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DIAGNOSTIC AND PROGNOSTIC BIOMARKERS AT IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION

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Introduction. Idiopathic pulmonary arterial hypertension (IPAH) is a subtype of pulmonary arterial hypertension (PAH). IPAH is characterized by a progressive increase in pulmonary vascular resistance (PVR), which can lead to right ventricular heart failure and even mortality. The aim was to study the levels of C-reactive protein (CRP), endothelin-1 (ET-1) and interleukin-6 (IL-6) in patients with IPAH, as well as to assess their relationship with clinical and hemodynamic parameters.

Materials and methods. Expression of CRP, ET-1 and IL-6 in blood serum samples of patients with IPAH (n=53) and control group (n=52) of the appropriate age/gender was determined using enzyme immunoassay (ELISA). Demographic, clinical characteristics and hemodynamic parameters were studied in patients with IPAH according to catheterization of the right heart (CRH).

Result and discussion. The average age range of patients with IPAH was 35.0-51.0 years, there were 46 (86.8%) women in this group. The average age of the participants in the control group was 31.0-42.0 years, there were 46 (88.5%) women. The levels of ET-1 ($p < .016$) and IL-6 ($p < .001$) were higher in patients with IPAH compared to patients in the control group, whereas the level of CRP ($p = .270$) was no different. Meanwhile, the level of ET-1 positively correlated with the average pressure in the right atrium ($r = .728$, $p < .001$) and pulmonary vascular resistance ($r = .360$, $p = .008$), while IL-6 positively correlated with the functional class of heart failure according to the classification of the New York Heart Association (NYHA FC).

Conclusion. Levels of IL-6 and ET-1 can be included in the diagnostic algorithm for assessing the severity and prognosis of the disease.

Key words: idiopathic pulmonary arterial hypertension; c-reactive protein; endothelin-1; interleukin-6

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive pulmonary vascular disease with high morbidity and mortality [21]. Idiopathic pulmonary arterial hypertension (IPAH) corresponds to a sporadic disease without any family history of PAH or a known provoking factor. The prevalence of PAH among the adult population was registered in the range of approximately 15-26 cases and 4.6-9 cases per million, respectively. About half of patients with PAH worldwide have hereditary, idiopathic, or drug-induced PAH [18]. Despite the fact that this disease is rare, the 5-year survival rate is only 65% even with modern treatment, which underlines the importance of prognostic assessment. Risk stratification is necessary to inform about the prognosis, to select treatment options, to monitor treatment response or disease progression [8]. Therefore, early diagnosis is crucial to improve the prognosis in patients with IPAH. One of the solutions to this problem may be the search for new biomarkers to predict the risk of IPAH development.

IPAH is characterized by proliferation of smooth muscle cells, fibroblasts and endothelial cells in the walls of small pulmonary arteries. Some scientists suggest that the inflammatory response and inflammatory pathways play the important role in the pathogenesis of PAH [3]. Perivascular inflammation is an important feature of the pathogenesis of PAH, but the exact role of the inflammatory pathway remains controversial. Many studies have confirmed the role of interleukin-6 (IL-6) in the pathogenesis of

pulmonary hypertension (PH). One study described that lung function in patients with PAH is inversely correlated with increased blood serum concentrations of IL-6 [5]. IL-6 is a small molecular glycoprotein encoded by the 7p15-21 chromosome, which consists of four α-structures and usually exists in the form of a monomer [10]. IL-6 is also a pleiotropic cytokine, which is known to play a crucial role in the progression of PAH. Blood plasma levels of IL-6 are increased in both patients and animal models of PAH [20].

