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Liver transplantation does not increase morbidity or mortality in women undergoing surgery for breast cancer

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Abstract

Purpose: The incidence of breast cancer following solid organ transplantation is comparable to the age-matched general population. The rate of de novo breast cancer following liver transplantation varies. Furthermore, there is limited information on the management and outcomes of breast cancer in liver transplant recipients. We aim to evaluate the impact of liver transplantation on breast cancer surgery outcomes and compare the outcomes after breast cancer surgery in liver transplant recipient in transplant versus non-transplant centers.

Methods: National Inpatient Sample database was accessed to identify liver transplant recipient with breast cancer. Mortality, complications, hospital charges, and total length of stay were evaluated with multivariate logistic regression testing. Weighted multivariate regression models were employed to compare outcomes at transplant and non-transplant centers.

Results: Ninety-nine women met inclusion criteria for liver transplantation + breast cancer and were compared against women with breast cancer without liver transplantation (n = 736,527). Liver transplantation + breast cancer had lower performance status as confirmed via higher Elixhauser Comorbidity Index (20.5% vs 10.2%, $p < 0001$). There were significantly more complications in the liver transplantation cohort when compared to the non-liver transplant recipient (15.0% vs 8.2%, $p = 0.012$). However, on multivariate analysis, liver transplantation was not an independent risk factor for post-operative complications following breast cancer surgery (odd ratio, 1.223, $p = 0.480$). Cost associated with breast cancer care was significantly higher in those with liver transplantation (2.621, $p < 0.001$). Breast conservation surgery in liver transplantation had shorter length of stay as compared to breast cancer alone (odds ratio, 0.568, $p = 0.027$) in all hospitals.

Conclusion: Liver transplantation does not increase short-term mortality when undergoing breast cancer surgery. Although there were significantly more complications in the liver transplantation cohort when compared to the non-liver transplant recipient (15.0% vs 8.2%, $p = 0.012$), on multivariate analysis, liver transplantation was not an independent risk factor for postoperative complications following breast cancer surgery. Breast cancer management in liver transplant recipient at non-transplant centers incurred higher charges but no difference in complication rate or length of stay when compared to transplant centers.

Keywords

breast cancer, breast surgery, hospital length of stay, liver transplantation, solid-organ transplantation

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Introduction

Liver transplantation (LT) is the standard treatment for those with acute and chronic liver disease, as well as those with various types of liver neoplasms. Livers are the second most commonly transplanted organ in the United States.[1] The number of liver transplants performed in the United States has steadily increased over the past 20 years. Almost 9000 liver transplants were performed in 2020.[2] The 1, 3, and 5-year survival rate for women over the age of 40 following LT is 88.2%, 81.4%, and 76.7%, respectively.[3]

Chronic immunosuppressive therapy, essential for allograft survival, remains the most important long-term risk factor contributing to morbidity following LT. Both infectious and neoplastic complications are much more common in the immunosuppressed host. Malignancies in transplant recipients often have a more rapid progression, an unfavorable prognosis, and a poor response to standard treatment.[4–6] Therefore, as both the number of liver transplants performed and survival increases, identification and management of complications in these patients is paramount.

Breast carcinoma (BC) is the leading cause of new cancer diagnosis in women. Approximately 13% of women in the United States will develop breast cancer during their lifetime.[7] Treatment for breast cancer is individualized. However, the current mainstay of curative BC treatment is breast surgery. While the outcomes of those undergoing breast surgery are well documented in the general population, little is known regarding how patients fare if they have previously undergone a liver transplant.

