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The impact of kidney transplantation on heart failure risk varies with candidate body mass index

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Abstract

Background—The relationship of body mass index (BMI) with heart failure (HF) risk before and after kidney transplant is not well-described.

Methods—We examined United States Renal Data System records for 67,591 kidney transplant candidates (1995–2004) with Medicare insurance and BMI data at listing. HF diagnoses were ascertained from Medicare billing claims. BMI was categorized per World Health Organization criteria. We modeled time-dependent associations (adjusted hazard ratio, aHR) of transplant with HF risk after listing compared to waiting in each BMI group by multivariable, stratified Cox regression. The time-dependent exposure variables partitioned relative risk of HF following transplant versus waiting into early (≤90d) and late (>90d) posttransplant periods.

Results—The BMI distribution of listed candidates was: 3.7% under, 40.4% normal, 32.0% over, 16.2% obese, and 7.7% morbidly-obese weight. The prevalence of HF among patients awaiting transplant reached 57.4% by three years. Deceased donor transplant was associated with increased early HF risk compared to continued waiting – aHRs ranged from 2.23 for normal-BMI to 2.82 for morbidly obese patients. However, transplant reduced the risk of HF in the late posttransplant period, from 54% (aHR 0.46) in normal BMI to 32% (aHR 0.68) for morbidly obese patients. Relative benefits were largest for normal weight candidates who received live-donor transplants (aHR 0.31).

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Conclusions—HF risk improves in obese patients in the long-term after kidney transplant, but not as much as for non-obese. There is need for close monitoring and for new strategies to reduce HF risk in obese patients before and after transplant.

Keywords

Body mass index; Heart failure; Kidney transplantation; Medicare; Registry

Introduction

Heart failure (HF) is common among patients with end-stage renal disease (ESRD). Concomitant dysfunction of the heart and kidneys results in part from shared risk factors, as well as from a "vicious cycle" of reciprocal causation [1]. Overt HF portends a poor prognosis in dialysis-dependent patients 2, and even asymptomatic cardiac dysfunction in kidney transplant candidates bears an independent association with mortality 3. Kidney transplantation improves a number of factors predisposing to HF including volume overload, uremic toxicity and anemia. Although left ventricular systolic dysfunction was previously considered a contraindication to kidney transplantation, reversals of cardiac dysfunction after transplant have been documented 4–6.

Obesity, a risk factor for HF in the general population [7], predicts increased risks of mortality and perioperative complications in kidney transplant recipients including delayed graft function, elevated transplant costs, and allograft loss 8–10. Single-center and registry-based observational studies have reported higher frequencies of HF after kidney transplant in obese compared to non- obese recipients 11–14. However, the joint effects of BMI and transplantation upon HF after listing are not well-described despite the increasing prevalence of obese patients on the transplant waiting list. Therefore, to advance understanding of the risks of HF before and after kidney transplantation, we performed a retrospective study of a national cohort of recent renal allograft candidates recorded in the United States Renal Data System (USRDS). We aimed to describe the frequency of total and new-onset HF diagnoses after listing, and to estimate the time-dependent relative risk of HF associated with deceased or living donor kidney transplantation, compared to continuing waiting, in early and late post-transplant periods. The joint effects of candidate BMI with transplant-related HF risk were considered across BMI classifications.

Methods

Data Sources

We performed sample selection, outcomes ascertainment, and covariate determinations using registry data collected by the USRDS that incorporates information from the Organ Procurement and Transplantation Network (OPTN) and Medicare billing claims records. Details of the source USRDS data, as well as limitations of Medicare claims data, have been described previously [15]

Participant Selection

The primary sample included adult (≥18 years-old) ESRD patients listed for kidney transplantation from January 1995 to December 2004 with Medicare Part A and B benefits and available BMI data at listing. We identified Medicare beneficiaries per the "Payer History" file of the USRDS. In secondary analyses we studied patients with one-year of continuous Medicare coverage before listing, with continuity defined to allow unlimited gaps up to three days (administrative gaps) and/or a single gap of four to sixty days, and no indication of pre-listing HF as defined below.

Definitions of Outcomes and Covariates

Heart failure—HF was defined by identification of qualifying Medicare bills with a HF diagnosis per the claims definition of the USRDS Annual Data Report (ADR) (International Classification of Diseases Code 9th Edition (ICD-9) codes 398.91, 422, 425, 428, 402.×1, 404.×1, 404.×3) 16. We defined claims-based HF diagnosis as ≥1 inpatient Part A institutional claim or ≥2 Part B physician/supplier claims. The date of the earliest claim was taken to define HF onset. We recently demonstrated this algorithm to have 92.5% sensitivity for detection of clinically diagnosed HF events in a validation study among kidney transplant recipients 17. Pre-listing HF diagnosis also included indications of HF on the United Network for Organ Sharing (UNOS) Candidate Registration Form and the Center for Medicare and Medicaid Studies (CMS) Form 2728, which queries select comorbidities at the time of ESRD reporting.

BMI at listing and other baseline patient traits—Candidate demographic and clinical information were obtained from the CMS Form 2728 and the OPTN Transplant Candidate Registration Form, including age, gender, race, Hispanic ethnicity, primary cause of ESRD, and date of first dialysis, and comorbidities (coronary disease or myocardial infarction, cerebrovascular disease, peripheral vascular disease, tobacco use and alcohol dependence). BMI (kg/m^2) was computed from height and weight information reported at waitlist entry, and was categorized by World Health Organization criteria into five categories ranging from underweight to morbidly obese weight (Table 1).

Statistical Analysis

Baseline demographic and clinical traits of the study patients are described as counts and proportions. Continuous variables were categorized into clinically relevant strata. Missing categorical covariate data were grouped with the absence of a characteristic when such categories were relevant, or into a category distinct from the reference group.

At-risk time for all the time-to-event analyses was censored at end of Medicare enrollment, death not concurrent with HF diagnosis, or end of study (December 31, 2004). Time to first post-listing HF diagnosis in the full study sample was examined to describe the burden of clinically recognized HF in the target population (cumulative prevalence). Time to first post-listing HF diagnosis in a sample selected as free of indicated HF before listing in the registry was also examined as a representation of cumulative incidence. We estimated the observed, cumulative frequencies and 95% confidence intervals (CI) of HF after listing and after transplant by the product-limit (Kaplan-Meier) method. At-risk time for the Kaplan-Meier estimates while waiting was also censored at transplantation to constrain these frequency estimates to the period between listing and transplant. Waitlist entry was considered according the principle of “intention to treat”, and thus risk-time was not censored at waitlist removal for reasons other than transplant or death.

