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**Augmented renal clearance in critically ill trauma patients:
a pathophysiologic approach using renal vascular index.**

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ABSTRACT

BACKGROUND: The aim of the present study was to explore the relationship between creatinine clearance (Cl_{Cr}), cardiac index (CI) and renal vascular index (RVI) in order to assess the potential mechanisms driving ARC in critically ill trauma patient. The secondary objective was to assess the performance of RVI for prediction of ARC.

METHODS: Every trauma patient who underwent cardiac and renal ultrasound measurements during their initial ICU management was retrospectively reviewed over a 3-month period. ARC was defined by a 24-hr measured $Cr_{CL} \geq 130$ ml/min/1.73m². A mixed effect model was constructed to explore covariates associated with Cl_{Cr} over time. The performance of RVI for prediction of ARC was assessed by receiver operating characteristic (ROC) curve and compared to the ARCTIC (ARC in trauma intensive care) predictive scoring model.

RESULTS: Thirty patients, contributing for 121 coupled physiologic data, were retrospectively analysed. There was a significant correlation between Cl_{Cr} values and RVI ($r = -0.495$; $p = 0.005$) but not between Cl_{Cr} and CI values ($r = 0.023$; $p = 0.967$) at day 1. Using a mixed effect model, only age remained associated with Cl_{Cr} variations over time. The area under the ROC curve of RVI for predicting ARC was 0.742 (95%CI: 0.649 – 0.834; $p < 0.0001$), with statistical difference when compared to the ROC curve of ARCTIC (0.842 [0.771 – 0.913]; $p < 0.0001$).

CONCLUSION: Ultrasonic evaluation of CI and RVI didn't allow approaching the haemodynamic mechanisms responsible for ARC in patients. RVI was inaccurate and not better than clinical score for predicting ARC.

1 **KEY WORD**

2

3 • Augmented renal clearance

4 • Renal vascular index

5 • Renal ultrasound

6 • Trauma

7 • Critical illness

8

1 **BACKGROUND**

2

3 For several years, augmented renal clearance (ARC) has been increasingly investigated in critical care
4 practice, currently defined by an increased urinary creatinine clearance (Cl_{Cr}) exceeding 130 ml/min/1.73m² [1].
5 This is a major concern as ARC has been recognised as one of the leading causes of subtherapeutic antibiotic
6 exposure, potentially responsible for poor clinical outcome in septic patients [2-4]. Although a prompt
7 recognition of ARC should be crucial for optimising empirical antibiotic dosing, few screening tools available at
8 the bedside have shown adequate predictive abilities for identifying patients with ARC [5, 6].

9

10 Moreover, the pathophysiologic mechanisms responsible for ARC in critically ill patients remain mainly
11 unknown, although alterations in both glomerular filtration and renal tubular function have been observed [7].
12 The most widespread theory involves an increase in cardiac index (CI), resulting in an enhanced renal blood
13 flow (RBF) and therefore an increased glomerular filtration rate (GFR) [8]. On the other hand, some authors
14 suggested that changes in vasomotor tone and intra-glomerular filtration pressure were potentially the main
15 mechanism underlying ARC in critically ill patients [9].

16

17 Renal Doppler vascular index (RVI) has been used to reflect regulation of renal vascular tone in the
18 critical care settings [10]. A recent meta-analysis suggested that abnormally high RVI was associated with
19 further renal impairment in septic critically ill patients [11]. In addition, RVI seems to be of interest in
20 evaluating changes in renal perfusion as a consequence of therapeutic interventions [12-14]. The ability of RVI
21 to predict ARC remains questionable and still needs to be demonstrated.

22

23 The main objective of this study was thus to investigate the relationship between Cl_{Cr} , RVI and CI in
24 critically ill trauma patients with or without ARC. The secondary objective was to assess the performance of RVI
25 for the early prediction of ARC.

26

1 **METHODS**

2

3 **1. Design, population and settings**

4

5 This study is a retrospective analysis of our local database (declared to the French Data Protection
6 Authority: declaration number 2166637v0) prospectively collected in a 25-bed Surgical and Trauma Intensive
7 Care Unit (ICU). Ethical approval for this analysis was obtained from the Ethics Committee of the French Society
8 of Anaesthesia and Intensive Care Medicine (IRB number: CERAR 00010254-2018-089). The patients and/or
9 next of kin were informed about the inclusion of their anonymised health data in the database, and none
10 declined participation.

11

12 During the study period, every trauma patient who underwent cardiac and renal ultrasound during the
13 initial ICU management was included. The ultrasound measurements were performed by one of our attending
14 physician as part of a standard care over a 3-month period. Non-inclusion criteria were pregnancy, age < 18
15 years, end-stage renal failure or indication for renal replacement therapy, known renal artery stenosis,
16 cirrhosis, congestive heart failure, atrial fibrillation or arrhythmia.

