Original Article

Initial kidney graft resistance index and the long-term cardiovascular mortality in transplanted patients: a paired grafts analysis

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Abstract

Background. Cardiovascular complications remain the most frequent cause of death in kidney transplant recipients. We analysed the prognostic value of early measured resistance index (RI) in the aspect of long-term cardiovascular mortality. In order to eliminate potential donor-related confounders, we analysed the mortality of recipients, transplanted with organs procured from the same donor, in whom the initial RI values differed. Methods. Doppler sonography was performed in 725 consecutive kidney graft recipients early after transplantation. We identified 133 pairs (266 patients) who received their kidney grafts from the same donor and their initial RI values differed by >0.1. Results. During 109 ± 37 months of follow-up after transplantation, 84 patients lost their graft and 29 died, 14 of them due to cardiovascular causes. Two groups of paired patients with higher RI and lower RI did not differ significantly with respect to their age, BMI, HLA mismatch and cold ischaemia time. There were more patients with diabetes in the higher RI group (14.3 versus 6.8%). Survival analysis revealed a higher mortality for cardiovascular (8.3 versus 2.3%, P = 0.02) and all causes (14.3 versus 7.5%, P = 0.06) among patients with higher initial RI values. In the Cox regression model, not including age, a higher RI value was a strong predictor of cardiovascular death (HR = 4.88), independent of previous cardiovascular episodes (HR = 6.78). Both these variables lost its significance as a predictors after inclusion of age in the regression model. Conclusion. Increased intrarenal resistance index in the early posttransplant period may help to identify the recipients with increased cardiovascular risk.

Keywords: cardiovascular death, Doppler ultrasound, kidney transplantation, outcome, predictor

Introduction

Kidney transplantation is an optimal method of treatment in patients with chronic kidney disease (CKD) in terms of morbidity, mortality and quality of life [1]. Nevertheless, the overall mortality in kidney transplant recipients remains higher than in the general population, and death with a functioning allograft is one of the major causes of allograft losses [2]. Patients with CKD are at high risk for the development of cardiovascular disease (CVD) [3], both atherosclerosis and arteriosclerosis [4]. After kidney transplantation, the cardiovascular mortality is still substantially higher than in the general population [5], as a consequence of the coexistence of numerous traditional (hypertension, diabetes, lipid disturbances and left ventricular hypertrophy—LVH) and nontraditional, specific for CKD (anaemia, systemic inflammation, calcium-phosphate disturbances and oxidative stress), risk factors [6, 7].

Kidney graft resistance index (RI), which is calculated based on the Doppler spectrum measured in the segmental arteries, is an integration of arterial compliance, pulsatility and peripheral resistance [8]. In stable kidney transplant recipients, RI correlated significantly with recipient age and arterial pulse pressure [9, 10]. Moreover, it was demonstrated that other markers of atherosclerosis and arterial stiffness, namely, pulse wave velocity (PWV), carotid intima-media thickness (IMT), and ankle-brachial index, also independently influence RI values [8, 11]. Thus, in the landmark Radermacher study, the RI value over 0.8
has been associated with worse long-term allograft and patient survival in stable kidney transplant recipients [12]. In contrast, during the early posttransplant period, RI value reflects mainly the degree of interstitial oedema within the graft, developed as a consequence of ischaemia-reperfusion injury. Of note, numerous clinical complications, such as an acute tubular necrosis, an acute rejection episode or calcineurin inhibitor nephrotoxicity, may also increase the kidney graft RI value [13, 14]. In addition, an initial RI value may be also influenced by donor hypotension episodes or catecholamine treatment as well as lower donor kidney excretory function (eGFR) prior to organ procurement, episodes or catecholamine treatment as well as lower donor kidney excretory function (eGFR) prior to organ procurement, and donor age [15, 16]. Recently, Kramann et al. have pointed out the relationship between the timing of RI measurement after transplantation and RI predictive value for graft failure or death, simultaneously denying such a value for RI measured within the first 6 months post-transplantation on a small subset of patients [17]. On the contrary, our recent work demonstrated that high RI values measured in segmental arteries of the kidney graft in the early posttransplant period are the predictor of worse kidney graft function and all-cause graft loss, including patient death [18]. However, the association between an early RI value and the cardiovascular mortality, which predominates in this population, has never been investigated. Hence, in the present study, we aimed to demonstrate the prognostic impact of noticeably higher posttransplant RI value on the long-term patient cardiovascular mortality. In order to eliminate potential donor-related confounders, as well as transplant era-related confounders, we analysed the mortality of recipients transplanted with kidneys procured from the same donor, in whom the early posttransplant RI values substantially differed.

