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Risk of myeloid neoplasms after solid organ transplantation

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Abstract

Solid organ transplant recipients have elevated cancer risks, due in part to pharmacologic immunosuppression. However, little is known about risks for hematologic malignancies of myeloid origin. We linked the US Scientific Registry of Transplant Recipients with 15 population-based cancer registries to ascertain cancer occurrence among 207,859 solid organ transplants (1987–2009). Solid organ transplant recipients had significantly elevated risk for myeloid neoplasms, with standardized incidence ratios (SIRs) of 4.6 (95% confidence interval 3.8–5.6; N=101) for myelodysplastic syndromes (MDS), 2.7 (2.2–3.2; N=125) for acute myeloid leukemia (AML), 2.3 (1.6–3.2; N=36) for chronic myeloid leukemia, and 7.2 (5.4–9.3; N=57) for polycythemia vera. SIRs were highest among younger individuals and varied by time since transplantation and organ type (Poisson regression P<0.05 for all comparisons). Azathioprine for initial maintenance immunosuppression increased risk for MDS (P=0.0002) and AML (2–5 years

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CONFLICTS OF INTEREST

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after transplantation, P=0.0163). Overall survival following AML/MDS among transplant recipients was inferior to that of similar patients reported to US cancer registries (log-rank P<0.0001). Our novel finding of increased risks for specific myeloid neoplasms after solid organ transplantation supports a role for immune dysfunction in myeloid neoplasm etiology. The increased risks and inferior survival should heighten clinician awareness of myeloid neoplasms during follow-up of transplant recipients.

INTRODUCTION

In the United States (US), nearly 30 000 patients annually undergo solid organ transplantation.[1] Clinical advances have led to substantial improvements in survival following transplantation, increasing the public health and clinical importance of understanding the long-term health effects of solid organ transplantation. The elevated cancer risks experienced by transplant recipients, largely due to pharmacologic immunosuppression to prevent graft rejection, are a key cause of morbidity and mortality following transplantation.[1–3]

Post-transplantation lymphoproliferative disorders (PTLDs) are among the most common serious complications of transplantation,[1] but much less is known about the risks for hematologic malignancies of myeloid origin. Increased risks have been reported after solid organ transplantation for all myeloid neoplasms combined[4, 5] and for acute myeloid leukemia (AML).[6, 7] However, myeloid neoplasms comprise a range of diseases – including AML, myelodysplastic syndrome (MDS, which may progress to AML), chronic myeloid leukemia (CML), and other rarer entities such as polycythemia vera.[8] Survival following a myeloid neoplasm diagnosis is generally poor, with estimated 5-year relative survival of 22% for AML, 41% for MDS, and 68% for CML in the US.[9] Exposure to ionizing radiation and cytotoxic chemotherapy are established risk factors for certain myeloid neoplasms,[10] but otherwise the causes of these malignancies remain unclear.[8, 11] Evidence increasingly supports a role for immune dysfunction in the development of myeloid neoplasms, with elevated risks observed for individuals with a history of certain infections and autoimmune disease[12–15] or HIV/AIDS.[16, 17]

We therefore conducted the first comprehensive investigation of the spectrum of risks for specific myeloid neoplasms among 207 859 solid organ transplants occurring in the US during 1987–2009 in the Transplant Cancer Match Study.[2]

METHODS

Transplant Cancer Match Study

The Transplant Cancer Match Study (www.transplantmatch.cancer.gov)[2] provides comprehensive, systematic cancer ascertainment for solid organ transplant recipients by linking data from the Scientific Registry of Transplant Recipients (SRTR) with population-based cancer registries. The SRTR includes detailed information on all US solid organ transplants since 1987. Structured data are obtained regularly from transplant centers, including information on recipients (e.g., demographics, medical history, indication for

transplant [Supplemental Table]), type of organ transplanted, and medications used for induction and baseline maintenance of immunosuppression to prevent graft rejection.

During 2008–2012, serial record linkages were completed between the SRTR and 15 population-based cancer registries: California (years of coverage: 1988–2008), Colorado (1988–2009), Connecticut (1973–2009), Florida (1981–2009), Georgia (1995–2008), Hawaii (1973–2007), Illinois (1986–2007), Iowa (1973–2009), Michigan (1985–2009), North Carolina (1990–2007), New Jersey (1979–2006), New York (1976–2007), Seattle/Puget-Washington (1974–2008), Texas (1995–2006), and Utah (1973–2008). Transplant recipients residing in these registry areas during the specified time periods were eligible for this analysis (46% of the US transplant population). We further excluded transplant recipients with unknown race/ethnicity (N=1421) or history of HIV (N=238). The study was approved by human subjects research review committees at the National Cancer Institute and, as required, participating cancer registries.

