



# Renal transplant recipients suffer significantly more complications but not mortality after breast cancer surgery and benefit from treatment at transplant centers

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**Background:** Breast carcinoma has the highest incidence of any cancer in adult females. The impact of a previous kidney transplant (KT) on breast cancer surgery outcomes has not been examined. We aim to evaluate the influence of a KT on the short-term outcomes of mastectomy or lumpectomy to inform future treatment decisions in this population.

**Methods:** A retrospective cohort analysis was conducted using Nationwide Inpatient Sample (NIS) data between 2005 and 2014. Population included adult females with KT surgically treated for breast malignancy. Weighted multivariate regression models were employed to compare outcomes at transplant and non-transplant centers.

**Results:** Three hundred and ninety-eight women met the inclusion criteria. KT recipients (KTR) had higher Elixhauser Comorbidity Index (ECI). We noted longer length of stay ( $P<0.001$ ), higher expenditure ( $P=0.001$ ), and complications ( $P<0.001$ ). Specifically, rates of hematomas ( $P=0.041$ ), acute renal failure ( $P<0.001$ ), blood transfusion ( $P<0.001$ ), fresh frozen plasma transfusion ( $P<0.001$ ), cardiovascular ( $P<0.001$ ), and other complications ( $P=0.012$ ) were increased. There was no mortality in transplant recipients. Weighted multivariate analyses highlight that rates of complication ( $P=0.040$ ), and length of stay ( $P<0.001$ ) are lower at transplant centers (TCs).

**Conclusions:** History of KT has a significant impact on the outcomes of mastectomy or lumpectomy. These patients suffer more post-operative adverse events. However, KTR experience superior outcomes at TCs.

**Keywords:** Breast cancer; kidney transplant (KT); transplant center (TC); ethnicity; complications

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## Introduction

The number of kidney transplants (KT) has increased annually over the past decade (1). Survival rate among KT

recipients (KTR) has also improved in that time period, closely mirroring improvements in graft survival. There were nearly 220,000 individuals living with a renal allograft

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in 2017 (2). History of an organ transplant is a known risk factor for developing a malignancy (3). As the rates of KTs continue to climb, the number of KTR diagnosed with cancer is likely to grow.

Breast carcinoma is the leading cause of new cancer diagnosis in women (4). It was also identified in 4.7% of *de novo* cases in those with history any transplant (5). Breast carcinoma was the most frequently encountered gynecologic malignancy in KTR (6). They are also more likely to have advanced disease burden at diagnosis (7). Others observed higher mortality in renal allograft recipients diagnosed with Stage III or Stage IV breast cancer (8). However, there is limited information on the management and outcomes in KTR. Single center trials have demonstrated comparable prognoses between transplant and non-transplant cohorts (9).

It is imperative to develop a greater understanding of the outcomes of breast surgery in KT patients. Our purpose is to evaluate the influence of KT history on the short-term outcomes of mastectomy or lumpectomy in women at transplant and non-transplant centers. We present the following article in accordance with the STROBE reporting checklist (available at <http://dx.doi.org/10.21037/abs-20-56>).

## Methods

The Nationwide Inpatient Sample (NIS) is the largest database of hospital discharges in the United States. It is a product of the Healthcare Cost and Utilization Project and includes approximately 7 million annual hospitalizations. NIS enables researchers to formulate national estimates because of its 20% stratified sample. We obtained NIS data from 2005 to 2014 and classified individuals who underwent lumpectomy or mastectomy (ICD 9 code: 85.20–85.23, 85.33–85.36, and 85.41–85.48). Within this subset, we selected for those with history of KT (ICD9: V42.0).

