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Outcomes of Coronary Artery Bypass Grafting for Asymptomatic Patients Referred for Renal Transplant

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ABSTRACT

Background: The optimal management of incidental coronary artery disease (CAD) for renal transplant candidates is not well-defined. This study examined transplant and survival outcomes in patients undergoing coronary artery bypass grafting (CABG) for asymptomatic CAD.

Methods: A retrospective review of patients undergoing CABG solely to facilitate renal transplant was conducted at four tertiary centers. Exclusion criteria were symptoms or acute coronary syndrome (ACS). The primary outcomes were successful renal transplant and survival analyzed using Kaplan-Meier curves with log-rank testing, compared to US Renal Data System (USRDS)-predicted life expectancy matched for age and gender.

Results: 86 patients (59.0 [IQR 51.0,65.0] years, 88% male) were identified. At follow-up of 4.41 (2.74,6.04) years, 19.8% ($n = 17$) had successful renal transplant; 29.1% ($n = 25$) were never listed, 44.2% ($n = 38$) listed but removed (29 permanently, 9 temporarily), 7.0% ($n = 6$) awaiting transplant. Pre- and intraoperative characteristics were similar between those transplanted and not. For the entire cohort, CABG was associated with worse 1-year survival, similar 5-year survival, and better 8-year survival compared to USRDS-predicted life expectancy (log-rank $p = 0.027$). Considering those not transplanted, 8-year survival was similar to USRDS (log-rank $p = 0.94$).

Conclusions: In patients with Stage V CKD and asymptomatic CAD, renal transplant rates are low. Whether surgical revascularization offers survival benefit due to successful renal transplant or due to revascularization remains an area of future study. Longer follow-up, study of patient/procedural factors, and multidisciplinary efforts may improve patient selection and transplantation rates.

Abbreviations: ACS, acute coronary syndrome; AUC, appropriate use criteria; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; ESRD, end-stage renal disease; HD, hemodialysis; LAD, left anterior descending artery; LIMA, left internal mammary artery; STS, Society of Thoracic Surgeons; USRDS, United States Renal Data System.

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1 | Introduction

Coronary artery disease (CAD) is common in patients with chronic kidney disease (CKD), with 63% of dialysis patients with or without angina having significant (≥75% stenosis) CAD and an average of 3.3 lesions [1]. If left untreated, CAD may preclude transplant listing due to the concern for perioperative myocardial infarction and poor cardiovascular outcomes complicating renal transplant. The optimal management of asymptomatic CAD discovered on screening for renal transplant is not well-defined. Although the 2017 appropriate use criteria (AUC) document rates coronary artery bypass grafting (CABG) as "Appropriate" for renal transplant [2], the benefit of surgical revascularization is based on the premise that these patients will subsequently undergo renal transplant. A single-institution study previously identified low rates of solid abdominal organ transplantation following CABG performed to achieve transplant candidacy [3]. Therefore, we aimed to conduct a multi-center study to investigate the outcomes of patients who underwent CABG for asymptomatic CAD identified on renal transplant workup, including 30-day perioperative outcomes, successful renal transplant, and all-cause mortality.

2 | Patients and Methods

A retrospective chart review of patients who underwent CABG solely for the indication of renal transplant clearance at four tertiary care academic medical centers was conducted. IRB approval was obtained from each institution (UTHSA IRB#HSC20200365E, 2020 May 20; IU IRB# #11626, 2021 May 13; U of M IRB# HUM00217819, 2022 May 23; and UF IRB# 202001453, 2020 Jul 29) and waivers of consent were granted. The primary source of data was each institution's Society of Thoracic Surgeons (STS) database and transplant division administrative database. Due to variations in database maintenance and data availability, the study period varied for each institution (Supporting Table).

2.1 | Data Variables, Definitions, and Outcome Measures

Inclusion criteria were patients who were referred for surgical revascularization of CAD identified on workup for renal transplant but who were asymptomatic, defined as the absence of angina or angina equivalent, as determined by review of clinical notes by each site investigator. Patients with angina, angina equivalent, or acute coronary syndrome (ACS) were excluded. The primary outcomes were successful renal transplant and survival at follow-up.

