UDC 575.
https://doi.org/10.2298/GENSR2201329S
Original scientific article

ASSOCİATİON OF *IL-1B* (-511 C / T) AND *IL-1B* (-31 T / C) GENE POLYMORPHİSM WİTH ENDOPLASMİC RETİCULUM STRESS MARKER LEVELS İN ACUTE DECOMPENSATED HEART FAİLURE WİTH LOW EJECTİON FRACTİON

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Sabırlı R., A. Köseler, E. Mete, I. Türkçüer (2022). *Association of ıl-1β (-511 c / t) and ıl-1β (-31 t / c) gene polymorphism with endoplasmic reticulum stress marker levels in acute decompensated heart failure with low ejection fraction.* - Genetika, Vol 54, No.1, 329-339.

Inflammatory processes play an important role in the pathogenesis of heart failure. The accumulation of unfolded proteins in the endoplasmic reticulum lumen and the unfolded protein response signal path is activated. The *IL-1B* gene is located in the Chromosome 2.q14 region. -31 and -511 single nucleotide polymorphisms (SNPs) were detected in the *IL-1B* promoter region. These two SNPs affect IL-1expression. This study aims to investigate the presence of *IL-1B* (-511 C / T) and *IL-1B* (-31 T / C) gene polymorphisms and the relationship between ER stress markers and inflammatory markers. Patients who applied to the department of emergency medicine with the findings of acute decompensated heart failure. Polymorphic sites of the *IL-1B* gene were determined by DNA sequencing. In all study, individuals with *IL-1B* (-31 T / C) T allele have higher serum PERK, GRP-78, CHOP and CRP levels median values than individuals with *IL-1B* (-31 T/C) C allele (p = 0.0001, p = 0.002, p = 0.002 and p = 0.011, respectively). Serum ERK and GRP-78 values in HF group were higher in individuals with *IL-1B* (-31 T / C) T allele compared to individuals with C allele (p = 0.0001 and p = 0.006). There was a statistically significant difference in serum CHOP levels in the control group with the *IL-1B* (-511 C / T) T allele and the individuals with the C allele in the HF group (p = 0.002). In conclusion, we consider that the inflammatory response caused by IL-1B (-31 T / C) gene polymorphism increased and the ER stress response increased, inflammatory

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pathway and ER stress of having *IL-1B* (-31 T / C) T / T genotype or T allele.

Keywords: IL-1B (-511 C / T), IL-1B (-31 T / C), Gene Polymorphism, Endoplasmic Reticulum Stress, Heart Failure.

INTRODUCTION

Heart failure (HF) is a clinical syndrome caused by structural or functional impairment of ventricular filling or blood pumping. The diagnosis of HF is largely based on a careful history and physical examination. In 2013 ACCF / AHA Heart failure guide, heart failure was divided into 2 groups according to the ejection fraction (EF). EF has preserved heart failure (HFpEF) and low EF with heart failure (HfrEF). It is defined as EF > 50 in HfpEF and EF ≤ 40% in HfrEF (YANCY *et al*. 2013).

Inflammatory processes play an important role in the pathogenesis of arrhythmia, pericarditis, myocarditis, sepsis-induced cardiomyopathy, myocardial infarction and heart failure (SZEKELY and ARBEL, 2018). IL-1 family cytokines play a role in the thrombogenic response of endothelial cells, endothelial and smooth muscle cell mitogenesis, leukocyte adherence, extracellular matrix production, lipoprotein metabolism and regulation of vascular permeability (LIBBY *et al*. 1988; DI GIOVINE *et al.* 1990). IL-1 is a proinflammatory cytokine and IL-1 elevation has been associated with disease, regardless of etiology in heart failure (YNDESTAD *et al*. 2006). Although IL-1 cytokine family has anti-inflammatory cytokines (IL-37), IL-1β is a pro-inflammatory cytokine (REN and TORRES, 2009). C-reactive protein is an indicator of IL-1 activity and is an independent predictor marker for the development of adverse outcome in heart failure (BRAUNWALD, 2008).

