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ORIGINAL ARTICLE

Early perioperative fluid overload is associated with adverse outcomes in deceased donor kidney transplantation

Hanying Jia[1,2,3,4,5], Fuhan Huang[6], Xing Zhang[1,2,3,4,5], Jun Cheng[1,2,3,4,5], Jianghua Chen[1,2,3,4,5] & Jianyong Wu[1,2,3,4,5]

1 Kidney Disease Center, College of Medicine, The First Affiliated Hospital, Zhejiang University, Hangzhou, China
2 Key Laboratory of Nephropathy, Hangzhou, China
3 Kidney Disease Immunology Laboratory, the Third-Grade Laboratory, State Administration of Traditional Chinese Medicine of China, Hangzhou, China
4 Key Laboratory of Multiple Organ Transplantation, Ministry of Health of China, Hangzhou, China
5 Institute of Nephropathy, Zhejiang University, Hangzhou, China
6 HuZhou Central Hospital, Affiliated Hospital of HuZhou Normal University, HuZhou, China

Correspondence
Jianyong Wu, Kidney Disease Center, the First Affiliated Hospital of Medicine College, Zhejiang University, Qingchun Road 79, Hangzhou 310003, China.
Tel./fax: +86 0571-87236189;
e-mail: wujianyong1964@zju.edu.cn

SUMMARY

Kidney transplant recipients are often treated with a large volume of infusion to attain adequate graft perfusion in the early perioperative period. However, it remains unknown whether this fluid therapy is renal responsive or a contributing factor to fluid overload complications. We conducted a retrospective cohort analysis of all recipients who received deceased donor kidney transplantation at an academic teaching hospital from January 2015 to April 2019. Our exposure of interest was early perioperative fluid balance. The primary outcome was graft function at 1, 6, and 12 months after transplantation. The secondary outcome was cardiopulmonary and gastrointestinal complications. Fluid balance was not significantly correlated with graft function in short- or long-term periods. Postoperative complications were higher in recipients with increased fluid balance. Delayed graft function was significantly related to cardiopulmonary and gastrointestinal complications. Cardiovascular disease and high BMI of recipients were strong risk factors for cardiopulmonary complications. Fluid overload was prevalent in the early perioperative period of kidney transplantation. It did not promote renal recovery, but was associated with a high risk of complications. Our findings might be a useful indicator to optimize the perioperative fluid management of kidney transplant recipients.

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Key words
fluid balance, graft function, kidney transplantation, perioperative complications

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Introduction

Kidney transplantation is considered as the best treatment for patients with end-stage kidney disease (ESKD), and early graft function is of utmost importance for the improvement of patient outcomes [1]. Various factors are associated with the recovery of renal function, including ischemia/reperfusion injury, allograft quality, dialysis vintage, and human leukocyte antigen (HLA) compatibility [2–5]. Most of these factors are no longer modifiable once the donated kidney has reached the implantation unit. Fluid management is one of the few manipulatable factors that has been recognized as an important measure for improving graft function [6–8]. Currently, there is a paucity of literature on the perioperative fluid management of patients undergoing kidney transplantation. This creates a dilemma for clinicians when they encounter a kidney transplant recipient with

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a high demand for fluid management. A questionnaire in current UK practice highlighted a high degree of heterogeneity regarding perioperative fluid therapy of kidney transplant recipients [9].

Previous studies have indicated that aggressive volume expansion targeting a mean arterial pressure (MAP) of >93 mmHg [10] and central venous pressure (CVP) of 15 mmHg [11] at the time of reperfusion was associated with better graft outcomes. The transplanted kidney is denervated and lacks neurogenic regulation of renal blood flow; moreover, vasodilation mediators accumulated in the ischemic period will further contribute to the potential decline in renal perfusion [12]. Therefore, maximal volume expansion for increasing renal perfusion is recommended in the perioperative care of renal transplant recipients [7,10,13].

Over the last few years, several studies have found an association between increased fluid administration or positive fluid balance (FB) and reduced renal recovery in critically ill patients [14–19]. Increased fluid intake (>1 l/day) in the early acute kidney injury (AKI) stage was an independent risk factor for progression to AKI stage III in the intensive care unit patients [17]. Similarly, positive FB (>2 l) at 48 h is increasingly associated with AKI development in severely injured trauma patients [19]. According to a meta-analysis of 22 studies, over 40% of critically ill patients are not fluid responsive [20]. Fluid resuscitation of patients who are not fluid responsive may cause tissue edema, damage the endothelial glycocalyx, and decrease oxygen delivery [21,22]. The kidney, an encapsulated organ, is particularly vulnerable to interstitial edema, which increases venous pressure and decreases the glomerular filtration rate. This was demonstrated by a study of 2 l intravenous infusion over 1 h to healthy volunteers, resulting in renal cortical edema and reduced renal perfusion as determined by MRI [23].

Kidney transplantation is a surgical procedure that involves ischemia-reperfusion injury, which also occurs in AKI and is further complicated by the interplay of donor and recipient factors, immune activation, transplanted kidney reperfusion, and denervation [24]. On the basis of previous evidence, increased fluid infusion may not be beneficial for renal recovery in patients with AKI and critically ill patients [15,17,19], and therefore, whether the concept of maximal hydration can improve immediate graft function in kidney transplantation needs to be re-evaluated.

Adverse outcomes of perioperative fluid overload have long been recognized in various clinical scenarios [25–29]. Patients undergoing major surgery with FB above 2000 ml intraoperatively were more likely to develop ICU-related complications and higher in-hospital mortality [25]. Chronic renal failure recipients usually have impaired cardiac function and reduced hemodynamic autoregulation ability [30]. Traditional fluid therapy based on maximal hydration to improve renal perfusion can expose these recipients to the risk of fluid overload, pulmonary edema, heart failure, and infections.

