ASSOCIATION BETWEEN EARLY RESISTIVE INDEX MEASUREMENT AND EARLY GRAFT FUNCTION AND LONG-TERM GRAFT SURVIVAL AFTER KIDNEY TRANSPLANTATION: AN EVIDENCE-BASED CLINICAL REVIEW

Pande M. W. Tirtayasa¹, Gede Wirya K. Duarsa¹, Gerhard R. Situmorang², I Wayan Yudiana¹, Kadec B. Santosa¹, Anak A. Gde Oka¹, Arry Rodjani², Nur Rasyid²

¹ Division of Urology, Department of Surgery, Faculty of Medicine Universitas Udayana / Sanglah Hospital, Bali, Indonesia.
² Department of Urology, Faculty of Medicine Universitas Indonesia / Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Pande Made Wisnu Tirtayasa, MD. Division of Urology, Department of Surgery, Faculty of Medicine Universitas Udayana - Sanglah Hospital. Jl. Diponegoro, Denpasar 80113, Bali, Indonesia. email: wisnu.tirtayasa@gmail.com.

ABSTRACT

Background: Resistive Index (RI) measurement is commonly performed to assess organ transplant function using Doppler ultrasonography. The RI test results are the best parameter to assess kidney transplant dysfunction. Several studies have shown the role of RI as a predictor of transplant failure but those studies used RI results that were not taken immediately post-transplantation. The purpose of this study is to identify the relationship between RI measurement performed immediately post-transplantation with initial kidney transplant function represented by delayed graft function (DGF) and immediate graft function (IGF) and long-term kidney transplant survival.

Method: A clinical review based on evidence was performed on studies published before May 2018 using sources from Medline, Science Direct, EMBASE, and Cochrane. Studies that measure RI immediately post-transplantation where the primary or secondary purpose is related to kidney transplant function and/or kidney transplant survival are included. Studies that measure RI results not immediately post-transplantation and without RI level are not included in this study. The Mantel-Haenszel method was used to analyze pooled risk ratio and 95% confidence interval, while heterogeneity was analyzed through the I2 level. Analysis was performed using Review Manager 5.3.

Results: Analysis was performed on nine studies with a total of 1802 patients post-kidney transplant. DGF was found in 19% (193/1015) of patients in the low RI group and 42.8% (337/787) of patients in 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 patients in the low RI group and 10.5% (28/268) of patients in the high RI group (RR 0.26 (95% CI 0.17-0.40), p < 0.00001, I² = 0%). Kidney transplant that was still functioning was found in 83% (701/845) of patients in the low RI group and 69.4% (395/569) of patients in the high RI group (RR 0.82 (95% CI 0.72-0.93), p = 0.002, I² = 63%), with follow-up between 60-144 months.

Conclusion: The results of this study confirm the relationship between RI measurement performed immediately post-transplantation with initial kidney transplant function and long-term kidney transplant survival. An increase in RI offers the opportunity to recognize patients with a long-term poor prognosis, even in the early stages post-kidney transplantation.

Key words: kidney transplantation, resistive index, resistance index, kidney transplant function.
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 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 piloted 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. 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. 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>
<thead>
<tr>
<th>Authors/ year</th>
<th>Study method</th>
<th>N</th>
<th>Follow-up (months)</th>
<th>Do nor source</th>
<th>Mean donor age (years)</th>
<th>Mean recipient age (years)</th>
<th>CIT (min)</th>
<th>RI values group</th>
<th>RI measurement (day after transplant)</th>
<th>RI examination (artery/ arteries)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mwipatayi et al2016</td>
<td>Retrospective</td>
<td>253</td>
<td>144</td>
<td>LD &amp; DD</td>
<td>49</td>
<td>46</td>
<td>534</td>
<td>&lt;0.8 &amp; &gt;0.8</td>
<td>&lt;1</td>
<td>Segmental</td>
</tr>
<tr>
<td>Conti et al2015</td>
<td>Prospective</td>
<td>79</td>
<td>a</td>
<td>LD &amp; DD</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>&lt;0.84 &amp; &gt;0.84</td>
<td>1-3</td>
<td>Renal-iliac anastomosis</td>
</tr>
<tr>
<td>Rodrigo et al2010</td>
<td>Retrospective</td>
<td>333</td>
<td>139</td>
<td>DD</td>
<td>n/a</td>
<td>49</td>
<td>1290</td>
<td>&lt;0.7 &amp; &gt;0.7</td>
<td>2-3</td>
<td>Interlobar &amp; segmental</td>
</tr>
<tr>
<td>Saracino et al2006</td>
<td>Retrospective</td>
<td>76</td>
<td>140</td>
<td>DD</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>&lt;0.635 &amp; &gt;0.635</td>
<td>&lt;28</td>
<td>Interlobar &amp; segmental</td>
</tr>
<tr>
<td>Kolonko et al2012</td>
<td>Prospective</td>
<td>364</td>
<td>60</td>
<td>LD &amp; DD</td>
<td>39</td>
<td>41</td>
<td>1200</td>
<td>&lt;0.73; 0.73-0.85 &amp; &gt;0.85</td>
<td>2-4</td>
<td>Segmental</td>
</tr>
<tr>
<td>McArthur et al2011</td>
<td>Retrospective</td>
<td>172</td>
<td>36</td>
<td>DD</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>&lt;0.74; 0.74-0.81 &amp; &gt;0.81</td>
<td>&lt;7</td>
<td>Interlobar</td>
</tr>
<tr>
<td>Akgul et al2009</td>
<td>Retrospective</td>
<td>121</td>
<td>63</td>
<td>LD &amp; DD</td>
<td>40</td>
<td>31</td>
<td>a</td>
<td>&lt;0.7 &amp; &gt;0.7</td>
<td>&lt;28</td>
<td>Interlobar &amp; segmental</td>
</tr>
<tr>
<td>Barba et al2011</td>
<td>Retrospective</td>
<td>343</td>
<td>120</td>
<td>LD &amp; DD</td>
<td>47</td>
<td>50</td>
<td>888</td>
<td>&lt;0.7 &amp; &gt;0.7</td>
<td>1</td>
<td>Interlobar &amp; segmental</td>
</tr>
<tr>
<td>Król et al2011</td>
<td>Prospective</td>
<td>61</td>
<td>48</td>
<td>DD</td>
<td>n/a</td>
<td>45</td>
<td>n/a</td>
<td>&lt;0.57; 0.57-0.7 &amp; &gt;0.7</td>
<td>0 (intraoperative)</td>
<td>Renal-iliac anastomosis</td>
</tr>
</tbody>
</table>

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
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: $RI = \frac{\text{peak systolic frequency shift} - \text{minimum diastolic frequency shift}}{\text{peak systolic frequency shift}}$. 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\textsuperscript{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\textsuperscript{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 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, I\(^2\) = 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, I\(^2\) = 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, I\(^2\) = 63\%] (Figure 4).

![Forest plot between low RI and high RI in terms of DGF incidence](image1)

![Forest plot between low RI and high RI based on IGF incidence](image2)
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.

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, in conformity with previous studies, and others set their RI cut-off point at 0.8 or closer to that point, based on a study by Radermacher et al which reported an RI of 0.8 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 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 $C_r$ and an inverse correlation with GFR estimated by $Cr$ clearance, both at early stages after transplantation or at later stages. In contrast, other studies did not find this relationship.

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. Chudek et al 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 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. 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. 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 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. 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.

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.

REFERENCES


