Pharmacophore

ISSN-2229-5402

Journal home page: http://www.pharmacophorejournal.com

Pharmacophore
an International Journal
ISSN 2229-5402

PROGNOSTIC VALUE OF LYMPHOPENIA TO PREDICT IN-HOSPITAL OUTCOME IN PATIENTS WITH CHRONIC HEART FAILURE

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ARTICLE INFO

Received:
03th Jun 2017
Accepted:
29th Nov 2017
Available online:
14th Dec 2017

Keywords: *Heart failure, Lymphocyte, Lymphopenia, Mortality, Complication*

ABSTRACT

Background: No comprehensive studies are available on the diagnostic value of lymphopenia in predicting outcomes in patients with heart failure. The present study aimed to address the prognostic value of lymphopenia on admission to predict in-hospital outcome of patients who hospitalized with the diagnosis of heart failure.
Methods: This historical cohort study was performed on 288 consecutive patients who hospitalized with the diagnosis of heart failure that admitted to Taleghani hospital in Urmia city, Iran in 2014. The lymphocyte count was determined on admission at laboratory of the hospital and the patients were assigned to lymphopenic group and normal lymphocyte count group.
Results: The prevalence of lymphopenia was 49.3%. The patients with lymphopenia had significantly higher function class compared with the control group (p = 0.004). In-hospital mortality was considerably higher in those with lymphopenia than in those with normal lymphocyte counts (13.4% versus 3.4%, p = 0.002). Also, MACE rate was significantly higher in former group (22.5% versus 11.0%, p = 0.008). But, no difference in mean hospital stay and ICU stay between the two groups. Based on multivariate logistic regression model, lymphopenia was significantly associated with early mortality with the presence of baseline confounders (OR = 3.401, 95%CI: 1.132 – 10.216, p = 0.029). In another regression model, lymphopenia could predict in-hospital MACE (OR = 1.938, 95%CI: 1.965 – 3.891, p = 0.033).
Conclusion: lymphopenia on admission can predict in-hospital mortality and complications in patients with chronic heart failure.

To Cite This Article: Reza Faramrza Zadeh, Venus Shahabi, Nader Jangi Oskoei, Aidin Enbesati, (2017), "Prognostic value of lymphopenia to predict in-hospital outcome in patients with chronic heart failure", ***Pharmacophore, 8(6S),*** *e-1173570*.

Introduction

Lymphopenia as a common finding in hospitalized patients is generally a transient and reversible complication, however in case of prolonged sustainability, this condition may affect patients 'prognosis [1]. Several pathological reasons have been proposed for the occurrence of lymphopenia in admitted patients including radiation, lymphopenia caused by tuberculosis, lupus, Hodgkin's disease, stress induced, and some medications and hormones such as corticosteroids [2,3]. It has been shown that prolonged lymphopenia are associated with poor prognosis mainly in special circumstances such as serious infectious diseases and cardiovascular diseases [4]. Recently, lymphopenia has been introduced as an inflammatory marker predicting new cardiovascular events [5,6]. In some animal studies, it has been revealed that lymphopenia has a possible role in the process of atherosclerosis. Also, evidences exist to show the close association between lymphopenia and poor prognosis in patients with chronic ischemic heart disease, acute coronary events or heart failure [7].
The relationship between lymphopenia and the severity of chronic heart failure progression has taken into consideration. In some reports, during the first two months of the diagnosis of heart failure, the lymphocyte count even reached less than 1,500 cells per cubic millimeter [8]. It has also been hypothesized that the occurrence of lymphopenia may be induced by other

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factors such as advanced age, stress and medications [9]. In this regard, no comprehensive studies are available on the diagnostic value of lymphopenia in predicting outcomes in patients with heart failure and the role of other underlying factors in exacerbating lymphopenia in these patients remained ambiguous. The present study aimed to address the prognostic value of lymphopenia on admission to predict in-hospital outcome of patients who hospitalized with the diagnosis of heart failure.

