

# Correlation of Interleukin-8, Pediatric Logistic Organ Dysfunction score and factors associated with systemic inflammatory response after cardiopulmonary bypass in children who have undergone open-heart surgery

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## Abstract

**Background** Cardiopulmonary bypass (CPB) provides a complex set of non-physiologic circumstances, induces systemic release of pro-inflammatory cytokines and initiates systemic inflammatory response. IL-8 is an important activator of neutrophil with chemotactic effect and are proposed to be major mediator of inflammation. The majority of general intensive care unit scoring system does not adequately address the specific characteristics of cardiac surgery patients. None of the study had been published the validation of PELOD score setting in pediatric cardiac intensive care unit (CICU).

**Objectives** To evaluate the correlation between interleukin-8 (IL-8), Pediatric Logistic Organ Dysfunction (PELOD) score and factors associated with systemic inflammatory response after bypass (SIRAB) in children undergone cardiopulmonary bypass surgery.

**Methods** A quasi-experimental study was conducted on children who have undergone cardiac surgery requiring CPB. There were 21 eligible children, two were excluded. Blood samples from mixed vein and coronary sinus were taken before, during and after surgery. The plasma level of IL-8 analyzed at 3 time points: baseline (before) CPB, at reperfusion period and 3 hours after aortic cross clamp-off. Cumulative organ dysfunctions were analyzed by PELOD score.

**Results** The plasma level of IL-8 highly increase at the reperfusion period. IL-8 plasma level correlated with bypass-time ( $r > 0.49$ ,  $p=0.003$ ) and aortic cross clamp-time ( $r > 0.55$ ,  $P=.014$ ). Moderate association between age and PELOD score ( $r > 0.47$ ,  $P=0.041$ ). The correlations were significant between age and mechanical ventilation time support ( $r > 0.47$ ,  $P=0.03$ ), age and length of stay in CICU ( $r > 0.44$ ,  $P=0.05$ ). No correlation between IL-8 plasma level and PELOD score.

**Conclusion** There was no correlation between IL-8 plasma level and PELOD score. IL-8 plasma level correlated with aortic cross clamp-time in children who undergo cardiopulmonary bypass surgery. [Paediatr Indones. 2010;50:245-51].

**Keywords:** Interleukin-8, Pediatric Logistic Organ Dysfunction score, cardiopulmonary-bypass surgery

The current trend in pediatric cardiac surgery is repairing the congenital heart defect early before the heart and the patient undergo deleterious adaptation to the abnormal physiology. In recent years in most centers, the approach to neonates with congenital heart defect

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has been toward complete surgical correction rather than palliation in order to avoid the pathophysiologic consequences and limit on neonatal growth. Cardiac surgery with cardiopulmonary bypass (CPB) is still necessary for the correction of congenital cardiac defect in pediatric patients. The development of surgical and catheter techniques for the diagnosis and treatment of critical heart disease in children has been paralleled by major advances of neonatal and pediatric intensive care, particularly pediatric cardiac intensive care. The improvement in diagnostic accuracy, surgical techniques and intensive care management have contribution in reduction the mortality.

CPB has a profound physiologic effect on most organ system and provokes a systemic inflammatory response syndrome after bypass (SIRAB). Until now, however the complex pathophysiology of this problem has not been solved. Contact of the blood components with the artificial surface of the bypass circuit, ischemia-reperfusion injury, endotoxemia and operative trauma are all possible causes of systemic inflammatory response syndrome (SIRS). CPB induces systemic release of proinflammatory cytokines, promoting enhanced neutrophil-endothelial adherence by up-regulated surface adhesive. Activation of complement, neutrophils, cytokines and coagulation cascades as well as free radical generation have been proposed to be responsible for the deleterious effects of cardiopulmonary bypass. The increase of neutrophil-endothelial adherence causes organ injury during clinical inflammatory conditions. Cytokines are endogenous polypeptides produced by a wide variety of cells and especially by activated monocytes and macrophages. Interleukin-6 (IL-6), interleukin 8 (IL-8) and tumor necrosis factors- $\alpha$  (TNF- $\alpha$ ) are cytokines involved in the induction of the inflammatory response in children undergoing cardiac surgery. IL-8 is an important activator of neutrophil with a chemotactic effect and activating peptide, which are proposed to be major mediator of inflammation. The systemic response that follows cardiopulmonary bypass are associated with increased capillary permeability, leucocytosis, accumulation of interstitial fluid and eventually end-organ impairment. The clinical pictures are often named as post-perfusion (reperfusion) syndrome. The inflammatory reaction may contribute to the development of post-operative complications

such as respiratory failure, renal and neurological dysfunction, myocardial dysfunction, bleeding disorders, altered liver function and ultimately multiple organ failure.

