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Diagnostic and prognostic significance of alpha-defensin in patients with chronic heart failure during 2-year follow-up

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Abstract

Background

Defensins play an important role in the processes associated with innate immunity. Their growth is observed in sites of intense inflammation, but also in less severe inflammation. Evaluation of alpha-defensin levels in patients with chronic heart failure (CHF) and its possible association with a long-term prognosis may be an interesting supplement to knowledge about the state of the immune system in heart failure.

The aim of the study was to compare the plasma concentration of alpha-defensin between the patients with chronic heart failure with impaired ventricular ejection fraction (LVEF) <45% and the control group, as well as to evaluate the prognostic value of alpha-defensin as a possible predictor of death during a 24-month observation period.

Methods

The study included 52 hospitalized patients with a primary diagnosis of CHF and LVEF <45%. 20 patients exhibited features of CHF exacerbation, the remaining 32 were hospitalized on schedule. The control group consisted of 28 healthy volunteers. The observation was conducted by telephone for 2 years. The end point of the study was death for all reasons.

Results

Patients with CHF had significantly higher levels of alpha-defensin than control subjects. Similarly, plasma hs-CRP levels were significantly higher in the study group than in the control group, although in both groups the median hs-CRP did not exceed 5 mg / L. It has not been shown that exacerbation has an effect on alpha-defensin concentration. During the two-year follow-up, statistically significant effects on the endpoint of the following parameters were observed: EF ($p = 0.035$, HR = 0.917), hs-CRP ($p = 0.036$; HR = 1.046) and NT-proBNP ($p < 0.001$, HR = 1.000078). ROC analysis showed that during both a 12-month (AUC = 0.333, $p = 0.116$) as well as a 24 month (AUC = 0.447, $p = 0.616$) observation period plasma concentration of alpha-defensin was not a good predictor of death in CHF patients.

Conclusions

Higher levels of alpha-defensin in patients with CHF confirm subclinical inflammatory activation in this population. However, this marker does not have predictive value for predicting death in the medium-term observation.

Key words: alpha-defensin, chronic heart failure.

Background

The price of the success of modern cardiology in the field of treatment of coronary heart disease is steadily increasing incidence of heart failure. Rapid and accurate diagnosis of patients with chronic heart failure (CHF) is extremely important both in clinical and economic terms. Finding new useful biomarkers in the diagnosis and risk stratification of patients with heart failure is, therefore, a matter of utmost importance.

Chronic heart failure (CHF) is a disease in which irrespective of etiology, proinflammatory activation is associated with chronic tissue ischemia, oxidative stress, and stimulation of hormonal compensatory mechanisms (adrenergic, RAA). Inflammation of minor severity is inherently accompanied by heart failure and, just as in ischemic heart disease, diabetes or renal failure, its intensity (measured most often by plasma c-reactive protein levels) is an important deterioration factor. The position of the C-reactive protein in cardiology indicates the potential associated with the assessment of inflammation in cardiovascular diseases, particularly in chronic heart failure [1-4].

Defensins are substances that play an important role in the processes associated with congenital resistance, their growth is observed in places of intense inflammation but also in less severe inflammatory conditions. Evaluation of alpha-defensin levels in patients with CHF and its possible association with long-term prognosis may be an interesting addition to the knowledge about the condition of the immune system in HF, and at the same time may become a valuable part of the treatment of these patients.

The aim of the study was to compare the plasma concentration of alpha-defensin between the population of CHF patients with impaired left ventricular ejection fraction and the control group, and to evaluate the prognostic value of alpha-defensin as a possible predictor of death during a 24-month observation period.

Methods

The study group consisted of 52 Caucasian patients hospitalized in the II Clinic of Cardiology CM UMK with diagnosed CHF NYHA classes II-IV (20 patients) or for planned medical procedures (32 patients). All patients received optimal pharmacological treatment in accordance with the guidelines of the European Society of Cardiology. The inclusion criteria in the study included: age over 18 years, HF with impaired left ventricular ejection fraction (LVEF) <45% assessed during current hospitalization or up to 6 months earlier. The exclusion criteria in the study were: acute coronary syndrome, acute heart failure, severe renal impairment (GFR <30ml / min), active tumor disease, active infection, fever of unknown etiology, autoimmune disease, corticosteroid therapy, decompensated diabetes requiring intravenous infusion of insulin, chronic obstructive pulmonary disease, substitution therapy with iron preparations and chronic inflammatory bowel disease.

