Value of the combination of renal resistance index and central venous pressure in the early prediction of sepsis-induced acute kidney injury

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Abstract

Purpose: Early prediction of acute kidney injury (AKI) in septic patients is difficult. This study aimed to assess the values of renal resistive index (RI), central venous pressure (CVP), and their combination in the early prediction of sepsis-induced AKI.

Methods: A prospective cohort study was performed in septic patients. The variables potentially associated with AKI were recorded at admission and compared between the AKI and non-AKI groups. The variables independently associated with sepsis-induced AKI were identified using multivariable logistic regression, and the area under the receiver operating characteristic curve (AUROC) analysis was calculated.

Results: A total of 124 septic patients were included. Septic shock (OR, 3.28; P = 0.002), high CVP (OR, 1.92; P = 0.012) and renal RI (OR, 2.58; P = 0.009), low diastolic perfusion pressure (DPP) (OR, 2.15; P = 0.010) at admission were independent risk factors for sepsis-induced AKI. The AUROC value of the combination of RI and CVP was greater compared with either RI or CVP alone in predicting sepsis-induced AKI (AUROC = 0.858, 0.811, and 0.780, respectively).

Conclusions: The combination of RI and CVP was more valuable than either of the two parameters in the early prediction for sepsis-induced AKI.

Key words: Acute kidney injury; Central venous pressure; Resistive index; Sepsis; Ultrasonography

Introduction

More than half of all critically ill patients develop acute kidney injury (AKI), and its most common cause is sepsis [1]. Sepsis-induced AKI has been associated with increased in-hospital mortality and the risk of chronic kidney disease after hospital discharge [2-4]. The Kidney Disease Improving Global Outcomes (KDIGO) clinical guidelines are used as the diagnostic criteria for AKI [5]. However, serum creatinine (SCr) lacks sensitivity for the early diagnosis of AKI because of the influence of age, gender, body weight, muscle mass, and protein intake [6, 7]. In last 10 years, many novel biomarkers, including neutrophil gelatinase–associated lipocalin, kidney injury molecule-1, tissue inhibitor of metalloproteinases-2, and insulin-like growth factor binding protein-7, have been assessed for the early prediction of AKI [8-10]. However, these biomarkers have not yet been verified to improve the diagnosis or treatment of sepsis-induced AKI.

Bedside Doppler ultrasound, a rapid, noninvasive, and repeatable tool for assessing renal perfusion, is widely used in critically ill patients [11-13]. The Doppler-based renal resistive index (RI) changes before the change in the SCr level during both the development and the recovery processes of AKI. Renal RI has been shown to predict AKI [14-16]. However, several physiological factors, such as vascular compliance and intra-abdominal pressure, influence RI. Central venous pressure (CVP) not only is a marker of resuscitation but also predominantly determines the microcirculatory perfusion pressure as an outflow obstruction. A higher CVP value is associated with impairment of microcirculatory blood flow and the development of AKI [17, 18]. The value of the combination of renal RI and CVP in the early prediction of sepsis-induced AKI has probably not been studied to date. Therefore, the main objective of this study was to evaluate the value of renal RI, CVP, and especially the combination

of these two parameters in the early prediction of sepsis-induced AKI.

Material and Methods

Patients

This was a prospective single-center cohort study. Between July 2015 and June 2016, consecutive patients admitted to the surgical intensive care unit (SICU) of Zhongshan Hospital Fudan University who met the following sepsis diagnostic criteria were included: (1) confirmed or suspected tissue or body cavity infection caused by pathogenic or potentially pathogenic microorganisms, and (2) systemic inflammatory response, which manifested as two or more of the following conditions: body temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min, and white blood cell count $>12 \times 10^9$/L or $<4 \times 10^9$/L. Septic shock was defined according to the Surviving Sepsis Campaign (SSC) guidelines [19]. The exclusion criteria were as follows: (1) age <18 years, (2) pregnant, (3) arrhythmia, (4) a history of chronic kidney disease, (5) confirmed abnormal renal structure, (6) confirmed renal artery stenosis, and (7) history of organ transplantation. The ethics committee of Zhongshan Hospital approved the study, and all included patients or their legal representatives gave written informed consent.

Study protocol and data collection

The SSC guidelines were followed to treat all eligible patients [19]. The patients were resuscitated according to a non-CVP-guided treatment protocol with the following resuscitation goals: mean arterial pressure (MAP) ≥60 mm Hg, superior vena cava oxygenation saturation ($ScvO_2$) ≥70%, and urine output ≥0.5 mL/kg · h. A systemic

hemodynamic assessment was achieved by continuous invasive monitoring of arterial blood pressure and $ScvO_2$ measurements through blood gas analysis using a central venous catheter. The CVP was also measured through the central venous catheter.

