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Review article

Renal resistive index as a predictive factor of delayed graft function: A meta-analysis

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ABSTRACT

Background: Delayed graft function represents a major complication of kidney transplantation, leading to high rates of short and long-term morbidity. The aim of the present meta-analysis is to assess the role of renal resistive index measurement in the post-transplant period and evaluate its efficacy in the prediction of delayed graft function.

Methods: Medline, Scopus, Cochrane Central Register of Controlled Trials CENTRAL, Clinicaltrials.gov and Google Scholar databases were systematically searched. Statistical analysis was performed with Review Manager 5.3, R 3.4.3 and Open Meta-Analyst software.

Results: Fourteen studies were included with a total of 2741 kidney recipients. Patients with delayed graft function presented significantly higher rates of elevated renal resistive index (Odds Ratio: 1.96, 95% CI: [1.37, 2.81]). Also, renal resistive index values were significantly higher in patients with delayed graft function compared both to those with slow (Mean Difference: 0.04, 95% CI: [0.01, 0.07]) and immediate (Mean Difference: 0.10, 95% CI: [0.07, 0.12]) graft function. The pooled sensitivity for the detection of delayed graft function was estimated at 47.2% (95% CI: [30.9, 64.2]), the specificity at 69.3% (95% CI: [54.1, 81.2]) and the area under the curve at 0.613.

Conclusions: The present meta-analysis suggests the promising role of renal resistive index evaluation early after kidney transplantation, since its high values were significantly associated with higher incidence of delayed graft function. Future large-scale studies should define the most appropriate cut-off value and should incorporate renal resistive index in combined models in order to achieve optimal predictive accuracy.

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1. Introduction

Delayed graft function (DGF) is a common complication of kidney transplantation, occurring early in the postoperative period, mainly in deceased donors transplants [1]. It represents a form of acute kidney injury, necessitating dialysis within the first week after transplantation, resulting in increased rate of short-term morbidity, longer hospital stay and higher costs [2]. Its incidence varies from 3 to 35%, depending on the implemented definitions, which may be based on dialysis requirements, urine output, serum creatinine values, functional imaging or renal biopsy [3]. In the recent years, the frequency of DGF remains high, probably due to the rise of expanded criteria donors (ECD) and after cardiac death donations [4]. Although the pathophysiology of DGF is complex and multifactorial, ischemia-reperfusion injury in conjunction with the upregulation of innate and adaptive immunity responses leading to increased complement activation, oxidative stress and cell death constitute established pathogenetic steps [5].

Since an effective treatment is not currently available, early prediction is essential to recognize the recipients that would benefit the most from measures of prevention or prompt intervention [6]. Several predictive models have been developed, identifying cold-ischemia time, human leukocyte antigen (HLA) mismatches, as well as various donor and recipient-specific demographical and clinical factors as potential markers of increased DGF risk [7]. Moreover, much interest has been devoted on the evaluation of novel biomarkers as potential tools for DGF detection, with neutrophil gelatinase-associated lipocalin (NGAL) [8], interleukin 18 [9] and monocyte chemoattractant protein-1 (MCP-1) [10] to be the most promising. However, the development of an optimal model for the accurate prediction of DGF remains still under investigation.

Renal resistive index (RRI) measurement is a reproducible and non-invasive Doppler ultrasonographic study, used to evaluate renal microcirculation. It is assessed at the level of arcuate or interlobar arteries in the upper, mid and lower kidney poles and represents a marker of vascular impedance [11]. Apart from renal capillary wedge pressure, several extra-renal factors, such as heart rate, aortic stiffness and pulse pressure, may exert significant influence on its values [12]. In the native kidney, high RRI measurements have been associated with adverse clinical outcomes in hypertension due to renal artery stenosis [13], as well as with increased risk of acute kidney injury both in the postoperative setting [14] and in critically ill patients [15]. Recent research has focused on the potential utility of RRI evaluation in kidney transplant recipients, proposing that elevated values are linked to increased rates of acute allograft rejection [16] and long-term mortality [17]. Nevertheless, the interpretation of RRI values may be confounded by several parameters, such as aortic stiffness, diastolic blood pressure and atherosclerotic burden [18], especially in old-aged and diabetic kidney recipients.

The value of RRI as a tool for DGF prediction has been evaluated in several observational studies, although no firm consensus exists regarding its exact efficacy. The present meta-analysis aims to accumulate current literature knowledge in the field, in order to assess the predictive

efficacy of RRI and determine whether its elevated values are associated with an increased risk of DGF.

