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Short- and Long-Term Outcomes of Cardiac Surgery in Kidney Transplant Recipients: A Review

—Kidney Transplant and Cardiac Surgery

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Abstract

Background: Cardiovascular diseases remain the leading cause of death in kidney transplant patients and increasing proportion of these patients are referred to cardiac surgery. Data on short- and long-term outcomes of these patients are limited to single center reports with no randomized trials and no prospective studies published previously. The aim of this review was to report both short- and long-term outcomes of these patients. **Methods:** Literature review was conducted using three databases from inception to June 2022. Multiple search terms were used and limited to English language. Thirty-one relevant articles were included. Outcomes of interest were short-term mortality, long-term survival, renal allograft failure and infection in kidney transplant patients undergoing cardiac surgery. **Results:** Cardiac risk factors (diabetes mellitus, hypertension, hyperlipidemia) were prevalent in kidney transplant patients. 30-days mortality ranged across the studies from zero to 18.8%. The 1-year survival ranged from 71% - 97% and 5-years survival ranged from 31% - 95.7%. Commonest causes of death were cardiac and sepsis. Multiple predictors of mortality were reported. Postoperative acute kidney injury ranged from 0 - 74% with most of them being transient. Kidney graft failure ranged from 0 - 45% with 5-year kidney graft survival rates ranged between 37% - 80%. Post-operative infection rates ranged from 1% - 25% and the most common sites were pneumonia followed by septicemia and surgical site infections. **Conclusion:** Cardiac surgery can be performed in kidney transplant patients with good short- and long-term results.

Keywords

Kidney Transplant, Cardiac Surgery, Graft Failure, Dialysis, Immunosuppression

1. Introduction

Since the first case reported of successful coronary artery bypass graft (CABG) surgery in a patient with kidney transplantation in 1975 [1], there have been numerous cases and small series supporting the use of cardiac surgery in patients with kidney transplantation [2]-[6]. Cardiovascular diseases remain the leading cause of death in kidney transplant recipients and it is a major barrier to improve the long-term survival of kidney transplant patients. There are multiple risk factors for cardiovascular disease in these patients which include both traditional and transplant-specific risk factors [3] [4]. Traditional risk factors (such as Diabetes Mellitus, hypertension, hyperlipidemia) are prevalent in kidney transplant recipients. Transplant-specific risk factors include immunosuppression therapy, infections, cellular and antibody related rejection and other factors. The outcomes of such patients are constantly improving due to improvement in surgical techniques, perioperative care and organ preservation with improvement in immunosuppression therapy. The aim of this review was to examine and report the short- and long-term outcomes of kidney transplant recipients with functioning renal allograft undergoing cardiac surgery. Predictors of graft failure and long-term survival were also examined and discussed. Understanding these outcomes can lead to the development of preventative strategies and improved outcomes in these patients.

2. Materials and Methods

2.1. Literature Review, Inclusion and Exclusion Criteria

Literature review was conducted in PubMed, Google scholar, Embase databases from inception to 1st June 2022. Literature search was limited to English language only. The following search terms were used [cardiac surgery and renal transplant], [cardiac surgery and abdominal solid organ transplant], [valve surgery and renal transplant], [coronary artery bypass and renal transplant], [renal failure and cardiac surgery], [dialysis and cardiac surgery], [immunosuppression and cardiac surgery]. All titles were screened, and relevant abstracts were extracted. All relevant articles were then reviewed, analyzed and summarized. Individual references from the reference list of each relevant article were also manually searched to expand the search criteria. Case reports and small case series of less than 10 patients were excluded from the study. In the event of duplicate publications from same authors or institution, the largest study was included only. Studies examining the outcomes of cardiac surgery on patients with abdominal solid organ transplantation (ASOT) were included in the study if individual data were available for kidney transplant subset or the kidney transplant subset constituted more than one third of the study population. In addition, articles comparing outcomes of dialysis patients to functioning renal transplants following cardiac surgery were included if the authors provided individual relevant data to kidney transplant groups. Records identified through initial search was 2230. A total of 2199 records were excluded after reviewing of abstracts, eli-

mination of duplicate publication and exclusion of small case series and reports. The number of relevant articles meeting the above criteria included in this analysis was 31 articles [3]-[33]. Outcomes of interest were short-term mortality, predictors of mortality, long-term survival, acute kidney injury post-operatively, renal allograft failure and infections. Outcome variables were tabulated in relevant tables with reference to each published article.

2.2. Definitions of Outcome Variables

Short term mortality was defined as 30-Day mortality following cardiac surgery. Acute kidney injury referred to the use of temporary/permanent dialysis in a patient with no prior history of use preoperatively or worsening of kidney function that was managed conservatively postoperatively. Kidney graft failure referred to the resumption of permanent dialysis or the requirement of re-transplantation following cardiac surgery. Infectious complications referred to surgical site infections (sternum and leg wound) whether deep or superficial, pneumonia or sepsis.

