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Assessment of thrombin-activatable fibrinolysis inhibitor levels in essential hypertension

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ABSTRACT

Objectives: Most research in this field has highlighted the significance of the fibrinolytic system in essential hypertension, revealing anomalies within the coagulation and fibrinolytic pathways that contribute to a hypercoagulable condition. We aim to investigate thrombin-activatable fibrinolysis inhibitor (TAFI) levels in individuals diagnosed with high blood pressure.

Methods: We compared 40 newly diagnosed cases of essential hypertension, who were not receiving antihypertensive medication, with 40 normotensive individuals as controls. Various parameters and TAFI levels were assessed in all subjects and compared between the groups. Additionally, hypertensive patients were classified based on whether they exhibited high or normal cholesterol levels (≥200 mg/dL).

Results: The concentrations of TAFI were significantly higher in the hypertensive cohort compared to the normotensive counterparts (116.95±29.76 and 77.72±32.78 (ng/mL) , respectively; P<0.001). In addition, the high blood pressure cohort exhibited a notably higher mean body mass index (BMI) in contrast to the normotensive group (29.55±4.82 vs. 24.93±3.07 kg/m2, respectively; P<0.001). On the other hand, the remaining results showed no statistically significant differences between the two cohorts. Linear regression analysis revealed that blood pressure status and BMI independently correlated with plasma TAFI levels.

Conclusions: The concentrations of TAFI are elevated in patients with high blood pressure compared to individuals with normal blood pressure, irrespective of high cholesterol levels. Further exploration is necessary to clarify the involvement of TAFIs in the pathophysiology of primary hypertension, necessitating advanced investigatory initiatives.

Keywords: Thrombin activatable fibrinolysis inhibitor, cardiovascular diseases, thrombosis, fibrinolysis

Essential hypertension (PHT) accounts for 85-90% of all cases of hypertension. Hypertension represents a substantial risk factor for cardiovascular diseases, which stand as the foremost cause of mortality globally. The asymptomatic presentation of primary hypertension frequently results in diagnostic delays and unfavorable cardiovascular consequences [1]. Additionally, it induces abnormalities in the coagulation and fibrinolytic systems, leading to disruption in the balance of coagulation [2]. Thrombin-activatable fibrinolysis Inhibitor (TAFI) has garnered growing attention in recent years regarding its

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implications for the interplay among atherosclerosis, hypertension, and hemostasis. Moreover, it belongs to the group of metalloproteinases, acting as a proenzyme for carboxypeptidase. TAFI is activated by thrombin, leading to the inhibition of fibrin degradation, which is essential for preserving the delicate equilibrium between fibrinolysis and coagulation [3-5]. In addition, circulating concentrations of this marker are elevated in pathologies which characterized by hypercoagulability. Hypertension (HT) represents a predisposing factor for the majority of these conditions [6].

In addition to its role in coagulation/fibrinolysis and inflammatory processes, some studies suggest a potential association between plasma TAFI levels and hyperlipidemia. Some studies have shown that Low low-density lipoprotein cholesterol (LDL) is a significant determinant of plasma TAFI in studies involving individuals with type 2 diabetes [7].

In previous studies, researchers observed that women diagnosed with hypercholesterolemia showed markedly elevated TAFI levels compared to women without this risk factor, while exploring the correlation between our markers and traditional cardiovascular risk factors [8].

In subsequent scientific studies demonstrating the effects of simvastatin treatment, it was observed that TAFI levels decreased significantly following simvastatin therapy [9].

Based on these findings, it is suggested that due to the biochemical properties of TAFI, it could influence the relationship between hyperlipidemia and PHT. Therefore, additional research is necessary. Consequently, we examined TAFI levels in patients diagnosed with PHT and hypercholesterolemia and meticulously controlled prospective clinical trials.

METHODS

The study involved 40 individuals newly diagnosed with primary hypertension and the same number of control groups. Primary hypertension was characterized by blood pressure (BP) readings ≥140/90 mmHg, without an identifiable secondary cause [10].

The exclusion criteria included kidney diseases, endocrine disorders, diabetes, and antilipidemic medication users. This thesis was conducted at Istanbul Şişli Hamidiye Etfal Training and Research Hospital.

Comprehensive clinical patient information including medication usage was obtained. The body mass index (BMI) of the individuals was determined through measurements of their height and weight.