17

18

2. Data collection and ultrasound measurements

Our local database included daily metabolic, haemodynamic and ultrasound measurements prospectively collected as part of a standard care in every trauma patient. Data collection started within 48 hours of ICU admission and was discontinued at 1) ICU discharge, 2) development of severe renal impairment ($Cl_{Cr} < 30$ ml/min/1.73m²) or institution of renal replacement therapy, 3) removal of invasive monitoring or 4) day 5, whichever came first. Plasma and urinary samples were recorded during the first five days after admission and measured Cl_{Cr} was calculated as follows: $\frac{24\text{-hr urinary volume (ml/day)} \times \text{urinary creatinine (mmol/L)}}{\text{plasma creatinine } (\mu\text{mol/L})}$, converted in ml/min and normalised to a body surface area of 1.73 m² (Dubois formula). As previously described, ARC was defined by a measured $Cl_{Cr} \geq 130$ ml/min/1.73m² [1]. A predictive scoring model called ARCTIC (ARC in trauma intensive care) was also calculated each day as originally described [15]: SCr < 62 μ mol/L (3 points), male sex (2 points), Age < 56 years (4 points) or 56-75 years (3 points).

All cardiac and renal ultrasound measurements were performed using a General Electric Vivid S6 machine (GE Healthcare, Wauwatosa, WI, USA) by an experienced physician unaware of the measured Cl_{Cr} . As previously described, RVI was obtained from the most representative proximal interlobar arteries [10]. The peak systolic velocity (V_{max}) and the minimal diastolic velocity (V_{min}) were determined by pulse wave Doppler, and RVI was calculated as $(V_{max} - V_{min})/V_{max}$. The results from three consecutive similar-appearing waveforms were averaged for each kidney (**Figure 1**). Using echocardiography, stroke volume (SV) was calculated as the product of the aortic valve area ($\pi/\text{diameter}^2/4$) by the area under the envelope of the pulsed-wave Doppler measured at the aortic annulus and averaged over three consecutive measurements. Cardiac output was calculated as the product of heart rate (HR) and stroke volume, indexed to the body surface area (L/min/m²). Intra-observer variability coefficient, assessed in ten patients before the study, was $5 \pm 3\%$ for RVI and $4 \pm 3\%$ for VTI.

1 **3. Statistical analysis**

2

3 Results are expressed as mean \pm standard deviation or median (25% to 75% interquartile range) for
4 continuous variables and as numbers (percentages) for categorical variables. The data distribution was
5 analysed by a Kolmogorov-Smirnov test. Non-paired analysis of continuous variables was performed using the
6 Student *t* test or the Mann–Whitney test as appropriate. Categorical variables were compared using the chi-
7 square test or Fisher’s exact test as appropriate.

8

9 The first paired data were compared using Spearman’s correlation coefficient. To model changes of Cl_{Cr}
10 over time, a random components mixed-effects model was constructed [1]. Relevant covariates were added as
11 a forward stepwise procedure to obtain the smallest Akaike information criterion (AIC). The addition of
12 covariates was stopped when no further decrease of AIC was obtained.

13

14 For the secondary outcome of the study, the accuracy of RVI to predict ARC was assessed using a receiving
15 operator curve (ROC) analysis. The best threshold values were chosen to maximize Youden index. A threshold
16 analysis was also performed using a grey zone approach [16]. Furthermore, recent data have been suggesting
17 that an ARCTIC score of 6 or higher was an appropriate cutoff to screen for ARC, although external validation is
18 lacking. We thus aimed to compare areas under ROC curves between RVI and ARCTIC score using the DeLong
19 test [17].

20

21 A *p* value < 0.05 was considered statistically significant. Statistical analyses were performed using XLSTAT
22 2017 for Windows (Addinsoft Paris, France).

23

1 **RESULTS**

2

3 **1. Population**

4

5 The final dataset consisted of 121 coupled individual data of Cl_{Cr} , RVI and CI collected from 30 trauma
6 patients. Overall, 67% (20/30) of the patients manifested ARC on at least one occasion during the first five
7 study days. The characteristics of the population are resumed **Table 1**.

8

9 Mean value for Cl_{Cr} was 128 ± 57 ml/min/1.73m² and ARC was found in 61/121 urinary samples (50%).
10 Representation of Cl_{Cr} , RVI and CI over time is shown in **Supplementary data**. The intra-patient variability
11 coefficients were $15 \pm 10\%$ for Cl_{Cr} , $6 \pm 4\%$ for RVI and $19 \pm 9\%$ for CI without significant difference over the
12 three consecutive days.

13

14 **2. Relationship between Cr_{Cl} , RI and systemic hemodynamic data**

15

16 There was a significant correlation between Cl_{Cr} values and RVI ($r = -0.495$; $p = 0.005$) but not between Cl_{Cr}
17 and CI values ($r = 0.023$; $p = 0.967$) at day 1 (**Figure 2**). There was a significant correlation between RVI values
18 and age ($r = 0.676$; $p < 0.0001$). There was no correlation between RVI and MAP ($p = 0.679$), whether in patients
19 with or without ARC. For a given MAP, lower RVI values were observed in ARC patients (**Supplementary data**).

20

21 Using a mixed effect model, only age (AIC 1069.8; $p < 0.001$) and RVI (AIC = 1083; $p < 0.047$) remained
22 associated with Cl_{Cr} over time. Gender, mechanical ventilation, CI, mean MAP or norepinephrine doses were
23 not predictive of daily Cl_{Cr} . A model parameterized with the two covariates (i.e. age and RVI, *model n + 1*) had
24 an AIC of 1071 and was no statistically different from the *model n* (i.e. age) by the likelihood ratio test ($p =$
25 0.34). The random component variance (RVI or CI) didn't have a significant effect on the global model.

