Evaluation of Preoperative Abdominal Adipose Tissue–, Inflammation-, Muscle Mass–, and Nutritional Status–based Prognostic Markers to Assess Renal Dysfunction in Living Kidney Donors

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ABSTRACT

Background. Living kidney donors (LKDs) are at high risk of renal dysfunction after undergoing a donor nephrectomy (DN), resulting in poor prognosis associated with the development of cardiovascular or cerebrovascular disease. Decreasing this risk can improve the survival rate of LKDs. We investigated the effects of preoperative conditions in LKDs on renal dysfunction after DN using abdominal adipose tissue, inflammation, nutritional status, and muscle mass as markers for this assessment.

Methods. Our retrospective study included 79 LKDs. Body composition markers were assessed using preoperative unenhanced computed tomographic images. Inflammation- and nutritional status–based markers were assessed using preoperative laboratory blood tests. The association between each marker was investigated, and prognostic markers for renal dysfunction after DN were identified.

Results. The LKDs in this cohort comprised 30 men and 49 women. The median age at the time of DN and the preoperative estimated glomerular filtration rate were 58 years and 81.9 mL/min/1.73 m^2, respectively. Abdominal subcutaneous adipose tissue and muscle mass significantly differed between the sexes. Each adipose tissue–, inflammation-, nutritional status–, and muscle mass–based marker showed an association with each other. Abdominal visceral adipose tissue and nutritional status could be independent prognostic markers for renal dysfunction after DN.

Conclusions. Our findings suggest that the preoperative condition of LKDs (assessed using specific markers such as abdominal visceral adipose tissue mass per volume and nutritional status) could affect renal dysfunction after DN. Optimal preoperative management can lead to better outcomes in LKDs. Further research is needed to establish appropriate exercise programs and nutritional interventions.

Ethics Approval and Consent to Participate:The institutional review board of the Nara Medical University approved this study. The reference number is 1605. As the data for the study was obtained through retrospective chart review, a waiver of informed consent was approved by the institutional review board of the Nara Medical University.

Availability of Data and Material: The datasets generated and/or analyzed during the current study are not publicly available because of our hospital policy but are available from the corresponding author on reasonable request.

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KIDNEY transplant is the most successful treatment for patients with end-stage renal disease (ESRD) and leads to improved survival and quality of life [1]. However, globally there exists a gross discrepancy between the demand and supply of organs. In addition to HLA matching and ABO blood type compatibility, the donor's medical status also needs to be thoroughly assessed, particularly in marginal donors.

Although deceased donor kidney transplant is known to reduce mortality in patients with ESRD compared with those receiving maintenance hemodialysis, living donor kidney transplant reportedly shows better outcomes than those observed following deceased donor kidney transplant. Thus, transplant communities widely recommend living donor kidney transplant [2–5]. In our practice, most donor kidneys are obtained from living kidney donors (LKDs). Optimal management of LKDs is important in the clinical setting. Okamoto et al reported that survival rates of LKDs at 5-, 10-, 20-, and 30-year time periods after donor nephrectomy (DN) were 98.3%, 94.7%, 86.4%, and 66.2%, respectively, and the mean age at the time of death was 70 (SD, 11) years. Mortality in LKDs after DN was attributable to malignancy, cardiovascular, and cerebrovascular disease [6]. Previous studies describing long-term follow-up in LKDs have reported that approximately 50% of LKDs developed hypertension and obesity or became overweight after DN, and an increased prevalence of microalbuminuria or diabetes mellitus was observed after DN [7,8]. Therefore, long-term follow-up of LKDs is important.

Our previous report suggested that preoperative abdominal visceral adipose tissue area (VAT) and nutritional status could predict postoperative renal function in Japanese LKDs [9]. Multivariate analysis revealed that a high VAT measured at the level of the fourth and fifth lumbar vertebrae (L4–5) and a low prognostic nutritional index (PNI) were independent markers for renal dysfunction after DN. Usually, obesity serves as a risk factor for the development of chronic kidney disease (CKD), and LKDs tend to develop obesity and CKD related to obesity because of the increasing prevalence of obesity that is being observed in this patient population [10,11]. The LKD guidelines in Japan state that a body mass index (BMI) ≤ 30 kg/m^2 is an optimal value in LKDs and a BMI > 30 kg/m^2 is undesirable. Rankinen et al suggested that BMI could not accurately evaluate obesity and that the measurement of waist circumference is the best marker for obesity [12,13]. Lee et al reported that the measurement of waist circumference was inaccurate because it could not distinguish between VAT and subcutaneous adipose tissue (SAT), and that in LKDs, the visceral-to-subcutaneous adipose tissue volume ratio (VSR) is superior to BMI as a marker for renal function recovery after DN [14].

We aimed to evaluate preoperative abdominal adipose tissue, inflammation, nutritional status, and muscle mass as markers for renal dysfunction after DN. An understanding of the association between a donor's preoperative general condition and renal function could help in long-term follow-up and also to achieve better preoperative management in LKDs, resulting in good prognosis.

METHODS

Patient Selection, Data Collection, and Study Design

Figure 1A shows a schematic representation of the present study. We studied 98 consecutive LKDs who underwent DN for renal transplant between January 2008 and December 2016 at our hospital. Among these, 19 LKDs (19.4%) were excluded from the analysis because of a lack of preoperative computed tomography images or a follow-up period < 12 months. Therefore, we retrospectively reviewed the medical charts of 79 LKDs included in this study and obtained clinical and radiographic data from their medical charts. We also obtained laboratory data in patients, including the estimated glomerular filtration rate (eGFR, expressed as mL/min/1.73 m^2), which was used as an indicator of renal function. Postoperative renal function was evaluated at the time of discharge, and at 1-, 3-, 12-, 24-, and 36-month time periods. The number of LKDs who could be followed up for 24 and 36 months was 63 and 33, respectively. We evaluated whether preoperative conditions in LKDs indicated by abdominal adipose tissue, inflammation, muscle mass, and nutritional status affect postoperative renal dysfunction in this group of individuals. Our study protocol for this research project was approved by the Institutional Review Board for Clinical Studies (Medical Ethics Committee ID: NMU−1605), which waived the requirement for informed patient consent because of the retrospective nature of the analysis.

