Kidney-pancreas transplant recipients experience higher risk of complications compared to the general population after undergoing coronary artery bypass grafting

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Abstract

Background: This retrospective analysis aims to identify differences in surgical outcomes between pancreas and/or kidney transplant recipients compared to the general population undergoing CABG. Methods: Using NIS data from 2005 to 2014, patients who underwent CABG were stratified by either no history of transplant, or history of pancreas and/or kidney transplant. Multivariate analysis was used to calculate odds ratio (OR) to evaluate in-hospital mortality, morbidity, length of stay (LOS), and total hospital charge in all centers. Results: Overall, 2,678 KTx, 184 PTx, 254 KPTx, and 1,796,186 Non-Tx met inclusion criteria. KPTx experienced higher complication rates compared to Non-Tx (78.3% vs. 47.8%, $p<0.01$). Those with PTx incurred greater total hospital charge and LOS. On weighted multivariate analysis, KPTx was associated with an increased risk for developing any complication following CABG (OR 3.512, $p<0.01$) and emergency CABG (3.707, $p<0.01$). This risk was even higher at transplant centers (CABG OR 4.302, $p<0.01$; emergency CABG OR 10.072, $p<0.001$). KTx was associated with increased in-hospital mortality following emergency CABG, while PTx and KPTx had no mortality to analyze. Conclusion: KPTx experienced a significantly higher risk of complications compared to the general population after undergoing CABG, in both transplant and non-transplant centers. These outcomes should be considered when providing perioperative care.

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Introduction:

Kidney transplant is the standard intervention for ESRD. In transplant recipients, cardiovascular disease (CVD) is the leading cause of death with functioning graft[1,2]. Kidney transplant recipients are at an increased risk for CVD for several reasons. Diabetes and hypertension associated with kidney disease are independent CVD risk factors. Additionally, the resultant kidney failure leads to arterial calcification and metabolic derangements[3]. ESRD increases the risk of CAD by more than 50%[4] and kidney potential transplant recipients wait longer for organs. Following transplantation, immunosuppressive regimens themselves accelerate underlying coronary artery disease[3,5-7]. The risk of CVD may be highest early after transplantation, with incidence up to 11% at 3 years after[1,8,9].

The addition of pancreas transplantation limits diabetic complications, improves lipid profile, and enhances quality of life for type 1 diabetics with renal failure[10-15]. The normalization of blood glucose levels reduces progression of atherosclerosis, and by extension, lowers the risk of CVD[12,13]. Kidney-pancreas transplant recipients show improved survival compared to those who remain on dialysis[14,15]. Likely as a result, the number of kidney-pancreas transplants in 2019 were the highest recorded in over a decade[16].

As post-transplant survival improves, those with kidney and pancreas transplants are likely to undergo CABG due to increased pre- and post-transplant risk of CVD. It is estimated that there are nearly 400,000 CABG operations performed annually in the United States[17]. While renal transplant appears to be the most well-researched organ in terms of outcomes and surgical complications, less is known about the risks in pancreas and kidney-pancreas transplants. Previous literature evaluating outcomes in abdominal organ transplants undergoing cardiac surgery has yielded variable results[3,7]. Surgical outcomes in pancreas and kidney-pancreas transplant recipients undergoing CABG requires further exploration.

Due to the risk of developing coronary artery disease, there is increased need to identify outcomes in kidney and pancreas transplant recipients undergoing CABG. We aim to evaluate in-hospital mortality, complications, length of stay (LOS), and total hospital charges in both transplant and non-transplant centers. Understanding these outcomes in this unique population is critical to improve perioperative and post-operative care as the need for CABG in transplant recipients grows.

Materials and Methods

Inclusion Criteria

The Nationwide Inpatient Sample (NIS) through the HCUP (Healthcare Cost and Utilization Project) records data from over 7 million hospitalizations each year. Information from the database was collected and analyzed in this review. Patients who underwent CABG or cardiopulmonary bypass from 2005 to 2014 were identified by the ICD-9 procedure codes: 36.10 to 36.19 and 39.61 to 39.66. CABG procedure types were stratified as either elective or urgent/emergent. Appropriate ICD-9 V codes were used to identify those with a history of kidney transplant (ICD-9 code: V42.0), pancreas transplant (ICD-9 code: V428.3), and both pancreas and kidney transplant. Those with history of or complication from another organ transplant were excluded. Basic patient demographic information and hospital characteristics were also collected. Transplant centers were defined as having performed at least one renal transplant between 2005 to 2014. The Elixhauser comorbidity index scores were calculated using preexisting medical conditions available in the NIS data[18].

