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Authors

Halabi, Wissam J
Jafari, Mehraneh D
Nguyen, Vinh Q
et al.

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Colorectal Surgery in Kidney Transplant Recipients: A Decade of Trends and Outcomes in the United States

Wissam J. Halabi, M.D.,* Mehraneh D. Jafari,* Vinh Q. Nguyen, Ph.D.,† Joseph C. Carmichael, M.D.,* Steven Mills, M.D.,* Alessio Pigazzi, M.D., Ph.D.,* Michael J. Stamos, M.D.,* Clarence E. Foster III, M.D.*

From the *Department of Surgery, University of California, Irvine School of Medicine, Irvine, California; and the †Department of Statistics, University of California Irvine, Irvine, California

There is paucity of data evaluating the trends and outcomes of colorectal surgery (CRS) in kidney transplant recipients (KTRs). Using the Nationwide Inpatient Sample 2001 to 2010, a retrospective review of CRS performed in KTRs was performed. Trends, demographics, indications, and outcomes were examined for elective and emergent cases and compared with the general population (GP) on multivariate logistic regression. A total of 2616 KTRs underwent CRS, 50 per cent of which were done emergently. KTRs developed colon and rectal cancer at a younger age and had significantly higher incidence of comorbidities compared with the GP. Diverticular disease was the most common indication for surgery (48%) followed by cancer (30.6%). Compared with the GP, KTRs had higher rates of mortality (6.29 vs 3.64%), wound complications (8.02 vs 5.37%), and acute renal failure (ARF) (17.14 vs 7.10%) (all $P < 0.05$). No difference was seen in the incidence of anastomotic leak. On multivariate analysis, KTRs had higher associated odds of ARF (odds ratio, 2.02; $P < 0.001$), whereas the odds of mortality, wound, and anastomotic complications were similar to the GP. Emergency surgery in KTRs was associated with worse outcomes compared with the elective setting. KTRs undergoing CRS have unique characteristics that are different than the GP. They are at an increased risk of complications, especially acute renal failure.

Over the past decade, the number of kidney transplants performed annually in the United States has grown from approximately 12,000 cases in 1998 to more than 16,000 cases in 2008.¹ With a 5-year graft survival rate ranging from 72 to 91 per cent, there were over 144,000 patients living with a functioning transplanted kidney in 2008 compared with 83,000 patients in 1999.¹ The increased 5-year survival rate is the result of a change in immunosuppression regimens and the use of more effective immunosuppressants, lowering the risk of kidney allograft failure from acute rejection.

An increase in long-term survival along with the obligated use of therapeutic immunosuppression makes kidney transplant recipients more prone to diseases that affect the general population. Kidney transplant recipients (KTRs) have a well-documented increased risk for colorectal malignancies, a risk that is two- to threefold higher than their age-matched control subjects.²⁻⁵ Moreover, the rate of acute diverticulitis in the immunosuppressed population is higher than the baseline population with significantly worse outcomes.⁶⁻⁸

Available reports on colon and rectal pathologies in kidney transplant recipients have focused mainly on demographics, demonstrating an earlier age of onset of colorectal

malignancy in this population.⁵ However, there is a paucity of data examining the outcomes of colorectal surgery in this unique population. Most reports come from single-center experiences and are thus limited by small sample sizes precluding meaningful analyses. Moreover, to date there are no reports describing the trends of colorectal surgery in KTRs at the national level.

This is a large retrospective review of colorectal surgical procedures performed in KTRs in the United States over a 10-year period analyzing trends, demographics, indications, and outcomes of surgery in the elective and emergent setting. Comparisons were made to the general population.

Methods

Patient Population

Using the Healthcare Cost and Utilization Project–Nationwide Inpatient Sample (NIS) from 2001 to 2010, we performed a retrospective review of cases with a history of a transplanted kidney that underwent subsequent colorectal surgical procedures. The NIS is the largest all-payer inpatient care database in the United States and contains information from 95 per cent of all hospital discharges in the United States. Data elements within the NIS are drawn from hospital discharge abstracts, which provide information on patient characteristics, length of stay, procedure performed postoperative morbidity, and in-hospital mortality. Approval for the use of the NIS patient-level data in this study was obtained from the Institutional Review Board of the University of California–Irvine Medical Center and the NIS.

