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Can Split Renal Volume Assessment by Computed Tomography Replace Nuclear Split Renal Function in Living Kidney Donor Evaluations? A Systematic Review and Meta-Analysis

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Abstract

Background: As part of their living kidney donor assessment, all living donor candidates complete a computed tomography (CT) angiogram, but some also receive a nuclear renogram for split renal function (SRF%).
Objective: We considered whether split renal volume (SRV%) assessed by CT can predict SRF%.
Design: Systematic review and meta-analysis.
Setting: Living donor candidates undergoing evaluation as potential living kidney donors.
Patients: Living donor candidates who received both a nuclear renogram for split function and CT for SRV as part of their living donor work-up.
Measurements: Split renal volume from CT scans and SRF from nuclear renography.
Methods: We performed a systematic review and meta-analysis of the literature, abstracting data and digitizing plots where possible. We searched Medline, EMBASE, and the Cochrane Library. We added data from donor candidates assessed in London, Ontario from 2013 to 2016. We used fixed and random-effects models to pool Fisher's *z*-transformed Pearson's correlation coefficient (*r*). We conducted random-effects meta-regression on digitized and aggregate data. Studies were restricted to living kidney donors or living donor candidates.
Results: After pooling 19 studies (n = 1479), we obtained a pooled correlation of $r = 0.74$ (95% confidence interval [CI] = 0.61-0.82). By linear regression using individual-level data, we observed a 0.76% (95% CI = 0.71-0.81) increase in SRF% for every 1% increase in SRV%. Split renal volume had a specificity of 88% for discriminating SRF at a threshold that could influence the decision of which kidney is to be removed (between-kidney difference ≥10%). Predonation SRV and SRF both moderately predicted kidney function 6 to 12 months after donation: $r = 0.75$ for SRV and $r = 0.73$ for SRF; $\Delta r = 0.05$ (–0.02, 0.13).
Limitations: Most studies were retrospective and measured SRV and SRF only on selected living donor candidates. Efficiency gains in removing the SRF from the evaluation will depend on the transplant program.
Conclusion: Split renal volume has the potential to replace SRF for some candidates. However, it is uncertain whether it can do so reliably and routinely across different transplant centers. The impact on clinical decision-making needs to be assessed in well-designed prospective studies.
Trial registration: The digitized data are registered with Mendeley Data (doi10.17632/dyn2bfgxxj.2).

Abrégé

Contexte: Dans le cadre de leur évaluation comme donneur, tous les candidats au don de rein vivant passent une angiographie par tomodensitométrie (CT), mais certains sont également soumis à un rénogramme nucléaire qui mesure la fonction rénale séparée (% de la FRS).
Objectif: Nous souhaitions vérifier si le volume rénal séparé (% du VRS) évalué par tomodensitométrie pouvait prédire le pourcentage de la FRS.
Type d'étude: Une revue systématique et une méta-analyse.
Cadre: Évaluation des candidats au don d'un rein de leur vivant.

Sujets: Les candidats au don d'organes vivants qui, dans le cadre de leur évaluation, ont été soumis à un rénogramme nucléaire (mesure de la FRS) et à une tomodensitométrie (mesure du VRS).
Mesures: Le volume rénal séparé mesuré par tomodensitométrie et la fonction rénale séparée mesurée par rénogramme nucléaire.
Méthodologie: Nous avons effectué une revue systématique et une méta-analyse de la littérature sur Medline, EMBASE et Cochrane Library dont nous avons extrait les données et, dans la mesure du possible, numérisé les schémas. Les données des candidats donateurs évalués à London, en Ontario, entre 2013 et 2016 ont été ajoutées. Nous avons utilisé des modèles à effets fixes et aléatoires pour regrouper la transformation de Fisher du coefficient de corrélation de Pearson (*r*). Nous avons procédé à une méta-régression des données numérisées et agrégées. Les études ont été limitées aux donneurs vivants d'un rein ou aux candidats au don d'organes vivants.
Résultats: Après la mise en commun de 19 études (n = 1 479 sujets), nous avons obtenu une corrélation combinée (*r*) de 0,74 (IC à 95 %: 0,61-0,82). Par régression linéaire, en utilisant les données individuelles, nous avons observé une augmentation de 0,76 % (IC à 95 %, 0,71-0,81) du pourcentage de la FRS pour chaque augmentation de 1 % du VRS. Ce dernier présentait une spécificité de 88 % pour la discrimination de la FRS à un seuil qui pourrait influencer la décision dans le choix du rein à retirer (différence entre les reins ≥ 10 %). Le VRS et la FRS pré-don se sont tous deux avérés modérément sensibles pour prédire la fonction rénale six à douze mois après le don: r = 0,75 pour le VRS et r = 0,73 pour la FRS; Δr = 0,05 [-0,02 à 0,13].
Limites: La plupart des études retenues étaient rétrospectives et ne mesuraient le VRS et la FRS que pour certains candidats. Les gains d'efficacité obtenus en supprimant la mesure de la FRS de l'évaluation dépendront du programme de transplantation.
Conclusion: La mesure du VRS pourrait remplacer la mesure de la FRS chez certains candidats. On ignore toutefois s'il est possible de le faire de manière fiable et systématique dans différents centres de transplantation. L'impact de ce remplacement sur la prise de décision clinique doit être évalué dans le cadre d'études prospectives bien conçues.

Keywords
living kidney donor, split kidney volume, split renal function, computed tomography

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What was known before

There was correlation between split renal volume and split renal function, but the interpretability of Pearson's *r* made next steps difficult to convey. Knowledge on this topic was limited to results of individual studies, which is not enough to inform clinical decision-making.

What this adds

To our knowledge, this is the first systematic review and meta-analysis of this topic. This study highlights the work done to date and suggests future directions for improvement in a real-world setting. We recommend that prospective studies with a clear goal should be designed and tested, rather than continuing to perform retrospective analyses that will add little additional value.

Introduction

The living kidney donor evaluation has been estimated to take 8 to 16 months from the time the donor's evaluation starts until donation.[1,2] During this time, some recipients may start dialysis before their transplant, adversely affecting patient quality of life and post-transplant outcomes.[3,4] More time on dialysis also has substantial costs to the health care system.[3,4] Although some of these outcomes are unavoidable, there have been recent calls to improve the efficiency of the living donor evaluation process.[2,5-8] One strategy is to remove any unnecessary tests from the evaluation without jeopardizing the safety and quality of the evaluation.

Deciding which kidney is most suitable for donation is a necessary part of the donor candidate evaluation. The left kidney is generally preferred because the left renal vein is longer and may reduce the surgical complexity of the transplant.[9] However, this decision also depends on other factors, including (1) the number of accessory arteries and veins serving each kidney (the kidney with less vascular complexity may be chosen); (2) the presence of benign or resectable anomalies on each kidney, including small stones or cysts (the kidney with greater anomaly may be chosen for donation leaving the donor with the "better" kidney); and (3) the relative function of each kidney if they are suspected to have a clinically

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relevant difference (the lower-functioning kidney may be chosen, again leaving the donor with the "better" kidney).[7,10,11] For the latter consideration, if early imaging identifies a clinically significant size difference (≥1 cm or ≥10%) between the right and left kidneys, a nuclear renogram is ordered in many programs to measure the function of each kidney (the split renal function [SRF]).[7,12] However, as a standard part of their evaluation, living donors at most transplant centers also complete a computed tomography (CT) scan, which can be used to accurately map out the vasculature, identify anomalous findings, and potentially measure the donor's glomerular filtration rate (GFR).[13-15] More recently, CT imaging has also been suggested to be as reliable as nuclear renography (the gold standard) for measuring the SRF using the split renal volume (SRV) as a surrogate.[16] If true, this may eliminate the need to perform nuclear renography for some donor evaluations.

