

Novel non-invasive and quantitative assessment of the renal function of transplanted kidneys using Doppler ultrasonography with the vascular index of superb microvascular imaging

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Purpose: This study assessed the reproducibility and clinical value of the vascular index (VI), derived from superb microvascular imaging (SMI) using Doppler ultrasonography, for evaluating renal function in transplanted kidneys.

Methods: This retrospective study included 63 renal transplant patients who underwent grayscale and Doppler ultrasonography with SMI from January 2022 to February 2023. The VI of the transplanted kidneys was measured using three methods (VI_{box} , VI_{F1} , VI_{F2}). The VI was compared across chronic kidney disease (CKD) groups categorized by estimated glomerular filtration rate (eGFR) and Kidney Disease: Improving Global Outcomes (KDIGO) CKD risk groups based on eGFR and albuminuria. The correlation between VI and renal function was evaluated. Univariate and multivariate linear regression analyses were used to identify predictors of eGFR.

Results: Significant differences in VI were observed among CKD groups based on eGFR (VI_{box} , $P=0.001$; VI_{F1} , $P<0.001$; VI_{F2} , $P<0.001$) and KDIGO CKD groups based on eGFR and albuminuria (VI_{box} , $P=0.039$; VI_{F1} , $P=0.001$; VI_{F2} , $P<0.001$). VI_{F1} and VI_{F2} demonstrated moderate/high correlations with eGFR ($r=0.627$, $P<0.001$ and $r=0.657$, $P<0.001$, respectively) and serum creatinine ($r=-0.626$, $P<0.001$ and $r=-0.649$, $P<0.001$, respectively). VI_{box} moderately correlated with eGFR ($r=0.445$, $P<0.001$). Multivariate regression identified the urine albumin-creatinine ratio (ACR) (adjusted odds ratio [aOR], 1.122; 95% confidence interval [CI], -0.007 to, 0.000; $P=0.030$) and VI_{F2} (aOR, 1.114; 95% CI, 0.466 to 1.235; $P<0.001$) were independently associated with eGFR.

Conclusion: The VI measured by drawing a region of interest along the border of the transplanted kidney in SMI (VI_{F2}) is highly reproducible and correlates well with eGFR. Both VI_{F2} and ACR independently predict eGFR.

Keywords: Ultrasonography; Color Doppler ultrasonography; Kidney transplantation; Glomerular filtration rate

Key points: The vascular index measured on superb microvascular imaging with a freehand region of interest along the outer margin of the transplanted kidney, excluding renal sinus fat, correlates well with estimated glomerular filtration rate (eGFR) and is an independent predictor of eGFR. Vascular index measurement on superb microvascular imaging is a non-invasive and quantitative method for assessing renal function in the transplanted kidney.

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Introduction

As the prevalence of chronic kidney disease (CKD) increases globally, the number of kidney transplantations has risen dramatically over the years [1,2]. In 2021, the total number of kidney transplantations in the United States reached 25,487 [2]. Although kidney transplantation is the most effective treatment for end-stage renal disease, the 5-year graft loss rate is reported to be approximately 30%, and nearly 50% of patients lose their graft within 10 years, despite advances in immunosuppression [3].

One of the key factors in the development of CKD in the kidney allograft is microvascular rarefaction [4]. The loss of peritubular capillaries is associated with lower long-term estimated glomerular filtration rate (eGFR) in the transplanted kidney [4]. Steegh et al. [5] reported that early peritubular capillary loss during the first 3 months after transplantation predicts lower renal function at 1 year. Although renal biopsy is the gold standard for assessing graft status, including microvasculature, percutaneous core needle biopsy is invasive and carries a risk of bleeding [6,7].

Ultrasonography (US) is a completely non-invasive method for the gross evaluation of the renal allograft [8]. Doppler US can depict the vascularity of the renal allograft and assess its vascular complications [8,9]. Conventional color Doppler US is effective for evaluating medium to large vessels; however, its ability to assess small and low-flow vessels is limited [10]. Various advanced techniques, including power Doppler imaging (PDI) and contrast-enhanced US (CEUS), have been explored for assessing renal microvasculature [10–14]. However, PDI is vulnerable to respiratory motion and probe movement due to its low frame rate [10], and while CEUS is relatively safe for evaluating renal vascularity, it is limited by longer examination times and high cost.

Recently, superb microvascular imaging (SMI) has been introduced as a novel technique that visualizes microvasculature and low-velocity flow using an adaptive algorithm [15–17]. SMI offers advantages over conventional color Doppler and PDI, providing high resolution, high frame rate, increased sensitivity, and fewer motion artifacts [15–17]. However, data regarding renal allograft evaluation using SMI remain scarce, and few studies have employed SMI for renal allografts [14,18]. Moreover, an optimal quantification method for renal allograft vascularity using SMI has not yet been established. Therefore, this study aimed to investigate the reproducibility and value of the vascular index (VI) derived from SMI in Doppler US for assessing renal function in the transplanted kidney.

