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Clinical value of heart type fatty acid binding protein (H-FABP) in acute pulmonary thromboembolism

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ABSTACT

Introduction: To investigate factors which could possibly be prognostic, to decide on thrombolytic therapy as soon as possible, and to determine the prognostic value of H-FABP, which is a new marker, in pulmonary thromboembolism.

Material and Method: In our study, a patient group, consisting of 58 patients diagnosed with PTE and a control group of 30 healthy individuals were investigated. According to their risk of mortality, patients were analyzed in three groups: high, moderate and low. The moderate mortality risk groups were categorized into two groups according to PAP and patients with PAP≥45 mmHg were "Group 1" and PAP<45 mmHg were "Group 2". Differences in levels of H-FABP and other cardiac prognostic markers between these groups were analyzed.

Results: H-FABP level was measured as 507.6±99.3 pg/ml in the control group and 3203.1±2389.3 pg/ml in the patient group. H-FABP level was found to be the highest in the high mortality risk group, and the lowest in the low mortality risk group ($p<0.001$). Moreover, in the subgroups of moderate mortality risk group, H-FABP levels were significantly higher in group 1 compared to group 2. For the evaluation of other cardiac markers in PTE subgroups, pro-BNP level was the highest in the high mortality risk group, and the lowest in the low mortality risk group.

Conclusion: The findings in this study show that, H-FABP is a superior marker in determining the prognosis compared to pro-BNP and troponin. High PAP level is one of the important prognostic markers that should be considered along with the electrocardiography findings.

Keywords: Pulmonary thromboembolism, H-FABP, cardiac enzymes, prognostic factors, thrombolytic treatment

INTRODUCTION

Pulmoner tromboembolism (PTE) is one of the most common diseases that is difficult to be diagnosed and that has high mortality and morbidity (1,2).

The diagnosis of PTE and initiation of proper treatment requires urgency. The severity of the disease should be determined swiftly because it might change the treatment approach for the patients diagnosed with PTE (3). In assessment of the severity of the disease, the following approaches are used: clinical evaluation (e.g., hyper-tension, shock), electrocardiograph (ECO), thorax computerized tomography angiography, brain natriuretic peptides (BNP), and cardiac troponins (4,5).

In instances of cardiac injury, heart type fatty acid binding protein (H-FABP) is released to blood stream faster than troponins and it shows up in blood circulation approximately 30 minutes after the symptom emerges. It reaches peak levels in six hours. Recent studies on PTE diagnosed patients suggest that H-FABP levels during first introductioncan predict early negative clinical incidents with higher accuracy and specificity than cardiac troponin can do (6-8). Moreover, H-FABP levels in Chronic thromboembolic pulmonary hypertension patients are found to be associated with risk of death in the long run (6,9). The main purpose in this study is to research the changes in H-FABP levels, as a new marker, based on the type of pulmonary thromboembolism and compare it with other prognostic markers.

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MATERIAL AND METHOD

The study was carried out with the permission of Yıldırım Beyazıt University Non-Interventional Clinical Researches Ethics Committee (Date: 18/06/2014; Decision No: 19). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study was conducted from January 2015 through June 2016 as part of a prospective study in our hospital.

Patients Inclusion and Study Design

The sample consists of 58 patients and a randomly selected healthy 30 individuals to serve as the control group. Patients with hematologic problems, those below the age of 18 and pregnant patients are not included in the study. Further, patients diagnosed with acute myocardial infarction and patients diagnosed with heavy cardiac insufficiency are not also included in the study because the H-FABP levels of such patients could increase as a result of their condition. Patients with systemic illness history are not included in the control group. All patients diagnosed with pulmonary thromboembolic disease using multi-sectorial (with 16 and 64 detectors) thorax computed tomography pulmonary angiography are included in the study.

Patients with venous thrombus are identified employing lower- and upper-extremity venous doppler ultrasonography. ECO results and all symptoms indicated by the patients are recorded along with the demographic characteristics such as age, sex, profession, symptoms on hospital admission, history of risk factors, vital signs, D-dimer, troponin T, CK-MB, Pro-BNP and CRP levels and other background information on the patients are also recorded.

