

Relationship Between Shock Index and Serum Cystatin C Values with the Incidence of Acute Kidney Injury in Critical Patients with Vasodilation Shock at Dr. Soetomo Hospital, Surabaya

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KEYWORDS

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y shock

ABSTRACT:

Introduction: Acute kidney injury (AKI) is linked to a higher death rate in individuals experiencing vasodilatory shock exceeding 50%. Early detection and intervention are very important in improving prognosis. Some promising tests for early diagnosis of acute kidney injury are serum Cystatin C (CysC) and shock index (SI). **Objectives:** The main focus of this research is to examine the possibility of early diagnosis of AKI using serum CysC biomarkers in critically ill patients with vasodilatory shock compared with shock index. **Methods:** This cross-sectional study with a simple random method involves 36 samples which included adult patients with critical illness with vasodilatory shock who were treated in ICU of Dr. Soetomo Hospital, Surabaya. **Results:** There is a significant association between SI and delta creatinine ($r=0.352$; $p=0.035$); between serum Cystatin C and delta creatinine ($r=0.535$; $p=0.001$); and between SI and AKI incidence ($r=0.432$; $p=0.034$). While the relationship test between serum Cystatin C and AKI incidence was not significant ($r=0.025$; $p=0.449$). ROC curve test showed that the SI had an AUC of 0.725 with a sensitivity of 55.0% and a specificity of 81.25% while serum Cystatin C had an AUC of 0.747 with a sensitivity of 60.0% and a specificity of 93.75%. **Conclusions:** Shock index and serum Cystatin C could serve as valuable early indicators for anticipating AKI occurrences in critical patients experiencing vasodilatory shock. Cystatin C outperforms Shock Index in predicting AKI, showing superior results in terms of AUC, sensitivity, and specificity.

1. Introduction

Acute kidney injury (AKI) is a severe condition that significantly impacts patient morbidity and mortality (Febriyani et al., 2021). The traditional way to identify AKI is by looking for higher levels of serum creatinine and/or decreased urine production (Christin et al., 2023), reflecting a sharp decline in glomerular filtration rate (GFR). GFR, calculated using endogenous filtration markers like serum creatinine, remains a key indicator of kidney function in health and disease. However, serum creatinine as a diagnostic marker for AKI has limitations, including inaccuracies in specific populations (Anesthesia et al., 2018; Kister et al., 2023).

AKI associated with sepsis quadruples the mortality risk compared to non-AKI sepsis in critically ill patients (Prasetyawan et al., 2020). Notably, AKI in sepsis patients often manifests within 24 hours of ICU admission. Although serum creatinine remains the standard for diagnosing AKI, its levels may only rise days after kidney function has declined by 50%, leading to delayed detection and therapeutic intervention (Prasetyawan et al., 2020). At Dr. Soetomo Hospital in 2021, the AKI mortality rate in the ICU was 30.43%, predominantly affecting male patients aged 50–59 years (Febriyani et al., 2021). A study at Dr. Soetomo Hospital in 2023 reported a mortality rate of 41.2% among patients with vasodilatory shock and found that shock index values correlated with mortality (Prasetyawan et al., 2020). Vasodilatory shock involves activation of ATP-sensitive potassium channels, nitric oxide

production, and vasopressin deficiency (Lahiry et al., 2019). The shock index, obtained by dividing the HR by the SBP, proves to be a valuable tool for examining hemodynamic stability and forecasting patient outcomes in emergency cases (Pomalango, 2020).

In addition, recent studies have explored the utility of serum cystatin C (CysC) as an alternative biomarker for diagnosing and predicting AKI in critically ill patients. Serum CysC, a 13-kDa protein produced by nearly all nucleated cells, may provide a more accurate reflection of GFR than serum creatinine (Hong et al., 2022). Evidence suggests that CysC is a reliable and accurate indicator of kidney function (D. C. Chen et al., 2022; Z. Chen et al., 2021). Furthermore, CysC has been recognized as a more reliable indicator of kidney function and the likelihood of cardiovascular issues when compared to creatinine (Ogawa-Akiyama et al., 2018). Due to the importance of serum CysC in detecting and assessing the risk of AKI in critically ill individuals, the purpose of this research is to examine how the severity of shock, as indicated by the Shock Index (SI), correlates with serum CysC levels and how this relationship affects the occurrence of AKI in patients experiencing vasodilatory shock.