Persons with a history of another organ transplant (ICD9: V42.1, V42.2, V42.6, V42.7, V42.8, V42.81, V42.82, V42.83, V42.84, V42.89, V42.9) were excluded. Individuals with complications from prior organ transplants were also excluded (ICD9 codes: 996.80, 996.82, 996.83, 996.84, 996.85, 996.86, 996.87, 996.88, 996.89). Other exclusion criteria were benign tumor, age younger than 18 years, and male gender. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

## Statistical analysis

After applying exclusion and inclusion criteria, hospital and patient-level characteristics between KT and non-KT recipients were compared with *t*-test, Mann-Whitney test, and chi square test. In order to adjust for comorbidities, Elixhauser Comorbidity Index (ECI) scores were calculated from NIS data. The outcomes of interest were mortality, complications, total hospital charge and length of stay. Logistic regression models were created for mortality and complications as binary outcomes. Linear regressions were used to build models for length of stay and charges as numeric outcomes to find the role of KT as a risk factor. In addition to the multivariate logistic regression, we adjusted and normalized total charges and length of stay to further minimize bias. Total charges were adjusted based on consumer price index (CPI) 2020. We observed that both total charges and length of stay were positively skewed. We normalized these two variables by creating log transformation. This was the best method to normalize the data without changing the direction of skew. Since there was no mortality in the KTR cohort, only three of the outcomes were assessed in a multivariate fashion.

Multivariate logistic regressions were performed to compare short-term breast surgery outcomes sorted by hospital designation. Specifically, we analyzed the results for sub-cohorts of KTR treated at transplant centers (TCs), teaching organizations, and all hospitals. We identified TC as locations with at least one transplant performed during the timeframe of the study. Teaching institutions were defined by the presence of an Accreditation Council for Graduate Medical Education (ACGME) approved residency program, membership in the Council of Teaching Hospitals (COTH), or a resident to bed ratio of 0.25 or higher. Finally, we considered outcomes for allograft recipients undergoing immediate breast reconstruction following lumpectomy or mastectomy at TC.

The NIS database has the advantage of collecting both patient and hospital characteristics. Patient and hospital characteristics had some statistically significant and non-significant values. To reduce any bias, we entered all the patient and hospital characteristics in the multivariate logistic and linear regression models along with the surgical procedures because they were either statistically significant or clinically relevant. All results were calculated after applying the sampling weight built in NIS.

## Results

### Demographics

The sample population consisted of 737,017 individuals who underwent lumpectomy, unilateral mastectomy, or bilateral mastectomy between 2005 and 2014. In this group, 398 had a prior KT after application of inclusion and exclusion criteria. Demographic characteristics are outlined in *Table 1*. An assessment demonstrated that KTR obtaining treatment were significantly younger (57.3 *vs.* 59.8,  $P<0.001$ ) and had fewer individuals older than 65 (24.70% *vs.* 37.2,  $P<0.001$ ). The overall breast operation population was predominantly made up of white females (62.1%), however they constituted a smaller portion of the KT cluster (47.6%,  $P<0.001$ ). In comparison, a greater percentage of African-American (21.0% *vs.* 10.1%,  $P<0.001$ ) and Hispanic (9.8% *vs.* 6.6%,  $P=0.01$ ) women undergoing surgery were transplant recipients than otherwise. The overall rate of carcinoma *in situ* was 18.0%. There was no significant difference based on KT and non-KT (14.3% *vs.* 18.0%,  $P=0.054$ ).

### ECI

Participants were classified into ECI categories  $<-1$ , 0–2, 3–10, and  $>10$ . Our analysis demonstrated that KTR had a higher median comorbidity score (6) compared to the non-transplant division (0). Significantly fewer with an allograft were in the  $<-1$  ( $P<0.001$ ), and 0–2 ( $P<0.001$ ) groups. Furthermore, meaningfully more recipients were in the 3–10 ( $P<0.001$ ), and  $>10$  (24.1% *vs.* 10.2%,  $P<0.001$ ) comorbidity index classes.

### Procedures

The most common surgical treatment was unilateral mastectomy (67.1%). Breast reconstruction was performed in 10.3% of cases. In those instances, 97.1% of reconstructions were immediate. Significantly fewer transplant recipients underwent reconstruction (6.5% *vs.* 10.3%,  $P=0.012$ ). There was no variation between immediate and delayed reconstruction based on KT history, but all recipients underwent immediate reconstruction.

### Insurance

A majority of the entire operative population was privately insured (50.8%). However, Medicare was the primary payer

for significantly more KTR (43.3% *vs.* 36.6%,  $P=0.006$ ). There was no difference in median household incomes across quartiles 1 and 4 of the transplant and comparison group. There were significant variances in quartiles 2 and 3, with most KTR located in quartile 2 (28.3% *vs.* 22.5%,  $P=0.007$ ).

