Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2024.275884.3239 Volume 30, Issue 9.1, December. 2024, Supplement Issue
Manuscript ID ZUMJ-2403-3239
DOI 10.21608/ZUMJ.2024.275884.3239
Original Article

The Predictive Value of Follistatin-Like Protein 1 in Pediatric Patients with Hypoxia-Induced Pulmonary Hypertension: A Case-Control Study

Heba Mohamed Abdelazeem Mahmoud[*1], M.M.Romih[1], Amal S. El-Shal[2, 3], Eman M.M. El-Hindawy[1]
[1] Pediatrics Department, Faculty of Medicine, Zagazig University, Egypt
[2]Medical Biochemistry and Molecular Biology Department, Faculty of Medicine, Zagazig University, Egypt
[3] Medical Biochemistry and Molecular Biology Department, Armed Forces college Of Medicine (AFCM), Egypt

Corresponding author*:

Heba Mohamed Abdelazeem Mahmoud

Email: hebaaboelmge@gmail.com

Submit Date 10-03-2024
Revise Date 24-03-2024
Accept Date 25-03-2024

ABSTRACT

Background: Right ventricular hypertrophy and elevated pulmonary arterial pressure are the results of abnormal pulmonary artery smooth muscle cell (PASMC) migration and proliferation, which cause pulmonary vascular remodeling and pulmonary hypertension (PH), which is still a fatal condition. Secreted glycoprotein follistatin-like protein 1 (FSTL1) reduces tissue remodeling in cardiovascular injury. However, the function of FSTL1 in aberrant pulmonary arteries is still unknown.**Aim:** To evaluate the relationship between the plasma levels of FSTL1 and hypoxia-induced pulmonary hypertension in pediatric patients.**Methods:** This case–control study was conducted in the Pediatrics and Medical Biochemistry Departments of the Faculty of Medicine, Zagazig University. Thirty-nine subjects were divided into three groups: group (I): 13 subjects with no history of pulmonary or cardiovascular disease and not receiving any medication composed the control group; group (II): 13 patients with pulmonary hypertension and no history of pulmonary disease; and group (III): 13 patients with hypoxia-induced pulmonary hypertension. Plasma levels of FSTL1 were measured in all subjects.**Results:** Plasma FSTL1 levels were significantly higher in patients with hypoxia-induced pulmonary hypertension compared to healthy controls and patients with pulmonary hypertension and no history of pulmonary disease. FSTL1 can significantly predict hypoxia-induced pulmonary hypertension in pediatric patients (AUC= 0.982, P value <0.001) at a cut-off > 63.435µg/L with 92.31% sensitivity and 100% specificity.

Conclusion: Plasma levels of FSTL1 were found to be a significant predictor of hypoxia-induced pulmonary hypertension in pediatric patients.

Keywords: Follistatin-like protein 1, Hypoxia, Pulmonary

INTRODUCTION

Vascular remodeling and proliferation are hallmarks of the condition known as pulmonary hypertension (PH), which affects the tiny pulmonary arteries. It causes the mean pulmonary arterial pressure to rise by more than 25 mm Hg, and the pulmonary vascular resistance to gradually increase **[1].**

Since follistatin-like proteins are members of the major family of secreted protein, acidic and rich in cysteine (SPARC) that share a high degree of primary sequence and domain structural homology with the activin-binding protein follistatin (FST), they appear to be intriguingly. These homologous proteins play a role in controlling how cells interact with their surroundings **[2].**

Because it is expressed in the majority of mesenchymal cell types, FSTL1 has an impact on lung tissue. It has been demonstrated that a reduction in FSTL1 in mice causes respiratory failure, which in turn causes postnatal death. Furthermore, the creation of the cartilaginous base of the respiratory tract is disrupted by the

inactivation of the FSTL1 gene. This is shown by a halt in development and a reduction in the tracheal trunk's overall number of produced semicircles **[3].**

Because no previous studies have investigated pulmonary hypertension in humans and its relationship with FSTL1, this study aimed to evaluate the relationship between plasma levels of FSTL1 and hypoxia-induced pulmonary hypertension in pediatric patients.