On admission to hospital all patients in the study group received peripheral blood morphology, creatinine concentration, ion concentration, iron concentration, LDL, HDL, plasma concentration of high-sensitivity C-reactive protein with turbidimetry method (hs-CRP), plasma Ferritin concentration and plasma concentration of natriuretic N-terminal natriuretic propeptide (NT-proBNP). In addition, a blood sample was also collected from each patient, which was then stored at -80 ° C until the alpha-defensin concentration was determined, within a period not exceeding 3 months. A commercially available ELISA kit (USCN Life Science, code no. SEB 705Hu) was used to determine the plasma level of alfa-defensin. The observation was conducted by telephone - every 3 months since the inclusion in the study telephone contact took place, during which the appearance of the endpoint was evaluated. The endpoint of the study was death for all causes in a 24-month follow-up. The control group consisted of 28 healthy volunteers.

The results were analyzed using Statistica ver. 12. The probability of $p < 0.05$ was statistically significant. The normality of the analyzed parameters was checked with the Shapiro-Wilk test. In the absence of normal distributions, nonparametric analyzes were performed. Plasma concentration of alpha-defensin, Hs-CRP, ferritin, NT-proBNP, troponin T heart (TnT), iron, hemoglobin (Hb), HDL, LDL, BMI, LVEF were compared in total and depending on the occurrence of death in the-24 month observation using the Mann-Whitney test. NYHA class, sex, age, diabetes, GFR and etiology were compared using the χ 2 and χ 2 tests with the Yates correction. Evaluation of the diagnostic power of the alpha-defensin test in predicting death during a 24-month follow-up was based on ROC (ROC) analysis. Analysis of correlation between alpha-defensin, hs-CRP, ferritin, NT-proBNP, TnT, Hb, class NYHA and EF was performed to estimate Spearman rank correlation coefficients. A comparison of individual parameters between the study and the control group as well as between the patients with exacerbation of CHF and stable patients was performed with the Mann-Whitney test. The relative risk (HR) of the markers was calculated on the basis of univariate and multivariate COX regression. The comparison of plasma concentration of alpha-defensin between patients classified in NYHA class II and patients classified in NYHA class III or IV was performed using the Mann-Whitney test.

Results

The study included 52 patients with CHF with impaired LVEF whose mean age was 60 ± 13 years; male accounted for 86.5% of all patients; 32 patients were in stable clinical

condition; CHF exacerbation syndromes occurred in 20 patients. The clinical and laboratory characteristics of the study group are shown in Table 1. During the two-year follow-up period, 14 patients (26.92%) died. Patients who died had significantly statistically lower LVEF and higher plasma concentrations of troponin T and NT-proBNP. The control group consisted of 28 healthy volunteers whose average age was 50 ± 7 years and male accounted for 39.3% of the volunteers.

Patients with CHF had significantly higher concentration of alpha-defensin than patients in the control group (Table 2). Similarly, the plasma level of hs-CRP was significantly higher in the study group than in the control group, although in both groups the median hs-CRP did not exceed 5 mg / l. In the study group between patients with exacerbation of CHF and clinically stable patients there was no significant difference in the alpha-defensin concentration and no difference in overall mortality during both one-year and the two-year follow-up (Table 3).

Table 1. Basic characteristics of the studied population, depending on the occurrence of the endpoint.

