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Outcomes Following Colorectal Resection in Kidney Transplant Recipients

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Abstract

Background—Kidney transplant recipients (KTR) are at increased risk of requiring colorectal resection compared to the general population. Given the need for lifelong immunosuppression and the physiologic impact of years of renal replacement, we hypothesized that colorectal resection may be riskier for this unique population.

Methods—We investigated the differences in mortality, morbidity, length of stay (LOS), and cost between 2,410 KTR and 1,433,437 non-KTR undergoing colorectal resection at both transplant and non-transplant centers using the National Inpatient Sample between 2000–2013, adjusting for patient and hospital level factors.

Results—In hospital mortality was higher for KTR in comparison to non-KTR (11.1 vs 4.3%, $p < 0.001$; adjusted odds ratio [aOR] 2.68_{3.59}_{4.81}) as were overall complications (38.5 vs 31.5%, $p = 0.001$; aOR 1.08_{1.30}_{1.56}). LOS was significantly longer (10 vs 7 days, $p < 0.001$; ratio 1.42_{1.53}_{1.65}) and cost was significantly greater (\$23,056 vs \$14,139, $p < 0.001$; ratio 1.42_{1.54}_{1.63}) for KTR compared to non-KTR. While LOS was longer for KTR undergoing resection at transplant centers compared to non-transplant centers (aOR 1.68 vs 1.53, $p = 0.03$), there were no statistically significant differences in mortality, overall morbidity, or cost by center type.

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Conclusions—KTR have higher mortality, higher incidence of overall complications, longer LOS, and higher cost than non-KTR following colorectal resection, regardless of center type. Physicians should consider these elevated risks when planning for surgery in the KTR population and counsel patients accordingly.

Keywords

general surgery; kidney transplantation; colorectal resection; colectomy

INTRODUCTION

More than 300,000 colectomies are performed annually in the United States for a variety of pathologies, including diverticulitis and cancer.[1,2] Because transplant recipients are at increased risk of these diseases, they are more likely to require colorectal resections compared to the general population. For example, transplant recipients have 2.6× higher incidence of colorectal cancer than non-transplant recipients[3], with a 5-year cumulative incidence rate of 0.5%.[4] Kidney transplant recipients (KTR) also have a higher incidence of diverticular disease and acute diverticulitis than the general population (0.94% vs 0.02%). [5–7] Furthermore, as post-transplant survival improves and the KTR population ages, the number of KTR requiring colorectal resection will increase proportionally.[7,8] An improved understanding of mortality, morbidity, length of stay, and associated cost of colorectal resection in this population is important for peri-operative planning and risk stratification.

A systematic review of single-institution studies of immunosuppressed patients demonstrated a 23% mortality rate for colorectal resection for diverticulitis[5], while another found 17.5% mortality following resection for colonic perforation[6], both significantly higher than anticipated in the general population.[1] As with other types of general surgery in KTR, single-institution case series have demonstrated a prolonged length of stay (LOS) following colorectal resection, with one study reporting a median LOS of 22.2 days compared to a national average of 9.3 days for open colectomy.[6,9–11] Given concerns of increased operative risk, it has been suggested that any increased morbidity, LOS or cost might be reduced if transplant recipients receive their surgical care at transplant centers.[12–14]

We used the National Inpatient Sample (NIS), a large, nationally representative database, to investigate the differences in mortality, morbidity, length of stay and cost between KTR and non-KTR undergoing colorectal resection in the United States. We also investigated post-resection outcomes based on the location of surgical care at transplant centers compared to non-transplant centers.

MATERIALS AND METHODS

Data Source

Patients were drawn from the NIS. Available through the Health Care Cost and Utilization Project, the NIS contains data from approximately 7 million hospital stays yearly, and is

made up of a stratified sample of 20% of the non-federal hospitals in the United States. The stratified sample is self-weighted to allow for population based estimates.[15] Information provided in the NIS includes patient level hospital discharge data such as patient demographics, as well as diagnostic and procedural ICD-9 codes for the index hospital admission. All study methods were approved by the Johns Hopkins Hospital Institutional Review Board.

