Association between Early Resistive Index Measurement and Early Graft Function and Long-Term Graft Survival after Kidney Transplantation: an Evidence-based Clinical Review

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ABSTRAK

Latar belakang: *pemeriksaan Resistive Index (RI) sering dilakukan untuk menilai fungsi organ transplant dengan menggunakan alat Doppler ultrasonography. Hasil pemeriksaan RI merupakan parameter terbaik untuk menilai disfungsi ginjal transplant. Beberapa studi telah menunjukkan peran RI sebagai prediktor kegagalan transplantasi namun studi-studi tersebut menggunakan hasil RI yang tidak segera pasca transplantasi. Tujuan studi ini untuk mengidentifikasi hubungan antara hasil pemeriksaan RI yang dilakukan segera pasca transplantasi dengan fungsi awal ginjal transplant yang direpresentasikan oleh delayed graft function (DGF) dan immediate graft function (IGF) beserta angka kelangsungan hidup ginjal transplant dalam jangka waktu lama.* ***Metode:*** *artikel yang merupakan tinjauan klinis berbasis bukti dilakukan pada penelitian yang dipublikasikan sebelum Mei 2018 menggunakan sumber dari Medline, Science Direct, EMBASE dan Cochrane. Penelitian yang mengukur hasil RI segera pasca transplantasi dimana tujuan utama atau tujuan sekundernya berkaitan dengan fungsi ginjal transplant dan/atau angka kelangsungan hidup ginjal transplant dimasukkan ke dalam studi ini. Penelitian yang mengukur hasil RI tidak segera pasca transplantasi dan tanpa kelompok tingkat RI, tidak dimasukkan ke dalam studi ini. Metode Mantzel-Haenzel digunakan untuk menganalisis pooled risk ratio dan 95% interval kepercayaan, sementara heterogenitas dianalisis melalui tingkat I2. Analisis menggunakan program Review Manager 5.3.* ***Hasil:*** *analisis dilakukan pada sembilan penelitian dengan total pasien sebanyak 1802 pasca transplantasi ginjal. DGF ditemukan pada 19% (193/1015) pasien di kelompok RI rendah dan 42.8% (337/787) pasien di kelompok RI tinggi (RR 2.04 (95% IK 1.72-2.41), p < 0.00001, I2 = 28%). IGF ditemukan pada 39.5% (62/157) pasien di kelompok RI rendah dan 10.5% (28/268) pasien di kelompok RI tinggi (RR 0.26 (95% IK 0.17-0.40), p < 0.00001, I2 = 0%). Ginjal transplant yang masih berfungsi ditemukan pada 83% (701/845) pasien di grup RI rendah dan 69.4% (395/569) pasien di grup RI tinggi (RR 0.82 (95% IK 0.72-0.93), p = 0.002, I2 = 63%), dengan follow-up antara 60-144 bulan.* ***Kesimpulan:*** *hasil studi ini menegaskan hubungan antara hasil pemeriksaan RI yang dilakukan segera pasca transplantasi dengan fungsi awal ginjal transplant dan kelangsungan hidup ginjal transplant dalam jangka waktu lama. Peningkatan RI memberikan peluang untuk mengenali pasien dengan prognosis jangka panjang yang buruk, bahkan disaat-saat awal pasca transplantasi ginjal.*

Kata kunci: *transplantasi ginjal, resistive index, resistance index, fungsi ginjal transplant.*

