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Transplantation. Author manuscript; available in PMC 2026 June 23.

Published in final edited form as:

Transplantation. 2025 October 01; 109(10): 1611–1625. doi:10.1097/TP.0000000000005377.

Risk Factors for Solid Organ Graft Failure and Death in Solid Organ Transplant Recipients Undergoing Hematopoietic Cell Transplantation- A Retrospective Center for International Blood and Marrow Transplant Research (CIBMTR) and Organ Procurement & Transplantation Network (OPTN) Study

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DISCLOSURES:

Dr. Schoettler reports consulting and honorarium from Omeros and Alexion

Dr. Battiwalla reports research support to their Institution from Novartis.

Dr. Hamilton reports (ad hoc) advisory boards for Nkarta, Sanofi, Incyte, Rigel, Maat; consultancy with ACI Group, Therakos/ Mallinkrodt speaker fees; data safety monitoring committee for Angiocrine; adjudication committee with CSL Behring.

Dr. Schoemans reports having received personal fees from Incyte, Janssen, Novartis, Sanofi and from the Belgian Hematological Society (BHS) paid to her institution; and serves as a volunteer for the EBMT.

Dr. Sorror reports receiving honoraria from JAZZ Pharmaceuticals Canada and research funding per a contract with Massachusetts General Hospital.

Dr. Ahmed reports Research support to institution for clinical trials from Seattle Genetics, Merck, Xencor, Chimagen and Tessa Therapeutics, has membership on Tessa Therapeutic's and Chimagen scientific advisory committee, she serves on Data Safety Monitoring Board for Myeloid Therapeutics; she is a consultant for ADC therapeutics, KITE/Gilead.

Dr. Maakaron reports his institution receives research funding on his behalf from Gilead, Atara, CRISPR, Precision Biosciences, Scripps Research Institute, VOR Bio, and Affimed.

Dr. Maziarz reports serving as consultant for Autolous, Kite/Gilead, Novartis; research support from Gamida, OrcaBio, and Novartis, participating in DSMB for Athersys, Novartis, Century Therapeutics and VorPharma and a patent with Athersys.

Dr. William reports advisory board for Genmab and BMS; and consulting for Guidepoint Global.

Dr. Shaw reports consulting for Orcabio and Mallinkrodt.

Dr. Phelan reports compensation from bluebird bio: advisory board; Amgen: research funding (ended December 2021).

Dr. Porter reports Stock and Other Ownership Interests: Genentech, Roche (Spouse former employment); Consulting or Advisory Role: Novartis, Kite/Gilead, Janssen, BMS, Angiocrine, Mirror Biologics, Capstan Therapeutics, Sana Biotechnology, Verismo Therapeutics; Research Funding: Novartis; BMS (consortium); Patents, Royalties, Other Intellectual Property: Novartis, Tmunity. (Dr. Porter is a patent inventor for use of CAR T cells in CD19+ malignancies) and Elsevier (Deputy editor, Transplant and Cell Therapy (ASTCT Journal).

DATA USE STATEMENT:

CIBMTR supports accessibility of research in accord with the National Institutes of Health (NIH) Data Sharing Policy and the National Cancer Institute (NCI) Cancer Moonshot Public Access and Data Sharing Policy. The CIBMTR only releases de-identified datasets that comply with all relevant global regulations regarding privacy and confidentiality.

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Abstract

Background: There is a growing population of solid organ transplant (SOT) survivors who subsequently require a hematopoietic cell transplant (HCT), though there are limited data on survival, risk factors for SOT graft loss, and death in this cohort.

Methods: This retrospective Center for International Blood and Marrow Transplant Research (CIBMTR) study included recipients of SOT followed by HCT between 1989 and 2017. HCT data were merged with organ transplant data from the Organ Procurement & Transplantation Network.

Results: Eighty-three patients with a SOT underwent an HCT. Organs transplanted included heart/lung (thoracic, n=15), kidney (n=42), and liver (n= 26); 24 (29%) received a living donor graft and 59 (71%) a deceased graft. Forty-one (49.4%) received an allogeneic HCT and 42 (50.6%) an autologous HCT. Three-year overall survival (OS) from HCT in the entire cohort was 38.6%. There were no significant differences in OS by SOT type, though 3-year OS appeared lowest in the kidney SOT group at 29.9%, compared to liver 40.6%, and thoracic SOT at 58.2%. The incidence of SOT graft failure 3 years post-HCT was 59.1%. There were no significant

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differences in SOT graft failure by organ type: 3-year failure probability 67.2% for kidney, 56.5% for liver 56.5%, and 46.2% for thoracic. Shared risk factors for death and graft failure included HCT indication (leukemia, lymphoma and non-malignant diseases), HCT type (allogeneic), and SOT type (kidney).

Discussion: While some SOT recipients may benefit from HCT, the incidence of SOT graft failure was high and OS was poor, particularly after allogeneic HCT.

INTRODUCTION

Nearly 40,000 patients undergo solid organ transplantation (SOT) annually in the United States[1]. As a result of substantial advancements in clinical care, immunosuppression regimens, and understanding of the long-term effects of SOT on overall health, survival after SOT has improved significantly[2–4]. Post-transplant malignancy is a known risk in the setting of prolonged immunosuppression and accounts for up to 30% of deaths in transplant recipients[5–10]. While Kaposi sarcoma (>50-fold), lip cancer (>10-fold), and non-melanoma skin cancer (>10-fold) are among the most common malignancies in this population, hematologic malignancies can also occur. SOT recipients who develop malignancies have significant morbidity and mortality.

Hematopoietic cell transplantation (HCT) offers the best curative option for select hematologic malignancies, non-malignant blood disorders, and immune deficiency/dysregulation diseases[16–19]. Unique risks when undergoing HCT in SOT recipients include compromised solid organ graft longevity, risk of graft-versus-host disease (GVHD) targeting the SOT, toxicities from medications or changes in immunosuppression therapies, and rejection or failure of either graft[9,20–22]. However, there are limited data on outcomes of SOT recipients who subsequently receive an HCT. The objective of this study was to assess overall survival, SOT graft loss, and associated risk factors in a large cohort of patients using data from the Center for International Blood and Marrow Transplant Research (CIBMTR) and Organ Procurement Transplantation Network (OPTN).

METHODS

Data Sources Statement

The CIBMTR® (Center for International Blood and Marrow Transplant Research®) is a research collaboration between the Medical College of Wisconsin and NMDP. It comprises a voluntary working group of more than 380 participating centers worldwide that contribute detailed data on cellular and gene therapies. Participating centers are required to report all HCTs consecutively and data audits are performed to ensure data quality. Studies conducted by the CIBMTR are performed in compliance with all applicable US 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. Globally, as required by that country's laws and regulations governing human subjects and privacy protection, the center is responsible for obtaining any necessary institutional review and approval of protocols. The center obtains consent of each patient participating in the research protocol.

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The Organ Procurement and Transplantation Network (OPTN) is a public-private partnership that links all professionals involved in the U.S. solid organ donation and transplantation system. The United Network for Organ Sharing (UNOS) is an independent contractor employed by the United States Congress to run the OPTN, which collects data on every solid organ donation and transplant event occurring in the U.S. since October 1, 1987. The registry is a 24/7, secure, internet-based database created to enable the organ transplant institutions in the United States to register patients for transplants, match donated organs, and manage the data of all patients, before and after solid organ transplantation. This system is being used by all United States organ transplant programs, organ procurement organizations, and histocompatibility (tissue typing) laboratories.

Study Design/Data Acquisition

This is a retrospective cohort study of patients registered in the CIBMTR and OPTN/UNOS between 1989 and 2017. Data in the UNOS registry were collected by the OPTN from hospitals and organ procurement organizations (OPOs) across the United States. Subjects registered in both the CIBMTR and OPTN/UNOS were identified using social security number and date of birth. Data from both registries were merged and de-identified by the National Marrow Donor Program (NMDP). The primary investigators of the study received separate de-identified datasets from each vendor and merged them for analysis using the subjects' unique UNOS ID as the identifier. Appropriate CIBMTR review committee study approval, HRSA agreements, and IRB approvals for this study were obtained prior to data merging.

