


ORIGINAL



Performance of Doppler-based resistive index and semi-quantitative renal perfusion in predicting persistent AKI: results of a prospective multicenter study

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Abstract

Purpose: The Doppler-based resistive index (RI) and semi-quantitative evaluation of renal perfusion using color Doppler (SQP) have shown promising results for predicting persistent acute kidney injury (AKI) in preliminary studies. This study aimed at evaluating the performance of RI and SQP to predict short-term renal prognosis in critically ill patients.

Methods: Prospective multicenter cohort study including unselected critically ill patients. Renal Doppler was performed at admission to the intensive care unit. The diagnostic performance of RI and SQP to predict persistent AKI at day 3 was evaluated.

Results: Overall, 371 patients were included, of whom 351 could be assessed for short-term renal recovery. Two thirds of the included patients had AKI ($n = 233$; 66.3%), of whom 136 had persistent AKI (58.4%). Doppler-based RI was higher and SQP lower in AKI patients and according to AKI recovery. Overall performance in predicting persistent AKI was however poor with area under ROC curve of respectively 0.58 (95% CI 0.52–0.64) and 0.59 (95% CI 0.54–0.65) for RI and SQP. Optimal cutoff was respectively 0.71 and 2 for RI and SQP. At optimal cutoff, sensitivity and specificity were 50% (95% CI 41–58%) and 68% (62–74%) for RI and 39% (32–45%) and 75% (66–82%) for SQP.

Conclusion: Although statistically associated with AKI occurrence, RI and SQP perform poorly in predicting persistent AKI at day 3. Further studies are needed to adequately describe factors influencing Doppler-based assessment of renal perfusion and to delineate whether these indicators may be useful at the bedside.

Clinicaltrial.gov: NCT02355314.

Keywords: Acute kidney injury, Doppler, Resistive index, Sensitivity, Specificity, Renal replacement therapy

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Introduction

Acute kidney injury (AKI) is common in intensive care unit (ICU) patients and remains associated with a dismal prognosis [1–3]. Prompt diagnosis of AKI is hampered by several important limitations of its usual markers [4]. Oliguria is unspecific, and serum creatinine elevation is delayed and only occurs after a prolonged decrease in the glomerular filtration rate [1, 5]. These limits urge KDIGO experts to recommend validation of an alternate marker allowing the early diagnosis, differential diagnosis, or prognostic evaluation of AKI [6].

Doppler-based renal resistive index (RI) measurement is a rapid and non-invasive tool that was proposed for early AKI detection [7–9] or to differentiate transient from persistent AKI in ICU patients [7, 9, 10]. Semi-quantitative evaluation of renal perfusion (SQP) using color Doppler has also been proposed as a simple tool and showed similar performance [11]. Although suggesting promising performance of these tools to predict short-term prognosis of AKI, most of these studies were performed in an expert center with limited patient samples [7, 9, 12, 13]. A recent meta-analysis confirmed this diagnostic performance but also reported a high heterogeneity between studies [14]. Actually, these results must be tempered by the high risk of bias associated with these preliminary studies and the numerous confounding factors known to influence RI [15, 16]. Indeed, discrepant studies showed limited diagnostic performance of RI [12, 17].

Therefore, a multicenter prospective cohort study was undertaken to evaluate the performance of Doppler-based RI and SQP to predict persistent AKI in a large cohort of unselected critically ill patients. The secondary objective was to assess the performance of these tools to predict the need for renal replacement therapy (RRT).

Methods

Patients

The study was approved by the Saint-Etienne institutional review board. Patients and their next of kin were informed, and informed consent was obtained before inclusion. The study protocol was registered in clinical-trial.gov (NCT02355314).

Seven university hospital ICUs and one community-based hospital ICU in France participated in the study between June 2013 and June 2016. Consecutive adults admitted to these ICUs and requiring mechanical ventilation were included. Patients with obstructive renal disease, underlying severe chronic kidney disease (stage IV or V), with previously known renal artery stenosis or renal vein thrombosis, with cardiac arrhythmia precluding renal Doppler measurement, persons deprived of liberty or under guardianship or curators, patients with

expected hospital stay < 72 h, patients with AKI having already recovered according to our definition, and pregnant patients were not included. Last, patients with hospital stays < 72 h, since they could not be classified as having transient or persistent AKI according to our definitions, were secondarily excluded. Screening was ongoing as long as two investigators trained in Doppler were available.

Although the study was open, investigators were blinded to the primary objective of this study.

Definitions

Acute kidney injury was defined as any degree of AKI at study inclusion according to the KDIGO definition (plasma creatinine level increase of 26.4 $\mu\text{mol/l}$ or more, plasma creatinine increase $\geq 150\%$ from baseline, or urine output < 0.5 ml/kg/h for 6 h or more) [18]. For patients whose baseline plasma creatinine level was unknown, this variable was estimated according to Modification of Diet in Renal Disease (MDRD) formula back-calculation [18]. AKI severity was defined according to the KDIGO definition [18].