Calculation of eGFR and Classification of the Stages of Chronic Kidney Disease

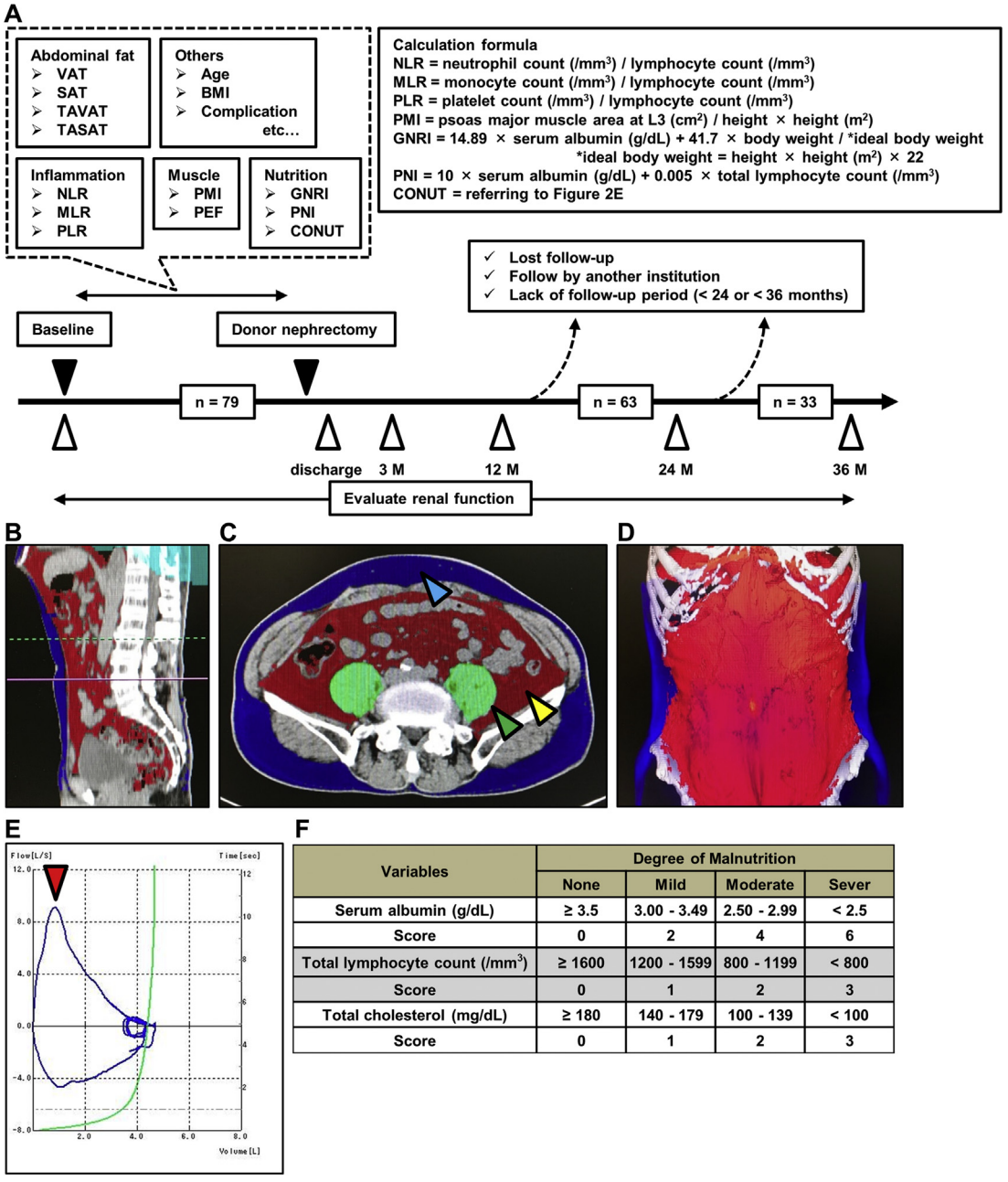
The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [15]. The stage of CKD was classified based on the Kidney Disease: Improving Global Outcomes guidelines published in 2012: CKD G1, ≥ 90; CKD G2, 60–89.9; CKD G3a, 45–59.9; CKD G3b, 30–44.9; CKD G4, 15–29.9; CKD G5, < 15 mL/min/1.73 m^2 [16].

Measurement of Abdominal Adipose Tissue– and Muscle Mass–Based Markers

Unenhanced computed tomography images obtained for preoperative screening or examination of vascular structures were analyzed using the Volume Analyzer SYNAPSE VINCENT image analysis system (Fujifilm Medical, Tokyo, Japan) to quantify abdominal adipose tissue and muscle area and/or volume. The cross-sectional area of abdominal SAT and VAT at L4–5 was measured using the analysis system. Total abdominal subcutaneous adipose tissue volume (TASAT) and total abdominal visceral adipose tissue volume (TAVAT) were also measured using the analysis system. The VSR was calculated to determine the distribution of abdominal adipose tissue. Similarly, the cross-sectional area of the psoas major muscle at the level of the third lumbar vertebra (L3) was measured using the analysis system. The measured values were normalized for height to obtain the psoas muscle index (PMI). Representative images used for analyses of abdominal adipose tissue and muscle mass are shown in Fig 1B-D.

