Original Paper

In-Hospital Mortality and Major Adverse Cardiovascular Events after Kidney Transplantation in the United States

Abhinav Goyal^a Kshitij Chatterjee^b Roy O. Mathew^c Mandeep S. Sidhu^d
Sripal Bangalore^e Peter A. McCullough^{f,g} Janani Rangaswami^{h,i}

^aDepartment of Digestive Diseases and Transplantation, Einstein Medical Center, Philadelphia, PA, USA; ^bDepartment of Hematology and Oncology, University of Arkansas for Medical Sciences, Little Rock, AR, USA; ^cDivision of Nephrology, WJB Dorn VA Medical Center, Columbia, SC, USA; ^dDivision of Cardiology, Albany Medical College and Albany Medical Center, Albany, NY, USA; ^eNew York University School of Medicine, New York, NY, USA; ^fBaylor University Medical Center, Dallas, TX, USA; ^gBaylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, TX, USA; ^hDivision of Nephrology, Department of Medicine, Einstein Medical Center, Philadelphia, PA, USA; ⁱSidney Kimmel College of Thomas Jefferson University, Philadelphia, PA, USA

Keywords

Kidney transplantation · Major adverse cardiovascular events · Cardiovascular disease · End-stage kidney disease

Abstract

Background: Kidney transplantation (KT) is the treatment of choice for end-stage kidney disease. Cardiovascular disease is a major determinant of morbidity and mortality in patients with KT. Temporal trends in perioperative cardiovascular outcomes after KT are understudied, especially in light of an aging KT waitlist population. **Methods:** We performed a retrospective observational cohort study using the National Inpatient Sample for the years 2004–2013. All adult patients undergoing KT were identified using the appropriate International Classification of Diseases, 9th Revision, Clinical Modification codes. Demographic and hospital characteristics, discharge disposition, payer status, and major adverse cardiovascular events (MACEs) were summarized using summary statistics. Multivariate logistic regression was used to identify predictors of MACEs in the perioperative period of KT. **Results:** A total of 147,431 KTs were performed between 2004 and 2013. The mean age at KT went up from 48.1 to 51.8 years from 2004 to 2013. Medicare was the primary payer for 59.6% of the KTs. Overall average perioperative mortality was 0.5%, median length of stay was 5 days, and 6.5% of patients experienced an MACE, 78% of which were heart failures (HFs). Important predictors of perioperative MACEs were age ≥ 65 years (OR = 2.14), Medicare as primary payer (OR = 1.51), diabetes (OR = 1.46), recreational drug use (OR = 1.72), pulmonary circulation disorders (OR = 3.28),

Abhinav Goyal, MD
Suite 363, Klein Building, Einstein Medical Center
5501 Old York Road
Philadelphia, PA 19141 (USA)
E-Mail goyalabh@einstein.edu

and malnutrition (OR = 1.91). **Conclusion:** Despite increases in age at the time of KT, the absolute risk of perioperative MACEs has remained stable from 2004 to 2013. HF is a major component of postoperative MACEs in KT. Malnutrition and pulmonary hypertension are major nontraditional predictors of perioperative MACE outcomes.

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Introduction

Kidney transplantation (KT) is the treatment of choice for patients with end-stage kidney disease (ESKD), resulting in reduced morbidity, mortality, and health care costs when compared to chronic dialysis [1, 2]. Cardiovascular disease (CVD) is a major cause of adverse outcomes in patients with ESKD, before and after KT. CVD is the most common cause of mortality in patients with functioning allografts at all times after KT [3]. The expected burden of CVD after KT is expected to continue to rise, based on national trends reported in transplantation registries. Specifically, the 2016 annual Organ Procurement and Transplantation Network report on KT showed that the KT waitlist continued to age, with ongoing increases in the proportions of candidates aged 50–74 years [4]. The proportion of candidates with diabetes as a cause of ESKD increased to 36.2% of waitlisted candidates, and >20% of listed candidates had been on dialysis for at least 6 years from their most recent listing [4].

