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Splenic and Renal Doppler Resistive Indices for Early Detection of Hypoperfusion in Septic Shock Patients: A Prospective Observational Study

Ahmed Mostafa[1], Mohamed Barwa[1], Amr Elhadidy[1], Mohamed Abouelwafa[1]*

[1]*Department of Critical Care Medicine, Faculty of Medicine, Cairo University, Cairo, 11956, Egypt.*

Abstract

One of the circulatory shock symptoms is hypoperfusion, which reflects an imbalance in oxygen supply and demand. microcirculatory dysfunction may continue even when macrocirculatory parameters improve, so monitoring microcirculatory parameters in situations of circulatory shock may be essential for improving treatment. 120 sepsis patients at the Critical Care Department, Kasr El-Ainy Hospitals, Cairo University meeting the inclusion/exclusion criteria were enrolled in the study. Abdominal ultrasound and sonographic assessment of renal and splenic perfusion measuring RDRI and SDRI were done for the enrolled participants The goal of this study was to assess the impact of RDRI and SDRI in the early prediction of hypoperfusion in sepsis patients and to determine the cut-off value for hypoperfusion. Multivariate logistic regression analysis was performed. There was a significant relationship between APACHE scores, SOFA scores, mortality rates, serum lactate levels, and CO_2 gap values to the values of RDRI and SDRI. The best cutoff value for detection of perfused patients' pre-resuscitation using RDRI pre <0.755 with sensitivity=100% and specificity=98.5%. While the best cutoff value for detection of perfused patients' pre-resuscitation using SDRI pre <0.74 with sensitivity=98.2% and specificity=98.5%. The best cutoff value for detection of perfused patients' post-resuscitation using RDRI post <0.75 with sensitivity=98.8% and specificity=100%. The best cutoff value for detection of perfused patients post resuscitation using splenic artery RI pre <0.71 with sensitivity=97.6% and specificity=100%. RDRI and SDRI are surrogate markers of overall tissue perfusion. In addition, their combination with CO_2 gap, SVO_2, and serum lactate is more significant in predicting clinical outcomes than each one index separately.

Keywords: Renal Doppler Resistive Index, Spleen Doppler Resistive Index, Hypoperfusion, Septic patients, ICU, Quality of life.

Full length article **Corresponding Author*, e-mail: *mohamedbarwa@Kasralainy.edu.eg*

1. Introduction

Circulatory shock is a clinical condition characterized by clinical and biochemical tissue hypoperfusion, resulting in insufficient oxygen consumption by cells, with or without low blood pressure (systolic blood pressure < 95 mmHg). One of its symptoms is hypoperfusion which reflects the global metabolic and circulatory effects of an imbalance in oxygen supply and demand. Clinical indicators of shock are typically seen when three body windows are examined, notably the skin, kidneys, and brain. Examples of biochemically sensitive and reliable traditional criteria for the early detection of hypoperfusion are serum lactate level (hyperlactemia), a decreased mixed or central venous oxygen saturation ($SvCO_2$, SvO_2), and an elevated veno-arterial carbon dioxide difference (the "pCO_2-gap") [1]. In cases of septic shock, goal-directed therapy has been used to monitor macrohemodynamic targets like blood mean arterial pressure, cardiac output, peripheral resistance, etc. Although macro-circulatory variables may have improved or maintained, microcirculatory dysfunction has been shown to occasionally continue and change, initially showing up as hypoperfusion and subsequently as cryptic shock [1]. Because microcirculatory dysfunction may continue even when macro-circulatory parameters improve, monitoring microcirculatory parameters in situations of circulatory shock may be essential for improving treatments [2]. Recent ultrasound applications that attempt to evaluate visceral end-organ perfusion may help to better understand this facet of shock pathogenesis. Splanchnic organs (kidneys, spleen, liver, etc.) make up only 10–12% of the total body weight but they receive a significant amount (up to 40%) of the total cardiac output during resting hemodynamic conditions. This aspect of shock pathophysiology may be better understood through ultrasound applications that try to evaluate visceral end-organ perfusion.