Severe multiorgan complications are associated with excessive fluid intake, while fluid restriction may confer risk to develop renal hypoperfusion. Therefore, it is essential to seek a balance between the benefits and harms of different aspects of fluid management in kidney transplant recipients. The above considerations raise the question of whether rapid, high volume fluid administration is beneficial for renal recovery and whether fluid overload is a risk factor for postoperative complications in this population. To the best of our knowledge, studies regarding the effect of early perioperative FB on kidney transplant recipients are scarce. Therefore, we conducted this retrospective cohort analysis to study early perioperative FB and its associated outcomes in deceased donor kidney transplant (DDKT) recipients.

Materials and methods

Data source and participants

This single-center, retrospective study was conducted at the First Affiliated Hospital, Zhejiang University. We conducted a retrospective data analysis on DDKT performed between January 2015 and April 2019. Perioperative data were obtained from the digital medical records of the patients. The data analyzed in this article will be shared on reasonable request to the corresponding author. All participants had to meet the following inclusion criteria: age over 18 years, first and single kidney transplantation. Patients who underwent transplantation from pediatric donors or experienced a second operation due to surgical complications (urinary, vascular, or wound-related complications) during the hospital stay were excluded. Participants were followed up until 1 year after transplantation. The study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (Approval No: 20196681), and informed consent for data sharing was obtained from patients included in the study. All donor kidneys in this study were procured for donation after the donor's death in accordance with the guidelines of

The National Program for Deceased Organ Donation in China. None of the transplanted kidneys were procured from prisoners. All kidney donations were voluntary, unpaid, and compliant with the Helsinki Declaration and Istanbul Declaration.

Measurement of exposure of interest

Exposure of interest was the FB from the start of the operation to 6:00 AM on the second postoperative day and included all intravenous infusion and oral intake. FB was calculated as follows: (fluid input-fluid output in milliliters)/hospital admission weight in kilograms*100%. Fluid output included urine output, fluid drainage, and volumes of stool and vomit.

Covariates

The following covariates were considered: (i) recipient factors such as age; sex; body mass index (BMI); history of hypertension, diabetes mellitus, and cardiovascular disease (CVD); dialysis duration; cause of ESKD; and immunosuppressive therapy; (ii) donor factors: donor type [donation after cardiac death (DCD); donation after brain death (DBD)], cause of death, donor age, sex, terminal serum creatinine (μmol/l), BMI, and comorbidities; and (iii) allograft/transplant factors: cold ischemia time (CIT) (in hours), warm ischemia time (WIT) (in minutes), and human leukocyte antigen (HLA) mismatches. MAP at the time of reperfusion was recorded. The use of diuretic and inotropic drugs within the perioperative period was recorded. Delayed graft function (DGF) was defined as the need for dialysis during the first week after transplantation.

Measurement of outcomes

Our primary outcome was the estimated glomerular filtration rate (eGFR), which was calculated using the CKD-EPI equation at 1, 6, and 12 months after transplantation. The secondary outcome was cardiopulmonary (CP) complications and gastrointestinal (GI) complications during hospitalization. The severity of complications was scored according to the Clavien-Dindo classification [31] (Table S1). Cardiac complications included new onset arrhythmia requiring treatment, congestive cardiac failure, acute coronary syndromes confirmed by an electrocardiography (ECG), or blood samples showing myocardial damage biomarkers with chest discomfort. Pulmonary complications were defined as pneumonia treated with antibiotic therapy or atelectasis requiring physiotherapy and respiratory failure [partial pressure of oxygen in the blood/fraction of inspired oxygen (PO_2/FiO_2) < 200]. Gastrointestinal complications included bowel obstruction, vomiting, or diarrhea more than three times a day.

Perioperative kidney transplant management

During the surgery, an infusion of Ringer's lactate solution was initiated to maintain a CVP of 8–15 mmHg and systolic blood pressure of 130–160 mmHg. If hypotension occurred and could not be corrected by fluid resuscitation or anesthesia adjustment, the recipients received one or more doses of dopamine or phenylephrine. Continuous fluid infusion based on urine volume was recommended to all recipients within 24 h after operation.

Statistical analysis

Categorical variables are described as frequencies and percentages, while continuous variables are reported as mean, standard deviation, or median, range. Categorical variables between different FB levels were analyzed by the chi-square test. Continuous variables between different FB levels were analyzed by the Kruskal-Wallis test or ANOVA as appropriate. We first grouped FB by quartiles into four categories (low, middle low, middle high, and high) and examined the association of FB as a categorical predictor with postoperative complications by using univariate logistic regression analysis. Variables that were considered to be clinically relevant or showed a univariate relationship with the outcome ($P < 0.1$) were entered into multivariate analysis. Multiple linear regression was performed to evaluate correlations between different FB groups and eGFR at 1, 6, and 12 months after transplantation. Multiple logistic regression analysis was used to examine the association of FB with postoperative complications. We also used restricted cubic spline (RCS) to determine the association between FB as a continuous exposure of interest and postoperative complications. The validity of logistic regression was assessed using the Hosmer-Lemeshow test. *C*-statistic was calculated by the area under curve (AUC) for receiver operating characteristic (ROC). Donor details were missing for 2.7% of the cohort, and eGFR levels of recipients at 1, 6, and 12 months after transplantation were missing for 0.5%, 3.1%, and 2.2% of the cohort, respectively. With these exceptions, cohort data were complete for all other covariates and outcomes.