Successful transplant was defined as a patient undergoing a renal transplant after CABG, regardless of post-transplant mortality or morbidity, and was determined by each site's transplant surgeon investigator upon review of the institutional transplant database. Patients not transplanted were further analyzed by waitlist status at follow-up using institutional documentation from transplant surgeons and transplant committees. Patient survival was defined as time from surgery to last follow-up or date of death. Survival analysis was performed using Kaplan-Meier curves with log-rank testing. To eliminate the impact of CABG postoperative mortality on the ability to be evaluated for transplant, survival time was calculated starting 90 days after CABG to the last follow-up or date of death. Four patients who were deceased prior to the cutoff time were excluded from the survival analysis. A comparison cohort was generated using US Renal Data System (USRDS) life expectancy tables (Table 1) [4], matched for age and gender with each individual patient in the study. Twenty simulated survival times in an exponential distribution for each patient's predicted life expectancy were generated to create a comparison survival curve.

TABLE 1 | Predicted life expectancy.

	ESRD patients, 2019				General US population, 2018	
	Dialysis		Transplant			
Age	Female	Male	Female	Male	Female	Male
40–44	10.2	11.1	29.9	28.2	40.4	36.5
45–49	9.1	9.6	26.0	24.3	35.8	32.1
50–54	7.8	8.2	22.3	20.6	31.3	27.8
55–59	6.8	6.9	18.9	17.3	26.9	23.8
60–64	5.9	5.8	15.7	14.3	22.8	20.0
65–69	5.0	4.9	12.7	11.7	18.8	16.4
70–74	4.3	4.1	10.3	9.5	15.0	13.0
75–79	3.7	3.5	8.3[a]	7.6[a]	11.5	9.9
80–84	3.2	2.9			8.4	7.2
85+	2.7	2.4			4.3	3.7

Note: Adapted from the United States Renal Data System. 2021 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2021. https://usrds-adr.niddk.nih.gov/2021/end-stage-renal-disease/6-mortality.

[a]This is for 75+.

Major morbidity outcomes included re-operation for bleeding or cardiac reason, stroke, intubation >48 h or reintubation, and deep sternal wound infection.

2.2 | Statistical Analysis

Continuous variables are expressed as mean ± SD for normally distributed variables and median with interquartile range (IQR) for non-normally distributed variables. Categoric variables are presented as proportion and absolute number. Differences between groups were detected using the $\chi 2$ test or the Fisher exact test for categoric variables and 2-tailed *t*-test for continuous variables.

Survival analysis was performed using Kaplan-Meier curves with log-rank testing. Data management and statistical analyses were performed using R 4.2.1 software (R Foundation for Statistical Computing) with the *lubridate* [5]and *survminer* [6] packages.

TABLE 2 | Characteristics of patients by transplanted status.

	Not transplanted ($n = 69$)	Transplanted ($n = 17$)	p value
Age	60 [52, 65]	56 [51, 65]	0.540
Gender			0.506
Male	76.8 (53)	88.2 (15)	
LVEF			0.728
<40%	20.3 (14)	11.8 (2)	
Diabetes			0.501
Type I	66.7 (46)	52.9 (9)	
Type II	33.3 (16)	35.3 (6)	
None	10.1 (7)	11.8 (2)	
ESRD etiology			0.729
Diabetes	87.0 (60)[a]	88.2 (15)	
Hypertension	23.2 (16)[a]	5.9 (1)	
Nephrotic syndrome	1.4 (1)	5.9 (1)	
Polycystic	1.4 (1)	0 (0)	
Autoimmune	1.4 (1)	0 (0)	
Dialysis type			0.357
Hemodialysis	66.7 (46)	52.9 (9)	
Peritoneal	24.6 (17)	41.2 (7)	
None	8.7 (6)	5.9 (1)	

Note: Continuous variables are reported as median [IQR]; categorical variables as proportion (count).
Abbreviations: ESRD, end-stage renal disease; LVEF, left ventricular ejection fraction.
[a]10 patients had both diabetic and hypertensive nephropathy and have been listed under both.

TABLE 3 | Operative characteristics.

	Not transplanted ($n = 69$)	Transplanted ($n = 17$)	p value
# Vessels bypassed			0.065
1	7.2 (5)	17.6 (3)	
2	30.0 (20)	35.3 (6)	
3	44.9 (31)	17.6 (3)	
4	18.8 (13)	23.5 (4)	
5	0 (0.0)	5.9 (1)	
# IMA grafts			0.290
0	2.9 (2)	11.8 (2)	
1	88.4 (61)	82.4 (14)	
2	8.7 (6)	5.9 (1)	
LAD graft			0.048
Any IMA	95.7 (66)	76.5 (14)	
In-situ LIMA	87.0 (60)	64.7 (11)	
Free LIMA	7.2 (5)	17.6 (3)	
In-situ RIMA	0 (0)	0 (0)	
Free RIMA	1.4 (1)	0 (0)	
SVG	4.3 (3)	17.6 (3)	

Note: Categorical variables are reported as proportions (count).
Abbreviations: IMA, internal mammary artery; LAD, left anterior descending; LIMA, left internal mammary artery; RIMA, right internal mammary artery; SVG, saphenous vein graft.