Prior observational data have reported higher frequencies of cardiovascular events in the early post-KT period (<3 months) as well as within 1 year post KT [5–7]. Medicare billing claims estimate the cumulative incidence of myocardial infarction to range from 8.7 to 16.7% by 3 years after active KT listing, and from 4.7 to 11.1% after KT [5, 8]. However, in the backdrop of an aging waitlisted population, a higher proportion of diabetics, and increasing dialysis vintage pre KT, rates of major adverse cardiovascular events (MACEs) in the perioperative KT period have not been well defined over the past decade. This study examines trends in mortality and the frequency of MACEs in the perioperative period after KT using the National Inpatient Sample (NIS). We also explored the trends in KT recipient demographics and transplantation center-related factors that potentially influence CVD outcomes post KT.

Materials and Methods

Data Source

Data from the NIS for the years 2004–2013 was used for this study. The NIS was developed by the Agency for Healthcare Research and Quality as a part of Healthcare Utilization Project. It is the largest all-payer inpatient database in the United States. Prior to 2012, the NIS contained data from a 20% stratified sample of all U.S. hospitals. In 2012, the NIS was redesigned to include samples of discharges from all hospitals participating in the Healthcare Utilization Project in the participating states, representing over 95% of the U.S. population. For trend analysis after the redesigning of the NIS in 2012, new sampling weights (trend weights) were provided for the years prior to 2012 to account for the difference in database design. These weights are used to produce national-level estimates. Each hospitalization contains information regarding patient characteristics such as demographics and comorbidities as well as primary and up to 24 secondary discharge diagnoses. It does not include data on laboratory parameters, hemodynamic parameters, or medications. Data on prior cardiovascular interventions were not available in the NIS. The International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes are used to record diagnoses and procedures in the NIS.

Study Objectives

The objectives of the study were to determine the prevalence and predictors of the composite outcome of MACEs, comprising cerebrovascular accidents (CVAs), acute myocardial infarction (AMI), heart failure (HF), and all-cause mortality after KT during the index admission between 2004 and 2013.

Study Design

This was a retrospective cohort study using data from the NIS between 2004 and 2013. All adult patients (≥ 18 years at the time of admission) with an ICD-9-CM procedure code 55.60, 55.61, or 55.69 were included in this analysis (see online suppl. Table 1; see www.karger.com/doi/10.1159/000492731 for all online suppl. material). All hospitalizations with missing information on key demographic variables such as age and sex were excluded. All patients who underwent simultaneous dual organ transplantation were excluded. These were identified using simultaneous presence of any of the ICD-9-CM procedure codes for heart, liver, pancreas, or intestine transplantation (see online suppl. Table 1). Demographic characteristics (age, sex, race), hospital characteristics (location, teaching status), discharge disposition, Elixhauser comorbidities, and primary payer were summarized using summary statistics [9]. The outcomes of these hospitalizations, including death (in-hospital mortality), length of stay, HF, CVA, and AMI, were recorded using their respective ICD-9-CM codes (see online suppl. Table 1) [10, 11]. Annual trends in key variables and outcomes were also recorded from 2004 to 2013.

Statistical Analysis

Manufacturer-provided sampling weights were used to produce national estimates for all data. Additionally, the complex survey design of the NIS was incorporated into all analyses. All continuous variables were summarized using mean $\pm$ SD and compared using Student's *t* test. Categorical variables were summarized using percentages and compared using the χ^2 test. Demographic characteristics, in-hospital mortality, and length of stay were compared between those who experienced the composite outcome event and those who did not. Trend of proportions was tested using the Cochran-Armitage test through the “*p* trend” command in Stata, while linear regression was used for continuous variables. Age-adjusted incidence rate was calculated using the standard U.S. census population for the year 2000.

To determine the potential predictors of MACEs among patients undergoing KT, a multivariate logistic regression model was used. Independent variables included in the model were demographic characteristics (age, sex, race, and socioeconomic status), hospital characteristics (rural versus urban location and teaching status), primary insurance payer, discharge disposition, and Elixhauser comorbidities (such as pulmonary hypertension [PH] and malnutrition). The output of logistic regression is reported as OR for ease of understanding. Stata 14.0 (StataCorp, College Station, TX, USA) and SPSS 23.0 (SPSS Inc., Chicago, IL, USA) were used to perform all statistical analyses. A *p* value < 0.05 was considered statistically significant.