Definition of Sarcopenia and Baseline Respiratory Muscle Strength

Hamaguchi et al reported a new diagnostic cutoff value for sarcopenia based on a study involving 541 adult living donors for liver transplant. The cutoff value was defined as PMI < 6.36 cm^2/m^2 for men and PMI < 3.92 cm^2/m^2 for women [17]. Our study used this definition for analysis. Regarding respiratory muscle strength, the



Variables	Degree of Malnutrition			
	None	Mild	Moderate	Sever
Serum albumin (g/dL)	≥ 3.5	3.00 - 3.49	2.50 - 2.99	< 2.5
Score	0	2	4	6
Total lymphocyte count (/mm^3)	≥ 1600	1200 - 1599	800 - 1199	< 800
Score	0	1	2	3
Total cholesterol (mg/dL)	≥ 180	140 - 179	100 - 139	< 100
Score	0	1	2	3

Fig 1. Schematic representation of the study workflow, representative images used for analyses of abdominal adipose tissue– and muscle mass–based markers, and the scoring system used to assess the controlling nutritional status score. This study included 79 donors. Information regarding preoperative conditions was obtained retrospectively through assessment of abdominal adipose tissue–, inflammation-, nutritional status–, and muscle mass–based markers. Abdominal adipose tissue– and muscle mass–based markers were measured using preoperative unenhanced computed tomographic images and inflammation- and nutritional status–based markers were calculated using preoperative laboratory blood tests. The estimated glomerular filtration rate was used to evaluate renal function and was assessed preoperatively, at the time of discharge, and at 3-, 12-, 24-, and 36-month time periods **(A)**. The Volume Analyzer SYNAPSE VINCENT image analysis system was used to reconstruct 3-dimensional images as follows: sagittal plane for quantification of the visceral adipose tissue area at the level of the lumbar vertebrae 4 and 5 (L4–5) and the psoas muscle area at the level of the third lumbar vertebra (L3) **(B)**; coronal plane for assessment of the abdominal subcutaneous adipose tissue area (blue area indicated by blue arrow), abdominal visceral adipose tissue area (red area indicated by yellow arrow), and the psoas muscle area (green area indicated by green arrow) **(C)**; 3-dimensional image used for quantification of abdominal subcutaneous and visceral adipose tissue volumes **(D)**; spirometry data for measurement of peak expiratory flow (red arrow) to assess the strength of respiratory muscles **(E)**; The controlling nutritional status (CONUT) score was determined using serum albumin, total lymphocyte count, and total cholesterol levels **(F)**.

peak expiratory flow (PEF) is determined by the strength of respiratory muscles in patients without lung disorders [18]. The PEF was expressed in liters per minute and categorized as normal or reduced based on the cutoff values defined by Berglund et al [19]. Because spirometry was routinely performed preoperatively, PEF values could be easily obtained for LKDs. Representative spirometry images used for analyses of PEF are shown in Fig 1E.

Measurement of Inflammation- and Nutritional Status–Based Markers

Preoperative inflammation and nutritional status were evaluated using inflammatory markers (neutrophil-lymphocyte ratio [NLR], monocyte-lymphocyte ratio [MLR], and platelet-lymphocyte ratio [PLR] and nutritional status-based markers (geriatric nutritional risk index [GNRI], PNI, and controlling nutritional status score [CONUT]. These markers were calculated using laboratory data obtained over a period of < 30 days prior to the DN. The inflammatory markers were calculated using the ratio of each cell count (per mm^3). The GNRI was originally reported as a prognostic marker after hospitalization in elderly patients and was subsequently used for patients undergoing maintenance hemodialysis [20,21]. The GNRI was calculated using the following formula: 14.89 × serum albumin (g/dL) + 41.7 × current body weight (kg)/ ideal body weight (kg), where ideal body weight was calculated using the following formula: height × height (m^2) × 22. The PNI was proposed as a marker to determine the feasibility of resection and anastomosis in different segments of the gastrointestinal tract and was reported as a prognostic factor associated with survival in patients with cancer [22,23]. The PNI was calculated using the following formula: 10 × serum albumin (g/dL) + 0.005 × total lymphocyte count (/mm^3) (Fig 1A). The CONUT score was also an independent prognostic marker for colorectal cancer. This score was determined using the serum albumin (g/dL), peripheral lymphocyte count (/mm^3), and the total cholesterol levels (mg/dL) (Fig 1F).

Statistical Analysis

Statistical analyses were performed and figures were plotted using the GraphPad Prism 7.0 (GraphPad Software, San Diego, Calif, United States). Data have been represented using bar charts or box plots. The *t* test or the Mann-Whitney test was used for statistical analysis. The interrelationship between each marker was examined using the Spearman rank correlation coefficient. To identify prognostic factors for renal dysfunction after DN, the development of CKD G3b 12 months after DN was defined as an event. Univariate and multivariate analyses were performed via logistic regression analysis using the SPSS software, version 21 (IBM, Armonk, NY, United States). The cutoff value for each marker was determined using the receiver operating characteristic curve analysis. Two-sided tests were used in all cases and a *P* value < .05 was considered statistically significant in all analyses.

RESULTS

Patient Characteristics

Table 1 shows the baseline clinical characteristics, preoperative renal function, comorbidities, and perioperative data for the cohort comprising 79 LKDs. The median age and BMI at DN were 58 years and 22.6 kg/m^2, respectively (interquartile range [IQR], 48–64 and 21.1–24.8, respectively). BMI ≥ 30 kg/m^2 was observed in 4 LKDs and 3 of them were men. The preoperative median serum creatinine level and eGFR were 0.64 mg/dL and 81.9 mL/min/1.73 m^2, respectively (IQR, 0.58–0.78 and 73.5–91.6, respectively). This cohort of LKDs comprised 30 men (38%) and 49 women (62%). A Charlson comorbidity index ≥ 1 was observed in 4 donors (5%), and no LKD showed proteinuria ≥ 150 mg/gCr. Hypertension was observed in 13 LKDs (16%). More than 50% of DN procedures were performed via hand-assisted laparoscopic surgery, and only 3 LKDs underwent pure laparoscopic surgery. No patient experienced blood loss requiring transfusion, and no major perioperative complications (> grade 2 of the Clavien classification) were reported in any patient. During follow-up, no new-onset hypertension, diabetes, and proteinuria were observed in any patient, and no progression was observed in 2 donors with known diabetes.

