ORIGINAL ARTICLE

Usefulness of Interleukin-6 and High-sensitivity C-reactive Protein as Prognostic Markers in Outpatients with Heart Failure and Reduced Ejection Fraction

Utilidad de la interleucina-6 y de la proteína C reactiva ultrasensible como marcadores pronósticos en pacientes ambulatorios con insuficiencia cardíaca y fracción de eyección reducida

DANIEL A. CHIRINO NAVARTA[1], GRACIELA TREJO[1], MARIELA S. LEONARDI[1], MARÍA P. FOSSATI[2], MIRTA GURFINKEL[2], FRANCISCO TELLECHEA[1], MARÍA L. RODRÍGUEZ VÁZQUEZ[1], CLAUDIO DIZEO[1*]

ABSTRACT

Background: The aim of this study was to assess whether interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) associated with B-type natriuretic peptide (BNP) are independent markers of adverse events in outpatients with heart failure and reduced ejection fraction (HFrEF).
Methods: Patients older than 65 years of age with HFrEF who were followed-up on an outpatient basis were prospectively included. Baseline BNP, IL-6 and hsCRP levels were assessed. Patients with HF after recent myocardial infarction (<6 months), and recent hospitalization (<3 months) due to a condition that could increase inflammatory markers were excluded from the analysis. The composite endpoint was all-cause mortality and hospitalization for decompensated heart failure (DHF).
Results: A total of 130 patients aged 75 ± 5 years and with EF of 33 ± 11% were included in the study. The composite endpoint was observed in 31.5% (n=41) of patients during a follow-up period of 450 ± 210 days. In the multivariate analysis, elevated BNP (>442 pg/ml) and elevated IL-6 (>7.2 pg/ml) were independent predictors of the primary endpoint [HR 2.60 (95% CI 1.14-5.9), p=0.02 and HR 2.49 (95% CI 1.08-5.7), p=0.03, respectively], but not hsCRP >6.9 mg/l, p=0.2. IL-6 presented an area under the ROC curve (AUC) of 0.70, BNP 0.73 and hsPCR 0.63, without significant differences between them.
Conclusions: BNP and IL-6 were independent markers of the composite endpoint, but not CRP. The discrimination ability of IL-6 and BNP was moderate.

Key words: Heart failure - Biomarkers - Interleukin-6 - C-Reactive Protein – Prognosis

RESUMEN

Objetivo: Evaluar si la interleucina-6 (IL-6) y la proteína C reactiva ultrasensible (PCRus) asociadas al péptido natriurético tipo B (BNP) son marcadores independientes de eventos en pacientes ambulatorios con insuficiencia cardíaca con fracción de eyección reducida (IC-FEr).
Materiales y Métodos: Se incluyeron en forma prospectiva pacientes mayores de 65 años con IC-FEr controlados en forma ambulatoria. Se realizó la medición basal del BNP, la IL-6 y la PCRus. Se excluyeron los pacientes con IC posinfarto de miocardio reciente (<6 meses), con internación reciente (<3 meses) por un cuadro que pudiera aumentar los marcadores inflamatorios. Se consideró el punto final combinado de mortalidad de cualquier causa e internación por insuficiencia cardíaca descompensada (ICD).
Resultados: Se incluyeron 130 pacientes de 75 ± 5 años, con FE de 33 ± 11%. Con un seguimiento de 450 ± 210 días, el punto combinado se observó en el 31,5% (n = 41). En el análisis multivariado, el BNP elevado (>442 pg/ml) y la IL-6 elevada (>7,2 pg/ml) fueron predictores independientes del punto primario (HR 2,60 (IC95%: 1,14-5,9), p = 0,02 y HR 2,49 (IC95%: 1,08-5,7), p = 0,03, respectivamente), no así la PCRus (>6,9 mg/l), con p = 0,2. La IL-6 presentó un área bajo la curva (AUC) de 0,70, el BNP, de 0,73 y la PCRus de 0,63, sin diferencias significativas entre las curvas.
Conclusiones: El BNP y la IL-6 fueron marcadores independientes del punto combinado, no así la PCRus. La capacidad de discriminación de la IL-6 y el BNP fue moderada.

