INDONESIAN JOURNAL OF ANESTHESIOLOGY AND REANIMATION
Volume 3 (2), July 2021 : 62-70

Original Article

VALIDITY OF URINE SYNDECAN-1 AS A PREDICTOR OF ACUTE KIDNEY INJURY IN PEDIATRIC SEPSIS PATIENTS

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ABSTRACT

Introduction: AKI (Acute Kidney Injury) complications in sepsis patients generally occur 24 hours after admission to ICU. Creatine Serum Concentration is a standard parameter to diagnose AKI. Unfortunately, the changes in creatine serum concentration will only be seen several days after the decrease of renal function to 50%. The low detection ability has been linked with time loss before preventive therapy is commenced. Furthermore, this instigates the need for biomarkers to ensure early detection. **Objective:** This study aimed to identify cut-off points of urine syndecan-1 and to measure the prediction ability of urine syndecan-1 towards the AKI occurrence in pediatric sepsis patients. **Materials and methods:** This study was a prospective cohort study performed at a single center in Dr. Soetomo General Hospital, Surabaya. The inclusion criterion was all children admitted to the resuscitation room from October until December 2019. Furthermore, urine sampling is carried out at 0, 6, 12, and 24 hours for a syndecan-1 urine examination, and every procedure performed on the patient will be recorded. This action were continued up to the third day and aimed to evaluate some factors related to AKI at 48-72 hours of admission. **Result and Discussion:** Out of 41 pediatric sepsis patients, 30 patients fulfilled the inclusion criteria and 57% had AKI. The value of urine syndecan-1 at hour-0 and hour-6 was significantly featured a cut-off point. **Conclusion:** The value of urine syndecan-1 at hour-0 and hour-6 are valid parameter to predict the occurrence of AKI grade 1, 2, and 3 in pediatric septic patients at 48-72 hours after their hospital admission. The best cut-off value of urine syndecan-1 at the 0th hour was 0.67 ng/ml.

Keywords: Acute Kidney Injury; Creatinine Serum; Medicine; Pediatric Septic Patient; Predictor of AKI; Urine Syndecan-1

ABSTRAK

Pendahuluan: Komplikasi acute kidney injury (AKI) pada pasien sepsis umumnya terjadi 24 jam setelah masuk ICU. Konsentrasi kreatinin serum merupakan parameter yang umum digunakan untuk mendiagnosis AKI. Sayangnya, perubahan konsentrasi kreatinin serum ini akan terlihat setelah beberapa hari saat sudah terjadi penurunan 50% fungsi ginjal. Kemampuan deteksi yang rendah ini mengakibatkan upaya pencegahan AKI lebih dini tidak dapat dilakukan. Oleh sebab itu perlu dicari biomarker yang memiliki kemampuan deteksi AKI lebih dini. **Tujuan:** Penelitian ini bertujuan untuk mencari *cut off point* kadar syndecan-1 dalam urine (urine syndecan-1) dan mengukur kemampuan sebagai prediktor kejadian AKI pada pasien sepsis anak. **Bahan dan Metode:** Penelitian ini merupakan studi kohort prospektif yang dilakukan di RSUD Dr. Seotomo Surabaya. Kriteria inklusi adalah semua anak yang dirawat di ruang resusitasi mulai Oktober hingga Desember 2019. Selanjutnya pengambilan sampel urin dilakukan pada jam 0, 6, 12, dan 24 jam untuk pemeriksaan urin sindekan-1, dan setiap prosedur yang dilakukan pada pasien akan dicatat. Kegiatan Ini dilanjutkan sampai dengan hari ketiga dan bertujuan untuk mengevaluasi faktor-faktor yang berhubungan dengan AKI pada 48-72 jam setelah masuk rumah sakit. **Hasil dan Pembahasan:** Dari total 41 pasien anak sepsis, 30 memenuhi kriteria inklusi, dan 57% mengalami AKI. Kadar syndecan-1 dalam urin pada jam-0 dan jam-6 secara signifikan menggambarkan *cut off point*. **Kesimpulan:** Kadar syndecan-1 dalam urine pada jam-0 dan jam-6 merupakan parameter yang valid untuk memprediksi kejadian AKI grade 1, 2, dan 3 pada pasien sepsis anak dalam kurun 48-72 jam setelah masuk rumah sakit. Nilai *cut-off* terbaik kadar syndecan-1 dalam urine pada jam ke-0 adalah 0,67 ng /ml

