transplant (HR, 1.34; *P*=.046), and HCT-CI ≥1 versus 0 (HR, 1.26 to 1.56; $P < .0001$) significantly increased the risk of NPT (Figure 2). In contrast, year of HCT 2014 or later (HR, .70; $P < .0001$), conditioning without TBI (HR, .60; *P*=.0002) and use of TBI-based NMA conditioning versus TBI-based MAC (HR, .57; $P < .0001$), and platelet recovery (HR, .29; $P < .001$) were associated with a significantly lower risk of NPT (Table 3). We also analyzed the impact of the inclusion of in vivo T cell depletion (antithymocyte globulin and alemtuzumab) in the conditioning regimen and use of granulocyte colony-stimulating factor post-transplantation but did not find any significant association with NPT in the multivariable models.

Table 2
Cumulative Incidence of NPT after AlloHCT

Outcomes	N	Probability, % (95% CI)
NPT (IPS, DAH, or COP)	21,508	
3 mo		4.0 (3.8-4.3)
6 mo		5.9 (5.6-6.2)
1 yr		8.1 (7.7-8.5)
3 yr		10.3 (9.8-10.7)
IPS	21,526	
3 mo		2.6 (2.4-2.8)
6 mo		3.8 (3.5-4)
1 yr		4.9 (4.7-5.2)
3 yr		5.8 (5.5-6.2)
DAH	21,552	
3 mo		1.4 (1.3-1.6)
6 mo		1.8 (1.6-2)
1 yr		2.1 (1.9-2.3)
3 yr		2.3 (2.1-2.5)
COP	21,553	
3 mo		.2 (.1-.2)
6 mo		.3 (.3-.4)
1 yr		.7 (.6-.8)
3 yr		1.0 (.8-1.1)

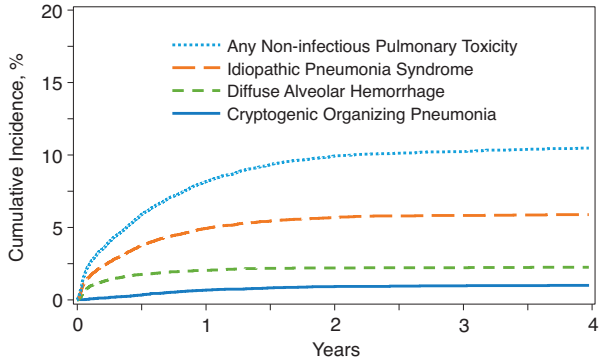

Figure 1. Cumulative incidence of NPT after alloHCT.

Risk factors for IPS included HCT-CI ≥1 versus 0 (HR, 1.26 to 1.59; *P*=.0002), whereas alloHCT in 2014 or later (HR, .80; *P*=.002) and platelet recovery (HR, .34; $P < .0001$) decreased the risk of IPS (Table 3). The analysis showed a significant interaction between TBI conditioning intensity and the time-dependent variable of grade II-IV acute GVHD (*P*=.002): patients receiving TBI-based NMA and non-TBI-based regimens had a significantly lower risk of IPS if they did not develop grade II-IV acute GVHD (HR, .48; and .52, respectively; $P < .0001$ for both), but not if they had acute GVHD (HR, .75; P=.06 and .88, respectively; *P*=.21), compared with TBI-based MAC recipients (irrespective of acute GVHD onset). For DAH, significant risk factors included severe pulmonary dysfunction (HR, 1.66; $P < .0001$); underlying chronic myelogenous leukemia, myelodysplastic syndrome, or myeloproliferative neoplasm (HR, 1.52; *P*=.0006); and grade II-IV acute GVHD (HR, 1.49; *P*=.0006). In contrast, alloHCT performed in 2014 or later (HR, .58; $P < .0001$), TBI-based NMA and non-TBI-based conditioning versus TBI-based MAC (HR, .60; *P*=.0004 and HR, .54; $P < .0001$, respectively), and platelet recovery (HR, .15; $P < .0001$) were associated with a significantly decreased risk of DAH (Table 3). Finally, grade II-IV acute GVHD (HR, 1.81; *P*=.001) significantly increased the risk of COP, whereas platelet recovery (HR, .50; *P*=.001) and non-TBI-based conditioning (HR, .47; *P*=.002) were associated with significantly decreased risk (Table 3).

