



# Renal resistive index as predictor of acute kidney injury after major surgery: A systematic review and meta-analysis



Ioannis Bellos<sup>a,\*</sup>, Vasilios Pergialiotis<sup>a</sup>, Konstantinos Kontzoglou<sup>a,b</sup>

<sup>a</sup> Laboratory of Experimental Surgery and Surgical Research N.S. Christeas, Athens University Medical School, National and Kapodistrian University of Athens, Greece

<sup>b</sup> 2nd dept of Propedeutic Surgery, "Laikon" General Hospital, National and Kapodistrian University of Athens, Greece

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## ABSTRACT

**Purpose:** To determine the efficacy of Doppler renal resistive index in the prediction of acute kidney injury after major surgery.

**Methods:** A systematic review and meta-analysis of cohort studies was conducted. Medline (1966–2018), Scopus (2004–2018), [Clinicaltrials.gov](http://Clinicaltrials.gov) (2008–2018) and Google Scholar (2004–2018) databases were systematically searched. Prospective studies that examined the diagnostic accuracy of renal resistive index in postoperative acute kidney injury were included.

**Results:** The meta-analysis was based on 10 studies, including a total number of 911 patients. Patients who developed acute kidney injury presented higher renal resistive index values preoperatively (MD: 0.02, 95% CI: [0.00–0.03]), immediately after surgery (MD: 0.07, 95% CI: [0.04–0.11]) and 24 hours postoperatively (MD: 0.07, 95% CI: [0.04–0.09]). The pooled sensitivity was 81.8%, the specificity 77.6% and the area under the curve 0.866. Fagan's nomogram indicated that the post-test probability was increased to 60.6% (positive test) and decreased to 9.5% (negative test), when the pre-test probability was 30%.

**Conclusions:** Renal resistive index represents a useful marker with fair performance in the prediction of postoperative acute kidney injury. Future cohorts should establish the optimal timing of measurement and evaluate the most appropriate cut-off value that should be used in the clinical setting.

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## 1. Introduction

Acute kidney injury (AKI) represents a major postoperative complication and a significant contributor of both short and long-term morbidity and mortality [1]. Its incidence is higher after cardiac surgery, ranging from 5 to 42% [2], while 1–5% of patients require renal replacement therapy (RRT) [3]. The pathophysiology of postoperative AKI is multifactorial, as it is based on the interplay of various events, including renal vasoconstriction, inflammation, ischemia-reperfusion injury and the administration of drugs with nephrotoxic properties [4]. Several predisposing factors have been identified, such as preoperative cardiovascular and pulmonary disorders and the intraoperative cardiopulmonary bypass (CPB) and aortic clamp time [5]. Early prediction is essential in order to identify patients at high risk of AKI and to offer preventive and early treatment measures. For this reason, recent research has focused on the development of predictive models that stratify patients according to several clinical factors [6]; however, these models tend to recognize predominantly the most severe cases requiring dialysis therapy, while their applicability is limited by the large number of

parameters needed to be evaluated [7]. Furthermore, a variety of serum and urinary biomarkers [8], such as neutrophil gelatinase-associated lipocalin (NGAL) [9] and interleukin 18 [10], has been assessed, although their predictive efficacy seems to be modest [11].

Renal resistive index (RRI) is a non-invasive tool of evaluating renal circulation, which is measured through the Doppler waveforms at the level of arcuate or interlobar arteries [12]. It represents a pulsatility and vascular compliance index [13], while it is affected by both renal and extrarenal factors, including renal capillary wedge pressure, heart rate and aortic stiffness [14]. Elevated RRI values are observed after an acute rise in renal interstitial pressure, presenting thus high performance in the diagnosis of hydronephrosis [15,16]. Increased RRI is also associated with type 2 diabetes mellitus [17], as it is related to higher insulin resistance [18] and adverse long-term outcomes in patients with diabetic nephropathy [19]. Moreover, there is evidence that RRI is a useful marker in the setting of sepsis [20] or mechanical ventilation [21], as it is able to discriminate persistent from transient acute kidney injury in critically ill patients [22].

