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Clinical Usefulness of Preoperative Levels of Leukocyte and D-Dimer in Predicting Perioperative Outcomes of Cardiovascular Disease

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The present study was retrospectively designed to define whether preoperative levels of leukocytes and D-dimer are potentially useful factors in predicting perioperative outcomes of coronary heart disease (CHD). There was no relationship between preoperative leukocyte counts (Pre-OP leukocyte) and preoperative D-dimer levels (Pre-OP D-dimer). Pre-OP leukocyte counts each had positive correlation with cardiac troponin-I, creatine kinase-MB or C-reactive protein (cardiac markers) levels at preoperative and postoperative periods. Pre-OP D-dimer levels were positively associated with each cardiac marker at the same periods. Pre-OP leukocyte counts positively related with aspartate aminotransferase and alanine aminotransferase (liver markers), whereas Pre-OP D-dimer level positively or negatively correlated with bilirubin (liver marker), creatinine (renal marker) or glucose levels at preoperative and/or postoperative periods. Pre-OP leukocyte and Pre-OP D-dimer were inversely associated with Pre-OP high density lipoprotein cholesterol levels or left ventricular ejection fraction. Pre-OP leukocyte counts each had positive correlation operation duration and postoperative mechanical ventilation-time (PMVT), whereas Pre-OP D-dimer levels had positive relationship with PMVT, intensive care unit-staying period and hospitalization. The retrospective data suggest that Pre-OP leukocyte and Pre-OP D-dimer levels may be clinically useful factors for predicting perioperative outcomes in patients with CHD.

Key words : Leukocyte, D-dimer, cardiac marker, biochemical marker, coronary heart disease, perioperative outcomes

Introduction

Coronary heart disease (CHD) continues to be a leading cause of morbidity and mortality among adults in the whole world. In the United States, CHD accounts for nearly 40% of all deaths each year [11]. In Korea, it becomes a major factor of mortality together with cerebrovascular accidents and cancers.

It is well established that inflammation plays a pivotal role in the development and progression of atherosclerosis, including plaque rupture which triggers coronary thrombosis and myocardial infarction. The risk factors have included age, gender, hypertension, cigarette smoking, serum total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and diabetes [38]. Furthermore, factors such as obesity, left ventricular hypertrophy, and family history of premature CHD have also been considered in defining CHD risk [23].

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However, these factors cannot explain all of the excess risk; approximately 40% of CHD deaths occur in persons with serum cholesterol levels that are lower than the population average [18].

Several lines of evidence have suggested that leukocyte counts and D-dimer levels may be implicated in the development of CHD. Nevertheless, we have a few studies for the effects of preoperative levels of leukocyte and D-dimer on perioperative outcomes in patients with CHD in Korea.

We have retrospectively designed this study to investigate whether there is an association between preoperative levels of leukocytes and/or D-dimer and perioperative variables. Preoperative levels of leukocytes and D-dimer are recognized as potentially useful factors in predicting perioperative outcomes in eighty adult patients that underwent off-pump coronary artery bypass grafting surgery (OPCAB).

Materials and Methods

Study population

Data for eighty patients that underwent off-pump coro-

nary artery bypass grafting surgery (OPCAB) were postoperatively reviewed and analyzed. Blood or other samples were never collected from the patients and additional test were not performed for the present study. All patients were discharged from the hospital. We only evaluated the recorded-data for this study.

Analysis of variables

That following variables were preoperatively or postoperatively analyzed and recorded.

Left ventricular ejection fraction (LVEF)

All patients' LVEFs were preoperatively measured with echocardiography.

Total leukocyte counts

Blood samples were preoperatively taken from the patients and three ml of blood was infused EDTA-contained bottle. The sample bottle was gently mixed and total leukocyte counts were measured by CD-3700 (Abbott Co., Los Angeles, USA).

Plasma D-dimer

Immunoturbidimetric method was applied for determination of plasma D-dimer. At the preoperative period, three ml of blood collected from the patients was infused with 3.2% sodium citrate-tube and centrifuged into plasma at 4℃, 3,000 rpm for 10 min. The plasma was analyzed by Sysmex CA 7000 (Sysmex Co., Tokyo, Japan) with Innovance D-dimer assay kit (Siemens Healthcare, Munich, Germany). Its normal value is <0.5 μg/ml.