The patients are classified into three mortality risk categories: (1) High risk, (2) Middle risk, (3) Low risk, based on the Acute Pulmonary Embolite Diagnosis and Treatment Manual, published by European Society of Cardiology in 2019 (4). Additionally, the patients are also subjected to a second layer of classification based on their pulmoner artery pressure (PAP) value: those who have a PAP value of 45mm Hg and above are classified in Group 1 (high mortality risk), those with a PAP value less than 45 mm Hg are considered in Group 2 (low mortality risk). Distribution of the patients in these groups are shown in **Table 1**. We have examined the differences of major cardiac prognostic markers such as H-FABP levels, troponin T, creatine kinase-muscle/brain /(CK-MB), pro-brain natriuretic peptide (pro-BNP).

Biochemical Analysis

We take 3 cc blood from PTE patients at the time of hospitalization using tubes containing lithium heparin and then analyse them in our biochemistry laboratory in less than two hours. Therefore, we have also analysed in these blood samples from the PTE patients to measure the the H-FABP levels with the sandwich method using Hycult biotech HK 401 and Human H-FABP Elisa kits.

Statistical Analysis

Statistical analyses were performed with SPSS for Windows version 17.0 (SPSS Inc., Chicago, III., USA). The Kolmogorov-Smirnov test was applied to determine the probability distribution. In comparing the mean differences between two groups, we used Student's t test, more than two groups we used One-Way-ANOVA (Analysis of Variance) when there were. Relationship between two quantitative variables is tested using Spearman's Correlation test. We have accepted $p<0.05$ as the threshold value for statistical significance.

RESULTS

The mean ages of the patient and control groups are 63.8±16.1 and 62.1±18.2, respectively. Control groups have not yielded any significant differences ($p>0.05$). The patient group was composed of 32 females (55.2%) and 26 males (44.8%). The control group was comprised of 13 females (43.3%) and 17 males (56.7%). Chi square test results have not shown any significant relationship between sexes and groups ($p>0.05$).

When we compared the pulmoner artery pressure (PAP) among different mortality risk groups of PTE patients, we found that patients in the high-risk group to have higher PAP values (mean: 55±8.7; range: 50-80) than those in the low-risk group and those in Group 2 of the moderate risk group ($p<0.001$) (**Table 2**).

The most common symptom at the time of first arrival to the hospital were shortness of breath (93.1%) and chest pain (55.2%). The frequency of syncope and chest pain among high mortality risk group was significantly higher than other PTE groups ($p<0.05$).

Table 1. Classification of patients based on mortality risk

	(n)	Shock or hipertension[a]	Right ventricle dysfunctions (ECO findings)
High risk (Massive)	15	+	+
Moderate risk (Submasssive)	Group 1	13	(+)b
	Group 2	12	(+)c
Low risk (Low emboli)	18	-	-

a: 40mm Hg decrease in daily average arterial tension or having an arterial tension of ≤90/60 mm Hg. b: If PAP≥45mm Hg c: If PAP<45mm Hg

Table 2. Distribution of pulmonary emboli groups based on PAP levels

		High risk (n=15)	Moderate risk		Low risk (n=18)	Significance
			Group 1 (n=13)	Group 2 (n=12)		
Sex	Female/Male	6/9	5/8	6/6	9/9	0.878
PAP	45mm Hg<n	0	0	12 (%100)	18 (%100)	<0.001
	45 mm Hg≥n	15 (%100)	13 (%100)	0	0	
PAP value* (mm Hg)		55±8.7 (50-80)	55 ±9.4 (45-70)	40± 4.6 (35-40)	Normal	<0.001

*: PAP values include mean±standard deviation and the minimum & maximum in parenthesis

The vital symptoms of the patients were found the following measures: an average pulsation count of 117±15/min, mean systolic tension of 112±16 mm Hg, mean diastolic tension of 71±12 mm Hg, an average respiratory rate of 24±6.8/min, and 88.6%±6.7 oxygen saturation rate. Significant differences were detected in vital measures across PTE sub-groups. For instance, the average number of puls and respiratory rates of patients in high risk group were significantly higher than all other PTE groups (p<0.001). The oxygen-free saturation among patients in the low mortality risk group were significantly higher than other PTE groups (p<0.001). Likewise, the systolic and diastolic blood pressure of patients in the low-risk group was significantly higher than other patients (p<0.001).

