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The Effect of Emergency Department Visits and Inflammatory Markers on One-Year Mortality in Patients with Heart Failure

Ataman Köse[1] · Ahmet Çelik[2] · Ersin Altınsoy[1] · Seyran Bozkurt Babus[1] · Semra Erdoğan[3]

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Abstract

The neurohumoral and inflammatory pathways proposed for the development and progression of heart failure (HF) remain up-to-date. We aimed to investigate the effect of emergency department (ED) visits and inflammatory markers on mortality in HF patients. Two-hundred patients with stable chronic HF followed by the cardiology clinic were included in this study. The patients were divided into two groups as patients who had visited the ED due to worsening HF symptoms within the last 6 months (ED visit Group) and who had not (No ED visit Group). The demographical properties, clinical characteristics, and laboratory values including inflammatory markers of the patients were recorded. During the follow-up period, 38 patients (19%) died. In HF patients with previous ED visits, the mortality risk was 2.091 times higher (relative risk, RR). It was identified that the HF patients who died during the follow-up had higher initial NLR ($p=0.004$), IG% ($p=0.029$), hs-CRP ($p=0.001$), and NT-proBNP ($p=0.004$) values. It was observed that the area under the curve (AUC) values, NLR (AUC: 0.705, $p<0.001$), IG% (AUC: 0.652, $p=0.003$), and hs-CRP (AUC: 0.732, $p<0.001$) were very strong predictors of the 1-year mortality. According to the cut-off points, the mortality risk (RR) was 3.39 times higher in patients with NLR > 3.7 (95% CI 1.783–6.444), 2.39 times higher when IG% > 0.4 (95% CI 1.16–4.957), and 4,2 times higher when hs-CRP > 9.9 mg/dl (95% CI 2.16–8.16) ($p<0.05$). The patients with chronic stable HF who visited the ED within the last six months and having increased NLR, IG%, and CRP levels among inflammatory markers were associated with a higher mortality risk at 1 year.

Keywords Emergency department · Heart failure · Inflammatory markers · Mortality

Introduction

It was known that patients with decompensated heart failure (HF) had a poor prognosis. 7% to 16% of HF patients may be re-admitted to the hospital due to cardiovascular (CV) causes and 45% may re-visit the emergency department within 30 days [1]. The 1-year mortality rate of these patients after the admission has been reported at varying rates of 20–50% [1, 2]. HF is a chronic disease that requires a multi-disciplinary approach and requires many specialties to cooperate and provide care together [3]. Most HF patients are followed up and treated by HF specialists and/or cardiologists. The ED has a very important role in the initial care, diagnosis, and management of HF patients. It has been reported that early clinic follow-up (especially by doctors that know the patient) is related to better outcomes for HF patients [4]. There are also many studies about HF care and the outcomes depending on the specialty (cardiology, family physician, or primarily responsible practitioner, internal diseases, etc.) [1, 3]. However, the information about the clinical approach to HF in the ED and the long-term outcomes of these cohorts is limited [5–7]. Furthermore, most studies about the epidemiology and outcomes of HF have focused on patients who are hospitalized. However, the outcomes of stable HF patients with previous ED visits who regularly followed-up by a cardiologist and/or heart failure specialist are not well known.

Many prognostic and trigger factors have been described for HF. The neurohumoral and inflammatory pathways are

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✉ Ataman Köse
ataberk76@yahoo.com.tr

[1] Faculty of Medicine, Department of Emergency Medicine, Mersin University, Mersin, Turkey

[2] Faculty of Medicine, Department of Cardiology, Mersin University, Mersin, Turkey

[3] Faculty of Medicine, Department of Biostatistics and Medical Informatics, Mersin University, Mersin, Turkey

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two fundamental mechanisms proposed for the development and progression of HF. The presence of inflammatory processes may indicate deterioration of functional capacity and poor prognosis [8–11]. Among the inflammatory markers, the white blood cell count (WBC) and its components (such as the neutrophil–lymphocyte ratio, NLR) and high-sensitivity C-reactive protein (CRP) are simple, easily available and widely used markers. It is proposed that in some populations there is a relationship between WBC, NLR, CRP and, CV diseases (acute myocardial infarction (AMI), stroke, peripheral arterial disease, and vascular death) [11–14]. Inflammatory markers at higher levels (NLR and CRP) have been associated with increased severity, mortality, and morbidity in both chronic and acute HF patients [9, 15–19]. However, no studies were found about the role of immature granulocytes (IG) among these inflammatory markers in HF patients. The presence of increased IG numbers is an important criterion in the diagnosis of the systemic inflammatory response, and IG has been reported to be a useful prognostic marker of infection and inflammation [20, 21].

We aimed to find the possible effects of previous ED visits and inflammatory markers such as NLR, IG percentage (%), and CRP on hospitalization for HF and/or CV death in patients with chronic stable HF patients who are regularly followed up by a cardiologist and/or heart failure specialist.