Cardiac markers

A preoperative (Pre-OP) and postoperative 24 hr (PO-24 hr) level of plasma high sensitive C-reactive protein (CRP) was measured by Hitachi 7600-210 instrument (Hitachi, Tokyo, Japan) with commercial CRP kit (Denka Co., Kyoto, Japan) (normal value; <0.5 mg/dl). A preoperative level of plasma cardiac troponin- I was determined by Access immunoassay system (Sanofi Diagnostic Pasteur, Inc., Paris, France) with commercial cTnI kit (Boehringer Mannheim, Munich, Germanny) (normal value <0.05 ng/ml).

A preoperative level of plasma creatine kinase-MB was analyzed by Toshba instrument (Toshba Co., Tokyo, Japan) with CK-MB kit (Wako Co., Tokyo, Japan) (normal value; <15 IU/l).

Biochemical markers

At the preoperative (Pre-OP) and postoperative 24 hr (PO-24 hr) period, three ml of blood that was collected from the patients was infused in a serum separate-tube and centrifuged into serum at 3,000 rpm for 10 min. The serum was analyzed by Hitachi 7600-210 (Hitachi, Tokyo, Japan).

Operative procedures

All of the patients received general anesthesia. After median sternotomy, left internal mammary artery, left radial artery, and the great saphenous vein were harvested from the patients for OPCAB. 80-100 mg of heparin was intravenously injected and the heart was exposed. Cardiac apex was lifted for fixing appointed sites of anastomoses using cardiac holding apparatus (Octopus, Medtronic Inc., New York, USA), and one to five vessels were anastomosed by one operator. After the anastomoses, blood flow vessels were reopened [assessment by HT 107 medical volume flow-meter (Transonic systems Inc., New York, USA) (normal flow; >20 ml/min)] and 0.8-1.0-fold protamine of used heparin was administered.

Perioperative variables

Operation time (OP-time), vessel grafting-numbers, postoperative mechanical ventilation-time (PMVT), intensive care unit (ICU) staying periods and hospitalized-days were recorded.

Statistical analysis

Data are presented as mean±SD (standard deviation). Paired *t*-test was utilized for comparison of the difference between Pre-OP and PO-24 hr variables. Pearson's correlation-analysis was applied for the determination of association between preoperative levels of leukocyte or D-dimer and perioperative variables (SAS program). Statistical significance was accepted with $p \leq 0.05$.

Results and Discussion

Clinical characteristics of study population

Table 1 shows clinical characteristics of study population. Mean values of systolic and diastolic blood pressure (SBP and DBP, respectively) were within normal ranges, whereas left ventricular ejection fraction (LVEF) was significantly lower than the normal value, indicating that coronary heart

Table 1. Clinical characteristics of study population

Parameter	Mean	SD
Number of patient	80	
Sex (M : F)	54:26	
Age (year)	62.85	9.60
Weight (kg)	66.50	10.38
BSA (m^2)	1.74	0.19
LVEF (%)	48.93	15.01
SBP (mmHg)	127.37	21.10
DBP (mmHg)	78.52	12.63
OP-time (min)	301.31	49.90
PMVT (hr)	17.25	16.57
ICU-period (hr)	71.74	29.28
Hospitalization (day)	17.55	6.02
Graft-number (no.)	3.79	1.26

Abbreviation: M, meal; F, female; BSA, body surface area; left ventricular ejection fraction; OP, operation; PMVT, post-operative mechanical ventilation; ICU, intensive care unit; Graft-number, number of vessel for coronary artery bypass surgery.

disease (CHD) causes LV dysfunction and heart failure. This result suggests that CHD may occur in individuals with normotension. CHD characterized by stenosis and obstruction of coronary arteries can result in a decreased supply of oxygen and nutrients in the myocardium, leading to myocardial injury and dysfunction.

