# CORRELATION BETWEEN INTERCELLULAR ADHESION MOLECULE-1 WITH D-DIMER, LACTATE LEVEL, AND MORTALITY IN PATIENTS WITH VASODILATORY SHOCK

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**Background and aims:** The mortality of vasodilatory shock patients in the ICU is more than 50%. Vasodilatory shock is mostly due to excessive inflammation. Intercellular adhesion molecule (ICAM)-1 is expressed in the response process, playing a role in leukocyte emigration, intracellular signaling, and activation of proinflammatory cascades. We analyzed the relationship between ICAM-1 to D-Dimer levels, lactate levels, mortality, and vasopressor doses in critically ill patients in vasodilatory shock.

**Methods:** Observational analytic study with cross-sectional design. The data were obtained from patients in the ICU and ER of RSUD Dr. Soetomo Surabaya. Measurement of ICAM-1, D-Dimer, lactate, mortality, and vasopressor dose (norepinephrine) at 1-3 and 24 hours of initial treatment. Data were analyzed using EZR version 1.61.

**Results:** Twenty of 43 (46.5%) patients died by day 28 of treatment. The Mean Arterial Pressure (MAP) was lower in the non-survivors compared to the survivors and significantly different ($p=0.015$). Lactate level and vasopressor dose were elevated in the non-survivors ($p<0.05$). ICAM-1 levels were significantly associated with D-dimer levels ($p=0.0001$), but not with lactate levels, vasopressor dose, or mortality.

**Conclusion:** There is an association between ICAM-1 and D-dimer levels. Therefore, a correlation between inflammation and coagulophaty degree in patients with vasodilatory shock is related. Correlation between ICAM-1 levels with indicators of tissue hypoxia (lactate), vasopressor dose, and mortality needs further research.

**Keywords**: Vasodilatory shock, ICAM-1, D-Dimer, lactate

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## INTRODUCTION

Vasodilatory shock represents a life-threatening condition characterized by cardiovascular failure, where systemic vascular resistance is impaired despite the use of high-dose vasopressor medications. Approximately 7% of critically ill patients will encounter refractory vasodilatory shock, which carries a short-term mortality rate exceeding 50%. This condition arises due to uncontrolled vasodilation and reduced responsiveness of blood vessels to natural vasoconstrictors, leading to a failure in the body's vasoregulatory mechanisms (Jentzer et al., 2018). Moreover, patients requiring vasopressor doses greater than 1 g/kg/min of norepinephrine (NE) or an equivalent, who continue to deteriorate clinically, face an alarming mortality rate of 80-90%.

Surviving Sepsis Campaign (SSC) guidelines recommend prompt antimicrobial therapy, early fluid resuscitation, and the use of vasopressors in patients with persistent hypotension despite adequate fluid resuscitation to address the high incidence of shock-related diseases. Catecholamine vasoactive agents, with NE as the primary choice, remain the mainstay of vasoactive therapy to maintain a target mean arterial pressure (MAP) of 65 mmHg or higher. If NE administration fails to sustain a MAP of at least 65 mmHg, other vasoactive agents like arginine vasopressin, epinephrine, or rescue therapy with dopamine or phenylephrine may be considered (Evans et al., 2021). Initiation of norepinephrine following sufficient fluid resuscitation may reduce the association between vasopressor dose intensity and increased mortality (Ammar et al., 2022). In a study investigating 28-day survival in septic shock patients requiring high doses of vasopressors, 42 individuals survived with a mortality rate of 60.4% at 28 days

(Auchet et al., 2017).