Materials and Methods:

This historical cohort study was performed on 288 consecutive patients who hospitalized with the diagnosis of heart failure that admitted to Taleghani hospital in Urmia city, Iran in 2014. The diagnosis of chronic heart failure was based on symptoms of dyspnea, general fatigue, and congestion; medication with diuretics, angiotensin-converting enzyme inhibitors, and digoxin; and an echocardiographically determined ejection fraction at rest of <45%. The lymphocyte count was determined on admission at laboratory of the hospital and the patients were assigned to lymphopenic group with lymphocyte count less than 1500 per microliter as the case group and those with normal lymphocyte count as the control group. Baseline characteristics and clinical information including comorbidities, medications, and laboratory parameters were extracted from the hospital recorded files. The patients in both groups were also followed within the hospitalization regarding mortality as well as early MACE defined as the occurrence of at least one of the events of cerebrovascular accidents, need to ventilation, sepsis, pneumonia, prolonged hospital stay or prolonged ICU stay.

For statistical analysis, results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using T test or Mann-Whitney U test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using chi-square test. Multivariate logistic regression analysis was used to determine main correlates of in-hospital mortality and MACE with the presence of baseline variables. For the statistical analysis, the statistical software SPSS version 20.0 for windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

Results:

In total, 288 patients were assessed. The mean age was 70.58 ± 13.16 years (ranged 29 to 91 years) and 56.2% were male. Regarding cardiovascular risk factors, 37.2% were diabetics, 28.1% had history of renal failure (with mean creatinine level 2.63 ± 1.48 mg/dl), and 27.4% had history of atrial fibrillation. With respect to functional class, 2.1% had class I, 11.8% had class II, 44.1% HAD CLASS III, and 42.0% had class IV. the overall in-hospital mortality rate was 8.3% with early MACE rate 16.7%. the mean total hospital stay was 6.11 ± 5.50 days and mean ICU stay 2.27 ± 3.59 days.

The prevalence of lymphopenia was 49.3%. Comparing baseline characteristics between the patients with and without lymphopenia (table 1).

Table 1: Baseline characteristics in patients with and without lymphopenia

Item	*Group with lymphopenia*	*Group without lymphopenia*	*p-value*
Gender			0.789
Male	81 (57.0)	81 (55.5)	
Female	61 (43.0)	65 (44.5)	
Age, year	71.51±12.51	69.68±13.74	0.240
Diabetes mellitus	45 (31.7)	62 (42.5)	0.058
Renal failure	39 (27.5)	42 (28.8)	0.806
Atrial fibrillation	44 (31.0)	35 (24.0)	0.182
Creatinine (mg/dl)	2.97±1.17	2.31±1.43	0.700
Sodium (mmmol/l)	137.63±5.05	137.36±12.06	0.802
Glucose (mg/dl)	152.45±91.22	159.60±82.15	0.485
Function class			0.004
I	1 (0.7)	5 (3.4)	
II	12 (8.5)	22 (15.1)	
III	60 (42.3)	67 (45.9)	
IV	69 (48.6)	52 (35.6)	

showed no difference in gender distribution, diabetes mellitus, renal failure, atrial fibrillation, mean age, mean weight, mean serum creatinine level, mean serum sdium level, and mean glucose level between the two groups. However, those with lymphopenia had significantly higher function class compared with the control group (p = 0.004). Regarding in-hospital events,

in-hospital mortality was considerably higher in those with lymphopenia than in those with normal lymphocyte counts (13.4% versus 3.4%, p = 0.002). Also, MACE rate was significantly higher in former group (22.5% versus 11.0%, p = 0.008). But, no difference in mean hospital stay and ICU stay between the two groups (table 2).

Table 2: In-hospital mortality in patients with and without lymphopenia

Item	Group with lymphopenia	Group without lymphopenia	p-value
In-hospital mortality	19 (13.4)	5 (3.4)	0.002
In-hospital MACE	32 (22.5)	16 (11.0)	0.008
Hospital stay	2.52±4.34	2.03±2.68	0.494
ICU stay	6.71±6.90	5.54±3.64	0.077

Based on multivariate logistic regression model (table 3).