METHODS

This case–control study was conducted in the Pediatrics and Medical Biochemistry Departments of the Faculty of Medicine, Zagazig University, from August 2022 to February 2023. Thirty-nine subjects were divided into three groups: group (I): 13 subjects with no history of pulmonary or cardiovascular disease and not receiving any medication composed the control group; group (II): 13 patients with pulmonary hypertension and no history of pulmonary disease; and group (III): 13 patients with hypoxia-induced pulmonary hypertension.

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University (IRB number 9735). The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

The inclusion criteria

Group (I); pediatric patients with hypoxia-induced pulmonary hypertension (a. pulmonary parenchymal disease, including extensive pneumonia, bronchopulmonary dysplasia, interstitial lung disease, and hypoplasia of the lungs; b. inadequate ventilator drive, including obesity, hypoventilation, and the central nervous system; c. disorders of the chest wall, including kyphoscoliosis and weakness or paralysis of the skeletal muscles). Group (II); pediatric patients without history of pulmonary diseases (large left to right shunt lesions (patent ductus arteriosus-ventricular septal defect, pulmonary venous hypertension due to mitral stenosis-chronic heart failure, and primary pulmonary vascular disease)). Group (III); healthy controls.

The exclusion criteria

Pediatric patients with autoimmune diseases, inflammatory diseases, or bronchial asthma and those with tumors were excluded from the study.

All subjects subsequently underwent a questionnaire interview that collected personal information, sociodemographic information, and a thorough medical history with a focus on age, sex, and length of sickness; symptoms of pulmonary hypertension (cough, dyspnea, recurrent chest infection, haemoptysis, chest wheezing); anti-failure drugs received (number, types, doses and duration); previous hospital and ICU admissions (number and drugs received during admission); clinical examination; local examination of the heart; laboratory investigations, including complete blood count (CBC); C-reactive protein (CRP); liver and kidney functions; and plasma FSTL1 levels, which were measured by an enzyme-linked immunosorbent assay (ELISA) kit for humans. Conventional echocardiographic evaluation was performed by the same experienced physician using an ultrasound system computer sonograph equipped with 2.5 to 3.5 MHz phased array transducers (with a Hewlett Packard 5500 ultrasound system with a 2.5 to 3.5 MHz transducer) (HP, Andover, MA).

Statistical analysis

Statistical analysis was performed with SPSS v26 (IBM Inc., Armonk, NY, USA). ANOVA (F) with a post hoc test (Tukey) was used to analyse quantitative parametric data, the Kruskal–Wallis test was used to analyse quantitative non-parametric data with the Mann–Whitney test to compare each group, the chi–square test was used to analyse qualitative variables, Pearson's correlation was performed to estimate the degree of correlation between two quantitative parametric variables and Spearman's correlation was performed to estimate the degree of correlation between two quantitative non-parametric variables. ROC curve analysis was used to evaluates the overall test performance (where the area under the curve >50% denotes acceptable performance and area about 100% is the best performance for the test).

RESULTS

SBP was significantly high in group I than in groups II and III (P =0.035 and <0.001, respectively), and it was significantly higher in group II than in group III (P =0.001). DBP was significantly higher in group I than in group III (P value =0.003), with no significant difference between groups I and II or between groups II and III. Pulses and RRs were significantly lower in group I than in groups II and III (P value <0.001), with no significant difference between groups II and III. Oxygen saturation was significantly higher in group I than in groups II and III (P value <0.001), with no significant difference between groups II and III. Pulmonary artery pressure was significantly lower in group I than in groups II and III (P value <0.001), and it was significantly lower in group III than in group II (P value =0.010). (Table1). FSTL1 plasma levels was significantly higher in group III than in groups I

and II (P value <0.001), with no significant difference between groups I and II (Table 2).