2. Objectives

The main focus of this study was to examine how serum Cystatin C levels and the shock index are connected in patients experiencing vasodilatory shock and their potential impact on the risk of developing AKI. The goal was to establish a possible correlation between elevated levels of serum Cystatin C and higher shock index values with an increased risk of developing AKI. The researchers aimed to uncover possible signs of kidney damage in patients experiencing vasodilatory shock by examining different factors. The objective was to enhance knowledge on how these markers could aid in forecasting and handling AKI in real-world medical settings. The investigation aimed to offer valuable perspectives that could support enhanced monitoring, prompt identification, and care of kidney issues in this particular group of patients.

3. Methods

This study was conducted as an observational analytic research with a cross-sectional design. The research took place in the intensive care unit (ICU) of Dr. Soetomo General Hospital, Surabaya. The study commenced in December 2023 and was projected to span six months, with an estimated completion by May 2024. The population of this study included all adult critically ill patients admitted to the ICU with vasodilation shock. Vasodilation shock was defined as a condition unresponsive to a minimum of 1000 mL of fluid administration and requiring vasopressor support at a dose of more than 0.1 µg/kg/min (Semedi et al., 2023).

The prevalence of AKI in critically ill patients was reported to be 60% in previous studies. The diagnostic performance of serum CysC in AKI showed a sensitivity of 84% and a specificity of 82% (Semedi et al., 2023). Hence, the required amount of data for this research was determined using the data provided. For both sensitivity and specificity estimations, a minimum of 31 Shock Index measurements was required for each. Allowing for a 10% dropout rate, the final sample size was determined to be 36 Shock Index measurements. The study employed a simple random sampling method to select eligible critically ill patients meeting the inclusion criteria.

Patients over the age of 18 who were suffering from vasodilation shock were eligible to participate in the research, based on specific outlined criteria. Those with a previous history of chronic kidney disease, prior consumption of nephrotoxic drugs, cancerous kidney conditions, or blockage in the urinary tract were not considered for inclusion. These strict standards were enforced to maintain consistency within the study group and minimize any variables that could impact the results.

The primary variables in this study were the Shock Index, serum CysC levels, and the incidence of AKI in critically ill patients with vasodilation shock. Shock Index was used as a measure of the severity of vasodilation shock. Serum CysC levels were evaluated as a biomarker for kidney function, and AKI incidence was assessed as the main clinical outcome. Several potential confounding variables were considered, including patient age, gender, body mass index, history of comorbidities, and use of medications that could influence kidney function.

Data were gathered and analyzed with SPSS version 26.0. Descriptive statistics were used to describe the Shock Index characteristics. Normality tests were conducted to check data distribution. Relationships between the Shock Index, serum CysC levels, and delta creatinine values were analyzed using Pearson or Spearman correlation tests, depending on data distribution. Logistic regression analysis was used to determine the relationship between the Shock Index, serum CysC levels, and the incidence of AKI. Diagnostic tests to establish optimal cut-off values for the Shock Index and serum CysC in predicting AKI were performed using Receiver Operating Characteristic (ROC) curve analysis. These methods were chosen to ensure a robust analysis of the data and to derive meaningful conclusions regarding the relationships between Shock Index, serum CysC levels, and AKI incidence in critically ill patients with vasodilation shock.

4. Results

Demographics of the Study

The study involved 36 participants, whose demographic characteristics are summarized in Table 1. Based on the Shapiro-Wilk normality test, the data for age, length of stay (LOS), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and Glasgow Coma Scale (GCS) did not follow a normal distribution ($p < 0.05$). In contrast, body weight (BW), height (HT), body mass index (BMI), and heart rate (HR) were normally distributed ($p > 0.05$).

Table 1: Demographic and Characteristics Data

Characteristics	n (%)	Range (Median)	Mean $\pm$ SD	p-value (normality)
Gender				
Male	25 (69.4%)	-	-	-
Female	11 (30.6%)	-	-	-
Age	36 (100%)	20–66 (57.5)	53.19 $\pm$ 12.56	<0.001
BW	36 (100%)	40–80 (60.0)	60.28 $\pm$ 10.76	0.317*
HT	36 (100%)	150–170 (160.0)	159.67 $\pm$ 5.03	0.073*
BMI	36 (100%)	15.63–35.56 (23.47)	23.65 $\pm$ 4.19	0.594*
LOS	36 (100%)	3–34 (8.50)	11.08 $\pm$ 7.92	<0.001
SBP	36 (100%)	77–92 (87.5)	86.19 $\pm$ 4.42	0.002
DBP	36 (100%)	43–53 (50.0)	49.00 $\pm$ 3.024	0.007
HR	36 (100%)	84–134 (110.0)	111.92 $\pm$ 11.66	0.309*
GCS	36 (100%)	244–456 (400.5)	394.86 $\pm$ 64.60	<0.000
MAP	36 (100%)	56–65 (61.5)	61.44 $\pm$ 2.27	0.039
Vasopressor				
Yes	36 (100%)	-	-	-
No	0 (0%)	-	-	-
28-days mortality				
Yes	11 (30.6%)	-	-	-
No	25 (69.4%)	-	-	-