Materials and Methods

Compliance with Ethical Standards

This single-center retrospective study was approved by the authors' affiliated Institutional Review Board (IRB No. 2023-05-010), and the requirement for informed consent was waived due to its retrospective design.

Study Design and Patients

From January 2022 to February 2023, 84 consecutive patients with renal transplantation underwent renal US with Doppler imaging, including the SMI technique, for clinical purposes. Patients were excluded if the SMI was obtained at a low frame rate, if raw SMI data for VI measurement were unavailable, if marked flash artifacts (defined as a definite flash artifact in perirenal fat adjacent to the renal cortex or parenchyma) were present, or if the imaging did not include the entire longitudinal diameter of the transplanted kidney.

Renal US Examination

All ultrasound examinations of the transplanted kidney were performed using one of four identical US machines (Aplio i800 System, Canon Medical Systems Corporation, Tokyo, Japan) with a multi-frequency convex transducer (i8CX1) operating at a center frequency of 4 MHz. Patients were scanned in the supine position. A board-certified radiologist with 10 years of experience in renal US and 5 years of experience in SMI conducted all examinations while remaining blinded to the patients' clinical information, including serum creatinine, eGFR, and albuminuria. The US examination included grayscale imaging, a color Doppler study, a spectral Doppler study with measurement of the resistive index (RI), and SMI.

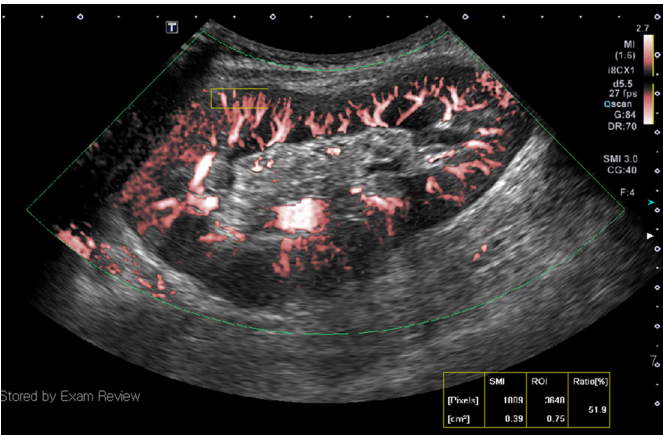
On grayscale imaging, the kidney size, the distance from the skin to the transplanted kidney, renal parenchymal echogenicity, and the presence of hydronephrosis or focal lesions were evaluated. The size of the transplanted kidney was measured in three planes: the transverse and anteroposterior lengths on the transverse scan and the longitudinal length on the longitudinal scan. For RI measurement, both color and spectral Doppler modes were used. RI values were measured at least three times in the upper, mid, and lower poles at the level of the interlobar or arcuate arteries, and the average value was recorded.

SMI was obtained using the following scan parameters: time gain of 40; color velocity scale of 2.3 cm/s; frame rate of 27 fps; and color frequency of 3.0 MHz. From the stored SMI still image of the transplanted kidney, one radiologist retrospectively drew a region of interest (ROI) to measure the VI, defined as the percentage ratio between the Doppler signal pixels and the grayscale pixels within the ROI. Three methods were used to measure the VI of

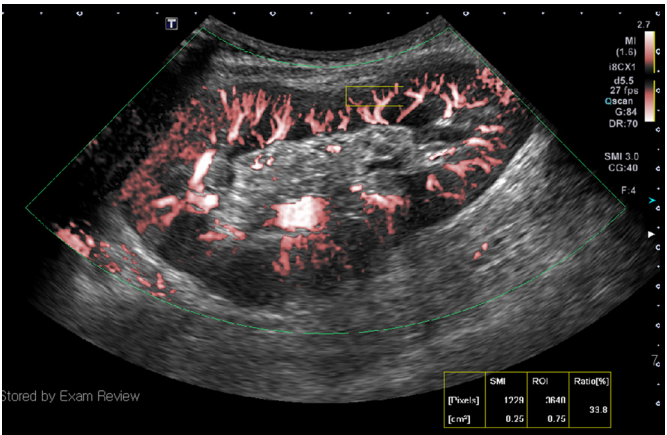
the transplanted kidney. VI_{box} was defined as the average of three vascular indices measured from 1.5×0.5-cm box ROIs placed in the upper, mid, and lower pole cortices. VI_{F1} was defined as the VI obtained from a freehand ROI manually drawn along the outer margin of the transplanted kidney. VI_{F2} was defined as the VI derived

from a freehand ROI manually drawn along the outer margin of the transplanted kidney, excluding the renal sinus fat (Fig. 1).