Transient AKI was defined as AKI with recovery occurring before H72 [7, 19, 20]. Short-term renal recovery was defined as a decrease of at least one stage in AKI severity according to the KDIGO criteria (i.e., a decrease of serum creatinine, reversal of oliguria in the absence of diuretic therapy, and absence of RRT requirement) [7]. Persistent AKI was defined by any degree of AKI not meeting the criteria for transient AKI. Diuretic use was defined as the use of diuretics at any time during the first 24 h in the ICU.

The Logistic Organ Dysfunction (LOD) score was calculated at study inclusion [21] and the Knaus scale score at ICU admission [22].

Sepsis and septic shock were diagnosed using the criteria developed at the American College of Chest Physicians/Society of Critical Care Medicine consensus conference [23].

Estimation of short-term renal recovery was performed by the senior attending physician, uninvolved in Doppler measurement. This estimation was the “estimation of probability of remaining free of AKI or of experiencing short-term renal recovery within 72 h” and was assessed by a Likert scale ranging from 0 to 100%.

Study protocol, data collection, and resistive index (RI) measurement

Assessments of renal perfusion and function as well as estimation of the probability of short-term renal recovery were performed concomitantly at study inclusion.

In line with already published methodology, during each study period, 27 investigators (all certified

physicians) attended a half-day training session on Doppler evaluation of renal perfusion. After a discussion of relevant theoretical considerations, practical training was provided in locating the kidneys, identifying the intrarenal vessels using color Doppler, grading renal perfusion using the previously published semi-quantitative color Doppler scale, and measuring the RI [11]. Feasibility and reliability of both Doppler-based RI and SQP were assessed and found to be adequate [11].

The following clinical variables were collected from each patient before the measurement session: heart rate; systolic, diastolic, and mean blood pressures; urine output; respiratory rate; tidal volume; positive end-expiratory pressure; inspired fraction of oxygen; plateau pressure; type and dose of sedative; and type and dose of vasoactive drugs.

In each patient, renal sonography for RI measurement was performed at study inclusion by a physician not involved in patient management. After kidney visualization in grayscale and color Doppler modes, the absence of signs of chronic renal damage was checked. Renal perfusion was assessed by color Doppler using the semi-quantitative scale (Table S1) [11]. An interlobar or arcuate artery was then selected, and measurements were obtained using pulse-wave Doppler. The Doppler gain was set to obtain a clear outline of flow waves with minimal background noise. The Doppler spectrum was considered optimal when at least three similar consecutive waveforms were visualized. The resistive index was calculated as (peak systolic velocity – end diastolic velocity)/peak systolic velocity. The mean of three to five RI values was computed.

Statistical analysis

Data are described as median and interquartile range (IQR) or number and percentage. Categorical variables were compared using Fisher's exact test and continuous variables using the nonparametric Wilcoxon test, Mann-Whitney test, or Kruskal-Wallis test. The Friedman test was used to compare continuous variables across the three patient groups (no AKI, transient AKI, and persistent AKI).

Based on previous findings, we estimated our sample size as follows [7, 19]. Four hundred patients would be needed to obtain 100 patients without AKI, 100 with transient AKI, and 100 persistent AKI, taking into account a loss to follow-up rate of 10% and a rate of failure to obtain Doppler-based RI of 10%. This would allow:

- Detecting an absolute change >0.03 in RI between groups with a statistical power of 0.95, alpha risk of 0.05, assuming an RI of 0.67 in patients without AKI [7].

- Delineating diagnostic test performance with CI of ± 0.05 assuming an area under the receiver-operating characteristic (AUROC) curve of 0.80 [14, 24].
- Assessing factors independently associated with persistent AKI, adjusting for nine variables in addition to RI or SQP [25].

Assessing diagnostic performance of the Doppler-based resistive index and semi-quantitative renal perfusion over the first 24 h in predicting persistent AKI, we plotted the receiver-operating characteristic (ROC) curves of the proportion of true positives against the proportion of false positives to classify patients as having persistent AKI. The confidence interval of the AUC was calculated and AUROC curves compared according to the DeLong method [26, 27]. The sensitivity, specificity, and confidence interval were approximated using bootstrapping methods [27, 28]. The optimal cutoff point was defined according to the optimal Youden's J statistic [29].

Independent predictors of persistent AKI and need for RRT were assessed using logistic regression and mixed logistic models. First, a logistic regression model was built. Variables of interest were selected according to their relevance and statistical significance in univariate analysis. We used conditional stepwise regression with 0.2 as the critical P value for entry into the model and 0.1 as the P value for removal. It was planned a priori to force semi-quantitative perfusion or RI in the model should these variables not be selected. Interactions and correlations between the explanatory variables were carefully checked. Continuous variables for which log linearity was not confirmed were transformed into categorical variables according to the median or IQR. Renal perfusion indices being strongly correlated with AKI severity (AKI stage), the latter was not inserted in the final model.