Study Population

After inclusion and exclusion criteria were applied, four groups were identified: pancreas transplant alone (PTx), kidney transplant alone (KTx), both kidney and pancreas transplant (KPTx), and non-transplant (Non-Tx). Mortality, complications, LOS, and total hospital charges were calculated during the primary CABG admission. Intra-operative and post-operative complications were identified using ICD-9 codes.

Statistical Analysis

Continuous data was expressed in terms of mean +/- standard deviation or median (IQR) and compared with ANOVA or Mann-Whitney U test. Categorical data was evaluated using chi-squared test. Multivariate logistic regression for weighted outcomes was utilized to compute odds ratio for in-hospital mortality and complications. We considered non-emergency CABG and emergency CABG separately and performed the analysis for all centers and transplant centers for each. Total hospital charges and LOS were evaluated with linear regression testing. In the linear and logistic regression testing, the general population (no history of transplant or immunosuppression, or Non-Tx) was set as the reference category. The multivariate analysis was adjusted for potential confounding factors. In order to attain robust statistical conclusions, total hospital change and LOS values were transformed to normal distribution via log-transformation procedure. Additionally, we adjusted the total charges based on consumer inflation index (CPI) 2020 to be able to compare the charges present. Statistical analysis was performed using IBM's Statistical Package for Social Sciences (SPSS) software version 25 (IBM Corp, Armonk, NY).

Results:

Patient Characteristics

Patient demographic characteristics are outlined in Table 1. Transplant recipients who underwent CABG were younger, with the youngest ages seen in PTx and KPTx (51 years). KPTx had the greatest percentage of CABGs performed emergently (56.0%) and the highest Elixhauser Comorbidity Index score (11).

Hospital Characteristics

Table 2 outlines hospital characteristics. Most CABGs in KPTx were performed at large (80.4%), private, non-profit (59.3%), urban, teaching hospitals (63.5%). Overall, transplant recipients had a greater proportion of CABGs performed at transplant centers (39.6% for KTx, 66.0% for PTx, and 37.4% for KPTx), compared to Non-Tx (27.7%).

Post-Operative Outcomes and Complications

Table 3 outlines post-operative outcomes for each transplant category. The main destination in all groups was routine discharge to home. KTx had 3.9% mortality rate, while there was no mortality in PTx and KPTx. KPTx experienced the highest rate of post-operative complications at 78.3%, which included acute renal failure (26.7%), respiratory (8.0%), post-operative infection (1.9%), SIRS (3.9%), and graft complication (8.0%) PTx had the second highest post-operative complication rate (75.9%), which included acute renal

failure (40.7%), respiratory (5.6%), accidental cut, puncture, or hemorrhage (2.7%), post-operative infection (5.9%), SIRS (8.0%), and graft complications (8.2%). On average, median total hospital charge ($276,012) and median length of stay (14 days) was greatest in PTx.

Blood Product Usage

On average, transplant recipients required more blood products that Non-Tx, with PTx leading all categories. In CABG procedures in PTx, platelets were needed in 13.7% of cases, fresh frozen plasma in 16.8%, and packed red blood cells in 48.9%. Except for platelets (3.8%), KPTx utilized more blood products on average than Non-Tx.

Multivariable Analysis

Multivariable logistic regression using weighted outcomes data from table 3 was analyzed to calculate odds ratios for in-hospital mortality, complications, LOS, and total hospital charge for transplant recipients. These results are outlined in Table 4, with Non-Tx as the reference. As there was no mortality in PTx and KPTx, there was no multivariable comparison made. The risk of developing any complication was greatest in KPTx (OR 3.512, $p<0.01$), followed by PTx (OR 2.174, $p<0.01$), then KTx (1.674, $p<0.01$). In the adjusted outcomes, LOS and total hospital charge were not increased in transplant recipients. Table 5 shows the multivariate analysis in transplant centers. The risk of any complication was highest in KPTx (OR 4.302, $p<0.01$), followed by PTx (OR 2.413, $p<0.01$), then KTx (OR 1.362, $p<0.01$). Of note, KTx showed increased in-hospital mortality in transplant centers (OR 1.913, $p<0.01$), although the overall mortality rate was low in this cohort (3.9%).