Methods

Study Design and Patient Selection

This study was conducted in the Cardiology and Emergency Medicine Clinics of the Mersin University Medical Faculty. A retrospective cohort study was performed by assessing the medical records of 200 patients who presented to the hospital with the diagnosis of HF between February 2017 and February 2019. Patients older than 18 years of age diagnosed with chronic HF who were regularly followed-up by the cardiology clinic were included in the study. These patients were separated into two groups: patients who visited the ED with complaints of shortness of breath and/or edema and required treatment for worsening HF within the last 6 months (ED visit group), and patients who did not visit the ED for worsening HF (no ED visit group). The patients were followed up for 1 year. We compared the demographic characteristics, clinical, laboratory, and echocardiographic (ECHO) findings and assessed the risk factors and inflammatory markers that affected mortality. Patients with an active infection, active cancer, patients who were younger than 18 years of age, and patients who had no regular follow-up data were excluded from the study.

All data were independently verified by the hospital electronic data processing system Nucleus, which is a national administrative database that contains the records of all visits to our hospital at the patient-level, the data records of the primary physician who follows up the patient, medulla, and e-nabiz (e-pulse) system queries. The 1-year mortality after the admission to the cardiology clinic and the ED within 6 months and hospitalization for HF were assessed. Death and causes of death were obtained by reviewing the hospital database [the KPS (Turkish Identity Information Sharing System) mode of the nucleus system), the e-nabız (e-pulse) system, and the death reporting system. A phone visit was made with a cardiologist for data that could be obtained from the database. This study protocol was assessed and approved by Mersin University Ethical Review Committee.

Outcomes

Outcomes concerning CV death during the follow-up of 12 months after the index ED visit were assessed. The primary endpoint of the present study is CV death in 1 year. The secondary endpoint demonstrates the relationship between inflammatory markers (hs-CRP, NLR, and IG%) and all-cause mortality at one year. CV death included death resulting from acute coronary syndrome, all unexpected sudden deaths, death due to HF, stroke, and other cardiovascular causes.

Statistical Analysis

Normality controls for continuous measurements were tested using the Shapiro Wilk test. The Student *t*-test was used for the differences in continuous measurements according to the department at presentation. The mean and standard deviation values were presented as descriptive statistics. The Pearson Chi-square and likelihood ratio Chi-square tests were used for differences regarding the categorical variables. Numbers and percentages were used as descriptive statistics. The receiver operating characteristic curve (ROC) analysis was used to identify the cut-off points for the parameters that affect mortality. With this analysis, the area under the ROC curve (AUC), sensitivity, specificity, and cut-off statistics were presented. The "relative risk coefficient and confidence interval" statistics were presented in the assessment of risk factors that affect mortality. The statistical significance level of the data was taken as $p < 0.05$. The www.e-picos.com NY, New York Biostatistical software and, Medcalc statistical program bundle were used to assess the data.

Results

The baseline characteristics of patients who presented to the ED within the last 6 months due to worsening HF and patients with diagnosed chronic HF with no ED visits were

reviewed and their descriptive statistics are presented in Table 1. It was identified that among the HF patients who had visited the ED within the last 6 months, 37% were New York Heart Association (NYHA) Class III/IV and 70.4% of them had heart failure with reduced ejection fraction (HFrEF), 53.7% of them had Diabetes mellitus (DM), 78% used loop diuretics, and their mean heart rate was higher than the heart rate means of HF patients followed up by the cardiology clinic (Table 1). There is no correlation between fasting glukose levels and inflammatory markers. The assessment of the ECHO findings showed that the mean left ventricular ejection fractions (LVEF) and tricuspid annular plane systolic excursion (TAPSE) of HF patients who visited the ED were lower and that their mean left ventricular end-diastolic (LVEDD), estimated systolic pulmonary artery pressure (esPAP), and right ventricle (RV) diameter were higher (Table 1). In the analysis of the laboratory parameters, it was identified that the average WBC, NLR, IG%, hs-CRP, blood glucose, aspartate aminotransferase (AST), and N-terminal probrain natriuretic peptide (NT-proBNP) levels of HF patients who had visited the ED within the last 6 months were significantly higher compared to the patient group with no ED visits (Table 1). It was also observed that the means hemoglobin and sodium levels of patients who had visited the ED were significantly lower. During the follow-up (12 months), 38 patients (19%) died. It was identified that 27 (25%) of these were HF patients who had visited the ED within 6 months, and 11 (12%) were HF patients who had not visited the ED and were being followed by the cardiology clinic ($p = 0.019$). It was also identified that the rate of hospitalization due to worsening HF was higher in the group with ED visits (Table 1).