Evaluation of regional splanchnic hemodynamics by color Splenic Doppler resistive index (SDRI) and Renal Doppler resistive index (RDRI) is a useful method for identifying early hemodynamic abnormalities associated with organ dysfunction before the occurrence of biochemical or macrohemodynamic changes [3–5]. The goal of this study was to assess the impact of RDRI and SDRI in the early prediction of hypoperfusion in sepsis patients and to determine the cut-off value for hypoperfusion.

2. Materials and Methods

Between October 2021, and October 2022, 120 sepsis patients at the Critical Care Department, Kasr El-Ainy Hospitals, Cairo University meeting the inclusion/exclusion criteria were enrolled in the study. Patients who were 16 years or older with sepsis defined according to Surviving Sepsis Campaign 2021 sepsis: Suspected or documented infection in addition to an increase in SOFA score 2 points or more from the baseline were eligible. Patients who meet the defined exclusion criteria were excluded from participation: (i) Other causes of shock (ii) Renal artery stenosis, (iii) Morbid obese patients with BMI >35. All enrolled patients were subjected to a full medical history, a complete physical examination including vital signs, central venous pressure, and urine output, and laboratory tests. Two scoring systems; the Acute Physiology and Chronic Health Evaluation II (APACHE II) score and the Sequential Organ Failure Assessment (SOFA) score were used for ICU mortality estimation. The characteristics of the patients and their data are shown in Table 1. Abdominal ultrasound and sonographic assessment of renal and splenic perfusion measuring RDRI and SDRI were done for the enrolled participants on admission using a 2-5 MHz phase array transducer, provided with a color-pulsed wave doppler device US equipment (GE LOGIQ). According to the urine output assessment, patients were categorized into hypoperfused and perfused groups. Those with hypoperfused status (low urine output) were subjected to resuscitation either as fluid responders only or as fluid non-responders (vasopressor). For the fluid responders, boluses of 300-500 cc of normal saline over 20 minutes were administered according to the patient's condition until non-responding. For fluid non-responders, initiating or increasing doses of vasopressors (Noradrenaline) for hemodynamic support was administered according to clinical condition. The RDRI and SDRI sonographic assessments were taken on the patient's admission, pre-resuscitation, and post-resuscitation. The RDRI and SDRI measurements were compared to assess the cut-off point for the differentiation between the perfused and hypoperfused patients. The study was approved by the local ethics committee of Cairo University and all patients meeting the inclusion criteria gave written informed consent. The statistical software for the social sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA) was used to code and enter the data. For quantitative data, the mean, standard deviation, median, minimum, and maximum were used; for categorical data, frequency (count) and relative frequency (%) were used. The non-parametric Kruskal-Wallis and Mann-Whitney tests were used to compare quantitative variables. The non-parametric Friedman and Wilcoxon signed rank tests were employed to compare serial measurements within each patient (Chan, 2003a). Using the Chi-square test, categorical data were compared. The Spearman correlation coefficient was used to determine correlations between quantitative variables (Chan, 2003c). The trial was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The trial was approved by the Research Ethics Committee (REC) of the Faculty of Medicine, Cairo University (NO.: MD-75-2021 on 28/4/2021). Informed consent was obtained from all individual participants.

3. Results and Discussion

The biochemical predictors of the hypoperfusion were significantly different between the perfused and hypoperfused patients. As shown in Table 2, there was a statistically significant difference between both groups regarding the Apache II score and its estimated mortality with p-value <0.001. Serum lactate level, SVO_2, and CO_2 gap exhibited a statistically significant difference between both groups with p-value <0.001.

3.1. RDRI Pre/ Post Resuscitation

There was a statistically significant difference regarding RDRI pre-resuscitation in both perfused and hypoperfused patients as 0.57 ± 0.10 and 1.08 ± 0.25 for each group, respectively (P value <0.001). Also, there was a statistically significant difference regarding RDRI post-resuscitation in both perfused and hypoperfused patients as 0.59 ± 0.08 and 1.18 ± 0.26 for each group, respectively (P value <0.001) with a maximum value of RDRI 0.74 and 1.61 in perfused and hypoperfused patients, respectively (Table 3). It is worth noting that some patients shifted from hypoperfused to perfused post-resuscitation explaining RDRI value of 1.42 in perfused patients' pre-resuscitation. Figure 1 represents a case of a 53-year-old female admitted with Urinary tract infection and severe dehydration with RDRI during hypoperfusion measured at 1 pre-resuscitation and 0.67 post-resuscitation with fluids and improvement of urine output.