Of the 1,312,249 records available in the UNOS/OPTN registry, 345 SOT records matched to HCT records in the CIBMTR. A total of 265 records were excluded: 71 duplicates, 6 never received HCT, 73 who never received SOT, 21 who received more than 1 SOT or HCT, and 10 who did not consent to CIBMTR research. One additional record was excluded because the death dates did not match. Of the remaining matching records, 80 subjects underwent initial HCT followed by subsequent SOT (outcomes reported in companion manuscript), leaving 83 subjects who underwent SOT followed by HCT (Figure 1).

Statistical Analysis

Descriptive statistics were used to summarize patient, disease, and treatment characteristics. Subjects were stratified by solid organ transplant type: thoracic, kidney, and liver. Subject-level variables and transplant variables included recipient and donor demographics, Karnofsky/Lansky score, pre-transplant conditioning regimen and intensity, primary disease or indication for transplant, HCT donor type, SOT donor type, transplant date, risk status, and HCT-comorbidity index (HCT-CI). HCT-CI is a comorbidity index that comprises 17 different categories of organ dysfunction. The composite score predicts overall survival as well as non-relapse mortality risk after HCT[24]. Risk status for malignant disease is a stratified variable. Low risk includes chronic phase chronic myelogenous leukemia (CML), chronic lymphocytic leukemia (CLL) with complete (CR) or partial (PR) remission, and Hodgkin's disease (HD) in CR. High risk includes acute myelogenous leukemia (AML), acute lymphocytic leukemia (ALL), myelodysplastic syndrome (MDS), multiple myeloma

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(MM), Non-Hodgkin's lymphoma (NHL), and HD, CML blast phase, active MM/AML/ALL, or CR2–3+ among AML/ALL.

Time between sequential transplants was defined as time from date of SOT to date of HCT. Disease risk index (DRI) scores for patients with AML, MDS, and B-ALL are calculated as described previously[25]. Acute graft versus host disease was graded and staged using Consensus criteria[26]. Solid organ transplant (SOT) graft failure was defined by the OPTN if the organ was no longer functioning as determined by the transplant center (i.e. return to dialysis), patient death, or re-transplantation at last follow up[3]. Categorical variables were summarized using frequencies and proportions, and continuous variables were expressed as medians and inter-quartile ranges (IQR). The cumulative incidence of SOT graft failure was calculated from HCT day 0 and stratified by organ type. Gray's test was used to compare cumulative incidence by organ type. Overall survival was estimated using the Kaplan Meier method, and survival rates by organ type were compared using the log-rank test. Univariable Cox proportional hazards regression model was used to identify variables associated with overall survival from the time and solid organ graft failure after HCT. Multivariable analysis was not performed due to limited sample size. SAS 9.4 (Cary, NC) was used for analysis, and statistical significance was set at 0.05[27].

RESULTS

Patient, Disease and SOT Characteristics

From 1985–2017, the CIBMTR and UNOS/OPTN identified 83 patients who underwent a solid organ transplant followed by a hematopoietic cell transplant. Most patients were Caucasian (80.7%), male (65.1%), and the median age at the time of SOT was 47.0 years (interquartile range, IQR, 24–56). SOT types included thoracic (n= 15, 18.1%), kidney (n= 42, 50.6%), and liver (n=26, 31.3%). Thoracic SOT types included heart (n=9) and lung (n=6). Known indications for thoracic SOT included amyloid restrictive cardiomyopathy (n=4), other cardiomyopathies (n=5), and obstructive lung disease (n=4). Common indications for kidney SOT included hypertension (n=5), glomerular disease (n=5), polycystic kidneys (n=4), and congenital obstructive nephropathy (n=3). Liver failure requiring liver SOT was due to viral hepatitis (n=3), fulminant failure and autoimmune disorders (n=5), alcoholic cirrhosis (n=3), primary sclerosing cholangitis (n=2), primary hepatic malignancy (n=2), and treatment-induced disease (n=1). There were 24 (28.9%) patients who underwent living donor SOT: 22 kidneys (52.4%) and 2 livers (7.7%) (Table 1).

HCT Characteristics

Malignancy after SOT was the most common indication for HCT (n=70; 84.3%). The most common malignant diseases included leukemia/myelodysplastic syndrome (n=23, 27.7%), lymphoma (n=27,32.5%), and multiple myeloma/plasma cell disorder (n=18, 21.7 %). Thirteen patients (15.7%) underwent HCT for a non-malignant disease. The median time from SOT to HCT was 58.2 months (IQR: 16.4–138.2). However, the median time from SOT to HCT varied by organ type; those who received a thoracic SOT proceeded to HCT at a median of 13.4 months (IQR 8.1–125.8), compared to longer times between SOT and HCT in liver (median 41.1 months, IQR 5.7–117.4), and kidney (median 93.8 months, IQR

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43.8–144.2) SOT. Most patients had a high (3+) HCT-comorbidity index (HCT-CI) (n=62, 74.7%). Most patients received a myeloablative (MA) conditioning regimen (n=57, 69%) -- the proportion of patients who received MA conditioning by organ type was: 87% among thoracic 62% among kidney, and 69% among liver SOR recipients.

Forty-one (49.4%) patients underwent an allogeneic HCT (Table 2) Most patients received a peripheral blood stem cell transplant (n=28, 68.3%)and had a related donor (n=19, 46.3%),. Tacrolimus in combination with other agents was the most commonly used drug for GVHD prophylaxis (n= 24, 29%) in the group. Across organs, one thoracic (6.7%), 13 kidney (31.0%), and 5 liver (19.2%) recipients underwent HCT from an HLA-identical sibling or non-HLA identical relative. Data to determine if living SOT and allogeneic HCT donors were the same individuals were unavailable. Forty-two patients underwent autologous HCT, with the most common indication for HCT being lymphoma (n=22, 53.4%) and plasma cell disorders (n=19, 42.9%, Table 3). Of note, thoracic SOT recipients underwent more autologous HCTs (n=11, 73.3%), while kidney and liver had 45.2% (n=19) and 46.2% (n=12) autologous HCTs, respectively.

Overall patient survival after HCT

The median follow-up time from HCT was 57.9 months (IQR: 44.9–95.5 months). The overall estimated 1-year, 3-year and 5-year survival after HCT in this cohort was 57.2% (95% CI 46.3– 67.7%), 38.6% (95% CI 28.1–49.6%), and 31.4% (95% CI 21.1–42.7%) respectively. Survival did not differ by organ type, though it appeared higher in thoracic organ recipients, 3-year overall survival (OS) among thoracic SOT was 58.2% (95% CI 32.6– 81.6), kidney SOT was 29.9% (95% CI 16.6–45.1%), and liver SOT 40.6% (95% CI 22.5–60.1%) (Figure 2). Causes of death were similar across SOT type; recurrence of primary indication for HCT accounted for 39% of deaths, followed by infection (15%) and organ failure (15%). Three (6%). patients died of secondary malignancy.

Survival differed by HCT type: among autologous HCT recipients, 3-year OS of thoracic SOT (n=11) was 63.6% (95% CI 34.5–88.1%), kidney SOT (n=19) was 45.5% (95% CI 22.6–69.5%) and liver SOT (n=12) was 41.7% (95% CI 16.5–69.4%). Over time, survival appeared to decrease most significantly in the kidney SOT cohort, with a 5-year OS of 18.2% (95% CI 0.6–52.1) compared to 63.6% (95% CI 34.5–88.1) for thoracic, and 41.7% (95% CI 16.5 – 69.4) for liver SOT recipients. However, there were no statistically significant differences among autologous HCT recipient OS rates by organ type (p=0.220) (Figure 3A).

