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The role of Interleukin-6 with Heart Failure: A Case-Control study

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Abstract

Background: Systemic inflammatory response has been documented as a common physiopathologic feature of heart failure (HF). Plentiful studies have shown that patients with HF have increased expression and release of inflammatory cytokines. IL-6 is associated with LVEF in people, independent of probable confounders. The objective of this work was to pinpoint and describe the association between IL-6 and heart failure. Material and methods: The study was a case-control, including 160 participants, comprising 80 patients with HF and a random group of 80 healthy control subjects. A left ventricular ejection fraction of less than 50% was used to identify HF with diminished ejection fraction. All participants were subjected to a hematological assessment of IL-6, and the results were matched with the control group. Results: Significantly higher IL-6 serum levels among the patients compared with the control and also among NYHA classes of HF. A non-significant difference in heart failure patients between the non-anemic and anemic patients regarding IL-6 levels. A highly significant negative correlation between IL-6 and LVEF% among patients with HF was also found. Conclusion: The results of the present study point to a strong relationship between IL-6 and HF and provide preliminary support for further research into any potential therapeutic uses of IL-6 in the prevention of HF. In general pubulation, interleukin-6 may be a promising biomarker for the emergence of HF.

Keywords

heart failure, IL-6, EF%, inflammation, interleukin.

The fact that the immune system and inflammatory processes are implicated in a number of immunological, cardiovascular, mental, neurological disorders, and physical health conditions that account for the majority of morbidity and mortality in the modern world is one of the most significant medical discoveries of the past 20 years. [1-6]. Inflammation has been documented as a mutual physiopathologic feature of heart failure (HF) [7, 8]. People over 70 years old now account for more than 10% of HF prevalence in industrialized countries [9]. In particular, inflammation has been connected to the onset, progression, and complications of disease and is an independent predictor of poor outcomes from conventional indices such left ventricular ejection fraction (LVEF) or NYHA functional class. [10, 11]. Plentiful revisions have shown that HF subjects have increased expression and release of inflammatory cytokines. [12].

Interleukin (IL)-6, a key signaling chemokine of innate immune response [13], appears to be at the center of the rapidly developing inflammatory response and atherosclerosis [14]. Main interventional trials more than 20 years ago, shown that baseline levels of IL-6 are just as stronger predictor of future vascular events as baseline levels of low-density lipoprotein cholesterol [15], and this tendency persists to the contemporary days [3]. IL-6 is linked independently with new-onset LVEF% in people [16].

Nevertheless, efforts to invent novel anti-inflammatory HF pharmaceutical therapies have mainly fallen short, which is likely due to our limited

understanding of the complex inflammatory panel that contributes to the varied HF syndrome. We must therefore increase our understanding of the particular inflammatory mechanisms that contribute to HF problems. Based on that, the objective target of this work was to pinpoint and describe the association between IL-6 and heart failure.

Materials and methods

Study design and sampling

This case-control study was piloted at Al-Hussein Teaching Hospital between 20 February 2021 and 16 April 2022. 95 out of the total 160 participants (which were aged 20 to 75) in the study, were males. Only 80 out of 123 recruited patients, who fulfill the inclusion criteria and were diagnosed with heart failure (based on echocardiographic findings), were selected. The rest 80 participants were selected as a healthy control group. All HF patients were inspected and categorized for four NYHA classes of HF [17]. Those with a history of kidney disease, diabetes mellitus, stroke, tumors, thyroid disorder, cigarette smoking, autoimmune disorders, and pregnancy were excluded from the study.

Hematological assays

The biochemical analyses of IL-6 and ferritin were done by IL-6 ELISA kit and Ferritin ELISA kits, “Shenzhen New Industries, China-Maglumi”. The "Hematology analyzer (Abbott-USA)" was used to measure hemoglobin (Hb). According to WHO guidelines, anemic patients were identified if their hemoglobin levels were less than 13g/dl in males and 12g/dl in females.

Echocardiography assessment

Using "The vivid E9 ultrasound machine, GE Healthcare USA," all patients completed an echocardiographic study. The subjects were checked by two different specialized echocardiographers who were blind to the study methodology, and the "left ventricular ejection fraction (LVEF %)" calculated to estimate severity of HF according to the NYHA classification. Cases of heart failure are those whose LVEF is lower than 50% [18].