The pathology underlying vasodilatory shock involves the upregulation of plasma catecholamines and activation of the renin-angiotensin system (RAS), leading to increased nitric oxide (NO) expression in various cell types, including vascular smooth muscle and endothelial cells (Júnior et al., 2020). The endothelium plays a crucial role in the blood coagulation system and is essential for maintaining hemostasis. Among its functions are the regulation of vascular tone, cellular adhesion, smooth muscle cell proliferation, and vascular wall inflammation (Yau et al., 2015). Coagulation activation generally occurs due to endothelial damage, leading to the exposure of blood to extravascular tissue factors (Schwameis et al., 2015). Sepsis-associated coagulopathy is characterized by coagulation activation, downregulation of physiological anticoagulants, and inhibition of fibrinolysis, resulting in the formation of various fibrin-related markers, including D-Dimer (Meini et al., 2021). D-Dimer has been identified as a prognostic marker in various critical conditions, including septic shock (Schwameis et al., 2015). Observations in septic shock also indicate that coagulation activation and fibrinolysis inhibition are associated with hyperlactatemia. This points to tissue hypoxia resulting directly from the imbalance in coagulation or fibrinolysis and helps explain the organ system failure and mortality observed in septic shock (Hartemink et al., 2010).

In vasodilatory shock, arterial hypotension reduces oxygen delivery, leading to regional and global tissue hypoxia. Concurrently, vasodilatory shock often involves a stress-induced hyperdynamic state that leads to aerobic glycolysis. The cumulative effect is a state of hyperlactatemia further compounded by acidemia. Hyperlactatemia has consistently been recognized as a hallmark of poor prognosis in vasodilatory shock (Wieruszewski & Khanna, 2022). Additionally, hyperlactatemia is associated with increased release of plasminogen activator inhibitor (PAI) due to impaired hemostasis. PAI contributes to microvascular thrombosis, resulting in cellular hypoxia. This cellular hypoxia perpetuates anaerobic metabolism, leading to further accumulation of lactate metabolites.

Intercellular adhesion molecule (ICAM)-1 is induced during the process of endothelial injury in vasodilatory shock pathology. ICAM-1 is an immunoglobulin (Ig)-like cell adhesion molecule expressed by various cell types, including leukocytes and endothelial cells. A soluble form of ICAM-1 (sICAM-1) has been identified in plasma. Apart from its well-established role in facilitating leukocyte emigration, ICAM-1 also initiates intracellular signaling (outside-to-inside signaling) leading to actin cytoskeleton rearrangement, aiding leukocyte diapedesis, and activating proinflammatory cascades that can result in a sustained inflammatory response (Lawson & Wolf, 2009).

The hypoxia that occurs in vasodilatory shock triggers an inflammatory response, which stimulates the release of inflammatory mediators, including reactive oxygen species (ROS). ROS are involved in mediating both physiological and pathophysiological signal transduction. Intercellular adhesion molecule (ICAM)-1 is one of the mediators released under the influence of ROS. The release of ROS and ICAM-1 contributes to the activation of the proinflammatory cascade. This ongoing proinflammatory cascade causes organ damage, leading to the development of multiple organ dysfunction syndrome (MODS) and ultimately culminating in mortality.

Given the background and phenomenon described above, the objective of this study is to analyze the relationship between intercellular adhesion molecule (ICAM)-1 and various factors such as D-Dimer levels, lactate levels, mortality, and vasopressor doses in critically ill patients experiencing vasodilatory shock.

## METHODS

The methodology employed in this study was an observational analytic design with a cross-sectional approach. The primary objective of the research was to investigate the relationship between intercellular adhesion molecule (ICAM)-1 and various factors, including D-Dimer levels, lactate levels, mortality, and vasopressor doses, in critically ill patients experiencing vasodilatory shock. The study was conducted at the Intensive Care Unit (ICU), resuscitation room, and intensive observation room (ROI) of the Emergency Department (ED) at Dr. Soetomo Regional General Hospital (RSUD) in Surabaya, over a period spanning from February to April 2022. Prior to commencing the study, informed consent was obtained from the patients' families, and ethical approval was obtained from the relevant ethics committee. The data collection process continued until the required sample size, meeting the inclusion criteria, was achieved.

*Inclusion criteria* for the study encompassed critically ill patients with vasodilatory shock who were receiving treatment at the designated hospital units and whose families consented to their participation, with informed consent duly signed. The patients were required to be aged 18 years or older and receiving norepinephrine vasopressor therapy. Conversely, certain *exclusion criteria* were applied, which included patients with congenital heart disease and those with end-stage renal disease (ESRD) requiring hemodialysis.

