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Higher recipient body mass index is associated with post-transplant delayed kidney graft function

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Abstract

Delayed graft function (DGF) complicates kidney allograft outcomes in the immediate post-transplantation period. We hypothesized that in hemodialysis patients, high pre-transplant body mass index (BMI) is associated with higher risk of DGF.

Linking 5-year hemodialysis patient data of a large dialysis organization to the Scientific Registry of Transplant Recipients, we identified 11,836 hemodialysis patients who underwent kidney transplantation during 7/2001-6/2007. We conducted multivariate logistic regression analyses to assess the association between pre-transplant BMI and post-transplant DGF.

Patients were 49±14 (mean±SD) years old, had a BMI of 26.8±6.0 kg/m², and included 38% women, 27% Blacks and 26% diabetics. After adjusting for relevant covariates, pre-transplant BMI remained an independent predictor of DGF. One SD increase in pre-transplant BMI was associated with a 35% higher risk of DGF (OR=1.35; 95% confidence interval [CI]: 1.27-1.44). Compared to patients with pre-transplant BMI of 22-24.99 kg/m², patient with overweight (BMI

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Relevant Potential Conflict of Interest:

Dr. Krishnan is an employee of DaVita. Dr. Kalantar-Zadeh is the medical director of DaVita Harbor-UCLA/MFI in Long Beach, CA. Other authors have not declared any conflict of interest.

25-29.99 kg/m²), mild obesity (BMI 30-34.99 kg/m²) and moderate to severe obesity (BMI ≥ 35 kg/m²) had 30%, 42% and 118% higher risks of DGF, respectively (p < 0.05). Similar associations were observed in all patients subgroups.

Pre-transplant overweight/obesity is associated with incrementally higher risk of DGF.

Keywords

Pre-transplant weight; delayed graft function; kidney transplantation; obesity; overweight; body mass index; overnutrition; weight reduction

Introduction

Delayed graft function (DGF) is a well-known complication affecting kidney allograft outcomes in the immediate post-transplantation period and is defined as the need for at least one session of dialysis treatment in the first week after receiving a kidney transplant.[1] DGF is attributed to ischemia-reperfusion and immunological injury of the graft.[2] The prevalence of DGF varies from 4% to 10% in living donor [2] and 5% to 50% in deceased donor kidney transplants.[3-7] The occurrence of DGF may significantly complicate the immediate post-transplant management by increasing morbidity and mortality,[8, 9] prolonging patient hospitalization [10] and inflating health care costs.[10-12]

Overweight (body mass index [BMI] 25- < 30 kg/m²) and obesity (BMI > 30 kg/m²) at the time of kidney transplantation are common among North American dialysis patients.[13] Some studies report poorer long-term post-kidney transplant outcomes in obese dialysis patients [14-17] mainly due to cardiovascular complications,[18] whereas other studies have found no association between pre-transplant BMI and long-term post-transplant outcomes, [19-22] including our recent study in 10,090 kidney transplant recipients.[23] In contrast, pre-transplant obesity is usually associated with such untoward short-term complications as surgical wound infections or dehiscence.[24] More recent studies report that obese renal transplant recipients have higher risk of developing diabetes mellitus or diverse post-operative complications.[19, 22, 24-26] However, it is not known whether overweight or obesity has a negative impact on other short-term complications in particular DGF. To the best of our knowledge, only a small case-control study (n=80) by Espejo *et al* showed that obese patients have higher risk of DGF after kidney transplantation,[27] whereas Yamamoto *et al.* (n=28) found no meaningful association between obesity and DGF.[28] Obesity is associated with higher sympathetic activity,[29, 30] which, along with imminent administration of calcineurin inhibitors may lead to renal vasoconstriction and decreased kidney perfusion, resulting in DGF. Moreover, obesity is associated with longer operative time and longer ischemic time,[31] which is associated with elevated risk of DGF.[32, 33] Given these biologically plausible hypotheses and the foregoing inconsistent data, we sought to examine whether recipients' high BMI has a bearing on early post-transplant graft function in a large and contemporary, incident cohort of kidney transplant recipients throughout the United States. We hypothesized that higher pre-transplant BMI during the months immediately prior to kidney transplantation is associated with higher prevalence of DGF in post-transplant patient.

