Nutrition, Metabolism & Cardiovascular Diseases (2015) **25**, 1033–1040

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

The lymphocyte-to-monocyte ratio: An added value for death prediction in heart failure

N. Silva [a,b,c,*], P. Bettencourt [a,d], J.T. Guimarães [b,c,e]

[a] Unidade I&D Cardiovascular do Porto, Faculdade de Medicina da Universidade do Porto, 4202-451 Porto, Portugal
[b] Departamento de Bioquímica, Faculdade de Medicina da Universidade do Porto, 4202-451 Porto, Portugal
[c] Serviço de Patologia Clínica, Centro Hospitalar São João, 4202-451 Porto, Portugal
[d] Serviço de Medicina Interna, Centro Hospitalar São João, 4202-451 Porto, Portugal
[e] EPIUnit, Instituto de Saúde Pública da Universidade do Porto, 4050-600 Porto, Portugal

Received 26 February 2015; received in revised form 18 June 2015; accepted 13 July 2015
Available online 26 July 2015

KEYWORDS
Leukocyte differential;
Lymphocyte-to-monocyte ratio;
Heart failure;
Death

Abstract *Background and aim:* Leukocytes and their subpopulation have been long implicated in the progression of the syndrome of heart failure (HF), especially heart infiltration cells. Previous reports have suggested that they can predict worse outcome in patients with HF, and can also affect the function of other cells and myocardial extracellular matrix remodeling process. However, the lymphocyte-to-monocyte ratio (LMR) and its possible value as prognostic marker have not been evaluated.
Methods and results: A total of 390 patients with acute HF were recruited and followed for 6 months. Their total blood count with leukocyte differential was obtained. Two groups were formed according to the endpoints of HF death and optimal cut-off value of LMR, and were compared. A multivariate Cox-regression model was used to establish the prognostic value with the endpoints of HF and all-cause mortality. Median age of the patients was 78 years and 48.5% of them were men. No major difference was observed between the clinical characteristics of the two groups. Patients who died of HF had significantly higher values of B-type natriuretic peptide and lower values of LMR. Leukocyte and monocyte counts revealed a multivariate-adjusted risk for both endpoints, whereas relative lymphocyte counts had only significant value for all-cause mortality. The multivariate-adjusted hazard ratios for the 6-month HF and all-cause mortality in patients with LMR values < 2.0 were, respectively, 2.28 (95% CI: 1.25–4.15) and 2.39 (95% CI: 1.39–4.10).
Conclusion: Our results show that, upon discharge from hospital after an episode of acute HF, a lower value of LMR is independently associated with a higher risk of mortality within 6 months.

Introduction

Pathophysiology of heart failure (HF) is no longer regarded as an isolated cardiac entity, but rather an increasingly more complex and systemic condition. The types of prognostic factors associated with the risk of HF morbidity and mortality have been increasing [1–3], with a special emphasis on markers associated with inflammation, such as interleukin-6, tumor necrosis factor-α, and C-reactive protein (CRP) [4–7]. However, regardless of its pathogenesis, the major causes of HF progression are still ventricular remodeling and fibrosis. It is shown that mechanisms of inflammation may be evident in this maladaptive progression of distinct HF etiologies [8]. Heart infiltration

* Corresponding author. University of Porto, Cardiovascular R&D Unit, Al. Prof. Hernâni Monteiro, 4200-319 Porto, Portugal. Tel.: +351 912821468.
E-mail address: nunosilva.box@gmail.com (N. Silva).

http://dx.doi.org/10.1016/j.numecd.2015.07.004
0939-4753/

cells, including granulocytes, monocytes, macrophages, dendritic cells, mast cells, and T- and B-lymphocytes, can produce and secrete various cytokines, modulating the inflammatory response and affecting the functions of other cells and myocardial extracellular matrix remodeling process [9,10].

As both lymphocytes and monocytes play important roles in HF-related inflammation and remodeling/fibrosis, and considering the heterogeneity of HF, we aim to test if the LMR is also a useful parameter in discriminating the HF patients at a higher risk of mortality.