The multivariate analysis was repeated for emergency CABG, as shown in Table 6. The risk of complication was highest among KPTx (OR 3.707, $p<0.01$), followed by KTx (OR 1.803, $p<0.01$). PTx was not associated with increased risk. Table 7 outlines the same multivariate analysis in transplant centers. Again, the risk of developing any complication was highest in KPTx (OR 10.072, $p<0.001$). KTx had increased in-hospital mortality (4.965, $p<0.01$) in transplant centers. In the adjusted outcomes, LOS and total hospital charge were not increased in transplant recipients.

Discussion

In this analysis, KPTx was associated with a 3.5-fold higher occurrence of any complication following CABG, and even higher after emergency CABG (OR 3.707, $p<0.01$). Previous literature has shown that transplant patients undergoing cardiac procedures may experience higher complication rates compared to the general population[7,19,20]. Each transplant group in this study carried a significantly higher Elixhauser comorbidity index score (calculated by preexisting comorbidities) compared to Non-Tx, which may reflect an increased baseline risk. However, it has also been demonstrated that transplant recipients have comparable mortality and long-term survival to non-transplanted individuals[3,20,21]. It remains critical to investigate surgical complications and risk factors in this unique population to establish preventative measures and comprehensive management protocols.

Emergency surgeries in transplant patients have been associated with worse surgical outcomes[3,6,22,23]. Non-elective surgery has been identified as a risk factor for major postoperative morbidity and mortality, including decline in renal function[3,6]. Emergency abdominal surgery in solid organ transplant is associated with up to 32.7% morbidity and 17.5% mortality[22], findings significantly higher than the general population. This association is likely explained by greater case complexity, greater incidence of complication, or immunosuppressive regimens that predispose to certain issues, such as infections[5,23].

Compared to the non-transplant population, KPTx had the highest complication following CABG (78.3% vs. 47.8%). Cardiovascular issues occurred evenly among all groups regardless of transplant status. However, rates of respiratory complications were significantly higher among transplant patients, with the highest in KPTx (8.0%). After excluding renal dysfunction, John et al. demonstrated that most transplant recipients required ventilatory support after cardiac surgery (11.4%)[3]. Pulmonary morbidity after cardiac surgery is common regardless of transplant status, including pleural effusions, pneumonia, and atelectasis. Transplant

recipients may be at increased risk for pulmonary issues due to chronic immunosuppression, as well as changes in pulmonary compliance from pre-transplant fluid overload of ESRD[24].

The incidence of SIRS was increased in all transplant recipients, with significantly higher rates in PTx (8.0%). Following cardiac surgery, rates of major infection in the transplant population may be as high as 19%[20]. Transplant recipients face a unique post-operative infection burden due to lifelong immunosuppression. These regimens downregulate inflammatory mediators, impair T-cell activation, and interfere with critical phases of wound healing[25]. Sirolimus may predispose to wound complications, including deep infections, cellulitis, and fascial dehiscence[26]. Likewise, chronic corticosteroid use is associated with a 2 to 5-fold increase in wound complications rates when compared to those not taking steroids[27]. However, we were unable to evaluate the risk in specific treatment regimens as the NIS database does not provide this detail.

Acute renal failure was a significant complication in all transplant groups following CABG. PTx had the highest risk of acute renal failure (40.7%), followed by KTx (35.7%), and KPTx (26.7%). Cardiopulmonary bypass itself may pose a risk of kidney injury due to hypoperfusion or inflammatory reactions inherent to the bypass mechanism[28]. Postoperative kidney dysfunction appears to be significantly more common in transplant patients after cardiac surgery[3]. Elevated preoperative serum creatinine (SCr >2 mg/dL) confers a higher risk and predisposes to postoperative kidney failure[3,6]. Transplant recipients may be at even greater risk from the nephrotoxic maintenance immunosuppressive regimens which lower baseline GFR. Off-pump surgery (beating heart surgery) has demonstrated fewer postoperative kidney complications and may show promise in transplant patients[28]. Larger studies are needed to evaluate whether this approach should be preferred.