The role of RRI in the diagnosis of postoperative acute kidney injury has been recently explored by several observational studies, although no consensus exists regarding its exact predictive value. The present meta-analysis aims to accumulate, for the first time, current literature

\* Corresponding author at: 15B, Ag. Thoma str., Athens 115 27, Greece.  
E-mail address: [bellosg@windowslive.com](mailto:bellosg@windowslive.com) (I. Bellos).

knowledge in the field in order to determine the pattern of postoperative RRI elevation and to assess its efficacy in predicting AKI in patients undergoing major surgery.

**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) guidelines [23]. Eligibility criteria were predetermined by the authors. Language or date restrictions were not applied during the literature research to avoid language bias. The studies were selected in three consecutive stages. Firstly, the titles and abstracts of all electronic articles were screened to assess their eligibility. Secondly, the articles that met or were presumed to meet the criteria were retrieved as full texts. In the final stage, all observational studies that reported the outcome of interest were selected. More specifically, studies that provided preoperative or postoperative RRI measurements in patients that developed acute kidney injury after surgery were judged as eligible. Cases of kidney transplantation were not included in this study. Animal studies, case reports and review articles were excluded. Any discrepancies regarding the methodology, retrieval of articles and statistical analysis were resolved through 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) and [Clinicaltrials.gov](http://Clinicaltrials.gov) (2008–2018) databases. Google Scholar (2004–2018) databases, as well as the reference lists of the selected studies, were also searched in order to identify additional sources. The date of the last search was set at 05 April 2018. The search strategy included the following algorithm: “(renal resistive index OR RRI) AND (surgery OR postoperative OR acute kidney OR AKI OR renal failure)” and is schematically presented in the PRISMA flowchart (Fig. 1). Two authors (I.B. and V.P) independently screened all articles for eligibility, while the third author (K.K) resolved any discrepancies during the literature search process. The extracted data from each study included: author names, year of publication, country, study design, eligibility criteria, AKI definition, type of surgery, ultrasonography characteristics, number of patients, renal resistive index values, mean age, gender, body mass index, number of patients with diabetes mellitus or hypertension, preoperative creatinine values, cardiopulmonary bypass time, cross-clamp time and number of patients requiring renal replacement therapy. In order to construct the 2 × 2 table, sensitivity and specificity of RRI, along with the cut-off value used in each study were also extracted.

**2.3. Quality assessment**

The quality of the included studies was evaluated using the Risk Of Bias In Non-randomized Studies (ROBINS-I) assessment tool, which

