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Prognostic significance of Absolute Neutrophil Count in Patients with Heart Failure with Preserved Ejection Fraction

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ABSTRACT

Background: The role of inflammation and neutrophil/lymphocyte ratio has been defined in systolic heart failure (HF) and coronary artery disease, but it is uncertain if such a relationship exists in HF with preserved ejection fraction (HFpEF) patients (pts). We sought to identify the prognostic impact of Absolute Neutrophil Count (ANC) in HFpEF in the absence of coronary artery disease history (CAD Hx).**Methods:** In this retrospective cohort, the institutional HF data base was queried to identify HFpEF pts diagnosed in 2006 (registry initiation date) based on symptoms, BNP, and Echocardiogram with no CAD Hx. Measured outcomes were cardiovascular disease (CVD) mortality and number of HF re-admissions (poor outcome if > 2 HF re-admissions). **Results:** We identified 125 eligible pts. Mean age was 70.8 ± 11.7 years. Women constituted 56.6%. Mean follow up was for 8.75 ± 0.17 years. The CVD mortality rate was 7.1%. Poor outcome was identified in 52.6%. Mean ANC was 6.3 ± 3.2, and in multivariate regression analysis, including baseline demographic, clinical, and biochemical covariates, ANC remained significantly associated with poor outcome and an independent predictor of mortality (OR 1.14, 95% CI 1.02-1.29, *P*=0.04 after adjustment for age, sex, hypertension, and other risk factors)(table).
Conclusion: In HFpEF pts, ANC is a significant predictor of poor outcome as well as mortality in the absence of coronary artery disease. Accordingly, ANC can be utilized as one of the non-invasive prognostic markers in HFpEF patients.
Keywords: Absolute Neutrophil Count; Heart Failure with Preserved Ejection Fraction; Cardiovascular disease mortality.

Introduction

The relationship of markers of inflammation including white blood cells (WBCs) and their subtypes, and cardiovascular disease has been examined in many studies, especially the association with coronary artery disease (CAD). It was shown that total WBCs, neutrophil count and lymphocyte count were independent risk factors of mortality and MI in patients with CAD, and worsening of their CAD [1-3]. Less so, it has also been studied in patients with heart failure (HF); markers of inflammation, like Interleukin (IL)-6 and tumor necrosis alpha (TNF)-alpha have also been found to be associated with increased incidence of heart failure [4-8], Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were also described as predictors of developing HF [9,10]. This could be explained as a causal relationship where these inflammatory mediators actually play a role in the development of heart failure or merely their presence being a marker of the underlying process causing left ventricular modelling and HF. All the available data were from patient with systolic heart failure but no study to date evaluated the significance of such as association in heart failure with preserved ejection fraction (HFpEF). Given the scarce evidence in the literature we aimed to evaluate the prognostic impact of absolute neutrophil count in patients with HFpEF.

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Patients and methods

This study was conducted following the approval of our Institutional Review Board. In this retrospective cohort, our institutional heart failure database was reviewed. All patients HFpEF diagnosis on 2006 were

included. All patients with confirmed HFpEF diagnosis based on symptoms, brain natriuretic peptide (BNP), and transthoracic echocardiogram were included. Ejection fraction of 50% or more was considered as cut off for the diagnosis.

Primary outcome was identified cardiovascular disease mortality. Secondary outcome included number of heart failure re-admissions with poor outcome defined as more than two re-admissions during the follow up period of 9 years.

Statistical Analysis

All data including patient's demographics, medical history, medications, clinical presentation, ECG, and echocardiographic details were obtained from advocate Illinois masonic clinical records and our prospectively collected databases. In addition, the source for follow-up information was subsequent clinic visits, hospital admissions, emergency room visits, and written correspondence from local physicians. Descriptive statistics for data with normal distribution were presented as means and standard deviations from the mean, while any other type of data distribution was presented using median with range. Counts and percentages were used for dichotomous and categorical data. Comparison between two groups was tested for continuous and dichotomous variables using Student's paired *t* test and $\chi 2$, respectively. Cox regression modelling and multivariate analysis were used to assess the independent contribution of all relevant clinical variables to the outcome. Probability value (*p*-value) of ≤ 0.05 was identified as a cut-off for statistical significance.