Results

The original 5-year (07/2001-06/2006) national database of all DaVita dialysis patients included 164,789 adult subjects. This database was linked via unique identifiers to the national SRTR registry that included all transplant waitlisted people and kidney transplant recipients until 06/2007 (Figure 1). Out of 37,766 DaVita dialysis patients who were identified in the SRTR database 17,629 had undergone one or more kidney transplantations during their life time, including 14,508 patients who had undergone their first kidney transplantation between 7/2001 and 7/2007. After excluding those without electronically recorded data (n=1), peritoneal dialysis patients (n=2092) subjects who lacked data from the baseline quarter or those with outlier values for age (> 99 or <16 years; n=579), there were 11,836 hemodialysis patients who met all inclusion and exclusion criteria and who subsequently underwent their first kidney transplantation during the observation period.

Table 1 compares the demographic, clinical, transplant related and pre-transplant laboratory characteristics of the patients with (n=2628) and without (n=9208) DGF. Patients with DGF were 2 years older and more likely to be diabetic or African-American or to have Medicare as their primary insurance. Patients with DGF had lower serum albumin and hemoglobin levels and were more likely to receive kidneys from deceased donors with longer cold ischemic time. Additionally, patients with DGF had a higher pre-transplant BMI by 1.2 kg/m² than those without DGF (Table 1).

Table 2 shows the results of multivariate logistic regression analyses. Pre-transplant BMI was an important predictor of DGF in univariate analysis. One standard deviation (SD=6.0 kg/m²) increase of pre-transplant BMI was associated with 30% higher risk of DGF (OR=1.30; 95%CI: 1.24-1.36). The association between pre-transplant BMI and the risk of DGF in the entire cohort are shown in Figure 2 and Figure S1 in the Appendix. After adjusting for case-mix and MICS variables, pre-transplant BMI remained an independent and significant predictor of DGF (Table 2). This association remained significant after adjusting for transplant related variables: one SD increase of pre-transplant BMI was associated with a 35% higher risk of DGF (OR=1.35; 95%CI: 1.27-1.45). Compared to patients with pre-transplant with BMI in high normal range (22-24.99 kg/m²) the patient groups with overweight (25-29.99 kg/m²), mild obesity (30-34.99 kg/m²), and moderate to severe obesity (>=35 kg/m²) had 30%, 42% and 118% higher risk of DGF in the fully adjusted model (p<0.05) (Figure 2). Patients with pre-transplant BMI higher than 35 kg/m² had 87% higher risks of DGF than individuals with pre-transplant BMI lower than 35 kg/m² (OR=1.87; 95%CI: 1.52-2.30). Qualitative similar results were found when different cut-off points for BMI were used (Table 2). The association of BMI with DGF was monotonously incremental when BMI was modeled as a continuous variable and using fractional polynomials and cubic splines (Figure S1). These associations persist in sensitivity analyses including after inclusion of peritoneal dialysis patients (Figure S2).

Similar associations were observed in all subgroups. Figure 3 shows fully adjusted OR (and 95%CI) of DGF associated with each SD higher pre-transplant BMI across various patient subgroups. The OR of DGF across all examined subgroups was greater than one, indicating a higher risk. Most interaction tests did not exhibit small p-values indicating lack of major

effect modification by the examined characteristics, except for diabetes and EDC. The association between pre-transplant BMI and DGF was stronger in non-diabetic patients and in recipients of an EDC kidney (Table S1). Of note, in deceased donor subgroup each SD increase of BMI was associated with 36 % risk of DGF (OR (95% CI): 1.36 (1.26-1.46)). In living donor subgroup each SD increase of BMI associated with 33 % (OR (95% CI): 1.33 (1.14-1.56)) risk of DGF. The interaction term was not significant ($p=0.88$) (Table S1).

Discussion

In 11,836 kidney transplant recipients with comprehensive pre- and post-transplant data, higher pre-transplant BMI during the last calendar quarter of hemodialysis treatment was associated with higher risk of DGE during the first post-transplant week. Compared to patients with pre-transplant BMI between 22-24.99 kg/m², the overweight and obese patients with higher pre-transplant BMI (25-29.99 kg/m², 30-34.99 kg/m², and ≥ 35 kg/m²) had incrementally higher risk, i.e., 30%, 42% and 118% higher risk of DGF, whereas lower BMI <22 kg/m² tended to show approximately 25% lower DGF risk. The associations between pre-transplant BMI and DGF were rather consistent across diverse demographic, clinical and laboratory subgroups. These findings may have important implications for pre-transplant management of waitlisted patients.

