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Analysis of post coronary bypass surgery risk factors and scoring system with study of immunogenetic epidemiology

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Introduction

The fact that the mean mortality rate of 5.59% after coronary bypass surgery at the Indonesian National Cardiac Center (Harapan Kita Hospital) has not changed significantly in the last 10 year period (1990-2000) warrants reassessment. The available literature reflects the opinion that the outcome of coronary bypass surgery patients could not be easily laid-out, which reflects the complexity of the problems affecting the patients' condition before and during surgery.

Published predictors of surgical mortality have been available in the form of scoring systems, for instance: Parsonnet score in the US, Euro score in Europe, Melbourne score in Australia. As data varies, so are the scorings. In some centers, agreement on post surgical mortality exists which are influenced by: progression of age, left ventricular dysfunction, and emergent surgery. On the other hand, opinions differ when it comes to: field of gender, obesity, diabetes, hypertension, and renal dysfunction.

Mortality is reported most often due to heart failure and the worsening of myocardial contractility. This disturbance is caused by damaged of myocardial tissue due to ischemia; i.e. due to coronary ischemia before surgery (arteriosclerosis) as well as ischemia during surgery. Ischemia initiates the discharge of free radicals intracellular as well as into the circulation. The proinflammatory cytokine TNF α is a free radical that has quite a large role compared to other cytokines. The role of this particular cytokine is still under debate, among others as an apoptotic trigger causing the dissemination of myocardial damage.

Due to the complexity of the issue, in this study, an assessment will be done on biological and clinical features, as well as assessment by statistical analysis. A search will be conducted for risk factors contributing to post coronary bypass surgical mortality. Biological analysis is aimed at the assessment on the rise of TNF α proinflammatory cytokine concentrations, which are suspected to cause postoperative clinical worsening of patients.

The increase in circulatory cytokine concentration is caused by many factors, including among others, genetic changes. Genetic abnormality found is the presence of gene polymorphism at 308 positions (promoter) in the form of adenine substitution of guanine.

In the clinical setting, analysis will be done on preoperative risk factors, including age, gender, body mass index, presence of diabetes mellitus or hypertension, cardiac dilatation in the form of left ventricular dilatation or the increase cardio thoracic ratio. These conditions are often accompanied by the impairment of myocardial contractility.

Aim of study

1. To prove that on coronary heart disease patients with polymorphism -308, a rise in TNF α concentrations will occur after undergoing coronary bypass surgery.
2. To prove that clinical manifestations after coronary bypass surgery is affected by increased TNF α concentrations in blood circulation.
3. To construct a model to predict mortality risk after coronary bypass surgery based on pre- and intraoperative risk factors, including also immunogenetic factors.

Theoretical background

Arteriosclerosis in coronary arteries results in decreased blood flow to myocardial fibers. The following ischemia triggers proinflammatory cytokine production, among others TNF α, which majority is produced by heart muscles, besides macrophages. So, in ischemia, circulating TNF α concentration is increased.

Although still in controversy, myocardial ischemia progresses during surgery. Ischemia causes increased pro-

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duction of TNF α, and also the production of the anti-inflammatory cytokine IL-10. If TNF α concentration in the circulatory increases, the contractility of myocardial fibers will lessen due to the negative isotropic effects. The following ischemia produced will cause apoptosis, which in turn will worsen myocardial function.

Concept of hypothesis

The deterioration of patients' clinical condition is thought to be in relevance with the high circulating concentration of proinflammatory cytokines. The increase in the concentration of cytokines is under genetic regulation (suspected by the role of polymorphism -308). If in this study the relationship polymorphism -308 and the increase of TNF α concentration are not proven, other factors influencing the increase of circulating TNF α will be sought. (**Figure 1**).

Hypothesis

1. Myocardial ischemia during surgery will cause an increase in circulating TNF α.
2. The increase of TNF α will be higher in coronary heart disease patients with DNA polymorphism -308 as compared to those without polymorphism -308.
3. The diversity of clinical manifestations of patients after coronary artery bypass surgery is influenced by the increase of blood TNF α concentrations.

Method

The study design is a prospective study with 280 samples; utilizing univariate, bivariate and multivariate analysis as well as by survival analysis study.

To view preoperative characteristics, analysis will be done by case control design. By homogeneity testing, the relative risk ratio (RRR) will be calculated and multivariate analysis using multinomial regression analysis. A scoring method is anticipated to be constructed such as encountered in other studies.