Among allogeneic HCT recipients, 1-year, 3- year, and 5- year OS was 35.7% (95% CI 21.8–51), 27.5% (95% CI 14.7–42.4%) and 21.6% (95% CI 10.1–36.1%) respectively. While OS was not significantly different by SOT type (p=0.35), survival appeared lowest in kidney SOT recipients [n= 23, 3-year OS 17.4% (95% CI 5–35.1, Figure 3B). Three-year OS among thoracic (n=4) and liver (n=14) SOT recipients was 37.5% (95% CI 0.6–89.4%) and 40.2% (95% CI 16.2–67%), respectively. Grade II-IV acute GVHD occurred in 10 patients (24.4%) after HCT: 1 thoracic (25.0%), 6 kidney (26.1%), and 3 liver (21.4%) SOT recipients. Grade III-IV acute GVHD occurred in 6 recipients (14.6%) after HCT: 1 thoracic

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(25.0%), 3 kidney (13%), and 2 liver (14.3%). The estimated incidence of chronic GVHD was 25.1% (95% CI 12.2– 40.8) at one-year post-HCT.

Among all patients (n=83), risk factors for death included: HCT type, allogeneic versus autologous HCT (HR 2.09, 95% CI 1.21– 3.60), low risk disease status compared to high risk (HR 5.38, 95% CI 1.17–24.83), and HCT indication: leukemia/myelodysplastic syndrome (HR 3.71, 95% CI: 1.53–8.98), lymphoma (HR: 2.69, 95% CI: 1.13–6.37), and non-malignant hematologic diseases (HR: 3.21, 95% CI: 1.18–8.66) compared to plasma cell disorders or multiple myeloma. Recipient female sex (HR 0.42, 95% CI 0.22–0.78), and thoracic SOT (HR 0.36, 95% CI 0.15– 0.86) compared to kidney SOT were associated with a decreased risk of death (Table 4).

Solid Organ Graft Survival after SOT-HCT

The incidence of SOT graft failure was not significantly different by SOT graft type (p=0.16). Among all patients and SOT graft types, the 1-year, 3-year and 5-year incidence of SOT graft failure after HCT was 41.7% (95% 29.9–54%), 59.1% (95% CI 46.7–70.9%) and 66.1% (95% CI 53.1–78%), respectively. By SOT type, 3-year incidence of SOT graft loss was notable: liver 56.5% (95% CI 35.6–76.3%), kidney 67.2% (95% CI 48.1–83.7%), and thoracic 46.2% (95% CI 19.7–73.9%); Figure 4. Over time, kidney SOT recipients appeared to experienced a greater rate of SOT graft loss; 5-year post-HCT graft loss by organ type was 46.2% (95% CI 19.7–73.9%) in thoracic SOT, 62% (95% CI 40.3–81.4%) in liver, and 80.1% (95% CI 58.1–95.2%) in kidney SOT.

Among allogeneic HCT recipients, 3-year SOT graft failure overall was 72.7% (95% CI 55.9–86.8%) and varied by graft type: thoracic 66.7% (95% CI 3.2–100%), kidney 82.4 % (95% CI 58.5–97.2%), and liver 61.5% (95% CI 32.9–86.4%). Among autologous HCT recipients, 3-year SOT graft failure overall and by graft type was 45.1% (95% CI 27.8–62.9%): thoracic 40% (95% CI 12.0–72.2%), kidney 44.6% (95% CI 16.3–75.0), and liver 50% (95% CI 19.0–81.0%), Figure S1).

Etiologies of post-HCT solid organ failure were largely missing from the dataset (n=37; 44.6%). Among patients with kidney SOT, the known causes of organ graft failure included acute rejection (n=2), chronic rejection (n=1), and vascular thrombosis (n=1). Liver graft loss was attributed to infection in 1 patient, and the etiology of graft loss in thoracic organ transplant recipients was unknown. Significant risk factors for SOT graft loss included HCT indication; leukemia/MDS (HR 3.34, 95% CI 1.24–8.97), lymphoma (HR 2.96, 95% CI 1.14–7.67), and non-malignant disease (HR 3.39, 95% CI 1.2–9.57) had a higher risk of SOT graft loss compared to patients with plasma cell disorders or multiple myeloma. Thoracic SOT recipients (HR 0.39, 95% CI 0.15–0.97) had a significantly lower risk of SOT graft failure compared to kidney SOT recipients. Allogeneic compared to autologous HCT was also a significant risk factor for SOT graft failure (HR 2.48, 95% CI 1.33–4.62). Among the recipients of allogeneic HCT, patients with an unrelated donor (n=12) had a lower risk of SOT graft failure (HR 0.27, 95% CI 0.09–0.80), when compared to the patients with HLA-identical sibling donor. SOT recipients with a deceased organ transplant had a lower risk of graft loss than those with a live organ donor (HR 0.39, 95% CI 0.21–0.74, Table 5).

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DISCUSSION

Both living and deceased organ donation rates continue to increase annually in the United States, and advances in surgical and medical techniques have resulted in rising numbers of SOT recipient long-term survivors[5–11,28]. However, there is scant literature to date describing outcomes in this population. The previously largest published series described outcomes in 28 patients who underwent allogeneic HCT from a European registry[29–32]. We add to this literature with this retrospective, descriptive study of 83 SOT recipients; in line with prior reports, overall survival was poor and SOT graft loss incidence was high. Overall, post-SOT patients have two- to four-fold increased malignancy risk and worse oncologic outcomes when compared to non-transplant patients with the same diagnosis[11,28,33]. In this study, malignant diseases accounted for 84% of patients requiring HCT and the most common indications were lymphoma (32.5%), leukemia/myelodysplastic syndrome (27.7%), and multiple myeloma/plasma cell disorder (21.7%). Aligned with our findings, other authors have reported lymphomas as one of the most common malignancies associated with solid organ transplantation with up to 40-fold increased risk after kidney transplant[7]. A link between SOT and myeloid neoplasms has also been previously reported, which served as indication for HCT in 27.7% of our cohort. Morton et al. studied 319 patients with myeloid neoplasms after SOT and found an increased risk for acute myeloid leukemia (2.7-fold), chronic myeloid leukemia (2.3-fold), myelodysplastic syndromes (4.6-fold), and polycythemia vera (7.2-fold) among SOT recipients when compared to the general population[14].

We hypothesize that the etiologies for poor survival in SOT recipients after HCT are multi-factorial. Most patients (74.7%) had a high HCT-Comorbidity Index (3+) at the time of HCT, and among those with a hematologic malignancy, 21 (30%) had high-risk disease; these are well described features associated with increased risk of non-relapse related mortality and relapse respectively. Given the heterogeneity of this cohort, including HCT indication, allogeneic and autologous HCT recipients, a wide age range, and HLA mismatch, comparing overall survival rate in this cohort to patients without a SOT is challenging. While the most common causes of death were recurrence of primary disease as the indication for HCT (39%), deaths from infection (15%) and organ failure (15%) are higher thanthe general SOT population not undergoing HCT, survival appears comparable to survival in HCT recipients during this time frame who did not receive a SOT. The primary causes of death were also comparable to national data without an apparent excessive risk in organ failure[35]. Like the general population, autologous HCT recipients in this study had a lower mortality rate than allogeneic HCT recipients.

Survival rates among allogeneic HCT recipients in this study were comparable to other published outcomes in patients who receive SOT followed by allogeneic HCT. Five-year OS in this cohort was 21.6% (95% CI 10.1–36.1) compared to 5-yr OS of 33% (95% CI 8–62) in a prior report of allogeneic HCT recipients after SOT[30]. Risk factors for death included SOT type (kidney compared to thoracic and liver), HCT type (allogeneic HCT) and leukemia, lymphoma and non-malignant diseases compared to multiple myeloma), sex (males high risk compared to females), and low-risk disease at the time of HCT compared

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to high-risk. Low-risk disease is not an expected risk factor for death; thus we attribute these statistical findings to a small number of patients with low -risk disease (n=2).