3. Results

3.1. Prevalence of Risk Factors in Kidney Transplant Patients Undergoing Cardiac Surgery

Table 1 is the summary of patients demographics of the included articles. As shown, majority of patients were males (57% - 90%) in their 4^{th}-6^{th} decade of life. Interval from kidney transplantation to cardiac surgery ranged from 3.5 years to 12 years. Cardiac risk factors were prevalent with hypertension occurring in 15% - 100% of patients, diabetes mellitus (DM) occurring in 19% - 93% of patients and hyperlipidemia occurring in 17% - 80% of kidney transplant patients. History of coronary artery disease reported to occur in 11% - 100% of cases. The incidence of endocarditis ranged from zero to 17%. All articles included were retrospective observational studies of single center with exception of five studies which were retrospective analysis of nationwide data system of USA [10] [18] [21] [23] [25].

3.2. Short-Term 30-Days Mortality and Long-Term Survival Following Cardiac Surgery

Short-term 30-Days mortality ranged across the studies examined from zero to 18.8%. Commonest causes of death (in order of frequency) were cardiogenic, sepsis, gastrointestinal complications, strokes and pulmonary embolism. Long-term follow-up periods varied between the studies and ranged from 2 to 6.5 years. The survival rate for 1 year ranged from 71% to 97%. Survival at 5-years ranged from 31% to 95.7%. Survival beyond 5-years ranged from 12% to 59%. These results are shown in Table 2. Predictors of 30-days mortality included pre-operative, intra-operative and post-operative factors (Table 3). Pre-operative factors were age, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), peripheral vascular disease (PVD), left ventricular

Table 1. Demographics and preoperative variables in the studies reviewed.

Study	Mean Age (years)	Male (%)	Hypertension (%)	Diabetes (%)	Hyperlipidemia (%)	Coronary artery disease (%)	Endocarditis (%)	Type of cardiac surgery	Duration between kidney transplant to cardiac surgery
Hundemer [3]	60	71	95	55	NR	77	NR	CABG/valve/combination	6.3 years
Bolman [4]	42	64	50	36	NR	71	14	CABG/valve/combination	67 months
Dressler [5]	55	73	NR	NR	NR	71	8.9	CABG/valve/combination	57 months
Mitruka [6]	51	65	98	43	NR	30	15	CABG/valve/combination	53 months
Fergusson [7]	44	69	15	33	NR	49	none	CABG	NR
Ono [8]	54	67	89	43	NR	43	4	CABG/valve/combination	76 months
Reddy [9]	43	58	50	19	77	92	7.7	CABG/valve/combination	79 months
Herzog [10]	Age 45 - 64 accounted for 59% of patients	71	NR	NR	NR	NR	none	CABG	7.8 years
Massad [11]	58	59	78	50	44	38	NR	CABG/valve/combination	NR
Moazami [12]	54	57	87	57	NR	57	NR	CABG/valve/combination	3.5 years
Zhang [13]	55	72	70	54	42	75	7	CABG/valve/combination	60 months
Deb [14]	52	NR	87	43	62	26	4.0	CABG/valve/combination	79 months
John [15]	52	71	83	93	51	37	NR	CABG/valve/combination	NR
Musci [16]	54	81	NR	NR	NR	NR	19	CABG/valve/combination	87 months
Rahmanian [17]	52	62	72	38	NR	35	17	CABG/valve/combination	45 months
Sharma A [18]	Age 45 - 64 accounted for >50% of patients	63	NR	13	NR	7.0	NR	Valve	NR
Shayan [19]	52	74	86	67	44	100	none	CABG	NR
Sharma R [20]	56	73	83	30	67	21	NR	CABG/valve/combination	10.8 years
Lenihan [21]	58	69	77	61	NR	24	none	CABG	6 years
Rocha [22]	57	64	88	61	45	20	4.0	CABG/valve/combination	8.2 years
Vargo [23]	58	66	NR	25	NR	24	NR	CABG/valve/combination	NR
Basic-Jukic [24]	68*	62	100	23	NR	NR	none	CABG/valve/aorta	65 months
Tooley [25]	Age 18 - 60 accounted for 59% of patients	67	72	56	NR	11.5	NR	CABG	NR
Farag [26]	59	71	94	29	74	25	NR	CABG/valve/combination	9.6 years
Kohmoto [27]	58	76	93	52	NR	30	NR	CABG/valve/combination	9 years

Continued

Bozso [28]	66	90	NR	35	NR	NR	NR	Valve ± CABG	12 years
Komagamine [29]	55	83	NR	22	35	NR	NR	CABG/valve/combination	80 months
Mace [30]	55	65	92	62	69	41	6.0	CABG/valve/combination	6.4 years
Bianco [31]	60	74	95	62	80	43	NR	CABG/valve/combination	NR
Fabio [32]	59	68	59	13	17	39	13	Valve	87 months
Fazmin [33]	63	66	81	29	NR	NR	NR	CABG/valve/combination	81 months

CABG: coronary artery bypass graft. NR: not reported. *Median value.

dysfunction, congestive heart failure (CHF), mitral valve disease, lower creatinine clearance, acute renal failure and solid organ transplantation. Intra-operative factors were urgent operation, combined valve surgery, combined cardiac surgery, cardiopulmonary bypass time, blood transfusion and mechanical mitral valve replacement. Post-operative factors were infection, septicemia and new onset dialysis. Predictors of long-term mortality (Table 3) included: Age, female gender, low body mass index (BMI), DM, chronic atrial fibrillation, history of stroke, COPD, higher number of preoperative myocardial infarctions (MI), preoperative unstable angina, congestive heart failure, ejection fraction <30%, renal transplantation before cyclosporin use, urgent surgery, previous CABG, dialysis dependence and solid organ transplant.