Preoperative levels of leukocyte and D-dimer

Pre-OP levels of leukocyte and D-dimer were summarized in Table 2. Although there were differences, mean values of Pre-OP leukocytes were within normal ranges. As is well known, leukocytes in peripheral blood play a critical role for host defense and immune system. The roles of leukocytes include humoral (production of antibodies) and cellular immunity. In general, elevated leukocyte counts in peripheral blood represent an infectious disease and/or systemic inflammatory response. Moreover, myocardial infarction (MI) can lead to an increase of leukocyte counts in peripheral blood.

Even though the heart in atherosclerosis is a multifactorial disease, with dyslipidemia, dysglycemia, smoking and other causes of endothelial injury, and genetic predisposition all contributing to pathogenesis, previous studies proposed that atherogenesis represents an active, inflammatory process rather than simply a passive injury with an infiltration of lipids [26]. Leukocytes play a major role in these inflammatory processes, which may be either adaptive or maladaptive, and acute or chronic. Margolis et al. [21] have recently demonstrated that leukocyte counts, a stable, well-standardized, widely available and inexpensive measure of systemic inflammation, are an independent predictor of CHD events and all-cause mortality in postmenopausal women. Leukocyte counts greater than 6.7×10^3 cells/μl may identify high-risk individuals who are not currently identified by traditional CHD risk factors.

Table 2. Preoperative levels of leukocyte and D-dimer

Variable \ Time	Preoperative
Leukocyte (10^3/ul)	7.86±3.35
D-dimer (ug/ml)	1.11±0.94

Data are expressed as mean±SD.

In the present study, mean leukocyte counts of patients participating in this study were 7.86±3.35×cells/μl, suggesting that they had an already high-risk of coronary events.

On the other hand, mean values of preoperative plasma D-dimer were abnormally higher than the normal range (<0.5 μg/ml). D-dimer is the degradation product of cross-linked fibrin. Increased levels of plasma D-dimer are indicative of a hypercoagulable state, as found in acute coronary syndromes (ACS). Plasma concentrations of D-dimer reflect the extent of fibrin turnover in the circulation, as this antigen is present in several degradation products from the cleavage of cross-linked fibrin by plasmin. Highly elevated D-dimer values occur in various disorders in which the coagulation system is excessively activated, such as acute venous thromboembolism [20]. It has been indicated that modestly increased circulating D-dimer levels reflect minor elevations in blood coagulation, thrombin formation, and turnover of cross-linked intravascular fibrin, which is partly intra-arterial to CHD [20].

In recent, D-dimer has gained increasing interest for several reasons. First, it can be considered as a global marker of the turnover of cross-linked fibrin and activation of the hemostatic system. Second, in contrast to other markers of hemostasis, D-dimer assays are more stable and more practical to measure and therefore may be more suitable for routine clinical and epidemiological purpose [20].

The present data on plasma D-dimer imply that CHD can contribute to an elevation of circulating levels of D-dimer.

Perioperative levels of cardiac markers

Perioperative levels of cardiac markers are summarized in Table 3. Pre-OP levels of plasma cTNI and CRP were

Table 3. Perioperative levels of cardiac markers

Marker \ Time	Pre-OP	PO-24 hr
cTNI (pg/ml)	3.12±0.65	2.60±2.31*
CK-MB (U/l)	15.50±5.86	19.82±17.58
CRP (mg/dl)	2.04±1.83	6.98±5.94*

Data are expressed as mean±SD.
*, $p<0.05$ (compared with Pre-OP levels).
Abbreviation: Pre-OP, preoperative period; PO-24 hr, 24 hr after the end of cardiovascular surgery; cTNI, cardiac troponin-I; CK-MB, creatine kinase-MB; CRP, C-reactive protein.

greater than their normal ranges, whereas that of plasma CK-MB was similar to the normal range. PO-24 hr cTNI levels were lower compared with Pre-OP levels, but higher than the normal range. However, CK-MB and CRP levels in PO-24 hr were higher than their Pre-OP levels. cTNI is a regulatory protein with both cytosolic and structural pools in the heart. Best data indicate that cardiac troponin is released from the myocardium when myocardial necrosis occurs [1]. CK-MB is a cytosolic carrier protein for high-energy phosphates. Even though measurement of CK-MB has been suggested to be the gold standard for the diagnosis of MI, it may increase in non-cardiac disorders [22]. In addition, CRP, which is an acute-phase reactant protein made in the liver, also increases in non-cardiac diseases. There is no doubt of the fact that cTNI is the strongest predictor on marker for the diagnosis of a myocardial injury and/or necrosis attributable to coronary artery disease.