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Kata kunci: *Acute Kidney Injury*; Serum Kreatinin; Kedokteran; Pasien Sepsis Anak; Prediksi AKI; Urin Sindekan-1

Article info: Received March 2nd 2021, Received in Revised March 16th 2021, Accepted July 1st 2021

INTRODUCTION

AKI (Acute Kidney Injury) is one of the complications reported in sepsis patients, often related to poor outcomes and mortality. Based on a global study, this challenge occurs in a fifth of pediatric cases (1), and sepsis generally appears within 24 hours of admission to the ICU (2). In current clinical practice, AKI diagnosis involves the measurement of creatinine serum concentration. However, this parameter barely changes until several days, when about 50% of kidney function has lost. Therefore, the time to perform preventive therapy is not available due to low detection ability (3); hence biomarkers for early recognition are needed.

Sepsis disturbs oxygen delivery within the microcirculation that leads to a possible decline inflow, and other diffusion disorders, resulting from edema and organ inflammation. Despite the poor understanding of the exact consequences from this modifications, sepsis increases the expression of inflammatory cytokines and leukocyte activity, subsequently causing a capillary and micro-thrombus blockage. This leads to reactive oxygen species production and induction of nitric oxide synthase which responsible for further damages in the endothelium and glycocalyx, affiliated with structural and functional changes (4–6). The presence of glycocalyx in the kidney is an early indicator of microcirculation disorders during sepsis, and the degradation process further contributes to the reported symptoms (7).

The endothelial cell surface is coated with a carbohydrate-rich layer, featuring an average thickness of 0.1 to 2 mm. The endothelial cell surface consists of hyaluronic acid (HA) string, heparan sulfate (HS) chain, and about 50-90% endothelial glycosaminoglycans, consists of two proteoglycan families of syndecan and glypican. Furthermore, the unique structural location provides a passive barrier to water and solute transport (regulation of vascular permeability) and interactions between circulatory and endothelial cells (regulation of leukocyte trade). The site also functioned as a sensor of mechanical strength in terms of voltage and pressure, protects cell surface receptors, and prevents receptor hyperactivation. However, this structure is vulnerable, with a tendency to degrade under the influence of various stressors, including endotoxins, ischemia/hypoxia/reperfusion, and oxidative stress. Some studies detect the change in 20 minutes to 6 hours post-insult (8,9).

Syndecan-1 is the main constituent of endothelial glycocalyx (a protective layer luminally covering the endothelium) measured in plasma as a biomarker of possible damage. However, the compound is also expressed in renal tubular cells. Studies have shown the ability to limit kidney damage after ischemia-reperfusion injury and promote tubular damage recovery; hence extensive expression is implicated in kidney injury (10–12). Subsequently, there is a damage in glomerular endothelium, known to perform filtration functions. This barrier destruction caused the release of syndecan-1, which will be detected in urine (12).

The mechanism of kidney damage reported in sepsis patients is related to changes in renal tubular epithelial cells. Besides, the initiation phase is characterized by a decline in renal blood flow to levels that are affiliated

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with cellular ATP depletion, followed by injury and acute tubular epithelial cell dysfunction. Moreover, renal ischemia in vivo rapidly induces several structural and functional changes in renal proximal tubular epithelial cells, and the extent depends on the severity and duration of ischemic injury. These changes usually fail to kill cells but interfere with renal tubular epithelial and endothelial blood vessel cells' ability to maintain normal kidney function (5,6).