3.3. Acute Kidney Injury (AKI) Including the Use of Temporary/Permanent Dialysis and Permanent Kidney Graft Failure Following Cardiac Surgery

Post-operative AKI (with or without dialysis) in kidney transplant patients following cardiac surgery ranged from zero to 74% and the majority were transient (Table 4). Permanent kidney graft failure (defined as return to permanent dialysis or requirement of another kidney re-transplantation) was reported between zero to 45% in different studies. 5-years renal graft survival rates ranged 37% - 80%. One study reported an 8-year kidney graft survival rate at 49% [22] and another study reported a 10-year kidney graft survival at 53% [30]. Interestingly, one study that compared off pump CABG to on pump CABG [19] showed no difference between the two groups in the incidence of AKI or kidney graft failure. Factors predicting kidney graft failure (Table 3) were: preoperative serum creatinine level, DM, hyperlipidemia, preoperative intra-aortic balloon pump use, transient renal failure requiring dialysis post-op, deceased kidney donor, high preoperative trough level of Calcineurin inhibitors.

3.4. Infection Rates and Sites of Infections in Kidney Transplant Patients Undergoing Cardiac Surgery

Postoperative infections in kidney transplant patients undergoing cardiac surgery (Table 5) ranged from 1% to 25.7%. Commonest reported sites (in terms of frequency of occurrence) were pneumonia, septicemia, and surgical site infections

Table 2. Short-term mortality and long-term survival in kidney transplant patients undergoing cardiac surgery.

Author/year	Number of patients	30-Day mortality	Cause of death	Follow-up	Long-term survival
Bolman [4]/1984	14	14%	1) Graft failure. 2) Arrhythmia	Mean 31 months	78.6% at 31 months
Dresler [5]/1997	45	8.8%	1) sepsis 2) GI complication 3) Cardiogenic	Mean 44 month	1-year: 88% 5-years: 85%
Mitruka [6]/1997	64 patients with ASOT (62.5% were kidney transplants)	3%	1) Sepsis 2) Arrhythmia	Mean 23 months	2-years: 80%.
Ferguson [7]/1999	45 patients (CABG only)	7%	Cardiogenic	Median 65.9 months	1 year: 93% 5-years: 59.5% 10-years: 30%
Ono [8]/2002	60 ASOT patients (77% were kidney transplants)	5%	1) Cardiogenic 2) Neurological	Mean 38.7 months	3-years: 71% 5-years: 67%
Reddy [9]/2002	26	7.7%	1. GI complication 2.PE	Mean 38 months	69%
Herzog [10]/2004	2661 (only CABG patients)	CABG no IMA 9.4% CABG with IMA 5%	Not reported	Mean 25 months	2-years survival was 74% (no IMA) and 83% (with IMA)
Massad [11]/2005	32 (only CABG)	6.2%	Cardiogenic	Mean 63 months	1-year: 92% 3-years: 87% 5-years: 79%
Moazami [12]/2006	26	Zero	No death	Not reported	3-year: 69%
Zhang [13]/2006	57	5.3%	Cardiogenic	Median 34 months	3-year: 71%
Deb [14]/2006	47 ASOT patients (72% were kidney transplants)	2 %	Cardiogenic	Mean 39 months	1-year: 97% 5-years: 82%
John [15]/2007	70 ASOT patients (83% were kidney transplants)	1.4%	Neurological	Mean 1 month	Not reported
Musci [16]/2007	39 patients with kidney or heart transplants (41% were kidney transplants)	18.8% kidney transplant	Sepsis	Mean 39 months	3-years: 81.3%
Rahmanian [17]/2009	29	3.4%	Sepsis	Mean 2.6 years	1 year: 89% 5-years: 50%
Sharma A [18]/2010	1335 (only valve surgery)	14%	1) Cardiogenic 2) Sepsis	Mean 34.4 months	1 year: 70.8% 5-years 38.4% 10-years: 16%