Intensive care scoring systems are devised to determine probable outcome of the patients being admitted into the intensive care unit (ICU). Cardiac surgery remains a difficult area for outcome prediction in ICU. The majority of general ICU scoring system does not adequately address the specific characteristics of cardiac surgery patients. In 2002, a consensus by the Society of Critical Care Medicine (SCCM) published the concept of criteria and definition or pediatric for sepsis and organ dysfunction. The creation of pediatric logistic organ dysfunction (PELOD) scoring system is age dependent physiologic variables. Organ dysfunction viewed with the more than five organs was used to score the severity of multiple organ dysfunction syndrome (MODS) in children. The predictive value of the PELOD scored accurately during the first 5 days of admission to PICU.

PICU scoring systems are mostly studied for developed nations settings. The PELOD score is subjected to a validation study in PICU's across Europe and North America. Data from developing nations has conflicting results. Until now, none of the study had been published the validation PELOD score setting in pediatric cardiac intensive care unit, eventually in developing country like ours. To our knowledge, this study marks the first time that PELOD score has been employed to predict organ dysfunction in children who have undergone cardiac surgery requiring CPB. This study is aimed to evaluate the correlation between IL-8, PELOD score and factors that associated with systemic inflammatory response after bypass (SIRAB) in children who have undergone cardiopulmonary bypass surgery. We hypothesized that PELOD score correlate with IL-8 and factors associated SIRAB in pediatric cardiac surgery.

## Methods

We conducted a quasi-experimental study between 1<sup>st</sup> June 2008 until 30<sup>th</sup> Juli 2008, in Integrated Cardiac Services – Dr.Cipto Mangunkusumo hospital, Jakarta. The study was approved by the local ethics

committee. The setting was pre and post operative in cardiac intensive care unit (CICU). Subjects were children who have undergone open-heart surgery due to the heart-defect. All of the patients were operated by the same two surgeons. The CPB management was ruled according to the standard protocol in Integrated Cardiac Services of Dr. Cipto Mangunkusumo hospital. Patients were ventilated (Servo-i, Maquet, Swedia), mechanical ventilation

was discontinued according to standard weaning protocol. Post-operative inotropic support was done according to age-adapted reference value for blood pressure and clinical variables using dopamine or dobutamine as a single or combination. Blood samples from mixed vein and coronary sinus were taken before, during and after surgery. The plasma level of IL-8 was analyzed at three time points: baseline/before CPB (1), at reperfusion period (2)

**Tabel 1.** Demography data and clinical characteristic

	Diagnosis	AGE	Body Weight	BSA	Operation time	Bypass time	Aorta cross clamp time	Cardioplegy temperature	Inotrope dose	MV time	LOS in CICU
		(mnth)	(kg)	(m2)	(mnt)	(mnt)	(mnt)	(0 C )	(mcg/kg/mnt)	(hr)	(day)
1	ToF	30	8,00	0,42	120	60	27	30,20	2,00	216	18
2	ToF	180	33,00	1,16	120	60	24	29,90	3,00	4	1
3	DORV	29	8,50	0,43	135	68	30	29,40	2,00	6	1
4	Large PM VSD + severe RCC prolapse + mod-sev AR +PH	204	39,00	1,29	375	142	112	31,50	2,00	6	1
5	VSD	60	23,00	0,85	50	47	21	30,50	2,89	5	1
6	Severe val + infundib stenosis	144	21,00	0,83	150	51	23	32,80	2,00	5	1
7	Large ASD II, deficient posterior rim + PH (high flow low resistance)	24	8,00	0,42	90	21	5	33,20	3,00	8	1
8	VSD DCSA	44	12,00	0,55	105	39	20	30,00	1,00	8	1
9	ToF	12	5,80	0,34	149	87	45	28,00	3,00	120	7
10	VSD	96	5,50	0,32	120	39	20	32,40	4,80	6	1
11	Severe MR + MVP AML + chordae rupture+ Mild-moderate TR ec. RHD	192	45,50	1,39	195	85	71	27,80	3,00	6	1
12	ToF	128	41,00	1,29	180	92	41	29,60	1,00	6	1
13	ToF	15	9,00	0,43	105	38	34	30,60	2,00	72	3
14	ToF with small PDA	24	14,00	0,61	186	50	21	32,20	2,00	6	1
15	Large perimembranous VSD	24	11,00	0,35	150	48	30	31,40	2,00	8	1
16	ToF	120	15,00	0,69	135	42	21	30,60	2,00	13	1
17	ToF	132	22,00	0,89	240	91	35	31,50	2,00	16	1
18	ToF	43	11,00	0,52	135	58	25	30,50	2,70	6	1
19	ToF	24	11,00	0,51	135	55	28	30,00	2,42	9	1