MATERIALS AND METHODS

Study Design, Setting, and Patient Selection

This research was a prospective cohort study performed at a single center in Dr. Soetomo General Hospital, Surabaya. The inclusion criterion was all children admitted to the resuscitation room from October to December 2019. Therefore, the consented patients were enrolled into the study protocol: pediatric patients aged over three months - 18 years with a suspected sepsis and septic shock diagnosis, assessed according to the PELOD-2 score criteria by Consensus on Sepsis Management in Pediatrics. However, the exclusion criteria were patients with 1) pre-existing kidney disease, 2) pre-existing heart disease, 3) malignancy, intoxication history, infection, 4) sepsis diagnosed by a previous hospital. 4) PELOD-2 score < 7.

Data Collection and Procedures

The patient's demographic data and medical history were evaluated on admission into the resuscitation room. According to the guidelines for sepsis treatment, a standard protocol for proper handling was carried out(13). The amount of fluid entering and leaving was observed, and the researcher quantitatively evaluated the urine every hour. Furthermore, vasopressors, inotropic drugs, and ventilator applications were noted. This procedures were followed by standard laboratory tests and repeated daily laboratory examinations to determine the occurrence of AKI up to the third day. Also, PELOD-2 and PRISM scores were assessed to stratify the disease severity.

Biomarker Measurement

Urine syndecan-1 examination uses an ELISA kit produced by ELABSCIENCE® with catalog number E-EL-H1298. In addition, the detection distance was 0.16-10 ng / ml, with sensitivity of 0.1 ng / mL, and variation coefficient of <10%. The assessment process was performed four times, from admission into the resuscitation room, the 3rd, 6th, 9th, 12th, 15th, 24th, to 27th hours. Also, 2 ml of new urine was collected from the catheter to obtain the appropriate sample.

Outcome

The primary study output includes the occurrence of AKI in 48 to 72 hours after hospital admission, based on the Kidney Disease Improving Outcomes (KDIGO) definition (4). The primary study output inferred this result because of the increased of serum creatinine levels, and stage 1 AKI has defined as 1.5-1.9 times the initial value, or 0.3 mg / dL increase in 48 hours. Furthermore, stage 2 is characterized by up to 2-2.9 times upsurge from the primary value and three times for stage 3. Based on the urine output, the respective values were <0.5 ml / KgBB / hour for 6-12 hours, <0.5 ml / KgBB / hour for >12 hours, and <0.3 ml / kg / hour for 24 hours or anuria for 12 hours (4).

Statistical Analysis

Continuous variables were compared using the t-test or the Mann-Whitney test, while the categorical variables were evaluated using the Chi-Square or Fisher's exact test. Subsequently, this study performed descriptive analysis, and the cut-off determination used the ROC curve, where the AUC ascertains validity and Younden's Index verifies the best cut-off from

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others. Furthermore, sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios were calculated. This was followed by the Kappa association test and the Mc Nemar comparison test.

RESULTS AND DISCUSSION

This research included forty-one participants, and 11 excluded because death was reported in less than the first 24 hours. Based on the final analysis results, 30 patients were selected after fulfilling the inclusion criteria, and AKI was prevalent, implicated in 57% of all pediatric sepsis cases. This data was evidenced by the data of demographics, disease origin, characteristics of therapy, and outcome, as shown in Table 1. The data recorded showed no significant differences between patients with and without AKI.

Table 1. The demographic, origin of the disease, therapy, and outcome

Parameter	(n = 13) Non-AKI	(n = 17) AKI gr. 1-3	*p*-value
Demographic Parameter			
Age (months), median (range)	22 (8 – 67)	11 (3 – 86)	0.232*
Male, n (%)	9 (69.2)	12 (70.6)	1.000*
PELOD-2 score, median (range)	11 (7 – 17)	12 (7 – 17)	
Lactate when entering, median (range)	1.71 (0.64 – 7.14)	2.2 (0.7 – 7.6)	0.32* 0.983*
PRISM-3 score, mean±SD	18.08±6.47	20.18±5.2	0.333****
IL-6, median (range)	175.02 (15,1-1280,4)	298.18 (12,39-5919)	0.250*
Origin of Disease			
Respiration, n (%)	4 (30.8)	7 (41.2)	0.708**
Cardiovascular and shock, n (%)	5 (38.5)	11 (64.7)	0.269**
neurology, n (%)	7 (53.8)	9 (52.9)	1.000**
Gastrointestinal, (%)	9 (69.2)	12(70.6)	1.000**
Therapy Characteristics			
Ventilator, n (%)	11 (84.6)	17 (100)	0.179**
Vassopressor and Inotropic agents, n (%)	5 (38.5)	8 (47.1)	0.721**
Diuretic, n (%)	0 (-)	2 (11.8)	0.492**
Outcome			
Ventilator (days), median (range)	4 (0 – 16)	4 (1 – 34)	0.445*
PICU LOS (days), median (range)	4 (2 – 16)	6 (1,5 – 34)	0.487*
Mortality, n (%)	4 (30.8)	8 (47.1)	0.465**