Study Population

We studied 2,410 KTR and 1,433,437 non-KTR undergoing colorectal resections from January 1, 2000 – December 31, 2013. We limited the study to patients who had an International Classification of Disease, Ninth Revision (ICD-9) procedure code for laparoscopic or open colorectal resection and included both elective and urgent/emergent indications. KTR were distinguished from non-KTR by the presence of ICD-9 diagnosis codes consistent with prior kidney transplantation. We excluded patients with ICD-9 codes indicating a history of other solid or non-solid organ transplants (Appendix A) and patients who underwent both kidney transplantation and colorectal resection during the same hospital admission.

Patient, Hospital, and Procedure Characteristics

Basic demographic information was examined and the Charlson Comorbidity Index Score was calculated for each patient.^{1,2} Hospital and procedure characteristics included standard NIS categories of location (rural or urban), size (small, medium, large), teaching status, region (Northeast, Midwest, South, or West), surgical approach (laparoscopic vs open), case status (elective vs urgent/emergent), and calendar year. In addition, we categorized hospitals as transplant centers (a hospital where at least one kidney transplant was performed during the study period) or non-transplant centers.

Clinical Outcomes

We defined mortality as death during the primary surgical hospital admission. Morbidity, defined as intraoperative or postoperative complications during the primary surgical hospital admission, were identified by ICD-9 code and categorized into system-based groups as established in previous studies (Appendix B).³ Incidence of mortality and morbidity were modeled using hierarchical logistic regression. Length of stay was examined using hierarchical negative binomial regression. Mixed linear regression was used to examine log-transformed costs, which were determined using the NIS cost-to-charge ratio files.

All models included random intercepts for each hospital and were adjusted for patient (sex, age, African American race, Charlson Comorbidity Index, primary insurance status) and hospital factors (location, size, region, teaching status, and transplant center status). Secular trends were evaluated by adjusting all models for calendar year. **Variables for urgent/emergent vs. elective case status and laparoscopic vs. open surgical approach were not associated with the outcomes of interest in univariable or multivariable models, and therefore did not change any of our study inferences. Further, the inclusion of these variables in our multivariable models resulted in inferior model fit based on the Akaike**

information criterion. Therefore, to optimize model parity, we excluded these variables in our reported models.

Effect Modification by Transplant Center

We investigated effect modification for the above outcomes based on whether the colorectal resection was performed at a transplant center or a non-transplant center. To evaluate the effect of transplant center status on the relationship of KTR and the outcomes above, we created an interaction term for KTR status with transplant center status in the regression models described above.

Statistical Analysis

We used χ^2 tests to evaluate categorical variables and Student's t test for continuous variables to draw between-group comparisons. For all analyses, a two-tailed p-value of < 0.05 was considered statistically significant. Confidence intervals are reported as per the method of Louis and Zeger.[16] Statistical analysis was performed using Stata 14.0 (StataCorp, College Station, Texas).

RESULTS

Study Population

In total, 2,410 KTR and 1,433,437 non-KTR underwent colorectal resection during the study period. KTR were younger (58.2 vs 65.1 years, $p < 0.001$), more likely to be male (58.7% vs 46.2%, $p < 0.001$), African American (20.2% vs 10.2%, $p < 0.001$), have public insurance (68.4% vs 59.1%, $p < 0.001$) and have higher Charlson Comorbidity Index scores (43.2% vs 35.7% with score ≥ 3). KTR were less likely to have a laparoscopic colorectal resection (20.4% vs 30.5%, $p = 0.002$) and less likely to undergo an elective procedure (47.3% vs 61%, $p > 0.001$) (Table 1).