Survival rates among allogeneic HCT recipients in this study were comparable to other published outcomes in patients who receive SOT followed by allogeneic HCT. 5-year OS in this cohort was 21.6% (95% CI 10.1–36.1) compared to 5-yr OS of 33% (95% CI 8–62) in a prior report of allogeneic HCT recipients after SOT[30].

The incidence of SOT graft failure was strikingly high in this cohort. Out of 83 patients in this cohort, with a median follow-up time of almost five years, 51% experienced solid organ failure after HCT; this is much higher than the general population of SOTs. The 5-year national incidence of graft loss in kidney, heart, lung, and liver SOT in patients who have not received an HCT is approximately 20%[38,39], 15%[40], 65%[41], and 5%[42] respectively. This cohort underwent HCT a median of 5 years post SOT, so the most appropriate comparison time point is 1 year post HCT. The incidence of SOT graft loss in this study 1-yr post HCT by SOT type was: 52.4% (95% 33.7– 70.8) kidney, 23.1% (95% 4.6– 50) thoracic, 39.1% (95% 20.2–60) liver. Risk factors for SOT graft loss in this study included HCT indication nonmalignant disease, leukemia/MDS, and lymphoma compared to plasma cell disorder/ multiple myeloma and allogeneic HCT compared to autologous. This cohort had a slightly higher rate of graft loss than a prior European Society for Bone Marrow Transplantation (EBMT) multicenter study which reported a 32.8% cumulative incidence of solid organ graft failure one year after HCT. Unfortunately, missing data precluded us from determining if patients received both transplants from the same donor, which could impact the rejection risk.

The mechanism of SOT graft failure post HCT is unclear. Human leukocyte antigen (HLA) class I and II haplotypes are matched with the recipient, but not with the solid organ previously transplanted. One could hypothesize this would result in an increased risk of solid organ rejection. However, high rates of kidney SOT graft failure were noted in our cohort after both autologous and allogeneic HCT. Transplanted SOT may be unusually sensitive to medications required in the HCT setting, perhaps predisposing them to graft loss. However, it is unclear why the SOT graft loss rates are higher in this study than many previously reported.

Notably, mortality rates and graft loss incidence appeared highest in kidney SOT recipients after both autologous and allogeneic HCT. Data of OS by SOT type is contradicting in the literature- kidney SOT recipients are reported to both have a better survival than other SOT types[30] and a trend for decrease survival compared to liver SOT[32,37]. In patients who have not undergone HCT, kidney SOT graft failure rates are lower compared to other organ types-- a stark contrast to this cohort. Etiologies for early death and graft loss in kidney SOT recipients are also likely multifactorial: 45% of kidney SOT patients died of relapse and 16% died of organ failure. Renal insufficiency prior to HCT from chronic calcineurin inhibitors predisposes patients to renal impairment post HCT and may put these patients uniquely at risk for graft injury and loss post HCT, contributing to death. Further, renal insufficiency can impact the intensity of the preparative regimen selected, and reduced intensity preparative regimens are a known risk factor for relapse. Lastly, the

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impact of prolonged immune suppression post-HCT, which is necessary to maintain the SOT graft, may impact graft-versus leukemia and relapse risks, though this is currently not well understood.

Our study has several limitations. First, this is a retrospective, descriptive cohort study. There were some missing data, including if living donors were the same for SOT and HCT. This is particularly important as there are emerging data that HCT can induce tolerance of SOT, leading to successful withdrawal of immune suppression and may impact both overall survival and the incidence of graft rejection[43]. There were also significant missing data on the etiology of SOT graft loss. The sample size precluded a multivariable analysis. Further, given the sample size, the analysis may be underpowered to detect statistically significant differences. To address these limitations, estimates (hazard ratios, survival and SOT graft loss) were provided with 95% confidence intervals for full transparency in lieu of emphasizing p-values. However, this study analyzes the largest cohort of SOT recipients who then undergo HCT patients to date. Further, merging two large databases allowed a rich description of the outcomes of this otherwise poorly described cohort.

In summary, in this cohort, OS in SOT recipients was poor, particularly among allogeneic recipients, and graft loss incidence was high, particularly among renal SOT recipients. Additional investigation is needed to understand the mechanism of SOT graft loss post HCT and novel strategies are needed to mitigate the risk of both SOT graft loss and death in SOT recipients after HCT. When counseling SOT recipients prior to HCT, it is important to note that syngeneic HCT and kidney transplants may have better outcomes, though we could not determine this in this study. Also, there have been many advances in transplant approaches since the start of this study; non-relapse related mortality rates have improved[36] and novel approaches to acute graft versus host disease prophylaxis including in-vivo and ex-vivo T-cell depletion allow safer transplantation of HLA mismatched donors. Contemporary outcomes of SOT recipients may also be better, additional studies capturing granular data are merited.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

FUNDING:

CIBMTR is supported primarily by the Public Health Service U24CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases (NIAID); 75R60222C00011 from the Health Resources and Services Administration (HRSA); and N00014-23-1-2057 and N00014-24-1-2057 from the Office of Naval Research. Support is also provided by the Medical College of Wisconsin, NMDP, Gateway for Cancer Research, Pediatric Transplantation and Cellular Therapy Consortium and from the following commercial entities: AbbVie; Actinium Pharmaceuticals, Inc.; Adaptive Biotechnologies Corporation; ADC Therapeutics; Adienne SA; Alexion; AlloVir, Inc.; Amgen, Inc.; Astellas Pharma US; AstraZeneca; Atara Biotherapeutics; BeiGene; BioLineRX; Blue Spark Technologies; bluebird bio, inc.; Blueprint Medicines; Bristol Myers Squibb Co.; CareDx Inc.; CSL Behring; CytoSen Therapeutics, Inc.; DKMS; Editas Medicine; Elevance Health; Eurofins Viracor, DBA Eurofins Transplant Diagnostics; Gamida-Cell, Ltd.; Gift of Life Biologics; Gift of Life Marrow Registry; GlaxoSmithKline; HistoGenetics; Incyte Corporation; Iovance; Janssen Research & Development, LLC; Janssen/Johnson & Johnson; Jasper Therapeutics; Jazz Pharmaceuticals, Inc.; Karius; Kashi Clinical Laboratories; Kiadis Pharma; Kite, a Gilead Company; Kyowa Kirin; Labcorp; Legend Biotech; Mallinckrodt Pharmaceuticals; Med Learning Group; Medac GmbH; Merck & Co.; Mesoblast; Millennium, the Takeda Oncology Co.; Miller Pharmacal

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Group, Inc.; Miltenyi Biomedicine; Miltenyi Biotec, Inc.; MorphoSys; MSA-EDITLife; Neovii Pharmaceuticals AG; Novartis Pharmaceuticals Corporation; Omeros Corporation; OptumHealth; Orca Biosystems, Inc.; OriGen BioMedical; Ossium Health, Inc.; Pfizer, Inc.; Pharmacyclics, LLC, An AbbVie Company; PPD Development, LP; REGiMMUNE; Registry Partners; Rigel Pharmaceuticals; Sanofi; Sarah Cannon; Seagen Inc.; Sobi, Inc.; Stemcell Technologies; Stemline Technologies; STEMSOFT; Takeda Pharmaceuticals; Talaris Therapeutics; Vertex Pharmaceuticals; Vor Biopharma Inc.; Xenikos BV.