DGF is a common short-term post-transplant complication and occurs in 5% to 50% of all kidney transplant recipients. It is especially more frequent with deceased donor kidneys. [3-6] The well known deleterious effects of DGF in the immediate post-transplant period are multiple and include complications of the immediate post-transplant patient care in the hospital. However, there may be even long-term impact of DGF. Most,[34, 35] but not all[36, 37] studies report an association between DGF and reduced long-term graft survival rate. A systematic review reported that DGF is associated with a 41% increased risk of graft loss,[8] 38% increased risk of acute rejection in the first year and a higher serum creatinine concentration at 3.5 years of follow-up.[8]

Overweight and obesity are highly prevalent at the time of kidney transplantation.[13] Previous reports have described conflicting associations between BMI and various outcomes in kidney transplant recipients. Early studies showed higher risk of post-operative complications[31] and early surgical wound infections[24] in obese patients. Lentine *et al.* reported higher incidence of cardiovascular event including heart failure and atrial fibrillation and early postoperative complications in obese versus non-obese patients.[18] Several other studies, however, did not find any association between pre-transplant BMI and mortality.[19, 21, 22] Chang *et al.* reported that obesity per se was not associated with poorer kidney transplant outcomes, although it was associated with factors that led to poorer graft and patient survival.[38] Indeed, patients with a BMI ≥ 30 receiving single pediatric kidneys had better death-censored graft survival rates when compared to non-obese patients. [39] Zaydfudim *et al.* reported that pre-transplant overweight and obese status did not affect physical quality of life after kidney transplantation.[40]

In our study the association between pre-transplant BMI and the risk of DGF was rather linear, incremental, consistent across virtually subgroups and robust even after adjusting for

several important confounders. Only few studies examined the association between BMI and DGF and found conflicting or equivocal results. A small case-control study (n=80) showed the obese patients have higher risk of DGF after kidney transplantation,[27] whereas Yamamoto et al.(n=28) found no association between obesity and DGF.[28] These studies were likely underpowered and used an inconsistent definitions of DGF.

Several potential mechanisms may contribute to the observed associations. A biologically plausible explanation is that obesity is associated with longer operative time of longer and warm ischemic time,[31] which are per se risk factors of DGF.[32, 33] Obesity is associated with high sympathetic activity,[29, 30] which results in renal vasoconstriction. Moreover the prompt administration of calcineurin inhibitors after transplantation, probably in higher doses given overweight or obesity, may aggravate vasoconstriction and further compromise graft perfusion, increasing the risk of DGF. Another potential explanation is the linkage between obesity and increased pro-thrombotic activity and endothelial dysfunction.[41] Body fat mass, in particular central obesity, is associated with higher levels of thrombin generation. [42, 43] Obesity is also a risk factor for venous thrombo-embolic disease. [44] Increased pro-thrombotic activity and endothelial dysfunction may contribute to the risk of graft micro-thrombosis,[45] which per se may play an important role in DGF.[46]

There are potential limitations to our study. Like all observational studies, ours too cannot prove causality. Patients who were excluded from analyses were likely different from the included ones, but their proportion was relatively small. In the SRTR dataset more detailed data about immunosuppression therapy such as calcineurin inhibitor dose or blood level or the induction therapy, which may also have an effect on the risk of DGF, do not exist. Additional limitation is the uncertainty about the use of BMI as a measure of obesity. BMI per se may not be an appropriate measure to characterize nutritional status, body composition, obesity or muscle mass in dialysis patients.[47-52] To better characterize nutritional status, additional parameters such as waist circumference would be needed.[48, 50-52] To the best of our knowledge our study is the first examining the association between pre-transplant BMI and immediate post-transplant DGF in such a large and nationally representative patient population. Other strengths of our study include the high number of patients, the multilevel adjustments including for laboratory data, and the contemporary nature of the cohort (2001-20017).

