Thieme

Correlation of early contrast-enhanced ultrasound parameters with postoperative graft function and at six months after kidney transplantation

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ABSTRACT

Purpose We analyzed which contrast-enhanced ultrasound (CEUS) parameters are associated with reduced kidney function in the early postoperative period and are prognostic for kidney function six months after transplantation.

Materials and Methods This prospective observational study included 74 patients in whom quantitative CEUS analysis and Doppler ultrasound were performed early after kidney transplantation (10 ± 6 days). For each region of interest (ROI) the time-to-peak intensity (TTP) and the respective delta between ROIs within interlobar artery, cortex, and medulla were compared. Results were correlated with kidney function at the time of imaging and six months later.

Results Patients with an eGFR < 30 ml/min at the time of investigation had significantly slower cortical enhancement with a longer cortical TTP (cTTP: 16.1 ± 0.9 vs. 11.7 ± 0.7 sec, $p < 0.001$), as well as a significant delay between the arterial and cortical phases (c–a), as shown in longer ΔTTP (c–a): 8.2 ± 0.9 vs. 4.2 ± 0.5 sec, $p < 0.001$. There was a significant negative correlation between cTTP and eGFR with a correlation coefficient of −0.37 ($p < 0.001$), as well as between ΔTTP (c–a) and eGFR with a correlation coefficient of −0.40 ($p < 0.001$). Reduced kidney function after 6 months correlated significantly with the findings of the initial CEUS examination ($p = 0.005$, correlation coefficient −0.39).

Conclusion CEUS revealed significant differences in temporal enhancement dynamics in patients with reduced kidney function after transplantation. Quantitative CEUS might therefore be able to depict graft function regarding microvascular damage and be of prognostic value regarding long-term renal outcomes.

Purpose

Ultrasound is the method of choice for identifying vascular and surgical complications after kidney transplantation, and contrast-enhanced ultrasound (CEUS) has become an established tool for assessing focal processes, renal infarcts, and cortical necrosis [1]. Doppler ultrasound is the common method used to evaluate the

perfusion status of the renal graft. Resistive index (RI) is still a commonly used indicator for parenchymal pathologies such as acute rejection, acute tubular necrosis, and calcineurin inhibitor toxicity, all of which are associated with higher RI values [2]. These conditions may involve pathological changes that affect peritubular and glomerular capillaries, a type of vessel that cannot be directly quantified with Doppler ultrasound. To date, no ultrasonographic parameter has been established for diagnosing parenchymal pathologies that are associated with delayed or decreasing graft function.

High RI values have been shown to be associated with worse renal outcomes in the first years after transplantation [3, 4] but there is still controversy if they truly indicate intrarenal pathology or rather reflect recipient atherosclerotic disease [5]. Due to low sensitivity and specificity, RI values may rather be a nonspecific sign of interstitial edema and renal vascular resistance [5]. Additionally, RI seems to be highly influenced by extrarenal factors such as recipient age and hemodynamics [2, 5–8]. In healthy patients, RI usually increases with age [9]. In kidney transplant patients, RI is considered normal if it is < 0.7, indeterminate between 0.7 and 0.8, and elevated if > 0.8. Interpretation is important in combination with the hemodynamic status and the timing of the investigation as interstitial edema results in elevated RI due to an absent end-diastolic flow [10, 11].

Serum creatinine, or estimated glomerular filtration rate (eGFR), together with clinical judgement remain the main indicators as to whether parenchymal pathology is present, and kidney biopsy as the gold standard of diagnosis should be performed [12]. A new noninvasive parameter detecting parenchymal damage earlier and with higher specificity than eGFR and RI would have a relevant clinical impact in the early and later postoperative period.

Due to the lack of nephrotoxicity and the low anaphylactic reaction rates of the contrast medium, as well as the excellent ability to evaluate the microcirculatory perfusion status in real time, CEUS has unique advantages over traditional Doppler imaging for patients who underwent renal transplantation [13, 14]. In recent years, research as to whether CEUS could be of use in this setting has emerged. Using commercially available quantification tools, contrast-enhanced ultrasound can be used to characterize true renal perfusion dynamics with time-intensity curves. However, little is known about its role in displaying kidney function. Correlating CEUS parameters with standard kidney function tests like eGFR as well as with clinical outcomes would be the first step towards more sensitive and possibly more kidney-specific follow-up parameters in kidney transplantation and has the potential to add prognostic value to our ultrasound examination. We, therefore, analyzed which CEUS parameters correlated with impaired kidney function in the early postoperative period and assessed their prognostic values for reduced eGFR up to 6 months after transplantation.