In this study, we assessed whether SRV on CT can reliably estimate measures of SRF on nuclear renogram. We performed a chart review of living kidney donor candidates in London, Ontario, Canada, and conducted a systematic review and meta-analysis of the literature.

Methods

Chart Review

We reviewed the medical records of all living donor candidates who were evaluated at London Health Sciences in Ontario, Canada. To be eligible, donor candidates were required to have had a nuclear renogram performed between 2013 and 2016. Kidney dimensions were measured from CT scans using a 64-slice scanner following infusion of intravenous iodinated contrast. Tri-planar images were obtained with a maximum thickness of 3 mm. Renal dimensions were obtained from each scan and were measured by 2 authors (C.G.-O. and G.B.), independent of knowledge of the others' results and the SRF. Transverse and anteroposterior measurements were obtained on the axial images, whereas the length was obtained on the sagittal images (Supplemental Appendix 1). We used the ellipsoid formula (length × width × depth × $\pi/6$) to calculate renal volume (note that variants of the ellipsoid formula exist, yet for the calculation of SRV%, the constant [eg, $\pi/6$] cancels out).[17] At our medium-sized center, we do not have software to conduct volume calculations using more accurate means (eg, 3-dimensional [3D] rendering), which would also be true for many other transplant centers that currently evaluate living kidney donor candidates worldwide. The left kidney SRV% was calculated using left kidney volume/(left + right kidney volume). The left SRF% was abstracted from nuclear renogram reports, which were reported as a percentage of the total GFR that came from the left (and right) kidney. Nuclear renograms were performed using the radionuclide technetium-99m (Tc99m) conjugated to mercaptoacetyltriglycine (MAG3) or diethylenetriaminepentaacetic acid (DTPA).

Systematic Review and Meta-Analysis

We conducted and reported this systematic review and meta-analysis according to the PRISMA guidelines (Supplemental Appendix 2). We searched Medline (via PubMed), EMBASE (via OVID), and the Cochrane Library on August 11, 2017, using the key terms "split renal function" and "computed tomography" or "ultrasound." Reference lists and the "related articles" feature in PubMed were scanned for relevant articles. As some studies that included donors were not captured by this search strategy, we conducted a second search using the terms "donor nephrectomy and (nuclear or split function or volume*)." Eligible articles were written in English and reported both SRF and SRV. Conference abstracts were excluded.

Study variables. Two authors (S.H. and C.G.-O.) extracted the following information from the studies: mean age of study population, the CT technique, the contrast medium used (if any), slice thickness to measure volume, region of the kidney measured (ie, whole kidney, cortex only, parenchyma only), the volumetric calculation method (ie, 3D rendering, ellipsoid method), the tracer used for nuclear renography, and the reported Pearson's correlation coefficient between SRV% and SRF%. A third author (G.B.) served as arbiter if there were any uncertainties about data abstraction. As indicators of the quality of the method used, we recorded which studies indicated technicians were blinded (unaware) to the nuclear renogram results when measuring SRV. We also documented whether the *method of patient ascertainment* was comprehensive (eg, all patients received both scans, either through prospective recruitment or standard protocol) or opportunistic (eg, patients were selected retrospectively because they had both scans). We also recorded the time between CT scan and nuclear renogram, as these can change over time for patients with kidney disease (this may be relevant for donor candidates who are screened out due to the presence of kidney disease). We reported the number of studies with an upper-case N and the number of patients as lower-case n.

Study outcomes. The primary analysis was the correlation of SRV% from CT with SRF% from nuclear renography, with the measure of association being Pearson's correlation coefficient (r). For studies that did not report r, we calculated it where possible by abstracting individual-level data from the published tables. Alternatively, the figures of studies presenting scatterplots (SRV vs SRF as a percentage or a ratio) and/or their respective Bland-Altman plots were digitized (https://automeris.io/WebPlotDigitizer/), and r was estimated directly from the extracted data. Digitization enables otherwise inaccessible information to be pooled in individual patient meta-analyses.[18,19] The digitized data are provided in Supplemental Appendix 3. We also attempted to contact the authors of 3 studies to obtain missing values of r, but we were unsuccessful.

The secondary analysis was the ability of SRV to discriminate between a clinically important difference in relative kidney function (at least a 10% difference between the 2 kidneys; eg, at least 45%/55% SRF). This difference is large enough to influence decision-making (the donor usually retains the higher-functioning kidney).[12] The digitized data were used for these calculations if not reported by study authors. Finally, we summarized the associations of SRV and SRF with postdonation kidney function.

Statistical Methods

To pool Pearson's correlation coefficients, we transformed r into Fisher's z, where $z = 0.5 \times ln(1 + r)/(1 - r)$.[20] The z-values were pooled using random effects using the inverse of the squared standard error (SE) as the weight (weight $= 1/SE^2 = n - 3$). The pooled z-value (and 95% confidence limits) was then back-transformed into r. A general rule of thumb is that an r of 0.5 to 0.7 represents a moderate positive correlation, and $r > 0.7$ a high or very high positive correlation.[21] Transformation and back-transformation were performed using the Microsoft Excel functions FISHER() and FISHERINV(), respectively. Meta-regression was performed to estimate the association of study-specific factors on Fisher's z using the metareg procedure in Stata. Analysis of publication bias was performed using Egger's test and presented with a funnel plot.

Given the potential biases associated with comparing correlation coefficients from different studies (as the value of the correlation depends on the standard deviation (SD) of both the SRV and SRF), we used the digitized data to estimate the association of SRV and SRF using linear regression via mixed models (proc mixed in SAS).[22,23] In these models, SRF was treated as the dependent (y) variable and the SRV as the only individual-level predictor. The study indicator was included as a random-effects variable to accommodate within-study clustering. From this model, the proportion of the variability in SRF that could be accounted for by between-study differences could be calculated. Other study-level factors were included as fixed effects (eg, year of publication, type of nuclear scan, and method of volumetric assessment). We reported β coefficients with 95% confidence intervals (CIs), which signifies the change in SRF (per percent in left kidney function) due to a 1-unit increment for each continuous predictor or a change in the level of a categorical predictor compared with its reference category. Analyses were conducted using Review Manager 5.3, STATA (v13.0; StataCorp LP, College station, TX, USA), and Statistical Analysis Software (SAS Institute, Cary, NC, USA).

Results

Chart Review

A total of 115 living kidney donor candidates had a nuclear renogram performed for SRF in London, Ontario, between 2013 and 2016. The donor candidates were a mean 49 (SD = 12.4) years of age, 80 (70%) were women, and 57 (50%) ultimately donated by January 2018. Of these 115 candidates, 93 (81%) also had a CT scan for SRV performed a median (25th, 75th percentile) of 1 (–6, 33) day after the nuclear renogram. Only 11/93 (12%) of the CT reports provided bilateral measurements (length, width, and depth) for volumetric calculations, and so all available CT scans were obtained and dimensions measured (n = 87). The total kidney volume was a mean 299 (SD = 66) mL as measured by 1 technician and 282 (65) mL by the other (Pearson's $r = 0.80$ for total volume, $r = 0.56$ for SRV%). The kidney volume (average of the 2 technicians) was a mean 142.8 mL (SD = 32.5 mL) for the left and 139.2 mL (SD = 38.7 mL) for the right.

