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ORIGINAL ARTICLE

Impact of metformin on malignancy in solid organ transplantation

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Abstract

Malignancy after solid organ transplant is a common occurrence that is associated with increased morbidity and mortality. Literature in the general diabetic population has identified possible antineoplastic properties of metformin. This retrospective study aims to determine if metformin results in a malignancy risk reduction in a cohort of diabetic kidney, liver, and heart transplant recipients. The population included transplant recipients without use of metformin at any time point (DMO arm, n = 147) and those with use of metformin (DMM arm, n = 172); the two arms were matched based on organ type and transplant date prior to application of exclusion criteria. Recipients with prior malignancy, malignancy before diabetes diagnosis, and metformin duration <30 days were excluded. The primary endpoint of malignancy first occurrence post-transplant was not found to be statistically significant at 1, 5, 10, and 15 years. In the subgroup of heart transplant recipients, there was a significant reduction in malignancy at 15 years post-transplant. Older age and Caucasian race were identified as significant risk factors for malignancy, while never smoker was a protective factor. Metformin use in this solid organ transplant cohort was not found to significantly reduce malignancy risk compared to use of other anti-diabetic agents.

KEYWORDS

metformin, neoplasms, transplantation

1 | INTRODUCTION

Long-term survival after solid organ transplant (SOT) is limited by malignancy, with rates reported to be double that of the general population. Non-Hodgkin's lymphoma, lung, liver, kidney, and cutaneous cancers are among the highest prevalence in this population. The heightened risk is a consequence of multiple factors including long-term immunosuppression and exposure to oncogenic viruses.[1] In addition to malignancy risk, SOT recipients are burdened with common chronic diseases, such as post-transplant diabetes mellitus, as adverse events of the immunosuppressive agents prescribed.

Metformin is the preferred management strategy in type 2 diabetes per the American Diabetes Association due to its favorable toxicity profile and potential cardiovascular benefits.[2] In the last decade, literature has emerged regarding metformin's antineoplastic potential in diabetic patients.[3,4] The estimated risk reduction in those patients receiving metformin is 37% compared to those diabetic patients not on metformin,[4] with some studies showing a larger risk reduction with longer duration of metformin use.[5] The mechanism behind this property involves inhibition of LKB1, a tumor suppressor kinase, which is a regulator of the AMPK pathway of glucose regulation.[6] The activation of AMPK inhibits the mammalian target

of rapamycin (mTOR) pathway, which impacts both hyperinsulinemia and the energy consumption of neoplastic cells.[7,8] The mechanism of metformin continues to evolve as literature emerges on its benefits in diabetes, malignancy, and cardiovascular disease.

With the established risks of malignancy and diabetes after SOT, understanding metformin's role in this population is necessary. A registry analysis of kidney transplant recipients between 2007 and 2013 found that only 4.7% of patients had been prescribed metformin within the first year post-transplant despite metformin use being associated with a reduction in all-cause mortality, including malignancy-related death, as well as all-cause graft failure.[9] A recent publication reported that use of metformin in heart transplant recipients was associated with a 90% reduction in risk of malignancy in their diabetic population.[10] The aim of the present study is to supplement the literature cited above by analyzing differences in malignancy rates in kidney, liver, and heart transplant recipients with diabetes at a large transplant center.

2 | MATERIALS AND METHODS

This was a single-center, retrospective study of kidney, liver, and heart transplant recipients approved by the Washington University in St. Louis Institutional Review Board with waiver of consent. Data were collected through manual chart review of the electronic medical record.

2.1 | Population

Adult patients (18 years and older) who underwent kidney, liver, and heart transplant or a combination thereof between January 1, 2002, and August 1, 2017, were included in this study. All patients had a diagnosis of diabetes (either type 1 or type 2) pre- or post-transplant. Diabetes diagnosis was defined by the American Diabetes Association[11] and/or the presence of anti-diabetic medications. Exclusion criteria included history of previous transplant, malignancy diagnosis before transplant, malignancy diagnosis prior to diabetes diagnosis, malignancy diagnosis before initiation of anti-diabetic agent, diet-controlled diabetes, metformin use <30 days duration, death or loss of follow-up within 30 days, or transplant at an outside hospital. Data on medications were pulled based on prescription order and refill history; therefore, the decision to exclude patients with metformin use <30 days was made to eliminate potential patients who did not start the medication despite a prescription being written. Eligible patients were divided into two arms, those who had never received metformin (DMO) and those who received metformin (as monotherapy or in combination) at any time (DMM). History of prescribed anti-diabetic agents was identified through previous orders as well as documentation within provider notes. Patients in the DMO arm were matched based on organ type and date of transplant to patients in the DMM arm; the closest transplant date available was used to match.