Last, a mixed model was performed using previously selected variables using center as random effect. This model adjusting for center effect is reported in the article. All models were assessed for calibration, discrimination, and relevancy. Residuals were plotted and the distributions inspected.

In a post hoc analysis, performance of perfusion indices was tested in subgroups (namely patients with AKI defined by serum creatinine, patients with AKI defined by oliguria, and patients without missing baseline serum creatinine) to ensure homogeneity of the results. Criteria to define AKI were found to be associated with the AKI severity and rate of short-term renal recovery [19, 30]. This sensitivity analysis therefore aimed to assess consistency of the results in groups considered to have different risks of short-term renal recovery.

All tests were two sided, and P values < 0.05 were considered statistically significant. Analyses were done using

R software version 3.4.4 (<https://www.r-project.org>), including the *pROC*, *lme4*, and *lmerTest* packages.

Results

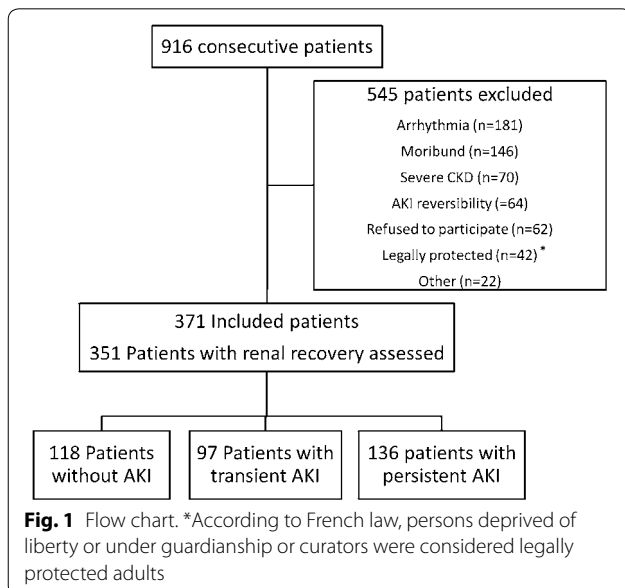
Overall, 916 patients were screened, of whom 371 were ultimately included within 24 h of ICU admission (1 day, IQR 0–1). Main reasons for non-inclusion were cardiac arrhythmia and expected hospital stay < 72 h (Fig. 1).

Study population

The main characteristics of the study population are reported in Table 1. Overall, 371 patients were included, of whom 20 were secondarily excluded as non-evaluable at H72. Of the 351 patients admitted, two thirds had AKI according to the KDIGO definition ($n=233$; 66.3%). Overall severity was AKI stage 1 in 149 patients (64.9%), stage 2 in 33 patients (14.2%), and stage 3 in 51 patients (21.9%). Criteria to define AKI were diuresis only in 135 patients, serum creatinine only in 30 patients, and presence of both criteria in 68 patients. Of the included patients with AKI, 97 recovered within 72 h and were classified as having transient AKI (41.6%) and 136 had a persistent AKI (58.4%). Older age, underlying comorbidities, illness severity as assessed by the LOD score, septic shock, emergency surgical status, hypovolemia, and number of nephrotoxic agents were associated with AKI and persistent AKI (Table 1).

Performance of the Doppler-based resistive index (RI) and semi-quantitative perfusion (SQP) in predicting persistent AKI

Doppler-based RI and SQP were obtained in all of the patients.



The resistive index was higher, and SQP lower, in AKI patients and according to short-term renal recovery (Table 1; Figs. 2a, b, 3a, b).

Overall performance in predicting persistent AKI was however poor with an area under the ROC curve of 0.58 (95% CI 0.52–0.64) and 0.59 (95% CI 0.54–0.65) for Doppler-based RI and SQP, respectively (Table 2; Fig. 4a, b). The optimal cutoff was respectively 0.71 and 2 for RI and SQP. At optimal cutoff, sensitivity and specificity were 50% (95% CI 41–58%) and 68% (62–74%) for RI and 39% (32–45%) and 75% (66–82%) for SQP (Table 2).

Before adjustment, SQP was associated with persistent AKI (OR 0.63 per point; 95% CI 0.47–0.85). After adjustment for confounders, logistic regression identified SQP as associated independently with persistent AKI (OR 0.69 per point; 95% CI 0.50–0.95).

Before adjustment, RI was associated with persistent AKI (OR 12.41 per 0.01 unit; 95% CI 1.65–98.25). When included in the stepwise selection, Doppler-based RI was not selected in the final model. When forced, RI was not associated with persistent AKI and did not change the model (OR 2.52 per 0.01 unit; 95% CI 0.27–22.83).

