

Effect of Monocyte-to-Lymphocyte Ratio on Heart Failure Characteristics and Hospitalizations in a Coronary Angiography Cohort

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Abstract

Inflammation is a shared mechanism in coronary artery disease (CAD) and subsequent heart failure (HF) and circulating monocyte and lymphocyte counts predict CAD severity and outcomes. We investigated whether the monocyte-to-lymphocyte ratio (MLR) correlates with biomarkers of HF and extent of CAD, as well as future HF hospitalizations in patients undergoing coronary angiography (CAG). Therefore, we studied 1754 patients undergoing CAG for stable CAD, unstable angina or myocardial infarction (MI). MLR was determined at blood draw prior to angiography and related cross-sectionally to HF biomarkers (ejection fraction [EF], N-terminal pro-B-type natriuretic peptide [NTproBNP] levels) and CAD severity, as well as longitudinally with risk of HF hospitalizations during follow-up. In the entire cohort, median (interquartile range) MLR was 0.32 (0.24-0.43). High MLR was defined as the upper quartile and significantly associated with non-stable CAD (unstable angina [Odds ratio=1.13; 95% confidence interval 1.06-1.21] or MI [OR=1.10; 1.04-1.16]), more severe CAD (OR=1.39; 1.15-1.68), poorer EF (OR=1.63; 1.29-2.05) and higher NTproBNP levels (β =0.78; 0.59-0.96), all $p<0.001$. The associations with non-stable CAD and NTproBNP remained highly significant after covariate adjustment. Over a mean follow-up of 1.3 years, 46 HF hospitalizations occurred. A high MLR was significantly and independently predictive of HF hospitalizations during follow-up (HR 2.1 [1.1-4.1], $p=0.039$) after adjustment for covariates and addition of MLR to the basic model significantly improved reclassification. In conclusion, MLR is strongly related to HF markers and predicts HF hospitalizations during follow-up in CAD patients.

Key words: heart failure (HF); coronary artery disease (CAD); monocyte-to-lymphocyte ratio (MLR); lymphocyte-to-monocyte ratio (LMR); inflammation

Introduction

The role of inflammation and inflammatory cells in cardiovascular disease has been demonstrated in countless studies, showing that leukocyte¹, monocyte², neutrophil counts³ and ratios hereof⁴ are related to coronary artery disease (CAD) severity and outcome. The monocyte-to-lymphocyte ratio (MLR) has recently been introduced as a potent predictor of mortality among coronary angiography (CAG) patients.^{5,6} In addition to its role in coronary atherosclerosis, inflammation is also involved in the pathogenesis of heart failure (HF). Although a number of studies have investigated clinical factors⁷ and imaging modalities⁸, evidence for the predictive capacity of circulating inflammatory cells in HF prediction is lacking. Given the close relation of higher monocyte levels and lower lymphocyte levels⁵ with myocardial injury and subsequent HF, and the strong association of MLR with (cardiovascular⁵) mortality⁶, we investigated the relation of MLR to HF biomarkers and HF hospitalizations during follow-up among patients with varying degrees of CAD.

Methods

In this study, we included CAG patients from the Utrecht Coronary Biobank (UCORBIO) cohort⁹ with available MLR (1754/1845 patients). Indications for CAG were stable CAD (complaints of dyspnea or chest pain upon exertion and >50% stenosis in one of the coronary arteries), unstable angina or MI. Patients undergoing CAG for other indications were excluded from the current analyses. The medical ethics committee of the UMCU approved the study and all patients provided written informed consent. UCORBIO is registered under the clinicaltrials.gov ID: NCT02304744. The study conforms to the Declaration of Helsinki.

Clinical data were collected as described previously.¹⁰ In brief, demographic data, history of acute coronary syndrome (ACS), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), cerebrovascular accident/transient ischemic attack (CVA/TIA) and peripheral arterial disease (PAD), medication use, cardiovascular risk factors: diabetes mellitus, body mass index (BMI), hypertension, hypercholesterolemia, smoking and the indication for CAG, the angiographic severity of CAD and procedural details were collected at the moment of enrollment.

