

## Potential of Monocyte Count for the Assessment of Cardiovascular Disease

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### Abstract

Atherosclerosis is a chronic inflammatory disease proceeding from an imbalance in lipid metabolism and immune responses. Since leukocytes, especially monocytes and monocyte-derived macrophages, play pivotal roles in the progression of atherosclerosis, it is possible that monocyte count is a beneficial marker for predicting cardiovascular disease (CVD). Many epidemiologic and clinical studies have indicated monocytosis to be an independent predictor of cardiovascular events, both in healthy individuals at baseline and in patients with CVD or with high risk diseases for CVD, such as diabetes, dyslipidemia, hypertension and chronic kidney disease. This relationship has been observed in prospective and retrospective cohort studies, and endures after adjustment for several CVD risk factors. Other indicators utilized monocyte count, such as lymphocyte-to-monocyte ratio, monocyte-to-lymphocyte ratio and monocyte-to-high-density lipoprotein cholesterol ratio, were also independently associated with cardiovascular events and its mortality. In this review, we discussed the clinical utility of the monocyte count as a predictive marker in atherosclerotic diseases.

**Keywords:** Monocyte count; Cardiovascular disease; Cardiovascular mortality; Predictive marker

### Introduction

Atherosclerotic diseases, including cardiovascular disease (CVD) and peripheral artery disease (PAD), are one of the leading causes of disability and death in the developed countries. Atherosclerosis is now recognized as a chronic inflammatory process characterized by early leukocyte recruitment which followed by plaque maturation and rupture [1]. Therefore, the increase in the number of leukocyte in blood may influence the degree of atherosclerosis. The leukocyte count has been reported to correlate with coronary heart disease (CHD) since 1920s [2]. In addition, many epidemiologic studies have reported that an increased leukocyte count is a strong and independent risk factor for cardiovascular events [3-10] and for the prevalence and progression of subclinical carotid atherosclerosis [11-16], suggesting that leukocyte count is useful as a clinical marker to predict atherosclerotic diseases. On the other hand, leukocyte count includes several types of cells which have different participation form in atherogenesis. In particular, monocytes and monocyte-derived macrophages play a central role in the early phase of atherogenesis [1,17-19]. In this review, we focus on the correlation between peripheral blood monocyte count and atherosclerotic diseases.

### Possibility of monocyte count as a marker for atherosclerotic diseases

Prentice et al. reported for the first time to analyze differential leukocyte counts, and they indicated that increasing neutrophil and eosinophil counts were both related to the development of CHD within two years, and suggested a similar relationship with monocyte count [20]. Thereafter, Paris Prospective Study II revealed that, after

adjustment for other variables, the risk of CHD increased 1.15 times for each increase of 100 cells/mm<sup>3</sup> in monocyte count [21]. We retrospectively investigated the association between monocyte count and future cardiovascular events in patients with coronary artery disease (CAD) [22]. Kaplan-Meier analysis demonstrated a higher probability of cardiovascular events in the high monocyte count ( $\geq 360/\text{mm}^3$ ) group compared with the low monocyte count ( $<360/\text{mm}^3$ ) group (log-rank test,  $p=0.047$ ) [22]. Multivariate Cox hazard analysis indicated that a high monocyte count is an independent predictor of cardiovascular events (hazard ratio (HR): 1.63, 95% confidence interval (CI):1.05-2.51,  $p=0.028$ ) [22]. In addition, multiple regression analysis in our study showed that the monocyte count was a significant and independent factor associated with reactive hyperemia peripheral arterial tonometry index (adjusted  $R^2=0.126$ ,  $p<0.001$ ) in CAD patients, suggesting that the monocyte count was a predictor for peripheral endothelial dysfunction [22]. Monocyte count has also been shown to be related to body mass index in middle-aged men [23], and that in the cross-sectional study it was independently and significantly associated with specific features of clustering of metabolic syndrome and prevalence of ischemic cardiovascular diseases in patients with type 2 diabetes [24]. Medical Research Council Cognitive Function and Ageing Study, which was a population based cohort study and focused on the relatively healthy elderly population, revealed that monocyte count was significantly associated with cardiovascular history [25]. Kim et al. also reported in the cross-sectional study that monocyte counts were associated with an increased risk of cardiovascular and cancer-related mortality in the elderly population [26]. In the prospective observational study investigated the association between monocyte count and preclinical CVD in an asymptomatic population, monocyte count was found to have the strongest, independent relationship with overall CVD risk by backgrounds linear regression modeling [27]. On the other hand, Nasir