ABBREVIATIONS:

ALL	Acute Lymphocytic Leukemia
AML	Acute Myelogenous Leukemia
B-ALL	B Cell Acute Lymphoblastic Leukemia
CIBMTR	Center for International Blood and Marrow Transplant Research
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myelogenous Leukemia
CR	Complete Response
GVHD	Graft Versus Host Disease
HR	Hazard Ratios
HCT	Hematopoietic Cell Transplantation
HCT-CI	Hematopoietic Cell Transplantation Comorbidity Index
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myelogenous Leukemia
CR	Complete Response
HD	Hodgkin’s Disease
HLA	Human leukocyte antigen
IQR	Inter-Quartile Range
MCW	Medical College of Wisconsin
MDS	Myelodysplastic Syndrome
MM	Multiple Myeloma
NMDP	National Marrow Donor Program
NHL	Non-Hodgkin’s Lymphoma
OPO	Organ Procurement Organization
OPTN	Organ Procurement & Transplantation Network

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OS	Overall Survival
PR	Partial Response
RF	Risk Factors
SOT	Solid Organ Transplant
UNOS	United Network for Organ Sharing

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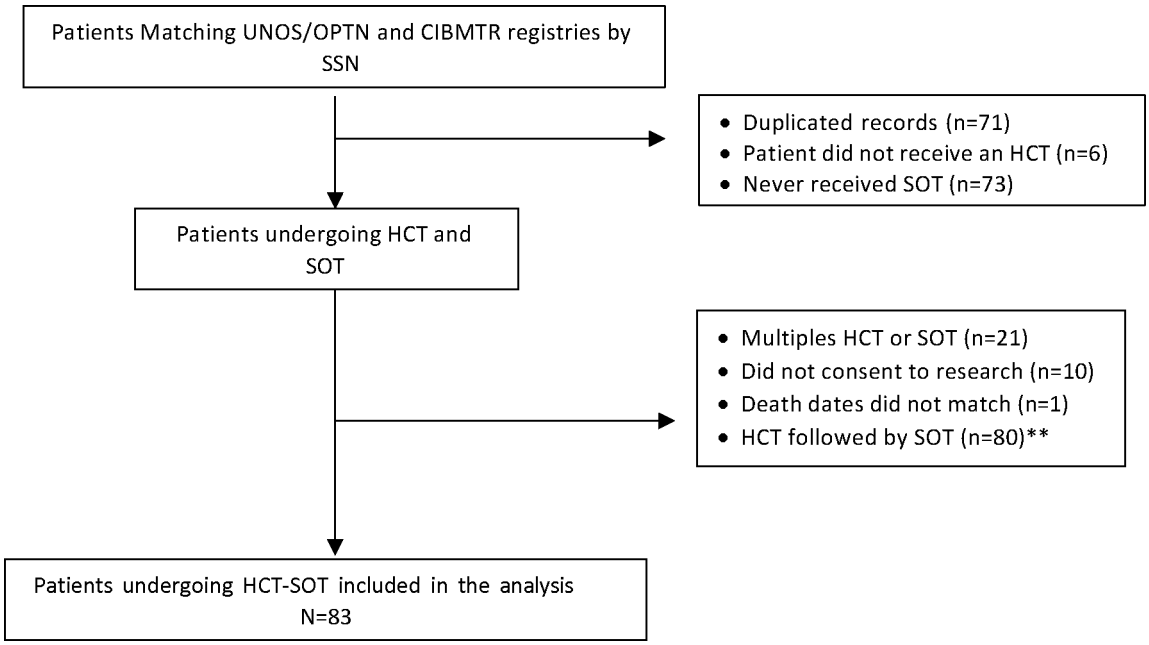

Figure 1:

Patients were matched from the United Network for Organ Sharing (UNOS) and Organ Procurement & Transplantation Network (OPTN) and Center for International Blood and Marrow Transplant Registry (CIBMTR) using social security numbers (SSN). There were 71 duplicate records, 6 patients who never received a hematopoietic cell transplant (HCT), and 73 who never received a solid organ transplant (SOT) who were excluded. Of the 195 patients who received both transplant types, an additional 112 were excluded, including 80 patients who received an HCT and then SOT. **Outcomes for these 80 patients are reported in a companion manuscript.

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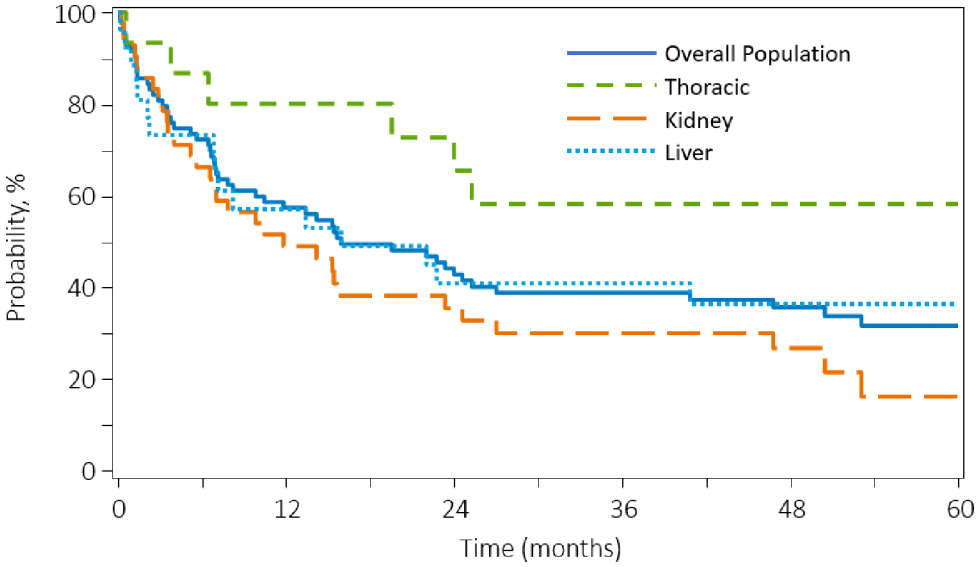

Figure 2:
Among the entire cohort (n=83), there were no significant differences in OS by SOT type (p=0.06).

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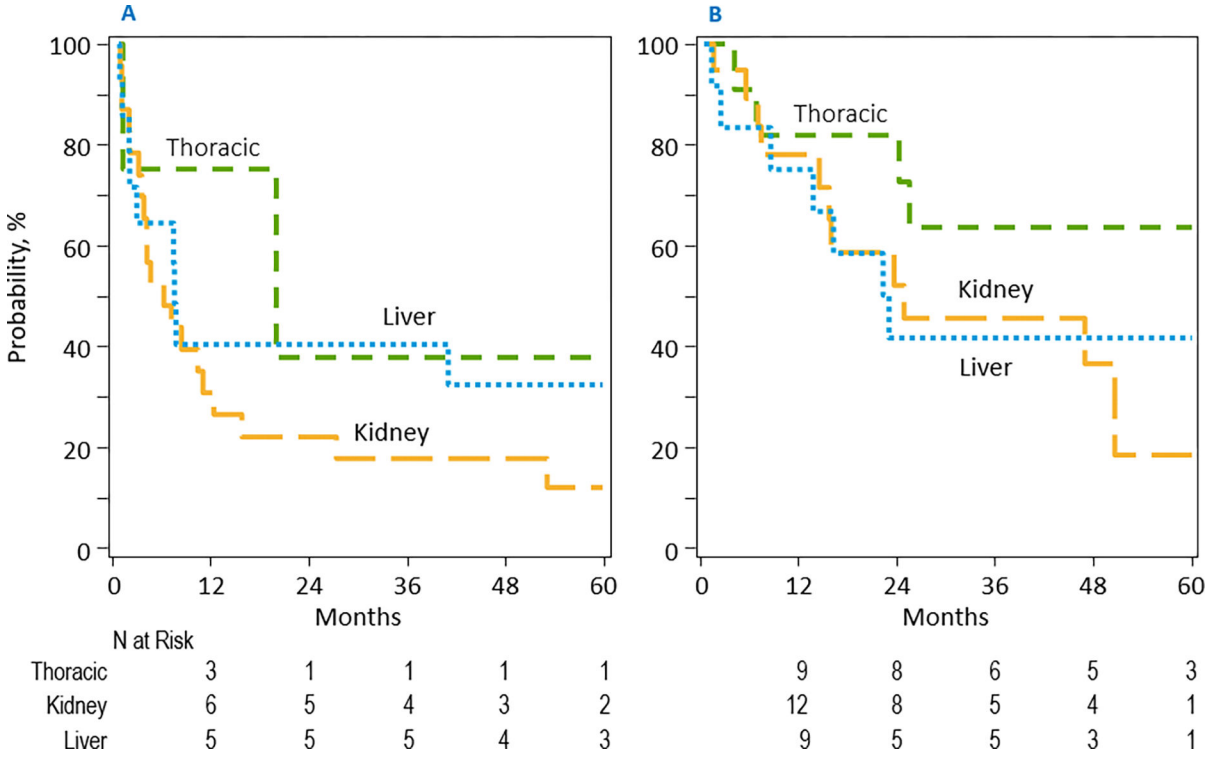

Figure 3:

There were no statistically significant differences in overall survival among autologous HCT recipients (A) or allogeneic recipients (B), though survival appeared lower in the kidney SOT recipients.