The baseline characteristics of the patients were assessed based on their mortality and their descriptive statistics are presented in Table 2. It was identified that 71.1% of the patients who died during the follow-up had ED visits due to worsening HF within the last 6 months, and that 28.9% comprised patients with no ED visits within the last 6 months. It was observed that 67.6% of the dead patients were NYHA III/IV symptomatic and 76.3% had heart failure with reduced ejection fraction (HFrEF). Among the patients who died, the usage rate of loop diuretics was lower, and the usage rate of beta-blockers and mineralocorticosteroid receptor antagonists (MRA) were similar to the patients who survived (Table 2). It was identified that the mean resting baseline heart rate was higher, the mean LVEF was lower, TAPSE was lower, and the esPAP was higher in patients who died (Table 2). The assessment of laboratory parameters showed that the initial NLR, IG%, hs-CRP, creatinine, and NT-proBNP values of the HF patients who died during the follow-up were higher and that their hemoglobin and sodium levels were lower (Table 2).

The cut-off points for each parameter that affected mortality were obtained from the results of the ROC analysis. It was observed that the parameters NLR, IG%, hs--CRP, and NT-proBNP were very strong in distinguishing HF patients who survived and died and that this was statistically significant (Table 3). Parallel to this, it was observed that the NLR, IG%, hs-CRP, and NT-proBNP were stronger predictors of the 1-year mortality. Also, when the ROC curves are compared for these parameters, the area under the curve (AUC) values were similar in terms of their ability to distinguish survival and mortality (Fig. 1).

The cut-off points for each parameter that affected mortality were obtained from the results of the ROC analysis and the relative risk (RR) of the risk factors that affect mortality was assessed using E-PICOS in relation to the cut-off points. The relative risk analysis of categorical variables comparing positives with non-positive was also performed using E-PICOS. It was identified that the relative risk according to the cut-off points was high and meaningful for the parameters NLR, IG%, heart rate, hs-CRP, NT-proBNP, LVEF, TAPSE, esPAP, hemoglobin, creatinine, and sodium ($p < 0.05$). The other parameters were not significant. The mortality risk of patients with ED visits was 2.091 times higher than that of patients with no ED visits. The mortality risk was 3.39 times higher in patients with NLR > 3.7, 2.398 times higher in patients with IG% > 0.4, 4.2 times higher in patients with hs-CRP > 9.9 mg/dL, and 3.839 times higher in patients with NT-proBNP > 3270 ($p < 0.05$). Table 4 summarizes the RR values of factors that affect mortality.

Discussion

Firstly, in our study, more than half of chronic HF patients presented to the ED within six months and mortality occurred within 1 year for 25% of these patients. One other finding is that inflammatory markers (NLR, IG%, and hs-CRP), hospitalization rates, and the one-year mortality risk (RR: 2.091) were two times higher in HF patients. Among the chronic HF patients who were included in the study, it was observed that the ability to predict mortality was stronger at the cut-off values NLR > 3.7, IG% > 0.4, and hs-CRP > 9.9 mg/L. According to these cut-off values, inflammatory markers are associated with the one-year mortality risk of HF patients. In these patients, it was identified that the mortality risk was 3.39 times higher in patients with NLR > 3.7, 2.39 times higher in patients with IG% > 0.4, and 4.2 times higher in patients with hs-CRP > 9.9 mg/L.

In general, it is predicted that HF patients who present to the ED are acute, more severe, and have more negative outcomes. Between 2008 and 2014, 41% of HF patients presented to the outpatient clinics, 11% to EDs, and 47% directly to hospitals. However, data from this study show

Table 1 The Baseline characteristics of the patients according to emergency department visit