Mortality and Morbidity

Mortality was higher following colorectal resection for KTR compared to non-KTR (11.1% vs 4.3%, $p < 0.001$). After adjusting for patient and hospital characteristics, the odds of mortality following colorectal procedures in KTR was 3.59-fold higher than non-KTR (aOR 2.68_{3.59}^{4.81}). KTR were more likely than non-KTR to have postoperative complications during their surgical hospitalization (38.5% vs 31.5%, $p = 0.001$). Specifically, KTR had more wound complications (6.2% vs 2.4%, $p < 0.001$), infectious complications (7.7% vs 4.2%, $p < 0.001$), cardiovascular complications (5.2 vs 2.7%, $p < 0.001$), pulmonary complications (8.0% vs 5.3%, $p = 0.008$) and intraoperative complications (6.5% vs 3.9%, $p = 0.003$) than non-transplant recipients (Table 2). After adjustment, the odds of overall morbidity were 1.30-fold higher in KTR than non-KTR (aOR 1.08_{1.30}^{1.56}). Specifically, KTR had higher odds of cardiovascular (aOR 1.45_{2.19}^{3.31}), wound (aOR 1.35_{1.97}^{2.87}), infectious (aOR 1.08_{1.52}^{2.13}), pulmonary (aOR 1.21_{1.70}^{2.39}), and intraoperative (aOR 1.15_{1.66}^{2.38}) complications when compared to non-KTR (Table 3).

Length of Stay and Cost

Median length of stay (LOS) was longer in KTR compared to non-KTR (10 days vs 7 days, $p < 0.001$). Following adjustment, KTR had a 53% longer LOS than non-KTR (ratio 1.43_{1.53}_{1.65}). Cost of care was higher for KTR than non-KTR, with a median difference of \$9,000 dollars (\$23,056 vs \$14,139, $p < 0.001$). Following adjustment, cost was 54% higher in KTR than non-KTR (ratio 1.42_{1.53}_{1.63}) (Tables 2 & 3).

Transplant Center

KTR were more likely to be treated at kidney transplant centers than non-KTR (29.9% vs 8.9%, $p > 0.001$) (Table 1). There was no statistically significant difference in mortality for KTR treated at transplant centers compared to those treated at non-transplant centers (aOR 3.95 vs 3.43, interaction $p = 0.6$). There was also no statistically significant difference in overall complications or most system-specific complications (Table 4). However, KTR were less likely to have infectious complications at transplant centers compared to non-transplant centers (aOR 0.75 vs 1.99, interaction $p = 0.03$). LOS was 15% longer for KTR treated at transplant centers (ratio 1.68 vs 1.53, interaction $p = 0.03$). There was no significant difference in cost of care for KTR between transplant center types (Table 4).

DISCUSSION

In this national, 14-year study of 2,410 kidney transplant recipients undergoing colorectal resection, we found that KTR had a 3.6-fold increase in mortality and 1.3-fold increase in overall morbidity when compared to non-KTR. KTR were more susceptible to wound (6.2 vs 2.4%), infectious (7.7 vs 4.2%), cardiovascular (5.2 vs 2.7%), pulmonary (8.0 vs 5.3%) and intraoperative (6.5 vs 3.9%) complications than non-KTR. Cost was 1.5-fold higher for KTR compared to non-KTR. KTR also had a 1.5-fold longer LOS than non-KTR, with an additional 15% increase in LOS when KTR are treated at transplant centers.

Our findings of significantly higher mortality in KTR undergoing colorectal resection are consistent with and expand on single-institution studies of solid organ transplant recipients which document 7 to 10% mortality rates from colorectal disease complications.[17–19] A recent national study of emergency colorectal surgery reported a 9.3% mortality rate,[1] appropriately higher than the rate we report for the non-transplant population (4%), given that our sample contains both elective and urgent/emergent surgical resections. However, considering nearly half of the transplant recipients in our study population had elective resections, the 3.6-fold increase in mortality that we report after adjustment is striking.

Furthermore, we found the rate of overall complications to be significantly higher in KTR. Specifically, we found that KTR suffered more wound, infectious, cardiovascular, pulmonary, and intraoperative complications than non-KTR. These findings are consistent with a recent systematic review of gastrointestinal complications in solid organ transplant recipients that reported a 33% incidence of complications following resection for diverticular disease, and several single institution case series reporting between 60–100% complication rate for colorectal resections for diverticulitis or lower gastrointestinal perforations.[6,7,17]