Palabras clave: Insuficiencia cardíaca - Biomarcadores - Interleucina-6 – Proteína C reactiva - Pronóstico

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Address for reprints: Daniel A. Chirino Navarta - La Rioja 951 - CP 1221 CABA - E-mail: daniel.chirino@hotmail.com

[1] Cardiology Service, Hospital César Milstein, Buenos Aires, Argentina
[2] Laboratory Service, Hospital César Milstein, Buenos Aires, Argentina

INTRODUCTION

The prevalence of chronic heart failure (CHF) has increased in recent decades, and despite advances in treatment strategies it continues to have high morbidity and mortality. (1, 2) Chronic heart failure is known to be a complex syndrome that involves not only the cardiovascular system but also the renal, neuroendocrine and immune systems. (3) Although neurohormonal activation is the main pathophysiological mechanism (3, 4), it has been shown that significant inflammatory activation occurs in CHF, also contributing to disease progression. (5)

Elevation of numerous inflammatory markers in heart failure (HF) have been associated with the severity of the disease and worse prognosis (6). Interleukin 6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) are known proinflammatory markers that have been studied in HF. The former is a cytokine with proinflammatory and vasoconstrictive properties (6) that has been associated with poorer prognosis in both acute HF (7) and CHF, (8) while high-sensitivity C-reactive protein is one of the most studied inflammatory markers in numerous cardiovascular diseases, and in HF is associated with worse prognosis (9).

On the other hand, B-type natriuretic peptide (BNP) and its amino-terminal fraction (NT-proBNP) are the most studied biomarkers and their use for diagnostic confirmation, evaluation and management of HF is recommended in different treatment guidelines. (10, 11) However, these different biomarkers are an expression of diverse altered pathophysiological mechanisms involved in HF, so it has been suggested that the strategy of combining biomarkers may improve the prognostic stratification in HF. (12)

The objective of the present study was to evaluate whether IL-6 and hsCRP associated with BNP are independent markers of global mortality and hospitalization for decompensated HF (DHF) in outpatients with HFrEF.

METHODS

Patients referred to the HF program of an institution that exclusively cares for elderly patients were prospectively included between July 2016 and July 2017. The inclusion criteria were patients with HF in functional class II-III of the New York Heart Association (NYHA) and with left ventricular ejection fraction (LVEF) ≤40% (measured by Simpson's biplane method). Patients with HF after recent myocardial infarction (<6 months) and those with recent hospitalization (<3 months) due to a condition that could have increased inflammatory markers, such as infectious processes, acute coronary syndrome, bleeding, HF and patients with active malignancies were excluded from the analysis.

Anamnesis of all the patients was carried out in order to obtain their medical history and cardiovascular risk factors, and they all underwent physical examination during the first visit to record systolic (SBP) and diastolic blood pressure (DBP), heart rate (HR) and the presence of signs of congestion. The echocardiogram was performed with an Acuson Sequoia c512 ultrasound machine (Siemens), in the institution's echocardiography service. All patients underwent laboratory analysis assessing BNP, IL-6, and hsCRP within 15 days of the first consultation.

Follow-up was carried out through periodic clinical check-ups corresponding to the hospital's HF program. The frequency of these controls was established in each patient according to the criteria of the treating medical team. In addition, telephone follow-up was performed in case of not attending the scheduled controls.

The primary endpoint was all-cause mortality and hospitalization for DHF. The discharge report was requested from all the patients who were hospitalized in order to assign the event as hospitalization for DHF.

Laboratory analyses

The analyses were carried out in the institution's central laboratory in accordance with the following protocol: first, blood was withdrawn by venipuncture and the sample was separated into two 10 ml tubes, one with EDTA and one for serum. The tubes were subsequently centrifuged for 10 minutes at 3,000 revolutions per second. Brain natriuretic peptide was immediately processed on an ADVIA Centaur CP (Siemens) immunoassay system. The serum tube was subdivided into two aliquots of 2 ml each and stored in a freezer at -20° C until processing. Both IL-6 and hsCRP were processed in batches every 2 months, using an IMMULITE 1000 system (Siemens).