Statistical examinations

Measurements are displayed as means/±SD. The statistical software that was available (SPSS/25, USA) was operated for the statistical examination. With the use of the “Student's T-test” for categorical variables, variations between the study groups were assessed. Unpaired Student-T and ANOVA tests were utilized to analyze variations in continuous variables. In order to verify the associations between the important variables, analyses utilizing linear regression were utilized. Statistical significance was indicated by a P value lower than 0.05.Ethical issue

The health institution's ethical committee permitted the study design, and each participant gave informed consent before participating. The study was conducted following the Helsinki Declaration's guidelines.

Results

Main characteristics of the participants

Table 1 demonstrates the characteristics of the two studied groups. All study parameters of the control and patients were comparable apart from the mean levels of IL-6, LVEF%, and incidence of hypertension. A highly significant lower EF% levels, higher IL-6 serum levels, and presence of hypertension among the patients with HF.

Table 1: Basal characteristic features of the two study groups (mean ±SD)

Parameter		Control	Patient	p-value
Age (yrs)		60.42± 8.01	62.51±9.12	P>0.05
Sex	Men	47 (58.75%)	48 (60%)	P >0.05
	women	33 (41.25%)	32 (40%)	
Body mass index Kg/mI		26.61±3.4	25.49±3.01	P>0.05
Echocardiographic LVEF%		66.79 ±7.3	37.55±9.5	P<0.0001
Fasting glucose (mg/ dl)		93.31 ± 10.59	92.82 ± 8.80	P>0.05
Presence of hypertension (%)		0	12 (9.8)	P<0.05
Ferritin µg /dl		102±56.6	96.14±66.2	P>0.05
NYHA functional class		--	2.6 ±0.6	P<0.0001
Interleukin-6 (pg/ml)		1.65 ± 0.25	5.88 ±3.3	P<0.0001
Hb g/dl		12.09 ± 1.9	12.47±1.7	P>0.05
Systolic pressure (mmHg)		129.8 (20.0)	137.2 (41.0)	P>0.05
Diastolic pressure (mmHg)		71.0 (19.4)	88.4 (11.4)	P>0.05

Comparison of interleukin-6, ferritin, and hemoglobin among patients between anemic and non-anemic patients with heart failure

Table 2 exposed a non-significant difference in heart failure patients between the non-anemic and anemic patients regarding IL-6 (P>0.05), while ferritin and Hb were highly significantly lower among the anemic subjects (P<0.001).

Table 2: Iron status and hematological parameters (Mean ± SD) among cases with heart failure, according to the iron status (anemic and non-anemic)

Presence of anemia	IL-6 pg/ml	Ferritin µg/dl	Hb g/dl
Non anemic	6.01 ± 3.8	129.3±60.1	13.6±0.9
Anemic	5.04 ± 1.5	55.2±45.9	10.84±1.4
Significance	P>0.05	P<0.001	P<0.001

Comparison of interleukin-6, ferritin, and hemoglobin among patients according to NYHA classes of heart failure

ANOVA test was analyzed to compare the result of the four classes of heart failure regarding interleukin-6, ferritin, and hemoglobin (Table 3). The IL-6 show highly significant differences among classes (P<0.001). While the other two parameters were not significantly differing (P>0.05).

Table 3: Multiple comparisons of interleukin-6, ferritin, and hemoglobin among patients according to "NYHA classification of heart failure"

Parameters	NYHA I (32)	NYHA II (20)	NYHA III (15)	NYHA IV (13)	P-value
IL-6 pg/ml	4.04 ±0.6	5.57 ±0.9	6.5 ±1.4	14.075±3.8	P<0.001
Ferritin µg/dl	111.1±69.5	88.3±75.2	87.9±53.1	102.05±21.3	P>0.05
Hb g/dl	12.7±2.1	12.6±1.2	11.9±1.6	12.52±0.7	P>0.05

"Post Hoc comparisons" between each pair of heart failure classes (according to NYHA classification) regarding IL-6, ferritin, and hemoglobin were shown in Table 4. In all paired comparisons, the IL-6 revealed significant differences between the classes other than between classes II and III. While there were non-significant differences between all other pairs of classes regarding both ferritin and hemoglobin (P.0.05).

Table 4: Multiple comparisons of IL-6, ferritin, and hemoglobin among patients according to NYHA classes of heart failure

Parameters	Class I vis II	Class I vis III	Class I vis IV	Class II vis III	Class II vis IV	Class III vis IV
IL-6 pg/ml	S	S	S	NS	S	S
Ferritin µg/dl	N/S	N/S	N/S	N/S	N/S	N/S
Hb g/dl	N/S	N/S	N/S	N/S	N/S	N/S

Correlation between serum interleukin-6 and ferritin with the ejection fraction:

Table 5 shows the correlation between plasma interleukin-6 and ferritin with the EF%, which shows a highly significant negative correlation between IL-6 and LVEF% among patients with HF. whereas, ferritin exposed a highly significant positive correlation (P<0.001) with LVEF%.