Methods

Study population

We conducted a prospective observational study between January 2009 and December 2010. In this study, patients admitted to the department of internal medicine of a central Portuguese hospital center, with the primary diagnosis of HF, either worsening or *de novo* HF, were included. However, patients with acute coronary syndromes, with symptoms attributable to causes other than HF, or with no echocardiographic structural or functional cardiac abnormality were excluded from the study.

An echocardiogram was performed in all eligible patients within 72 h of admission. A comprehensive echocardiographic assessment was performed using a multifrequency matrix probe (Vivid S6, GE Healthcare). The diagnosis of HF was made in accordance with the guidelines of the European Society of Cardiology [11]. All HF etiologies were admitted. Both groups of patients with left ventricular systolic dysfunction (LVSD) and HF with preserved ejection fraction were included in the study. A left ventricular ejection fraction (LVEF) of above 50% was defined as normal systolic fraction. Treatment decisions, timing of discharge, and discharge medication were at discretion of the attending physician, and the physicians were aware of the ongoing study.

Fasting venous blood samples were collected from all patients between 7 and 8 am on the day of discharge. Clinical and demographic data were collected, and other relevant information was obtained by interview upon the collection of the blood samples. Plasma B-type natriuretic peptide (BNP) was measured by a chemiluminescent immunoassay in the Architect i2000 automated analyzer (Abbott), and serum creatinine and CRP were measured in the automated clinical chemistry Olympus AU5400 analyzer (Beckman Coulter Inc.). Data on hemoglobin level and complete blood count (CBC) with leukocyte differential were obtained in a Sysmex XE-5000 automated blood counter (Sysmex).

Comorbidities were also recorded for each patient. Coronary heart disease was verified with a history of myocardial infarction, history or electrocardiographic evidence of ischemia, or confirmation of coronary angiography. Diabetes mellitus was confirmed with a history of diabetes or the current prescription of either an oral hypoglycemic agent or insulin. Anemia was found to be present when the hemoglobin level was <13 and <12 g/dL in men and women, respectively. Arterial hypertension was confirmed with the presence of previous diagnosis or evidence of antihypertensive pharmacological treatment. Renal dysfunction was suspected when creatinine levels exceeded 1.5 mg/dL. Alcohol habits of the patients were determined by clinician evaluation. Estimated glomerular filtration rate (EGFR) was calculated by the Cockcroft–Gault equation [12].

Patients were followed up for a period of 6 months after discharge, by means of consultation in the hospitals and/or telephone contact. The obtained endpoints were HF death, including worsening congestion because of progressive pump failure and sudden cardiac death, and all-cause mortality.

It is worth noting that all patients provided written informed consent to participate in the study. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki, and was approved by the local ethics committee.

Statistical analysis

Continuous variables are presented as median (interquartile range (IQR)) because of the skewed distribution, and categorical variables as counts and proportions. Normality of the variables was determined by the Shapiro–Wilk test.

Patients were divided according to the endpoint of HF death and the optimal cut-off value of LMR. This value was calculated through receiver operating characteristic (ROC) curves and the Youden index. The Youden index is useful in the calculation of the maximum vertical distance or difference between the ROC curve and the diagonal or chance line, which represents the cut-point that optimizes the differentiating ability of the biomarker when sensitivity and specificity are given equal importance. Groups were formed and compared. A chi-squared test was used for the comparison of categorical variables, and a Mann–Whitney test was used for comparing continuous variables once their distribution was skewed.

A univariate Cox-regression analysis was used for the assessment of prognostic power of the variables under study. Variables that were found to be of prognostic significance or known to influence HF prognosis were included in the developed multivariate models. Variables with significant prognostic power in the multivariate models were also divided into groups according to their optimal cut-off values to evaluate their influence on stratification of our patients.

The Kaplan–Meier test was used for estimating the survival function of patients in the 6-month follow-up with both outcomes in study, and according to the cut-off value calculated by the Youden index.

It was considered that $p = 0.05$ is statistically significant with a confidence interval of 95%.

Data were stored and analyzed using software packages such as SPSS Statistics 20.0 (SPSS Inc., Chicago, IL, USA) and MedCalc 14.8.1 (MedCalc Software bvba, Ostend, Belgium).