26

27

1 **3. Performance of RVI in predicting the occurrence of ARC**

2

3 The area under the ROC curve of RVI for predicting ARC was 0.742 (95%CI: 0.649 – 0.834; $p < 0.0001$)

4 (**Figure 3**). A threshold of RVI < 0.68 had a sensitivity and specificity of 0.84 (95%CI: 0.71 – 0.91) and 0.65

5 (95%CI: 0.51 – 0.76) respectively. The grey zone approach was comprised between 0.57 and 0.70, with 64% of

6 RVI measurements falling in the inconclusive grey zone.

7

8 On the other hand, an ARTIC score > 6 had a sensitivity and specificity of 0.82 (95%CI: 0.70 – 0.90) and 0.73

9 (95%CI: 0.61 – 0.83) respectively. The area under the ROC curve of ARCTIC for predicting ARC was 0.842

10 (95%CI: 0.771 – 0.913; $p < 0.0001$) with statistical difference when compared to RVI ($p = 0.049$).

1 DISCUSSION

2
3 To our knowledge, this is the first study assessing the potential hemodynamic mechanisms underlying ARC
4 using RVI in critically ill trauma patients. The hypothesis pertaining to this study was that 1) lower RVI for a
5 given MAP should reflect the inhibition of arteriolar tone responsible for ARC in critically ill patients; 2) the
6 sustained vasodilatation may contribute to kidney autoregulation impairment, 3) RBF and GFR becoming
7 dependent of changes in systemic haemodynamics. Despite an inverse correlation between RVI and Cl_{Cr} ,
8 neither RVI nor CI remained associated with ARC after adjustment for confounding covariates. Age remained
9 the only independent variable associated with Cl_{Cr} over time.

10
11 The demographic characteristics of ARC patients should reflect the higher renal functional reserve in
12 younger patients [18]. Renal functional reserve is defined by the ability of the kidney to respond to an
13 increased physiological demand through a combination of nephron recruitment, increase in renal blood flow
14 and/or glomerular hyperfiltration. This hypothesis was also suggested by Udy et al. who demonstrated an
15 elevation of glomerular filtration and high renal plasma flow using exogenous markers in 20 critically ill patients
16 with ARC [9]. For a given renal plasma flow, authors observed considerable variations in filtration fraction.
17 These data indicate that changes in intra-glomerular filtration pressure (due to variable afferent and efferent
18 arteriolar tone) are potentially a key mechanism underlying ARC in critically ill patients [9]. In agreement with
19 these data, some authors thus assumed that the combination of an inhibition of arteriolar vascular tone
20 coupled with an increased renal blood flow in patients with a greater physiological reserve should be
21 accepted as the leading mechanism for ARC [7].

22
23 However, our study failed to estimate arteriolar vascular tone using RVI in a specific population at risk for
24 ARC. Several factors should explain our negative results. First, determinants of RVI are multiple, including renal
25 vascular resistances (RVR) and compliance, renal interstitial pressure, ureteral pressure or systemic arterial
26 pressure [19]. Former data demonstrated that the relationship between vascular resistance and RVI was linear
27 only when vascular compliance was normal [20, 21]. In this context, age-related arterial stiffening may greatly
28 influence RVI values [22]. Moreover, most of patients with ARC displayed physiological range of RVI reported in
29 healthy subjects (0.60 ± 0.01) [23]. Physiological RVI values can't be interpreted as a decreased vascular tone

1 explaining supraphysiological Cl_{Cr} values. The correlation between RVI and Cl_{Cr} may thus be explained by the
2 interdependence between age and these two covariates. Finally, we didn't observe any statistical association
3 between RVI and MAP, although ARC patients displayed lower RVI values for a given MAP. Although RVI is not a
4 valuable reflect of RBF, Lerolle et al. previously demonstrated a negative relationship between MAP and RVI
5 which could be consistent with the physiological increase in RVR in hypoperfusion situations [24]. This
6 assessment was challenged by Dewitte et al. in which such a relationship was only observed in patients without
7 persistent AKI, suggesting that RVI could only reflect renal autoregulation before the occurrence of renal
8 vascular or tubular damage [25]. The ability of RVI to reflect renal autoregulation thus remains questionable
9 and still need to be demonstrated.

10

11 In this context, RVI was inaccurate and not better than the ARCTIC score for predicting ARC in critically ill
12 trauma patients. The considerable overlap in RVI values between patients with and without ARC precludes the
13 use of RVI as a screening marker for ARC. The ARCTIC score is a practical and pragmatic system that can help
14 the clinician to consider dosing adjustments. Our results corroborate the predictive value of a score greater
15 than or equal to 6 as an appropriate threshold for ARC screening [15]. On the other hand, a prompt recognition
16 of ARC is crucial in critically ill patients to optimise empirical antibiotic dosing. Commonly used formulas
17 underestimate measured Cr_{Cl} and frequently misclassify ARC [5, 6]. Measured Cl_{Cr} remains the reference and
18 should be monitored daily in at-risk patients [1].