AKI was diagnosed based on the changes in SCr levels and urine output according to the KDIGO clinical practice guidelines [5]. The patients were divided into AKI and non-AKI groups based on the diagnosis of AKI. The following clinical characteristics and variables potentially associated with AKI according to previous studies were recorded at admission: age, gender, body mass index (BMI), heart rate, systolic and diastolic blood pressure (SBP / DBP), MAP, CVP, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, sequential organ failure assessment (SOFA) score, SCr, total bilirubin, platelet count, pH value, ratio of arterial oxygen partial pressure to fractional inspired oxygen, partial pressure of carbon dioxide, lactate, procalcitonin, ScvO2, use of vasoactive drugs, comorbid conditions associated with AKI, sepsis severity (septic shock or not), and sepsis sources. The values of heart rate, SBP, DBP, MAP, and CVP immediately upon SICU arrival were used for following statistical analysis. Renal diastolic perfusion pressure (DPP) defined as DBP minus CVP was also recorded. Each participant also underwent a bedside renal Doppler ultrasound examination within 3 h after admission. The renal size and RI were recorded in this examination. Each patient was observed until death, hospital discharge, or day 28, whichever came first. The duration of intensive care unit (ICU) stay and hospitalization was recorded.

RI calculation

The RI was calculated using a CX50 CompactXtreme Ultrasound System (Philips, MA, USA) and a 2–5 MHz curved array transducer by an attending doctor

experienced in this technique. In most patients, the RI of the right kidney was calculated. The size of the kidney (length and width) was measured through visualization in gray scale. The renal perfusion was assessed using color Doppler. An interlobar or arcuate artery was selected to calculate the RI using pulse-wave Doppler. The Doppler gain was set at its optimum condition to obtain a clear outline of flow waves with minimal background noise. When at least three similar consecutive waveforms were visualized, the Doppler spectrum was considered as optimal. RI was calculated according to the following expression: (peak systolic velocity – end-diastolic velocity)/peak systolic velocity. The mean of three distinct RI calculations was considered.

Statistical analysis

The data were statistically analyzed using SPSS version 21.0 (IBM Corporation, NY, USA). The distribution of data was evaluated by the Shapiro–Wilks test. Continuous variables were expressed as mean ± standard deviation and analyzed using the Student *t* test or the Mann–Whitney *U* test. Categorical variables were compared using the χ^2 test or Fisher's exact test. The multivariable logistic regression was performed using the forward stepwise method for the variables considered to be risk factors for sepsis-induced AKI in the univariate analysis with a *P* value <0.1. The results were depicted as odds ratio (OR) and 95% confidence interval (95% CI). The area under receiver operating characteristic curve (AUROC) analysis was performed to determine the predictive values of the risk factors. The predicted value of AKI incidence obtained by logistic regression of renal RI and CVP was defined as a new variable. The AUROC value of the new variable was also analyzed. The AUROC values were interpreted as follows: <0.70 = poor, 0.70–0.80 = fair, 0.80–0.90 = good, and >0.90 = excellent. The optimal cutoff value was calculated using the Youden index. The cumulative

probability of survival in the AKI and non-AKI groups was estimated using the Kaplan–Meier survival analysis. A *P* value <0.05 (two sided) was considered as statistically significant.

Results

General characteristics of participants

A total of 2704 patients were admitted into the SICU of Zhongshan Hospital between July 2015 and June 2016. Of these, 124 patients (74 males and 50 females, with a mean age of 62.4 ± 5.9 years) met the inclusion criteria and were enrolled for the analysis (Fig. 1). The mean values of APACHE II and SOFA scores were found to be 14.3 ± 4.9 and 4.0 ± 1.1, respectively, and the mean value of BMI was found to be 22.6 ± 4.9. A total of 75 (60.5%) patients were admitted to the SICU after operation, and 27 (21.8%) patients were diagnosed as septic shock at admission. The presumed or confirmed sepsis sources were as follows: abdominal (59, 47.6%), respiratory tract (29, 23.4%), bloodstream (22, 17.7%), urinary tract (6, 4.8%), skin and soft tissues (5, 4.0%), and other sites (3, 2.4%).

The AKI group comprised 52 (41.9%) patients who developed sepsis-induced AKI, and the non-AKI group comprised 72 (58.1%) patients who did not develop this condition. AKI was confirmed on an average in 4.2 ± 2.6 days in the AKI group. The overall 28-day mortality rate was 30.6% (38/124). The development of AKI was significantly associated with 28-day mortality: 40.4% (21/52) versus 23.6% (17/72), *P* = 0.027 (Fig. 2). The AKI group had a significantly longer duration of ICU stay and hospitalization compared with the non-AKI group (16.5 ± 5.2 days vs 12.8 ± 4.1 days, *P* = 0.009; 21.3 ± 6.9 days vs 17.9 ± 5.3 days, *P* = 0.005, respectively).