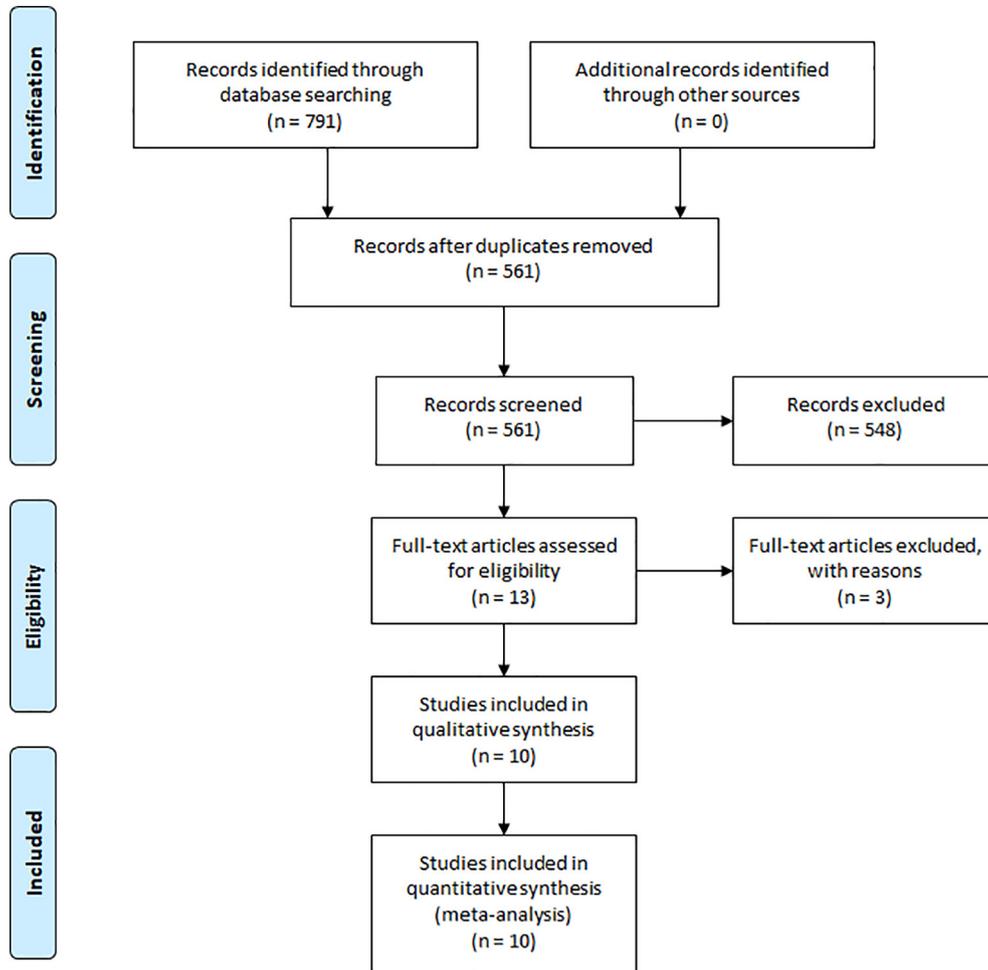


Fig. 1. Search plot diagram.

assesses the potential bias due to confounding, selection, classification, deviation from intended intervention, missing data, measurement and reporting of the outcomes [24]. Subsequently, the methodological quality of the studies included in the diagnostic accuracy analysis was also judged with the QUADAS-2 tool, which consists of 4 domains: patient selection, index test, reference standard, flow and timing [25]. Both tools were independently implemented by two authors (I.B. and V.P.), while potential disagreements were resolved by the consensus of all authors.

#### 2.4. Definitions

Renal resistive index was estimated using the following formula: (peak systolic velocity - end-diastolic velocity)/peak systolic velocity, measured transparietally at the level of arcuate or interlobar arteries [26]. Acute kidney injury was defined with creatinine (postoperative increase compared to preoperative baseline value) and/or urine (urine output <0.5 ml/kg/h) criteria. The RIFLE (Risk, Injury, Failure, Loss, and End-stage renal disease) [27], AKIN (Acute Kidney Injury Network) [28] or KDIGO (Kidney Disease: Improving Global Outcomes) [29] guidelines were applied.

#### 2.5. Statistical analysis

Statistical meta-analysis of the data regarding RRI values among AKI and non-AKI cases was performed with the RevMan 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Confidence intervals were set at 95%. The inter-study heterogeneity was assessed using the inconsistency index ( $I^2$ ) [30]. When significant heterogeneity was present ( $I^2 > 50\%$ ), the DerSimonian-Laird random effect model was applied to provide pooled estimates of the mean difference (MD) and the 95% confidence intervals (95% CI). Subgroup analysis was conducted on the basis of the timing of RRI measurement (preoperatively, 0 h, 24 h or RRI<sub>max</sub> during 48 hours postoperatively).