Variables	All patients ($n=200$)	ED visit group ($n=108$, %54)	No ED visit group ($n=92$, %46)	p
Clinical features				
Sex *n* (%)				0.788
Male	146 (73.0)	78 (72.2)	68 (73.9)	
Female	64 (27)	30 (27.8)	24 (26.1)	
Ischemic etiology (%)	114 (57.0)	69 (63.9)	45 (48.9)	0.330
NYHA Class, *n* (%)				**0.001**
I/II	141 (72.7)	68 (63)	73 (84.9)	
III/IV	53 (27.3)	40 (37)	13 (15.1)	
HF type, *n* (%)				**0.008**
HfrEF	124 (62.0)	76 (70.4)	48 (52.2)	
HfpEF	76 (38.0)	32 (29.6)	44 (47.8)	
Age (mean, SD)	65.0 ± 13.6	66.2 ± 13.4	63.6 ± 13.5	0.178
Systolic blood pressure (mm Hg), (Mean, SD)	134.57 ± 25.79	134.91 ± 29.72	134.13 ± 19.70	0.827
Diastolic blood pressure (mm Hg), (Mean, SD)	79.0 ± 14.97	79.74 ± 18.02	78.04 ± 9.71	0.407
Heart rate (beats/min), (Mean, SD)	82.01 ± 21.25	87.5 ± 21.33	75.34 ± 19.25	**< 0.001**
Medical history *n* (%)				
CABG	69 (34.5)	39 (36.1)	30 (32.6)	0.604
Diabetes mellitus	88 (44.0)	58 (53.7)	30 (32.6)	**0.030**
Hypertension	120 (60.0)	65 (60.2)	55 (59.8)	0.954
Cerebrovascular disease	20 (10)	14 (13.0)	6 (6.5)	0.202
Chronic kidney disease	63 (31.5)	40 (37.0)	23 (25.0)	0.680
Chronic lung disease	25 (12.5)	17 (15.7)	8 (8.7)	0.133
Smoke	28 (14.0)	19 (17.6)	9 (9.8)	0.113
ICD	37 (18.5)	19 (17.6)	18 (19.6)	0.901
CRT	13 (6.5)	6 (5.6)	7 (7.6)	
Pacemaker	5 (2.5)	3 (2.8)	2 (2.2)	
Medications, *n* (%)				
RAASi	109 (54.5)	58 (53.7)	51 (55.4)	0.806
Beta-blockers	167 (83.5)	90 (83.3)	77 (83.7)	0.945
Loop diuretic	141 (70.5)	85 (78.7)	56 (60.9)	0.060
MRAs	95 (47.5)	53 (49.1)	42 (45.7)	0.629
Digoxin	33 (16.5)	21 (19.4)	12 (13.0)	0.224
Aspirin	118 (59.0)	65 (60.2)	53 (57.6)	0.712
Ivabradine	25 (12.5)	16 (14.8)	9 (9.8)	0.284
Nitrates	31 (15.5)	19 (17.6)	12 (13.0)	0.376
ECG rhythm, *n* (%)				
Sinus rhythm	150 (75.0)	82 (75.9)	68 (73.9)	0.687
Atrial fibrillation	34 (17.0)	19 (17.6)	15 (16.3)	
Pace rhythm	16 (8.0)	7 (6.5)	9 (9.8)	
Echocardiography datas (Mean, SD)				
LVEF (%)	36.28 ± 14.63	33.60 ± 14.43	39.43 ± 14.32	**0.005**
LVEDD (cm)	5.75 ± 0.87	5.87 ± 0.83	5.60 ± 0.89	**0.032**
LVESD (cm)	4.49 ± 1.23	4.62 ± 1.13	4.32 ± 1.32	0.111
*LA*D (cm)	4.42 ± 0.82	4.44 ± 0.72	4.39 ± 0.92	0.679
LA *volume* (mL)	100.56 ± 48.76	103.28 ± 49.15	97.40 ± 48.03	0.444
LVEDV (mL)	145.06 ± 67.21	146.27 ± 68.13	143.65 ± 66.55	0.805
LVESV (mL)	95.30 ± 56.40	100.40 ± 57.55	89.39 ± 54.83	0.216
TAPSE (mm)	19.20 ± 5.37	18.27 ± 6.30	20.30 ± 3.75	**0.012**
esPAP (mmHg)	40.18 ± 13.79	43.32 ± 14.05	36.32 ± 12.50	**0.01**

Table 1 (continued)

Variables	All patients ($n=200$)	ED visit group ($n=108$, %54)	No ED visit group ($n=92$, %46)	p
RV diameter (cm)	3.79 ± 0.86	4.03 ± 0.91	3.51 ± 0.70	**< 0.001**
Laboratory values (Mean, SD)				
WBC count ($\times 10^3$ /uL)	9.11 ± 3.10	9.98 ± 3.48	8.07 ± 2.17	**< 0.001**
NLR	4.25 ± 3.52	5.34 ± 4.28	2.95 ± 1.53	**< 0.001**
IG index (%)	0.55 ± 0.45	0.65 ± 0.55	0.42 ± 0.22	**< 0.001**
Hemoglobin (g/dL)	12.54 ± 2.04	12.23 ± 2,05	12.91 ± 2.07	**0.019**
Platelets ($\times 10^3$ /uL	246.20 ± 83.77	244.10 ± 92.33	248.72 ± 72.61	0.694
hs-CRP (mg/L)	16.24 ± 23.88	22.40 ± 27.56	7.83 ± 14.30	**< 0.001**
Glucose (mg/dl)	139.63 ± 59.18	152.51 ± 67.46	122.53 ± 41.16	**< 0.001**
Creatinine (mg/dl)	1.30 ± 1.03	1.43 ± 1.26	1.17 ± 0.66	0.071
AST (U/L)	28.15 ± 37.03	33.23 ± 47.49	22.03 ± 15.53	**0.022**
ALT (U/L)	25.68 ± 52.25	28.76 ± 67.57	22.0 ± 22.86	0.363
Potassium (mEq/L)	4.6 ± 0.56	4.56 ± 0.56	4.64 ± 0.56	0.378
Sodium (mEq/L)	137.91 ± 4.15	136.69 ± 4.40	139.54 ± 3.25	< 0.001
NT-proBNP (pg/mL)	6694.43 ± 8322.71	8172.38 ± 8559.62	4534.36 ± 7516.10	0.006
Ferritin	121.76 ± 144.75	131.63 ± 139.23	109.59 ± 151.56	0.383
Outcomes *n* (%)				
1-year mortality	38 (19.0)	27 (25.0)	11 (12.0)	**0.019**
Hospitalization	82 (41.0)	67 (62.0)	15 (16.3)	**< 0.001**