A landmark analysis was conducted at day +100 post-alloHCT to evaluate the impact of platelet recovery on NPT risk (Figure 3A-D). The risk of DAH was significantly lower in patients who had achieved platelet recovery by day +100 (HR, .37; *P*=.0007) (Figure 3D), whereas the risk of IPS and COP was not significantly affected by platelet recovery by day +100 (Figure 3B,C).

Survival Outcomes

The 3-year OS probability for the study cohort was 48.9% (95% CI, 48.1% to 49.6%). Multivariable analysis for OS

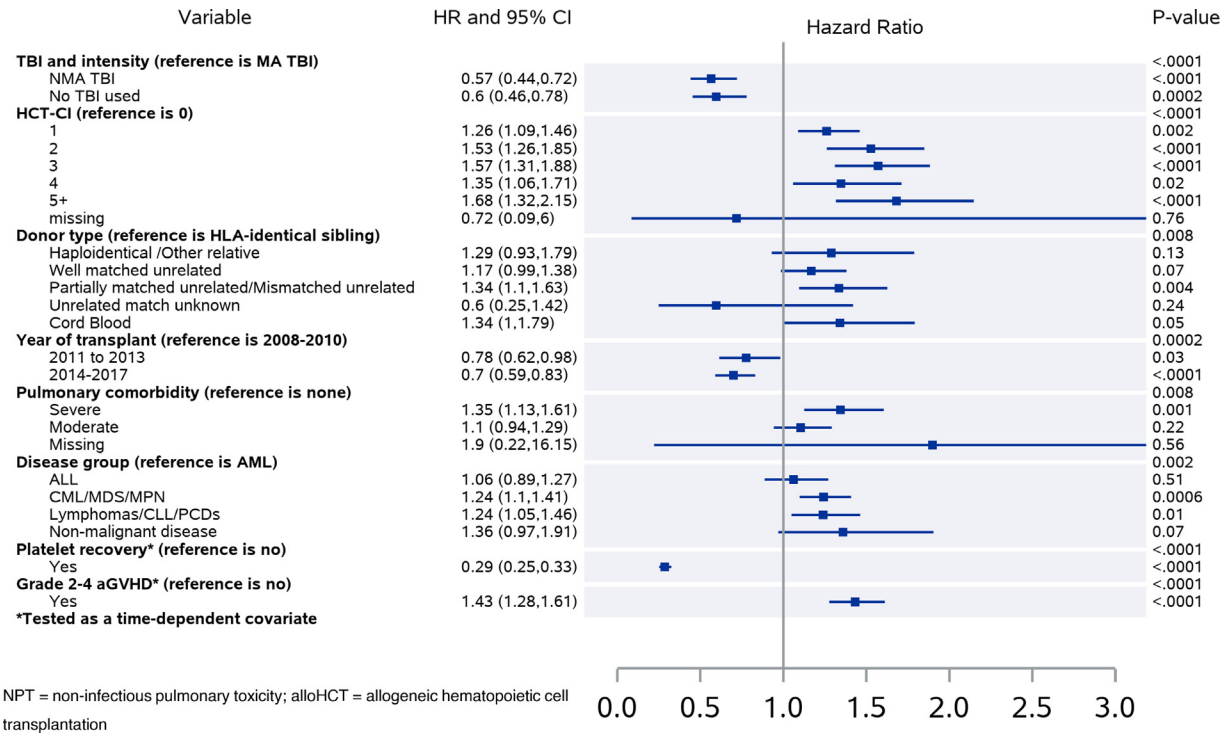

Figure 2. Multivariable analysis: forest plot of risk factors for NPT after alloHCT.