Blood samples were obtained from participants following a 12-hour overnight fasting period. Serum was collected into tubes with a gel separator, while plasma was collected into tubes containing 3.2% trisodium citrate solution as a blood thinner. The biological materials were centrifuged according to the protocol, aliquoted, and stored at -80°C. Lipid profile tests and C-reactive protein (CRP) serum levels were conducted using the Abbott-Aeroset automated analyzer at Abbott Diagnostics, Illinois, USA.

Fibrinogen, as one of the coagulation tests, was assessed using the Clauss method on the ACL Advance automated analyzer (San Diego, Instrumentation Laboratory, USA). The concentrations of TAFI antigen used as a research kit were measured using an enzyme-linked immunosorbent assay (ELISA) kit. (American Diagnostica Inc Imunclone, USA). The group diagnosed with primary hypertension and the normotensive group were also divided into two groups based on high cholesterol levels (total cholesterol levels ≥ 200 mg/dL and those < 200 mg/dL). As a result, our study continued with four groups based on these criteria.

Statistical Analysis

It was conducted using the SPSS 22.0 software package. Descriptive statistics including mean and standard deviation were presented for normally distributed numerical variables. Normality of variables was assessed visually using histogram and probability graphs, as well as analytically using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Student's t-test and One-Way ANOVA were employed for comparisons between two groups and multiple groups, respectively. For variables that did not follow a normal distribution, median, interquartile range (IQR), minimum, and maximum values were reported, and the Mann-Whitney U test was used for comparisons between the two groups. Statistical remarkable levels were defined as ($P<0.050$). Linear regression analysis was utilized to independent variables associated with TAFI antigen concentration. Pearson correlation analysis was applied to parameters showing homogeneous distribu-

tion, while Spearman correlation analysis was used for parameters not showing homogeneous distribution. The statistical power of the study was computed using this software [11]. The study's statistical power was determined to be 0.80, with a significance level (α) of 0.05 and a power of 80% (β=0.20). In our study, a Type II error rate of 20% and a Type I error rate of 0.05 with a 95% confidence interval were chosen to achieve 80% statistical power. The sample size was calculated using information from a previous study, where the average TAFI levels were reported as 104.91±27.43 (ng/mL) in the group with high blood pressure and 87.59±25.82 (ng/mL) in the group without high blood pressure.

RESULTS

The basic clinical features and biochemical tests of the hypertensive and normotensive groups are presented in Table 1. While statistically significant differences were observed in BMI, CRP, and TAFI levels, no differences were found between the two groups in most lipid profile and coagulation parameters, fibrinogen. (Table 1). Moreover, TAFI antigen did not significantly differ between hypercholesterolemic and normocholesterolemic patients (98.5±37.1 and 95.1± 37.0 (ng/mL), respectively; P=0.570)). Similarly, there was no remarkable disparity in TAFI levels based on hypertensive and normotensive groups. After dividing the two groups into subgroups based on high cholesterol levels (<200 mg/dL and ≥200 mg/dL), we compared the TAFI levels between these subgroups. Analysis revealed no statistically significant differences in TAFI levels among the subgroups of both hypertensive and normotensive individuals categorized by total cholesterol levels (P=0.471 and P=0.839, respectively) (Fig. 1). Table 2 provides a detailed overview of the linear regression analysis findings related to the factors associated with serum TAFI levels. The data indicate that TAFI levels are independently associated with both BMI and essential hypertension. In our study, correlation analysis revealed a positive and significant relationship between age and BMI (r=0.267, P=0.017); TAFI and BMI (r=0.455, P<0.001); age and CRP (r=0.349, P=0.002); and fib-

Table 1. Demographic characteristics and biochemical parameters of cases

	Hypertensive group (n=40)	Normotensive group (n=40)	P value
Systolic blood pressure (mmHg)	161.87±16.43	116.02±4.84	**<0.001**
Diastolic blood pressure (mmHg)	100.62±11.44	75.12±6.25	**<0.001**
Age (year)	47±7.57	46.15±4.31	0.539
Weight (kg)	77.35±12.84	68.75±10.37	**0.001**
Height (cm)	162.88±9.03	166.38±7.50	0.063
BMI (kg/m^2)	29.55±4.82	24.93±3.07	**<0.001**
Total cholesterol (mg/dL)	195.20±37.91	194.27±41.55	0.917
Triglyceride (mg/dL)	122±54	127±88	0.516
HDL cholesterol (mg/dL)	43.8±9.7	42.2±11.9	0.512
LDL cholesterol (mg/dL)	126.50±32.69	126.24±36.96	0.973
Fibrinogen (mg/dL)	328.35±60.67	328.72±65.59	0.979
TAFI (ng/mL)	116.95±29.76	77.72±32.78	**<0.001**
CRP (mg/dL) *	3.14±2.72 (0.01-25.70)	2.17±3.56 (0.01-24.00)	**0.030**