3.2. SDRI Pre/ Post Resuscitation

There was a statistically significant difference regarding SDRI pre-resuscitation in both perfused and hypoperfused patients as 0.57 ± 0.08 and 1.07 ± 0.24 for each group, respectively (P value <0.001). Also, there was a statistically significant difference regarding SDRI post-resuscitation in both perfused and hypoperfused patients as 0.60 ± 0.07 and 1.17 ± 0.24 for each group, respectively (P value <0.001) with a maximum value of SDRI 0.74 and 1.60 in perfused and hypoperfused patients, respectively (Table 3). It is worth noting that some patients shifted from hypoperfused to perfused post-resuscitation explaining SDRI value of 1.30 in perfused patients' pre-resuscitation.

3.3. Statistical Relationship of RDRI, SDRI with Biochemistry Parameters

As shown in Table 4, patients with higher APACHE scores, SOFA scores, and higher mortality rates have a significantly higher value of RDRI and SDRI with p-values <0.001. Additionally, significantly higher values of RDRI and SDRI in the group of patients with higher serum lactate levels, p-value < 0.001 (Figure 2**).** The statistical analysis revealed that larger CO2 gap values and is associated with significantly higher values of RDRI and SDRI, with p-value < 0.001.

Figure 3 describes the relationship between nephropathy grade and RDRI numbers. The higher the nephropathy grade, the higher the RDRI values with p-values of 0.013 and 0.026 for patients' pre-resuscitation and post-resuscitation, respectively.

3.4. Cutting-off Values of RDRI and SDRI Pre-resuscitation

The best cutoff value for detection of perfused patients' pre-resuscitation using RDRI pre <0.755 with sensitivity=100% and specificity=98.5%. The area under the curve = 100% (95% CI: 99.9% to 100%). While the best cutoff value for detection of perfused patients' pre-resuscitation using SDRI pre <0.74 with sensitivity=98.2% and specificity=98.5%. The area under the curve (AUC= 99.4% (95% CI:98.1% to 100%) as shown in Table 5 and Figure 4.

3.5. Cutting-off Values of RDRI and SDRI Post-resuscitation

The best cutoff value for detection of perfused patients' post-resuscitation using RDRI post <0.75 with sensitivity=98.8% and specificity=100%. The area under the curve (AUC) = 100% (95% CI:99.9% to 100%). The best cutoff value for detection of perfused patients post resuscitation using splenic artery RI pre <0.71 with sensitivity=97.6% and specificity=100%. The area under the curve (AUC) = 99.4% (95% CI:99.8% to 100%). Targeted therapies in the case of circulatory shock have focused on the improvements of the macrocirculatory hemodynamic targets like cardiac output, peripheral resistance, mean arterial blood pressure, and others. However, despite improvement or stability of macrocirculatory targets, cases of microcirculatory dysfunction have been found and reported to persist and change as hypoperfusion and then shock. Thus, managing microcirculatory parameters in cases of circulatory shock may be crucial for optimizing treatments and ICU patient's quality of life [1-2]. In this study, there was a statistically significant difference regarding RDRI in both perfused and non-perfused patients with a maximum value for RDRI 0.755 in perfused patients with p-value <0.001.