demonstrated that the development of NPT significantly increased the risk of overall mortality (HR, 4.19; $P < .0001$) (Table 4). The multivariable models for IPS, DAH, and COP individually showed an increased mortality risk, with respective HRs of 4.16, 5.6, and 1.93 ($P < .0001$ for all). The effects of other variables on the probability of OS after alloHCT are shown in Table 4 and Supplementary Table S2. Importantly, smoking history (HR, 1.11; $P < .0001$), HCT-CI ≥1 (HR, 1.10-1.45; $P < .01$) and severe pulmonary comorbidity (HR, 1.27; $P < .0001$) significantly increased mortality risk. We also conducted a day +100 landmark analysis to evaluate the impact of NPT on OS after alloHCT (Supplementary Table S3, Figure 4A-D), which showed a significantly decreased OS in patients who developed NPT. Patients who were alive and developed NPT by day +100 had a 1-year OS of 58.4% (95% CI, 54% to 63%), compared with 74.7% (95% CI, 74% to 75.3%) in patients who survived until day +100 without developing NPT ($P < .0001$). Similarly, 3-year OS was significantly improved in patients who survived without NPT by day +100 (57% versus 39%; $P < .0001$).

DISCUSSION

This retrospective analysis of 21,574 patients in a registry-based study examined the incidence of and risk factors for NPT as well as its effect on survival after allogeneic transplant. We identified a 1-year cumulative incidence of 4.9% for IPS, 2.1% for DAH, and .7% for COP. Our analysis demonstrated that TBI-based MAC and HCT-CI score ≥1 increased the risk for IPS, whereas severe pulmonary comorbidity, myelodysplastic and myeloproliferative disorders (ie, chronic myelogenous leukemia, myelodysplastic syndrome, and myeloproliferative neoplasm) were significant risk factors for DAH, and TBI-based MAC and acute GVHD were predictive for both DAH and COP. Severe, but not moderate, pulmonary comorbidity on pre-transplantation PFT and use of mismatched unrelated donor and cord blood transplants were associated with a significantly higher risk of NPT. In contrast, alloHCT performed in 2014 and later, use of non-TBI-based and TBI-based NMA conditioning regimens, and platelet recovery were associated with a lower risk of NPT. The occurrence of acute GVHD abrogated the favorable effect of non-TBI-based and NMA conditioning regimens on the risk of IPS. The more frequent use of reduced-intensity conditioning/NMA regimens and less frequent use of MAC with TBI in the last decade, along with improved supportive care, likely explain the decreased risk of NPT between 2014 and 2017 versus 2008 to 2010.

NPT after alloHCT represents a varied and multifaceted set of problems with significant contributions to morbidity and mortality [23]. Many of the previously reported studies included single-institution retrospective datasets with smaller sample sizes with significant heterogeneity, thereby limiting our understanding of the epidemiology of and outcomes associated with NPT. Previous studies have reported incidence rates ranging from 2% to 15% for IPS, from 2% to 14% for DAH, and from 1% to 10% for COP [4,15,19,24]. Identified risk factors for IPS include MAC (particularly with TBI), age >40 years, and severe acute GVHD [5,25], and those for DAH include older age, MAC (especially with TBI), and acute GVHD [26,27]. Further work suggested delayed or failed neutrophil engraftment as a risk factor for DAH, with delayed platelet engraftment a risk factor after cord blood transplants [28]. COP, in contrast, has been associated with HLA disparity, female donor to male recipient alloHCT, use of peripheral blood stem cell grafts, and acute and chronic GVHD [18,29].