All parameters were shown as mean ± standard deviation. *CRP values are shown as median (Interquartile range) (minimum-maximum). TAFI=Thrombin-Activatable Fibrinolysis Inhibitor, BMI=Body Mass Index, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, CRP=C-Reactive Protein

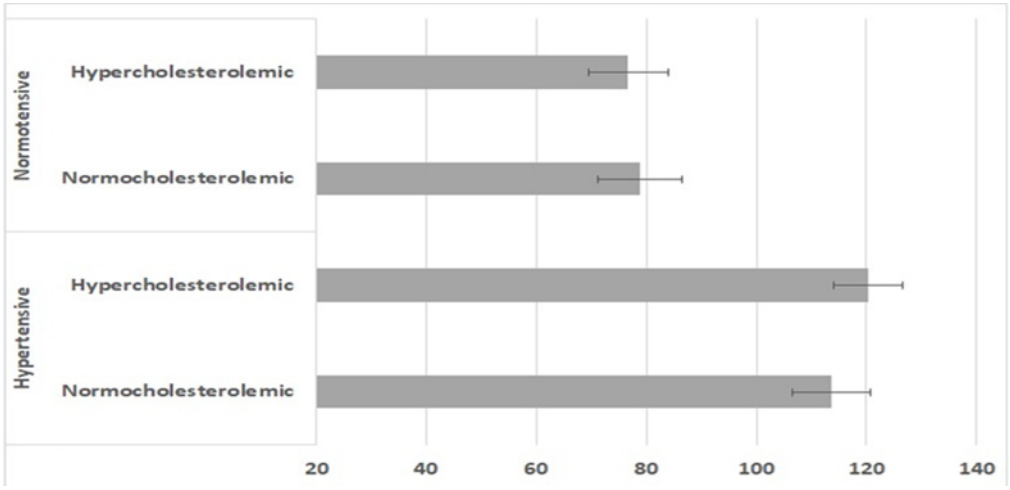

Fig. 1. Serum TAFI levels (ng/mL); TAFI=Thrombin-Activatable Fibrinolysis Inhibitor.

rinogen and CRP (r=0.386, P<0.001). No significant relationship was found among other biochemical parameters (Table 3).

DISCUSSION

The objective of this investigation was to assess TAFI levels in individuals with PHT who had not undergone any antihypertensive treatments. Upon comparison between the hypertensive and normotensive groups, it was observed that our markers were notably increased in the hypertensive group (Table 1). Additionally, the hypertensive group exhibited significantly higher BMI and CRP values compared to the normotensive group.

The main goal of the current study was to determine TAFI Antigen concentrations in individuals diagnosed with PHT who had not undergone any antihypertensive interventions. Upon comparison between the hypertensive and normotensive cohorts, it

Table 2. Linear regression analyses of the parameters related to TAFI levels

	B	P value	95% CI for B	
			Lower bound	Upper bound
(Constant)	71.443	0.139	-23.704	166.591
Age (year)	-0.833	0.173	-2.041	0.375
Gender (female/male)	-3.494	0.665	-19.500	12.512
Groups (normotensive/hypertensive/)	-28.739	**0.001**	-44.764	-12.715
BMI (kg/m^2)	2.173	**0.023**	0.306	4.041
HDL cholesterol(mg/dL)	0.338	0.345	-0.371	1.047
LDL cholesterol(mg/dL)	0.001	0.994	-0.217	0.218
Triglyceride(mg/dL)	0.048	0.335	-0.051	0.147
Fibrinogen(mg/dL)	0.094	0.194	-0.049	0.237
CRP (mg/dL)*	-0.322	0.732	-2.192	1.548