Table 1. Patients' background

Variables	Number of donors	%
Total	79	100
Age at operation		-
Median (IQR)	58 (48 - 64)	
BMI (kg/m^2)		-
Median (IQR)	22.6 (21.1 - 24.8)	
Serum creatinin (mg/dL)		-
Median (IQR)	0.64 (0.58 - 0.78)	
eGFR (mL/min/1.73m^2)		-
Median (IQR)	81.9 (73.5 - 91.6)	
Sex		
Men	30	38
Women	49	62
Proteinuria		
No	0	0
Yes	79	100
CCI		
0	75	95
≥1	4	5
Hypertension		
No	66	84
Yes	13	16
Diabetes		
No	77	97
Yes	2	3
Hyperlipidemia		
No	68	86
Yes	11	14
Hyperuricemia		
No	75	95
Yes	4	5
Type of donor nephrectomy		
Hand assisted	59	75
Laparoscopic	3	4
Open	17	21
Operative time (min)		
Median (IQR)	252 (220 - 310)	-
Perioperative complications		
No	74	94
Yes	5	6

BMI, body mass index; IQR, interquartile range; eGFR, estimate glomerular filtration rate; CCI, Charlson comorbidity index.

Table 2. Baseline abdominal adipose tissue-, inflammation-, muscle-, nutrition-based markers in 79 donors for renal transplantation

Variables	Median (IQR) or n (%)	Mean ± SD	*P* value
BMI (kg/m2)	22.6 (21.1 - 24.8)	23.4 ± 3.2	
Men	22.5 (21.1 - 24.8)	23.4 ± 3.2	0.48 †
Women	22.6 (21.1 - 24.8)	23.4 ± 3.2	
Abdominal adipose tissue markers			
VAT at L4-5 (cm^2)	84.1 (49.9 - 122.3)	92.5 ± 59.2	
Men	81.0 (49.8 - 122.4)	92.5 ± 59.6	0.78 †
Women	84.1 (49.8 - 122.1)	92.6 ± 59.8	
SAT at L4-5 (cm^2)	149.1 (95.7 - 208.4)	153.7 ± 77.6	
Men	147.9 (95.6 - 205.8)	152.8 ± 77.7	0.0003 †
Women	154.1 (98.2 - 210.5)	156.8 ± 75.9	
TAVAT (cm^3)	2041.5 (1086.9 - 3389.8)	2305.8 ± 1505.6	
Men	2044.5 (1086.4 - 3410.4)	2311.3 ± 1514.6	0.6 †
Women	2041.5 (1085.9 - 3348.5)	2299.6 ± 1517.7	
TASAT (cm^3)	3263.9 (1844.7 - 4926.3)	3498.6 ± 1958.7	
Men	3245.8 (1830.9 - 4967.7)	3485.4 ± 1967.9	<0.0001 †
Women	3543.6 (1998.9 - 5009.1)	3561.1 ± 1941.4	
VSR	0.56 (0.42 - 0.95)	0.77 ± 0.59	
Men	0.57 (0.42 - 0.95)	0.78 ± 0.59	<0.0001 †
Women	0.55 (0.42 - 0.94)	0.72 ± 0.45	
Inflammation markers			
CRP (mg/dL)	0.1 (0 - 0.1)	0.1 ± 0.12	-
NLR	1.8 (1.5 - 2.3)	2.0 ± 0.9	-
MLR	0.21 (0.17 - 0.27)	0.24 ± 0.10	-
PLR	141.7 (107.9 - 164.3)	141.2 ± 44.4	-
Muscle markers			
PMI at L3 (cm^2/m^2)	5.88 (4.78 - 7.49)	6.14 ± 1.90	
Men	5.91 (4.80 - 7.52)	6.16 ± 1.91	<0.0001 †
Women	5.83 (4.77 - 7.56)	6.14 ± 1.93	
normal	68 (86)	-	-
sarcopenia	11 (14)	-	
PEF (L/min)	438.6 (366.0 - 507.6)	443.3 ± 110.7	
Men	436.8 (365.7 - 510.3)	443.2 ± 111.4	<0.0001 †
Women	435.0 (365.4 - 502.2)	442.4 ± 111.8	
normal	59 (75)	-	-
decreased	20 (25)	-	
Nutrition markers			
GNRI	107.2 (104.2 - 109.5)	106.8 ± 4.3	-
PNI	53.0 (51.0 - 55.5)	53.7 ± 3.9	-
CONUT score	0 (0 - 1)	0.54 ± 0.66	-

IQR, interquartile range; SD, standard deviation; BMI, body mass index; VAT, visceral adipose tissue; L4-5, at the level of the fourth and fifth lumbar vertebra; SAT, subcutaneous adipose tissue; TAVAT, total abdominal visceral adipose tissue; TASAT, total abdominal subcutaneous adipose tissue; VSR, visceral-to-subcutaneous adipose tissue volume ratio; CRP, C-reactive protein; NLR, neutrophil-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; PLR, platelet-lymphocyte ratio; PMI, psoas muscle index; L3, at the level of the third lumbar vertebra; PEF, peak expiratory flow; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; CONUT, controlling nutritional status.
†Mann-Whitney U test.

Baseline Values of Abdominal Adipose Tissue–, Inflammation-, Muscle Mass–, and Nutritional Status–Based Markers

The preoperative baseline median (IQR) and mean (SD) values for each marker including the abdominal adipose tissue (VAT, SAT, TAVAT, TASAT, and VSR), inflammation (C-reactive protein, NLR, MLR, and PLR), muscle mass (PMI, sarcopenia status, and PEF), and nutritional status (GNRI, PNI, and CONUT) are shown in Table 2. There was no significant difference in BMI between men and women. Although VAT and TAVAT tended to be higher in men than in women, this difference was not statistically significant. In contrast, the SAT and TASAT were significantly higher in women than in men ($P < .001$ and $P < .001$, respectively). The VSR, which indicates the distribution of abdominal adipose tissues, was significantly higher in men than in women ($P < .001$), and this result could be attributed to the difference in TASAT between the 2 sexes. The PMI and PEF were significantly higher in men than in women ($P < .001$ and $P < .001$, respectively). Moreover, among the 79 LKDs studied, 11 (14%) showed sarcopenia and 20 (25%) were diagnosed as having decreased respiratory muscle strength.