Myeloid Neoplasm Ascertainment

Incident diagnoses of myeloid neoplasms were identified through the cancer registries using International Classification of Diseases for Oncology, 3rd Edition morphology codes,[18] grouped according to the World Health Organization[8] classification into AML (9840, 9861, 9866–9867, 9870–9874, 9891, 9895–9897, 9910, 9920, 9930–9931), MDS (9980–9989), CML (9863, 9875–9876), chronic myelomonocytic leukemia (CMML; 9945–9946), polycythemia vera (9950), and other chronic myeloproliferative disorders (9960–9964, 9975; combined due to small numbers of observed cases). CMML, MDS, polycythemia vera, and other chronic myeloproliferative disorders only became reportable to cancer registries in 2001 and, thus, were not ascertained prior to 2001.

Statistical Analysis

For each transplant, follow-up began on the date of transplantation, start of cancer registry coverage, or (for evaluation of CMML, MDS, polycythemia vera, and other chronic myeloproliferative diseases) January 1, 2001, whichever came last. Follow-up ended at the earliest of: myeloid neoplasm diagnosis, graft failure, re-transplantation, death, loss to follow-up, or end of cancer registry coverage. Follow-up time ended at graft failure or re-transplantation due to substantial changes in clinical status (e.g., immunosuppression medication use) associated with these events.

To quantify risk of myeloid neoplasms after solid organ transplantation in comparison with the general population, we used standardized incidence ratios (SIRs). Expected numbers of cases were calculated by applying myeloid neoplasm incidence in the cancer registry areas to the person-time at risk of the transplant recipients, stratifying on age (5-year groups), sex, race/ethnicity, calendar year, and registry. Exact 95% confidence intervals (CIs) about the SIR were computed based on the Poisson distribution. We compared myeloid neoplasm SIRs for recipient subgroups (e.g., defined by age at transplantation or organ type) using a Wald test ($P_{homogeneity}$) derived from multivariate Poisson regression models that included terms for age at transplantation, sex, race, transplanted organ, and year of transplantation.

We conducted a sensitivity analysis restricted to those transplants performed during years when cancer registries captured the cancers of interest (i.e., transplants for which follow-up began at the date of transplantation). For AML and CML, this analysis included transplants occurring after the start of cancer registry coverage (N=202 626 transplants). For CMML, MDS, polycythemia vera, and other chronic myeloproliferative disorders, this analysis included transplants occurring in 2001 or later (N=105 130 transplants). Because the occurrence of a previous cancer may alter risk of subsequent myeloid neoplasms, we conducted a second sensitivity analysis restricting the cohort to individuals with no history of cancer prior to transplantation and censoring people when they developed any cancer (for AML and CML: N=194 355 transplants; for CMML, MDS, polycythemia vera, and other chronic myeloproliferative disorders: N=105 130). Results from these sensitivity analyses were similar to the main results and, thus, are not presented.

To understand the clinical impact of myeloid neoplasms in solid organ transplant recipients, we conducted two types of analyses. First, we estimated the relative risk (RR) of mortality from any cause associated with myeloid neoplasm development using hazard ratios (HRs) and 95% CIs derived from multivariate Cox regression models. Models used time since transplantation as the time scale and were adjusted for age at transplantation, sex, race, transplanted organ, and year of transplantation, with a time-dependent covariate indicating myeloid neoplasm diagnosis. Second, we constructed Kaplan-Meier curves for overall survival (i.e., time before death due to any cause) after myeloid neoplasm diagnosis, comparing transplant recipients to individuals with the same diagnoses reported to 17 SEER cancer registries.[9] Because demographic factors are important determinants of overall survival, we individually-matched 10 SEER cases (selected randomly) to each case from the transplant population by age and calendar year of myeloid neoplasm diagnosis (±5 years), sex, and race/ethnicity. Overall survival was then compared between the two patient populations using the log-rank test.

RESULTS

Among 207 859 solid organ transplants occurring during 1987–2009 (950 464 person-years of follow-up), kidney was the most frequently transplanted organ (58%), followed by liver (22%), heart (10%), lung (4%), and other or multiple organs (6%, Table 1). The majority of recipients were male (61%) and non-Hispanic white (62%), and most transplants occurred at ages 35–64 years (67%). Recipient characteristics varied by type of transplanted organ. In particular, the proportion of males ranged from 52% for lung recipients to 75% for heart recipients, and the proportion of individuals aged ≥50 years at transplantation ranged from 21% for recipients of other/multiple organs to 59% for lung recipients.

