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Correlation between Angiopoietin-2 and IL-6 as inflammation biomarkers on the severity of coagulopathy and mortality in vasodilated shock patients

Dini Septian[1], Christrijogo Soemartono W[1], Bambang Pujo Semedi[1*], Prihatma Kriswidyatomo[1], Lucky Andriyanto[1], Budi Utomo[2]

[1]Department of Anesthesiology and Reanimation, Faculty of Medicine, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, Indonesia;
[2]Department of Public Health and Preventive Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.

*Corresponding author:
Bambang Pujo Semedi;
Department of Anesthesiology and Reanimation, Faculty of Medicine, Dr. Soetomo General Hospital, Universitas Airlangga, Surabaya, Indonesia;
bambang-p-s@fk.unair.ac.id

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ABSTRACT

Background: Sepsis and vasodilatory shock are serious medical conditions and cause high mortality rates worldwide. It is known that IL-6 and Angiopoietin-2 levels have a role in the etiology of shock in ICU patients. Consequently, this research aims to examine the involvement of Angiopoietin-2 and IL-6 in the severity of coagulation problems in patients with vasodilatory shock.

Methods: The study's design is observational analytic with a cross-sectional study design, and the data came from those treated in the ICU room and the Emergency Room at RSUD Dr. Soetomo Surabaya from February 2020 to March 2022. Data collected included age, respiratory rate, DIC score, APACHE II score, mortality, IL-6 levels, and Angiopoietin-2 levels. The data was then analyzed using Easy R (EZR).

Result: 27 of the 44 patients (61.4% of the total) belonged to the DIC group. A correlation between IL-6 levels and DIC incidence and mortality at first ICU admission and after 24 hours in the ICU was shown to be significant ($p<0.05$). There was also a significant correlation between Angiopoietin-2 and both DIC incidence and mortality upon admission to the ICU and after 24 hours in the ICU ($p<0.05$). It was found that the test specificity and sensitivity of Angiopoetin-2 and IL-6 levels on the severity of coagulation disorders and mortality in patients with vasodilatation shock were 85.9% for Angiopoetin-2 and 71.6% for IL-6.

Conclusion: There is a correlation between the severity of coagulation disorders in vasodilated shock and increased IL-6 and Angiopoietin-2. IL-6 and Angiopoietin-2 were to be correlated with mortality and Angiopoietin-2 has higher specificity and sensitivity than IL-6. Multicenter prospective studies are needed to confirm study results.

Keywords: Angiopoietin-2, APACHE, DIC, IL-6, ISTH criteria, Shock.
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INTRODUCTION

Sepsis and vasodilatory shock are serious medical conditions and cause high mortality rates worldwide. It is estimated that around 5.3 million people worldwide die from sepsis and organ failure each year, which is equivalent to 30% of sepsis patients who die.[1,2] In the United States, more than 1.5 million people experience vasodilatory shock each year, most of which is caused by sepsis.[3] Vasodilatory shock is the most common cause of shock in the Intensive Care Unit (ICU).[4] Approximately 25% of patients admitted to the ICU experience a course of disease leading to severe sepsis and vasodilatory shock, which has a mortality rate of more than 50%.[5] Approximately 6-7% of patients treated in the ICU experience an increased mortality rate of 50% due to this vasodilatory shock.[6] Vasodilated shock patients also frequently experience disseminated intravascular coagulation. Disseminated intravascular coagulation (DIC) is defined by the International Society on Thrombus and Haemostasis (ISTH) as a variety of syndromes acquired by activation of intravascular coagulation that arise from a variety of infectious and non-infectious disorders.[6] Therefore, early detection and aggressive therapy are needed to reduce mortality in patients with vasodilatory shock.

Severe systemic inflammation and endothelial damage are one of the mechanisms by which vasodilatory shock occurs.[7] Including sepsis and non-sepsis, the risk of coagulation disorders increases due to endothelial cell dysfunction.[8] Previous studies have shown that increased levels of IL-6 are related to the mechanism of hypercoagulation due to endothelial damage.[9] An increase in Angiopoietin-2 is also associated with conditions with endothelial abnormalities[10], which shows the potential of Angiopoietin-2 and IL-6 as predictor markers of severity and mortality in patients with vasodilatory shock. Although Angiopoietin-2 has been studied as a predictor of survival or mortality in patients[11,12,13], until now there is no definite predictor marker for the event rate parameter and mortality in

cases of vasodilatory shock in the ICU.

This study aims to examine the relationship between Angiopetin-2 and IL-6 levels with the severity of coagulation disorders and mortality in patients with vasodilatory shock. This research is expected to make an important contribution to the field of treatment and care for patients with vasodilatation shock in the ICU, as well as open up opportunities for further research in the future.