### Hospital characteristics

Hospital characteristics are compiled in *Table 2*. We noted that significantly more women with a KT received operative management for breast cancer at large hospitals by bed number ( $P<0.001$ ). Comparatively, those without renal replacement surgery visited medium sized hospitals more frequently ( $P<0.001$ ). More KTR sought treatment at TCs ( $P<0.001$ ).

Private non-profit hospitals were the site for most breast surgeries. KTR preferentially utilized government owned centers compared to the cohort (34.4% *vs.* 27.9%,  $P<0.002$ ). Transplant patients obtained care at urban, teaching hospitals (61.9% *vs.* 54.3%,  $P<0.001$ ) and less likely to visit rural ( $P=0.011$ ), or non-teach urban institutions ( $P=0.041$ ). Fewest kidney recipients underwent breast cancer surgeries in the Northeast ( $P=0.016$ ).

### Outcomes

*Table 3* features the short-term results of univariate analysis for breast surgeries. The renal transplant population had significantly different outcomes. There was no mortality in the KTR, but complication rates were nearly double (16.5% *vs.* 8.2%,  $P<0.001$ ). Specifically, the most frequently encountered complications were cardiovascular ( $P<0.001$ ), acute renal failure ( $P<0.001$ ), hematomas ( $P=0.041$ ), and other ( $P=0.012$ ). Furthermore, allograft recipients required more fresh frozen plasma ( $P<0.001$ ), and packed red blood cell (pRBC) transfusions ( $P<0.001$ ) after surgery. KTR had longer length of stay after their procedures ( $P<0.001$ ) along with higher total expenditures ( $P<0.001$ ). Median charge was nearly \$8,000 more for treatment. Despite this, no one with an allograft met SIRS criteria compared to 0.2% for the cohort ( $P<0.001$ ).

Weighted multivariate adjusted outcomes for all KTR based on transplant, and teaching designations can be found in *Table 4*. Weighted analyses highlight meaningful differences compared to other hospitals. TC illustrated significantly lower rates of suffering any complication after

**Table 1** Patient characteristics considered in the study

Characteristics	No KT (n=736,619)		KT (n=398)		Total (n=737,017)		P value
	n	%	n	%	n	%	
Age >65	273,865	37.20	98	24.70	273,963	37.20	<0.001
Age, mean (SD), year	59.8 (14.3)		57.3 (10.2)		59.8 (14.2)		<0.001
Race							
White	457,650	62.1	190	47.6	457,840	62.1	<0.001
Black	74,320	10.1	83	21.0	74,403	10.1	<0.001
Hispanic	48,574	6.6	39	9.8	48,613	6.6	0.01
Asian or pacific islander	22,562	3.1	16	3.9	22,578	3.1	0.271
Native American	2,882	0.4	0	0.0	2,882	0.4	0.21
Other	17,956	2.4	10	2.6	17,967	2.4	0.929
Race unknown	112,675	15.3	60	15.1	112,735	15.3	N/A
Elixhauser Comorbidity Index							
≤-1	258,111	35.0	0	0.0	258,111	35.0	<0.001
0-2	319,991	43.4	31	7.7	320,022	43.4	<0.001
3-10	83,252	11.3	272	68.2	83,524	11.3	<0.001
>10	75,265	10.2	96	24.1	75,361	10.2	<0.001
Median (IQR)	0 (-1.0 to 1.0)		6 (5.0-10.0)		0 (-1.0 to 2.0)		<0.001
Breast carcinoma in situ	132,859	18.0	57	14.3	132,916	18.0	0.054
Procedures							
Unilateral mastectomy	494,261	67.1	273	68.6	494,534	67.1	0.526
Bilateral mastectomy	161,704	22.0	87	21.9	161,791	22.0	0.964
Lumpectomy	91,151	12.4	38	9.5	91,189	12.4	0.087
Reconstruction	736,619	10.3	26	6.5	76,185	10.3	0.012
Immediate reconstruction	64,343	97.1	26	100.0	64,369	97.1	0.376
Primary expected payer							
Medicare	269,372	36.6	172	43.3	269,545	36.6	0.006
Medicaid	63,858	8.7	35	8.7	63,892	8.7	0.948
Private insurance	373,975	50.8	186	46.8	374,161	50.8	0.102
Self-pay	10,957	1.5	5	1.3	10,962	1.5	0.701
No charge	2,542	0.3	0	0.0	2,542	0.3	0.652
Other	15,032	2.0	0	0.0	15,032	2.0	0.004
Payer unknown	883	0.1	0	0.0	883	0.1	N/A
Zip code income quartile							
First quartile	154,390	21.0	94	23.5	154,484	21.0	0.234
Second quartile	165,927	22.5	113	28.3	166,039	22.5	0.007
Third quartile	178,786	24.3	75	18.9	178,861	24.3	0.009
Forth quart	222,409	30.2	112	28.1	222,521	30.2	0.303
Zip code unknown	15,107	2.1	5	1.1	15,111	2.1	N/A