To assess a potential center effect, a sensitivity analysis was performed replicating multivariable analysis using a mixed model with center included as random effect. This analysis did not change the model, impact of selected variables, or impact of SQP or RI (Table 3).

Performance of Doppler-based resistive index (RI) and semi-quantitative perfusion (SQP) in predicting need for renal replacement therapy at day 3

Overall, 36 patients (10.3%) required RRT at day 3 (Table S2).

The resistive index was higher, and SQP lower, in patients requiring RRT (Table S2).

Overall performance in predicting need for RRT was however poor with an area under the ROC curve of respectively 0.65 (95% CI 0.57–0.73) and 0.66 (95% CI 0.58–0.75) for Doppler-based RI and SQP (Figure S1 and S2).

The optimal cutoff was respectively 0.74 and 2 for RI and SQP. At optimal cutoff, sensitivity and specificity were 74% (95% CI 69–79%) and 51% (34–68%) for RI and 41% (25–58%) and 81% (76–85%) for SQP.

Before adjustment, SQP was associated with the need for RRT (OR 0.43 per point; 95% CI 0.26–0.68). After adjustment for confounders, logistic regression identified SQP as associated independently with the need for RRT (OR 0.56 per point; 95% CI 0.33–0.93) along with illness severity as assessed by the norepinephrine dose (OR 4.15 per $\mu\text{g}/\text{kg}/\text{min}$; 95% CI 2.02–9.43) and FiO_2 level (1.03 per %; 95% CI 1.01–1.04).

Before adjustment, RI was associated with the need for RRT (OR 74.04 per point; 95% CI 3.22–1743). When

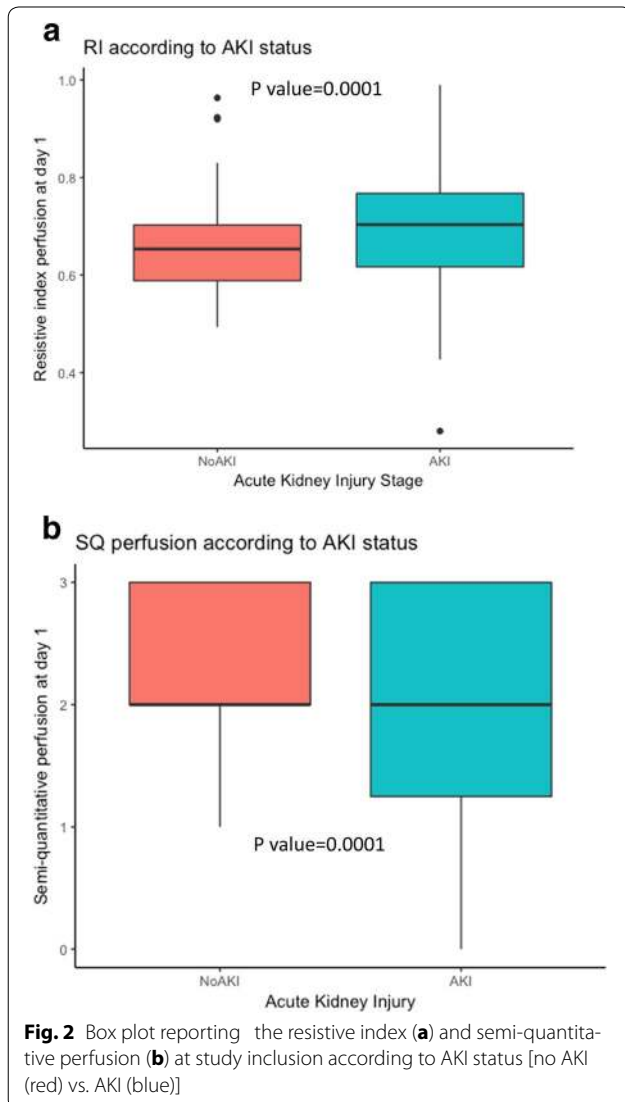
Table 1 Characteristics of patients according to renal dysfunction and short-term renal recovery, reported as number (%) or median [IQR]