Meta-analysis of RRI diagnostic accuracy was carried out in R (3.4.3 version), using the MADA package [31]. A bivariate model was fitted to provide summary estimates of sensitivity and specificity, since it takes into account the possible correlation between these two quantities, due to threshold effect [32,33]. A summary receiver operating characteristic (SROC) curve was constructed and the area under the curve (AUC) was calculated. Subgroup analysis was performed in order to explore the effect of several potential confounders on the overall outcome, as well as to compare the efficacy of RRI in different settings. The examined variables were: type of surgery, timing of measurement, cut-off values, definition of AKI, use of urine criteria, region, mean patient age and percentage of AKI cases requiring RRT. Moreover, as a secondary analysis, a univariate approach was implemented to provide pooled estimates of likelihood ratios (LR) and diagnostic odds ratio (DOR) of the test. A Fagan's nomogram [34] was drawn, which determines the post-test probability, according to the calculated positive and negative likelihood ratios. The pre-test probability was set at 30%. The presence of publication bias was evaluated with the Deeks' funnel plot, by plotting the inverse of square root of the effective sample size (ESS) against the  $\ln(\text{DOR})$  [35].

#### 2.6. Sensitivity analysis

Leave-one-out analyses were performed to explore the influence of individual studies. One study was sequentially omitted at a time, in order to assess its effect on the overall outcomes of sensitivity, specificity and AUC. The analysis was performed in R 3.4.3 (MADA package) [31].

### 3. Results

#### 3.1. Included studies

Ten studies [36–45] were finally included in the present analysis, with a total number of 911 patients. Among them, 345 patients were diagnosed with postoperative AKI. The methodological characteristics of the included studies (country, study design, exclusion criteria, type of surgery, ultrasound characteristics and criteria used for AKI definition) are described (Supplementary Table 1). The most important patients' characteristics that were extracted included number, age, gender, body mass index (BMI), presence of diabetes or hypertension, preoperative serum creatinine levels, cardiopulmonary bypass and aortic clamp time, as well as the number of patients requiring RRT (Supplementary Table 2). Four studies that reported their results of RRI values in terms of mean and standard deviation were included in the quantitative analysis, while the rest were evaluated qualitatively. All studies were eligible for the diagnostic accuracy analysis, since they provided adequate data for the construction of the  $2 \times 2$  table. Sensitivity and specificity of each study are illustrated in forest plots (Supplementary Fig. 1).

#### 3.2. Excluded studies

Three studies [46–48] were excluded from the present review after reading the full text. Specifically, two studies [46,47] did not report the outcome of interest, while the population of the third study consisted exclusively of neonates [48].

#### 3.3. Quality assessment

The outcomes of ROBINS-I tool are presented in Table 1. The overall risk of bias was judged to be moderate in the majority of studies. As depicted in Fig. 2, the QUADAS-2 tool indicated a higher risk of bias in the domain of index test, as 8 studies did not use pre-determined cut-off values, but the optimal ones to estimate the sensitivity and specificity of RRI.

#### 3.4. Qualitative analysis

The results of all studies were evaluated qualitatively (Supplementary Table 3). Preoperative RRI values were provided in 6 studies [36,38,40,42,43,45]. In two of them [40,43] a significant increase was noted in patients that developed AKI postoperatively, while in the rest four [36,38,42,45] this elevation did not reach statistical significance. Six studies [37,38,40,42,43,45] evaluated RRI immediately after surgery and demonstrated a significant rise in the AKI group. RRI was also increased in AKI cases when measured 4 [42], 6 [38,45], 24 [38,42,45] and 48 h [45] after surgery. In addition, the maximum RRI value observed during sequential Doppler evaluations during the first 48 h after surgery was found to be increased in AKI patients [36,45]. It is important to state that two studies [36,38] discriminated AKI into transient and persistent, depending on the recovery within the first 3 postoperative days. More specifically, Wu et al. [36] indicated that RRI was elevated in both transient and persistent AKI, although persistent cases presented significantly higher values. On the contrary, Guinot et al. [38] observed a significant increase of RRI only in the subgroup of persistent postoperative AKI.