2.2 | Protocol

All patients at Barnes-Jewish Hospital receive initial maintenance immunosuppression consisting of a calcineurin inhibitor, antimetabolite, and corticosteroids with adjustments made at the prescriber's discretion. The target tacrolimus trough concentration in the early post-transplant period is 7-10 ng/mL for kidney transplants, 4-8 ng/mL for liver transplants, and 8-12 ng/mL for heart transplants. The majority of kidney transplant recipients are maintained on prednisone lifelong, while liver and heart transplant recipients are tapered off. Induction with rabbit antithymocyte globulin (rATG; 3-6 mg/kg) or basiliximab is used for kidney transplants. Heart transplant recipients receive rATG (5 mg/kg), basiliximab, or no induction at the provider's discretion, while liver transplant recipients receive basiliximab or no induction. Opportunistic infection prophylaxis consists of acyclovir or valganciclovir, depending on CMV serostatus, sulfamethoxazole/trimethoprim, and fluconazole or clotrimazole troches.

2.3 | Objectives

The primary endpoint was incidence of post-transplant malignancy first occurrence. Post-transplant malignancy was identified based on provider documentation in the electronic medical record and/or biopsy results. Secondary endpoints included time to post-transplant malignancy first occurrence, graft loss, mortality, and a composite endpoint of malignancy, graft loss, and mortality. Mortality, including both malignancy-related and cardiovascular-related mortality, was defined by provider documentation. Malignancy, graft loss, and mortality were assessed at 1, 5, 10, and 15 years post-transplant. Safety endpoints included incidence of cardiovascular events (myocardial infarction and cerebrovascular accident), lactic acidosis, and metformin discontinuation. Cardiovascular events were defined by documentation in the electronic medical record and/or confirmation on imaging. Lactic acidosis was defined by a pH < 7.35 with a lactate >5 mmol/L. Metformin discontinuation was defined by order end date and/or provider documentation with or without documentation of reasoning; patients may have been reinitiated on metformin at a later time point, if deemed appropriate. Laboratory values within 3 months of the time point assessed were included for analysis; for A1c, values within 1 year were used. Pre-defined subgroup analyses included assessment of outcomes in each organ type.

2.4 | Statistical analyses

Differences between categorical data were analyzed using the Pearson chi-square test or Fischer's exact test as appropriate. Differences between continuous data were analyzed using Mann-Whitney *U* or *t* test as appropriate. Kaplan-Meier curves were compared using the log-rank test comparing the DMO and DMM arms following anti-diabetic medication initiation. Patients with graft loss, death, or loss of follow-up were included and censored with the last observation carried forward method. To determine the impact of

independent factors on the primary endpoint, a multivariable Cox proportional hazards model with time-dependent covariables was performed. Variables associated with malignancy in the univariable analysis ($P < .05$) as well as variables identified as predictors of malignancy in previous literature were eligible for entry into the model. Metformin use was included as a time-varying covariable in the multivariable analysis. *P*-values less than .05 were considered statistically significant. All data analyses were conducted using IBM SPSS Statistics version 22 (IBM Corp.).

3 | RESULTS

3.1 | Population

A total of 319 patients were included in the analysis, with exclusions detailed in Figure 1. There were 147 patients in the DMO arm and 172 patients in the DMM arm. Median follow-up time post-transplant was 88.9 months in the DMO arm and 97.5 months in the DMM arm ($P = .07$). The median age in the DMO arm was 57 years compared to 54 years in the DMM arm ($P = .07$). At the time of transplant, more patients in the DMO arm had a diagnosis of diabetes mellitus compared to the DMM arm (68.7% vs 48.3%; $P < .01$), with the primary anti-diabetic agent being insulin (51.0% vs 17.4%; $P < .01$). Aspirin use at the time of transplant was 48.6% in the DMO arm compared to 37.7% in the DMM arm ($P = .05$). Additional baseline characteristics are found in Table 1.