Inclusion Criteria

All KTRs were identified by the *International Classification of Diseases, 9th Revision, Clinical Modification* CM diagnosis code V42.0. We selected cases admitted electively or emergently that underwent colorectal surgical procedures. The following indications for surgery were included: colon and rectal cancer, benign polyps, diverticular disease, ischemic colitis, and *Clostridium difficile* colitis. The following procedure types were included in our analysis: right and left colectomy, transverse colectomy, sigmoidectomy, anterior resection, abdominoperineal resection, and partial and total colectomy. The use of laparoscopy and conversion rates was also considered as well as the use of stoma.

Exclusion Criteria

Patients with a history of kidney–pancreas, liver–kidney, or heart–kidney transplant were excluded from our analysis to minimize heterogeneity that may result from disparity in immunosuppressive regimens. We also excluded patients with inflammatory bowel disease, rheumatoid arthritis, collagen vascular disease, polyarteritis nodosa, sarcoidosis, history of transplanted organs other than kidney, and patients with AIDS. Because our aim was to investigate the effect of immunosuppression on outcomes in KTRs, we believe that other regimens and causes of immunosuppression

may confound this effect. Patients with a history of a transplanted kidney who are back on dialysis were excluded from the KTR population. Missing variables including admission status (elective vs emergent) were excluded from our analysis as well.

Study Variables

Patient characteristics that were examined included: age, gender, race, payer type, and comorbidities provided by NIS and based on the Elixhauser comorbidity index⁹ as well as a comorbidity score based on the Elixhauser-Van Walraven's model to investigate the functional status of KTR.¹⁰ Indication for surgery, procedure types, the use of stoma, laparoscopy, and the associated conversion rates were also examined and accounted for on multivariate regression analysis. KTRs and the general population were split into two groups based on the admission type: elective *versus* urgent/emergent. Admission type was also accounted for on multivariate regression analysis.

End Points

The following end points were chosen *a priori* and analyzed on multivariate analysis: mortality, infectious complications (wound complications, pneumonia, urinary tract infection), noninfectious complications (cerebrovascular accident, cardiac complications, respiratory failure, ileus, urinary retention, deep venous thrombosis, postoperative bleeding), acute renal failure, anastomotic leakage, and wound complications.

Statistical Analysis

All statistical analyses were conducted using SAS, Version 9.3, and the R Statistical Environment. χ^2 with Yates' correction was used for univariate analysis. Multivariate logistic regression was used to compare end points between KTRs and the general population (GP) after controlling for the variables previously listed. Estimates of adjusted mean differences and adjusted odds ratios (ORs) were obtained with 95 per cent confidence intervals (CIs). Statistical significance was declared if P values were < 0.05.

Results

Based on our sampling criteria, we identified a total of 2,273,829 patients who underwent colorectal surgical procedures in the study period. Of these cases, only 2,616 (0.12%) had a history of a transplanted kidney (Table 1). The number of colorectal surgical procedures performed in the KTR population in the United States remained relatively low over the study period showing a modest average yearly increase of 6 per cent.

TABLE 1. Estimated Number of Colorectal Surgical Procedures Performed in the United States and the Number of Procedures Performed in Kidney Transplant Recipients (KTRs) during the Study Period

Year	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	Total
Colorectal surgeries in GP	227,188	234,441	228,785	227,662	229,393	224,170	230,573	235,070	221,379	212,552	2,271,213
Colorectal surgeries in KTRs	232	172	234	312	263	233	287	259	289	335	2,616
Percent KTRs	0.10	0.07	0.10	0.14	0.11	0.10	0.12	0.11	0.13	0.16	0.12

GP, general population.

Patients in the transplant group were younger than the general population with a mean age of 59 years compared to 65 years in the GP (Table 2). On subgroup analysis, KTRs undergoing colon cancer surgery were younger compared with the general population (60 vs 70 years; $P < 0.001$). Similar findings were observed for rectal cancer (KTR 45.8 years vs GP 46.5 years; $P < 0.001$).

Patients in the transplant group were more likely to have anemia, diabetes, hypertension, congestive heart failure, chronic liver disease, and peripheral vascular disease. As expected, comorbidity scores in the KTR group were higher than the general population (Table 2).