METHODS

This research is an analytic observational study with a cross-sectional study design. The research was conducted in the ICU and Emergency Room of RSUD Dr. Soetomo Surabaya from February 2022 to March 2022. The sample is all patients with a critical state of vasodilation shock due to sepsis or non-sepsis at the Hospital. The inclusion criteria in this study were patients over 18 years of age and patients with vasodilatory shock in the ICU and Emergency Department. Critical patients are patients with unstable vital signs, hypotension (systolic blood pressure less than 90 mmHg or mean arterial pressure (MAP) less than 65 mmHg) who do not improve with vasopressors and hypoperfusion and are life-threatening and require special patient care. Patients were excluded if their families refused, had congenital heart disease, and patients with end-stage renal disease (ESRD). Data collection was carried out through IL-6 and Angiopoetin-2 laboratory tests. Blood samples were put into a 5 ml venoject tube with EDTA anticoagulant and collected to examine Angiopoietin 2 and Interleukin 6 levels using the ELISA kit method. Subjects are still undergoing hemodynamic monitoring and resuscitation according to the protocol. Samples were taken according to the number of research samples fulfilled. Data were analyzed using the SPSS 24.0 program.

RESULTS

Angiopoietin-2 and IL-6 Levels on the Severity of Coagulation Disorders and Mortality in Patients with Vasodilatation Shock

The results of the Spearman correlation test showed that there was a significant correlation between IL-6 levels at the time of admission and the first 24 hours ($p < 0.05$). The results of the Spearman correlation test showed that there was a significant positive correlation between the mean IL-6 and Angiopoetin-2 on the level of coagulation disorders with a value of r=0.367 and p=0.014 ($p<0.05$) for IL-6 and r=0.651 and p =0.0001 ($p<0.05$) for Angiopoetin-2 (Table 1).

Table 1. Correlation between IL-6 and Angiopoetin-2 levels on the severity of coagulation disorders (DIC)

Variable	R	p
Mean IL-6 (pg/mL)	0.367	0.014
IL-6-$_0$ (pg/mL)	0.353	0.019
IL-6-$_1$ (pg/mL)	0.359	0.017
Rerata Angiopoein-2 (pg/mL)	0.651	0.0001
Angiopoetin-2-$_0$ (ng/mL)	0.644	0.0001
Angiopoetin-2-$_1$ (ng/mL)	0.645	0.0001

Table 2. Correlation of IL-6 and Angiopoetin-2 levels on mortality in patients with vasodilatation shock

Variable	R	p
IL-6-$_0$ (pg/mL)	0.514	**0.0001**
IL-6-$_1$ (pg/mL)	0.482	**0.001**
Angiopoetin-2-$_0$ (ng/mL)	0.863	**0.0001**
Angiopoetin-2-$_1$ (ng/mL)	0.863	**0.0001**

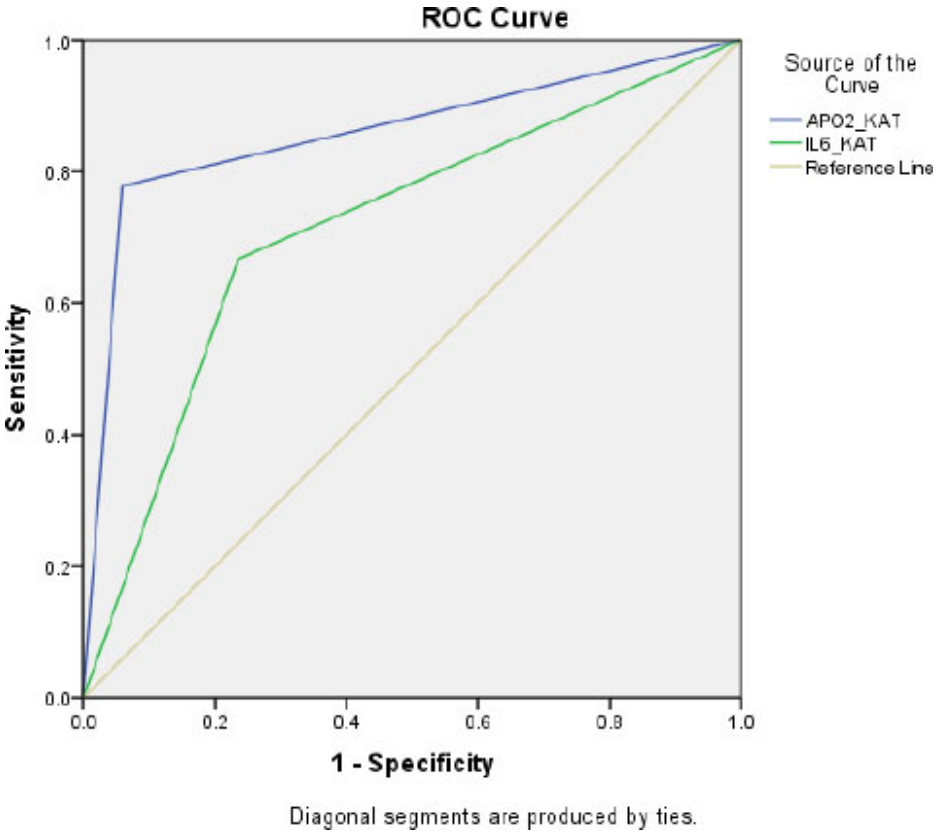

Figure 1. Specificity and sensitivity test of Angiopoietin-2 and IL6 on the severity of coagulation disorders and mortality in research subjects.

