

Relation of Neutrophil to Lymphocyte Ratio to Risk of Incident Atrial Fibrillation



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Clinical and experimental data support a critical role for inflammation in cardiovascular disease. The purpose of the current study was to examine the relation between an inflammatory marker, neutrophil-to-lymphocyte ratio (NLR), and incident atrial fibrillation (AF) in asymptomatic adults. We investigated 21,118 self-referred men and women who were annually screened in a tertiary medical center. All subjects were free of AF at baseline and had their serum NLR calculated at the first annual visit. Subjects were divided into 2 groups based on their baseline NLR: Low (<2.83; n = 17,524) and high (≥2.83; n = 3,594; Upper Sextile). The primary endpoint was new onset AF during follow-up. Mean age of study population was 48 ± 10 years and 72% were men. A total of 563 (2.7%) incident events occurred during an average follow-up of 7.5 ± 5 years. Unadjusted Cox regression analysis demonstrated that each 1 unit increase in NLR was associated with a significant 14% increase in risk of occurrence of a first AF event (95% confidence interval 1.06 to 1.23, p < 0.001) and 20% increased risk of death. Kaplan-Meier's survival analysis showed that the cumulative probability of incident AF was significantly higher among subjects with high NLR compared with low NLR group (p = 0.006). Interaction analysis with adjustment to clinical parameters showed that NLR-related risk was age-dependent, such that in the younger age-group (< =50 years) high NLR group had two folds increased risk for AF event compared with low NLR group (95% confidence interval 1.08 to 3.51; p = 0.027) whereas among older subjects the rate of events was similar between both NLR groups (p = NS; p for interaction = 0.024). In conclusion, our findings suggest that high NLR is associated with increased risk of new onset AF. This finding is more pronounced among young adults. © 2018 Elsevier Inc. All rights reserved. (Am J Cardiol 2019;123:396–401)

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. With an estimated prevalence of 1.5% to 2.0% in the general population it represents a major public health problem.^{1,2} It is associated with hemodynamic impairment, disabling symptoms, and decreased

life-expectancy and as such causes significant morbidity, mortality, and financial cost.³ Inflammation has a critical role in cardiovascular disease, and the role of inflammatory markers in cardiovascular diseases has been studied extensively. Systemic inflammation has been found associated with both paroxysmal and persistent AF.^{4,5} Inhibition of inflammatory pathways has been suggested as a possible approach to reduce AF prevalence and burden.⁵

Neutrophil-to-lymphocyte ratio (NLR) is a marker of oxidative stress damage. It is a prognostic marker of mortality in both cardiac and noncardiac diseases⁶ and is associated with higher AF recurrence rate among patients with paroxysmal AF and with higher rates of postoperative AF.⁷ However, little is known about the impact of NLR on new onset AF. The purpose of the current study was to examine the relation between NLR and the risk of incident AF.

Methods

The study population has been described previously.⁸ Approximately 9,000 annual examinations are performed at the Institute for Medical Screening of the Chaim Sheba Medical Center. Computerized database established in 2000, is the source of data. All subjects are asymptomatic self-referred men and women attending periodic health screening examination. A nurse at the center measures the height and weight of all subjects at each visit. After

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Statements: The Institutional Review Board of the Sheba Medical Center approved this study on the basis of strict maintenance of participants' anonymity during database analyses (approval number 8995–11–SMC). Data from subjects were recorded anonymously. No individual consent was obtained.

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completing a standard questionnaire, including any unusual medical event since previous follow-up, a physical examination in performed by a physician at the center. A blood test, which is analyzed at the center's lab, and a blood pressure measurement, are obtained at each encounter. In addition, all subjects complete a maximal exercise stress test according to the Bruce protocol at each annual visit. The complete database includes 29,449 subjects who visited the center between 2000 and 2017. Subjects with at least 2 consecutive visits to the center with a baseline blood count analysis were included in the present study. Subjects were excluded if they had a single visit to the center ($n = 7,966$) or had a history of AF at their first (baseline) visit ($n = 365$). Thus, the final study sample comprised 21,118 subjects.