KT, kidney transplant.

**Table 2** Hospital characteristics considered in the study

Characteristics	No KT (n=736,619)		KT (n=398)		Total (n=737,017)		P value
	n	%	n	%	n	%	
<b>Hospital ownership</b>							
Government or private	205,267	27.9	137	34.4	205,404	27.9	<0.002
Public	60,810	8.3	29	7.4	60,839	8.3	0.546
Private, non-profit	384,947	52.3	184	46.3	385,131	52.3	0.039
Private, investor owned	70,272	9.5	39	9.7	70,311	9.5	0.771
Private	11,439	1.6	0	0.0	11,439	1.6	0.013
Ownership unknown	3,884	0.5	9	2.3	3,894	0.5	N/A
<b>Hospital bed capacity</b>							
Small	99,616	13.5	54	13.7	99,670	13.5	0.869
Medium	174,021	23.6	45	11.4	174,066	23.6	<0.001
Large	459,099	62.3	289	72.6	459,388	62.3	<0.001
Capacity unknown	3,884	0.5	9	2.3	3,894	0.5	N/A
<b>Location/teaching status</b>							
Rural	64,416	8.7	20	4.9	64,436	8.7	0.011
Urban, non-teaching	268,258	36.4	123	30.8	268,381	36.4	0.041
Urban, teaching	400,060	54.3	247	61.9	400,306	54.3	<0.001
Teaching status unknown	3,884	0.5	9	2.3	3,894	0.5	N/A
<b>Region</b>							
Northeast	180,189	24.5	77	19.3	180,265	24.5	0.016
Midwest	151,407	20.6	91	23.0	151,498	20.6	0.254
South	250,009	33.9	145	36.5	250,155	33.9	0.294
West	155,014	21.0	85	21.3	155,099	21.0	0.878
Kidney transplant center	171,164	23.2	175	43.9	171,339	23.2	<0.001

KT, kidney transplant.

operations ( $P=0.040$ ) and shorter length of stay ( $P<0.001$ ). Teaching institutions produced a higher adjusted odds ratio (aOR) for any complication (1.937,  $P=0.001$ ). Those KTR with immediate breast reconstruction surgery benefitted from a lower total charge ( $P=0.015$ ) and shorter LOS ( $P=0.003$ ) at transplant hospitals.

## Discussion

History of solid organ transplant (SOT) is linked to an increased risk of developing a malignancy (3). Our aim was to investigate short term post-operative outcomes in

women with KT undergoing surgery for breast cancer at transplant and non-transplant centers. Previous publications have examined surgical results in kidney recipients. After undergoing appendectomies and cholecystectomies, they had increased expenses and length of stay (10,11) KTR also sustained increased expenses, length of stay, overall complication, and mortality rate after colorectal resection (12).