Conclusions

In our large and contemporary national cohort of 11,836 kidney transplant recipients, pre-transplant BMI is associated with risk of DGF even after extensive multivariate adjustment. The association between pre-transplant BMI and DGF was consistent in all examined subgroups. Despite data indicating an obesity paradox with greater survival of overweight and obese hemodialysis patients,[47, 49, 53, 54] careful trials of closely supervised weight reduction may be indicated to examine whether immediate post-transplant outcomes including risk of DGF can be improved.

Methods

Patients

We linked data on all kidney transplant recipients listed in the *Scientific Registry of Transplant Recipients* (SRTR) up until June 2007 to a list of individuals with chronic kidney disease stage 5D, who underwent maintenance hemodialysis (MHD) treatment from July 2001 to June 2006 in one of the outpatient dialysis facilities of a US-based large dialysis organization (DaVita Inc, prior to its acquisition of former Gambro dialysis facilities). The study was approved by the Institutional Review Committees of both Los Angeles Biomedical Research Institute at Harbor-UCLA and DaVita Clinical Research. The study was conforming to the principles of the Declaration of Helsinki. Because of the large sample size, the anonymity of the patients studied and the non-intrusive nature of the research the requirement for informed consent was waived.

Clinical and Demographic Measures

The creation of the national DaVita MHD patient cohort has been described previously.[51, 54-57] Demographic data and details of medical history were collected, including information on age, gender, race, type of insurance, marital status, presence of diabetes, height, post-hemodialysis dry weight (to calculate averaged body mass index [BMI]) and dialysis vintage. Dialysis vintage was defined as the duration of time between the first day of dialysis treatment and the day of kidney transplantation.

To minimize measurement variability, all repeated measures for each patient during any given calendar quarter, i.e., over a 13-week or 3-month interval, up to the time of kidney transplantation, were averaged and the quarterly means in each of the 20 calendar quarters were used in our analyses. Each patient had up to 39 recoded post-hemodialysis weights corresponding thrice weekly MHD treatment. All values were averaged into one single quarterly value per patient per each calendar quarter. In the present study we used the average of a number of BMI measurement in the last quarter before transplantation.

After deleting extreme outliers (BMI<12 or >60 kg/m²) we divided pre-transplant BMI into six *a priori* selected categories or underweight (=<19.99 kg/m²), low normal weight (20-21.99 kg/m²), high normal weight (22-24.99 kg/m²), overweight (25-29.99 kg/m²), mild obesity (30-34.99 kg/m²), and moderate to severe obesity (>=35 kg/m²). These increments were consistent with our previous studies.[58]

Laboratory Measures

Blood samples were drawn using uniform techniques in all of the DaVita dialysis clinics and were transported to the DaVita Laboratory in Deland, Florida, typically within 24 hours. All laboratory values were measured by automated and standardized methods in the DaVita Laboratory. Most laboratory values were measured monthly, including serum urea, creatinine, albumin, calcium, phosphorus, bicarbonate, and total iron binding capacity (TIBC). Serum ferritin was measured at least quarterly. Hemoglobin was measured at least monthly in essentially all patients and weekly to bi-weekly in most patients. Most blood samples were collected *pre-dialysis* with the exception of the post-dialysis serum urea

nitrogen that was obtained to calculate urea kinetics. Kt/V (single pool) was calculated using urea kinetic modeling equations as described elsewhere.[56] Albumin-corrected calcium was calculated by subtracting 0.8 mg/dL for each g/dL serum albumin below 4.0 g/dL.[59]

Definition of DGF

DGF was defined as the need for any dialysis therapy in the first week after transplantation. [1]

Statistical Methods

Data were summarized using proportions, means (\pm standard deviation [SD]) or medians (interquartile range [IQR]) as appropriate. Categorical variables were analyzed with chi-square tests and continuous variables were compared using Student's t-tests or the Mann-Whitney U tests, Kruskal-Wallis H tests or ANOVA as appropriate. In all statistics two-sided tests were used and the results were considered statistically significant if p was <0.05 . Logistic regression models were employed to estimate the odds ratio (OR) (and 95% confidence interval [95%CI]) of post-transplant DGF based on pre-transplant BMI during the calendar quarter preceding the kidney transplantation.