Table 5: Correlation between IL-6, ferritin, with EF% among the patients with heart failure

Variables	r	Significance
Interleukin-6	-0.548	P < 0.001
Ferritin	0.168	P < 0.001

In the existing study, gender revealed no significant variations regarding IL-6, ferritin, and hemoglobin among the patients with heart failure (P>0.05), Table 6.

Table 6: The differences in serum interleukin-6, ferritin, and hemoglobin according to the gender of patients with heart failure

Parameter	Male	Female	P-value
IL6 pg/dl	5.2±2.3	6.5±4.3	P>0.05
Ferritin µg /dl	100.6±63.5	103.8±71.4	P>0.05
Hb g/dl	12.3±2.2	12.1±2.15	P>0.05

Discussion

The present work demonstrates that higher serum IL-6 levels are linked to a greater risk of HF development. Interestingly, our study revealed a statistically significant relationship between IL-6 and the HF development. Our study extends earlier research emphasizing the significance of interleukin-6 in HF cases to the population, supporting the notion that IL-6 might be a promising marker for the onset of HF.

The study's findings support the recent finding that IL-6 has a significant role in LVEF%. In the BIOSTAT-CHF cohort, a sizable and heterogeneous analyses of HF patients, increased IL-6 concentrations were shown to be a reliable predictor of HF with preserved EF% [19].

Our findings do not differ from those of the previous "In the Health, Aging, and Body Composition Study", a cohort of older patients, in which, Kalogeropoulos et al. demonstrated that IL-6 was related to incident HF [20]. As a rebuttal to this point, other scientists have failed to repeat such observations and exposed that only a restricted group possibly will benefit from IL-6 estimation in acute HF [21]. They discovered that an initial rise in IL-6 levels is neither always associated with a positive clinical outcome nor useful as a prognostic indicator.

The heterogeneity in population samples of the studies is most probable to be to cause for the disparity between these findings, which possibly influences IL-6 results [22, 23].

Based on previously established normal values of IL-6 (1.2-2.0 pg/ml), the information acquired in this study indicates that more than half of the patients had unusually increased serum IL-6 values. Interleukin-6 was correlated negatively with the deterioration of ventricular systolic EF%. These results are consistent with an earlier study that showed IL-6 substantially correlated with echo indicators of diastolic ventricular dysfunction and was found to suppress the production of “sarcoplasmic reticulum Ca2+-ATPase (SERCA2)” channels in cardiac myocytes [24]. SERCA2 mediates Ca reabsorption in the sarcoplasmic reticulum, which contributes to diastolic cardiomyocyte relaxation. In addition, through decreasing titin phosphorylation, IL-6 heightens cardiomyocyte stiffness [25]. The negative significant correlation between IL-6 and LVEF% may be explained by these processes in turn.

The data from this study showed a non-significant variation in HF patients between the non-anemic and anemic patients regarding IL-6. A similar phenomenon was published by Yook C. et al., last year [16], which found that higher IL-6 concentrations in the population are related to a greater risk of developing HF, independent of potential confounders including iron levels. In contrast, Markousis G. et al. concluded that lower iron concentrations were a reliable predictor of greater serum concentration of IL-6, and patients with higher IL-6 levels had a greater frequency of anemia and/or deranged iron homeostasis [19]. Hepcidin peptide is an “acute phase protein" that is synthesized as a result of the liver's acute-phase response being activated by interleukin-6 signaling [26, 27]. Hepcidin regulates systemic iron metabolism and induces hypoferremia via IL-6 [28].

Anemia is a significant factor in HF because anemia has been associated with a poor prognosis, could influence one's ability to exercise, their risk of developing depression, and possibly even directly affect their myocardium [29]. Despite having small sample sizes, earlier research on chronic cardiac failure demonstrated no correlation between serum hepcidin and IL-6 concentrations [16] with LVEF%. These results when combined with of our study findings, specify that IL-6 signaling is a crucial bio-mechanism that contributes to HF and may therefore merit further research for modifying these pathologic processes [19].

In the current study, gender revealed no significant variations regarding IL-6 and ferritin. This finding is consistent with that of Markousis G. et al., who reported that IL-6 serum concentrations correlated positively with LVEF%, even after correcting for the effect of sex [19].

Conclusion

The results of the present study point to a strong relationship between IL-6 and HF and provide preliminary support for further research into any potential therapeutic uses of IL-6 in the prevention of HF. In people, interleukin-6 may be a viable biomarker for the emergence of HF.

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