ABSTRACT

Background: *resistive index (RI) is highly utilised to assess the graft function using Doppler ultrasonography. The RI has been shown as the best ultrasound parameter to assess kidney allograft dysfunction. Several studies have established the role of the RI as a predictor of transplant failure. However, these studies were using RI measurement in the later stages post transplantation. The present study has conducted to identify the association between early RI measurement and early graft function represented as delayed graft function (DGF) and immediate graft function (IGF), as well as long-term graft survival.* ***Methods:*** *an evidence-based clinical review of studies published before May 2018 was conducted from Medline, Science Direct, EMBASE and Cochrane databases. Studies on early measurement of RI whereby the primary or secondary goals of the study related to graft function and/or graft survival were included. Studies using late RI measurement and without RI value groups were excluded. The Mantzel-Haenzel method was used to analyse pooled risk ratio and 95% confidence interval, while the heterogeneity of the study was calculated through I2 value. Data analysis was performed using Review Manager 5.3.* ***Results:*** *nine studies with a total of 1802 patients who had undergone a kidney transplant were analysed. DGF was found in 19% (193/1015) of the low RI group and in 42.8% (337/787) of the high RI group (RR 2.04 (95% CI 1.72 - 2.41), p < 0.00001, I2 = 28%). IGF was found in 39.5% (62/157) of the low RI group and in 10.5% (28/268) of the high RI group (RR 0.26 (95% CI 0.17 – 0.40), p < 0.00001, I2 = 0%). Long-term graft survival, with follow up between 60-144 months, was found in 83% (701/845) of the low RI group and in 69.4% (395/569) of the high RI group (RR 0.82 (95% CI 0.72 – 0.93), p = 0.002, I2 = 63%).* ***Conclusion:*** *the results of this study emphasise the association between early measurement of RI and early graft function, and long-term graft survival. An elevated RI provides the chance of recognizing the patients with poor long-term prognosis, from the first moment after kidney transplant.*

Keywords: *kidney transplant, resistive index, resistance index, graft function.*

INTRODUCTION

Kidney transplantation is the best method of treatment in patients with end-stage kidney disease from the perspective of morbidity, mortality, quality of life, and cost-effectiveness as compared to dialysis.[1-3] Several risk factors have been reported that affect short- and long-term graft survivals, namely donor and recipient age, human leukocyte antigen (HLA) mismatch, prolonged cold ischaemia time (CIT), acute rejection episodes and delayed graft function (DGF).[4-6] In the early period post-transplant, many crucial factors may influence kidney graft function, such as rejection episodes and acute immunosuppressive drug toxicity, and also vascular complications.[7]

Delayed graft function (DGF) is known to be one of the most important factors affecting the results of kidney transplantation.[3,8] DGF is a delayed decrease in serum creatinine after kidney transplantation, apparently resulting in much worse graft survival compared to immediate graft function (IGF).[9,10] Therefore, early diagnosis of DGF may help to optimise long-term graft survival by allowing an immediate modification of immunosuppressive drug treatment.[11-12]

Resistive index (RI), is a physiological value that indirectly reflects the degree of resistance of the renal and intrarenal vessels, and is highly utilized to assess the graft function using Doppler ultrasonography. The RI has been shown to be the best ultrasound parameter to assess kidney allograft dysfunction.[13,14] Many factors may increase the RI, such as intrarenal factors, including transplant rejection, acute tubular necrosis, and graft nephritis; extrarenal factors, including ureteric obstruction, allograft compression due to perinephric collection, and vascular stenosis/compression; or systemic factors, including heart rate, patient age, and hypotension.[15,16] The correlations between RI and allograft histology, presence of acute rejection, and acute tubular necrosis have been investigated.[13,17-19] Several studies have established the role of the RI as a predictor of transplant failure. However, these studies were using RI measurement in the later stages post transplantation.[13,20]

Previous studies have reported the role of early RI measurement in predicting long-term kidney allograft function. The present study conducted a meta-analysis to comprehend the

role of early RI measurement in early graft function as well as long-term graft survival.

METHODS

This study was reported and conducted under guidance with previously published guidelines[21,22] using a pre-specified protocol.

Searching Relevant Studies

Studies from Medline, Science Direct, EMBASE and Cochrane databases published before May 2018 were screened using the search terms 'kidney transplant', 'resistance index', 'resistive index', and 'graft function'. We pilot-tested the strategies and we modified them to ensure that we addressed known eligible studies. The eligibility of each study was assessed and the full-text of each study was retrieved for any study considered potentially relevant. We did manual references checking to make sure identify all articles that might be relevant and also complemented the search by using the 'related articles' feature on PubMed to spot additional and grey literatures. Two independent reviewers (PMWT and GWKD) screened the studies and those considered potentially relevant were retrieved for further assessment. Both reviewers assessed the eligibility of each full-text study, resolving disagreements by turning to another reviewer (GRS).