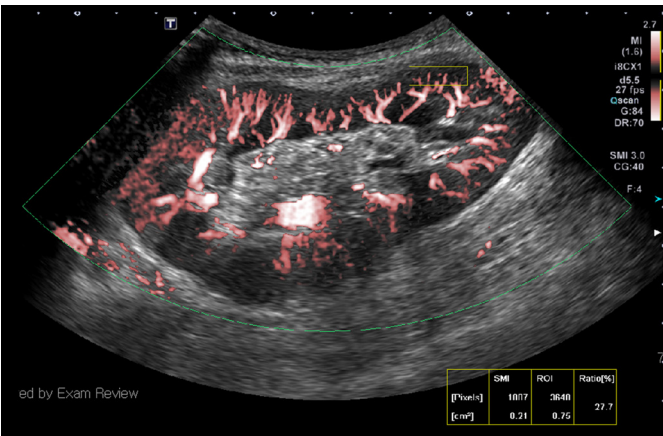
To assess interobserver agreement, the VI of 30 patients was measured independently by a second radiologist (with 6 years of experience in renal US and 1 year of experience in SMI) using all



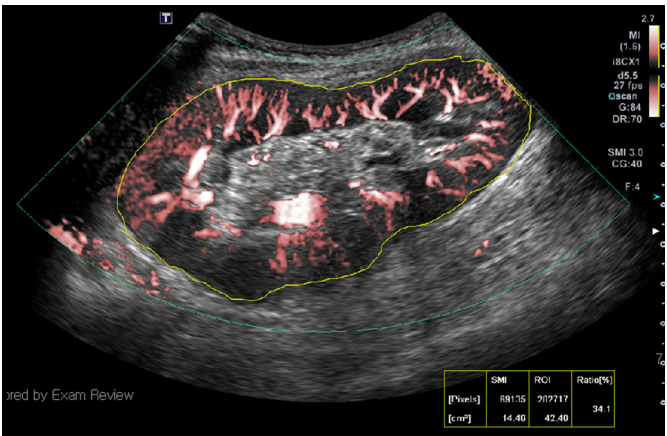
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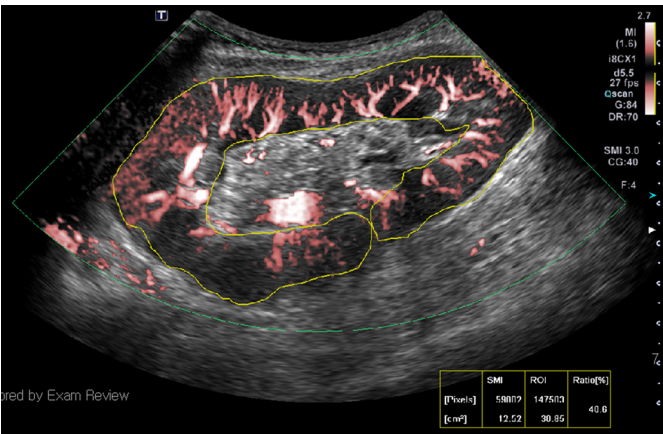
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D



E

Fig. 1. Three methods of measuring the vascular index (VI) of the transplanted kidney. VI_{box} is defined as the average of three VI_{box} values measured in the upper (A), middle (B), and lower (C) pole of the transplanted kidney. VI_{F1} is defined as the VI derived from a region of interest (ROI) drawn along the outer margin of the transplanted kidney (D). VI_{F2} is defined as the VI derived from an ROI drawn along the outer margin of the transplanted kidney, excluding renal sinus fat (E). SMI, superb microvascular imaging.

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012			Persistent albuminuria categories		
			Normal to mildly increased	Moderately increased	Severely increased
			<30 mg/g	30-300 mg/g	>300 mg/g
eGFR group 1	Normal or high	≥ 90			
	Mildly decreased	60–89			
eGFR group 2	Mildly to moderately decreased	45–59			
	Moderately to severely decreased	30–44			
eGFR group 3	Severely decreased	15–29			
	Kidney failure	<15			
GFR categories (mL/min/1.73m ²)					
Green: low risk			Yellow: moderately increased risk		Orange: high risk, Red: very high risk
Low risk group (KDIGO group 1)			Moderate risk group (KDIGO group 2)		High risk group (KDIGO group 3)

Fig. 2. Kidney Disease: Improving Global Outcomes (KDIGO) risk groups. CKD, chronic kidney disease; GFR, glomerular filtration rate; eGFR, estimated glomerular filtration rate.

three methods (VI_{box} , VI_{F1} , and VI_{F2}).