The rate of reported de novo breast cancer following LT varies. There is a general consensus that the risk of BC does not appear to be increased in those having undergone solid organ transplant.[8–15] Nonetheless, once cancer develops in transplant recipients, the post-treatment outcomes may be worse than expected in the general population.[16] Despite this, little is known regarding the outcomes of breast surgery in liver transplant recipient (LTR). Koonce et al. reported no significant complications following breast reconstructive surgery in those who previously underwent a solid organ transplant. However, this cohort consisted of only 17 women, 2 of whom underwent an LT.[17] Similarly, in a case report by Nakakimura et al.,[18] no severe adverse events were observed in one woman who underwent breast surgery and chemotherapy following an LT. Others observed higher mortality when diagnosed with higher stage breast cancer after LT.[19]

Breast cancer surgery outcomes data following solid organ transplantation has largely focused on those with kidney transplantation.[20] Consequently, little attention has been afforded to LTR subsequently treated for BC. Since LT has become a common procedure and recipients live with allografts, it is imperative to develop a greater understanding of the outcomes of breast cancer surgery in this cohort. Our purpose is to evaluate the influence of LT on the short-term outcomes of breast cancer surgery in women at transplant and non-transplant centers (TCs).

Methods

Data from the National (Nationwide) Inpatient Sample (NIS), between 2005 to 2014 on Breast Lumpectomy and Mastectomy were isolated for this retrospective cohort review.[21] The NIS is the largest publicly available all-payer inpatient healthcare database designed to produce U.S. regional and national estimates of inpatient utilization, access, charges, quality, and outcomes. A history of liver transplant was determined within this subset. As such, the cohort was breast surgery patients who had a history of prior liver transplant. Exclusion criteria included concomitant history of prior organ transplant, complications related to prior organ transplants, benign breast tumor, age younger than 18, and male gender. Hospital and patient-level characteristics between breast cancer with and without liver transplant were compared with *t*-test, Mann–Whitney test, and chi-square test. The power of the study was calculated to be 80%.

The Elixhauser Comorbidity Index (1988) categorized and scored comorbidities. The Elixhauser Comorbidity Index is a method of categorizing comorbidities of patients based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data.[22] A greater score is associated with worse prognosis.[23] The influence of LT on mortality and morbidity was evaluated with logistic regression testing. Total hospital charge and length of stay (LOS) were converted to a binary variable based on their median. The role of LT on the total hospital charge and LOS was evaluated with logistic regression testing, where the dependent variable was LOS or total hospital charge below or above median. Similarly, the effect of LT on total hospital charge and LOS was measured with linear regression. Total charges were adjusted based on consumer price index (CPI) 2020. Since there was no mortality in the LT cohort, only three of the outcomes were assessed in a multivariate fashion.

Statistical analyses

Multivariate logistic regressions were performed to compare outcomes sorted by TC, teaching centers, and patients who underwent reconstruction following breast cancer surgery. The selected co-variates were standard patient and hospital characteristics in NIS which were statistically significant between LT and no LT. These include race, comorbidity, primary expected payer, zip code income quartile, hospital ownership, location/teaching status, and region. Missing values are reported in Tables 1 and 2 and were coded for the co-variates. There was no exclusion in the result of multivariate logistic regression. We identified TC as hospitals with at least one liver transplant performed during the timeframe. All results were calculated after

Table 1. Patient characteristics.

	No LT (n = 736,527)		LT (n = 99)		TOTAL (n = 736,626)		p value
	Number	%	Number	%	Number	%	
Age > 65 years	273,841	37.2	34	34.7	273,876	37.2	0.559
Age, mean (SD), year	59.8 (14.3)		59.7 (11.2)		59.8 (14.3)		0.945
Race							
White	457,621	62.1	65	65.3	457,685	62.1	<0.001
Black	74,295	10.1	15	15.2	74,310	10.1	<0.001
Hispanic	48,565	6.6	5	5.0	48,570	6.6	<0.001
Asian or pacific islander	22,562	3.1	5	4.6	22,567	3.1	<0.001
Native American	2882	0.4	0	0.0	2882	0.4	<0.001
Other	17,956	2.4	10	9.9	17,966	2.4	<0.001
Race unknown	112,645	15.3	0	0.0	112,645	15.3	N/A
Elixhauser co-morbidity category							
⩽–1	258,101	35.0	20	20.2	258,121	35.0	0.002
0–2	319,982	43.4	10	10.1	319,992	43.4	<0.001
3–10	83,208	11.3	49	49.2	83,256	11.3	<0.001
>10	75,237	10.2	20	20.5	75,257	10.2	0.001
Elixhauser co-morbidity index, median (IQR)	0 (–1.0 to 1.0)		4.0 (1.0 to 8.0)		0 (–1.0 to 1.0)		<0.001
Zip code income quartile							
First quartile	154,371	21.0	10	10.6	154,381	21.0	0.008
Second quartile	165,913	22.5	19	19.4	165,932	22.5	0.235
Third quartile	178,762	24.3	35	35.8	178,798	24.3	0.017
Forth quart	222,375	30.2	34	34.2	222,409	30.2	0.264
Zip code unknown	15,107	2.1	0	0.0	15,107	2.1	N/A
Carcinoma in situ of breast	132,850	18.0	21	21.0	132871	18.0	0.441
Procedures							
Unilateral mastectomy	494,188	67.1	69	69.7	494,257	67.1	0.582
Bilateral mastectomy	161,699	22.0	15	15.2	161,714	22.0	0.102
Lumpectomy	91,137	12.4	15	15.2	91,152	12.4	0.401
Reconstruction	76,159	10.3	15	15.2	76,174	10.3	0.116
Immediate reconstruction	64,343	97.1	15	100	64,358	97.1	0.501