A demographic analysis outlined statistically significant variations. KTR undergoing breast operations were generally younger. The mean age was 57.3 years as opposed to 59.8 in the cohort. The percentage older than 65 years

**Table 3** Outcome variables considered in the study and results

Characteristics	No KT (n=736,619)		KT (n=398)		TOTAL (n=737,017)		P value
	n	%	n	%	n	%	
Death in hospital	599	0.10	0	0.00	599	0.10	1.0
Patient disposition (uniform)							0.010
Unknown	66	0.00	0	0.00	66	0.00	
Home health care	148,588	20.20	99	24.90	148,687	20.20	
Transfer to SNF, ICF, or other	24,196	3.30	0	0.00	24,196	3.30	
Transfer to short term hospital	839	0.10	0	0.00	839	0.10	
Routine	561,561	76.20	299	75.10	561,860	76.20	
Other	770	0.10	0	0.00	770	0.10	
Any complication	60,419	8.20	66	16.50	60,485	8.20	<0.001
Cardiovascular	3,567	0.50	10	2.60	3,577	0.50	<0.001
Respiratory	2,435	0.30	0	0.00	2,435	0.30	0.251
Peripheral vascular complication	223	0.00	0	0.00	223	0.00	1.0
Central nervous system complication	329	0.00	0	0.00	329	0.00	1.0
Hematomas	23,684	3.20	20	5.10	23,704	3.20	0.041
Accidental cut, puncture or hemorrhage during a procedure	871	0.10	0	0.00	871	0.10	1.0
Complications of operative wound	1,467	0.20	0	0.00	1,467	0.20	1.0
Post-operative infection	3,266	0.40	0	0.00	3,266	0.40	0.430
Other	2,489	0.30	5	1.20	2,494	0.30	0.012
Acute renal failure	4,497	0.60	10	2.50	4,507	0.60	<0.001
Urinary complications	1,405	0.20	0	0.00	1,405	0.20	1.0
Digestive system complications	1,869	0.30	0	0.00	1,869	0.30	0.632
Acute vascular insufficiency-intestine	30	0.00	0	0.00	30	0.00	1.0
Platelet transfusion	990	0.10	0	0.00	990	0.10	1.0
Fresh frozen plasma transfusion	1,467	0.20	5	1.40	1,473	0.20	<0.001
pRBC transfusion	24,307	3.30	29	7.40	24,337	3.30	<0.001
SIRS	1,339	0.20	0	0.00	1,339	0.20	<0.001
Complication of graft	3,272	0.40	6	1.40	3,277	0.40	0.395
Length of stay, day, median [IQR]	2 [1–2]		2 [1–3]		2 [1–2]		<0.001
Total charges, \$, median [IQR]	43,005 [26,953–71,034]		50,670 [32,632–73,966]		43,009 [26,957–71,046]		<0.001

Total charges were adjusted based on inflation price index 2020. CPH, cut, puncture, hemorrhage; SNF, skilled nursing facility; ICF, intermediate care facility; pRBC, packed red blood cells; SIRS, systemic inflammatory response syndrome; IQR, interquartile range; KT, kidney transplant.

**Table 4** Weighted multivariate adjusted outcome for kidney transplant recipients based on center designation and reconstruction

Characteristics	Adjusted odds ratio	Confidence interval	Co-efficient	Standard error	P value
All centers					
In hospital mortality	N/A	N/A			N/A
Any complication	1.254	0.958–1.640			0.100
Total charge			0.001	0.014	0.274
Length of stay			–0.001	0.009	0.312
Transplant centers					
In hospital mortality	N/A	N/A			N/A
Any complication	0.579	0.344 to 0.975			0.040
Total charge			–0.004	0.019	0.064
Length of stay			–0.010	0.013	<0.001
Reconstruction at TC					
In hospital mortality	N/A	N/A			N/A
Any complication	N/A	N/A			N/A
Total charge			–0.008	0.047	0.015
Length of stay			–0.011	0.033	0.003
Teaching centers					
In hospital mortality	N/A	N/A			N/A
Any complication	1.937	1.428 to 2.627			0.001
Total charge			0.001	0.017	0.390
Length of stay			0.001	0.011	0.621

(I) N/A, not applicable because of zero mortality and zero complications in only reconstructed patients. (II) Total charges were adjusted based on consumer price index 2020. (III) The multivariable analyses were adjusted for age, gender, race, co-morbidity, primary expected payer, zip code income quartile, hospital ownership, hospital bed capacity, location/teaching status, region, operations (lumpectomy vs. mastectomy), and breast conservation surgery to reduce bias. TC, transplant center.

was also meaningfully lower. This is not unexpected. Organ transplant and immunosuppressive treatments are well established risk factors for malignancies (3). These are likely contributing factors in the development of breast cancer at an earlier age.

