European Review for Medical and Pharmacological Sciences 2012; 16: 839-844

Significance of bacteriuria and leukocyturia in the outpatients with heart failure

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Abstract. – *Aim:* **To investigate the relationship between severity of illness and hospitalization with the presence of leukocyturia and bacteriuria in outpatients with heart failure (HF).**

Patients and Methods: **Four hundred three patients admitted with the diagnosis of HF to cardiology outpatient clinic were included in this study. According to New York Heart Association (NYHA) classification, the patients were divided into two groups to be group A (decompensated) as stage 3 or 4 and group B as stage 1 or 2 (compensated HF). All subjects underwent standard 12-lead ECG and echocardiography. In all patients, full blood, biochemical tests as liver and kidney function tests, full urinary analysis (FUA) and thyroid function tests were analyzed. Mid-stream urine for culture was taken for the leukocytes number ≥ 5 mm^3.**

Results: **The mean leukocyte number (MLN) in urine of patients was 16.56 ± 13.63 in Group A and was 3.74 ± 5.31 in Group B ($p < 0.000$). The moderately positive correlation was found between the MLN and NHYA class in all patients ($r = 0.526$; $p < 0.000$). In receiver operating characteristic (ROC) curve analysis, the optimal cut-off value of leukocytes in urinalysis to predict hospitalization of CHF was ≥ 5, with 76.1% sensitivity and 75.7% specificity (area under the curve 0.825, 95% confidence interval 0.781 to 0.862, $p = 0.000$).**

Conclusions: **We found that the numbers of leukocytes in urinalysis of hospitalized patients with HF were significantly higher than non-hospitalized persons. Also, number of leukocyte in urinalysis was positively correlated with NYHA class of HF patients. Namely, leukocyturia may be an indicator of decompensations in HF patients.**

Key Words:

Bacteriuria, Heart failure, Urinalysis, Pyuria.

Introduction

Heart failure (HF), which leads to high morbidity and mortality, is a prevalent and progressive clinical syndrome. Recurrent hospitalizations of HF patients are associated with increased mortality rates and decreased quality of life. Also, hospitalizations lead to a substantial increase in health care costs[1,2]. Because of the increased mortality rates and costs, the management of HF has prioritized attention toward risk factor modification to prevent future hospitalizations. Many researches are conducted to reduce the healthcare costs of this group of patients. Any kind of infection can be a precipitating factor for worsening HF, which increases the hospitalization rates[3].

Leukocyturia (LU) is defined as the presence of leukocytes in urine. LU may be due to urinary infections or non-infectious factors. Bacteriuria (BU) without LU can be encountered especially in some conditions such as chronic renal failure, heart failure, and diabetes mellitus[4] LU associated with urinary tract infection (UTI) is considered to be significant when it is ≥10/mm^3 in women, 5-10 ≥ leukocytes/in men[5]. Studies have shown that LU is a predictive value for BU. BU is the presence of bacterium in urine in person without symptoms of urinary system. Significant BU is the presence of ≥ 10^5 cfu/ml of bacteria at mid-stream urine sample[6]. BU is common in all age groups. However, it is more common in individuals with advanced age[7].

We think that there is an association between grade of LU and BU with HF. We hypothesize that these two urinary pathologies are independent factors to demonstrate the severity of HF and hospitalization. In this study, we aimed to in-

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vestigate the relationship between severity of illness and hospitalization with the presence of LU and BU in outpatients with HF admitted to our Cardiology Clinic.

Materials and Methods

Study Population

Four hundred three patients admitted with the diagnosis of HF to the cardiology clinic of Abant Izzet Baysal University Hospital between November 2010 and February 2012 were included in the study. Clinical data such as age, gender, hyperlipidemia, hypertension, diabetes mellitus, coronary artery disease, family history of a heart disease, smoking, use of medications, New York Heart Association (NYHA) classification and compliance with the diet of all patients were recorded.

According to NYHA classification, the patients were divided into two groups to be group A (Decompensated) as stage 3 or 4 and group B as stage 1 or 2 (Compensated HF). The patients with decompensated HF (Group A) were hospitalized[8].