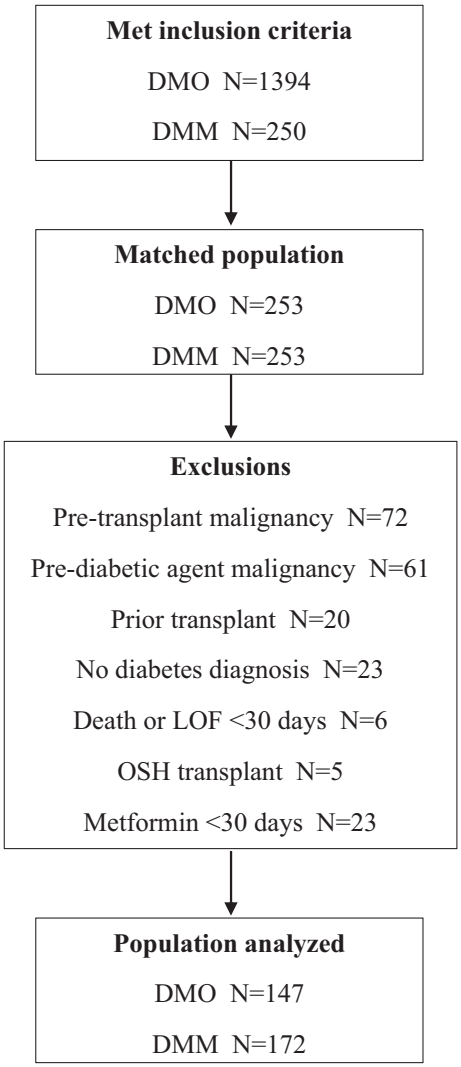


FIGURE 1 Study population inclusion and exclusion criteria applied; DMM, diabetes mellitus with metformin use; DMO, diabetes mellitus without metformin use, LOF, loss of follow-up; OSH, outside hospital

The population primarily included kidney transplant recipients (47.6% vs 40.7%). For induction immunosuppression, 62.6% of the DMO arm received rATG compared to 53.5% in the DMM arm ($P = .10$). Overall exposure to lymphocyte-depleting agents across the follow-up period was higher in the DMO arm compared to the DMM arm (68.0% vs 56.4%; $P = .03$; Table 2), including treatment of rejection episodes in 15.0% of the DMO arm and 12.2% of the DMM arm ($P = .47$). Of the kidney transplant recipients, the estimated glomerular filtration rate (eGFR) at 1 year post-transplant was 51.7 mL/min/1.73 m^2 in the DMO arm and 62.1 mL/min/1.73 m^2 in the DMM arm ($P < .01$). Similarly, in the non-kidney transplant recipients, the eGFR at 1 year post-transplant was 52.0 mL/min/1.73 m^2 in the DMO arm and 62.1 mL/min/1.73 m^2 in the DMM arm ($P < .01$).

In the DMM arm, 74.4% of the population was on metformin for greater than 1 year. Insulin use was more prominent in the DMO arm during the follow-up period compared to the DMM arm (73.5% vs 50.0%, $P < .01$; Table 3). Overall A1c control at 1, 5, 10, and 15 years was similar between the two arms.

3.2 | Primary endpoint

The difference in incidence of malignancy at 1, 5, 10, and 15 years was not statistically significant between the DMO arm and the DMM arm. At 15 years, 25.9% of the DMO arm and 17.4% of the DMM arm had developed a malignancy ($P = .07$). Similarly, there was no difference in malignancy-free survival at 15 years as assessed by Cox regression with metformin as a time-varying covariable (Figure 2). Malignancy rate did not differ when comparing longer duration of metformin use to shorter duration of use. Cutaneous malignancies constituted the most common type of malignancy (52.6% in the DMO arm vs. 63.3% in the DMM arm, $P = .38$). The incidence of skin-limited squamous cell carcinoma was 34.2% in the DMO arm compared to 43.3% in the DMM arm ($P = .44$). Of the entire study population, only one patient developed a lymphoma (DMM arm). 47.4% of the DMO arm and 30.0% of the DMM arm developed other malignancies ($P = .15$). Other malignancies in the DMO arm consisted primarily of prostate, breast, and colon cancer, whereas prostate, bladder, and lung cancer were more prevalent in the DMM arm. In the univariable analysis of malignancy-free survival, age (HR = 1.06; 95% CI, 1.03-1.09; $P < .01$), Caucasian race (HR = 2.60; 95% CI, 1.22-5.52; $P = .01$), and never smoker (HR = 0.58; 95% CI, 0.35-0.95, $P = .03$) significantly impacted the outcome. In the multivariable analysis, age and Caucasian race increased the risk of malignancy, while never smoker was protective (Table 4).