Considerably greater proportions of African-American and Hispanic women with KT required surgical intervention for breast carcinoma. These findings are particularly interesting due to the demographic prevalence of breast cancer and KT. Since 1988, more than twice as many White females (n=100,378) as African American females (n=46,196) underwent KT. An even smaller number of Hispanic women (n=26,102) received a renal allograft over the same time period (1). The age-adjusted rate of breast cancer per 100,000 has been very similar between

Whites (126.1) and African Americans (124.0) whereas the Hispanic rates were far lower (93.9) (13). Although our analysis was limited by size, the appreciably higher number of African American and Hispanic females in the sample was curious and of note nonetheless. Researchers have encountered greater tacrolimus clearance in African-Americans, compared to Non-Hispanic Whites, which require higher doses to reach therapeutic levels (14). Others concluded that Hispanic KTR do not suffer similar effects and in fact require less immunosuppressive therapy (15). The variability in drug regimen and dosing could explain increased rates of breast malignancy in African-American and Hispanic women compared to their non-transplanted cohort.

The ECI uses 31 unique diagnostic categories to predict

charges, length of stay, and in-patient mortality (16). Each condition is assigned a point value ranging from -7 to +12, corresponding to the strength of association with death prior to discharge. Next, an algorithm is used to generate a score between -19 and +89 (17). In general, a higher ECI score points to an increased likelihood of mortality and provides a good framework to measure disease burden and resource utilization. Our investigation demonstrated that significantly more KTR with breast cancer had ECI between 3–10 (68.2%) and over 10 (24.1%), which was drastically higher than the 11.3% and 10.2%, in the higher Elixhauser categories respectively, for those without prior transplants.

This paints the KTR cohort as a generally sicker population with numerous risk factors requiring more hospital resources and placing them at increased risk of in-hospital mortality. This is not entirely unexpected as several conditions that heavily influence ECI are common in transplant recipients. Comorbidities such as hypertension, diabetes mellitus (DM), DM with complication, and renal failure can be precursors to KT. Whereas coagulopathies, fluid and electrolyte abnormalities, and anemias are seen in KTR and they are important considerations in the ECI scoring.

A substantially larger segment of the KTR utilized Medicare as the primary payer for their breast cancer procedures despite a minority of patients being over 65. There were no marked differences in coverage by Medicaid, private insurance, or self-pay. It is important to note that those under 65 with end stage renal disease and an allograft are covered by Medicare for 36 months after their transplant. The variations in insurance coverage paired with the younger age of KTR point to additional factors that may be involved. We could not track duration of time between KT and breast carcinoma treatment.

A review of short-term breast cancer surgery outcomes across the study populations featured some distinct outcomes. We discovered that KTR had longer post-operative hospital stays. The median length of hospitalization was the same at 2 days. However, the range was larger in the KTR group with 1–3 days compared to 1–2 days in the control.

We identified that total hospital charges were higher in the transplant cohort. Median expenditure was nearly \$8,000 higher. The increased length of stay and cost match the outcomes predicted by the ECI given the majority were in the high risk 3–10 and >10 comorbidity score clusters.

Next, KTRs were more likely to require pRBC and fresh frozen plasma transfusions during their breast surgery recovery. Prior research has indicated that anemia is a common and under-treated diagnosis following kidney transplantation (18). Although prevalence of anemia decreases following KT, it can persist for years in up to one third of cases (19).

Finally, transplant recipients experienced nearly double the rate of post-operative complications at 16.5% compared to 8.2%. Our analysis specifically tracked any short term in-hospital adverse events. This is consistent with previous publications that have categorized the influence of prior renal transplant on future surgical outcomes. In cases of cholecystectomy, appendectomy, and colorectal resection the reports confirmed that KTR experienced more in-hospital complications compared to others (10–12). Similar to our results, all three of these projects emphasized rates of any short-term ailments.