Although the underlying cause for our findings of increased mortality and complications is multifactorial, it is likely heavily influenced by immunosuppression. The impact of immunosuppression on wound healing and infection is well documented, particularly in the immediate post-transplant setting.[20,21] Even with improved immunosuppressant regimens, higher rates of wound healing issues and infectious complications have been documented in KTR.[22,23] **Given our findings of increased wound and infectious complications in the KTR population following colorectal resection and current literature that suggests laparoscopic resection decreases the risk of wound complications in high risk patients, we would encourage surgeons to utilize a laparoscopic approach when technically feasible to mitigate these elevated risks.**[24] In addition, we have demonstrated that cardiovascular, pulmonary and intraoperative complications are more frequent in KTR. The global tissue damage caused by years of renal failure and/or dialysis is potentially responsible for an increase in complications associated with these organ systems and subsequent mortality.[25]

We found the median length of stay for kidney transplant recipients to be significantly longer than non-transplant recipients (10 vs 7 days), particularly when treated at a transplant center (11 vs 7 days). The median LOS we report for the general population is similar to other reports that document LOS of 6–9 days following open colorectal resection, as only 20% of patients in our study underwent laparoscopic approach.[2,9] Our findings are consistent with longer LOS documented in other smaller, single institutions studies of transplant recipients undergoing general surgical procedures.[10,11,26] Additionally, we reported significantly higher cost for kidney transplant recipients compared to non-transplant recipients. A recent national study of colectomy reported median costs ranging from \$12,071 – 14,141 depending on surgical approach for the general population, which is similar to our finding of median cost of \$14,139 for non-transplant recipients.[2] However, median cost for kidney transplant recipients was 54% higher following adjustment. While this difference is significant, the nature of our study data precluded a more granular examination of costs.

Despite the sentiments expressed in multiple opinion pieces including book chapters and editorials, we did not find better outcomes for transplant recipients at transplant centers. [13,14,27] In fact, we found that KTR had a 15% longer LOS when treated at transplant centers. Given the constellation of similar mortality, morbidity and cost in the setting of longer LOS at transplant centers, the longer LOS does not appear to be attributable to a difference in illness severity at transplant centers compared to non-transplant centers. This is potentially suggestive of more conservative discharge criteria and behavior at transplant centers.

This study has some limitations that warrant further discussion. An important limitation was the lack of clinical granularity of NIS data. While the admitting diagnosis was routinely recorded and helpful in determining the indication for surgery, it was often vague, hindering our ability to adjust for colorectal resection indication. Without detailed information on the specific costs and events occurring during a hospital stay, we were also unable to determine the underlying reasons for cost and length of stay differences between KTR and non-KTR, and between transplant centers and non-transplant centers. We were unable to determine

whether, for example, those KTR presenting to non-transplant centers who were sicker were transferred to transplant centers for care. An additional limitation inherent in the design of the NIS was the lack of longitudinal follow-up across multiple hospitalizations, and the lack of linkage to transplant registries, thereby limiting our ability to study later graft or patient outcomes. The magnitude of the NIS, however, offers an understanding of the national outcomes of colorectal resections in KTR and avoids the bias and limited power associated with single-center studies. It also allows us to perform multivariable analyses, investigate interactions, and study outcomes at transplant vs non-transplant centers.

CONCLUSION

In this large national study, kidney transplant recipients had higher mortality, greater morbidity, and higher cost when compared to non-transplant recipients following colorectal resection, regardless of center type. Kidney transplant recipients also have longer length of stay, which is particularly increased when colorectal resection is performed at transplant centers. Our findings suggest that surgeons should consider these elevated risks when planning for surgery in the KTR population and counsel patients accordingly.

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Appendix A

International Classification of Diseases, 9th Revision, codes for procedure, inclusion and exclusion criteria. **Procedure codes for laparoscopic resections are nested as subcodes of the applicable resection in cases where the name reads “open and other”.** For cases that are not specifically listed as “open and other”, specific subcodes for laparoscopic procedures have been listed.