#### 3.5. Quantitative analysis

The pooled RRI values were significantly increased among AKI patients measured preoperatively (MD: 0.02, 95% CI: [0.00–0.03],  $p$ -value = 0.01), 0 h (MD: 0.07, 95% CI: [0.04–0.11],  $p$ -value < 0.001) and 24 h after surgery (MD: 0.07, 95% CI: [0.04–0.09],  $p$ -value < 0.001). The maximum RRI during the first postoperative days was also elevated in the AKI group (MD: 0.08, 95% CI: [0.06–0.10],  $p$ -value < 0.001).

**Table 1**  
ROBINS-I evaluation.

Risk of bias in non-randomized studies - of interventions (ROBINS-I) tool								
Year; author	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall bias
2017; Wu	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
2017; Qin	Moderate	Moderate	Low	Low	Moderate	Low	Moderate	Moderate
2016; Regolisti	Low	Moderate	Low	Low	Low	Low	Low	Low
2016; Hertzberg	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
2016; Marty	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate
2015; Marty	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate
2014; Kararmaz	Moderate	Low	Low	Low	Low	Low	Moderate	Low
2014; Giustiniano	Moderate	Low	Moderate	Low	Low	NI	Low	Moderate
2013; Guinot	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
2011; Bossard	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate

(Supplementary Fig. 2). The summary sensitivity and specificity of RRI for the detection of postoperative AKI were 0.818 (95% CI: [0.726–0.884]) and 0.776 (95% CI: [0.676–0.852]), respectively. AUC was calculated at 0.866 and the summary ROC (SROC) curve is depicted in Fig. 3. The outcomes of the subgroup analysis are presented in Table 2. SROC curves were plotted for the three cut-off subgroups and compared (Fig. 4). The pooled diagnostic odds ratio was 18.766 (95% CI: [7.928–44.417]), while the positive likelihood ratio was calculated at 3.584 (95% CI: [2.425–5.298]) and the negative at 0.245 (95% CI: [0.153–0.392]). Fagan's nomogram indicated that the post-test probability was increased to 60.6% and decreased to 9.5%, when the pre-test

probability was 30% (Fig. 5). The Deeks' funnel plot revealed no evidence of publication bias (*p-value* = 0.2711) (Supplementary Fig. 3).

3.6. Sensitivity analysis

The outcomes of the leave-one-out analysis revealed that no single study was found to significantly affect the overall outcome (Supplementary Table 4). By omitting one study at a time, sensitivity ranged from 0.796 to 0.832, specificity from 0.752 to 0.797 and AUC from 0.834 to 0.877.



Fig. 2. QUADAS-2 evaluation.

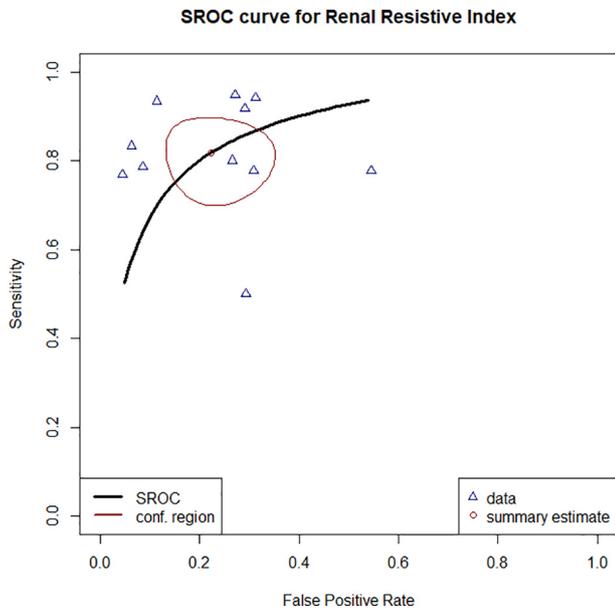


Fig. 3. Summary Receiver Operating Characteristics (ROC) curve (bivariate model) for the performance of renal resistive index in the detection of postoperative acute kidney injury.