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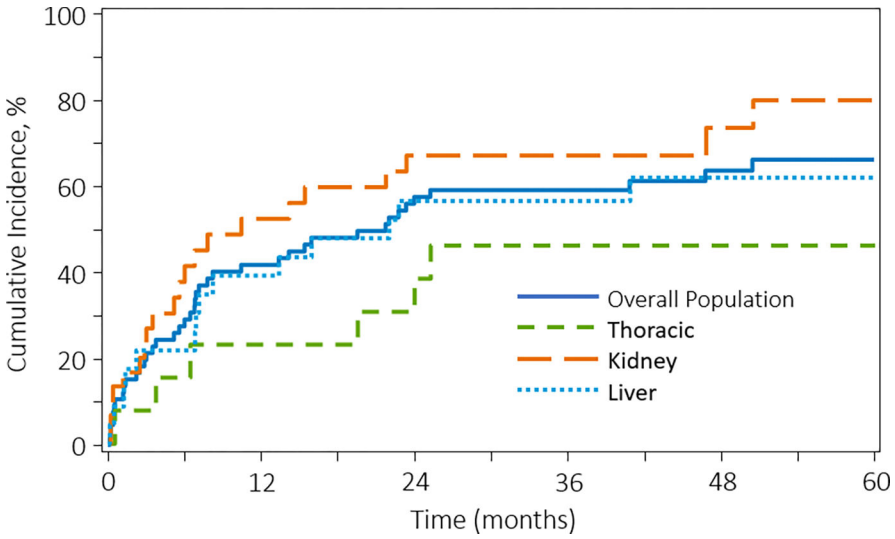

Figure 4:

There were no significant differences in the cumulative incidence of solid organ transplant (SOT) graft loss by organ type (p=0.640).

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TABLE 1:

Demographic and Solid Organ Transplant Characteristics

Characteristic	Total	Thoracic	Kidney	Liver
No. of patients	83	15	42	26
Recipient race - no. (%)				
Caucasian	67 (80.7)	13 (86.7)	32 (76.2)	22 (84.6)
African-American	11 (13.3)	2 (13.3)	5 (11.9)	4 (15.4)
Other	2 (2.4)	0 (0.0)	2 (4.8)	0 (0.0)
Not reported	3 (3.6)	0 (0.0)	3 (7.1)	0 (0.0)
Recipient sex - no. (%)				
Male	54 (65.1)	9 (60.0)	31 (73.8)	14 (53.8)
Female	29 (34.9)	6 (40.0)	11 (26.2)	12 (46.2)
Time from solid organ waitlist to transplant, months				
Median (25th-75th pctl)	5.7 (1.8–16.2)	3.2 (0.7–6.3)	13.4 (5.5–20.0)	2.5 (0.6–9.6)
Age of recipient, at SOT				
Median (25th-75th pctl)	47.0 (24.0–56.0)	44.0 (28.0–58.0)	46.0 (37.0–55.0)	48.5 (11.0–57.0)
Age of recipient, at SOT - no. (%)				
0–17	13 (15.7)	1 (6.7)	3 (7.1)	9 (34.6)
18–40	23 (27.7)	6 (40.0)	14 (33.3)	3 (11.5)
41–60	36 (43.4)	6 (40.0)	21 (50.0)	9 (34.6)
>60	11 (13.3)	2 (13.3)	4 (9.5)	5 (19.2)
Living/deceased solid organ donor - no. (%)				
Living	24 (28.9)	0 (0.0)	22 (52.4)	2 (7.7)
Deceased	59 (71.1)	15 (100.0)	20 (47.6)	24 (92.3)
Year of SOT - no. (%)				
< 1995	7 (8.4)	1 (6.7)	4 (9.5)	2 (7.7)
1995–1999	19 (22.9)	2 (13.3)	12 (28.6)	5 (19.2)
2000–2005	12 (14.5)	1 (6.7)	8 (19.0)	3 (11.5)
2006–2010	30 (36.1)	6 (40.0)	15 (35.7)	9 (34.6)
2011–2015	15 (18.1)	5 (33.3)	3 (7.1)	7 (26.9)
Time in months from SOT to HCT				
Median (25th-75th pctl)	58.2 (16.4–138.2)	13.4 (8.1–125.8)	93.8 (43.8–144.2)	41.4 (5.7–117.4)
Time in months from SOT to HCT (months) - no. (%)				
0 - <6 months	10 (12.0)	2 (13.3)	1 (2.4)	7 (26.9)
6 - <12 months	5 (6.0)	3 (20.0)	0 (0.0)	2 (7.7)
12 - <18 months	7 (8.4)	5 (33.3)	1 (2.4)	1 (3.8)
18 months - <2 years	4 (4.8)	0 (0.0)	2 (4.8)	2 (7.7)
2 - <5 years	16 (19.3)	1 (6.7)	11 (26.2)	4 (15.4)
5 - <10 years	13 (15.7)	0 (0.0)	9 (21.4)	4 (15.4)
≥ 10 years	28 (33.7)	4 (26.7)	18 (42.9)	6 (23.1)

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TABLE 2:

Allogeneic Hematopoietic Cell Transplant Characteristics

Characteristic	Total	Thoracic	Kidney	Liver
No. of patients	41	4	23	14
HCT primary disease - no. (%)				
Leukemia/MDS	23 (56.1)	1 (25.0)	17 (73.9)	5 (35.7)
Lymphoma/non-Hodgkin's disease	5 (12.2)	0 (0.0)	5 (21.7)	0 (0.0)
Non-malignant diseases	13 (31.7)	3 (75.0)	1 (4.3)	9 (64.3)
Recipient age at HCT, years				
Median (25th-75th pctl)	49.2 (22.4–62.9)	41.1 (22.6–58.6)	55.7 (43.1–60.9)	25.8 (11.6–65.6)
Recipient age, at HCT - no. (%)				
0–17	8 (19.5)	1 (25.0)	1 (4.3)	6 (42.9)
18–40	8 (19.5)	1 (25.0)	4 (17.4)	3 (21.4)
41–60	14 (34.1)	1 (25.0)	13 (56.5)	0 (0.0)
>60	11 (26.8)	1 (25.0)	5 (21.7)	5 (35.7)
HCT Karnofsky/Lansky score - no. (%)				
90–100	16 (39.0)	0 (0.0)	12 (52.2)	4 (28.6)
< 90	24 (58.5)	4 (100.0)	11 (47.8)	9 (64.3)
Not reported	1 (2.4)	0 (0.0)	0 (0.0)	1 (7.1)
HCT-Comorbidity Index - no. (%)				
0	2 (4.9)	0 (0.0)	1 (4.3)	1 (7.1)
1	4 (9.8)	0 (0.0)	0 (0.0)	4 (28.6)
2	4 (9.8)	1 (25.0)	3 (13.0)	0 (0.0)
3+	28 (68.3)	3 (75.0)	17 (73.9)	8 (57.1)
Not reported	3 (7.3)	0 (0.0)	2 (8.7)	1 (7.1)
GVHD Prophylaxis - no. (%)				
Ex-vivo T-cell depletion and CD34 selection	6 (14.6)	2 (50.0)	2 (8.7)	2 (14.3)
Post-CY + other(s)	4 (9.8)	1 (25.0)	1 (4.3)	2 (14.3)
CNI + MMF ± other(s) (except post-CY)	15 (36.6)	1 (25.0)	8 (34.8)	6 (42.9)
CNI + MTX ± other(s) (except MMF, post-CY)	10 (24.4)	0 (0.0)	9 (39.1)	1 (7.1)
CNI ± other(s) (except MMF, MTX, post-CY)	5 (12.2)	0 (0.0)	2 (8.7)	3 (21.4)
Other(s)	1 (2.4)	0 (0.0)	1 (4.3)	0 (0.0)
HCT graft type - no. (%)				
Bone marrow	6 (14.6)	2 (50.0)	1 (4.3)	3 (21.4)
Peripheral blood	28 (68.3)	2 (50.0)	19 (82.6)	7 (50.0)
Umbilical cord blood	7 (17.1)	0 (0.0)	3 (13.0)	4 (28.6)
HCT donor type - no. (%)				
HLA-identical sibling	14 (34.1)	1 (25.0)	11 (47.8)	2 (14.3)
Other related	5 (12.2)	0 (0.0)	2 (8.7)	3 (21.4)
Unrelated	15 (36.6)	3 (75.0)	7 (30.4)	5 (35.7)