The level of circulating IL-6 in patients with PAH may be prognostic marker, because some studies have demonstrated the correlation between IL-6 levels and long-term survival outcomes [9]. Although IL-6 may be a poor predictor of hemodynamics in patients with PAH, and a strong correlation has been shown between IL-6 levels and right ventricular dysfunction [2]. In addition, the recent study showed that pulmonary artery endothelial cells from patients with IPAH have increased regulation of membrane-bound IL-6 receptors [6]. Increased expression of IL-6 contributed to the antiapoptotic phenotype in pulmonary artery endothelial cell dysfunction in patients with IPAH, but not in the control group. Simpson et al. [16] demonstrated that the increased concentration of IL-6 in the blood is associated with remodeling of pulmonary vessels in patients with PH. It has been proven that IL-6 can become the potential therapeutic target for early diagnostic markers of diseases and treatment of PAH, including PAH associated with connective tissue diseases (CTD-PAH). Increased levels of IL-6 can predict mortality and have been associated with the survival of patients with PAH of group 1 [11].

C-reactive protein (CRP) has both pro-inflammatory and anti-inflammatory effects. Quarck et al. demonstrated that CRP levels in patients with PAH or chronic thromboembolic pulmonary hypertension (CTPH) were higher than in control subjects, and CRP level in patients with PAH correlated with NYHA functional class, right atrial pressure, 6-minute walking time, response to therapy and overall survival [11].

Endothelin-1 (ET-1) is a peptide that acts as a powerful vasoconstrictor and has a wide range of both physiological and pathological functions [2]. ET-1 is a mediator of functional and morphological vascular abnormalities of pulmonary hypertension, expressed basally in pulmonary epithelial cells [4, 12]. In recent years, the focus has been on the contribution of the ET-1 annex. This has led to the development of various ET receptor antagonists, some of which are approved for the treatment of PAH [1, 15].

The aim of the study was to consider the levels of CRP, IL-6 and ET-1 in patients with IPAH and to assess the relationship with clinical and hemodynamic parameters of the disease.

MATERIALS AND METHODS

Participants. The study included 53 patients with IPAH examined at the specialized National Scientific Cardiac Surgery Center (Astana city) in the period from 2016 to 2022. All patients were over the age of 18. The diagnosis of IPAH in all patients was confirmed by catheterization of the right heart (CRH) after the comprehensive clinical examination and exclusion of pulmonary hypertension caused by other causes (left heart defects, lung diseases, thromboembolism, etc.). Demographic and clinical characteristics of all examined persons were studied. The severity of heart failure was assessed in accordance with the criteria of the functional class according to the classification of the New York Heart Association (NYHA FC). All participants signed the informed consent regarding the purpose and procedure of the study. The control group consisted of practically healthy individuals (n=52) comparable in age and gender with no personal or family history of PAH or other cardiovascular diseases (such as congenital heart defects, coronary heart disease, chronic heart failure, arterial hypertension).

Ethics statement. The scientific study was approved by the Ethics Committee of Karaganda medical university NC JSC (Protocol No. 62 dated 12.04.2021).

Molecular analysis. Blood plasma samples of all patients with IPAH and the control group were analyzed by enzyme immunoassay (ELISA) for biomarkers: CRP, endothelin-1 and interleukin-6. The analysis was performed using kits for endothelin-1 (ELISA – CEA482Ni), CRP (Vector Best A-9002), interleukin-6 (Vector Best A-8768). Biomarker levels were measured in peripheral venous blood samples taken from patients with IPAH. Peripheral venous blood samples were collected, stored on ice and centrifuged for 30 minutes. Samples were stored at the temperature of -80 °C prior to analysis. The biochemical study was conducted on the basis of Shared laboratory of Karaganda medical university NC JSC (Karaganda city).

Statistical analysis. Descriptive statistics were calculated and presented as medians (*Mdn*) and interquartile range (*IQR*) for continuous data with non-normal distribution. Distribution of the data was evaluated by analyzing Skew and Kurtosis, as well as the visual inspection of histograms. Levene's test was utilized to assess the assumption of homogeneity of variance. Frequencies (*n*) and percentages (%) were presented for categorical data. For continuous data, Mann – Whitney U-test was used to compare median values of two data series. Whereas Kruskal-Wallis test was employed for multiple comparisons. Wilcoxson Rank Sum test was utilized for pairwise comparisons. Univariate association with IPAH was examined with Pearson's Chi-Square test. Odd ratio

was used as an index of effect size. Spearman's rank correlation coefficient is used to assess the relationship between two continuous variables. Statistical level of significance was accepted as $p < .05$. The probability values, which fall in the range ≥ 0.05 to < 0.10, were regarded as a trend towards statistical significance. Statistical analysis was performed utilizing R version 4.4.1 (R Core Team, 2024).