History of AF at baseline was based on medical records, self-report, or electrocardiographic documentation of AF at the first visit. Subjects were considered to have diabetes mellitus or hypertension if their primary care physicians treated them for these disorders or based on self-report. If abnormal lab values or physical findings were identified during the visit, further evaluation was conducted, with newly diagnosed and treated subjects appropriately documented on the next follow-up visit.

The primary outcome of the current study was the first occurrence of AF during follow-up. A new diagnosis of AF was based on an electrocardiogram recorded at the time of the annual visit, 24h-Holter monitoring, and on medical records from the primary healthcare provider. All newly diagnosed events were recorded on medical summaries of annual visits. All atrial fibrillation events were adjudicated by 2 study investigators (AB and AY) who were blinded to patients' baseline characteristics. Data on AF type (paroxysmal, persistent, or chronic), management, and treatment strategies were not available.

Patients with NLR values in the upper sextile were pre-specified to the high-NLR group (≥ 2.83 ; $n = 3,594$) whereas the rest were assigned to the low-NLR group (< 2.83 ; $n = 17,524$). Similarly, patients were considered to be young if they were less than 50 years old. Continuous data

were compared with Student *t* test and one-way ANOVA. Categorical data were compared with the use of chi-square test or Fisher exact test. Multivariable Cox proportional hazard regression modeling was used to evaluate hazard ratios for a first AF event with NLR as a continuous and dichotomous variable. In the model that assessed the association between baseline NLR and the risk for the development of de novo AF, additional prespecified baseline covariates included age, gender, body mass index, hypertension, diabetes mellitus, ischemic heart disease, previous stroke, chronic kidney disease, and cholesterol levels. The probability of new AF event during follow-up by the pre-specified NLR and age groups was estimated and graphically displayed according to the method of Kaplan-Meier, with comparison of cumulative events across strata by the log-rank test. Subanalysis of 14,695 (70%) subjects with C-reactive protein value at first visit was used to evaluate the effect of an additional inflammatory marker on AF events. The Kaplan-Meier method was used to compare the probability of AF event between patients with low CRP (lowest quintile) to high CRP (quintiles 2 to 6). Statistical significance was accepted for a 2-sided $p < 0.05$. The statistical analyses were performed with IBM SPSS version 23.0 (Chicago, Illinois).

Results

Final study population comprised 21,118 individuals, of whom 15,166 (72%) were men. Mean age was 49 ± 11 years. Mean NLR was 2.17 ± 0.9 with a median of 2.02 and interquartile range of 1.61 to 2.55. Baseline clinical and laboratory characteristic by the prespecified NLR groups are presented in Table 1. Notably, patients with low NLR were younger with fewer co-morbidities, and were less likely to be active smokers. During a mean follow-up time of 7.5 ± 5 years (Median 6.5, interquartile range 3 to 12) the primary study outcome occurred in 563 (2.7%) subjects. Unadjusted Cox regression analysis demonstrated that advanced age, gender, body mass index, hypertension, diabetes mellitus, ischemic heart disease, previous stroke,

Table 1
Population characteristics

Variables	Neutrophil to lymphocyte ratio			p value
	Low (N = 17,524)	High (N = 3,594)	All (N = 21,118)	
Age (years)*	48 (10.4)	50 (11.2)	48 (10.6)	<.001
Men (%)	72	72	72	0.75
Neutrophil to lymphocyte ratio*	1.9 (0.5)	3.6 (1.1)	2.2 (0.9)	<.001
Body mass index (kg/m ²)*	25.9 (3.9)	26.1 (4.3)	26.0 (4.0)	NS
Hypertension (%)	12	17	13	<.001
Coronary heart disease (%)	3.4	5.5	3.8	<.001
Diabetic mellitus (%)	4	6	4.3	<.001
Low density lipoprotein (mg/dl)*	120 (31)	117 (32)	120 (31)	<.001
High density lipoprotein (mg/dl)*	48 (13)	47 (13)	48 (13)	<.001
Creatinine (mg/dl)*	1.03 (0.18)	1.04 (0.24)	1.01 (0.19)	<.001
Systolic blood pressure (mm Hg)*	122 (21)	124 (23)	122 (22)	<.001
Diastolic blood pressure (mm Hg)*	77 (13)	77 (14)	77 (13)	NS
Hemoglobin (g/dl)*	14.5 (1.3)	14.6 (1.7)	14.5 (1.4)	NS
Active smoker (%)	17	19	17	0.016

* Values are expressed as mean \pm SD.