Endoplasmic reticulum (ER) homeostasis is impaired due to conditions such as endoplasmic reticulum stress (ER) viral infection, oxidative stress, hyperlipidemia and calcium metabolism disorders. The accumulation of unfolded proteins in the ER lumen and eventually the unfolded protein response (UPR) signal path is activated. When ER stress persists for a long time, apoptosis pathways are activated (ZHANG, 2015; LUO and LEE, 2013). ER stress has been shown to trigger inflammatory processes by stimulating the multi-protein signaling platform, called inflammazom, inducing the release of proinflammatory cytokines in macrophages (MENU *et al.* 2012; STROWING *et al.* 2012). It has also been shown that IL-1B induces ER stress (LIU *et al* 2015; VERMA *et al*. 2010).

The *IL-1B* gene is located in the q14 region of the Chromosome 2 and two single nucleotide polymorphisms (SNPs) at positions -31 and -511 were detected in the *IL-1B* promoter region. These two SNPs affect *IL-1B* expression (BHAT *et al* 2014).

In the literature, *IL-1B* gene polymorphism has been studied in many diseases, (RAI *et al* 2016; TABREZ *et al*. 2017; KIMANG 2012; GORACY *et al*. 2019; CHEN *et al*. 2019; YADAV *et al.* 2017; KANDIL *et al.* 2013; TSIMIKAS *et al.* 2014; JAKOVLJEVIC *et al.* 2020) but we did not find the study in the group of patients with heart failure in our literature review. We did not find a study examining the relationship between *IL-1B gene* polymorphism, ER stress marker level and inflammatory marker levels in heart failure. This study aims to investigate the presence of *IL-1B* (-511 C / T) gene (-511 SNP) and *IL-1B* (-31 T / C) gene (-31 SNP) polymorphisms and the relationship between ER stress markers and inflammatory markers.

MATERIAL AND METHODS

Patients and Methods

Study Type

Ethical approval numbered 60116787-020 / 13220 was obtained from Pamukkale University Ethics Committee prior to the study. The study is a prospective, case-control study.

Study Population

A total of 90 patients with acute decompensated heart failure and 90 volunteers without any disease were included in the study. Patients who applied to the emergency department of Pamukkale University hospital with the findings of acute decompensated heart failure (YANCY *et al.* 2013; GHEORGHIADE *et al*. 2013; MEYER 2018) were included in the study. The patient group and healthy control group were informed about the study and a written consent form was obtained from all patients wishing to participate in the study. Healthy patients without any known chronic or acute diseases and drug use were taken as control group. After the participants of the study were evaluated according to the inclusion and exclusion criteria, they were divided into two groups as hearth failure group (HF) and Healthy group (Control).

Hearth failure group (HF): According to the 2013 ACCF / AHA Guideline for the Management of Heart Failure guide,[1] patients with HfrEF and acute decompensated heart failure were divided into the heart failure (HF) group.

Healthy group (Control): This group consists of people with no known acute, subacute or chronic disease history, no medication, and written consent to participate in the study. It was chosen as a partner in terms of age and gender with the group of healthy and patient patients.
The exclusion criteria included the diagnosis of kidney and liver failure, pregnancy, acute pulmonary embolism, chronic inflammatory disease (e.g. autoimmune disease, rheumatic disease) cancer diagnosis, asthma, chronic obstructive pulmonary disease, cerebrovascular disease, EF > 40, and having infectious diagnosis. All the individuals signed informed consent form before including the study.

Blood samples and Measurement of CHOP, PERK, GRP78 Level

CHOP, PERK, GRP78 Level Measurement

Detection of Serum Human Glucose Regulated Protein 78 (GRP78)

Serum GRP78 levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Human Glucose Regulated Protein 78 (GRP78) ELISA Kit, SunLong, SL2048Hu, China), per the manufacturer's protocol. The detection rate of this kit is 16 pg/mL.

Detection of Serum Human C/EBP homologous protein (CHOP)

Serum Human C/EBP homologous protein (CHOP) levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Human C/EBP homologous protein (CHOP) ELISA Kit, SunLong, SL2631Hu, China), per the manufacturer's protocol. The detection rate of this kit is 6 pg/mL.

Detection of Serum Human Phospho Extracellular Signal Regulated Kinase (PERK)

Serum Human PERK (Phospho Extracellular Signal Regulated Kinase) levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit Human PERK (Phospho Extracellular Signal Regulated Kinase) ELISA Kit, MyBioSource.com, MBS014568, USA), per the manufacturer's protocol. The detection rate of this kit is 18.75 pg/mL.