The main assessment is made by analyzing all risk factors, including preoperative risk factors, intraoperative risk factors, and immunogenetic influence.

The assessment in this study differs from scoring assessment found in literature. For analysis, this study will profile itself on: proportional hazard assumption assessment, hazard ratio calculation, and median value by means of 'time at risk'. Analytical results will be used as factors to construct a scoring system. It is hoped that the result-

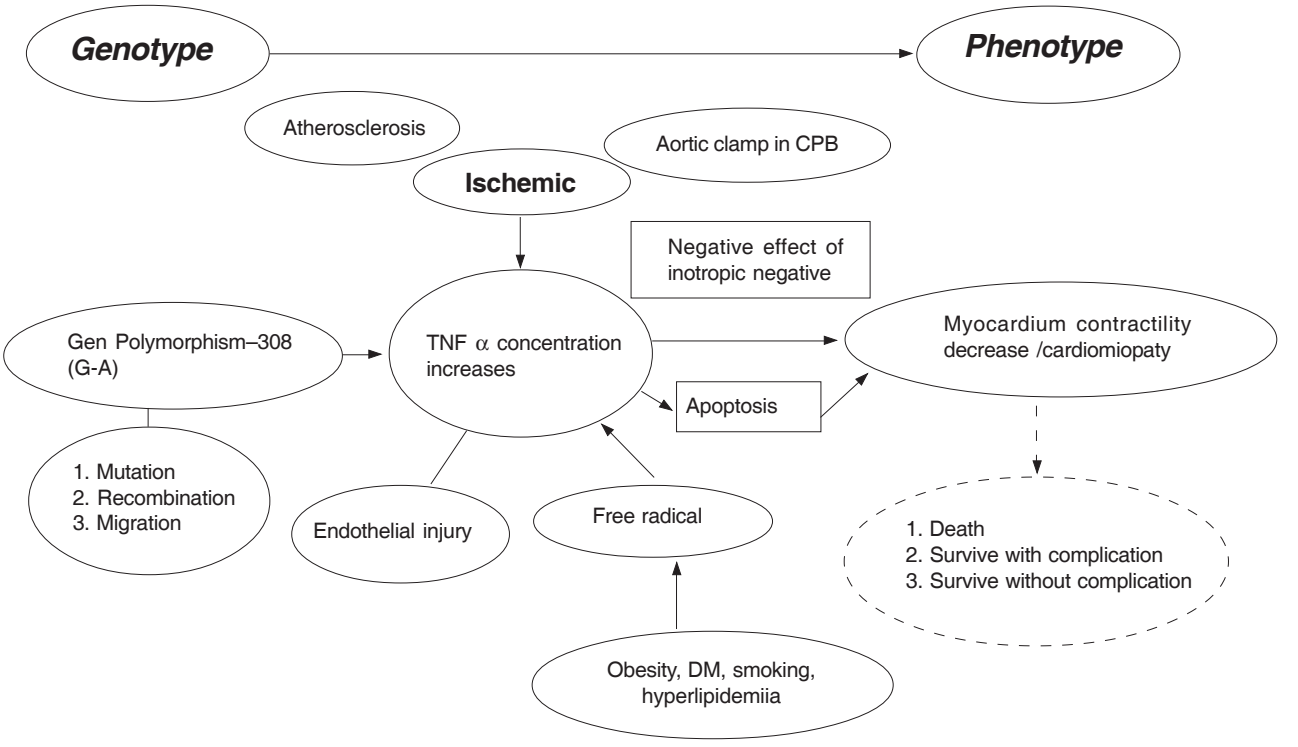

FIGURE 1. CONCEPT BACKGROUND CORRELATION BETWEEN GENE POLYMORPHISM –308, INCREASE TNF α CONCENTRATION AND CLINICAL MANIFESTATION IN CORONARY PATIENTS.

ing scoring system would be able to predict mortality after coronary by pass surgery. If the results differ from data encountered in literature, then these results will reflect the characteristic of the Indonesian population or the Malay ethnic. Available data in the literature have been reflecting studies on Caucasian subjects.

Special analysis for immunogenetic factor is done by gene studies to see the 308 position and to measure the TNF α concentration before and after surgery. The TNF α concentration is determined by Elisa using quantikine kit immunoassay. The immunogenetic map of coronary heart disease patients is not well known, so the results of this study will be new to our knowledge. Statistical analysis on this study utilizes Stata 7.0 software.