TAFI=Thrombin-Activatable Fibrinolysis Inhibitor, BMI=Body Mass Index, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, CRP=C-Reactive Protein, OR=Odds ratio, CI=confidence interval

*P value=0.030

Table 3. **Correlation analysis of the parameters**

		Age (year)	BMI (kg/m^2)	HDL cholesterol (mg/dL)	LDL cholesterol (mg/dL)	Triglyceride (mg/dL)	Fibrinogen (mg/dL)	TAFI (ng/mL)
Age (year)	r		0.267*	-0.042	0.124	0.15	-0.126	-0.04
	P value		**0.017**	0.714	0.272	0.184	0.266	0.724
BMI (kg/m^2)	r	0.267*		0.072	0.064	0.128	0.05	0.455*
	P value	**0.017**		0.528	0.571	0.257	0.658	**<0.001**
HDL cholesterol (mg/dL)	r	-0.042	0.072		0.124	-0.069	-0.075	0.166
	P value	0.714	0.528		0.274	0.542	0.51	0.14
LDL cholesterol (mg/dL)	r	0.124	0.064	0.124		0.02	0.208	0.024
	P value	0.272	0.571	0.274		0.862	0.064	0.832
Triglyceride (mg/dL)	r	0.15	0.128	-0.069	0.02		0.008	0.07
	P value	0.184	0.257	0.542	0.862		0.941	0.539
Fibrinogen (mg/dL)	r	-0.126	0.05	-0.075	0.208	0.008		0.107
	P value	0.266	0.658	0.51	0.064	0.941		0.344
TAFI (ng/mL)	r	-0.04	0.455*	0.166	0.024	0.07	0.107	
	P value	0.724	**<0.001**	0.14	0.832	0.539	0.344	
CRP (mg/dL)**	r	0.095	0.349*	-0.115	-0.099	0.168	0.386	0.141
	P value	0.403	**0.002**	0.309	0.382	0.137	**<0.001**	0.211

TAFI=Thrombin-Activatable Fibrinolysis Inhibitor, BMI=Body Mass Index, HDL=High Density Lipoprotein, LDL=Low Density Lipoprotein, CRP=C-Reactive Protein, r=Pearson correlation coefficient, rs=Spearman correlation coefficient

*Correlation is significant at the 0.05 level

**Spearman Correlation Analysis

was observed that the TAFI levels in the hypertensive group were markedly elevated, as delineated in Table 1. Additionally, the hypertensive cohort exhibited notably higher BMI and CRP values in contrast to the normotensive group. Within this dataset, linear regression analyses were conducted to explore the factors associated with TAFI Antigen, aiming to ascertain whether TAFI elevation in the hypertensive cohort remained independent of BMI and CRP concentrations (Table 2), which were notably elevated within this group. Essentially, the rise in TAFI levels among hypertensive individuals was determined to be linked to hypertension status, irrespective of BMI and CRP values (Table 2).

Based on the correlation analysis performed in our study, a statistically significant positive association was identified between CRP and both age and fibrinogen levels. Additionally, a significant positive correlation was observed BMI and age, as well as between BMI and TAFI levels.

Multiple pathways might elucidate the heightened TAFI levels observed in PHT patients. Animal studies indicate TAFI's expression as an acute-phase protein [12]. Furthermore, this antigen elicits inflammatory and coagulation cascades [13, 14]. Anticoagulation play a role in decreasing inflammation, as inflammatory conditions can lead to blood clot formation. Moreover, research shows that higher levels of TAFI are linked to markers of endothelial cell damage, such as thrombin-antithrombin complexes and thrombomodulin. This suggests a relationship between inflammation, endothelial damage, and the risk of clot formation [15]. The presence of inflammation-induced endothelial dysfunction exacerbates the susceptibility to thrombotic events in individuals diagnosed with pulmonary hypertension disease [16]. Elevated levels of TAFI, originating from endothelial sources, may escalate due to endothelial damage, consequently fostering a state of hypercoagulability [17]. These observations align with numerous studies within the existing literature.

In prior research on renal transplant recipients, Malyszko *et al*. found that hypertensive patients had increased levels of TAFI compared to those with normal blood pressure [18].