Echocardiographic EF was grouped into 4 categories: <30%, 30-39%, 40-49% and >50%.

An arterial blood sample was drawn from the arterial sheath inserted for CAG before any procedure-related drugs were administered. Differential blood counts were performed in accordance with routine clinical practice using the Abbott Cell-Dyn hematology analyzer. All hematological parameters were subsequently stored in and extracted from the Utrecht Patient-Oriented Database (UPOD).¹¹

Patients are followed-up for 5 years, of which 3 years had passed at the moment of writing. Every year, patients received a questionnaire to ask for hospital hospitalizations for any reason. When patients reported a potential event or when the patient did not return the questionnaire, the general practitioner or the said hospital was contacted for confirmation of the hospitalization. In case of hospitalization, medical records were requested and a panel of cardiologists adjudicated the event.

All analyses were performed on data with imputed covariates in order to avoid bias caused by data missing-not-completely-at-random. Covariates, but not outcomes (MLR and HF hospitalizations during follow-up) were imputed using multiple imputation (“mice” package for R, $m=10$). Pooled results from the analyses performed on the 10 imputed datasets are shown in this paper, unless stated otherwise. Baseline characteristics were compared using t-tests for normally distributed continuous data, Kruskal-Wallis tests for non-normally distributed continuous data and chi-square tests for categorical data. HF markers (left ventricular ejection fraction [EF] and NTproBNP levels) were cross-sectionally related to MLR in univariable and multivariable linear regression analyses. All available covariates were included: age, sex, diabetes, hypertension, hypercholesterolemia, BMI, smoking, indication for CAG, angiographic severity of CAD, treatment of CAD, history of acute coronary syndrome, PCI, CABG, CVA or PAD, kidney failure, medication use (ACE inhibitor, beta-blocker, statin, diuretic, P2Y12 inhibitor), NTproBNP levels (not for the NTproBNP analysis), EF (not for the EF analysis), troponin I levels and hsCRP levels.

Furthermore, the prediction of future HF hospitalizations by MLR was evaluated in multivariable Cox regression analysis (deceased patients were censored, $n=115$). For prediction, MLR was dichotomized into high MLR for all values in the upper quartile (>0.43) and low or normal MLR for the 3 lower quartiles (≤ 0.43). Covariates for the survival analyses were identical to those in the cross-sectional analysis. Because of the known influence of MI on monocyte and lymphocyte counts, we tested for interaction between indication for angiography and MLR in the analysis for outcome.

This interaction turned out to be significant and therefore stratified univariable analyses were performed for the indications for CAG. For MLR, we calculated integrated discrimination improvements (IDIs) and continuous net reclassification improvements (cNRI) as described previously.⁶

Because of a positively skewed distribution, MLR, NTproBNP, TnI and hsCRP levels were log-transformed for analysis. All analyses were performed in the Rstudio environment for the R statistical programming software. Tests were two-tailed, a p-value <0.05 was deemed significant.

Results

Table 1 summarizes baseline patient characteristics, stratified by low/normal and high MLR. Unstable angina and MI as compared to stable CAD were related to significantly higher MLR (analyzed as logMLR because of positive skewing) as shown in figure 1A. Univariably, a 1-point increase in logMLR resulted in an odds ratio (OR) of 1.13 [1.06-1.21], $p < 0.001$ for unstable angina vs. stable CAD. Similarly, a 1-point increase in logMLR resulted in an OR of 1.10 [1.04-1.16], $p < 0.001$ for MI vs. stable CAD. In the multivariable model the OR for unstable angina vs. stable CAD was 1.13 [1.05-1.21], $p < 0.001$ and OR for MI vs. stable CAD 1.06 [0.99-1.13], $p = 0.08$. In a univariable model, logMLR was significantly associated with the number of affected coronary arteries (OR=1.38 [1.14-1.67], $p < 0.001$, figure 1B), but this relation was inverted after multivariable adjustment (OR=0.78 [0.63-0.99], $p = 0.040$).

