A pilot study on the association between early fluid status indicators after kidney transplantation and graft function recovery

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Supplementary Material

Patients and Methods

Table S1. Characteristics of patients included in the study

Table S2. Univariate analysis of factors associated with Day 30 estimated glomerular filtration rate

Table S3. Association between fluid status indicators levels within the first 72h after kidney transplantation from cadaveric donors and Day-30 eGFR: summarize of the different regression models after inclusion of KDPI

Figure S1. Daily fluid load and fluid balance within the first 72h after kidney transplantation

Figure S2. Predicted Day 30 eGFR *versus* fluid status indicators levels within the first 72h after kidney transplantation

Patients and Methods

Patients

We performed a pilot single-center study at University Hospital of Reims (France) using the dataset of a previous prospective study of our group in which patients were well-characterized for both donor, recipient, and perioperative characteristics as well as for all fluid status indicators of interest. All patients older than 18 years and not protected by the law undergoing kidney transplantation at University Hospital of Reims (France) between May 1^{st} 2017 and April 30^{th} 2019 who provided written informed consent to participate were included in the study. Patients for whom fluid status indicators monitoring was incomplete (dysfunction of monitoring device, transfer, detransplantation, death) were excluded from analysis. This study was approved by ethics committee (CPP Sud Mediterranée IV, Montpellier. March 14th, 2017) and was registered in Clinicaltrial.gov (NCT03478176). All adult patients undergoing kidney transplantation at University Hospital of Reims (France) between May 1^{st} 2017 and April 30^{th} 2019 were approached to participate. All included subjects provided written informed consent.

Graft function recovery

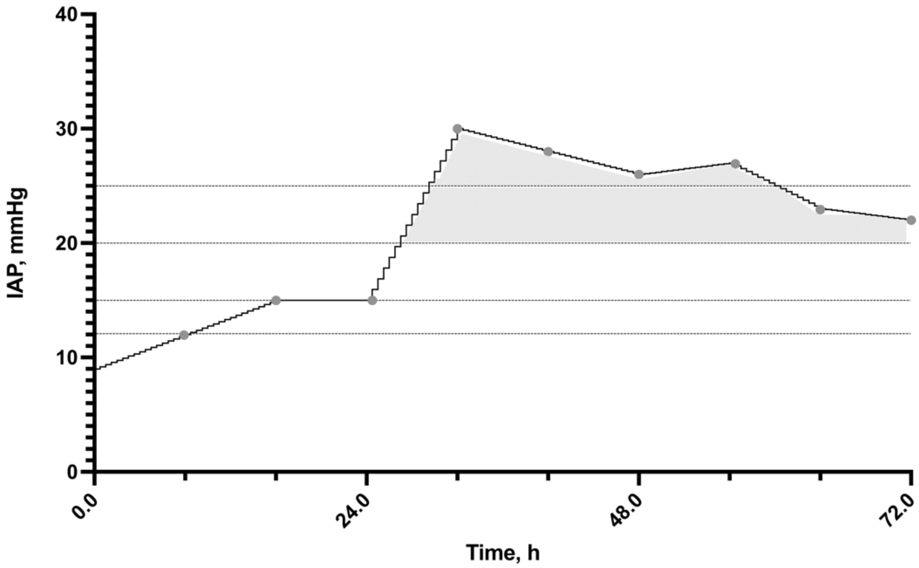
For each patient, we recorded the Day 3 creatininemia and the occurrence of delayed graft function (DGF, defined as renal replacement therapy requirement beyond Day 1 and within the first week after kidney transplantation) to describe short term graft function. To distance from the very first days, we focused on Day 30 eGFR calculated with CKD-EPI equation. The occurrence of biopsy-proven acute rejection within the first month was also recorded.