RESULTS

Clinical characteristics of IPAH patients. In total, 105 persons were included in the study: 53 (50.5%) with IPAH and 52 (49.5%) relatively healthy people. The age range of patients with IPAH was 35.0-51.0 years, 46 (86.8%) of them were female. At the same time, the age of the surveyed in the control group was 31.0–42.0 years, 46 (88.5%) of them were female. According to the results of the study, the relationship of IPAH with age was determined (*OR* = 1.09, *95%CI* = [1.04-1.14]), although no relationship between IPAH and gender was registered (*OR* = 1.17, *95%CI* = [0.36-3.74]). Among patients with IPAH, NYHA functional class I (FC I) of chronic heart failure (HF) was diagnosed in 3 patients (5.7%), FC II – in 17 (32.1%), FC III – in 28 (52.8%), FC IV – in 5 (9.4%). At the same time, the median values of mPAP and mRAP were 33.0 (28.0–45.0) and 4.0 (5.0–6.0) mmHg, respectively. The average PVR was 6.0 (10.6–14.6) WU, whereas the average CI value according to Fick was 2.3 (1.9–2.7) l/min/m^2 (Table 1).

CRP, ET-1 and IL-6 expressions in IPAH patients and controls. The results show that there was no significant difference in the level of CRP between patients with IPAH (*Mdn* = 3.45) and the control group (*Mdn* = 4.79), *U* = 1205.5, p = 0.270. The ET-1 value was significantly higher in patients with IPAH (*Mdn* = 17.09) than in the control group (*Mdn* = 15.53), *U* = 1754.5, p = 0.016. In addition, it was found that patients with IPAH had significantly higher level of IL-6 (*Mdn* = 4.97) than practically healthy people (*Mdn* = 3.26), *U* = 1954.0, *p* <0.00022. The data is shown in Figure 1 (A, B, C).

Correlation of Il-6, CRP and ET-1 with clinical characteristics in IPAH patients. Table 2 presents the assessment of the association of CRP, ET-1, IL-6 and the characteristics of patients with IPAH.

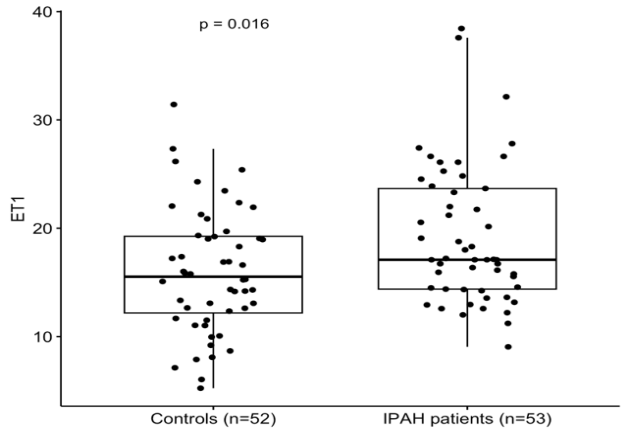
The results demonstrated that there was no significant correlation between CRP and the clinical characteristics of patients with IPAH. The same pattern was observed for IL-6 level, which did not correlate with the clinical characteristics of patients with IPAH. However, the ET-1 level was significantly associated with mRAP (r = 0.728, *p* <0.001) and PVR (r = 0.360, p = 0.008).