There was a positive correlation between IL-6 at admission and 24 hours on mortality but statistically significant. Angiopoetin-2 levels on mortality at admission and 24 hours of stay in the ICU have a positive correlative value and are statistically significant (Table 2).

After analysis, the mean cut-off values for Angiopoetin-2 levels for the severity of coagulation disorders and mortality were

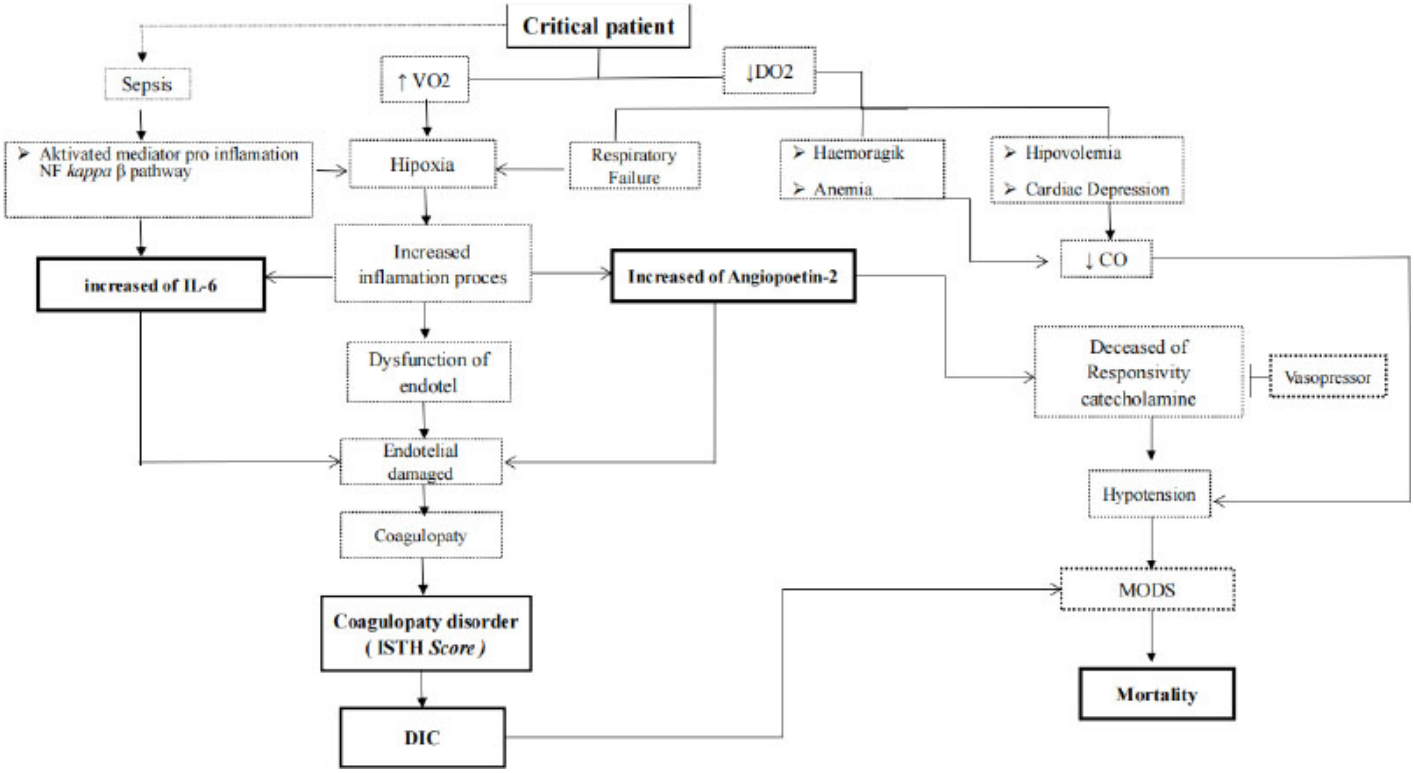

Figure 2. Pathophysiology of Angiopoietin-2 and IL-6 as inflammation biomarkers on the severity of coagulopathy and mortality in vasodilated shock patients.

7.75 and 72.79. Meanwhile, the mean cut-off values for IL-6 levels for coagulation disorders and mortality severity were 72.9 and 72.9, respectively. It was found that the test specificity and sensitivity of Angiopoetin-2 and IL-6 levels on the severity of coagulation disorders and mortality in patients with vasodilatory shock were 85.9% for Angiopoetin-2 and 71.6% for IL-6 (Figure 1).

DISCUSSION

Critical patients in the ICU can be caused by infection due to sepsis. Systemic inflammation due to sepsis causes the formation of proinflammatory cytokines, including TNF-a, IL-10 and IL-6. Cytokine storms can trigger endothelial damage. Endothelial abnormalities also cause an increase in Angiopoietin-2 and can inhibit anticoagulants, namely thrombomodulin, where the process can directly exacerbate hypercoagulability. Critical patients experience an imbalance between oxygen supply (Delivery oxygen/DO2) and oxygen demand (oxygen consumption/VO2) which can cause hypoxia. Hypoxic conditions can trigger an increase in inflammatory mechanisms in the tissue, thereby triggering endothelial damage. Endothelial damage or dysfunction will also be further exacerbated by an increase in Angiopoetin-2 in the blood. This mechanism will continue until vasodilation shock can cause MODS and end in mortality (Figure 2).