Increased CK-MB and CRP levels in PO-24 hr might be attributed to surgical procedures (e.g. vessels harvested and skin incision and sutures etc.)

Finally, the present findings of postoperatively lower cTNI and higher CK-MB and CRP levels represent the patients' hearts recovering from their illness

Biochemical markers

Table 4 shows Pre-OP and PO-24 hr levels of biochemical markers. Mean values of Pre-OP aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were slightly higher than their normal ranges (10-35 and 0-35 IU/L, respectively). Pre-OP levels of glucose were significantly higher, whereas those of high density lipoprotein cholestrerol (HDL) were significantly lower than the each normal values (76-110 or 45-74 mg/dl, respectively). Pre-OP levels of the others were within normal ranges. On PO-24 hr, ALT, blood urea nitrogen (BUN), and creatinine levels returned to the normal ranges with decreased levels. Bilirubin levels were postoperatively elevated, but within

Table 4. Perioperative levels of biochemical markers

Marker \ Time	Pre-OP	PO-24 hr
AST (IU/l)	39.03±14.38	53.30±34.87*
ALT (IU/l)	38.04±14.33	33.77±25.06
Bilirubin (mg/dl)	0.71±0.29	1.00±0.51*
BUN (mg/dl)	18.15±7.97	17.50±7.50
Creatinine (mg/dl)	1.08±0.27	1.04±0.30
Glucose (mg/dl)	155.51±55.42	NM
Triglyceride (mg/dl)	157.56±98.15	NM
T-cholesterol (mg/dl)	190.79±44.15	NM
HDL (mg/dl)	37.31±10.30	NM
LDL (mg/dl)	111.76±36.88	NM

Data are expressed as mean±SD.
*, $p<0.05$ (compared with Pre-OP levels).
Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; T, total; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; BUN, blood urea nitrogen; ND, not measured.

normal values. However, PO-24 hr levels of AST were significantly greater than Pre-OP levels. Glucose, triglyceride, total cholesterol, HDL, and low dinsity lipoprotein cholesterol (LDL) levels were not measured in the postoperative period. Circulating concentrations of liver amino transferase, AST and ALT have been recognized as markers of non-alcoholic fatty liver disease.

Clark et al. [4] recently described that elevated aminotransferase was strongly associated with adiposity and other features of the metabolic syndrome. Schindhelm et al. [33] also demonstrated that ALT was a predictor for the development of CHD events.

In the present study, although there was difference among the patients, it is possible that increased AST and ALT levels partly contribute to CHD. Especially, we believe that preoperatively high glucose and low HDL levels may be pivotal contributors.

On the one hand, it is interesting that bilirubin concentrations were elevated at PO-24 hr. For many years, the bile pigment bilirubin was considered a toxic waste product formed during heme catabolism. However, more recent evidence suggests that bilirubin is a potent physiological antioxidant that may provide important protection against atherosclerosis, CHD, and inflammation [10]. Substantial evidence has documented that the development of CHD involves lipid peroxidation, and formation of oxygen free radicals and inflammation are associated with the production of oxygen and peroxyl radicals [25]. The antioxidant capacity of bilirubin and its ability to provide potent scavenging of peroxyl radicals have led to suggestions that mildly in-

creased circulatory bilirubin may have a physiologic function to protect against disease processes that involve oxygen and peroxyl radical. Therefore, the observation that postoperative bilirubin levels were higher compared with preoperative levels may indicate a physiological compensatory mechanism for the recovery from the illness. Nevertheless, we cannot explain the clinical significance for postoperatively increased AST levels. Further studies are needed to clarify it.