Bold values indicate statistical significance at $p < 0.05$

Data are expressed as mean ± SD, or number (percentage)

NYHA New York Heart Association heart failure, *HFrE* heart failure with reduced ejection fraction, *HFpEF* heart failure with preserved ejection fraction, *CABG* coronary artery bypass grafting, *ICD* implantable-cardioverter defibrillato, *CRT* cardiac resynchronization therapy; renin angiotensin aldosteron system inhibitor (RAASi; ACEİ: ARB: ARNİ), *MRA* mineralocorticosteroid receptor antagonists, *LVEF* left ventricular ejection fractions, *LVEDD* left ventricularend-diastolic, *LVESD* end-systolicdiameter, *LAD* left atrium diameter, *LVEDV* left ventricular end-diastolic volüme, *LVESV* left ventricular endsystolic volüme, *TAPSE* tricuspid annular plane systolic excursion, *esPAP* systolic pulmonary artery pressure, *RV* right ventricle diameter, *WBC* white blood cell count, *NLR* neutrophil-to-lymphocyte ratio, *IG* index *(%)* ımmature granulocyte percentage; *hs-CRP* high-sensitivity C-reactive protein, *AST* Aspartate aminotransferase, *ALT* Alanine aminotransferase, *NT-proBNP*N terminal probrain natriuretic peptides

that the incidence of ED visits related to HF may have increased starting from 2011 [22]. In our study, more than half of the HF patients who had been followed by cardiology had visited the ED within the last 6 months. It has been reported that if the CV follow-up of HF patients is performed regularly by a doctor (family physician, cardiologist, or general internalist), they have better outcomes (fewer ED visits, less rehospitalization, and lower mortality rates) despite their high rate of comorbid diseases. In a newly published study, the WBC, ALT, and blood glucose levels were significantly higher and the sodium levels were significantly lower in HF patients presenting to the ED (emergency physician group) when compared to the group seen by cardiologists (cardiologist group) [3]. In our study, among HF patients who visited the ED, higher WBC, NLR, IG%, hs-CRP, glucose, AST, NT-proBNP, and lower hemoglobin and sodium levels were detected. It has been reported that HF care provided by cardiologists is associated with significantly lower ratios of negative outcomes when compared to care not provided by cardiologists [23, 24]. However, these reports assessed the management of patients hospitalized in the index hospital ≥ 24 h after presentation at the ED and do not reflect the characteristics of the initial ED application. In contrast, in a recent analysis of the records of REALITY-AHF that included 1682 patients, it was stated that there was no difference related to a specialty in short-term or long-term mortality between patients managed by emergency physicians and patients managed by cardiologists [3]. In HF patients treated and discharged from the ED, it was established that early follow-up by their primary physicians was associated with lower mortality and better outcomes [4, 25]. In the study by Gorlicki et al. ED visits did not appear to be related to mortality, and a hospital care process including the cardiology clinic was associated with increased in-hospital survival among AHF patients [26]. A study that compared HFrEF patients according to the final destination (cardiology unit, short-term care unit, general internal diseases clinic, and patients discharged directly from the ED) presented similar short-term outcomes regardless of

Table 2 Comparison of the baseline characteristics of patients according to mortality