Materials and Methods

Patients

Of all patients undergoing kidney transplantation between 01/2021 and 01/2023 at our transplant center, 92 patients agreed to participate in this prospective observational study, which was approved by the medical ethics committee and conducted in accordance with the Declaration of Helsinki. Cadaveric and living donors were included. Exclusion criteria were known allergy to ultrasound contrast media, compressing perirenal hematoma, high-grade hydronephrosis, renal artery stenosis, right-to-left heart shunt, severe pulmonary hypertension, cardiovascular instability, and lack of written informed consent. Immunosuppressive medication after transplantation was administered according to the center-specific standard with tacrolimus, enteric coated mycophenolic acid, and corticosteroids. Patients were followed up closely within the first 6 months after transplantation in order to ensure appropriate trough levels.

Ultrasound examination

All patients were examined under standard conditions by the same sonographer with CEUS experience, using the Philips iU22 ultrasound machine with a 3–5 MHz convex transducer. A standardized protocol was used for B-mode and Doppler ultrasound examination. RI values were measured at six different interlobar arteries at the upper and lower pole, as well as the pars intermedia, and the mean value was calculated.

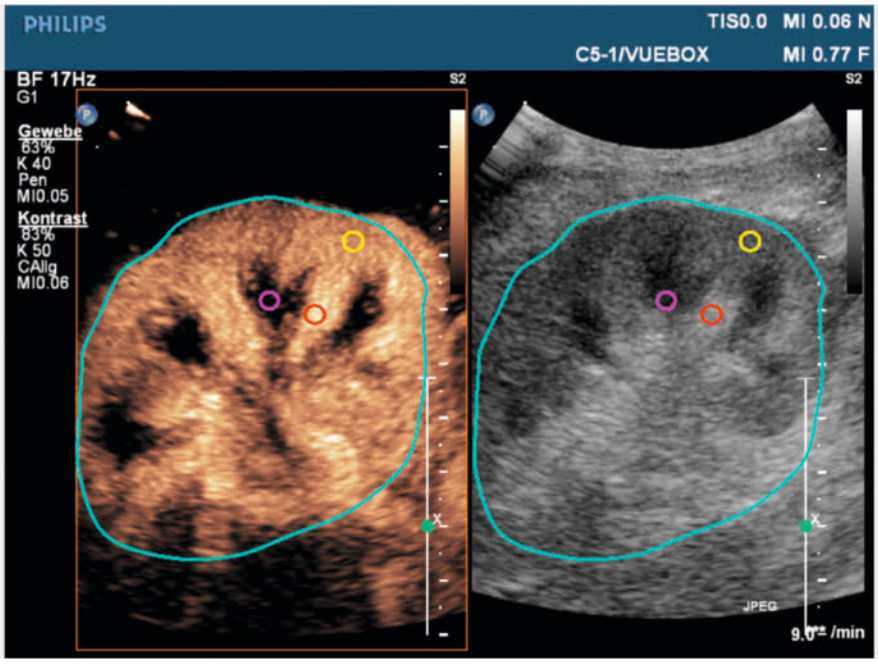
For the contrast study a contrast-specific preset was used and set to a mechanical index of 0.06, a frame rate of 12 Hz, and a dynamic range of 50 dB. Depth and gain were optimized for each individual. Focus was fixed at the bottom of the image. All parameters remained unchanged during the procedure. The ultrasound contrast agent SonoVue (Bracco, Milan, Italy) was used in all patients and a bolus of 1.8 ml was injected over a 20 G needle using a 3-way tap, followed by a saline flush. The kidney was visualized in the longitudinal axis, encompassing the hilum, interlobar arteries, medulla, and cortex. The enhancement was recorded for over 90 seconds in a cine loop file starting at the time of injection and stored as DICOM file.

Contrast-Enhanced Ultrasound Quantification

For quantification of contrast enhancement, the Bracco software Vuebox (Bracco, Milan, Italy) was used and the bolus perfusion model was chosen. A clip length of 60 seconds was analyzed starting at arrival time of the contrast agent within the delimitation to factor out circulation time. Two regions of interest (ROIs) with an area of 10 mm^2 were placed in each of the interlobar arteries, the cortex, and the medulla as shown in ▶ **Fig. 1**. Time-intensity curves were generated and the calculated quantitative parameters of the two ROIs for each region were averaged. Only the temporal parameter time to peak (TTP) was included in the analysis. TTP was defined as the time from zero to maximum intensity within the delimitation. In addition, the time difference in TTP was calculated between the arteries, cortex, and medulla and named ΔTTP (c–a), ΔTTP (m–a), and ΔTTP (m–c), respectively. Only temporal parameters were chosen for this study as they have shown to be more robust than intensity-related parameters [15, 16].