Data and Statistical Analysis

Patients were categorized into three groups based on eGFR (G1, eGFR >60 mL/min/1.73m²; G2, eGFR 45–60 mL/min/1.73m²; G3, eGFR <45 mL/min/1.73m²) and into three groups according to the Kidney Disease: Improving Global Outcomes (KDIGO) CKD risk classification based on eGFR and albuminuria (low, moderate, and high risk) [19]. In this study, the "high risk" and "very high risk" categories were combined into a single high-risk group (Fig. 2). Clinical data—including age, sex, kidney donor type, transplantation vintage, etiology of CKD, and renal function test results (serum creatinine, eGFR, and urine albumin-creatinine ratio [ACR])—were collected from electronic medical records. Laboratory results were obtained from tests performed within one week before or after the ultrasound examination.

VI values measured by the three methods were compared among CKD groups based on eGFR and among KDIGO risk groups using one-way analysis of variance (ANOVA) with Dunnett's post hoc test for pairwise comparisons. Comparisons of clinical data among CKD groups were performed using one-way ANOVA or the Kruskal-Wallis test, as appropriate, with the Shapiro-Wilk test assessing normality for continuous variables. Pearson's correlation analysis was used to evaluate the relationship between VI and renal function, as

indicated by serum creatinine or eGFR. The intraclass correlation coefficient (ICC) was calculated to assess interobserver agreement for the three VI measurement methods [20]. Reliability was classified as excellent (ICC >0.75), fair to good (ICC = 0.40–0.75), or poor (ICC ≤ 0.40) [21]. Univariate and multivariate linear regression analyses were used to identify factors predictive of eGFR. Statistical analyses were performed using Rex 3.1.2 (<https://rexsoft.org/>), with statistical significance defined as $P < 0.05$.

Results

Patients

Of the 84 eligible patients, 21 were excluded for the following reasons: SMI obtained with a low frame rate ($n=9$), unavailable raw SMI data for VI measurement ($n=6$), a marked flash artifact on SMI ($n=4$), and imaging that did not include the entire longitudinal diameter of the transplanted kidney ($n=2$). Ultimately, 63 patients (36 men and 27 women) who underwent renal US with Doppler imaging including SMI were included (Fig. 3). The mean age was 56.8 years (standard deviation, 9.62; range, 38 to 77 years). Patient demographics are detailed in Table 1. Among the KDIGO risk groups, the low-risk group contained a significantly higher proportion of women ($P=0.019$). No other significant differences in patient characteristics were observed among the eGFR groups or KDIGO risk groups.

Comparison of VIs Measured by Three Methods According to Renal Function

Statistically significant differences in VI were observed among CKD groups based on eGFR (VI_{box} , $P=0.001$; VI_{F1} , $P<0.001$; VI_{F2} , $P<0.001$) and KDIGO CKD risk groups based on eGFR and albuminuria (VI_{box} , $P=0.039$; VI_{F1} , $P=0.001$; and VI_{F2} , $P<0.001$) (Table 2). VI_{box} and VI_{F1} demonstrated a statistically significant difference between the eGFR group 1 (G1) and group 3 (G3) (VI_{box} , $P=0.005$ and VI_{F1} ,

$P<0.001$) and between group 2 (G2) and G3 (VI_{box} , $P=0.020$ and VI_{F1} , $P=0.000$). However, no statistically significant difference was found between G1 and G2 (VI_{box} , $P=0.543$ and VI_{F1} , $P=0.163$). VI_{F2} showed statistically significant differences in all between-eGFR group comparisons (G1 vs. G2, $P=0.016$; G1 vs. G3, $P<0.001$; and G2 vs. G3, $P=0.005$, respectively) (Fig. 4). All three VI measurement methods revealed statistically significant differences between KDIGO CKD groups 1 (low-risk group) and 2 (moderate-risk group) and between groups 1 and 3 (high-risk group), but with no statistically significant difference between groups 2 and 3 (Fig. 5).

Correlations between VI of the Transplanted Kidney, eGFR, and Serum Creatinine

Among the three methods of measuring the VI of the transplanted kidney, VI_{F1} and VI_{F2} showed moderately high correlations with eGFR ($r=0.627$, $P<0.001$ and $r=0.657$, $P<0.001$, respectively) and serum creatinine ($r=-0.626$, $P<0.001$ and $r=-0.649$, $P<0.001$, respectively). VI_{box} exhibited a moderate correlation with eGFR ($r=0.445$, $P<0.001$) and serum creatinine ($r=-0.447$, $P<0.001$) (Fig. 6).