Study Eligibility

Our inclusion criteria for this study were as follows: 1) randomized controlled trials, cohort or case control studies on early measurement of RI using RI value groups whereby the primary or secondary goals of the study were related to early graft function and/or long-term graft survival; 2) follow up at least 12 months afterwards for long-term graft survival and 3) involving adult living-donor and/or deceased-donor transplantation. We excluded studies in languages other than English; studies using late RI measurement and without RI value groups; and studies involving paediatric populations.

Quality Assessment

The quality of each study was reviewed in accordance to Hayden criteria.23 Six main points of potential bias were reviewed as follows: 1) study population clearly defined; 2) study attrition or completeness of follow-up; 3) prognostic factors measured appropriately; 4) outcome measured appropriately; 5) confounding measurement and accountability; 6) Analysis was appropriate. Studies were graded as 'good' if they met five or six criteria, 'fair' if they met three to four criteria and 'poor' if they met less than three criteria.

Outcomes

The outcomes measured in this study were DGF and IGF as a marker of early graft function along with long-term graft survival as second outcome.

Statistical Analysis

We reviewed DGF, IGF and long-term graft survival in patients with low RI values compared to those with high RI values. Statistical analysis used a fixed or random effects model with the Mantzel-Haenzel method used to assess the pooled risk ratio and 95% confidence interval by comparing the DGF, IGF and long-term graft survival in patients with low and high RI values. We determined the heterogeneity by calculating the I2 statistic. The heterogeneity was deemed low (I2 25%-50%), moderate (I2 50%-75%) and high (I2 >75%). All analyses were performed using Review Manager 5.3.

RESULTS

A comprehensive database search retrieved 516 citations. Authors excluded 486 publications based on title and abstract screening. Full-text review and detailed evaluation of the remaining 30 articles resulted in 9 studies that met inclusion and exclusion criteria of our study. Therefore, these 9 studies were included in our meta-analysis.[7,12,24-30] The outcome identified DGF in 9 studies, IGF in 2 studies and long-term graft survival in 5 studies. **Figure 1** describes the flow diagram for literature searching.

Table 1 and **2** present the study characteristics and study populations in the 9 publications included in the meta-analysis. The 9 publications included a total of 1802 patients who underwent kidney transplantation. Six studies were using retrospective cohort methods and three studies were using prospective cohort methods. Five studies included living-donor kidney transplant

