Correlation between elevated TNF-a, syndecan-1

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Correlation between elevated TNF-α, syndecan-1, and urine IL-18 levels in acute kidney injury following on pump cardiac surgery

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Abstract

***Objective*: This study aims to determine the correlation between elevated tumor necrosis factor alpha (TNF-α) and syndecan-1 with urine interleukin (IL)-18 levels as post-cardiac surgery-related acute kidney injury (AKI) marker.**

***Design*: This study was an analytical observational study with a cross sectional design.**

***Setting*: This study was conducted at Dr. Wahidin Sudirohusodo Central General Hospital. The period of study was from October 2019 to February 2020.**

***Patients and participants*: Population of study was all patients who underwent adult on pump cardiac surgery. Study samples were patients who were included in inclusion criteria. Patient's characteristics were presented as frequency and percentage.**

***Measurement and results*: All interval data with normal distribution were analyzed using T-pair test. Spearman correlation test was performed to determine the correlation between TNF-α, syndecan-1, and IL-18 levels toward AKI incidence. The data was presented with odds ratio (OR) 95% confidence interval (CI). There were 33 subjects who underwent adult cardiac surgeries including coronary artery bypass grafting (CABG), valve, and congenital disorder surgeries. Twenty-one people (63.6%) had AKI and 12 people (36.4%) did not. In AKI patients there was an increased syndecan-1 level of 61.94±36.58 ng/ml with relative risk (RR)=1.11 (95% CI 1.02-1.21), TNF-α level of 6.85±4.05 pg/ml, RR=2.61 (95% CI 1.19-5.71), and IL-18 level of 205.5±121.35 pg/ml, RR=1.38 (95% CI 1.06-1.79). There was a significant correlation between syndecan-1, TNF-α, and IL-18 levels. AKI incidence in post-cardiac surgery patients had a significant elevated IL-18 level (p=0.016), with RR=1.38 (95% CI 1.06-1.79).**

***Conclusion*: Elevated syndecan-1, TNF-α, and IL-18 levels were correlated with AKI incidence in post-cardiac surgery patients.**

Key words: Acute kidney injury, IL-18, on pump cardiac surgery, syndecan-1, TNF-α.

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Introduction

Post-cardiac surgery-related acute kidney injury (AKI) is a complex problem and commonly occurs with an incidence of up to 30% in Europe and leads to an increased mortality in near and long term. (1) Data on post-cardiac surgery AKI incidence in Indonesia from a previous study showed an estimated incidence of 36.4% in post-pediatric heart surgery. (2)

To improve the accuracy of AKI diagnosis and management, it is necessary to detect AKI and its related complications as early as possible, therefore further deterioration of kidney function could be prevented. (3) Mechanism of injury that might be involved in AKI events after cardiac surgery includes microembolization, neurohormonal activation, exogenous and endogenous toxics, meta-

bolic factors as well as hemodynamic and inflammatory factors, ischemic reperfusion injury, and oxidative stress. (4)

Tumor necrosis factor (TNF)-α is one of the most important cytokines in heart surgery, where elevated level of TNF-α marks a more severe disease progression. (5) This represents the role of TNF-α on vascular endothelial damage as one of the pathomechanisms of post-cardiac surgery AKI, therefore it is one of variables that was included in this study.

Glycocalyx is one of the most susceptible structure towards oxidative stress, because reactive oxygen species (ROS) will trigger glycocalyx degradation, leading to vasoconstriction, leukocyte adhesions, and direct activation of immune reaction. (6) Glycocalyx is a vascular endothelial cells component that function as a barrier between blood and endothelium, maintains homeostasis by regulating vascular permeability, vascular tone, and leukocyte attachment. (7)

Several studies have been conducted to examine syndecan-1 level in cardiac surgery. A study reported a correlation of increased syndecan-1 level with acute renal failure incidence after pediatric heart surgery. (8) The cause of increased syndecan-1 level in correlation to elevated TNF-α level in adult heart surgery is still unknown. The lack of studies that examined syndecan-1 level as a marker of post-cardiac surgery AKI is an area of interest to study further, by examining its correlation to TNF-α level as a trigger for inflammatory mediators.