Variables	Absence of AKI <i>n</i> = 118	Transient AKI <i>n</i> = 97	Persistent AKI <i>n</i> = 136	<i>P</i> value	<i>P</i> value (transient vs. persistent)
Age (years)	57.5 [44–67]	65 [52–72]	64 [55–71]	0.004	0.988
Female gender	52 (44.1%)	33 (34.0%)	44 (32.4%)	0.125	0.901
Body weight (kg)	74 [62–82]	72 [63–84]	81 [70–95]	< 0.001	0.004
Case mix and severity					
Inclusion day (from ICU admission)	1 [0–2]	1 [0–1]	1 [0–1]	0.165	0.966
Knaus score				0.001	0.221
A	63 (53.4%)	35 (36.1%)	44 (32.4%)		
B	42 (35.6%)	31 (32.0%)	61 (44.9%)		
C	12 (10.2%)	28 (28.9%)	28 (20.6%)		
D	1 (0.8%)	3 (3.1%)	3 (2.2%)		
LOD score	7.0 [5.0–9.0]	9.0 [6.0–11.0]	9.0 [6.0–12.0]	< 0.001	0.279
Main reason for ICU admission					
Septic shock	15 (12.7%)	28 (28.9%)	29 (21.3%)	0.014	0.243
Acute respiratory failure	45 (38.1%)	36 (37.1%)	59 (43.4%)	0.561	0.409
Acute kidney injury/metabolic	2 (1.7%)	14 (14.4%)	20 (14.7%)	0.001	1.00
Coma	40 (33.9%)	31 (32.0%)	35 (25.7%)	0.334	0.372
Burn	19 (16.1%)	8 (8.2%)	14 (10.3%)	0.166	0.765
Case mix				0.079	0.07
Elective surgery	4 (3.4%)	1 (1.0%)	8 (5.9%)		
Medical patient	73 (61.9%)	66 (68.0%)	98 (72.1%)		
Urgent surgery	41 (34.7%)	30 (30.9%)	30 (22.1%)		
Main risk factors for AKI					
Absolute or relative hypovolemia	47 (39.8%)	54 (55.7%)	69 (50.7%)	0.054	0.541
Sepsis	46 (39.0%)	46 (47.4%)	61 (44.9%)	0.430	0.799
Cardiovascular comorbidities	6 (5.1%)	15 (15.5%)	21 (15.4%)	0.018	1.00
Chronic kidney disease	4 (3.4%)	7 (7.2%)	10 (7.4%)	0.345	1.00
Hypertension	38 (32.2%)	42 (43.3%)	71 (52.2%)	0.006	0.227
Diabetes	18 (15.3%)	19 (19.6%)	30 (22.1%)	0.384	0.769
Number of nephrotoxic agents				0.038	0.916
None	59 (50.0%)	33 (34.0%)	42 (30.9%)		
One	26 (22.0%)	31 (32.0%)	43 (31.6%)		
Two	20 (16.9%)	24 (24.7%)	39 (28.7%)		
Three or more	13 (11.0%)	9 (9.3%)	12 (8.8%)		
Organ support and dysfunction at study inclusion					
Norepinephrine infusion	47 (39.8%)	57 (58.8%)	80 (58.8%)	0.004	1.00
Norepinephrine dose (µg/kg/min)	0.00 [0.00–0.12]	0.09 [0.00, 0.36]	0.05 [0.00–0.30]	0.001	0.687
Use of other inotrope or vasopressor	2 (1.7%)	7 (7.2%)	16 (11.8%)	0.008	0.355
Ramsay score	5 [4–6]	5 [4–6]	5 [4–6]	0.38	0.697
Ventilator setting					
Respiratory rate	20 [16–24]	20 [17–26]	20 [18–25]	0.222	0.564
Tidal volume (ml)	460 [426–505]	465 [430–520]	450 [420–500]	0.363	0.213
FiO ₂ (%)	40 [30–50]	40 [30–50]	48 [30–60]	0.195	0.175
Total PEEP	5 [5–7]	5 [5–7]	6 [5–9]	0.002	0.001
Plateau pressure (cmH ₂ O)	18 [15–22]	18 [15–22]	17 [17–24]	0.004	0.022
Renal function at study inclusion					
Baseline serum creatinine (µmol/l)	80 [68–97]	88 [71–97]	88 [71–97]	0.105	0.451
Creatinine at study inclusion (µmol/l)	64 [53–80]	92 [71–138]	101 [66–160]	< 0.001	0.754

Table 1 continued

Variables	Absence of AKI <i>n</i> = 118	Transient AKI <i>n</i> = 97	Persistent AKI <i>n</i> = 136	<i>P</i> value	<i>P</i> value (transient vs. persistent)
Diuresis at study inclusion (ml/kg/h)	0.88 [0.64–1.17]	0.31 [0.18–0.48]	0.26 [0.12–0.42]	< 0.001	0.023
AKI stage				< 0.001	< 0.001
No AKI	118 (100%)	0	0		
Stage 1	0	76 (78.4%)	73 (53.7%)		
Stage 2	0	11 (11.3%)	22 (16.2%)		
Stage 3	0	10 (10.3%)	41 (30.1%)		
Estimators of persistent AKI					
Physician estimation (%)*	92.5 [80–100]	80 [60–95]	80 [50–99]	< 0.001	0.555
Doppler-based resistive index (UI)	0.65 [0.59–0.70]	0.69 [0.62–0.77]	0.71 [0.62–0.76]	0.001	0.659
Semi-quantitative perfusion	2.00 [2.00–3.00]	2.00 [2.00–3.00]	2.00 [1.00–2.75]	0.002	0.153

*Physician estimation was the “estimation of probability of remaining free of AKI (for patients without AKI) or of experiencing renal recovery within 72 h (for patients with AKI)”



included in the stepwise selection, Doppler-based RI was not selected in the final model, and, when forced, RI was not associated with the need for RRT (OR 17.51; 95% CI 0.51–608) and did not change the model (Table S3).