Correlation of leukocyte counts to D-dimer levels

The relationship of leukocyte counts with D-dimer levels at the preoperative period is summarized in Table 5. There was no significant correlation between leukocyte and D-dimer levels at the preoperative period ($p>0.05$). Carobbio et al. [3] recently showed that leukocytosis is a risk factor for thrombosis in essential thrombocythemia, which is Philadelphia-chromosome-negative myeloproliferative disorder. Many studies have reported that leukocytes can cause hypercoagulability and CHD [9]. However, previous studies analyzed a relationship between leukocyte counts and D-dimer level. Based on the previous reports, it is evident that leukocytes contribute to thrombogenesis, and the present data suggest that other factors can be involved in thrombus formation.

Correlation of Pre-OP levels of leukocyte or D-dimer with concentrations of cardiac markers

Table 6 shows the relationship of Pre-OP levels of leukocyte or D-dimer with perioperative concentrations of cardiac markers. Pre-OP leukocyte counts each had positive correlation with Pre-OP and PO-24 hr cTNI, CK-MB or CRP (excepting PO-24 hr CRP) levels ($p<0.05$, $p<0.01$ or $p<0.0001$). These data imply that Pre-OP levels of leukocyte and D-dimer are powerful predictors for diagnosis and prognosis of CHD.

Margolis et al. [21] have recently demonstrated that leukocyte counts, a stable, well-standardized, widely available and inexpensive measure of systemic inflammation, are an independent predictor of CHD events and all-cause mortality in postmenopausal women. Leukocyte counts greater than 6.7×10^3 cells/μl may identify high-risk individuals who are not currently identified by traditional CHD risk factors.

As mentioned earlier, mean leukocyte counts of patients participated in this study were 7.86±3.35×cells/μl, suggesting that they had an already high-risk of coronary events.

As early as 1954, Cole et al. [5] made the observation that patients with myocardial infarction (MI) with increased leukocyte counts had a four-fold higher risk of death compared with patients with leukocyte counts in the normal range. Leukocytes can generate systemic inflammation. Systemic levels of inflammatory markers are associated with elevated cardiovascular risk in adult populations. This association has been reported for peripheral blood leukocyte counts, CRP and interleukin-6 [39]. In general, this relationship has been attributed to inflammation and atherosclerosis occurring in the arterial wall [15]. Alternatively, leukocytes may facilitate vascular occlusion by modifying platelet activity and promoting thrombus formation [6]. Various types of inflammatory cells, including monocytes, lymphocytes, eosinophils, and neutrophils, have been implicated in CHD [28]. Numerous epidemiologic and clinical studies have shown the leukocyte count to be an independent risk factor for CHD, a risk factor for future cardiovascular events in individuals apparently without cardiovascular disease (CVD), and a prognostic marker of future events in patients who already have CVD [39].

Our proposition that a preoperative leukocyte count is a clinically useful marker for the diagnosis and prognosis of CHD is supported by previous studies.

Table 5. Correlation of preoperative leukocyte counts to preoperative D-dimer levels

Variable	Leukocyte	D-dimer
Leukocyte (*r*)	1.0	0.17¶
D-dimer (*r*)	0.17¶	1.0

r, correlation coefficient.
¶, $p>0.05$ (not significant).

Table 6. Correlation of preoperative levels of leukocyte or D-dimer to concentrations of cardiac markers at perioperative period

Marker	Pre-OP leukocyte	Pre-OP D-dimer
cTNI		
Pre-OP (*r*)	0.48++	0.59++
PO-24 hr (*r*)	0.33*	0.25*
CK-MB		
Pre-OP (*r*)	0.39+	0.29*
PO-24 hr (*r*)	0.29*	0.18¶
CRP		
Pre-OP (*r*)	0.49++	0.17¶
PO-24 hr (*r*)	0.20¶	0.25*

r, correlation coefficient.
*,$p<0.05$; +,$p<0.001$; ++,$p<0.0001$ (significant correlation);
¶, $p>0.05$ (not significant).