This study discovered a significant relationship between IL-6 levels and coagulation problems at the time of ICU admission and after 24 hours (p0.05). At the first ICU admission and after 24 hours in the ICU, patients with coagulation abnormalities had greater IL-6 levels than those without coagulation disorders. A link was also discovered between IL-6 levels and DIC scores. Other researchers have discovered elevated IL6 levels in vasodilatory shock.[14-17] Furthermore, this study discovered that IL-6 levels in blood serum remained high in DIC patients for the first 24 hours after admission to the ICU (89.80 (65.90-108.30) pg/mL vs. 92.20 (67.60-112) pg/mL). A similar study found that serum IL-6 levels were high in the first 48 hours following ICU admission (70.0 pg/mL on admission; 50.0 pg/mL at 48 hours). These findings may point to an additional anti-inflammatory mechanism involved in vasodilatory shock due to greater endothelial damage in vasodilatory shock patients. The function of IL-6 in diagnosis and prognosis is debatable. According to one recent study, IL-6 levels can be utilized as a predictive marker in individuals with organ dysfunction.[18] Another study discovered that IL-6 had a better diagnostic and prognostic value than PTX3 and PCT in sepsis and vasodilatation shock cases.[19] In another investigation, serum IL-6 levels were found to have a better diagnostic value than PCT, presepsin, and CRP in instances with vasodilation shock.[20] Other research has demonstrated that IL-6 serves mostly as a prognosis signal rather than a diagnostic tool.[15,21] High IL-6 levels during hospitalization are related to shorter survival than patients with low IL-6 levels. Another study found that IL-6 performed better in evaluating antibiotic efficacy and proposed utilizing IL-6 as a prognostic diagnostic in patients with sepsis and septic shock.[20] As a result, IL-6 monitoring can be valuable clinically in diagnosing disease in the acute phase and evaluating medication success. This is in contrast to watching a decrease in the inflammatory

response, which can be disastrous for the patient.[22,23]

In the intensive care unit, there is a correlation between IL-6 and mortality. Patients who did not survive had much greater IL-6 levels than survivors. These findings are consistent with earlier research suggesting IL-6 is related to mortality in ICU patients.[18,24,25] Previous research has even found that IL-6 outperforms other mortality measures in patients with sepsis and septic shock, such as PTX3, PCT, and CRP.[25] The IL-6 marker is also an independent risk factor for mortality in patients with sepsis and vasodilatation shock, with high IL-6 levels related to death.[25] This study shows that IL-6 is linked to death in people suffering from sepsis and septic shock. This study reveals novel findings, namely that in individuals with vasodilatation shock and coagulation problems, IL-6 levels can rise and be related to mortality. As a biomarker, the IL-6 marker is significant in patients because it allows prompt aggressive therapy, early identification, and lower mortality. T-lymphocytes, fibroblasts, endothelial cells, and monocytes produce interleukin-6 (IL-6), a pro-inflammatory cytokine.[26,27] IL-6 has been shown in studies to influence platelet activation, resulting in platelet depletion.[28] In severe shock, IL-6 levels promote platelet-endothelial cell contact, which also occurs in sepsis.[29] The main cause of vasodilatory shock is poor vascular reactivity, which includes uncontrolled pathological vasodilation (vasoplegia).[30] In DIC situations, two conditions can occur: cytokine storms and endothelial disruptions caused by shock.[31-33] A combination of decreased platelets, increased fibrinogen/fibrin degradation products, and prolonged prothrombin time (PT) is characteristic of DIC.[34] As a result, IL-6 levels in DIC patients are elevated due to vasodilatory shock.

This study discovered a significant relationship between Angiopoietin-2 and coagulation problems at the time of ICU admission and 24 hours later ($p<0.05$). Angiopoietin-2 levels were higher in patients with coagulation problems than in non-DIC patients at both the initial ICU admission and after 24 hours in the ICU. Angiopoietin-2 levels were also found to have a favorable connection with DIC scores. Similar investigations have reported elevated Angiopoietin-2 levels in ICU patients with coagulation problems.[35-38] Furthermore, patients with coagulation abnormalities caused by sepsis had higher Angiopoietin-2 levels.[38] Angiopoietin-2 levels have been found to rise in patients with sepsis and vasodilation shock in prior research.[36,39,40] Furthermore, in patients with coagulation abnormalities, blood Angiopoetin-2 levels remained high for the first 24 hours following admission to the ICU ((10.37 (6.95-10.71) versus 10.32 (7.08-10.85)). This was also discovered in Feng's prior studies.35 Angiopoetin-2 regulates the endothelium and is implicated in a number of pathways connected to organ dysfunction.[41] When the endothelium is damaged, the levels rise. Angiopoietin-2 also functions as a proinflammatory mediator, causing fluid leakage via the vascular endothelium.[42] Angiopoietin-2 is linked to endothelial damage and increased vascular permeability in individuals with coagulation problems caused by severe trauma, according to research.[43] Furthermore, these situations occur in vasodilatory shock linked with coagulation problems. Therefore, elevated levels of Angiopoietin-2 play a role in the development of coagulation disorders in patients with vasodilatation shock.