applying the sampling weight built in NIS. The NIS Data Use Agreement (DUA) governs the disclosure and use of the data, including affirmations to protect individuals, establishments, and the database itself. NIS data use for this research includes adherence to the DUA.

Results

A total of 736,626 women underwent surgery for breast cancer. Of these, 99 received LT. There was no statistical difference in terms of age at the time of diagnosis of breast cancer. The majority of women in each cohort were white, with a significantly higher percentage of women in the LT group being white (65.3% vs 62.1%, $p < 0.001$). Of the 99 LTR, 69.7% had an Elixhauser comorbidity score of 3 or greater (median score of 4), while only 21.5% of non-LT patients had a score of 3 or greater (median score of 0) ($p < 0.001$, Table 1). Socioeconomic status for the LTR cohort was higher than the non-LTR cohort, as these women belonged mostly to the higher-income quartile (third quartile 35.8% vs 24.3%, p 0.017). There was no statistical difference in the frequency or type of surgical procedure, lumpectomy, or mastectomy (Table 1).

The dominant payment method was private insurance (50.8%). However, Medicare was a more common method of payment for the LTR group compared to the non-LTR group (65.0 vs 36.6%, $p < 0.001$). Most centers were public hospitals, with large bed size, and urban teaching affiliates. Although there were some statistical differences in the components of these variables, overall, these hospitals were comparable (Table 2).

The rate of complication was significantly higher in the LTR group compared to the non-LTR group (15.0 vs 8.2%, $p < 0.012$); the most common complication was acute renal failure in the LTR group (9.9 vs 0.6%, $p < 0.001$). Other complications were comparable (Table 3).

Liver transplant recipients underwent breast cancer surgery predominantly in TCs when compared to non-LTR (35.0% vs 23.2%, $p = 0.004$). There were no deaths in the 99 liver transplant recipients. There were significantly more complications in the LT cohort when compared to the non-LTR (15.0% vs 8.2%, $p = 0.012$). However, on multivariate

Table 2. Hospital characteristics.