The study dates and annual renal transplant volumes over the study periods for each center are shown in the Supporting Table.

3 | Results

3.1 | Primary Outcomes

A total of 86 patients with a median age of 59.0 (IQR 51.0,65.0) years, of whom 88% were male. Patient demographics and renal and cardiac preoperative factors are shown in Table 1. There were no significant differences in the baseline characteristics of those who underwent transplant and those who did not (Table 2). At a median follow-up of 4.41 (IQR 2.74, 6.04) years, 19.8% ($n = 17$) had undergone successful renal transplant at 426 (IQR 315, 660) days, with the incidence of transplant after CABG ranging from 13.6% to 38.9% among centers. Of the remaining patients, 30.2% (26) were never listed, 43.0% (37) were listed but then removed from listing (28 permanent, 9 temporary), and 7.0% (6) are awaiting transplant. The reasons for non-listing were not documented for a majority of patients. Of the patients who were permanently delisted, the cause was death in 17 (60.7%), malignancy in 2 (7.1%), and unknown in 9 (32.1%). All-cause mortality at follow-up was 42.0% in those not transplanted and 5.9% in those transplanted (Chi-square $p = 0.004$) (Table 5).

When compared to the USRDS predicted life expectancy matched for age and gender, CABG was associated with worse survival at 1-year, similar survival at 5-years, and better survival at 8 years (log-rank $p = 0.032$, Figure 1A). When considering only those not transplanted, survival was similar to USRDS through 8 years (log-rank $p = 0.91$, Figure 1B).

3.2 | Intraoperative and Perioperative Outcomes

Intraoperative characteristics are shown in Table 3. The number of vessels bypassed did not differ between groups ($p = 0.065$), although those not transplanted had more vessels bypassed (≥3 vessels, 63.7% vs. 47%) and had a non-significantly higher proportion of IMA conduits (97.1% vs. 88.3%, $p = 0.29$). Patients not-transplanted were more likely to receive an IMA graft to the left anterior descending artery (LAD) (95.7% vs. 76.5%, $p = 0.048$); however, two patients had a LIMA-diagonal graft, and the overall arterial graft numbers did not differ between groups (Table 3).

Major morbidity was 18.8% versus 11.8% ($p = 0.725$) in not transplanted versus transplanted, with pulmonary complications

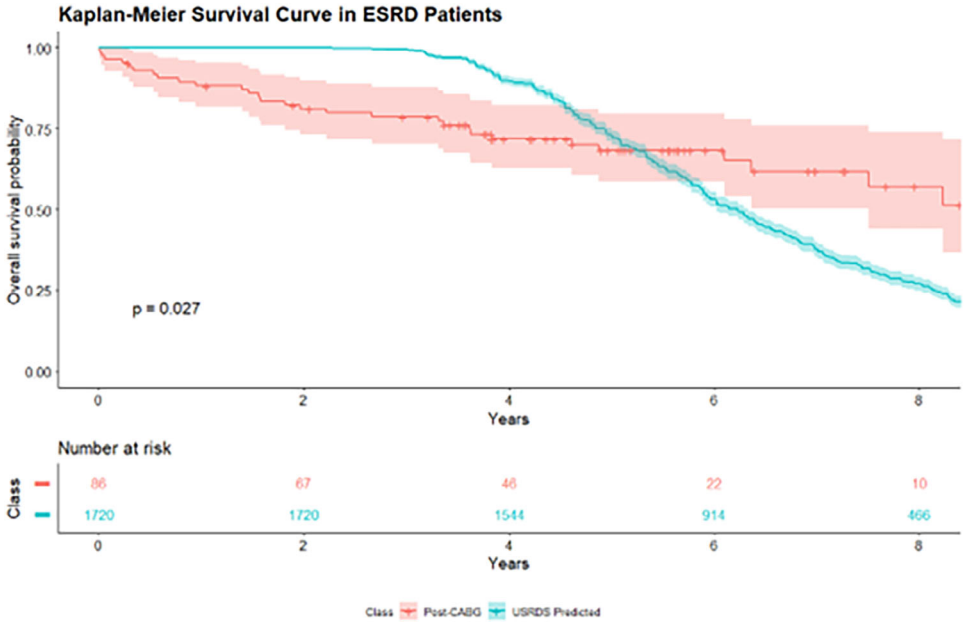


FIGURE 1 | Appropriate use score for patients undergoing renal transplantation. Numbers indicate the appropriate use score (1–9). A indicates appropriate; AA, antianginal; BB, beta blockers; CABG, coronary artery bypass graft; LMCA, left main coronary artery; M, may be appropriate; PCI, percutaneous coronary intervention; R, rarely appropriate; SYNTAX, synergy between PCI with taxus and cardiac surgery trial.

being the most common. Overall, 30-day mortality was 3.5% (n = 3).