To assess a potential effect of center effect, a sensitivity analysis was performed replicating multivariable analysis using a mixed model with center included as random effect. This analysis did not change the model, impact of selected variables, or impact of SQP or RI.

Accuracy of physician prediction of short-term renal recovery or need for renal replacement therapy

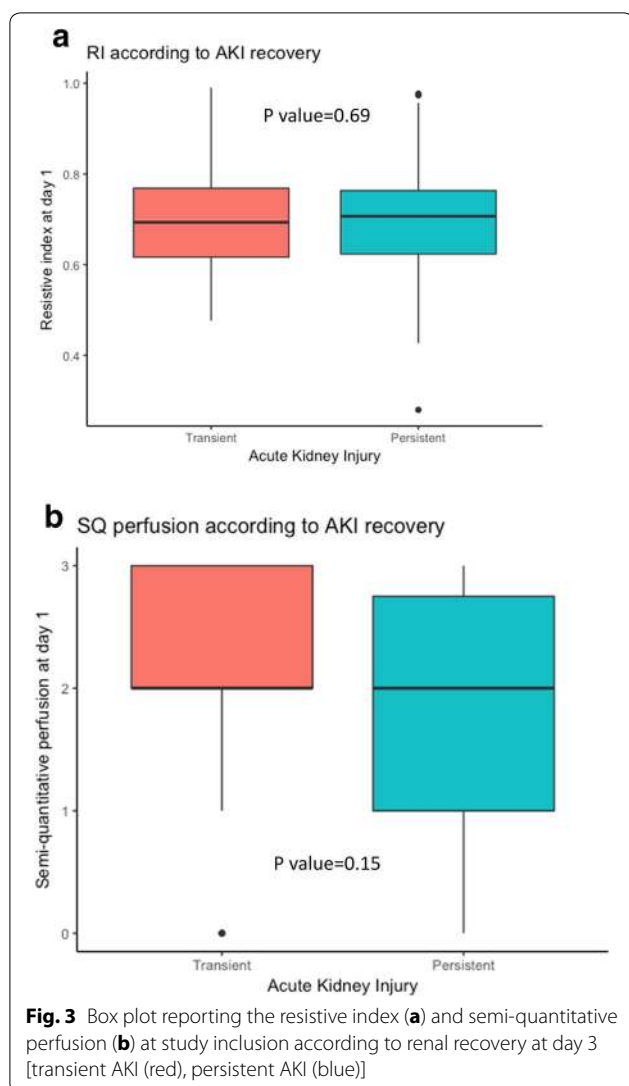
Physician estimation of probability for short-term renal recovery at study inclusion had similar performance in predicting persistent AKI (AUC ROC 0.59; 95% CI 0.52–0.65) or need for RRT (AUC ROC 0.76; 95% CI 0.66–0.85) than both Doppler-based perfusion estimators (Figure S2a and S2b).

Sensitivity analysis according to criteria defining AKI and availability of baseline serum creatinine

Performance of the perfusion index in predicting persistent AKI was not different in patients with AKI defined by serum creatinine, in patients with AKI defined by oliguria, and in patients without missing baseline serum creatinine (Table S4).

Discussion

This multicenter study is the largest to date assessing performance of Doppler-based RI and SQP in predicting persistent AKI and need for RRT. According to our results, neither Doppler-based RI nor SQP is useful in predicting persistent AKI. Although they might be able to predict need for RRT, performance in this regard is also poor.