2. Materials and methods

2.1. Study design

The present meta-analysis was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [19] and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines [20]. Study selection was performed consecutively in 3 stages. Firstly, the titles and/or abstracts of all electronic articles were screened to evaluate their eligibility. All articles that were presumed to meet the criteria were retrieved as full-texts. Finally, all observational studies (both prospective and retrospective) that reported RRI values among transplant recipients with delayed, slow or immediate graft function were selected. Case reports, conference abstracts or posters, review articles and animal studies were excluded from the present review. No date/language restrictions were applied. Any possible discrepancies concerning retrieval of articles and statistical analyses were resolved by the consensus of all authors.

2.2. Literature search and data collection

Literature search was primarily conducted using the Medline (1966–2018), Scopus (2004–2018), Cochrane Central Register of Controlled Trials (CENTRAL) (1999–2018) and Clinicaltrials.gov (2008–2018) databases. Google Scholar (2004–2018) database and the reference list of all the included studies were also searched in order to recognize potential additional articles. The date of the last search was set at 26 December 2018. The search strategy included the following algorithm: “(renal resistive index OR rri OR resistance index OR arterial resistance or vascular resistance) AND (((renal OR kidney) AND (transplant OR transplantation)) OR (delayed graft function) OR dgf)” and is schematically illustrated in the PRISMA flowchart (Suppl. Fig. 1).

2.3. Investigated indices

The data extracted from each included study were the following: name of first author, year of publication, country, study design, eligibility criteria, DGF definition criteria, timing of RRI measurements, ultrasound characteristics, inter- and intra-observer coefficient of variation, patients' number, mean age, gender, systolic blood pressure, presence of diabetes mellitus, dialysis duration prior to transplantation, cold-ischemia time (CIT), HLA mismatches, degree of proteinuria and RRI cut-off. The examined donor characteristics included number of living donors, donor age, gender and presence of hypotension. The outcomes of interest were the rate of RRI elevation in DGF patients, as well as the comparison of RRI absolute values among recipients with delayed, slow or immediate graft function.

2.4. Definitions

Renal resistive index is calculated with the formula: (peak systolic velocity - end-diastolic velocity)/peak systolic velocity, measured transparietally at the level of arcuate or interlobar arteries, under Color Doppler guidance. Three waveforms at the superior, median and lower kidney segments are obtained and subsequently RRI is estimated as the mean of the above measurements [21]. DFG was detected when need for dialysis was present within the first post-transplantation week [22].

2.5. Quality assessment

The methodological quality of all the included studies was judged with the Risk Of Bias In Non-randomized Studies (ROBINS-I) assessment tool [23], which evaluates the possible risk of bias due to confounding, selection, classification and deviation from intended intervention, as well as due to missing data, measurement and reporting of the outcomes. Moreover, the quality of the studies that were eligible for the diagnostic accuracy analysis was also assessed with the QUADAS-2 tool [24], which includes 4 basic domains: patient selection, index test, reference standard, flow and timing. Both tools were implemented by two researchers independently, while potential disagreements were resolved through the consensus of all authors.

2.6. Statistical analysis

The statistical meta-analysis was conducted in Review Manager 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011), Open Meta-Analyst software [25], as well as in R (3.4.3 version) using the “metafor” package [26]. Confidence intervals were set at 95%. The inter-study heterogeneity was assessed with the inconsistency index (I^2) [27]. When significant heterogeneity was noted ($I^2 > 50\%$), a random effects model was implemented to provide pooled estimates of odds ratio (OR) or mean difference (MD) along with the 95% confidence intervals (95% CI).

Heterogeneity was also evaluated with a Galbraith radial plot [28], which was constructed by plotting the standardized effect size against the inverse of the standard error. Studies exceeding the 95% CI lines were considered as outliers. In addition, heterogeneity detection was performed using a Baujat plot [29] which indicates the contribution of each study to the overall heterogeneity, as assessed by the Cochrane's Q statistic (Q_i) versus its influence on the overall outcome, expressed as the squared difference of the meta-analytic estimate with and without the n^{th} study, divided by the calculated variance without the n^{th} study. The presence of countable sources of heterogeneity was further investigated by conducting meta-regression analysis. The examined parameters were pre-specified to be the following: country, sample size, gender, percentage of living kidney donors, RRI cut-off, timing of measurement and risk of bias. The potential presence of publication bias was explored with the visual inspection of the funnel plot, while its asymmetry was evaluated using both the Egger's regression [30] and Begg's rank correlation [31] tests.

Trial sequential analysis was performed with the TSA version 0.9.5.5 software (Copenhagen: The Copenhagen Trial Unit, 2016) in order to investigate the possible presence of type I and II errors [32]. O'Brien-Fleming α -spending function was used, permitting adjustment of the desired statistical significance level. The risk for type I errors was set at 5% and for type II errors at 80%. The cumulative Z-curve and the two-sided 5% symmetrical significance boundaries were both plotted. During the analysis, it was also evaluated whether the total information size reached the required one to ensure sufficient power.