A significant relationship was found between Angiopoietin-2 and mortality in the ICU. Non-survivor patients had significantly higher levels of Angiopoietin-2 than survivors. These results align with previous studies that Angiopoietin-2 is associated with mortality in patients in the ICU, namely patients with sepsis and vasodilation shock.[36,44,45] Previous research also found an increase in Angiopoietin-2 compared to the control group in patients in the ICU due to sepsis and vasodilatory shock.[36,45] Angiopoetin-2 is known to be associated with endothelial dysregulation, tissue hypoxia, and thrombin formation, so patients with sepsis and coagulation disorders can experience an increase in serum Angiopoietin-2 levels as experienced by the sample in this study. Angiopoietin-2 is ultimately useful for patients treated in the ICU, both septic and non-septic, to predict death. The aim is that patients with high levels of Angiopoietin-2 can immediately get aggressive treatment and reduce mortality. Studies have found that high Angiopoetin-2 levels are associated with a worse prognosis in patients with sepsis.[46-49] Recent studies have also found that Angiopoetin-2 levels are associated with a worse prognosis in patients with DIC-related sepsis.[36] However, the underlying mechanism is still unclear. Studies report that Angiopoetin-2 can increase inflammation and vascular permeability, leading to the development of ARDS.[49-55] Moreover, a positive relationship between Angiopoetin-2 and IL-6 has been observed.[48] Therefore, an increase in Angiopoietin-2 is associated with the severity of shock.

CONCLUSION

This study demonstrates a correlation between changes in Angiopoietin-2 and IL-6 levels on the severity of coagulation disorders and mortality in patients with vasodilatory shock.

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ETHICS CLEARANCE

This research was approved by ethical clearance from the Ethics Committee of the Faculty of Medicine, Airlangga University/ Dr. RSUD. Soetomo (Registration No. 0348/KEPK/XII/2021).

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTION

All authors have contributed equally from the conceptual framework, data acquisition, and data analysis until the study results are reported through publication.