The variable	Total number (n=52)	Survial (n=38; 73,08%)	Death (n=14; 26,92%)	p
Age (years)*	59,81±12,72	58,71±13,14	62,79±11,42	0,6425
Men	86,54%	86,84%	85,71%	0,9158
Ischemic etiology	48,08%	52,63%	37,71	0,2788
BMI (kg/m2)*	28,36±5,22	28,28±5,45	28,57±4,74	0,7491
NYHA class II/III/IV	26,92%/61,54%/11,54%	34,21%/55,26%/10,53%	7,14%/78,57%/14,29%	0,1486
DM	38,46%	36,84%	42,86%	0,6925
EF (%)*	27,04±8,11	28,61±8,28	22,786±6,03	0,0273
GFR <60 / >60 (%)	44,23%/55,77%	36,84%/63,16%	64,29%/35,71%	07716
Hb (g/dl)**	14,15 (13,05-15,10)	14,20 (13,20-15,10)	13,92 (12,20-15,00)	0,6499
Fe (µg/dl)**	68,50 (53,00-91,50)	74,50 (54,00-96,00)	61,00 (46,00-76,00)	0,3121
Alfa-defensin (ng/ml)**	175,46 (159,62-187,54)	176,85 (164,34-186,32)	165,48 (135,90-190,76)	0,5705
hs-CRP (mg/L)**	4,08 (1,82-8,32)	3,67 (1,68-7,37)	6,02 (3,82-13,80)	0,0968
Ferritin(µg/dl)**	138,00 (86,50-224,00)	141,00 (88,00-223,00)	127,00 (78,00-241,00)	0,6499
TnT (µg/l) **	0,020 (0,014-0,036)	0,019 (0,013-0,030)	0,035 (0,020-0,048)	0,0137
NT-proBNP (pg/ml)**	1179 (697-4297)	1017 (566-2229)	4521,5 (1169-6702)	0,0006
LDL (mg/dl)**	101,5 (79-133,5)	101,5 (80-127)	111 (71-164)	0,5846
HDL (mg/dl)**	38 (30,5-48,5)	40,5 (34-47)	33 (28-51)	0,3919
ACEi	78,85%	78,95%	78,57%	>0,05
ARB	23,08%	21,05%	28,57%	>0,05
statin	86,54%	92,11%	71,43%	>0,05
beta-blocker	100%	100%	100%	>0,05
ASA	48,08%	50,00%	42,86%	>0,05
digoxin	32,69%	28,95%	42,86%	>0,05
spironolacton	75,00%	71,05%	85,71%	>0,05
eplerenon	19,23%	21,05%	14,29%	>0,05

The results were presented as:
* average ± standard deviation
** median (bottom quartile − upper quartile)

Table 2. Comparison of study group with control group.

Parameter	Study group (n=52)	Control group (n=28)	p
Age*	59,81±12,72	50,00±6,97	**<0,001**
Male	86,54%	39,29%	
BMI*	28,36±5,22	22,80±2,62	**<0,001**
Alfa-defensin (ng/ml)**	175,46 (159,62-187,54)	128,53 (111,68-150,83)	**0,0000**
Hb (g/dl)**	14,15 (13,05-15,10)	13,90 (13,00-15,15)	0,8401
Hs-CRP (mg/L)**	4,08 (1,82-8,33)	1,00 (0,60-1,50)	**<0,001**

The results were presented as:
* average ± standard deviation
** median (bottom quartile − upper quartile)

Table 3. Comparison of alpha-defensin concentration and overall mortality between patients with CHF exacerbation and clinically stable patients.

The variable	Total number (n=52)	Clinically stable patients (n=32; 61,5%)	Patients with CHF exacerbation (n=20; 38,5%)	p
Alfa-defensin (ng/ml)*	175 (160-188)	177 (165-188)	170 (131-188)	0,137
Mortality during 1-year follow-up	n=10 (19,23%)	n=4 (12,50%)	n=6 (30,00%)	0,120
Mortality during 2-year follow up	n=14 (26,92%)	n=8 (25,00%)	n=6 (30,00%)	0,581

The results were presented as:
* median (bottom quartile − upper quartile)
n − numbers of patients

Univariate Cox-propotional hazard analysis during the 1-year follow-up showed that only plasma concentration of NT-proBNP (p <0.001; HR = 1) significantly statistically affected the occurrence of the endpoint (Table 4), whereas during the 2-year follow-up statistically significant effects on the endpoint of the following parameters were observed: LVEF (p = 0.035; HR = 0.917), hs-CRP (p = 0.036; HR = 1.046) and NT-proBNP (p <0.001; HR = 1) (Table 5).

Table 4. Univariate Cox-propotional hazard analysis – 1-year follow-up; statistically significant correlations are presented in bold ($p < 0.05$).