The diagnostic accuracy meta-analysis was carried out in the “mada” package of R (3.4.3 version) [33]. A bivariate model was implemented to provide summary estimates of sensitivity and specificity, as it takes into

consideration the potential correlation between these two quantities, due to threshold effect [34]. A summary receiver operating characteristic (SROC) curve was also constructed and the area under the curve (AUC) was estimated.

2.7. Sensitivity analysis

Leave-one-out analysis was performed in order to investigate the effect of individual studies on the overall outcome. To achieve this, one study was sequentially omitted at a time and its influence on the meta-analysis estimate was assessed. Moreover, the main outcome was calculated with both the random and fixed effects model, in order to evaluate whether the result was significantly affected by the statistical method. The effect of RRI elevation on DGF incidence was also assessed in specific study subgroups, which were pre-defined to be the following: studies with sample size >250 patients, prospective cohort design, mean patient age >50 years, living donors $>30\%$, RRI cut-off: 0.70, RRI measurements ≤ 5 days postoperatively and studies with a low risk of bias as evaluated by the ROBINS-I tool. In addition, in order to define the predictive nature of RRI, its diagnostic accuracy was separately calculated including only the studies which performed their measurements early in the postoperative period (≤ 5 days after transplantation).

3. Results

3.1. Included studies

Fourteen studies [35–48] were finally included to the present systematic review, with a total of 2741 kidney transplant recipients. Among them 695 were diagnosed with delayed graft function, while the rest 2046 patients served as the control group. Thirteen studies were evaluated both qualitatively and quantitatively, while one study [37] was only included in the qualitative synthesis, as it provided its outcomes in terms of median and interquartile range. The diagnostic accuracy analysis was based on 10 studies, which provided adequate data for the construction of the 2×2 table. The methodological characteristics of the included studies (country, study design, exclusion criteria, DGF definition, timing of measurement and RRI cut-off) are exhibited in Table 1. All studies were cohorts, with 4 of them [42,43,45,47] to present a prospective design. DGF was detected by the need of dialysis within the 1st postoperative week in the majority of studies; however, in one study it was defined as the need of >1 dialysis procedures. Five studies also included a group of patients with slow graft dysfunction (SGF), defined as serum creatinine $>264 \mu\text{mol/L}$ at day 3 after transplantation. RRI was evaluated before the 5th postoperative day in 10 studies, while intraoperative measurements were available in one of them. No study reported the use of machine perfusion for kidney preservation. The most important patients' characteristics (age, gender, systolic blood pressure, presence of diabetes mellitus, dialysis duration before the transplantation, CIT, HLA mismatches and degree of proteinuria) are presented in Suppl. Table 1, while donor characteristics (number of living donors, age, gender and presence of hypotension) are described in Suppl. Table 2. It should be noted that in the majority of studies, increased mean patients' age was associated with higher RRI values, as broadly reported in the literature.

3.2. Excluded studies

Six studies [49–54] were excluded from the analysis after reading the full-text, since they did not report the outcomes of interest. It should be noted that in three of them [51–53], a significant correlation of high RRI measurements with increased rates of DGF was observed, although neither the absolute RRI values nor the number of DGF patients with a high RRI were provided.

Table 1

Study characteristics. NR: not reported; DGF: delayed graft function; PC: prospective cohort; RC: retrospective cohort; ATN: acute tubular necrosis; CV: coefficient of variation.

Year; Author	Country	Study design	Exclusion criteria	DGF definition	Timing of measurement	RRI cut-off
2003; Radermacher	Germany	RC	Kidney compression, ATN at measurement, renal artery stenosis $\geq 50\%$, hydronephrosis grade ≥ 2 , acute rejection	Need of dialysis during the 1st week after transplantation	≥ 3 months after transplantation	0.8
2006; Chudek	Poland	PC	Acute rejection within the first month, primary graft non-function	Need of >1 dialysis procedures	2–4 days postoperatively	–
2006; Saracino	Italy	RC	Acute rejection, rapid renal function deterioration, renal artery stenosis, urinary tract obstruction	Need of dialysis during the 1st week after transplantation	Within 1st month postoperatively	0.635
2009; Akgul	Turkey	RC	Clinical signs of acute rejection, renal artery stenosis, urinary tract obstruction, cyclosporine toxicity	Need of dialysis during the 1st week after transplantation	Within 1st month postoperatively	0.7
2010; Rodrigo	Spain	RC	Vascular thrombosis, death during the 1st week postoperatively, renal artery stenosis, hydronephrosis grade ≥ 2	Need of dialysis during the 1st week after transplantation	2–3 days postoperatively	0.7
2011; Grzelak	Poland	RC	NR	Need of dialysis during the 1st week after transplantation	3–5 days postoperatively	–
2011; Krol	Poland	PC	Early acute rejection, early graft loss, primary graft non-function	Need of dialysis during the 1st week after transplantation	Intraoperatively	0.7
2012; Kolonko	Poland	PC	Acute rejection at measurement, primary graft non-function	Need of dialysis during the 1st week after transplantation	2–4 days postoperatively	0.73
2012; Winther	Denmark	RC	Any apparent intercurrent illness	Need of dialysis during the 1st week after transplantation	≥ 3 months after transplantation	0.66
2015; Contti	Brazil	PC	Renal vein thrombosis, renal artery thrombosis or stenosis	Need of dialysis during the 1st week after transplantation	1–3 days postoperatively	–
2016; Mwipatayi	Australia	RC	Renal artery stenosis, perinephric collection, urinary tract obstruction	Need of dialysis during the 1st week after transplantation	Within 24 h postoperatively	0.8
2017; Schwarz	Austria	RC	NR	Need of dialysis during the 1st week after transplantation	Within 48 h postoperatively	–
2018; Comai	Italy	RC	Combined heart and kidney transplantation	Need of dialysis during the 1st week after transplantation	Within 24 h postoperatively	0.7
2018; Venkatesh	India	RC	NR	Need of dialysis during the 1st week after transplantation	Within 5 h postoperatively	0.7