SRV% from CT and SRF% from nuclear renography. Split renal volume was weakly correlated with SRF, regardless of technician ($r = 0.22$-0.28; Figure 1A). For comparison, the split renal length was similarly only weakly correlated with SRF ($r = 0.24$; Figure 1B).

Systematic Review and Meta-Analysis

Study selection. A total of 562 studies were identified after automatically removing duplicates. After screening titles and abstracts, 19 additional duplicates were identified, 476 were not relevant, and 9 were case reports, editorials, or reviews. Fifty-eight articles received full-article screening. Of these, we excluded the following: 22 studies were not relevant; 10 studies only included patients with kidney disease (and not kidney donors);[24-33] 4 studies did not report Pearson's r and data could not be extracted;[34-37] and 1 study compared SRF with SRV in mL/min rather than as a percent and was inappropriate for pooling.[38] The 21 eligible studies are described in Table 1 and were mathematically combined in meta-analysis along with the results from the London, Ontario chart review.

Study characteristics. Most studies (N = 14) were conducted in countries with predominantly white persons. Most studies used Tc99-MAG3 (N = 8), Tc99-DTPA (N = 5), or Tc99-dimercaptosuccinic acid (DMSA; N = 4) as the sole radionuclide, or otherwise used some combination. Most studies measured the renal volume of the kidney parenchyma and used either a series of slices to calculate the volume (calculated as the area/slice times slice thickness) or used software to reconstruct a 3D image of the kidney to automatically calculate the volume (Tables 1 and 2). Only 2 studies reported the ellipsoid formula. Blinding of SRV calculation to the SRF measurement was reported in 7 studies. Most studies were retrospective analyses that included patients who had both scans, although 4 studies indicated that SRF was routinely measured for all donor candidates. As reported in 9 studies, the time between the CT scan and the nuclear renogram was mostly within 3 months (Table 2).

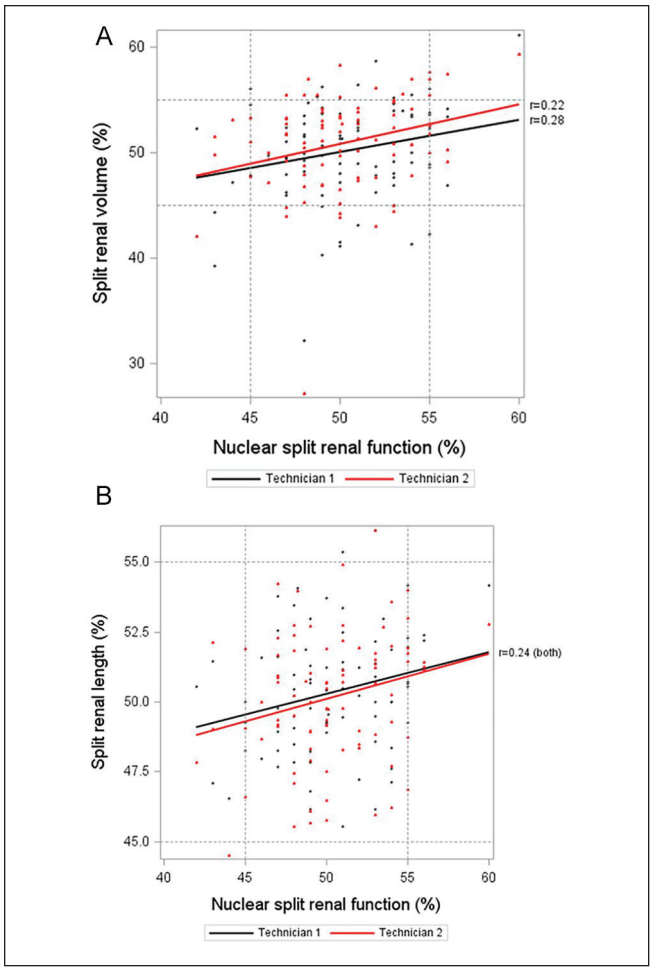

Figure 1. Correlation of split renal function percent with (A) split renal volume by computed tomography by technician and (B) split renal length by ultrasound or computed tomography.
Note. Split function, length, and volumes were calculated and presented as the absolute value of the *left* kidney as a proportion of the total (left + right). The diagonal line represents the line of best fit with Pearson's correlation coefficient, *r*. The horizontal and vertical long-dashed lines provide reference to the clinically relevant 45% and 55% split values.

Digitization. Among studies that reported Pearson's correlation and presented a scatterplot or Bland-Altman plot for digitization, we assessed the accuracy of digitizing data points from graphs to recalculate *r*. A very strong linear correlation was observed between the reported and the digitized-recalculated Pearson's correlation coefficients ($r = 0.998$, N = 11; Figure 2). Confident in the accuracy, the digitized data were included in the meta-analyses and regressions.

Correlation of SRV% with SRF%. Nineteen studies reported Pearson's correlation coefficient (*r*) directly or could be derived from digital images (N = 19; n = 1479; Table 2). The pooled *r* was 0.74 (95% CI = 0.61-0.82); however, there was significant heterogeneity across studies ($I^2 = 94\%$, $P < 0.0001$; Figure 3A). There was no evidence of publication bias (Egger's test $P = 0.30$; Figure 3B, omitting this study). Using the digitized individual patient data (N = 16, n = 850), the calculated *r* was 0.72 (95% CI = 0.69-0.75; Figure 4A). The Bland-Altman plot suggests good agreement, with 94% of the data points falling within −7.4 and +7.2%, 86% within ±5%, and 99% within ±10% (Figure 4B and C).

Meta-regression—aggregate data. To examine various factors that may explain the heterogeneity between studies, we conducted meta-regression on the aggregated data (N = 19; n = 1479). In terms of study characteristics of quality, the magnitude of Fisher's *z* was not associated with the study sample size ($P = .32$), measurement blinding ($P = .48$), method of patient ascertainment (eg, opportunistic versus routine; $P = .67$), or method of CT volumetry (eg, ellipsoid versus 3D rendering versus area × slice thickness; $P = .79$). However, Fisher's *z* was significantly lower if studies did not report Pearson's correlation coefficient and had to be digitized: $r = 0.45$ (95% CI = 0.25-0.60), N = 4 if not reported versus $r = 0.80$ (95% CI = 0.69-0.88), N = 14 if reported; $P = .03$. Regarding other study characteristics, Fisher's *z* was not associated with the type of nuclear scan (ie, MAG3, DMSA, DTPA; $P = .73$), whether CT volume was measured using the parenchyma ($P = .44$ vs cortical or whole kidney volume), whether the method used to calculate SRV was through 3D reconstruction, the ellipsoid formula, or the summation of slice areas times their thickness ($P = .67$), or CT slice thickness ($P = .14$). Fisher's *z* was lower in more recently published studies ($P = .03$; Figure 5A) and non-significantly higher among studies with an older study population ($P = .07$; Figure 5B).