Procedure

Total intra-abdominal colectomy 45.8

Laparoscopic total intra-abdominal colectomy 45.81

Open and other partial excision of large intestine 45.7

Open and other multiple segmental resection of large intestine 45.71

Open and other cecectomy 45.72

Open and other right hemicolectomy 45.73

Open and other resection of transverse colon 45.74

Open and other left hemicolectomy 45.75

Open and other sigmoidectomy 45.76

Open and unspecified partial excision of large intestine 45.79

Laparoscopic partial excision of large intestine 17.31–17.39

Pull through resection of rectum 48.4

Laparoscopic pull through resection of rectum 48.42

Abdominoperineal resection of rectum 48.5

Laparoscopic abdominoperineal resection of rectum 48.51

Inclusion

Kidney transplant recipient: V42.0

Exclusion

Other (non-kidney) transplant recipients: V42.1, V42.2, V42.6, V42.7, V42.8, V42.81, V42.82, V42.83, V42.84, V42.89, V42.9

Complications from history of other (non-kidney) transplant: 996.80, 996.82, 996.83, 996.84, 996.85, 996.86, 996.87, 996.88, 996.89

Appendix B

International Classification of Diseases, 9th Revision, clinical modification codes for postoperative in-hospital complications. *Adapted from Guller et al.*

Mechanical Wound

Delayed wound healing, 998.83

Postoperative hematoma, 998.12

Postoperative seroma (non-infected), 998.13

Disruption of operative wound, 998.3 Persistent postoperative fistula, 998.6

Infectious

Postoperative infection, 998.5
 Postoperative skin abscess, 998.59
 Postoperative septic wound complications, 998.59
 Postoperative skin infection, 998.59
 Postoperative intraabdominal abscess, 998.59
 Postoperative subdiaphragmatic abscess, 998.59
 Postoperative infected seroma, 998.51

Cardiovascular
 Postoperative stroke, 997.02
 Phlebitis or thrombophlebitis from procedure, 997.2
 Cardiac arrest/insufficiency during or resulting from a procedure, 997.1

Thromboembolic
 Postoperative deep venous thrombosis, 997.79
 Postoperative pulmonary embolism, 415.11

Pulmonary
 Postoperative atelectasis, 997.3
 Postoperative pneumonia, 997.3
 Postoperative acute respiratory insufficiency, 518.5
 Postoperative acute pneumothorax, 512.1
 Adult respiratory distress syndrome, 518.5
 Postoperative pulmonary edema, 518.4

Gastrointestinal tract
 Postoperative small-bowel obstruction, 997.4
 Postoperative ileus, 997.4
 Postoperative ileus requiring nasogastric tube, 997.4
 Postoperative nausea, 997.4
 Postoperative vomiting, 997.4
 Postoperative pancreatitis, 997.4
 Complication of anastomosis of gastrointestinal tract, 997.4

Urinary
 Postoperative urinary retention, 997.5
 Postoperative urinary tract infection, 997.5

Intraoperative
 Accidental puncture or laceration, complicating surgery, 998.2
 Foreign body accidentally left during procedure, 998.4
 Hemorrhage/bleeding complicating procedure, 998.11

Table 1

Characteristics, hospital and procedure details for kidney transplant recipients (KTR) and non-KTR undergoing colorectal resection between 2000–2013.

	KTR (n=2,410)	Non-KTR (n=1,433,437)	p-value
Age, mean (SD)	58.2 (11.9)	65.1 (15.5)	<0.001
Female, %	41.3	53.8	<0.001
African American, %	20.2	10.2	<0.001
Charlson Comorbidity Index, %			<0.001
0	22.8	31.1	
1	10.2	11.8	
2	23.8	21.4	
3	43.2	35.7	
Insurance Status, %			<0.001
Public	68.4	59.1	
Private	29.7	36.1	
Other	1.8	4.8	
Hospital bed size, %			<0.001
Small	3.9	11.7	
Medium	20.6	24.9	
Large	75.6	63.4	
Hospital location/teaching status, %			<0.001
Rural	2.9	10.0	
Urban non-teaching	24.8	44.2	
Urban teaching	72.3	45.8	
Hospital region, %			0.47
Northeast	23.0	23.6	
Midwest	19.3	17.5	
South	37.7	40.4	
West	20.0	18.5	
Laparoscopic, %	20.4	30.5	<0.001
Performed at transplant center, %	29.9	8.9	<0.001
Elective case, %	47.3	61.0	<0.001

Table 2

Unadjusted outcomes following colorectal resection in kidney transplant recipients (KTR) vs non-KTR.