Results

In this study of 280 cases of coronary heart disease, polymorphism -308 percentage was at 8.6%, consisting of heterozygote polymorphism (G-A) at 4.64% and homozygote polymorphism (A-A) at 3.93%.

This percentage is larger than polymorphism found on normal individuals without coronary heart disease, which has been at 3.5-3.7% (Irawan Yusuf). A different result is obtained if compared to the study conducted by Li Wang (2000) in Sydney, wherein he reports a polymorphism-308 incidence of 30.1% consisting of heterozygote polymorphism (G-A) 25.4% and homozygote polymorphism (A-A) 4.7%. This figure suggests genetic difference between ethnic groups.(**Table 1**)

Mean values obtained by 'geometric mean' show TNF α concentrations without polymorphism to be 338.79 pg/ml, whilst patients with heterozygote polymorphism (G-A) had a higher mean value of 336.41 pg/ml. Higher still was the mean value of homozygote polymorphism (A-A) of 447.78 pg/ml. Although statistical analysis shows an insignificant result, this data reflects TNF α concentration higher than patients with polymorphism-308, particularly the homozygote variant; in concordance with the hypothesis made. (**Table 2**)

The presurgical measurement of TNF α concentration on coronary heart disease patients yields range of values from the lowest value of 245.6781 pg/ml to the highest value of 886.3500 pg/ml. These values exceed by far, values found on normal individuals of less than 100.0000 pg/ml. No comparison data exists to date regarding the value of TNF α, suggesting that this data is newly acquired information.

On patients with polymorphism -308 undergoing coronary bypass surgery, a change in TNF α concentration occurs. albeit not in all conditions. A decrease has even been noted in some patients. Although circulatory concentrations vary, the mean value still show an increase; especially in patients with homozygote polymorphism. These results are anticipated, but further studies are recommended, especially regarding those cases with the occurrence of a decrease of post surgical TNF α concentration.

Analysis on patients who died after surgery compared to those with better results yielded different characteristics. TNF α concentrations on patients who died

Table 1. Distribution of patients with polymorphism -308 at the Coronary heart disease

Research by	Without polymorphism (G-G)	Polymorphism heterozygote (G-A)	Polymorphism homozygote (A-A)
Li –Wang (Sidney-Australia)	448 (69, 9%)	163 (25, 4%)	30 (4, 7%)
Tri Wahyu (Jakarta-Indonesia)	256 (91, 43%)	13 (4, 64%)	11 (3, 93%)

Table 2. Mean value of the group with or without polymorphism from clinical characteristic during surgery

Clinical characteristic	Without polymorphism		With polymorphism heterozygote (G-A)		With polymorphism homozygote (A-A)	
	Mean	95% CI means	Mean	95% CI means	Mean	95% CI means
Surgical time	309,24	(300,74; 317,75)	315,92	(269,88; 361,97)	339,73	(271,19; 408,27)
TNF pre surgery	344,80	(326,33; 363,26)	411,25	(296,53; 525,97)	482,07	(262,55;701,60)
TNF post surgery	350,19	(329,55;370,84)	434,80	(295,16;574,44)	486,11	(266,24;727,64)
ICU stay	1,89	(1,65;2,12)	2,09	(1,50;2,65)	1,82	(1,41;2,22)

after surgery was lower than patients who lived (survive). (**Table 3**).

This differs from the hypothesis, which predicted that the high TNF α concentration would worsen the post surgical clinical manifestation. The study shows low TNF α concentration at the start of surgery and the slight increase at the completion. The deliberation is as follows:

1. On the opinion that circulating TNF α concentration is influenced by the presence of others cytokines; proinflammatory, as well as anti-inflammatory.
2. TNF α cannot be produced by damaged myocardial tissue, and that production by macrophages is also decreased because of exhaustion. Bivariate analysis on this study show an insignificant value, but the characteristic picture of TNF α concentration can contribute data for further studies. (**Table 4**).

TNF α concentration of more than 500.00 pg/ml can be correlated to 4 risk factors; 70.59% (12/17) diabetics, 5/17 (29.41%) senile patients (>62 years). High values are also found on 308 polymorphism 5/17 (29.41%) and only 4/17 (23.53%) on patients with an ejection fraction of <35%. These 4 factors warrant extra attention on the analysis to construct a scoring system.