	No LT (n = 736,527)		LT (n = 99)		TOTAL (n = 736,626)		p value
Primary expected payer							
Medicare	269,300	36.6	64	65.0	269,364	36.6	< 0.001
Medicaid	63,848	8.7	10	10.1	63,858	8.7	0.830
Private insurance	373,971	50.8	25	24.9	373,995	50.8	< 0.001
Self-pay	10,957	1.5	0	0.0	10,957	1.5	0.445
No charge	2542	0.3	0	0.0	2542	0.3	0.0794
Other	15,027	2.0	0	0.0	15,027	2.0	0.335
Payer unknown	883	0.1	0	0.0	883	0.1	N/A
Hospital ownership							
Government or private	205,257	27.9	25	25.5	205,282	27.9	0.637
Public	60,805	8.3	15	14.8	60,820	8.3	0.036
Private, non for profit	384,870	52.3	49	49.6	384,919	52.3	0.640
Private, investor owned	70,272	9.5	10	10.1	70,282	9.5	0.758
Private	11,439	1.6	0	0.0	11,439	1.6	0.349
Ownership unknown	3884	0.5	0	0	3894	0.5	N/A
Hospital bed size							
Small	99,611	13.5	15	15.1	99,626	13.5	0.694
Medium	174,011	23.6	14	14.6	174,026	23.6	0.061
Large	459,020	62.3	70	70.2	459,090	62.3	0.194
Bed size unknown	3884	0.5	0	0	3894	0.5	N/A
Location/teaching status							
Rural	64,412	8.7	0	0.0	64,412	8.7	0.006
Urban, non-teaching	268,225	36.4	50	50.0	268,275	36.4	0.012
Urban, teaching	400,005	54.3	49	50.0	400,055	54.3	0.456
Teaching status unknown	3884	0.5	0	0	3894	0.5	N/A
Region							
Northeast	180,178	24.5	11	10.6	180,189	24.5	0.002
Midwest	151,372	20.6	20	20.6	151,393	20.6	0.931
South	249,991	33.9	45	45.3	250,036	33.9	0.016
West	154,986	21.0	23	23.5	155,009	21.0	0.593
Transplant center	99,260	13.5	30	35.3	99,290	13.5	0.004

analysis, undergoing LT was not an independent risk factor for post-operative complications followed breast cancer surgery (odds ratio (OR), 1.223 p = 0.480; Table 4). Total hospital charges for breast cancer surgery were higher in the liver transplant group ($63,724 vs $43,003, p < 0.001; Table 3) LOS for breast cancer surgery in the reconstructed group was significantly shorter in the liver transplant group (LOS > 2 days OR 0.170, p = 0.002; Table 4).

Discussion

Organ transplantation has significant survival and quality-of-life benefits compared to best medical (non-transplant) management. One of the most important factors that has allowed for prolonged allograft survival has been the advances in immunosuppressive regimens. Although de novo malignancies are known long-term complications of organ transplantation, breast cancer is not increased in the transplant population when compared against age-matched SEER general population data. Incident rates in published literature show age-specific breast cancer incidence after 50 years old in those with LT similar to that of the general population. Our sample size is small when compared to the overall incidence in the literature of de novo breast cancers in those with liver transplants. Nonetheless, after weighting, our results reflect a realistic appraisal of patients with breast cancer and LT.

The care of the liver transplant recipient requires a lifelong multidisciplinary effort by a wide range of specialists. Clinicians must not only consider all of the transplant-related complications but also typical age-related comorbidities. Moreover, chronic immunosuppressive therapy can induce or accelerate some conditions that the non-transplant patient may not be routinely monitored for, specifically malignancy.

Centralized and specialized management of breast cancer in the liver transplant recipient is paramount. On univariate analysis, the complication rate, especially in acute renal failure was higher in LTR group. Currently most of breast surgery was performed in the outpatient setting. LTR might show the elevation of creatinine in perioperative workup since LTR require immunosuppression drugs

Table 3. Outcomes.