TABLE 2. Demographic Characteristics and Associated Comorbidities of Patients in the General Population and Kidney Transplant Recipient (KTR) Undergoing Colorectal Surgery*

Age (years)	65 (55–77)	59 (51–67)	< 0.01
Gender			
Male	47.42	58.13	< 0.001
Female	52.58	41.87	
Ethnicity			
White	61.17	56.40	< 0.001
Black	6.66	13.01	< 0.001
Hispanic	3.99	4.99	0.01
Other	2.79	2.82	0.95
Missing	25.39	22.78	
Primary payer			
Medicare	29.60	38.61	< 0.001
Private including HMO	23.55	21.26	< 0.01
Medicaid	2.53	2.17	0.28
Other	3.24	1.52	< 0.001
Missing	41.09	36.44	
Comorbidities			
Anemia	14.57	25.81	< 0.001
Diabetes	15.28	29.50	< 0.001
Hypertension	45.69	65.72	< 0.001
Obesity	6.12	4.55	< 0.001
Congestive heart failure	7.09	10.41	< 0.001
Chronic pulmonary disease	15.39	8.46	< 0.001
Chronic liver disease	1.43	2.17	0.002
Peripheral vascular disease	3.72	6.51	< 0.001
Smoking	15.96	8.68	< 0.001
Comorbidity score†	5 (0–10)	9 (5–12)	< 0.001

* Percentages are given for categorical variables, whereas absolute numbers are used for continuous variables (age and comorbidity score).

† Based on the Elixhauser-VanWalraven comorbidity index.

The indications for surgery in KTR and the GP are listed in Table 3. Emergent procedures accounted for 50.11 per cent in KTRs compared with 38.23 per cent in the GP ($P < 0.001$). KTRs were more likely to be operated on for diverticular disease, which constituted the most common indication for surgery: 47.7 per cent compared with 33.2 per cent in the GP. Cancer was the second most common indication in KTRs and accounted for 30.58 per cent of cases, whereas it was 50.76 per cent in the GP. Interestingly, KTRs were operated on more frequently for benign polyps of the colon compared with the GP ($P < 0.001$). Colectomy for ischemic colitis was performed in 9.1 per cent of KTRs versus 4.5 per cent of cases in the GP ($P < 0.001$).

TABLE 3. Indication for Colorectal Surgical Procedures in Kidney Transplant Recipients (KTRs) and the General Population (GP) in the Elective and the Emergent Settings*

	Elective			Emergent		
	GP (n = 1,402,020)	KTR (n = 1,305)	P Value	GP (n = 869,193)	KTR (n = 1,311)	P Value
Colon benign polyps	13.93	17.83	< 0.01	4.33	4.76	0.52
Colon cancer	37.89	33.91	< 0.01	35.70	14.29	< 0.01
Diverticular disease	28.86	36.09	< 0.01	40.14	59.31	< 0.01
Ischemic colitis	1.03	2.61	< 0.01	10.01	15.58	< 0.01
<i>Clostridium difficile</i> colitis	0.23	0	—	1.57	2.16	0.12
Rectal benign polyps	0.80	0.43	0.22	0.25	0	—
Rectal cancer	17.26	9.13	< 0.01	8.00	3.90	< 0.01

* Numbers represent percentages.

The use of laparoscopy, conversion rates, and the use of stoma are listed in Table 5. The use of stoma for all the procedures considered (excluding abdominoperineal resection (APR) and total colectomy) was higher in the KTR group compared with the GP (26.9 vs 15.5%; $P < 0.001$). Again, a stoma was more likely to be used in KTRs undergoing emergent surgery compared with cases performed electively (44.6 vs 9.1%; $P < 0.001$) (Table 4). No difference was observed in the use of laparoscopy between KTRs and the GP. Laparoscopy was used in 10.8 per cent of cases in the KTR group versus 13.2 per cent in the GP ($P = 0.14$). The associated conversion rates were similar as well. In KTRs, the use of laparoscopy was more common in the elective setting as compared with the emergent setting (16.5 vs 5.2%; $P < 0.001$).

TABLE 4. Use of Laparoscopy, Conversion Rates, and Ostomy Creation in Kidney Transplant Recipients (KTRs) and the General Population (GP) in the Elective and the Emergent Settings*

	Elective			Emergent		
	GP (n = 1,402,020)	KTR (n = 1,305)	P Value	GP (n = 869,193)	KTR (n = 1,311)	P Value
Use of laparoscopy	17.02	16.52	0.68	7.01	5.2	0.01
Conversion rates	18.05	21.05	0.79	25.98	16.66	0.68
Stoma creation	6.29	9.13	0.11	30.34	44.59	< 0.001

* Total numbers are provided in the third row. Results for use of laparoscopy, conversion rates, and ostomy creation are given in percentages.