-	p	HR	(-95%; 95% confidence interval for HR)
Age	0,115	0,185	(0,99; 1,10)
Sex	0,506	0,591	(0,13; 2,78)
BMI	0,845	1,012	(0,90; 1,14)
HF etiology	0,879	0,908	(0,26; 3,14)
Diabetes	0,879	0,608	(0,18; 2,10)
NYHA	0,432	0,608	(0,18; 2,10)
EF	0,092	0,921	(0,84; 1,01)
Hb	0,371	0,820	(0,53; 1,27)
Alfa-defensin	0,076	0,985	(0,97; 1,00)
NT-proBNP	**<0,001**	**1,00019**	**(1,000097; 1,000282)**
hs-CRP	0,417	1,026	(0,96; 1,09)
Ferritin	0,642	0,999	(0,995; 1,003)
TnT	0,185	1187,918	(0,03; 42226303)

Table 5. Univariate Cox-propotional hazard analysis – 2-year follow-up; statistically significant correlations are presented in bold ($p < 0.05$).

-	p	HR	(-95%; 95% confidence interval for HR)
Age	0,274	1,025	(0,98; 1,07)
Sex	0,861	0,875	(0,196; 3,91)
BMI	0,910	1,005	(0,91; 1,11)
HF etiology	0,358	1,670	(0,56; 4,99)
Diabetes	0,665	0,791	(0,27; 2,28)
NYHA	0,102	0,183	(0,02; 1,40)
EF	**0,035**	**0,917**	**(0,85; 0,99)**
Hb	0,215	0,764	(0,50; 1,17)
Alfa-defensin	0,242	0,991	(0,98;1,01)
NT-proBNP	**<0,001**	**1,000078**	**(1,000039; 1,000116)**
hs-CRP	**0,036**	**1,046**	**(1,003; 1,091)**
Ferritin	0,805	1,000	(0,998; 1,002)
TnT	0,181	1182,846	(0,037; 37912315)

In multivariate analysis, both the 1-year and the 2-year follow-up showed that NT-proBNP plasma concentration was the only independent statistically significant factor affecting mortality in the observed patient group (Table 6).

Table 6. Multivariate Cox-propotional hazard analysis – 1-year and 2-year follow-up ($p < 0,05$).

-	p	HR	(-95%; 95% confidene interval for HR)
NT-proBNP – 1-year follow-up	<0,001	1,000190	(1,000097; 1,000282)
NT-proBNP – two-year follow-up	<0,001	1,000077	(1,000038; 1,000115)

The ROC analysis showed that during the 12-month (AUC = 0.333; confidence interval (-95%; 95%) = 0.126-0.541; p = 0.116) and the 24-month (AUC=0,447; confidence interval (-95%; 95%) - 0.242-0.653; p = 0.616) follow-up plasma concentration of alfa-defensin did not appear to be a valuable prognostic factor for predicting death for all causes in patients with CHF.

The comparison of plasma alpha-defensin concentration between patients classified in NYHA class II as well as in NYHA class III or IV did not show statitically significant differences in alpha-defensin concentration between these patients (p = 0.34), as shown in Figure 1.