	No LT (n = 736,527)		LT (n = 99)		TOTAL (n = 736,626)		
	Number	%	Number	%	Number	%	*p* value
Death	599	0.1%	0	0.0%	599	0.1%	0.776
Disposition of patient (uniform)							0.747
Unknown	66	0	0	0	66	0.1	
Home health care	148,568	20.2%	16	16.0%	148,584	20.2%	
Transfer to SNF, ICF, or other	24,187	3.3%	0	0.0%	24,187	3.3%	
Transfer to short-term hospital	839	0.1%	0	0.0%	839	0.1%	
Routine	561,498	76.2%	83	84.0%	561,581	76.2%	
Other	770	0.1	0	0	770	0.1	
Any complication	60,372	8.2%	15	15.0%	60,387	8.2%	0.012
Cardiovascular	3567	0.5%	0	0.0%	3567	0.5%	0.488
Respiratory	2435	0.3%	0	0.0%	2435	0.3%	0.567
Peripheral vascular complication	223	0.0%	0	0.0%	223	0.0%	0.863
Central nervous system complication	329	0.0%	0	0.0%	329	0.0%	0.833
Hematomas	23,670	3.2%	5	5.0%	23,675	3.2%	0.300
Accidental cut, puncture, or hemorrhage during a procedure	871	0.1%	0	0.0%	871	0.1%	0.732
Complications of operative wound	1467	0.2%	0	0.0%	1467	0.2%	0.657
Post-operative infection	3266	0.4%	0	0.0%	3266	0.4%	0.507
Other	2489	0.3%	0	0.0%	2489	0.3%	0.562
Acute renal failure	4487	0.6%	10	9.9%	4497	0.6%	<0.001
Urinary complications	1405	0.2%	0	0.0%	1405	0.2%	0.664
Digestive system complications	1869	0.3%	0	0.0%	1869	0.3%	0.616
Acute vascular insufficiency-intestine	30	0	0	0	30	0	1.000
Platelet transfusion	990	0.1%	0	0.0%	990	0.1%	0.715
Fresh frozen plasma transfusion	1458	0.2%	0	0.0%	1458	0.2%	0.658
pRBC transfusion	24,280	3.3%	5	5.0%	24,285	3.3%	0.328
SIRS	1339	0.2%	0	0.0%	1339	0.2%	0.671
Complication of graft	3263	0.4%	0	0.0%	3263	0.4%	0.507
Length of stay, day, median (IQR)	2.0 (1.0–2.0)		2.0 (1.0–2.0)		2.0 (1.0–2.0)		0.493
Total charges associated with breast cancer surgery, $, median (IQR)	43,002 (26,952–71,027)		63,724 (33,068 – 91,809)		43,003 (26953 – 71,032)		<0.001

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.
Total charges were adjusted based on inflation price index 2020.

Table 4. Weighted multivariate adjusted outcome for liver transplant patients based on type of center.

	All centers	
	P value	OR
Any complication	0.480	1.223
Total charge > 43,000 USD	<0.001	2.621
Length of stay > 2 days	.027	.568
	Transplant Centers	
	P value	OR
Any complication	.0.651	1.254
Total charge > 43,000 USD	.146	1.782
Length of stay > 2 days	.186	.516
	Non-liver transplant center	
Any complication	.732	1.126
Total charge > 43,000 USD	<0.001	2.802
Length of stay > 2 days	.078	.590
	Teaching centers	
	P value	OR
Any complication	.064	1.942
Total charge > 43,000 USD	<0.001	2.891
Length of stay > 2 days	.189	.625
	Reconstruction	
	P value	OR
Any complication	N/A	N/A
Total charge > 43,000 USD	.907	1.067
Length of stay > 2 days	.002	.170

Note:
1. N/A, not applicable because of zero mortality and zero complications in only reconstructed patients.
2. Total charges were adjusted based on consumer price index 2020.
3. The multivariable analyses were adjusted for race, co-morbidity, primary expected payer, zip code income quartile, hospital ownership, location/teaching status, region.

and adjustment of the doses frequently according to serum creatinine levels. However, after adjustment and on multivariate analysis, LTR was not an independent risk factor for developing a post-operative complication (OR 1.223 p 0.480; Table 4). This suggests that factors other than LT are associated with development of post-operative complications.

A significantly higher proportion of LTR had an Elixhauser comorbidity score of ⩾3 (69.7% vs 21.5%, $p < 0.001$, Table 1), indicating that LT patients suffered from a higher degree of co-morbidity. However, our data show that despite the LTR having significantly more comorbidities, there were no differences in mortality, complication rate, total charge, or LOS when these patients were managed at a TC (Table 4). Breast cancer management in LTR at non-TCs incurred higher charges but no difference in complication rate nor LOS when compared to breast cancer management in LTR at TCs.