Continued

Shayan [19]/2011	43 (CABG only)	7%	1) Cardiogenic 2) GI complication 3) Sepsis	Mean 4.3 years	1 year: 76% 5-years: 61% 8-years: 32%
Sharma R [20]/2012	36 kidney and liver transplants (30 were kidney transplants)	ZERO	No death	Mean 4 years	1 year: 94% 5-years: 80% 10 years: 59%
Lenihan [21]/2013	1594 (CABG only)	5%	1) Cardiogenic 2) Sepsis	Median 3.6 years for CABG patients	2-years survival 76% 5-years survival 55%
Rocha [22]/2014	92	11%	1) Cardiogenic 2) Sepsis 3) GI complication	Mean 4.2 years	1-year survival 72% 5-year survival 47% 8-year survival 30%
Vargo [23]/2015	3535 ASOT patients (77% were kidney transplants)	7%	Not reported	Not reported	No long term follow-up
Basic-Jukic [24]/2015	13	15%	Not reported	No follow-up	No long term follow-up
Tooley [25]/2016	2146 (CABG only)	2.7%	Not reported	No follow-up	No long term follow-up.
Farag [26]/2017	70 ASOT patients (70% were kidney transplants)	12.2% kidney transplant.	1) Sepsis 2) Cardiogenic	Median 32 months	1-year: 74% 5-years 66% 10-years: 56%
Kohmoto [27]/2018	115 ASOT patients (71% were kidney transplants)	4% kidney transplant.	1) Cardiogenic 2) Sepsis 3) GI complication	Median 39 months	3-years: 60% 5-Years: 31% 10-years: 12%
Bozso [28]/2019	20 patients with kidney, liver, lung, bone-marrow. (70% were Kidney transplants)	Zero	No death.	Median 3.9 years	2-years: 66% 5-years: 50% 10-years: 50%
Komagamine [29]/2020	23	4.3%	Sepsis	Mean 78 months	1-year 95.7% 5-years 95.7% 10-years: 58.2%
Mace [30]/2020	179	6%	Not reported	Mean 1 year	1-year: 82.4%
Bianco [31]/2020	129 ASOT (65% were Kidney transplants)	2%	Not reported	Mean 5 years	5-years: 75%
Fabio [32]/2021	129 ASOT patients (76% were kidney transplants). Only valve surgery.	14%	1) Sepsis 2) Cardiogenic	Median 51 months	5-years: 59% 10-years: 47% 15-years:40%
Fazmin [33]/2021	38	15.8%	Not reported	Not reported	1-year: 79% 5-year: 63%

ASOT: abdominal solid organ transplants. CABG: Coronary artery bypass graft surgery. GI complication: gastrointestinal complication. IMA: internal mammary artery. PE: pulmonary embolism.

Table 3. Predictors of mortality (short and long term) and predictors of dialysis in kidney transplant patients undergoing cardiac surgery.

Author/year	Predictors of mortality/ kidney graft failure
Ferguson [7]/1999	Predictors of long-term mortality: Diabetes mellitus, higher number of pre-CABG myocardial infraction, renal transplantation before cyclosporine use, older age, unstable angina prior to CABG.
Ono [8]/2002	Predictors of long-term mortality: female gender, low BMI, non-elective surgery. Predictors of long-term kidney graft loss: preoperative serum creatinine level.
Herzog [10]/2004	Predictors of long-term mortality: age > 75 years old, CHF, diabetic end stage renal disease.
Massad [11]/2005	Predictors of 1 year mortality: ejection fraction < 30%, history of CVA/stroke, previous CABG, chronic atrial fibrillation, No beta blockers, dialysis dependence.
Zhang [13]/2006	Predictors of 30-Day mortality and adverse outcomes: preoperative renal insufficeinecy, mitral valve disease and left ventricular dysfunction.
John [15]/2007	Predictors of 30-Day mortality were: preoperative CHF, non-elective surgery, prolonged CPB, peripheral vascular disease, and lower creatinine clearance.
Sharma A [18]/2010	Predictors of 30-Day mortality: age, Diabetes mellitus and combined valve surgery.
Shayan [19]/2011	Predictor of 30-Day mortality: age only.
Sharma R [20]/2012	Predictors of long-term mortality were: increasing age and solid organ transplant.
Rocha [22]/2014	Predictors of 30-Day mortality: age > 65 years old, Ejection fraction < 35%, and combined cardiac surgery. Predictors of permanent dialysis post cardiac surgery were: diabetes, hyperlipidemia, pre-op IABP, preoperative creatinine > 2 mg/dl, transient renal failure requiring dialysis.
Vargo [23]/2015	Predictors of in-hospital mortality: age and acute renal failure.
Farag [26]/2017	Predictors of 30-Day mortality: solid organ transplantation, intra-operative transfusion, and post-operative increase in bilirubin concentration., new onset dialysis, septicemia.
Bianco [31]/2020	Predictors of 5-year mortality: COPD and CHF.
Fabio [32]/2021	Predictors of 30-Day mortality: COPD, urgent operation, mechanical mitral valve replacement, post-operative infection, and CPB time.
Hundemer [3]/2021	Predictors of Acute kidney injury: deceased donor and high pre-operative trough level of Calcineurin inhibitors.

BMI: Body mass index. CABG: coronary artery bypass graft. CHF: congestive heart failure. COPD: chronic obstructive pulmonary disease. CPB: cardiopulmonary bypass. CVA: cerebrovascular accident. IABP: intra-aortic balloon pump.

Table 4. Post-operative acute kidney injury requiring dialysis and permanent kidney graft failure.