Post kidney transplantation fluid management

Fluid management was fulfilled in all patients according to a standardized protocol as previously described. Briefly, hourly diuresis was systematically compensated with NaCl 0.6% (or NaCl 0.9% if plasma sodium was below 136mmol/L, or $NaHCO_3$ 1,4% if plasma bicarbonate was below 16mmol/L) until daily diuresis stabilized below 8 liters per day. Fluid administration was used to maintain CVP above 5cmH2O without exceeding a 8 to 10% increase in Δweight. Daily fluid loads and fluid balances were recorded in all included patients.

Fluid status indicators

Four fluid status indicators (Δweight, CVP, MAP and IAP) were measured every 8 hours within the first 72h after kidney transplantation. As previously described, CVP was measured by a jugular catheter using a pressure manometer, MAP was measured in a non-invasive way, and IAP was assessed by intravesical pressure measurement with the Unometer™ Abdo-Pressure™ device. Δweight was calculated as the percentage of variation compared to dry weight. The abdominal perfusion pressure (APP= MAP-IAP) and mean perfusion pressure (MPP= MAP-CVP) were calculated as indicated. Each variable was interpolated to obtain 1 value every 30 minutes and then analyzed with a dedicated computer program using the R package DescTools (R package version 0.99.34, R Foundation for Statistical Computing, Vienna, Austria). For each fluid status indicator, we predefined a priori (based on clinical practice and existing definitions) four different thresholds for which the program identified, for each patient, the sections when the variable was continuously above the threshold considered. For each fluid status indicator, we tested 4 different thresholds to identify the more relevant one regarding the Day 30 eGFR: 0-5-10 and 15% for Δweight, 65-75-85 and 95mmHg for MAP, 5-10-15 and 20cmH_2O for CVP, 12-15-20-25mmHg for IAP and 55-65-75 and 85mmHg for MPP and APP. For each combination of fluid status indicator and threshold, the program calculated the area above threshold (AAT), *i.e.* the area between the variable curve and the threshold line, which reflects both the time spent above the predefined threshold (duration) and the magnitude of derivation from the threshold (see Definition of the area above threshold Figure hereafter).



Definition of the area above threshold
For each fluid status indicator, data were interpolated every 30 min within the first 72h after kidney transplantation based on the measurements recorded every 8h (grey dots) in all patients. To test the association between each fluid status indicator level and Day 30 eGFR, we predefined four thresholds per variable, and calculated, for each combination of variable and corresponding threshold, the area above threshold (AAT), which reflects both the time spent above the threshold (duration) and the magnitude of the derivation (severity). The AAT for intraabdominal pressure (IAP) above 20mmHg (grey area) is shown as an example.

Statistical analysis

Normal distribution of continuous data was tested using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean±standard deviation and categorical variables were expressed as counts(percentages).

We used different univariate linear regression and multivariate stepwise backward analysis of covariance models to test the association between each AAT (corresponding to one threshold for one fluid status indicator) within the first 72h and Day 30 eGFR. The linearity of the relationship between each AAT and Day 30 eGFR was first confirmed using scatter plot. Each model included the AAT corresponding to one threshold for one fluid status indicator, and all other variables significantly associated with Day 30 eGFR in univariate analysis with a *p*-value <0.20 as well as other variables that might also impact Day 30 eGFR, regardless of univariate analysis. Because early kidney graft function is expected to differ between recipients from cadaveric and living donors, we also reperformed all univariate and multivariate analysis models after exclusion of recipients from living donors. Statistical analysis was performed using R package version 0.99.34. To take into account multiplicity, we systematically applied the Bonferroni correction to the *p*-values obtained in univariate and multivariate analysis. A *p*-value <0.05 was considered statistically significant. All data underlying this article are available from the corresponding author upon reasonable request.