Clinical and Doppler US Factors Associated with eGFR

Univariate linear regression analysis revealed that the urine ACR

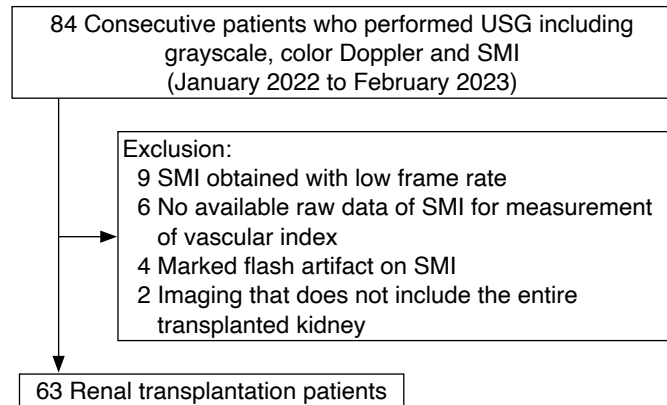


Fig. 3. Flowchart of the study. SMI, superb microvascular imaging; USG, ultrasonography.

Table 1. Patient characteristics by eGFR groups and KDIGO CKD risk groups

	eGFR group				KDIGO group			
	G1 (n=31)	G2 (n=16)	G3 (n=16)	P-value	Low (n=21)	Moderate (n=20)	High (n=22)	P-value
Age (year)	56.81±10	55.44±7.3	58.5±11.16	0.653	56.38±10.49	59.2±10.5	55.27±7.81	0.408
Sex				0.529				0.019
Male	16	11	9		7	15	14	
Female	15	5	7		14	5	8	
Donor				0.257				0.144
Living donor	23	12	15		14	16	20	
Deceased donor	8	4	1		7	4	2	
KT vintage (year)	9.55±8.6	7.94±8.77	10.38±11.28	0.764	10.14±9.54	6.7±6.8	11±10.73	0.219
CKD etiology				0.309				0.238
Unknown	9	4	4		6	7	4	
DM	7	1	6		4	4	6	
Hypertension	7	3	1		6	4	1	
Glomerular disease	8	8	5		5	5	11	
Creatinine (mg/mL)	0.97±0.2	1.35±0.18	1.76±0.43	<0.001	0.89±0.14	1.33±0.23	1.56±0.48	<0.001
eGFR (mL/min/1.73 m ²)	76.63±12.73	54.38±4.62	38.82±7.7	<0.001	80.21±12.12	55.8±11	48.47±15.79	<0.001
ACR	15.60 (6.70–50.30)	35.90 (15.30–91.50)	72.95 (29.65–145.05)	0.023	9.60 (5.60–15.60)	21.70 (11.2–59.35)	129.05 (67.22–422.55)	<0.001

Values are presented as mean±SD, number, or median (IQR).

eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; CKD, chronic kidney disease; KT, kidney transplantation; DM, diabetes mellitus; ACR, urine albumin-creatinine ratio.

Table 2. Comparison of VI measured by three methods according to CKD groups

	eGFR group				KDIGO group			
	G1 (n=31)	G2 (n=16)	G3 (n=16)	P-value	Low (n=21)	Moderate (n=20)	High (n=22)	P-value
VI _{box}	36.03±12.09	32.63±14.66	20.56±12.1	0.001	36.62±12.8	29.29±15.63	27.87±12.95	0.039
VI _{F1}	31.01±7.9	27.21±8.62	17.37±8.11	<0.001	32.19±7.46	24.7±10.32	22.93±9.22	0.001
VI _{F2}	32.64±8.98	25.51±9.18	17.41±7.78	<0.001	34.56±8.87	24.04±10.48	22.36±8.66	<0.001

Values are presented as mean±SD.