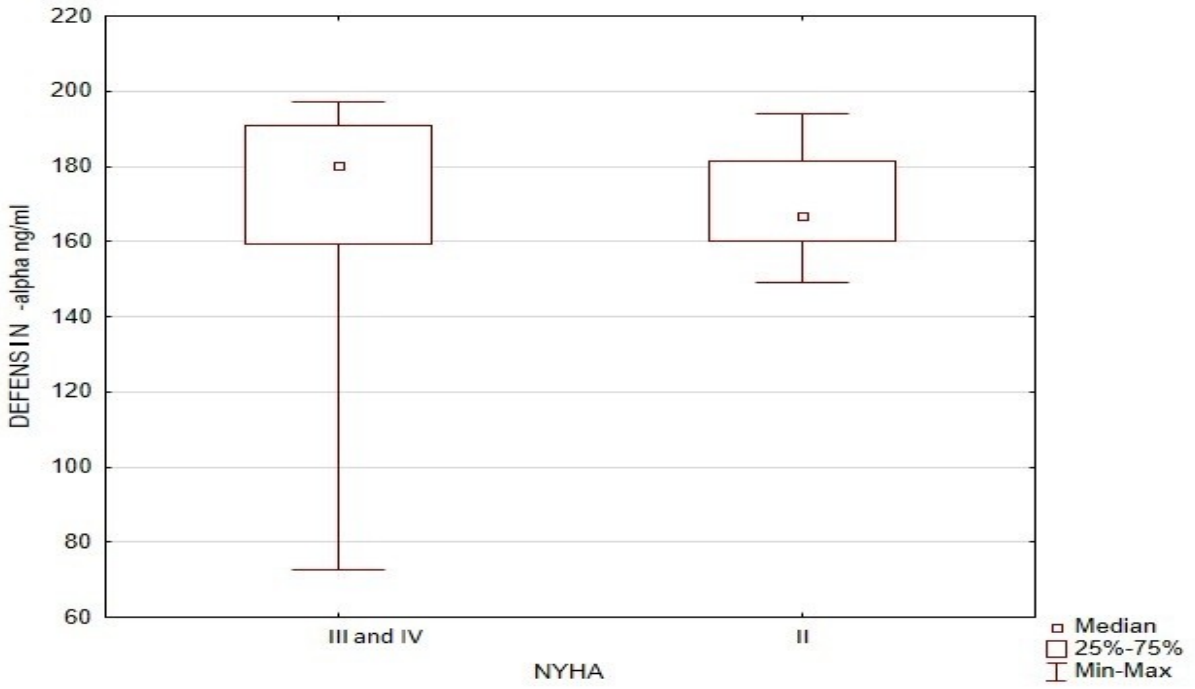

Figure 1. Plasma concentrations of alpha-defensin depending on NYHA class (p = 0.34). The comparison of plasma alpha-defensin concentration between patients classified in NYHA class II as well as in NYHA class III and IV.

In addition, a correlation analysis was performed between each of the prognostic markers, estimating Spearman`s rank correlation coefficients, as shown in Table 7.

Table 7. Spearman`s rank correlation between the prognostic markers. Statistically significant correlations are presented in bold ($p < 0.05$).

-	CRP	TnT	NT-proBNP	FERRYTYNA	Alfa-defensyna	Hb	EF	NYHA
CRP	1,000	**0,346**	**0,347**	-0,079	-0,258	-0,112	0,012	0,127
TnT	**0,346**	1,000	**0,464**	-0,148	-0,137	-0,099	-0,136	0,197
NT-proBNP	**0,347**	**0,464**	1,000	**-0,279**	-0,083	-0,144	**-0,430**	0,218
FERRYTIN	-0,079	-0,148	**-0,279**	1,000	-0,128	**0,384**	0,103	-0,188
Alfa-defensyna	-0,258	-0,137	-0,083	-0,128	1,000	0,006	0,144	0,136
Hb	-0,112	-0,010	-0,144	**0,384**	0,006	1,000	-0,119	0,09
EF	0,0120	-0,136	**-0,430**	0,103	0,144	-0,119	1,000	-0,009
NYHA	0,127	0,197	0,218	-0,188	0,136	0,09	-0,009	1,000

Discussion

Defensins are small (3-5 kDa) antimicrobial peptides with a β-harmonica structure. In their structure defensins usually contain six cysteine residues linked by three disulfide bonds. They are conventionally divided into: α-, β-, θ-defensins. Human alpha-defensins (6 of them have been carefully characterized) HNP-1,2,3,4 (human neutrophil alpha-defensins) are produced in neutrophil granulocytes and HD-5,6 defensins (human defensins) in Panetha cells and epithelial cells in female reproductive tract [1-4]. Every day the human body produces 2×10^9 neutrophils / kg of body weight, which translates to 10 mg of defensins in this mass unit. Human genes for defensin alpha are mainly located in the 8p23.1 chromosome (10% of the population does not have HNP3 defensin gene) [5]. Defensins are one of the most conservative, oldest phylogenetic elements of the immune system. They belong to the family of antimicrobial proteins (AMP - antimicrobial proteins), having antimicrobial, antiparasitic, antiviral and antifungal properties. Alpha-defensin concentration increases in inflammation sites, and in serum - in systemic infections. This increase in plasma defensives occurs 2-4 hours after contact with the triggering agent. Patients with lack of defenses due to neutrophil granulomas (SDG) are more likely to suffer from acute bacterial infections [6]. Defensins activate mast cells leading to their degranulation, the release of histamine and prostaglandin D2, which are known mediators of inflammation. These peptides may further increase the production of tumor necrosis factor (TNF) and interleukin-1 (IL-1), and reduce the production of anti-inflammatory interleukin 10 (IL-10) [7,8]. Alpha-defensins act chemotactically on CD8 T lymphocytes, immature dendritic cells, and immature T lymphocytes, enhancing or suppressing activation of the classical complement pathway [9,10].