Patients with hypothyroidism, malignity, immunosuppressive drug using, hyperthyroidism, Alzheimer's disease, Parkinson's disease, cerebrovascular disease, stroke, active infection other than UTI, respiratory system disease (Chronic obstructive pulmonary disease, acute pulmonary diseases), acute coronary syndromes, and congenital heart disease were excluded from the study.

The study was approved by the Ethics Committee of Abant Izzet Baysal University School of Medicine.

Laboratory Measurements

In all patients, full blood count (Beckman Coulter LH780, Fullerton, CA, USA), biochemical tests including liver and kidney function tests (Architect CI8200, Abbott Laboratories, Abbott Park, North Chicago, IL, USA), thyroid function tests (Immulite 2000, Siemens Healtcare Diagnostics Inc., Tarrytown, NY, USA) were analysed. Full urinary analysis (FUA) was done with original kits by IQ 200 (Iris Diagnostics, Chatsworth, CA, USA).

Mid-stream urine was taken for culture. All the urinary samples were passaged into Sheep-Blood and Eosin-Methylen Blue agars and evaluated after 24 sd hours. Cultures which yielded only one bacterial species grown at a concentrarion of $\geq 10^5$ cfu/ml were evaluated and the pathogen was identified with Gram stain, biochemical techniques, and automatic analyzer as VITEK-2. (BioMèrieux, Marcy L'Etoile, Craponne, France). Antibiotic sensitivity tests were done by Kirby Bauer disc diffusion technique according to criteria of Clinical and Laboratory Standards Institute. The sensitivity tests of the some stains were repeated by automatic analyzer as VITEK-2.

Electrocardiographic and Echocardiographic Measurement

All patients were evaluated by transthoracic M mode, two dimensional (2-D), pulsed-wave (PW), continuous wave (CW), colour-flow Doppler ecocardiograph. All examinations were performed with the GE-Vivid-3 ultrasound system (GE Vingmed, Horten, Norway) using a 2-4 MHz transducer at a dept of 16 cm by an experienced cardiologist. All patients were imaged in the left lateral decubitus position. 2-D and conventional Doppler examinations were obtained in the parasternal and apical views according to the guidelines of the American Society of Echocardiography[8]. Left ventricular (LV) diameters and wall thicknesses were measured by M-mode echocardiography. LV ejection fraction (EF) was calculated using the apical two-and four-chamber views by Simpson's method.

All subjects underwent standard 12-lead ECG, acquired using the MAC 5500 electrocardiograph (GE Healthcare, Milan, Italy) at a paper speed of 25 mm/s and 10 mm/mV. All recordings were performed in a quiet room, in the supine position.

Statistical Analysis

All analyses were performed using the SPSS for Windows 15.0 software package (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as the mean ± standard deviation. Categorical variables were presented as the percentage. Pearson's and Spearman correlation exponents were used to establish a relationship between continuous variables. Linear regression analysis was used to determine the independent predictors of hospitalization (including; age, weight, height, EF, gender, chronic renal failure (CRF), DM, HT, HL, cigarette smoking, and leukocytes in urinalysis), which incorporate variables that correlated with a P value of less than 0.1 in the correlation analysis. A value of $p < 0.05$ was considered statistically significant.

Results

Four hundred three (403) patients were included in this study. Forty-four patients were excluded from the study because of exclusion criteria. Therefore, three hundred sixty two patients were evaluated. Clinical and baseline characteristics of the patients were shown in Table I.

The leukocyte number (LN) was ≥ 5 mm^3 in FUA of 222 patients. However, leukocyte did not exist in urine of 51 patients and the leukocyte number was between 1-4 /mm^3 in the remaining patients. The mean leukocyte number (MLN) was 16.56 ± 13.63 in urine of patients in Group A and 3.74 ± 5.31 in Group B ($p < 0.000$). A strong positive correlation was found between the MLN and NHYA classes of all the patients (r=0.526; $p < 0.000$). Also, a significant positive correlation was observed between the MLN and the hospitalization days in group-A patients (r=0.439; $p < 0.000$) (Figure 1).

Table I. Baseline charecteristics of patients.