The data was analyzed by Easy R software (EZR) version 1.61. Biivariate analysis techniques such as the

independent t-test, Chi-Square test, and Mann-Whitney test were utilized, with a significance level set at P<0,05. Additionally, the Spearman's rank correlation test was applied to explore the relationships between different variables. Prior to the analysis, a preliminary assessment was conducted to verify the normality of data distribution.

## RESULTS

### Demographic Characteristics of Study Subjects

In the non-survivor group, there were higher male (11) than female (9) patients. The median age of the study subjects was 51 years (range: 17-77 years). The mean Body Mass Index (BMI) in the non-survivor group was 23.71 kg/m2 with a standard deviation of 3.67 kg/m2, and there was no significant difference when compared to the survivor group (p = 0.360). However, the mean systolic blood pressure of non-survivor patients was lower than that of the survivor group, and this difference was found to be statistically significant (p = 0.01). Similarly, the mean MAP in the non-survivor group was lower than that in the survivor group, and this difference was also statistically significant (p = 0.015).

Furthermore, this study assessed lactate levels and increased norepinephrine (NE) doses, as presented in Table 1. Lactate levels were found to be significantly different between the survivor and non-survivor groups at all measured times (p < 0.05), with higher lactate levels observed in the non-survivor group. Similarly, NE doses were also significantly different between the two groups at all times (p < 0.05), with the non-survivor group receiving higher NE doses.

Table (1) Characteristics of Critically Ill Patients with Vasodilatory Shock

| | Total | Survivor 23 (53,5%) | Non-survivor 20 (46,5%) | P value |
|---|---|---|---|---|
| Age, years (median (min-max)) | 51 (17-77) | 47 (17-77) | 51 (18-71) | 0.797 |
| Gender | | | | |
| Man [N (%)] | 26 (60,5%) | 14 (60,9%) | 11 (55%) | 0.729 |
| Woman [(N (%)] | 17 (39,5%) | 9 (39,1%) | 9 (45%) | |
| Systolic blood pressure (mmHg) (Mean (SD)) | 94.6 (18.2) | 101.1 (16.6) | 85.9 (17.0) | 0.010 |
| BMI (kg/m$^2$)(Mean (SD)) | 23.71 (3.67) | 23.22 (3.84) | 24.35 (3.43) | 0.360 |
| MAP (Mean (SD)) | 68.729 (13.935) | 73.824 (12.617) | 62.043 (13.029) | 0.015 |
| 1-3 hours Lactate, (median (min-max)) | 3 (0,5-21) | 2 (0,5-2) | 4 (2,5-21) | 0.010 |
| 24-hour Lactate,(median (min-max)) | 3 (0,7-25) | 2 (5-2) | 5 (3,5-25) | <0.001 |
| Changes Lactate, (Mean(SD)) | -0.04 (1.86) | -1.16 (1.50) | 1.43 (1.13) | 0.009 |
| NE usage for 1-3 hours, (median (min-max)) | 150 (50-200) | 100 (50-200) | 150 (100-200) | 0.016 |
| NE usage for 24 hours, (median (min-max)) | 100 (50-250) | 75 (50-150) | 250 (200-250) | <0.001 |
| Change of Usage NE, (median(min-max)) | 0 (-50-150) | -25 (-50-25) | 100 (50-150) | <0.001 |
| D-Dimer for 1-3 hours, (median (min-max)) | 925.43 (439.42-6886.79) | 990.07 (439.42-4803.91) | 841.64 (573.50-6886.79) | 0.495 |
| D-Dimer for 24 hours, (median (min-max)) | 961.34 (434.64-6379.24) | 1155.27 (592.65-4801.51) | 842.83 (434.64-6379.24) | 0.089 |
| D-Dimer changes, (Mean (SD)) | 16.76 (-2963.93) | 93.37 (-402.21-1752.50) | -50.28 (-1211.43-414.18) | 0.195 |