Regression coefficients with corresponding relative risks are reported as odds ratios (ORs) with 95% confidence intervals (CIs). Differences with a P value of <0.05 were considered to be statistically significant. Analyses were conducted using R (version 3.2.4) and ggplot2 package (version 4.5).

Sensitivity analyses

To assess the robustness of our findings, we reduced the FB calculation period from the start of the operation to 6:00 AM on the first postoperative day.

Results

Patient baseline characteristics and perioperative data by FB levels

A total of 955 DDKTs were performed at our hospital between January 2015 and April 2019, of which 103 were excluded from the analysis (36 recipients were younger than 18 years, 20 recipients had combined and second transplants, 31 were pediatric kidneys, and 16 patients experienced second operations in the perioperative period). A total of 852 recipients met our inclusion criteria for analysis: 120 (14.1%) recipients experienced DGF, and 732 (85.9%) recipients did not experience DGF (non-DGF; Fig. 1). Table 1 shows baseline characteristics of all recipients by FB level. The mean (±standard deviation) age was 42.4 ± 9.9 years, and 529 (62.1%) recipients were male. Among the 852 recipients of DDKT, the mean (±standard deviation) FB was 45.7 ± 25.0 ml/kg. The median FB calculation period was 37 h (range, 36–40 h). High FB occurred more frequently in DGF recipients than in non-DGF recipients (60.1 ± 20.2 ml/kg vs. 43.3 ± 24.9 ml/kg, $P < 0.001$). Compared to recipients with high FB, those with low FB were more likely to be male and overweight. Hypertension, diabetes, and CVD were more prevalent among recipients with low FB. Recipients with high FB had longer dialysis years than those with low FB (4.8 ± 2.7 vs. 3.9 ± 2.4 years, $P = 0.002$). Donor terminal creatinine was higher in the group with higher levels of positive FB [75.0 (55.7–97.0)] vs. 91.0 (61.0–144.5) μmol/l, $P < 0.001$). Although recipients with high FB were more frequently on inotropes than those with low FB, the former group had lower MAP at reperfusion (96.9 ± 11.1 vs. 102.6 ± 11.8 mmHg, $P < 0.001$). Diuretics were more frequently used in the high FB group (21.1% vs. 58.9%, $P < 0.001$).

Overall analysis of recipient outcomes by FB levels

Figure 2 shows the postoperative eGFR values by different FB levels. The mean (±standard deviation) eGFR values at 1, 6, and 12 months after transplantation were 60.7 ± 22.3, 66.2 ± 19.7, and 67.6 ± 20.6 ml/min/1.73 m^2 ($P < 0.001$). One-way ANOVA revealed that different FB levels affected eGFR at 1, 6, and 12 months after transplantation ($P = 0.004$, 0.027, and 0.006,

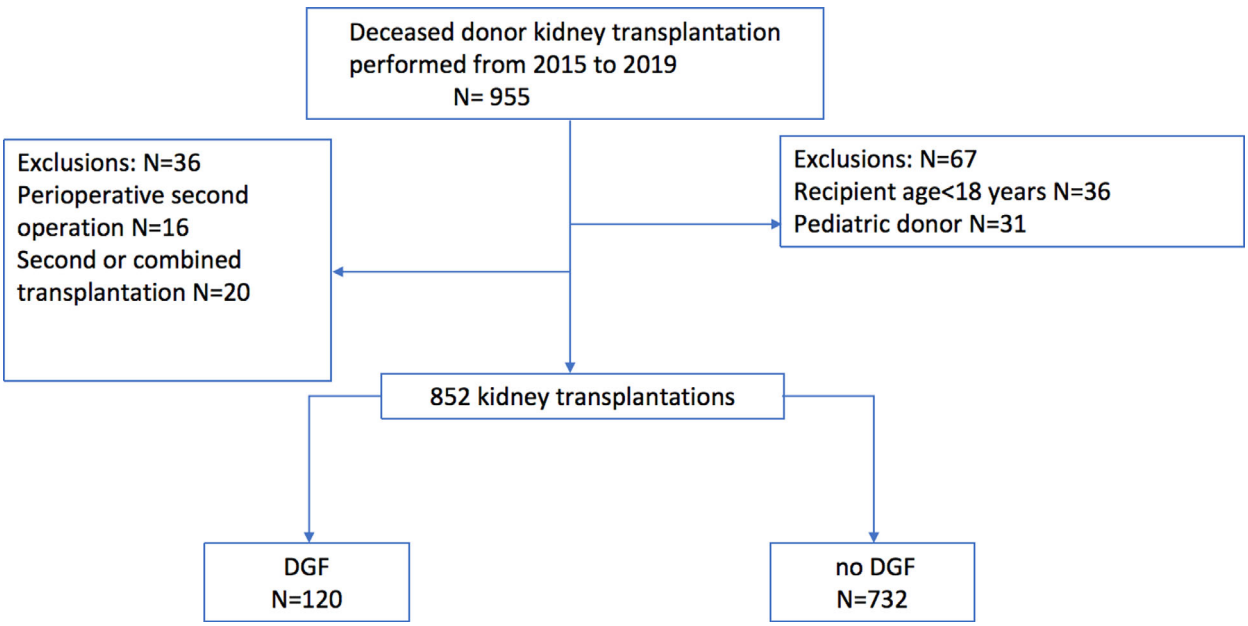

Figure 1 Study flow diagram.

Table 1. Cohort characteristics and perioperative data by fluid balance.