3.3. Quality assessment

The outcomes of the ROBINS-I tool are demonstrated in Suppl. Table 3, indicating a moderate to low overall risk of bias. More specifically, moderate bias risk was identified in 7 studies, mainly coming from potential confounding and deviations from intended interventions. The results of QUADAS-2 evaluation are illustrated in Suppl. Fig. 2, suggesting an overall fair quality of the studies. Sources of bias were recognized in the domain of index test in one study not using pre-defined RRI cut-off values [38], as well as in the domain of flow and timing in 4 studies [35,38,40,48] that evaluated RRI after DGF diagnosis, while applicability concerns were raised in one study [46], since it included patients with combined kidney and liver transplantation.

3.4. Qualitative synthesis

The outcomes of the qualitative synthesis are summarized in Suppl. Table 4. RRI was treated as a categorical variable in 10 studies, while continuous data were provided in 5 studies. The most frequently used RRI cut-off was 0.70, implemented in 5 of the included studies. Elevated values above the defined threshold were significantly more common in

DGF compared in IGF patients in all the 10 studies evaluating RRI early in the postoperative period. On the contrary, this finding was not present in the rest 4 studies, which measured RRI after DGF diagnosis. SGF was assessed in 5 studies, indicating that it was linked to increased rates of RRI elevation compared to IGF. Concerning absolute RRI values, a similar trend was present, since patients diagnosed with DGF and SGF showed significantly higher RRI levels than IGF patients.

3.5. Quantitative synthesis

Elevated RRI was associated with a significantly increased incidence of DGF (OR: 1.96, 95% CI: [1.37, 2.81], 2454 patients) (Fig. 1). Recipients with DGF showed significantly higher RRI values compared to those with IGF (MD: 0.10, 95% CI: [0.07, 0.12], 462 patients) and SGF (MD: 0.04, 95% CI: [0.01, 0.07], 319 patients). In addition, patients with SGF presented significantly higher RRI than those with IGF (MD: 0.06, 95% CI: [0.05, 0.07], 361 patients) (Suppl. Fig. 3). The SROC curve for DGF detection is depicted in Fig. 2. The AUC was calculated to be 0.613, while summary sensitivity was estimated at 47.2% (95% CI: [30.9, 64.2]) and specificity at 69.3% (95% CI: [54.1, 81.2]).

The Galbraith radial plot suggested that no studies exceeded the 95% lines, suggesting no remarkable heterogeneity. Similarly, the Baujat plot

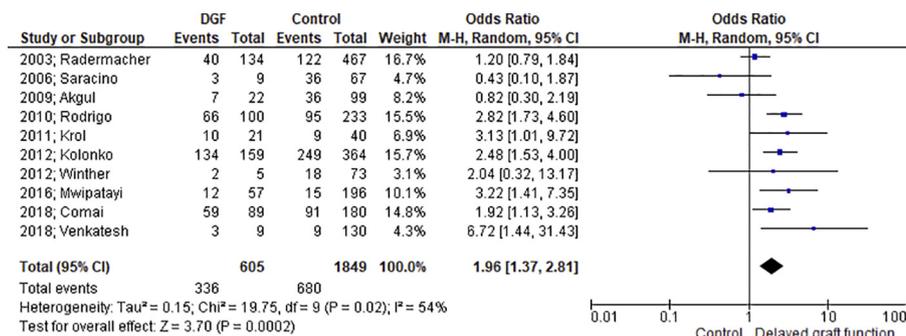


Fig. 1. Forest plot comparing the incidence of elevated renal resistive index among patients with delayed graft function and the control group.