The best cutoff value for detection of perfused using RDRI <0.755 with sensitivity=100%, specificity=98.5%, and AUC =100% (95% CI:99.9% to 100%). These results are in alignment with the study conducted by Dewitte et al. [6]. The authors claimed that RDRI > 0.75 was sensitive in detecting occult hypovolemic shock associated with hypoperfusion in 96 patients. Furthermore, Rozemeijer et al. discussed in a study conducted on 92 patients with RDRI cut-off mean value of 0.751 for hypoperfusion, that compared to patients without shock, people with shock have greater RDRI values [7]. Low membrane capacitance, preadmission renal impairment, and systemic circulation pressure indices were independent predictors of increased RDRI. Slight differences in the cut-off value between our RDRI results and other studies' results were reported as well. For instance, Corradi et al conducted a study on 49 patients when peripheral arterial oxygenation was normal, RDRI > 0.7 identifies organ-specific supply and demand imbalances, showing an early vascular response to systemic tissue hypoxia, similarly, in a prospective cohort study done by Haitsma Mulier et al. [8]. RDRI of 0.70 was set as the cut-off value for hypoperfusion in 99 mixed ICU patients with or without shock [9]. A case report published by Anile et al. considered RDRI > 0.7 very sensitive in detecting occult hypovolemic shock in postoperative patients [10]. Fotopoulou et al discussed the cut-off value of RDRI for hypoperfusion as 0.70 suggesting that RDRI could detect overall tissue hypoperfusion and provides evidence for the novel concept of the ultrasound-based assessment of visceral end-organ perfusion in septic patients [11]. Our RDRI results suggest that the reproducibility and repeatability of RDRI are often sufficient, if not superior. When measurements were made by skilled personnel, the range of intra-observer variability was 2.07 to 5.1 percent, whereas the range of interobserver variability was 3.61 to 6.2 percent. Variations in RDRI values between 0.02 and 0.04 between observers, including intra- and inter-observer, should be considered negligible [12].

That could account for the small difference in cut-off value between our results and other reported results. Furthermore, the utility of RDRI in clinical practice is limited by the knowledge of all renal and extra-renal pathophysiological factors that can interact to affect RDRI values differently in different individuals. On the other hand, SDRI in our study showed a statistically significant difference in both perfused and non-perfused patients with a maximum value for SDRI 0.74 in perfused patients with P-value <0.001. So, the best cutoff value for detection of perfused using SDRI <0.74 with sensitivity=98.2%, specificity=98.5%, and AUC =99.4% (95% CI:98.1% to 100%). This goes with the study done by Brusasco et al, with a slight difference in cutoff value, the study conducted on 49 patients considered SDRI > 0.71 to be very sensitive in detecting occult hypovolemic shock and can titrate the adequacy of resuscitation targeting persistent occult hypoperfusion in polytrauma patients [13]. The authors recommend the diagnostic value of RDRI and SDRI in the context of using ultrasonographic RDRI and SDRI as guidance for early detection of hypoperfusion and improvement of hemodynamics not alone but supported by other clinical and ultrasonographic measures. Also, RDRI and SDRI could be used as guidance for the improvement of hemodynamics and perfusion with serial measurements and reduction in their values to nearly perfused cut-off values with other clinical data and ultrasonographic measures like LVOT VTI or IVC collapsibility. The prognostic value of RDRI and SDRI is suggested as the applicability of RDRI and SDRI in the early estimation of critically ill patients guided by other scores of mortality estimation. Limitations of this study involve the relative novelty of the technique lies in the lack of a uniform cut-off value for the diagnosis. The patient has to comply and hold his breath for the sonographer to see the best path for the renal artery. If the critically ill patient is unable to hold his breath, it will be difficult to set an accurate Doppler signal. Confounding factors like age and abnormal arterial stiffness, which may have affected RDRI and SDRI weren't included in the study design. Finally, the recording period was relatively short because the aim was to study acute physiological responses to hypoperfusion and fluid challenge, thus possibly missing late physiological responses due to fluid balance restoration or fluid redistribution.

Table 1: Patient characteristics and parameters.

Patient (n=120) Characteristics	Mean			
Age	61.06			
Sex	Male = 67		Female = 53	
CKD	Yes = 16		No = 104	
Nephropathy grade	0 = 47	1 = 14	2 = 45	3 = 14
SOFA estimated mortality %	<33 % = 77	50% = 25	>95% = 18	
Urine Output Pre-resuscitation	Yes = 55		No = 65	
Urine Output Post-resuscitation	Yes = 82		No = 38	
Mortality	Yes = 54		No = 66	

Table 2: Data and Biochemistry Parameters of Perfused and Hypoperfused Patients.