Compared with the general population, solid organ transplant recipients had significantly and substantially elevated risks for myeloid neoplasms, with risks (SIRs) increased 2.7-fold (95%CI 2.2–3.2) for AML, 4.6-fold (3.8–5.6) for MDS, 2.3-fold (1.6–3.2) for CML, and 7.2-fold (5.4–9.3) for polycythemia vera (Table 2). Risks were non-significantly elevated 2.1-fold (0.8–4.6) for CMML (N=6) and 1.8-fold (1.0–2.9) for other chronic myeloproliferative disorders (N=16), but the small numbers of observed cases for these entities precluded further analysis.

Incidence of AML and MDS increased with increasing age at transplantation, reaching 32.2 and 25.7 cases/100 000 person-years, respectively, for individuals aged ≥65 years at transplantation (Figure 1). In contrast, incidence of CML was approximately 5 cases/100 000 person-years for ages 35–49, 50–64, and ≥65 years, whereas incidence of polycythemia vera was approximately 12 cases/100 000 person-years for ages 20–34, 35–49, and ≥65 years but only 5 cases/100 000 person-years for ages 50–64. Unlike the incidence patterns, SIRs for all myeloid neoplasms (reflecting risk relative to the general population) were highest in young recipients and decreased monotonically with increasing age, with the exception of polycythemia vera.

For AML and polycythemia vera, SIRs also varied significantly by time since transplantation (Figure 2). Risks for AML were increased 2.0-fold during the first year following transplantation and peaked at 4.6-fold during 1–1.9 years following transplantation, with declining risk thereafter ($P_{homogeneity}$=0.0456). In contrast, polycythemia vera risk was increased 22.0-fold during the first year following transplantation, with SIRs dropping precipitously thereafter, yet remaining significantly increased 2.9–6.7-fold ($P_{homogeneity}$=0.0003). For MDS, risks appeared to decline consistently during the first five years following transplantation and increase again thereafter, although these changes were not statistically significant ($P_{homogeneity}$=0.5170). For CML, risk did not vary by time since transplantation ($P_{homogeneity}$=0.8049).

In analyses by type of organ transplanted, risk patterns differed for specific myeloid neoplasms (Table 2). For MDS, risks were strikingly high among lung recipients (SIR=14.3) and recipients of other/multiple organs (SIR=14.0) but substantially lower, albeit still significantly elevated compared with the general population, among heart (SIR=4.5), liver (SIR=4.4) and kidney (SIR=3.8) recipients ($P_{homogeneity}$=0.0001). Risks for AML also were highest among lung recipients (SIR=6.5) but were lowest for recipients of other/multiple organs (SIR=1.4; $P_{homogeneity}$=0.0126). In contrast, risks for polycythemia vera were 9.0-fold increased among kidney recipients and 21.7-fold increased among recipients of other/multiple organs, although these differences in risk by organ type were not significant ($P_{homogeneity}$=0.1580); the strikingly elevated risk for polycythemia vera in the first year following transplantation also was evident across organ type (data not shown). Risks for CML did not differ significantly by organ type ($P_{homogeneity}$=0.9997).

To further understand differences in myeloid neoplasm risk by the type of organ transplanted, we explored risks according to receipt of immunosuppressive medications to prevent graft rejection and indication for transplantation. Individuals who received azathioprine for initial maintenance of immunosuppression had significantly higher risk for MDS (SIR=8.4 *vs.* 3.5, P=0.0002) and for AML occurring 2–5 years after transplantation (SIR=6.6 *vs.* 1.7, P=0.0163; with no association for AML occurring <2 or >5 years after transplantation), whereas no association was observed for CML or polycythemia vera. Inclusion of azathioprine in the multivariate Poisson regression models for AML and MDS reduced the heterogeneity in risks observed by organ type. No other therapies for induction of immunosuppression at the time of transplantation (monoclonal antibodies, polyclonal antibodies, alemtuzumab, or interleukin-2 receptor antagonists) or for initial maintenance of immunosuppression (cyclosporine, tacrolimus, mycophenolate mofetil, mTOR inhibitors,

steroids) were associated with myeloid neoplasm risk (data not shown). We also did not observe significantly increased risks of myeloid neoplasms associated with broadly defined indications for transplantation (data not shown).

Within the cohort of transplant recipients, risk of death was significantly increased 14.4-fold (95%CI 11.8–17.6) following the diagnosis of AML, 6.8-fold (5.2–8.7) following MDS, and 2.4-fold (1.3–4.4) following CML, but not significantly increased following the diagnosis of polycythemia vera (RR=1.2, 95%CI 0.6–2.4). Compared to patients reported to SEER cancer registries, overall survival was consistently inferior among transplant patients with AML (median survival: transplant patients=0.31 years, SEER patients=0.83 years; log-rank P<0.0001) and MDS (median survival: transplant patients=1.07 years, SEER patients=2.90 years; P<0.0001) (Figure 3). In contrast, overall survival following CML and polycythemia vera was lower, but not significantly, in transplant patients compared to patients reported to SEER cancer registries (P=0.5464 and 0.2105, respectively).