19

20 The current study has some limitations. First, the design was monocentric with a retrospective analysis
21 over a relatively short period, with potential selection bias that limits the generalizability of the results.
22 Moreover, we acknowledge a limited number of patients, although contributing for numerous ultrasound
23 measurements, prospectively collected and blinded for Cl_{Cr} values. Second, RVI and CO levels were measured
24 once per day whereas Cl_{Cr} was recorded from the 24-hr urinary samples. As those parameters may vary widely
25 over 24h in ICU patients, it is uncertain that Cl_{Cr} data correspond to the actual Cl_{Cr} at the time of other
26 physiologic parameters measurements. This limitation could explain the poor correlation between CI and 24-hr
27 Cl_{Cr} when compared to other studies assessing continuous CI measurements [8]. Finally, 24-hr measured Cl_{Cr} is
28 known to overestimate glomerular filtration rate and RVI is far from being the most valuable marker of renal
29 vascular resistance or plasma renal flow [27]. On the other hand, the clinical evaluation of renal autoregulation

1 is restricted because of the lack of non-invasive RBF assessment at the bedside [18]. Standardised and valuable
2 measurements of GFR and RBF by exogenous markers, contrast-enhanced ultrasound and/or magnetic
3 resonance imaging might be necessary to corroborate the hypothesis pertaining to this study.

4

5

1 **CONCLUSION**

2

3 Ultrasonic evaluation of CI and RVI doesn't allow approaching the haemodynamic mechanisms responsible
4 for ARC in patients. RVI was inaccurate and not better than the ARCTIC score for predicting ARC in critically ill
5 trauma patients. Further studies are thus needed to explore haemodynamic determinates in this specific
6 population at risk for ARC.

7

1 **LIST OF ABBREVIATIONS**

2

3 • ARC = augmented renal clearance

4 • CI = cardiac index

5 • Cr_{CL} = creatinine clearance

6 • GFR = glomerular filtration rate

7 • HR = heart rate

8 • ICU = Intensive Care Unit

9 • RBF = renal blood flow

10 • RVI = renal vascular index

11 • RVR = renal vascular resistance

12 • ROC = receiving operator curve

13 • SV = stroke volume

14 • V_{max} = peak systolic velocity

15 • V_{min} = minimal diastolic velocity

16

17

1 **DECLARATIONS**

2

3 **1. Ethics approval and consent to participate**

4

5 Ethical approval for this single-centre, non-interventional study was obtained from the Ethics Committee
6 of the French Society of Anaesthesia and Intensive Care Medicine (IRB number: CERAR 00010254-2018-089),
7 which waived the need for written consent. According to the French law, the database was declared to the
8 French Data Protection Authority (declaration number: 2166637v0). The patients and/or next of kin were
9 informed about the inclusion of their anonymised health data in the database, and none declined participation.

10

11 **2. Consent for publication**

12

13 Not applicable

14

15 **3. Availability of data and material**

16

17 The datasets used and/or analysed during the current study are available from the corresponding author
18 on reasonable request.

19

20 **4. Competing interests**

21

22 The authors declare that they have no competing interests.

23

24

1 **5. Funding**

2

3 Only departmental funds were used for this study. No external funds were obtained.

4

5 **6. Authors' contributions**

6

7 CC helped to conceive the study and design the trial, helped to analyse the data and to draft the
8 manuscript. AL performed all ultrasound measurements and supervised data collection. SR and LP helped to
9 analyse the data and to draft the manuscript. HDC and MB helped to provide statistical advice and to draft the
10 manuscript. All authors read and approved the final manuscript.

11

12 **7. Acknowledgements**

13

14 Not applicable

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15

1 **FIGURES LEGEND**

2

3 **Figure 1.** Principles of measurements of renal Doppler vascular index (RVI). (A) Visualization of proximal
4 interlobar arteries in color-Doppler mode. (B) Peak systolic velocity (V_{max}) and minimal diastolic velocity (V_{min})
5 determined by pulsed Doppler from three consecutive similar-appearing waveforms. RVI calculated as $(V_{max} -$
6 $V_{min})/V_{max}$ [10].

7

8 **Figure 2.** Relationship between creatinine clearance (Cl_{Cr}) and renal Doppler vascular index (RVI) at day 1 in 30
9 critically ill trauma patients. Correlations were assessed using Spearman correlation coefficient ($R^2 = 0.245$, $p =$
10 0.005).

11

12 **Figure 3.** A) ROC curves of RVI (continuous line, AUC = 0.742 [95%CI: 0.649 – 0.834]; $p < 0.0001$) and ARTIC
13 score (dotted line, AUC = 0.842 [95%CI: 0.771 – 0.913; $p < 0.0001$]) for predicting augmented renal clearance (p
14 = 0.049). B) The inconclusive grey zone of RVI is displayed as a grey rectangle for an RVI between 0.57 and 0.70
15 (64% of RVI measurements).

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Figure 1. Principles of measurements of renal Doppler vascular index (RVI). (A) Visualization of proximal interlobar arteries in color-Doppler mode. (B) Peak systolic velocity (V_{\max}) and minimal diastolic velocity (V_{\min}) determined by pulsed Doppler from three consecutive similar-appearing waveforms. RVI calculated as $(V_{\max} - V_{\min})/V_{\max}$ [19].