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Characteristic	Total	Thoracic	Kidney	Liver
Cord blood	7 (17.1)	0 (0.0)	3 (13.0)	4 (28.6)
Year of HCT - no. (%)				
2003–2005	3 (7.3)	0 (0.0)	2 (8.7)	1 (7.1)
2006–2010	23 (56.1)	2 (50.0)	14 (60.9)	7 (50.0)
2011–2017	15 (36.6)	2 (50.0)	7 (30.4)	6 (42.9)
Follow-up from subsequent transplant				
Median (range)	75.9 (6.0–127.2)	75.9 (12.1–75.9)	72.7 (47.7–127.2)	95.5 (6.0–100.8)
25th-75th pctl	57.9–96.9	12.1–75.9	60.2–127.2	57.9–96.9

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TABLE 3:

Autologous Hematopoietic Cell Transplant Characteristics

Characteristic	Total	Thoracic	Kidney	Liver
No. of patients	42	11	19	12
HCT primary disease - no. (%)				
Lymphoma/non-Hodgkin's disease	22 (52.4)	4 (36.4)	9 (47.4)	9 (75.0)
Plasma cell disorder/multiple myeloma	18 (42.9)	6 (54.5)	10 (52.6)	2 (16.7)
Other malignancies	2 (4.8)	1 (9.1)	0 (0.0)	1 (8.3)
Recipient age at HCT, years				
Median (25th-75th pctl)	56.5 (43.7–63.7)	49.6 (25.8–61.2)	56.8 (48.1–64.7)	58.8 (40.1–63.1)
Recipient age, at HCT - no. (%)				
0–17	2 (4.8)	1 (9.1)	0 (0.0)	1 (8.3)
18–40	5 (11.9)	2 (18.2)	1 (5.3)	2 (16.7)
41–60	22 (52.4)	5 (45.5)	12 (63.2)	5 (41.7)
>60	13 (31.0)	3 (27.3)	6 (31.6)	4 (33.3)
HCT Karnofsky/Lansky score - no. (%)				
90–100	21 (50.0)	6 (54.5)	10 (52.6)	5 (41.7)
< 90	20 (47.6)	5 (45.5)	9 (47.4)	6 (50.0)
Not reported	1 (2.4)	0 (0.0)	0 (0.0)	1 (8.3)
HCT-Comorbidity Index - no. (%)				
0	4 (9.5)	2 (18.2)	0 (0.0)	2 (16.7)
1	1 (2.4)	0 (0.0)	1 (5.3)	0 (0.0)
2	3 (7.1)	1 (9.1)	2 (10.5)	0 (0.0)
3+	34 (81.0)	8 (72.7)	16 (84.2)	10 (83.3)
Year of HCT - no. (%)				
2006–2010	12 (28.6)	4 (36.4)	3 (15.8)	5 (41.7)
2011–2017	30 (71.4)	7 (63.6)	16 (84.2)	7 (58.3)
Follow-up from subsequent transplant				
Median (range)	52.5 (2.3–114.3)	58.0 (33.8–96.6)	48.3 (2.3–114.3)	56.2 (36.0–58.6)
25th-75th pctl	36.0–74.3	48.0–81.8	35.3–114.3	44.9–58.6

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Table 4:

Univariable Hazard Ratios for Death after HCT

HCT characteristics	Category	N	HR	95% CI	P-value
Recipient age at HCT	0–17	10	1.00	.	
	18–49	26	1.36	0.50– 3.69	0.5478
	50+	47	1.55	0.60– 3.99	0.3674
Recipient sex	Male	54	1.00	.	
	Female	**29**	**0.42**	**0.22– 0.78**	**0.0065**
Recipient race	Caucasian	67	1.00	.	
	Afr. American	11	0.63	0.27– 1.48	0.2880
	Other	**2**	**5.44**	**1.27– 23.22**	**0.0222**
	Not reported	3	3.29	0.99– 10.89	0.0511
Karnofsky/Lansky Score	90–100	37	1.00	.	
	<90	44	1.17	0.68– 2.02	0.5652
	Not reported	2	0.94	0.13– 6.99	0.9517
HCT-CI	0–1	11	1.00	.	
	2	7	1.09	0.31– 3.87	0.8939
	≥3	62	1.53	0.65– 3.62	0.3280
	Not reported	3	1.68	0.34– 8.33	0.5263
Disease	Plasma cell disorder/MM	18	1.00	.	
	Leukemia/MDS	**23**	**3.71**	**1.53– 8.98**	**0.0036**
	Lymphoma/NHL	**27**	**2.69**	**1.13– 6.37**	**0.0251**
	Other malignancies	2			
	Nonmalignant	**13**	**3.21**	**1.18– 8.66**	**0.0216**
Conditioning	RIC/NST	24	1.00	.	
	MAC	57	0.59	0.33– 1.05	0.0738
	Not reported	2	2.69	0.62– 11.75	0.1888
Disease status	High risk	21	1.00	.	
	Intermediate	40	0.69	0.36– 1.32	0.2679
	Low risk	**2**	**5.38**	**1.17– 24.83**	**0.0309**
	Other malignant/nonmalignant	15	0.88	0.38– 2.02	0.7592
	Not reported	5	1.30	0.43– 3.95	0.6401
Transplant type	Auto	42	1.00	.	
	Allo	**41**	**2.09**	**1.21– 3.60**	**0.0079**
Donor	Auto	42		--	
	HLA-id sib	14	1.00	.	
	Other related	5	2.80	0.94 – 8.30	0.0635
	Unrelated	15	0.51	0.21– 1.23	0.1318
	Cord blood	7	1.40	0.52– 3.79	0.5119
HCT Donor sex	Male	19	1.00	.	