For each analysis, four models were examined based on the level of multivariate adjustment: **(I)** An unadjusted model; **(II)** Case-mix adjusted models included age, gender, race-ethnicity (African Americans and other self-categorized Blacks, Non-Hispanic Whites, Asians, Hispanics and others), diabetes mellitus, dialysis vintage, primary insurance (Medicare, Medicaid, private and others), marital status (married, single, divorced, widowed and other or unknown), the standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dose as indicated by Kt/V (single pool), presence or absence of a dialysis catheter, and **(III)** Malnutrition-inflammation-complex syndrome (MICS) adjusted models which included all of the covariates in the case-mix model as well as 11 surrogates of nutritional status and inflammation, including 10 laboratory variables with known association with clinical outcomes in HD patients, i.e. nPCR as an indicator of daily protein intake, also known as the normalized protein nitrogen appearance (nPNA)[60], serum or blood concentrations of albumin, creatinine, TIBC, ferritin, phosphorus, calcium, bicarbonate, peripheral white blood cell count (WBC), lymphocyte percentage and hemoglobin; and **(IV)** Case-mix, MICS and transplant data adjusted models included all of the above plus 7 transplant-related variables: (1) donor type (deceased or living), (2) donor age, (3) panel reactive antibody (PRA) titer (last value prior to transplant), (4) number of HLA mismatches, (5) cold ischemia time, (6) transfusion before transplantation and (7) extended donor criteria (EDC) using standard definition (donor history of hypertension and/or serum creatinine of donor > 1.5 mg/dL and/or cause of death in donor is cerebrovascular event).

In sensitivity analyses, we reexamined all associations after 1,962 peritoneal dialysis patients were added to 11,836 hemodialysis patients, leading to a total sample size of 13,798 kidney transplanted recipients. Missing covariate data in the last (pre-transplant) calendar quarter were imputed by medians or means including from prior calendar quarters as appropriate. All analyses were carried out using STATA version 11.1 (STATA Corporation, College Station, TX).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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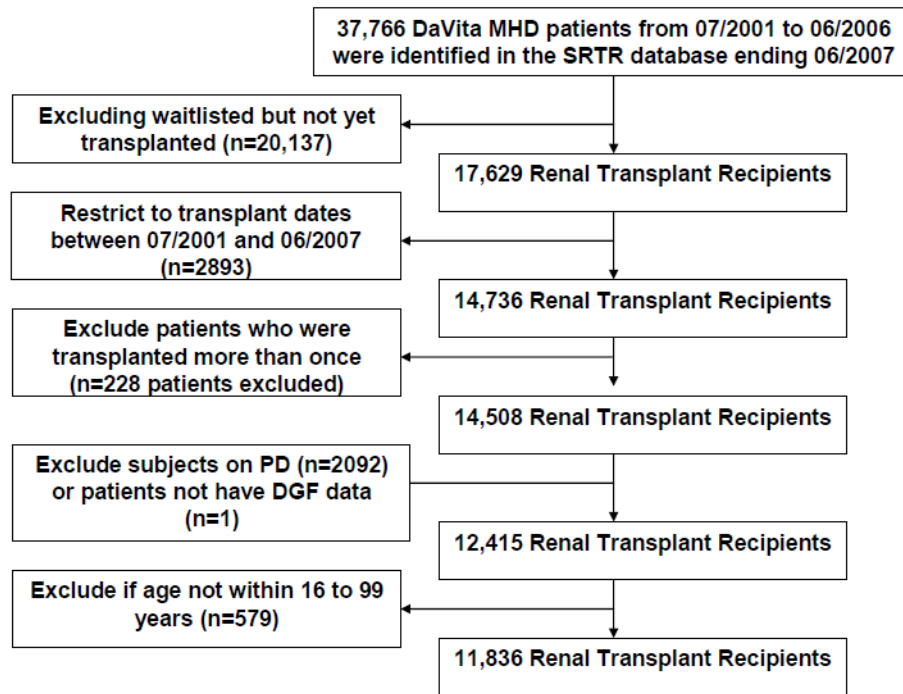


Figure 1.
Flow chart of the patient selection (see text)