A

		Age	BMI	Abdominal Fat				Inflammation			Muscle		Nutrition	
				VAT	SAT	TAVAT	TASAT	NLR	MLR	PLR	PMI	PEF	GNRI	PNI
Age	*P* value													
	Spearman r													
BMI	*P* value	.88												
	Spearman r	0.017												
VAT	*P* value	.34	<.0001											
	Spearman r	0.11	0.7											
SAT	*P* value	.94	<.0001	<.0001										
	Spearman r	−0.0088	0.69	0.58										
TAVAT	*P* value	.22	<.0001	<.0001	<.0001									
	Spearman r	0.14	0.62	0.9	0.55									
TASAT	*P* value	.58	<.0001	<.0001	<.0001	<.0001								
	Spearman r	−0.063	0.53	0.49	0.86	0.6								
NLR	*P* value	.45	.72	.93	.16	.072	.13							
	Spearman r	−0.086	−0.041	−0.19	−0.16	−0.2	−0.17							
MLR	*P* value	.78	.91	.99	.43	.95	.56	<.0001						
	Spearman r	0.032	−0.013	0.00091	−0.09	−0.0074	−0.067	0.61						
PLR	*P* value	.49	.18	.012	.25	.014	.22	<.0001	<.0001					
	Spearman r	−0.078	−0.15	−0.28	−0.13	−0.27	−0.14	0.6	0.49					
PMI	*P* value	.96	.51	.96	.005	.84	.0007	.15	.065	.81				
	Spearman r	−0.0069	0.082	−0.0069	−0.34	0.025	−0.4	0.18	0.22	−0.029				
PEF	*P* value	.091	.17	.5	.0074	.5	.0019	.33	.34	.42	<.0001			
	Spearman r	−0.19	0.16	0.076	−0.3	0.076	−0.34	0.11	0.11	−0.092	0.62			
GNRI	*P* value	.31	.075	.72	.29	.89	.59	.29	.53	.92	.42	.16		
	Spearman r	−0.11	0.2	0.041	0.12	0.015	0.062	0.12	0.071	0.011	0.1	0.16		
PNI	*P* value	.078	.81	.37	.46	.15	.22	.0012	.0038	<.0001	.82	.73	<.0001	
	Spearman r	−0.2	0.028	0.1	0.084	0.16	0.14	−0.36	−0.32	−0.48	0.029	0.039	0.61	

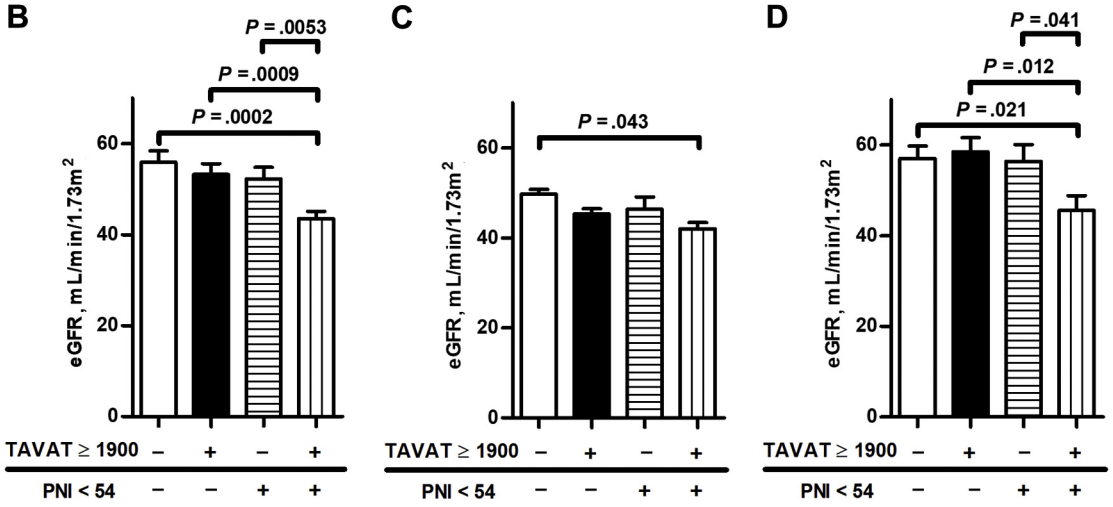


Fig 2. Correlation between abdominal adipose tissue–, inflammation-, nutritional status–, and muscle mass–based markers and comparison of renal function at 12 months based on risk stratification. The following 13 markers were compared with each other: age, body mass index (BMI), visceral adipose tissue area (VAT), subcutaneous adipose tissue (SAT), total abdominal visceral adipose tissue volume (TAVAT), total abdominal subcutaneous adipose tissue volume (TASAT), neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), platelet-lymphocyte ratio (PLR), psoas muscle index (PMI), peak expiratory flow (PEF), geriatric nutritional risk index (GNRI), and prognostic nutritional index (PNI). No significant correlation was observed between age and the other markers. Elderly donors tended to show a low PNI. BMI showed a positive correlation with abdominal adipose tissue-based markers and abdominal adipose tissue–based markers showed a positive correlation with each other. The VAT and TAVAT showed a negative correlation with the PLR. However, SAT and TASAT showed a negative correlation with muscle mass–based markers. Inflammation-based markers showed a significantly positive correlation with each other and a negative correlation with PNI. Muscle mass– and nutritional status–based markers showed a positive correlation with each other **(A)**. Postoperative renal function in donors with TAVAT $\geq$ 1900 and PNI $<$ 54 was significantly diminished compared with that of donors showing TAVAT $<$ 1900 and PNI $\geq$ 54, TAVAT $\geq$ 1900 and PNI $\geq$ 54, and TAVAT $<$ 1900 and PNI $<$ 54 **(B)**. In donors with preoperative eGFR $<$ 80 mL/min/1.73 m^2, postoperative renal function in those with TAVAT $\geq$ 1900 and PNI $<$ 54 was significantly diminished compared with those showing TAVAT $<$ 1900 and PNI $\geq$ 54 **(C)**. In donors with preoperative eGFR $\geq$ 80 mL/min/1.73 m^2, postoperative renal function in those with TAVAT $\geq$ 1900 and PNI $<$ 54 was significantly diminished compared with those showing TAVAT $<$ 1900 and PNI $\geq$ 54, TAVAT $\geq$ 1900 and PNI $\geq$ 54, and TAVAT $<$ 1900 and PNI $<$ 54 **(D)**.