Author/year	Number of patients	Post-operative AKI (%) including dialysis	Permanent post-operative kidney graft failure (%)	Comment
Bolman [4]/1984	14	Zero	Zero	
Dresler [5]/1997	45	Zero	8.9	
Mitruka [6]/1997	64 patients with solid organ transplants (40 were kidney transplants)	10	5	
Ferguson [7]/1999	83 (45 post transplant revascularization)	Zero	Zero	No graft loss seen in postoperative cardiac surgery
Ono [8]/2002	60 ASOT patients (46 kidney transplant)	8.7	Zero	3 and 5 years graft survival were both 80%.
Reddy [9]/2002	26	11.5	3.8	11.5% graft loss at mean follow up.
Massad [11]/2005	32	6	6	
Moazami [12]/2006	26	7.7	Zero	
Zhang [13]/2006	57	14	3.5	
Deb [14]/2006	47 patients ASOT (kidney transplant was 34)	3	3	
John [15]/2007	70 ASOT patients (kidney transplant 58)	32.6	9.3	
Musci [16]/2007	39 heart and kidney transplant patients (kidney transplant 16)	6	6	
Rahmanian [17]/2009	29	3.4	3.4	
Shayan [19]/2011	43	72	26	No difference in off pump vs. on pump CABG in renal allograft failure or post operative acute kidney injury.
Sharma R [20]/2012	36 kidney and liver transplants (30 were kidney transplants)	8.3	Zero (all recovered)	
Rocha [22]/2014	92	21	3.3	Freedom from dialysis at: 1 year: 90%, 5 years: 66%, 8 years: 49%
Vargo [23]/2015	3535 ASOT patients (2712 were kidney transplant patients)	37.5	2 (kidney transplant subset)	

Continued

Basic-Jukic [24]/2015	13	30.8	15.4	
Farag [26]/2017	70 ASOT patients (49 were kidney transplants)	17.1	12.9	
Kohmoto [27]/2018	115 patients with kidney, liver, kidney-pancreas transplants. (82 were kidney transplants)	7	37	Long term graft loss in kidney transplant subset was 37%
Bozso [28]/2019	20 patients with kidney, liver, lung or bone-marrow. Kidney transplants were 14 patients.	50	Zero	
Komagamine [29]/2020	23	13	14 at 1 year	Freedom from renal graft failure at: 1-year: 86% 5-years: 80%
Mace [30]/2020	179	5	3.4	Freedom from renal graft failure at: 1-year: 95%, 5-years:79%, 10-years: 53% Predictor of long-term renal allograft loss was preoperative serum creatinine > 1.9 mg/dl.
Bianco [31]/2020	129 patients with solid organ transplants. Kidney transplant patients were 84 patients.	10	4	
Fabio [32]/2021	129 patients with solid organ transplants (97 patients were kidney transplants)	19	9.3	
Hundemer [3]/2021	83	46	10	Highest incidence of AKI was seen in patients who received a deceased donor and high Calcineurin inhibitor trough level.
Fazmin [33]/2021	38	74	45	

AKI: acute kidney injury. ASOT: abdominal solid organ transplants. CABG: coronary artery bypass graft.

(SSI). Interestingly, 3 studies have reported zero incidence of SSI in their series [29] [31] [33].

Table 5. Infections and site of infections in kidney transplant patients undergoing cardiac surgery.

Author/year	Number of patients	Infection rate (%)	Site of infections
Bolman [4]/1984	14	14	Pneumonia
Mitruka [6]/1997	64 patients with solid organ transplants (40 were kidney transplants)	19	1) pneumnia 2) sepsis 3) mediastinitis 4) Leg wound 5) UTI 6) C.Diff
Ono [8]/2002	60 ASOT patients (46 kidney transplant)	5	1) Pneumonia 2) sepsis 3) mediastinitis
Reddy [9]/2002	26	3.8	Leg wound
Massad [11]/2005	32	12	Leg wound infection
Moazami [12]/2006	26	8.5	1) pneumonia 2) sepsis 3) sternal wound
Zhang [13]/2006	57	17.5	1) UTI 2) Pneumonia 3) Sepsis 4) mediastinitis
Deb [14]/2006	47 patients ASOT (kidney transplant was 34)	6.4	1) pneumonia 2) Leg wound infection
John [15]/2007	70 ASOT patients (kidney transplant 58)	2.9	1) sepsis 2) leg wound 3) pneumonia
Musci [16]/2007	39 heart and kidney transplant patients (kidney transplant 16)	12.5	1) sepsis
Rahmanian [17]/2009	29	6.9	1) sepsis
Shayan [19]/2011	43	21	Not specified
Sharma R [20]/2012	36 kidney and liver transplants (30 were kidney transplants)	16.6	1) Leg wound 2) endocarditis 3) sepsis
Lenihan [21]/2013	1594 (compared to 678 PCI patients)	8.6	Not specified
Rocha [22]/2014	92	3.3	Wound infection (sternum and leg)
Vargo [23]/2015	3535 ASOT patients (2712 were kidney transplant patients)	6.2	1) pneumonia: 6.2% 2) wound infection: 1.3%
Basic-Jukic [24]/2015	13	15.4	1) pneumonia
Tooley [25]/2016	2146	2.5	1) pneumonia: 2.5% 2) sepsis: 1.3% 3) SSI: 1.3%
Farag [26]/2017	70 ASOT patients (49 were kidney transplants)	25.7	1) Sepsis: 10% 2) Pneumonia: 7.1% 3) SSI: 5.7%