VI, vascular index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

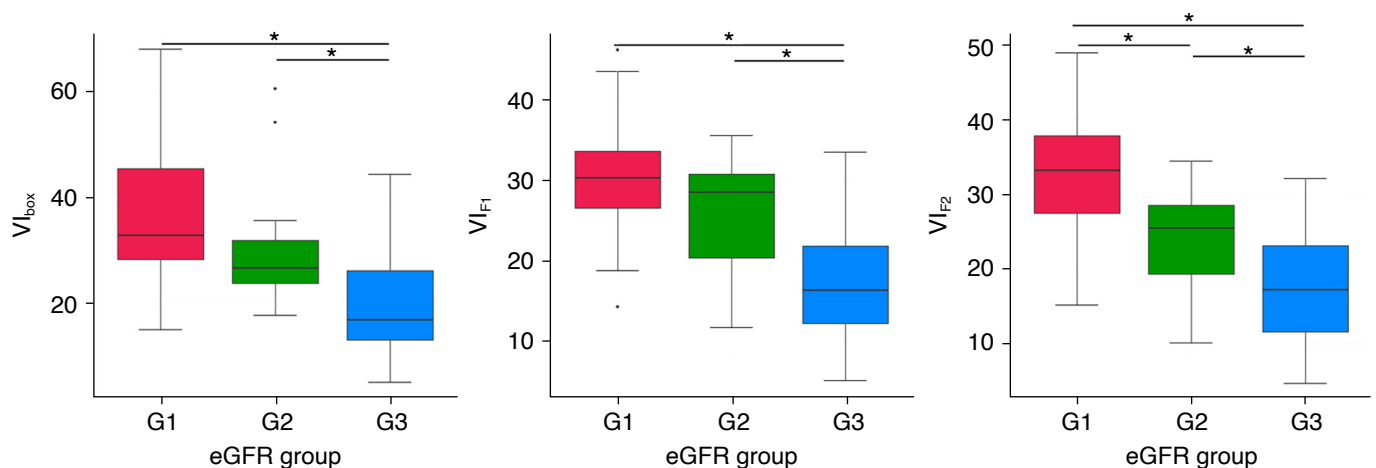


Fig. 4. Comparison of the vascular index (VI) values measured using three methods in groups based on the estimated glomerular filtration rate (eGFR). VI_{F2} shows a statistically significant difference in all between-group comparisons. VI_{box} and VI_{F1} exhibit statistically significant differences in G1 vs. G3 and G2 vs. G3, and with no significant difference between G1 vs. G2. *P<0.05.

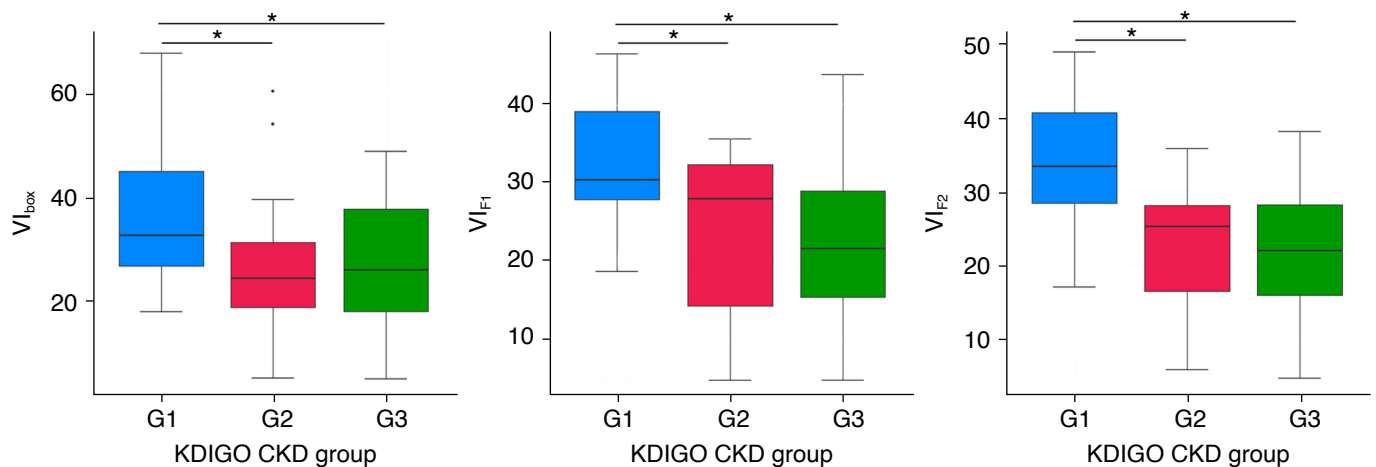


Fig. 5. Comparison of vascular index (VI) values measured by three methods in the Kidney Disease: Improving Global Outcomes (KDIGO) chronic kidney disease (CKD) groups. The VI measured by all three methods showed statistically significant differences in G1 vs. G2 and G1 vs. G3. *P<0.05.