et al. reported the correlation between leukocyte subtype counts and PAD in the cross-sectional study of the U.S. population [28]. They revealed that monocytes were the only white blood cell subtype significantly and independently associated with PAD after adjustment for other inflammatory markers [28]. Concerning a cerebrovascular disease, the prospective study indicated that monocyte count was associated with lacunar infarcts in hypertensive patients [29]. Eventually, it is possible that monocyte count is useful as a predict marker for several atherosclerotic diseases.

### **Monocyte count as a predictive marker for cardiovascular mortality**

Regarding the cardiovascular mortality, the Atherosclerosis Risk in Communities (ARIC) study found that the highest quartiles of monocyte was associated with respective increase of 40% in cardiovascular disease mortality relative to the lowest quartiles [30]. On the other hand, Kato et al. prospectively studied the predictive value of monocyte count for total and cardiovascular death in hemodialysis patients [31]. Kaplan-Meier analysis revealed that the highest tertile of the baseline monocyte (>270  $\mu$ l) count had a significantly lower survival rate compared to the middle and the lowest tertiles [31]. Cox hazards analysis after adjustment for other conventional risk factors revealed that monocyte counts of >270/ $\mu$ l became a determinant of total death compared with those of <180/ $\mu$ l (hazards ratio 1.98 [1.10-3.57],  $p=0.02$ ) [31]. Therefore, monocyte count may be a beneficial predictor for cardiovascular death, as well as CVD.

### **Monocyte count as a marker for carotid atherosclerosis**

Several lines of reports for the correlation between monocyte count and carotid atherosclerosis estimated by ultrasonography were accumulated. Huang et al. reported that the presence of carotid atherosclerosis was associated with significant increases in the counts of monocyte after adjustments for age and body mass index in male non-smokers [32]. Boyajian et al. also reported that monocytes as a percentage of circulating leukocytes was independently associated with carotid stenosis [33]. The community-based Carotid Ultrasound Disease Assessment Study revealed that monocyte count is a better independent predictor of intima media thickness (IMT) and plaque formation in common carotid artery (CCA) than IL-6, hs-CRP, fibrinogen, and WCC in a healthy community population [11]. We also revealed in the cross-sectional study that monocyte counts were positively correlated with both mean CCA-IMT and maximum CCA-IMT in patients with type 2 diabetes [34]. The prospective study concern with monocyte count and carotid atherosclerosis revealed that for one standard deviation increase in monocyte count, the risk of being in a higher plaque category increased by 18% (OR, 1.18; 95% CI, 1.08 to 1.29) [13]. Moreover, in the highest monocyte quartile, the risk for having plaque compared with the lowest quartile was 1.85 (OR) (95% CI, 1.41 to 2.43) [36]. Therefore, monocyte count could be an independent predictor of future plaque formation in subjects without pre-existing carotid atherosclerosis.

### **Monocyte count as a marker for future CVD after intervention**

After intervention therapy for atherosclerotic vessels, it is possible that monocyte count is one of the prognosis determining factors. Schillinger et al. reported that pretreatment monocyte counts were