Results

There were a total of 147,431 KT procedures performed in the United States between January 2004 and December 2013. The demographic characteristics of these patients are described in Table 1. Overall, mean age at KT was 50.3 ± 13.8 years, with 60.7% of patients being between 45 and 60 years of age. In this time frame, mean age at KT went up from 48.1 to 51.8 years (Fig. 1), male sex was more common (60.3% compared to 39.7% females), 24% of patients had diabetes mellitus, and 6.2% had chronic pulmonary disease. Medicare was the primary payer for 59.6% of KTs and private insurance for 33.4%. In-hospital mortality post KT remained low between 2004 and 2013 (Fig. 2), with an overall mean of 0.5%. Length of stay decreased from a median of 6 to 5 days, and the incidence of MACEs decreased from 7.1 to 6.1% (Fig. 3). As the age at KT has increased, the age-adjusted incidence of MACEs was also calculated and is shown in online supplementary Figure 2.

There were 9,592 MACE outcomes experienced by the KT recipients (6.5%). Of these, 19.2% were AMIs, 1.76% were CVAs, 78% were HF, and 7.14% were in-hospital deaths. Transplant recipients who experienced an MACE outcome, compared to those who did not, were significantly older (55.9 vs. 49.9 years, $p < 0.001$), had a higher proportion of males (63.3 vs. 60.1%, $p < 0.001$), diabetes (35.5 vs. 23.2%, $p < 0.001$), and patients with chronic pulmonary disorders (9.8 vs. 5.9%, $p < 0.001$). Patients with MACEs were more likely to be Medicare beneficiaries (73.2 vs. 58.7%) and stayed in the hospital longer (median length of stay 7 vs. 5 days, $p < 0.001$). All comparisons are shown in Table 1.

Table 1. Demographic characteristics, comorbidities, and outcomes of patients undergoing KT in the United States between 2004 and 2013

	All patients (<i>n</i> = 147,431) (100%)	MACEs (<i>n</i> = 9,592) (6.5%)	No MACEs (<i>n</i> = 137,839) (93.5%)	<i>p</i> value
<i>Patient characteristics</i>				
Mean (SD) age, years	50.3 (13.8)	55.9 (12.0)	49.9 (13.8)	<0.001
Age categories				
18–39 years	34,226 (23.2%)	1,064 (11.1%)	33,162 (24.1%)	<0.001
40–64 years	89,424 (60.7%)	5,976 (62.3%)	83,448 (60.5%)	
≥65 years	23,781 (16.1%)	2,553 (26.6%)	21,228 (15.4%)	
Female	58,587 (39.7%)	3,521 (36.7%)	55,066 (39.9%)	<0.001
Chronic pulmonary disease	9,123 (6.2%)	940 (9.8%)	8,183 (5.9%)	<0.001
Diabetes	35,439 (24.0%)	3,402 (35.5%)	32,038 (23.2%)	<0.001
Primary health insurance				<0.001
Medicare	87,921 (59.6%)	7,022 (73.2%)	80,898 (58.7%)	
Medicaid	5,572 (3.8%)	283 (3.0%)	5,289 (3.8%)	
Private insurance	49,184 (33.4%)	2,023 (21.1%)	47,161 (34.2%)	
Other/missing	4,754 (3.2%)	263 (2.7%)	4,491 (3.3%)	
<i>Outcomes</i>				
In-hospital mortality	685 (0.5%)	685 (7.1%)	–	n/a
Median (IQR) length of stay, days	5 (3)	7 (6)	5 (3)	<0.001
<i>MACEs</i>				
Heart failure	7,480 (5.1%)	7,480 (78%)	–	–
Cerebrovascular accident	169 (0.1%)	169 (1.8%)	–	–
Acute myocardial infarction	2,843 (1.3%)	2,843 (19.2%)	–	–
All-cause in-hospital mortality	685 (0.5%)	685 (7.1%)	–	–

Of the 147,431 patients, 9,592 (6.5%) had a MACE event during hospitalization. MACEs included cerebrovascular accident, acute myocardial infarction, acute heart failure, and death. The comparison of the baseline characteristics and outcomes between those who did and did not experience MACEs is also shown (*p* value). Values represent *n* (%) unless otherwise specified. All percentages were rounded to the closest decimal. KT, kidney transplantation; MACE, major adverse cardiovascular event; n/a, not applicable.