Table 3. Logistic Regression of Baseline Prognostic Variables for Development of CKD G3b after 12 Months

	Univariate Analysis			Multivariate Analysis		
Variables	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Age						
< 60	1					
≥ 60	2.7	1.0–7.2	.06			
Sex						
Men	1					
Women	0.4	0.2–1.1	.09			
BMI						
< 22	1					
≥ 22	2.3	0.8–6.3	.15			
eGFR						
≥ 80	1			1		
< 80	5.4	1.9–14.9	.001	4.3	1.4–12.7	.009
Hypertension						
No	1					
Yes	2.7	0.8–9.0	.12			
VAT at L4–5						
< 80	1			1		
≥ 80	3	1.1–7.8	.03	1.7	0.3–9.1	.56
SAT at L4–5						
< 170	1					
≥ 170	2.4	0.9–6.1	.09			
TAVAT						
< 1900	1			1		
≥ 1900	3.2	1.2–8.7	.03	4.2	1.3–13.7	.02
TASAT						
< 3800	1					
≥ 3800	2	0.8–5.2	.16			
VSR						
< 0.7	1			1		
≥ 0.7	3.6	1.4–9.5	.01	1.2	0.3–4.5	.84
CRP						
< 0.2	1					
≥ 0.2	1.5	0.5–4.0	.47			
NLR						
< 1.9	1			1		
≥ 1.9	3.8	1.5–9.6	.007	0.5	0.1–1.7	.26
MLR						
< 0.24	1					
≥ 0.24	1.4	0.5–3.7	.62			
PLR						
< 141	1					
≥ 141	0.7	0.3–1.7	.48			
PMI at L3						
< 6.4	1			1		
≥ 6.4	3.2	1.1–9.1	.04	3.3	0.5–21.9	.21
PEF						
Normal	1					
Decreased	1.1	0.4–3.0	1			
Sarcopenia						
No	1					
Yes	0.9	0.2–4.3	1			
GNRI						
≥ 111	1					
< 111	4.7	0.6–39.9	.15			
PNI						
≥ 54	1			1		
< 54	4.1	1.4–11.8	.009	5.1	1.5–17.6	.009
CONUT						
0	1					
≥ 1	1.2	0.5–3.0	.81			

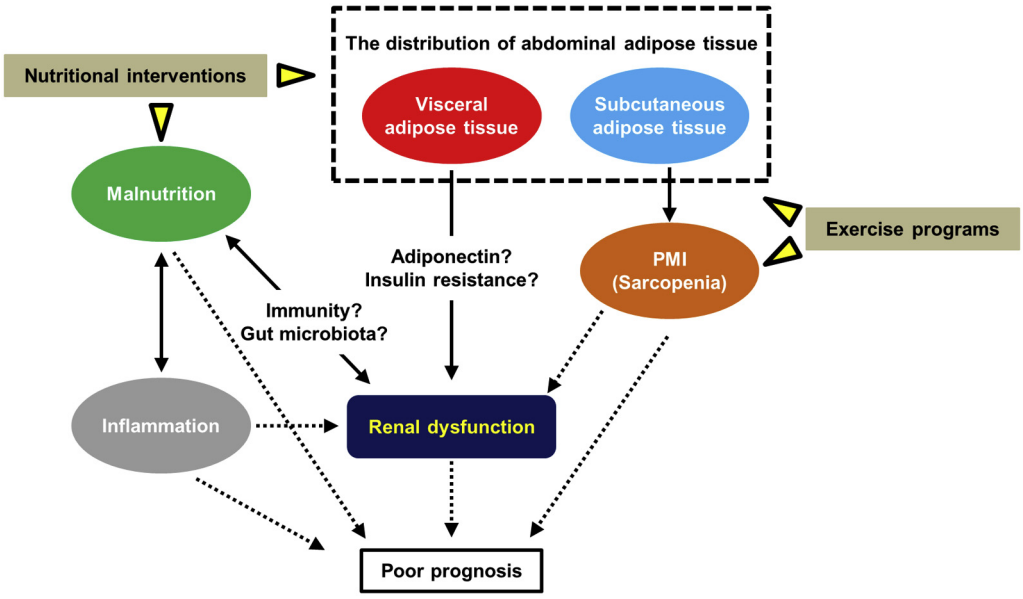


Fig 3. Schematic summary of this study. Parameters such as abdominal adipose tissue, inflammation, nutritional status, and muscle mass, which indicate preoperative conditions in living kidney donors, are correlated with each other. An increase in visceral adipose tissue is related to diminished renal function. Although the exact mechanisms remain unclear, various cytokines including adiponectin and insulin resistance could affect renal function. Abdominal subcutaneous adipose tissue was negatively correlated with muscle mass–based markers; thus, preoperative sarcopenic obesity might be a factor associated with renal dysfunction and consequently a poor prognosis. Malnutrition and renal function are closely correlated with each other. Eating habits could affect gut microbiota and host immunity. Thus, malnutrition might lead to renal dysfunction. Malnutrition is also correlated with inflammation and might affect prognosis. We emphasize that improvements in these parameters, managing inflammation and malnutrition prior to donor nephrectomy, can ensure improved renal function after donor nephrectomy and a good prognosis in living kidney donors. Appropriate exercise programs and nutritional interventions prior to a donor nephrectomy will lead to better outcomes in donors.