On the other hand, the preoperative D-dimer level was significantly associated with Pre-OP cTNI and CK-MB or PO-24 hr cTNI and CRP levels ($p<0.05$ or $p<0.0001$). Many prospective studies have shown independent associations of CHD events (MI and CHD death) with CRP or D-dimer levels in both middle-aged and the older population [7,16]. D-dimer, a fibrin degradation product, is a marker not only of thrombin generation but also of cross-linked fibrin turnover. Procoagulant reactions producing fibrin activate fibrinolysis to produce plasmin, which degrades fibrin to produce D-dimer. Coagulation factor levels predict arterial thrombosis in epidemiological studies [7]. Several studies have showed that D-dimer predicted future MI in men and women over age 65 years [7]. In patients with CAD, fibrinogen and D-dimer are independently associated with incident coronary events among postmenopausal women [27]. The present findings that Pre-OP levels of leukocyte and D-dimer had significant correlation with Pre-OP and PO-24 hr cardiac markers (cTNI, CK-MB or CRP) suggest that leukocyte counts and D-dimer levels are useful indicators for predicting the development and diagnosis of CHD.

Moreover, our observations reveal that preoperative levels of leukocyte and D-dimer were associated with postoperative levels of cardiac markers and thus they also might be good markers for prognosing postoperative cardiac condition and inflammation.

Interestingly, Pre-OP leukocyte counts related with Pre-OP CRP levels, whereas Pre-OP D-dimer levels correlated with PO-24 hr CRP levels, suggesting that leukocyte or D-dimer independently contribute to the coronary events. Especially, CRP is considered as a high risk factor of CHD as well as an inflammatory marker. CRP is the best characterized of the currently available inflammatory biomarkers and has emerged as a potential marker for cardiovascular risk. CRP is a circulating pentraxin that plays a major role in the human innate immune response. Even though generally considered to be an acute-phase reactant, CRP is also produced in smooth muscle cells within human coronary arteries and is expressed preferentially in diseased vessels [2]. CRP may directly affect expression of adhesion molecules, impact fibrinolysis, and alter endothelial dysfunction [34]. Danenbery et al. [8] and Paul et al. [26] recently have demonstrated that transgenic mice expressing human CRP have an increased thrombotic risk and perhaps elevated atherogenesis.

Consequently, in the present, Pre-OP or PO-24 hr CRP levels might be clinically serviceable for the diagnosis and prognosis of CHD.

Association of Pre-OP leukocyte and D-dimer levels to perioperative biochemical markers

Associations of Pre-OP levels of leukocyte or D-dimer to perioperative concentrations of biochemical markers were summarized in Table 7. Pre-OP leukocyte counts had positive correlation with Pre-OP and PO-24 hr concentrations of AST or ALT ($p<0.01$ or $p<0.0001$), whereas Pre-OP D-dimer levels had a positive relationship with Pre-OP and PO-24 hr levels of bilirubin ($p<0.01$ or $p<0.0001$). The pre-OP D-dimer levels were associated with Pre-OP glucose levels (positively, $p<0.05$) and PO-24 hr creatinine levels (negatively, $p<0.05$). Both Pre-OP leukocyte and D-dimer levels were inversely related to Pre-OP HDL levels ($p<0.05$).

It is a well-known fact that AST and ALT are clinical liver markers. However, clinical physicians began recognizing them as risk factors involved in the development of CHD. Recently, Saely et al. [32] have shown that ALT, ALT/AST

Table 7. Association between preoperative levels of leukocyte or D-dimer with perioperative concentrations of biochemical markers

Marker	Pre-OP leukocyte	Pre-OP D-dimer
Pre-OP AST (*r*)	0.50^{++}	0.15¶
PO-24 hr AST (*r*)	0.34**	0.18¶
Pre-OP ALT (*r*)	0.40^{++}	0.14¶
PO-24 hr ALT (*r*)	0.34**	0.18¶
Pre-OP bilirubin (*r*)	0.11¶	0.44^{++}
PO-24 hr bilirubin (*r*)	0.19¶	0.38**
Pre-OP BUN (*r*)	0.08¶	0.09¶
PO-24 hr BUN (*r*)	0.11¶	0.10¶
Pre-OP creatinine (*r*)	0.08¶	0.10¶
PO-24 hr creatinine (*r*)	0.19¶	-0.22*
Pre-OP glucose (*r*)	0.18¶	0.21*
PO-24 hr glucose (*r*)	NM	NM
Pre-OP triglyceride (*r*)	0.14¶	0.15¶
PO-24 hr triglyceride (*r*)	NM	NM
Pre-OP T-cholesterol (*r*)	0.12¶	0.09¶
PO-24 hr T-cholesterol (*r*)	NM	NM
Pre-OP HDL (*r*)	-0.23*	-0.35**
PO-24 hr HDL (*r*)	NM	NM
Pre-OP LDL (*r*)	0.11¶	0.07¶
PO-24 hr LDL (*r*)	NM	NM