Fluid balance Variables	Total (*n* = 852)	Low (*n* = 213) <31 ml/kg	Middle low (*n* = 212) 30–45 ml/kg	Middle high (*n* = 213) 45–60 ml/kg	High (*n* = 214) >60 ml/kg	*P*
Age (years)	42.4 ± 9.9	42.3 ± 10.3	41.9 ± 9.6	43.4 ± 10.0	42.0 ± 9.7	0.364
Male (*n*, %)	529 (62.1%)	153 (71.8%)	146 (68.9%)	133 (62.4%)	97 (45.3%)	<0.001
BMI (kg/m^2)	21.6 ± 2.9	22.4 ± 3.1	22.2 ± 2.9	21.5 ± 2.9	20.2 ± 2.4	<0.001
Comorbidities, *n* (%)						
Hypertension	752 (88.3%)	202 (94.8%)	189 (89.2%)	182 (85.4%)	179 (83.6%)	0.002
Diabetes status	229 (26.9%)	88 (41.3%)	47 (22.2%)	60 (28.2%)	34 (15.9%)	<0.001
Cardiovascular disease	371 (43.5%)	116 (54.5%)	100 (47.2%)	84 (39.4%)	71 (33.2%)	<0.001
Cause of ESRD						
Polycystic kidney	45 (5.3%)	6 (2.8%)	9 (4.2%)	16 (7.5%)	14 (6.6%)	0.138
Glomerulonephritis	583 (68.7%)	176 (83.0%)	176 (83.0%)	162 (76.1%)	169 (79.7%)	
Diabetes	76 (9.0%)	5 (2.4%)	9 (4.2%)	4 (1.9%)	2 (0.9%)	
Hypertension	60 (7.1)	10 (4.7%)	10 (4.7%)	8 (3.8%)	8 (3.8%)	
Autoimmune disease	26 (1.9%)	3 (1.4%)	1 (0.5%)	7 (3.3%)	5 (2.4%)	
Other	59 (5.8%)	12 (5.7%)	7 (3.6%)	16 (7.5%)	14 (6.6%)	
Dialysis exposure						
Non	32 (3.8%)	12 (5.6%)	5 (2.4%)	7 (3.3%)	8 (3.7%)	<0.001
Hemodialysis	505 (59.3%)	96 (45.1%)	134 (63.2%)	134 (62.9%)	141 (65.9%)	
Peritoneal	315 (37.0%)	105 (49.3%)	73 (34.4%)	72 (33.8%)	65 (30.4%)	
Dialysis time (years)	4.3 ± 2.6	3.9 ± 2.4	4.1 ± 2.3	4.3 ± 2.7	4.8 ± 2.7	0.002
WIT (min)	10.1 ± 7.5	9.6 ± 7.6	11.1 ± 8.4	10.0 ± 7.1	9.8 ± 6.8	0.319
CIT (h)	7.0 ± 3.7	6.8 ± 3.6	6.9 ± 4.0	6.9 ± 3.5	7.3 ± 3.9	0.509
HLA mismatches	2.9 ± 1.3	3.0 ± 1.3	2.9 ± 1.3	2.9 ± 1.3	3.0 ± 1.2	0.904
Immunosuppression						
Tac + MPA + Ster	787 (92.4%)	196 (92.0%)	194 (91.5%)	194 (91.1%)	203 (94.9%)	0.450
CyA + MPA + Ster	65 (7.7%)	17 (8.0%)	18 (8.5%)	19 (8.9%)	11 (5.1%)	
Donor characteristics						
Age (years)	42.5 ± 13.9	41.0 ± 14.8	41.8 ± 13.3	44.2 ± 13.7	43.0 ± 13.9	0.095
BMI (kg/m^2)	23.1 ± 3.2	23.0 ± 3.0	22.9 ± 3.2	23.6 ± 3.5	22.8 ± 3.1	0.060
Creatinine (mol/l)	80 (58-120)	75 (55-97)	75 (55-106)	87 (61-130)	91 (61-144)	<0.001
Donor type (DBD)	224 (26.3%)	68 (31.9%)	63 (29.7%)	52 (24.4%)	41 (19.3%)	0.013
Comorbidities, *n* (%)						
Hypertension	122 (14.5%)	26 (12.4%)	29 (14.0%)	34 (16.1%)	33 (15.6%)	0.694
Diabetes mellitus	19 (2.3%)	6 (2.8%)	4 (1.9%)	4 (1.9%)	5 (2.4%)	0.904

Table 1. Continued.

Fluid balance Variables	Total (n = 852)	Low (n = 213) <31 ml/kg	Middle low (n = 212) 30–45 ml/kg	Middle high (n = 213) 45–60 ml/kg	High (n = 214) >60 ml/kg	P
Cause of death						
Stroke	273 (32.0%)	56 (26.3%)	74 (34.9%)	72 (33.8%)	71 (33.2%)	0.021
Trauma	496 (58.2%)	141 (66.2%)	121 (57.1%)	117 (54.9%)	117 (54.7%)	
Anoxia	64 (7.5%)	10 (4.7%)	14 (6.6%)	23 (10.8%)	17 (7.9%)	
Other	19 (2.2%)	6 (2.8%)	3 (1.4%)	1 (0.5%)	9 (4.2%)	
Perioperative data						
Total fluids (ml/kg)	159.4 ± 71.9	189.3 ± 93.2	148.7 ± 64.5	139.5 ± 59.0	160.1 ± 55.1	<0.001
Perioperative time (h)	37 (36-40)	37 (36-39)	37 (36-43)	37 (36-40)	37 (35-42)	0.213
Diuretic use, n%	361 (42.4%)	45 (21.1%)	76 (35.8%)	114 (53.5%)	126 (58.9%)	<0.001
Inotrope use, n%	286 (33.6%)	45 (21.1%)	67 (31.6%)	76 (35.7%)	98 (45.8%)	<0.001
MAP (mmHg)	96.9 ± 11.1	102.6 ± 11.8	99.3 ± 11.9	98.5 ± 11.2	96.9 ± 11.1	<0.001

BMI, body mass index; CIT, cold ischemia time; DBD, donation after brain death; ESRD, end-stage renal disease; MAP, mean arterial pressure; MPA, mycophenolate acid; Ster, steroid; Tac, tacrolimus; WIT, warm ischemia time.

respectively; Table 2). Multiple linear regression analyses showed that FB had no significant effect on graft function after transplantation (P = 0.324, 0.644, and 0.742, respectively).