**Materials and Methods**

The Bioethics Committee of the Medical University of Silesia granted the permission for this study. Informed consent was not deemed necessary; all data were analysed anonymously based on centre transplant database and the information from other transplant centres.

Seven hundred twenty-five consecutive adult recipients of deceased donor kidney transplant operated on in our centre between January 1998 and June 2009 were studied. Patients with primary graft nonfunction were excluded from further analysis. Finally, we identified 133 pairs (266 patients) who received their kidney grafts from the same donor and their initial RI values differed by >0.1. We have set such a difference to overcome the potential bias caused by both interobserver variability and intraobserver reproducibility of RI measurements in our centre, which were established as <0.05 and 0.03, respectively. Additionally, no patient within these pairs has been diagnosed with the transplant renal artery stenosis during the first week after transplantation.

The majority of patients were followed in our out-patient department. Thus, their clinical data were prospectively collected using a centre-operated database. The long-term follow-up data of patients transferred to other transplant centres were collected retrospectively in an effort to increase the completeness of follow-up.

In the analysed group of patients, the causes of chronic renal disease were as follows: chronic glomerulonephritis (47.7%), interstitial nephritis (11.3%), polycystic kidney disease (9.0%), diabetic nephropathy (8.6%), hypertensive nephropathy (7.5%), other disease and unknown conditions (15.9%).

After transplantation, most of the patients received triple immunosuppression therapy, which consisted of cyclosporine or tacrolimus, mycophenolate or azathioprine or sirolimus and steroids (Table 1). Twenty-five patients received basiliximab (Simulect®, Novartis, Basel, Switzerland) or antithymocyte globulin (ATG®, Fresenius, Bad Homburg, Germany) as an induction therapy. Notably, the analysed subgroups did not differ in terms of initial immunosuppressive regimen, including the induction therapy.

In all patients, the first Doppler sonography of the kidney graft was performed between the second and third days post-transplantation. All Doppler examinations were performed with an Acuson machine (Aspen, Mountain View, CA, USA), equipped with 2.5–4.0 MHz micro-convex-array transducer. After visualization of several segmental arteries in each patient, the Doppler spectrum was recorded and analysed. The kidney segmental arterial resistance index was calculated as \( RI = 1 - \left( \frac{V_{\text{max}}}{V_{\text{mean}}} \right) \). Results from three measurements, comprising both renal poles and its middle part, were averaged. The examinations were performed by three experienced sonographers, the majority of them by the principal investigator (A.K.).

Initial graft function was defined as immediate (IGF), slow (SGF) or delayed (DGF) graft function. IGF was defined as the serum creatinine concentration \( S_{\text{Cr}} \) at Day 3 posttransplant below or equal 264 µmol/l (3 mg/dl), SGF was defined as \( S_{\text{Cr}} \) above 264 µmol/l at Day 3, and DGF was defined as a need of dialysis therapy during the first week after transplantation.

The blood concentrations of calcineurin inhibitors reported in Table 1 were measured at the time of initial Doppler examination after transplantation.

Early acute rejection (AR) episode was defined by AR occurrence within the 3 months posttransplant, and late AR when AR was diagnosed later than 3 months after kidney transplantation. AR episodes were diagnosed based on clinical signs and symptoms and/or biopsy was proven if the diagnosis was uncertain.

The kidney graft function during the follow-up period was estimated using the eGFR calculated according to the Modification of Diet in Renal Disease (MDRD) formula (serum creatinine measurements were not IDMS-traceable) 3 months after transplantation and every consecutive 6 months.