We employed multivariable, stratified Cox regression to estimate the time-dependent relative risk (adjusted hazard ratio, aHR) of HF diagnosis (total and new-onset) associated with deceased or living donor kidney transplantation compared to continuing waiting without transplant for each BMI group. Living donor renal allografts tend to function more promptly and have superior long-term graft survival compared to deceased donor transplants for reasons such as less pre-transplant ischemia. As an underlying hypothesis of this analysis was that restoration of kidney function may improve HF risk in ESRD patients in the long-term, living and deceased donor transplantations were considered as distinct exposure events. Kidney transplant time-dependent exposure variables partitioned relative risk associated with transplant versus waiting into early (≤90 days) and late (>90 days) post-transplant periods based on an *a priori* hypothesis that HF risk differs peri-operatively compared to late after transplant. Stratification by BMI group at the time of listing established patients within a given

BMI category who remained without transplant as references, while allowing estimation of all time-dependent variables within a single model and thus facilitating direct comparison of effect estimates. Models were adjusted for baseline patient demographic and clinical traits at listing including age, gender, race, ethnicity, cause of ESRD, duration of dialysis prior to listing, dialysis modality, reported comorbidities and listing year. To assess consistency of effects across demographic groups, subgroup analyses limited by gender or race were performed.

Authorship and Funding

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Results

BMI distribution and baseline characteristics according to BMI

There were 180,233 unique adults listed for kidney transplantation per USRDS records in the study period, of whom 89,297 had Medicare primary insurance at the time of listing. Of these Medicare-insured transplant candidates, 67,591 (75.7%) also had BMI data at listing and were selected for analysis. The BMI distribution of this sample of waitlisted subjects was: 3.7% underweight, 40.4% normal, 32.0% overweight, 16.2% obese, and 7.7% morbidly obese weight. Forty-one percent of the sampled patients were women and 34% were black race. The distribution of patient characteristics according to BMI at listing is shown in Table 1. Trait distributions varied significantly according to listing BMI, with overweight, obese and morbidly groups having higher prevalence of black race, ESRD due to diabetes, listing before dialysis initiation and listing in the most recent years of the study compared to normal weight candidates. Overweight and obese candidates were more likely to be aged >45 years and to have known coronary artery disease and peripheral vascular disease at listing. Morbidly obese and underweight candidates were more commonly female. Of 38,997 candidates with continuous Medicare coverage for at least one year before transplant, 21,120 (54%) did not have identified HF prior to listing. The BMI distribution of this sub-sample was similar to that of the full cohort (Table 2).

Fifty four percent (36,433) of the full cohort were transplanted during the observation period, after a median waiting period of 411 days in those who received an allograft. BMI at transplant could be calculated for 78.4% (28,550) of these subjects. Among transplant recipients with complete BMI data at transplant and listing, the median change in BMI from listing to transplant was 0 kg/m2 (interquartile range: −1.26 to 0.45 kg/m^2). Because not all candidates were transplanted and because HF risk was considered from the candidate's perspective, BMI at listing was used to classify patients in the analytic models.

Cumulative frequencies of HF on the waitlist and after transplant

HF was common after waitlist entry. By three years, the cumulative prevalence of HF diagnoses on the waitlist was 57.4% (95% CI 56.8–57.9%). Among candidates without a diagnosis of HF prior to listing, the incidence of new-onset HF was 46.1% (95% CI 45.2–47.0%) at three years. The crude frequencies of total and new-onset HF diagnoses varied significantly by baseline BMI strata (P<0.0001 by Log-Rank test) (Figure 1). Specifically, among obese or morbidly obese candidates the cumulative prevalence of HF at three years after listing was 59.6% (95% CI 58.5–60.6%) compared to 55.0% (95% CI 54.2–55.8%) in normal weight candidates. In obese or morbidly obese candidates the cumulative incidence of HF at three

years after listing was 48.4% (95% CI 46.5–50.3%) compared to 43.2% (95% CI 41.8–44.7%) in normal weight candidates.

Among patients transplanted during observation, 36.1% (95% CI 35.5–36.6%) acquired HF diagnoses by three years after transplant. The cumulative frequency of HF rose most sharply early after transplant and then achieved a more gradual slope (Figure 1). The prevalence of HF at three years after transplant was lower among recipients of living compared to deceased donor allografts, 28.2% (95% CI 27.0–29.5%) vs. 37.8% (95% CI 37.2–38.4%). Post-transplant HF was more common among transplant recipients with higher BMI at listing (Figure 1). Estimates of HF prevalence according to BMI at transplant in the subgroup with these data available were very similar (point estimates at three years within 0 to 1.5%).

Relative risk of HF within 90 days of transplant compared to waiting

Associations of kidney transplantation with relative risk of HF compared to waiting were examined by time-dependent regression. Figure 2 displays the time-dependent relative risks of HF associated with transplant within the first 90-day period post-transplant, compared to continued experience without transplant, including the joint effect of candidate BMI. Deceased-donor kidney transplant was associated with increased early (≤90 days) HF risk compared to waiting without transplant: aHRs ranged from approximately 2.23 (95% CI 2.08–2.39) for normal weight candidates (BMI group 2) to an aHR of 2.82 (95% CI 2.41–3.30) for morbidly obese patients (BMI group 5). Living-donor kidney transplant was also associated with increased early HF risk. Notably, normal weight candidates who received living-donor allografts faced a modest 20% relative risk increase (aHR 1.21, 95% CI 1.02–1.44) in the early post- transplant period, but early relative risk was more than two times that of waiting (aHR 2.36 95% CI 1.74–3.21) for morbidly obese patients receiving a living donor transplant. Patterns were similar for the relative risk of new-onset HF early after kidney transplant, with both deceased and living donor transplantation predicting increased risk, but suggestion of lowest relative risk in normal weight patients transplanted with living-donor grafts.

Relative risk of HF late after transplant compared to waiting

In contrast, there was significant reduction in HF risk late (>90 days) after transplant compared to waiting (Figure 3). For deceased donor transplant, late risk reduction varied from 54% (aHR 0.46, 95% CI 0.43–0.96) in normal weight candidates to 32% (aHR 0.68, 95% CI 0.58–0.79) in morbidly obese patients. Relative benefits were largest for normal weight candidates receiving living donor transplants, who achieved up to 69% relative risk reduction (aHR 0.31, 95% CI 0.27–0.36). Patterns were similar for the relative risk of new-onset HF late after transplant, with both deceased and living donor transplants predicting benefit across candidate BMI strata, but appearance of a graded decline the long-term protective effect of transplantation in patients at higher BMI levels.

Subgroup analyses

Associations of transplant with early and late HF risk compared to waiting were similar in men compared to women, and in persons of black, white and other races, albeit with some loss of statistical precision (wider confidence intervals) due to smaller sample sizes (Table 3).

Discussion

Heart failure is a common but serious complication in patients with renal failure. We examined the joint effects of kidney transplantation and patient BMI on acquisition of HF diagnoses among a large national sample of transplant candidates, and observed several main findings. 1) HF is common among ESRD patients awaiting transplantation, with incidence and prevalence rising progressively with waiting time. 2) Kidney transplantation is associated with

a brief early rise in HF risk compared to experience without transplant. 3) Both deceased and living donor kidney transplants are associated with significant long-term reductions in HF risk. This benefit appears more pronounced for recipients (especially normal weight) of living donor allografts. 4) There is variation in the apparent benefit of kidney transplantation for HF risk according to candidate BMI –while obese patients experience benefit in long-term HF risk with transplant compared to waiting, their benefit is less than for non-obese patients.