All essays were run with their respective high and low controls.

Statistical analysis

Continuous variables are expressed as mean±standard deviation and categorical variables as percentage. To compare between groups with and without events, Student's t test was used for continuous variables if the distribution was normal, or the Wilcoxon test in case of non-normal distribution. Categorical variables were compared using the chi-square test and Fisher's exact test if any of the variables had a frequency <5.

First, univariate analysis for the composite endpoint was performed using Cox regression analysis including IL-6 and hsCRP, as well as for known prognostic variables such as age, LVEF, kidney function (serum creatinine), serum sodium, SBP, and BNP. These variables were analyzed as continuous variables and in the case of IL-6, hsCRP and BNP, they were also dichotomized using the cutoff points obtained through the analysis of the ROC curve. Subsequently, a multivariate model was built with the proportional hazzard regression method using IL-6, hsCRP and BNP as continuous and then dichotomized variables, adding the variables that were significant in the univariate analysis. In addition, survival was analyzed with the Kaplan-Meier method, using dichotomized BNP, IL-6 and hsCRP variables.

To establish the discrimination power of the different markers, ROC curves were built and the area under the curve (AUC) was calculated, comparing the different AUCs with the Hanley-Mc Neil test. A p value <0.05 was considered significant. Epi-info 7 and Statistix 8 softwares were used for the general analysis. To build and compare ROC curves, the Epidat 3.1 program was used.

Ethical considerations

The protocol was approved by the institutional ethics committee and the patients signed an informed consent.

RESULTS

Among a total of 240 treated patients, 180 presented the inclusion criteria, and both biomarkers (IL-6 and hsCRP) were obtained in 130 patients. Mean age was 75±5 years, 43% were female, 30% diabetic, 77% hypertensive, and mean EF was 33±11%. In 45% of cases, patients had a history of atrial fibrillation (AF), 27% had previous infarction and 20% chronic kidney failure. The most frequent etiology was ischemic-necrotic (45%), and 9% had chagasic etiology. Table 1 shows baseline population characteristics.

Median follow-up was 443 days (interquartile range 234-659) and the composite endpoint was found in 31.5% of cases (41 patients), with an overall mortality of 10.7% (14 patients). The group with event presented higher BNP [799 (197-1576) vs. 380 (170-789) pg/ml, p <0.001], higher IL-6 [10.2 (5.6-19.5) vs. 4.9 (3.3-9.7) pg/ml, p <0.001] and higher hsCRP [8.2 (3.9-15.8) vs. 4.1 (2.0-8.0) mg/l, p=0.01]. The cutoff points found were: >442 pg/ml for BNP (elevated BNP), >7.2 pg/ml for IL-6 (elevated IL-6) and >6.9 mg/l for hsCRP (elevated CRP); 53.1% of patients (n=69) had elevated BNP, 44.6% (n=80) elevated IL-6, and 40.8% (n=87) elevated CRP.

In the univariate analysis, the following variables presented a significant association with the compos-