In 2008, new *International Classification of Diseases, 9th Revision* procedure codes were introduced. These codes are specific for laparoscopic colorectal cases. We performed a subgroup analysis to examine the use of laparoscopy in the GP and KTR

from 2001 to 2008 and from 2009 to 2010. We found an increase in the use of laparoscopy when comparing the 2001–2008 period with the 2009–2010 period in KTR and GP (Table 5).

TABLE 5. The Use of Laparoscopy in Kidney Transplant Recipients and the General Population from 2001 to 2008 and from 2009 to 2010

Data Years	General Population			Kidney Transplant Recipients		
	2001–2008	2009–2010	<i>P</i> Value	2001–2008	2009–2010	<i>P</i> Value
Numbers	1,837,283	433,930		1,992	624	
Open cases	1,688,567 (91.90)*	275,654 (63.52)*	< 0.001	1,878 (94.28)*	466 (74.68)*	< 0.001
Laparoscopic cases	148,716 (8.10)*	158,276 (36.48)*	< 0.001	114 (5.72)*	158 (25.32)*	< 0.001
Conversion rates	25.20	14.57	< 0.001	29.82	22.15	0.20

* Values represent raw numbers with percentages listed in parentheses. Conversion rates are given in percent proportions.

The length of stay of KTRs undergoing elective colorectal surgical procedures was 9 days (range, 5 to 9 days) compared with only 7 days for the GP (range, 5 to 8 days). Length of stay was longer in the emergent setting: 15 days in the KTR group (range, 8 to 18 days) compared with 13 days in the GP (range, 7 to 16 days).

KTRs undergoing elective colorectal surgery had higher mortality rates compared with the GP (3.04 vs 1.29%; $P < 0.001$). This difference in mortality rates was observed in the emergent setting as well: 9.52 per cent in KTRs versus 7.45 per cent in the GP ($P = 0.005$) (Table 5). On subgroup analysis, mortality rates were analyzed after colon cancer surgery as well as diverticular disease. We noted that although mortality rates after colon cancer surgery were similar in KTRs compared with the GP in the elective setting (1.38 vs 2.56%; $P = 0.07$), emergency surgery for colon cancer was associated with a higher mortality rate in KTRs compared with the GP (9.09 vs 5.46%; $P = 0.04$). This observation was also noted for diverticular disease in which the mortality rate for KTRs undergoing elective resection was similar to the GP (0.63 vs 1.20%; $P = 0.14$). However, when performed emergently, surgery for acute diverticulitis was associated with a 7.30 per cent mortality rate for KTRs compared with 4.91 per cent in the GP with a statistically significant P value of 0.002.

Postoperative complications in the KTRs and the GP in the elective and emergent settings are listed in Table 6. We note that the incidence of certain complications such as acute renal failure and wound complications were higher in KTRs both in the elective and the emergent setting.

TABLE 6. Postoperative Outcomes in Kidney Transplant Recipients (KTRs) and the General Population (GP) in the Elective and the Emergent Settings*

	Elective			Emergent		
	GP (n = 1,402,020)	KTR (n = 1,305)	P Value	GP (n = 869,193)	KTR (n = 1,311)	P Value
In-hospital mortality	1.29	3.04	< 0.001	7.45	9.52	0.005
Cerebrovascular accident	0.11	0	—	0.19	0	—
Cardiac complications	2.03	1.74	1	2.89	2.16	0.12
Respiratory failure	3.52	2.17	0.009	10.72	12.55	0.03
Pneumonia	2.30	1.74	0.23	6.84	6.49	0.65
Ileus/bowel obstruction	16.55	16.52	0.97	20.06	16.45	0.001
Anastomotic leak	11.37	10.10	0.61	14.18	16.15	0.45
Acute renal failure	4.28	11.74	< 0.001	11.65	22.51	< 0.001
Urinary tract infection	3.03	8.70	< 0.001	8.89	7.79	0.17
Urinary retention	2.06	2.61	0.20	2.16	1.92	0.59
Deep vein thrombosis	0.24	0	—	0.89	0.43	0.13
Wound complications	4.22	7.39	< 0.001	7.24	8.66	0.04
Postoperative bleeding	1.91	4.35	< 0.001	2.16	1.73	0.36

* Absolute total numbers are provided in the third row. The remaining values represent percentages.