Multivariate logistic regression analysis was done to identify the predictors of MACE outcomes (Fig. 4). Older age (40–64 years: OR = 1.86, *p* < 0.001; ≥65 years: OR = 2.44, *p* < 0.001; reference: 18–39 years), male sex (OR = 1.15, *p* = 0.02), African-American ethnicity compared to Caucasian (OR = 1.24, *p* = 0.002), Medicare beneficiaries compared to private payers (OR = 1.51, *p* < 0.001), diabetes (OR = 1.46, *p* < 0.001), recreational drug use (OR = 1.72, *p* = 0.01), pulmonary circulation disorders (largely driven by PH as shown in online suppl. Fig. 1; OR = 3.28, *p* < 0.001), malnutrition (OR = 1.91, *p* < 0.001), and urban hospital location compared to rural (OR = 1.64, *p* < 0.001) were independent predictors of perioperative MACE outcomes in KT recipients.

Discussion

Our study describes several important findings in the trends of perioperative MACEs following KT in the time period of January 2004 to December 2013. The most common contributor to MACEs after KT was HF, rather than an ischemic event such as stroke or AMI. Preoperative evaluation of KT patients focuses extensively on the detection and management

Fig. 1. Mean age at kidney transplantation for all adults in the United States from 2004 to 2013.

Fig. 2. In-hospital mortality post kidney transplantation for all adults in the United states from 2004 to 2013.

of coronary artery disease, yet AMI was far less frequent than the development of HF. Thus, despite the increasing burden of CVD risk factors such as age, diabetes, and dialysis vintage in potential KT recipients [4], the overall absolute rates of in-hospital AMI following KT have remained low and stable over time as a result of heightened awareness and proactive

Fig. 3. Incidence of major adverse cardiovascular events (MACEs) post kidney transplantation in all adults in the United States from 2004 to 2013.

Fig. 4. Forrest plot of OR for important predictors of perioperative major adverse cardiovascular events in kidney transplant recipients, obtained from logistic regression. All values in the right column represent OR (95% CI).

management of coronary artery disease. Additionally, nontraditional risk factors such as malnutrition (weight loss prior to KT) and the presence of PH significantly increased the risk of perioperative MACEs after KT because the dominant component of MACEs was HF.

The effect of the malnutrition-inflammation complex in patients with CKD and ESKD on increased mortality has been demonstrated in previous studies [12–14]. A time-dependent survival model that linked national databases of a large dialysis organization and the Scientific Registry of Transplant Recipients over 6 years showed that transplantation-waitlisted hemodialysis patients with lower body mass index or muscle mass and/or unintentional weight or muscle loss experienced higher mortality rates [15]. The association between good pre-KT nutritional status as quantified by body mass index and surrogate measures of muscle mass and better post-KT long-term patient and allograft survival has also been documented [16]. Our analysis demonstrates a similar association between pre-KT malnutrition and short- rather than long-term cardiovascular outcomes in patients undergoing KT. Thus, optimizing nutritional status prior to KT may be an opportunity to reduce perioperative MACEs in KT.

The burden of PH is disproportionately high in patients with CKD and has been shown to drive higher mortality rates in CKD and ESKD [17]. Our study demonstrated that pulmonary circulation disorders (PH in particular) are a significant predictor of short-term perioperative MACE outcomes in patients undergoing KT. The deleterious effect of persistent PH post KT on long-term patient and allograft outcomes has been reported in previous observational studies. In a cohort of 215 KT recipients, Issa et al. [18] found that pretransplantation pulmonary artery systolic pressure >50 as compared to <50 mm Hg was associated with nearly four times higher posttransplantation mortality over a mean follow-up of 22.8 months (adjusted HR = 3.75, $p = 0.025$). Similarly, in a cohort of 638 KT recipients, patients with (versus without) PH prior to transplantation had a lower graft survival rate at 5 years (54.6 vs. 76.0%, $p < 0.05$) and were nearly twice as likely to experience all-cause graft failure (adjusted HR = 1.8, 95% CI 1.11–1.51) during the study period [19]. Given the significant effect of PH on perioperative MACEs in KT, particularly HF, optimization of PH preoperatively is an important target to reduce the burden of perioperative MACEs in this population.