DISCUSSION

By combining national data on solid organ transplantation with systematic cancer ascertainment from population-based registries, we provide the first comprehensive study demonstrating that transplant recipients have significantly elevated risk for a range of myeloid neoplasms. Although these malignancies are relatively rare, the increased risks as well as the inferior survival following diagnosis, particularly for AML and MDS, should heighten the clinical awareness of myeloid neoplasms during long-term follow-up of solid organ transplant recipients.

Our results support a role for immune dysfunction in myeloid neoplasm etiology, consistent with the observations of increased myeloid neoplasm risk among individuals with HIV/AIDS[16, 17] or a history of autoimmune disease and infections.[12–15] The persistently elevated risks for myeloid neoplasms following transplantation varied by type of organ transplanted and time since transplantation, with no clear association with specific indications for transplantation. Our findings contrast with the U-shaped pattern of risk by time since transplantation for NHL,[19, 20] for which early-onset disease risks are attributed to Epstein-Barr virus infection and receipt of T-cell depleting polyclonal antibodies, and later-onset disease risks are attributed to longer-term immunosuppression.[19, 21, 22]

AML and MDS were the most commonly occurring myeloid neoplasms in solid organ transplant recipients. The higher risks we observed for lung recipients compared with recipients of other organs were attributable in part to the increased use of azathioprine, which was associated with increased risk of AML and MDS. Our findings are consistent with a previous study of AML among solid organ transplant recipients[6] and confirm previous reports of increased AML/MDS risk associated with use of azathioprine or other antimetabolites.[6, 23–28] In current clinical practice in the US, azathioprine is used infrequently in solid organ transplant recipients, having been largely replaced by mycophenolate mofetil.[29] Although the lack of association between myeloid neoplasm risk and mycophenolate mofetil or any of the other immunosuppressive drugs we evaluated is reassuring, our results should be interpreted cautiously in light of the potential for

incomplete ascertainment of medication use, lack of information on long-term use, and our inability to evaluate drug doses.[30] Clinical awareness of myeloid neoplasm risk after solid organ transplantation is particularly relevant for MDS/AML due to the improved outcomes for patients treated for MDS before progression to AML.

We also observed elevated risks for CML and polycythemia vera. CML is a relatively rare malignancy with a largely unknown etiology. The elevated risks observed in our study were consistent with those reported previously in the Transplant Cancer Match study,[2] as well as another study.[5] Albeit based on small numbers of cases, we did not observe significant variation in CML risk by recipient subgroup, unlike the other myeloid neoplasms. Our finding of elevated risks for polycythemia vera among solid organ transplant recipients, particularly in the first year following transplantation, has not been reported in the literature. This association may be spurious, particularly the strikingly elevated risks in the first year following transplantation, for example resulting from misdiagnosis among kidney recipients with a history of erythropoietin use[31] or incidental diagnosis of previously undetected disease, particularly in liver recipients with Budd-Chiari syndrome.[32] However, risks of polycythemia vera remained significantly elevated for the duration of post-transplantation follow-up in this study, supporting a causal role for transplantation in polycythemia vera development.

Further research is warranted to explore the biological mechanisms that may contribute to the development of myeloid neoplasms following solid organ transplantation. Pharmacologic immunosuppression to prevent graft rejection may result in loss of critical immunosurveillance function, as described for CML.[33] Alternatively, a role for immune stimulation in AML etiology is supported by a recent report of elevated serum kappa and lambda immunoglobulin free light chains (FLCs) prior to the development of AML.[34] That observation is particularly intriguing in light of similar observations for lymphoma risk after solid organ transplantation[35] or HIV/AIDS.[36] Further research also is warranted to clarify the importance of direct cytotoxicity versus immunosuppression intensity or duration of certain immunosuppressive agents in myeloid neoplasm etiology.

The incidence of most myeloid neoplasms increased with increasing age. However, the SIR for each specific myeloid neoplasm type was significantly higher among younger versus older individuals at transplantation, and the median age at diagnosis among transplant recipients compared with SEER population-based cases ranged from 17 years younger for MDS to 5 years younger for CML. This risk pattern may result from intrinsic susceptibility of young individuals to the direct or indirect carcinogenic effects of immunosuppressive medications. Alternatively, transplantation may have a larger relative effect in younger individuals, who have had less time to accumulate carcinogenic exposures that may lead to myeloid neoplasm development.

We present the first large-scale analysis demonstrating that overall survival in transplant recipients was significantly inferior for AML and MDS compared with patients diagnosed with these malignancies reported to SEER cancer registries. Optimal treatment approaches for myeloid neoplasms following transplantation are not known, although normal kidney and liver function are required for a number of standard chemotherapeutic regimens.