Ischemic refusion of kidneys is also an important factor of AKI after cardiopulmonary bypass (CPB) by initiating IL-18 expression, therefore increasing inflammatory response in kidneys. (9) Serum IL-18 is a sensitive biomarker for tubular injury assessment. (10) Urine IL-18 level gives more promising diagnostic value in clinical practice after CPB than serum creatinine and urine urine neutrophil gelatinase-associated lipocalin (NGAL) for diagnosis. (11) In this study, researchers will use urine IL-18 to assess post-cardiac surgery AKI incidence predictive value by comparing Kidney Disease: Improving Global Outcomes (KDIGO) criteria as a standard assessment of AKI incidence and assessing three biomarkers predictive and cut-off values for post-cardiac surgery AKI incidence.

Materials and methods

This study was an observational analytic study with a cross sectional study design. The population included in this study were patients who would undergo adult heart surgery on pump procedure. The study sample was patients who would undergo adult heart surgery procedures that met the inclusion criteria. The sample size formula for correlation test was used, that met a minimum sample size of 33 patients. Before the study was carried out, the researchers requested ethical approval (ethical clearance) from Biomedical Study Ethics Commission in Humans of Faculty of Medicine, Hasanuddin University and study permission (data collection) from Dr. Wahidin Sudirohusodo General Hospital. This study was in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Adult patients who underwent adult heart surgery procedures and met the inclusion criteria had given their written consent.

Adult patients who gave their written consent were subject to standard general anesthesia for their heart surgery. Hemodynamic assessment and preoperative sampling for TNF-α, syndecan-1, and IL-18 levels were conducted after anesthesia induction and intubation. Sampling were also conducted 2 hours after off-pump for TNF-α, syndecan-1, and urine IL-18 levels. Data analysis was carried out after all samples were collected within 4 months of study.

All patients were given standard perioperative management based on institutional guidelines. Anesthesia induction was carried out with intravenous midazolam (0.05-0.07 mg/kg) and sufentanil (1.5-2 µg/kg) or fentanyl 2-4 µg/kg and maintenance was conducted with inhaled sevoflurane and continuous fentanyl. Heparin was given at an initial dose of 300 IU/kg to reach activated clotting time (ACT) above 480 seconds or 3-4 times the patient's ACT baseline value. CPB circuit was primed with 1.6 l priming solution containing 100 ml of 20% albumin, 20% mannitol (0.5 g/kg), sodium bicarbonate (20 mEq), heparin (5000 IU), and natrium chloride (NaCl) or Ringer's lactate (RL). Non-pulsatile pump flow rate was maintained at a speed of 1.8-2.4 l/min/m^2 with mild hypothermia (32-33 °C). After CPB weaning, heparin antagonist, protamine sulfate (3 mg/kg), was given. All patients were transferred to intensive care unit (ICU) after surgery.

Norepinephrine (up to 0.5 µg/kg/min) was used as the first-line vasopressor and vasopressin (up to 4 IU/hour) was used as the second-line vasopressor. Milrinone or dobutamine was given to treat ventricular systolic dysfunction. Hematocrit level was maintained above 20% during CPB and 25% before and after CPB with packed red cells (PRC) transfusion and ultrafiltration/reinfusion of intraoperative blood rinse during CPB. Allogenic plasma products including fresh frozen plasma (FFP) and thrombocyte concentrate (TC) were

transfused according to clinician's advice based on prothrombin time (PT)/activated partial thromboplastin time (aPTT) and platelet count.

Venous blood samples were taken during anesthesia induction and 2 hours after surgery, centrifuged at a speed of 1000 x g for 15 minutes and stored at -80 °C for further analysis according to the company's kit instructions. Enzyme-linked immunosorbent assay (ELISA) method was used to measure serum syndecan-1, serum TNF-α, and urine IL-18 levels.

Serum creatinine level was assessed 1 day before surgery and every day for 1 week postoperatively. Additional measurements were made according to clinician's advice, with serum creatinine level measurement was performed within 7 days after surgery that was used for AKI diagnosis and grading.