REFERENCES

1. Angus, D. C., and van der Poll, T. 2013. 'Severe sepsis and septic shock'. *N Engl J Med, 369*(9), 840-851. doi:10.1056/NEJMra1208623
2. Singer, M., Deutschman, C. S., Seymour, C. W., Shankar-Hari, M., Annane, D., Bauer, M., Bellomo, R. *et al.* 2016. 'The third international consensus definitions for sepsis and septic shock (sepsis-3)'. *JAMA, 315*(8), 801-810. doi:10.1001/jama.2016.0287
3. Hershey, T. B., and Kahn, J. M. 2017. 'State sepsis mandates - a new era for regulation of hospital quality'. *N Engl J Med, 376*(24), 2311-2313. doi:10.1056/NEJMp1611928
4. Vincent, J. L., and De Backer, D. 2013. 'Circulatory shock'. *N Engl J Med, 369*(18), 1726-1734. doi:10.1056/NEJMra1208943
5. Divatia, J. V., Amin, P. R., Ramakrishnan, N., Kapadia, F. N., Todi, S., Sahu, S., Govil, D. *et al.* 2016. 'Intensive care in india: The indian intensive care case mix and practice patterns study'. *Indian J Crit Care Med, 20*(4), 216-225. doi:10.4103/0972-5229.180042
6. Jenkins, C. R., Gomersall, C. D., Leung, P., and Joynt, G. M. 2009. 'Outcome of patients receiving high dose vasopressor therapy: A retrospective cohort study'. *Anaesthesia and Intensive Care, 37*(2), 286-289. doi:10.1177/0310057x0903700212
7. Hultström, M., Fromell, K., Larsson, A., Quaggin, S. E., Betsholtz, C., Frithiof, R., Lipcsey, M. *et al.* 2021. 'Elevated angiopoietin-2 inhibits thrombomodulin-mediated anticoagulation in critically ill covid-19 patients'. *medRxiv*. doi:10.1101/2021.01.13.21249429
8. Williams, G. W., Berg, N. K., Reskallah, A., Yuan, X., and Eltzschig, H. K. 2021. 'Acute respiratory distress syndrome'. *Anesthesiology, 134*(2), 270-282. doi:10.1097/ALN.0000000000003571
9. Bester, J., and Pretorius, E. 2016. 'Effects of il-1beta, il-6 and il-8 on erythrocytes, platelets and clot viscoelasticity'. *Sci Rep, 6*, 32188. doi:10.1038/srep32188
10. Statz, S., Sabal, G., Walborn, A., Williams, M., Hoppensteadt, D., Mosier, M., Rondina, M. *et al.* 2018. 'Angiopoietin 2 levels in the risk stratification and mortality outcome prediction of sepsis-associated coagulopathy'. *Clin Appl Thromb Hemost, 24*(8), 1223-1233. doi:10.1177/1076029618786029
11. Kumpers, P., David, S., Haubitz, M., Hellpap, J., Horn, R., Brocker, V., Schiffer, M. *et al.* 2009. 'The tie2 receptor antagonist angiopoietin 2 facilitates vascular inflammation in systemic lupus erythematosus'. *Ann Rheum Dis, 68*(10), 1638-1643. doi:10.1136/ard.2008.094664
12. Siner, J. M., Bhandari, V., Engle, K. M., Elias, J. A., and Siegel, M. D. 2009. 'Elevated serum angiopoietin 2 levels are associated with increased mortality in sepsis'. *Shock, 31*(4), 348-353. doi:10.1097/SHK.0b013e318188bd06
13. Ziegler, T., Horstkotte, J., Schwab, C., Pfetsch, V., Weinmann, K., Dietzel, S., Rohwedder, I. *et al.* 2013. 'Angiopoietin 2 mediates microvascular and hemodynamic alterations in sepsis'. *J Clin Invest, 123*(8), 3436-3445. doi:10.1172/JCI66549
14. Cioara, A., Valeanu, M., Todor, N., Cristea, V., and Lupse, M. 2016. 'Early sepsis biomarkers and their relation to mortality'. *Rom J Anaesth Intensive Care, 23*(2), 159-160. doi:10.21454/rjaic.7518/232.psi
15. Gentile, L. F., Cuenca, A. G., Vanzant, E. L., Efron, P. A., McKinley, B., Moore, F., and Moldawer, L. L. 2013. 'Is there value in plasma cytokine measurements in patients with severe trauma and sepsis?'. *Methods, 61*(1), 3-9. doi:10.1016/j.ymeth.2013.04.024
16. Nainggolan, S. C., Aman, A. K., and Hanafie, A. 2019b. 'The relationship between the level of interleukin-6 and procalcitonin in severe sepsis patients at the adam malik hospital'. *Indonesian Journal of Clinical Pathology and Medical Laboratory, 25*(1). doi:10.24293/ijcpml.v25i1.1488
17. Riedel, S., and Carroll, K. C. 2013. 'Laboratory detection of sepsis: Biomarkers and molecular approaches'. *Clin Lab Med, 33*(3), 413-437. doi:10.1016/j.cll.2013.03.006
18. Takahashi, W., Nakada, T. A., Yazaki, M., and Oda, S. 2016. 'Interleukin-6 levels act as a diagnostic marker for infection and a prognostic marker in patients with organ dysfunction in intensive care units'. *Shock, 46*(3), 254-260. doi:10.1097/SHK.0000000000000616
19. Song, J., Park, D. W., Moon, S., Cho, H. J., Park, J. H., Seok, H., and Choi, W. S. 2019. 'Diagnostic and prognostic value of interleukin-6, pentraxin 3, and procalcitonin levels among sepsis and septic shock patients: A prospective controlled study according to the sepsis-3 definitions'. *BMC Infect Dis, 19*(1), 968. doi:10.1186/s12879-019-4618-7