Clinical and laboratory data

Blood samples were routinely collected on the day of examination including serum creatinine, eGFR, tacrolimus trough levels, and hemoglobin. eGFR was calculated using the CKD-EPI formula. Kidney function tests were repeated 180 ± 30 days after transplantation.



▶ **Fig. 1** Selection of "ROI" (region of interest) in the Vuebox software within the cortex (yellow), medulla (purple) and interlobar artery (red).

Impaired kidney function was defined as an eGFR < 30 ml/min. Delayed graft function was defined as the need for dialysis between 24 hours and 7 days after transplantation.

Statistical analysis

SPSS 28.0 (SPSS Inc, Chicago, USA) was used for all statistical analyses. Demographic and clinical variables are presented as mean with standard deviation or as frequency with percentage. For comparison between groups, the Mann-Whitney U test was selected after the Shapiro-Wilk test showed no normal distribution. For correlation testing, Spearman correlation was used. Differences were considered significant at $p < 0.05$.

Results

From 01/2021 to 01/2023, 92 kidney transplant recipients were enrolled in this study and ultrasound examination was performed 10 ± 6 days after surgery. No adverse effects were seen following contrast injection. Of the initial 92 patients, 19 patients were excluded because the ROIs could not be positioned optimally in the CEUS image within the quantification software (mostly due to technical issues regarding the video recording), leading to a cohort of 73 patients eligible for analysis. All patients received triple immunosuppressive therapy with Tacrolimus, Mycophenolate mofetil, and Methylprednisolone. Delayed graft function occurred in 10 patients, all of whom were deceased kidney transplant recipients. Because of the small sample size, statistical analysis of this subgroup was not performed.

Impaired kidney function on the day of ultrasound examination was defined as an eGFR ≤ 30 ml/min and patients were categorized accordingly. Patients with reduced graft function at the time of examination (N = 36) were significantly more likely to have a transplant from a deceased donor ($p = 0.016$) and to have experienced delayed graft function ($p < 0.001$). In patients with impaired graft function, there was a tendency toward older recipient age ($p = 0.046$) and higher BMI ($p < 0.001$) with a longer waiting time to transplantation ($p = 0.044$), as well as older donors ($p = 0.028$) with a higher rate of arterial hypertension in their medical history ($p = 0.018$), which is shown in ▶ **Table 1**.

Ultrasound parameters in patients with reduced kidney function during initial evaluation

Patients with an eGFR ≤ 30 ml/min on the day of examination showed significant differences in the cortical perfusion parameter cTTP compared to patients with an eGFR > 30 ml/min (16.1 ± 0.9 vs. 11.7 ± 0.7 sec, $p < 0.001$, ▶ **Fig. 2a**). We saw significant temporal delay between enhancement of the arterial and cortical ROI resulting in higher ΔTTP(c–a) values when comparing patients with an eGFR ≤ 30 ml/min to patients with an eGFR > 30ml/min (8.2 ± 0.9 vs. 4.2 ± 0.5 sec. $p < 0.001$, ▶ **Fig. 2b**). There was a moderate negative correlation between cTTP and eGFR with a correlation coefficient of −0.37 ($p < 0.001$), as well as between ΔTTP(c–a) and eGFR with a correlation coefficient of −0.40 ($p < 0.001$).

Patients with impaired kidney function on the day of examination had significantly higher RI values (0.70 vs. 0.74, $p = 0.014$, ▶ **Fig. 2c**) than patients with an eGFR > 30 ml/min. Correspondingly, higher RI values correlated significantly with a lower eGFR (correlation coefficient: −0.35, $p = 0.003$). All analyzed parameters are shown in ▶ **Table 2** and visualized in **supplementary Fig. 1**.