Our finding that HF is a progressively frequent diagnosis among ESRD patients awaiting kidney transplantation is sobering but not unexpected. Prior studies have demonstrated that chronic kidney disease is an independent risk factor for HF and that a significant proportion of patients with ESRD have left ventriculuar hypertrophy (LVH) and/or reduced left ventricular (LV) systolic function [18–20]. Even among chronic kidney disease patients with normal LV systolic function, there is a high prevalence of impaired myocardial performance as seen using modern tissue Doppler techniques 21. Indeed, authors have recognized the pathobiologic interplay of cardiac and kidney dysfunction in the increasingly used term “cardiorenal syndrome” 1.

Given the baseline high degree of cardiac structural abnormalities in patients with ESRD, the increase in HF in the early posttransplantation period (<90 days) seen in our study may be explained by several mediating factors. These include perioperative stresses, fluid overload and delayed or impaired graft function. The predictors of early HF following kidney transplant have not been well studied. In a recent study of 132 kidney transplant recipients, early HF was common and was associated with post-transplant anemia, allograft dysfunction, duration of dialysis prior to transplant, and degree of pretransplant LVH [22]. Of note, in our study sample the relative rise in HF risk early after transplant was smaller with living compared to deceased donor transplantation across BMI strata, possibly reflecting superior early graft function in this cohort. It is also possible that the increase in early HF is affected by ascertainment bias, in that patients receive close follow-up early after transplant, compared to more intermittent clinical assessments of patients on the waitlist.

Importantly, however, transplant was associated with significantly decreased risk for late HF as compared to ongoing waiting in our analysis. There are several likely explanations for this observation. First, it has been demonstrated that dialysis imparts specific hemodynamic stressors that may predispose patients to adverse cardiac remodeling and subsequent HF. In a recent study utilizing implantable hemodynamic monitoring, patients undergoing hemodialysis three times weekly were demonstrated to have significant increases in right ventricular and pulmonary artery pressures between dialysis sessions [23]. Similarly, LV mass, LV myocardial interstitial edema and LV intraventricular synchrony have been shown to adversely fluctuate between hemodialysis sessions, all potentially leading to negative cardiac remodeling and subsequent heart failure [24, 25]. The degree of overt fluid retention and weight gain between hemodialysis sessions is an independent risk factor for all-cause cardiovascular death [26]. A recent study demonstrated that dialysis patients have significant alterations in systolic and diastolic function by tissue Doppler even if LV ejection fraction is normal [27]. It is therefore plausible that kidney transplantation may significantly lower HF risk by restoring renal function, interrupting the ongoing stressors listed above related to dialysis, as well as possibly improving other mediators of HF such as anemia and inflammatory markers.

Our findings of HF risk reduction after transplant resonate with serial echocardiographic observations of average increases in ejection fraction and regression of left ventricular hypertrophy following kidney transplantation [5, 6], as well as retrospective data demonstrating reduced HF incidence in diabetic patients following transplant [28]. Pilot studies have suggested that regression of ventricular hypertrophy requires adequate allograft function [4], which is congruent with our finding of larger long-term, relative HF risk reductions with living

compared to deceased donor grafts. Others have demonstrated that LVH regression is also significantly dependent on degree of posttransplant blood pressure control [29–31].

Another key observation of the current study was variation in the apparent benefit of kidney transplant for HF risk according to candidate BMI. We found that obese patients, who composed nearly 25% of our study population, had higher risk of HF after listing than normal weight candidates. While obese patients did acquire benefit in long-term HF risk with transplant compared to waiting, their benefit was less than for non-obese patients. In the Framingham Heart Study, obesity was shown to be a significant independent risk factor for the development of HF as well as overall cardiovascular mortality [7, 32]. Similarly, increased BMI and abdominal adiposity were recently shown to be strong independent risk factors for HF hospitalizations and HF mortality in a middle-aged to older adult population [33]. However, the implications of obesity in ESRD are complex and controversial. High BMI is associated with a mortality benefit in dialysis patients [34–37] and a large, registry-based study found no apparent survival benefit with weight loss among transplant candidates [37]. These relationship are confounded by underlying comorbidities and malnutrition that both reduce BMI and increase death risk [38].

Several prior studies including clinical record and registry-based data have shown higher risk of HF in obese compared to non-obese kidney transplant candidates. Additionally, retrospective studies have suggested that BMI at time of transplant and posttransplant weight gains are associated with acquisition of cardiovascular risk factors and decreased patient and graft survival [9, 39]. Recently, in a retrospective study of 1102 patients who underwent kidney transplant between 1991 and 2004 a one center, we found that elevated BMI at transplant predicted significantly increased risk of posttransplant HF and atrial fibrillation [11]. The current study expands on this knowledge by examining a large, national cohort of ESRD patients with analyses performed to compare HF risk before and following transplant. Our findings indicate that obesity at listing modifies the impact of transplantation on HF by increasing the early risk to some degree and, most notably, attenuating the long-term risk reduction associated with transplantation.

Limitations of this study include the retrospective design. We were unable to objectively confirm or grade severity of HF diagnoses based on the use of Medicare claims as binary outcome measures, and the ICD9 coding scheme does not distinguish uremia as a cause of HF. Notably, the claims-based algorithm employed was recently shown to have very good sensitivity for detection of clinically diagnosed HF events in a validation study among a similar population [17], but misclassification of other conditions such as primary fluid retention with HF diagnosis codes cannot be excluded. Claims data for beneficiaries of insurance systems other than Medicare are not captured in the USRDS and our results may not generalize to privately insured patients. However, as Medicare is the single largest payer for end-stage renal disease services in the United States due to disease-specific entitlement, sampling of Medicare beneficiaries captures a large and relevant portion of the target population. The USRDS registry lacks quantitative information on clinical parameters such as blood pressure, cardiac ejection fractions, laboratory values such as hemoglobin, and the use of cardiovascular medications. Because follow-up in the registry is not protocol based, there is potential for ascertainment bias. In particular, early monitoring in the peri-transplant period may account for some of the increase in HF diagnoses early after transplant compared to waiting.

In conclusion, in this large retrospective study of Medicare-insured kidney transplant candidates, we found that the incidence and prevalence of HF increases during the waiting period for an allograft. Kidney transplantation is associated with a brief rise in HF risk early following transplant compared to risk in patients who remained on the waiting list. However, both deceased and living donor transplants are associated with significant long-term reductions in HF risk. There is variation in the benefit of transplantation on HF risk according to candidate

BMI – while HF risk is reduced in obese patients in the long-term after kidney transplant, the benefit is not as much as for non-obese patients. There is need for close monitoring and for new strategies to reduce HF risk in obese ESRD patients before and after transplant.