Continued

Kohmoto [27]/2018	115 patients with kidney, liver, kidney-pancreas transplants. (82 were kidney transplants)	5	1) pneumonia: 5% 2) SSI: 1%
Bozso [28]/2019	20 patients with kidney, liver, lung or bone-marrow. Kidney transplants were 14 patients.	1	1) sepsis
Komagamine [29]/2020	23	4.3	Pneumonia No SSI
Mace [30]/2020	179	12	1) pneumonia: 12% 2) SSI : 1%
Bianco [31]/2020	129 patients with solid organ transplants. Kidney transplant patients were 84 patients.	6	1) Pneumonia: 6% 2) sepsis: 2% No SSI
Fabio [32]/2021	129 patients with solid organ transplants (97 patients were kidney transplants)	18	1) pneumonia 2) mediastinitis /wound
Fazmin [33]/2021	38	21	Pneumonia: 18% Other infection: 21% No SSI

ASOT: abdominal solid organ transplants. C.Diff: Clostridium Difficile infection. UTI: Urinary tract infection. SSI: surgical site infection.

4. Discussion

4.1. Cardiovascular Disease and Risk Factors in Kidney Transplant Patients

Cardiovascular disease remains the major cause of death after renal transplant and renal transplant recipients continue to have a higher incidence of fatal and non-fatal cardiovascular events than the general population. Traditional cardiac risk factors (such as hypertension, DM, hyperlipidemia) are prevalent in renal transplant patients and are affected by the immunosuppression treatment. Hypertension can be caused or worsened by steroids and Calcineurin inhibitors. Dyslipidemia is prevalent in more than half of renal transplant patients and can be caused by steroids, Calcineurin inhibitors and Sirolimus. The high incidence of post-transplant DM is not surprising due to steroid and Calcineurin inhibitors induced hyperglycemia, and this is compounded by the high prevalence of obesity at the time of renal transplant with estimated 60% being overweight or obese. Many non-traditional risk factors that exacerbate cardiac risk in patients with end stage renal disease also operate after renal transplantation including renal graft loss, proteinuria, anemia, chronic inflammation, hyperhomocysteinemia, hypercoagulation and left ventricular hypertrophy [34]. In a prospective study of 344 consecutive renal transplant patients free of cardiovascular disease, it was

found that 7.8% of the cohort developed coronary event. The authors observed that inflammation plays a role in the pathogenesis of atherosclerosis in renal transplant recipients [35]. Similarly, in an autopsy series of 18 renal transplant recipients, cardiovascular pathological findings were evident in 15 out of 18 patients which included severe coronary atherosclerosis with acute MI, left/right ventricular hypertrophy, left/right ventricular dilatation, left/right atrial dilatation and valvular abnormalities [36]. Another paper examined a cohort of 922 patients transplanted between 1993 and 1998. Cardiovascular events (both fatal and non-fatal) occurred in 21% of patients [37]. Multivariate analysis of cardiac events post kidney transplants showed the following factors as predictors: prior cardiovascular event, DM, tobacco history, obesity at transplant, multiple rejections, Dialysis > 1 year. Multivariate analysis of mortality following kidney transplantation showed the following as predictors: Tobacco and deceased donor, age > 45 years, DM pre-transplant, prior cardiovascular event, pulse pressure of 61 mm Hg or greater, dialysis > 1 year and hypercholesterolemia at transplant. The incidence of cardiovascular disease in kidney transplant patients was twice that of the general population. Even young transplant recipients (aged 35 - 45 years) experienced an almost 10-fold increase in cardiovascular disease-related mortality [37]. The commonest cause of late mortality after kidney transplantation was cardiovascular diseases accounting for 40% - 55% of all deaths [14]. As the number of kidney transplantations increases annually, cardiac events are also expected to rise in this population with an increasing number being referred for cardiac surgery. Kidney transplant recipients represents a challenging patient population because of potentially increased risk of postoperative sepsis related to immunosuppression treatment, temporary or permanent allograft failure because of intraoperative non-pulsatile flow of cardiopulmonary bypass and allograft failure. As such, knowledge on the expected post-operative outcome is important to give informed consent to patients and guide clinicians to manage these patients. In addition, the expected long-term survival and kidney graft failure are of paramount importance to predict and reduce its incidence leading to improved survival and outcome. The aim of this review is to summarize the main results of data published over 4 decades with particular emphasis on the outcome data, operative mortality and long-term survival. This review will help clinicians in drawing the proper decision in the management strategies when presented with kidney transplant patients.