Table S1. Characteristics of patients included in the study

Variables	All patients (n=55)
Kidney transplant recipients	
Age, *years*	49±12
Male, *n (%)*	29 (53)
BMI, *kg/m²*	26±5
Causal Nephropathy, *n (%)*	
Diabetic	4 (7)
Glomerulopathy	20 (36)
Interstitial	7 (13)
Hypertension	4 (7)
ADPKD	17 (31)
Uropathy	3 (5)
Urine output > 500mL, *n (%)*	31 (56)
Heart failure, *n (%)*	4 (7)
Anti-HLA immunization, *n (%)*	23 (42)
Renal replacement therapy, *n (%)*	
Preemptive	8 (15)
Peritoneal dialysis	12 (22)
Hemodialysis	35 (64)
Dialysis exposure time, *months*	42±41
Perioperative management	
Cold ischemia time, *minutes*	830±474
Machine perfusion, *n(%)*	14 (256)
Vascular fluid load during surgery, *mL/kg*	45±19
Kidney transplant donors	
Age, *years*	52±16
BMI, *kg/m²*	26±5
Creatininemia, *µmol/L*	78±50
Living donor, *n (%)*	6 (11)
Cadaveric donor, *n (%)*	49 (89)
KDRI	1.26±0.52
KDPI, *%*	59±31
Cardiac arrest, *n (%)*	17 (35)
Atheroma, *n (%)*	13 (24)
Vascular calcification, *n (%)*	9 (16)
Immunosuppressive therapy	
Induction	
Thymoglobulin, *n (%)*	19 (35)
Basiliximab, *n (%)*	36 (66)
Maintenance	
MMF, *n (%)*	49 (89)
Ciclosporin, *n (%)*	27 (49)
Tacrolimus, *n (%)*	28 (51)
Corticosteroids, *n (%)*	55 (100)
Early kidney graft outcomes	
Day 3 creatininemia, *µmol/L*	307±227
DGF, *n (%)*	10 (18)
Acute rejection within first month, *n (%)*	0 (0)
Day 30 eGFR, *mL/min/1.73m²*	47.6±21.8

Data are expressed as mean±standard deviation or number (%). BMI, body mass index; KDRI, kidney donor risk index; KDPI, kidney donor profile index; MMF, mycophenolate mofetil; DGF, delayed graft function; eGFR, estimated glomerular filtration rate.

Table S2. Univariate analysis of factors associated with Day 30 estimated glomerular filtration rate

Variables	Day 30 eGFR, *mL/min/1.73m²*	Univariate analysis *p*
Kidney transplant recipients		
Age		**0.01**
Male		0.37
Yes (n=23)	46.6±18.2	
No (n=32)	48.6±25.2	
Causal Nephropathy		0.45
Diabetic (n=4)	53.5±38.4	
Glomerulopathy (n=20)	50.8±26.3	
Interstitial (n=7)	54.5±11.8	
Hypertension (=4)	42.3±24.3	
ADPKD (n=17)	40.6±13.8	
Uropathy (n=3)	46.0±21.0	
Urine output >500mL per day, *n (%)*		0.78
Yes (n=31)	47.7±17.8	
No (n=24)	47.0±26.6	
Anti-HLA immunization		0.09
Yes (n=23)	54.3±25.4	
No (n=32)	42.3±17.6	
Renal replacement therapy		0.35
Preemptive (n=8)	38.2±14.6	
Peritoneal dialysis (n=12)	51.2±20.6	
Hemodialysis (n=35)	48.1±23.5	
Kidney transplant donors		
Creatininemia		0.18
Donor type		**0.01**
Living (n=6)	67.3±19.2	
Deceased (n=49)	44.9±21.1	
Perioperative management		
Cold ischemia time		0.58
Machine perfusion		0.94
Yes (n=14)	47.1±26.8	
No (n=41)	47.4±20.3	
Immunosuppressive therapy		
Calcineurin inhibitor type		**0.04**
Ciclosporin (n=27)	41,56±16.7	
Tacrolimus (n=28)	52.9±24.9	
Fluid status indicators levels within the first 72h		
Weight gain		
AAT ΔWeight> 0, %/h		0.88
AAT ΔWeight> 5, %/h		0.87
AAT ΔWeight> 10, %/h		0.77
AAT ΔWeight> 15, %/h		0.43
Mean arterial pressure (MAP)		
AAT MAP> 65mmHg, mmHg /h		0.08
AAT MAP> 75mmHg, mmHg /h		0.07
AAT MAP> 85mmHg, mmHg /h		**0.05**
AAT MAP> 95mmHg, mmHg /h		**0.05**
Central venous pressure (CVP)		
AAT CVP> 5cmH_2O, mmH_2O /h		0.20
AAT CVP> 10cmH_2O, cmH_2O /h		0.39
AAT CVP> 15cmH_2O, cmH_2O /h		0.88
AAT CVP> 20cmH_2O, cmH_2O /h		0.75