DNA isolation and genotyping

Blood sample from each participant were collected in EDTA tubes (Becton Dickinson, U.K.). DNA was extracted using the standard phenol chloroform DNA extraction method (BARBARO *et al*. 2004). All subjects were included in the study after giving informed consent, and this study was approved by the Ethics Committee of Pamukkale University Faculty of Medicine.

Two sets of oligonucleotide primers were used for the amplification of the polymorphic regions of the IL-1β gene from genomic DNA. The DNA amplification primers are shown in Table 1. PCR was carried out following the procedure described by Zeng et al (Zeng et al. 2003). Polymorphic sites of the IL-1β gene were determined by DNA sequencing (ABI PRISM 310, Analysis System, USA). Non-radioactive fluorescence dye-based DNA sequencing was performed using the ABI PRISM 310 analysis system.

Statistical Analysis

Similarly, since there is no regulated reference study, as a result of the power analysis, at least 172 people (at least 86 people for each group) are included in the study in order to obtain 90% power with 95% confidence, assuming that the effect size we expect from the study will be high (f = 0.6) was found to be necessary. The data were analyzed with SPSS package program. Continuous variables were given as mean ± standard deviation, median (IQR) and categorical variables as numbers and percentages. When parametric test assumptions were not provided, Mann-Whitney U test and Kruskal Wallis variance analysis were used to compare independent group differences. The fit of the population to the Hardy-Weinberg equation was analyzed with the Goodnes of fit test. In all examinations, $p < 0.05$ was considered statistically significant.

RESULT

The power obtained in the study for this effect size was 90.5% at 95% confidence level. In the control group, the frequency of -31 T allele was higher than the HF group (83.3% vs 61.1% and OR = 1.364 (95% CI 1.193-1.559). There was a statistically significant factor between groups in terms of -31 allele frequencies ($p = 0.0001$). *IL-1B* -511 SNP gene T and C allele frequencies were similar in both groups ($p = 0.652$). The carriers of the -31 SNP C variant have a 3.3 fold risk increase of heart failure compared to TT homozygotes (with $p<0.0001$). And also the carriers of the -511 T allele have a 4.59 fold risk increase of HF ($p<0.0001$) (Table 1).
In all study group (HF + Control group), serum PERK, GRP-78, CHOP and CRP median levels were higher value in individuals who have *IL-1B* -31 T allele ($p = 0.0001$, $p = 0.002$, $p = 0.002$ and 0.011 respectively). Serum CHOP level median value is found higher in individuals who have -511 T allele ($p = 0.025$) (Table 2).

Table 1. Genotype and allele frequencies of the groups

		Heart Failure Group (N=90)	Control Group (N=90)	OR (95%CI)	p Value
Genotypes		*N (%)*	*N (%)*		p Value
IL-1β (-31 T/C)	T/T	34 (37.8%)	60 (66.7%)	2.745 (1.474-5.111)[1]	<0.0001
	T/C	42 (46.7%)	30 (33.3%)	2.059 (1.086-3.904)[2]	0.0001
	C/C	14 (15.5%)	0 (0%)	3.294 (1.788-6.07)[3]	<0.0001
IL-1β (-511 C/T)	C/C	16 (17.8%)	42 (46.7%)	0.392 (0.251-0.612)	0.0001
	C/T	74 (82.2%)	48 (53.3%)	1.76 (1.385-2.242)	<0.0001
	T/T	0 (0%)	0 (0%)	4.594 (2.336-9.034)[4] 3.349 (1.713-6.549)[5]	<0.0001
Alleles		*N (%)*	*N (%)*		
IL-1β (-31 T/C)	T Allele	110 (61.1%)	150 (83.3%)	1.364 (1.193-1.559)	
	C Allele	70 (38.9%)	30 (16.7%)	0.429 (0.295-0.623)	0.0001
IL-1β (-511 C/T)	C Allele	124 (68.9%)	120 (66.7%)		
	T Allele	56 (31.1%)	60 (33.3%)		0.652

[1]Odds ratio is calculated for the -31 SNP TT vs TT+TC genotypes.
[2]Odds ratio is calculated for the -31 SNP TT vs TC genotypes.
[3]Odds ratio is calculated for the carriers of the C variant (-31 SNP)
[4]Odds ratio is calculated for the carriers of T allel (-511 SNP)
[5]Odds ratio is calculated for the -511 CC vs CT genotypes