In our present cohort, IPS and DAH were more likely to develop earlier in the post-transplantation course than COP, with a median time to onset of 112 and 50 days post-alloHCT for IPS and DAH, respectively, compared with 246 days for COP. This likely reflects the differences in the underlying pathophysiology of each disorder. In IPS, for example, data from murine models suggest that conditioning agents trigger lung epithelial injury, followed by excessive activation of pulmonary macrophages and alloreactive T lymphocytes [2]. The

Table 3
Multivariable Analysis of NPT after AlloHCT

Variable	N	HR	95% CI	*P* Value
NPT				
TBI and conditioning intensity				
MAC TBI	4216	1		<.0001
NMA TBI	4010	.566	.442-.725	<.0001
No TBI	12,937	.596	.455-.78	.0002
HCT-CI (minus pulmonary)				
0	8514	1		<.0001
1	5193	1.262	1.09-1.461	.0019
2	2287	1.527	1.261-1.849	<.0001
3	2300	1.568	1.307-1.882	<.0001
≥4	2385	1.484	1.231-1.788	<.0001
Donor type				
HLA-identical sibling	5492	1		.0089
Haploidentical/other relative	2612	1.288	.929-1.786	.1288
Well-matched unrelated	8161	1.169	.988-1.383	.0694
Mismatched unrelated	1867	1.33	1.092-1.621	.0046
Cord blood	2845	1.342	1.005-1.792	.0465
Year of transplantation				
2008 to 2010	6318	1		.0003
2011 to 2013	4413	.777	.615-.982	.0346
2014 and after	10,432	.702	.592-.833	<.0001
Pulmonary comorbidity				
None	12,443	1		.0071
Severe	3171	1.352	1.132-1.615	.0009
Moderate	5081	1.105	.944-1.294	.2127
Disease group				
AML	7889	1		.0021
ALL	2469	1.061	.887-1.27	.5145
CML/MDS/MPN	6646	1.245	1.099-1.41	.0006
Lymphomas/CLL/PCDs	3073	1.239	1.049-1.462	.0114
Nonmalignant disease	1086	1.36	.971-1.903	.0734
Platelet recovery				
No	2325	1		<.0001
Yes	18,838	.286	.252-.325	<.0001
Grade II-IV acute GVHD				
No	12,480	1		<.0001
Yes	8683	1.434	1.276-1.611	<.0001
IPS				
HCT-CI (minus pulmonary)				
0	8508	1		<.0001
1	5188	1.26	1.075-1.477	.0044
2	2281	1.437	1.173-1.761	.0005
3	2301	1.595	1.308-1.944	<.0001
≥4	2381	1.489	1.211-1.83	.0002
TBI and conditioning intensity, acute GVHD				
MAC TBI, no acute GVHD	2264	1		.0018
NMA TBI, no acute GVHD	2460	.478	.3788-.6031	<.0001
No TBI, no acute GVHD	7740	.5149	.4335-.6117	<.0001
MAC TBI, acute GVHD	1947	1.0066	.7878-1.2862	.9579
NMA TBI, acute GVHD	1547	.7469	.5494-1.0153	.0625
No TBI, acute GVHD	5186	.8785	.7157-1.0784	.2156
Year of transplantation				
2008 to 2010	6315	1		.0081
2011 to 2013	4411	.848	.716-1.004	.0561
2014 and later	10,418	.801	.695-.923	.0022
Platelet recovery				
No	2311	1		<.0001

(*continued*)

Table 3 (*Continued*)