### Relationship between Increased Levels of Intercellular Adhesion Molecule (ICAM-1) and Increased Levels of D-Dimer in Critically Ill Patients Experiencing Vasodilatory Shock

The results of the Spearman correlation test revealed a statistically significant correlation between ICAM-1 levels and D-Dimer levels at both 1-3 hours and 24 hours (p < 0.05). The positive correlation observed indicates that a decrease in ICAM-1 levels corresponds to a decrease in D-Dimer levels in the non-survivor group, as shown in Table 2. Table 5.1 illustrates this relationship, displaying lower levels of both D-Dimer and ICAM-1 in the non-survivor group.

Table (2) Correlation of intercellular adhesion molecule (ICAM)-1 levels to D- Dimer levels in critically ill patients who experienced vasodilatory shock

| Variable | Correlation coefficient | p *value* |
|---|---|---|
| A1 – B1 | 0.858 | **<0.001**[a] |
| A2 – B2 | 0.819 | **<0.001**[a] |

A1 = ICAM-1 1-3 hours; A2 = ICAM-1 24 hours; B1 = D-Dimer 1-3 hours; B2 = 24-hour D-dimer;
a = Spearman correlation

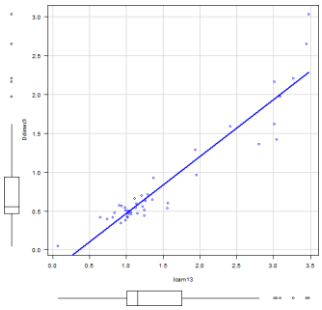

Figure 2. Scatter plot of correlation between D-dimer and ICAM-1 levels in the first 1-3 hours

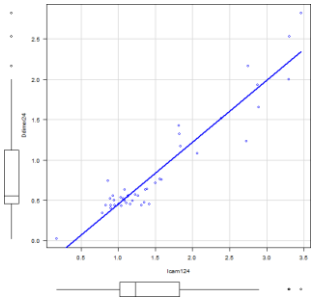

Figure 3. Scatter plot of correlation between 24th hour D-Dimer and ICAM-1 levels

**Relationship of Increased Levels of Intercellular Adhesion Molecule (ICAM)-1 to Increased Lactate Levels in Critically Ill Patients Experiencing Vasodilatory Shock**

The Spearman correlation test results indicated that there was no statistically significant correlation between ICAM-1 levels and lactate levels at all measured sampling hours ($p < 0.05$). This finding is presented in Table 3.

Table (3) Correlation of intercellular adhesion molecule (ICAM)-1 levels with lactate levels in critically ill patients experiencing vasodilatory shock.

| Variable | Correlation coefficient | p *value* |
|---|---|---|
| A1 – L1 | -0.031 | 0.842[a] |
| A2 – L2 | -0.198 | 0.204[a] |

A1 = ICAM-1 1-3 hours; A2 = ICAM-1 24 hours; L1 = Lactate 1-3 hours;
L2 = Lactate 24 hours; a = Spearman Correlation

**Relationship of Increased Levels of Intercellular Adhesion Molecule (ICAM)-1 to Mortality in Critically Ill Patients Experiencing Vasodilatory Shock**

Analysis of the results through the Spearman correlation test revealed a non-significant correlation between ICAM-1 levels and mortality at all examination times ($p < 0.05$). This finding is presented in Table 4.

Table (4) Correlation of increased levels of intercellular adhesion molecule (ICAM)-1 with mortality in critically ill patients who experienced vasodilatory shock

| Variable | Correlation coefficient | p *value* |
|---|---|---|
| A1-M | 0.082 | 0.598[a] |
| A2-M | 0.120 | 0.443[a] |

A1 = ICAM-1 first 1-3 hours, A2 = ICAM-1 24th hour M = mortality
a = Spearman correlation

**Relationship of Increased Levels of Intercellular Adhesion Molecule (ICAM)-1 to the Need for Vasopressors in Critically Ill Patients Experiencing Vasodilatory Shock**

The results obtained from the Spearman correlation test, examining the relationship between ICAM-1 levels and vasopressor doses (NE) administered at all sampling times, indicated no significant relationship ($p < 0.05$). This finding is presented in Table 6.