In hypoxia-induced pulmonary hypertensive patients, there was a significant negative correlation between FSTL1 and O_2 saturation (r= -0.644, P =0.018), while there was a significant positive correlation between FSTL1 and pulmonary artery pressure (r= 0.556, P =0.049). There were no significant correlations between FSTL1 and age, BMI, SBP, DBP, pulse, RR, Hb, WBCs, platelets, ALT, AST, creatinine, or CRP (Table 3).

In pulmonary hypertensive patients without hypoxia, there was a significant negative correlation between FSTL1 and AST (r= -0.653, P =0.016), while there was no significant correlation between FSTL1 and age, BMI, SBP, DBP, pulse, RR, O_2 saturation, pulmonary artery pressure, Hb, WBCs, platelets, ALT, creatinine, or CRP (Table 4).

In all pulmonary hypertensive patients, there was a significant positive correlation between FSTL1 and creatinine (r= 0.543, P =0.004), while there was a significant negative correlation between FSTL1 and SBP (r= -0.424, P =0.031) and pulmonary artery pressure (r= -0.462, P =0.017). There were no significant correlations between FSTL1 and age, BMI, DBP, pulse, RR, O_2 saturation, Hb, WBCs, platelets, ALT, AST, or CRP (Table 5).

FSTL1 can significantly predict hypoxia-induced pulmonary hypertension in pediatric patients (AUC= 0.982, P value <0.001) at a cut-off > 63.435µg/L, 92.31% sensitivity, 100% specificity, 100% PPV and 92.9% NPV (Table 6).

Table 1: Demographic, clinical and basic laboratory data of the studied groups

		Group I (n=13)	Group II (n=13)	Group III (n=13)	P value	
Age (years)	**Median**	3	1.6	6	0.561	
	IQR	2 - 4	0.6 - 4.5	0.8 - 8		
Gender (n)	**Male**	8 (61.54%)	7 (53.85%)	8 (61.54%)	0.899	
	Female	5 (38.46%)	6 (46.15%)	5 (38.46%)		
Weight (kg)	**Median**	12.5	11	22	0.442	
	IQR	11 - 15	7.9 - 13	9 - 26		
Height (cm)	**Mean ± SD**	96.85 ± 21.98	91.62 ± 28.24	97.85 ± 30.09	0.820	
	Range	75 - 145	65 - 154	55 - 145		
BMI (kg/m^2)	**Mean ± SD**	16.78 ± 3.02	16.34 ± 2.76	18.61 ± 2.91	0.121	
	Range	13.5 - 25	12.2 - 21.9	13 - 22.9		
SBP (mmHg)	**Mean ± SD**	109 ± 6.44	100.23 ± 10.52	86.92 ± 8.3	**<0.001***	P1 **=0.035*** P2 **<0.001*** P3 **=0.001***
	Range	100 - 120	85 - 125	70 - 100		
DBP (mmHg)	**Mean ± SD**	67.85 ± 10.95	58.08 ± 17.2	50.69 ± 7.05	**0.005***	P1 =0.127 P2 **=0.003*** P3 =0.298
	Range	50 - 85	44 - 95	40 - 60		
Pulse (beats/min)	**Mean ± SD**	82.77 ± 9.97	136.15 ± 22.47	132.85 ± 17.01	**<0.001***	P1 **<0.001*** P2 **<0.001*** P3 =0.887
	Range	66 - 100	100 - 165	110 - 160		
RR (breaths/min)	**Mean ± SD**	23.15 ± 4.93	46.69 ± 10.88	46.85 ± 12.97	**<0.001***	P1 **<0.001*** P2 **<0.001*** P3 =0.999
	Range	13 - 30	30 - 62	32 - 67		
O_2 saturation (%)	**Mean ± SD**	97.85 ± 1.21	92 ± 2.52	91.54 ± 1.9	**<0.001***	P1 **<0.001*** P2 **<0.001*** P3 =0.819
	Range	95 - 99	89 - 97	89 - 95		