Variable	N	HR	95% CI	*P* Value
Yes	18,833	.338	.281-.407	<.0001
DAH				
Disease group				
AML	7892	1		.0076
ALL	2468	.992	.724-1.36	.9622
CML/MDS/MPN	6655	1.517	1.197-1.922	.0006
Lymphomas/CLL/PCDs	3074	1.292	.959-1.741	.0915
Nonmalignant disease	1088	1.373	.867-2.174	.1769
Pulmonary comorbidity				
None	12,449	1		.0003
Severe	3172	1.665	1.3-2.132	<.0001
Moderate	5085	1.373	1.093-1.725	.0064
TBI and conditioning intensity				
MAC TBI	4220	1		<.0001
NMA TBI	4012	.598	.449-.797	.0004
No TBI	12,945	.542	.426-.69	<.0001
GVHD prophylaxis				
Ex vivo T cell depletion/CD34$^+$ cell selection	669	1		<.0001
PTCy ± other(s)	2198	1.031	.535-1.987	.9269
CNI + MMF	5936	1.559	.867-2.8	.1377
CNI + MTX	9668	.828	.457-1.501	.535
CNI + other	2109	1.049	.548-2.008	.8858
Year of transplantation				
2008 to 2010	6319	1		<.0001
2011 to 2013	4419	.644	.497-.833	.0008
2014 and later	10,439	.582	.462-.733	<.0001
Grade II-IV acute GVHD				
No	12,490	1		.0006
Yes	8687	1.486	1.185-1.864	.0006
Platelet recovery				
No	2327	1		<.0001
Yes	18,850	.15	.116-.194	<.0001
COP				
TBI and conditioning intensity				
MAC TBI	4218	1		.007
NMA TBI	4013	.753	.423-1.338	.333
No TBI	12,947	.471	.29-.765	.002
Grade II-IV acute GVHD				
No	12,490	1		.001
Yes	8688	1.815	1.26-2.613	.001
Platelet recovery				
No	2327	1		
Yes	18,851	.502	.329-.765	.001

Haplo indicates haploidentical; CNI, calcineurin inhibitor.

association of IPS with higher HCT-CI and TBI-based MAC suggests that a preexisting pulmonary comorbidity (eg, chemotherapy-associated interstitial pneumonitis, smoking-related emphysema) coupled with subsequent conditioning regimen-related toxicity drive the development of IPS. In contrast, the pathogenesis of DAH is thought to be prompted by alveolar epithelial injury, leading to inflammation followed by dysregulated cytokine release, resulting in capillary endothelial injury [30]. Our study demonstrates a strong association of DAH with platelet recovery, as the onset of DAH at a median of 1.7 months post-alloHCT correlated with nonengraftment of platelets. Post-transplantation thrombocytopenia may be associated with thrombotic microangiopathy, which also has been reported as a risk factor for DAH [28]. Furthermore, transfusion-related acute lung injury and transfusion-associated circulatory overload, byproducts of supportive care treatment, can damage the capillary endothelium and worsen preexisting alveolar injury [31]. Based on the increased risk of DAH and COP in patients who develop acute GVHD and the decreased risk in recipients of non-TBI-based conditioning regimens, the data suggest a role for alloreactivity in conjunction with regimen-related toxicity in the development of NPT [32].

This study has several limitations, including its retrospective nature, the observational database of the registry notwithstanding. One caveat of this analysis is the inherent possibility of misdiagnosis or delayed diagnosis of NPT. We acknowledge the possibility that NPT might not have been diagnosed correctly, thereby affecting the incidence estimates. Intrinsically, these entities can have overlapping clinical features with infectious and other noninfectious processes (such as cardiac or