r, correlation coefficient.
ND, not measured.
*, $p<0.05$; **, $p<0.01$; +, $p<0.001$; ++, $p<0.0001$ (significant correlation); ¶, $p>0.05$ (not significant).

ratio, and gamma-glutamyl transferase were significantly and independently associated with the metabolic syndrome. The metabolic syndrome may be associated with the development of CHD.

Therefore, the present data suggest that leukocytes contribute to increased AST and ALT levels, resulting in the metabolic syndrome, which may cause CHD.

An association of Pre-OP D-dimer to Pre-OP and PO-24hr bilirubin may represent an antithrombogenic role of bilirubin. Serum bilirubin acts as a natural antioxidant in several in vitro systems [6]. Furthermore, bilirubin, especially with albumin, appears to be cytoprotective [12]. Very recently, Ghem et al. [12] have demonstrated that reduced serum levels of bilirubin were shown to be associated with a higher prevalence of CAD emerging as a new potential risk factor marker.

A relationship between Pre-OP D-dimer and glucose levels suggests that hyperglycemia or diabetes is a high risk factor for inflammation and/or thrombogenesis, leading to CHD. Reliable studies have documented there is a strong correlation between hyperglycemia (or diabetes) and CHD [31].

In the present study, negative correlation of Pre-OP leukocyte or D-dimer to Pre-OP HDL reflects a significant role of HDL in the prevention of CHD.

HDL plays a central role in many events involved in the development of atherosclerosis, and there is an inverse relationship between plasma HDL levels and cardiovascular risk [14]. The atheroprotective role of HDL is often related to its ability to promote reverse cholesterol transport [29]. However, HDL presents several other antiatherogenic properties, such as inhibition of LDL aggregation and LDL non-enzymatic oxidation, which prevent cellular inflammatory events mediated by phospholipids [30]. Furthermore, HDL exerts a protective effect on endothelial cells and monocytes [24]. Wannamethee et al. [37] recently suggested that there is a significant association between HDL level and D-dimer for the development of CHD. Nevertheless, further studies should be carried out to explain a clinical significance for the association of Pre-OP leukocyte or D-dimer with PO-24 hr creatinine levels. In some respects, Pre-OP AST, ALT, bilirubin, glucose and HDL levels may be very important indicators for predicting CHD. Finally, individuals with lower HDL levels may suffer decreased antiinflammation and increased oxidative stress and thereby elevation of leukocyte and D-dimer levels, resulting in CHD.

Association of Pre-OP leukocyte or D-dimer levels with other perioperative variables

Table 8 shows the association of Pre-OP leukocyte or D-dimer levels with other perioperative variables. Pre-OP leukocyte or D-dimer levels were inversely associated with Pre-OP LVEF value ($p<0.05$), suggesting that increased preoperative levels of leukocyte and D-dimer can contribute to decreased LVEF. Reduced LVEF means heart failure, leading to other organ dysfunctions and/or complications, including systemic edema. Leukocytosis with neutrophilia and monocytosis is associated with the nonrecovery of left ventricular function in patients with left ventricular dysfunction [36]. Leukocytosis may cause an increased production of proinflammatory cytokines and thrombus. A significant increase in the level of D-dimer can be found in participants with generalized arterosclerosis, with a LVEF $\leq$40% as well as those with left ventricular aneurysm [35]. Pre-OP leukocyte counts were positively associated with Pre-OP DBP, where Pre-OP D-dimer levels were positively associated with Pre-OP SBP and DBP, indicating that hypertension can cause an increased production of D-dimer in circulation [17]. Pre-OP leukocyte counts were positively correlated with DBP levels, OP-time or PMVT, whereas Pre-OP D-dimer levels were positively associated with SBP and DBP levels, PMVT, ICU-period, or hospitalization ($p<0.05$ or $p<0.001$).