Intra-abdominal pressure (IAP)	
AAT IAP> 12mmHg, mmHg /h	**<0.01**
AAT IAP > 15mmHg, mmHg /h	**<0.01**
AAT IAP > 20mmHg, mmHg /h	**<0.01**
AAT IAP > 25mmHg, mmHg /h	**<0.01**
Mean perfusion pressure (MPP)	
AAT MPP> 55mmHg, mmHg /h	**0.04**
AAT MPP> 65mmHg, mmHg /h	**0.03**
AAT MPP> 75mmHg, mmHg /h	**0.02**
AAT MPP> 85mmHg, mmHg /h	**0.01**
Abdominal perfusion pressure (APP)	
AAT APP> 55mmHg, mmHg /h	**<0.01**
AAT APP> 65mmHg, mmHg /h	**<0.01**
AAT APP> 75mmHg, mmHg /h	**<0.01**
AAT APP> 85mmHg, mmHg /h	**<0.01**

Data are expressed as mean±standard deviation or number (%). eGFR, estimated glomerular filtration rate; ADKPD, autosomic dominant polycystic kidney disease; *HLA*, Human leucocyte antigen.

Table S3. Association between fluid status indicators levels within the first 72h after kidney transplantation from cadaveric donors and Day-30 eGFR: summarize of the different regression models after inclusion of KDPI

Variables	Multivariate analysis	
	β coefficient ± SE	*p* value
Weight gain		
AAT ΔWeight> 0, %/h	-	-
AAT ΔWeight> 5, %/h	-	-
AAT ΔWeight> 10, %/h	-	-
AAT ΔWeight> 15, %/h	-	-
Mean arterial pressure (MAP)		
AAT MAP> 65mmHg, mmHg /h	0.02±0.12	0.82
AAT MAP> 75mmHg, mmHg /h	0.02±0.12	0.83
AAT MAP> 85mmHg, mmHg /h	0.03±0.14	0.78
AAT MAP> 95mmHg, mmHg /h	0.04±0.14	0.75
Central venous pressure (CVP)		
AAT CVP> 5cmH_2O, mmH_2O /h	-	-
AAT CVP> 10cmH_2O, cmH_2O /h	-	-
AAT CVP> 15cmH_2O, cmH_2O /h	-	-
AAT CVP> 20cmH_2O, cmH_2O /h	-	-
Intra-abdominal pressure (IAP)		
AAT IAP> 12mmHg, mmHg /h	-0.46±0.11	<0.01
AAT IAP > 15mmHg, mmHg /h	-0.42±0.11	<0.01
AAT IAP > 20mmHg, mmHg /h	-0.38±0.10	<0.01
AAT IAP > 25mmHg, mmHg /h	-0.31±0.10	<0.01
Mean perfusion pressure (MPP= MAP-CVP)		
AAT MPP> 55mmHg, mmHg /h	0.10±0.14	0.52
AAT MPP> 65mmHg, mmHg /h	0.12±0.15	0.49
AAT MPP> 75mmHg, mmHg /h	0.13±0.16	0.46
AAT MPP> 85mmHg, mmHg /h	0.13±0.16	0.45
Abdominal perfusion pressure (APP= MAP-IAP)		
AAT APP> 55mmHg, mmHg /h	0.29±0.11	0.02
AAT APP> 65mmHg, mmHg /h	0.30±0.11	0.01
AAT APP> 75mmHg, mmHg /h	0.32±0.10	<0.01
AAT APP> 85mmHg, mmHg /h	0.34±0.10	<0.01