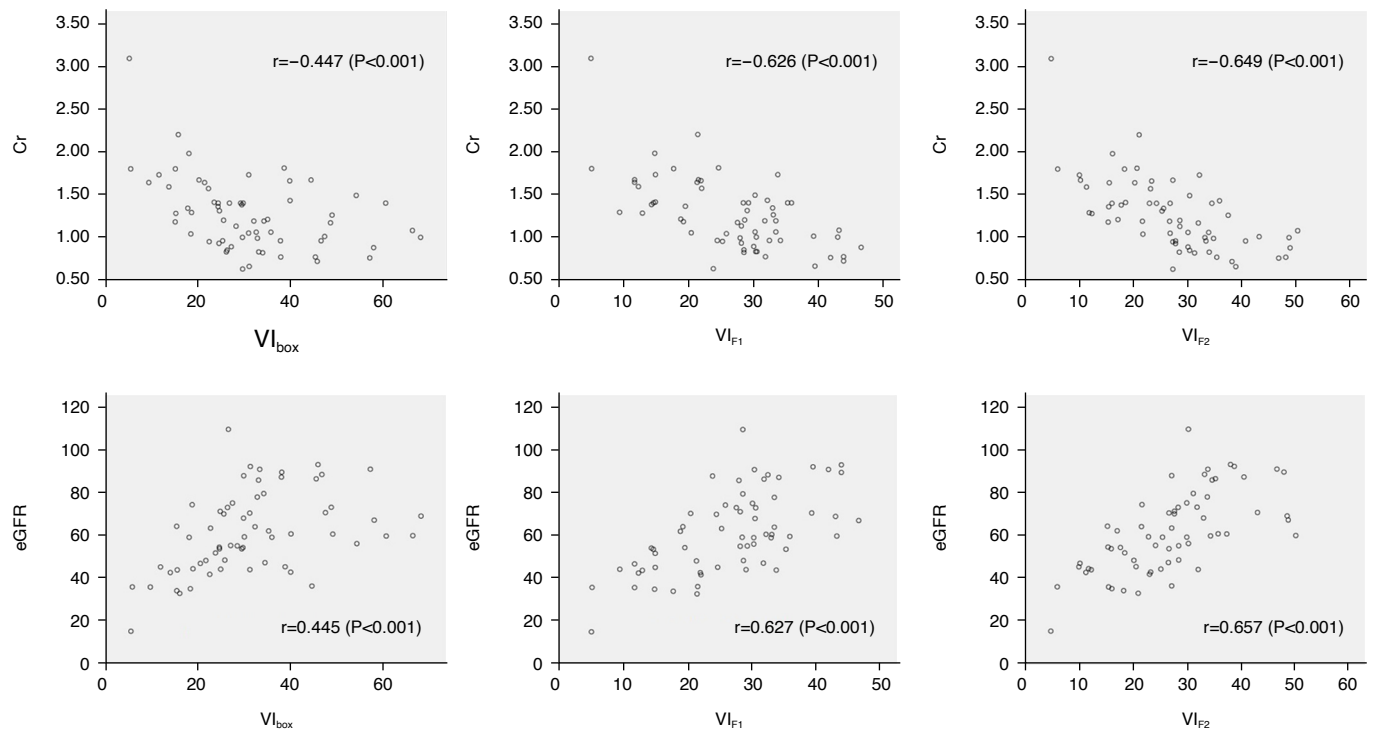


Fig. 6. Correlation between the vascular index (VI) of the transplanted kidney, estimated glomerular filtration rate (eGFR), and serum creatinine (Cr). A strong correlation was defined as a correlation coefficient of >0.5 ; moderate correlation, correlation coefficient ≥ 0.4 to ≤ 0.75 ; and poor correlation, a correlation coefficient of <0.4 .

Table 3. Clinical and Doppler ultrasound factors associated with eGFR

Parameter	Univariate			Multivariate			
	β	95% CI ^{a)}	P-value	β	OR	95% CI ^{a)}	P-value
Age	-0.304	-0.865 to 0.256	0.279	—	—	—	—
Sex	4.032	-6.547 to 14.612	0.446	—	—	—	—
Post-KT period ^{b)}	-0.000	-0.002 to 0.001	0.210	—	—	—	—
Donor type ^{c)}	-12.817	-32.755 to 7.120	0.201	—	—	—	—
ACR	-0.006	-0.010 to -0.002	0.003	-0.004	1.122	-0.007 to 0.000	0.030
Kidney volume	0.054	-0.060 to 0.168	0.344	—	—	—	—
Vascular index ^{d)}	0.989	0.606 to 1.372	<0.001	0.850	1.114	0.466 to 1.235	<0.001

eGFR, estimated glomerular filtration rate; CI, confidence interval; OR, odds ratio; KT, kidney transplantation; ACR, urine albumin-creatinine ratio

^{a)}95% CI for odds ratio, Wald confidence intervals were calculated. Stepwise selection method is used for the multivariate analysis. ^{b)}Post-KT period was defined as the time from the date of kidney transplantation to the date of ultrasound examination (days). ^{c)}The donor type was dichotomized into living and deceased donors. ^{d)}Vascular index derived from a ROI drawn along the outer margin of the transplanted kidney, excluding renal sinus fat (VI_{F2}).

($P=0.003$) and VI_{F2} ($P<0.001$) were associated with eGFR. Other parameters (age, sex, post-kidney transplantation period, and donor type) exhibited no associations with eGFR.

Multivariate linear regression analysis showed that the ACR (adjusted odds ratio [aOR], 1.122; 95% confidence interval [CI], -0.0007 to -0.000; $P=0.030$), and VI_{F2} (aOR, 1.114; 95% CI, 0.466 to 1.235; $P<0.001$) was independently associated with eGFR (Table 3).

Inerobserver Agreement of the Three VI Measurement Methods

The interobserver agreement of VI measurements was excellent between the two radiologists for all three methods (ICC: VI_{Box}, 0.953; VI_{F1}, 0.988; VI_{F2}, 0.932, respectively) (Table 4).

