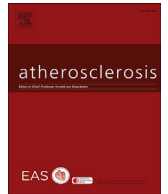




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Prognostic significance of circulating leukocyte subtype counts in patients with coronary artery disease

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ABSTRACT

Background and aims: This study investigated the association of leukocyte subtype counts with vascular endothelial dysfunction and future cardiovascular events in patients with coronary artery disease (CAD). **Methods:** The study included 389 consecutive CAD patients (259 male, 130 female; mean age, 70.1 ± 9.9 years). The patients underwent coronary angiography, and measurement of blood parameters, including leukocyte subtype counts.

Results: There were 84 cardiovascular events during a mean follow-up of 586 ± 378 days. Kaplan–Meier analysis showed a higher probability of cardiovascular events in the high-monocyte group ($\geq 360/\text{mm}^3$) compared with the low-monocyte group ($< 360/\text{mm}^3$) (log-rank test, $p = 0.047$). Multivariate Cox hazard analysis identified a high monocyte count as an independent predictor of cardiovascular events (hazard ratio: 1.63, 95% confidence interval: 1.05–2.51, $p = 0.028$). Peripheral endothelial function in 355 of the CAD patients was assessed by reactive hyperemia peripheral arterial tonometry index (RHI) to examine the association of ln-RHI with leukocyte subtype counts. Total leukocyte, monocyte and neutrophil counts were significantly higher in CAD patients with low ln-RHI (< 0.57 : the mean ln-RHI value) compared with those with high ln-RHI (≥ 0.57). Univariate analyses revealed that ln-RHI in CAD patients was positively correlated with ln-total leukocyte ($r = -0.187$, $p < 0.001$), ln-monocyte ($r = 0.316$, $p < 0.001$), and neutrophil ($r = -0.175$, $p = 0.001$) counts. Multiple regression analysis showed that the monocyte count was a significant and independent factor associated with ln-RHI (adjusted $R^2 = 0.126$, $p < 0.001$).

Conclusions: A high monocyte count was an independent and incremental predictor of cardiovascular events in CAD patients. The monocyte count was also significantly correlated with peripheral endothelial dysfunction in CAD patients.

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1. Introduction

Coronary artery disease (CAD) is now the leading cause of death worldwide, and its prevalence is associated with aging of the population, and with the prevalence of obesity, type 2 diabetes mellitus (DM), and metabolic syndrome [1]. Because cardiovascular

events are the main cause of death in CAD patients, risk stratification for future cardiovascular events in these patients can provide valuable information in the clinical setting. Vascular endothelial function plays a key role in the pathophysiology and prognosis of cardiovascular diseases, including atherosclerosis, ischemic heart disease, and heart failure [2,3]. In addition, vascular endothelial dysfunction in high risk patients is found from the early phase of arteriosclerosis to advanced atheroma, resulting in obstructive CAD [4] and cardiovascular events [5,6]. Previous reports showed that vascular endothelial dysfunction, as assessed by forearm flow-mediated vasodilation is closely associated with various cardiovascular diseases [7,8]. Using fingertip reactive hyperemia

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Abbreviations list

CAD	coronary artery disease
DM	diabetes mellitus
RH-PAT	reactive hyperemia peripheral arterial tonometry
RHI	reactive hyperemia peripheral arterial tonometry index
CAG	coronary angiography
SVD	single-vessel disease
MVD	multiple-vessel disease
eGFR	estimated glomerular filtration rate
UMIN	University Hospital Medical Information Network
HDL cholesterol	high-density lipoprotein cholesterol
LDL cholesterol	low-density lipoprotein cholesterol
TG	triglycerides

BNP	B-type natriuretic peptide
hs-troponin T	high-sensitivity troponin T
hs-CRP	high-sensitivity C-reactive protein
HR	hazard ratio
CI	confidence interval
E/e'	ratio of early transmitral flow velocity to tissue doppler early diastolic mitral annular velocity
BMI	body mass index
LVEF	left ventricular ejection fraction
ACEI	angiotensin-converting enzyme inhibitor
ARB	angiotensin II receptor blocker
CCB	calcium channel blockers
HMG-CoA RI	hydroxymethylglutaryl coenzyme-A reductase inhibitors

peripheral arterial tonometry (RH-PAT), we previously reported that the RH-PAT index (RHI) correlated inversely with various cardiovascular risk factors [9–12], indicating the practical usefulness of the RH-PAT test.