Analysis of risk factors

Demographic characteristics, clinical characteristics, and potential risk factors of sepsis-induced AKI were recorded at admission (Table 1). Each patient underwent a bedside renal Doppler ultrasound examination within 3 h after SICU admission. No significant difference was observed in the renal size between the AKI and non-AKI groups. However, the renal RI of the AKI group was significantly higher compared with that of the non-AKI group (0.76 ± 0.11 vs 0.63 ± 0.12, P = 0.008) (Fig. 3). The univariate analysis revealed that patients with AKI were older, with lower DBP and DPP, higher CVP, lactate values, APACHE II score, septic shock percentage and renal RI than the non-AKI patients (P < 0.1) (Table 1). No significant differences were found in other demographic and clinical characteristics between the two groups. According to multivariate analysis, high CVP (OR, 1.92; 95% CI, 1.32–3.58; P = 0.012), low DPP (OR, 2.15; 95% CI, 1.48–4.16; P = 0.010), high renal RI (OR, 2.58; 95% CI, 1.84–4.29; P = 0.009), and septic shock (OR, 3.28; 95% CI, 1.98–4.86; P = 0.002) at admission were independent risk factors for sepsis-induced AKI (Table 2).

Predictive value of the risk factors

The AUROC values of RI and CVP were calculated. The sensitivity and specificity of RI ≥ 0.695 for predicting sepsis-induced AKI were 52% and 87%, respectively (AUROC = 0.811; 95% CI, 74–89). The sensitivity and specificity of CVP ≥ 11.5 mm Hg for predicting sepsis-induced AKI were 54% and 85%, respectively (AUROC = 0.780; 95% CI, 70–86) (Fig. 4). The AUROC value of the predicted value of AKI incidence was bigger than that of either RI or CVP (AUROC = 0.858; 95% CI, 79–93) (Fig. 4). The sensitivity and specificity of DPP ≤ 42.5 mm Hg for predicting sepsis-induced AKI were 87% and 46%, respectively (AUROC = 0.835; 95% CI, 76–90).

Discussion

Based on the findings of this study, septic shock, high renal RI and CVP, and low renal DPP were considered independent risk factors of sepsis-induced AKI, and the predicted value of AKI incidence obtained by integrating RI and CVP was a better indicator for sepsis-induced AKI than either of the two parameters. With the development of AKI, the 28-day mortality rate increased and the duration of ICU stay and hospitalization prolonged.

Age, gender, muscle mass, and so on, influence the traditional AKI evaluation indicators, such as urine and SCr, to a great extent. Therefore, such indicators might not permit the early detection of AKI and result in missing the opportunity for early treatment [20, 21]. The concepts of the pathogenesis of sepsis-induced AKI have suffered profound change in recent years. The pathological characteristics of AKI are more complex than the previous thought of simple acute renal tubular necrosis and glomerular injury [22]. Inflammation, oxidative stress, microvascular dysfunction, and the adaptive response of the tubular epithelial cell to septic insult are all involved in sepsis-induced AKI [23 - 25]. The microvascular dysfunction characterized by a decrease of continuous flow and a concomitant increase of intermittent or no flow in vessels might be resulted from the capillary leukocytic infiltration, altered endothelial cells, and renal tissue edema [26 - 28]. Renal Doppler is considered to be a reliable and easy-to-perform bedside assessment method for monitoring renal perfusion in critically ill patients [29]. Inexperienced operators can be made to perform this technique after a brief training, and the side-to-side difference is usually <5% [13]. A significantly increased renal RI at admission has been shown to be associated with

AKI in critically ill patients [14,15]. Even in patients using vasoactive drugs, the renal RI had good sensitivity and specificity in the diagnosis of AKI [30, 31]. Darmon et al. found that renal RI could distinguish between transient or persistent AKI in critically ill patients on mechanical ventilation. An RI >0.795 predicted persistent AKI with 82% sensitivity and 92% specificity [30]. The evaluation criteria of renal RI were different in various diseases inducing AKI [15,32]. In the present study, the SCr levels of the AKI and non-AKI groups were in the normal range with no significant difference at admission. However, the renal RI of the AKI group was significantly higher compared with that of the non-AKI group, and indicated an earlier subclinical change in renal blood flow in patients with sepsis-induced AKI. We thought it was a marker of downstream obstruction related to inflammation, microvascular dysfunction and other mechanisms, and characterized by low velocity and high resistance. According to the renal artery spectrum, the velocity of blood flow in the AKI group was relatively slower compared with that in the non-AKI group, and this phenomenon was more obvious in diastole than in systole. Therefore, the pulsed-wave Doppler spectrum of the AKI group showed a narrow and steep waveform character, which resulted in a high renal RI value.