*Mann-Whitney test **Fisher-exact test ***Chi-square test ****2 sample *t*-test

Table 2 showed the median value of each Urine syndecan-1 collected and compared between participants with and without AKI. The result identified higher values in patients with AKI.

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Table 2. Comparison of Urine Syndecan-1 value and AUC between group 'No AKI' and 'AKI' to the incidence of acute kidney injury

Syndecan-1 (hour)	Non-AKI (n=13)	AKI gr. 1-3 (n = 17)	p-value
0^{th}	0,55 (0,11-3,44)	1,31 (0,17 – 2,91)	**0.021**
6^{th}	0,46 (0,08 – 2,26)	1,18 (0,08 – 6,81)	**0.034**
12^{th}	0,98 (0,06 – 2,4)	1,07 (0,13 – 5,72)	0.451
24^{th}	1,16 (0,16 – 6,17)	1,29 (0,1 – 7,91)	0.786
0^{th} + 6^{th}	0,5 (0,08-3,44)	1,255 (0,08-6,81)	**0.003**
All	0,73 (0,06-6,17)	1,19 (0,08-7,91)	**0.005**

*Mann-Whitney test

A urine assessment of syndecan-1 was performed. The significant values recorded at the 0th and 6th hours, and all outcomes were combined into one considerable value. Figure 1 shows the significant amount of Syndecan-1 in the urine, based on the comparison made with AUC-ROC, which differentiate the occurrence of AKI into grade 1, 2, or 3.

The urine syndecan-1 value recorded at the 0th hour has a balanced sensitivity and specificity value at 0.67 ng/ml. In comparison, 0.78 ng/ml was reported on the 6th hour, with the sensitivity and specificity values shown in Table 3. Furthermore, the cut-offs have equality and association with AKI occurrence in the next 48 to 72 hours, thus validating syndecan-1 urine as a valid predictor of AKI in pediatric sepsis patients.