Inflammation, characterized by early leukocyte recruitment, is known to be closely associated with vascular endothelial dysfunction and atherosclerosis [4]. Previous epidemiologic studies have reported that an increased leukocyte count is a strong and independent risk factor for progression of atherosclerosis [13], and also for cardiovascular events [13–16]. However, the association between leukocyte subtype counts and vascular endothelial function in patients with CAD has not been fully elucidated. Therefore, the aim of this study was to investigate the associations between leukocyte subtype counts and vascular endothelial function, and the prognostic usefulness of leukocyte subtype counts in patients with CAD.

2. Materials and methods

2.1. Study subjects and protocol

Consecutive stable patients with suspected CAD who were referred for hospitalization and scheduled for coronary angiography (CAG) at Kumamoto University Hospital between January 2008 and August 2013 were registered. Based on the results of CAG, patients with atherosclerotic organic coronary artery stenosis ($\geq 75\%$) were diagnosed as having CAD (diameter of stenosis in vessels ≥ 1.5 mm). On the basis of the CAG results, CAD patients were classified into single-vessel disease (SVD) or multiple-vessel disease (MVD) groups according to the number of diseased vessels to evaluate the severity of CAD. Patients were excluded for the following reasons: heart failure, history of a coronary artery bypass graft, active infective disease, history of malignancy, and end stage of renal disease (estimated glomerular filtration rate [eGFR] < 15 mL/min/1.73 m²). Finally, a total of 389 patients were enrolled in the study, and followed prospectively until February 2014 or until the occurrence of a cardiovascular event. The RHI was used to assess peripheral endothelial function and was measured in 350 study participants before CAG using fingertip RH-PAT by EndoPAT2000 (Itamar Medical Ltd., Caesarea, Israel) to assess the relationship between vascular endothelial dysfunction and leukocyte subtype counts in CAD (Supplemental Fig. 1).

The study protocol conformed to the principles of the Declaration of Helsinki and the study has been approved by an institutional review committee at Kumamoto University Hospital. Written

informed consent was obtained from all patients. This study is registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000018886).

2.2. Definition of coronary risk factors

DM was defined as the presence of symptoms of diabetes and a resting plasma glucose concentration ≥ 200 mg/dL, a fasting plasma glucose concentration ≥ 126 mg/dL, a 2-h plasma glucose concentration ≥ 200 mg/dL in a 75 g oral glucose tolerance test, or taking medication for DM. Hypertension was defined as $> 140/90$ mmHg or taking antihypertensive medication. Current smoking was defined as smoking at the time of admission. Dyslipidemia was defined as high-density lipoprotein (HDL) cholesterol < 40 mg/dL or low-density lipoprotein (LDL) cholesterol ≥ 140 mg/dL, triglycerides (TG) > 150 mg/dL, or taking medication for dyslipidemia.

2.3. Measurement of blood parameters

Blood samples were taken early in the morning in the fasting state before any medications were administered and stored at -80 °C until analysis. The levels of plasma B-type natriuretic peptide (BNP), high-sensitivity troponin T (hs-troponin T), serum high-sensitivity C-reactive protein (hs-CRP), and other relevant biochemical markers were measured.

2.4. Follow-up and cardiovascular events

Patients were followed up until February 2014 or until the occurrence of a cardiovascular event, such as cardiovascular death, nonfatal myocardial infarction, unstable angina pectoris, nonfatal ischemic stroke, hospitalization for heart failure decompensation, or coronary revascularization. Cardiovascular death was defined as death as a result of myocardial infarction (within 28 days of onset), heart failure, or documented sudden death in the absence of non-cardiovascular causes. Myocardial infarction was diagnosed by the rise or fall of cardiac biomarkers (plasma creatine kinase-MB and cardiac troponin-T) above the 99th percentile of the upper limit of the normal range, with evidence of myocardial ischemia, as indicated by at least one of the following: electrocardiogram changes (new ST-T changes, left bundle branch block, pathological Q wave) or imaging evidence of new loss of viable myocardium or new abnormalities in regional wall motion. Unstable angina pectoris was diagnosed by new or accelerating symptoms of myocardial ischemia accompanied by new ischemic ST-T changes. Ischemic

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