So far, the impact of alpha-defensin on the cardiovascular system has been assessed in relatively small studies. Alpha-defensin promotes the accumulation of lipoprotein (a) significantly contributing to the formation of foam cells, endothelial dysfunction and atherosclerotic plaque development [11-13]. The presence of elevated concentrations of this peptide as a manifestation of inflammatory processes has been observed in atherosclerotic plaques [14-16]. Nassar and co-authors also showed that elevated alpha-defensin concentration in skin biopaths is an independent factor that determines the severity of coronary artery disease observed during coronary angiography [16]. Elevated alpha-defensin levels are observed in Behcet's disease, and patients with type 1 diabetes with higher alpha-defensin concentration have a higher incidence of cardiovascular disease and higher cardiovascular mortality. In addition, significantly higher levels of this peptide were observed in diabetic nephropathy and accompanying albuminuria [17,18].

CHF is characterized by increased activity of the immune system and chronic inflammation, which results in an increase in the concentration of a number of proinflammatory cytokines, chemokines and adhesion molecules. The precise mechanism leading to these changes is unknown, but at present significant importance is attributed to unfavorable haemodynamic changes, oxidative stress, toll-like receptor hyperactivity (TLR), molecular mimicry and chronic immune system stimulation by bacterial antigens, and gastric endotoxin extrusion. Changing the ratio of proinflammatory factors - anti-inflammatory factors not only leads to the development and progression of CHF, but also to the deterioration of the function of other organs, which is associated with worse prognosis of patients with CHF [19-21]. The first study that showed a relationship between inflammatory intensity expressed by elevated CRP and clinical deterioration in patients with CHF was the study by Elster and co-authors. [22].

Our study was conducted among patients of the Polish population who belong to the high risk population, as confirmed by two large epidemiological studies - NATPOL PLUS and WOBASZ. The NATPOL PLUS study (n = 2399) showed that our country was characterized by high CRP levels - mean hs-CRP was 2.03 ± 2.14 mg / l [23]. In the WOBASZ study (n = 6561) it amounted to 2.7 ± 4.8 mg / l [24]. For comparison, in highly developed European countries as well as in Japan, CRP is significantly lower [25,26]. In this study, the median of CRP plasma, in patients with chronic severe disease, is undoubtedly relatively low for HF, which is most likely due to numerous exclusion criteria for patients with chronic inflammation of differentiated etiology.

All the more important is the observation of elevated alpha-defensin levels in patients with chronic heart failure. In our opinion, the observed phenomenon indicates the presence of inflammation in patients with CHF even at low CRP values. This is confirmed by numerous reports of the existence of proinflammatory stimulation resulting from many of the processes involved in the development of CHF, including hypoxia, oxidative stress or bacterial antigenic stimulation. The results of this study may point to the need to assess inflammation in this group of patients, and possibly other cardiovascular disease patients, using other, more sensitive inflammatory markers, or a set of markers.

According to our knowledge, this is the second study in the world that evaluates the prognostic value of alpha-defensin in patients with CHF. The results of our study indicate that alpha-defensin has no prognostic value in this group of patients. Christensen et al. [27] demonstrated significant prognostic value of alpha-defensin in CHF patients. However, the data analysis presented in our study is not an exact replicate of the analysis by Christensen et al. On the basis of the alpha-defensin concentration the quoted authors divided the study group into quartiles. Moreover, logarithmic transformations were used to present alpha-defensin concentration, and thus the statistics can be ambiguous. In the study by Christensen et al., there was no significant difference between the alpha-defensin concentration in the study group and the control group: 496 (307-685) mg / L vs. 486 (348-624) mg / l, p = 0.25, significant differences were observed with clinical deterioration: NYHA III-IV 599 (368-830) mg / L vs. NYHA I-II 486 (317-655) mg / l, p = 0.002), which also creates some interpretation difficulties and raises doubts as to the fairness of such data presentation.

Patients in our study were characterized by lower values of LVEF. Moreover, patients classified in NYHA class III and IV represented the majority of all patients that participated in the study, which may also affect the results. The pharmacological therapy used in patients in the study by Christensen et al. may also raise doubts, where in subsequent terciles β-blocker took 33.5 / 30.2 / 29.7% of the patients, whereas ACEi / Sartan sequentially 72.3 / 87.3 /

67.7% of the patients. In our study, 100% of the study group received β-blocker and ACEi / sartan.