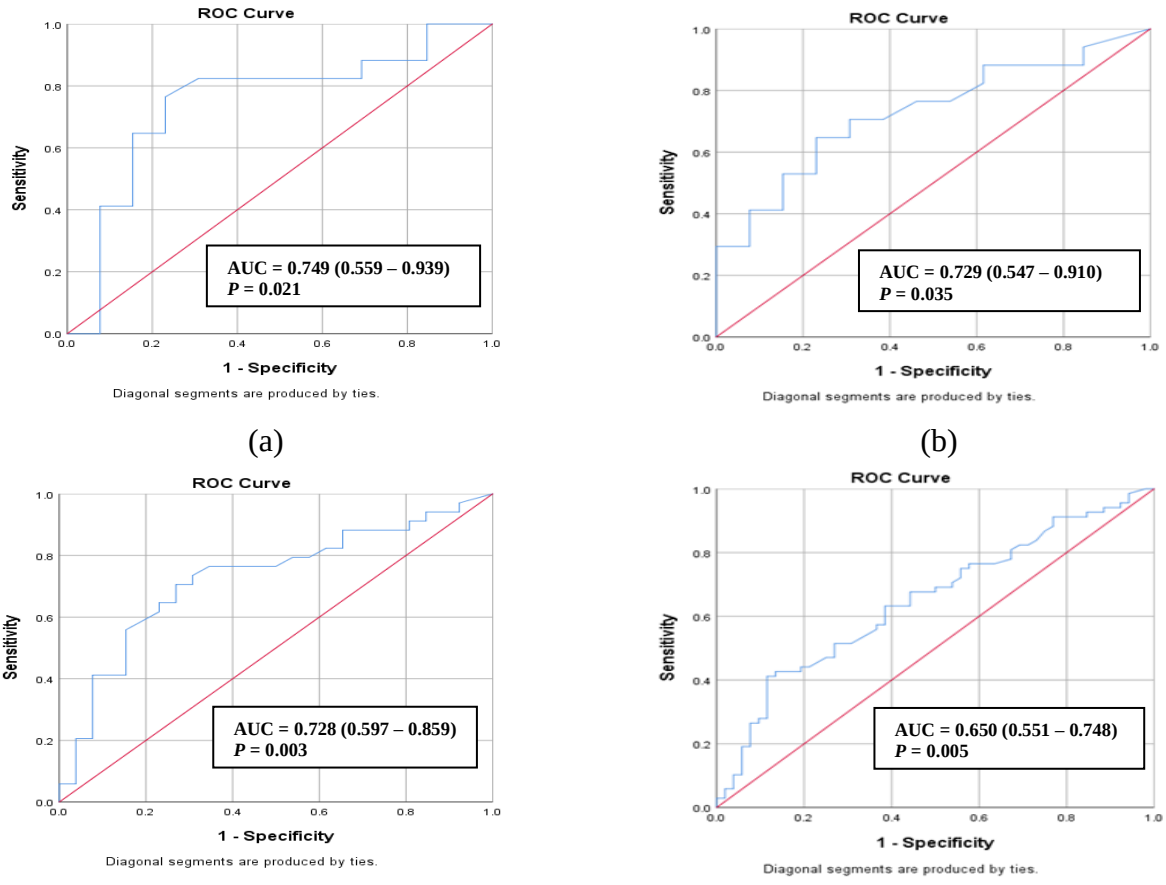

Figure 1. Ability to diagnose Urine syndecan-1 at the 0th hour (a); 6th hour (b); 0th+6th hours (c); and all results (d) to detect AKI

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Therefore, it was essential to derive a cut-off value for both the 0th and 6th hours because of the significant differences achieved by combining both values. The cut-off value was estimated at 0.71 ng/ml, with varied sensitivity and specificity. Therefore, a ROC curve is made because the overall syndecan-1 ratio between AKI and no AKI was significant. A cut-off value of 1 ng/ml was obtained, characterized by similarities in sensitivity and specificity in both the 0th and 6th hours (Table 3). A cut-off value of 1 ng/ml was obtained, characterized by similarities in sensitivity and specificity in both the 0th and 6th hours (Table 3).

Table 3. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), likelihood ratio (LR), McNemar, Kappa, and AUC on Urine Syndecan-1 *cut-off*

Parameter	Results					
	Syndecan-1 (hour)					
	0th	0th	0th	6th	6th	6th
Cut-off	0.67 ng/ml	0.71 ng/ml	1 ng/ml	0.78 ng/ml	0.71 ng/ml	1 ng/ml
Sensitivity (%)	76	71	65	71	71	65
Specificity (%)	77	77	77	69	69	77
Positive predictive value (%)	81	80	79	75	75	79
Negative predictive value (%)	71	67	63	64	64	63
Likelihood ratio (+)	3.31	3.06	2.8	2.29	2.29	2,8
Likelihood ratio (-)	0.31	0.38	0.46	0.42	0.42	0,46
Prevalence	57	57	57	57	57	57
Likelihood ratio (*p*)	8.86 (0.004)	6.946 (0.008)	5.336 (0.021)	4.81 (0.028)	4.81 (0.028)	5.336 (0.021)
Mc Nemar test (*p*)	1.000	0.727	0.508	1.000	1.000	0.508
Kappa (*p*)	0.529 (0.004)	0.467 (0.024)	0.405 (0.024)	0.395 (0.03)	0.395 (0.03)	0.405 (0.024)
Relative risk	2.84 (1.202-6.727)	2.4 (1123-5.127)	2.095 (1.052-4.174)	2.1 (0.984-4.48)	2.1 (0.984-4.48)	2.095 (1.052-4.174)
Youden's Index	0.53	0.48	0.42	0.4	0.4	0.42