Table 2. Laboratory parameter levels in each genotypes and alleles of whole study members

			Laboratory Parameters				
			pERK (pg/ml) Median (IQR)	GRP78 (pg/ml) Median (IQR)	CHOP (pg/ml) Median (IQR)	CRP (mg/dl) Median (IQR)	hsTnT (µg/L) Median (IQR)
Alleles	IL-1β (-31 T/C)	C Allele (N=100)	540.5 (446-648)	93.5 (69-152)	37 (29-76)	0.215 (0.125-0.641)	0.011 (0.006-0.048)
		T Allele (N=260)	592.5 (529-719)	96 (81-298)	58 (33-84)	0.284 (0.169-0.685)	0.009 (0.005-0.021)
		p^1 Value	0.0001	0.002	0.002	0.011	0.068
	IL-1β (-511 C/T)	C Allele (N=244)	577.5 (496-662)	94 (79-175)	40 (31-76)	0.283 (0.153-0.829)	0.009 (0.005-0.021)
		T Allele (N=116)	592.5 (518-663)	95 (69-381)	61.5 (31-96)	0.274 (0.153-0.472)	0.115 (0.006-0.026)
		p^1 Value	0.709	0.643	0.025	0.588	0.191
Genotypes	IL-1β (-31 T/C)	C/C (N=14)	518 (346-532)	94 (54-267)	71 (29-172)	0.142 (0.065-0.305)	0.006 (0.005-0.092)
		T/C (N=72)	575 (452-659)	81 (69-144)	36 (29-63)	0.296 (0.135-1.296)	0.012 (0.007-0.475)
		T/T (N=94)	597 (549-734)	96 (81-381)	63 (36-103)	0.284 (0.24-0.65)	0.007 (0.005-0.021)
		p^2 Value	0.001	0.005	0.0001	0.009	0.018
	IL-1β (-511 C/T)	C/C (N=58)	573 (496-662)	112 (81-179)	37 (31-72.75)	0.215 (0.142-0.338)	0.009 (0.005-0.021)
		C/T (N=122)	591 (518-663)	91 (72-307)	61.5 (32-103)	0.315 (0.24-0.685)	0.011 (0.006-0.027)
		T/T (N=0)	NE	NE	NE	NE	NE
		p^1 Value	0.830	0.246	0.033	0.027	0.382

p^1 - values are derived from Mann Whitney U test. p^2 - values are derived from Kruskal Wallis test. IQR, interquartile range; PERK, Protein Kinase RNA-like Endoplasmic Reticulum Kinase; GRP78, Glucose Regulated Protein; CHOP C / EBP homologous protein; CRP, C-reactive protein; hsTnT, high sensitive troponin T

Serum PERK, GRP-78, CHOP, CRP and hsTnT levels were significantly different in individuals with -31 C/C, T/C and T/T genotypes (p = 0.001, p = 0.005, p = 0.0001, p = 0.009, and p = 0.018 respectively). Serum PERK level median value is was higher in individuals with -31 T / T genotype. Serum GRP-78 and CHOP values were lower in individuals with -31 T / C genotype than the other two groups. Serum CRP and HsTnT levels were higher in individuals with -31 T/C genotype (Table 2).

Table 3. ER Stress markers, CRP and hsTnT levels of the Control and HF groups

	Control Group		HF Group		
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	p Value
PERK (pg/ml)	653±197.18	591 (549-734)	572.8±140.47	577 (480-654)	0.028
GRP-78 (pg/ml)	180.4±144.49	96 (81.5-262	219.88±305.05	90 (70.5-215.25)	0.083
CHOP (pg/ml)	80.33±66.01	63 (36-84)	65.17±63.84	39 (27-77.25)	0.001
CRP (mg/dl)	0.22±0.87	0.24 (0.142-285)	1.83±2.79	0.65 (0.231-2.55)	0.0001
hsTnT (µg/L)	0.007±0.004	0.006 (0.004-0.009)	0.11±0.228	0.021 (0.011-0.932)	0.0001