A recent study by Lee et al. [19] has shown that D-dimer levels were strongly associated with postoperative outcomes, especially PMVT, ICU-stay, and hospitalization, suggesting that D-dimer is a good marker for prognosing postoperative outcomes of patients that underwent car-

Table 8. Association between preoperative levels of leukocytes or D-dimer with perioperative variables

Index \ Variable	Pre-OP leukocyte	Pre-OP D-dimer
LVEF (*r*)	-0.23*	-0.44+
SBP (*r*)	0.19¶	0.33*
DBP (*r*)	0.25*	0.27*
OP-time (*r*)	0.22*	0.12¶
Graft-number (*r*)	0.07¶	0.09¶
POMV-time (*r*)	0.28*	0.44+
ICU-period (*r*)	0.19¶	0.42+
Hospitalization (*r*)	0.16¶	0.46+

r, correlation coefficient.

*, $p<0.05$; +, $p<0.001$ (significant correlation); ¶, $p>0.05$ (not significant).

diovascular surgery. To date, many clinical physicians have analyzed and utilized several markers to diagnose and prognose patients with CHD. The electrocardiogram (ECG) is critical for the initial evaluation of patients with suspected acute coronary syndromes (ACS). However, in 20-50% of cases, the ECG is nondiagnostic at hospital admission [13], thus, biochemical cardiac markers have become important diagnostic tools for ACS. It is currently standard that patients presenting with chest pain to an emergency room are evaluated not only by ECG but also by determination of biochemical cardiac markers such as cTNI CK-MB and CRP.

To identify patients with ACS or CHD, serial assessment of CK-MB and cTNI at 4 to 6 hr intervals is obligatory because of the time lag of CK-MB and cTNI increases after the onset of chest pain. However, all these markers merely detect myocardial necrosis after MI but totally fail to detect unstable angina pectoris. Moreover, there is a relatively long time lag before these markers increase.

Therefore, measurements of leukocyte and D-dimer levels, which with a relatively short time lag, low cost and reliable results, may be clinically useful for the diagnosis, prediction and prognosis of ACS and CHD.

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초록 : 심혈관질환의 수술기주위 결과예측에 있어 수술 전 백혈구 수 및 D-dimer 농도의 임상적 유용성

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이 연구는 관상동맥질환 수술기주위의 결과예측에 있어 수술 전 백혈구 및 D-dimer 수치가 유용한 인자가 될 수 있는지를 규명하기 위해 회고적으로 실시하였다. 수술 전 백혈구 수는 수술 전 및 후의 심장표지자인 troponin-I, creatine kinase-MB, C-반응단백 각각의 농도와 정의 상관성이 있었다. 수술 전 D-dimer 농도 역시 수술기주위의 심장표지자들과 정의 상관관계를 보였다. 수술 전 백혈구 수는 간표지자인 aspartate aminotransferase 및 alanine aminotransferase의 수술 전후 농도와 정의 상관관계를 보였는데 비해, 수술 전 D-dimer 농도는 수술 전후 빌리루빈 농도, 수술 전 글루코스 농도, 수술 후 크레아티닌 농도와 각각 정 또는 역의 상관관계가 있었다. 수술 전 백혈구 및 D-dimer 수치 둘 다 수술 전 고밀도콜레스테롤 농도 및 좌심실구출계수와 각각 역의 상관관계가 있었다. 수술 전 백혈구 수는 수술시간 및 수술 후 기계보조 호흡시간과 각 정의 상관관계를 보였고, 수술 전 D-dimer 농도는 수술 후 기계보조 호흡시간, 중환자실 치료기간, 재원기간과 각 정의 상관관계가 있었다. 이 회고적 조사의 결과는 수술 전 백혈구 및 D-dimer 수치가 관상동맥수술 환자들의 수술기주위 결과예측에 있어 임상적으로 유용한 인자들이 될 수 있음을 시사하고 있다.