Table 4. Inter-observer agreement of the VI measurement methods

	VI _{box}	P-value	VI _{F1}	P-value	VI _{F2}	P-value
ICC	0.953 (0.896–0.978)	<0.001	0.988 (0.976–0.994)	<0.001	0.932 (0.857–0.967)	<0.001

The data in parentheses are the 95% confidence intervals.

VI, vascular index; ICC, interclass correlation coefficient.

Discussion

This study demonstrated that the VI measured by SMI is significantly lower in patients with reduced eGFR and that both ACR and VI_{F2} are independently associated with eGFR. Moreover, the interobserver agreement was excellent for all three VI measurement methods. These findings suggest that the VI derived from SMI can serve as a reliable indicator of renal function in transplanted kidneys, with VI_{F2} emerging as the most robust measurement method. In contrast, VI_{box} and VI_{F1} were not independently associated with eGFR. The VI_{box} method may be limited by its evaluation of only a small region of the transplanted kidney, whereas the VI_{F1} method may be confounded by the inclusion of renal sinus fat and large vessels within the ROI.

Assessing the cortical microvasculature is crucial for predicting microvascular rarefaction in kidney allografts. Although renal biopsy remains the most definitive method for analyzing the kidney microvasculature, it is an invasive procedure. A previous study reported that quantifying relative renal blood volume using enhanced computed tomography (CT) correlated with capillary rarefaction [22]; however, CT exposes patients to ionizing radiation, and iodine contrast may induce nephrotoxicity.

SMI is a state-of-the-art Doppler technique for detecting slow flow and small vessels using a novel clutter suppression algorithm, which separates flow signals from tissue motion artifacts with a high frame rate [15,23,24]. The kidney is an ideal organ for evaluation with Doppler US to obtain functional and vascular information [25]. A recent study demonstrated that SMI is more sensitive than color Doppler or power Doppler US in depicting cortical microvasculature in native kidneys [24].

However, the utility of SMI for evaluating both native and transplanted kidneys remains uncertain. Few studies have investigated the use of SMI in transplanted kidneys [14,18]. Kim et al. [14] reported that VI measured by the VI_{box} method on SMI was not significantly different between rejection and non-rejection groups, which contrasts with the findings of the present study; however, their study relied solely on the VI_{box} method, which may have limited the evaluation of overall kidney vascularity. In contrast, Gurbuz et al. [18] demonstrated that the distance between the kidney capsule and SMI-detected vessels could predict the chronic allograft damage index.

This study found that VI_{F2} had a strong correlation with eGFR and was independently associated with eGFR. The authors believe that the VI_{F2} method minimized selection bias by capturing the ratio of color to grayscale pixels across the entire renal parenchyma. However, unlike the eGFR groups, VI_{F2} did not reflect a stepwise difference across KDIGO risk groups. This discrepancy may stem from the complexity of the KDIGO grading system, which incorporates both eGFR and albuminuria. Since albuminuria reflects both glomerular and tubular damage, it may account for the observed differences between KDIGO risk groups and VI [26]. To the authors' knowledge, this study is the first to use the entire renal parenchyma of an image for acquiring the VI of the transplanted kidney. The excellent interobserver agreement supports that VI measurement on SMI is highly reproducible and suitable as a quantitative marker for renal function evaluation.

This study has several limitations. First, its retrospective design and relatively small sample size may introduce selection bias. Second, renal biopsy results were not analyzed because not all kidney transplant patients undergo allograft biopsy regardless of renal function, and biopsy is an invasive procedure with bleeding risk. Third, only single-vendor US machines were used, and the quantitative measurement of microvascular imaging (VI) is a unique feature of these machines. Fourth, the study provided only an indirect assessment of allograft vascularity using a two-dimensional VI from SMI, which does not quantify blood flow velocity because it is based on a pixel-counting method within the ROI. Fifth, the VI_{F2} method did not exclusively capture small vessels but also included some larger vessels within the ROI. Owing to the nature of manual ROI delineation, isolating only small vessels is challenging, and VI_{F2} was selected as a practical alternative with a clearly defined contour. Finally, renal function was assessed at a single time point, so whether VI can predict future allograft function remains unknown. Future longitudinal studies are warranted to evaluate the relationship between VI on SMI and the prognosis of transplanted kidneys.

In conclusion, the VI measured by drawing a freehand ROI along the border of the transplanted kidney in SMI (VI_{F2}) is a highly reproducible method that correlates well with eGFR. Both VI_{F2} and ACR are independent predictors of eGFR. The VI derived from SMI in Doppler US provides a non-invasive, quantitative, and reproducible

assessment of renal function in transplanted kidneys.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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