p-values are derived from Mann Whitney U test. SD, standart deviation; IQR, interquartile range; PERK, Protein Kinase RNA-like Endoplasmic Reticulum Kinase; GRP78, Glucose Regulated Protein; CHOP C / EBP homologous protein; CRP, C-reactive protein; hsTnT, high sensitive troponin T
All p Values are derived from Mann Whitney U test.
p^1 values indicate the result of statistical analysis of the laboratory parameters between allele groups in HF group.
p^2 values indicate the result of statistical analysis of the laboratory parameters between allele groups in control group.
PERK, Protein Kinase RNA-like Endoplasmic Reticulum Kinase; GRP78, Glucose Regulated Protein; CHOP C / EBP homologous protein; CRP, C-reactive protein; hsTnT, high sensitive troponin T

Table 4. Laboratory parameter levels in each genotypes in HF and Control groups

				Laboratory Parameters				
				pERK (pg/ml)	GRP78 (pg/ml)	CHOP (pg/ml)	CRP (mg/dl)	hsTnT (µg/L)
				Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Genotypes		HF Group (N=90)	T/T	628 (565-746)	161 (80.5-345)	44 (30.7-87.7)	0.868 (0.24-2.55)	0.021 (0.016-0.07)
			T/C	549 (445-626)	85 (68-95)	33 (25.7-49.5)	0.865 (0.237-3.84)	0.026 (0.13-0.1)
			C/C	518 (346-532)	94 (54-267)	71 (29-84)	0.142 (0.06-0.3)	0.006 (0.005-0.092)
		p^1 Values		0.001	0.004	0.102	0.0001	0.049
	IL-1B (-31 T/C)	Control Group (N=90)	T/T	582 (549-734)	93.5 (81-381)	68 (37-103)	0.264 (0.169-0.285)	0.005 (0.004-0.007)
			T/C	648 (573-662)	112 (94-152)	37 (33-63)	0.142 (0.125-0.215)	0.007 (0.007-0.009)
			C/C	NE	NE	NE	NE	NE
		p^2 Values		0.643	0.879	0.001	0.009	0.018
	IL-1B (-511 C/T)	HF Group (N=90)	C/T	594 (485-659.25)	93 (68.75-277)	39 (27.75-81.75)	0.472 (0.159-1.603)	0.019 (0.009-0.083)
			C/C	525.5 (453.5-613)	85.5 (79.5-159.75)	39.5 (24.75-72)	2.54 (0.87-5.36)	0.081 (0.022-0.111)
			T/T	NE	NE	NE	NE	NE
		p^2 Values		0.183	0.598	0.751	0.002	0.007
		Control Group (N=90)	C/T	591 (549-734)	91 (79-381)	70 (63-210)	0.267 (0.24-0.325)	0.006 (0.004-0.007)
			C/C	610 (514-767)	132 (84-240.2)	37 (31.5-75.75)	0.161 (0.129-0.267)	0.007 (0.004-0.0112)
			T/T	NE	NE	NE	NE	NE
		p^2 Values		0.884	0.080	0.0001	0.001	0.105

p^1 values are derived from Kruskal Wallis test. p^2 values are derived from Mann Whitney U test. PERK, Protein Kinase RNA-like Endoplasmic Reticulum Kinase; GRP78, Glucose Regulated Protein; CHOP C / EBP homologous

When HF and control groups are analyzed separately, there is a statistically significant difference between HF and control group in terms of serum PERK, CHOP, CRP and hsTnT levels (p = 0.028, p = 0.001, p = 0.0001 and p = 0.0001 respectively) (Table3) Serum PERK and

CHOP levels were found higher, serum CRP and hsTnT levels were found in control group (Table 3).

In HF group, serum PERK, GRP-78 and CRP levels median values were higher in individuals with -31 T/T genotype than other genotypes ($p = 0.001$; $p = 0.004$ and $p = 0.0001$ respectively). Serum CRP and hsTnT levels median values were higher in individuals with -511 T/T genotype ($p = 0.002$ and $p = 0.007$ respectively) (Table 4).

In control group, serum CHOP and CRP levels median values were found higher in individuals with -31 T/T genotype than C/C genotype ($p = 0.001$ and $p = 0.009$ respectively). Serum CHOP levels were found higher and serum CRP levels were found lower in individuals with -511 T/T genotype ($p = 0.0001$ and $p = 0.001$) (Table 4).