*normal if p value >0.05

Shock Index

The shock index was calculated by dividing HR by systolic blood pressure. The normality test determined the appropriate statistical method for analysis; Parametric techniques were applied to data that followed a normal distribution, whereas non-parametric techniques were used for data that did not meet this criteria. The shock index ranged from 0.96 to 1.44, with a mean of 1.21 ± 0.12 . The Shapiro-Wilk normality test yielded a p-value of 0.679, indicating that the shock index data were normally distributed.

Cystatin C Levels

Cystatin C levels were measured using clinical laboratory methods, specifically nephelometry or turbidimetry. The levels ranged from 0.77 to 1.41, with a mean of 1.12 ± 0.18 . The Shapiro-Wilk normality test produced a p-value of 0.179, indicating that the data were normally distributed.

Delta Creatinine

Delta creatinine represents the change in creatinine levels from baseline to day two. Across the 36 samples, delta creatinine values ranged from -0.40 to 3.10. Negative delta creatinine values indicate a decrease in creatinine levels, while positive values indicate an increase. The Shapiro-Wilk normality test returned a p-value of 0.000, showing that delta creatinine data were not normally distributed.

Acute Kidney Injury (AKI)

AKI was established based on the KDIGO 2012 guidelines. These criteria involves an increase in serum creatinine levels of greater than 0.3 mg/dL within a 48-hour period or an increase to more than 1.5 times the baseline within the prior seven days. Baseline serum creatinine was defined as the level upon ICU admission. Among the 36 participants, 20 (55.6%) developed AKI, while 16 (44.4%) did not.

Association Between Demographics and AKI

Chi-square tests were used for categorical data, independent t-tests for normally distributed continuous data, and Mann-Whitney tests for non-normally distributed continuous data (Table 2). The analysis revealed that gender, age, BW, HT, and BMI were not significantly associated with AKI. Additionally, LOS, SBP, DBP, HR, MAP, GCS, and 28-day mortality were not significantly associated with AKI. These findings suggest that general demographic characteristics do not confound the occurrence of AKI.

Table 2: Demographic Characteristics with Acute Kidney Injury (AKI)

Demography	N	AKI		p value*
		Yes	No	
Gender				
Male	25	15 (60,0%)	10 (40,0%)	0,483
Female	11	5 (45,5%)	6 (54,5%)	
Age (Range Median)	36	20 – 66 (59,50)	24 – 64 (57,00)	0,577
Weight (Mean ± SD)	36	58,50 ± 9,93	62,50 ± 11,66	0,274
Height (Mean ± SD)	36	160,05 ± 4,08	159,19 ± 6,12	0,616
BMI (Mean ± SD)	36	22,81 ± 3,63	24,70 ± 4,71	0,184
LOS (Range Median)	36	3 – 28 (9,50)	4 – 34 (8,00)	0,936
SBP (Range Median)	36	78 – 92 (87,50)	77 – 90 (87,50)	0,576
DBP (Range Median)	36	43 – 53 (49,50)	44 – 53 (50,00)	0,328
Heart Rate (Mean ± SD)	36	112,45 ± 13,32	111,25 ± 9,57	0,755
MAP (Range Median)	36	56 – 64 (61,50)	56 – 65 (61,50)	0,723
GCS (Range Median)	36	244 – 456 (356)	334 – 456 (450,50)	0,359
Vasopressor				
Yes	36	20 (55,6%)	16 (44,4%)	-
No	0	0 (0,0%)	0 (0,0%)	
28 Day Mortality				
Yes	11	6 (54,5%)	5 (45,5%)	1,000
No	25	14 (56,0%)	11 (44,0%)	

*significant if p value >0.05

Association Between Shock Index and Cystatin C With Delta Creatinine

The relationship between shock index and Cystatin C with delta creatinine was assessed using Spearman correlation tests. Significant associations were found, with p-values of 0.035 and 0.001, respectively (Fig 1). The correlation coefficients (r-values) were 0.352 for shock index and 0.535 for Cystatin C, indicating a positive relationship between these variables and delta creatinine. The connection between shock index and delta creatinine was found to be lacking in strength, whereas the relationship between Cystatin C and delta creatinine was deemed to be of moderate level.