Ultrasound parameters in patients with reduced kidney function 6 months after transplantation

Recipients of deceased donor kidneys, whose kidney function was impaired 6 months after transplantation had a significantly

▶ **Table 1** Baseline characteristics of patients with reduced and normal kidney function on the day of ultrasound examination.

	eGFR ≤ 30 ml/min n = 36	eGFR > 30 ml/min n = 37	p-value
Recipient			
Demographics and comorbidities			
Age (years)	51 ± 12	45 ± 14	**0.05**
Sex (male)	17 (46)	20 (54)	0.18
BMI	27 ± 4	23 ± 5	**< 0.001**
Arterial hypertension	32 (89)	30 (81)	0.35
Diabetes mellitus	4 (11)	2 (5)	0.38
Transplantation			
Renal replacement time to transplant (years)	7 ± 5	5 ± 4	**0.04**
Living kidney donation	7 (19)	17 (46)	**0.02**
Cold ischemia time (minutes)	608 ± 319	508 ± 387	0.06
Delayed graft function	10 (28)	0 (0)	**< 0.001**
Kidney function			
Creatinine on the day of CEUS (mg/dl)	5.4 ± 3.1	1.6 ± 0.6	**< 0.001**
eGFR on the day of CEUS (ml/min)	14 ± 8	50 ± 13	**< 0.001**
Creatinine 6 months after transplantation (mg/dl)	1.8 ± 0.7	1.4 ± 0.5	**0.01**
eGFR 6 months after transplantation (ml/min)	46 ± 19	57 ± 17	**0.01**
Tacrolimus trough level on the day of CEUS (ng/ml)	7.8 ± 2.5	8.4 ± 2.9	0.32
Donor			
Age (years)	57 ± 12	49 ± 14	**0.03**
Arterial hypertension	17 (46)	7 (19)	**0.02**
Sex (male)	23 (64)	20 (54)	0.40
Time from TPL to CEUS (days)	11 ± 6	11 ± 6	0.47

All data are presented as mean (± SD) or percentage (%). BMI: body-mass index, TPL: transplantation, CEUS: contrast-enhanced ultrasound, eGFR: estimated glomerular filtration rate.

longer cortical TTP (cTTP: 19.3 ± 6.4 sec vs. 13.7 ± 4.9 sec, p = 0.022, ▶ **Fig. 3a**) and slower arterio-cortical transit time (ΔTTP(c–a): 11.0 ± 6.4 vs. 5.8 ± 4.4. p = 0.049, ▶ **Fig. 3b**) in their initial CEUS examination compared to patients with an eGFR > 30ml/min. In these patients, eGFR after 180 days correlated with cTTP and ΔTTP(c–a) at the time of examination (p = 0.005, correlation coefficient −0.39, respectively).

In opposition to CEUS values, RI values at the initial evaluation did not correlate with kidney function after 6 months but with recipient age (p < 0.001, correlation coefficient 0.614).