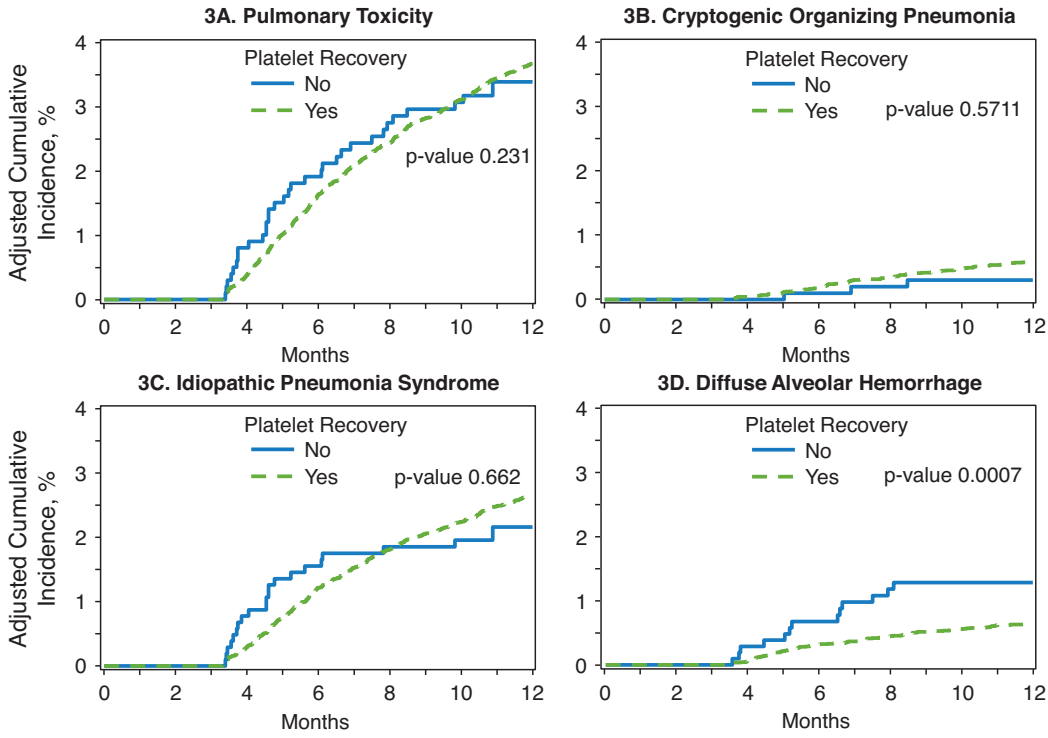

Figure 3. Cumulative incidence of NPT after alloHCT by platelet recovery. (A) NPT; (B) COP; (C) IPS; (D) DAH.

renal) and lung biopsy may be needed to confirm the diagnosis, which may not be feasible. Underutilization of invasive diagnostic procedures may be due to obvious safety concerns in already compromised transplantation recipients. Patchy distribution of disease also may limit the yield of bronchoscopic biopsies compared with surgical lung biopsies [33]. Our data show that the diagnosis of NPT was based largely on clinical context, and that only a small percentage of patients underwent an invasive diagnostic procedure, and that data were not reported in a significant proportion of these. Inherent with real-world practice, diagnostic pathways for NPT often are not universally established and/or implemented across transplantation centers. This study is also limited by the fact that the registry does not capture the details of NPT diagnosis, such as its severity (eg, proportion of patients needing mechanical ventilation after developing NPT), treatments, and subsequent responses. Another limitation is the inability to ascertain the effect of infections, including respiratory, on the development of NPT. Pretransplantation therapies that can increase the predisposition to pulmonary complications, such as bleomycin, checkpoint inhibitors, and thoracic irradiation, could not be included as variables in the analysis; nonetheless, we presume that those patients had residual effects of therapy-induced interstitial pneumonitis on pretransplantation PFTs that were captured in our analysis.

Despite these limitations, however, our results represent real-world evidence regarding of post-transplantation NPT diagnosed based on clinical grounds with imaging, laboratory, and histopathologic support. A prospective study with an algorithmic approach to diagnosing and managing NPT mandated in the protocol will minimize this limitation. More frequent utilization of invasive diagnostic testing, such as transbronchial or thoracoscopic lung biopsy, will increase the probability of an accurate diagnosis. As the clinical presentation of various NPTs can overlap, making diagnosis difficult, the use of a composite NPT endpoint incorporating all 3 entities circumvented the potential limitation of capturing a misclassified NPT (eg, IPS in lieu of COP) in our analysis.