Pulmonary artery pressure (mmHg)	**Mean ± SD**	13.31 ± 1.25	56.69 ± 10.67	48.46 ± 4.74	**<0.001***	P1 **<0.001*** P2 **<0.001*** P3 **=0.010***
	Range	12 - 16	40 - 67	45 - 55		
Hb (g/dl)	**Mean ± SD**	11.1 ± 0.99	10.86 ± 0.63	11.02 ± 1.72	0.876	
	Range	9.5 - 13.2	9.5 - 11.9	7.8 - 13.5		
WBCs (x10^9/L)	**Mean ± SD**	10 ± 3.89	9.77 ± 3.73	9.9 ± 3.73	0.988	
	Range	5 - 16.2	5.2 - 17.2	6.4 - 18		
Platelets (x10^9/L)	**Mean ± SD**	332.31 ± 111.02	362.15 ± 97.9	357.15 ± 73.34	0.697	
	Range	150 - 540	166 - 547	234 - 467		
ALT (U/L)	**Median**	18	15	17	0.842	
	IQR	15 - 25	13 - 20	14 - 22		
AST (U/L)	**Median**	27.2	33.7	26	0.194	
	IQR	17.5 - 31	28.2 - 45.7	20.5 - 47		
Creatinine (mg/dl)	**Median**	0.32	0.3	0.42	0.123	
	IQR	0.2 - 0.4	0.21 - 0.37	0.36 - 0.56		
CRP (mg/dl)	**Median**	9	12.8	12	0.252	
	IQR	6 - 11	6 - 24	9 - 24		

BMI: body mass index, IQR: interquartile range, SD: standard deviation, SBP: systolic blood pressure, DBP: diastolic blood pressure, RR: respiratory rate, Hb: hemoglobin, WBCs: white blood cells, ALT: alanine transaminase, AST: aspartate aminotransferase, CRP: C-reactive protein, *:significant as P value ≤ 0.05, P1: P value between group I and II, P2: P value between group I and III, P3: P value between group II and III.

Group (I): control subjects with no history of pulmonary or cardiovascular disease and not receiving any medication; group (II): patients with pulmonary hypertension and no history of pulmonary disease; and group (III): patients with hypoxia-induced pulmonary hypertension.

Table 2: FSTL1 of the studied groups

		Group I (n=13)	**Group II (n=13)**	**Group III (n=13)**	**P value**	
FSTL1 (µg/l)	**Mean ± SD**	52.53 ± 7.58	54.31 ± 8.79	110.25 ± 26.73	**<0.001***	P1 =0.961 P2 **<0.001*** P3 **<0.001***
	Range	40.324 - 63.435	44.274 - 76.132	61.126 - 148.891		

FSTL1: Follistatin-like protein 1, *: significant as P value ≤ 0.05, P1: P value between group I and II, P2: P value between group I and III, P3: P value between group II and III

Group (I): control subjects with no history of pulmonary or cardiovascular disease and not receiving any medication; group (II): patients with pulmonary hypertension and no history of pulmonary disease; and group (III): patients with hypoxia-induced pulmonary hypertension.

Table 3: Correlation between FSTL1 and different parameters in hypoxia-induced pulmonary hypertensive patients

	FSTL1 (µg/l)	
	r	**P value**
Age (years)	-0.171	0.577
BMI (kg/m^2)	-0.028	0.928
SBP (mmHg)	0.205	0.502
DBP (mmHg)	0.150	0.624
Pulse (beats/min)	0.316	0.293
RR (breaths/min)	0.104	0.737
O_2 saturation (%)	-0.644	**0.018***
Pulmonary artery pressure (mmHg)	0.556	**0.049***
Hb (g/dl)	-0.249	0.412
WBCs (x10^9/L)	-0.485	0.093
Platelets (x10^9/L)	-0.255	0.401
ALT (U/L)	0.064	0.835
AST (U/L)	0.143	0.642
Creatinine (mg/dl)	0.451	0.122
CRP (mg/dl)	-0.547	0.053