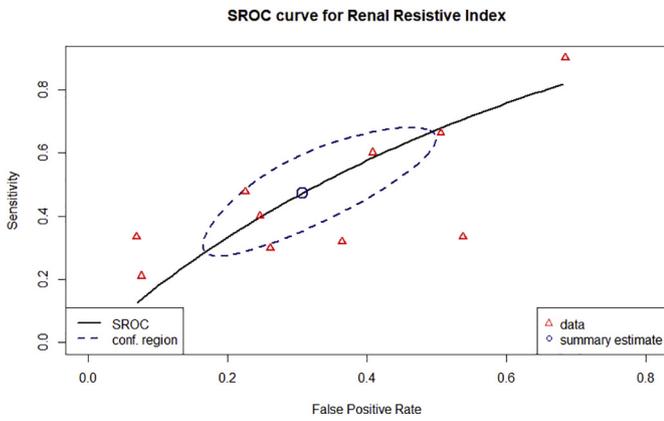


Fig. 2. Summary receiver operating characteristic (SROC) curve of renal resistive index for the detection of delayed graft function.

indicated that all studies were placed in the left lower quadrant, demonstrating the existence of no outliers (Fig. 3). Meta-regression analysis proposed that country, sample size, gender, percentage of living donors

and RRI cut-off did not affect the outcome; on the contrary, timing of measurement ($r = 0.862, p\text{-value} < 0.001$) and risk of bias ($r = 0.736, p\text{-value} = 0.001$) were suggested to significantly influence the overall results, indicating that RRI elevation lead to higher rates of DGF in studies in which measurements were conducted early in the postoperative period (≤ 5 days after transplantation) and in those with low risk of bias as assessed by the ROBINS-I tool (Table 2).

Trial sequential analysis demonstrated that the Z-curve surpassed both the conventional and trial sequential monitoring boundaries, while the required information size (RIS = 1669) was reached, suggesting that there was enough evidence to support the statistical significance of the results (Fig. 4). The visual inspection of the funnel plot supported no evidence of publication bias (Suppl. Fig. 4), while both Egger's ($t = 0.225, p\text{-value} = 0.83$) and Begg's ($t = 0.111, p\text{-value} = 0.73$) tests revealed no asymmetry.

3.6. Sensitivity analysis

Leave-one-out analysis indicated that the meta-analysis estimate remained stable, since no single study exerted significant effect on the overall outcome (Fig. 5). Interestingly, excluding the only study measuring RRI >3 months post-transplantation [40] did not alter the statistical