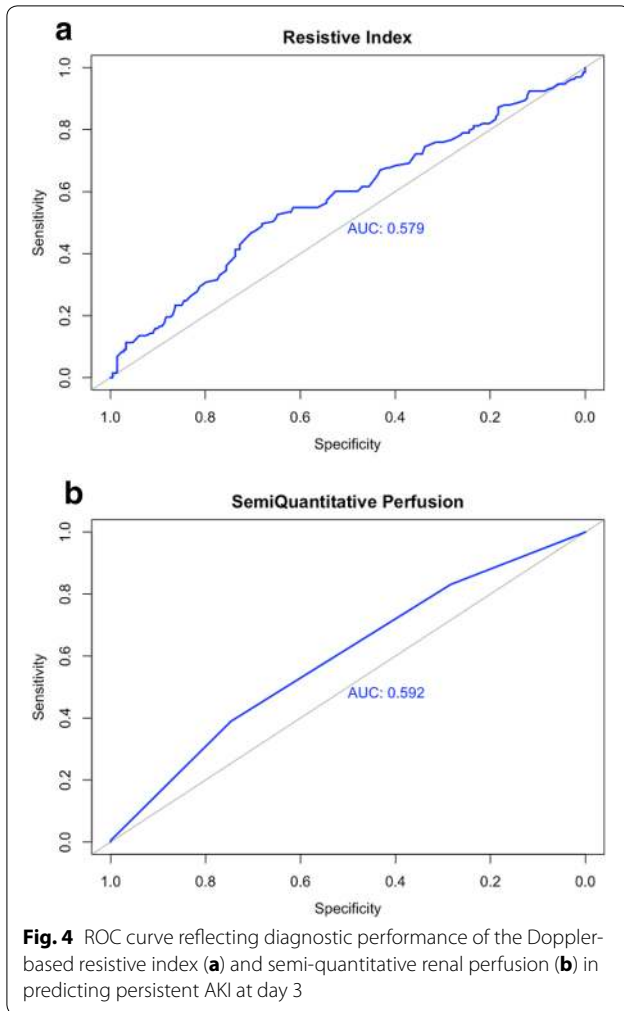


Limits of usual markers of renal dysfunction, namely the insensitive serum creatinine [6] or the unspecific oliguria [1], urge KDIGO experts to recommend validation of a marker other than serum creatinine allowing the early diagnosis, differential diagnosis, or prognostic evaluation of AKI [18, 20]. Several studies suggested renal Doppler might help in predicting development of renal dysfunction [8] or short-term renal prognosis [14]. Although several preliminary studies conducted in the 1990s suggested that RI might help to separate transient from persistent AKI [10, 31, 32], these studies included limited numbers of patients, and both patient selection and definitions of transient and persistent AKI are unclear in most of these studies. In recent studies focusing on critically ill patients, RI measured at admission was significantly higher in patients with persistent or worsening of AKI [7, 9, 11]. In these studies, RI performed better than most of the urinary indices including urinary cystatin C [7, 9, 11]. A recent meta-analysis suggested a very good performance of renal Doppler in predicting short-term reversibility [14]. Several limits were however noted to these positive findings. First, discordant results were noted, with some studies reporting limited or poor performance of RI [12, 17]. Furthermore, most of the studies performed were at high risk of bias; numerous confounding factors have been described to influence RI, explaining the high heterogeneity noted among results of studies performed so far [14–16].

In addition to clinical data, several experimental studies suggested vast heterogeneity and inadequate comprehension of RI significance. RI has been assumed to faithfully reflect renal vascular resistance [33, 34]. In experimental studies, however, the association between Doppler-based RI and renal vascular resistance was weak. Large, non-physiologic, pharmacologically induced changes in renal vascular resistance translated into only small RI changes [33]. In addition, several intrarenal or systemic hemodynamic factors have been demonstrated to influence both RI and the association between RI and renal vascular

Table 2 Diagnostic performance of the Doppler-based resistive index, semi-quantitative perfusion, and physician estimation in predicting persistent AKI and need for renal replacement therapy

Performance of tests	AUC ROC curve (95% CI)	Optimal cutoff	Sensitivity (95% CI)	Specificity (95% CI)
Persistent AKI at day 3				
Doppler-based resistive index	0.58 (0.52–0.64)	0.71	50% (41–58%)	68% (62–74%)
Semi-quantitative renal perfusion	0.59 (0.54–0.65)	2.0	39% (32–45%)	75% (66–82%)
Physician estimation	0.59 (0.53–0.65)	78%	45% (36–53%)	70% (64–77%)
Renal replacement therapy at day 3				
Doppler-based resistive index	0.65 (0.57–0.73)	0.73	51% (34–69%)	76% (70–80%)
Semi-quantitative renal perfusion	0.66 (0.58–0.75)	2	36% (31–41%)	86% (72–97%)
Physician estimation	0.76 (0.67–0.85)	75%	63% (49–77%)	77% (72–81%)



resistance. In several studies, arterial stiffness (vascular compliance) was a major determinant of RI [33–35]. In addition, the relationship between vascular resistance and RI became weaker as arterial stiffness increased [34]. Furthermore, increases in interstitial or intraabdominal pressure reduce the transmural pressure of the renal arterioles, thereby diminishing arterial distension, decreasing vascular compliance and ultimately increasing RI [35]. Last, several hemodynamic factors including the pulse pressure index, mean arterial pressure, and heart rate have direct and dramatic effects on RI values [7, 8, 33, 34, 36]. Each of these factors may act as a confounder. The numerous factors involved in RI changes, along with the strong influence of preexisting vascular stiffness, have led to the hypothesis that RI might reflect renal and vascular history and therefore explain the previously demonstrated association between RI and the renal prognosis or pathologic mechanism of renal dysfunction [14, 37].