3.3 | Comment

As the writing group of the 2017 ACU document acknowledged, there is a lack of experience or data from controlled studies to develop meaningful scenarios for the cohort of patients referred for revascularization of CAD prior to organ transplantation [2]. Nevertheless, appropriate use of CABG is rated "May be appropriate" for the majority of imaging and risk findings combinations, with "Appropriate" reserved for patients who had intermediate/high risk noninvasive findings, regardless of symptom status (Figure 1). The ACU document does not provide any evidentiary literature for these ratings. Considerations of clinical benefit for asymptomatic patients include reduced mortality or improved quality of life deriving from successful transplant, and/or mortality benefit from decrease in cardiovascular mortality. These benefits must be weighed against the additional operative mortality and morbidity risk imposed by end-stage renal disease (ESRD) status, especially for patients who are asymptomatic. Both sequelae of postoperative complications and progression of other comorbidities have the potential to render a patient unfit for renal transplantation. Furthermore, predicted CABG graft patency must also be accounted for in the decision to operate. With time, vein graft patency decreases, and native CAD can progress, which may lead to recurrent myocardium at risk if there is a long interval between revascularization and renal transplantation. Multi-arterial graft options are limited to bilateral IMAs in these patients, given the need to preserve upper extremity vascular dialysis options. We suggest that all these considerations should be discussed in a multidisciplinary fashion with the referring physicians, transplant team, the patient, and their family (Figure 2).

Intuitively, patients referred for renal transplantation would seem to be a selected group with an improved comorbidity profile and decreased surgical risk compared to the broader group of all ESRD patients. However, Matthews et al., who found that only 3 of 22 patients went onto successful renal transplant, also found that there were no differences in 30-day operative mortality or morbidity between those undergoing CABG for renal transplant candidacy versus non-transplant patients [3]. In addition to the short-term safety of CABG for ESRD patients, the findings of this study suggest that there may be a longer-term mortality benefit compared to predicted life expectancy based on USRDS. Mid-term all-cause mortality at 8 years in the CABG cohort was superior to historical controls using USRDS life expectancy tables. However, this benefit was not seen when restricting survival analysis to those not transplanted. Given the small number of patients and limited follow-up despite the inclusion of multiple institutions, this should be interpreted with caution. Certainly, no causative relationship can be declared. It is possible that other comorbidities are responsible for both non-transplantation and mortality at follow-up. Still, the leading cause of death in ESRD patients is cardiovascular disease, accounting for 46.9% of deaths [7].

When counseling ESRD patients regarding the risk-benefit ratio of CABG, mortality benefit is an area with scant evidence, and further studies are needed to better define the magnitude, if it exists. The majority of patients will be focused more on renal transplantation candidacy as the benefit to CABG. In this study, we found a wide variation in transplantation rates. Factors accounting for this variation may be patient or program-related. A low rate of transplantation suggests that greater scrutiny of patient comorbidities that affect transplant candidacy and not just CABG candidacy may be an opportunity for improvement. Unfortunately, the reasons for never listing or for delisting were missing in many cases, rendering any clinical recommendations