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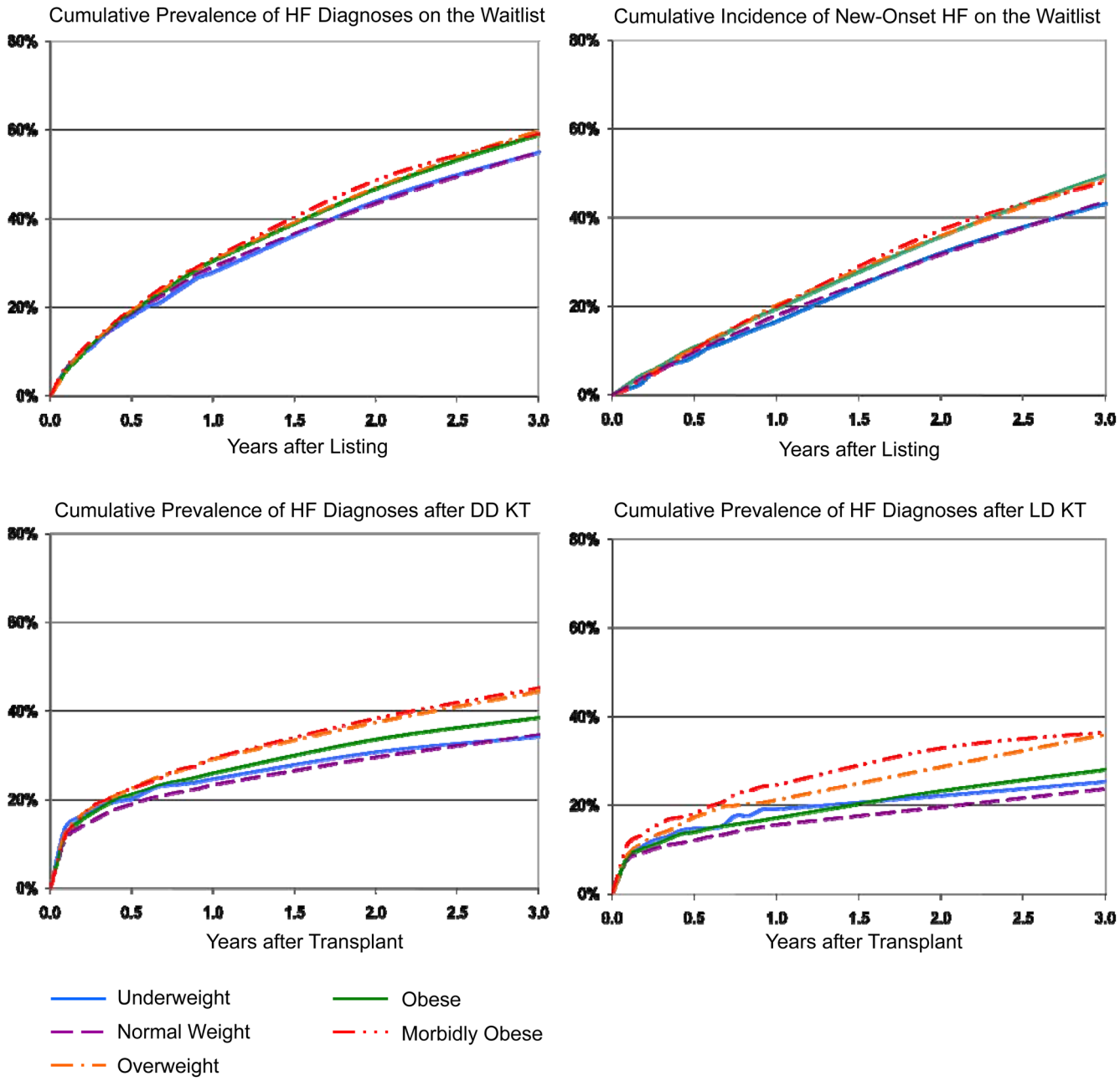

Figure 1. Frequency of heart failure diagnoses after kidney transplant listing and after transplantation, according to listing BMI category