4.2. Short-and Long-Term Mortality with Predictors of Mortality in Kidney Transplant Patients

As shown in **Table 6**, most of the studies [5] [6] [8]-[15] showed 30-Days mortality rates ≤ 10%. Only five studies [15] [23] [26] [27] [33] compared the short-term outcomes of kidney transplant patients undergoing cardiac surgery to non-transplant patients using a variety of matching techniques. Ranjit *et al.* [15] retrospectively reviewed kidney transplant patients undergoing cardiac surgery over a 10 years' period in a single center (70 patients with kidney transplants

Table 6. Summary of outcomes stratified as percentages.

Outcome	Number of studies reporting outcome	References
30-Days mortality		
≤10%	21 studies	5, 6, 8 - 15, 17, 19 - 21, 23, 25, 27 - 31.
>10%	8 studies	4, 16, 18, 22, 24, 26, 32, 33.
Survival at 5 years		
≥50%	15 studies	5, 7, 8, 11, 14, 17, 19 - 21, 26, 28, 29, 31 - 33.
<50%	3 studies	18, 22, 27.
Survival beyond 5 years		
≥50%	4 studies	20, 26, 28, 29.
<50%	6 studies	7, 18, 19, 22, 27, 32.
AKI/Dialysis		
≤10%	14 studies	4 - 8, 11, 12, 14, 16, 17, 20, 27, 30, 31.
>10%	13 studies	3, 9, 13, 15, 19, 22 - 24, 26, 28, 29, 32, 33.
Permanent kidney graft failure		
≤10%	21 studies	3 - 9, 11 - 17, 20, 22, 23, 28, 30 - 32.
>10%	6 studies	19, 24, 26, 27, 29, 33.
Infection rate		
≤10%	14 studies	8, 9, 12, 14, 15, 17, 21 - 23, 25, 27 - 29, 31.
>10%	12 studies	4, 6, 11, 13, 16, 19, 20, 24, 26, 30, 32, 33.

AKI: Acute Kidney Injury.

were matched to 895 controls). The authors showed that kidney transplant patients were on average 9 years younger with higher incidence of DM, PVD, chronic renal failure and unstable angina when compared to controls. Prior kidney transplant was not a predictor of 30 days' mortality in that study and multivariate analysis of 30-Days mortality were: preoperative CHF, urgent surgery, prolong cardiopulmonary bypass, PVD and lower creatinine clearance. Vargo *et al.* [23] retrospectively analyzed 3535 ASOT patients (kidney transplants were 2712 patients) from a nationwide inpatient sample over 4 years' period and these were propensity matched in 1:3 to non-transplant patients undergoing cardiac surgery. The authors found no significant difference in in-hospital mortality between transplant and non-transplants patients (7% vs. 4%, respectively). However, total hospital costs were significantly higher for transplant patients. Farag *et al.* [26] retrospectively reviewed single center database of 70 patients with ASOT (49 patients were kidney transplants) over 13 years' period and matched them in 1:1 with non-transplant patients undergoing cardiac surgery based on age, gender and cardiac risk factors. The authors found that 30-Days mortality was significantly higher in the kidney transplant group compared to controls (12.2% vs. 5.7%) with higher long-term mortality over median follow-up time of 32 months (36% vs. 11.4%). Transplant survival compared to controls at 1-year, 5-years and 10-years were significantly lower than controls (74% vs. 93% at 1 year, 66% vs. 88% at 5-years, 56% vs. 81% at 10 years). Multivariate predictors of mortality were organ transplant (Hazard ratio

3.7), intra-op transfusion (Hazard ratio 1.0) and post-op increase in bilirubin concentration (Hazard ratio 1.3). Kohmoto *et al.* [27] retrospectively reviewed 115 patients with ASOT undergoing cardiac surgery over 16 years' period in a single center and performed propensity match (1:3) to 345 patients with no prior transplant. The study showed no difference in the rate of 30-Days mortality between the two groups (4% for transplants vs. 2% for controls). Fazmin *et al.* [33] retrospectively reviewed 38 patients with kidney transplant patients matched as 1:2 to 76 patients with no prior transplant over 8 years' period in a single center. Matching was based on age, gender, left ventricular function, body mass index, preoperative creatinine level, logistic EURO SCORE, operation urgency and operation category. The study showed higher in-hospital mortality in transplant patients compared to controls (15.8% vs. 1.3% respectively) with significantly lower 5-years survival in kidney transplant patients compared to controls (63% vs. 91%, respectively). Most of the studies reviewed [5] [7] [8] [11] [14] showed 5-years survival in kidney transplant patients undergoing cardiac surgery to be ≥ 50% (**Table 6**).