LogMLR was also strongly related to EF in univariable analysis (OR=1.59 [95% CI 1.25-2.02], $p < 0.001$, figure 1C), indicating that a 1-point increase in logMLR gives 59% higher odds of 1-category poorer EF (e.g. a deterioration from moderately impaired to poor EF). In multivariable analysis the significance of this relation was diminished (OR=1.07 [0.82-1.41], $p = 0.59$).

In univariable analysis there was a strong relation between logMLR and logNTproBNP ($\beta = 0.78$ [95% CI 0.59-0.97], $p < 0.001$), indicating that for every 1-point increase in logMLR the logNTproBNP increased with 0.78 points (figure 1D). This relation remained statistically significant after adjustment for confounders ($\beta = 0.32$ [0.13-0.51], $p < 0.001$). There also was a significant correlation between hsCRP and MLR; Pearson's $r = 0.24$ (0.18-0.31), $P < 0.001$.

During a mean follow-up duration of 484 days, 46 HF hospitalizations occurred. Only 1 patient experienced MI during follow-up and prior to HF hospitalization. For prediction, MLR was categorized in low/normal MLR and high MLR, as described above. Unadjusted for confounding factors, patients with a high MLR had an almost 4-fold higher risk of getting HF symptoms (hazard ratio [HR] 3.9 [2.2-7.0], $p < 0.001$, figure 2). After adjustment for covariates, including EF, NTproBNP, Troponin I (TnI) and hsCRP, high MLR remained a significant predictor of HF hospitalizations (HR 2.1 [1.1-4.1], $p = 0.039$). Hazard ratios of these covariates are presented in supplementary table 1.

Moreover, IDI en cNRI for addition of MLR to the full HF prediction model proved to be significant, albeit of modest size. The IDI was 0.01 (95% confidence interval 0.00-0.06), $p = 0.05$ and the cNRI was 0.32 (0.01-0.45), $p < 0.001$. These data suggest that risk prediction would improve when MLR would be taken into account. The predictive value of high MLR far exceeded that of high monocyte counts (HR 0.5 [0.3-1.2], $p = 0.12$) or low lymphocyte counts (HR 1.6 [0.8-3.1], $p = 0.2$) alone, which were both non-significant in multivariable analysis.

There was a borderline significant interaction between high MLR and indication for CAG for the prediction of HF hospitalizations ($p_{\text{interaction}} = 0.065$), suggesting that MLR would have slightly more prognostic value in stable/unstable angina than in MI patients (supplementary table 2). No interaction was found for sex ($p_{\text{interaction}} = 0.44$) or EF ($p_{\text{interaction}} = 0.61$), indicating that MLR could have similar prognostic value between men and women and in patients with preserved or reduced EF, respectively.

Discussion

In CAD patients, MLR was strongly associated with NTproBNP levels and EF. Furthermore, high MLR showed predictive value on top of an extensive clinical risk prediction model for the prediction of HF hospitalizations after CAG. Our data show that MLR is closely related to HF parameters and future HF admissions in CAD patients. This is in line with preclinical studies showing that NF κ B P50 in bone marrow-derived cells (and not in cardiomyocytes) determines adverse remodeling independent of infarct size.¹² The current research connects to previous evidence on the predictive value of MLR in cardiovascular disease. In this regard, MLR relates to the severity of CAD¹³ and is a predictor of cardiovascular mortality.^{5,6} Moreover, MLR associates with adverse long-

term outcomes in HF patients.¹⁴ These data indicate that MLR has predictive value not only in atherosclerosis, but also in the prediction of development of de novo HF and of adverse outcome in manifest HF.