DD, deceased donor; HF, heart failure; LD, living donor; KT, kidney transplant

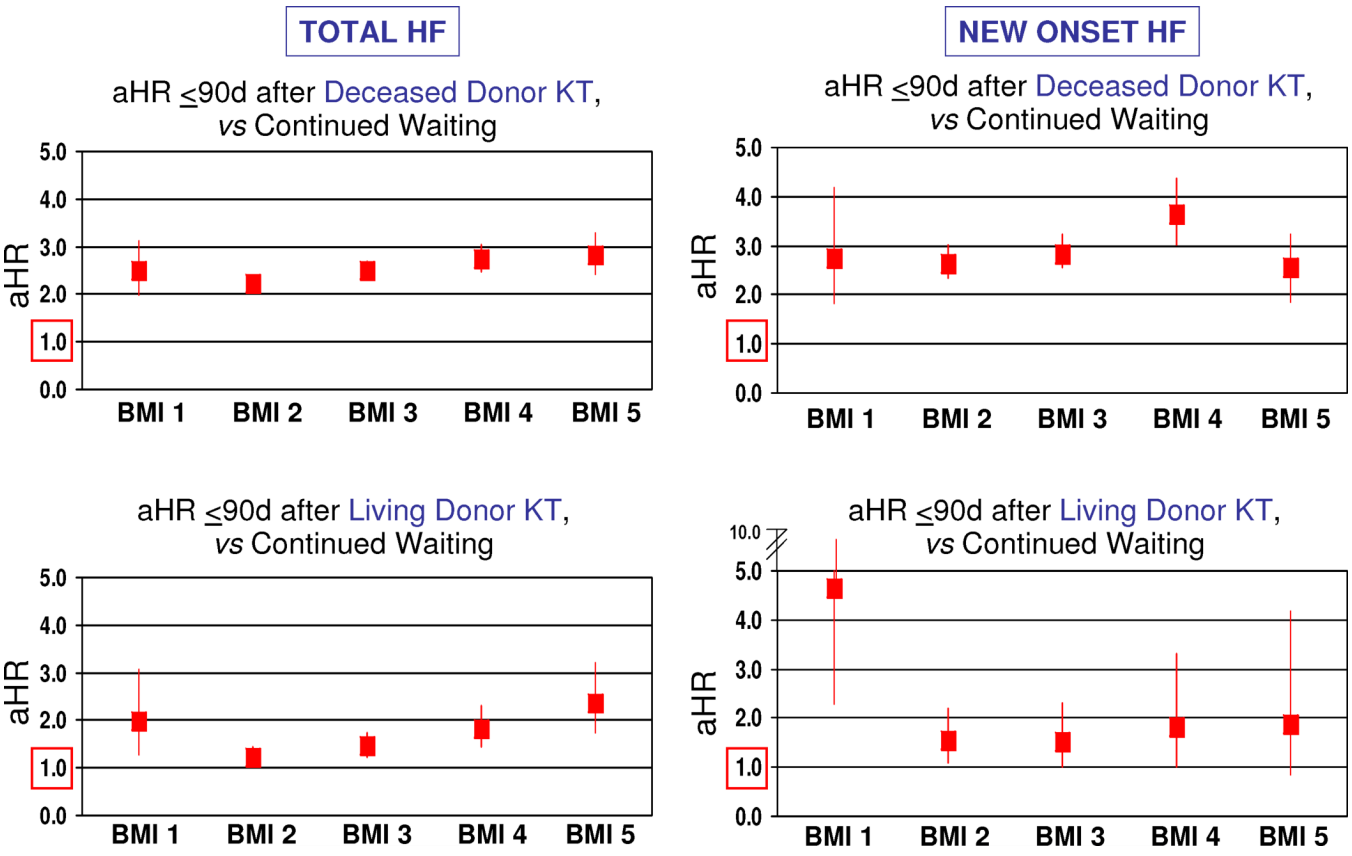

Figure 2. Early increases in heart failure risk after kidney transplant comparing to waiting, by candidate BMI and donor type. *

* Transplant modeled as a time-dependent predictor of HF after listing in stratified multivariable regression. Models were adjusted for baseline patient traits and comorbidities as listed in Tables 1 and 2. Reference groups are patients in a given BMI category who remain without transplant. BMI group by WHO: 1-Underweight (<18.5); 2-Normal weight (18.5 to <25); 3-Overweight (25 to <30); 4-Obese (30 to <35); 5-Morbidly obese (≥35).

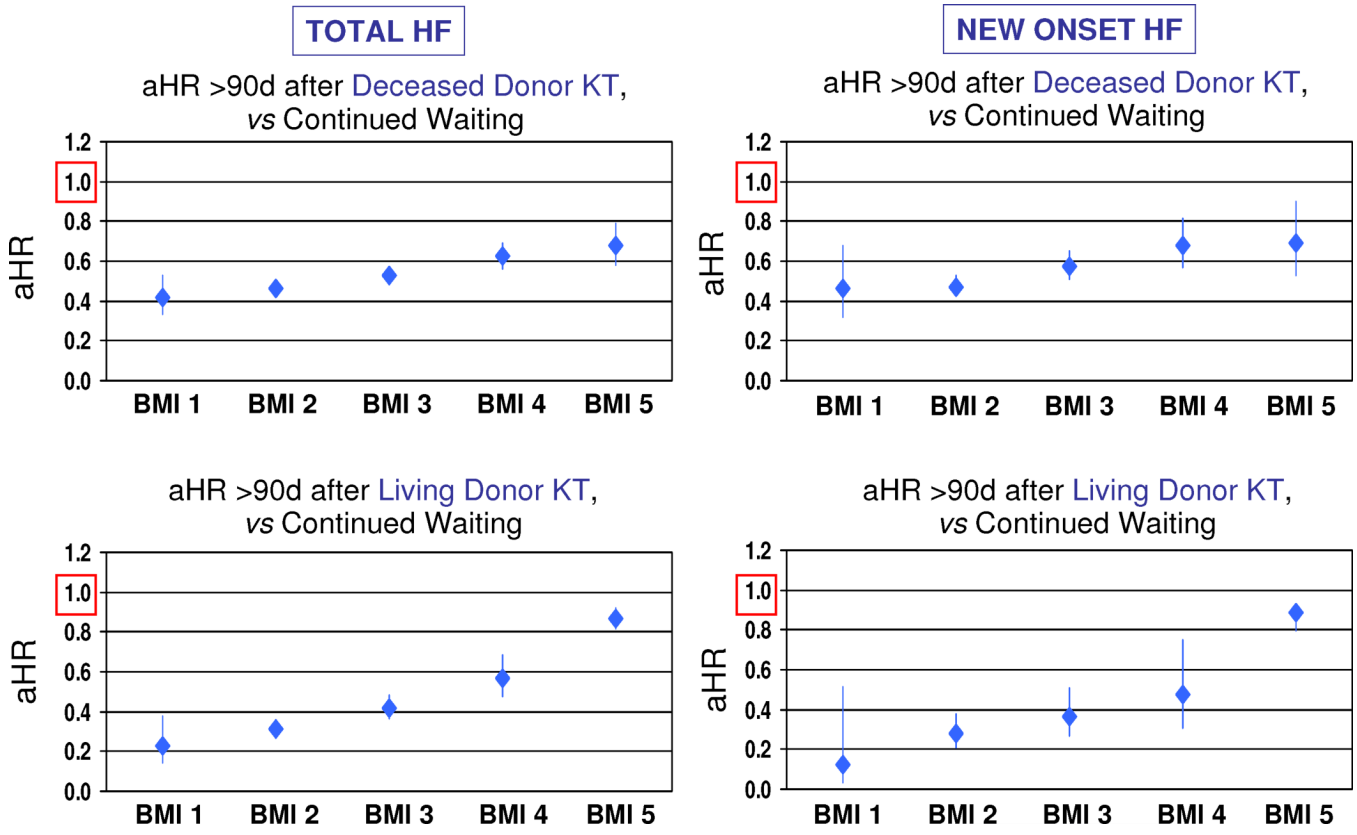

Figure 3. Late reductions in heart failure risk after kidney transplant comparing to waiting, by candidate BMI and donor type

* Transplant modeled as a time-dependent predictor of HF after listing in stratified multivariable regression. Models were adjusted for baseline patient traits and comorbidities as listed in Tables 1 and 2. Reference groups are patients in a given BMI category who remain without transplant. BMI group by WHO: 1-Underweight (<18.5); 2-Normal weight (18.5 to <25); 3-Overweight (25 to <30); 4-Obese (30 to <35); 5-Morbidly obese (≥35).

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Table 1

Baseline characteristics of the full study cohort at listing for kidney transplantation.