The endothelial glycocalyx functioned as an excellent permeability barrier and a binding deterrent against blood. Furthermore, a disorder in this structure has known to increase capillary permeability, instigate the attachment of leukocytes and platelets, alongside tissue edema and inflammation, leading to an increase in the procoagulant state (14). The extent of damage is indicated by syndecan-1, which serves as a biomarker, characterized by an increase after cardiac surgery (14,15) or heart failure (16). Despite not being a kidney-specific indicator, there is an evidence of endothelial injury playing an essential role in the pathophysiology of AKI, especially the sepsis-related form (17).

Another thing is that syndecan-1 is inversely proportional to kidney function. The

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renal vascular endothelium is a significant target in several disease processes. Those processes are including glomerular nephritis, vasculitis, lupus nephritis, preeclampsia, hemolytic uremic syndrome, ischemic acute renal failure, renal transplant rejection, and chronic progressive kidney disease. During sepsis, the immune system is first activated and becomes hyperactive, leading to uncontrolled excessive immune reactions, with a tendency to harm rather than protect. The hyperactive phase features the presence of proinflammatory cytokines, structural and functional modification. This is assumed to support the septic process in leukocyte adhesion with endothelial cells, which then switch from anticoagulant to procoagulant state, subsequently changing the barrier function, increasing permeability, and vasomotor tone disorders.

Furthermore, an upsurge in renal vascular resistance results from sepsis induced vasoconstriction, endothelium leakage, tissue edema, leukocyte adhesion to endothelial cells, and micro thrombosis. The kidney is a unique organ with two layers of capillaries, glomerulus and peritubular, linked with the arterioles. The structure is observed as different vascular compartments connected in series with separate circuits for each, with the inherent microcirculation and macrocirculation appearing connected and dependent on one another (14–17). This series connection explains why syndecan-1 is detected in urine, regardless of tubular injury (14).

Following experimental ischemic injuries, the upsurge in Syndecan-1 expression influenced survival and tubular repair in mice (10). However, syndecan-1 in human is identified in the renal allografts, with terms associated with functional improvement (11). The concentration was evaluated at the beginning of the hospital admission, with the assumption of kidney injury on hospitalization and reflecting severity. This application is due to the ability of syndecan-1 as a biomarker during kidney regeneration (18).

Other studies revealed that the mean urine ACR was 10.5 (3-88) mg/g, and the mean syndecan-1 level was 27.7 (SD 2.24) ng/mL (19).

This study is expected to bring about significant changes, since based on the research, 56.7% of patients suffered from AKI septic disease (20).

CONCLUSION

In conclusion, the urine syndecan-1 evaluated at the 0th and 6th hours was established as a valid predictor of AKI within 48-72 hours in pediatric sepsis patients. The best outcome was observed at the 0th hour, featuring a cut-off of 0.67 ng/ml and the highest Younden's index.

Research Limitations

This study had several limitations, including the use of one center, a relatively low number of patients included, and flawed cost analysis. Therefore, it was difficult to derive definitive conclusions about the use of urine syndecan-1 to predict AKI occurrence. However, the technique was estimated to function as a potential non-invasive biomarker. The ELISA syndecan-1 test is only available for research use and not for diagnostic or therapeutic purposes. Hence, there is a need to develop analytical tests for proper validation and support in clinical practice.

REFERENCES

1. Fitzgerald J, Basu R, Akcan-Arikan A, Izquierdo L, Hassinger A, Olave BP, et al. Acute Kidney Injury in Pediatric Severe Sepsis. Crit Care Med. 2016;44(12):2241–50.