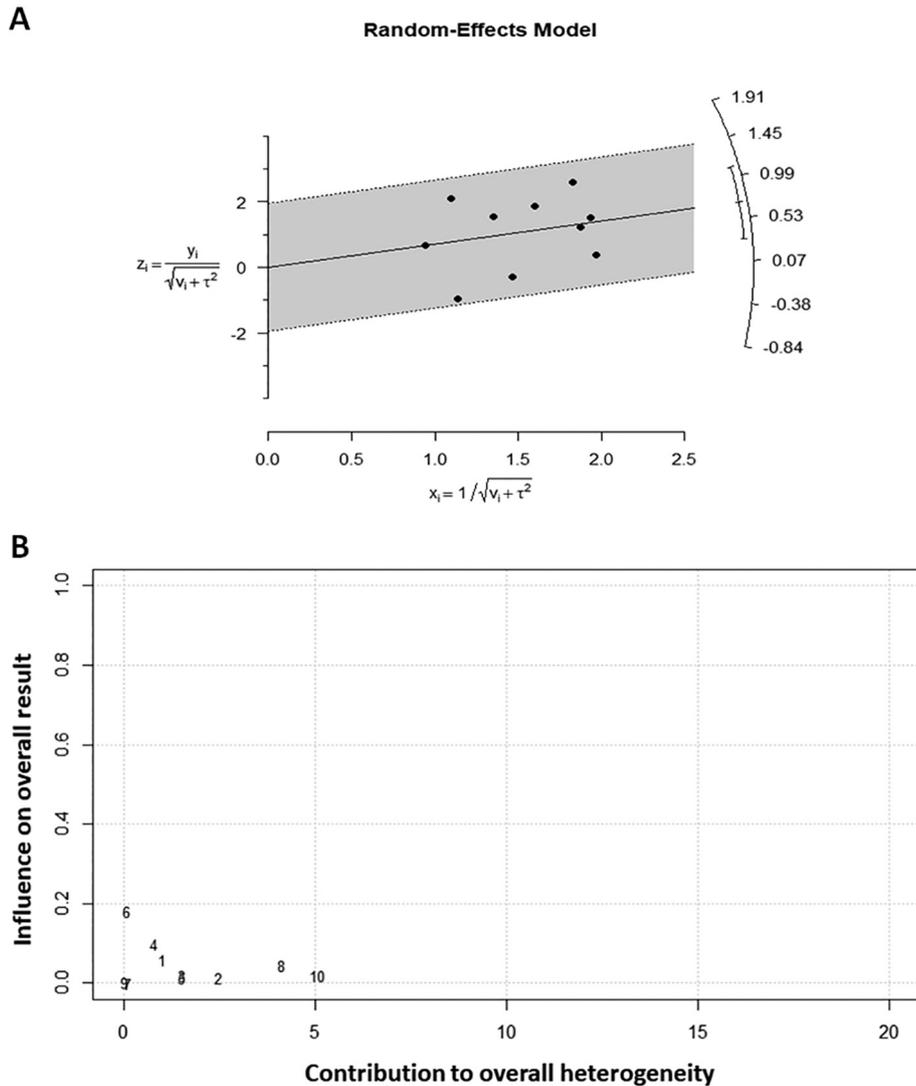


Fig. 3. Heterogeneity investigation. The Galbraith radial plot (A) indicates that no study exceeds the 95% confidence interval lines. The arc on the right side shows the estimated individual effect size for each point, if a line from 0 (0,0) is projected through that point towards the arc. The Baujat plot (B) shows that all studies are in the left lower quadrant, suggesting no significant heterogeneity and the existence of no outliers.

Table 2
Outcomes of the meta-regression analysis.

Covariate	Level	Studies	Coefficient	Standard error	p-value
Sample size	–	10	0.000	0.001	0.775
Gender	–	9	–0.011	0.011	0.280
Percentage of living kidney donors	–	9	–0.003	0.006	0.652
Country	Europe ^a	7	–		
	Other	3	0.160	0.398	0.689
Renal resistive index cut-off	Other ^a	5	–		
	0.70	5	0.252	0.305	0.408
Timing of measurement	>5 days	4	–		
	≤5 days postoperatively ^a	6	0.862	0.230	<0.001
Risk of bias	Moderate ^a	5	–		
	Low	5	0.736	0.227	0.001

Bold indicates statistically significant

^a Reference variable.

significance of the meta-analytic result (OR: 2.19, 95% CI: [1.54, 3.12]). Moreover, the fixed-effects model lead to a similar result compared to the random-effects model (OR: 1.96, 95% CI: [1.56, 2.36] vs. 1.98, 95% CI: [1.37, 2.81]). As presented in Table 3, the outcome remained statistically significant in all the examined subgroups. It is important to note that the highest OR was observed when the analysis was limited to studies conducted early after the transplantation (OR: 2.54, 95% CI: [1.96, 3.30]), as well as to studies with a low risk of bias (OR: 2.50, 95% CI: [1.92, 3.26]). Interestingly, $I^2 = 0$ was observed in these subgroups. Correspondingly, the predictive efficacy of RRI was also calculated to be higher in studies performing their measurements during the first 5 postoperative days (AUC: 0.66; sensitivity: 52.2%, 95% CI: [27.6, 75.7], specificity: 71.9%, 95% CI: [46.8, 88.2]).

4. Discussion

Delayed graft function constitutes a major source of morbidity in transplant kidney recipients, while its increased duration has been

associated with both short and long-term adverse outcomes. Effective risk stratification is essential, since it would enable the offer of early intervention and would guide clinical decisions concerning the optimal timing for dialysis initiation [55]. More specifically, identifying patients at increased risk of DGF would indicate the necessity of close monitoring, volume status optimization and maintenance of calcineurin inhibitor levels within the therapeutic range [56]. An efficient predictive tool is also useful for the future clinical trials evaluating DGF preventive measures, since early administration of the candidate interventions in high-risk patients may enhance their effectiveness [57].

The present meta-analysis evaluated the potential role of RRI in the post-transplant setting, supporting that elevated RRI values are significantly linked to an increased DGF incidence. Importantly, as demonstrated by the sensitivity analysis, this association was more pronounced when measurements were performed early in the postoperative period, suggesting the predictive nature of RRI elevation. Nevertheless, the estimated diagnostic accuracy of early RRI rise was moderate (AUC: 0.66, sensitivity: 52.2%, specificity: 71.9%), indicating that evaluation of RRI alone was not adequate to efficiently predict the occurrence of DGF. Patients with SGF presented also significantly higher RRI than those with IGF, although the small number of studies limited the interpretation of this comparison.

The impact of DGF etiology on RRI values had been assessed in one of the included studies using contrast-enhanced ultrasonography, suggesting that both delayed contrast medium distribution in the renal parenchyma and elevated RRI were more prominent in patients with acute rejection compared to those with acute tubular necrosis [44]. The pathogenesis of this observation may be attributed to the inflammation-induced endothelial dysfunction leading to microthrombosis and the subsequent increase of vascular bed resistance [58]. Intraoperative RRI measurements were conducted in one study using Doppler flowmeter on the renal graft artery, observing that low RRI values were associated with IGF, as well as with higher glomerular filtration rate on the long-term [42]. It is also interesting that the combination of RRI and serum amylase evaluation was able to efficiently predict DGF, enhancing the accuracy of either marker alone [46].