FSTL1: Follistatin-like protein 1, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, RR: respiratory rate, Hb: hemoglobin, WBCs: white blood cells, ALT: alanine transaminase, AST: aspartate aminotransferase, CRP: C-reactive protein, *: significant as P value ≤ 0.05, r: correlation coefficient

Table 4: Correlation between FSTL1 and different parameters in pulmonary hypertensive patients without hypoxia

	FSTL1 (µg/l)	
	r	**P value**
Age (years)	0.262	0.387
BMI (kg/m^2)	0.170	0.578
SBP (mmHg)	0.078	0.800
DBP (mmHg)	0.173	0.573
Pulse (beats/min)	0.031	0.920
RR (breaths/min)	-0.030	0.924
O_2 saturation (%)	-0.110	0.720
Pulmonary artery pressure (mmHg)	0.176	0.566
Hb (g/dl)	-0.219	0.472
WBCs (x10^9/L)	-0.426	0.147
Platelets (x10^9/L)	0.402	0.174
ALT (U/L)	-0.519	0.069
AST (U/L)	-0.653	**0.016***
Creatinine (mg/dl)	0.203	0.507
CRP (mg/dl)	-0.225	0.460

FSTL1: Follistatin-like protein 1, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, RR: respiratory rate, Hb: hemoglobin, WBCs: white blood cells, ALT: alanine transaminase, AST: aspartate aminotransferase, CRP: C-reactive protein, *: significant as P value ≤ 0.05, r: correlation coefficient

Table 5: Correlation between FSTL1 and different parameters in pulmonary hypertensive patients

	FSTL1 (µg/l)	
	r	**P value**
Age (years)	0.150	0.465
BMI (kg/m^2)	0.326	0.104
SBP (mmHg)	-0.424	**0.031***
DBP (mmHg)	-0.175	0.392
Pulse (beats/min)	0.035	0.864
RR (breaths/min)	0.045	0.828
O_2 saturation (%)	0.103	0.618
Pulmonary artery pressure (mmHg)	-0.462	**0.017***
Hb (g/dl)	-0.085	0.680
WBCs (x10^9/L)	-0.222	0.276
Platelets (x10^9/L)	-0.050	0.808
ALT (U/L)	-0.093	0.650
AST (U/L)	-0.180	0.379
Creatinine (mg/dl)	0.543	**0.004***
CRP (mg/dl)	-0.127	0.538

FSTL1: Follistatin-like protein 1, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, RR: respiratory rate, Hb: hemoglobin, WBCs: white blood cells, ALT: alanine transaminase, AST: aspartate aminotransferase, CRP: C-reactive protein, *: significant as P value ≤ 0.05, r: correlation coefficient

Table 6: Diagnostic accuracy of FSTL1 in diagnosis of hypoxia-induced pulmonary hypertension

	Cut-off	AUC	Sensitivity	Specificity	PPV	NPV	P value
FSTL1 (µg/l)	>63.435	0.982	92.31	100	100	92.9	**<0.001***

FSTL1: Follistatin-like protein 1, AUC: area under the curve, PPV: positive predictive value, NPV: negative predictive value, *: significant as P value ≤ 0.05

DISCUSSION

In our investigation, there was no significant difference between groups I and II; however, the FSTL1 of group III was significantly greater than that of groups I and II (P value <0.001).

Similar to NDRG1, a hypoxia-induced gene that reduces hypoxic injury, FSTL1 protein expression was shown in a previous study to be significantly elevated under hypoxia in primary human trophoblasts, which is consistent with our findings **[4].**

Furthermore, FSTL1 was observed to increase in the circulation or in the explanted failing heart in individuals with acute coronary syndrome (ACS) or heart failure, respectively, according to studies by Lara-Pezzi et al. [5] and Widera et al**. [6].**

Additionally, **Shimano et al. [7]** reported that transverse aortic constriction (TAC) significantly increased the cardiac transcript level of Fstl1 in mice sevenfold, demonstrating the role of FSTL1 as an antihypertrophic "cardiokine" in response to pressure overload.