Variables	All patients ($n=200$)	Survival ($n=162$, %81)	Death ($n=38$, %19)	p
Clinical features				
ED presentation (n, %)	108 (54.0)	81 (50.0)	27 (71.1)	**0.019**
Hospitalization (n,%)	82 (41.0)	54 (33.3)	28 (73.7)	**< 0.001**
Sex n (%)				0.359
Male	146 (73.0)	116 (71.6)	30 (78.9)	
Female	64 (27)	46 (28,4)	8 (21.1)	
Ischemic etiology, n (%)	114 (57)	91 (56.2)	23 (60.5)	0.626
NYHA class				**< 0.001**
I/II	141 (72.7)	129 (82.2)	12 (32.4)	
III/IV	53 (27.3)	28 (17.8)	25 (67.6)	
Heart failure type				**0.043**
HFrEF	124 (62.0)	95 (58.8)	29 (76.3)	
HFpEF	76 (38.0)	67 (41.4)	9 (23.7)	
Age (mean, SD)	65.0 ± 13.6	64.6 ± 13.5	66.6 ± 13.73	0.422
Systolic blood pressure (mm Hg), (Mean, SD)	134.57 ± 25.79	136.70 ± 24.01	126.03 ± 30.88	0.053
Diastolic blood pressure (mm Hg), (Mean, SD)	79.0 ± 14.97	69.94 ± 14.61	75.23 ± 16.04	0.083
Heart rate (beats/min), (mean, SD)	82.01 ± 21.25	80.32 ± 20.41	89.05 ± 23.44	**0.023**
Medical history n (%)				
CABG	69 (34.5)	57 (35.2)	12 (31.6)	0.674
Diabetes mellitus	88 (44.0)	68 (42.0)	20 (52.6)	0.234
Hypertension	120 (60.0)	98 (60.5)	22 (57.9)	0.768
Cerebrovascular disease	20 (10.0)	14 (8.6)	6 (15.8)	0.226
Chronic kidney disease	63 (31.5)	46 (28.4)	17 (44.7)	0.051
Chronic lung disease	25 (12.5)	16 (9.9)	9 (23.7)	**0.031**
Smoking	28 (14.0)	21 (13.0)	7 (18.4)	0.383
ICD	37 (18.5)	30 (18.5)	7 (18.4)	0.474
CRT	13 (6.5)	9 (5.6)	4 (10.5)	
PACE	5 (2.5)			
Medications, n (%)				
RAASi	109 (54.5)	90 (55.6)	19 (50.0)	0.536
Beta-blockers	167 (83.5)	133 (82.1)	34 (89.5)	0.270
Loop diuretic	141 (70.5)	109 (67.3)	32 (84.2)	**0.039**
MRAs	95 (47.5)	76 (46.9)	19 (50.0)	0.732
Digoxin	33 (16.5)	23 (14.2)	10 (26.3)	0.070
Asetil salysilic acid	118 (59.0)	97 (59.9)	21(55.3)	0.603
Ivabradine	25 (12.5)	19 (14.7)	6 (15.8)	0.507
Nitrates	31 (15.5)	22 (13.6)	9 (23.7)	0.121
ECG rhythm, n (%)				
Sinus rhythm	150 (75.0)	124 (76.5)	26 (68.4)	0.577
Atrial fibrillation	34 (17.0)	26 (16.0)	8 (23.1)	
Pace rhythm	16 (8.0)	12 (7.4)	4 (10.5)	
Echocardiography data (mean, SD)				
LVEF (%)	36.28 ± 14.63	37.31 ± 14.80	31.92 ± 13.28	**0.041**
LVEDD (cm)	5.75 ± 0.87	5.72 ± 0.85	5.87 ± 0.97	0.333
LVESD (cm)	4.49 ± 1.23	4.46 ± 1.17	4.61 ± 1.47	0.546
*L*AD (cm)	4.42 ± 0.82	4.42 ± 0.80	4.41 ± 0.91	0.932
LA *volume* (mL)	100.56 ± 48.76	100.06 ± 50.80	102.77 ± 37.87	0.784
LVEDV (mL)	145.06 ± 67.21	144.10 ± 67.45	148.97 ± 67.17	0.715
LVESV (mL)	95.30 ± 56.40	93.09 ± 57.08	104.28 ± 53.50	0.316
TAPSE (mm)	19.20 ± 5.37	19.78 ± 5.47	16.71 ± 4.14	**0.002**

Table 2 (continued)

Variables	All patients ($n=200$)	Survival ($n=162$, %81)	Death ($n=38$, %19)	p
esPAP (mmHg)	40.18 ± 13.79	39.02 ± 13.98	45.21 ± 11.83	**0.020**
RV diameter (cm)	3.79 ± 0.86	3.77 ± 0.87	3.92 ± 0.81	0.386
Laboratory values, (mean ± SD)				
WBC count ($\times 10^3$ /uL)	9.11 ± 3.10	8.98 ± 3.08	9.68 ± 3.16	0.214
NLR	4.25 ± 3.52	3.84 ± 3.28	5.98 ± 4.01	**0.004**
IG index (%)	0.55 ± 0.45	0.50 ± 0.38	0.75 ± 0.64	**0.029**
Hemoglobin (g/dl)	12.54 ± 2.05	12.75 ± 2.01	11.66 ± 2.06	**0.003**
Platelets ($\times 10^3$ /uL)	246.20 ± 83.77	247.71 ± 82.92	239.84 ± 88.10	0.604
hs-CRP (mg/L)	16.24 ± 23.88	11.91 ± 16.24	34.05 ± 38.30	**0.001**
Glucose (mg/dl)	139.63 ± 59.18	141.04 ± 60.5	133.79 ± 53.71	0.505
Creatinine (mg/dl)	1.30 ± 1.03	1.20 ± 0.71	1.80 ± 1,79	**0.049**
AST (U/L)	28.15 ± 37.03	27.57 ± 40.15	30.58 ± 19.29	0.653
ALT (U/L)	25.68 ± 52.25	25.37 ± 56.99	26.99 ± 32.97	0.864
Potassium (mEq/L)	4.6 ± 0.56	4.61 ± 0.544	4.52 ± 0.62	0.386
Sodium (mEq/L)	137.91 ± 4.15	138.35 ± 3.80	136.11 ± 5.10	**0.003**
NT-proBNP (pg/mL)	6694.43 ± 8322.71	5524 ± 7445.10	11,372.41 ± 9997.82	**0.004**
Ferritin	121.76 ± 144.75	127.44 ± 152.86	92.87 ± 144.75	0.308