Correlation Analyses of Each Marker

We evaluated the correlation between the abdominal adipose tissue–, inflammation-, muscle mass–, and nutritional status–based markers. Spearman correlation coefficient analysis was performed using selected continuous variables such as age, BMI, VAT, SAT, TAVAT, TASAT, NLR, MLR, PLR, PMI, PEF, GNRI, and PNI. Figure 2A summarizes the P values and the Spearman r values obtained using correlation coefficient analyses. BMI showed a strong and significantly positive correlation with all the abdominal adipose tissue–based markers ($P < .001$). Four abdominal adipose tissue–based markers, that is, the VAT, SAT, TAVAT, and TASAT, showed a strong and significantly positive correlation with each other ($P < .001$). Three inflammation-based markers, that is, the NLR, MLR, and PLR, also showed a strong and significantly positive correlation with each other ($P < .001$). Additionally, 2 muscle mass–based markers and 2 nutritional status–based markers showed a strong and significantly positive correlation with each other (both $P < .001$). However, VAT and TAVAT showed a significantly negative correlation with PLR (both $P = .01$ and $P = .01$). The SAT showed a significantly negative correlation with PMI and PEF ($P = .005$ and $P = .007$, respectively). The TASAT also showed a significantly negative correlation with PMI and PEF ($P < .001$ and $P = .002$, respectively). Furthermore, PNI showed a significantly negative correlation with all 3 inflammation-based markers (NLR, $P = .001$; MLR, $P = .004$; PLR, $P < .001$). No significant correlation was observed between age and the other markers.

Prognostic Values of Renal Function Based on Abdominal Adipose Tissue–, Inflammation-, Muscle Mass–, and Nutritional Status–based Markers

Univariate and multivariate analysis were performed to determine the prognostic value of preoperative abdominal adipose tissue–, inflammation-, muscle mass–, and nutritional status–based markers to assess renal function after DN (Table 3). The development of CKD G3b 12 months after DN was defined as an event. Cutoff values for selected markers were determined using receiver operating characteristic curve analysis. Univariate analysis revealed that preoperative eGFR < 80 mL/min/1.73 m^2 was a statistically significant positive prognostic factor for renal dysfunction (odds ratio [OR], 5.4; 95% CI, 1.9–14.9; $P = .001$). The VAT, TAVAT, and VSR were statistically significant positive prognostic factors for renal dysfunction among abdominal adipose tissue–based markers (OR, 3.0; 95% CI, 1.1–7.8; $P = .03$; OR, 3.2; 95% CI, 1.2–8.7; $P = .03$; OR, 3.6; 95% CI, 1.4–9.5; $P = .01$, respectively). Among the inflammation-based markers, only NLR was observed to be a statistically significant positive prognostic

factor for renal dysfunction (OR, 3.8; 95% CI, 1.5–9.6; $P = .007$). The PMI was also a statistically significant positive prognostic factor for renal dysfunction (OR, 3.2; 95% CI, 1.1–9.1; $P = .04$). Moreover, among the nutritional status–based markers, only PNI was observed to be a statistically significant positive prognostic factor for renal dysfunction (OR, 4.1; 95% CI, 1.4–11.8; $P = .009$). Multivariate analysis revealed that the preoperative eGFR, TAVAT, and PNI were independent prognostic factors for renal dysfunction (OR, 4.3; 95% CI, 1.4–12.7; $P = .009$; OR, 4.2; 95% CI, 1.3–13.7; $P = .02$; OR, 5.1; 95% CI, 1.5–17.6; $P = .009$, respectively). Figure 2B-D shows a comparison of renal function after 12 months allocated by TAVAT and PNI. The postoperative eGFR in all LKDs with TAVAT $\geq$ 1900 and PNI $<$ 54 was significantly lower than these values in LKDs with TAVAT $<$ 1900 and/or PNI $\geq$ 54, indicating that achieving a TAVAT of $<$ 1900 or a PNI $\geq$ 54 preoperatively is important to ensure preservation of renal function (Fig 2B). In LKDs with preoperative eGFR $<$ 80 mL/min/1.73 m^2, effectively maintaining the TAVAT to $<$ 1900 and PNI $\geq$ 54 was important to avoid a decline in postoperative renal function (Fig 2C). Regarding LKDs with preoperative eGFR $\geq$ 80 mL/min/1.73 m^2, the postoperative eGFR of LKDs with TAVAT $\geq$ 1900 and PNI $<$ 54 was significantly lower than this parameter in LKDs with TAVAT $<$ 1900 and/or PNI $\geq$ 54 (Fig 2D).

DISCUSSION

The present study shows that the effect of preoperative donor conditions, which can be effectively assessed using abdominal adipose tissue–, inflammation-, nutritional status–, and muscle mass–based markers, significantly affect renal function/dysfunction after DN in LKDs. Abdominal adipose tissue–based markers and muscle mass–based markers show a characteristic difference between men and women as is expected and understandable. In this study, these markers showed a correlation with each other. Although the BMI did not differ between the sexes, a positive correlation was observed between the BMI and abdominal adipose tissue-based markers. The VAT and TAVAT showed a negative correlation with PLR. The SAT and TASAT showed a negative correlation with muscle mass–based markers, and inflammation based–markers showed a negative correlation with PNI. Multivariate analysis showed that among these markers, TAVAT and PNI served as independent markers for renal dysfunction. Figure 3 summarizes the present study. Although the mechanism by which abdominal VAT produces adverse effects on renal function is unclear, adiponectin or insulin resistance could be involved. Malnutrition and renal dysfunction are closely correlated with each other, and malnutrition might affect immunity and gut microbiota, resulting in renal dysfunction. Renal dysfunction concomitant with inflammation and/or sarcopenia might lead to poor prognosis in donors, including cardiovascular and/or cerebrovascular disease. Living kidney donors are originally healthy and their eGFRs are often $>$ 80 mL/min/1.73 m^2. However, owing to the increase in kidney transplantation and the shortage of deceased organ donation, the number of marginal donors has shown a marked increase. It is well known that LKDs develop CKD triggered by DN; thus, pre- and postoperative management are important. We hypothesize that preoperative exercise programs and nutritional interventions could improve prognosis in LKDs.