Furthermore, permanent left anterior descending coronary artery ligation (LAD) increased serum FSTL1 to three times its baseline level and increased the transcript level of the ischemic heart by thirteen times. A clinically significant secreted factor called FSTL1 has been suggested by emerging data to be highly regulated and to have a protective function against cardiovascular insults **[8].**

Zhang et al. [9] discovered that a mouse model of hypoxia-induced PH (HPH) and patients with PH associated with chronic obstructive pulmonary disorders (COPDs) have increased serum levels of FSTL1. Nevertheless, following a 4-week hypoxic challenge, the level of FSTL1 in phosphate-buffered saline controls was significantly lower than that in mice that received exogenous FSTL1 intravenously, leading to somewhat improved heart hyperfunction. Therefore, the inability of increased FSTL1 expression to protect against HPH may be explained by insufficient hypoxia-induced FSTL1. Notably, there was no discernible change in Fstl1 mRNA or protein levels in lung tissue from baseline during the 4 weeks of hypoxia. FSTL1 was first shown to confer resistance to damage caused by hypoxia, possibly for the purpose of protecting organs. The protective mechanisms in the lung eventually

decompensate as HPH progresses, and negative outcomes follow, resulting in a decrease in Fstl1 transcript and expression. However, further research is needed to determine the exact mechanism underlying the elevated serum FSTL1 found during hypoxia exposure.

Furthermore, skeletal muscle has been found to release FSTL1, a novel "myokine" that either facilitates ischemic limb reperfusion or inhibits the establishment of vascular neo intimal formation **[10].**

All of these findings corroborate our findings that patients with dysfunctional pulmonary arteries had elevated FSTL1 levels; this is significant because it protects against PH. Patients with idiopathic pulmonary fibrosis and mouse models of bleomycin-induced lung injury **[11],** CCl4-induced liver injury **[12],** and kidney injury following unilateral ureteral obstruction all exhibit higher levels of FSTL1 expression than healthy tissue. Reduced expression of Fstl1 through siRNA or haplodeficiency of Fstl1 reduces the formation of collagen in liver and lung injuries **[13].**

According to **Liu et al. [14],** FSTL1 may play a role in the early development of lung mesenchyme-derived airway smooth muscle (SM). FSTL1was highly expressed in the SM cells of the developing lung.

Xu and Cao [15] aimed to explore the relationship between FSTL1 and lung fibroblast activation triggered by oxidative stress under simulated hypoxic conditions. The levels of the oxidative stress markers malondialdehyde (MDA) and catalase (CAT) tended to increase with prolonged hypoxia treatment, while the antioxidant tempol effectively mitigated oxidative stress. Western blot analysis revealed parallel changes in the expression of alpha smooth muscle actin (α-SMA) and FSTL1 in response to oxidative stress. Silencing of FSTL1 protein expression led to decrease in the oxidative stress index and decrease in the protein levels of collagen 1 and α-SMA. Immunohistochemical staining of α-SMA exhibited variations. Fibroblasts were demonstrated to be activated by intermittent hypoxia in a rat model, which supports these findings. Periodic hypoxia causes oxidative stress, which in turn activates fibroblasts; the production of the FSTL1 protein seems to be involved in this process.

In our study, in pulmonary hypertensive patients without hypoxia, there was a significant negative correlation between FSTL1 and AST (r= -0.653, P =0.016), while there was no significant correlation between FSTL1 and age, BMI, SBP, DBP, pulse, RR, O_2 saturation, pulmonary artery pressure, Hb, WBCs, platelets, ALT, creatinine, or CRP.

In our study, in hypoxia-induced pulmonary hypertensive patients, there was a significant positive correlation between FSTL1 and O_2 saturation (r= 0.644, P =0.018), while there was a significant negative correlation between FSTL1 and pulmonary artery pressure (r= -0.556, P =0.049). There were no significant correlations between FSTL1 and age, BMI, SBP, DBP, pulse, RR, Hb, WBCs, platelets, ALT, AST, creatinine, or CRP.