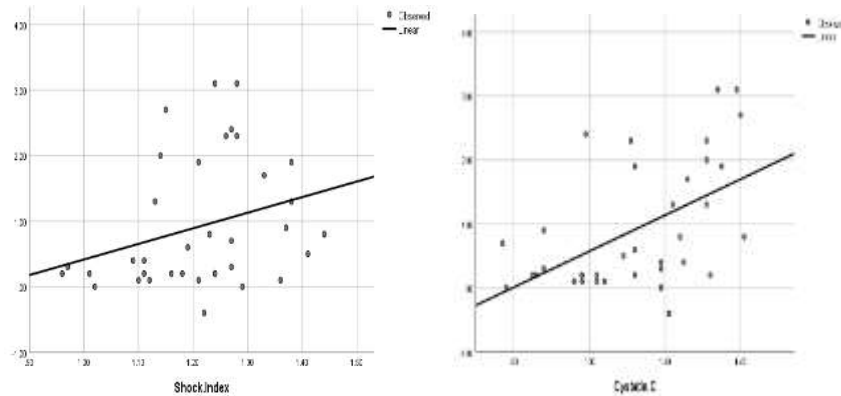


Figure 1: Scatter plot of shock index (left) and cystatin C (right) with delta creatinine.

Association Between Shock Index and Cystatin C With AKI

A logistic regression analysis was carried out to assess the correlation between shock index and Cystatin C with AKI. These factors include ratio and nominal categorical data. Table 3 presents the results, indicating significant associations with p-values of 0.034 for shock index and 0.025 for Cystatin C. The regression coefficients were 0.432 for shock index and 0.449 for Cystatin C, signifying a moderate relationship between these variables and AKI.

Table 3: Analysis of Association Between Shock Index and Cystatin C With AKI

	n	AKI		p value	r
		Yes (Mean±SD)	No (Mean±SD)		
Shock index	36	1.25±0.116	1.16±0.110	0.034	0.432*
Cystatin C	36	1.18±0.187	1.043±0.149	0.025	0.449*

*significant if p value >0.05

Diagnostic Analysis of Shock Index and Cystatin C for AKI

ROC curve analysis was employed to evaluate the diagnostic utility of shock index and Cystatin C for AKI (Fig 2). This analysis provided values for the area under the curve (AUC), cutoff points, sensitivity, specificity, and relative risk (RR). Table 4 shows that the shock index had a significant p-value of 0.022, with an AUC of 0.725, indicating a 72.5% diagnostic accuracy for AKI. The optimal cutoff for the shock index was >1.24, with a sensitivity of 55.0%, specificity of 81.25%, and RR of 1.921 (95% CI: 1.084–3.403). For Cystatin C, the analysis yielded a p-value of 0.012 and an AUC of 0.747, indicating a 74.7% diagnostic accuracy for AKI. The optimal cutoff for Cystatin C was >1.21, with a sensitivity of 60.00%, specificity of 93.75%, and RR of 2.654 (95% CI: 1.484–4.746). These results suggest that Cystatin C is a more robust diagnostic marker for AKI compared to the shock index, as evidenced by its higher AUC, sensitivity, specificity, and relative risk.

Table 4: Diagnostic Analysis of Shock Index and Cystatin C for AKI

	N	p value	AUC	Cut-off	Sensitivity	Specificity	RR (CI 95%)
Shock index	36	0.022	0.725	> 1.24	55.00 %	81.25 %	1.921 (1.084 – 3.403)
Cystatin C	36	0.012	0.747	> 1.21	60.00 %	93.75 %	2.654 (1.484 – 4.746)

*significant if p value >0.05

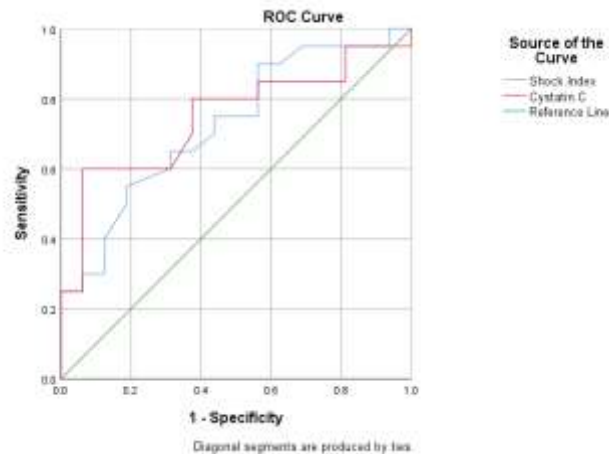


Figure 2: ROC of shock index dan Cystatin C according to AKI.