A major strength of this analysis is its large, diverse, and contemporaneous cohort of alloHCT recipients with mature follow-up data. The study population included a variety of malignant and nonmalignant diseases treated with different conditioning and GVHD prophylaxis regimens, donor types, and graft sources, adding to the generalizability of our results. This analysis focused on NPT occurring early in the post-transplantation period, which encompassed the bulk of the IPS, DAH, and COP burden, and was shown to have onset even after the first year post-alloHCT. It is important to note that we excluded bronchiolitis obliterans syndrome in this analysis, given its typical presentation later in the course after alloHCT and its association with chronic GVHD [4,34]. Periengraftment respiratory distress syndrome, which manifests with fever, diffuse infiltrates on imaging, hypoxemia, and an erythematous rash in the absence of infection, occurs in patients with engraftment syndrome (diffuse systemic capillary leak disorder), may be considered to represent a subset of IPS, and is not individually captured in the CIBMTR database [4,35,36].

In conclusion, this registry-based analysis of alloHCT recipients highlights several risk factors for the development of early NPT, including severe pulmonary dysfunction, TBI-based MAC, and acute GVHD. Identification of baseline pretransplantation variables can help elucidate the risk of development of NPT and guide the selection of conditioning, graft source, and GVHD prophylaxis. Because post-transplantation NPT is associated with a several-fold higher mortality risk, it is therefore, prudent to consider the risk of NPT in patients with severe pulmonary dysfunction based on pretransplantation PFT; counseling patients to stop smoking early and tailoring the conditioning to non-TBI-based MAC regimens would be important considerations. It remains to be seen whether

Table 4
Multivariable Analysis for OS Examining the Effect of NPT after AlloHCT

Variable	N	HR	95% CI	*P* Value
NPT				
No	19641	1		<.0001
Yes	1828	4.187	3.782-4.635	<.0001
Disease group				
AML	8001	1		<.0001
ALL	2505	.912	.855-.974	.0059
CML/MDS/MPN	6745	.93	.887-.976	.0033
Lymphomas/CLL/PCDs	3121	.782	.729-.84	<.0001
Nonmalignant diseases	1097	.56	.471-.666	<.0001
Age group				
18-39 yr	5062	1		<.0001
40-64 yr	12036	1.343	1.274-1.417	<.0001
≥65 yr	4371	1.638	1.524-1.761	<.0001
Race				
Caucasian	15914	1		.0011
African American	1643	1.19	1.081-1.311	.0004
Asian/Pacific Islander	1336	.979	.851-1.127	.769
Hispanic	1800	1.054	.971-1.145	.2099
KPS				
>90	3849	1		.0001
≤90	17221	1.187	1.096-1.286	<.0001
History of smoking				
No	12170	1		<.0001
Yes	8499	1.108	1.063-1.153	<.0001
HCT-CI (minus pulmonary)				
0	8636	1		<.0001
1	5264	1.105	1.047-1.167	.0003
2	2311	1.214	1.129-1.305	<.0001
3	2332	1.225	1.135-1.322	<.0001
≥4	2429	1.45	1.351-1.556	<.0001
Pulmonary comorbidity				
None	12624	1		<.0001
Severe	3220	1.27	1.194-1.351	<.0001
Moderate	5144	1.031	.975-1.09	.2806
Prior autologous HCT				
No	20202	1		<.0001
Yes	1267	1.226	1.136-1.323	<.0001
GVHD prophylaxis				
Ex vivo T cell depletion/CD34 selection	687	1		<.0001
PTCy ± other(s)	2235	.989	.782-1.251	.9277
CNI + MMF	5999	1.148	.932-1.415	.1933
CNI + MTX	9762	.974	.777-1.22	.8164
CNI ± other	2118	1.017	.803-1.29	.8863
Year of transplantation				
2008 to 2010	6379	1		<.0001
2011 to 2013	4471	.824	.772-.879	<.0001
2014 and later	10619	.739	.693-.787	<.0001
Donor type, graft source				
HLA-identical sibling BM	636	1		<.0001
HLA-identical sibling PBSCs	4925	1.284	1.089-1.513	.0029
Haplo-related BM	846	1.407	1.167-1.697	.0003
Haplo-related PBSCs	1814	1.543	1.281-1.86	<.0001
Matched unrelated BM	1436	1.341	1.151-1.563	.0002
Matched unrelated PBSCs	6826	1.339	1.147-1.564	.0002
Mismatched unrelated BM	366	1.778	1.458-2.169	<.0001
Mismatched unrelated PBSCs	1521	1.644	1.373-1.967	<.0001
Cord blood	2904	1.711	1.376-2.127	<.0001