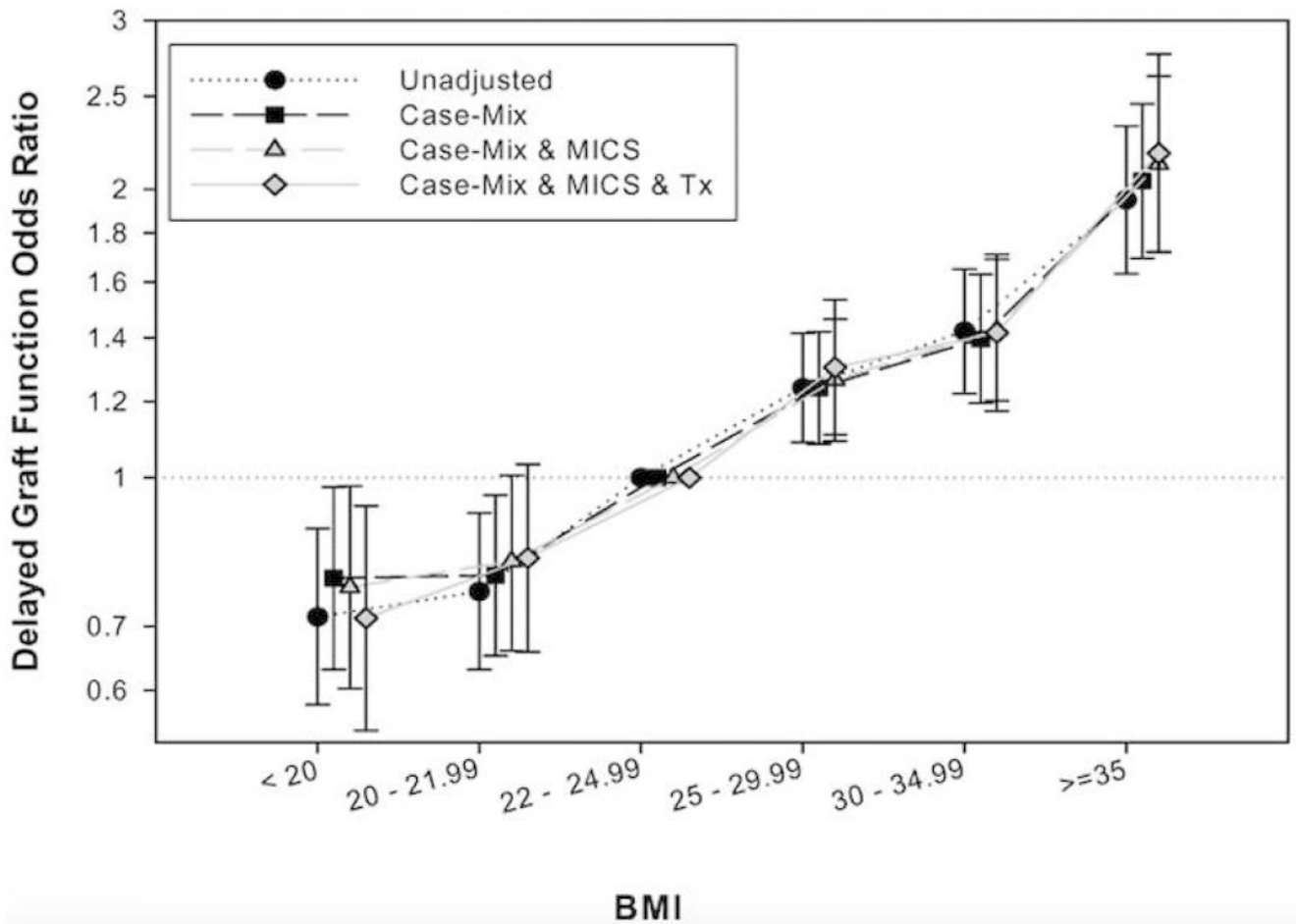


Figure 2. Multivariate analysis of logistic regression models showing pre-transplant BMI and OR (and 95% CI as error bars) of delayed graft function in four different models (Reference: BMI 22- 25 kg/m^2)