Meta-regression—individual-level (digitized) data. To account for heterogeneity between studies using the individual-level digitized data (N = 16; n = 850), we fit a linear mixed model. Using SRV as the only predictor and accommodating for clustering by study, the β coefficient for SRV was 0.76 (95% CI = 0.71-0.81), $P < .0001$, and between-study differences accounted for only 1.7% of the total variability in SRF ($P = .10$). Heteroskedasticity was not observed in residual-versus-predictor or residual-versus-fitted plots (Supplemental Appendix 4). After adding other study-level (eg, aggregate) variables to the model, there was no association between SRF and year of publication (β = −0.04 [95% CI = −0.16 to 0.08] per year; $P = .51$), slice thickness (β = 0.12 [95% CI = −0.33 to 0.56] per millimeter; $P = .57$), average age of study cohort (β = −0.05 [95% CI = −0.11 to 0.02] per year; $P = .14$), blinding of measurements (β = 0.27 [95% CI = −0.68 to 1.23]; $P = .55$), or method of patient ascertainment (β = 0.36 [95% CI = −0.92 to 1.64] for routine versus opportunistic imaging; $P = .55$).

Discrimination of 45/55% SRF. Only 7 studies evaluated the relative difference in right and left kidney function and volume.[42,46,48,50,51,55,56] Variable reporting made this difficult

Table 1. Study Demographics.

References	Mean age	*N*	Country	Population	Blinding	Patient ascertainment[a]	Time between SRF and SRV	Kidney region measured for volume
Nilsson et al[39]	48	27	Sweden	Donors	NR	Clinical	NR	Parenchyma
Wu et al[40]	46	28	Taiwan	Donors	NR	Clinical	NR	NR
Hackstein et al[41]	53	26	Germany	Donors and patients[b]	NR	Clinical	Within 4 weeks	Parenchyma
Summerlin et al[42]	40	152	United States (Alabama)	Donors	Yes	Clinical	NR	Parenchyma
Jeon et al[43]	41	222	Korea	Donors	Yes	Research	NR	NR
Knox et al[44]	47	54	Canada (Alberta)	Donors	Yes	Clinical	Mean 30 days	Parenchyma
Miyazaki et al[45]	53	60	Japan	Donors	NR	Research (unsure)	Within 5 days	Whole kidney
Kato et al[46]	56	28	Japan	Donors	NR	Clinical	Median 1 month	Parenchyma
Gupta et al[47]	65	36	U.S. (MA)	CKD and controls (eGFR >60)	Yes	Clinical	Within 2 weeks	Parenchyma
Soga et al[48]	44	38	U.S. (MA)	Donors	Yes	Clinical	Average 32 days	Parenchyma
Halleck et al[49]	49	167	Germany	Donors	NR	Routine	NR	Cortex
Diez et al[50]	40	65	U.S. (Indiana)	Donors	NR	Clinical	NR	Parenchyma
Patankar et al[51]	49	12	Australia	Donors	yes	Clinical	Within 2 months	Whole, cortex, and medulla
Tanriover et al[52]	44	96	U.S. (New York)	Donors, ≥10% renal size mismatch	NR	Clinical	NR	Whole kidney
Yanishi et al[53]	52	35	Japan	Donors	NR	Routine	NR	Whole kidney
Yokoyama and Ishimura[54]	53	46	Japan	Donors	NR	Clinical	NR	NR
Barbas et al[55]	50	88	Canada (Ontario)	Donors	NR	Routine	Within 1 to 2 weeks	Parenchyma
Weinberger et al[56]	53	13	Germany	Donors	NR	Clinical	NR	Cortex
Wahba et al[16]	50	101	Germany	Donors	NR	Clinical	NR	Parenchyma
Mitsui et al[57]	61	34	Japan	Donors	NR	Clinical	NR	Cortex, parenchyma
Lee et al[58]	42	264	Korea	Donors	NR	Routine	NR	Parenchyma
This study	49	13	Canada	Donors and candidate	Yes	Clinical	Median 1 day	Whole kidney

Note. SRF = split renal function by nuclear renography; SRV = split renal volume by computed tomography scan; NR = not reported; U.S. = United States; MA = Massachusetts; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.
[a]Describes whether patient ascertainment was comprehensive (eg, all patients received both scans, either through prospective recruitment [research] or standard protocol [routine]) or opportunistic (eg, patients were selected retrospectively because they had both scans [clinical]).
[b]Only the donor data were extracted.

to pool. After digitization, we calculated the ability of SRV and SRF to identify a clinically significant difference between the right and left kidneys (≤45% or ≥55% relative volume or function). Sixteen percent of CT scans and 18% of nuclear renograms identified such a clinically significant difference with 78% overall agreement (proportion where SRF and SRV were both abnormal or both normal; Table 2). Using SRF as the gold standard, CT volumetry had a sensitivity of 35%, a specificity of 88%, a positive predictive value of 40%, and a negative predictive value of 86% to detect an SRF where 1 kidney provided at least 55% of total function or more (Table 3).

Prediction of postdonation residual kidney function among live donors. Nine studies reported on the ability of both predonation SRF and SRV to predict postdonation absolute GFR (estimated by different methods) in kidney donors (Table 4).[16,55,51,40,49,52,53,57,58] Studies varied by the duration of follow-up and most studies reported Pearson's correlation coefficients. The pooled correlation with estimated glomerular filtration rate (eGFR) measured 6 to 12 months postdonation was $r = 0.75$ (95% CI = 0.71-0.78) for SRV and $r = 0.73$ (95% CI = 0.69-0.76) for SRF (Figure 6A). The difference in Fisher's z-transformed Pearson's correlation (Δz) was calculated for each study (z for CT volumetry vs eGFR minus

Table 2. Correlation and Agreement Between Split Function and Volume.

References	Nuclear GFR tracer	Computed tomography characteristics				Individual patient data and discrimination of >55% split					Pearson's[a] correlation, *r*
		Technique	Contrast medium	Slice thickness (mm)	Volume calculation	IPD	n/N data points digitized	% SRF >55% or <45%	% SRV >55% or <45%	% agreement	
Nilsson et al[39]	MAG3	CTA	Iohexol	2	Area × thickness	✓	27/27 (100%)	1 (4%)	0 (0%)	26 (96%)	.90
Wu et al[40]	NR	CTA	NR	NR	NR	×	0/28 (0%)	—	—	—	NR
Hackstein et al[41]	MAG3	Helical (triphasic)	Iopromide	4	Patlak; area × thickness	✓	26/26 (100%)	12 (46%)	8 (31%)	22 (85%)	.9056
Summerlin et al[42]	NR	Spiral	Iohexol	3	3D-reconstruction	✓	127/152 (84%)	12 (9%)	25 (20%)	100 (79%)	.61
Jeon et al[43]	DTPA	Helical	Iopamidol	1	Area × thickness	×	0/222 (0%)	—	—	—	.453
Knox et al[44]	DMSA	MDCT	Iopamidol	1.25	Area × thickness	✓	49/54 (91%)	6 (12%)	3 (6%)	44 (90%)	.61[b]
Miyazaki et al[45]	DTPA	MDCT	NR	10	Area × thickness	×	0/60 (0%)	—	—	—	.907
Kato et al[46]	DMSA	MDCT	NR	1	3D reconstruction	✓	28/28 (100%)	2 (7%)	1 (4%)	27 (96%)	.9352
Gupta et al[47]	DTPA	MDCT	Iohexol	5	3D reconstruction	✓	35/36 (97%)	29 (83%)	21 (60%)	27 (77%)	.95
Soga et al[48]	MAG3 or DTPA	Helical	Iodinated	NR	Area × thickness; area × thickness × mean attenuation; mod ellipsoid; length × width; length	✓	38/38 (100%)	5 (13%)	8 (21%)	33 (87%)	.84
Halleck et al[49]	DTPA, MAG3	MDCT	Iopromide	0.5	3D reconstruction	×	0/167 (0%)	—	—	—	.93
Diez (2014)[50]	MAG3	MDCT	Iodinated	1	3D reconstruction	✓	60/65 (92%)	19 (32%)	9 (15%)	38 (63%)	.59
Patankar et al[51]	DMSA	MDCT	Iohexol	0.8	Attenuation area	✓	12/12 (100%)	2 (17%)	0 (0%)	10 (83%)	.451[b]
Tanriover et al[52]	DMSA	MDCT	Iohexol	2.5	3D reconstruction	✓	90/96 (94%)	15 (17%)	13 (14%)	78 (87%)	.78
Yanishi et al[53]	MAG3	3D-CT	NR	NR	NR	✓	34/35 (97%)	5 (15%)	0 (0%)	29 (85%)	.714
Yokoyama and Ishimura[54]	MAG3 (ERPF)	3D-CT	NR	NR	3D reconstruction	✓	46/46 (100%)	8 (17%)	2 (4%)	38 (83%)	.441
Barbas et al[55]	DTPA	CTA	NR	NR	Attenuation method	✓[e]	88/88 (100%)[e]	3 (3%)	13 (15%)	72 (82%)	.51
Mitsui et al[57]	MAG3	MDCT	Iopamidol	1	3D reconstruction	✓	34/34 (100%)	32 (94%)	33 (97%)	33 (97%)	.942[c]
Wahba et al[16]	MAG3	MDCT	Iohexol	2	Voxel, ellipsoid	✓	100/101 (99%)	25 (25%)	22 (22%)	63 (63%)	.36[b]
Weinberger et al[56]	MAG3	MDCT	Iodinated	0.5-1.0	3D reconstruction	✓	13/13 (100%)	3 (23%)	6 (46%)	6 (46%)	.19[b,d]
Lee et al[58]	DTPA	Helical	NR	2.5	3D reconstruction	×	0/264 (0%)	—	—	—	.949[c]
This study	MAG3 or DTPA	MDCT	Various	Various	Ellipsoid	—	—	8 (9%)	22 (25%)	63 (72%)	.28[d]
Total	—	—	—	—	—	—	1150/1202 (96%)	297 (25%)	296 (25%)	953 (80%)	—