Table (5) Correlation of intercellular adhesion molecule (ICAM)-1 levels with vasopressor requirements in critically ill patients experiencing vasodilatory shock.

| Variable | Correlation coefficient | p *value* |
|---|---|---|
| A1 – V1 | -0.254 | 0.100 |
| A2 – V2 | -0.267 | 0.083 |

A1 = ICAM-1 1-3h; A2 = ICAM-1 24h; V1 = NE 1-3h;
V2 = NE 24 hours; a = Spearman Correlation

**DISCUSSION**

Vasodilatory shock is characterized by persistent hypotension despite adequate fluid resuscitation and is considered a terminal condition of various shock types, being a leading cause of mortality among critically ill patients in the ICU (Priyanka et al., 2022; Ukor & Walley, 2019). However, the underlying pathophysiology of vasodilatory shock remains incompletely understood, which can complicate its diagnosis and management (Ukor & Walley, 2019).

The pathophysiology of vasodilatory shock shares similarities with sepsis, involving intricate interactions between different immune system molecules and cells, including soluble adhesion molecules (Zonneveld et al., 2014). Adhesion molecules play a vital role in mediating cell-to-cell interactions, inflammation, and immune responses. When cells are activated or damaged, fragments of these proteins, termed soluble adhesion molecules, are released into the bloodstream. Several soluble adhesion molecules have been linked to sepsis, including E-selectin, L-selectin, P-selectin, ICAM-1, and VCAM-1 (Xing et al., 2018; Zonneveld et al., 2014). Evidence suggests that the endothelial cell surface expresses these adhesion molecules, mediating leukocyte extravasation and causing vascular endothelial damage, ultimately leading to shock and organ dysfunction (Xing et al., 2018). Additionally, increased inflammation in critically ill patients, including those with vasodilatory shock, may result in the activation or shedding of these molecules from the cell surface, leading to their accumulation in the blood (Zonneveld et al., 2014). The present study aimed to investigate ICAM-1, a soluble adhesion molecule, in the serum of critically ill patients with vasodilatory shock to determine its association with patient mortality.

Regarding the demographic characteristics, there were no significant differences in age, gender, and BMI between the survivor and non-survivor groups, which is advantageous as these variables could have acted as confounding factors. However, the mean systolic blood pressure and MAP were notably lower in the non-survivor group. The non-survivor group had a mean systolic blood pressure of 85.9 mmHg with a standard deviation of 17.0 mmHg and a mean MAP of 62.043 mmHg with a standard deviation of 13.029 mmHg. MAP, commonly used as a target for sepsis or vasodilatory shock management, has been associated with ICU mortality in previous studies (Khanna et al., 2023). Systolic blood pressure (SBP) is closely linked to MAP, and one study found that SBP was associated with mortality in sepsis patients (Tang et al., 2017). The Surviving Sepsis Campaign guidelines recommend a target MAP of at least 65 mmHg for patients (Asfar et al., 2014; Russell, 2020). Another study indicated that a MAP of at least 60 mmHg was crucial for adequate tissue perfusion and to prevent hypoperfusion-related organ failure (Fei, 2020).

Norepinephrine is a commonly utilized vasopressor to increase Mean Arterial Pressure (MAP) and achieve hemodynamic stability in the management of vasodilatory shock (Dugar et al., 2020). It has been demonstrated as the preferred option for managing vascular dysfunction in septic shock (Uhel & van der Poll, 2020). Compared to other vasopressors, norepinephrine is more effective in reducing the occurrence of arrhythmias and is considered safe for use in septic shock (Ruslan et al., 2021). In the present study, the use of norepinephrine was notably higher and significantly greater in the non-survivor group. The median norepinephrine dosage at 1-3 hours and 24 hours in the non-survivor group was 150 (100-200) and 250 (200-250), respectively, displaying a median increase of 100 (50-150). Similar findings have been observed in previous studies involving patients with septic shock, where increased norepinephrine usage was associated with higher mortality rates (Sato et al., 2021; Yeo et al., 2021). Meanwhile, the use of Ang-2 has potential to be a regimen for patients with vasodilatory shock (Semedi et al., 2023).