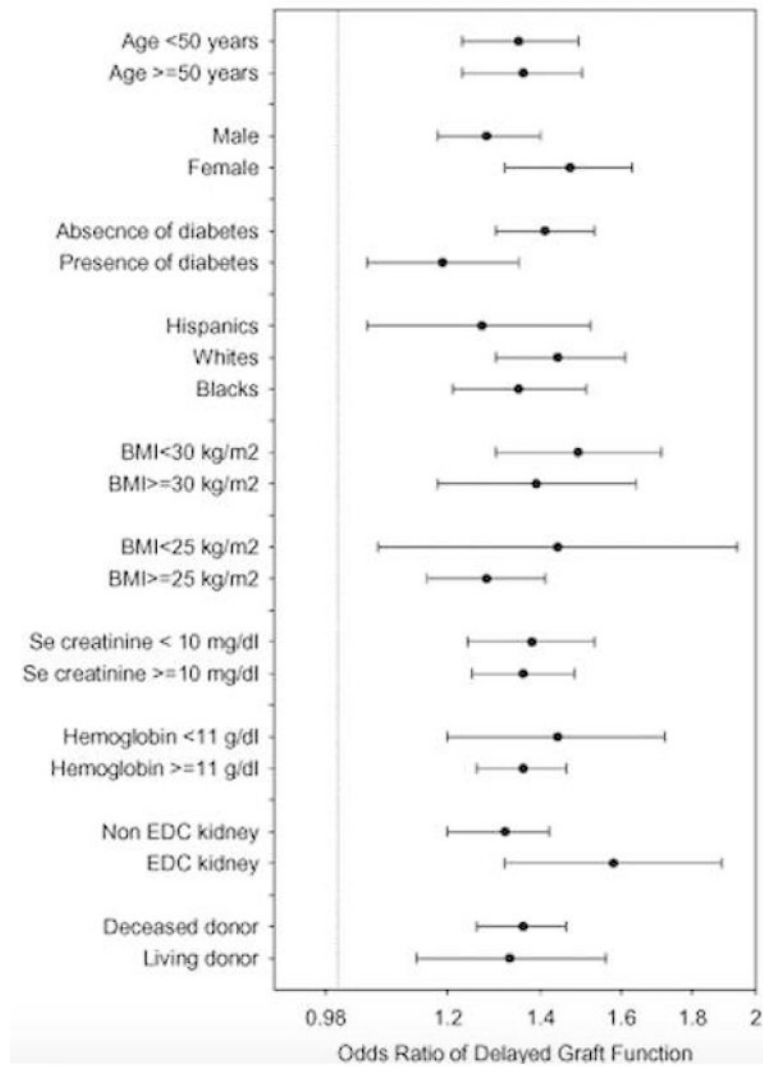


Figure 3. Multivariate analysis of fully adjusted (for case-mix, MICS and transplant covariates) logistic regression models showing pre-transplant BMI and OR (and 95% CI as error bars) of delayed graft function for each standard deviation higher BMI in different sub-group of patients

Table 1

Demographic, clinical and laboratory characteristics for 11,836 long-term hemodialysis patients who received kidney transplants. Data are from the last or second to last calendar quarter prior to transplantation. Values are in percentage or mean \pm SD or median (IQR), as appropriate

Variables	All	With DGF	Without DGF	p-value
N (%)	11,836 (100)	2,628 (22.2)	9,208 (77.8)	N/A
Age (years)	49 \pm 14	50 \pm 13	48 \pm 14	<0.001
Gender (% women)	38	34	39	<0.001
Diabetes mellitus (%)	26	29	26	<0.001
Race/Ethnicity (%)				
Whites	46	39	48	<0.001
African Americans	27	35	25	<0.001
Hispanics	14	14	14	0.85
Asians	4	3	4	0.01
Dialysis vintage time (%):				
<6 months	12	6	14	<0.001
6-24 months	28	19	31	<0.001
2-5 years	36	41	35	<0.001
>5 years	24	34	21	<0.001
Primary insurance (%)				
Medicare	52	59	50	<0.001
Medicaid	3	3	3	0.47
Private Insurance	16	14	17	0.003
Other	20	14	22	<0.001
Marital Status (%)				
Married	47	46	48	0.26
Divorced	6	6	6	0.65
Single	27	28	27	0.17
Widowed	3	3	3	0.98
BMI (kg/m ²)	26.8 \pm 6.0	28.0 \pm 6.7	26.4 \pm 5.7	<0.001
Kt/V (dialysis dose)	1.61 \pm 0.35	1.60 \pm 0.33	1.62 \pm 0.36	0.055
nPCR (g/kg/day)	1.05 \pm 0.25	1.06 \pm 0.25	1.05 \pm 0.26	0.01
Serum albumin (g/dL)	4.02 \pm 0.37	4.00 \pm 0.37	4.03 \pm 0.38	<0.001
creatinine (mg/dL)	10.6 \pm 3.2	11.1 \pm 3.1	10.5 \pm 3.2	<0.001
bicarbonate (mg/dL)	21.9 \pm 3.4	22.2 \pm 3.3	21.8 \pm 3.4	<0.001
TIBC (mg/dL)	212 \pm 40	208 \pm 39	213 \pm 41	<0.001
ferritin (ng/mL) *	469 (249-731)	534 (299-786)	448 (236-717)	<0.001
phosphorus (mg/dL)	5.95 \pm 1.54	5.97 \pm 1.57	5.94 \pm 1.53	0.41
calcium (mg/dL)	9.43 \pm 0.74	9.42 \pm 0.77	9.44 \pm 0.73	0.23