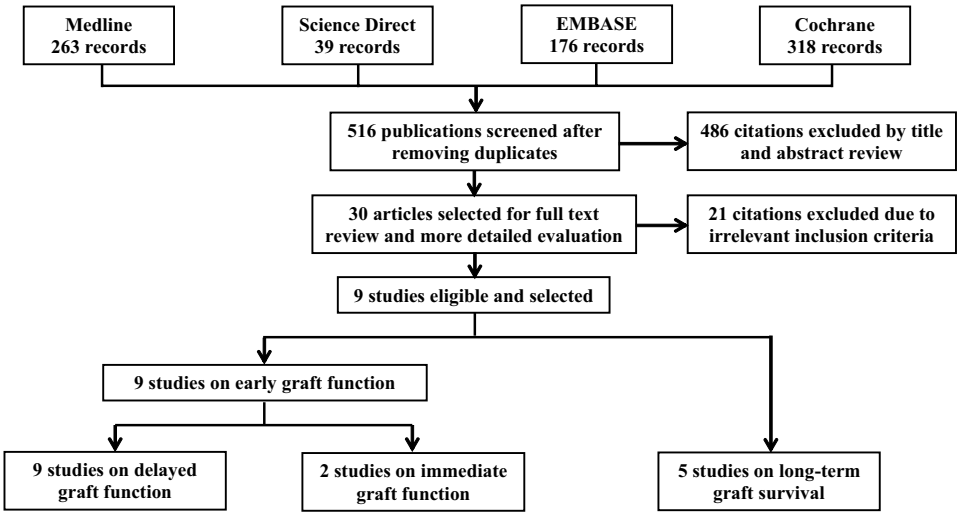

Figure 1. Flow diagram for literature searching

Table 1. Characteristics of all studies included in the review

Authors/ year	Study method	N	Follow-up (months)	Do nor source	Mean donor age (years)	Mean recipient age (years)	CIT (min)	RI values group	RI measurement (day after transplant)	RI examination (artery/ arteries)
Mwipatayi et al[24]/ 2016	Retrospective	253	144	LD & DD	49	46	534	<0.8 & >0.8	<1	Segmental
Contti et al[25]/2015	Prospective	79	a	LD & DD	n/a	n/a	n/a	<0.84 & >0.84	1-3	Renal-iliac anastomosis
Rodrigo et al[26]/2010	Retrospective	333	139	DD	n/a	49	1290	<0.7 & >0.7	2-3	Interlobar & segmental
Saracino et al[27]/2006	Retrospective	76	140	DD	n/a	n/a	n/a	<0.635 & >0.635	<28	Interlobar & segmental
Kolonko et al[7]/2012	Prospective	364	60	LD & DD	39	41	1200	<0.73; 0.73-0.85 & >0.85	2-4	Segmental
McArthur et al[28]/2011	Retrospective	172	36	DD	n/a	n/a	n/a	<0.74; 0.74-0.81 & >0.81	<7	Interlobar
Akgul et al[29]/2009	Retrospective	121	63	LD & DD	40	31	a	<0.7 & >0.7	<28	Interlobar & segmental
Barba et al[30]/2011	Retrospective	343	120	LD & DD	47	50	888	<0.7 & >0.7	1	Interlobar & segmental
Król et al[12]/2011	Prospective	61	48	DD	n/a	45	n/a	<0.57; 0.57-0.7 & >0.7	0 (intraoperative)	Renal-iliac anastomosis

CIT, cold ischaemia time; RI, resistive index; a, not available; n/a, not applicable; LD, living donor; DD, deceased donor.

recipients, while the rest included only deceased-donor kidney transplant recipients. The length of follow-up for these studies ranged from 36 to 144 months. The mean donor age ranged from 39 to 49 years, and the mean recipient age ranged from 31 to 50 years. The cold ischaemia time ranged from 534 to 1290 minutes. The time of RI measurement ranged from 0 (intraoperative) to 28 days after transplant. **Table 3** shows the summary of findings of DGF, IGF and long-term graft survival in low and high RI groups.

The renal Doppler ultrasonography used

Table 2. Characteristics of study populations in all studies

Authors	DGF definition	DGF incidence (%)	IGF definition	IGF incidence (%)	Long-term graft survival (%)	Quality
Mwipatayi et al	Dialysis within first week POD	22.5	a	a	87.3	Good
Contti et al	Dialysis within first week POD	50.6	a	a	a	Good
Rodrigo et al	Dialysis within first week POD	30	a	a	59.5	Good
Saracino et al	Dialysis within first week POD	11.8	a	a	a	Good
Kolonko et al	Dialysis within first week POD	43.7	Cr <3mg/dl by POD 3	19.5	83.8	Good
McArthur et al	Dialysis within first week POD	35.5	a	a	a	Good
Akgul et al	Dialysis within first week POD	18.1	a	a	76.1	Good
Barba et al	Dialysis within first week POD	17.8	a	a	81.9	Good
Król et al	At least 1 dialysis except for hyperkalemia or volume overload reasons within first week POD	34.4	Cr <3mg/dl by POD 3	31.1	a	Good

DGF, delayed graft function; IGF, immediate graft function; POD, post-operative day; Cr, serum creatinine; [a], not available.

