Fırat Tıp Derg/Firat Med J 2016; 21(4): 204-208

Clinical Research

Is Monocyte Count a Marker in the Decompensation of Heart Failure?

Hakan GÜNEŞ[1], Tarık KIVRAK[1,a], Mustafa ADEM TATLISU[1], Hakkı KAYA[2], Dursun AKASLAN[1], Mehmet Birhan YILMAZ[2]

[1]*Sivas Numune Hastanesi, Kardiyoloji Kliniği, Sivas, Türkiye*
[2]*Cumhuriyet Üniversitesi Tıp Fakültesi, Kardiyoloji Anabilim Dalı, Sivas, Türkiye*

ABSTRACT

Objective: The aim of this study is to investigate the association of monocytes count with cardiovascular mortality in patients with acute decompensated heart failure (ADHF).
Material and Method: The study is a retrospective cohort study including 237 consecutive patients with ADHF admitted to cardiology. Clinical follow-up was performed by telephone interviews with the patient and/or relatives and by review of hospital medical records.
Results: These patients were divided into two groups: the deceased group (group 1), who died during hospitalization or the follow-up period, and the survival group (group 2). There was a significant difference in the mean percentage of monocytes and monocyte count between the two groups (p=0.003; p=0.006, respectively). ROC curve was drawn (AUC=0.618, 95% confidence interval: 0.544-0.693, p=0.003).
Conclusion: In summary monocyte-related cytokines play an important role in ADHF. Our study shows that monocytes can be used in patients with ADHF as a independent predictor of mortality; moreover it is inexpensive and easy to perform. Nonetheless, further larger-scale and multicenter studies needed to confirm these findings.

Keywords: *Acute Decompensation of Heart Failure, Monocyte Count, Heart Failure.*

ÖZET

Monosit Sayısı Dekompanse Kalp Yetersizliğinde Belirteç midir?

Giriş: Çalışmanın amacı akut dekompanse kalp yetersizliği (ADKY) olan hastalarda kardiyovasküler mortalite ile monosit sayısı arasındaki ilişkinin araştırılmasıdır.
Gereç ve Yöntem: Çalışma kardiyolojiye ardışık başvurmuş 237 hasta içeren retrospektif kohort çalışmasıdır. Klinik takipler telefon görüşmesi veya hastanenin medikal kayıtlarından yapıldı.
Bulgular: Hastalar iki gruba ayrıldı: 1. Grup takipte veya hastanede yatışı sırasında ölenlerden, 2. grup yaşayan hastalardan oluşturuldu. İki grup arasında monosit yüzdesi ve sayısı arasında anlamlı farklılık vardı (p=0.003; p=0.006, sırasıyla). ROC eğrisi ile değerlendirildi (AUC=0.618, %95 GA:0.544-0.693, p=0.003).
Sonuç: Monosit ile ilişkili sitokinler ADKY de önemli rol oynarlar. Çalışmamız monositlerin ADKY olan hastalarda mortalitenin bağımsız prediktörü olabileceği, ucuz ve kolay ulaşılabileceğini gösterdi. Bununla birlikte geniş çaplı ve çok merkezli çalışmalar ile bulgular desteklenmelidir.

Anahtar Sözcükler: *Akut Dekompanse Kalp Yetersizliği, Monosit Sayısı, Kalp Yetersizliği.*

Heart failure (HF) is a pathophysiologic process in which the heart muscle is unable to meet the body's needs for blood and oxygen caused by cardiac structural and/or functional impairment. Acute decompensated heart failure (ADHF) is characterized by neurohormonal activation and acute change in hemodynamic condition in patients with existing HF (1, 2).

The inflammatory mechanisms play an important role in this complex syndrome involving acute and chronic heart failure process and atherosclerosis (3, 4). Leukocytes and its subgroups play key roles in the presence of active inflammation. Monocytes are important components of the immune system constituting 3-8% of peripheral blood leukocytes. It is also known that inflammatory process plays a role in the pathophysiology of HF and atherosclerosis (5-7).

The objective of this study was to investigate the association of monocytes count with cardiovascular mortality in patients with ADHF.