We also determined the effect of NYHA FC in patients with ILPAH on CRP and ET-1 levels. It was found that NYHA FC HF did not affect CRP level *(H* (3) = 4.71, *p* = .194) and ET-1 (*H* (3) = 5.87, *p* = .118). However, NYHA FC significantly affected IL-6 level of (*H* (3) = 16.12, *p* = 0.001). The results of

Table 1 – Clinical characteristics of IPAH patients and controls

Characteristic	Patients with IPAH (n=53)	Controls (n=52)	p
Age, *Mdn (IQR)*	45.0 (35.0–51.0)	33.5 (31.0–42.0)	< .001
Sex, *n (%)*			
Male	7 (13.2%)	6 (11.5%)	.795
Female	46 (86.8%)	46 (88.5%)	
NYHA FC, *n (%)*			
I	3 (5.7%)	-	-
II	17 (32.1%)	-	-
III	28 (52.8%)	-	-
IV	5 (9.4%)	-	-
mPAP (mmHg), *Mdn (IQR)*	33.0 (28.0–45.0)	-	-
PVR (WU), *Mdn (IQR)*	6.0 (10.6–14.6)	-	-
mRAP(mmHg), *Mdn (IQR)*	4.0 (5.0–6.0)	-	-
Fick CI (l/min/m^2), *Mdn (IQR)*	2.3 (1.9–2.7)	-	-

Note: IPAH – idiopathic pulmonary arterial hypertension; IQR – interquartile range; Mdn – median; mPAP – mean pulmonary artery pressure; PVR – pulmonary vascular resistance; mRAP – mean right atrial pressure; CI – cardiac index, NYHA FC – New York Heart Association Functional Classification



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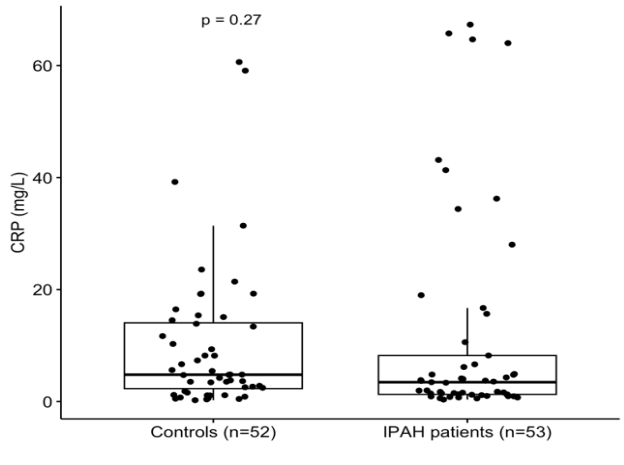

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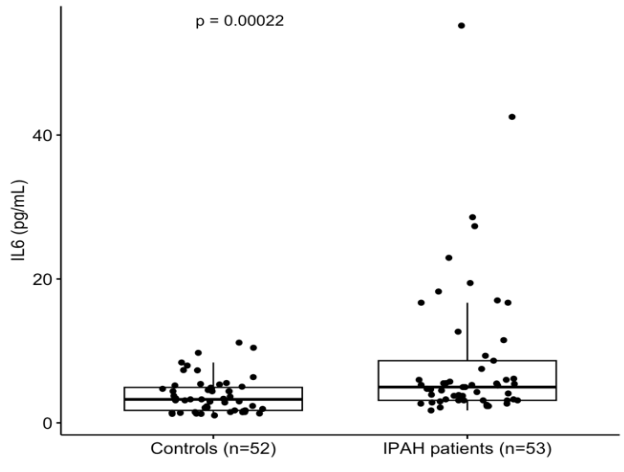
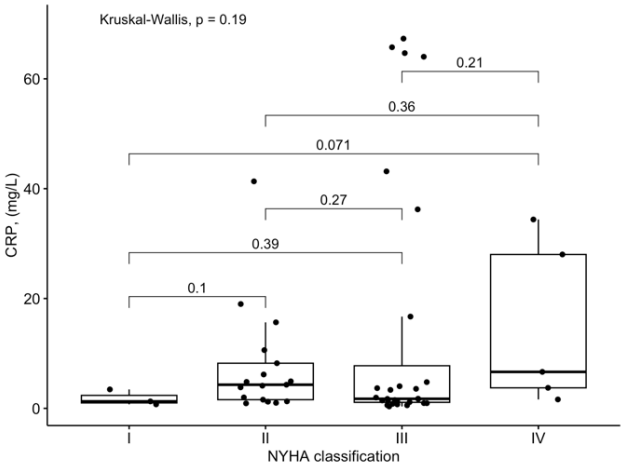