After adjusting for age, gender, ethnicity, comorbidity score, disease type, the use of laparoscopy, and the admission status (elective vs emergent), we observed that KTRs had higher odds of postoperative acute renal failure compared with the GP (OR, 2.02; 95% CI, 1.50 to 2.71; $P < 0.001$). Interestingly, having a transplanted kidney was not associated with higher odds of mortality, infectious complications, anastomotic leak, or wound complications. The odds of noninfectious complications were lower in KTRs (OR, 0.74; $P = 0.04$) (Table 7).

TABLE 7. Multivariate Regression Analysis of Selected Outcomes*

	Odds Ratios (95% confidence interval)	P Value†
In-hospital mortality	1.21 (0.76–1.95)	0.84
Wound complications	0.93 (0.64–1.36)	0.87
Anastomotic leakage	0.82 (0.58–1.16)	0.80
Infectious complications	1.02 (0.78–1.34)	0.87
Noninfectious complications	0.74 (0.59–0.93)	0.04
Acute renal failure	2.02 (1.50–2.71)	< 0.001

* Comparison is made between kidney transplant recipients and the general population. The latter was used as control group.

† P values were adjusted for multiple comparisons using Holm's method.

Discussion

Although the number of kidney transplants performed in the United States has increased over the past decade with an associated increase in the life expectancy of patients living with a transplanted kidney,¹ it would be intuitive to think that the number of cases referred for colorectal surgical procedures would show a parallel increase as well. Our results showed only a 6 per cent yearly increase in the number of KTRs

undergoing colorectal surgery. This rate is significantly lower than the average increase in the number of patients living with a transplanted kidney or the increase in the number of kidney transplants per year. The modest increase may be the result of the relatively small sample size or other factors such as pre-transplant screening colonoscopies of prospective transplant candidates. Alternatively, the publication of several reports highlighting the importance of aggressive colonoscopic screening in this population may have led to more frequent screening colonoscopies and subsequent colonoscopic management of early polyps that may otherwise rapidly develop into cancer. Third, several reports have highlighted the high mortality of acute diverticulitis in immunosuppressed patients,^{6, 7, 11} which may have led to prophylactic surgery before receiving a transplanted kidney.

KTRs represent a unique population, which, despite their relatively younger age, has a higher incidence of comorbidities and a worse functional status compared with the GP. Also, the indications for colorectal surgical procedures are different than those usually observed in the GP. The important finding is that half of all surgical procedures performed in this population are done on an emergent basis, which is independently associated with worse outcomes as seen in our results and other studies.¹²

Diverticular disease is the most common indication for colon surgery in the kidney transplant population, accounting for 48 per cent of cases. Several studies have shown an increased incidence of acute diverticulitis in the kidney transplant population.^{7, 8} In a systematic review of diverticulitis in transplant patients, Hwang et al.¹¹ found that the incidence of acute diverticulitis in patients with transplants was 1 per cent, which is substantially higher than the GP, estimated to be approximately 0.02 per cent. When examining transplant patients who had diverticulosis diagnosed before transplantation, Qasabian et al. found that the likelihood of progression to acute diverticulitis was 22 times higher than the GP.¹¹ Our results show that the mortality rate after elective sigmoid resection in KTRs is no different than the GP. However, when considering emergent operations for acute diverticulitis, mortality rates were significantly higher in KTRs compared with the GP (7.3 vs 4.91%). These findings are in line with a recent review of sigmoid colectomies performed for acute diverticulitis in solid organ transplant recipients.¹³ Therefore, our findings should raise the possibility of a screening program to address the issue of diverticular disease in KTRs before it progresses to a complicated or emergent stage.