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HCT characteristics	Category	N	HR	95% CI	P-value
	Female	22	1.32	0.65– 2.68	0.4503
	Auto tx	42			
Graft type	Bone marrow	6	1.00	.	
	Peripheral blood	28	2.30	0.68– 7.73	0.1787
	Cord blood	7	3.34	0.83– 13.49	0.0905
	Auto tx	42			
Recipient CMV	Negative	21	1.00	.	
	Positive	61	1.48	0.76– 2.87	0.2480
	Not reported	1			
Donor CMV	Negative	21	1.00	.	
	Positive	19	0.67	0.32– 1.40	0.2841
	Not reported	1			
	Auto tx	42			
Chronic GVHD (allo only)	No	25	1.00	.	
	Yes	12	0.87	0.29– 2.62	0.8077
Year of HCT	2003–2010	38	1.00	.	
	2011–2017	45	0.75	0.44– 1.30	0.3080
SOT characteristics					
Solid organ	Kidney	42	1.00	.	
	Thoracic	**15**	**0.36**	**0.15– 0.86**	**0.0223**
	Liver	26	0.78	0.42– 1.40	0.3999
Recipient age at SOT	0–17	13	1.00	.	
	18–49	33	0.96	0.43– 2.15	0.9166
	50+	37	0.88	0.39– 1.98	0.7566
SOT donor status	Living	24	1.00	.	
	Deceased	59	0.71	0.40– 1.25	0.2397
SOT donor gender	Male	50	1.00	.	
	Female	33	1.24	0.72– 2.13	0.4342
SOT donor race	Caucasian	62	1.00	.	
	Afr. American	9	1.25	0.56– 2.77	0.5917
	Other	12	0.50	0.20– 1.27	0.1452
Time from SOT to HCT	0.9 yrs	15	1.00	.	
	1.9 yrs	11	0.60	0.22– 1.65	0.3182
	4.9 yrs	16	0.71	0.30– 1.71	0.4469
	5+ yrs	41	1.00	0.48– 2.07	0.9983
Time from wait list to SOT	0–0.9 yr	46	1.00	.	
	1–1.9 yrs	18	1.19	0.62– 2.28	0.6073
	2+ yrs	9	0.55	0.17– 1.80	0.3224
	Not reported	10	1.29	0.59– 2.83	0.5179

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HCT characteristics	Category	N	HR	95% CI	P-value
SOT donor age	0–17	14	1.00	.	
	18–49	52	1.22	0.54– 2.75	0.6305
	50+	17	1.28	0.50– 3.25	0.6058

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Table 5:

Univariable hazard ratios for SOT graft loss (n=66)

Characteristic	Category	N	HR	95% CI	P-value
Recipient age at HCT	0–17	9	1.00	.	
	18–49	21	1.04	0.37– 2.97	0.9359
	50+	36	1.28	0.49–3.36	0.6188
Recipient sex	Male	42	1.00	.	
	Female	24	0.52	0.27–1.03	0.0604
Recipient race	Caucasian	54	1.00	.	
	Afr. American	11	0.53	0.21–1.35	0.1811
	Not reported	1	1.70	0.23–12.60	0.6021
Karnofsky/Lansky Score	90–100	31	1.00	.	
	<90	33	1.10	0.59–2.04	0.7669
	Not reported	2	0.93	0.12–7.03	0.9464
HCT-CI	0–1	10	1.00	.	
	2	5	1.20	0.30–4.81	0.8008
	≥3	48	1.29	0.54–3.11	0.5672
	Not reported	3	1.45	0.29–7.18	0.6521
Disease	Plasma cell disorder/MM	16	1.00	.	
	Leukemia/MDS	**16**	**3.34**	**1.24–8.97**	**0.0170**
	Lymphoma/NHL	**20**	**2.96**	**1.14–7.67**	**0.0258**
	Other malignancies	1			
	Nonmalignant	**13**	**3.39**	**1.20–9.57**	**0.0212**
Conditioning	RIC/NST	18	1.00	.	
	MAC	46	0.56	0.29–1.10	0.0914
	Not reported	2	2.53	0.56–11.39	0.2277
Disease status	High risk	16	1.00	.	
	Intermediate	31	0.76	0.36–1.59	0.4638
	Low risk	0			
	Other malignant/nonmalignant	14	1.13	0.47–2.68	0.7849
	Not reported	5	1.41	0.45–4.41	0.5568
Transplant type	Auto	33	1.00	.	
	Allo	**33**	**2.48**	**1.33–4.62**	**0.0044**
Donor	Auto	33			
	HLA-id sib	9	1.00	.	
	Other related	5	1.64	0.53–5.07	0.3939
	Unrelated	**12**	**0.27**	**0.09–0.80**	**0.0188**
	Cord blood	7	0.87	0.30–2.52	0.7916
HCT Donor sex	Male	16	1.00	.	
	Female	17	1.04	0.48– 2.30	0.9138

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Characteristic	Category	N	HR	95% CI	P-value
	Auto tx	33			
Graft type	Bone marrow	6	1.00	.	
	Peripheral blood	53	2.49	0.72– 8.58	0.1500
	Cord blood	7	2.97	0.74– 12.00	0.1262
	Auto tx	33			
Recipient CMV	Negative	16	1.00	.	
	Positive	49	1.53	0.71– 3.32	0.2781
	Not reported	1			
Donor CMV	Negative	18	1.00	.	
	Positive	14	0.69	0.30– 1.59	0.3844
	Not reported	34	6.51	0.71– 59.42	0.0968
	Auto tx	33			
Chronic GVHD (allo only)	No	19	1.00	.	
	Yes	10	0.42	0.09– 1.81	0.2432
Year of HCT	2003–2010	31	1.00	.	
	2011–2017	35	0.92	0.50– 1.71	0.7954
SOT characteristics					
Solid organ	Kidney	30	1.00	.	
	Thoracic	**13**	**0.39**	**0.15– 0.97**	**0.0419**
	Liver	23	0.66	0.34– 1.29	0.2233
Recipient age at SOT	0–17	12	1.00	.	
	18–49	25	1.04	0.43– 2.52	0.9371
	50+	29	0.99	0.42– 2.36	0.9830
SOT donor status	Living	17	1.00	.	
	Deceased	**49**	**0.39**	**0.21– 0.74**	**0.0040**
SOT donor gender	Male	43	1.00	.	
	Female	23	1.40	0.75– 2.60	0.2886
SOT donor race	Caucasian	48	1.00	.	
	Afr. American	8	1.16	0.48– 2.79	0.7403
	Other	10	0.47	0.16– 1.33	0.1522
Recipient CMV at SOT	Negative	19	1.00	.	
	Positive	30	0.71	0.36– 1.40	0.3209
	Not reported	17	0.50	0.21– 1.19	0.1157
Recipient EBV at SOT	Negative	11	1.00	.	
	Positive	26	1.05	0.44– 2.50	0.9081
	Not reported	29	0.54	0.22– 1.34	0.1809
Donor CMV at SOT	Negative	25	1.00	.	
	Positive	35	0.85	0.45–1.62	0.6240

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Characteristic	Category	N	HR	95% CI	P-value
	Not reported	6	1.71	0.57–5.17	0.3393
Donor EBV at SOT	Negative	5	1.00	.	
	Positive	26	1.41	0.41–4.81	0.5883
	Not reported	35	1.17	0.35–3.94	0.7963
Time from SOT to HCT	0–0.9 yrs	15	1.00	.	
	1–1.9 yrs	11	0.59	0.22–1.64	0.3146
	2–4.9 yrs	11	0.93	0.38–2.29	0.8699
	5+ yrs	29	0.82	0.38–1.80	0.6221
Time from wait list to SOT	0–0.9 yr	38	1.00	.	
	1–1.9 yrs	13	1.20	0.55–2.60	0.6462
	2+ yrs	7	0.55	0.13–2.35	0.4213
	Not reported	8	2.74	1.22–6.17	0.0149
SOT donor age	0–17	10	1.00	.	
	18–49	41	1.32	0.51–3.45	0.5657
	50+	15	1.68	0.58–4.86	0.3370
Cause of SOT donor death	Anoxia	8	1.00	.	
	Cerebrovascular/Stroke	13	0.77	0.25–2.44	0.6617
	Head trauma	24	0.91	0.32–2.53	0.8485
	Other	2	0.85	0.10–7.34	0.8791

17/83 patients have solid organ either fail (n=3) or lost to follow up (n=14) by the time of HCT – all were excluded (n= 2 lung transplants, 12 kidney transplants and 3 liver transplants); remaining n=66.