Of women who received a liver transplant, LOS following breast cancer surgery was significantly shorter in the group which underwent breast reconstruction. ($OR < 1$, $p = 0.002$; Table 4). This may be due to the fact that, in general, immediate breast reconstruction is performed by careful selection of those patients who are possibly overall healthier. We do not have knowledge of pre- and post-transplant performance status, immunosuppressive regimens, or pretransplant health that may overall lend to healthier LTR and thus ability to withstand an immediate breast reconstruction with acceptable outcomes and LOS. We have found a significantly shorter LOS after reconstruction in the liver transplant cohort compared to the non-liver transplant cohort most likely explained by better selection of appropriate candidates. The liver transplant patients underwent probably simpler implant-based reconstruction as opposed to non-liver transplant patients who underwent autologous

tissue-based reconstructions usually associated with more than double the LOS.

Our analyses revealed no statistical difference when comparing the overall survival of the two cohorts. This mirrors previous reports. Jeong et al. compared the prognosis of post-transplant breast cancer patients receiving immunosuppressants to general breast cancer survivors. All individuals had previously undergone either a liver or kidney transplant. They discovered that after matching by tumor size, lymph node metastasis, and age, disease-free survival, breast-cancer specific survival, and overall survival were not significantly different between the two cohort.[24]

A final, notable point is the fact that total hospital charges for breast cancer surgery were higher in the liver transplant group, even after controlling for other variables (OR 2.621, $p < 0.001$; Table 4). This may be explained by LTR suffer from a higher degree of co-morbidity. An analysis of 126,664 individuals with breast cancer, revealed the average medical cost per patient with comorbidity was higher compared to the average medical cost per person without comorbidity ($p < 0.05$).[25] We hypothesize that increased comorbidities in the LT cohort may have played a role in these women incurring higher costs for breast cancer surgery.

This analysis is not without limitations, as there is inherent weakness of large database analysis. The NIS has a data structure such that each observation represents a discrete health care encounter and includes a set of administrative diagnosis and procedure codes that correspond with that encounter, thus there is no ability to track patients longitudinally. Time between LT and breast cancer surgery was not known. Prolonged periods of immunosuppressive treatment may induce DNA damage and inhibit immune surveillance mechanisms, thus increasing risk of lymph node metastases which would require more extensive BC surgery, possibly axillary node dissection, with locally advanced disease at presentation.[24] In addition, immunosuppressive medications are unknown. This prevented us from stratifying outcomes based on type of immunosuppressive agent. Furthermore, information on the breast cancer stage and neoadjuvant chemotherapy treatment prior to surgery is unknown. Thus, we were unable to assess outcomes on early versus advanced disease. Similarly, long-term patient outcomes are not available due to database limitations, and could not be assessed, and may differ from the reported short-term outcomes in our analyses. Furthermore, there are no data available on cancer stage distribution or method of breast cancer detection or screening rates in those with LT.

Additional research is needed to more comprehensively understand the difficulties that post-liver transplant breast cancer survivors face following breast cancer surgery compared to the general breast cancer population. Future analyses should consider factors such as breast cancer stage, type of immunosuppressive therapy for both BC and LT, and time to breast cancer surgery and treatment since LT.

Conclusion

This is the largest and first-reported analyses that determines that prior LT does not increase morbidity nor mortality in women undergoing surgery for breast cancer. Total hospital charges for breast surgery were significantly higher in LTR. These results may be used to guide clinical practice when treating women for breast cancer who have undergone a liver transplant.

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All authors contributed to the study conception and design. All authors read and approved the final article.

Author contribution(s)

Gregory Veillette: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing—original draft.
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Data

Data from the National Inpatient Sample (NIS), between 2005 and 2014 on Breast Lumpectomy and Mastectomy were isolated (ICD 9 code: 85.20-85.23 and 85.33-85.36 and 85.41 – 85.48).

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

NIS Data use and acknowledgements include adherence to the Data Use Agreement (DUA). The DUA governs the disclosure and use of the data, including affirmations to protect individuals, establishments, and the database itself. This study was approved by the New York Medical College Institutional Review Board # 14177.

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Informed consent

This protocol does not meet the definition of human subjects research according to Federal Regulations at 45 CFR 46, thus informed consent is not relevant.

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Supplemental material

Supplemental material contains ICD 9 procedure and diagnosis codes isolated for this study.

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