The incidence of adenocarcinoma of the colon and rectum is increased by two- to threefold in KTRs.²⁻⁵ Colorectal cancer in KTRs usually arises 4 to 11 years posttransplant^{14, 15} and is associated with significantly worse long-term oncologic outcomes,¹⁶ reduced 5-year survival,³ and a more aggressive phenotype.^{3, 15, 17} As demonstrated by Park et al.,⁵ the majority of cancers in KTRs arise de novo because most recipients are screened for malignancy before the transplant procedure. Immunosuppressive medications impair normal host cancer surveillance mechanisms enabling reactivation of oncogenic viruses.^{5, 18, 19} Taking into account pretransplant screening, we observed that malignancy still accounts for 31 per cent of the indications for surgery in the transplant group. Our findings add more evidence to the fact that there is an increased incidence of colorectal cancers in the transplant population. Our results also echo the findings of Johnson et al.³ who found that colorectal malignancy appears at

a younger age in the transplant population. What is also interesting is the relatively high percentage of KTRs operated on for cancer emergently and the associated substantial increase in mortality rates. Emergent operations for colon and rectal cancer are performed in cases of perforation and obstruction.²⁰ Currently there are no specific guidelines for screening colonoscopies in kidney or other solid organ transplant recipients, and our findings as well as others³ argue for more frequent screening policies in this patient population.³

The use of laparoscopy in the transplant population was similar to the GP with an associated similar conversion rate. It has increased in the 2009 to 2010 period, which could be the result of the use of specific codes for laparoscopic colorectal cases as we have previously demonstrated.²¹ The use of laparoscopy may prove beneficial in this patient population because laparoscopy has been found to be associated with a lower postoperative inflammatory response compared with open surgery.²² The higher use of stoma in the transplant population, especially in the emergent setting, may be related to concerns of poor healing associated with immunosuppression.

Consistent with the findings of other studies,^{23,24} we found higher mortality and morbidity rates in KTRs after surgery. However, this effect appears to be more related to the high incidence of comorbidities in this population rather than the effect of immunosuppression itself. Having a transplanted kidney does not appear to be independently associated with higher mortality rates after adjusting for multiple confounders. More interesting is the finding that the incidence of anastomotic leak and wound complication was no different compared with the GP on risk-adjusted analysis. Our results are in line with the findings of Khoury et al.¹⁶ who retrospectively reviewed 55 patients on chronic immunosuppressive therapy after solid organ transplant. In their study, postoperative morbidity in immunosuppressed patients was similar to the GP. All these findings may possibly be the result of the fact that KTRs may receive higher acuity of care, which also may explain why the incidence of noninfectious complications was lower compared with the GP.

Perhaps the most important finding of this study is the higher rate of postoperative acute renal failure in the transplant population. To our knowledge, this finding has not been reported because prior studies were limited by small sample sizes. Awareness of this potential complication argues for more aggressive measures to protect the transplanted kidney.

The main limitation of our study lies in its retrospective nature and its inherent biases. The use of an administrative database may be prone to coding errors.²⁵ The NIS also does not provide any information on the immunosuppressive medications used in KTRs. Given the relatively long study period, several changes in immunosuppressive regimens have occurred,¹ and the impact this change may have had on outcomes is unknown. Moreover, no information is given whether immunosuppressive medication was continued in the perioperative period. There could be several unmeasured confounders that may affect our results. We tried to account for the effect of unmeasured confounders by adjusting for a large numbers of variables. NIS only provides information related to one single hospital stay and as such, long-term data, readmission rates, and 30-day mortality rates are unknown. However, many of these limitations are likely to affect both groups equally. It would be important to understand the timeframe post-transplant

when cancer or complications from diverticular disease develop. Understanding the impact of time post-transplant would guide surveillance strategies for neoplasia and possibly guide dietary recommendations for diverticular disease in this high-cost population. Nevertheless, to our knowledge, this represents the largest report on the trends and outcomes of colorectal surgery in KTRs.

Conclusion

KTRs undergoing colorectal surgical procedures represent a very small population with unique characteristics. It is a relatively young patient population with many associated comorbidities. Moreover, KTRs appear to have an increased risk of colorectal cancer and complicated diverticular disease. More than half of colorectal surgical procedures in KTRs are performed emergently, which unfortunately worsens their outcomes. Based on these findings, more aggressive screening campaigns should be performed in this fragile population to avoid the detrimental effect of emergency. Acute renal failure appears to be the only postoperative complication independently associated with the presence of a transplanted kidney. The higher incidence of other postoperative outcomes in the transplant group appears to be more related to the poor functional status of this population and the often emergent presentation of their pathology rather than the effect of immunosuppression.

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Address correspondence and reprint requests to Clarence E. Foster III, M.D., Department of Surgery, 333 City Boulevard West, Suite 1200, Orange, CA 92868. E-mail: fosterc@uci.edu.