Unfortunately, data on myeloid neoplasm treatments, cytogenetic abnormalities, and comorbidities were not available for transplant recipients, and, thus, we could not determine whether the observed differences in survival may be explained by differences in these factors. Additionally, we lacked detailed data on cause of death, and some deaths in the transplant cohort may have been due to transplant-related disease.

The linkage of two major population-based data sources enabled us to conduct the first assessment of risk for the spectrum of myeloid neoplasms following solid organ transplantation. The population-based nature of the data eliminated the biases associated with previous clinical series, whereas the large sample size facilitated investigation of less common myeloid neoplasms as well as estimation of risks among patient subgroups. However, several limitations of our study should be considered in the interpretation of our results. Because cancer diagnoses were ascertained through central registries, standardized pathology review was not feasible. Although diagnostic criteria for specific myeloid neoplasms has changed over time,[8] the impact of these changes on our results was minimized by comparing myeloid neoplasm incidence in solid organ transplant recipients to that in the general population, which was presumably affected by similar changes. Risks may have been underestimated because cancers diagnosed in patients who had migrated out of the cancer registry areas were not ascertained, although analyses of migration of the transplant population suggest that this affects only a small number of individuals.[2] Finally, despite the large sample size, our statistical power for evaluating risks in certain patient subgroups remained limited.

In summary, we observed significantly elevated risks for AML, MDS, CML, and polycythemia vera after solid organ transplantation. Diagnoses of AML, MDS, and CML were associated with an increased risk of death within the transplant cohort, and overall survival following AML and MDS in transplant recipients was significantly inferior when compared with patients with the same diagnoses reported to SEER cancer registries. Our findings call for an increased awareness of myeloid neoplasms in the risk/benefit assessment for solid organ transplantation and during long-term follow-up of solid organ transplant recipients. Additionally, further research is needed to elucidate the role of immune dysfunction in myeloid neoplasm etiology and to identify optimal treatments for myeloid neoplasms in immunosuppressed individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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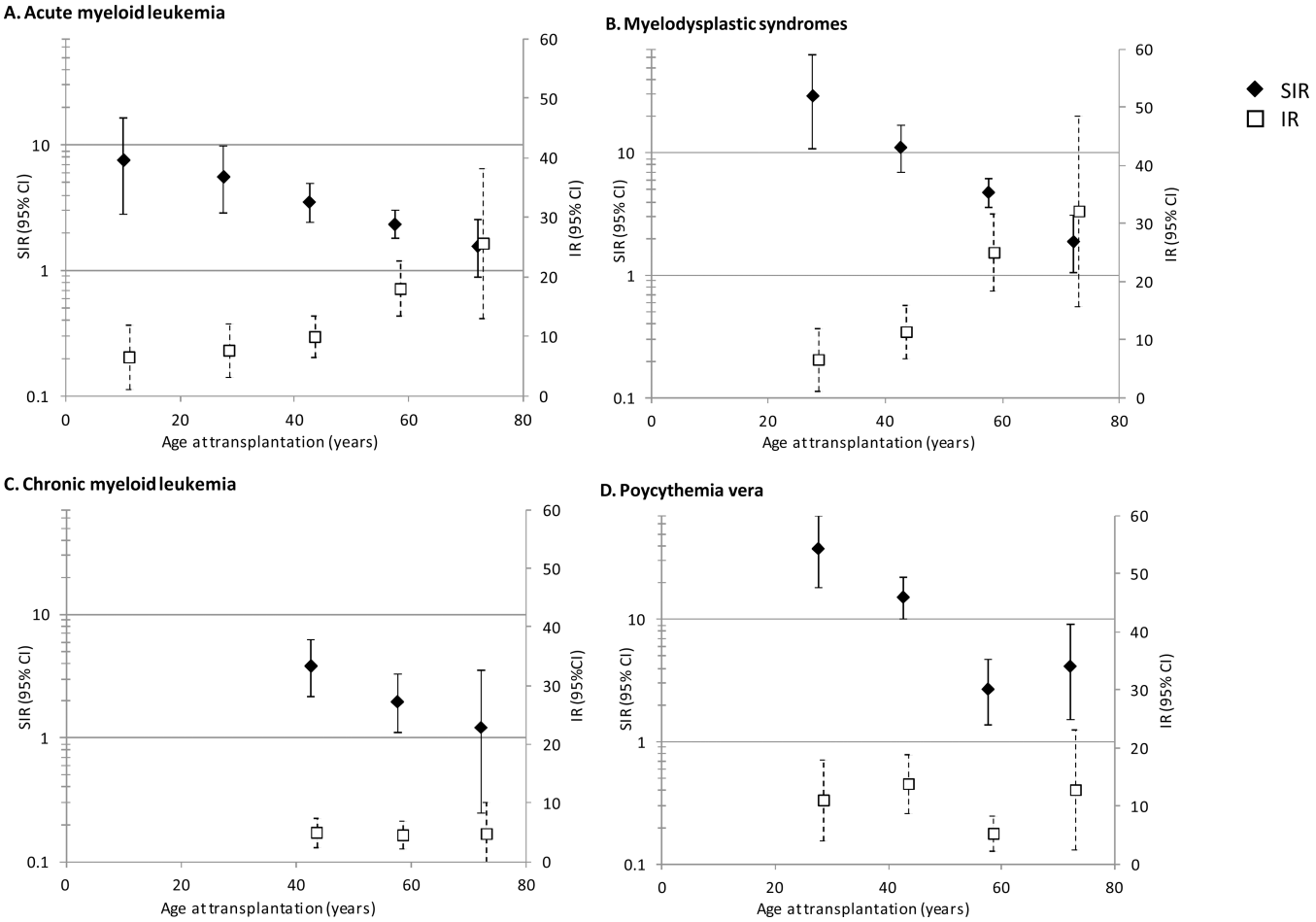