Table 1. Baseline characteristics

	With Event (n=41)	Without event (n=89)	p
Age (years, mean±SD)	75 ± 8	75± 7	0.58
Women–n(%)	20 (48)	36 (41)	0.23
History: n(%)			
HT	30 (73)	71 (80)	0.40
DSP	14 (34)	26 (29)	0.21
DBT	8 (19)	27 (30)	0.15
Smoking	2 (5)	9 (10)	0.22
Chronic AF	17 (41)	27 (30)	0.34
Ischemic etiology	19 (46)	40 (45)	0.12
CKF	12 (29)	14 (16)	0.07
COPD	5 (4)	7 (8)	0.42
LVEF (%, mean±SD)	32 ±10	34 ± 11	0.25
SBP (mmHg, mean±SD)	110 ± 14	113 ± 15	0.27
General laboratory (mean±SD)			
Ht (%)	39 ± 4	39 ±5	0.8
Hb (mg/dl)	13.1 ± 0.17	13.0 ± 0.2	0.7
WBC count. (count/µl)	6,797 ± 2,100	7,025 ± 1,839	0.5
Urea (mg/dl)	66 ± 45	60 ± 26	0.36
Creatinine (mg/dl)	1.52 ± 1.0	1.25 ± 0.45	0.18
Na (mEq/l)	137 ±3	138 ± 3	0.1
IL-6 (pg/ml)*	10.2 (5.6-19.5)	4.9 (3.3-9.7)	<0.001
hsCRP (mg/l)*	8.2 (3.9-15.8)	4.1 (2.0-8.0)	0.01
BNP (pg/ml)*	799 (197-1576)	380 (170-789)	<0.001
Dichotomized (n %)			
IL-6 >7.2 pg/ml	28 (68)	30 (34)	<0.001
hsCRP >6.9 mg/l	24 (58)	29 (33)	0.005
BNP >442 pg/ml	32 (78)	37 (42)	<0.001
Treatment n (%)			
ACEI	27 (66)	48 (54)	0.2
ARB	4 (9)	18 (20)	0.13
ANRI	3 (7)	12 (13)	0.30
BB	34 (83)	80 (91)	0.26
MRA	28 (68)	68 (77)	0.32
Furosemide	39 (95)	77 (87)	0.43
Ivabradine	5 (12)	13 (14)	0.37

HT: Hypertension. DSP: Dyslipidemia. DBT: Diabetes mellitus. Chronic AF: Chronic atrial fibrillation. CKF: Chronic kidney failure. COPD: Chronic obstructive pulmonary diseases. LVEF: Left ventricular ejection fraction. SBP: Systolic blood pressure. Ht: Hematocrit. HB: Hemoglobin. WBC count: White blood cell count. Na: Serum sodium. IL-6: Interleukin-6. hsCRP: High-sensitivity C-reactive protein. BNP: B-type natriuretic peptide. ACEI: Angiotensin-converting enzyme inhibitors. ARB: Angiotensin II receptor inhibitors. ANRI: Angiotensin and neprilysin receptor inhibitor. BB: Beta-blockers. MRA: Mineralocorticoid receptor antagonists. * Median (interquartile range).

ite endpoint: SBP [HR 0.96 (95% CI 0.94-0.99), p = 0.006], IL-6, and BNP, both as continuous [HR 1.04 (95% CI 1.02-1.05), p <0.001 and HR 1.008 (95% CI 1.005-1.01), p <0.001, respectively] and as dichotomized variables: elevated IL-6 [HR 4.82 (95% CI 3.9-8.7), p <0.001], elevated BNP [HR 4.29 (95% CI 3.5-8.3), p <0.001] and elevated CRP [HR 2.02 (95% CI 1.04-3.97), p = 0.03] (Table 2).

In the multivariate analysis, IL-6 [HR 1.04 (95% CI 1.01-1.06), p = 0.003], elevated IL-6 [HR 2.49 (95% CI 1.08-5.7), p=0.03], BNP [HR 1.008 (95% CI 1.005-1.01), p<0.0001] and elevated BNP [HR 2.60 (95% CI 1.14-5.9), p=0.02] were independent predictors of the composite endpoint (Table 3). The elevation of both markers (elevated BNP and elevated IL-6) resulted in a HR of 5.08 (95% CI 1.82-8.91), p<0.001.

The analysis of discrimination power showed that IL-6 presented an AUC of 0.70 (95% CI 0.62-0.77), BNP of 0.73 (95% CI 0.64-0.80) and hsCRP of 0.63 (95% CI 0.58-0.71). When comparing the curves, no significant differences were found (BNP vs. IL-6, p=0.54; BNP vs. hsCRP p=0.15; IL-6 vs. hsCRP p=0.20) Figure 1). Figure 2 shows the Kaplan-Meier curves with the dichotomized variables.

DISCUSSION

In the present work we evaluated the usefulness of IL-6 and hsCRP as event predictors in outpatients with HFrEF. We found that IL-6 was an independent predictor of overall death and hospitalization for DHF in stable patients with HRrEF, whereas hsCRP was not. Patients with IL-6 >7.2 pg/ml had more than 2-fold risk of events than those with lower IL-6. This result was obtained by adjusting with BNP, hsCRP and SBP values. IL-6 and BNP presented a moderate discrimination capacity (AUC 0.70 and 0.73, respectively), while, in the case of hsCRP, this capacity was poorer (AUC 0.63).