Each multivariate analysis model included the AAT corresponding to one of the fluid status indicators (weight gain, MAP, CVP, IAP, MPP or APP) and one predefined threshold within the first 72h after kidney transplantation, as well as all the following confounding variables: recipient age, anti-HLA immunization status (presence or absence of anti-HLA antibodies), calcineurin inhibitor (ciclosporin or tacrolimus), cold ischemia time and Kidney Donor Profile Index (KDPI). eGFR, estimated glomerular filtration rate; SE, standard error: AAT, area above threshold.

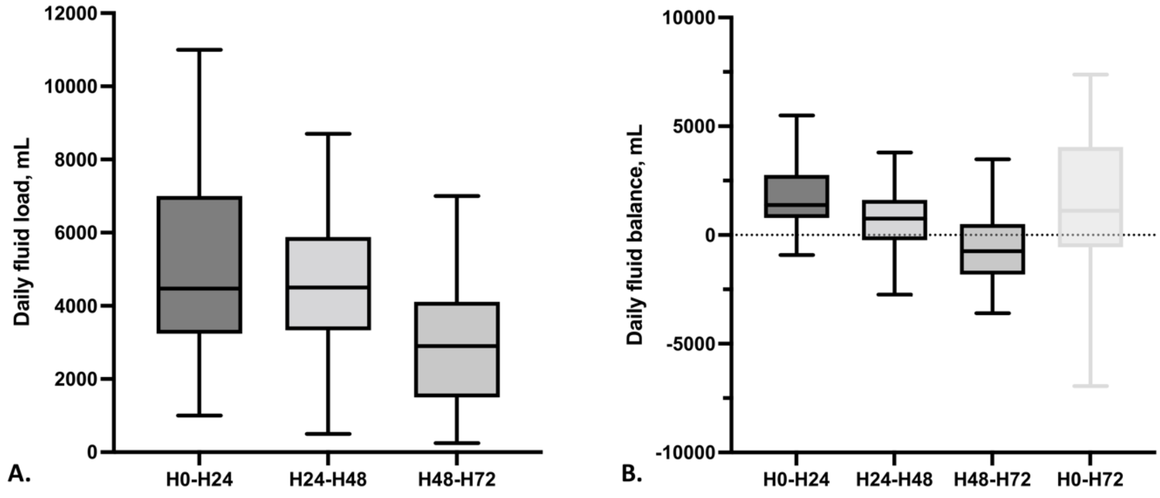


Figure S1 Daily fluid load and fluid balance within the first 72h after kidney transplantation

Evolution of daily fluid load (A) and daily fluid balance (B) within the first 72h after kidney transplantation. Results are shown as box plots.