MATERIAL and METHOD

The study was a retrospective cohort study including 237 consecutive patients with acute decompensated heart failure admitted to cardiology clinic from 1 June 2009 to 1 July 2011. Sample size was determined by simple random sampling. Demographic and clinical

[a]Yazışma Adresi: Dr. Tarık KIVRAK, Sivas Numune Hastanesi, Kardiyoloji Kliniği, Sivas, Türkiye
Tel: 0505 3729945 e-.mail: tarikkivrak@gmail.com
Geliş Tarihi/Received: 22.11.2015 Kabul Tarihi/Accepted: 21.03.2016

data including age, sex, heart failure function class, and laboratory data were assessed at baseline. Clinical follow-up was performed by telephone interviews with the patient and/or relatives and by review of hospital medical records. The study was approved by Cumhuriyet University Faculty of Medicine Ethics Committee.

Patients with New York Heart Association (NYHA) class III or IV systolic heart failure were included in this study. Patients with acute myocardial injury, acute and/or chronic infection, leukemia, lymphoma, inflammatory bowel disease, connective tissue disease were excluded from the study.

Statistical Analysis

Parametric data were expressed as mean±standard deviation, and categorical data as percentages. Data were processed using the Medcalc statistical software (v12.3.0, personallicence of MBY). Independent parameters were compared via the independent samples t-test, and via the Mann-Whitney U-test if there was an abnormal distribution. Categorical data were evaluated by the chi-square test as appropriate for the prediction of mortality, Receiver operating characteristic (ROC) curve analysis was performed to identify the optimal cut-off of monocyte percentage. Area under the curve (AUC) was calculated as measure of the accuracy of the test and compared with the use of the z-test. Outcome curves were generated using the Kaplan–Meier analysis for patients having above and below the monocyte percentage cut-off point and the groups were compared by the log-rank test. Patients were censored if alive at the end of the follow- up. A *p* value <0.05 was accepted as significant.

RESULTS

The mean age of the patients was 70.5 ±11.1 and one hundred fifty-five patients (65.4%) were male. These patients were divided into two groups: the deceased group (group 1), who died during hospitalization or the follow-up period, and the survival group (group 2). The mean age of the patients in group 1 and group 2 was 69.9±11.2 and 71.4±11.0 years, respectively. Their baseline demographic and clinical data are presented in Table 1. The two groups had similar age and sex distribution as shown in Table 1 (p=0.242; p=0.952, respectively).

Their baseline clinical and laboratory data, length of stay in hospital, frequency of hospitalization, and follow-up time are presented in Table 1. The mean monocyte count of patients in groups 1 and 2 was 0.69±0.28 and 0.59±0.25, respectively. The mean percentage of monocytes of patients in groups 1 and 2 was 7.90±2.18 and 7.18±2.68, respectively. There was a significant difference in the mean percentage of monocytes and monocyte count between the two groups as shown in Table 2 (p=0.003; p=0.006, respectively).

Table.I: The baseline demographic characteristics of the patients

	Group 1 (n=96)	Group 2 (n=141)	p
FPG, mg/dL	127.69±41.05	142.42±74.91	0.53
Üre, mg/dL	36.15±21.47	28.56±16.04	**0.02**
Creatinine, mg/dL	1.47±0.74	1.29±0.58	0.11
HDL, mg/dL	28.97±11.61	31.70±10.99	0.23
LDL, mg/dL	87.68±38.21	88.25±10.99	0.07
TG, mg/dL	86.24±43.20	99.56±61.91	0.09
TC, mg/dL	133.08±49.24	141.62±36.68	**0.01**
Na, mg/dL	135.16±4.76	136.11±4.43	0.22
K, mg/dL	4.76±0.78	4.47±0.56	0.01
Hb, g/dL	12.90±2.21	12.90±1.81	0.93
RDW,	16.81±2.74	15.68±2.34	0.01
HCT,	39.97±6.20	39.45±5.17	0.79
EF, %	32.07±10.91	28.23±9.70	0.01
The frequency of hospitalization	3.57±3.19	3.38±2.87	0.89
İndex follow-up period before hospitalization, month	34.03±26.45	22.58±15.93	0.15
DM, n (%)	79/17	120/21	0.47
HT, n (%)	29/67	36/105	0.45
CAD, n (%)	77/19	112/29	0.97
AF, n (%)	39/57	47/94	0.19
CABG, n (%)	17/79	32/109	0.33
LBBB, n (%)	9/87	12/129	0.81
CRT, n (%)	1/95	4/137	0.34