(C)

Figure 1 – Comparison of CRP, ET-1 and IL-6 between patients with IPAH and controls. A – comparison of CRP between IPAH patients and controls; B – comparison of ET-1 between IPAH patients and controls; C – comparison of IL-6 between IPAH patients and controls



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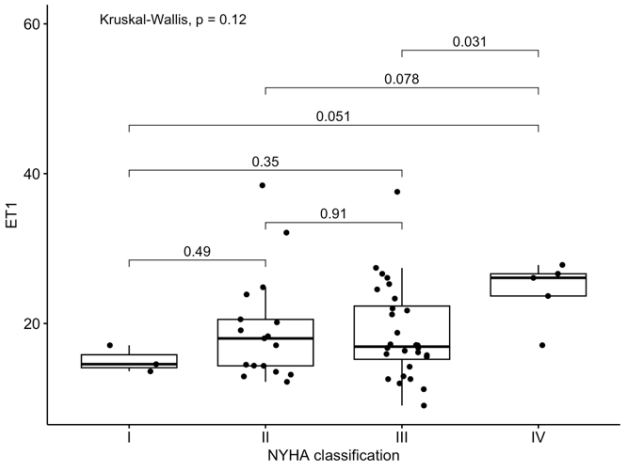

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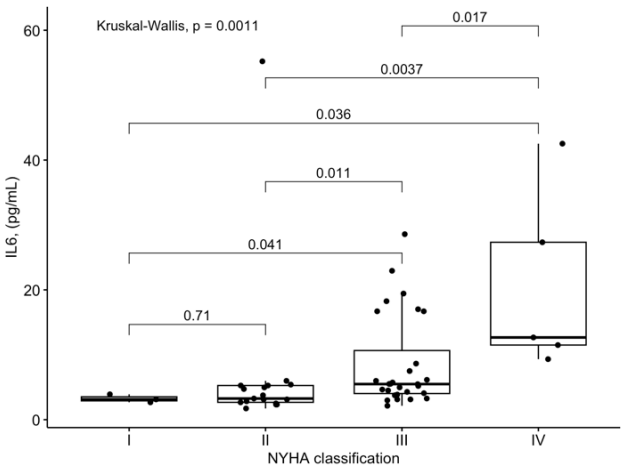

(C)

Figure 2 – Comparison of CRP, ET-1 and IL-6 levels in patients with IPAH according to WHO-FC grade. A – comparison of CRP between patients with IPAH and FC grade; B – comparison of ET-1 between patients with IPAH and FC grade; C – comparison of IL-6 between patients with IPAH and FC grade

Table 2 – Correlation of CRP, ET1, IL6 with characteristics of patients with IPAH

Characteristic	CRP		ET-1		IL-6	
	r	p	r	p	r	p
Age	.238	.086	.067	.636	.197	.158
Sex	.019	.948	-.224	.351	.486	.168
mPAP	-.027	.849	.728	< .001	.179	.201
PVR	.088	.533	.360	.008	.049	.726
mRAP	.116	.409	.036	.799	-.004	.979
Fick CI	.076	.590	-.192	.169	.120	.393

Note: CRP – C-reactive protein; ET-1 – endothelin-1; IL-6 – interleukin-6; mPAP – mean pulmonary artery pressure; PVR – pulmonary vascular resistance; mRAP – mean right atrial pressure; Fick CI – cardiac index by Fick

pairwise comparisons of IL-6 levels between NYHA functional classes suggested that IL-6 level did not differ significantly in patients with FC I and FC II ($W = 21.5$, $p = .710$). At the same time, the level of IL-6 in patients with IPAH with NYHA FC I was significantly lower than in patients with FC III ($W = 11$, $p = .0415$) and FC IV ($W = 0$, $p = .036$). Also, IL-6 level was significantly higher in patients with IPAH and FC III and IV ($W = 128.5$, $p = 0.011$) ($W = 5$, $p = .004$) than in patients with FC II. The results of the comparative assessment of IL-6 level depending on FC III and IV showed that IL-6 level was significantly lower in patients with IPAH and FC III than in patients with FC IV ($W = 22$, $p = .017$). The above data is shown in Figure 2.