Table 2
Predictors of atrial fibrillation

	Univariate hazard ratio (95% CI)	p value	Multivariate hazard ratio* (95% CI)	p value
Neutrophil to lymphocyte ratio (continuous)	1.14 (1.06-1.23)	<.001	1.03 (0.94-1.12)	0.53
High vs. low neutrophil to lymphocyte ratio	1.20 (1.00-1.44)	0.049	0.96 (0.79-1.17)	0.71

* Multivariate model is further adjusted to age, gender, body mass index, hypertension, diabetes mellitus, ischemic heart disease, previous stroke, chronic kidney disease, and cholesterol levels.

chronic kidney disease, and cholesterol levels were all associated with increased AF risk ($p < .01$ for all). In addition, the same model demonstrated that NLR was also associated with AF increased risk: each 1 unit increase in NLR was associated with a significant 14% increase in risk of occurrence of a first AF event (95% confidence interval [CI] 1.06 to 1.23, $p < 0.001$) and higher NLR group demonstrated a significant 20% increase in risk compared with low NLR group (Table 2). Kaplan-Meier’s survival analysis consistently showed that patients with high NLR showed a significantly higher event rate compared with low NLR group (p value = 0.006; Figure 1). Multivariate Cox regression model with adjustment to predictors of AF demonstrated that advanced age, male gender, obesity, hypertension, and ischemic heart disease were all independently associated with increased AF risk. However, the model failed to show a statistically significant relation between continuous or dichotomous NLR and new onset AF (Table 2).

Subgroup univariate analysis revealed that the occurrence of a first episode of AF during follow-up was age dependent (Table 3). Among patients in the younger age-group (≤ 50 years), those with high NLR showed a significantly higher event rate compared with those in the low NLR group whereas among older subjects the rate of events was similar between both NLR groups (p for interaction = 0.024). Multivariate Cox regression analysis among younger subjects, with adjustment for the previously mentioned factors, showed that subjects with high NLR were more than twice as likely to develop new onset AF during follow up compared with subjects with low NLR (hazard ratio [HR] = 1.95, 95% CI 1.08 to 3.51, $p = 0.027$). When assessed as a continuous covariate in the same model,

among the young age-group, each 1-unit increment in NLR was associated with a significant 34% increased risk in the development of AF (95% CI 1.17 to 1.52, $p < 0.001$). CRP levels were available for 14,695 (70%) subjects, with a follow up of 4.7 ± 2.7 years. Subanalysis of this cohort demonstrated no correlation between NLR levels and either continuous or dichotomous CRP levels. Kaplan Meier analysis of this cohort demonstrated that subjects in the lower CRP group quintile were less likely to develop AF (HR 0.66; 95% CI 0.49 to 0.90; $p = 0.009$; Figure 2). The association was not significant in a multivariate model with adjustment to other predictors of AF, and there was no interaction between age and CRP-related risk. During a mean follow-up time of 12 ± 5 years, 1,142 (4%) subjects died. Univariate Cox regression model showed that subjects with high NLR levels were 77% more likely to die (95% CI 1.54 to 2.02; $p < 0.001$), and that each 1 unit increase in NLR was associated with 20% increased AF risk ($p < 0.001$). Kaplan-Meier’s survival analysis yielded similar results such that the cumulative probability of death at 10 years was 5% in the high NLR group compared with 2% in the low NLR group (Figure 3). Multivariate Cox regression with adjustment for known predictors of poor survival showed that high NLR was not an independent predictor of mortality.

In addition to NLR, absolute neutrophil and lymphocyte counts were evaluated separately. Among younger subjects,

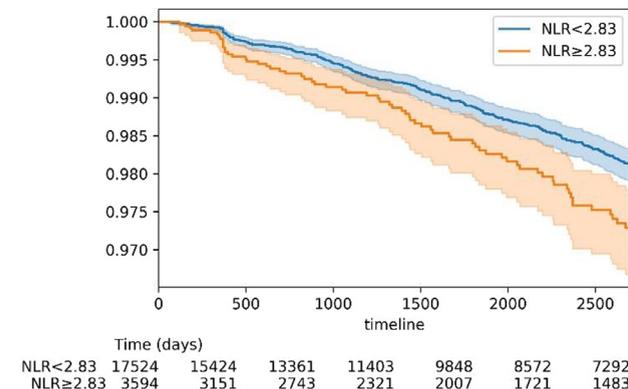


Figure 1. Kaplan-Meier’s survival analysis for incident AF events according to NLR groups.