Note. GFR = glomerular filtration rate; IPD = individual person data (obtained by digitization); SRF = split renal function; SRV = split renal volume; MAG3 = mercaptoacetyltriglycine; NR = not reported; DTPA = diethylenetriaminepentaacetic acid; DMSA = dimercaptosuccinic acid; ERPF = effective renal plasma flow; EDTA = ethylenediaminetetraacetic acid; 3D = 3-dimensional; CTA = computed tomography angiography; MDCT = multi-detector computed tomography.

[a]Pearson's correlation (*r*) of split renal volume percent (from computed tomography imaging) with split renal function percent (from nuclear scintigraphy).

[b]Digitized from scatterplot or Bland-Altman plot, or calculated using data from table provided in article.

[c]Split function and split volume were reported in mL/min/1.73 m^2 instead of a percentage. Conversion to a percentage was not possible as this required both left and right kidney volume and function measurements to be linked.

[d]Study reported Spearman's correlation.

[e]Fully digitized smaller subset (n = 88) with restricted to patients with 6-month follow-up. For purpose of discrimination, only points <45% or >55% were counted, and all remaining points were assumed to lie within the 45% to 55% range for both CT and nuclear scintigraphy.

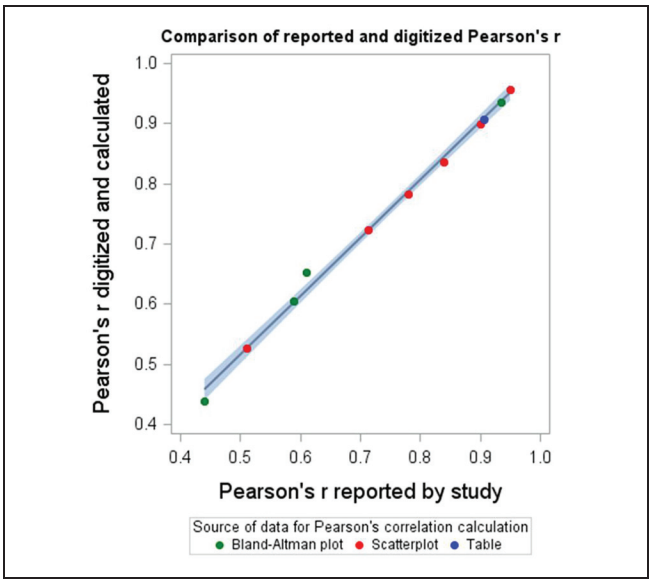

Figure 2. Comparison of reported and digitized Pearson's correlation coefficient when data were abstracted from Bland-Altman plots, scatterplots, or individual-level data were presented in tables.

Note. The solid line is the line of best fit from linear regression with a 95% confidence band (digitized $r = 0.0309 + 0.9685 \times$ actual r). Pearson's correlation was $r = 0.998$, $n = 11$.

z for nuclear GFR vs eGFR) and pooled (Figure 6B). The pooled Δz was back-transformed to obtain $\Delta r = 0.05$ (95% CI = −0.02 to 0.13), suggesting no difference between either method in the correlation with postdonation eGFR.

Discussion

In this meta-analysis, we found a moderate correlation between SRV by CT and SRF by nuclear renography. For every 1 mL/min increase in SRV%, the SRF% increased on average 0.76 mL/min, suggesting a less than 1:1 linear relationship between the 2 methods. However, in our own center we could not obtain such robust results, and the correlation between SRV by CT and SRF by nuclear renography was weak. Although reporting was sparse, there was no difference in predicting eGFR postdonation by either method, and the strength of this correlation was moderate.

If reliable, replacing nuclear renography with a CT scan for donor candidate evaluations would have many advantages, including reduced exposure to potentially harmful radioisotopes and reducing the number of tests needed to evaluate a candidate. This could also translate into an improved living donor experience, as well as reduced costs to the health care system (approximately CAD$220 per nuclear renogram).[59] Eliminating nuclear renograms for SRF may also result in the CT scan being performed earlier in the evaluation, which may result in a quicker time until approval (and a quicker time until transplant), which may translate into more donor candidates completing the evaluation.[60] A survey of transplant programs in Europe identified 7 centers in The Netherlands, 2 centers in Croatia, and 1 center in Belgium that rely solely on SRV% instead of SRF%.[49]

The ability of SRV to discriminate donor candidates with SRF >55% or <45% is a threshold that influences decision-making, as this is 1 criterion used to decide which kidney to leave with the donor. Using SRF as the gold standard, for every 100 CT volumetric examinations performed, 60 would be false positives (with no recognizable adverse consequences as the choice of kidney would not depend on SRF), but 14 would be false negatives that would result in the wrong kidney being chosen (assuming all other decision-altering factors are absent). This estimate was derived using available individual-level data, which came from studies that predominantly measured SRV on a selected subset of patients rather than all patients. The measures of agreement among such studies are subject to verification bias and should be confirmed in large unselected populations.[61,62]

In the living donor work-up in many centers, nuclear renography for SRF is performed for a select subset of donor candidates: those with a significant (>1 cm or >10%) difference in kidney length. Thus, the patient population selected for this study and those in the literature are less likely to have an SRF or SRV of 50/50, effectively increasing the prevalence of discrepant kidney function. Prevalence does not affect measures of sensitivity and specificity, but does influence predictive values.[63] Increasing the prevalence of the condition (ie, testing candidates more likely to have disparate relative kidney function) will reduce the negative predictive value (more false negatives). Thus, the current false negative rate of 14% is higher than would be anticipated had all candidates been tested. The predictive values presented in Table 3, therefore, may vary by living donor program depending on the criteria used to decide whether or not to perform SRF. As all donor candidates require a CT scan before donating (regardless of ultrasound results), this is less likely to be an issue.