TABLE 1 Baseline characteristics at the time of transplant

	DMO (N = 147)	DMM (N = 172)	*P*-value
Recipient-related			
Age (y), median (IQR)	57.0 (49.0, 64.5)	54.0 (47.0, 60.1)	.07
Male sex, N (%)	102 (69.4)	111 (64.5)	.36
Caucasian race, N (%)	104 (70.7)	120 (69.8)	.85
BMI (kg/m^2), median (IQR)	30.0 (25.0, 33.0)	30.0 (27.0, 33.3)	.17
Tobacco use, N (%)[a]	62 (42.5)	77 (45.3)	.61
Hypertension, N (%)	116 (78.9)	121 (70.3)	.08
Diabetes mellitus, N (%)	101 (68.7)	83 (48.3)	<.01
Baseline diabetic agent, N (%)[b]			
Insulin	75 (51.0)	30 (17.4)	<.01
Sulfonylurea	24 (16.3)	17 (9.9)	.09
Meglitinide	3 (2.0)	1 (0.6)	.24
Thiazolidinedione	6 (4.1)	3 (1.7)	.21
DPP-4 inhibitor	4 (2.7)	2 (1.2)	.31
Metformin	0 (0.0)	16 (9.3)	<.01
HCV RNA positive, N (%)[c]	10 (6.8)	11 (6.5)	.92
HBV RNA positive, N (%)[d]	1 (0.7)	3 (1.8)	.39
Baseline statin use, N (%)	62 (42.2)	62 (36.0)	.26
Baseline aspirin use, N (%)[e]	70 (48.6)	63 (37.7)	.05
Baseline eGFR in mL/min/1.73 m^2, median (IQR)			
Kidney transplant	7.4 (5.5, 11.3)	6.9 (5.0, 9.9)	.57
Non-kidney transplant	43.5 (14.0, 70.3)	57.5 (14.3, 79.4)	.22
Baseline hemodialysis, N (%)	83 (56.5)	82 (47.7)	.12
Donor-related			
Donor (y), median (IQR)	35.0 (24.0, 51.0)	33.0 (21.8, 47.0)	.28
Caucasian donor, N (%)[f]	98 (77.2)	128 (82.6)	.26
Transplant-related			
Type, N (%)			.38
Kidney	70 (47.6)	70 (40.7)	
Liver	47 (32.0)	55 (32.0)	
Heart	22 (15.0)	34 (19.8)	
Combined	8 (5.4)	13 (7.6)	
Induction, N (%)			
None	40 (27.2)	58 (33.7)	.21
rATG	92 (62.6)	92 (53.5)	.10
Basiliximab	18 (12.2)	23 (13.4)	.76
CMV high risk, N (%)[g]	31 (21.2)	41 (23.8)	.58
EBV high risk, N (%)[h]	2 (1.4)	2 (1.2)	.89

Abbreviations: BMI, body mass index; DMM, diabetes mellitus with metformin use; DMO, diabetes mellitus without metformin use; eGFR, estimated glomerular filtration rate; HBV, hepatitis B; HCV, hepatitis C; IQR, interquartile range.