Table 3
Multivariate Cox regression – subgroup analysis

A – age < 50	Hazard ratio	95% Confidence interval	p value
High neutrophil to lymphocyte ratio	1.95	1.08–3.51	0.027
Age (continuous)	1.07	1.01–1.13	0.027
Men gender	3.35	1.41–7.99	0.006
Body mass index (continuous)	1.01	0.94–1.09	0.724
Hypertension	1.76	0.79–3.89	0.165
Chronic kidney disease	1.13	0.155–8.25	0.9
Coronary heart disease	10.56	3.66–30.41	<0.001
B – age ≥ 50			
High NLR	0.96	0.76–1.20	0.71
Age (continuous)	1.07	1.06–1.09	<0.001
Male gender	1.44	1.11–1.87	0.006
Body mass index (continuous)	1.04	1.02–1.06	<0.001
Hypertension	1.28	1.04–1.58	0.019
Chronic kidney disease	0.96	0.73–1.25	0.74
Coronary heart disease	1.79	1.38–2.32	<0.001

The model is further adjusted for previous cerebrovascular event, diabetes mellitus, and cholesterol levels.

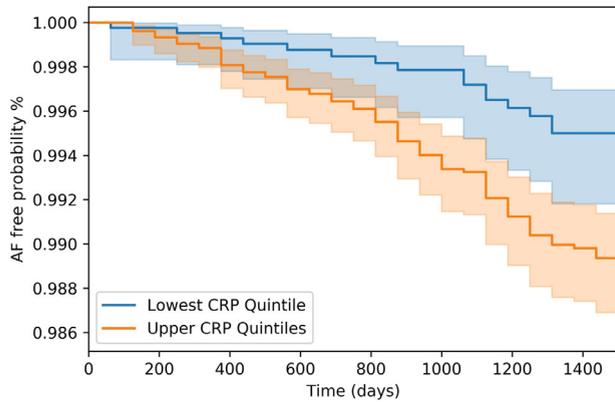


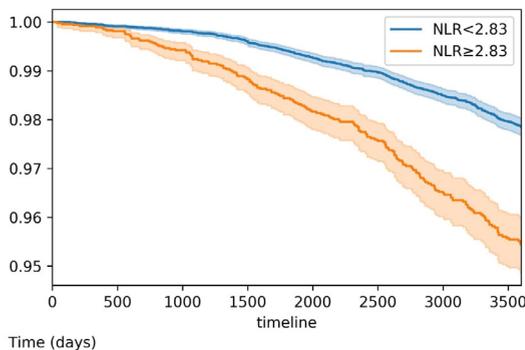
Figure 2. Kaplan-Meier's survival analysis for incident AF events according to CRP groups.

absolute neutrophil count was associated with incident AF events in both the univariate (HR = 1.005, CI 1.001 to 1.01, $p = 0.022$ for age < 50; HR = 0.99, CI 0.98 to 1.01, $p = 0.54$ for age ≥ 50) and multivariate model (HR 1.006, CI 1.002 to 1.01, $p = 0.006$ for age < 50; HR 0.99, CI 0.98 to 1.00, $p = 0.12$ for age ≥ 50). With respect to absolute lymphocyte count, a significant inverse association was noted in the entire cohort (HR 0.98, CI 0.97 to 0.99, $p = 0.003$). However, among the younger age group absolute lymphocytes count was no longer statistically significant ($p = 0.15$ for age < 50; $p = 0.233$ or age ≥ 50).

Discussion

The present study provides 3 important insights regarding the association between NLR and the risk for incident AF in apparently healthy middle-aged men and women: (1) NLR, as an inflammatory marker, is a marker for new-onset AF among patients younger than 50 years of age (2) In patients older than 50 years, other factors play a more significant role in the appearance of first event of AF (3) high NLR is associated with increased risk of mortality among all age groups.