DISCUSSION

IL-1B (-511 C / T) and *IL-1B* (-31 T / C) gene polymorphism have been frequently studied in the coronary artery disease in the literature. TABREZ *et al*. both polymorphisms have worked in CAD patients and have demonstrated that both nucleotide polymorphisms do not pose a risk for CAD, and allele frequencies are similar in the patient and healthy groups (TABREZ *et al.* 2017). In a metaanalysis investigating the risk of IL-1 gene polymorphism and coronary artery disease, 13 studies were evaluated (3219 cases-2445 controls) *IL-1B-511* gene polymorphism was not associated with CAD risk (OR = 0.98, 95% CI 0.87–1.09) (ZHOU *et al.* 2012). In a large case-control study -511 C allele was found to be a risk for CAD (OR = 1.36, $p = 0.041$) (RAI *et al.* 2016). In a meta-analysis performed in COPD patients, the risk was found to be reduced in individuals with -31 homozygous genotype (OR: 0.77, 95% CI: 0.63–0.94) (XIAO *et al*. 2014). In our study, we found that having the -31 T allele increased the risk of HF (OR = 1.364, 95% CI: 1.193-1.559). It is also noteworthy that -31 C/C and C/T genotype are in higher frequency in the patient group. It is also noteworthy that we determined that the -511 CT genotype caused an increase in HF risk. And also we found that the carriers of the -31 SNP C variant have a 3.3 fold risk increase of heart failure compared to TT homozygotes, and the carriers of the -511 SNP T allel have 4.5 fold risk increase of HF.

We have previously conducted a study of clinical prediction of serum ER stress marker levels in acute decompensated heart failure and found serum PERK levels high in patients with acute decompensated heart failure. We have found the serum GRP78 level higher in control group. Similarly, in our study, we found serum PERK level higher in the HF group. Unlike our previous study, we found the serum GRP78 level at a similar level among the groups (SABIRLI *et al.* 2019). This situation reveals the necessity of studying ER stress markers in wider populations in heart failure.

It is known that ER stress causes the release of proinflammatory cytokines through the effect on infamazomas and stimulates inflammatory processes, and IL-1B triggers ER stress (VERMA *et al* 2010; XIAO *et al* 2014; STROWIG *et al*. 2012). They found that IL-1B stimulates ER stress in pancreatic epithelial cell lines, dependent on c-JUN N-terminal kinase (JNK) (VERMA *et al.* 2010). We did not find any study investigating the effect of IL-1B gene polymorphism on ER stress in our literature review. In our study, high levels of serum PERK and GRP-78 in HF group individuals with -31 TT genotype is remarkable. In the control group, the CHOP level was found to be high in the TT genotype. Serum PERK and GRP-78 levels were found high in individuals

with T allele in the HF group. In individuals with T allele, only the CHOP level is high in the control group. This situation suggests that having -31 T allele in the case of heart failure, where inflammatory processes are prominent, triggers ER stress and proinflammatory processes.

In individuals with -511 T allele or -511 CT genotype, only CHOP level was found to be high. This relationship is similar to the relationship between -511 CT gene polymorphism and CRP level. While the ER stress marker level is not different in individuals with C and T alleles in the HF group, the high CHOP level in individuals with the T allele in the control group suggests that *IL-1B* (-511 C / T) polymorphism does not have a significant effect on ER stress marker levels.

It is known that ER stress stimulates infamazomas and triggers the inflammatory process (STROWIG *et al*. 2012; MENU *et al*. 2012). The polymorphism of nucleotides located in the -31 and -511 regions of the gene encoding the IL-1B protein regulates *IL-1B* expression (BHAT *et al*. 2014). In the study of LATKOVSKIS *et al.*, there was no difference in CRP levels between -511 genotypes in CAD patients (p = 0.127) (LATKOVSKIS *et al*. 2004). In another study, individuals with -511 CC genotype had higher CRP levels (ROGUS *et al*. 2008).In another study, serum CRP levels were found low in individuals with IL-1B -511 T allele (LIN *et al.*2007). Although the relationship between -511 gene polymorphism and CRP level has been frequently studied in the literature, the relationship between *IL-1B* (-31 T / C) gene polymorphism and CRP level has been studied less in number. Our study is the first study that has investigated relationship between *IL-1B* SNP's and CRP levels in patient who have HF.