[a]N = 146 and 170, respectively

[b]Of those with a diagnosis of diabetes at the time of transplant

[c]N = 146 and 168, respectively

[d]N = 147 and 171, respectively

[e]N = 144 and 167, respectively

[f]N = 127 and 155, respectively

[g]N = 146 and 172, respectively

[h]N = 142 and 164, respectively

3.3 | Secondary endpoints

Graft loss at 5, 10, and 15 years was significantly higher in the DMO arm compared to the DMM arm (*P* < .01); this difference was primarily driven by the rate of death with a functioning graft. Death at 5, 10, and 15 years was higher in the DMO arm with the rate at 15 years reaching 35.4% as compared to 9.9% in the DMM arm (*P* < .01). Of those who died, malignancy-related death occurred in 24.0% of the DMO arm and 13.3% of the DMM arm (*P* = .31). Cardiovascular-related death occurred in 36.0% of the DMO arm compared to 33.3% in the DMM arm (*P* = .85). Of note, 19.5% of patients had unknown or not documented causes of death. The composite outcome of malignancy, graft loss, and mortality at 15 years was observed in 55.1% of the DMO arm and 29.1% of the DMM arm (*P* < .01). Figure 3 depicts survival free of composite malignancy, graft loss, and mortality following anti-diabetic agent initiation (*P* = .02).

The incidence of cardiovascular events overall was higher in the DMO arm compared to the DMM arm, except at 1 year. At 5 years, 8.2% of the DMO arm compared to 3.5% of the DMM arm had an event, driven primarily by the difference in cerebrovascular accidents (*P* = .07). At 10 years, 15.6% of the DMO arm and 8.7% of the DMM arm had a cardiovascular event (*P* = .06). By 15 years, incidence of cardiovascular events was 18.4% in the DMO arm and 11.0% in the DMM arm (*P* = .06). Lactic acidosis occurred in 4.8% of the DMO arm compared to no patients in the DMM arm (*P* < .01). Metformin was discontinued in 52.9% of the DMM population over the follow-up period. The most commonly documented reasons for metformin discontinuation included escalation of therapy (18.7%), renal dysfunction (18.7%), or gastrointestinal-related adverse effects (16.5%).

TABLE 2 Post-transplant course characteristics

	DMO (N = 147)	DMM (N = 172)	*P*-value
Multiple transplants, N (%)	5 (3.4)	6 (3.5)	.96
Year 1 statin use, N (%)[a]	98 (70.0)	114 (68.3)	.74
Year 1 aspirin use, N (%)[b]	124 (92.5)	144 (90.0)	.45
Year 1 eGFR in mL/min/1.73 m^2, median (IQR)			
Kidney transplant	51.7 (43.1, 66.2)	62.1 (52.2, 75.1)	<.01
Non-kidney transplant	52.0 (41.6, 63.0)	62.1 (50.1, 79.0)	<.01
Year 1 maintenance immunosuppression, N (%)[c]			
Cyclosporine	13 (9.0)	8 (4.7)	.12
Tacrolimus	120 (83.3)	159 (93.0)	.01
Azathioprine	7 (4.9)	12 (7.0)	.42
Mycophenolate	106 (73.6)	125 (73.1)	.92
Corticosteroid	112 (77.8)	119 (69.6)	.10
Sirolimus	6 (4.2)	5 (2.9)	.55
Everolimus	1 (0.7)	2 (1.1)	.67
Belatacept	1 (0.7)	1 (0.6)	.76
Treated rejection episodes, N (%)	22 (15.0)	21 (12.2)	.47
Exposure to lymphocyte-depleting agent, N (%)	100 (68.0)	97 (56.4)	.03
Quantifiable CMV viremia, N (%)	12 (8.2)	16 (9.3)	.72
Quantifiable BK viremia, N (%)	5 (3.4)	4 (2.3)	.89
Quantifiable EBV viremia, N (%)	0 (0.0)	0 (0.0)	1.00

Abbreviations: CMV, cytomegalovirus; DMM, diabetes mellitus with metformin se; DMO, diabetes mellitus without metformin use; EBV, Epstein-Barr virus; GFR, glomerular filtration rate; IQR, interquartile range; rATG, rabbit antithymocyte globulin.

[a]N = 140 and 167, respectively

[b]N = 134 and 160, respectively

[c]N = 144 and 171, respectively

3.4 | Subgroup analyses

3.4.1 | Kidney transplant alone

There were 70 patients in the DMO arm and 70 patients in the DMM arm of the kidney transplant subgroup. Similar to the overall population, there was no significant difference in first malignancy occurrence at 1, 5, 10, and 15 years post-transplant. At 15 years post-transplant, 27.1% of the DMO arm and 21.4% of the DMM arm had developed malignancy (P = .43). When metformin was assessed as a time-varying covariable, it was not found to have a significant impact (P = .09).