	Mean	SD	%	N
Age (years)	65.89	7.19		
Gender (M/F)			47.8/52.2	170/192
BMI (kg/m^2)	28.2	4.3		
Etiology of CHF				
Ischemic			38.1	138
Dilated			46.4	168
Valvular			11.9	43
Other			3.6	13
Ejection fraction (%)	31.13	8.23		
LVDD (mm)	5.82	0.72		
LAD (mm)	4.74	0.83		
SPAP (mmHg)	48	19		
NYHA class				
Class I			5.8	21
Class II			23.5	85
Class III			37.0	134
Class IV			33.7	122
CRF			22.7	82
DM			36.2	131
HT			56.4	204
Dyslipidemia			24.6	89
BPH (for male)			48.2	82
Smoking			30.1	109
Rhythm (NSR/AF)			64.4/35.6	233/129
Hemoglobin (g/dl)	12.9	1.6		
CC (ml/min)	76	14		
Presence of anemia			24	88
Antiplatelet agents			72.4	262
Beta Blockers			70.5	255
ACE inh/ARB			66.8	242
Statins			20.4	74
Diuretics			91.2	330

*LVDD: Left ventricular diastolic diameter; LAD: Left atrial diameter; SPAP: Systolic pulmonary artery pressure; CC: Creatinine clearance.

In linear regression analysis of the patient population, NHYA class, EF, and the number of leukocytes in urinalysis were found as independent predictors of hospitalization (Table II).

All patients were divided into 2 groups according to the number of leukocyte in urinalysis as; ≥10 (Group 1) and <10 (Group 2). In the nonparametric analysis, the gender, CRF, diabetes mellitus, hypertension, hyperlipidemia, benign prostate hyperplasia (for male), etiology of CHF and smoking were not significantly different between the groups ($p > 0.05$). However, atrial fibrillation (AF) and hospitalization rate were statistically more frequent in the first group and NYHA Functional Class of the group 1 patients was higher. We also repeated this analysis according to the leukocyte number of ≥ 5 and < 5 in urinanalysis, and we found that NYHA and hospitalization were statistically more frequent in the group of leukocyte number ≥ 5 mm^3.

In ROC curve analysis, the optimal cut-off value of leukocytes in urinalysis to predict hospitalization of CHF was ≥ 5, with 76.1% sensitivity and 75.7% specificity (area under the curve 0.825, 95% confidence interval 0.781 to 0.862, $p = 0.000$; Figure 2). If the cut-off value of leukocytes in urinalysis to predict hospitalization of CHF was ≥10, the sensitivity and specificity were found as 66.1-91.3%.

The frequency of bacteriuria was 18.2% (n=66) in the study population. *Escherichia coli* was the most frequent isolated pathogen (60.6%). There was a significant difference between males and females in view of the frequency of BU (male: 30.3%, n=20, female: 69.7%, n=46; $p = 0.002$). The frequency of bacteriuria and distribution of infectious microorganisms were similar in both groups (Group A: 17.0 %, n=44; Group B: 12.6%, n=13; $p = 0.304$). The frequency of BU and distribution of microorganisms in all 66 admission records were similar ($p = 0.121$) and were listed in Table III.

Discussion

In this study, firstly we found that the number of leukocytes in urinalysis of hospitalized patients with HF was significantly higher than non-hospitalized persons. Secondly, number of leukocyte in urinalysis was positively correlated with