4.3. Acute Kidney Injury and Renal Allograft Failure in Kidney Transplant Patients

As shown in table 6, more than half of the studies reviewed [4]-[8] showed the incidence of acute kidney injury (AKI) with or without dialysis to be ≤ 10% with ≤10% rate of permanent kidney graft failure [11]-[17]. Only 6 previous studies were a matched case control design [3] [15] [23] [26] [27] [33]. Ranjit *et al.* [15] reported significant difference in the need of postoperative dialysis in kidney transplant patients compared to controls (11.7% vs. 1% respectively) and significantly higher incidence of AKI in transplant patients vs. controls (33% vs. 6%, respectively). However, this was all temporary and none of their transplant patients had permanent kidney graft failure. Vargo *et al.* [23] showed significantly increased risk of AKI in transplant patients vs. controls (38% vs. 27%, Odds ratio 1.6). However, kidney graft failure was only 2%. Farag *et al.* [26] showed significantly higher need for dialysis in transplant patients compared to controls (17% vs. 6%, respectively) with 12% kidney graft failure. Kohmoto *et al.* [27] showed no difference in the rate of AKI between transplant and non-transplant patients undergoing cardiac surgery. However, over 15-years follow-up, 37% of kidney transplant patients have lost their kidney graft function. Fazmin *et al.* [33], showed higher incidence of AKI in transplant patients compared to controls (74% vs. 38%, respectively) with higher requirement of dialysis in transplant patients (45% vs. 5%, respectively). However, the authors did not report the rate of permanent kidney graft failure. Hundemer *et al.* [3] investigated incidence and risk factors for AKI retrospectively over 3 years' period in patients with kidney transplants undergoing cardiac surgery and matched them 1:1 with control group. Matching was based on age, preoperative glomerular filtration rate and type of cardiac surgery. The study was conducted in 2 centers and showed that

renal transplant patients had significantly higher AKI rate compared to control (46% vs. 28%, Odds ratio 2.7). In addition, the study showed that the presence of diseased donors and high preoperative level of Calcineurin inhibitors had additive effect on incidence of AKI (88% for patients with these two risk factors vs. 25% for patients with neither).

4.4. Postoperative Infections in Kidney Transplant Patients

Post operative infection is a major complication with significant impact on kidney transplant patients undergoing cardiac surgery as these patients are on chronic immunosuppression therapy and steroids. These medications predispose such patients to both general systemic and opportunistic infections. As shown in **Table 6**, more than half of the studies reviewed [8] [9] [12] [14] [15] showed infection rates ≤ 10% in renal transplant patients undergoing cardiac surgery. Only 5 studies were matched case control design [15] [23] [26] [27] [33]. Ranjit *et al.* [15] showed no difference in the rate of postoperative infections in transplant patients compared to controls (2.9% vs. 2%, respectively) and no difference in the rates of sepsis (2.9% vs. 1.7%, respectively) or pneumonia (1.4% vs. 6.7%, respectively). However, patients with kidney transplants were less likely to have left internal mammary artery (LIMA) used for revascularization compared to controls (62% vs. 88%, respectively) and 73 of 74 patients that had kidney transplant underwent CABG either alone or in combination with valve surgery in the same study. The use of LIMA is a risk factor in postoperative infections post cardiac surgery. Vargo *et al.* [23], showed no difference between transplant patients and controls in the rate of wound infections (1.4% vs. 1.3%, respectively) or pneumonia (7.5% vs. 6%, respectively). Farag *et al.* [26], showed that sepsis was significantly higher in renal transplant patients compared to controls in patients undergoing cardiac surgery (10% vs. 1.4%). Rates of post-operative infections were also significantly higher in transplant patients compared to controls (25.7% vs. 12.9%, respectively). However, the rate of wound infections was not significantly different between the two groups (5.7% for transplants vs. 4.3% for controls). Kohmoto *et al.* [27] showed no difference in the rate of surgical site infections in kidney transplant patients compared to controls (1% for kidney transplants vs. 2% for controls) and no difference in postoperative pneumonia rate (5% each group). Fazmin *et al.* [33], showed that renal transplant patients had significantly higher incidence of non-wound and non-respiratory infections compared to non-transplant patients (21% vs. 4%, respectively). Wound infections were not different in the two groups in that study.

4.5. Future Directions

Key features in the perioperative management of renal transplant patients include appropriate management of immunosuppression, careful maintenance of renal perfusion before and during cardiopulmonary bypass, and monitoring of

renal function postoperatively. Ideally, patients at higher risk for mortality and renal allograft failure could be identified preoperatively and managed selectively to minimize their risk. Multidisciplinary approach (cardiac surgeons, intensivists, anesthetists, transplant clinicians and infectious disease specialists) is of foremost importance when managing these patients.

5. Limitations of the Study

Although this is a comprehensive review of the outcome of renal transplant recipients undergoing cardiac surgery, the review has several limitations. Firstly, the references used were solely observational studies and were mostly single center studies. Secondly, there was no prospective study and no randomized trial performed in these study population that was reported and as such, these studies will have inherent selection bias associated with them. Thirdly, although the general principles of management for the kidney transplant patients following cardiac surgery were applied in the various studied used, the management strategies differed between centers with lack of standardization between them. This might have biased the results of observed outcomes and partially explain the differences in outcomes seen between the studies examined.

6. Conclusion

Cardiac surgery can be safely performed in patients with prior functioning kidney transplants with good short-term morbidity and mortality. Long-term results are encouraging both in terms of survival and functionality of kidney graft. Understanding these observations may lead to improved outcomes in the future and improve detection and management strategies aiming at reducing the adverse outcomes.

Data Availability

All data were extracted from previously published articles reviewed from the three databases used in method section.

Conflicts of Interest

The author declares that there is no conflict of interest regarding the publication of this manuscript.

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