Table 3. Summary of findings: DGF, SGF and IGF incidence; and graft survival in low and high RI

Authors	N		DGF incidence (%)		IGF incidence (%)		Long-term graft survival (%)	
	Low RI	High RI	Low RI	High RI	Low RI	High RI	Low RI	High RI
Mwipatayi et al	226	27	19.9	44.4	a	a	89.4	70.4
Contti et al	33	46	19.4	72.1	a	a	a	a
Rodrigo et al	172	161	19.7	40.9	a	a	62.7	55.9
Saracino et al	37	39	16	8	a	a	a	a
Kolonko et al	115	249	21.7	53.8	38.3	10.8	87.8	81.5
McArthur et al	58	114	24.1	41.2	a	a	a	a
Akgul et al	85	36	17.6	19.4	a	a	83.5	58.3
Barba et al	247	96	14.6	26	a	a	88.7	64.6
Król et al	42	19	26.2	52.6	42.9	5.3	a	a

DGF, delayed graft function; IGF, immediate graft function; RI, resistive index; a, not available.

to measure RI in all studies was carried out by one, or more than one, experienced radiologists who were unaware of the patients' history or laboratory findings. RI was analysed in the renal iliac anastomosis in 2 studies, interlobar and segmental arteries in 4 studies, segmental arteries in 2 studies and interlobar arteries in 1 study. RI was calculated according to the following formula: RI = (peak systolic frequency shift – minimum diastolic frequency shift) / peak systolic frequency shift. Six studies differentiated RI values into low RI and high RI groups while the remaining 2 studies divided RI values into low RI, intermediate RI and high RI groups. The remaining 2 studies were modified into low RI and high RI groups to obtain a symmetrical analysis with other studies. In a study conducted by McArthur et al[28], the group with RI <0.74 were assumed as low RI, and other groups (RI 0.74-0.81 and RI >0.81) were assumed as high

RI. The same pattern also applied to the study by Król et al[12], whereby RI <0.57 and 0.57-0.7 were deemed as low RI; and RI >0.7 was deemed as high RI to obtain similarity with other studies in terms of the cut-off point for low RI and high RI values.

Delayed Graft Function

Data from 1802 patients from 9 studies, including 1015 patients in the low RI group and 787 patients in the high RI group, was analyzed. It was found that 193 out of the 1015 patients belonging to the low RI group suffered from DGF (19%) and 337 patients with DGF were identified from 787 patients in the high RI group (42.8%). Patients who had higher RI during early examination faced a higher risk of experiencing an episode of DGF after transplantation compared to those who had lower RI [pooled RR 2.04 (95% CI 1.72 - 2.41), p < 0.00001, I2 = 28%] (**Figure 2**).

Immediate Graft Function

Data was obtained from 425 patients from 2 studies, including 157 patients in a low RI group and 268 patients in a high RI group. It was found that 62 out of 157 patients in the low RI group had IGF (39.5%) and 28 out of 268 patients in the high RI group had IGF (10.5%). Patients who had lower RI during early examination after their kidney transplant tended to have IGF compared to those who had higher RI [pooled RR 0.26 (95% CI 0.17 – 0.40), p < 0.00001, I2 = 0%] (**Figure 3**).

Long-term Graft Survival

There were 5 studies, including 1414 patients, that addressed the relationship between early measurements of RI values and long-term graft survival. It was found that 701 out of 845 patients in the low RI group who had their kidney allograft survived (follow-up 60-144 months, 83%) and 395 out of 569 patients in the high RI group who had their graft survived (follow-up 60-144 months, 69.4%). The long-term graft survival was higher in patients with low RI during early measurements compared to those who had high RI [pooled RR 0.82 (95% CI 0.72 – 0.93), p = 0.002, I2 = 63%] (**Figure 4**).