In the group of patients with heart failure, we did not find any study of these two gene regions in our literature search. In our study, there was no difference between the CRP levels of those who had the T or C allele of -511 in the entire population (HF + Control), but individuals with the -511 CT genotype were found to be higher in CRP. The reason for the higher CRP level in individuals with CC genotype in the HF group and in individuals with the CT genotype in the control group would be probably because of the CC genotype frequency is low in the HF group. Also, in our study, the high serum CRP value in individuals with -31 T allele and individuals with T T genotype is remarkable, and -31 polymorphism of -511 is more effective than polymorphism. When both HF group, control group and whole population with -31 T allele or TC or TT genotype were examined together, serum CRP values were higher than other genotypes and alleles. It was thought that the *IL-1B* (-31 T/C) gene region may play a more active role in *IL-1B* gene expression.

The present study has some limitations such as the absence of IL-1B level. We consider that evaluating CRP level is sufficient to evaluate inflammation. Measuring the tissue levels of ER stress markers could also provide more benefit, but it was not possible to take tissue samples in the HF patient group.

CONCLUSIONS

In conclusion, in this study, we reported that the inflammatory response caused by IL-1B (-31 T / C) gene polymorphism increased and the ER stress response increased, inflammatory pathway and ER stress of having IL-1B (-31 T / C) T / T genotype or T allele. We consider it has a significant effect on it. We observed that the carriers of the -31 SNP C variant have a 3.3 fold risk increase of heart failure compared to TT homozygotes, and the carriers of the -511 SNP T allel have 4.5 fold risk increase of heart failure.

We think that IL-1B (-511 C / T) polymorphism has an effect on the level of CHOP protein, which plays an important role in the apoptotic pathway rather than the inflammatory pathway.

Received, September 07th, 2020
Accepted August 28th, 2021

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ASOCIJACIJA *IL-1B* (-511 C / T) I*IL-1B* (-31 T / C) GENSKOG POLIMORFIZMA SA ENDOPALZMATIČNIM RETIKULOM STRES MARKERIMA NIVOOM U AKUTNOJ DEKOMPEZATNOJ SRČANOJ SLABOSTI

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Izvod

Važnu ulogu u patogenezi srčane insuficijencije igraju inflamatorni procesi. Aktivira se akumulacija nesavijenih proteina u lumenu endoplazmatskog retikuluma i signalna putanja odgovora nesavijenog proteina. Gen IL-1B se nalazi u regionu hromozoma 2.k14. -31 i -511 pojedinačni nukleotidni polimorfizmi (SNP) otkriveni su u promotorskom regionu IL-1B. Ova dva SNP utiču na ekspresiju IL-1. Ova studija ima za cilj da istraži prisustvo polimorfizama gena IL-1B (-511 C / T) i IL-1B (-31 T / C) i odnos između markera ER stresa i markera zapaljenja. Pacijenti koji su se javili na odeljenje urgentne medicine sa nalazom akutne dekompenzovane srčane insuficijencije. Polimorfna mesta gena IL-1B određena su sekvenciranjem DNK. U svim studijama, osobe sa alelom IL-1B (-31 T / C) T imaju više srednje vrednosti nivoa PERK, GRP-78, CHOP i CRP u serumu od osoba sa alelom IL-1B (-31 T/C) C ($p = 0,0001$, $p = 0,002$, $p = 0,002$ i $p = 0,011$, respektivno). Serumske vrednosti ERK i GRP-78 u grupi HF bile su veće kod osoba sa IL-1B (-31 T / C) T alelom u poređenju sa osobama sa C alelom ($p = 0,0001$ i $p = 0,006$). Postojala je statistički značajna razlika u nivoima CHOP u serumu u kontrolnoj grupi sa alelom IL-1B (-511 C / T) T i kod osoba sa alelom C u grupi HF ($p = 0,002$). U zaključku, smatramo da se inflamatorni odgovor izazvan polimorfizmom gena IL-1B (-31 T / C) povećao i povećao odgovor na stres ER, inflamatorni put i ER stres od IL-1B (-31 T / C) T / T genotip ili T alel.

Primljeno 07.IX.2020.
Odobreno 28.VIII. 2021.