3.4.2 | Liver transplant alone

There were 47 patients in the DMO arm and 55 patients in the DMM arm of the liver transplant subgroup. Similar to the overall population, there was no significant difference in first malignancy occurrence at 1, 5, 10, and 15 years post-transplant. At 15 years post-transplant, 19.1% of the DMO arm and 14.5% of the DMM arm had developed malignancy (P = .53). When metformin was assessed as a time-varying covariable, it was not found to have a significant impact (P = .51).

3.4.3 | Heart transplant alone

There were 22 patients in the DMO arm and 34 patients in the DMM arm of the heart transplant subgroup. Similar to the overall population, there was no significant difference in first malignancy occurrence at 1, 5, and 10 years post-transplant. At 15 years post-transplant, 40.9% of the DMO arm and 14.7% of the DMM arm had developed malignancy (P = .03). When metformin was assessed as a time-varying covariable, it was not found to have a significant impact (P = .33).

4 | DISCUSSION

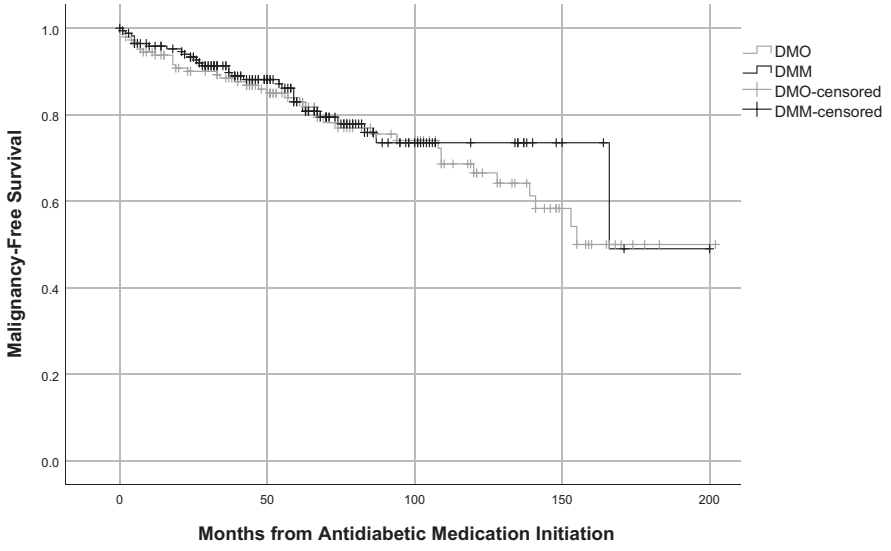
In this retrospective study, no reduction in malignancy risk was observed with use of metformin in the entire population of diabetic

kidney, liver, and heart transplant recipients. However, in the subgroup analysis of heart transplant recipients, there was a statistically significant reduction in malignancy at 15 years in the DMM arm. This finding supports that of Peled et al,[10] which found a significant malignancy risk reduction with use of metformin in a cohort of heart transplant recipients. The reduction in malignancy in this study is smaller in magnitude than described by Peled et al; however, Peled et al had a larger population of heart transplant recipients. The difference in findings between the entire population compared to the heart transplant population is unknown, but may be due to a reduction in the development of cardiac allograft vasculopathy (CAV) as reported in a recent study by Ram et al[12] which demonstrated metformin therapy was associated with a 91% reduction in the risk for CAV or cardiovascular mortality in a population of heart transplant recipients. The current study aimed to address limitations within the study by Peled et al including clarification of the definition for metformin exposure, detailed descriptions of immunosuppression used, and assessment of additional malignancy risk factors. Previous literature in the general diabetic population has identified a duration-dependent effect on malignancy risk,[5] which was not addressed by the Peled et al study. We deemed a duration of >30 days to be clinically significant exposure. Of those patients with a known duration of metformin use, 74.4% used metformin for at least 1 year. Interestingly, previous literature has identified a metformin duration of 3 years or longer to be associated with a risk reduction in prostate cancer.[13] However, in this study, use of metformin did not impact risk of malignancy development in the multivariable analysis, and similarly, duration of therapy >3 years did not change the outcome. Other risk factors for malignancy identified in the literature were described in the baseline characteristics, including but not limited to older age, male sex, Caucasian race, tobacco use, EBV serostatus, and use of lymphocyte-depleting agents.[4,10,14,15] The majority of these risk factors were well balanced between the two arms; however, use of lymphocyte-depleting agents was significantly higher in the DMO arm, driven by the rate of rATG for induction. It is possible that higher use of rATG in the DMO arm masked the difference in malignancy rates between the groups; however, lymphocyte-depleting therapy was not found to influence malignancy outcomes in the multivariable analysis. Multivariable analyses assessing the impact of various risk factors on malignancy development in the entire population revealed age and Caucasian race as the only predictors of malignancy. mTOR inhibitor use has been described as another potential protective factor against malignancy.[16] In this study, mTOR inhibitor use did not impact malignancy outcomes, but the effect was possibly confounded