Pre-transplant and post-transplant major adverse cardiovascular events (MACE) were defined as episodes of myocardial infarct, stroke or cardiac artery stenting/surgery, and recognized, based on the original medical records. Cardiovascular death was defined as death secondary to myocardial infarct, stroke, non-traumatic intracranial bleeding or vascular rupture (e.g. aortic aneurysm). The causes of all deaths were analysed based on the original medical records, not on the information from demographic registries or health care national payer.

Statistical analyses were performed using the STATISTICA 10.0 PL for Windows software package (StatSoft Polska, Kraków, Poland) and MedCalc 12.3.0.0. (Mariakerke, Belgium). Values are presented as means and 95% confidence intervals or...
Table 1. Clinical characteristics and laboratory parameters in patients with higher or lower kidney graft initial RI value after transplantation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Higher RI, n = 133</th>
<th>Lower RI, n = 133</th>
<th>ANOVA/Fisher test</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At transplantation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>44 (42–46)</td>
<td>41 (39–43)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>69/64</td>
<td>80/53</td>
<td>n.s.</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.7 (23.9–25.4)</td>
<td>23.9 (23.3–24.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Dialysis vintage (months)</td>
<td>37 (31–43)</td>
<td>29 (25–34)</td>
<td>0.05</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>110 (82.7)</td>
<td>119 (89.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>19 (14.3)</td>
<td>9 (6.8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>11 (8.3)</td>
<td>9 (6.8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>MACE, n (%)</td>
<td>6 (4.5)</td>
<td>10 (7.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>CIT (h)</td>
<td>19 (18–20)</td>
<td>19 (18–20)</td>
<td>n.s.</td>
</tr>
<tr>
<td>PRA &gt; 25, n (%)</td>
<td>5 (3.8)</td>
<td>4 (3.0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Second transplant, n (%)</td>
<td>14 (10.5)</td>
<td>6 (4.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>HLA mismatch class I</td>
<td>2.4 (2.3–2.6)</td>
<td>2.4 (2.2–2.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>HLA mismatch class II</td>
<td>1.0 (0.9–1.1)</td>
<td>0.9 (0.8–1.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Follow-up period</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension at 12-month timepoint (%)</td>
<td>95 (78.5)</td>
<td>106 (86.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Number of antihypertensive drugs (n)</td>
<td>2.1 (1.9–2.4)</td>
<td>2.0 (1.8–2.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>ACE/ARB, n (%)</td>
<td>23 (19)</td>
<td>18 (14.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Statin usage at 12-month timepoint, n (%)</td>
<td>31 (25.6)</td>
<td>23 (18.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Overall diabetes at follow-up, n (%)</td>
<td>48 (36.1)</td>
<td>38 (28.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>On insulin therapy, n (% of diabetics)</td>
<td>21 (43.8)</td>
<td>13 (34.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Metformin, n (% of diabetics)</td>
<td>14 (29.2)</td>
<td>13 (34.2)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Sulfonylurea derivatives, n (% of diabetics)</td>
<td>6 (12.5)</td>
<td>7 (18.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Early AR, n (%)</td>
<td>21 (15.8)</td>
<td>16 (12.0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Late AR, n (%)</td>
<td>16 (12.9)</td>
<td>14 (10.9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>CMV episode, n (%)</td>
<td>21 (15.8)</td>
<td>27 (20.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Early graft function (IGF/SGF/DGF)</td>
<td>16/45/72</td>
<td>32/74/27</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MACE, n (%)</td>
<td>20 (15.0)</td>
<td>7 (5.3)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Data shown as means ± 95% CI or frequencies.
RI, resistance index; BMI, body mass index; MACE, major adverse cardiac events; CIT, cold ischaemia time; PRA, panel-reactive antibodies; HLA, human leukocyte antigen; Tc, tacrolimus; CyA, cyclosporine A; MPA, mycophenolate; AZA, azathioprine; RAPA, sirolimus; ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; AR, acute rejection; CMV, cytomegalovirus; IGF, immediate graft function; SGF, slow graft function; DGF, delayed graft function; n.s., not significant.