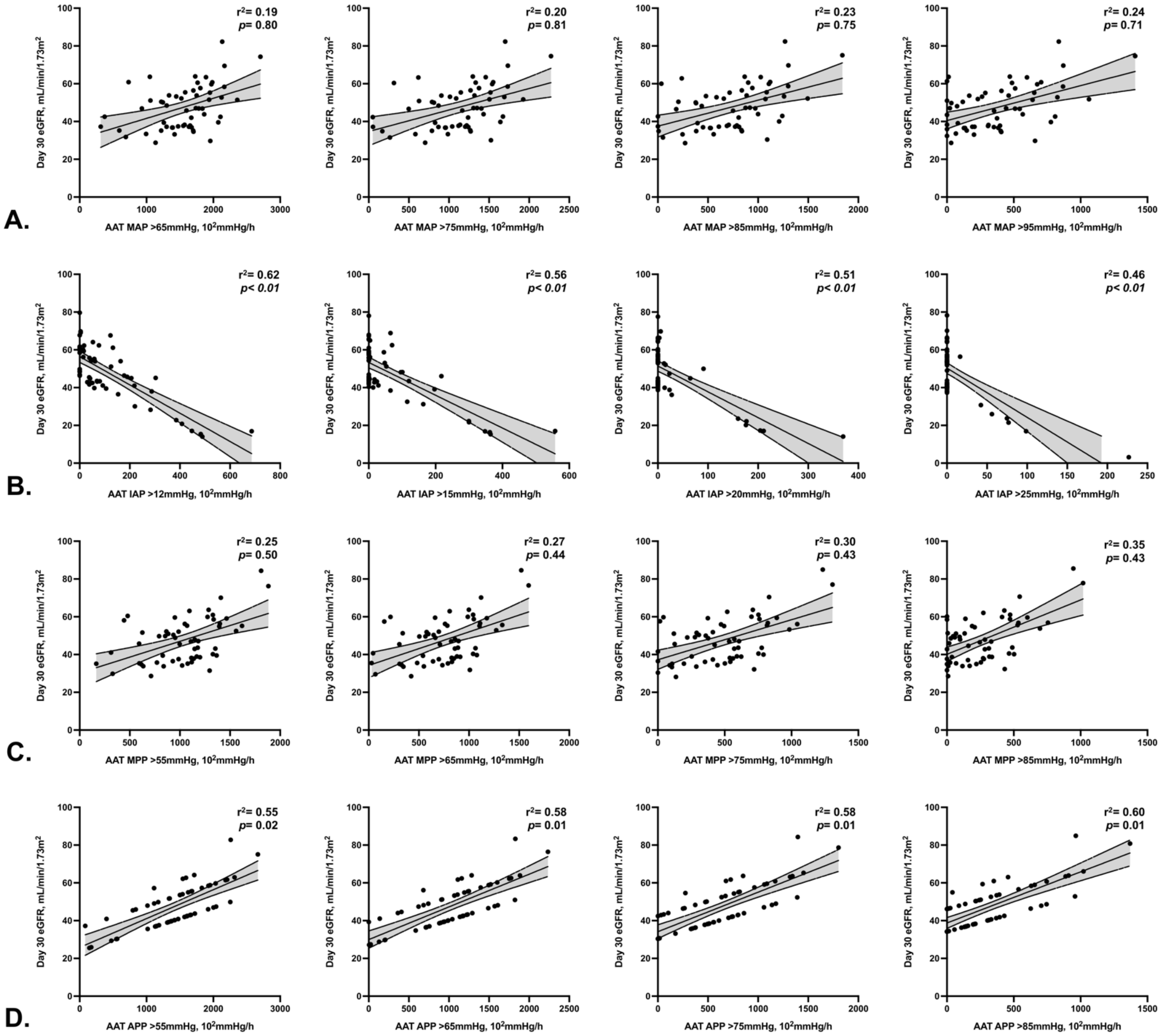


Figure S2. Predicted Day 30 eGFR *versus* fluid status indicators levels within the first 72h after kidney transplantation

Predicted multivariable-adjusted Day 30 eGFR (with 95% confidence intervals) *versus* the AAT for MAP (A), IAP (B), MPP (C) or APP (D) and predefined threshold within the first 72h after kidney transplantation. In each multivariate analysis model, our stepwise backward approach included the following confounding variables: recipient age, donor creatininemia, anti-HLA immunization status (presence or absence of anti-HLA antibodies), donor type (cadaveric or living kidney donor) calcineurin inhibitor (ciclosporin or tacrolimus) and cold ischemia time. eGFR, estimated glomerular filtration rate; AAT, area above threshold; MAP, mean arterial pressure; IAP, intraabdominal pressure; MPP (=MAP-central venous pressure), mean perfusion pressure; APP, abdominal perfusion pressure.