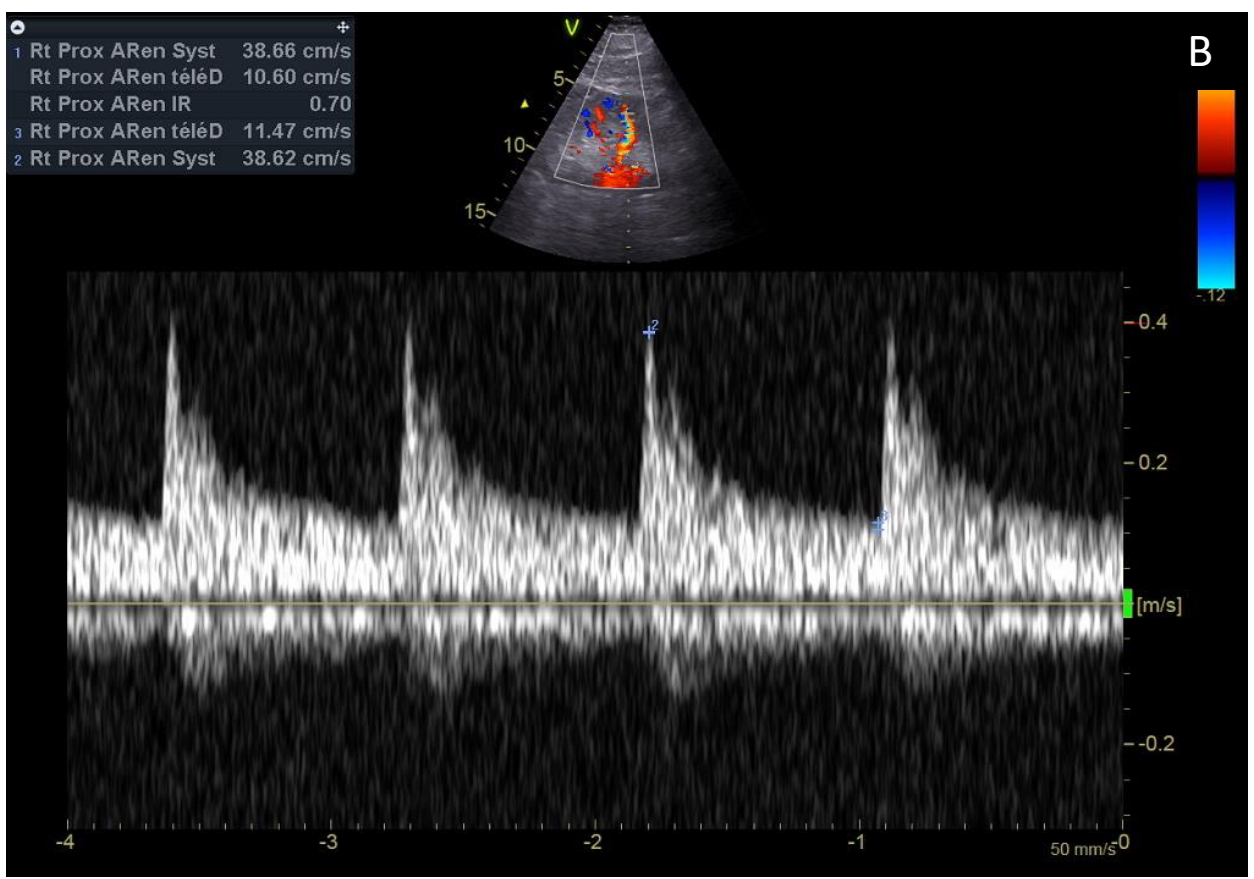
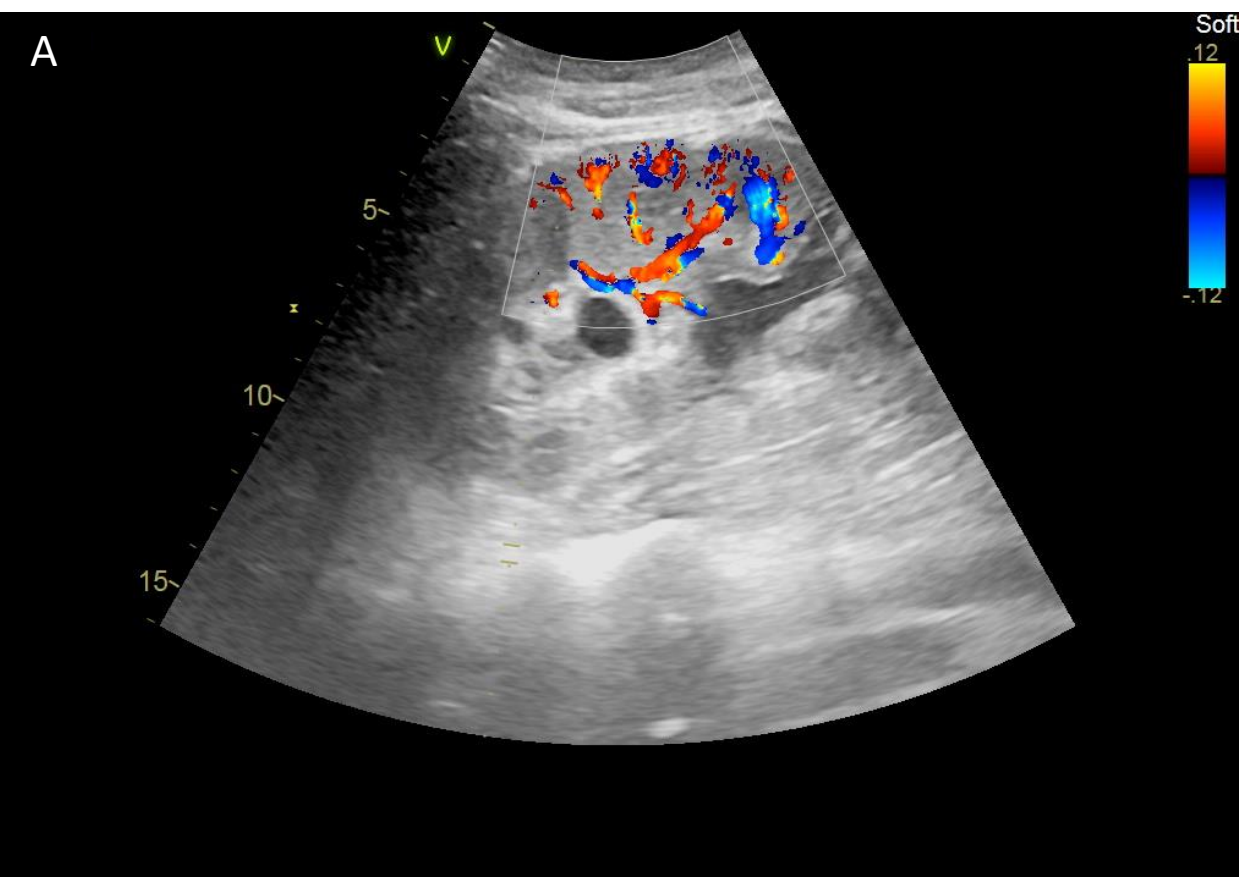