The incidence of CP and GI complications increased with FB (4.7% vs. 18.7%, $P < 0.001$; 27.2% vs. 46.3%, $P < 0.001$). According to the Clavien-Dindo classification, most of the recipients were between grade I and II complications (324, 92.0%). Severe complications including 9 (2.6%) cases of grade III and 19 (5.4%) cases of grade IV complications occurred (Fig. 3). The severity of complications increased significantly with the elevation of FB (P value for trend = 0.034). In univariate analysis, high FB was associated with a 4.7 times risk of CP complications and a 2.3 times risk of GI complications as compared to low FB (Tables 3 and 4). Recipients with CVD and high BMI were more likely to develop CP complications, while recipients with low BMI and hypertension were more prone to develop GI complications. DGF, diuretic use, and high terminal creatinine of donor (>100 (μmol/l) are the common risk factors of CP and GI complications. By using RCS function, we constructed a logistic model for the total composite complications, and the results showed a similar pattern (Fig. 4). Multivariate logistic regression analysis further confirmed this relationship (Tables 3 and 4). After adjusting for other covariates (BMI, dialysis year, comorbidities of recipient, terminal serum creatinine of donor (μmol/l), BMI of donor, donor type, diuretic and inotropic use, and DGF status), the incidence of CP and GI complications continually increased as the FB level increased. For CP complications, compared to low FB, the OR was elevated from middle high FB (OR 2.44, 95% CI 1.07–5.58) to high FB (OR 5.29, 95% CI 2.28–12.24). For GI complications, OR increased from middle high FB (OR 1.54, 95% CI 0.99–2.39) to high FB (OR 1.97, 95% CI 1.24–3.13; Table 4). Recipients with DGF were 2.5 and 1.6 times more likely to have CP and GI complications, respectively, than non-DGF recipients (OR 2.49, 95% CI 1.37–4.54; OR 1.60, 95% CI 1.05–2.45, respectively). Overweight and obese recipients showed a 2.9-fold (OR 2.91, 95% CI 1.60–5.28) and 3.4-fold (OR 3.40, 95% CI 2.28–12.24) increased risk of developing CP complications as compared to those with normal BMI. The incidence of CP complications appeared to be significantly increased in recipients with CVD. Diuretic use was only associated with a high risk of GI complications. The other factors did not reach statistical significance. The multivariate logistic regression for CP and GI complications achieved an AUC estimate of 0.77

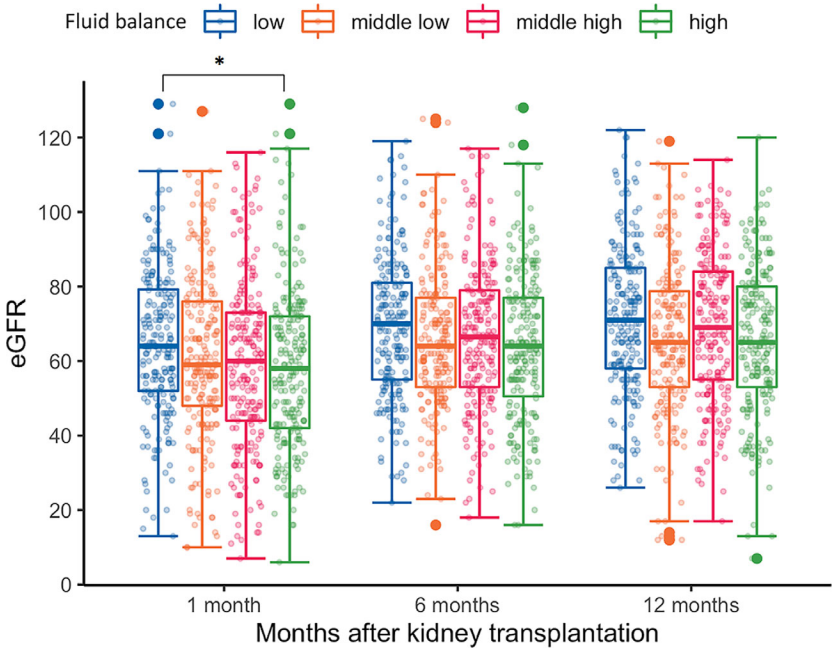

Figure 2 The eGFR at 1, 6, and 12 months after kidney transplantation in four fluid balance levels. Statistically significant differences were observed in eGFR at 1 month after kidney transplantation. *$P < 0.05$.

and 0.65 with Hosmer-Lemeshow test values of 0.332 and 0.491, respectively.

Sensitivity analysis

When we reduced the duration of FB calculation period to 6:00 AM in the morning of the first day after transplantation, sensitivity analysis yielded similar results (Tables S2–S4).

Discussion

In this retrospective analysis of 852 recipients of DDKT performed at a single-center teaching hospital, no apparent association was detected between early perioperative FB and graft function. However, we found an increase in the incidence of CP and GI complications with a rise in FB. DGF was significantly related to CP and GI complications. Diuretic use was associated with GI complications. CVD and abnormal BMI were also strong risk factors for CP complications, suggesting that this population needs to be carefully evaluated and infused.