This study also assessed D-Dimer and lactate levels at 1-3 hours and 24 hours. The results showed no significant difference in D-Dimer levels among the study subjects. In a recent study, sepsis patients with low D-Dimer levels within the normal reference range were found to have nearly 4 times higher risk of death compared to those with higher D-Dimer levels. However, another study reported that sepsis patients without elevated D-Dimer had a higher mortality rate compared to those with a moderate and marked increase in D-Dimer (Semedi et al., 2023). These findings suggest that vasodilatory shock and sepsis are complex and heterogeneous conditions, presenting with different clinical features and outcomes, which may impact the relationship between D-Dimer levels and mortality.

On the other hand, lactate levels were found to be significantly different and higher in the non-survivor group. The lactate levels in the non-survivor group at

1-3 hours and 24 hours were 4 (2-21) and 5 (4-25) mmol/L, respectively. Serum lactate level is an important marker of sepsis severity. Several studies have explored the association between high lactate levels and mortality in sepsis vasodilatory shock (Casserly et al., 2015; Liu et al., 2019; Mikkelsen et al., 2009). It has been established that lactate levels greater than 4.0 mmol per L can be used to identify patients at a higher risk of death (Casserly et al., 2015). In septic shock, a cutoff lactate level of ≥4 mmol/L exhibits the best test characteristics to predict increased mortality (Villar et al., 2019).

Positive correlation between ICAM-1 and D-Dimer levels was observed in critically ill patients who experienced vasodilatory shock, indicating that both ICAM-1 and D-Dimer levels were increased in the non-survivor group. Prior research on ICAM-1 and D-Dimer in vasodilatory shock has been limited, with a focus on their prognostic roles in sepsis patients. D-Dimer has been recognized as a significant prognostic factor in sepsis patients, but recent studies have shown its dependence on leukocytes and vasopressor administration, leading to inconsistent prognostic values for both low and high D-Dimer levels in sepsis patients (Han et al., 2021).

This correlation can be elucidated through the roles of ICAM-1 and D-Dimer in the pathophysiology of critically ill patients. As mentioned earlier, ICAM-1 is primarily involved in leukocyte recruitment and mobilization to tissues. Elevated ICAM-1 expression has been associated with increased neutrophil adhesion and migration to tissues (Kaur et al., 2021). Subsequently, neutrophil activation is linked to platelet activation and intravascular coagulation, resulting in impaired organ perfusion. Hypercoagulation, as represented by elevated D-Dimer, may be induced by the heightened inflammation in critically ill patients. Elevated D-Dimer levels may indicate thrombin generation and fibrinolytic degradation (Tripodi, 2011). The relationship between the immune system and coagulation processes could account for the observed correlation between these two markers, both of which may also occur in critically ill patients with vasodilatory shock.

On the other hand, we found no correlation between ICAM-1 and lactate levels in critically ill patients with vasodilatory shock. This can be explained by the mechanism of hyperlactatemia, which is not directly related to hypercoagulation during endothelial injury and the release of proinflammatory cytokines (PAI-1). Recent studies have suggested that elevated lactate levels serve as indicators of physiological stress, anaerobic metabolism, and are strong predictors of mortality (Bruno et al., 2021; Hayashi et al., 2020; Hernandez et al., 2019). The arterial hypotension observed in vasodilatory shock leads to regional and global tissue hypoxia, further contributing to excessive lactate production. This aligns with the findings of this study, where higher lactate levels were observed in the non-survivor group, despite serial measurements. Currently, there are no studies investigating the relationship between ICAM-1 and lactate levels.