TABLE 3 Post-transplant diabetes mellitus characteristics

	DMO (N = 147)	DMM (N = 172)	*P*-value
Metformin duration, N (%)			
<180 d	—	17 (9.9)	
180-365 d	—	13 (7.6)	
366-1825 d	—	79 (45.9)	
>1825 d	—	49 (28.5)	
Unknown	—	14 (8.1)	
Insulin use, N (%)	108 (73.5)	86 (50.0)	<.01
A1c, median (IQR)			
1 y	7.0 (6.2, 8.1)	6.7 (6.2, 7.6)	.12
5 y	7.0 (6.3, 8.1)	7.1 (6.3, 7.9)	.59
10 y	7.2 (6.3, 8.0)	7.5 (6.5, 8.5)	.34
15 y	6.7 (6.0, 7.1)	7.6 (7.2, 8.7)	.11

Abbreviations: DMM, diabetes mellitus with metformin use; DMO, diabetes mellitus without metformin use; IQR, interquartile range.



No. at risk	1 yr.	5 yrs.	10 yrs.	15 yrs.
DMO	134	85	35	3
DMM	168	121	53	6

FIGURE 2 Malignancy-free survival following anti-diabetic medication initiation (*P* = .57); DMM, diabetes mellitus with metformin use; DMO, diabetes mellitus with other agents use

by the low rate of mTOR use in the cohort. The incidence of de novo malignancy in each organ subgroup was comparable or increased in comparison to the rates described in previous literature.[14]

Although there was no difference in malignancy in the entire cohort, the difference in incidence of death at 5, 10, and 15 years was significantly higher in the DMO arm compared to the DMM arm. Malignancy-related deaths in the DMO arm were approximately double that of the DMM arm. Interestingly, in the multivariable Cox regression analysis with metformin use as a time-dependent covariable, metformin use was protective against death (HR = 0.51; 95% CI 0.28-0.92; *P* = .03) and graft loss (HR = 0.55; 95% CI 0.33-0.91; *P* = .02). Cardiovascular events were numerically higher in the DMO arm and it is possible that metformin decreased death rates by improvement in cardiovascular outcomes. These findings warrant future prospective studies.