CVP in patients with sepsis is conventionally measured using a central vena cava catheter, and is one of the fluid resuscitation goals mentioned in the SSC guidelines. However, higher CVP increases the afterload and backflow resistance of the kidneys, resulting in a decline in renal perfusion pressure [33]. Legrand et al observed an association between high CVP and development of new or persistent AKI in septic patients, which suggested the participation of venous congestion in the physiopathology of septic AKI [18]. A higher CVP has been shown to be closely related to a worse renal function and mortality, independent of the heart index or other

clinical factors [17, 34]. Moreover, previous study confirmed that CVP reduction could improve the renal function and clinical outcomes in patients with heart failure [35]. In this study, the CVP was significantly higher in the AKI group compared with that of the non-AKI group immediately upon SICU arrival, but no significant difference was found in the SBP, DBP, and MAP between the two groups. Therefore, the increasing renal backflow resistance caused by high CVP might decrease the renal perfusion, partly proved by the significantly lower DPP in AKI group, and result in reflux disorder and renal cortex edema. According to the results, low DPP was also a sensitive predictor for sepsis-induced AKI, since it integrated the potential low blood pressure in diastole and the venous congestion status, which was consistent with our experience and should be taken seriously in clinic.

As confirmed by logistic regression analysis, both high renal RI and CVP at admission were independent risk factors for sepsis-induced AKI, but one single parameter predicting AKI was still not accurate enough. The reason for this is both RI and CVP were influenced by many other physiological and pathological factors, including vascular compliance, intra-abdominal pressure, right ventricular dysfunction, and tricuspid valve disease. According to the AUROC results in this study, CVP (≥11.5 mm Hg) was a fair and RI (≥0.695) was a good predictor of sepsis-induced AKI, but the AUROC of the predicted value of AKI incidence obtained by the combination of RI and CVP was even greater than that of either RI or CVP in predicting sepsis-induced AKI. Our explanation behind the results was that the inflammation and microcirculation dysfunction caused the downstream obstruction which was reflected by the higher RI. Meanwhile, venous congestion, reflected by the CVP elevation, might aggravate the consequences.

According to the results, septic shock was also an independent risk factor for sepsis-

induced AKI, which demonstrated the importance of sepsis severity in the occurrence of sepsis-induced AKI just as reported in other articles. The mortality rate was significantly higher and the duration of ICU stay and hospitalization were significantly longer in the AKI group than in the non-AKI group, which were consistent with previous findings [36, 37]. Therefore, identifying patients with sepsis who were at high risk of AKI as early as possible and treating them without delay were extremely important to reduce the mortality, hospital stay, and hospitalization costs.

This study had several limitations. First, it was a single-center study with limited sample size. Second, Doppler examination was not conducted by the same attending doctor, and complete blinding of the clinical condition of patients to the ultrasonography operators at the time of RI measurement was almost impossible. Therefore, to minimize this bias, the operators were not involved in patient care. Finally, both RI and CVP were influenced by several other physiological and pathological factors, which might have influenced the results. Despite these limitations, these two integrative parameters could help in detecting early renal dysfunction in patients with sepsis. Additional well-designed studies with larger sample size are needed to confirm the aforementioned conclusions.

Conclusions

In summary, the mechanisms of sepsis-induced AKI were comprehensive, and early prediction was extremely difficult. Septic shock, high RI and CVP, and low DPP at the time of sepsis diagnosis were independent predictors of sepsis-induced AKI, and it was more valuable to combine RI and CVP in the early prediction of sepsis-induced

AKI.

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Table 1

Demographic characteristics and potential risk factors for sepsis-induced AKI at admission

	AKI group (n = 52)	Non-AKI group (n = 72)	P value
Age (year)	65.8 ± 5.5	60.9 ± 6.2	0.067
Male sex (n,%)	30 (57.7)	44 (61.1)	0.254
BMI	21.9 ± 4.7	23.1 ± 5.1	0.339
Heart rate (beat/min)	102 ± 14	98 ± 10	0.667
SBP (mm Hg)	117 ± 25	122 ± 28	0.282
DBP (mm Hg)	52 ± 12	59 ± 16	0.085
MAP (mm Hg)	63 ± 18	69 ± 16	0.365
CVP (mm Hg)	12.5 ± 2.7	9.2 ± 2.1	0.006
DPP (mm Hg)	40 ± 13	50 ± 17	0.003
APACHE II score	16.2 ± 5.2	12.9 ± 4.6	0.082
SOFA score	4.2 ± 1.2	3.8 ± 1.1	0.226
Postoperative (n, %)	30 (57.7)	45 (62.5)	0.586
SCr (μmol/L)	88 ± 12	83 ± 15	0.218
TB (μmol/L)	12.4 ± 3.2	10.9 ± 3.8	0.634
Platelet ($\times 10^9$/L)	155 ± 37	179 ± 46	0.257
pH	7.33 ± 0.15	7.38 ± 0.18	0.725
PaO_2/FiO_2 (mm Hg)	225 ± 38	236 ± 43	0.368