frequencies. Study subgroups with higher or lower RI values were compared using the Fisher and Armitage tests (qualitative variables) and ANOVA (quantitative variables). Multivariate Cox proportional hazard regression analyses were performed for the calculation of the risk of cardiovascular death in two separate models, including potential explanatory variables: age, pretransplant diabetes, pretransplant MACE, DGF occurrence, duration of dialysis therapy prior to transplant, second transplant and higher RI value within the pair of recipients. Interpretation of the results was based on P-values of regression coefficients (parameter), the values of respective hazard ratios (HR) and their 95% confidence intervals (95% CI). In all statistical tests, the P-values below 0.05 were considered statistically significant; however, for multivariate analyses, a P-value between 0.05 and 0.1 was interpreted as borderline statistical significance.

**RESULTS**

**Study patients**

The demographic and clinical characteristics of patients with higher (mean value 0.93 ± 0.10) or lower (mean value 0.71 ± 0.08) initial RI values in pairs of recipients, transplanted with kidney grafts procured from the same donor, are shown in Table 1. There were more second transplants and diabetic patients in the higher RI group. Additionally, they also had longer dialysis vintage prior to transplant. Of importance, the frequency of patients diagnosed with coronary artery disease or MACE before transplantation was similar. The study groups did not differ significantly in terms of cold ischaemia time, HLA matching and initial immunosuppression regimen.

The long-term follow-up data were available for all patients, including patients transferred to other centres. Of note, only a small subset of study patients in both groups were receiving ACE/ARB and/or statins.

**Donors**

Table 2 shows the characteristics of donors. They were relatively young, with low incidence of hypertension. Only 17.1% of them fulfilled the extended donor criteria.

**Kidney graft outcomes**

The frequency of DGF was more than twice as high in the higher RI group (45.1 versus 20.3%, P < 0.001). It was not related
to the greater rate of early acute rejection in these patients (Table 1). In both groups, 15% of DGF cases were explained by an AR episode. Of note, the corresponding calcineurin inhibitors levels were similar in both groups. Patients with higher RI initial values were characterized by significantly worse kidney graft function during the first 3 years after transplantation [eGFR-MDRD: 12 months: 47.6 (44.2–50.9) versus 53.2 (49.8–56.6), P = 0.02; 24 months: 46.5 (42.7–50.4) versus 53.6 (49.7–57.4), P = 0.01; 36 months: 46.2 (42.4–49.9) versus 52.1 (48.1–56.1), P = 0.03]. During the next years of observation, the difference in eGFR between both groups was subtle.

The incidence of late AR episodes and overt CMV infections was similar in both groups.

During the mean follow-up of 109 ± 37 months, 84 patients lost their graft. There was an equal number of graft losses in both study groups (log-rank P = 0.59).

Recipient outcomes

Overall, there were 29 post-transplant deaths (10.9%), including 14 deaths due to cardiovascular causes (5.3%). There were two times more deaths in the group with higher early post-transplant RI value [19 (14.3%) versus 10 (7.5%), P = 0.06]. A significant difference between these two groups was noticed for cardiovascular mortality [11 (8.3%) versus 3 (2.3%), P = 0.02]. Similar results were obtained applying the log-rank test (for overall mortality: $F = 1.93$, P = 0.05; for cardiovascular mortality: $F = 2.31$, P = 0.02) (Figure 1).

The model of multivariate Cox proportional hazard regression with backward selection, not including age, revealed that a higher RI value was a predictor of cardiovascular death (HR = 4.88), independent of the previous cardiovascular episodes (HR = 6.78). The significance of both higher RI value and previous MACE as a predictors was no longer observed (P = 0.15 and P = 0.08, respectively) after inclusion of age—model II (Table 3).

RI value related to the cardiovascular mortality

We have performed receiver operator curve (ROC) analysis to determine the cut-off RI value that discriminates cardiovascular mortality in the long-term follow-up period. The analysis revealed an RI value >0.8 as the discrimination threshold for cardiovascular death, with 73% sensitivity and 47% specificity.