Christensen et al. did not took into account any exclusion criteria while pereparing their study, and thus, it cannot be ruled out that the factor that significantly influenced the prognosis of patients was chronic inflammation resulting not from CHF, but from other co-morbid conditions. Higher alpha-defensin levels reflect inflammation that may have had an effect on prognosis, but the liberal selection of the group may have influenced the results and conclusions received.

We also did not see higher alpha-defensin concentration in patients with more advanced heart failure or in patients admitted with exacerbation. It seems that the causes of such a marker breakdown may lie in the selection and size of the study group. First, it was a relatively small population and, secondly, was characterized by severe left ventricular systolic dysfunction (mean LVEF 27%) and high clinical homogeneity - more than 60% of the patients were in NYHA class III.

As expected, the strongest, independent predictor of death was the plasma concentration of the recognized marker - NT-proBNP, confirming the unquestionable position of natriuretic peptides in the prognosis process in this group of patients. It also indirectly indicates the predominant influence of increasing haemodynamic disturbances on the prognosis of patients with heart failure. It appears that among patients with such CHF progression, inflammation is merely an accompanying pathology without a significant effect on and serious prognosis.

This study demonstrated that alpha-defensin cannot be a statistically significant predictor of death in patients with CHF. This result, despite a fairly long observation period, is only preliminary due to the relatively small sample size limiting the possibility of drawing far-reaching conclusions. Our study is a pilot study, and a full assessment of the possible prognostic value of alpha defensiveness will undoubtedly require wider analyzes in larger patient groups. The hope of alpha defensiveness seems to be all the more justified because another inflammatory marker - CRP - is an important prognostic factor in cardiovascular disease. The value of our observations is primarily confirmed by the new marker of chronic inflammation in a select group of heart failure patients with a relatively low CRP marker value. This may indicate the need to seek new markers more precisely defining pro-inflammatory-anti-inflammatory balance in CHF populations, or suggest the need for a set of biochemical factors that provide better insight into the clinical status of CHF patients.

Conclusions

1. Increased plasma concentration of alpha-defensin in patients with chronic heart failure with impaired left ventricular ejection fraction confirms subclinical inflammatory activation in this group despite relatively low CRP values.

2. Alpha-defensin did not prove to be a valuable predictor of death in CHF patients in both annual and biennial observation.

3. The only significant factor for poor prognosis was NT-proBNP, which confirms the strong position of natriuretic peptides not only in the diagnostic but also prognostic process in CHF patients.

Study limitations

The results of this study may not refer to patients with acute HF and in patients with CHF with left ventricular systolic function.

Abbreviations

CHF, chronic heart failure;
RAA,renin – angiotensin – aldosterone;
NYHA,New York Heart Association;
HF, heart failure;
LVEF, left ventricular ejection fraction;
GFR, glomerular filtration rate
LDL,low-density lipoprotein;
HDL, high-density lipoprotein;
hs-CRP high-sensitivity C-reactive proteine
NT-proBNP,N-terminal natriuretic propeptide
ELISA,enzyme-linked immunosorbent assay;
TnT, troponin T;
Hb, hemoglobin;
BMI,body mass index;
ROC, receiver operating characteristic;
AUC, Area Under the Curve;
HR, hazard ratio;
ACEi angiotensin-converting-enzyme inhibitor
α-defensin, alpha-defensin;

Declarations

Ethics approval and consent to participate

The research related to human use complied with all the relevant national regulations, institutional policies, and was in accordance with the tenets of the Helsinki Declaration. The study protocol was approved by the Ethical Committee of Collegium Medicum, Bydgoszcz, of Nicolaus Copernicus University, Torun, Poland**.** The Ethical Comitee consented in writing to the study.

During realization of tests, all participants provided informed consent and used all measures for maintaining anonymity of participants.

Consent to publish

Patients gave written informed consent to publish the study results anonymously.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

JB, ŁW, DR, WG, participated in the design of this study. DR, ŁW, KB, JB, performed the statistical analyses. JB, ŁW, DR, WG, KB, DK, PM, WZ, WS drafted the manuscript. ŁW,

DR, JB, WG, KB, DK, PM, WZ, WS were involved in data collection and/or made important intellectual contributions to the interpretation of data and the writing of paper. All authors critically revised and approved the final version.

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