$PaCO_2$ (mm Hg)	36.5 ± 5.2	39.2 ± 5.9	0.147
Lactate (mmol/L)	2.4 ± 1.0	1.7 ± 0.9	0.078
PCT (ng/mL)	5.6 ± 3.7	4.9 ± 2.8	0.118
$ScvO_2$ (%)	66 ± 13	69 ± 11	0.346
Use of vasoactive drugs (*n*, %)	29 (55.8)	37 (51.4)	0.539
Hypertension (*n*, %)	15 (28.8)	20 (27.8)	0.788
Diabetes (*n*, %)	11 (21.2)	14 (19.4)	0.622
Cardiovascular disease (*n*, %)	9 (17.3)	13 (18.1)	0.785
Septic shock (*n*, %)	20 (38.5)	7 (9.7)	0.001
Sepsis source (*n*, %)			0.393
Abdominal	26 (50.0)	33 (45.8)	
Respiratory tract	12 (23.1)	17 (23.6)	
Bloodstream	9 (17.3)	13 (18.1)	
Urinary tract	2 (3.8)	4 (5.6)	
Skin or soft tissue	2 (3.8)	3 (4.2)	
Other sites	1 (1.9)	2 (2.8)	
Renal size			
Length (cm)	10.2 ± 1.7	10.6 ± 1.9	0.575
Width (cm)	4.8 ± 0.8	5.1 ± 1.0	0.662

Renal RI	0.76 ± 0.11	0.63 ± 0.12	0.008

AKI, Acute kidney injury; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; CVP, central venous pressure; DPP, diastolic perfusion pressure; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; SCr, serum creatinine; TB, total bilirubin; PaO2/FiO2, arterial oxygen partial pressure to fractional inspired oxygen; PaCO2, partial pressure of carbon dioxide; PCT, procalcitonin; ScvO2, central venous oxygen saturation; RI, resistive index.

Table 2

Logistic regression analysis of risk factors associated with AKI

	OR	95% CI	*P* value
Age	1.07	0.86–1.86	0.136
DBP	0.86	0.32–1.55	0.207
CVP	1.92	1.32–3.58	0.012
DPP	2.15	1.48–4.16	0.010
APECHE II score	1.25	0.85–1.68	0.187
Lactate	1.39	0.82–1.54	0.242
Septic shock	3.28	1.98–4.86	0.002
Renal RI	2.58	1.84–4.29	0.009

AKI, Acute kidney injury; DBP, diastolic blood pressure; CVP, central venous pressure; DPP, diastolic perfusion pressure; APACHE, Acute Physiology and Chronic Health Evaluation; RI, resistive index.

Figure captions:

Fig. 1. Flow diagram of the study.

Fig. 2. Kaplan–Meier survival curve at 28 days for the AKI and non-AKI groups.

Fig. 3. Pulsed-wave Doppler spectrum of the AKI and non-AKI groups. (A) Pulsed-wave Doppler spectrum of a non-AKI patient, with RI = 0.582. (B) Pulsed-wave Doppler spectrum of an AKI patient with a narrow and steep waveform character, with RI = 0.679.

Fig. 4. Receiver operating characteristic curves of the risk factors. The AUROC value of RI, CVP, and the combination of these two parameters was 0.811, 0.780, and 0.858, respectively.

Highlights

1. Septic shock, high RI and CVP, low DPP at admission were independent predictors for sepsis-induced AKI.
2. The combination of RI and CVP was valuable in the early prediction of sepsis-induced AKI.
3. Sepsis-induced AKI was associated with 28-day mortality and hospitalization.