Rapidly administered, high volume fluid therapy remains a common approach in the early perioperative care of kidney transplant recipients because the fear of postoperative renal hypoperfusion may aggravate existing ischemic-reperfusion damage [7,10,13]. However, the effectiveness of the liberal use of high volume fluid resuscitation has been questioned in patients with AKI and critically ill patients. In an experimental animal model of sepsis, only the first fluid bolus transiently improved renal perfusion, but the latter two boluses failed to maintain any sustained improvements in renal function [32]. In a large multicenter ICU study in Beijing, fluid overload was found to increase the incidence and severity of AKI [33].

Similar to AKI observed in native kidneys, transplanted kidneys may experience identical physiological ischemia-reperfusion changes and often receive a large volume of fluid infusion. The infusion period often persists for hours to days after transplantation. In this early perioperative period, more than 95% of recipients were under positive FB in our study, which is far greater than that noted in patients who underwent general abdominal surgery. The function of transplanted kidneys depends on renal perfusion and intrinsic factors of the donor kidney, WIT/CIT, and physical fitness of recipients [2–5], and overemphasis on renal perfusion can lead to increased venous pressure and tissue edema, which might be injurious to the transplanted kidney.

Consistent with other studies, we found that recipients with excessive FB have more complications [34–38]. The harmful effects of fluid overload are often manifested as pulmonary edema, pleural effusions, and cardiac overload, thereby putting patients at a high risk

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Table 2. Comparisons of outcomes stratified by perioperative fluid balance.

Fluid balance Outcomes	Total (n = 852)	Low (n = 213) <31 ml/kg	Middle low (n = 212) 31–45 ml/kg	Middle high (n = 213) 45–60 ml/kg	High (n = 214) >60 ml/kg	P
Graft function						
eGFR at 1 month	60.7 ± 22.3	65.2 ± 20.4	60.9 ± 22.5	59.2 ± 23.3	57.7 ± 22.2	0.004
eGFR at 6 months	66.2 ± 19.7	69.1 ± 18.9	65.7 ± 18.8	66.6 ± 19.8	63.4 ± 20.8	0.027
eGFR at 12 months	67.6 ± 20.6	71.1 ± 19.8	65.6 ± 20.8	68.8 ± 20.3	64.8 ± 21.0	0.006
1-year graft loss	9 (1.1%)	1 (0.5%)	2 (0.9%)	1 (0.5%)	5 (2.3%)	0.324
1-year mortality	2 (0.2%)	0 (0%)	0 (0%)	1 (0.5%)	1 (0.5%)	0.874
Complications						
Cardiopulmonary	91 (10.7%)	10 (4.7%)	16 (7.5%)	25 (11.7%)	40 (18.7%)	<0.001
Gastrointestinal	306 (35.8%)	58 (27.2%)	64 (30.2%)	85 (39.9%)	99 (46.3%)	<0.001

eGFR, estimated glomerular filtration rate.

of heart and respiratory failure [34,37]. Our study showed that the complication rate first increased slowly as FB increased, followed by a rapid growth in complications with the continuous increase in FB. Recipients with DGF were under fluid accumulation and experienced more complications than non-DGF recipients. One could speculate that poor urine output associated with DGF will prompt the treating clinician to fluid challenge more aggressively in the hope of achieving better urine output, thereby leading to a higher level of positive FB. These recipients with higher positive FB will later develop complications such as cardiopulmonary decompensation. Fluid challenge in DGF recipients need to be rigorously evaluated to minimize fluid overload. Furthermore, recipients with a history of CVD or high BMI were at an increased risk of developing CP complications. The pathogenic cascade of fluid overload was complicated by baseline characteristics and graft function of recipients. The capacity of water-electrolyte balance in this population was reduced, thus making them vulnerable to overhydration. In addition to recipient factors, the quality of the deceased donor could also affect these outcomes. Recipients who receive extended criteria donor (ECD) kidneys are thought to be at increased risk of graft failure and CVD events [39]. Donor terminal creatinine was higher in the group who had higher levels of positive fluid balance, indicating the poor ability of urine production in this group. Therefore, personalized fluid infusion strategies should be developed through comprehensive consideration of recipient, donor, and graft factors.

Fluid therapy should be individualized and based on dynamic indices of intravascular volume in this specific population who often have impaired cardiovascular physiology and reduced hemodynamic autoregulation. Goal-directed fluid therapy (GDFT) uses a cardiac output monitor to individualize fluid therapy. Dynamic indices obtained by monitoring parameters such as stroke volume variation (SVV), pulse pressure variation (PPV), and systolic pressure variation provide a precise indication of fluid responsiveness [40]. It requires cardiac output monitoring that may be invasive and lacks easily identifiable target. Hence, it is challenging to implement this approach in routine clinical practice. Enhanced recovery after surgery (ERAS) is another paradigm shift in perioperative care, resulting in substantial improvements in clinical outcomes and cost savings [41]. A key element of the ERAS protocol is to seek fluid balance rather than use large volumes of intravenous fluids [41,42]. Timely vasopressor use is recommended in ERAS for no fluid-responsive patients