DISCUSSION

Evaluation of CRP, ET-1 and IL-6 levels in patients with IPAH and participants of the control group showed that ET-1 and IL-6 levels were higher in patients with IPAH compared with control subjects, whereas the level of CRP did not differ in the two groups. IL-6 level plays a significant role in the emergence and development of PAH. In patients with PAH, IL-6 level is not only the inflammatory factor, but it also performs a dual pro-inflammatory and anti-inflammatory function, and it is the «mediator» of PAH progression. In our study, the severity of heart failure was associated with the increased level of circulating IL-6 at IPAH. IL-6 level significantly affects NYHA FC HF, that is, the increase in severity of FC correlates with the progression of IL-6 level. Several researchers have shown that IL-6 level was significantly increased in patients with IPAH and HPAH. At the same time, IL-6 was identified as a more informative predictor of IPAH development than such traditional criteria as the 6-minute walk test or hemodynamic parameters [17]. Increased IL-6 levels can predict high mortality and are associated with the survival of patients with IPAH [7, 14]. In IPAH, there was the imbalance between vasoconstriction and vasodilation. Regardless of the provoking factor, vasoconstriction in combination with vascular fibrosis and proliferation of endothelial cells leads to pathogenic remodeling characteristic of PAH.

The results of our study show that the circulating level of the endothelin 1 biomarker increases significantly at IPAH and correlates with key cardiopulmonary hemodynamic parameters such as pulmonary vascular resistance and mean pressure in the right atrium (PVR and mPAP), which affect the prognosis of the disease. Similar results were reported in several other studies and were characterized by increased blood serum levels of endothelin-1 in patients with IPAH, correlated with pulmonary hemodynamics. Rubens et al. [13] found that there was the strong correlation between PAP, PVR, CI and ET-1 blood plasma levels. Blood serum ET-1 level may be the prognostic factor in patients with IPAH. The control reference ET-1 value, published by Carmine laboratory, ranges from 5 to 12 pg/ml, but the risk of death from IPAH increases by 10% with the increase of ET-1 level in blood plasma by 1 pg/ml [19]. Our study has some limitations, first of all, since IPAH is an orphan disease, the sample size in this study was small.

CONCLUSION

IPAH correlates with higher IL-6 and ET-1levels. In this regard, it can be assumed that these biomarkers in patients with IPAH can be included in the diagnostic algorithm for assessing the disease severity and predicting.

Authors' contributions:

D. Z. Taizhanova, G. Zh. Abildinova – conception and design of the study, editing.

T. T. Nurpisova – collection and processing of material, manuscript formation, design, statistical processing.

Conflict of interest. No conflict of interest has been declared.

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ДИАГНОСТИЧЕСКИЕ И ПРОГНОСТИЧЕСКИЕ БИОМАРКЕРЫ ПРИ ИДИОПАТИЧЕСКОЙ ЛЕГОЧНОЙ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ

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Введение. Идиопатическая легочная артериальная гипертензия (ИЛАГ) – представляет собой подтип ЛАГ, характеризующийся прогрессирующим увеличением легочного сосудистого сопротивления (ЛСС), что может привести к правожелудочковой сердечной недостаточности и даже смертности. Цель исследования – изучение уровня С-реактивного белка (СРБ), эндотелина-1 (ЭТ-1) и интерлейкина-6 (ИЛ-6) у пациентов с ИЛАГ, а также оценка их взаимосвязи с клиническими и гемодинамическими показателями.

Материалы и методы. Экспрессию СРБ, ЭТ-1 и ИЛ-6 в образцах сыворотки пациентов с ИЛАГ (n=53) и контрольной группы (n=52) соответствующего возраста/пола определяли с помощью иммуноферментного анализа (ИФА). У пациентов с ИЛАГ изучены демографические, клинические характеристики и гемодинамические показатели по данным катетеризации правых отделов сердца (КПОС).