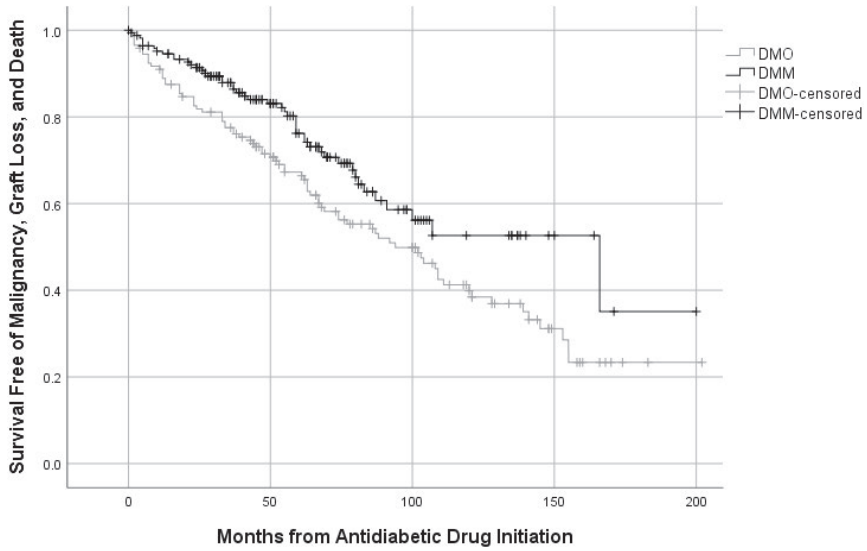
Vest et al[9] reported that the incidence of metformin use in a cohort of kidney transplant recipients within the first year post-transplant was <5.0%. Within this study, median 1 year eGFR in both arms was >50 mL/min/1.73 m^2, making metformin a viable option for the treatment of diabetes mellitus. Of note, over half of the patients on metformin in the present study discontinued the drug after initiation for multiple reasons, including 18.8% discontinuing for kidney dysfunction. Lactic acidosis has historically been a concern with metformin, especially when considering use in the kidney transplant population; however, there were no patients in the DMM arm with lactic acidosis within the follow-up period. With all of this in mind, it is likely that metformin is underutilized within the solid organ transplant population, especially with the known cardiovascular benefits in the general population.[17,18] Similarly, Ram et al[12] identified direct and indirect effects of metformin on the non-immune and immune-mediated pathophysiology of CAV specifically in heart transplant recipients. Cardiovascular disease burdens the SOT population and therefore appropriateness of metformin therapy should be assessed for all patients presenting with pre-transplant or new onset diabetes after solid organ transplantation.

This study is not without limitations. The retrospective design may limit the accuracy of the data with possible missing or misreported information from the electronic medical record. With the retrospective nature of this study, it was not possible to account for all possible malignancy risk factors. However, data were collected on the risk factors that could be feasibly captured in patient records. Medication regimen information was limited to prescription order start and stop dates, as well as documentation by providers; patient adherence to the regimen was unable to be assessed. Regarding follow-up post-transplant, the number of patients assessable at 15 years was limited; however, this is comparable to the data presented by Peled et al The small sample size at each time point may have limited the ability to see a statistically significant difference in

TABLE 4 Multivariable Cox Regression model of factors associated with risk for malignancy

Factor	Adjusted hazards ratio (95% CI)	*P*-value
Age (y)	1.08 (1.05-1.11)	<.01
Caucasian	2.60 (1.22-5.52)	.01
Never smoker	0.58 (0.35-0.95)	.03
Metformin use[a]	0.95 (0.56-1.60)	.85
mTOR inhibitor use	1.54 (0.69-3.40)	.29
Lymphocyte-depleting agent use	1.07 (0.63-1.80)	.81

[a]Metformin use included as time-dependent covariate



No. at risk	1 yr.	5 yrs.	10 yrs.	15 yrs.
DMO	133	81	31	3
DMM	168	120	51	5

FIGURE 3 Survival free of composite malignancy, graft loss, and death following anti-diabetic medication initiation (*P* = .02); DMO, diabetes mellitus with other agents use

endpoints. Finally, there is possible selection bias as the choice of anti-diabetic agent(s) was left up to the discretion of the prescriber.

In summary, metformin use was not associated with a reduction in risk of first malignancy occurrence in diabetic kidney, liver, and heart transplant recipients over a 15-year time span. However, the heart transplant subgroup had a significant reduction in malignancy at 15 years. Patients who had never received metformin had a higher incidence of mortality compared to those who had received metformin, although the reason for this difference is unknown. There was a numerically higher rate of malignancy-related deaths and cardiovascular events in the DMO arm. Although no differences in malignancy rates were found in the entire cohort of present study, the reduction in malignancy in the heart transplant subgroup, previously described cardiovascular benefits and the lack of lactic acidosis observed in this study suggest that metformin should be considered in diabetic patients after solid organ transplantation.

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CONFLICT OF INTEREST

The authors of this manuscript have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

Felicia Bartlett, Spenser January, April Pottebaum, Andrew F. Malone: concept/design, data collection, data analysis/interpretation; Felicia Bartlett, drafting article; Felicia Bartlett, Spenser January, Timothy Horwedel, statistics; Felicia Bartlett, Spenser January, April Pottebaum, Timothy Horwedel, Andrew F. Malone, critical revision of article; Spenser January, April Pottebaum, Timothy Horwedel, Andrew F. Malone, approval of article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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