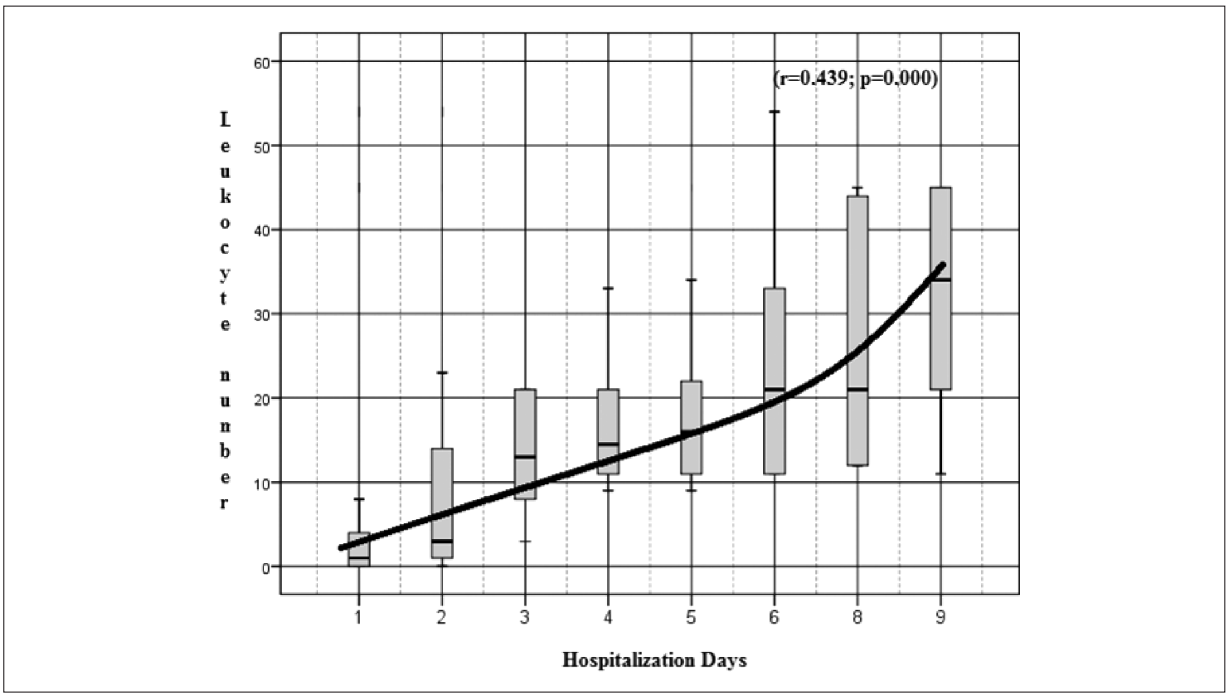

Figure 1. The positive correlation between the MLN and the hospitalization days.

NYHA class of patients with HF. Finally, the amount of leukocytes in urinalysis was found to be an independent predictive factor for the hospitalization rate. Thus, in ROC curve analysis, the optimal cut-off number of leukocytes in urinalysis to predict hospitalization of HF was > 5, with 76.1% sensitivity and 75.7% specificity.

Infections can lead to the worsening of the symptoms thus increases the hospitalization rate in patients with HF. Pneumonia is one of the most common infectious diseases in people with HF[9]. UTIs may be evaluated among the reasons triggering the severity of heart failure. However, it has not been reported a study to show the relationship between urinary tract inflammation or

Table II. Linear regression analysis was done to show the significant independent association to Hospitalizations days.

	Beta	Std. Error	p
(Constant)	0.913	0.301	0.003
Leukocyte, G/l	0.006	0.001	< 0.001
Age, years	0.000	0.002	0.815
Gender, n (%)	-0.010	0.024	0.676
BMI (kg/m^2)	0.000	0.001	0.229
Etiology of CHF	-0.188	0.001	0.811
Ejection fraction (%)	0.003	0.016	< 0.001
NYHA class	0.374	0.001	0.041
CRF	0.011	0.020	< 0.001
DM	0.024	0.027	0.690
HT	-0.009	0.024	0.312
Dyslipidemia	-0.016	0.023	0.697
Smoking (n, %)	-0.027	0.026	0.538
Rhythm	-0.013	0.025	0.282