Parameter	Perfused Group	Hypoperfused Group	*P*-Value
Age	58.63 ± 16.98	66.29 ± 11.06	0.021
APACHE score	16.33 ± 6.87	23.16 ± 4.97	<0.001
APACHE estimated mortality %	26.81 ± 16.41	43.61 ± 14.78	<0.001
Lactate (mmol)	2.98 ± 2.57	6.68 ± 3.59	<0.001
SVO_2	59.68 ± 10.46	53.18 ± 11.04	<0.001
CO_2 Gap	5.17 ± 1.26	6.58 ± 1.59	<0.001

Table 3: RDRI and SDRI values in both groups.

	Perfused			Hypoperfused			P value
	Mean	Minimum	Maximum	Mean	Minimum	Maximum	
RDRI pre-resuscitation	0.57± 0.10	0.31	0.75	1.08±0.25	0.75	1.63	<0.001
RDRI post-resuscitation	0.59±0.08	0.35	0.74	1.18±0.26	0.76	1.61	<0.001
SDRI pre-resuscitation	0.57±0.08	0.37	0.72	1.07±0.24	0.72	1.66	<0.001
SDRI post-resuscitation	0.60±0.07	0.38	0.74	1.17±0.24	0.72	1.60	<0.001

Table 4: RDRI, SDRI, and Microcirculatory Relation (n=120).

		RDRI pre-resuscitation	RDRI post-resuscitation	SDRI pre-resuscitation	SDRI post-resuscitation
APACHE score	**Correlation Coefficient**	0.413	0.442	0.415	0.464
	P value	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
APACHE estimated mortality %	**Correlation Coefficient**	0.463	0.442	0.460	0.469
	P value	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
SOFA score	**Correlation Coefficient**	0.460	0.531	0.462	0.535
	P value	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
Lactate (mmol)	**Correlation Coefficient**	0.472	0.487	0.471	0.492
	P value	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
CO_2 gap	**Correlation Coefficient**	0.393	0.357	0.374	0.459
	P value	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
Nephropathy grade	**Correlation Coefficient**	0.227	0.204	-	-
	P value	0.013	0.026	-	-

Table 5: Logistic Regression Models of RDRI and SDRI Cut-off Values Pre-resuscitation.

	AUC	P-value	95% Confidence Interval		Cut off	Sensitivity %	Specificity %
			Lower Bound	Upper Bound			
RDRI pre-resuscitation	1.000	< 0.001	0.999	1.000	0.755	100	98.5
RDRI post-resuscitation	0.910	< 0.001	0.861	0.959	0.665	92.7	75.4
SDRI pre-resuscitation	0.994	< 0.001	0.981	1.006	0.74	98.2	98.5
SDRI post-resuscitation	0.937	< 0.001	0.898	0.977	0.645	85.5	86.2