4. Discussion

Acute kidney injury constitutes one of the most common causes of postoperative morbidity, especially after cardiothoracic surgery. Prompt risk stratification is essential to guide preoperative decisions and to avoid potential aggravating interventions, such as dehydration and the use of nephrotoxic medications [49]. Furthermore, a variety of preventive measures has been suggested to reduce the incidence of AKI, with the administration of natriuretic peptide, fenoldopam and dexmedetomidine to be the most potent [50]. However, the unfavorable kinetics of creatinine, due to its constant release from skeletal muscle, limits its value as a predictive test in the early perioperative period [51]. As a result, there is growing interest in the identification of novel markers that would maximize the diagnostic performance of the existing clinical models, improving thus the management of patients at high risk of AKI [52].

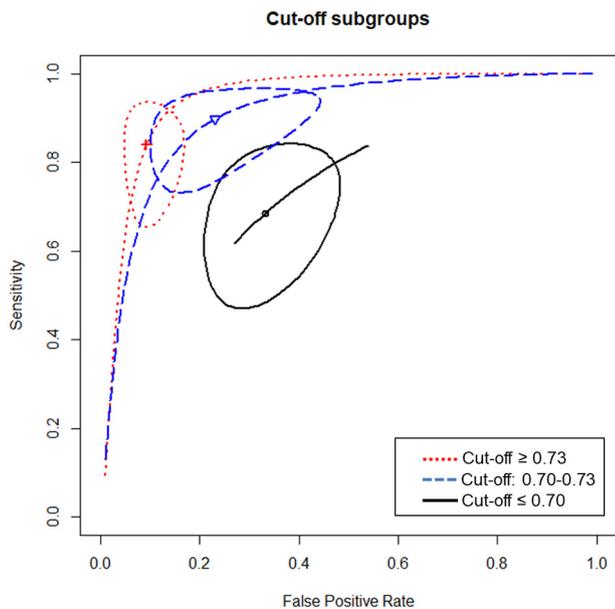


Fig. 4. Receiver operating characteristics (ROC) curves of the three cut-off subgroups.

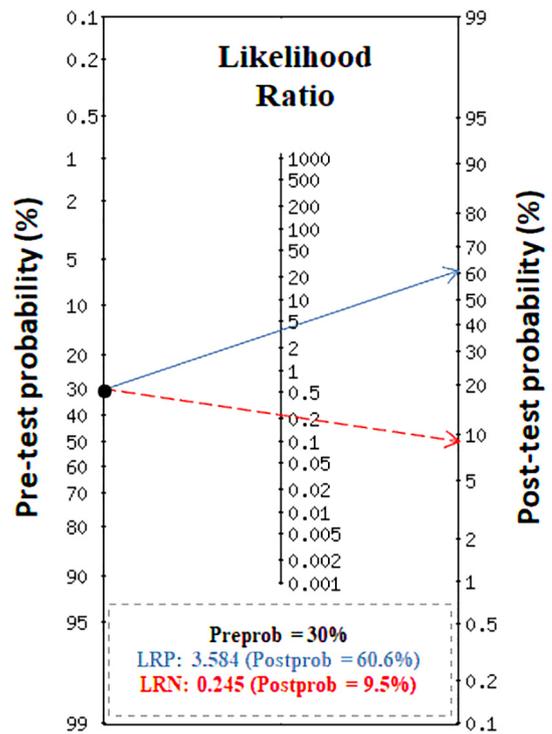


Fig. 5. Fagan's nomogram.