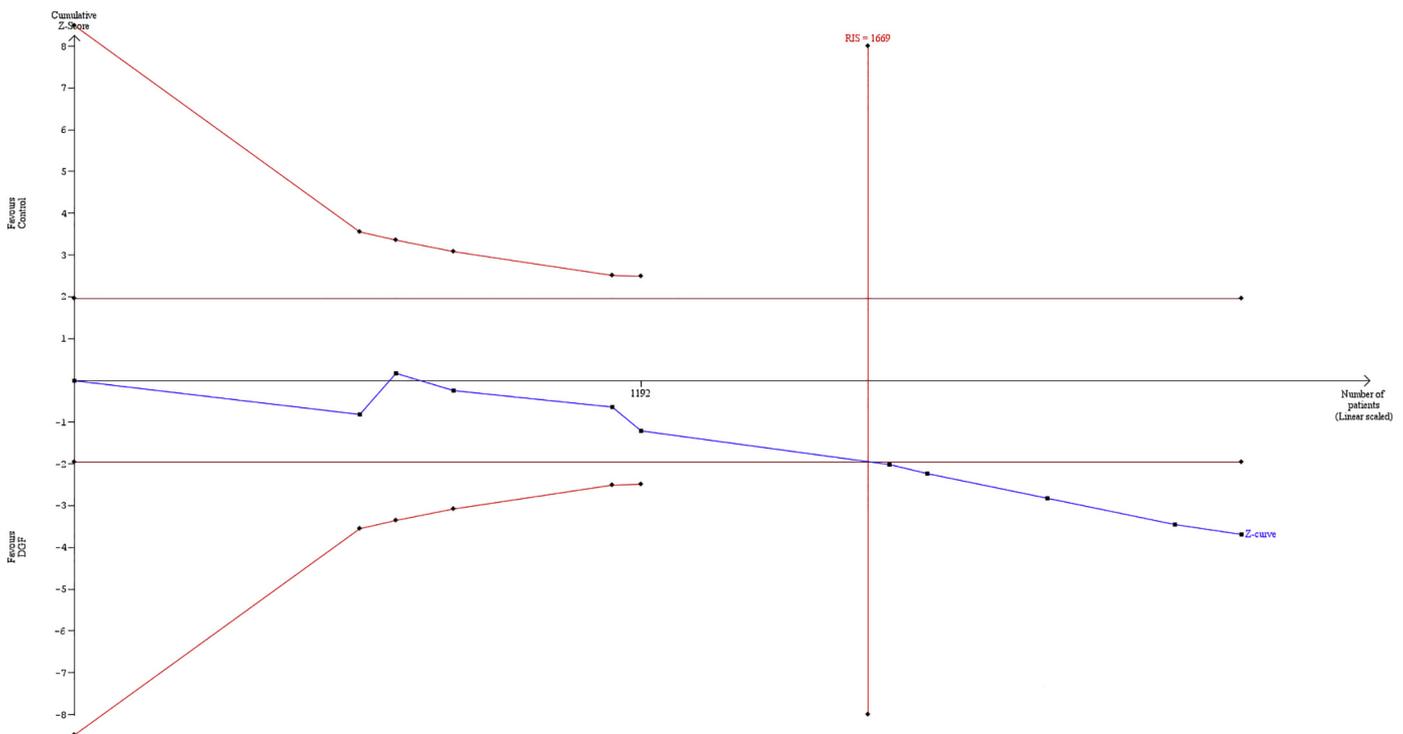


Fig. 4. Outcomes of the trial sequential analysis. The cumulative Z-curve crossed both the conventional and O'Brien–Fleming significance boundaries. RIS: required information size.

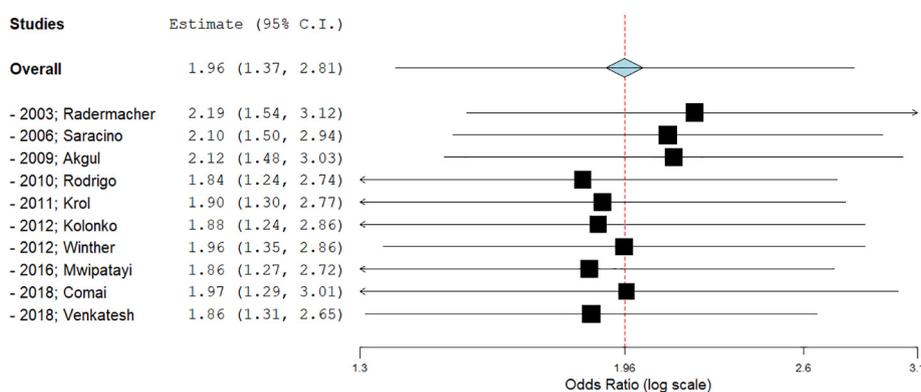


Fig. 5. Outcomes of the leave-one-out analysis. No single study significantly influenced the overall result.