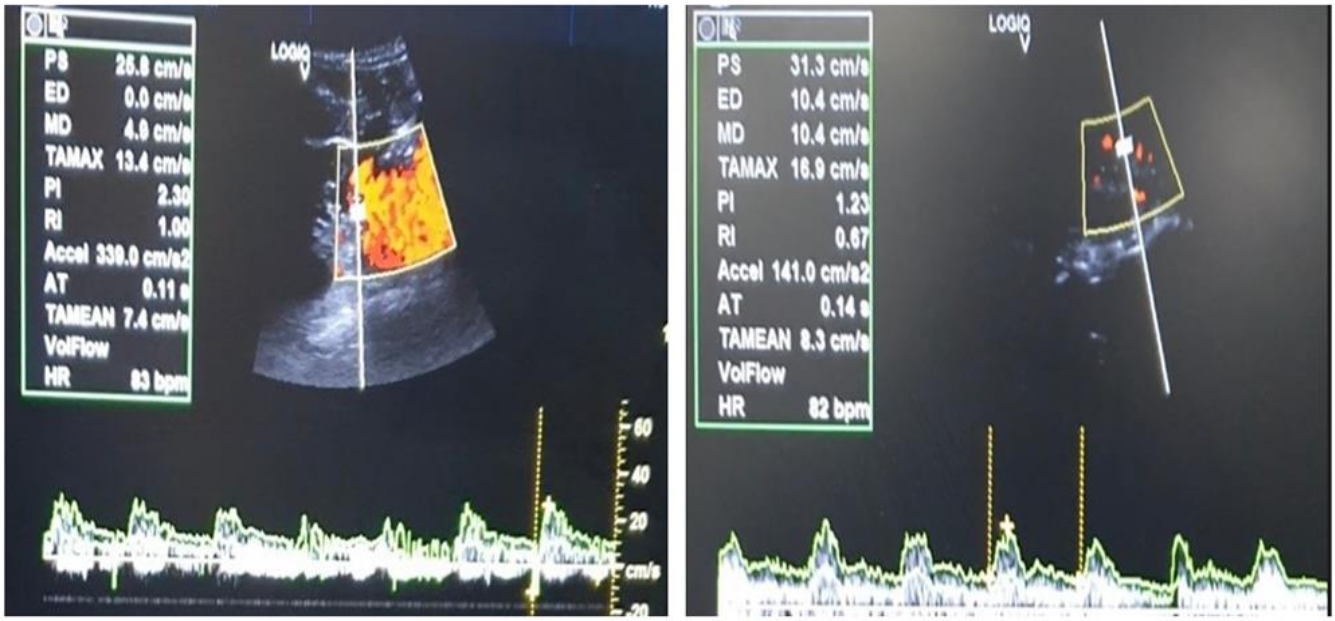

Figure 1: Sonographic image in a perfused patient post-resuscitation (hypoperfused pre-resuscitation) representing (a) RDRI of 1.00 pre-resuscitation and (b) RDRI of 0.67 post-resuscitation.