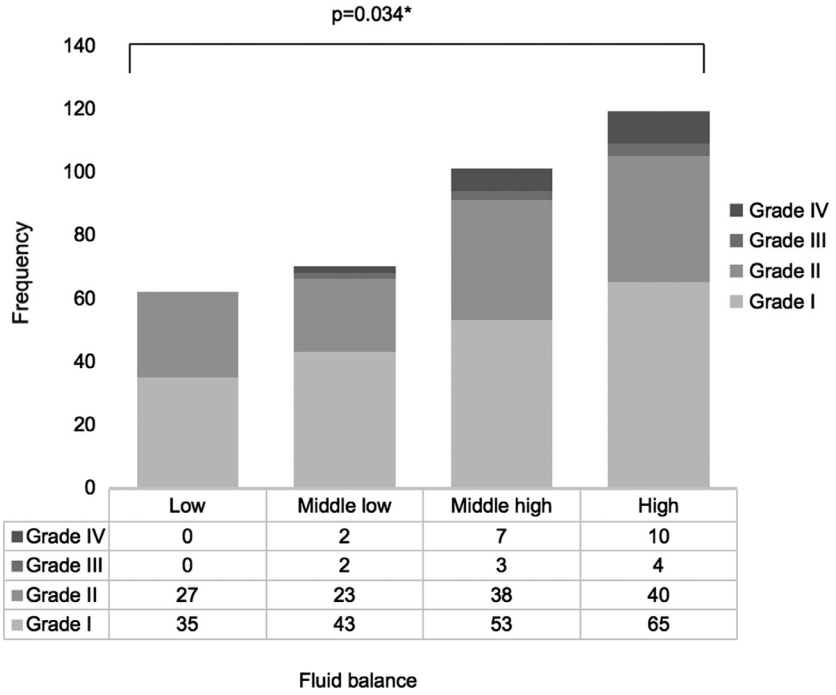

Figure 3 Complications by Clavien-Dino classification. *Mantel-Haenszel chi-square for linear trend. The severity of complications increased significantly with the elevation of fluid balance (*P* value for trend = 0.034).

Table 3. Logistic model analysis for cardiopulmonary complications.

	Univariate			Multivariate*		
Variable	OR	95% CI	*P*	OR	95% CI	*P*
Fluid balance			<0.001			<0.001
Low	Reference			Reference		
Middle low	1.66	0.73–3.74	0.224	1.58	0.67–3.70	0.297
Middle high	2.70	1.26–5.77	0.010	2.44	1.07–5.58	0.035
High	4.67	2.27–9.61	<0.001	5.29	2.28–12.24	<0.001
BMI			0.007			<0.001
Normal	Reference			Reference		
Low	0.58	0.26–1.32	0.195	0.47	0.20–1.09	0.080
Overweight	1.98	1.18–3.34	0.010	2.91	1.60–5.28	<0.001
Obesity	2.26	0.89–5.76	0.087	3.40	2.28–12.24	0.021
DGF	4.15	2.56–6.73	<0.001	2.49	1.37–4.54	0.003
Dialysis year	1.10	1.01–1.19	0.023	1.05	0.96–1.14	0.284
Comorbidities of recipient						
Cardiovascular disease	1.67	1.08–2.59	0.021	1.77	1.10–2.86	0.020
Hypertension	0.77	0.41–1.45	0.425	0.97	0.48–1.94	0.931
Diabetes mellitus	0.64	0.38–1.10	0.108	1.03	0.57–1.87	0.930
Terminal Cr of donor[†]	2.39	1.54–3.70	<0.001	1.39	0.81–2.38	0.228
Diuretic use	1.77	1.14–2.73	0.011	0.96	0.58–1.58	0.860
Inotropic use	1.91	1.23–2.96	0.004	1.34	0.83–2.20	0.223
Donor type	1.92	1.08–3.41	0.027	1.65	0.89–3.05	0.111

BMI, body mass index of recipient; CVD, cardiovascular disease; DGF, delayed graft function; Cr, creatinine; OR, odds ratio; CI, confidence interval.

*The model adjusted for BMI, dialysis year (in years), comorbidities of recipient, terminal serum creatinine of donor (μmol/l), diuretic and inotropic use, donor type (DBD), DGF.

[†]Terminal Cr of donor >100 μmol/l.

Table 4. Logistic model analysis for gastrointestinal complications.

	Univariate			Multivariate*		
Variable	OR	95% CI	*P*	OR	95% CI	*P*
Fluid balance			<0.001			0.022
Low	Reference			Reference		
Middle low	1.16	0.76–1.76	0.500	1.17	0.76–1.81	0.486
Middle high	1.78	1.18–2.67	0.006	1.54	0.99–2.39	0.057
High	2.30	1.54–3.45	<0.001	1.97	1.24–3.13	0.004
BMI			0.068			0.261
Normal	Reference			Reference		
Low	1.54	1.04–2.30	0.033	1.39	0.92–2.11	0.121
Overweight	0.85	0.57–1.27	0.440	1.01	0.66–1.53	0.978
Obesity	1.55	0.75–3.22	0.235	1.68	0.78–3.59	0.184
DGF	2.06	1.39–3.03	<0.001	1.60	1.05–2.45	0.030
Dialysis year	1.03	0.98–1.09	0.289	1.02	0.96–1.08	0.510
Comorbidities of recipient						
Hypertension	1.90	1.17–3.08	0.009	2.27	1.36–3.77	0.002
Diabetes mellitus	1.05	0.76–1.43	0.778	1.34	0.95–1.88	0.099
Cardiovascular disease	0.92	0.69–1.22	0.541	0.96	0.71–1.30	0.807
Terminal Cr of donor†	1.68	1.26–2.34	<0.001	1.23	0.88–1.71	0.225
Diuretic use	1.73	1.30–2.30	<0.001	1.47	1.07–2.01	0.018
Inotropic use	1.15	0.86–1.55	0.342	0.99	0.72–1.37	0.991
Donor type	0.77	0.56–1.06	0.103	1.31	0.93–1.85	0.129

BMI, body mass index of recipient; CI, confidence interval; Cr, creatinine; CVD, cardiovascular disease; DGF, delayed graft function; OR, odds ratio.