and 3 hours after aorta cross clamp-off (3). Plasma IL-8 was quantified by solid-phase 96-well plates enzyme linked immuno-absorbant assay (ELISA) using uncommercially kits (Human Interleukin-8 UltraSensitive / hIL-8 US, BioSource International Inc., USA). One hundred microliters of plasma were used for the IL-8 assays and concentrations were determined using a standard curve generated by regression analysis. The factors associated SIRAB were internal factors (age, gender, body surface area & type of congenital heart defect) and peri-operative factors represented as aortic cross clamp-time, CPB-time, hypothermic state and dose of inotrope. Cumulative organ dysfunctions was analyzed by PELOD score. Demographic data was collected in order to characterize the samples. The outcome for all cases was documented as survival or death. Length of hospital stay was also recorded. The associations between variables were performed by paired Wilcoxon non-parametric test and unpaired data were tested with Mann-Whitney U. The results scores were analyzed by using the Spearman test. We used SPSS for Windows version 15.0 software. Result were deemed significant if  $P < 0.05$ .

## Results

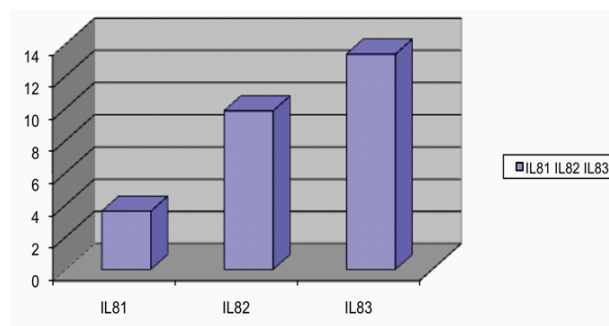
Twenty-one eligible children followed open-heart surgery with CPB, two were excluded because they didn't complete the study. Most of the patients were survived, only one child died in this study. **Table 1** shows the demography data and baseline clinical characteristic of the nineteen patients. The median of age was 44 months. Almost similar the amount of gender (boys and girls) and the heart defect type (cyanotic and non-cyanotic) with median body surface area was  $0.55 \text{ m}^2$ . The median of operation time was 2 hours 15 minutes, bypass time was 135 minutes and aortic cross-clamp time was 27 minutes. The median of temperature during cardioplegy was  $30.5^\circ\text{C}$  (mild hypothermia). Length of stay in CICU was 1 day with the median of inotrope dose was 2 microgram/kg/minute and the median of mechanical ventilation time was 6 hours.

The figures below presented the data of IL-8 plasma level in three different time points: baseline/ before CPB, at the reperfusion period and three

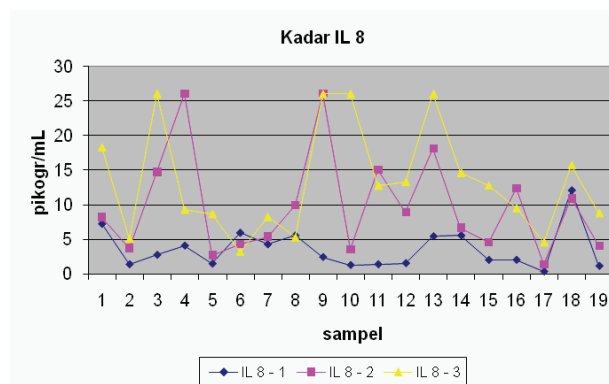
hour after aortic clamp-off. Before operation and at reperfusion period, level of IL-8 raised but it did not correlated significantly. IL-8 concentrations at three hour after aortic cross-clamp off were higher significantly than in the reperfusion period ( $r > .49$ ,  $P = 0.030$ ). (**Figures 1 and 2**).

Level of IL-8 correlated with the bypass time ( $r > .53$ ,  $P = 0.018$ ) as well as aortic cross-clamp time ( $r > .55$ ,  $P = 0.014$ ). (**Figure 3**).