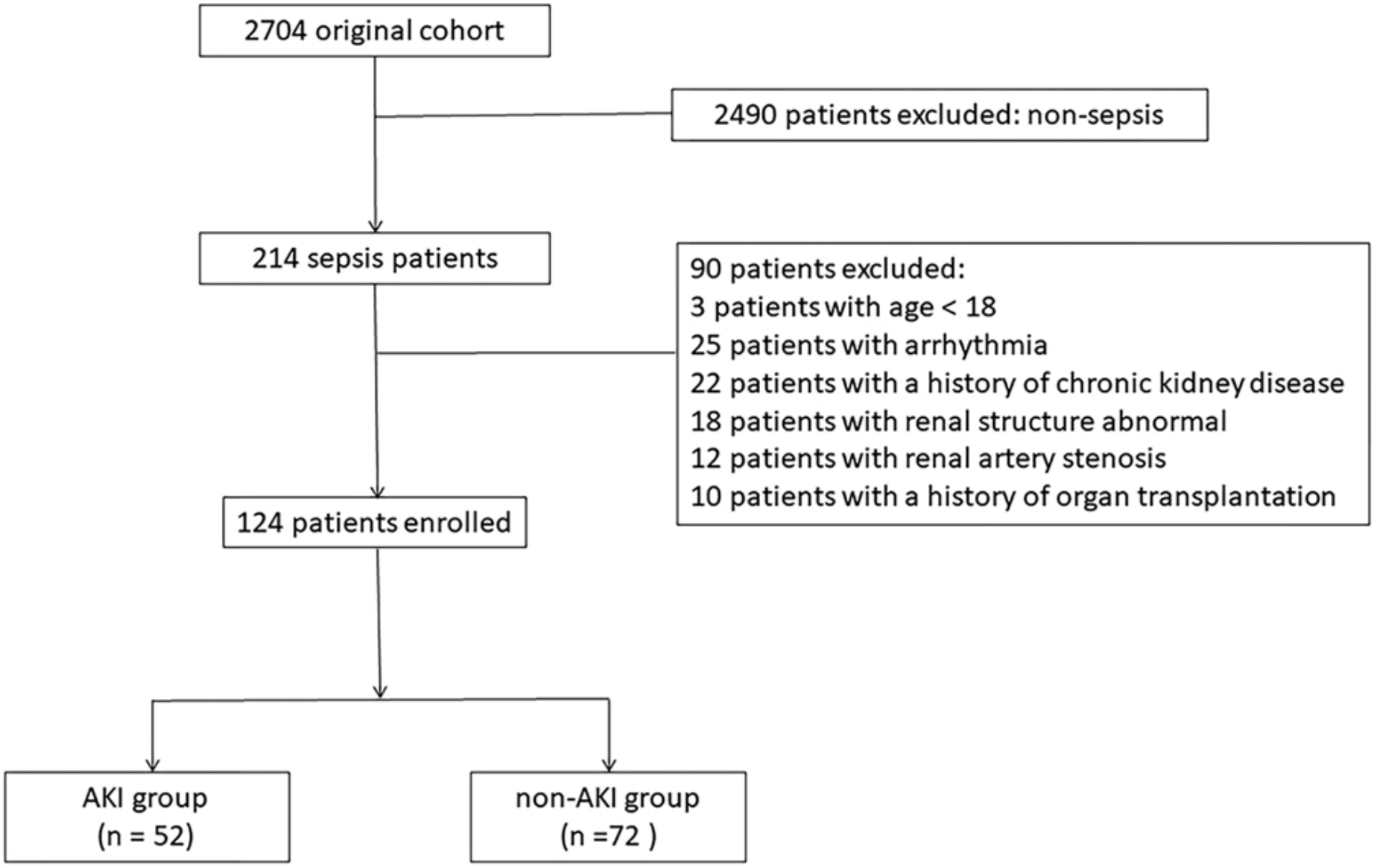
2704 original cohort
2490 patients excluded: non-sepsis
214 sepsis patients
90 patients excluded:
3 patients with age < 18
25 patients with arrhythmia
22 patients with a history of chronic kidney disease
18 patients with renal structure abnormal
12 patients with renal artery stenosis
10 patients with a history of organ transplantation
124 patients enrolled
AKI group
(n = 52)
non-AKI group
(n =72)