The Pearson correlation coefficient was the measure of choice for most studies, despite several caveats. First, the correlation coefficient is an unadjusted measure. Although adjustment was not anticipated to influence the relationship between SRV and SRF in the primary analysis, the correlation of predonation SRF or SRV with postdonation eGFR was much lower ($r = 0.73$-0.75) and subject to improvement by adjustment or risk stratification.[52] Prediction of postdonation residual kidney function may depend on predonation donor factors other than kidney size or function, including donor age, gender, body mass index, blood pressure, smoking, and other factors, which cannot be easily estimated using correlation alone.[64,65] Second, correlation coefficients have been criticized as unsuitable measures of effect for comparison across studies due to its dependence on the distribution of its inputs.[22,23] Using digitization to extract individual-level data with high accuracy, we were able to overcome this

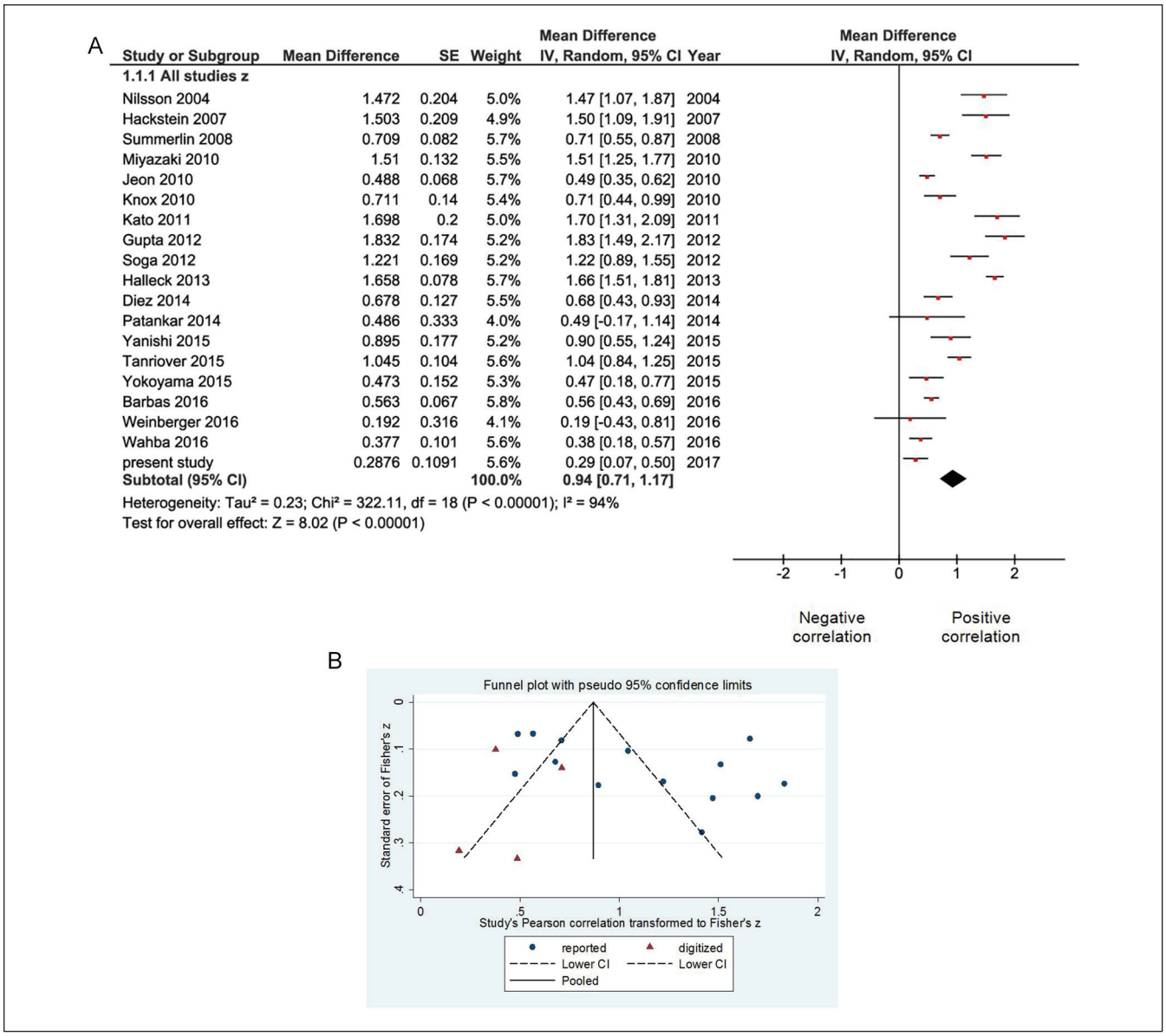

Figure 3. Meta-analysis of Pearson's correlation coefficients transformed to Fisher's *z* using aggregated study data. (A) Forest plot reporting pooled individual-study Pearson's correlation coefficients. (B) Funnel plot for publication bias excluding this study ($P = .30$ for publication bias when reported and digitized data are combined; $P = .11$ when digitized studies are omitted).
Note. CI = confidence interval.

limitation and found no association between SRF and any predictor variable. Although there was no evidence of publication bias, studies that had to be digitized to be meta-analyzed had a significantly lower correlation than those that reported Pearson's correlation. Third, because of its unitless property, correlation coefficients may be difficult to interpret. Using regression methods, we demonstrated only a moderate relationship between SRV and SRF. Fourth, Pearson's correlation assumes both variables are normally distributed. Although deviation from this assumption is less likely to influence the results in large sample sizes (ie, in a digitized and pooled dataset), the small sample size for each individual study may bias the individual study correlation coefficients. Finally, the potential for partial validation bias reduces the reliability of measures of agreement for clinical decision-making. This bias is frequently observed in 2-phase diagnostic tests, whereby the second diagnostic test (SRF) is only performed on a subset of patients that depends on the result of the first diagnostic test (SRV).[61] This strategy is expected to reduce the number of points falling within the normal range by both diagnostic tests (eg, within 5% difference). Omitting many of these data points due to this bias is not expected to influence the Pearson correlation or the linear regression coefficient as these are non-influential points.[66]