Detailed evaluations of immediate adverse events pointed to markedly increased rates of problems with hematomas, acute renal failure, and the cardiovascular system. Hematomas are likely a product of underlying anemia and coagulopathies associated with KT (18). Intuitively, one can point to a decreased baseline renal function in KTR, due to only one functioning kidney and nephrotoxic immunosuppressants as the cause behind cardiovascular and nephrology difficulties. Pre-existing comorbidities in recipients with high ECI scores are predictably a contributing factor. Challenges in managing post-operative fluid status paired with compromised filtration is likely the key in developing either of these complaints.

Others have focused on breast procedure outcomes in SOT recipients. They did not find an increased risk of complications (20). However, there were significant differences in the population and procedures tracked in these projects. Zellner *et al.* examined maladies following plastic surgery in SOT patients, but the sample only included 14 breast procedures across all organ transplants not limited to KT, and the majority of the cases were minor reconstruction revisions (n=6) and reduction mammoplasty (n=5) (20). In contrast, we specifically considered mastectomies and lumpectomies for breast cancer. Ongoing malignancies also carry unique risks that would not be evident in plastic surgery cases. For instance, postoperative venous thromboembolism is a known consequence of cancer, even in those established on oral anticoagulation and would necessitate additional monitoring (21,22).

Nonetheless, Zellner *et al.* revealed a complication rate of 14% in breast procedures, which is similar to our 16.5% rate (20).

We established that KTR were less likely to undergo reconstruction after mastectomy. There was no significance in rates of immediate reconstruction or variations in outcomes based on reconstruction status. Other researchers focusing on breast reconstruction after SOT also did not discern a difference in adverse events but observed 8 instances of minor side effects such as infected seromas and cellulitis. Their series only included 7 KTR in the total 17, and the research only focused on reconstructions and not operations to reduce tumor burden (23). Both examinations of plastic surgery after organ transplant suffered from KT sample size limitations. This makes stratification and comparisons across all SOT challenging given the nuances of post-operative immunosuppression and unique risk factors associated with different organ systems. For example, DM increases the possibility of breast wound infection after operations (21). DM is a common underlying condition in renal recipients and increases the risk of complications for KTR compared to another SOT.

Features of treatment centers were evaluated and correlated with patient outcomes. More KTR sought surgical care for breast cancer at large hospitals by bed capacity compared to the cohort. The majority of the treatment facilities were urban, teaching institutions. Comparatively fewer chose urban, non-teaching or rural establishments.

Private, non-profit hospitals were the most common source of treatment for all. KTR visited government owned centers more frequently than the comparison. It is plausible that this is an artifact of the abundant Medicare beneficiaries with an allograft.

There was also a preference for TCs for breast cancer surgery amongst KTR compared to the cohort. This is consistent with the current understanding in the literature. Nationwide investigations observed that more KTR underwent colorectal resection, appendectomy, and cholecystectomy at a TC (10-12). Some published opinion-based recommendations suggest transfer of care of transplant recipients even for non-allograft operations to TC because of their familiarity with the individual and expertise in management (24,25). It can also be postulated that KTR may choose to return to their TC for continuity of care.

A broader examination of the TCs in KTR breast

cancer surgery highlighted their superior performance. We identified that individuals treated at TC had lower rates of any complications, shorter post-operative stay, and lower expenditures. Prior works by DiBrito *et al.* have scrutinized hospital specific complications rates for abdominal procedures and concluded there were no differences by TC status (10-12). Nevertheless, it has been well established that the complications of breast surgeries differ from those of abdominal operations (21). The inherent differences in the types of procedures likely explains this discrepancy.

Next, post-operative length of stay was shorter at TC. This was again in contrast to the evidence for KTRs at TCs after colorectal resection and appendectomy (11,12). The differences in breast and abdominal complications again likely explain these differences. Breast operations have the benefit of not interfering with the prior KT site or incision and would reasonably require less intensive post-operative oversight for any graft complications. Furthermore, it may be speculated that TCs are better equipped to monitor the nuances of renal function in the KTRs and therefore more comfortable discharging patients earlier after breast surgery.

Total expenditures after breast surgeries were marginally lower at TCs compared to non-TCs but not statistically significant ( $P=0.064$ ). Again, this alters the current understanding for cost of care at TCs for procedures. DiBrito *et al.* identified that charges were higher after appendectomies and did not vary significantly for colorectal resection and cholecystectomies (11). It can be inferred that the lower expenditure is a function of the overall performance of TC after breast surgeries with fewer complications and a shorter length of stay.