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** 10.20473/ijar.V3I22021.62-70

2. Bagshaw S, George C, Bellomo R, Committee the ADM. Early acute kidney injury and sepsis: a multicentre evaluation. Crirtical care. 2008;12(2):47.
3. Wheeler D, Devarajan P, Ma Q, Et A. Serum neutrophil gelatinase-associated lipocalin (NGAL) as a marker of acute kidney injury in critically ill children with septic shock. Crit Care Med. 2008;36(4):1297–303.
4. Poston J, Koyner J. Sepsis associated acute kidney injury. Br Med J. :k4891.
5. Basile D, Anderson M, Sutton T. Pathophysiology of acute kidney injury. Compr Physiol. 2012;2(2):1303–53.
6. Zarbock A, Gomez H, Kellum J. Sepsis-induced acute kidney injury revisited: pathophysiology, prevention and future therapies. Curr Opin Crit Care. 2014;20(6):588–95.
7. Song J, Zullo J, Lipphardt M, Et A. Endothelial glycocalyx—the battleground for complications of sepsis and kidney injury. Nephrol Dial Transpl. 2018;33(2):203–11.
8. Annecke T, Fischer J, Hartmann H, Et A. Shedding of the coronary endothelial glycocalyx: Effects of hypoxia/reoxygenation vs ischaemia/reperfusion. Br J Anaesth. 2011;107(5):679–86.
9. Schmidt E, Yang Y, Janssen W, Et A. The pulmonary endothelial glycocalyx regulates neutrophil adhesion and lung injury during experimental sepsis. Nat Med. 2012;18(8):1217–23.
10. Celie J, Katta K, Adepu S, Et A. Tubular epithelial syndecan-1 maintains renal function in murine ischemia/reperfusion and human transplantation. Kidney Int. 2012;81(7):651–61.
11. Adepu S, Rosman C, Dam W, Et A. Incipient renal transplant dysfunction associates with tubular syndecan-1 expression and shedding. Am J Physiol Physiol. 2015;309(2):F137–45.
12. Haraldsson B. The endothelium as part of the integrative glomerular barrier complex. Kidney Int. 2014;85(1):8–11.
13. Davis A, Carcillo J, Aneja R, Deymann A, Lin J, Nguyen T, et al. American College of Critical Care Medicine Clinical Practice Parameters for Hemodynamic Support of Pediatric and Neonatal Septic Shock. Crit Care Med. 2017;45(6):1061–93.
14. Cavalcante C de MB, Branco KC, Júnior VP, Et A. Syndecan-1 improves severe acute kidney injury prediction after pediatric cardiac surgery. J Thorac Cardiovasc Surg. 2016;152(1):178–86.
15. Ferrer N, Cavalcante C de MB, Branco K, ET A. Urinary {Syndecan}-1 and acute kidney injury after pediatric cardiac surgery. Clin Chim Acta. 2018;485:205–9.
16. Parahyba M, Maria A, Martins C, Libório A. Syndecan-1 in Acute Decompensated Heart Failure. Circ J. 2015;79(7):1511–9.
17. Verma S, Molitoris B. Endothelial Injury and Microvascular Dysfunction in Acute Kidney Injury. Semin Nephrol. 2015;35(1):96–107.
18. Miyake M, Lawton A, Dai Y, Et A. Clinical implications in the shift of syndecan-1 expression from the cell membrane to the cytoplasm in bladder cancer. BMC Cancer. 2014;14(1).
19. Saragih R, Pudjiadi A, Tambunan T, Satari H, Aulia D, Bardosono S, et al. Correlation between urinary albumin to creatinine ratio and systemic glycocalyx degradation in pediatric sepsis. Med J Indones. 2018;27(3):194–200.
20. Budi NS, Utariani A, Hanindito E, Semedi BP, Asmaningsih N. The validity of urinary neutrophil gelatinase-associated lipocalin (Ngal) as a biomarker of acute

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** 10.20473/ijar.V3I22021.62-70

kidney injury in pediatric patients with sepsis. Crit Care Shock. 2021;24(2):93–103.

Available at https://e-journal.unair.ac.id/IJAR | **DOI:** 10.20473/ijar.V3I22021.62-70