Bold values indicate statistical significance at $p<0.05$

Abbreviations: see Table 1

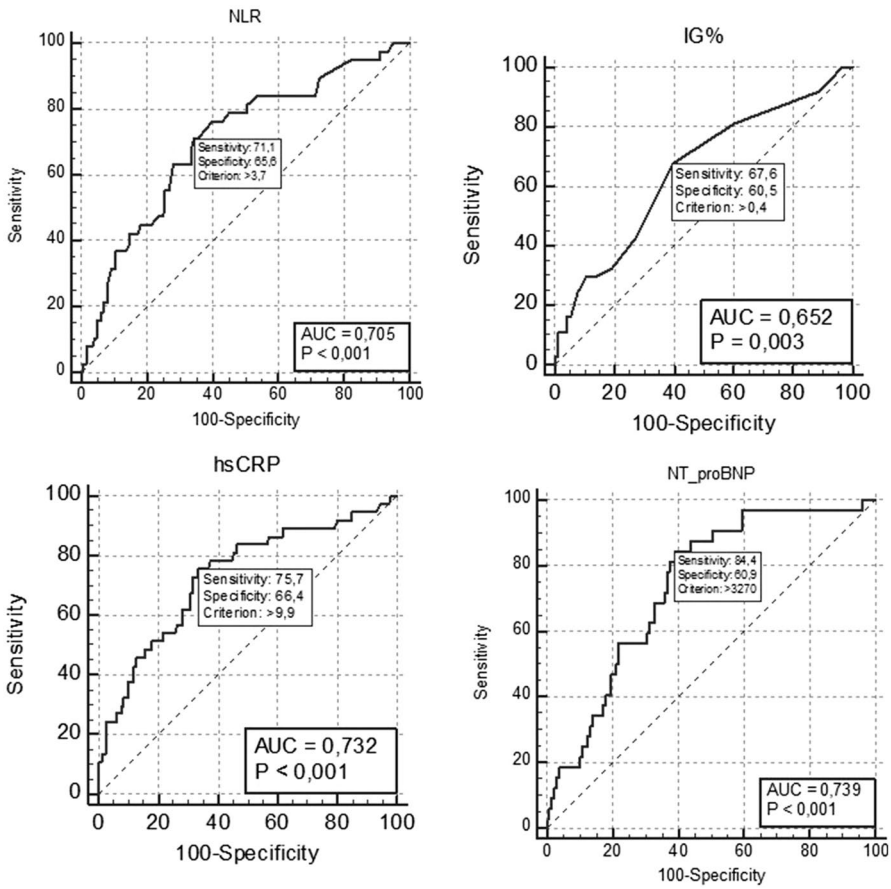

Fig. 1 In receiver operating characteristic curve analysis, the area under the curve of hs-NLR, IG%, hs-CRP, and NT-proBNP count to predict 12-month mortality was 0.705, 0.652, 0,732, and 0.739, respectively. The dotted line represents the diagonal reference line

Table 3 The ROC analysis of variables that may affect mortality

	Cut-off	AUC	Sensitivity (%)	Specificity (%)	*p*
NLR	> 3.7	0.705	71.1	65.6	< 0.001
IG %	> 0.4	0.652	67.6	60.5	0.003
hs-CRP	> 9.9	0.732	75.7	66.45	< 0.001
NT-proBNP	> 3270	0.739	84.4	60.9	< 0.001
LVEF	≤ 32	0.615	65.8	56.8	0.017
TAPSE	≤ 19	0.689	82.4	50.3	< 0.001
esPAP	> 48	0.662	57.6	77.6	0.004
Hemoglobin	≤ 13	0.651	81.6	47.2	0.001
Creatinine	> 1.4	0.673	52.6	80.9	< 0.001
Sodium	≤ 137	0.627	57.9	65,8	0,007
Heart rate	> 83	0.604	60.5	58.5	0,049

ROC receiver operating characteristic curve, *AUC* area under the curve, Abbreviations: see Table 1

Table 4 The logistic regression analysis of factors that may effect the mortality

Risk factors	Relative risk (RR)	95% confidence ınterval
ED presentation	2.091	1.099–3.98
Hospitalization	4.029	2.073–7.833
NLR	3.46	1.82–6.576
Heart rate	1.837	1.02–3.306
IG %	2.398	1.16–4.957
hs-CRP	4.2	2.16–8.16
NT-proBNP	3.839	2.022–7.288
LVEF	2.126	1.155–3.912
TAPSE	2.8	1.437–5.454
esPAP	2.846	1.639–4.942
Hemoglobin	3.207	1.484–6.931
Creatinine	2.508	1.64–3.834
Sodium	2.24	1.26–3.99

RR for variables in Table 4. Non-significant RR not shown. Abbreviations: see Table 1

the clinics that patients were referred to [24]. In our study, the one-year mortality rate was higher in patients who visited the ED despite being followed by the cardiology clinic (25%). The relative risk for mortality was 2.091 in HF patients who visited the ED.