In HF there is an important activation of the immune system, mainly expressed by the increase in numerous pro-inflammatory cytokines. This immune response is produced by various mechanisms. Increased activation of T lymphocytes has been documented in patients with HF, (13) and it is postulated that cardiomyocytes and endothelial cells also contribute to the secretion of cytokines, largely in response to elevated catecholamines, myocardial injury (5) and peripheral hypoperfusion. (14) Increased levels of various cytokines such as tumor necrosis factor alpha (TNF α), IL-6, and hsCRP have been associated with worse ventricular function (15, 16) and adverse events. (14, 15, 17)

IL-6 is secreted by endothelial cells, macrophages, lymphocytes, and adipocytes, among others. Its action is mediated by a soluble receptor to next bind to a cell membrane glycoprotein. It stimulates the differentiation of B and T lymphocytes, the liver secretion of acute phase reactants (6) and it is involved in remodeling and ventricular dysfunction. (5) It has also been observed that IL-6 levels correlate with procoagulant factors, such as the tissue and von Willebrand factors in acute (7) and stable HF patients. (18) Anti-inflam-

Table 2. Univariate analysis for the composite endpoint.

Variable	HR	95% CI	p
Age	0.98	0.94 – 1.03	0.2
SBP	0.96	0.94-0.99	0.006
LVEF	0.98	0.93-1.08	0.23
Serum Na	0.94	0.83-1.01	0.07
WBC count	1.00	0.92-1.05	0.21
IL-6	1.04	1.02-1.05	<0.001
IL-6 >7.2 pg/ml	4.82	3.9-8.7	<0.001
BNP	1.008	1.005-1.01	<0.001
BNP >442 pg/ml	4.29	3.5-8.3	<0.001
hsCRP	1.01	0.99-1,03	0.7
hsCRP >6.9 mg/l	2.02	1.04-4.41	0.03

Abbreviations as in Table 1.

Table 3. Multivariate analysis by proportional hazzard regression method using IL-6, BNP and hsCRP as continuous and dichotomized variables

	Continuouss			Dichotomized (*)		
Variable	HR	95% CI	p	HR	95% CI	p
IL-6	1.04	1.01-1.06	0.003	2.49	1.08-5.7	0.03
hsCRP	1.00	0.98-1.02	0.3	1.21	0.78-1,56	0.2
BNP	1.0008	1.0005-1.001	<0.001	2.60	1.14-5.9	0.02
SBP	0.98	0.95-1.00	0.2	0.97	0.94-1.02	0.9

Abbreviations as in Table 1. *IL-6 >7.2 pg/ml (elevated IL-6), hsCRP >6.9 mg/l (elevated hsCRP), BNP > 442 pg/ml (elevated BNP).