Data of patients' characteristics were presented with frequency and percentage. All variables with interval data types were tested for their distribution using paired T test. To determine the correlation between TNF-α, syndecan-1, and IL-18 levels on AKI incidence, Spearman correlation test was performed. Data were presented as odds ratio (OR) with 95% confidence level. P-value <0.05 was considered statistically significant for all comparisons.

Results

The number of subjects who experienced AKI and did not experience AKI can be seen in **Figure 1**. From a total of 33 subjects who underwent adult heart surgery which included CABG, valve and congenital abnormalities surgery, 21 people (63.6%) had AKI and 12 people (36.4%) did not have AKI (**Table 1**).

Comparison between the three biomarkers at anesthesia induction showed no significant differences between AKI and non AKI groups in syndecan-1 (77.24±24.39 ng/ml vs 66.47±17.06 ng/ml), TNF-α (8.54±2.70 pg/ml vs 7.35±1.69 pg/ml), and IL-18 (256.27±80.92 pg/ml vs 220.52±56.60 pg/ml) levels (p=0.187), however, post-operative levels of the three biomarkers showed significant differences between AKI and non AKI groups: syndecan-1 139.18±49.58 ng/ml vs 69.10±20.66 ng/ml, TNF -α 15.39±5.48 pg/ml vs 7.64±2.28 pg/ml, IL-18 461.76±164.49 pg/ml vs 229.26±68.55 pg/ml (p<0.0001) (**Table 2**).

The correlation between these three biomarkers is shown in **Table 3**. From statistical analysis, syndecan-1, TNF-α, and IL-18 levels have significant correlation at time of induction, post-surgery, and their increase. This shows that these three biomarkers have a correlation between one another.

A multiple logistic regression analysis, that was performed to determine the correlation between the three biomarkers with post-cardiac surgery AKI incidence, is shown in **Table 4**, where IL-18 level increase was significant (p=0.016) with a relative risk of 1.38 (95% CI 1.06-1.79). This shows that post-cardiac surgery patients have a 138 times AKI risk if IL-18 level markedly increase.

Syndecan-1, TNF-α, and IL-18 accuracy on predicting AKI incidence in post-cardiac surgery patients can be seen in **Table 5**. Accuracy level of the three biomarkers is similar, which is 93.9%. This shows that elevated levels of syndecan-1 level above 18.6, TNF-α above 2.45, and urine IL-18 above 6.17, have high accuracy value as a diagnostic tool for AKI incidence in post-cardiac surgery patients.

Discussion

In our study, 21 out of 33 patients (63.6%) experienced post-cardiac surgery AKI. AKI incidence in our study was higher than in some other studies. (1,12-14) Differences in diagnostic methods to determine AKI could be one of the causes for difference in AKI incidence for each study. KDIGO criteria, which is a combination of Acute Kidney Injury Network (AKIN) and Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE) classification, is commonly used in diagnosing post-cardiac surgery AKI. (4,15)

Data from our study showed a significant difference between the three biomarkers levels post-surgery between AKI and non AKI groups (syndecan-1 139.18±49.58 ng/ml vs 69.10±20.66 ng/ml, TNF-α 15.39±5.48 pg/ml vs 7.64±2.28 pg/ml, and IL-18 461.76±164.49 pg/ml vs 229.26±68.55 pg/ml) with p<0.0001.

In our study, subjects who experienced AKI, there was an elevated syndecan-1 level of 61.94±36.58 ng/ml with a relative risk of 1.11 (95% CI 1.02-1.21), an elevated TNF-α level of 6.85±4.05 pg/ml with a relative risk of 2.61 (95% CI 1.19 -5.71), and an elevated IL-18 level of 205.5±121.35 pg/ml with a relative risk of 1.38 (95% CI 1.06-1.79). These elevated levels were significant when comparing subjects in AKI vs non AKI groups after cardiac surgery.