TCs were further separated into teaching or non-teaching centers. We determined that teaching TC were associated with a higher risk of any complication. Yet they did not have any differences in LOS and total expenditure. DiBrito *et al.* adjusted the calculations based on teaching status but did not evaluate its impact on outcomes. A review of US hospitals discovered an association between teaching status and reduced mortality (26). These results were intriguing and require further examination to determine the underlying cause of the increased complications.

We also scrutinized the outcomes for breast reconstruction after mastectomy or lumpectomy at a TC. No mortality or complications were reported. There was an association between TCs and lower total charge for care and shorter post-operative length of stay. These findings are likely attributable to the expertise of TC in treating renal recipients.

### Limitations

This investigation has a few limitations primarily stemming from the design and limited sample size of KTR undergoing surgical treatment for breast carcinomas. The project relies on accurate diagnostic and procedural coding across the country for the NIS database. Next, our sample size far lower than those used by DiBrito *et al.* for the abdominal surgery series (10-12). Exclusion criteria and the narrow focus on breast cancers limited the sample. However, our analysis revealed robust significance across several categories. Furthermore, a single center trial estimated the incidence of post-transplant breast cancer at 0.5% after KT (9). There were approximately 200,907 people living with a functioning renal graft in 2014 (27). Transplant data between 1988–2014 suggests that women were the beneficiaries of roughly 40% of all KT (38.4–40.8%) (1). Approximately 80,000 women were living with a renal allograft in 2014. One would expect 400 cases (0.5%) of breast cancers from kidney recipients. Our population of 398 KTR with breast cancer, managed to include nearly all the predicted carcinomas despite the low number of cases. This is even more impressive considering NIS only captures 20% of the national inpatient sample.

Next, a crucial piece of information missing from our data was the specific immunosuppressive drug used in each patient. Reports have emphasized over a 3-fold increase in cancer incidence after renal transplant (28) New evidence has identified immunosuppression as the primary cause behind the increase (29). Tacrolimus is generally regarded as the preferred immunosuppressant after KT (30). But it has been associated with increased incidence of malignancy compared to cyclosporine-based drugs, that pose greater wound healing complications (31,32).

Another limitation was the lack of information regarding neoadjuvant treatment for breast cancer prior to surgical intervention. Previous chemotherapeutic intervention can influence the incidence of post-operative complications. Several groups have already quantified the impact of neoadjuvant therapy on breast cancer surgery. One analysis concluded that 18% of patients experienced major complications (33). Another discovered that adverse events are more frequent in cases of mastectomy with immediate reconstruction (34). Presumably those on immunosuppressants and receiving neoadjuvant chemotherapy would be even more susceptible to complications.

We identified increased rates of acute renal failure in KTR post-operatively. However, our methodology did not allow access to any kidney function test parameters such as GFR, Creatinine, or urinalysis. Finally, the lack of long-term data on recovery, graft function and failure were major drawbacks of the project. Nonetheless, this is the largest analysis of the outcomes of breast cancer surgery in KTR and we identified several novel findings.

### Conclusions

In this retrospective analysis, we identified that KTR underwent lumpectomy or mastectomy to treat breast carcinoma at a younger age but struggled with more comorbidities compared to the cohort. A higher proportion were African American and Hispanic women. Women with a renal allograft suffered nearly double the rate of complications and were more likely to need pRBC and fresh frozen plasma transfusions compared to nontransplant recipients. More KTR underwent breast surgery at a TC. TC demonstrated superior outcomes compared to other hospitals. Patients experienced fewer complications, and shorter post-operative stays at TCs.

This report advances the understanding of the unique risk factors of KTR undergoing breast surgery. Decreased morbidity at TCs is likely attributable to more experience in anticipating the needs of KTR and responding with a coordinated multidisciplinary approach to complicated cancer care. Our data supports the growing evidence that advocates for increased surgical treatment of KTR at TCs. We aim to inform future physician decision making in the treatment of transplant recipients. Although we establish the benefit of treatment at TC, further investigations of treatment methods at TCs are necessary to establish best practice guidelines for KTR.

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