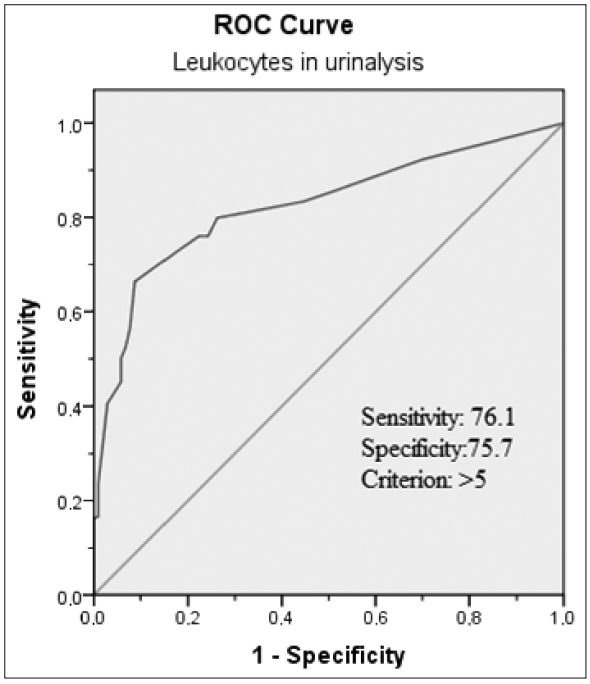

Figure 2. ROC curve for leukocytes in urinalysis prediction of hospitalization for HF.

Table III. Characteristics and distributions of microorganisms in patient who pathogen isolated.

	All patient	
	Group A	Group B
Proteus	5 (9.9)	2 (15.4)
Escherichia coli	33 (62.3)	6 (46.2)
Klebsiella	2 (3.8)	1 (7.7)
Streptococcus Staphylococcus	12 (22.6)	3 (23.1)
Other bacteria	1 (1.9)	1 (7.7)

*Data are presented as n (%).

infection with HF in the literature. In our study, a positive correlation was found between the presence of urinary leukocyte and the severity of the heart failure, but there was no relationship between the BU and the severity of the heart failure.

LU refers to a significant number of leukocytes in urine (more than 10,000 per milliliter). Also, it indicates urothelial inflammation and is required for the diagnosis of UTIs. Abundant LU can originate from the vagina and does not indicate aseptic LU. BU without LU indicates contamination of urine. Significant LU without BU (aseptic leukocyturia) can develop from various factors such as self-medication before urinalysis. Sterile LU may be associated with urinary stone, chronic interstitial nephritis (especially due to analgesics), urinary tract tumors, fastidious microorganisms requiring special culture mediums (*Ureaplasma urealyticum*, *Chlamydia, Candida*) (10). For these reasons, we evaluated FUA for all patients and did an urine culture in patients with 5 or more leukocytes in their FUA.

Urinary system symptomatology of the geriatric age group is more obscure than individuals of other age groups. Many elderly persons have chronic urinary tract symptoms[11]. In contrast, some elderly patients with UTIs may not have any urinary tract symptoms and urinary tract findings[12]. In our study population, the patients were over the age of 65 years, that is they were elderly population. For that reason, we did not use a urinary tract symptom questionnaire for the patients and FUA of all the patients were evaluated.

In 2008 ESC HFA guideline, urinalysis is recommended for all HF outpatients[8]. FUA was evaluated in all the outpatients with HF at their first admission. We found in this study that MLN was higher in hospitalized patients than non-hospitalized. Also, it was found that UL was an independent factor for hospitalization and had an association with NYHA class.

E. coli is the most common isolated pathogen from urinary tract of the patients with UTIs. Also, *Proteus* spp, *Klebsiella* spp, *Enterobacter* spp, *Pseudomonas* spp, and *Enterococcus* spp have been isolated, too[13-15]. In this study, our patients population were evaluated as complicated because of their advanced age. The most common isolated pathogen was *E. coli*. However, *Proteus spp.* and *Klebsiella spp*. were the other most common isolated pathogen. Also, we did not find that an association between the HF and BU.

Atrial fibrillation (AF) is one of the important reasons that give rise to worsening and decompensation of the HF[16]. In our study, NYHA class was higher and the hospitalization rate was statistically more frequent in the group with LN ≥ 10 /mm^3 than the group with LN < 10 /mm^3. Also, AF prevalence was more frequent in the group with LN ≥ 10 /mm^3 than the other group. For this reason, the patients were divided into two groups as LN < 5 mm^3 and LN ≥ 5 mm^3. AF prevalence was the same in these groups, and NYHA classes and the hospitalization rate were higher in the group with LN ≥ 5/mm^3 than the other group.

The limitation of our study, The limitation of our study may be stated as we did not do any urine culture in the patients, with LN < 5/mm^3 in their FUA, who were in elderly population group.

Namely, leukocyturia may be an indicator of decompensation in HF patients. To our knowledge, this has not been addressed previously in the literature.

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