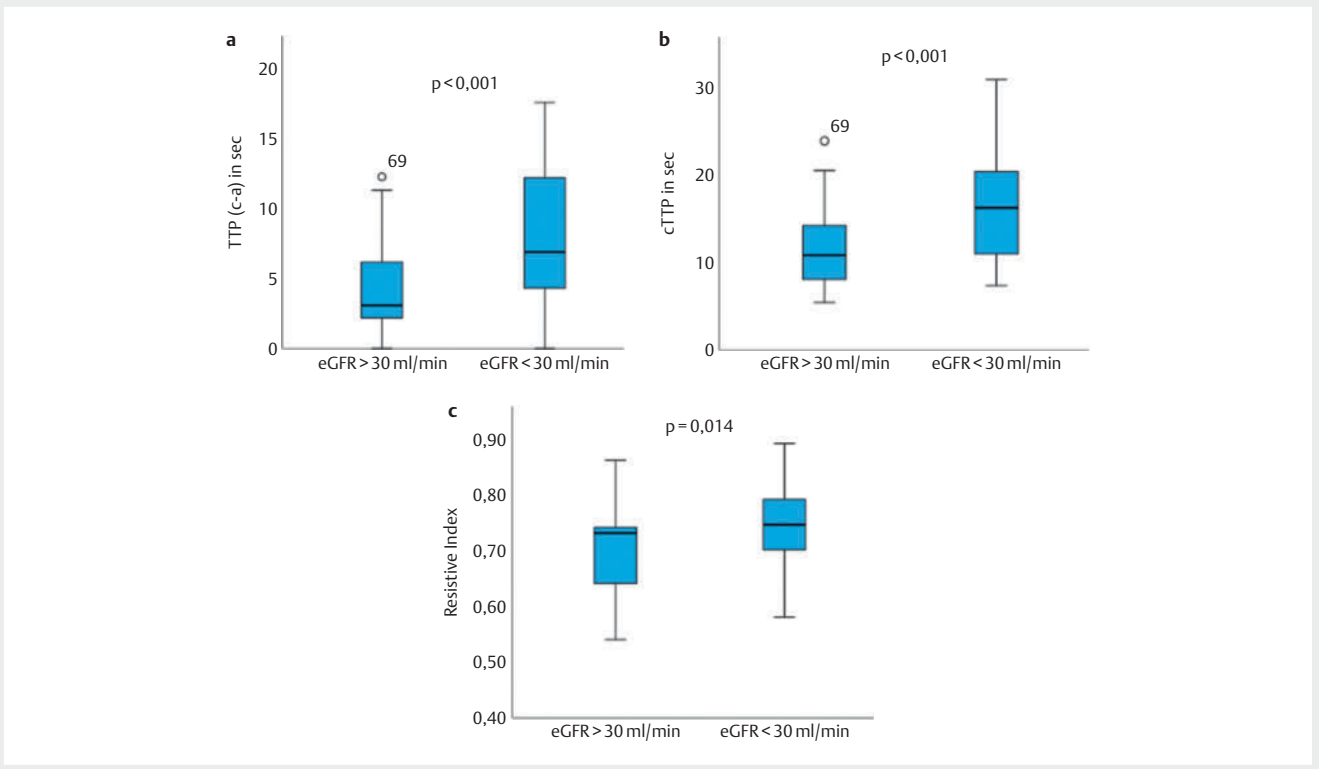
Conclusion

The main finding of our study was that impaired graft function with an eGFR ≤ 30 ml/min led to significantly higher RI values (i) and slower cortical enhancement with prolonged transit time between interlobar artery and cortex (ii) when compared to patients with an eGFR > 30 ml/min. CEUS parameters, but not the RI, were prognostic for sustained impairment of kidney function up to 6 months after surgery.

i. So far, RI is the standard follow-up parameter after kidney transplantation related to parenchymal disease [2]. In the present study, patients with impaired graft function at the time of ultrasound examination had significantly higher RI values than patients with an eGFR > 30 ml/min. This corresponds to previous studies showing an association between elevated RI and delayed graft function and early graft loss [17–19]. However, a high RI at the initial evaluation shortly after surgery did not correlate with reduced graft function after 6 months, indicating a reduced prognostic benefit in our study. This result is consistent with previous literature that found no prognostic utility for worse renal outcomes [20, 21]. In contrast, other study groups found early RI values to be prognostic of graft function and survival in the mid and long term [4, 17–19].

The correlation we found between RI and recipient age is well established and thought to be linked to generalized atherosclerosis of the recipient, likely accounting for its prognostic value regarding mortality and graft loss rather than intrarenal pathology [5–7].

ii. Recently, CEUS has become the method of choice when assessing the microvasculature of the kidney graft, showing perfusion in real time and high spatial resolution [1]. In our study, we found differences in cortical microperfusion in patients with and without impaired graft function in the early postoperative period,



▶ **Fig. 2** CEUS parameters in patients with impaired versus better kidney function in the initial investigation early after transplantation (10 ± 6 days). TTP (c–a): Time-to-peak difference between cortex and artery (**a**), cTTP: Cortical time-to-peak (**b**) and RI (resistive index) values (**c**)

▶ **Table 2** Ultrasound parameters in patients with reduced and normal kidney function on the day of CEUS examination.

	eGFR ≤ 30 ml/min n = 36	**eGFR > 30 ml/min n = 37**	**p-value**
RI	0.74 ± 0.07	0.70 ± 0.07	**0.01**
aTTP (sec)	7.87 ± 2.87	7.45 ± 3.06	0.40
cTTP (sec)	16.11 ± 5.93	11.68 ± 4.26	**< 0.001**
mTTP (sec)	22.10 ± 6.24	19.84 ± 5.88	0.12
ΔTTP (c–a) (sec)	8.24 ± 5.21	4.2 3 ± 3.31	**< 0.001**
ΔTTP (m–c) (sec)	5.99 ± 6.07	8.16 ± 4.29	0.09
ΔTTP (m–a) (sec)	14.23 ± 5.13	12.39 ± 4.30	0.13