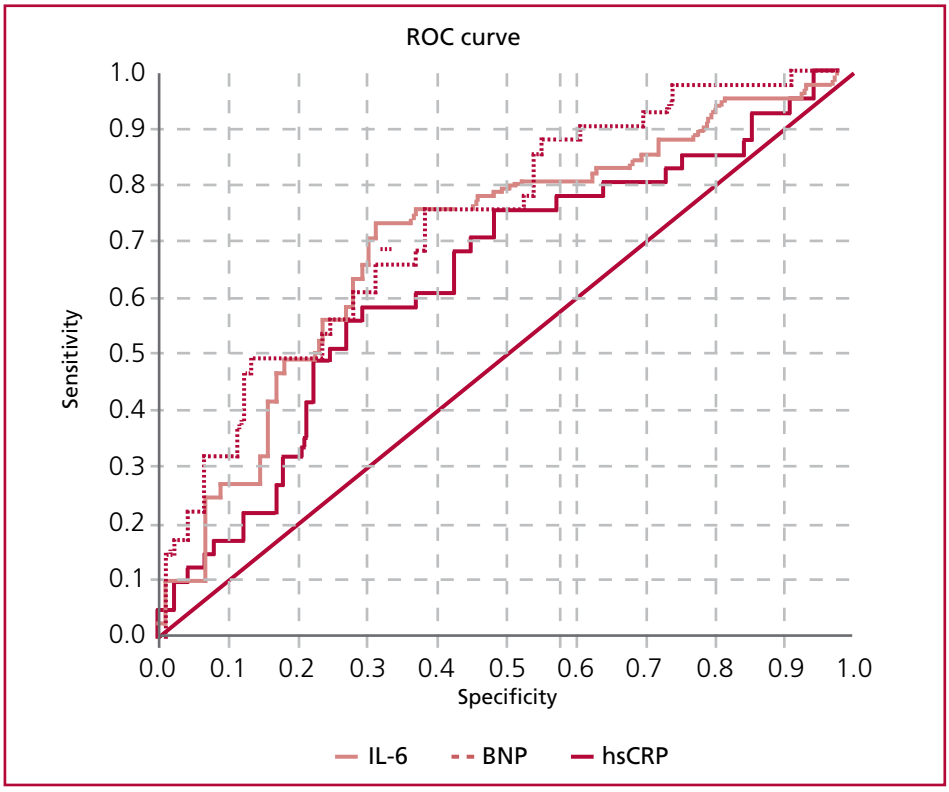

Fig. 1. ROC curves of BNP, IL-6 and hsCRP for the composite endpoint.

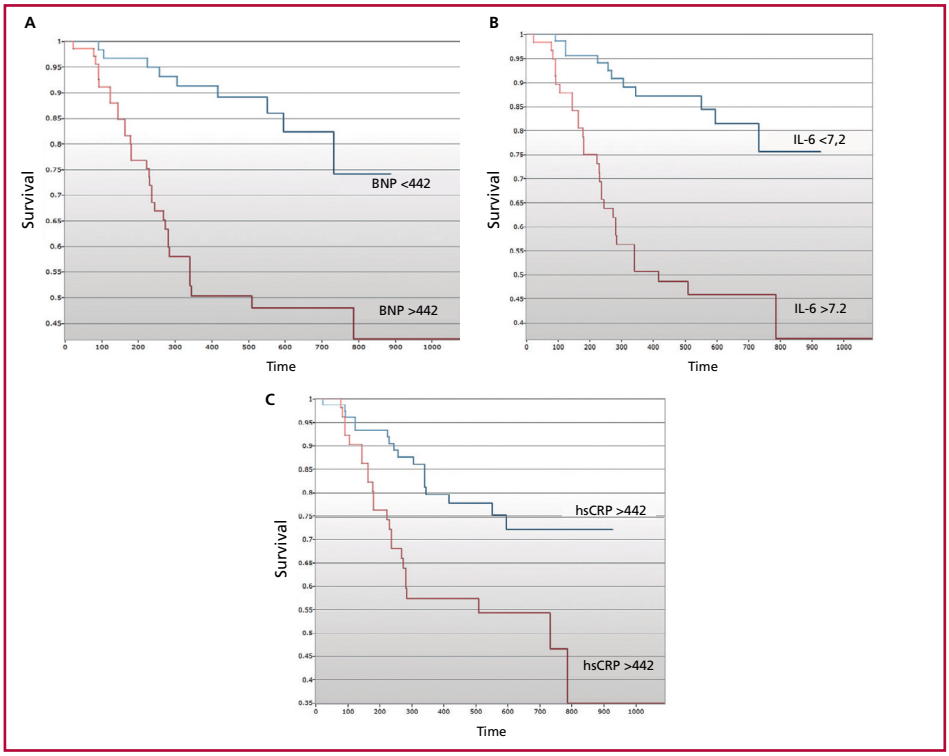

Fig. 2. Kaplan-Meier curves for the composite endpoint. A) BNP >442 pg/ml; B) IL-6 >7.2 pg/ml and C) hsCRP >6.9 mg/l.
A: BNP – Composite endpoint. B: IL-6 – Composite endpoint. C: hsCRP – Composite endpoint

matory and anti-apoptotic effects of IL-6 have also been described, so it is believed to be a modulator of the immune response. (6)