Результаты и обсуждение. У пациентов с ИЛАГ средний возрастной диапазон составил 35.0–51.0 года, из них женщин 46 (86,8%), а в контрольной группе 31.0–42.0 года, женщин было 46 (88,5%). ЭТ-1 (p <.016) и ИЛ-6 (p <.001) были увеличены у пациентов с ИЛАГ по сравнению с контрольной группой, тогда как уровень СРБ (p = .270) не отличался в двух группах. Между тем, ЭТ-1 положительно коррелировал со средним давлением в правом предсердии (r = .728, p <.001) и легочно-сосудистым сопротивлением (r = .360, p = .008), тогда как ИЛ-6 положительно коррелировал с функциональным классом сердечной недостаточности по классификации New York Heart Association (NYHA FC).

Заключение. ИЛ-6 и ЭТ-1 могут быть включены в диагностический алгоритм оценки тяжести и прогнозирования заболевания.

Ключевые слова: идиопатическая легочная артериальная гипертензия; с-реактивный белок; эндотелин-1; интерлейкин -6

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ИДИОПАТИЯЛЫҚ ӨКПЕЛІК АРТЕРИАЛДЫҚ ГИПЕРТЕНЗИЯДАҒЫ ДИАГНОСТИКАЛЫҚ ЖӘНЕ БОЛЖАМДЫҚ БИОМАРКЕРЛЕРІ

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Өзектілігі. Идиопатиялық өкпелік артериялық гипертензия (ИӨАГ) оң жақ қарыншаның жүрек жеткіліксіздігіне және ерте өлімге әкелуі мүмкін өкпе тамырларының кедергісін (ӨТК) үдемелі жоғарылауымен сипатталатын өкпелік артериалдық гипертензияның (ӨАГ) қосалқы түрі болып табылады.

Зерттеудің мақсаты. С-реактивті ақуыз (СРА), эндотелин-1 (ЭТ-1) және интерлейкин-6 (ИЛ-6) деңгейін ИӨАГ науқастарында зерттеу, сонымен қатар олардың клиникалық және гемодинамикалық көрсеткіштерімен байланысын бағалау.

Материалдар және әдістер. ИӨАГ науқастарының (n=53) және жасы/жынысы сәйкес келетін бақылау тобының (n=52) сарысу үлгілеріндегі СРА, ЭТ-1 және ИЛ-6 экспрессиясы иммуноферментті талдаудың (ИФА) көмегімен анықталды. ИӨАГ пациенттерінің демографиялық, клиникалық және оң жақ жүрек катетеризациясы көмегімен анықталған гемодинамикалық көрсеткіштері сипатталды.

Нәтижелер және талқылау. ИӨАГ бар науқастарда орташа жас диапазоны 35,0-51,0 жасты құрады, оның 46-сы (86,8%) әйелдер, ал бақылау тобында 31,0-42,0 жас, оның 46-сы (88,5%) әйелдер. ЭТ-1 (p < .016) және ИЛ-6 (p < .001) бақылау тобымен салыстырғанда ИӨАГ бар науқастарда жоғары, ал СРА деңгейі (p = .270) екі топ арасында ерекшеленбеді. Сонымен қатар, ЭТ-1 оң жақ жүрекшенің орташа қысымымен (r = .728, p < .001) және өкпе тамырларының қарсылығымен (r = .360, p = .008) оң корреляцияда болды, ал ИЛ-6 Нью-Йорк жүрек қауымдастығының (NYHA FC) классификациясына сәйкес жүрек жеткіліксіздігі функционалдық классымен оң корреляцияда болды.

Қорытынды. ИЛ-6 және ЭТ-1 ИӨАГ ауырлығы мен болжамын бағалау үшін диагностикалық алгоритмге қосуға болады.

Кілт сөздер: идиопатиялық өкпелік артериялық гипертензия; с-реактивті ақуыз; эндотелин-1; интерлейкин-6