Outcome	KTR (n = 2410)	Non-KTR (n = 1,443,437)	P value
Mortality, %	11.1	4.3	<0.001
Any Complication, %	38.5	31.5	0.001
System specific complications, ^a %			
Wound	6.2	2.4	<0.001
Infection	7.7	4.2	<0.001
Pulmonary	8.0	5.3	0.008
Cardiovascular	5.2	2.7	<0.001
Thromboembolic	0.4	0.3	0.7
Genitourinary	2.2	1.3	0.08
Gastrointestinal	18.4	19.3	0.6
Intraoperative	6.5	3.9	0.003
LOS, median days (IQR)	10 (6–20)	7 (5–11)	<0.001
At KT center	11 (7–24)	7 (5–12)	<0.001
At non-KT center	9 (6–18)	7 (5–11)	<0.001
Cost, median \$ (IQR)	23,056 (13,408–45,217)	14,139 (9,642–23,313)	<0.001
At KT center, median \$ (IQR)	21,360 (13,475–50,380)	15,615 (10,613 – 26,152)	<0.001
At non-KT center, median \$ (IQR)	23,899 (13,380–43,015)	13,964 (9,547 – 23,036)	<0.001

^a see Appendix B for breakdown of complications by system

Table 3

Adjusted outcomes^b following colorectal resection in kidney transplant recipients (KTR) vs non-KTR.

Outcome	KTR vs Non-KTR	95% CI
In hospital mortality, OR	3.59	2.68–4.81
Any complication, OR	1.30	1.08–1.56
System specific complications ^a , OR		
Wound	1.97	1.35–2.87
Infection	1.52	1.08–2.13
Pulmonary	1.70	1.21–2.39
Cardiovascular	2.19	1.45–3.31
Thromboembolic	1.22	0.30–4.95
Genitourinary	1.81	0.98–3.31
Gastrointestinal	0.91	0.72–1.15
Intraoperative	1.66	1.15–2.38
LOS, ratio	1.53	1.42–1.65
Cost, ratio	1.54	1.42–1.63

^a see Appendix B for breakdown of complications by system

^b adjusted for age, race, gender, Charlson comorbidity score, insurance status, hospital bed size, hospital region, teaching status, transplant center, calendar year

Table 4

Adjusted outcomes^b following colorectal resection for kidney transplant recipients (KTR) vs. non-KTR by center type.

Outcome	Transplant center	Non-transplant center	p-value for interaction
Mortality, OR	3.95 (2.39–6.51)	3.43 (2.39–4.91)	0.6
Any complication, OR	1.44 (1.02–2.01)	1.24 (0.99–1.55)	0.7
System specific complications ^a , OR			
Wound	1.84 (1.01–3.37)	2.05 (1.27–3.33)	0.8
Infection	0.75 (0.38–1.63)	1.99 (1.36–2.91)	0.03
Pulmonary	1.02 (0.52–2.03)	2.12(1.43–3.14)	0.07
Cardiovascular	2.93 (1.56–5.51)	1.83(1.07–3.16)	0.3
Thromboembolic ^c	1.99 (0.49–8.07)	-	-
Genitourinary	2.43 (0.98–6.03)	1.49 (0.66–3.38)	0.4
Gastrointestinal	1.02 (0.67–1.57)	0.87 (0.65–1.15)	0.5
Intraoperative	1.09 (0.53–2.24)	1.99 (1.31–3.02)	0.2
LOS, ratio	1.68 (1.50–1.87)	1.53 (1.43–1.65)	0.03
Cost, ratio	1.50 (1.33–1.68)	1.54 (1.41–1.68)	0.8

^a see Appendix B for breakdown of complications by system

^b adjusted for age, race, gender, Charlson comorbidity score, insurance status, hospital bed size, hospital region, teaching status, transplant center, calendar year

^c no thromboembolic events occurred at non-transplant centers