Baseline Characteristics	Full Sample of Candidates (N=67,591)	Underweight (BMI <18.5) (N=2,473)	Normal weight (BMI 18.5 to<25) (N=27,274)	Overweight (BMI 25 to <30) (N=21,678)	Obese (BMI 30 to <35) (N=10,970)	Morbidly Obese (BMI ≥35) (N=5,196)
	n (%)					
Age at listing (years)	§					
18–30	8,549 (12.6)	728 (29.4)	4,500 (16.5)	1,877 (8.7)	903 (8.2)	541 (10.4)
31–45	19,845 (29.4)	840 (34.0)	8,818 (32.3)	5,646 (26.0)	2,864 (26.1)	1,677 (32.3)
46–60	25,187 (37.3)	637 (25.8)	9,038 (33.1)	8,589 (39.6)	4,708 (42.9)	2,215 (42.6)
> 60	14,010 (20.7)	268 (10.8)	4,918 (18.0)	5,566 (25.7)	2,495 (22.7)	763 (14.7)
Female gender	27,543 (40.8) §	1,506 (60.9)	11,047 (40.5)	7,454 (34.4)	4,793 (43.7)	2,743 (52.8)
Race	§					
Black	23,076 (34.1)	653 (26.4)	8,497 (31.2)	7,508 (34.6)	4,177 (38.1)	2,241 (43.1)
White	39,416 (58.3)	1,483 (60.0)	16,237 (59.5)	12,787 (59.0)	6,183 (56.4)	2,726 (52.5)
Other	5,099 (7.5)	337 (13.6)	2,540 (9.3)	1,383 (6.4)	610 (5.6)	229 (4.4)
Hispanic ethnicity	11,427 (16.9) §	362 (14.6)	4,511 (16.5)	4,047 (18.7)	1,790 (16.3)	717 (13.8)
Cause of ESRD	§					
Diabetes	19,983 (29.6)	328 (13.3)	6,476 (23.7)	7,037 (32.5)	4,177 (38.1)	1,965 (37.8)
Hypertension	16,773 (24.8)	469 (19.0)	6,663 (24.4)	5,717 (26.4)	2,674 (24.4)	1,250 (24.1)
Glomerulonephritis	15,561 (23.0)	737 (29.8)	6,885 (25.2)	4,589 (21.2)	2,229 (20.3)	1,121 (21.6)
Other	15,274 (22.6)	939 (38.0)	7,250 (26.6)	4,335 (20.0)	1,890 (17.2)	860 (16.6)
Duration of dialysis prior to listing	§					
Not on dialysis	24,604 (34.6)	756 (30.6)	8,979 (32.9)	8,042 (37.1)	4,405 (40.2)	2,422 (46.6)
1–12 months	15,004 (22.2)	519 (21.0)	6,197 (22.7)	4,957 (22.9)	2,372 (21.6)	959 (18.5)
13–24 months	8,678 (12.8)	235 (9.5)	3,448 (12.6)	2,902 (13.4)	1,519 (13.9)	574 (11.1)
≥25 months	18,892 (27.9)	939 (38.0)	8,451 (31.0)	5,658 (26.1)	2,626 (23.9)	1,218 (23.4)
Unreported	413 (0.6)	24 (1.0)	199 (0.7)	119 (0.6)	48 (0.4)	23 (0.4)
Dialysis modality at listing	§					
Peritoneal	5,548 (8.2)	197 (8.0)	2269 (8.3)	1850 (8.5)	908 (8.3)	324 (6.2)
Hemodialysis, none or unreported	62,043 (91.7)	2,276 (92.0)	25,005 (91.7)	, (91.5)	10,062 (91.7)	4,872 (93.8)
Comorbidities						

Baseline Characteristics	Full Sample of Candidates (N=67,591)	Underweight (BMI <18.5) (N=2,473)	Normal weight (BMI 18.5 to<25) (N=27,274)	Overweight (BMI 25 to <30) (N=21,678)	Obese (BMI 30 to <35) (N=10,970)	Morbidly Obese (BMI ≥35) (N=5,196)
Coronary disease or myocardial infarction	3117 (4.6) §	43 (1.7)	983 (3.6)	1,228 (5.7)	673 (6.1)	190 (3.7)
Cerebrovascular disease	1,768 (2.6) ‡	55 (2.2)	674 (2.5)	637 (2.9)	290 (2.6)	112 (2.2)
Peripheral vascular disease	2,770 (4.1) §	62 (2.5)	1029 (3.8)	968 (4.5)	509 (4.6)	202 (3.9)
Tobacco use	1,459 (2.2) §	65 (2.6)	701 (2.6)	439 (2.0)	180 (1.6)	74 (1.4)
Alcohol dependence	311 (0.5) ‡	11 (0.4)	141 (0.5)	111 (0.5)	36 (0.3)	12 (0.2)
Listing year	§					
1995–1998	24,604 (36.4)	1,057 (42.7)	10,957 (40.2)	7,660 (35.3)	3,377 (30.8)	1,553 (29.9)
1999–2001	20,224 (29.9)	767 (31.0)	7,925 (29.1)	6,522 (30.1)	3,372 (30.7)	1,638 (31.5)
2002–2004	22,763 (33.7)	649 (26.2)	8,392 (30.8)	7,496 (35.6)	4,221 (38.5)	2,005 (38.6)

BMI, body mass index; ESRD, end-stage renal disease

Percentages reflect proportions within the full sample or BMI category with the indicated demographic or clinical traits (“column percentages”).

P-value for Chi-square test of differences in distributions of clinical characteristics according to BMI category:

‡ 0.002–0.01;

§ <0.001

Table 2

Baseline characteristics of the sample without heart failure before listing for kidney transplantation*.

Baseline Characteristics	Candidates Without HF before Listing (N=21,120)	Underweight (BMI <18.5) (N=811)	Normal weight (BMI 18.5 to<25) (N=8,596)	Overweight (BMI 25 to <30) (N=6,714)	Obese (BMI 30 to <35) (N=3,393)	Morbidly Obese (BMI ≥35) (N=1,606)
	n (%)					
Age at listing (years)	§					
18–30	2,973 (14.1)	265 (32.7)	1,526 (17.8)	644 (9.6)	315 (9.3)	223 (13.9)
31–45	6,884 (32.6)	283 (34.9)	3,031 (35.3)	1,991 (29.7)	1,033 (30.5)	546 (34.0)
46–60	7,744 (36.7)	198 (24.4)	2,804 (32.6)	2,688 (40.0)	1,381 (40.7)	673 (41.9)
> 60	3,519 (16.7)	65 (8.0)	1,235 (14.4)	1,391 (20.7)	664 (19.6)	164 (10.2)
Female gender	8,827 (41.8) §	512 (63.1)	3,474 (40.4)	2,378 (35.4)	1,568 (46.2)	895 (55.7)
Race	§					
Black	7,648 (36.2)	209 (25.8)	2,792 (32.5)	2,497 (37.2)	1,411 (41.6)	739 (46.0)
White	11,873 (56.2)	490 (60.4)	5,006 (58.2)	3,801 (56.6)	1,780 (52.5)	796 (49.6)
Other	1,599 (7.6)	112 (13.8)	798 (9.3)	416 (6.2)	202 (6.0)	71 (4.4)
Hispanic ethnicity	3,776 (17.9) §	130 (16.0)	1,537 (17.9)	1,336 (19.9)	562 (16.6)	211 (13.1)
Cause of ESRD	§					
Diabetes	4,971 (23.5)	99 (12.2)	1,639 (19.1)	1,751 (26.1)	1,009 (29.7)	474 (29.5)
Hypertension	5,528 (26.2)	150 (18.5)	2,175 (25.3)	1,858 (27.7)	925 (27.3)	420 (26.2)
Glomerulonephritis	5,399 (25.6)	257 (31.7)	2,351 (27.4)	1,630 (24.3)	766 (22.6)	395 (24.6)
Other	5,221 (24.7)	305 (37.6)	2,431 (28.3)	1,475 (22.0)	693 (20.4)	317 (19.7)
Duration of dialysis prior to listing	§					
Not on dialysis	7,665 (36.3)	249 (30.7)	2,800 (32.6)	2,495 (37.2)	1,376 (40.6)	745 (46.4)
1–12 months	590 (2.8)	18 (2.2)	265 (3.1)	192 (2.9)	89 (2.6)	26 (1.6)
13–24 months	4,457 (21.1)	119 (14.7)	1,764 (20.5)	1,503 (22.4)	784 (23.1)	287 (17.9)
≥25 months	8,238 (39.0)	412 (50.8)	3,682 (42.8)	2,478 (36.9)	1,130 (33.3)	536 (33.4)
Unreported	170 (0.8)	13 (1.6)	85 (1.0)	46 (0.7)	14 (0.4)	12 (0.8)
Dialysis modality at listing						
Peritoneal	1,772 (8.4)	77 (9.5)	712 (8.3)	586 (8.7)	290 (8.6)	107 (6.7)
Hemodialysis, none or unreported	19,348 (91.2)	734 (90.5)	7,884 (91.7)	6,128 (91.3)	3103 (91.5)	1,499 (93.3)
Comorbidities						