FPG:Fasting plasma glucose, **Üre**:Ürea, **HDL**:High Density Lipoprotein, **LDL**:Low Density Lipoprotein, **TG**:Triglyceride, **TC**:Total Cholesterol, **Na**:Sodium, **K**:Potassium, **HB**:Hemoglobine, **RDW**:Red Cell Distribution Width, **HCT**:Hematocrit, **EF**:Ejection Fraction, **DM**:Diabetes Mellitus, **HT**:Hypertension, **CAD**:Coronary Artery Disease, **AF**:Atrial Fibrilation, **CABG**:Coronary Artery Bypass Graft, **LBBB**:Left Bundle Branch Blocke, **CRT**:Cardiac Synchronise Theraphy

Table.II: Comparison of leukocyte and sub-groups of patients

	Group 1 (n=96)	Group 2 (n=141)	p
Leukocyte, × 10⁹/L	8.91±4.62	9.00±5.00	0.89
Neutrophil, × 10⁹/L	6.24±2.65	6.55±4.53	0.91
Lymphocyte, ×10⁹/L	1.79±3.54	1.65±1.67	0.46
Eosinophil, ×10⁹/L	0.14±0.12	0.16±0.17	0.68
Eosinophil, %	1.64±1.45	1.71±1.39	0.46
Basophil, ×10⁹/L	0.05±0.11	0.04±0.06	**0.01**
Basophil, %	0.55±0.89	0.53±0.48	0.29
Monocyte, ×10⁹/L	0.69±0.28	0.59±0.25	**0.01**
Monocyte, %	7.90±2.28	7.18±2.68	**0.01**

Statistically significant p<0.05 It was used sample t test or mann whitney u test.

ROC curve was constructed to evaluate the relationship mortality and monocyte count. ROC curve was drawn in figure 1 (AUC=0.618, 95% confidence interval: 0.544-0.693, p=0.003).

The results showed that monocyte percentage and count were not associated with follow-up time, length of stay in hospital, frequency of hospitalization. The cumulative mortality rates are presented in Figure 2.

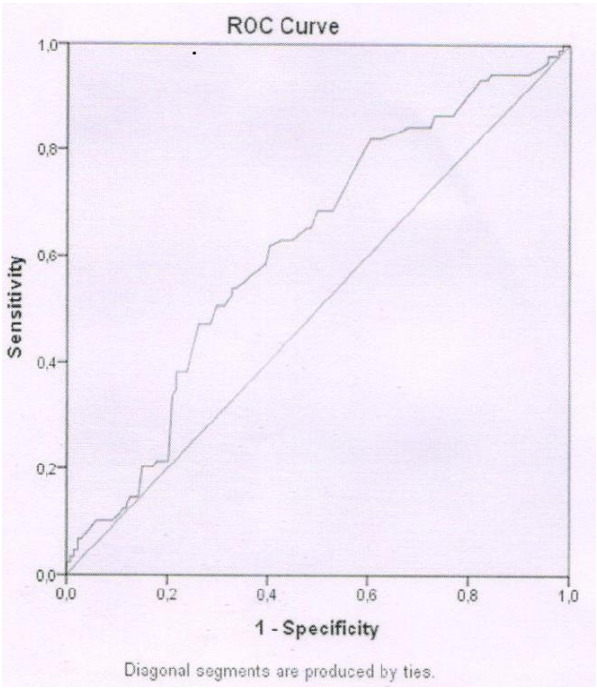

Figure 1. *Evaluation by Roc analysis of monocytes in patients whit acute decompensated heart failure*

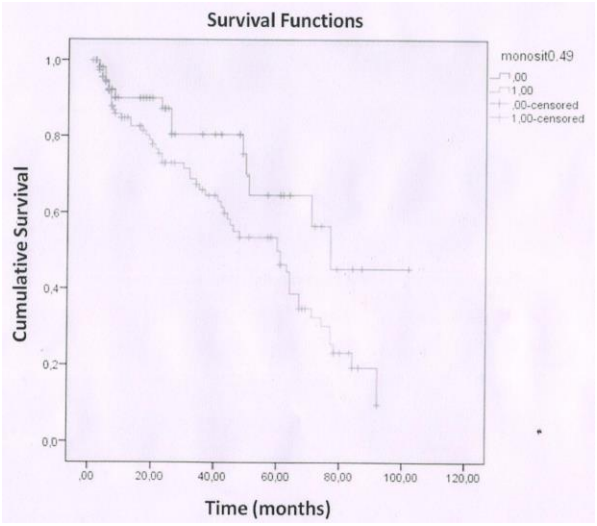

Figure 2.