Figure 1

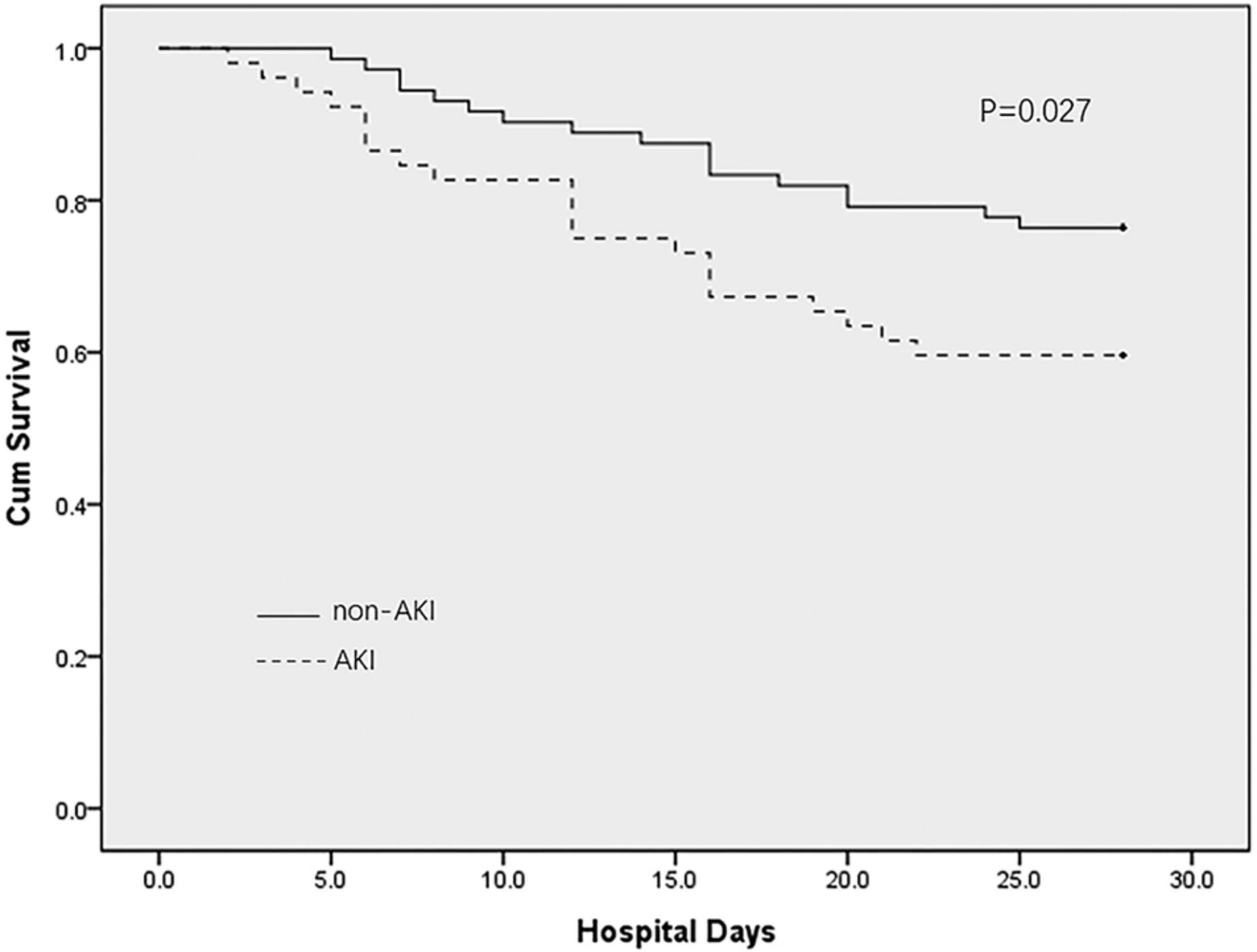
1.0
0.8
0.6
0.4
0.2
0.0
Cum Survival
P=0.027
non-AKI
AKI
0.0
5.0
10.0
15.0
20.0
25.0
30.0
Hospital Days

Figure 2

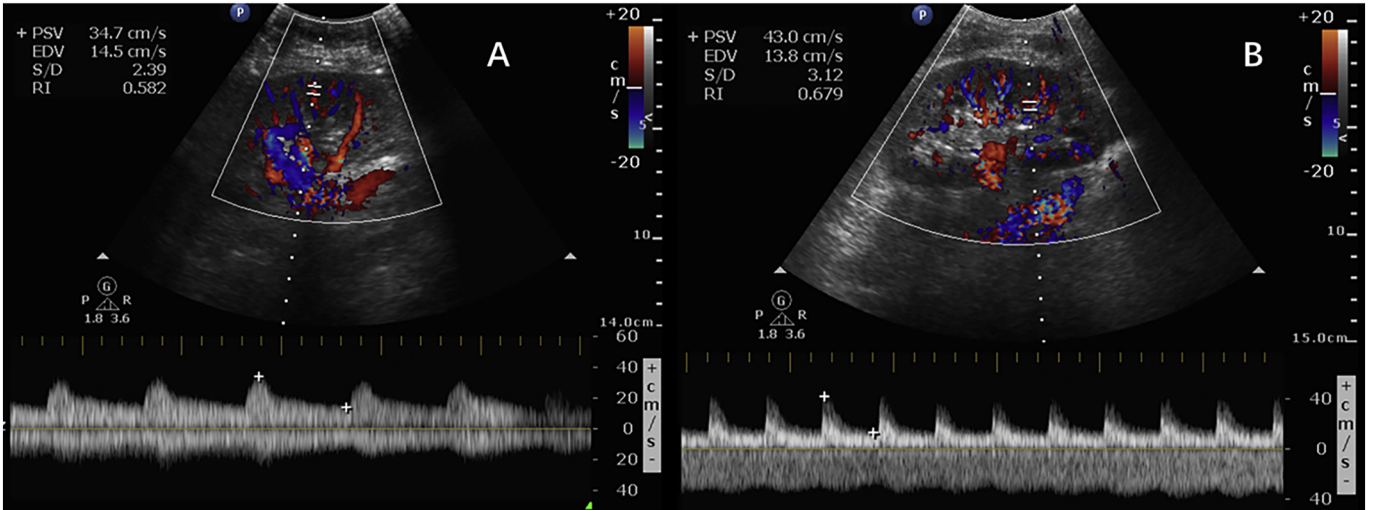
A
+ PSV 34.7 cm/s
EDV 14.5 cm/s
S/D 2.39
RI 0.582
+20
cm/s
-20
10
P G R
1.8 3.6
14.0cm
60
40
20
0
20
40
+ cm/s -
B
+ PSV 43.0 cm/s
EDV 13.8 cm/s
S/D 3.12
RI 0.679
+20
cm/s
-20
10
P G R
1.8 3.6
15.0cm
40
0
40
+ cm/s -