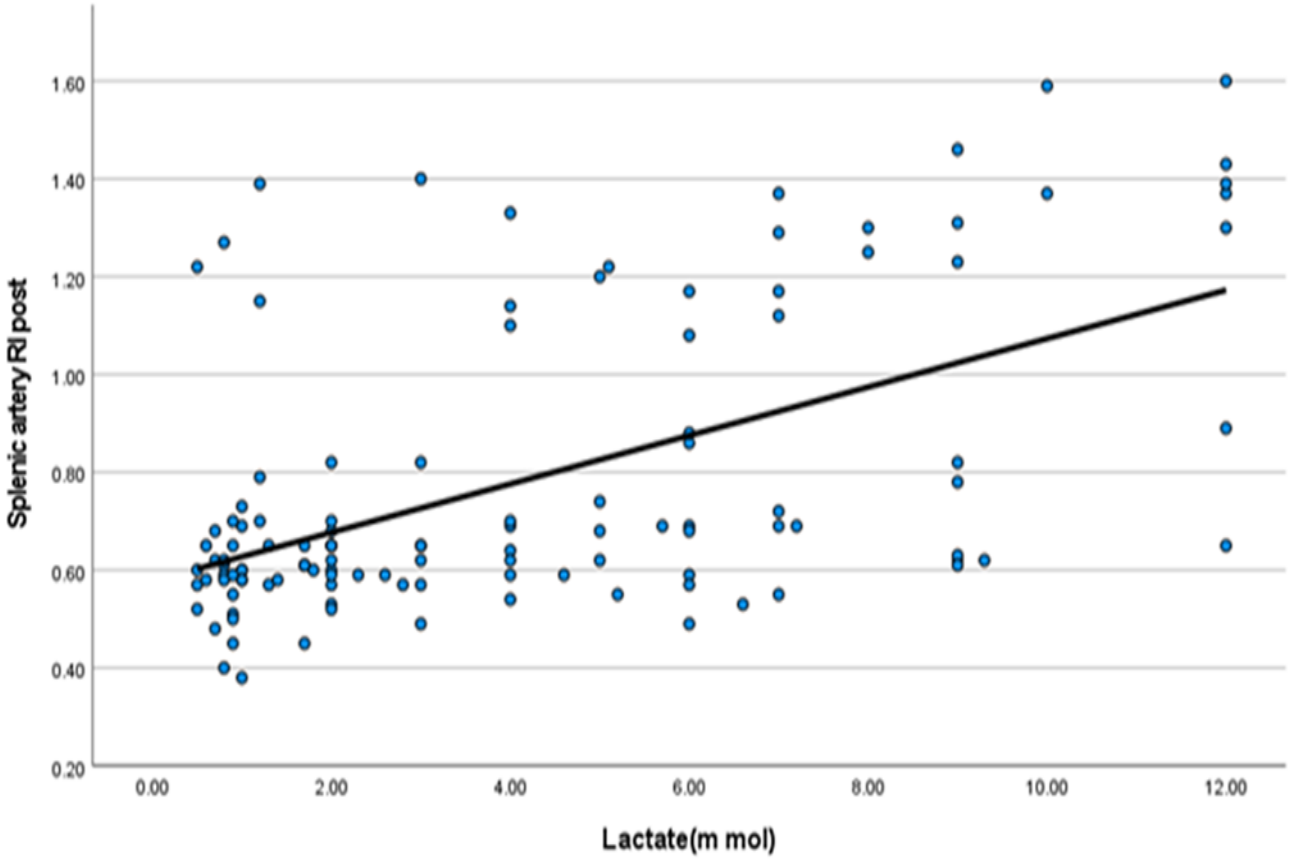

Figure 2: Serum Lactate Level and SDRI.