Blood lactate levels have been widely used as a marker to assess changes in tissue perfusion in critically ill patients (Vincent & De Backer, 2013). Normally, around 1 mEq/L of lactate is produced daily from various organs, including muscles, the gut, red blood cells, the brain, and skin (Levy, 2006). Elevated lactate levels, even small increases above 1.5 mEq/L, are associated with higher mortality rates or worse prognoses (A. D. Nichol et al., 2010; Singer et al., 2016). However, the complete mechanism leading to elevated lactate levels is not fully understood and may not necessarily be related to anaerobic metabolism (Kraut & Madias, 2014). Despite this lack of full understanding, elevated lactate levels have consistently been associated with high mortality rates and poor prognosis in shock patients (Cecconi et al., 2014; Haas et al., 2016; A. Nichol et al., 2011). Consistent with this study, lactate levels in the non-survivor group were found to be higher, even when measured serially. Additionally, the study found a statistically significant increase in lactate levels in the non-survivor group, in line with the suggestion from a previous study that serial lactate measurements may provide better clinical value than measurements taken at a single time point (Vincent et al., 2016).

Regarding ICAM-1 levels, the study results showed no significant difference between the survivor and non-survivor groups. Median ICAM-1 levels at 1-3 hours and 24 hours were lower in the non-survivor group, but an upward trend was observed in the non-survivor group. The median ICAM-1 levels at 1-3 hours and 24 hours in the non-survivor group were 1414.37 (568.37-6845.70) ng/L and 1359.86 (785.13-6770.19) ng/L, respectively. The median increase in ICAM-1 levels in the non-survivor group was 24.93 (-872.08-477.93). The Spearman correlation test did not reveal any significant correlation between ICAM-1 levels and mortality in critically ill patients experiencing vasodilatory shock.

The relationship between ICAM-1 as one of the soluble adhesion molecules and mortality in sepsis patients remains controversial. Some previous studies found no significant relationship between ICAM-1 and mortality in critically ill patients (Aird, 2005; Charalampos & Vincent, 2010; de Pablo et al., 2013; Kayal et al., 1998; Schuetz et al., 2011; Shapiro et al., 2010; Söderquist et al., 1999; van Griensven et al., 2006). ICAM-1 levels have been found to have an insignificant relationship with mortality and disease severity in both sepsis and non-sepsis patients (Aird, 2005). Furthermore, ICAM-1 is not an endothelial-

specific biomarker and can be elevated by other factors (Aird, 2005). Studies have shown that patients with moderate levels of soluble adhesion molecules, including ICAM-1, during sepsis have higher mortality rates and worse outcomes. This suggests that having higher levels of soluble adhesion molecules, including ICAM-1, may have a protective value (Zonneveld et al., 2014). On the other hand, there are studies that have found increased levels of sICAM-1 to be associated with mortality and the development of multiple organ failure. Serum levels of sICAM-1 on Days 1 and 7 have been considered valuable prognostic biomarkers for 90-day mortality in patients with severe sepsis and septic shock in the ICU (Amalakuhan et al., 2016; Fang et al., 2018; Kaur et al., 2021; Zonneveld et al., 2014).

Endothelial dysfunction has been linked to the pathogenesis and progression of various diseases presenting with systemic inflammatory response (SIRS), cardiovascular diseases, and hemorrhagic shock/trauma (Aird, 2005; Reinhart et al., 2002; Shapiro et al., 2010; Chatzizisis et al., 2008; Esper, 2006; Li et al., 2009; Matsutani et al., 2007). In cardiovascular research, endothelial dysfunction has been identified as an early marker of atherosclerosis, and in patients with acute coronary syndrome, it is associated with adverse conditions such as plaque rupture due to increased leukocyte adhesion, vasoconstriction, platelet activation, and thrombus formation (Esper, 2006). Large-scale clinical studies have also shown that endothelial markers correlate with the risk of cardiovascular events (Hwang et al., 1997; Ridker et al., 2000). Similarly, in trauma research, elevated levels of endothelial markers have been observed in experimental models of trauma and hemorrhagic shock (Li et al., 2009; Matsutani et al., 2007). Given that the etiology of vasodilatory shock can be sepsis or non-sepsis (trauma, cardiac disease, or hemorrhagic shock), the endothelial dysfunction theory can be applied to vasodilatory shock, forming the basis for investigating ICAM-1 as a potential molecule involved in vasodilatory shock.