This study has several strengths. First, the multicenter design, large sample size, and consecutive inclusions may

Table 3 Factors independently associated with persistent AKI using mixed logistic regression, taking center effect into account as random effect

Fixed effect	OR	95% CI	P value
Model 1*			
Logistic organ dysfunction score (/point)	1.09	1.02–1.16	0.015
Case mix			
Elective surgery	Ref	–	–
Medical	0.31	0.09–1.11	0.07
Urgent surgery	0.21	0.06–0.78	0.02
PEEP tot (/cmH ₂ O)	1.09	1.00–1.20	0.06
Number of nephrotoxic agents			
None	Ref	–	–
1	1.70	0.96–3.04	0.07
2	1.46	0.79–2.73	0.23
3+	0.92	0.39–2.18	0.85
Semi-quantitative renal perfusion (/point)	0.69	0.50–0.96	0.02
Model 2**			
Logistic organ dysfunction score (/point)	1.09	1.02–1.17	0.009
Case mix			
Elective surgery	Ref	–	–
Medical	0.31	0.09–1.07	0.06
Urgent surgery	0.22	0.06–0.79	0.02
PEEP tot (/cmH ₂ O)	1.10	1.00–1.20	0.04
Number of nephrotoxic agents			
None	Ref	–	–
1	1.73	0.97–3.10	0.06
2	1.58	0.85–2.96	0.15
3+	1.05	0.44–2.46	0.92
Doppler-based resistive index (/0.01)	2.48	0.27–22.83	0.42

Two models were performed to assess respectively semi-quantitative perfusion (model 1) and Doppler-based RI (model 2)

Stepwise variable selection. Resistive index and semi-quantitative perfusion were forced in the model if not selected

*Semi-quantitative renal perfusion was selected by the stepwise conditional procedure. Hosmer-Lemeshow statistic: $P=0.16$; marginal $R^2=0.130$, conditional $R^2=0.141$

**Doppler-based resistive index was not selected by the stepwise conditional procedure and was, according to the previously written protocol, forced in the final model. Hosmer-Lemeshow statistic: $P=0.86$; marginal $R^2=0.148$, conditional $R^2=0.154$

be expected to limit biases in assessing diagnostic test performance. The definition of persistent AKI was demonstrated as associated with relevant clinical end points, and training in renal Doppler was validated previously by our research group [11, 19]. Last, although negative, we ensured that this study had statistical power to detect relevant differences in RI between transient and persistent AKI and would have sufficient precision to allow a definite answer on this topic.

Our study also has limitations that may deserve to be discussed. First, our definition of transient AKI

significantly differs from the recently suggested definition of the ADQI group [20]. However, this study was initiated before publication of this definition. In addition, the chosen definition of persistent AKI was previously shown to be associated with relevant clinical end points [19]. Although no definite blinding was possible, we made efforts to limit biases by defining recovery objectively, ensuring renal Doppler was performed by a physician uninvolved in patient care and blinding clinicians to study objectives. In this line, indications for RRT were not standardized, which may have influenced our findings. However, attending physicians were not informed of the Doppler measurement results, investigators were uninvolved in patient care, and the clustering effect related to local practices should have been partly adjusted for by the mixed model adjusted for center effect. Moreover, this study was designed to assess discrimination of the tested marker. The poor discrimination observed in this study does not preclude potential influence of these markers in allowing risk stratification [38, 39]. Future studies may be needed to assess the usefulness of these tests in this regard. Last, lack of experience of some operators may have contributed to the negative results of this study. However, when adjusting for center effect, including expertise as part of the variability of results, an association between RI or SQP and persistent AKI was not modified, suggesting lack of center effect.

In conclusion, this multicenter study suggests measurement of Doppler-based RI and semi-quantitative renal perfusion to be feasible at bedside. Although statistically associated with AKI occurrence and persistence, these indicators perform poorly in predicting persistent AKI at day 3 or need for RRT. Further studies are needed to adequately describe factors influencing Doppler-based assessment of renal perfusion and to delineate whether these indicators may be useful at bedside. Meanwhile, our results suggest neither Doppler-based RI nor semi-quantitative renal perfusion should be used to assess short-term renal prognosis in the ICU setting.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-018-5386-3>) contains supplementary material, which is available to authorized users.

Abbreviations

AKI: Acute kidney injury; AUROC curve: Area under the receiver-operating characteristic curve; CI: Confidence interval; ICU: Intensive care unit; IQR: Interquartile range; LOD: Logistic organ dysfunction; MDRD: Modification of diet in renal disease; MV: Mechanical ventilation; OR: Odds ratio; RI: Doppler-based renal resistive index; ROC curve: Receiver-operating characteristic curve; RRT: Renal replacement therapy; SQP: Semi-quantitative perfusion.

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Compliance with ethical standards

Disclosures

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