4.1. Strengths and limitations of the study

The present meta-analysis gathered for the first time all the available literature knowledge concerning the role of RRI in the prediction of DGF in kidney transplant recipients. To achieve this, five independent literature databases were systematically searched, while any language or date restrictions were avoided. Risk of bias was evaluated in detail, using two different quality assessment tools (ROBINS-I and QUADAS-2); interestingly, the observed association was found to be stronger in studies with low risk of bias, as suggested by the sensitivity analysis. In addition, inter-study heterogeneity was thoroughly investigated by plotting a Baujat and a Galbraith radial plot, which identified no outliers. Extensive meta-regression and sensitivity analyses were performed, indicating that country, sample size, gender, percentage of living donors and RRI cut-off did not remarkably influence the overall outcome. The possibility of type I and II error was also tested by conducting a trial sequential analysis, supporting the robustness of the results. In order to limit the effect of RRI threshold heterogeneity, a bivariate statistical model was implemented for the diagnostic accuracy analysis, as it takes into account the possible correlation between sensitivity and specificity.

On the other hand, the existing heterogeneity can be attributed to the differentiations of the eligibility criteria implemented by each study, as well as to the variations regarding RRI measurement timing. More specifically, 3 studies did not report their exclusion criteria (Table 1), although they evaluated RRI early in the postoperative period, a fact that may limit risk of bias due to unnecessary exclusions. Moreover, patients with high RRI tended to present higher mean age and thus the influence of this parameter as a confounding factor cannot be safely excluded. Subjectivity in the measurements of RRI represents another inherent limitation of the method, while intra-observer and inter-observer variability were not reported in the majority of studies and thus the effect of this parameter could not be assessed. It is important to state that the analysis of RRI absolute values included a small number of studies, since the majority of them treated it as a categorical variable.

Table 3

Outcomes of the sensitivity analysis. CI: confidence intervals; RRI: renal resistive index.

Subgroup	Number of studies	Odds ratio [95% CI]	p-value	I ²
Sample size >250 patients	5	2.10 [1.46, 3.02]	<0.0001	58%
Prospective cohorts	2	2.57 [1.65, 3.99]	<0.0001	0%
Mean age > 50 years	3	1.47 [1.06, 2.02]	0.02	0%
Living donors >30%	4	1.98 [1.14, 3.44]	0.02	56%
RRI cut-off: 0.70	5	2.21 [1.62, 3.02]	<0.0001	47%
≤5 days postoperatively	6	2.54 [1.96, 3.30]	<0.0001	0%
Low risk of bias	5	2.50 [1.92, 3.26]	<0.0001	0%
Overall	10	1.96 [1.37, 2.81]	0.0002	54%

It should be also noted that since most studies did not perform a ROC analysis, the reported RRI diagnostic accuracy was based on the conventional cut-off values; therefore, the estimated sensitivity and specificity may be underestimated, while the optimal threshold for DGF diagnosis remains unknown.

4.2. Implications for current clinical practice and future research

The findings of the present meta-analysis support the promising role of RRI evaluation early after kidney transplantation, since its high values significantly associated with increased incidence of DGF. The predictive nature of this elevation was confirmed, as the observed association was found to be stronger in studies performed immediately postoperatively. As a result, RRI may serve as a useful non-invasive marker that may improve the diagnostic accuracy of the existing predictive models. However, it is important to state that the calculated sensitivity of the test was low and therefore RRI alone may not be able to effectively discriminate patients at risk of DGF. Thus, future large-scale studies should test its combination with conventional clinical risk factors, as well as with novel serum or urinary biomarkers, in order to construct a predictive model with optimal predictive efficacy. A prospective design should be followed, while defining DGF as the need of dialysis during the 1st postoperative week would limit inter-study heterogeneity. Potential confounders, such as age, cold-ischemia time and patients' comorbidities should be taken into account in order to investigate their effects. Finally, multiple cut-off values should be evaluated in order to find out the optimal RRI threshold that should maximize the sensitivity and specificity of the test.

5. Conclusions

The present meta-analysis suggests that high RRI values during the first postoperative days are significantly associated with an increased risk for delayed graft function. However, the sensitivity of the method was low and thus RRI alone was not able to adequately predict the occurrence of DGF. Future large-scale studies should evaluate the timing of measurement as well as the cut-off value that would maximize its efficacy. RRI should be tested in conjunction with conventional risk factors and novel biomarkers, in order to construct a combined predictive model with optimal diagnostic accuracy. The confounders mentioned in the present review should be taken into consideration to limit heterogeneity.

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