In our study, in all pulmonary hypertensive patients, there was a significant positive correlation between FSTL1 and creatinine (r= 0.543, P =0.004), while there was a significant negative correlation between FSTL1 and SBP (r= -0.424, P =0.031) and pulmonary artery pressure (r= -0.462, P =0.017). There were no significant correlations between FSTL1 and age, BMI, DBP, pulse, RR, O_2 saturation, Hb, WBCs, platelets, ALT, AST, or CRP.

In our study, FSTL1 was an insignificant predictor of pulmonary hypertension without hypoxia in pediatric patients. FSTL1 can significantly predict hypoxia-induced pulmonary hypertension in pediatric patients (AUC= 0.982, P value <0.001) at a cut-off >63.435 μg/L, 92.31% sensitivity, 100% specificity, 100% PPV and 92.9% NPV.

In our study, age, sex, weight, height, and BMI were not significantly different between the studied groups.

On the other hand, **Wang et al. [16]** discovered that, using univariate analysis, elevated BMI was associated with PH in COPD patients residing at high altitudes (HAs). Obesity and overweight are positively correlated with all-cause and cardiovascular mortality **[17].** Nonetheless, a prior study from the Southeast Iran Plateau revealed a significant correlation between low BMI and severe PH in COPD patients, suggesting that high BMI may be protective in individuals with severe PH. **[18].** This difference may be due to different inclusion criteria and different populations.

In our study, Hb, WBCs, platelets, ALT, AST, creatinine, and CRP were not significantly different between the studied groups.

WBC counts are strongly correlated with CRP levels, and some research has demonstrated that extended hypoxia can reduce inflammation, indicating that the vascular endothelium has adapted to hypoxia **[19].**

Wang et al. [16] showed that there was no significant difference in transaminases between COPD-PH patients at HA and COPD-PH patients at LA, which is consistent with our results.

According to earlier research, COPD-PH patients had greater levels of CRP, IL-1, and IL-6 than did COPD-NPH patients **[20].**

In contrast to our findings, a prior study revealed that hypoxia increases platelet activation and procoagulant factors in high-altitude polycythemia, a form of altitude sickness, indicating platelet participation in HPH **[16].** This discrepancy may be because the study was carried out at high altitudes.

To the best of our knowledge, no previous studies have investigated the correlation between FSTL1 and these different parameters.

CONCLUSION

FSTL1 levels were significantly higher in hypoxia-induced pulmonary hypertensive patients than in normal controls and pulmonary hypertensive patients without hypoxia. Additionally, FSTL1 was found to be a significant predictor of hypoxia-induced pulmonary hypertension in pediatric patients.