There is growing evidence linking inflammation with the development of AF.⁵ Bruins et al⁹ propose the inflammation-AF hypothesis. They revealed a link between



NLR < 2.83	24197	23879	22041	20638	19421	18021	16636	15176	13485
NLR \geq 2.83	4833	4765	4420	4172	3913	3662	3375	3117	2750

Figure 3. Kaplan-Meier's survival analysis for overall survival according to NLR groups.

peak CRP after coronary artery bypass surgery and the incidence of AF. CRP is an acute phase reactant produced by the liver. High levels of CRP are associated with increased risk of ischemic heart disease,¹⁰ ischemic stroke,¹¹ death,¹² and AF.¹³ Furthermore, elevated levels of CRP are associated with increased risk of AF burden.¹³ The CANTOS trial¹⁴ showed how anti-inflammatory therapy can reduce cardiovascular event rates. This randomized, double blinded trial, which included 10,061 patients with previous myocardial infarction and high levels of CRP successfully showed the beneficial therapeutic effect of a monoclonal antibody targeting interleukin-1 β . However, similar data on the clinical utility of such intervention to attenuate AF risk is lacking.

NLR is an inexpensive, accessible inflammatory marker.¹⁵ It is associated with numerous adverse outcomes among both patients with noncardiac diseases^{16–18} as well as in patients with cardiac diseases, including decompensated heart failure, acute coronary syndrome, and long-term mortality.^{15,19} Imtiaz et al followed 1,070 apparently healthy individuals. They showed that patients with chronic diseases such as hypertension and diabetes mellitus are more likely to be in the middle and highest tertile of NLR. Based on these findings they concluded that systemic inflammation measured by NLR has a significant association with prevalent chronic conditions. Our results are consistent with these previous studies by demonstrating an independent association between high NLR levels and the most prevalent cardiac arrhythmia.

Whereas our study is the first to suggest a correlation between high NLR levels and AF among young and apparently healthy adults, several well-conducted studies have investigated the correlation between NLR levels and AF. Karavelioglu et al⁷ demonstrated that high NLR is associated with higher rates of AF recurrence following cardioversion. In their study, 218 patients were followed following a successful conversion from AF to sinus rhythm. At a mean follow-up time for almost 2 years, 40% of patients had at least one event of AF. Higher NLR was associated with a significant 58% increased AF recurrence risk in a multivariate model. Their conclusions stand in contrast to the findings of Arbaş et al²⁰ who concluded that there is no link between high levels of NLR and the recurrence rate of AF after cardioversion. However, they included older patients with persistent AF with European Heart Rhythm Association (EHRA) classes II-III. These apparent conflicting results are consistent with our study that suggests that NLR-risk is age-dependent and is significant only in the younger age group. Other studies include the work of Gibson et al²¹ linking high NLR levels with postoperative AF in patients undergoing an coronary artery bypass surgery (mean age 65, $n = 275$) and a more recent study²² focusing on patients with diabetes mellitus. This recent study documented a significantly higher NLR levels among patients with persistent AF as compared with those without no history of AF. Using a similar cutoff to the one used in our analysis, their analysis revealed that NLR value of 2.38 had 76% sensitivity and 67% specificity for prediction of AF development in patients with diabetes mellitus. Finally, in a meta-analysis of 11 papers²³ involving more than 2,700 patients, high levels of NLR were associated with increased risk of AF occurrence and

recurrence. The author showed a significant association between baseline NLR and AF. This finding was true for patients undergoing cardioversion, ablation, or surgery.

This study has several limitations. First, it is a historical prospective, nonrandomized, nonblinded observational study examining the effect of NLR as an inflammatory marker on the risk of developing AF. As such, no direct intervention was suggested. Second, information regarding acute events that may have caused a temporary raise in values is missing. However, given this large population, exceptional events wouldn't have changed the main finding. Third, study population is composed of self-referred middle-aged men and women of high economic status with very low rates of ischemic heart disease and diabetes mellitus. It is, therefore, unclear whether our findings could be generalized to other populations. Moreover, a selection bias should be considered, and conclusions from this article should not be extrapolated to other populations.

In conclusion, NLR as an inflammatory marker is associated with an independent increased risk of developing AF among patients <50 years-old. In older patients other risk factors such as body mass index and hypertension have a more significant role in predicting AF risk.

Conflict of Interest

None declared.

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