Figure 1. Incidence rates (per 100 000 person-years) and standardized incidence ratios* for specific myeloid neoplasms by age at transplantation among 207 859 solid organ transplants in the United States, 1987–2009

Abbreviations: confidence interval (CI), incidence rate (IR), standardized incidence ratio (SIR). SIRs are presented for 0–19, 20–34, 35–49, 50–64, and 65+ years, with estimates centered over these intervals.

* IRs and SIRs are not presented when <3 cases were observed due to imprecise estimates.

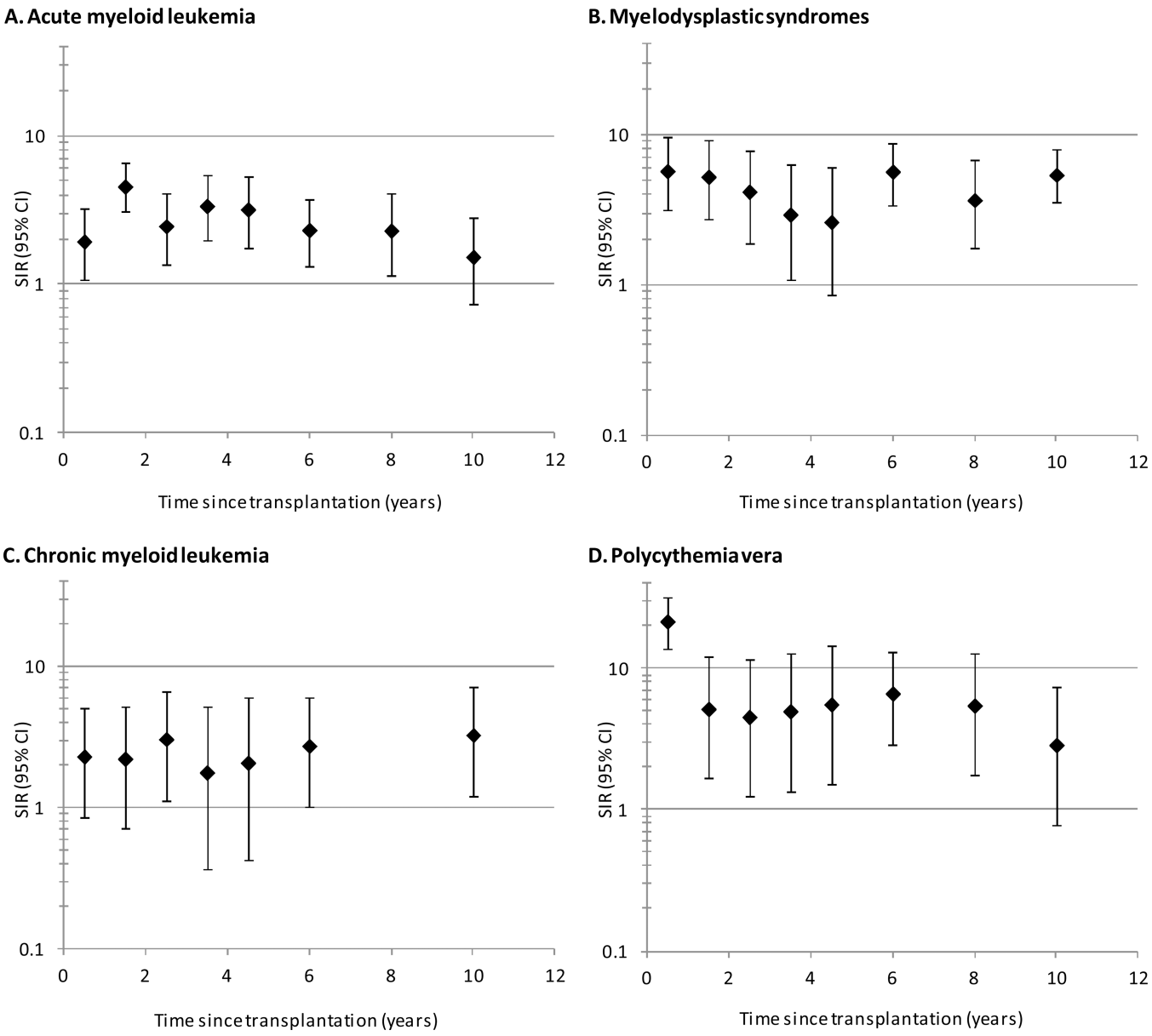
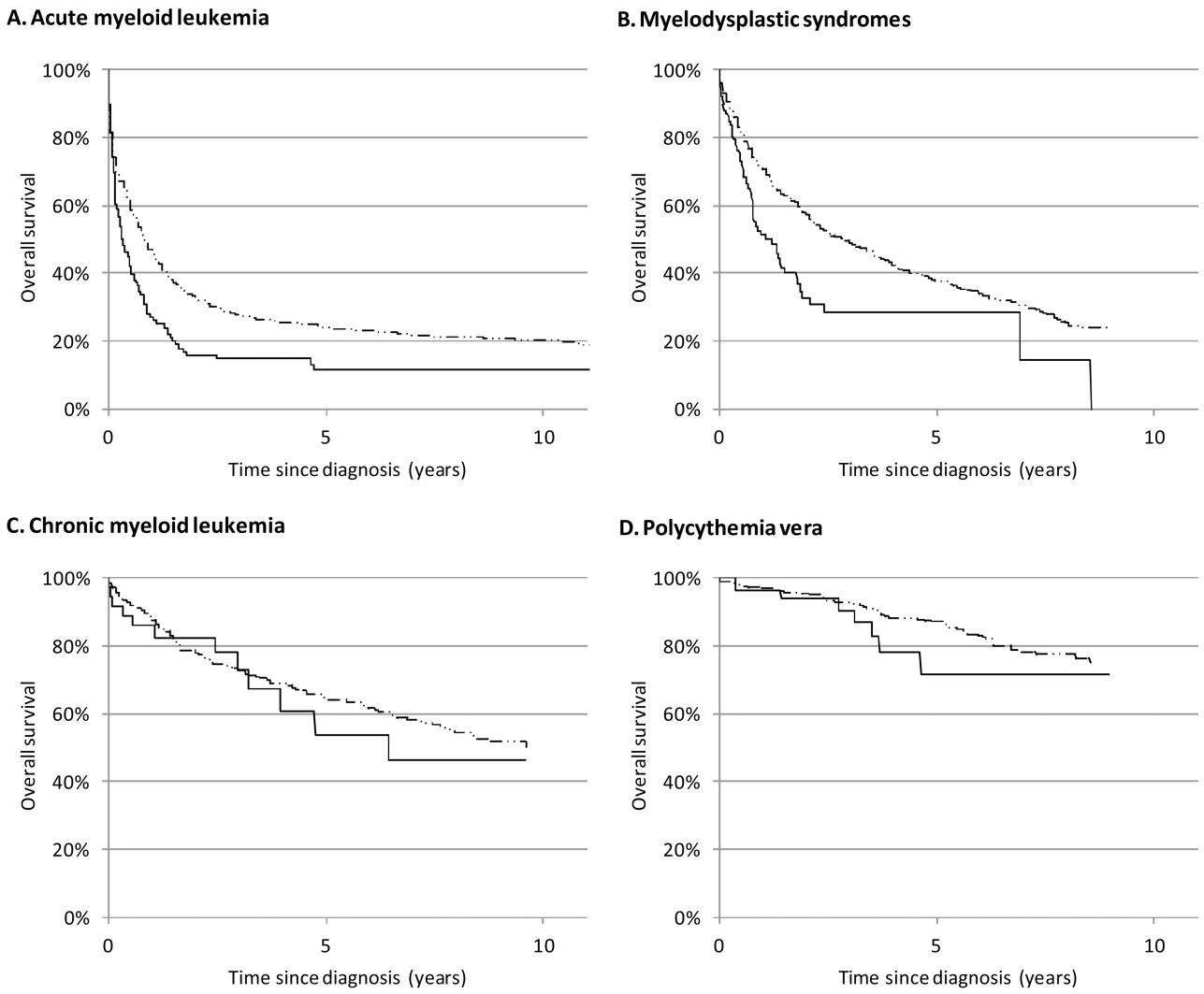


Figure 2. Standardized incidence ratios* for specific myeloid neoplasms by time since transplantation among 207 859 solid organ transplants in the United States, 1987–2009

Abbreviations: confidence interval (CI), standardized incidence ratio (SIR). SIRs are presented for <1, 1–1.9, 2–2.9, 3–3.9, 4–4.9, 5–6.9, 7–8.9, and 9+ years, with estimates centered over these intervals.