Results

Table 1: Baseline characteristics of patients with HFpEF (EF cutoff of >50%)

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Age	249	27	98	72.15	13.400
BMI (kg/m^2)	249	14.5	93.4	32.168	10.8590
Height (cm)	249	2.0	191.0	164.358	15.1083
Weight (kg)	249	42.3	852.0	91.335	57.4622
BSA (m^2)	249	1.40	197.00	3.9776	17.24746
Hb (g/dl)	249	1.5	16.4	10.972	2.0200
Hct	249	20.0	54.5	33.730	5.9931
Platelets	249	31.0	600.0	226.789	79.3638
WBC	249	3.3	20.1	8.730	3.0440
ANC	249	1.22	25.50	6.3059	3.23054
BNP	223	1.1	5000.0	587.270	726.9906
Creatinine (mg/dl)	249	.00	24.90	1.8155	1.82047
PA pressure (mmHg)	189	0	89	36.16	17.759
LA size (cm)	236	1.0	5.9	3.877	.8402

ANC: Absolute Neutrophil Count; BNP: Brain Natriuretic Peptide; BMI: Body Mass Index; BSA: Body Surface Area; Hb: Hemoglobin; Hct: Hematocrit; LA: Left atrium; PA : Pulmonary artery

Table 2: Multivariate regression analysis

Variable	OR	95.0% CI	p-value
Age (years)	1.0	0.97-1.02	0.73
Sex	1.11	0.77-1.60	0.59
BMI (kg/m^2)	0.99	0.97-1.01	0.55
ANC	1.14	1.02-1.29	0.04
Hemoglobin(g/dl)	0.88	0.73-1.06	0.18

ANC: Absolute Neutrophil Count; BMI: Body Mass Index;

Of the total of 249 patients studied, 125 eligible patients were included based on the inclusion criteria. The baseline characteristics of these patients are listed in Table 1: Baseline characteristics of patients with HFpEF (EF cutoff of >50%)Mean age was 72 ± 13, Women constituted 56.6%. Mean follow up was for 8.75 ± 0.17 years. BNP averaged 587 ± 727 and poor outcomes were identified in 52.6%. Mean ANC was 6.3 ± 3.2.In a multivariate analysis model to adjust for important baseline characteristics, including age, gender, cardiovascular risk factors, CAD, atrial fibrillation and optimum management, we found that among the parameters described in

Table 2, we found that ANC had statistically significant association with poor outcome (OR 1.14, 95% CI 1.02-1.29, *P*=0.04)

Discussion

Absolute neutrophilia has been shown to increase risk of developing HF after ischemic insult in a cohort study by Ypil et al [11], and in another cross-sectional study, absolute neutrophilia in the first 12 hours post-acute myocardial infarction (MI) is a predictor of increased risk of post-MI HF [12]. Although the underlying mechanism is yet to be known, but it has been proposed that increased neutrophil count and activity causes infarct expansion [13,14], possibly due to an increase in oxidative stress [13,15] , tissue destruction with proteolytic enzymes like myeloperoxidase, acid phosphatase, and elastase [16-19] or can contributed for by plugging capillary flow during reperfusion [20]. Whether neutrophilia also contributes to non-ischemic HF, and the mechanism of which is still unclear, it has been proposed it is induced by oxidative stress as well. It has been shown that oxidative stress can cause contractile dysfunction [21].
In a study of the incidence of hospitalization of HF patients has shown and independently from coronary events, and after adjustment for angina, that concentration of leukocytes is associated with increased risk of HF hospitalization in men with and without hypertension [22]. Yet hypertension has also been linked to increased inflammatory markers, and its role in the development of heart failure is well-known, similarly, subclinical coronary events can contribute to HF exacerbations and hospitalizations and coronary disease has been linked to increased leukocytes as described above. A retrospective analysis of the studies of left ventricular dysfunction also linked baseline increased WBC to all-cause mortality of patients with ischemic LV dysfunction but not with non-ischemic LV dysfunction [23]. Different white cell types have different mechanisms in inducing injury and inflammation, and conversely, lower lymphocyte counts have repeatedly been associated with increased risk of HF mortality and admissions [24-28]. Therefore, in an attempt to better elaborate the

relationship, 2 studies have been conducted recently combining neutrophilic and lymphopenic effects by Neutrophil to Lymphocyte ratio (NLR) in relation to acute heart failure prognosis and mortality [29,30]. NLR was also associated with increased severity of chronic heart failure NYHA classification in patients with idiopathic cardiomyopathy [30].When HF patients were divided into groups with preserved EF and reduced EF, significant increased mortality was demonstrated in both groups [30]. NLR was also an independent prognostic risk factor from ejection fraction in the second study by Vicente *et al*. [29].Despite the all the above evidence, it's still unclear if neutrophils have any direct rule in the failure of relaxation of the heart muscle (diastolic dysfunction) in the absence of ischemic insult or infarcted myocardial tissue.

Conclusion

ANC remains to be a significant predictor of morbidity and mortality in patients with HFpEF after correcting for all risk factors, despite the absence of coronary artery disease. This indicates that underlying inflammation might be contributing to the diastolic dysfunction in the presence of normal perfusion. Accordingly, ANC might be a very useful non-invasive marker that can be utilized in risk stratifying patients with HFpEF.

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