The potential mechanism of the effects of PH on perioperative MACEs in KT are unclear. One possibility is the fact that PH in itself is associated with delayed graft function post KT, which may in itself be a trigger for MACEs via the pathophysiological implications for type 3 cardiorenal syndrome [20]. Other possible mechanisms may include impaired left ventricular filling in the setting of right ventricular dysfunction, thereby contributing to higher rates of decompensated HF perioperatively, as seen in this study. This phenomenon is a consequence of prolonged contraction of the right ventricular free wall seen with right ventricular pressure overload, thus exceeding left ventricular pressures in early diastole and resulting in paradoxical septal movement leading to reduced left ventricular end-diastolic filling [21, 22]. The association between PH and perioperative MACEs after KT demonstrated in this analysis warrants future studies to better delineate potential mechanisms underlying these observations.

National trends in KT by age group over the time period 1998–2015, as summarized in the 2017 United States Renal Data System (USRDS) annual data report, showed a reduction in deceased-donor KT rates for those aged 65–74 years in 2015 [23]. This contrasts with KT rates for those aged 22–44 years rising sharply in 2015, with a 34.7% increase in counts that year. Prior to this, KT rates in the age group 22–44 years in the United States were declining from 2006 to 2014 while in the 65–74 years age group they were steadily rising from 1998 to 2014 [23]. This trend reversal temporally coincided with the implementation of the new Kidney Allocation System (KAS) policy in 2014, wherein allocation of the highest quality of donor kidneys (Kidney Donor Profile Index of $\leq 20\%$) is prioritized to younger recipients with the best expected posttransplantation survival scores [24]. The 2017 USRDS report also cited that the highest prevalence of ESKD per million population is currently in the age group of

65–74 years of age. In this backdrop, the low rates of in-hospital mortality and MACEs demonstrated in this study highlights the ability to successfully achieve favorable perioperative KT outcomes in older recipients. This is especially relevant in the changing landscape of organ allocation prioritization by age group post KAS implementation. Given that the data captured in this study extend till December 2013, the impact of the new KAS policy on postoperative MACEs after KT is unknown at this time.

The time frame of this analysis coincides with the publication of several societal guidelines on the perioperative cardiovascular risk stratification of potential KT recipients, with a wide range of recommendations on the extent of preoperative cardiac risk testing, modality, and frequency of follow-up while on the transplantation waitlist [25]. This is reflected in real-world practice by highly individualized center-specific criteria for CVD risk stratification pre KT, without a unified approach to listing higher-risk individuals or older potential recipients for KT. Given the beneficial effects of KT towards reduction in mortality and improvements in quality of life in older subjects when appropriately selected, it is important to ensure that the stable short-term mortality and MACE rates demonstrated in this study over time are considered when evaluating older potential KT recipients, who may derive benefits in terms of quantity and quality of life with KT [26].

Certain limitations of this study need to be acknowledged. As this was a retrospective observational study, the possibility of selection bias and residual confounding could not be eliminated. The time sequence of the development of MACE complications during a KT hospitalization could not be ascertained. The NIS is an administrative database which does not contain information regarding laboratory and clinical parameters such as glycemic control and medication use, which may have an impact on the incidence of MACEs post KT. Data on the severity of PH and cardiac parameters such as ejection fraction that have prognostic value for cardiovascular outcomes post KT were also not available for analysis. However, given that most centers have stringent criteria to screen patients for cardiovascular comorbidities prior to KT, it is unlikely that these patients had uncontrolled severe PH or cardiomyopathy pre KT. Data on donor kidney quality, cold and warm ischemia time, and incidence of postoperative delayed graft function were not available in this database and may be variables that influence MACE outcomes post KT. Finally, the proportion of cadaveric versus living donor KTs was not available in the NIS; however, given that cadaveric KT rates make up the majority of the renal allografts transplanted in the United States [4], our data are likely representative of MACE and in-hospital mortality outcomes from this donor type. Since the incidence of delayed graft function could not be ascertained using this database, it may potentially confound the rates of HF after KT. Finally, this study only captured short-term MACE outcomes using available data points within the NIS. Long-term MACE outcomes post KT and their stratification by recipient age are important areas of future study and will help optimize appropriate patient selection when evaluating potential KT recipients [27, 28].

Conclusions

Despite a trend for advancing age, the absolute risk of MACEs after KT is low and has remained relatively stable from 2004 to 2013. HF is the major component of MACEs after KT. Malnutrition and PH were important nontraditional predictors of perioperative MACE outcomes in patients undergoing KT.

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Statement of Ethics

The NIS is a commercially available de-identified database, therefore no institutional review board approval was required for this study.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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