Table 3: Main determinants of in-hospital mortality

Item	*P-value*	*Odds Ratio*	95% Confidence Interval	
			Lower limit	Upper limit
Lymphopenia	0.029	3.401	1.132	10.216
Male gender	0.981	1.012	0.385	2.658
Age	0.903	0.997	0.956	1.041
Function class	0.003	5.362	1.756	16.379
Diabetes mellitus	0.761	0.827	0.243	2.811
Renal failure	0.215	2.093	0.651	6.728
Atrial fibrillation	0.038	2.929	1.059	8.103
Creatinine	0.524	1.167	0.725	1.878
Sodium	0.446	0.986	0.952	1.022
Glucose	0.509	1.002	0.997	1.007

lymphopenia was significantly associated with early mortality with the presence of baseline confounders (OR = 3.401, 95%CI: 1.132 – 10.216, p = 0.029). In this regard, other correlates of mortality included high NYHA class and history of atrial fibrillation. In another regression model (table 4).

Table 4: Main determinants of in-hospital complications

Item	*P-value*	*Odds Ratio*	*95% Confidence Interval*	
			Lower limit	Upper limit
Lymphopenia	0.033	1.938	1.965	3.891
Male gender	0.523	1.248	0.632	2.464
Age	0.795	1.004	0.975	1.033
Function class	0.006	2.214	1.253	3.914
Diabetes mellitus	0.544	0.768	0.327	1.803
Renal failure	0.916	0.953	0.387	2.345
Atrial fibrillation	0.096	1.834	0.897	3.749
Creatinine	0.200	1.277	0.879	1.855
Sodium	0.159	0.967	0.923	1.013
Glucose	0.384	1.002	0.998	1.006

lymphopenia could predict in-hospital MACE (OR = 1.938, 95%CI: 1.965 – 3.891, p = 0.033). Along with lymphopenia, history of atrial fibrillation could also predict in-hospital MACE in heart failure patients.

Discussion:

As shown in some studies, increase in lymphocyte count has been demonstrated as an important marker for appearing ischemic heart diseases especially acute myocardial infarction. However, some investigations could show association between lymphopenia and poor prognosis in heart failure patients. the present study attempted to assess the role of lymphopenia for predicting in-hospital mortality and complications in chronic heart failure patients. We have shown that a notable number of patients with chronic heart failure experience lymphopenia that about half of them had lymphopenia. Also, we emphasize the correction of our primary hypotheses. First, the presence of lymphopenia was valuable to predict in-hospital mortality in these patients. Second, lymphopenia could effectively predict early complications within hospitalization in heart failure patients, but it was not associated with hospital stay and ICU stay. Our study was comparable with some similar studies. In a study by Turfan and colleagues, neutrophil to lymphocyte ratio could strongly predict mortality in heart failure patients with OR 1.2 [10]. Vaduganathan et al showed that by 10% decrease in plasma lymphocyte count, the risk for total mortality and cardiovascular related mortality increased 1.3 and 1.2 times respectively [11]. Charach et al indicated that the reduce of lymphocyte count lower than 1600 after 8 years was accompanied with considerable lower survival rate compared to those with lymphocyte count higher than 1600 (58% versus 72%) [12]. In another study by Núñez et al, an adverse association was observed between percentage of plasma lymphocytes and one-year mortality. In this context, lymphocyte percentage less than 7.5% and 5.0% was associated with cardiovascular increased risk as 1.95 times and 2.66 times, respectively [13]. Milo-Cotter et al showed that the patients with lymphocyte percentage less than 13% experienced lower improvement in dyspnea, more severe heart failure, longer hospital stay, and lower survival [14]. In a study by Ali, the lymphocyte percentage significantly lowers in those with uncompensated heart failure [15]. In a study by Huehnergarth et al, reduction n in lymphocyte count was associated with the increased risk for needing urgently hospitalization of heart failure patients [16]. In a prospective study by Sakatani et al, long-term mortality could be predicted by lymphocyte count lower than 20% [17]. In total and according to study results, it seems that not only lymphopenia can predict in-hospital mortality and morbidity, but also can predict long-term adverse events in heart failure patients.

In current study, along with the valuable role of lymphopenia to predict early mortality and MACE, there was an association between this marker and higher function class. On the other hand, lymphopenia could effectively predict low function capacity in heart failure patients. in this regard, monitoring this biomarker can be also used for assessing trend of improvement in functional capacity in these patients. in fact, the increase in plasma lymphocyte count can be accompanied with improvement of function class in heart failure patients that should be more assessed in further studies.

In conclusion, our study shows that along with low function class or other cardiovascular risk factor, lymphopenia can effectively predict in-hospital mortality and morbidity in patients with chronic heart failure.

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