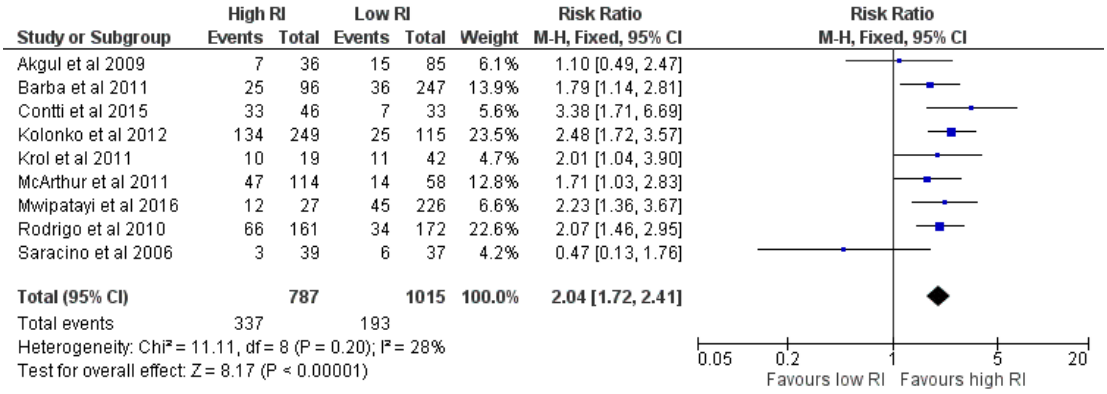

Figure 2. Forest plot between low RI and high RI in terms of DGF incidence

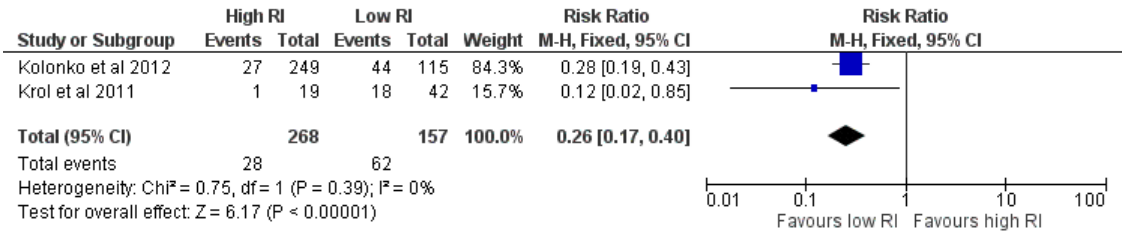

Figure 3. Forest plot between low RI and high RI based on IGF incidence

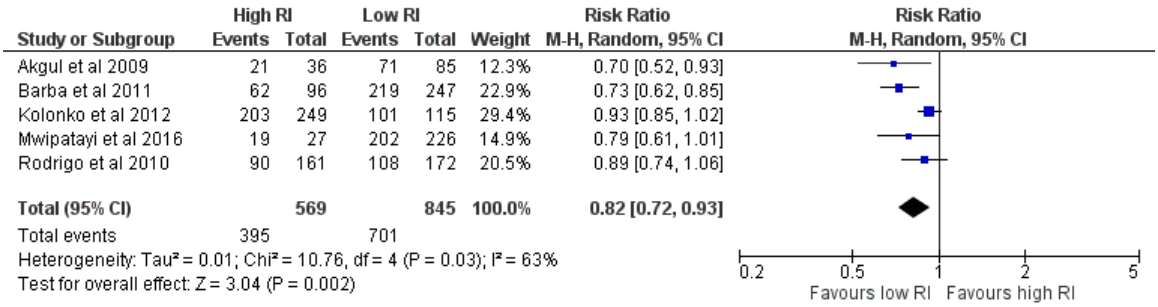

Figure 4. Forest plot between low RI and high RI in terms of long-term graft survival

DISCUSSION

The function and survival of the graft after kidney transplant has caused a lot of concern over the years, and this makes it crucial to identify any risk factors and variables that will enable us to foresee if the graft will succeed. The most useful factors are those that can be assessed early after transplantation and that might allow us to predict long-term graft survival. Early RI measurement after kidney transplant is suitable with those criteria. This measurement provides a real-time evaluation of graft structure and vascularization. Many centres have protocol to evaluate kidney allograft in an early manner by measuring RI using Doppler ultrasound, as this technique is valuable in the detection of many vascular events.[30]