Japanese LKD guidelines recommend that a BMI $\leq$ 30 kg/m^2 is desirable in LKDs and that LKDs with BMI $>$30 kg/m^2 should lose weight to attain a BMI $\leq$ 25 kg/m^2 [12]. Although BMI can be estimated using a simple calculation and is commonly used to assess the degree of obesity, BMI alone may not adequately assess the degree of obesity because of variability in readings [13]. In the present study, BMI showed a positive correlation with abdominal adipose tissue–based markers, and thus we suggest that BMI could be a marker of obesity, including VAT- and SAT-related obesity. However, univariate and multivariate analysis did not reveal BMI to be a prognostic marker for renal dysfunction after DN. In contrast, univariate analysis showed that abdominal VAT-based markers (VAT and TAVAT) and the abdominal adipose tissue distribution marker (VSR) were prognostic markers for renal dysfunction, and multivariate analysis showed that TAVAT was an independent marker for renal dysfunction after DN. Our results suggest that not only the BMI but also the abdominal VAT-based markers should be estimated in LKDs prior to performing a DN and that abdominal VAT affects renal dysfunction/function, thereby affecting the prognosis in LKDs undergoing DN. These assessments and information might be more relevant in marginal donors and should be taken into consideration prior to performing a DN.

Inflammation-based markers were observed to show a correlation with each other in this study. The NLR was shown to be a prognostic marker for renal dysfunction after DN using univariate analysis, but was not shown to be an independent marker using multivariate analysis. A high NLR is associated with poor prognosis in several cases of malignant tumors, and a high NLR has been shown to be a prognostic marker for muscle-invasive bladder cancer as previously described [24]. Regarding patients with CKD, a high NLR is a prognostic marker for cardiovascular and all-cause mortality in patients undergoing hemodialysis and for arterial stiffness in patients undergoing peritoneal dialysis [25–27]. Inflammation is also associated with mortality and cardiovascular events in patients with CKD stage 3 to 5 [28,29]. Most LKDs develop disease classified as CKD stage $\geq$ 2 after DN; thus, inflammation could be detrimental in LKDs. Systemic inflammation should be controlled prior to DN to decrease the risk of mortality and cardiovascular events.

Regarding nutritional status–based markers, the GNRI (a common assessment tool used in patients undergoing dialysis) and the PNI (an index to determine the feasibility of resection and anastomosis in different segments of the gastrointestinal tract) showed a correlation with each other. Moreover, multivariate analysis showed that the PNI was an independent prognostic marker for renal

dysfunction after DN [21,22]. The PNI showed a significant negative correlation with inflammation-based markers (NLR, MLR, and PLR). A satisfactory nutritional status prior to undergoing DN might positively affect renal function after DN, thereby improving the prognosis in LKDs. The exact relationship between nutritional status and renal function is unclear. In patients with CKD (patients with or without dialysis treatment), those with malnutrition are at a higher risk of mortality than those without malnutrition [30]. Recently, a few studies have reported that quantitative and qualitative abnormalities in the gut microbiota (known as dysbiosis) affect renal dysfunction and that gut microbiota also affect host immunity, resulting in renal dysfunction [31,32]. Therefore, daily eating habits significantly influence the nutritional status in LKDs, and, therefore, the importance of correct nutritional management in LKDs needs to be emphasized.

As the population of elderly recipients increases, the number of elderly LKDs is also increasing. Aging is associated with a loss of muscle mass leading to sarcopenia. A study involving Asians has shown that sarcopenia is associated with the risk of cardiovascular events, poor quality of life, and death [33]. In this study, LKDs with known sarcopenia prior to undergoing DN constituted 30% of the study population, and PMI was shown to be a prognostic marker for renal dysfunction after DN, although it was not an independent marker. The study performed in Asians showed that approximately 10% of patients were sarcopenic even with CKD stages 1 to 2 and that sarcopenia is associated with a decreased eGFR [34]. The LKDs develop CKD after DN, and patients with CKD concomitant with sarcopenia are at a high risk of mortality [35]. Thus, optimal preoperative management could be useful to reduce mortality rates. Additionally, muscle mass–based markers showed a negative correlation with abdominal SAT-based markers in this study, and this condition is called sarcopenic obesity. Aging is associated with inactivity and a nutritional imbalance causing a loss of muscle mass, an increase in body adipose tissue stores, malnutrition, and inflammation [36]. Sarcopenic obesity is associated with a high risk of mortality [36]. Therefore, preoperative management including appropriate exercise programs and nutritional interventions could improve prognosis in LKDs.

Limitations of our study include the following: (1) The sample size of this study was small. (2) Data regarding LKDs were collected retrospectively from a single hospital or center. (3) The follow-up period was relatively short to adequately evaluate donor prognosis. Optimal cutoff values for each marker need to be validated using a larger sample size including multi-institutional samples to establish a novel marker specific to LKDs. Evidence-based recommendations for an appropriate exercise program and nutritional education are essential for an improved prognosis in LKDs. Additionally, the measurement of serum concentrations of cytokines and/or adipokines should be considered to provide definitive scientific evidence to support these results.

CONCLUSIONS

Living kidney donors frequently gain weight and are at a high risk of renal dysfunction after DN, resulting in poor prognosis because of the development of cardiovascular and cerebrovascular diseases. We emphasize that preoperative conditions indicated by abdominal adipose tissue–, inflammation-, nutritional status–, and muscle mass–based markers show a correlation with each other and could serve as prognostic markers for renal dysfunction after DN in LKDs. An understanding of this information could ensure better preoperative management through the institution of appropriate exercise programs and nutritional interventions, resulting in better outcomes in LKDs. Further research is needed to develop appropriate exercise programs and nutritional interventions to improve the prognosis in LKDs.

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