Baseline Characteristics	Candidates Without HF before Listing (N=21,120)	Underweight (BMI <18.5) (N=811)	Normal weight (BMI 18.5 to<25) (N=8,596)	Overweight (BMI 25 to <30) (N=6,714)	Obese (BMI 30 to <35) (N=3,393)	Morbidly Obese (BMI ≥35) (N=1,606)
Coronary disease or myocardial infarction	425 (2.0) †	4 (0.5)	120 (1.4)	177 (2.6)	90 (2.7)	34 (2.1)
Cerebrovascular disease	467 (2.2)	19 (2.3)	197 (2.3)	161 (2.4)	62 (1.8)	28 (1.7)
Peripheral vascular disease	616 (2.9) ‡	12 (1.5)	241 (2.8)	238 (3.5)	83 (2.5)	42 (2.6)
Tobacco use	391 (1.8) ‡	15 (1.9)	187 (2.2)	122 (1.8)	53 (1.6)	14 (0.9)
Alcohol dependence	86 (0.4) ‡	1 (0.1)	46 (0.5)	31 (0.5)	7 (0.2)	1 (0.1)
Listing year	§					
1995–1998	8,154 (38.6)	389 (48.0)	3,638 (42.3)	2,489 (37.1)	1,112 (32.8)	526 (32.8)
1999–2001	6,217 (29.4)	226 (27.9)	2,451 (28.5)	2,053 (30.6)	1,005 (29.6)	482 (30.0)
2002–2004	6,749 (32.0)	196 (24.2)	2,507 (29.2)	2,172 (32.4)	1,276 (37.6)	598 (37.2)

BMI, body mass index; ESRD, end-stage renal disease

Percentages reflect proportions within the full sample or BMI category with the indicated demographic or clinical traits (“column percentages”).

* Restricted to patients with one-year of continuous Medicare coverage before listing and no indication of pre-listing HF.

P-value for Chi-square test of differences in distributions of clinical characteristics according to BMI category:

† 0.02–0.05;

‡ 0.002–0.01;

§ <0.001

Table 3

Associations of kidney transplantation with heart failure risk compared to waiting within gender and race-stratified sub-groups.*

Heart failure after listing in the full cohort according to candidate gender

	aHR ≤90d after KT vs Waiting		aHR >90d after KT vs Waiting	
	Men (N=40,048)	Women (N=27,543)	Men (N=40,048)	Women (N=27,543)
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Deceased Donor KT				
Underweight	3.56 (2.62–4.84)§	2.35 (1.74–3.16)§	0.56 (0.41–0.75)‡	0.40 (0.30–0.52)§
Normal weight	2.27 (2.08–2.47)§	2.27 (2.04–2.52)§	0.43 (0.39–0.46)§	0.51 (0.46–0.56)§
Overweight	2.41 (2.21–2.63)§	2.63 (2.34–2.97)§	0.50 (0.46–0.55)§	0.60 (0.54–0.67)§
Obese	2.58 (2.27–2.94)§	2.74 (2.37–3.17)§	0.61 (0.54–0.69)§	0.61 (0.54–0.70)§
Morbidly Obese	3.09 (2.50–3.81)§	2.67 (2.15–3.31)§	0.69 (0.57–0.84)‡	0.71 (0.59–0.85)‡
Living Donor KT				
Underweight	0.96(0.31–2.97)	2.78 (1.75–4.41)§	0.23 (0.09–0.54)‡	0.25 (0.14–0.44)§
Normal weight	1.05 (0.82–1.34)	1.49 (1.17–1.89)‡	0.28 (0.23–0.34)§	0.36 (0.29–0.44)§
Overweight	1.33 (1.05–1.67)†	1.63 (1.22–2.16)‡	0.36 (0.30–0.44)§	0.52 (0.42–0.65)§
Obese	1.52 (1.10–2.10)†	2.08 (1.48–2.91)§	0.59 (0.47–0.74)§	0.54 (0.40–0.73)§
Morbidly Obese	3.00 (1.93–4.65)§	1.99 (1.31–3.02)‡	0.86 (0.78–0.96)‡	0.88 (0.81–0.94)‡

Total HF after listing according to candidate gender

	aHR ≤90d after KT vs Waiting		aHR >90d after KT vs Waiting	
	Men (N=12,293)	Women Men (N=8,827)	(N=12,293)	Women (N=8,827)
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Deceased Donor KT				
Underweight	3.50 (1.88–6.53)§	2.81 (1.69–4.67)§	0.57 (0.35–0.93)†	0.44 (0.29–0.69)‡
Normal weight	2.48 (2.11–2.90)§	2.74 (2.26–3.32)§	0.41 (0.35–0.47)§	0.57 (0.48–0.67)§
Overweight	2.76 (2.34–3.26)§	3.23 (2.59–4.02)§	0.56 (0.49–0.65)§	0.64 (0.53–0.77)§

Total HF after listing according to candidate gender

	aHR ≤90d after KT vs Waiting		aHR >90d after KT vs Waiting	
	Men (N=12,293)	Women Men (N=8,827)	(N=12,293)	Women (N=8,827)
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Obese	3.24 (2.56–4.12)§	3.74 (2.91–4.79)§	0.66 (0.54–0.81)§	0.65 (0.52–0.82)‡
Morbidly Obese	2.71 (1.70–4.31)§	2.75 (1.82–4.16)§	0.61 (0.42–0.89)‡	0.76 (0.56–1.03)
Living Donor KT				
Underweight	2.76 (0.39–19.60)	5.48 (2.60–11.56)§	---	0.18 (0.04–0.71)†
Normal weight	1.09 (0.63–1.89)	1.97 (1.25–3.11)‡	0.26 (0.18–0.40)§	0.29 (0.19–0.44)§
Overweight	1.52 (0.88–2.63)	1.67 (0.87–3.22)	0.28 (0.18–0.45)§	0.54 (0.34–0.83)‡
Obese	1.32 (0.55–3.17)	2.15 (0.96–4.79)	0.68 (0.42–1.10)	0.16 (0.05–0.50)‡
Morbidly Obese	0.80 (0.11–5.66)	3.10 (1.29–7.47)†	0.90 (0.76–1.08)	0.90 (0.78–1.05)