Inflammation and neurohumoral activation are important for the pathogenesis, progression, severity and prognosis of HF [9, 14]. An increase in circulating myeloperoxidase, WBC count, and other inflammatory markers, particularly CRP, has been observed in patients with HF of various etiology suggesting that inflammatory activation may affect on the pathogenesis of HF. The importance of NLR has been recognized in patients with ischemic heart disease and AMI [13, 17]. Previous studies have shown that in decompensated HF patients, a high NLR is associated with increased long-term mortality risk [15, 16]. Uthamalingam et al. expressed in their study that high NLR (above median 9.6) was more valuable than the WBC count in predicting poor outcomes in HF [15]. Thus far, no generally accepted cut-off point has been identified to define critical NLR levels. In most acute CV diseases, the median values for the highest tertile of the NLR rate ranged between 1 and 10 [13, 15, 16]. In the study of Wasilewski et al. the 12-month mortality in patients in the NLR > 3.1 tertile was 3 times higher compared to the first tertile (< 2.1) and NLR was defined as an independent mortality factor [13]. In our study, the NLR cut-off point was above 3.7 and it was identified that above these values, the 12-month mortality rate was 3.39 times higher. Again, as a subpopulation of WBC, quickly and easily obtained IG has been used as a marker of inflammation,however, it is thought to be more important in local infections, sepsis, and septic shock [21, 27]. It has been reported that there is a strong relationship between the delta neutrophil index that reflects the number of IG in the circulation and the severity of diseases and increased mortality in patients with sterile inflammation such as AMI, pulmonary embolism, out-of-hospital cardiac arrest and upper gastrointestinal bleeding [27–30]. In these studies, it has been stated that IG can predict the severity and the mortality risk for diseases associated with severe inflammation reflecting increased pro-inflammatory cytokines and other mediators. As far as we know, this study of ours is the first to identify that the number of circulating IG can be used for the 1-year mortality risk in HF patients.

It has been defined that hs-CRP is of high value in predicting short- and long-term mortality after AMI and in patients with stable coronary heart disease (CHD) [11]. It was shown that hs-CRP > 0.77 mg/dl and NT-proBNP > 4.638 pg/mL at the admission in chronic stable HF patients are prognostic markers for 12-month mortality in the study by Park et al. [9]. Higher mortality risk was identified after a 120-day long-term follow-up of high CRP levels (2.9 to 10 mg/L) on the admission by Minami et al. [14], and after a 1-year follow-up of patients with CRP levels of > 10 mg/L on the admission by Siiril € a-Waris ve ark.[2]. To predict a more negative outcome, the best cut-off value for hs-CRP is once again heterogeneous and this could partially be associated with varying severity of HF among study populations [11]. In a previous study, it was discovered that moderately high CRP levels (> 3.23 mg/L) were associated with more severe HF features and long-term morbidity and mortality [31]. Therefore, CRP levels of approximately > 3 mg/L may reflect a chronic systemic inflammatory condition and could indicate a longer higher risk in patients with HF [12]. The cut-off value for CRP levels in our study was higher than 3 mg/L, which is recommended for the general population and stable CHD patients [9, 18]. However, it was compatible

with the CRP levels of > 9 mg/L defined for HF patients in previous studies [2, 14, 19]. Most studies show that the hospital re-visit and death risk was nearly 2 times higher in chronic HF patients with higher hs-CRP levels [2, 9]. Our study showed that when the hs-CRP cut-off value was higher than > 9.9 mg/L the death risk was nearly 4.2 times higher in HF patients. Must studies have shown that high NLR and hs-CRP levels are prognostic markers for mortality independent of LVEF, etiology of HF, blood pressure, kidney functions, and other hemodynamic variables [9, 11, 15, 16].

Conclusion

As a result, it has been shown that having presented to the ED within the last 6 months due to worsening HF in chronic HF patients was associated with hospital admission and death. In patients with chronic HF, increased levels of inflammatory markers such as NLR, IG%, and CRP are associated with higher 1-year mortality risk.

Limitations

The fact that our study was single-centered that our number of patients was low and that the data had been analyzed retrospectively is our main limitation. In addition, we only assessed inflammatory markers on presentation and did not include the follow-up inflammatory marker levels; therefore, it has not been possible to assess their changes over time and the effects of these changes on the outcomes of HF.

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Compliance with Ethical Standards

Conflict of interest All authors declares that they have no conflicts of interest.

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