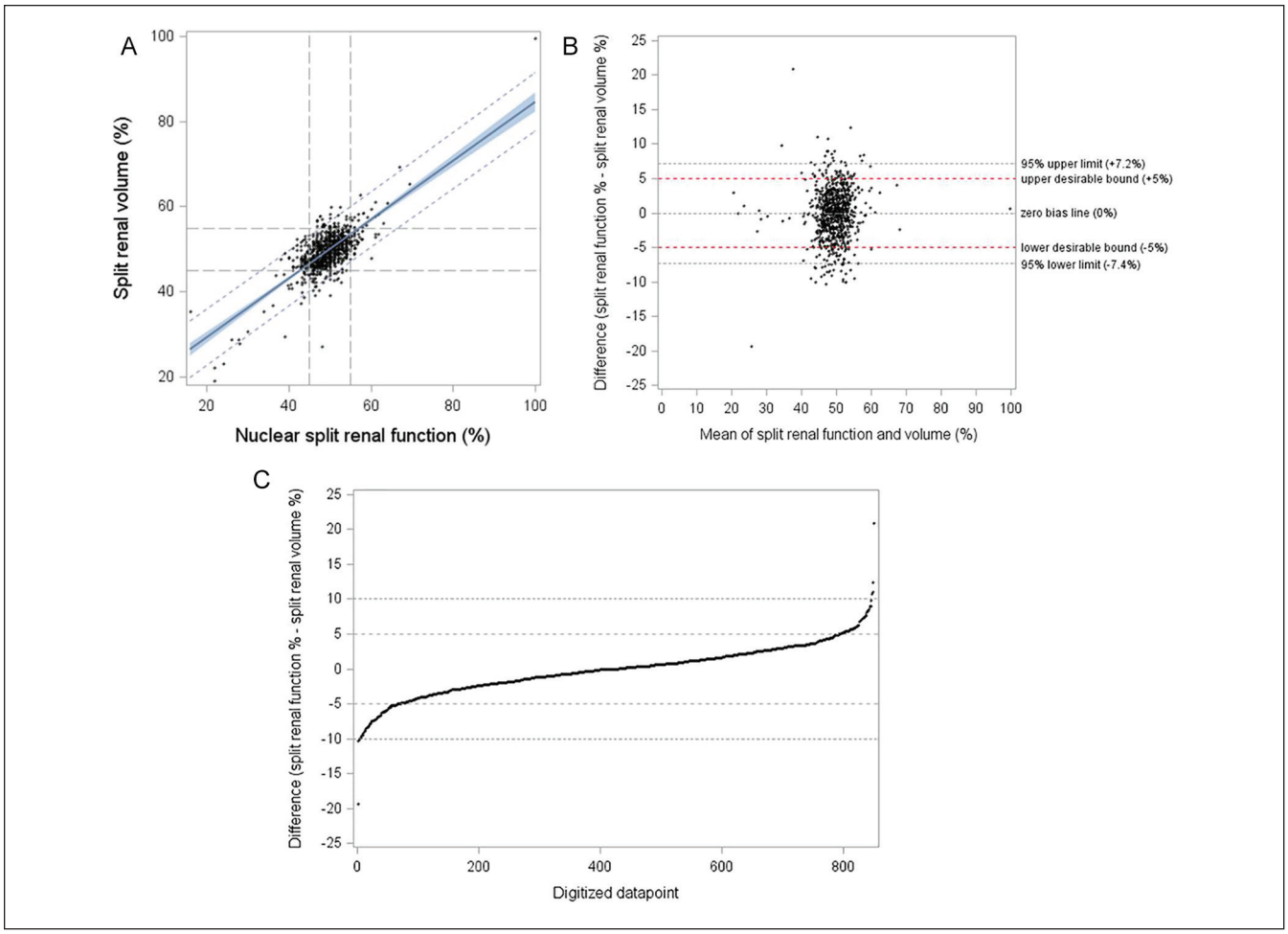

Figure 4. Correlation and agreement of split renal volume and split renal function from individual-level data. (A) Correlation of split renal function% with split renal volume% using all individual-level data. (B) Bland-Altman plot for agreement between split renal function and volume from all individual-level data. (C) Distribution of differences between split renal function and volume from all individual-level data.

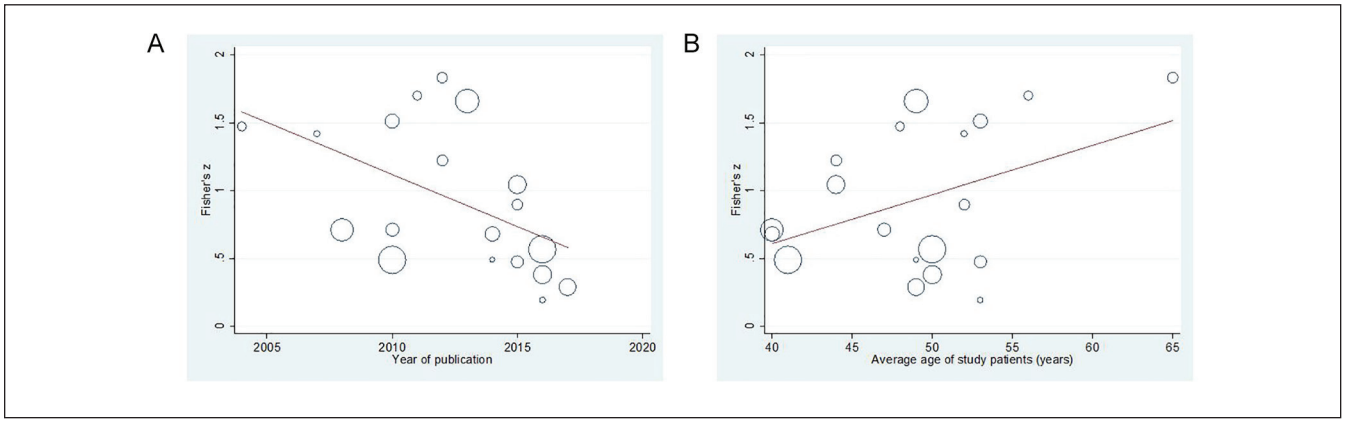

Figure 5. Bubble plots from meta regression of the correlation between split renal volume and split renal function by (A) publication year and (B) average age of the study population.
Note. The size of the bubble is proportional to the size of the study.

Table 3. Sensitivity and Specificity.

		Split renal function <45%/55%				
		Yes	No	Total	Sensitivity	54/155 = 35%
Split renal volume <45%/55%	Yes	54	82	136	Specificity	613/695 = 88%
	No	101	613	714	PPV	54/136 = 40%
	Total	155	695	850	NPV	613/714 = 86%

Note. Ability of split renal volume percent to discriminate a split renal function percent <45%/55%, a differential function deemed clinically significant. PPV = positive predictive value; NPV = negative predictive value.

Table 4. Prediction of Postdonation Donor eGFR.

	Donor follow-up period after living kidney donation				Assessment of kidney function at follow-up	Method of comparison	Comment
References	1 month	3 month	6 months	12 months			
Mitsui et al[57]	0.755 (nuclear) 0.679 (cortex) 0.806 (parenchyma)	0.615 (nuclear) 0.638 (cortex) 0.592 (parenchyma)	—	0.763 (nuclear) 0.747 (cortex) 0.764 (parenchyma)	MDRD	Correlation	
Barbas et al[55]	—	—	0.6808 (nuclear) 0.6997 (volume)	—	CKD-EPI	Correlation	
Yanishi et al[53]	—	—	—	0.634 (nuclear) 0.708 (volume)	Other equation	Correlation	
Wahba et al[16]	—	—	—	0.66 (nuclear) 0.71 (volume)	CKD-EPI	Correlation	Correlations were slightly higher if CG was used instead of CKD-EPI
Halleck et al[49]	—	—	0.85 (nuclear) 0.83 (volume)	—	Cockcroft-Gault	Correlation	
Patankar et al[51]	—	—	—	0.76 (nuclear) 0.85 (volume)	CKD-EPI	Correlation	
Wu et al[40]	—	—	—	—	Cockcroft-Gault	Correlation	The time of follow-up was not specified. $r = -0.201$ (nuclear) $r = 0.123$ (volume)
Lee et al[58]	0.685 (nuclear) 0.726 (volume)	0.688 (nuclear) 0.711 (volume)	0.711 (nuclear) 0.747 (volume)	—	MDRD	Correlation	
Tanriover et al[52]	—	—	—	$\beta = 16.8$, $P < .001$ (volume) $\beta = -0.203$, $P = .552$ (nuclear)	CKD-EPI	Multiple linear regression	Adjusted for donor eGFR, weight-adjusted donor renal volume, delta split function (%), and biopsy score

Note. Volume was measured by computed tomography. Presented in this table if the authors reported correlations for parenchyma and cortex separately. Correlation refers to Pearson's correlation coefficient (*r*) between predonation split kidney function (mL/min or mL/min/1.73 m^2) or total kidney function corrected by split kidney volume (mL/min or mL/min/1.73 m^2). eGFR = estimated glomerular filtration rate in mL/min or mL/min/1.73 $m,^2$ estimated by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration); MDRD (modification of diet in renal disease); or creatinine clearance by the Cockcroft-Gault equation; mGFR = measured glomerular filtration rate in mL/min/1.73 m^2.