Figure 2. Relationship between creatinine clearance (Cl_{Cr}) and renal Doppler vascular index (RVI) at day 1 in 30 critically ill trauma patients. Correlations were assessed using Spearman correlation coefficient ($R^2 = 0.245$, $p = 0.005$).

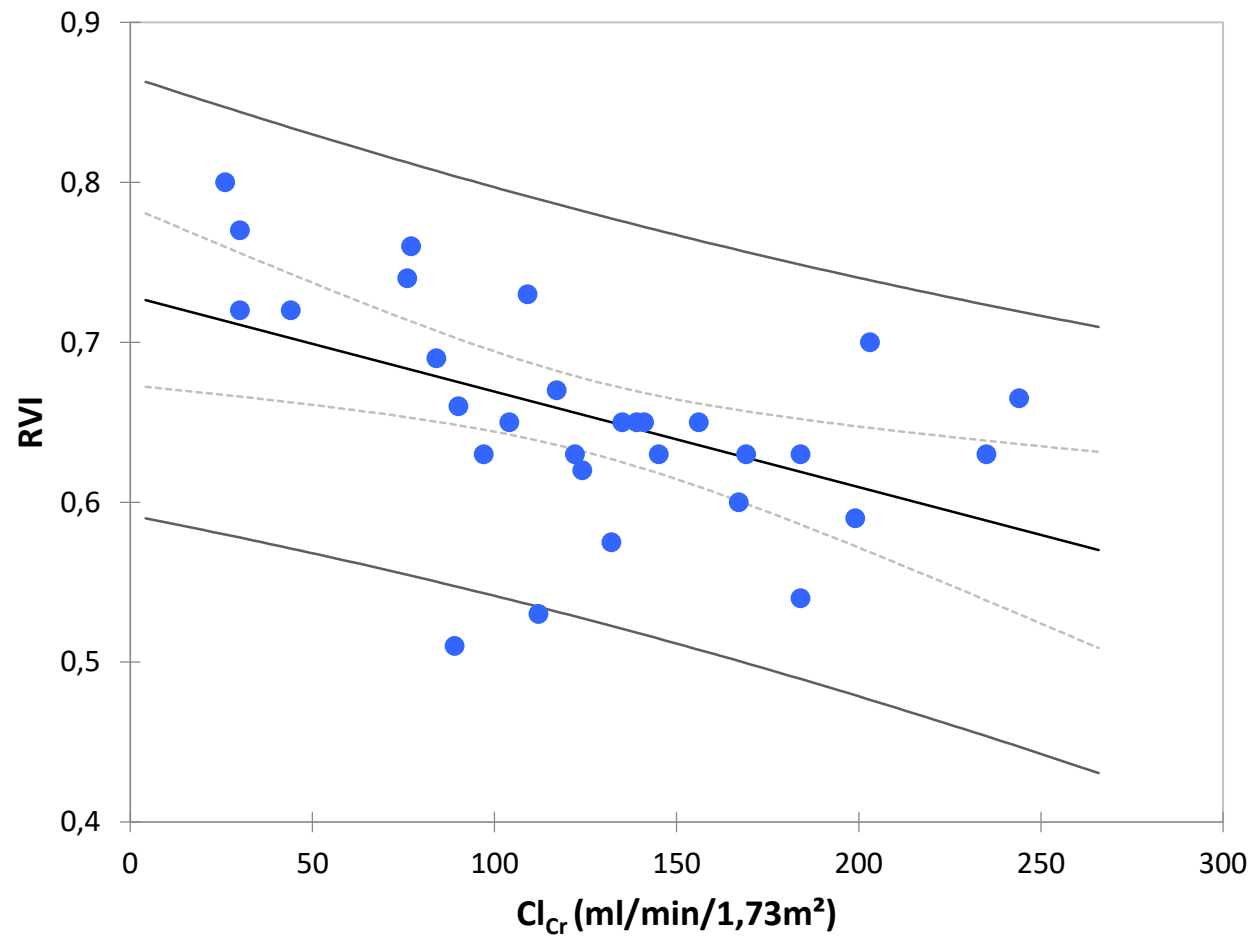


Figure 3. A) ROC curves of RVI (continuous line, AUC = 0.742 [95%CI: 0.649 – 0.834]; $p < 0.0001$) and ARTIC score (dotted line, AUC = 0.842 [95%CI: 0.771 – 0.913; $p < 0.0001$]) for predicting augmented renal clearance ($p = 0.049$). B) The inconclusive grey zone of RVI is displayed as a grey rectangle for an RVI between 0.57 and 0.70 (64% of RVI measurements).