Furthermore, they noted a relationship between the increase in TAFI and levels of the thrombin-antithrombin (TAT) complex, linking it to vascular endothelial injury observed in the hypertensive group. This endothelial damage led to increased TAT levels, subsequently promoting the formation of TAT complexes, which in turn heightened TAFI levels. Another investigation involving 72 hypertensive patients reported elevated levels of both TAFI and TAT, mutually reinforcing their relationship [18].

In our study, we observed increased TAFI levels among hypertensive patients, while levels of Activated Partial Thromboplastin Time (aPTT), fibrinogen, Prothrombin time (PT), TAT, and d-dimer remained unchanged. Therefore, we concluded that the increase in TAFI occurred independently of coagulation cascade activation. Özkan *et al*. [19] investigated the link between hypertension and fibrinolysis anomalies. Their study, which included 58 hypertensive subjects and 27 controls, revealed significantly elevated TAFI levels in the hypertensive group (P=0.03). Following one month of antihypertensive therapy, a statistically significant reduction in TAFI levels was observed (P=0.037). These results agree with the findings of our studies, in which illustrate a positive correlation between essential hypertension and TAFI Antigen concentrations.

According to Santos *et al*. [20] the crucial role of dyslipidemia as a major risk factor for atherosclerosis and coronary artery disease. It was observed that dyslipidemia negatively impacts the hemostatic system, resulting in impaired fibrinolysis and a subsequent increase in TAFI levels during cardiovascular conditions. Unlike their research focused on examining the association among clinical risk factors" (such as hypertension, BMI, smoking, etc.), gene polymorphisms (Alanin 147Thr (rs3742264), Threonin 325Ile (rs1926447) in the TAFI gene, and +1542C/G (rs940)) biochemical parameters and TAFI levels in 105 normolipidemic and 109 dyslipidemic cases. They found significantly elevated TAFI levels in dyslipidemic individuals with concurrent hypertension, increased BMI, and postmenopausal status. Additionally, certain alleles (Alanin 147, 325 Izolosin and C) were associated with lower TAFI levels, and the polymorphism rs3742264 was linked to dyslipidemia in male patients. Hence, the observation of elevated TAFI levels irrespective of dyslipidemia in their study corroborates our findings [20]. Additionally, our study found a significant relationship between BMI and TAFI, which supports the findings of the current study.

In another study, Santamaria *et al*. [8] compared TAFI levels with various hemostatic parameters such as FXII, Protein C, Fibrinogen, t-PA, and von Willebrand Factor, considering age and gender. Contrary to our findings, they did not find a significant difference between TAFI levels and hemostatic parameters. However, they observed significantly lower TAFI levels in female patients under the age of 30 as a notable finding. Moreover, they in female patients diagnosed with hypercholesterolemia. In addition, they conducted their study specifically on female patients with hypercholesterolemia. In our prospective study, TAFI levels were measured without grouping by age. We focused solely on age and gender to maintain group homogeneity. Our findings revealed significantly higher TAFI Antigen levels in patients with PHT compared to normotensive individuals (P<0.01). There was no statistically significant difference in TAFI and fibrinogen levels between the two groups (P>0.050).

In this comprehensive analysis, we exclusively quantified TAFI Antigen concentrations. Several investigations have found a correlation between circulating TAFI activity (TAFIa) and TAFI antigen concentrations [21, 22].

Although multiple investigations have identified a substantial correlation between TAFI levels and hypercholesterolemia, our study demonstrated that the elevation in TAFI levels among hypertensive patients occurred regardless of lipid level [6, 23, 24].
Yoshimasa *et al*. [23] investigated 136 participants diagnosed with type 2 diabetes. As a result, they did not find a statistically significant difference between metabolic parameters such as hs-CRP, insulin resistance, lipid levels, BMI, and PAI-1 level. Significantly, they observed that plasma TAFI levels correlated positively only with LDL cholesterol. Although they found a reverse correlation with Plasminogen Activator Inhibitor 1 (PAI-1), the level of alpha-2 antiplasmin did not show a corresponding negative correlation with TAFI. In conclusion, they highlighted the importance of assessing LDL cholesterol levels when examining TAFI in patients diagnosed with Type II diabetes mellitus. They emphasized the significance of the combined impact of metabolic syndrome and hypercholesterolemia, stating that it accelerates inflammatory processes. Additionally, they demonstrated a significant correlation between impaired fibrinolysis and elevated levels of PAI-1 and TAFI. Despite these outcomes, our study did not identify a statistically significant difference between TAFI and LDL cholesterol (P>0.05).