Case control study with multinomial regression analysis, for pre surgery risk factor. (**Table 5, Table 6,Table 7, and Table 8**).

On the analysis to construct a model for presurgical risk factors as related to the post surgical mortality, 5 variables were found to be of value: gender, age (in years), body mass index >25, creatinine concentration (in mg/dl), cardio thoracic ratio (in %). From these it could be obtained that individual characteristics as risk factors, multiplied by score value (designated score I for ICU stay ≥ 3 days) will result in the % of probability of ICU stay with complications. In the same way a predictor could be identified for the mortality risk factors. The result in the % of probability of post surgical mortality designated score I for mortality.

Survival analysis study with cox regression analysis

On survival analysis by compiling all presurgical risk factors, risk factors during surgery, and immunogenetic influence, we obtained a model designated as score II. On this model 5 variables were also identified as influencing the outcome; presence of polymorphism, presence of DM, age ≥ 62 years, low ejection fraction < 35% and surgical technique (Cardio Pulmonary Bypass). (**Table 9**).

Multivariate analysis results with good ROC area probability of 78, 63%, means that the scoring system available to use in Indonesia and the prediction power is 78,00%. (**Table 10, and Table 11**).

Risk factors in the scoring system each were measured based on the power test and yielded 82% power for the presence of polymorphism 308,91% power for low

Table 3. Clinical characteristic on patients who died after surgery with mean value of risk factors during surgery and after surgery

	Survive		Death	
Clinical characteristic	Mean	95% CI mean	Mean	95% CI mean
TNF pre surgery	358,42	(337,64;379,20)	309,19	(274,96;343,42)
TNF post surgery	365,48	(341,80;389,15)	310,32	(272,34;348,28)
Surgical time	310,46	(294,20;311,13)	324,14	(280,26;368,02)
ICU stay	1,79	(1,59;1,99)	3,79	(1,72;5,85)

Table 4. Distribution of TNF α concentration

	Concentration < 300 pg/ml	Concentration 300-499 pg/ml	Concentration > 500 pg/ml
Age > 62 y.o	13/53 (24, 53%)	22/63 (34, 92%)	5/17 (29, 41%)
DM	16/53 (30, 18%)	28/63 (44, 44%)	12/17 (70, 59%)
Low Ejection fraction (<35%)	6/42 (14, 28%)	5/49 (10, 20%)	4/17 (23, 53%)
With polymorphism – 308	4/55 (7, 71%)	4/63 (6,349%)	5/17 (29, 41%)

TABLE 5. DISTRIBUTION OF TNF α CONCENTRATION

Variable	Coefficient	RRR	95% CI RRR	P
Survive with ICU stay ≥ 3 days				
Sex (women)	1,448	4,25	1,31 ; 13,85	0,016
Age (year)	0,040	1,04	0,99 ; 1,09	0,114
Body mass index (≥25)	1,185	3,27	1,41 ; 7,59	0,006
Creatinin concentration	2,066	7,89	2,47 ; 25,18	0,000
Cardiothoracic ratio (%)	0,056	1,06	1,02 ; 1,10	0,006
Constant	-11,556			
Died				
Sex (woman)	-18,493	0,00	0,00 ; 0,00	0,000
Age (year)	0,149	1,16	1,05 ; 1,29	0,005
Body mass index (≥25)	1,402	4,06	0,82 ; 20,05	0,085
Creatinin concentration	1,756	5,79	0,67 ; 49,87	0,110
Cardiothoracic ratio (%)	0,072	1,07	1,00 ; 1,15	0,048
Constant	-0,257			

TABLE 6. FORM OF SCORING I PREDICTION POST SURGERY

Variable	Individual characteristic (IC))	Survive with ICU stay ≥ 3 days		Death	
		Score (S1)	IC x S1	Score (S2)	IC x S2
Sex					
Man		0		2	
Woman		2		0	
Age (year)		1		2	
Body mass index					
< 25		0		0	
≥ 25		2		1	
Creatinin concentration (mg/dl)		2		1	
Cardiothoracic ratio (%)		2		1	
Total (IC x S)			——		——

S1 = score of ICU stay ≥ 3 days; S2 = score of death.