Total HF after listing according to candidate race

	aHR ≤90d after KT vs Waiting			aHR >90d after KT vs Waiting		
	White (N=39,416)	Black (N=23,076)	Other (N=5,099)	White (N=39,416)	Black (N=23,076)	Other (N=5,099)
	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)	aHR (95% CI)
Deceased Donor KT						
Underweight	2.89 (2.24–3.72)§	2.82 (1.79–4.42)§	1.95 (0.81–4.71)	0.39 (0.30–0.50)§	0.74 (0.52–1.05)	0.33 (0.14–0.80)†
Normal weight	2.22 (2.04–2.41)§	2.28 (2.01–2.58)§	2.71 (2.12–3.47)§	0.44 (0.40–0.47)§	0.50 (0.45–0.56)§	0.47 (0.36–0.61)§
Overweight	2.33 (2.13–2.55)§	2.77 (2.45–3.13)§	3.00 (2.17–4.16)§	0.50 (0.46–0.55)§	0.61 (0.54–0.68)§	0.55 (0.39–0.77)‡
Obese	2.58 (2.28–2.91)§	2.79 (2.37–3.29)§	2.72 (1.60–4.64)‡	0.55 (0.49–0.62)§	0.75 (0.65–0.87)‡	0.45 (0.25–0.79)‡
Morbidly Obese	2.89 (2.39–3.49)§	2.93 (2.28–3.76)§	1.50 (0.37–6.02)	0.70 (0.59–0.83)§	0.75 (0.60–0.93)‡	---
Living Donor KT						
Underweight	2.37 (1.45–3.87)‡	2.33 (0.87–6.21)	0.94 (0.13–6.67)	0.19 (0.10–0.37)§	0.49 (0.22–1.09)	0.13 (0.02–0.94)†
Normal weight	1.24 (1.02–1.52)†	1.24 (0.84–1.82)	1.26 (0.63–2.53)	0.31 (0.27–0.37)§	0.37 (0.27–0.49)§	0.11 (0.04–0.29)§
Overweight	1.31 (1.05–1.63)†	1.81 (1.28–2.56)‡	1.62 (0.72–3.62)	0.38 (0.32–0.45)§	0.53 (0.40–0.69)§	0.47 (0.25–0.88)†

Total HF after listing according to candidate race

	aHR ≤90d after KT vs Waiting			aHR >90d after KT vs Waiting		
	White (N=39,416)	**Black (N=23,076)**	**Other (N=5,099)**	**White (N=39,416)**	**Black (N=23,076)**	**Other (N=5,099)**
	aHR (95% CI)	**aHR (95% CI)**	**aHR (95% CI)**	**aHR (95% CI)**	**aHR (95% CI)**	**aHR (95% CI)**
Obese	1.74 (1.32–2.30)§	1.73 (1.07–2.78)†	1.94 (0.62–6.06)	0.57 (0.46–0.71)§	0.55 (0.38–0.80)‡	0.64 (0.24–1.72)
Morbidly Obese	2.47 (1.73–3.51)§	2.38 (1.32–4.31)‡	---	0.88 (0.82–0.94)‡	0.87 (0.78–0.97)†	---

New-onset heart failure after listing according to candidate race (limited to candidates without HF before listing)

	aHR ≤90d after KT vs Waiting			aHR >90d after KT vs Waiting		
	White (N=11,873)	**Black (N=7,648)**	**Other (N=1,599)**	**White (N=11,873)**	**Black (N=7,648)**	**Other (N=1,599)**
	aHR (95% CI)	**aHR (95% CI)**	**aHR (95% CI)**	**aHR (95% CI)**	**aHR (95% CI)**	**aHR (95% CI)**
Deceased Donor KT						
Underweight	3.10 (1.95–4.93)§	2.81 (1.17–6.78)†	3.02 (0.74–12.28)	0.40 (0.26–0.61)§	0.88 (0.50–1.56)	0.37 (0.09–1.52)
Normal weight	2.59 (2.22–3.02)§	2.43 (1.93–3.05)§	3.04 (1.96–4.72)§	0.45 (0.39–0.51)§	0.50 (0.41–0.60)§	0.49 (0.32–0.76)‡
Overweight	2.58 (2.16–3.08)§	3.49 (2.82–4.31)§	3.61 (2.00–6.54)§	0.55 (0.48–0.64)§	0.67 (0.55–0.81)§	0.47 (0.24–0.91)†
Obese	3.95 (3.19–4.89)§	2.78 (2.04–3.78)§	3.13 (1.27–7.69)	† 0.56 (0.45–0.69)§	0.86 (0.68–1.08)	0.38 (0.14–1.05)
Morbidly Obese	2.72 (1.82–4.08)§	2.77 (1.69–4.54)§	3.04 (0.42–22.23)	0.69 (0.51–0.93)†	0.74 (0.51–1.05)	---
Living Donor KT						
Underweight	6.43 (3.20–12.90)§	---	---	0.18 (0.05–0.74)†	---	---
Normal weight	1.32 (0.86–2.03)	1.91 (0.95–3.83)	2.08 (0.66–6.53)	0.25 (0.18–0.36)§	0.37 (0.21–0.66) ‡	0.23 (0.06–0.95)†
Overweight	1.21 (0.67–2.18)	2.80 (1.54–5.07)‡	---	0.31 (0.20–0.47)§	0.64 (0.40–1.04)	---
Obese	1.84 (0.92–3.70)	1.58 (0.51–4.90)	---	0.46 (0.27–0.79)‡	0.47 (0.21–1.04)	0.45 (0.06–3.20)
Morbidly Obese	1.80 (0.67–4.79)	3.11 (0.78–12.45)	---	0.92 (0.82–1.04)	0.78 (0.53–1.15)	---

[*] Transplant modeled as a time-dependent predictor of HF after listing in multivariable regression within indicated gender and racial groups, adjusted for baseline patient traits and comorbidities as listed in Tables 1 and 2. Gender was excluded as a covariate in the gender-stratified analyses; race was excluded as a covariate in the race-stratified analyses. Reference groups for the aHR are patients in a given BMI category who remain without transplant. BMI group by WHO: 1-Underweight (<18.5); 2-Normal weight (18.5 to <25); 3-Overweight (25 to <30); 4-Obese (30 to <35); 5-Morbidly obese (≥35).

[†] P-value for statistical significance compared to reference: 0.02–0.05;

[‡] 0.002–0.01;

[§] <0.001

"--- " Not evaluable due to insufficient events within this category.