Syndecan-1 was markedly elevated after ischemic/reperfusion injury both in vivo and in vitro. (16) The critical role of hypoxia induces nuclear factor-kappa B (NF-κB) activation in CPB, therefore it leads to AKI due to glycocalyx damage. (17) Interestingly, this glycosaminoglycan epitope is known to provide a binding site for proinflammatory mol-

ecules such as IL-18, which is released by macrophages and is now an AKI biomarker after CPB. (18)

Statistical analysis in this study shows that the three biomarkers have a correlation between one another. This was confirmed through experimental animal studies which showed that TNF-α as an inflammatory mediator might reduce endothelial glycocalyx thickness. (19)

Endothelial injury is associated with inflammatory activation and structural alterations that might cause high expression of adhesion molecules and procoagulatory status associated with AKI pathophysiology. (20) Previous studies have reported that syndecan level in animal serum is directly correlated to inflammation severity. (21) This might be due to nuclear proteins cleavage that leads to extracellular domain delivery to matrix and then to circulation from several cytokines (IL-8, IL-17, TNF-α), which might induce nuclear protein cleavage by sheddases and directly interact with glycosaminoglycan chain. (22)

A study reported that perioperative syndecan-1 level was positively correlated with proinflammatory cytokines in patients undergoing cardiac surgery with CPB. (23) However, the correlation between elevated TNF-α level itself with syndecan-1 level has not been widely studied. A study found that elevated preoperative TNF-α level was associated with high syndecan-1 level. (24)

Preoperative inflammation that is presented by increased syndecan-1 level has a significant effect on subsequent post-CPB inflammation level, and is associated with a poor prognosis. (24) Serum syndecan-1 does not specifically originate from renal arteries because it is generally expressed during endothelial dysfunction and disruption of micro circulation at end organ dysfunction, and AKI might be considered as an example of end organ dysfunction that is often measured accurately after cardiac surgery. (16)

Our study shows that an elevated syndecan-1 level above 18.6 ng/ml, an elevated TNF-α level above 2.45 pg/ml, and an elevated urine IL-18 level above 61.7 pg/ml have high accuracy as a diagnostic tool for AKI incidence in post-cardiac surgery patients. Although some other studies showed a varying sensitivity and specificity syndecan cut-off levels and its correlation with postoperative complications, the suggested cut-off values were absolute levels, whereas in our study we used an elevated cut-off values for each biomarker and made this study different from previous studies. (24-28)

The strength of our study was that there was data showing a close correlation between the three biomarkers and acute renal failure incidence after cardiac surgery. However, this study could not show the evidence of other inflammatory factors which might be a confounding factor in analyzing the correlation between these three inflammatory biomarkers. Limited number of samples might also be the reason why statistical analysis results on several variables did not show a significant difference compared to other studies. Therefore, further study is needed with a larger number of samples and examine other biochemical factors that might act as confounding factors and having a role in AKI pathophysiology after cardiac surgery.

Conclusion

Elevated TNF-α level is associated with elevated syndecan-1 level in post-cardiac surgery patients. Increased syndecan-1 level is associated with increased urine IL-18 level in post-cardiac surgery patients. Increased TNF-α, syndecan-1, and urine IL-18 levels are associated with AKI incidence in post-cardiac surgery patients. An increase in syndecan-1 level above 18.6 ng/ml has a high accuracy and predictive value for AKI incidence in post-cardiac surgery patients, while an increase in urine IL-18 level above 61.7 pg/ml has a high accuracy and predictive value for AKI incidence in post-cardiac surgery patients. Further study with a larger sample needs to be conducted to determine the effects of perioperative factors for acute renal failure incidence after cardiac surgery. In addition, it is necessary to analyze other perioperative factors that might support AKI development after cardiac surgery.

Declaration of conflicting interests

The authors declare no potential conflicts of interests with respect to the research, authorship, and/or publication of this article.

Table 1. Comparison between AKI markers during anesthesia induction and post cardiac surgery in AKI and non AKI patients

Variables		AKI incidence		p value*
		Yes, n=21	No, n=12	
Syndecan-1 (ng/ml)	Induction	77.24±24.39	66.47±17.06	0.187
	Post-surgery	139.18±49.58	69.10±20.66	<0.0001
TNF-α (pg/ml)	Induction	8.54±2.70	7.35±1.69	0.187
	Post-surgery	15.39±5.48	7.64±2.28	<0.0001
IL-18 (pg/ml)	Induction	256.27±80.92	220.52±56.60	0.187
	Post-surgery	461.76±164.49	229.26±68.55	<0.0001

Legend: AKI=acute kidney injury; TNF-α=tumor necrosis factor alpha; IL-18=interleukin 18.
Data was tested with t-paired test. *p<0.05 is significantly statistic.