20. Behnes, M., Bertsch, T., Lepiorz, D., Lang, S., Trinkmann, F., Brueckmann, M., Borggrefe, M. *et al.* 2014. 'Diagnostic and prognostic utility of soluble cd 14 subtype (presepsin) for severe sepsis and septic shock during the first week of intensive care treatment'. *Crit Care, 18*(5), 507. doi:10.1186/s13054-014-0507-z
21. Vivas, M. C., Villamarin Guerrero, H. F., Tascon, A. J., and Valderrama-Aguirre, A. 2021. 'Plasma interleukin-6 levels correlate with survival in patients with bacterial sepsis and septic shock'. *Interv Med Appl Sci, 11*(4), 224-230. doi:10.1556/1646.2020.00006
22. Cho, S. Y., and Choi, J. H. 2014. 'Biomarkers of sepsis'. *Infect Chemother, 46*(1), 1-12. doi:10.3947/ic.2014.46.1.1
23. Pierrakos, C., and Vincent, J. L. 2010. 'Sepsis biomarkers: A review'. *Crit Care, 14*(1), R15. doi:10.1186/cc8872
24. Mat-Nor, M. B., Md Ralib, A., Abdulah, N. Z., and Pickering, J. W. 2016. 'The diagnostic ability of procalcitonin and interleukin-6 to differentiate infectious from noninfectious systemic inflammatory response syndrome and to predict mortality'. *J Crit Care, 33*, 245-251. doi:10.1016/j.jcrc.2016.01.002
25. Song, J., Park, D. W., Moon, S., Cho, H. J., Park, J. H., Seok, H., and Choi, W. S. (2019). Diagnostic and prognostic value of interleukin-6, pentraxin 3, and procalcitonin levels among sepsis and septic shock patients: A prospective controlled study according to the sepsis-3 definitions. In (Vol. 19).
26. Ma, L., Zhang, H., Yin, Y. L., Guo, W. Z., Ma, Y. Q., Wang, Y. B., Shu, C. *et al.* 2016. 'Role of interleukin-6 to differentiate sepsis from non-infectious systemic inflammatory response syndrome'. *Cytokine, 88*, 126-135. doi:10.1016/j.cyto.2016.08.033
27. Spittler, A., Razenberger, M., Kupper, H., Kaul, M., Hackl, W., Boltz-Nitulescu, G., Fugger, R. *et al.* 2000. 'Relationship between interleukin-6 plasma concentration in patients with sepsis, monocyte phenotype, monocyte phagocytic properties, and cytokine production'. *Clin Infect Dis, 31*(6), 1338-1342. doi:10.1086/317499
28. Oleksowicz, L., Mrowiec, Z., Isaacs, R., Dutcher, J. P., and Puszkin, E. 1995. 'Morphologic and ultrastructural evidence of interleukin-6 induced platelet activation'. *Am J Hematol, 48*(2), 92-99. doi:10.1002/ajh.2830480205
29. Shimizu, M., Konishi, A., and Nomura, S. 2018. 'Examination of biomarker expressions in sepsis-related dic patients'. *Int J Gen Med, 11*, 353-361. doi:10.2147/IJGM.S173684
30. Bassi, E., Park, M., and Azevedo, L. C. 2013. 'Therapeutic strategies for high-dose vasopressor-dependent shock'. *Crit Care Res Pract, 2013*, 654708. doi:10.1155/2013/654708
31. Iba, T., and Levy, J. H. 2018. 'Inflammation and thrombosis: Roles of neutrophils, platelets and endothelial cells and their interactions in thrombus formation during sepsis'. *J Thromb Haemost, 16*(2), 231-241. doi:10.1111/jth.13911
32. Levi, M., van der Poll, T., ten Cate, H., and van Deventer, S. J. 1997. 'The cytokine-mediated imbalance between coagulant and anticoagulant mechanisms in sepsis and endotoxaemia'. *Eur J Clin Invest, 27*(1), 3-9. doi:10.1046/j.1365-2362.1997.570614.x
33. Semeraro, N., Ammollo, C. T., Semeraro, F., and Colucci, M. 2015. 'Coagulopathy of acute sepsis'. *Semin Thromb Hemost, 41*(6), 650-658. doi:10.1055/s-0035-1556730
34. Iba, T., Nisio, M. D., Levy, J. H., Kitamura, N., and Thachil, J. 2017. 'New criteria for sepsis-induced coagulopathy (sic) following the revised sepsis definition: A retrospective analysis of a nationwide survey'. *BMJ Open, 7*(9), e017046. doi:10.1136/bmjopen-2017-017046
35. Feng, J., Wang, L., Feng, Y., Yu, G., Zhou, D., and Wang, J. 2022. 'Serum levels of angiopoietin 2 mrna in the mortality outcome prediction of septic shock'. *Exp Ther Med, 23*(5), 362. doi:10.3892/etm.2022.11289
36. Statz, S., Sabal, G., Walborn, A., Williams, M., Hoppensteadt, D., Mosier, M., Rondina, M. *et al.* 2018. 'Angiopoietin 2 levels in the risk stratification and mortality outcome prediction of sepsis-associated coagulopathy'. *Clin Appl Thromb Hemost, 24*(8), 1223-1233. doi:10.1177/1076029618786029
37. Thamm, K., and David, S. 2016. 'Role of angiopoietin-2 in infection - a double-edged sword?'. *Cytokine, 83*, 61-63. doi:10.1016/j.cyto.2016.03.019
38. Wada, T., Jesmin, S., Gando, S., Sultana, S. N., Zaedi, S., and Yokota, H. 2012. 'Using angiogenic factors and their soluble receptors to predict organ dysfunction in patients with disseminated intravascular coagulation