The ideal RI cut-off point for predicting graft function and long-term graft survival varies within the literature. Some studies used 0.7 as their RI cut-off point[12,26,29,30], in conformity with previous studies[31,32] and others set their RI cut-off point at 0.8 or closer to that point 7,24,25,28 based on a study by Radermacher et al[13] which reported an RI of 80 or higher to be the strongest predictor of allograft loss. However, some studies differentiated the low RI and high RI group by using the median RI values from their study population[27] and they did not adopt any ideal RI cut-off point that has been reported from previous literature. Regarding this issue, most of studies included in this meta-analysis were using two groups (low RI and high RI). However, some of studies using three groups (low RI, moderate RI and high RI). To overcome this problem, we have modified studies using three RI groups into two RI groups based on previous studies existed to maintain objectivity.

Many studies have reported that RI is closely related to kidney function post transplantation. RI has a significant direct correlation with Cr[13,33-36] and an inverse correlation with GFR estimated by Cr clearance[13,18,35], both at early stages after transplantation or at later stages. In contrast, other studies did not find this relationship.[27,37-39] Several previous studies reported that patients with DGF showed high RI quite similarly to patients with acute rejection, hence, RI differentiates patients with graft dysfunction, however, does not help to assure its cause.[35,36] Chudek et al[42] showed significant differences in RI values between patients with DGF and IGF who were measured between 2-4 days post-operative, which were 0.83 and 0.72, respectively (p = <0.001). Moreover, their analysis showed that RI >0.86 was characteristic for DGF. Rodrigo et al[26] showed for the first time that patients who suffered from DGF have more than a 3-fold risk of high RI values in early measurement, independent of donor and recipient characteristics and also that RI is predictive of DGF. Our study has shown that having high RI values in early measurement was related to incidence of DGF and having lower RI was related to IGF, which was in line with previous studies reported. Therefore, measurement of graft RI is a useful parameter to establish graft function in the early period after kidney transplant surgery.

A previous study reported that a high RI measured at least 3 months after surgery was associated with poor allograft function and death.[13] Patients with an RI >0.8 got an end-point of 50% or more decrease of creatinine clearance,

allograft failure or death at a significantly higher rate than those with low RI values. In addition, high RI also correlated with chronic allograft nephropathy.[13] In late RI measurement, higher RI values can depict recipient vascular compliance as a cardiovascular risk factor or as a marker of physical graft damage in patients with chronic allograft nephropathy. Rodrigo et al[26] found that the values of immediate RI measurement did not influence graft outcome in the very long term. They found that 1-year graft survival was worse in patients with high RI values, however, 3- and 5-year graft survival rates were not worse between high and low RI patients. Moreover, they explained that the acute effect of DGF over interstitial oedema and RI could disappear over time.[26] Our meta-analysis of five studies regarding association between early measurement RI and long-term graft survival has shown that patients with low RI in early measurement were more prone to having a higher long-term graft survival rate than those with high RI, which was in line with most of previous studies concerning this issue.

This study has some limitations. First, not all the studies included were in prospective fashion, some of them were retrospective studies, as such, there is always the risk of associated potential bias in terms of data collection. Second, the cut-off point of high and low RI was not homogenous. Moreover, some studies used three groups (low RI, intermediate RI, and high RI) instead of just two groups (low RI and high RI). In this case, the authors modified those three groups into two groups to obtain a symmetrical analysis, ensuring that modifications were as objective as possible.

CONCLUSION

The results of this study emphasise the association between early measurement of RI and early graft function and long-term graft survival. Early measurement of RI using Doppler ultrasound is exceptionally useful and feasible in the diagnosis of early graft function and can help us to predict long-term graft survival. An elevated RI provides the chance to recognise the patients with poor long-term prognosis, from the very first moment after kidney transplant.

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