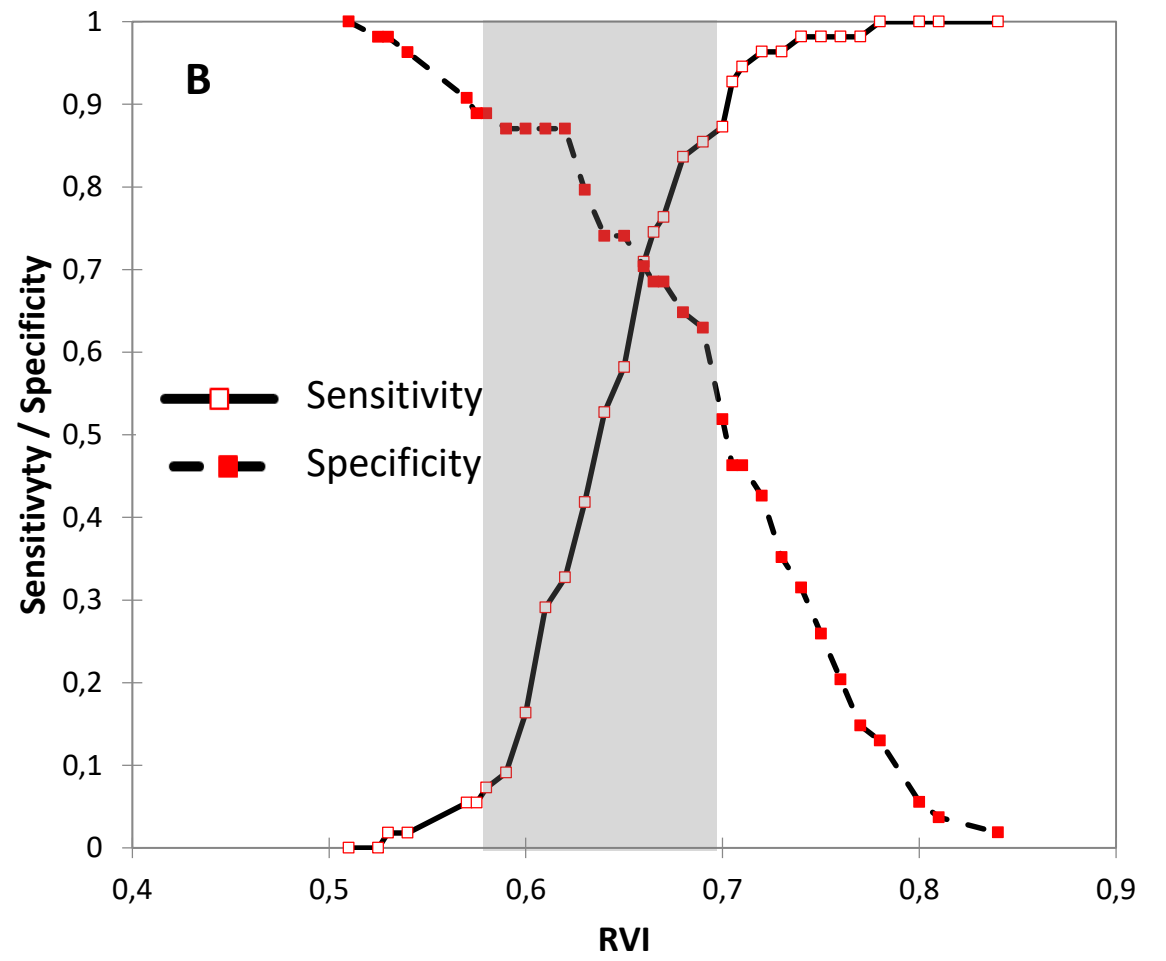
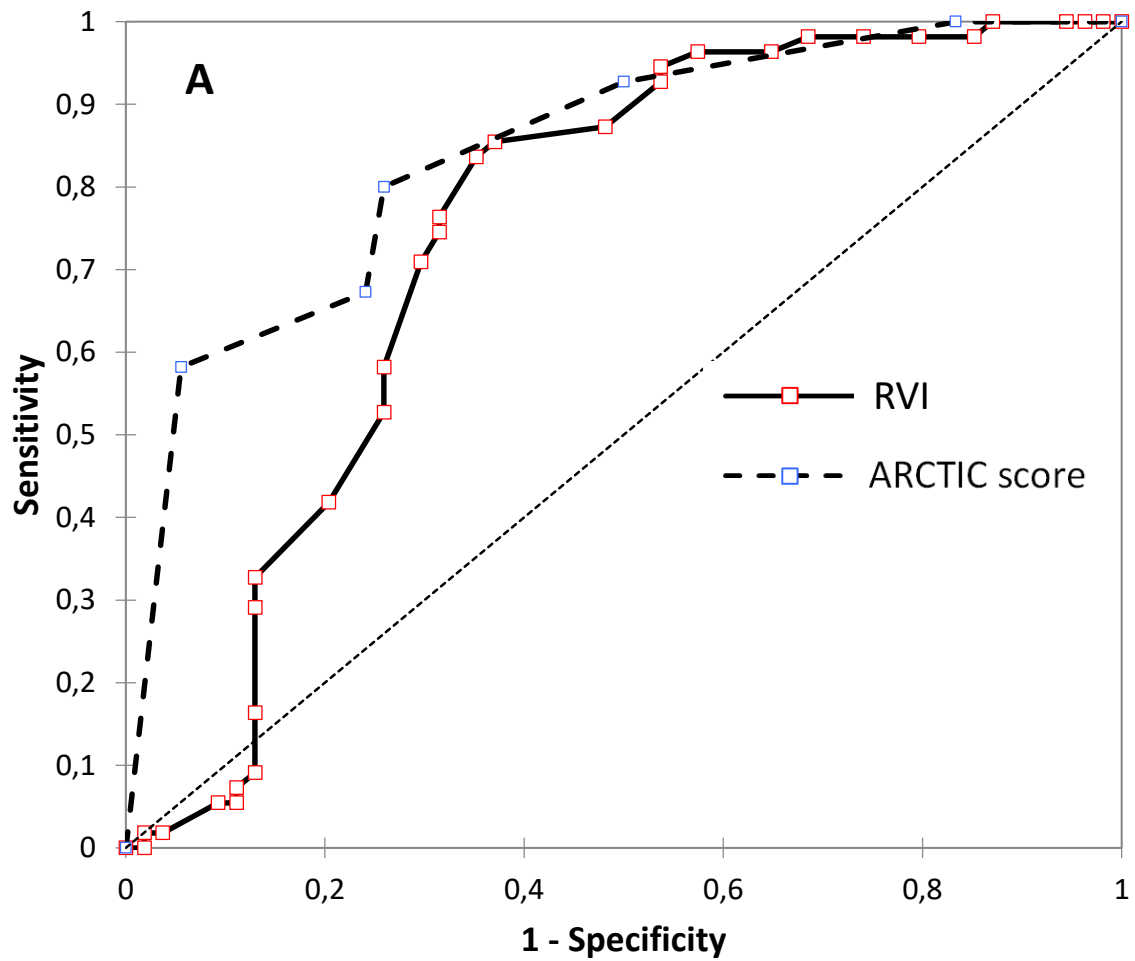