Elevated TAFI levels (near 126%) were associated with nearly a fourfold increase in the likelihood of acute coronary artery disease (CAD). Moreover, heightened TAFI levels have been linked to a substantial rise the probability of ischemic stroke and represent a considerable risk factor for coronary artery disease [25]. Previous studies have shown an increase in TAFI concentrations in individuals with stable angina pectoris and coronary artery disease identified via angiography [26]. It has been pointed out that elevated TAFI levels observed in metabolic syndrome contribute to the inhibition of fibrinolysis and accelerate disease progression [26, 27].
Unlike the earlier studies referenced, our research revealed no significant difference in triglyceride (P>0.05), LDL-cholesterol (P>0.05), and total cholesterol (P>0.05) levels between hypertensive and normotensive groups. This discovery led us to propose that the rise in TAFI levels could be directly caused by PHT.

Recent researches have shown that TAFIa serves as a promising target for addressing thromboembolic disorders. Presently, several studies are underway to develop TAFIa inhibitors for thrombosis treatment. However, no TAFIa inhibitor drug has been developed for clinical application thus far. Conversely, Toshimasa *et al*. [28] discovered a novel class of inhibitor molecules containing selenium, offering new avenues for drug development. This discovery represents a significant advancement toward the creation of novel therapeutic agents.

Yaoita *et al*. [29] investigated the effectiveness of drugs and TAFI values by inducing experimental thrombosis in rats using a renovascular hypertensive model. They assessed the impact of interventions including antiplatelet, anticoagulant, profibrinolytic, and antioxidative agents. After antihypertensive treatment, they noted a decrease in PAI-1, tissue factor, and TAFI levels. This finding, in line with our study, implies that in the context of the unknown origins of hypertension, TAFI levels may diminish with treatment, indicating a positive response to therapy.

Another study has indicated a notable reduction in blood clot formation in mice deficient in TAFI when subjected to FeCl3-induced vena cava thrombosis, implying a potential role for TAFI in pathology. In this

regard, numerous investigations have thoroughly explored the influence of TAFI levels or variations in the TAFI gene on the progression cardiovascular pathologies [30].

Furthermore, Aso *et al*. [23] found that low-density lipoprotein cholesterol independently affects plasma TAFI levels in 105 cases diagnosed with Type II diabetes mellitus. Additionally, subgroup analysis within this study revealed significantly higher plasma TAFI levels in two specific groups: diabetic patients with hypercholesterolemia, with or without accompanying metabolic syndrome [31].

Based on the studies, it is clear that TAFI may play a significant role in the process of essential hypertension and could impact post-treatment processes. Furthermore, it has been implicated in various diseases such as ulcerative colitis [32], antiphospholipid syndrome [33], chronic thromboembolic pulmonary hypertension [34], gestational diabetes [35], acute pancreatitis [36] and Deep Venous Thrombosis [37]. However, more studies are needed to uncover the specific role and mechanisms of TAFI in these conditions.

Limitations

Several limitations should be mentioned for this study. Initially, the number of study subjects was relatively small, which led to a wide range of TAFI levels. Aside from this TAFI can be an auxiliary parameter in explaining the relationship between hyperlipidemia and PHT, menopausal status which has similar demographic etiopathogenetic, and pathophysiological features. Additionally, since measuring only TAFI antigen levels may not fully represent the enzyme's functional status, the measurement of TAFI activity should also be conducted in future studies.

CONCLUSION

In conclusion, TAFI levels are higher in PHT patients than in normotensive individuals, and this is independent of serum cholesterol levels. Additionally, our study found a significant relationship between BMI and TAFI levels. Higher BMI was associated with increased TAFI levels, suggesting that adiposity may influence TAFI concentration and its role in the fibrinolytic system. The precise role and mechanistic pathways of TAFI in the pathogenesis of PHT should be elucidated in further advanced studies to understand its potential as a therapeutic target or biomarker.

Authors' Contribution

Study Conception: AY, NE; Study Design: AY, NE; Supervision: NE; Funding: AY, KO; Materials: AY, KO; Data Collection and/or Processing: AY; Statistical Analysis and/or Data Interpretation: AY, KO; Literature Review: AY; Manuscript Preparation: AY, KO, NE and Critical Review: NE, AY, KO.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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