Variables	All	With DGF	Without DGF	p-value
Blood hemoglobin (g/dL)	12.3±1.2	12.2±1.3	12.3±1.2	0.001
WBC ($\times 10^3/l$)	6.8±2.0	6.9±2.1	6.8±2.1	0.24
Lymphocyte (%total WBC)	23±8	23±8	23±8	0.22
Pre-transplant transfusion (%)	31	36	30	<0.001
Number of HLA mismatch *	4 (3-5)	4 (2-5)	4 (3-5)	<0.001
PRA (%) *	0 (0-3)	0 (0-4)	0 (0-3)	0.21
Cold Ischemia time (hours) *	14 (4-22)	19 (12-25)	12 (2-20)	<0.001
EDC kidney (%)	19	23	17	<0.001
Donor type (% Living)	32	10	38	<0.001
Donor age (years)	39±15	42±15	38±15	<0.001

BMI: body mass index, EDC: Extended Donor Criteria, HLA: human leukocyte antigen, TIBC: total iron binding capacity; nPNA: normalized protein nitrogen appearance, PRA: panel reactive antibody (last value prior to transplant), WBC: white blood cell.

* median (IQR)

Table 2

Multivariate logistic regression models showing pre-transplant weight and BMI and their Odds Ratios and 95% CI for delayed graft function

Pre-transplant weight	Unadjusted		Case-mix adjusted*		Case-mix & MICS adjusted**		Case-mix & MICS & Transplant data adjusted***	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Weight (kg) (+1 Standard Deviation)	1.29 (1.24-1.35)	<0.001	1.32 (1.25-1.39)	<0.001	1.33 (1.25-1.41)	<0.001	1.34 (1.26-1.44)	<0.001
BMI (kg/m ²) (+1 Standard Deviation)	1.30 (1.24-1.36)	<0.001	1.29 (1.23-1.36)	<0.001	1.33 (1.26-1.41)	<0.001	1.35 (1.27-1.44)	<0.001
BMI>25(kg/m ²) vs BMI≤25 (kg/m ²) (ref.)	1.48 (1.44-1.75)	<0.001	1.53 (1.38-1.69)	<0.001	1.53 (1.37-1.72)	<0.001	1.57 (1.39-1.79)	<0.001
BMI>30(kg/m ²) vs BMI≤30 (kg/m ²) (ref.)	1.54 (1.39-1.71)	<0.001	1.51 (1.35-1.68)	<0.001	1.50 (1.33-1.69)	<0.001	1.48 (1.30-1.70)	<0.001
BMI>35(kg/m ²) vs BMI≤35 (kg/m ²) (ref.)	1.78 (1.53-2.08)	<0.001	1.82 (1.55-2.13)	<0.001	1.84 (1.53-2.21)	<0.001	1.87 (1.52-2.30)	<0.001
BMI>40 (kg/m ²) vs BMI≤40 (kg/m ²) (ref.)	2.25 (1.72-2.96)	<0.001	2.34 (1.77-3.10)	<0.001	2.51 (1.80-3.50)	<0.001	2.78 (1.88-4.12)	<0.001