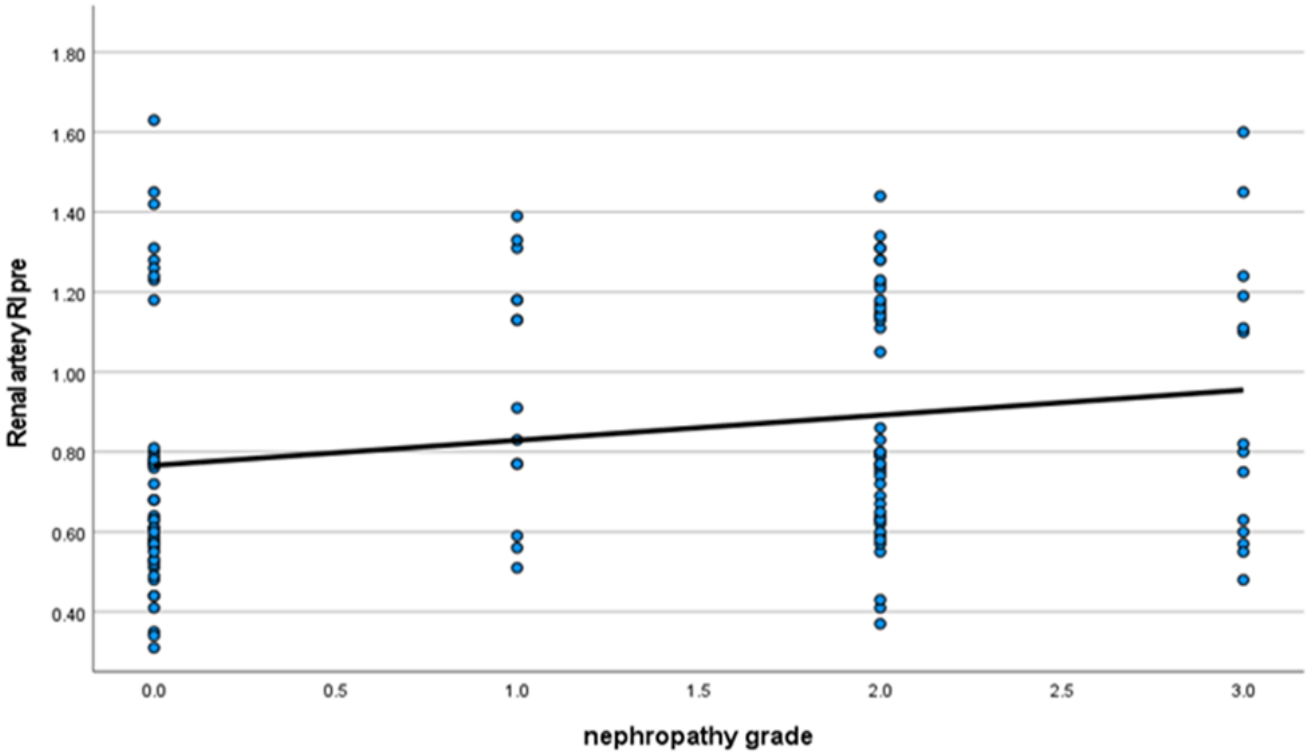

Figure 3. Nephropathy grade and RDRI.

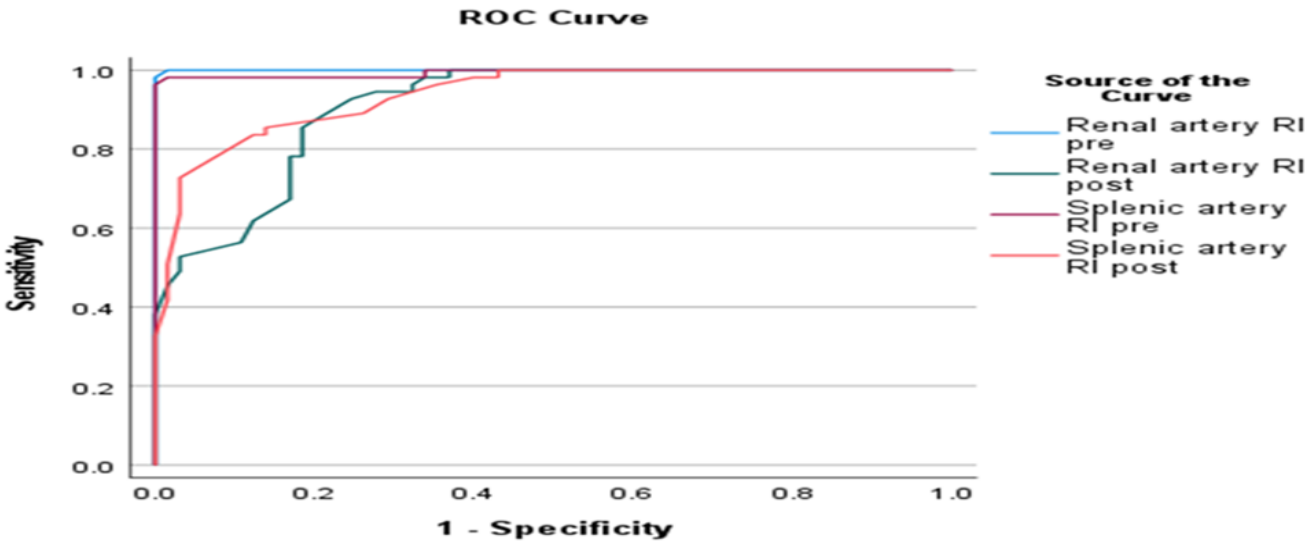

Figure 4: ROC Curve for RDRI and SDRI Cut-off Values Pre-resuscitation.

4. Conclusions

For summation, we have shown that RDRI and SDRI are surrogate markers of overall tissue perfusion. In addition, their combination with CO_2 gap, SVO_2, and serum lactate is more significant in predicting clinical outcomes than each one index separately. Hence, RDRI and SDRI could provide a potential warning for additional monitoring needs and for guiding the clinical management aiming at a better outcome for critically ill patients. Further studies investigating the role of RDRI and SDRI in ICU are necessary.

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Disclosure statement
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Authors Contribution
All authors have contributed equally

Availability of data and materials
The data sets during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval Statement
The Research Ethics Committee (REC) of the Faculty of Medicine, Cairo University has reviewed and approved the mentioned protocol, approval number MD-75-2021 on 28/4/2021.

Participation Consent
Informed consent was obtained from all individual participants included in the study.

Publication Consent
The authors affirm that human research participants provided informed consent for the publication of the images in the intended figures.

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