*The model adjusted for BMI, dialysis year (in years), comorbidities of recipient, terminal serum creatinine of donor (μmol/l), diuretic and inotropic use, donor type (DBD), DGF.

†Terminal Cr of donor >100 μmol/l.

in order to improve blood flow without causing fluid overload [42]. Our study, however, found no discernible benefits of vasopressor use in kidney transplant recipients. Vasopressor use may reflect the poor hemodynamic status and cardiac dysfunction of recipients requiring vasoactive medications and thus could introduce bias in our results. Diuretics were more frequently used in the high FB group; these were the same recipients who developed GI complications in our study. There is poor evidence to support the perioperative use of diuretics in kidney transplant recipients [43]. The choice and dosage of diuretics or no diuretics could be purely dependent on surgeon's preference and is not based on any robust clinical evidence. A thorough understanding of diuretics and vasopressors in ERAS is critical for the development of better fluid management strategies in kidney transplantation.

Our study provided insights into the effects of FB on graft function and postoperative complications. To the best of our knowledge, this is the first observational cohort study that evaluated the effect of early perioperative FB on associated outcomes in a large cohort of kidney transplant recipients. Most studies have focused on fluid therapy during transplantation. The postoperative phase that involves massive fluid volume is equally important. Moreover, this period often lacks intensive hemodynamic monitoring as compared to that during the intraoperative period; additionally, fluid therapy after kidney transplantation is heterogeneous among different transplant centers [9]. Our study expanded the duration of fluid balance to 6:00 AM on the second postoperative day, which allowed a more comprehensive analysis of perioperative fluid therapy. Data from many abdominal surgeries have suggested benefits of restrictive fluid therapy. Kidney transplantation was, however, an exception to restrictive fluid therapy. The strong relationship observed between positive FB and postoperative complications in the present study might prompt us to design clinical trials on fluid management in kidney transplant recipients.

Limitations of the present study are inherent to the retrospective analysis and to the limited study sample

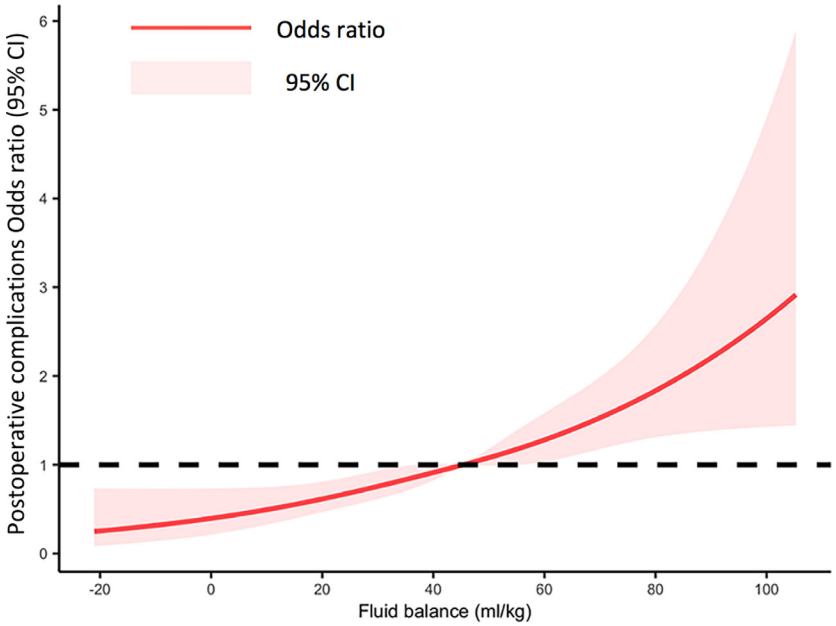

Figure 4 Restricted cubic spline plots of odds ratios for postoperative complications by fluid balance. The incidence of postoperative complications remains flat at negative or zero fluid balance and starts to rise apparently at high fluid balance, following adjustment for BMI, dialysis year, comorbidities of recipient, terminal serum creatinine of donor (μmol/l), BMI of donor, donor type, diuretic and inotropic use, and delayed graft function status.

obtained in a single center. Moreover, most of our recipients had fluid overload. This restricted our ability to detect the safe lower limit of FB. The range of the perioperative period was not uniform among the patients, although sensitivity analysis yielded similar results. In addition, we had no specific information on the dose of inotropes and diuretics for each patient, and the type of fluid was not considered for analysis. Further studies are required to characterize the role of inotropic or diuretic drugs and fluid type in the perioperative care of kidney transplant recipients.

In summary, we found that early perioperative positive FB did not promote renal function recovery and was associated with a high risk of postoperative complications in patients receiving kidney transplantation. These findings suggested caution to avoid unnecessary fluid infusion in this population. Further studies are needed to evaluate the optimal perioperative fluid therapy in kidney transplant recipients.

Authorship

JW, HJ and FH: designed the study. HJ, FH and JC: collected the data and prepared the figures and tables. XZ and JC: contributed analytical tools. HJ, FH and JW: wrote the paper and revised it critically.

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Conflict of interest

The authors have declared no conflicts of interest.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Classification of surgical complications.

Table S1. Comparisons of outcomes stratified by perioperative fluid balance*.

Table S1. Complications using fluid balance as design variables in univariate logistic regression.

Table S1. Complications using fluid balance as design variables in multivariable logistic regression.

Data S1. Supplementary Data

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