associated with restenosis after femoropopliteal percutaneous transluminal angioplasty (PTA) and stent implantation [35]. The study observed in-stent neointima after coronary stent implantation revealed that circulating monocytes increased after coronary stent implantation, and the peak monocyte count related to in-stent neointimal volume [36]. Hong et al. also reported the relationship between preinterventional peak monocyte count and neointimal growth after successful stent implantation using intravascular ultrasound [37]. They revealed that the preinterventional circulating monocyte count was significantly higher in the in-stent restenosis group than that in the group without in-stent restenosis [37]. Moreover, the neointima area associated with preinterventional monocyte count was largest among the patients in the highest tertile than that of the patients in the lowest or middle tertile [37]. On the other hand, Magri et al. reported that patients with critical limb ischemia have increased numbers of circulating monocytes, and the monocyte number decreases with resolution of ischemia after successful revascularization [38]. Taking their results, monocyte count may be a utility value as a predictor for success or failure of revascularization. Interestingly, Mocco et al. reported that preoperative monocyte count was independently associated with acute neurocognitive decline after carotid endarterectomy for asymptomatic stenosis [39].

### **Modified marker using monocyte count correlates with cardiovascular outcome**

Other predictive markers utilized monocyte count, such as lymphocyte-to-monocyte ratio (LMR), monocyte-to-lymphocyte ratio (MLR) and monocyte-to-high-density lipoprotein cholesterol ratio (MHR), were reported. Ozturk and Kurtul revealed in the cross-sectional study that LMR was significantly lower in the intermediate-high SYNTAX score group compared to low SYNTAX score group in acute coronary syndrome patients [40], and multivariate logistic regression analysis revealed that lower LMR was an independent predictor of intermediate-high SYNTAX score [40]. Furthermore, Gary et al. reported in the cross-sectional study that a decreased LMR is significantly associated with a high risk for critical limb ischemia in peripheral arterial occlusive disease [41]. On the other hand, the Utrecht Coronary Biobank cohort study revealed that MLR showed strong independent predictive value for cardiovascular mortality (HR 1.42 (1.11-1.81),  $p=0.005$ ) [42]. Other prospective study revealed that MLR was independently associated with all-cause mortality (HR 4.842; 95% CI, 2.091-11.214;  $P < 0.001$ ) and cardiovascular mortality (HR 6.985, 95% CI 1.943-25.115,  $P=0.003$ ) as continuous variables in hemodialysis patients [43]. In the study focused on MHR, increased MHR was associated with a worse cardiovascular profile and arose as independent predictors of major cardiovascular events in patients with chronic kidney disease [44]. Likewise, MHR was found to be independently correlated with in-hospital major adverse cardiac events and mortality after primary percutaneous coronary intervention (PCI) [45], and with major adverse cardiovascular events in patients undergoing coronary angiography [46] and in patients with acute coronary syndrome (ACS) [47]. Moreover, MHR arose as an independent predictor of in-stent restenosis [48]. As stated above, several lines of reports, which referred the benefit of monocyte count-applied predictive markers for CVD, were augmented. However, since it is still unclear what is the best beneficial marker for the prediction of atherosclerotic diseases, further studies are needed to clarify this issue.

## Conclusion

Monocytosis is associated with increased CVD risk and CVD-related mortality in various patient populations and clinical conditions. Monocyte count also emerges to be an independent risk factor for atherosclerotic diseases. However, some epidemiologic and prospective cohort studies indicated that monocytosis was not associated with CHD [49], cardiovascular death [50] or stroke [51]. Moreover, increased circulating monocyte count was correlated with good coronary collateral growth in patients with severely stenotic CAD [52] and with diabetes [53]. Thus, viewed from a different angle, the increased monocyte count may predict the protection of cardiac disorder. Although no one reported the apparent reason for the discrepancy, it is possible that the quality of monocytes may be related with this issue. In fact, it is important to note that monocyte subset count, such as CD14<sup>++</sup>CD16<sup>+</sup> monocytes, independently predicted the cardiovascular events, in patients with previous cardiovascular events [54], in patients with CKD [55] or in dialysis patients [56]. Therefore, to clarify the profitability of monocytosis on the prediction of CVD and cardiovascular mortality, detail examination including monocyte subset count might be needed. Further studies are required to determine the implications of using the monocyte count, monocyte count-utilized factors and monocyte subset count to predict clinical risk and outcome for CVD.

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