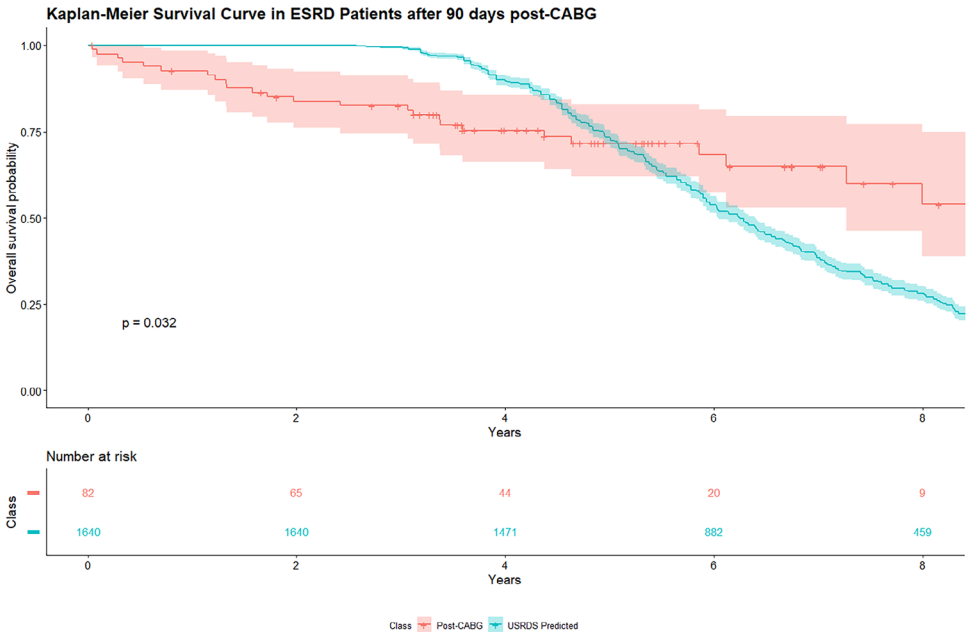


FIGURE 2 | (A) Survival analysis of entire patient cohort compared to US Renal Data System (USRDS) age and gender matched control population; (B) Survival analysis of non-transplanted cohort compared to US Renal Data System (USRDS) age and gender matched control population.

difficult to make. In addition to a multidisciplinary approach to patient selection, improved documentation and feedback on the ultimate success of achieving a renal transplant would be elements to incorporate in programs. Given the expansion of the donor kidney pool with strategies such as machine perfusion and preservation, more efficient use of high kidney donor profile index (KDPI) organs [8], donation after cardiac death, and kidney-paired exchanges, the issue of concomitant CAD and renal transplantation is expected to expand as well.

Other limitations of this trial include the use of number of vessels bypassed, rather than completeness of revascularization. The reasons for non-listing or removal from listing were not available in the majority of records. Patients may have had listing and transplantation at other centers. Comparison to the USRDS life expectancy table may be outdated, given that the tables cite data from 2018-2019. However, life expectancy in this population has not changed over time, as comparisons to older USRDS life expectancy tables show essentially stable figures, and the USRDS

TABLE 4 | Renal and mortality outcomes.

Outcomes	% (*n*)
Renal transplant status	
Underwent renal transplant	19.8 (17)
Awaiting renal transplant	7.0 (6)
Currently not listed	
Never listed after CABG	29.0 (25)
Temporarily removed from listing	10.5 (9)
Permanently removed from listing	33.7 (29)
Due to death	19.8 (17)
Due to cancer	3.5 (3)
Other/unknown	10.5 (9)
Cause of death	
Cancer	2
Cardiovascular	7
Other	5
Unknown	16

Note: Categorical variables are reported as proportions (count).
Abbreviation: CABG, coronary artery bypass grafting.

TABLE 5 | Cardiac and mortality outcomes.

	Not transplanted (n = 69)	Transplanted (n = 17)	*p* value
Perioperative CABG outcomes			
Re-operation	0 (0)	0 (0)	1
CVA	2.9 (2)	0 (0)	1
Intubation >48 h	4.3 (3)	5.9 (1)	1
DWSI	7.2 (5)	5.9 (1)	1
Re-intubation	8.7(6)	0 (0)	0.594
Any complication	18.8 (13)	11.8 (2)	0.725
30-day mortality	4.3 (3)	0 (0)	1
Cardiovascular event at 1 year	7.2 (5)	0 (0)	1
All-cause mortality at follow-up	42.0 (29)	5.9 (1)	0.004

Note: Categorical variables are reported as proportions (count).
Abbreviations: CABG, coronary artery bypass grafting; CVA, cerebrovascular accident; DWSI, deep sternal wound infection.

has been used as the standard in other studies of life expectancy in ESRD patients.[9] Finally, the study cohort may represent a selection bias of patients with a different comorbidity profile than an age and sex-matched USRDS cohort, given the association of CAD with other disease states such as peripheral vascular disease and cerebrovascular disease (Table 4).

4 | Conclusion

In patients with Stage V CKD and CAD, CABG as a bridge to renal transplant is associated with longer life expectancy than predicted; however, successful renal transplant rates are low, and early morbidity/mortality is not benign. Longer follow-up and study of factors involved may improve patient selection and transplantation rates and better define the role of CABG in this patient group.

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Disclosure

The work in this manuscript was presented as a poster at the Society of Thoracic Surgeons 58th Annual Meeting.

Consent

IRB approval and waiver of consent were granted (UTHSA IRB#HSC20200365E, 2020 May 20; IU IRB# #11626, 2021 May 13; U of M IRB# HUM00217819, 2022 May 23; UF IRB# 202001453, 2020 Jul 29).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.