5. Discussion

The demographic data of BMI from 36 shock index samples were collected. Shi et al. reported that individuals with abnormal BMI values have an increased risk of AKI, including BMI <18.5 (OR 1.68) and BMI $\geq$ 28.0 (OR 1.43). According to Cerceo, women have a lower risk of developing AKI (OR 0.72) and mortality (OR 0.78). Cerceo also explained that age correlates with worse outcomes, with each decade of age associated with a 20–32% increase in the likelihood of AKI and mortality.

The administration of norepinephrine to individuals suffering from acute kidney injury is a subject of debate due to the possible negative impact it may have on kidney function. Lauzier et al. found that vasopressin significantly improved creatinine clearance within the first 24 hours, unlike norepinephrine. Vasopressin is more effective in improving renal function than norepinephrine, particularly in patients classified as risk AKI, as vasopressin induces efferent arteriole vasoconstriction, thereby enhancing the GFR, as evidenced by increased creatinine clearance.

The FINNAKI study revealed that arterial hypotension with a MAP <73 is associated with AKI progression in sepsis patients in the ICU (Mo et al., 2022). This research demonstrates a link between hemodynamic disturbances and AKI in critically ill patients. The shock index reflects dynamic changes in circulatory function, making it valuable for early diagnosis of shock and patient deterioration. The normal shock index range is 0.5–0.7. A shock index of 1.0 or higher indicates worsening hemodynamic stability and is associated with higher mortality and morbidity rates (Berger et al., 2013). The shock index data from our 36 samples ranged from 0.96 to 1.44, indicating hemodynamic instability, reduced circulating volume, and decreased left ventricular end-diastolic pressure. The shock index can identify high-risk patients potentially overlooked by the qSOFA score (Koch et al., 2019).

Cystatin C is a biomarker for evaluating renal function, specifically GFR. Cystatin C levels are a better predictor of AKI than creatinine or creatinine-based eGFR. Normal serum Cystatin C levels range from 0.47 to 1.09 mg/L in individuals aged 20–70 years. The Cystatin C levels from our 36 samples ranged from 0.77 to 1.41 mg/L. These elevated levels indicate impaired renal function and reduced GFR (Mooney et al., 2019).

Delta creatinine refers to the difference between baseline creatinine and creatinine on day 2. Although its levels may not immediately increase, monitoring patient creatinine levels is essential to assess renal function (Goyal et al., 2021). Doi et al. found that 24 hours post-injury, serum creatinine increased less in septic mouse models (0.5 mg/dL) than in ischemic or cisplatin-treated cases (>1 mg/dL) (Doi et al., 2009).

Our results showed no significant correlation between demographic characteristics such as sex, age, weight, height, and BMI with the incidence of AKI. Similar findings were observed for clinical characteristics, including LOS, systolic and DBP, HR, MAP, GCS, and 28-day mortality. Conversely, AKI occurs in 1% of hospitalized patients in the United States and up to 67% of ICU patients.

Consequently, AKI is a significant factor prolonging LOS and increasing patient morbidity (Goyal et al., 2021).

Cystatin C is primarily eliminated from the body through glomerular filtration, followed by reabsorption and breakdown in the proximal tubules without any secretion occurring. Hence, the level of Cystatin C in the blood is mainly determined by the glomerular filtration rate (GFR). An increase in Cystatin C levels could indicate tubular dysfunction, making it an early warning sign of acute kidney injury (AKI). Notably, Cystatin C proves to be highly effective in critically ill patients, as it can detect tubular dysfunction before any damage to the glomeruli occurs. Therefore, Cystatin C has emerged as a valuable biomarker for detecting AKI at an early stage.