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

Funding information

None declared

REFERENCES

1. Roger I, Milara J, Montero P, Cortijo J. The role of JAK/STAT molecular pathway in vascular remodeling associated with pulmonary hypertension. *Int. J. Mol. Sci.*, 2021; *22*(9), 4980.
2. Parfenova OK, Kukes VG, Grishin DV. Follistatin-Like Proteins: Structure, Functions and Biomedical Importance. Biomedicines, 2021; 9(8), 999.
3. Liu X, Liu Y, Yang Z, Ning W. Cell type specific expression of Follistatin-like 1 (Fstl1) in mouse embryonic lung development. J. Mol. Histol., 2018; 49, 399-409.
4. Mouillet JF, Mishima T, do Amarante Paffaro AM, Parks TW, Ziegler JA, Chu T, et al. The expression and post-transcriptional regulation of FSTL1 transcripts in placental trophoblasts. Placenta, 2015; 36(11), 1231-1238.
5. Lara-Pezzi E, Felkin LE, Birks EJ, Sarathchandra P, Panse KD, George R, et al. Expression of follistatin-related genes is altered in heart failure. Endocrinology, 2008; 149(11), 5822-5827.
6. Widera C, Giannitsis E, Kempf T, Korf-Klingebiel M, Fiedler B, Sharma S, et al. Identification of follistatin-like 1 by expression cloning as an activator of the growth differentiation factor 15 gene and a prognostic biomarker in acute coronary syndrome. Clin. Chem., 2012; 58(8), 1233-1241.
7. Shimano M, Ouchi N, Nakamura K, van Wijk B, Ohashi K, Asaumi Y, et al. Cardiac myocyte follistatin-like 1 functions to attenuate hypertrophy following pressure overload. Proc Natl Acad Sci U S A, 2011; 108(43), E899-E906.
8. Oshima Y, Ouchi N, Sato K, Izumiya Y, Pimentel DR, Walsh K. Follistatin-like 1 is an Akt-regulated cardioprotective factor that is secreted by the heart. Circ., 2008; 117(24), 3099-3108.
9. Zhang W, Wang W, Liu J, Li J, Wang J, Zhang Y, et al. Follistatin-like 1 protects against hypoxia-induced pulmonary hypertension in mice. Sci Rep. 2017; Mar 31;7:45820.
10. Miyabe M, Ohashi K, Shibata R, Uemura Y, Ogura Y, Yuasa D, et al. Muscle-derived follistatin-like 1 functions to reduce neointimal formation after vascular injury. Cardiovasc. Res., 2014; 103(1), 111-120.
11. Murphy N, Gaynor KU, Rowan SC, Walsh SM, Fabre A, Boylan J, et al. Altered expression of bone morphogenetic protein accessory proteins in murine and human pulmonary fibrosis. Am J Pathol. 2016;186(3):600–615.
12. Vollmann EH, Cao L, Amatucci A, Reynolds T, Hamann S, Dalkilic-Liddle I, et al. Identification of novel fibrosis modifiers by in vivo siRNA silencing. Mol. Ther. Nucleic Acids. 2017; 7:314–323.
13. Dong Y, Geng Y, Li L, Li X, Yan X, Fang Y, et al. Blocking follistatin-like 1 attenuates bleomycin-induced pulmonary fibrosis in mice. J Exp Med. 2015;212(2):235–252.
14. Liu X, Liu Y, Li X, Zhao J, Geng Y, Ning W. Follistatin like-1 (Fstl1) is required for the normal formation of lung airway and vascular smooth muscle at birth. PloS one, 2017;12(6), e0177899.
15. Xu L, Cao J. Follistatin-like 1 promotes intermittent hypoxia-induced lung fibroblast activation in vitro and in vivo. 2019.
16. Wang L, Wang F, Tuo Y, Wan H, Luo F. Clinical characteristics and predictors of pulmonary hypertension in chronic obstructive pulmonary disease at different altitudes. BMC Pulm. Med., 2023; 23(1), 127.
17. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease: risk factor, paradox, and impact of weight loss. J Am Coll Cardiol. 2009;53(21):1925–32.
18. Fekri MS, Torabi M, Shoul SA, Mirzaee M. Prevalence and predictors associated with severe pulmonary hypertension in COPD. Am J Emerg Med., 2018; 36(2), 277-280.
19. Wood JG, Johnson JS, Mattioli LF, Gonzalez NC. Systemic hypoxia promotes leukocyte-endothelial adherence via reactive oxidant generation. J Appl Physiol 1999;87(5):1734–40.

20. Kwon YS, Chi SY, Shin HJ, Kim EY, Yoon BK, Ban HJ, et al. Plasma C-reactive protein and endothelin-1 level in patients with chronic obstructive pulmonary disease and pulmonary hypertension. J Korean Med Sci. 2010; 25(10):1487–91.

Citation

Mahmoud, H., Romih, M., El-Shal, A., El-Hindawy, E. The Predictive Value of Follistatin-like Protein 1 in Pediatric Patients with Hypoxia-Induced Pulmonary Hypertension: A Case-Control Study. *Zagazig University Medical Journal*, 2024; (4896-4904): -. doi: 10.21608/zumj.2024.275884.3239