Transplant recipients required more blood products than their Non-Tx counterparts, which may have further impacted their risk of complication. Perioperative red blood cell (RBC) transfusion increases the risk of AKI after cardiac surgery [29,30]. This may be the result of impaired oxygen handling by transfused RBCs, or faster breakdown causing more iron release and oxidative stress[29,30]. Additionally, blood transfusions pose a unique risk in the transplanted population. RBC transfusions increase HLA sensitization and antibody response which can increase the risk of future graft failure[31]. Sensitization can occur after a single transfusion, and nearly one-third of patients have already received a transfusion before being added to the transplant list[31]. Overly aggressive blood transfusions may increase the risk of perioperative AKI, future graft rejection, and render subsequent re-transplantation more difficult from the presence of reactive antibodies.

Rates of perioperative mortality in transplant patients have ranged from 1.4% to as high as 15.7%[3,32]. While there was no in-hospital mortality to analyze PTx and KPTx, the rate of KTx mortality in this report (3.9%) was similar to that of other reviews[33]. Three- and five-year survival rates in kidney transplants after CABG ranged from 70% and 66%, respectively[6,34], to as high as 85% for 5-year survival[35]. Importantly, although KPTx carried the greatest rate of complication, this did not influence in-hospital mortality. However, the data is unable to show how long-term survival is affected as a result.

We identified greater total hospital charge and LOS in transplant recipients on the univariate analysis. PTx had greatest median total charge overall ($276,012) and longer LOS following CABG (14 days in PTx vs. 8 days in Non-Tx). However, in the adjusted outcomes, LOS and total hospital charge were not increased in transplant recipients, despite being more likely to suffer a complication. Further analysis of pancreas transplant recipient surgical costs is needed to reconcile these conflicting results.

Our findings demonstrated increased risk in both non-transplant and transplant centers. It is unclear whether transplant centers provide superior care. Most surgeons believe care is better at transplant centers and recommend acute surgery be performed at these facilities[36]. However, in transplant recipients undergoing abdominal surgeries, DiBrito et al. found no statistically significant difference in complication rates at transplant centers vs. non-transplant centers[37,38]. Although we found increased in-hospital mortality in KTx at transplant centers, this was likely skewed by a greater proportion of deaths at these centers, as the overall mortality rate was 3.9% (or 106 out of 2678 patients).

Limitations

This investigation is limited by the retrospective nature, as well as small sample size of PTx and KPTx recipients specific to CABG. Given the small proportion of the population who undergo transplantation in general, this is a common theme within transplant literature. The lack of in-hospital mortality for PTx and KPTx limited our ability to compare trends in similar research. NIS data lacks detailed information about costs during hospital stay, so the reason for increased costs in PTx recipients cannot be determined. Additionally, NIS data does not permit longitudinal follow-up to evaluate subsequent readmissions or hospitalizations on patient or graft outcomes. Finally, the database does not include patient creatinine, GFR, or immunosuppressive regimens, which may influence perioperative risk.

Strengths

By using the NIS national database, we were able to avoid the bias and limited power of a smaller, single-institution study. Additionally, this permitted multivariable analysis to be performed to evaluate outcomes in transplants vs. non-transplant centers. Cardiac surgery has mostly been most studied in kidney and kidney-pancreas transplants, but also under the umbrella of solid abdominal organ transplant, which could also include pancreas and liver. By separating kidney, pancreas, and kidney-pancreas into independent groups, we evaluated outcomes specifically to each group. This appears to be the largest national investigation of CABG and emergency CABG outcomes in kidney and pancreas transplant recipients to date. It is not known from the NIS data whether the kidney-pancreas transplants are simultaneous pancreas-kidney transplant (SPKT) or pancreas-after-kidney (PAK), which may pose an interesting point of further research.

Conclusion

CABG is a common operation, and transplanted patients are increasingly likely to develop CVD. Kidney-pancreas transplant recipients showed significantly greater risk to develop a postoperative complication after CABG and emergency CABG, regardless of transplant center status. Surgeons should be aware of the perioperative risks of KPTx undergoing CABG. Delaying surgery is likely to increase the need for emergent operations, thereby increasing complications. In this analysis, in-hospital mortality was not affected in KPTx. However, it is not known how long-term outcomes are impacted as a result of perioperative morbidity. Further research should continue to evaluate risk factors for morbidity and mortality in transplant patients undergoing cardiac procedures.

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