Figure 3

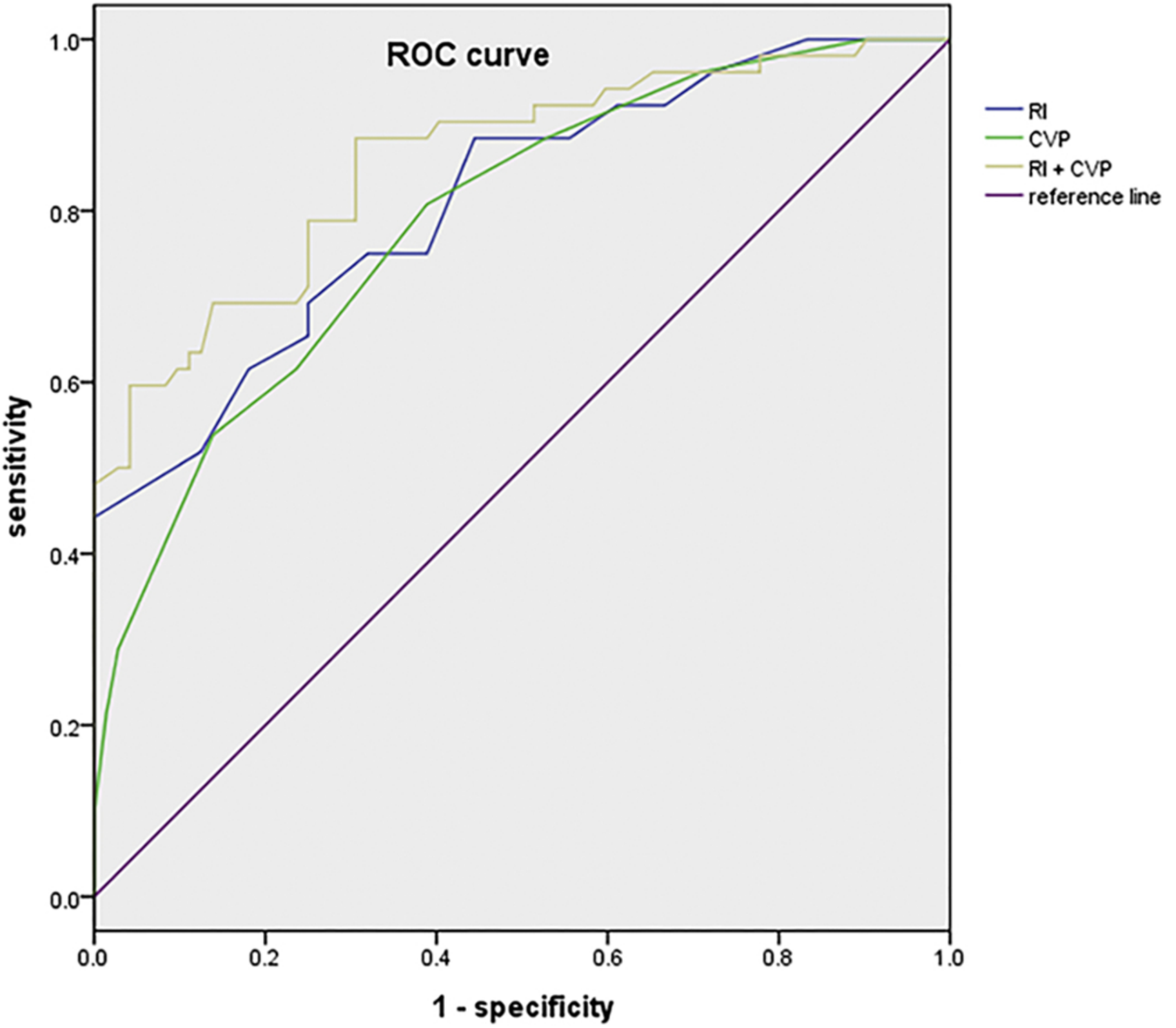
ROC curve
sensitivity
1 - specificity
0.0
0.2
0.4
0.6
0.8
1.0
RI
CVP
RI + CVP
reference line

Figure 4