Rather, this may influence the measures of agreement for discriminating kidneys with a significant functional difference. This cannot be accounted for in this study because the first-stage test may have been a renal ultrasound rather than a CT scan, introducing a differential verification bias that may be more difficult to correct.[62]

There are some limitations that may influence the potential efficiency gains resulting from omitting the nuclear renogram for split function. Although most centers included in this study conduct this test only if indicated, these indications may vary from center-to-center (eg, despite a 10% size difference, a program may not perform a nuclear renogram if the measured GFR is well above or below their donation threshold). Moreover, some centers performed this test for all candidates routinely and are therefore most likely to benefit from removing this additional test if this can be done without compromising the accuracy of the donor candidate evaluation (Table 1). Measured GFR (for total kidney function) is performed by some transplant programs for a selected subgroup of donor candidates, whereas other

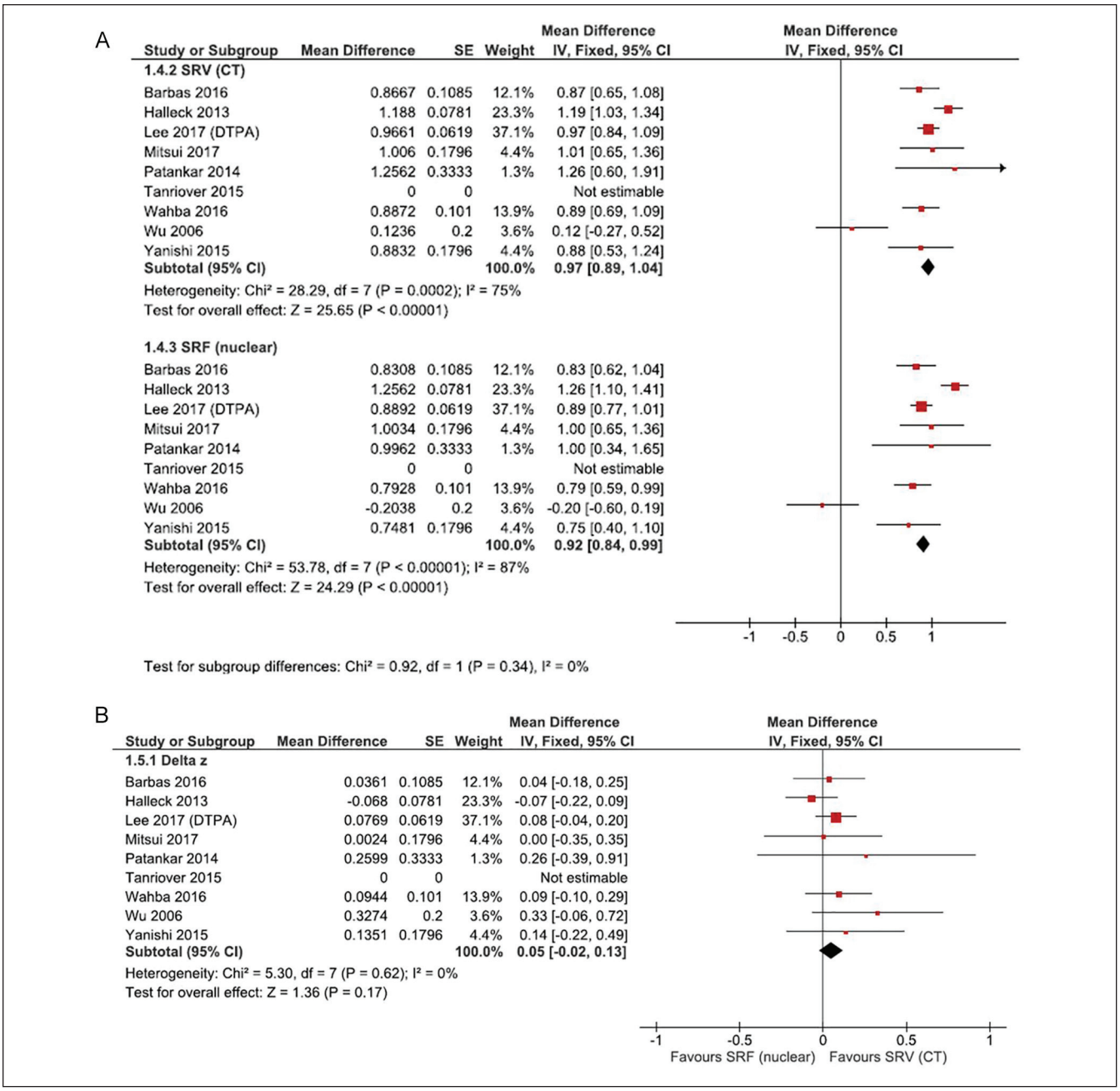

Figure 6. Comparison of split renal function (SRF, mL/min or mL/min/1.73 m^2) by nuclear renography and split renal volume (SRV, total kidney function corrected by split kidney volume, mL/min or mL/min/1.73 m^2) by computed tomography (CT) with estimated glomerular filtration rate of 6 to 12 months postdonation. (A) Forest plot for the Fisher's z-transformed Pearson's correlation coefficient for SRV (SRV_z; upper panel) and SRF (SRF_z; lower panel). (B) Forest plot for the difference in Fisher's z-transformed Pearson's correlation coefficient (delta z = SRV_z – SRF_z).
Note. CI = confidence interval.

programs conduct this test more routinely.[2] Eliminating the nuclear renogram for these candidates may still be valuable if the protocol for these 2 tests differ (eg, different contrast agents).[38,51] The availability of CT angiography relative to the nuclear renogram may also influence the efficiency gains of an individual program. Most centers in this study completed both scans within 1 month of each other, although it is not clear which test came first. These results may have a greater impact for transplant centers where the CT scan is readily available and can be conducted before the nuclear renogram without delaying the candidates' evaluation process.

In conclusion, further work is needed to establish whether SRV may replace SRF for the evaluation of living donor candidates. The present findings are supportive of this in some but not all transplant centers. However, neither method is ideal. Understanding the reasons behind the 14% false negative rate in the absence of verification bias is important to understand the potential impact of relying on SRV on clinical decision-making. The addition of additional retrospective studies based on opportunistic (rather than routine) testing is unlikely to advance our understanding of the performance characteristics of SRV assessment. Further work in a well-designed prospective setting is needed.

Ethics Approval and Consent to Participate

Research ethics approval was obtained from Western University (London, Ontario, Canada) (HSREB #107847).

Consent for Publication

As this was a retrospective analysis, patient consent was waived.

Availability of Data and Materials

Individual-level data were de-identified and published with Mendeley Data (doi: 10.17632/dyn2bfgxxj.2).

Author's Note

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Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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