DISCUSSION

It is known that neurohormonal and immune system play an important role in HF (7). The activation of inflammatory response is activated by these systems, either directly or indirectly. Monocytes play key roles in the activation of inflammatory response (6-9). There are limited data regarding the relationship between HF and monocytes. Based on the current literature, there is no study evaluating the association of monocytes with cardiovascular mortality in patients with ADHF.

The activation of monocytes is caused by ventricular distension, hypoxia and ischemia of tissues, increasing systemic congestion, and bacterial translocation. The activation of monocytes causes cytokine release such as interleukin (IL)-1b, IL-6, tumor necrosis factor (TNF) (10). However, myocardial injury also causes local cytokine release. Moreover, these cytokines create a positive feedback loop and reactivate the monocyte activation. Cytokines cause not only myocardial hypertrophy and fibrosis but also cardiac dysfunction via its effect on signal conduction system (10, 11).

It is known that high level of cytokines is associated with cardiac dysfunction in HF. Haugen *et al.* (5) showed that level of IL-1b, IL-6, IL-8, and TNF was higher in patients with HF than control group. Stumpf *et al.* (12) showed that level of TNF was higher in patients with congestive HF than healthy participants.

ADHF is one of the most common causes of the reasons for hospitalization in patients older than 65 years (13). Common causes of ADHF include myocardial ischemia and/or infarction, arrhythmias, severe hypertension, worsening of renal function, infection, severe thyroid disease, severe anemia, medication nonadherence, medical treatment such as non-steroidal inflammatory drugs, glitazones, negative inotropic agents (14, 15). There are several studies investigating relationship between cytokines and mortality and/or morbidity. Schulze *et al.* (16) showed that TNF level in patients with HF was higher than control group. They also showed that TNF level in patients with ADHF was higher than patients with compensated HF. Miettinen *et al.* found that the IL-6 level at 48 hours after admission in patient with ADHF was higher than patients with compensated HF. They also showed that high level of IL-6 and TNF were a independent predictor of 12-month mortality. Milani *et al.* (18) found that TNF level in patients with ADHF without cachexia was higher than healthy control group.

The activation of chemokines occurs in HF as a part of the inflammatory response. Chemokines, especially Monocyte Chemotactic Protein-1 (MCP-1) are polypeptides inducing monocyte mobilization from the bone marrow (19-21). Inflammatory cytokines contribute to activation of chemokines. Aukrust *et al.* (19) showed that chemokines were high in patients with NYHA class IV systolic heart failure. Also they found an inversely proportional relationship between left ventricular ejection fraction and chemokin level. Makarewicz-Wujek and Kozlowska-Wojciechowska (20) found that MCP-1 level was higher in patients with HF than control group. Cappuzello *et al.* (21) showed that MCP-1 level was higher in patients NYHA class II-IV heart failure than control group.

Monocytes play important roles in phagocytosis, antigen processing and presentation (22). Despite the important role of monocytes, there were few studies investigating prognostic role of monocytes in HF. Green *et al.* (23) found the association of monocyte count with poor prognosis in patients with HF admitted to hospital. Shantsila *et al.* (24) showed that high monocyte count was a independent predictor of mortality in patients with HF with preserved ejection fraction.

Interaction among monocytes, chemokines, and cytokines cause a vicious circle in HF. Many studies focused on monocyte-related cytokines. The aim of this study was to investigate the association of monocytes count with cardiovascular mortality in patients with ADHF. The results showed that monocyte percentage and count were associated with cardiovascular mortality.

This study had some limitations. This was a retrospective cohort and single-centered study. Another limitation to our study was the relatively small sample size.

In summary monocyte-related cytokines play an important role in ADHF. Our study shows that monocytes can be used in patients with ADHF as a independent predictor of mortality; moreover it is inexpensive and easy to perform. Nonetheless, further larger-scale and multi-center studies are needed to confirm these findings.