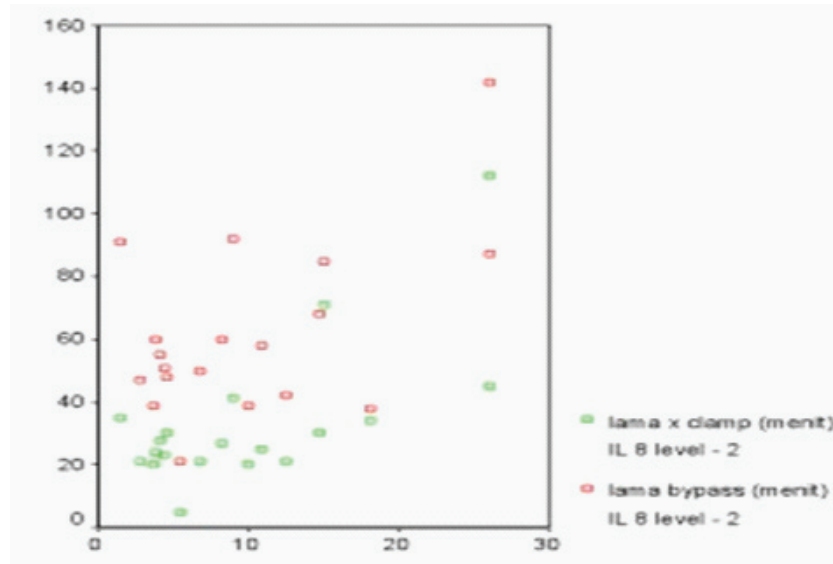
There was moderate associated between age and gender with PELOD scores ( $r > .47$ ,  $P = 0.041$ ). We found no correlation between IL-8 level and PELOD scores. There were significant correlation between age and mechanical ventilation time support ( $r > .47$ ,  $P = 0.030$ ), age and length of stay in CICU ( $r > .44$ ,  $P = 0.050$ ).



**Figure 1.** The median of plasma level IL-8 at the baseline/before CPB (1), reperfusion period (2) and 3 hours after aortic cross-clamp off (3)



**Figure 2.** Pattern of IL-8 plasma level at baseline (1), reperfusion period time (2) and 3 hours after aortic cross-clamp off (3) ( $r > .49$ ,  $P = 0.030$ )



**Figure 3.** Correlation  $\Delta$  IL-8 plasma level: between baseline and at reperfusion period and aortic cross-clamp time

## Discussion

CPB for the correction of congenital cardiac defects in pediatric patients has a profound physiologic effect on most organ systems. The deleterious effects of CPB are often more pronounced in neonates and infants, because many organs like the brain, lungs, coagulation system and endocrine system are still immature during infancy. Neonates and infants have high metabolic demands and require a high perfusion flow rate per body surface area. This may result in the high shear stress on the blood-cell components. CPB for pediatric cardiac procedures often requires the extreme temperature, hemodilution and perfusion flow rates. Younger age predisposes the myocardium to the adverse effects of CPB and hypothermic ischemia implicit in surgical-support techniques. Certain anatomic features will require alterations of bypass strategies, cannulation techniques or deep hypothermia with the circulatory arrest. A number of different strategies including new pharmacologic agents, CPB circuits and components, as well as surgical techniques have been performed during the last few years in to minimize the impact of SIRAB on the outcome of cardiac surgical.

After the correction of complex congenital heart defect, myocardial performance is usually normal

after two hour postoperative. The CPB-induced late neutrophil activation and free radical production up to 10 hour after CPB have been implicated as a potential mechanism of post operative cardiopulmonary dysfunction

Median time of operation (135 minutes) and cardiopulmonary bypass time (55 minutes) were less than other studies that have been reported. The short duration of median aortic cross-clamp time (27 minutes) similar with Anic et al<sup>14</sup> ( $31.7 \pm 12$  minutes) and Kotani et al<sup>17</sup> ( $0.9 \pm 0.6$  hours). The correlation between aortic cross-clamp time and  $\Delta$  IL-8 plasma level (baseline-reperfusion period) indicated the raising of inflammatory process during this period. The highly increased of IL-8 plasma level at reperfusion period compared to baseline value, did not concordance with the less difference of the pre and post operation PELOD score. The inflammatory reaction that responsible to SIRAB was very complicated. It needs another parameter and variables to indicated the prediction of organ dysfunction due to cardiopulmonary bypass in children.

In conclusion, IL-8 level correlates with aortic cross-clamp time in children who have undergone open heart surgery with cardiopulmonary bypass. No correlation is found between IL-8 and PELOD scores.

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