However, the results of this study showed no significant association between elevated ICAM-1 levels and mortality in critically ill patients with vasodilatory shock. The endothelial theory proposes that endothelial cells play a crucial role in the development of the inflammatory process, and various stimuli lead to endothelial activation and interactions with leukocytes, including leukocyte adhesion and extravasation. Activated endothelial cells express and release adhesion molecules, such as E-selectin, ICAM-1, and VCAM-1, which promote leukocyte extravasation (Leeuwenberg et al., 1992; Pigott et al., 1992). Cytokines further regulate the local mobilization of leukocytes to the inflammatory site, leading to increased expression of endothelial cell ligands (VCAM-1, ICAM-1, and E-selectin). These activated endothelial cells can be released and measured in the blood (Gearing & Newman, 1993). However, ICAM-1 is not specific to endothelial cells; it is also expressed by fibroblasts, leukocytes, and epithelial cells (Carlos & Harlan, 1994; Gearing et al., 1992; Söderquist et al., 1999). This lack of endothelial specificity may explain the lack of a significant association between ICAM-1 levels and mortality in the study subjects.

Furthermore, this study revealed no correlation between ICAM-1 levels and the dose of vasopressors in critically ill patients with vasodilatory shock. This lack of correlation could be attributed to the absence of differences in ICAM-1 levels between the survivor and non-survivor groups, while differences in vasopressor requirements were observed. Norepinephrine, a potent alpha-1, alpha-2, and beta-1-adrenergic agonist, is recommended as a first-line vasopressor agent in septic shock to improve vascular tone (Annane et al., 2018; Hamzaoui et al., 2017). Observational cohort studies have shown a positive correlation between the number of vasopressors needed and mortality rate (Brand et al., 2017). Additionally, an increase in the number of vasopressors has been associated with higher mortality rates in critically ill patients (Sviri et al., 2014). In this study, a significant relationship between vasopressor requirement and mortality was observed, with an increase in vasopressor use in the non-survivor group.

## CONCLUSION

Patients with vasodilatory shock, such as septic shock, often exhibit elevated levels of both ICAM-1 and D-dimer, indicating a systemic inflammatory response and a hypercoagulable state. Therefore, there is an association between ICAM-1 levels and D-dimer levels, and a correlation among inflammation and coagulopathy degree in patients with vasodilatory shock. However, no significant correlations were observed between ICAM-1 levels and lactate levels, mortality, and vasopressor doses administered to the patients. Early and adequate resuscitation may affect those result.

To obtain more comprehensive insights into the effects of intercellular adhesion molecule-1 and D-Dimer on lactate levels and mortality in vasodilatory shock patient, it is recommended to conduct prospective and multicenter follow-up studies. Additionally, efforts should be made to use more homogeneous underlying disease samples in future research. Exploring the role of ICAM-1 and other parameters associated with endothelial dysfunction in tissue hypoxia, coagulopathy, and mortality is also crucial for a better understanding.

## LIMITATIONS

Several limitations were identified in this study. Firstly, being a cross-sectional and single-center study, it inherently limits the ability to establish causal relationships, and the findings are confined to correlations only. Secondly, ICAM-1, being an endothelial adhesion molecule, serves as an indirect measure of endothelial activation or damage in the pathophysiology of vasodilatory shock, which might contribute to the lack of significant relationships observed in this study.

## AUTHORS' CONTRIBUTION

AHU, CSW and BPS: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to beaccountable for all aspects of the work. AHU : Data acquisition, interpretation, drafting, final approval and agree to be accountable forall aspects of the work.

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