REFERENCES

1. Dec GW. Management of acute decompensated heart failure. Curr Probl Cardiol 2007; 32: 321-66.
2. Summers RL, Sterling S. Early emergency management of acute decompensated heart failure. Curr Opin Crit Care 2012; 18: 301-7.
3. Onwuanyi A, Taylor M. Acute decompensated heart failure: pathophysiology and treatment. Am J Cardiol 2007 26; 99: 25-30.
4. Corrêa CR, Dias-Melicio LA, Calvi SA, Lastória S, Soares AM. Activation of monocytes and cytokine production in patients with peripheral atherosclerosis obliterans. J Inflamm 2011; 8: 23 doi:10.1186/1476-9255-8-23.
5. Haugen E, Gan LM, Isic A, Skommevik T, Fu M. Increased interleukin-6 but not tumour necrosis factor-alpha predicts mortality in the population of elderly heart failure patients. Exp Clin Cardiol 2008; 13: 19-24.
6. Ali S, Shahbaz AU, Nelson MD, *et al.* Reduced relative lymphocyte count in African-Americans with decompensated heart failure. Am J Med Sci 2009; 337: 156-60.
7. Korkmaz L, Kul S, Korkmaz AA, *et al.* Increased leucocyte count could predict coronary artery calcification in patients free of clinically apparent cardiovascular disease. Arch Turk Soc Cardiol 2012; 40: 223-8.
8. Vaduganathan M, Greene SJ, Butler J, Sabbah HN *et al.* The immunological axis in heart failure: Importance of the leukocyte differential. Heart Fail Rev 2013; 18: 835-45.
9. Lepage S. Acute decompensated heart failure. Can J Cardiol 2008; 24: 8-10.
10. Vaduganathan M, Greene SJ, Butler J, *et al*. The immunological axis in heart failure: Importance of the leukocyte differential. Heart Fail Rev 2013; 18: 835-45.
11. Pfister R, Sharp SJ, Luben R, Wareham NJ, Khaw KT. Differential white blood cell count and incident heart failure in men and women in the EPIC-Norfolk study. Eur Heart J 2012; 33: 523-30.
12. Stumpf C, Lehner C, Yilmaz A, Daniel WG, Garlichs CD. Decrease of serum levels of the anti-inflammatory cytokine interleukin-10 in patients with advanced chronic heart failure. Clin Sci (Lond) 2003; 105: 45-50.
13. Amin A. Hospitalized patients with acute decompensated heart failure: recognition, risk stra-tification, and treatment review. J Hosp Med 2008; 3: 16-24.
14. Varughese S. Management of acute decompensated heart failure. Crit Care Nurs Q 2008; 94-103.
15. Givertz MM, Teerlink JR, Albert NM, *et al.* Acute decompensated heart failure: Update on new and emerging evidence and directions for future research. J Card Fail 2013; 19: 371-89.
16. Schulze PC, Biolo A, Gopal D, *et al.* Dynamics in insulin resistance and plasma levels of adipokines in patients with acute decompensated and chronic stable heart failure. J Card Fail 2011; 17: 1004-11.
17. Miettinen KH, Lassus J, Harjola V-P, *et al.* Prognostic role of pro- and anti-inflammatory cytokines and their polymorphisms in acute de-compensated heart failure. Eur J Heart Fail 2008; 10: 396-403.
18. Milani RV, Mehra MR, Endres S, *et al.* The clinical relevance of circulating tumor necrosis factor-alpha in acute decompensated chronic heart failure without cachexia. Chest 1996; 110: 992-5.
19. Aukrust P, Ueland T, Müller F, Andreassen AK, *et al.* Elevated circulating levels of C-C chemokines in patients with congestive heart failure. Circulation 1998; 97: 1136-43.

20. Makarewicz-Wujec M, Kozlowska-Wojciechowska M. Nutrient intake and serum level of gamma-glutamyltransferase, MCP-1 and homocysteine in early stages of heart failure. Clin Nutr 2011; 30: 73-8.

21. Cappuzzello C, Di Vito L, Melchionna R, *et al.* Increase of plasma IL-9 and decrease of plasma IL-5, IL-7, and IFN-γ in patients with chronic heart failure. J Transl Med 2011; 21; 9-28.

22. Amir O, Spivak I, Lavi I, Rahat MA. Changes in the monocytic subsets CD14dimCD16+ and CD14++CD16- in chronic systolic heart failure patients. Mediators Inflamm 2012; 2012: 992-5.

23. Greene SJ, Harinstein ME, Vaduganathan M, *et al.* EVEREST Trial Investigators. Prognostic value of monocyte count in patients hospitalized for heart failure with reduced ejection fraction (from the EVEREST Trial). Am J Cardiol 2012; 110: 1657-62.

24. Shantsila E, Bialiuk N, Navitski D, *et al.* Blood leukocytes in heart failure with preserved ejection fraction: impact on prognosis. Int J Cardiol 2012; 155: 337-8.