* SIRs are not presented when <3 cases were observed due to imprecise estimates.



	SEER		Transplant		
	Overall % deceased	Median survival (years)	Overall % deceased	Median survival (years)	Log-rank P
Acute myeloid leukemia	75%	0.83	82%	0.31	<0.0001
Myelodysplastic syndromes	57%	2.90	59%	1.07	<0.0001
Chronic myeloid leukemia	38%	10.02	33%	6.45	0.5464
Polycythemia vera	15%	Not reached	14%	Not reached	0.2105

Figure 3. Overall survival following myeloid neoplasm diagnosis among 207 859 solid organ transplants in the United States, 1987–2009, compared with matched* patients reported to the SEER Program

Abbreviations: Surveillance, Epidemiology, and End Results (SEER), Scientific Registry of Transplant Recipients (SRTR).

* A sample of cases of each myeloid neoplasm type was selected from SEER, individually-matching 10 SEER cases per transplant case by age and calendar year of myeloid neoplasm diagnosis (±5 years), sex, and race.

Table 1

Recipient characteristics for 207 859 solid organ transplants* in the United States, 1987–2009

			Type of organ transplanted				
	Total (N=207 859)		Kidney (N=120 307)	Liver (N=45 742)	Heart (N=20 758)	Lung (N=8 543)	Other/ multiple** (N=12 509)
Characteristic	N	%	%	%	%	%	%
Sex							
Male	126 944	61	60	61	75	52	58
Female	80 915	39	40	39	25	48	42
Age at Transplantation, years							
0–19	18 356	9	7	12	15	6	6
20–34	31 621	15	19	6	8	13	24
35–49	64 871	31	33	29	20	21	50
50–64	75 430	36	32	44	48	51	19
65+	17 581	8	9	8	9	8	2
Race/Ethnicity							
White, Non–Hispanic	129 379	62	54	70	74	86	76
Black, Non–Hispanic	35 185	17	22	9	14	7	11
Hispanic	31 902	15	17	16	9	6	11
Asian/Pacific Islander	11 393	5	7	5	3	1	2
Transplant Number							
First	189 463	91	91	91	97	96	82
Second	16 816	8	9	8	3	4	16
Third or Higher	1 580	1	1	1	0	0	2
Calendar Year of Transplantation							
1987–1994	38 506	19	19	18	26	13	13
1995–1999	52 361	25	25	25	28	25	26
2000–2004	64 715	31	31	32	28	31	34
2005–2009	52 277	25	25	26	19	32	27

* Includes 207,859 transplants occurring among 192 562 individuals.

** Other/multiple includes kidney-pancreas (N=7267), pancreas (N=1892), kidney-liver (N=1743), heart-lung (N=427), kidney-heart (N=287), intestine (N=279), liver-intestine (N=229), pancreas-liver-intestine (N=181), and other rare solid organ transplants (N=204).

Table 2

Risk of specific myeloid neoplasms overall and by type of organ transplanted among 207 859 solid organ transplants in the United States, 1987–2009

	Acute myeloid leukemia			Myelodysplastic syndromes			Chronic myeloid leukemia			Polycythemia vera		
Characteristic	**N**	**SIR**	**95% CI**	**N**	**SIR**	**95% CI**	**N**	**SIR**	**95% CI**	**N**	**SIR**	**95% CI**
Total	125	2.7	2.2–3.2	101	4.6	3.8–5.6	36	2.3	1.6–3.2	57	7.2	5.4–9.3
Transplanted Organ												
Kidney	46	1.8	1.3–2.5	45	3.8	2.8–5.1	20	2.3	1.4–3.6	37	9.0	6.4–12.4
Liver	38	3.5	2.5–4.8	22	4.4	2.7–6.6	8	2.4	1.0–4.7	11	5.7	2.8–10.2
Heart	29	3.7	2.5–5.3	17	4.5	2.6–7.2	5	2.1	0.7–4.9	3	2.3	0.5–6.6
Lung	10	6.5	3.1–11.9	11	14.3	7.2–25.7	<3	2.1	0.1–11.6	0	0.0	0.0–12.2
Other/multiple	<3	1.4	0.2–5.1	6	14.0	5.2–30.5	<3	3.4	0.4–12.3	6	21.7	8.0–47.2
$P_{homogeneity}$*			0.0126			0.0001			0.9997			0.1580

Exact cell counts with <3 cases are not presented to protect patient confidentiality.

*P from a Wald chi-square test of homogeneity derived from a multivariate Poisson regression model adjusted for sex, age at transplantation, race, and calendar year of transplantation.