On the other hand, the shock index (SI) is a method used to assess the extent of hypovolemia in individuals experiencing shock. A high SI signifies inadequate circulation of blood, vasodilation, and impaired tissue perfusion. Apart from evaluating shock, the SI can also help in determining the severity of sepsis, with values exceeding 0.7 indicating more severe cases and poorer prognoses. Through Spearman's test, it was found that there were significant connections between SI ($p=0.035$), serum Cystatin C ($p=0.001$), and delta creatinine levels. Elevated SI and delta creatinine levels have been linked to unfavorable clinical outcomes and increased mortality rates among AKI patients, as an increased SI is indicative of cardiovascular instability, while a rise in delta creatinine signifies deteriorating renal function—both factors that forecast negative results, including in-hospital deaths. The correlation between shock index and serum Cystatin C with delta creatinine is unidirectional. This finding aligns with the physiological properties of serum Cystatin C, which responds faster to variations in renal function than serum creatinine, with a half-life of 1.5–2 hours compared to creatinine's 4-hour half-life. Studies suggest that serum Cystatin C can predict AKI as early as six hours post-renal injury. When serum Cystatin C levels increase, subsequent elevations in creatinine levels can be anticipated. This makes serum Cystatin C superior for early detection of GFR changes, which is crucial for predicting patients with progressive renal damage.

A meta-analysis by Zhang et al. revealed that serum Cystatin C has better diagnostic sensitivity (0.78–0.86) and specificity (0.82) for AKI. Martensson et al. demonstrated that serum Cystatin C outperforms creatinine in monitoring GFR in ICU patients as it is unaffected by variables that alter creatinine levels (Martensson et al., 2012). Furthermore, creatinine-based eGFR is highly correlated with muscle mass, complicating its use in children and the elderly (Grubb, 2017).

The shock index is determined as the comparison of HR to SBP. High SI values indicate insufficient circulating volume, vasodilation, and perfusion deficits (Berger et al., 2013). In sepsis, SI values >0.7 signify greater severity and worse outcomes (Koch et al., 2019). Sepsis, a leading cause of vasodilatory shock, can result in septic shock, characterized by systemic vasodilation that reduces vascular tone and blood pressure, impairing perfusion to vital organs despite normal or elevated cardiac output (Tumlin et al., 2018).

One of the most severe consequences of vasodilatory shock is AKI, a rapid yet reversible renal dysfunction marked by decreased GFR. Clinically, this manifests as increased serum creatinine or reduced urine output, indicating impaired renal perfusion and filtration (Tamargo et al., 2024). SI is particularly useful in detecting complications such as renal damage. Hemodynamic instability disrupts renal perfusion, impairing GFR and causing renal dysfunction. Persistent low perfusion deprives the kidneys of oxygen and nutrients, leading to ischemia in renal tubules, cell damage, and filtration impairment. In septic shock, cytokines and inflammatory mediators exacerbate endothelial dysfunction and disrupt renal blood flow autoregulation (Berger et al., 2013). Chronic hypotension increases renal sensitivity to nephrotoxic drugs and metabolic abnormalities, worsening AKI (Koch et al., 2019).

Based on the diagnostic test of shock index for AKI incidence using the ROC Curve test, the p -value was 0.022, indicating statistical significance ($p<0.05$). The diagnostic test showed an AUC of 0.725, suggesting that the shock index has a 72.5% ability to predict AKI. This aligns with Ran et al.'s study, which reported that the shock index predicts AKI and bleeding (Ran et al., 2021). The study found that

the shock index has low predictive value for AKI, comparable to the Mehran score, a well-known instrument for predicting AKI risk. Nevertheless, the shock index is beneficial as a quick and convenient tool for predicting early AKI by utilizing HR, SBP, and creatinine clearance, which are commonly found in most healthcare environments (Mehran et al., 2004).

Our study summarizes that while both shock index and serum Cystatin C can diagnose AKI, serum Cystatin C is more accurate, as indicated by higher AUC, sensitivity, specificity, and risk values. The ROC analysis showed that the cutoff value for serum Cystatin C in diagnosing AKI is >1.21 , with a sensitivity of 60.00%, specificity of 93.75%, and an RR of 2.654 (95% CI 1.484–4.746). The results of this study support the existing literature that suggests serum Cystatin C is more accurate in predicting AKI compared to creatinine or creatinine-based eGFR (Shlipak et al., 2011).

This study's limitations include the research was conducted by a single investigator, introducing potential bias and the study was undertaken at a single site, limiting generalizability to other locations.

6. Conclusion

There are significant relationships between the shock index and AKI incidence in critically ill patients with vasodilatory shock, also between serum Cystatin C and AKI incidence in critically ill patients with vasodilatory shock. Serum Cystatin C demonstrates superior diagnostic value compared to the shock index in critically ill patients with vasodilatory shock and AKI.

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DISCLOSURE

The authors have no conflicts of interest in this work. ETHICS APPROVAL

The research received approval from Dr. Soetomo General Hospital in Surabaya, Indonesia.

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