DISCUSSION

The most important finding of our study is the fact that among patients transplanted with kidneys procured from the same donor, those with higher RI values measured within the kidney graft during the first few days after transplantation present a significantly higher risk of cardiovascular death during the long-term observation. Moreover, after the exclusion of recipient age from the multivariate survival Cox model—as the variable which directly influences other potentially
analysed co-variables, i.e. pretransplant diabetes, previous cardiovascular episodes and even delayed graft function—we found that a higher RI value independently predicted greater cardiovascular mortality in our cohort.

In the early posttransplant period, a wide range of causes may influence the Doppler spectrum and the value of calculated parameters of intrarenal vascular resistance. Previously reported donor-derived factors include older age, a history of hypertension, increased serum creatinine concentration and/or episodes of hypotension prior to organ procurement [15, 16, 19]. Hence, in order to eliminate a potential influence of donor-related factors and to determine the genuine impact of higher kidney graft initial RI value on long-term cardiovascular mortality, we performed a paired kidney analysis with a reasonable within-pair RI value difference of >0.1, taking into account both potential intraobserver reproducibility and interobserver variability [20, 21], as well as the possible physiological differences between two kidneys from a single individual [22–24]. Considering the transplant factors, patients in both groups did not differ with regard to cold ischaemia time or HLA mismatch; the initial immunosuppression regimen and calcineurin inhibitor levels, corresponding with the time of initial Doppler examination, were also similar. However, there were more retransplanted patients in the higher RI group, with the borderline longer dialysis vintage. Significantly higher RI values measured within the first month after transplantation were previously shown in the recipients of the second kidney graft in comparison to first allograft recipients [25]. Nevertheless, that study included all living unrelated transplants, including some paediatric patients, and reported relatively great frequency of transplant kidney artery thrombosis or stenosis (>13% of all patients). In contrast, our present study analysed the consecutive cohort of deceased donor adult transplant recipients, and no kidney transplant artery stenosis was diagnosed in the analysed early posttransplant period. Finally, the multivariate regression analysis confirmed neither the independent influence of dialysis vintage nor retransplant on the long-term cardiovascular mortality.

Noticeably, there were more patients diagnosed with diabetes prior to transplantation in the higher RI group. The presence of diabetes has previously been shown to be associated with higher RI values in patients with [26, 27] and without underlying renal disease [27, 28]. In these studies, patients with diabetes also presented with significantly higher measures of arterial stiffness, namely, PWV and pulse pressure, than patients without diabetes [27, 28]. In kidney transplant recipients, the initial RI value was demonstrated to be independently influenced by the presence of pretransplant diabetes [29], and the percentage of diabetics was significantly greater in the highest initial RI tertile [30]. On the other hand, the presence of diabetes increased the risk of DGF [31, 32], which is clearly associated with markedly higher RI values in the early posttransplant period [16]. Obviously, the presence of pretransplant diabetes generally increases the risk of death in the long-term observation. Moreover, the development of new-onset diabetes after transplantation is also associated with high cardiovascular risk [33], posttransplant MACE and death [34]. It is worth noting that in the present study there was no significant difference in overall (pre- and post-transplant) diabetes prevalence during the whole follow-up period after transplantation. Moreover, in the multivariate analysis model, the authors did not show an independent influence of pretransplant diabetes on cardiovascular mortality.