Renal resistive index represents a tool of evaluating renal hemodynamics, with predictive value in a variety of vascular and kidney complications. More specifically, high RRI values have been linked to increased risk of cardiovascular events [53], as well as with more severe end-organ damage in patients with systemic atherosclerosis [54]. In addition, RRI has been shown to correlate with the progression of renal

Table 2

Outcomes of the subgroup analysis. AKIN: Acute Kidney Injury Network; RRT: renal replacement therapy; CI: confidence intervals; AUC: area under the curve.

Subgroup	Number of studies	Sensitivity (95% CI)	Specificity (95% CI)	AUC
<b>Type of surgery</b>				
Cardiothoracic	8	0.777 (0.669–0.858)	0.806 (0.667–0.896)	0.845
Other	3	0.903 (0.798–0.956)	0.727 (0.667–0.781)	0.863
<b>Timing of measurement</b>				
0 h	8	0.824 (0.695–0.906)	0.793 (0.703–0.861)	0.873
Other	3	0.796 (0.691–0.872)	0.746 (0.348–0.942)	0.796
<b>Cut-off value</b>				
≤0.70	4	0.685 (0.515–0.816)	0.668 (0.548–0.769)	0.726
0.70–0.73	4	0.898 (0.774–0.957)	0.769 (0.604–0.880)	0.904
≥0.73	3	0.839 (0.697–0.922)	0.907 (0.849–0.944)	0.94
<b>AKI definition</b>				
AKIN≥1	6	0.828 (0.663–0.922)	0.687 (0.556–0.795)	0.80
Other	3	0.839 (0.697–0.922)	0.907 (0.849–0.944)	0.94
<b>Urine criteria</b>				
Yes	6	0.834 (0.758–0.889)	0.762 (0.570–0.885)	0.846
No	3	0.765 (0.453–0.927)	0.856 (0.686–0.941)	0.887
<b>Region</b>				
Europe	8	0.824 (0.699–0.905)	0.743 (0.627–0.832)	0.851
Asia	3	0.839 (0.657–0.934)	0.879 (0.687–0.960)	0.916
<b>Mean age</b>				
≥65	6	0.838 (0.676–0.927)	0.758 (0.585–0.874)	0.868
<65	5	0.807 (0.705–0.880)	0.794 (0.665–0.883)	0.84
<b>AKI cases requiring RRT</b>				
≥10%	4	0.831 (0.702–0.911)	0.897 (0.769–0.958)	0.915
<10%	5	0.847 (0.641–0.945)	0.708 (0.539–0.834)	0.833

disease and the degree of albuminuria in hypertensive patients [55], while its measurement presents promising efficacy in the prediction of contrast [56] and sepsis-related [57] acute kidney injury. RRI can be performed on a routine basis and is reliably assessed even by the inexperienced operator, after a brief training course [58].

The findings of the present meta-analysis support that RRI is elevated in surgical patients developing AKI postoperatively and may serve as a promising marker given its sensitivity and specificity (81.8% and 77.6% respectively). It is remarkable that the estimated predictive efficacy of RRI (AUC: 0.866) was higher than the performance of urinary and serum biomarkers, such as urinary NGAL (AUC: 0.72), cystatin-c (AUC: 0.63) and interleukin 18 (AUC: 0.66), as reported in a recent meta-analysis [11]. The subgroup analysis indicated that the AUC of RRI was better when measured immediately postoperatively (Table 2), while the calculated specificity was increased in studies with higher rates of AKI cases requiring RRT. The use of cut-off values greater than the conventional threshold of 0.70 also achieved superior diagnostic accuracy. Of note, as reported by Marty et al., RRI was able to diagnose AKI 24 h earlier than the standard AKIN criteria, indicating thus the predictive nature of RRI measurements in the early postoperative period. It is important to mention that apart from AKI, elevated RRI was also associated with other serious postoperative complications, including septic shock and longer stay in the intensive care unit [39]. Moreover, two studies [41,42] measured RRI values both transperitoneally and transesophageally, proposing that the outcomes of the two ultrasound approaches did not differ significantly.