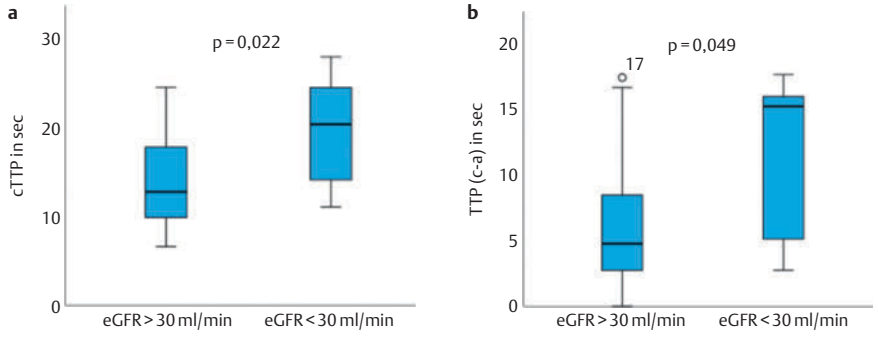
All data are presented as mean (± SD). RI: resistive index, TTP: time-to-peak, a(TTP): artery, c(TTP): cortex, m(TTP): medullar.

reflected by a longer cortical time to peak and delayed transit between the interlobar arteries and the cortex in patients with an eGFR ≤ 30ml/min. Preceding studies demonstrated a correlation between kidney function and cortical blood flow in patients with CKD [22, 23], in living kidney donors [24] as well as kidney transplant recipients [25, 26].

Studies concerning the long-term prognostic value of early CEUS are rare. We showed that patients with sustained impaired kidney function at 6 months post-transplantation already demonstrated a longer cortical time to peak and delayed transit between the interlobar arteries and the cortex in their initial ultrasound examination. This corresponds to the findings of Mori et al. who examined the prognostic value of conventional and CEUS parameters up to 12 months after transplantation. The authors found that higher cortical graft perfusion in the initial ultrasound examination was related to a better long-term eGFR [27]. Similar results were obtained by Schwenger et al., who showed that higher renal blood flow measured by CEUS one week after transplantation was prognostic for better kidney function up to one year after transplantation as well as for chronic allograft nephropathy in the long term. Of note, neither could be demonstrated for Doppler parameters such as the renal resistive index [25, 26].

Besides its possible prognostic value, CEUS is especially important for differentiating between infarction and ischemia with influence on clinical decision making such as the amount of immunosuppressive treatment in acute rejection therapy. Beyond that, CEUS can help to identify indeterminate transplant lesions, especially complicated renal cysts (EFSUMB guidelines) [28]. Interestingly, CEUS is seen as the modality of choice in post-transplant kidney disease compared to MRI and CT. However, the method is dependent on examiner experience [29].

In accordance to our findings, prolonged cortical TTP has been associated with severe transplant pathology and delayed graft function [30, 31] including acute vascular rejection [32, 33] and acute tubular necrosis [31] in previous studies. Fischer et al. were the first to show that especially vascular rejection was associated



▶ **Fig. 3** Initial CEUS parameters in patients with impaired versus better kidney function six months after transplantation. cTTP: Cortical time-to-peak (**a**), TTP(c–a): t = Time-to-peak difference between cortex and artery (**b**)

with delayed cortical enhancement and delayed arterio-cortical transit time [33], which reliably distinguished patients with vascular rejection from patients with normal kidney function. In our cohort, none of the patients receiving biopsy suffered from vascular rejection, so no analysis could be performed in this regard.

In our study, there was no significant difference in transit time from cortex to medulla between patients with normal and reduced kidney function. The literature shows that shorter cortico-medullary transit, possibly due to shunting in the face of high cortical resistance, could be seen in some studies in the later post-transplantation period [30, 34]. Other studies found no significant differences in TTP between delayed and normal graft function in the early postoperative period [34, 35].

iii. The present study has some limitations. First, this was a single-center study with a relatively small sample size, however, within the range of the previous studies on this topic. Second, although all exams where prospectively done by the same operator with the same settings, the timespan from transplantation to examination was not equal for all patients, which could have influenced the results with respect to its prognostic value. Third, eGFR and serum creatinine are encumbered by certain drawbacks and represent changes in a delayed manner, making them a suboptimal gold standard for kidney function. Histopathological correlation is therefore desirable.

In summary, our data show that quantitative CEUS examination within the early postoperative period can identify impaired graft function early after transplantation but also six months after surgery. CEUS might, therefore, be of use for illustrating microvascular damage resulting in impaired graft function. Further studies analyzing a correlation with histopathological vascular changes are needed to validate our findings.

Conflict of Interest

The authors declare that they have no conflict of interest.

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