As early as the 1990s, Tsutamoto et al. (14) evaluated serum levels of IL-6, atrial natriuretic peptide, and epinephrine in 100 patients with HF and moderate and severe ventricular function and found that IL-6 was an independent predictor of 6-month mortality. Later, other studies reported similar results when evaluating IL-6 along with other inflammatory markers and natriuretic peptides, both in patients with progressive (19) and stable HF. (8) Small studies

have also been published where IL-6 has not been an independent predictor of mortality, after adjusting for BNP (20) or other inflammatory markers. (17) Finally, the results of the BIOSTAT-CHF (21), a multicenter European registry of more than 2,500 patients, of which 89% had HFrEF, were recently published. It is the largest study where the role of IL-6 as a prognostic marker of HF has been evaluated. After adjusting for NT-proBNP, inflammatory markers such as TNF receptor 2), IL-1 receptor type 1/2 and the BIOSTAT-CHF risk score, IL-6 was an independent predictor of both the composite endpoint of mortality and all-cause hospitalization and overall mortality after a 2-year follow-up period. IL-6 improved the BIOSTAT-CHF risk model adjust, but did not increase the discrimination capacity.

The mentioned risk model includes NT-proBNP among other clinical and laboratory variables (22). In our work, the elevation of BNP >442 pg/ml and IL-6 >7.2 pg/ml almost doubled the risk for the composite endpoint, compared with each isolated condition.

C-reactive protein is synthesized by hepatocytes in response to various cytokines, mainly IL-6, which is considered an important inflammation marker. (5, 23) Several studies have shown that hsCRP is an important predictor of cardiovascular events such as myocardial infarction, stroke, peripheral vascular disease and cardiovascular mortality. (24, 25) A subanalysis of the Val-HeFT study (26), including 4,200 patients with HFrEF, showed that hsCRP behaved as an independent marker of overall mortality and of the composite endpoint of cardiovascular morbidity and DHF hospitalization. Some studies have found that hsCRP is a prognostic marker in patients with HF of ischemic-necrotic origin, but not in patients of non-ischemic etiology. (27, 28)

In our work, hsCRP was not an independent predictor of the composite endpoint. In the univariate analysis, hsCRP was not prognostic as a continuous variable, whereas dichotomizing it by the cut-off value (hsCRP >6.9 mg/l), it was associated with the composite endpoint. However, in the multivariate analysis, hsCRP was canceled by IL-6 and BNP. In this sense, although in a previous work Windram et al. (29) found that high levels of hsCRP were associated with mortality, when compared with NT-proBNP, the latter was a much stronger predictor (AUC 0.74 vs. 0.67). Moreover, in our study, the proportion of HF of ischemic origin was 45%, whereas in the Val-HeFT study it exceeded 60%.

Apparently, hsCRP seems to be more effective as a predictor in patients with HF and coronary heart disease. Most of our patients presented HF of non-ischemic origin, which could partially explain the low predictive value of this inflammatory marker in our population. On the other hand, in the aforementioned studies, hsCRP was not compared with IL-6. It is known that IL-6 stimulates the production of CRP in the liver and that, at the same time, it stimulates the secretion of IL-6 by a positive feedback mechanism. It has also been postulated that IL-6 mediates the actions of CRP. (6) This close pathophysiological relationship between the two markers could explain that, when evaluating the prognostic role of event occurrence, one of the markers (in our case IL-6) may cancel out the other in the multivariate analysis.

Limitations

Our work has the following limitations. It is a single center study, which exclusively cares for elderly patients (it is a specific PAMI subsidiary). Therefore, it is not representative of the entire spectrum of patients with HF. Moreover, it is a study of small dimensions, mainly due to the difficulty of accessing inflammatory biomarkers. This weakness was partially compensated by performing the multivariate analysis only with the variables that were significant in the univariate analysis, leaving 4 variables (BNP, IL-6, hsPCR and SBP) for 41 events.

CONCLUSIONS

In our outpatient population of HFrEF, BNP and IL-6 were independent markers of overall mortality and hospitalization for DHF. High sensitivity CRP was not a predictor of the composite endpoint. The discrimination ability of IL-6 and BNP was moderate.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material)

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