Monocytes are key players in atherosclerosis and have been shown to predict cardiovascular and all-cause mortality in cardiovascular disease patients.^{5,15} Monocytes are also involved in adverse remodeling, which may result in HF.¹⁶ However, the role of monocytes is not restricted to detrimental effects.¹⁷ Several subtypes (classical, intermediate, non-classical) with specific functional properties have been identified and their role in HF remains relatively unexplored. Yet, intermediate monocytes have been shown to associate with the occurrence of cardiovascular events¹⁸, low EF¹⁹ and larger end-diastolic left ventricular diameter.²⁰

In addition, our data are in line with the previously described relation between lower lymphocyte numbers and poorer functional class in HF patients.²¹ The underlying biological mechanism remains largely unclear. The majority of the lymphocyte population consists of T-cells, further subdivided into T-helper cells (CD4⁺), cytotoxic T-cells (CD8⁺) and regulatory T-cells (Tregs), with a cell type-specific response to cardiovascular events. Of these, Tregs are of great importance for the modulation and suppression of inflammation, which is key in limiting the development and progression of cardiac damage after various stimuli.²² This is reflected by the observation that Treg numbers correlate with cardiac function and that both the number and suppressive capacity of Tregs is decreased in HF patients.²³ In addition, several experimental studies have provided mechanistic evidence for the beneficial role of Tregs in hypertrophic remodeling and cardiac dysfunction after pressure-overload hypertrophy²⁴ and MI.²⁵ Data on T-cell subsets would therefore be of great interest. In contrast to T-cells, B-cells compose a small proportion of the total lymphocyte population and have been reported as causal players in atherosclerosis.²⁶ Conflicting evidence with respect to their relation to cardiac remodeling^{27,28} emphasizes that our understanding of the role of B cells is still in its infancy.

After adjusting for hsCRP levels, MLR remained a significant predictor of future HF hospitalizations, suggesting that MLR provides information beyond systemic inflammation as reflected by hsCRP levels, mediated by IL6. Although hsCRP and IL6 levels are related to CAD severity and prognosis, these associations often disappear after appropriate statistical adjustment.²⁹

MLR is related to HF markers and HF hospitalizations during follow-up after CAG, independent of NTproBNP. Our results therefore suggest a potential role for MLR alongside or in lieu of NTproBNP. For example, cardiac resynchronization therapy can lower inflammatory markers in plasma.³⁰ The response of MLR to HF therapy should be investigated as to evaluate its usability in therapy monitoring. The advantages of MLR are the ease of measurement and the low costs of measurement. While NTproBNP costs about €18 in the Netherlands, MLR can be measured for < €2, rendering it a cheap and attractive potential biomarker for risk stratification.

We acknowledge that our findings are limited to one cohort only; validation of our findings in an independent cohort is needed before considering clinical application. Ratios between specific monocyte and lymphocyte subsets, which were unavailable in our study, could further extend our understanding of the relation with HF indicators and improve prediction. Moreover, repeated MLR measurements in time would have been of immense value in order to better understand its role in HF progression. Also, data on the HF biomarkers galectin-3 and ST2 were not available in the current study, hindering direct comparison with MLR.

In conclusion, MLR related significantly to HF markers in CAD patients. Some of these associations remained significant after adjustment for amongst others EF, NTproBNP, TnI and hsCRP levels, suggesting an independent relation. Moreover, MLR had a significant and independent relation with HF hospitalizations during follow-up.

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Figure legends

Figure 1. Relation of MLR with CAD and HF characteristics

A: relation between MLR and indication for CAG. B: relation between MLR and severity of CAD. C: relation between MLR and left ventricular function. D: relation between MLR and NTproBNP levels (both on logarithmic scale). ^p-value results from univariable ordinal regression. *p-value results from univariable linear regression. *CAD: coronary artery disease; CAG: coronary angiography; MLR: monocyte-to-lymphocyte ratio; VD: vessel disease*

Figure 2. Age- and sex-adjusted occurrence of HF hospitalization for high vs. low/normal MLR

The occurrence of HF hospitalizations is shown stratified by MLR. Patients with a high MLR (upper quartile) had an almost 4-fold higher risk of getting HF symptoms (HR: 3.9 [2.2-7.0], $p < 0.001$) compared to those with low or normal MLR values. After further adjustment for covariates, including EF, NTproBNP, Troponin I and hsCRP, high MLR remained a significant predictor of HF hospitalizations (see text). *EF: ejection fraction; FU time; follow-up time; HF: heart failure; HR: hazard ratio; MLR: monocyte-to-lymphocyte ratio*