TABLE 7. CONVERSION SURVIVAL PREDICTORS WITH ICU STAY ≥ 3 DAYS (SCORING I FOR LONG ICU STAY)

Total score		Survival prediction with ICU stay ≥ 3 days
No risk	(< 159,60)	08,22
Low risk	(159,6 s/d170,19)	14,71
Moderate risk	(170,2 s/d 204,19)	25,71
High risk	(≥ 204,2)	50,00

TABLE 8. CONVERSION OF MORTALITY PREDICTION WITH TOTAL SCORE (SCORING I FOR MORTALITY)

Total score		Death prediction
No risk	(< 169,50)	00,00
Low risk	(169,5 s/d 185,99)	08,33
Moderate risk	(186,0s/d 205,39)	10,83
High risk	(≥ 205,4)	50,00

TABLE 9. MULTIVARIATE ANALYSIS AND SCORING

Variable	Koef.	SE coef.	HR	95% CI HR	Score
TNF-DNA (Polymorphism-308) status	0,862	1,228	2,37	(0,21;26,29)	1
DM (Yes)	0,985	0,820	2,68	(0,54;13,35)	2
Age (> 62 ty.o)	1,196	0,842	3,31	(0,64;17,21)	2
Ejection fraction (< 35%)	1,042	0,865	2,84	(0,52;15,46)	2
On pump technique)	1,379	0,857	3,97	(0,74;21,29)	2

TABLE 10. SCORING II WITH CHARACTERISTIC VARIABLE

Variable	Score	Characteristic subject
TNF-DNA status		
Normal	0	
Polymorphism-308	1	
DM		
No	0	
Yes	2	
Age		
< 62 y.o	0	
≥ 62 y.o	2	
Ejection fraction		
≥ 35%	0	
< 35%	2	
Surgical technique		
Off pump	0	
On pump	2	
TOTAL SCORE (0—9)		

TABLE 11. INTERPRETATION OF SCORING FOR MORTALITY RISK PREDICTION AFTER SURGERY

Total score	Risk	Death Proportion
≤ 1	No Risk	
2—3	Low Risk	1,06%
4—6	Moderate Risk	7.55%
≥ 6	High Risk	25.00%

ejection fraction (<35%) and 99% power for the presence of DM, age ≥ 62 years and surgical technique using CPB (on pump technique). (**Table 12**).

Conclusion

Based on the purpose of the study, the following data was obtained:

1. Coronary heart disease patients with 308 polymorphism (particularly heterozygote G-A polymorphism) have a higher circulating TNF a concentration compared to CHD patients without polymorphism.
2. The post surgical clinical manifestations were not proven to be influenced by circulating TNF α concentrations. It is thought that the increase was not enough to yield clinically manifestation.
3. A two scoring system could be designed for CHD patients;
   (1) Score I, prediction and probability the preoperative five risk factors (sex, age, BMI, creatinin concentration, CTR).
   (2) Score II prediction and probability by including all factors, which are presurgical factors, factors during surgery and also immunogenetic factors. Influencing 5 risk factors are old age (>62 years), presence of DM, low ejection fraction (<35%), surgical technique (on pump technique) including the presence or absence of

TABLE 12. POWER TEST OF RISK FACTOR

Variable	Unexposed	Exposed	HR	ϕ	$Z_{1-e/2}$ (α=90%)	$Z_{1-\beta}$	γ *
TNF-DNA status (Polymorphism-308)	251	24	2.37	10.5	1.96	0.895726	0.82
DM (Yes)	179	82	2.68	2.2	1.96	3.267504	0.99
Age (> 62 y.o)	198	77	3.31	2.6	1.96	4.341907	0.99
Ejection fraction (< 35%)	253	22	2.84	11.5	1.96	1.360544	0.91
Surgery technique (on pump)	160	83	3.97	1.9	1.96	5.247282	0.99

polymorphism. The power test yielded results of 82-99% on the scoring system made.

New informations obtained from this study are:

1. Polymorphism -308 incidences on CHD patients in this study is 8.6%.
2. CHD patients on this study had a very high TNF α concentration before surgery.
3. Patients who died after surgery had a TNF α concentration lower than survivors due to decreased production from macrophage (exhausted) or due to myocardial infarction.

Suggestion

1. This study warrants further investigation in pinpointing the data of augment the TNF α in coronary artery bypass surgery.
2. The scoring system need for further evaluation to improve the prediction results.
3. The Harapan Kita Hospital as the centre of the referral system has been expected to become as the major crossroad between service and research which is also expected to cover immunogenetic and epidemiology specific for the Indonesian.

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