associated with severe trauma'. *Crit Care, 16*(2), R63. doi:10.1186/cc11309
39. Liu, X., Yu, Y., and Zhu, S. 2018. 'Inflammatory markers in postoperative delirium (pod) and cognitive dysfunction (pocd): A meta-analysis of observational studies'. *PLoS ONE, 13*(4), e0195659. doi:10.1371/journal.pone.0195659
40. Szederjesi, J., Almasy, E., Lazar, A., Hutanu, A., and Georgescu, A. 2015. 'The role of angiopoietine-2 in the diagnosis and prognosis of sepsis'. *J Crit Care Med (Targu Mures), 1*(1), 18-23. doi:10.1515/jccm-2015-0004
41. van Meurs, M., Kumpers, P., Ligtenberg, J. J., Meertens, J. H., Molema, G., and Zijlstra, J. G. 2009. 'Bench-to-bedside review: Angiopoietin signalling in critical illness - a future target?'. *Crit Care, 13*(2), 207. doi:10.1186/cc7153
42. Maisonpierre, P. C., Suri, C., Jones, P. F., Bartunkova, S., Wiegand, S. J., Radziejewski, C., Compton, D. *et al.* 1997. 'Angiopoietin-2, a natural antagonist for tie2 that disrupts in vivo angiogenesis'. *Science, 277*(5322), 55-60. doi:10.1126/science.277.5322.55
43. Ganter, M. T., Cohen, M. J., Brohi, K., Chesebro, B. B., Staudenmayer, K. L., Rahn, P., Christiaans, S. C. *et al.* 2008. 'Angiopoietin-2, marker and mediator of endothelial activation with prognostic significance early after trauma?'. *Ann Surg, 247*(2), 320-326. doi:10.1097/SLA.0b013e318162d616
44. David, S., Mukherjee, A., Ghosh, C. C., Yano, M., Khankin, E. V., Wenger, J. B., Karumanchi, S. A. *et al.* 2012. 'Angiopoietin-2 may contribute to multiple organ dysfunction and death in sepsis*'. *Crit Care Med, 40*(11), 3034-3041. doi:10.1097/CCM.0b013e31825fdc31
45. Jesmin, S., Wada, T., Gando, S., Sultana, S. S., and Zaedi, S. 2013. 'The dynamics of angiogenic factors and their soluble receptors in relation to organ dysfunction in disseminated intravascular coagulation associated with sepsis'. *Inflammation, 36*(1), 186-196. doi:10.1007/s10753-012-9534-6
46. Giuliano, J. S., Jr., Lahni, P. M., Harmon, K., Wong, H. R., Doughty, L. A., Carcillo, J. A., Zingarelli, B. *et al.* 2007. 'Admission angiopoietin levels in children with septic shock'. *Shock, 28*(6), 650-654. doi:10.1097/shk.0b013e318123867b
47. Mankhambo, L. A., Banda, D. L., Group, I. P. D. S., Jeffers, G., White, S. A., Balmer, P., Nkhoma, S. *et al.* 2010. 'The role of angiogenic factors in predicting clinical outcome in severe bacterial infection in malawian children'. *Crit Care, 14*(3), R91. doi:10.1186/cc9025
48. Orfanos, S. E., Kotanidou, A., Glynos, C., Athanasiou, C., Tsigkos, S., Dimopoulou, I., Sotiropoulou, C. *et al.* 2007. 'Angiopoietin-2 is increased in severe sepsis: Correlation with inflammatory mediators'. *Crit Care Med, 35*(1), 199-206. doi:10.1097/01.CCM.0000251640.77679.D7
49. Ricciuto, D. R., dos Santos, C. C., Hawkes, M., Toltl, L. J., Conroy, A. L., Rajwans, N., Lafferty, E. I. *et al.* 2011. 'Angiopoietin-1 and angiopoietin-2 as clinically informative prognostic biomarkers of morbidity and mortality in severe sepsis'. *Crit Care Med, 39*(4), 702-710. doi:10.1097/CCM.0b013e318206d285
50. Fiedler, U., and Augustin, H. G. 2006. 'Angiopoietins: A link between angiogenesis and inflammation'. *Trends Immunol, 27*(12), 552-558. doi:10.1016/j.it.2006.10.004
51. Parikh, S. M., Mammoto, T., Schultz, A., Yuan, H. T., Christiani, D., Karumanchi, S. A., and Sukhatme, V. P. 2006. 'Excess circulating angiopoietin-2 may contribute to pulmonary vascular leak in sepsis in humans'. *PLoS Med, 3*(3), e46. doi:10.1371/journal.pmed.0030046
52. van der Heijden, M., van Nieuw Amerongen, G. P., Koolwijk, P., van Hinsbergh, V. W., and Groeneveld, A. B. 2008. 'Angiopoietin-2, permeability oedema, occurrence and severity of ali/ards in septic and non-septic critically ill patients'. *Thorax, 63*(10), 903-909. doi:10.1136/thx.2007.0873van der Poll, T., Levi, M., Hack, C. E., ten Cate, H., van Deventer, S. J., Eerenberg, A. J., de Groot, E. R. *et al.* 1994. 'Elimination of interleukin 6 attenuates coagulation activation in experimental endotoxemia in chimpanzees'. *J Exp Med, 179*(4), 1253-1259. doi:10.1084/jem.179.4.1253
53. Minanti BR, Soelistijo SA, Pranoto A. Characteristic profiles of patients with diabetes mellitus and COVID-19 during the second epidemic wave in East Java, Indonesia: a retrospective study. Bali Med J. [Internet]. 2023 Apr. 5 [cited 2023 Aug. 15];12(1):1120-6. Available from: https://www.balimedicaljournal.org/index.php/bmj/article/view/4208
54. Pangarsa EA, Setiawan B, Santosa D, Naibaho RM, Rizky D, - S, Tobing ML, Suharti C. Position paper from the Indonesian Society of Thrombosis and Hemostasis (InaSTH), Semarang chapter: Management of coagulopathy in COVID-19. Bali Med J. [Internet]. 2020 Jul. 14 [cited 2023 Aug. 15];9(2):482-8. Available from: https://www.balimedicaljournal.org/index.php/bmj/article/view/1841
55. Retnaningsih R, Tugasworo D, Andhitara Y, Ardhini R, Kurnianto A, Bunyamin J, Utami FS, Sogata IA, Hairuzaman H. Hemorrhagic transformation in SARS-CoV-2 infected patients: case reports from Indonesia. Bali Med J. [Internet]. 2021 Dec. 27 [cited 2023 Aug. 15];10(3):992-5. Available from: https://www.balimedicaljournal.org/index.php/bmj/article/view/2254.