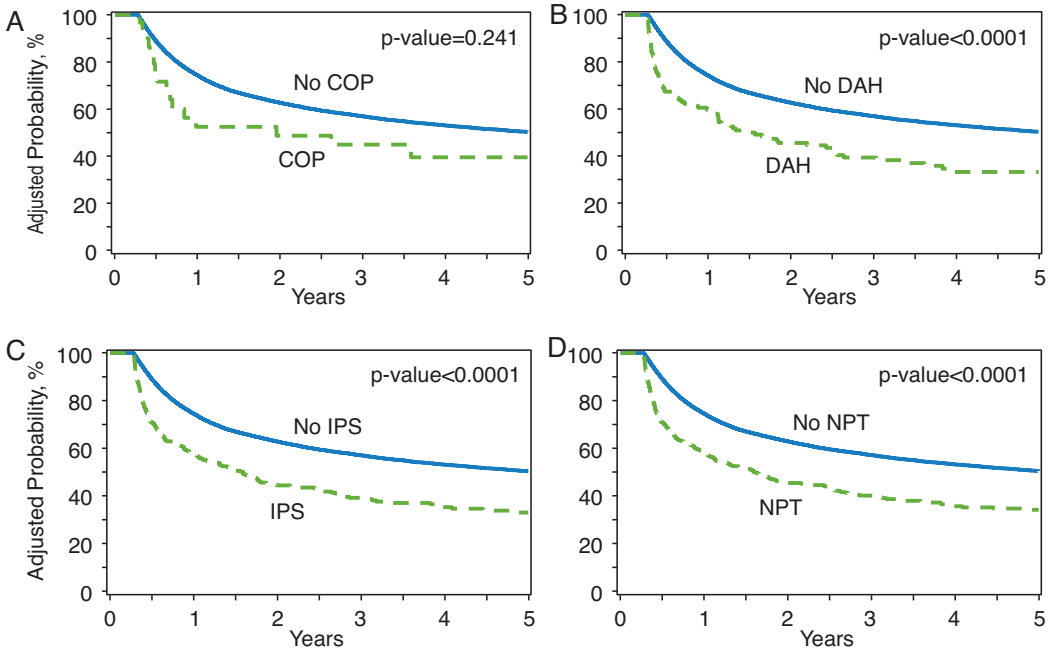

Figure 4. Day +100 landmark analysis for OS in patients with and without COP (A), with and without DAH (B), with and without IPS (C), and with and without any NPT (D).

recent changes in treatments for hematologic malignancies (targeted and immunotherapy approaches), novel transplantation conditioning and GVHD platforms (eg, post-transplantation cyclophosphamide for GVHD prophylaxis and ruxolitinib for severe acute GVHD) affect the risk of NPT and outcomes of NPT in alloHCT recipients. Future research should focus on exploring the mechanisms contributing to NPT development and identifying biomarkers to predict and risk-stratify these patients and to develop effective novel therapies. Advances in novel therapeutic approaches for NPT that will improve survival represent an area of significant unmet clinical need.

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Authorship statement: S.S.P., NS.M., B.K.H., K.W.A., and S.C. designed the study; C.B. acquired the data; K.W.A., M.K., S.S.P., and S.C. analyzed and interpreted the data; S.S.P. drafted the manuscript; and S.C. critically reviewed and revised the manuscript. All authors reviewed, critiqued, and approved the final manuscript.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2022.03.015.

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