It is important to stress that although the frequency of pretransplant cardiovascular episodes was similar in both groups, there was a considerably higher prevalence of cardiovascular complications during the long-term observation after kidney transplantation in patients with higher initial RI values. As a consequence, cardiovascular mortality was also significantly higher in this group. Hence, it could be argued that a higher early posttransplant RI seems to be an important additional predictor of increased cardiovascular risk in the long-term follow-up period. To date, in stable kidney transplant recipients, higher RI was associated with traditional cardiovascular risk factors, including age, systolic blood pressure, pulse pressure, body mass index, smoking and carotid IMT [8, 11, 35]. Furthermore, in the study of Bahous et al., the main parameters which predicted the posttransplant cardiovascular events were a past history of CVD, aortic PWV and Heart rate × Pulse pressure product [36]. Of note, pretransplant echocardiographic abnormalities such as LVH, ventricular dilatation and systolic dysfunction were associated with adverse patient outcome after transplantation [37]. On the other hand, a direct relationship has been recently found between kidney graft RI and LVH in stable kidney transplant recipients [38]. Similarly, higher renal RI values were independently related to age, pulse pressure, carotid IMT and left ventricular mass index in hypertensive patients [39], and were positively correlated with morphologic and haemodynamic alterations of the cardiovascular system. Also, in end-stage renal disease patients, prior cardiovascular disease, chronic inflammation, LVH, diabetes or advanced age identified patients at the highest risk for cardiovascular events [40]. Taking into account all above-mentioned results, we may assume that kidney graft RI is strongly correlated with the degree of arterial stiffness that is related to the damage to a recipient’s vasculature, and is partially related to age. In the same line, older recipient age was recently shown to be the strongest determinant of higher RI in the follow-up period [41]. Thus, increased RI would be a net effect of longer exposure to uraemic milieu, reflected by dialysis vintage and greater percentage of second transplants, more prevalent pretransplant diabetes, and slightly older population, resulting in noticeably greater, not proportional to age, vascular injury in the higher RI group.

Of interest, we have demonstrated that early RI values, but not DGF occurrence, predict the poor cardiovascular outcome, in concordance with our previous analysis of mortality among 364 consecutive kidney transplant patients [18]. It is well known that patients with DGF have initially increased RI values [16, 29]; however, the intrarenal interstitial oedema, related mostly to ischaemia-reperfusion injury, is not a sole RI value determinant. It could not be excluded that DGF patients with high cardiovascular risk have greater early posttransplant RI values. Previous reports concerning the DGF influence on mortality brought conflicted results [42, 43], and the percentage of cardiovascular deaths did not significantly differ in patients with and without DGF [42]. Hence, we may assume that the predictive significance of early RI value is related to
chronic vascular injury. In consequence, the predictive value of initial RI subsided after inclusion of age, the strongest determinant of arteriosclerosis in the regression model.

The main limitation of this study is the lack of protocol biopsies in the early posttransplant period, precluding the precise analysis of DGF causes. Nevertheless, the similar number of kidney graft losses in both study groups and comparable kidney graft function in remote observation subsides the potential bias related to worse early graft function in the higher RI group.

The statistical power of our findings is limited by the low number of deaths for cardiovascular causes, regardless of long follow-up period and complete patient outcome data. Noteworthy, the analysis did not include the fatal outcomes of our patients who lost their kidney graft and restarted dialysis therapy. On the other hand, such an analysis is not biased by the additional effect of further increase of the cardiovascular mortality accelerated by posttransplant haemodialysis therapy. In addition, the recent meta-analysis concerning the risk of death following kidney allograft failure, including 40 cohort studies, revealed that the first year of post-transplant dialysis therapy was associated with the highest mortality [44]. Of note, the authors pointed out the general high risk of bias and incompleteness of data in all included studies, and they could not sufficient information to summarize the annual mortality from cardiovascular events or any other specific causes.

Lastly, the time-dependent changes in immunosuppressive protocols throughout the analysed years may also be seen as a limitation of the study. However, the paired analysis used seems to annul this drawback.

In conclusion, our study provides new evidence facilitating the more precise evaluation of cardiovascular risk after kidney transplantation. It demonstrates that an increased intrarenal resistance index even in the early posttransplant period predicts higher cardiovascular mortality after kidney transplantation. However, this study did not establish the cut-off values that could help to identify the patients with increased cardiovascular risk on the basis of RI measurement early after kidney transplantation.

**CONFLICT OF INTEREST STATEMENT**

None declared.

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**R e s i s t a n c e i n d e x a n d c a r d i o v a s c u l a r m o r t a l i t y**

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Received for publication: 19.11.2014; Accepted in revised form: 4.3.2015