#### 4.1. Strengths and limitations of the study

The present systematic review combines for the first time current literature in the field and is based exclusively on prospective cohort studies. The quality of the included studies was extensively evaluated using two independent tools. A bivariate model was used to assess RRI diagnostic efficacy, as it takes into consideration potential threshold effects. Possible confounders were identified by conducting detailed subgroup and sensitivity analyses. A Fagan's nomogram was also plotted, since it is a clinically useful tool that allows the rapid determination of the post-test probability.

Nevertheless, the outcomes of the present analysis are derived from the pool of 10 studies with a moderate number of patients. As indicated by the QUADAS-2 tool, the tendency of studies to use optimal cut-offs may increase the risk of bias, overestimating the calculated diagnostic accuracy of the test. Additionally, most measurements were performed postoperatively; therefore the role of RRI preoperatively and intraoperatively remains to be determined. Furthermore, although all studies were eligible for the diagnostic accuracy meta-analysis, only 4 studies provided adequate data to evaluate quantitatively the difference of RRI values between AKI cases and controls. More specifically, 3 studies did not report the absolute RRI values, while the other 3 expressed their outcome in terms of median and interquartile range. As a result, the limited number of patients included in this analysis precludes the safe interpretation of the estimated mean differences of RRI. This limitation is more important in the subgroup of preoperative measurements, where the statistical significance of the outcome was marginal. Also, the majority of studies investigated cardiothoracic and orthopedic cases; therefore, data regarding prediction of AKI after other major operations is limited and further investigations are needed before safe conclusions can be drawn.

#### 4.2. Implications for current clinical practice and future research

This meta-analysis suggests that RRI has fair predictive efficiency and is a candidate marker of detecting patients at risk of postoperative AKI. High preoperative RRI values should imply an increased risk for renal dysfunction and therefore should prompt the implementation of interventions, such as hemodynamic optimization [59], intensive

glycemic monitoring [60] and avoidance of chloride-rich fluids [61]. Also, effective AKI prediction would allow recognition of patients that would benefit the most from minimization of CPB duration [62] and from red cell transfusions in order to maintain hemoglobin levels above 7 g/dl [63]. However, certain aspects remain to be elucidated before RRI measurements can be widely applied in clinical practice. Future large-scale cohort studies should evaluate RRI sequentially during the perioperative period in order to determine the optimum timing of measurement. More specifically, both preoperative and postoperative measurements are essential to clarify the exact pattern of RRI elevation. AKI should be defined according to the latest KDIGO guidelines [29], in order the inter-study heterogeneity to be reduced. As indicated by our analysis, possible confounders, such as age, severity of AKI and surgery type should be taken into consideration. Moreover, comorbidities and important extrarenal factors, including aortic valve disorders [46], with potential influence on RRI values should not be ignored. AKI cases should be discriminated into transient and persistent in order to clarify the differentiations of RRI in these two entities. Cut-off values have to be pre-defined to avoid overestimation of the reported diagnostic efficacy, while intraobserver and interobserver reproducibility should be measured and assessed in detail. Evaluation of RRI efficacy should also be assessed in abdominal surgeries, since AKI represents a common complication of these operations and is associated with adverse short-term adverse outcomes [64], longer intensive care unit stay [65] and increased mortality rates [66]. Finally, it would be important to assess RRI in conjunction with clinical predisposing factors, such as age, obesity and comorbidities, as well as with other novel biomarkers, in order to construct a combined model for the prediction of postoperative AKI.

## 5. Conclusions

The findings of this meta-analysis suggest that renal resistive index represents a promising marker for the detection of postoperative acute kidney injury. However, since the available evidence is drawn from small cohorts, future large-scale prospective studies are needed to confirm its predictive efficacy and to determine the optimal timing of measurement and cut-off value to be used in clinical practice.

## Declarations of interest

None.

## Acknowledgements

None.

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