Table 1. Characteristics of the population

	Overall (N = 30)	Non ARC patients (N = 10)	ARC patients (N = 20)	p
Demographic data				
• Age	48 [32 – 67]	69 [66 – 84]	37 [29 – 54]	0.002
• Male sex	27 (90)	10 (100)	17 (85)	0.197
• Body Mass Index (kg/m ²)	26 [22 – 29]	27 [23 – 30]	26 [21 – 28]	0.416
Reason for admission				
• Multiple trauma with brain trauma	13 (43)	4 (40)	9 (45)	0.794
• Isolated brain trauma	9 (30)	4 (40)	5 (25)	0.398
• Multiple trauma without brain trauma	8 (27)	2 (20)	6 (30)	0.559
SAPS II at ICU admission	42 [22 – 49]	50 [46 – 54]	31 [19 – 42]	0.0003
ISS	34 [29 – 50]	46 [29 – 57]	32 [28 – 42]	0.184
Mechanical ventilation at ICU admission	22 (73)	7 (70)	15 (75)	0.770
Norepinephrine at ICU admission	14 (47)	6 (60)	8 (40)	0.301
Median duration for norepinephrine infusion	1 [0 – 2]	1 [0 – 1]	1 [0 – 2]	0.697
Median values from day 1 to 5				
• Serum creatinine (μmol/L)	58 [50 – 79]	84 [56 – 106]	55 [46 – 65]	0.019
• 24-hr urinary Cr _{cl} (ml/min/1.73m ²)	127 [84 – 170]	64 [46 – 94]	157 [131 – 192]	< 0.0001
• RVI	0.65 [0.61 – 0.70]	0.72 [0.67 – 0.75]	0.63 [0.60 – 0.67]	0.008
• CI (L/min)	2.59 [2.16 – 3.26]	2.48 [1.95 – 2.81]	2.63 [2.26 – 3.37]	0.344
• MAP (mmHg)	87 [80 – 97]	91 [81 – 103]	86 [75 – 94]	0.06
• ARCTIC score	7 [5 – 9]	5 [5 – 6]	8 [6 – 9]	< 0.0001
Length of stay in ICU	12 [8 – 17]	14 [8 – 17]	12 [9 – 15]	0.203
Death in ICU	3 (10)	2 (20)	1 (5)	0.197

Results expressed in numbers (percentages) or median [25% to 75% interquartile range]. ARC patients = patients who manifested ARC ($Cr_{cl} > 130$ ml/min/1.73m²) on at least one occasion during the first five study days [1]. CI = Cardiac Index; Cr_{cl} = Creatinine Clearance; ICU = Intensive Care Unit; ISS = Injury Severity Score; MAP = Mean Arterial Pressure; RVI = Renal Vascular Index; SAPS = Simplified Acute Physiologic Score