Table 2. Correlation between syndecan-1, TNF-α, and IL-18 levels with post-cardiac surgery AKI incidence

Variables	AKI incidence		p value*	RR (95% CI)
	Yes, n=21	No, n=12		
Δ syndecan-1 (ng/ml)	61.94±36.58	2.64±16.49	0.016	1.11 (1.02-1.21)
Δ TNF-α (pg/ml)	6.85±4.05	0,29±1.82	0.016	2.61 (1.19-5.71)
Δ IL-18 (pg/ml)	205.50±121.35	8.74±54.70	0.016	1.38 (1.06-1.79)

Legend: TNF-α=tumor necrosis factor alpha; IL-18=interleukin 18; AKI=acute kidney injury.
Data was tested with logistic regression test. *p<0.05 is significantly statistic.

Table 3. Correlation between the three biomarkers (syndecan-1, TNF-α, and IL-18) in post-cardiac surgery patients

	Syndecan-1		TNF-α	
	r	p	r	p
Induction				
TNF-α	1.000	<0.0001	1.000	<0.0001
IL-18	1.000	<0.0001	1.000	<0.0001
Post-surgery				
TNF-α	1.000	<0.0001	1.000	<0.0001
IL-18	1.000	<0.0001	1.000	<0.0001
Delta				
TNF-α	1.000	<0.0001	1.000	<0.0001
IL-18	1.000	<0.0001	1.000	<0.0001

Legend: TNF-α=tumor necrosis factor alpha; IL-18=interleukin 18.
Data was tested with Spearman correlation test. *p<0.05 is significantly statistic.

Table 4. Multiple logistic regression analysis between syndecan-1, TNF-α, and IL-18 with post-cardiac surgery AKI incidence

Variabel	p value	RR (95% CI)
Δ IL-18	0.016*	1.38 (1.06-1.79)
Δ TNF-α	0.209	0
Δ syndecan-1	0.629	0

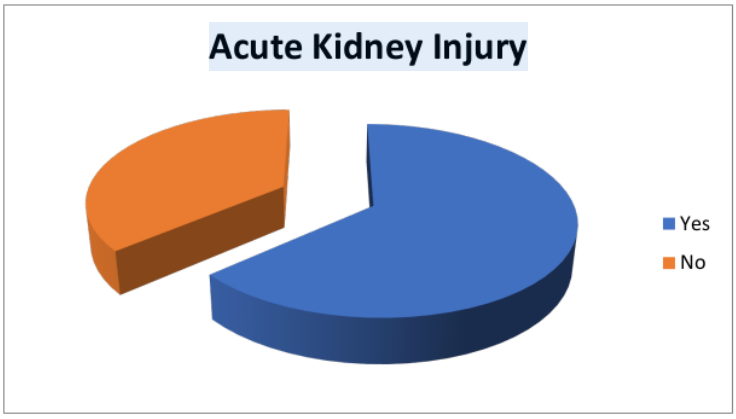
Legend: TNF-α=tumor necrosis factor alpha; IL-18=interleukin 18.
Data was tested with multiple logistic regression test. *p<0.05 is significantly statistic.

Table 5. Syndecan-1, TNF-α, and IL-18 accuracy on predicting post-cardiac surgery AKI incidence

Variables	Cut-off	Sensitivity	Specificity	PPV	NPV	Accuracy
Δ syndecan-1 (ng/ml)	18.6	0.952	0.917	0.952	0.917	93.9
Δ TNF-α (pg/ml)	2.45	0.905	1.000	1.000	0.857	93.9
Δ IL-18 (pg/ml)	61.7	0.952	0.917	0.952	0.917	93.9

Legend: TNF-α=tumor necrosis factor alpha; IL-18=interleukin 18; PPV=positive predictive value; NPV=negative predictive value.
Data was tested with diagnostic test.

Figure 1. Post-cardiac surgery AKI incidence



Legend: AKI=acute kidney injury.

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