With radiological tests, we have detected segmentary thrombus in 26 patients (44.8%), sub-segmentary thrombus in 14 patients (24.1%), thrombus at the bilateral main pulmonary artheries in 13 patients (22.4%), thrombus at unilateral main pulmonary arthery in 5 patients (8.6%).

The amount of radiological congestion of thrombus across PTE groups showed significant differences. The existence of thrombus at the bilateral main pulmanory arthery among patients in the high mortality risk group was significantly higher than other groups (p<0.001). Moreover, the H-FABP levels of 6560.3 (1959.6-7912) pg/ml, segmentary value 1997.5 (446.3-6210) pg/ml, and sub-segmentary valu e of 535.5 (446.6-3071) pg/ml among patients with thrombus at their bilateral pulmonary arthery were significantly higher than those with thrombus at their pulmonary arthery(p<0.001).

The H-FABP level in the patient group was significantly higher than the H-FABP level in the control group (p<0.001). An analysis of the H-FABP levels across PTE sub-groups showed significant differences (p<0.001). Besides, H-FABP level was higher in the Group 1 than it was in the Group 2 of the moderate risk group (p<0.001). The **Figure 1** is scatter plot diagram that shows the H-FABP levels across patient and control groups.

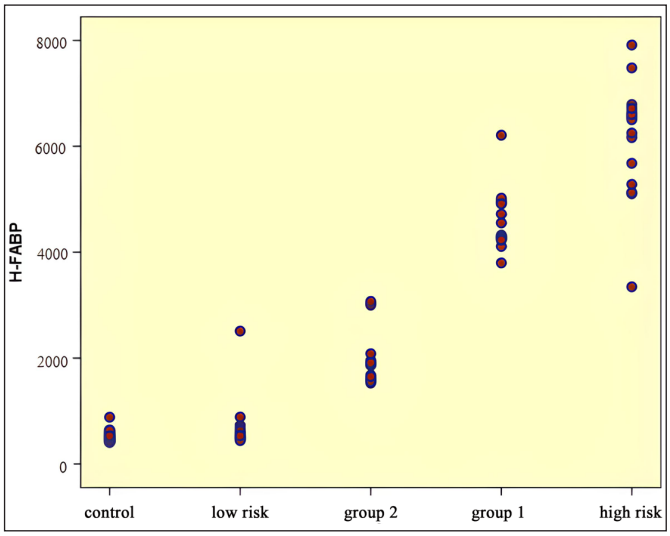

Figure 1. H-FABP levels in patient and control groups

Cardiac markers varied tremendously among PTE sub-groups (**Table 3**). For example, Pro-BNP level in high mortality risk group was the highes (3678 pg/ml) while it was the lowest in the low risk group (60 pg/ml). Troponin T level significantly higher in the high-risk group than both the moderate and low risk groups (p<0.001). Neither troponin T nor pro-BNP levels showed any significant differences between Group 1 and Group 2 of the moderate risk group. However, H-FABP levels were significantly higher than Group 2 (p<0.001).

Table 3. Cardiac markers, D-dimer & CRP levels across PTE groups

	Normal values	High risk (n=15)	Moderate risk		Low risk (n=18)
			Group 1 (n=13)	Group 2 (n=12)	
H-FABP (pg/ml)	*	6503.9 (3346.3-7912)	4553.0 (3798-6210)	1876.6 (1525.2-3071)	520.8 (446.3-886.8)
Pro-BNP (pg/ml)	0-198	3678 (102-9000)	320 (60-5578)	153.5 (60-9000)	60 (47-710)
Troponin T (pg/ml)	0-14	16 (3-55)	14 (7-63)	11 (7.5-19)	9.5 (3-66)
CK-MB (ng/ml)	0-4.9	2.3 (0.3-6.2)	1.6 (0.3-2.6)	1.5 (0.1-6.6)	1.2 (0.3-2.8)
D-dimer (ng/ml)	0-500	9300 (2300-10000)	3089 (1400-10000)	3421.5 (835-10000)	1590 (323-5632)
CRP (mg/dl)	0-0.8	9.4 (5.4-25)	8.3 (1.9-14)	6.7 (2.6-16.8)	2.0 (0.5-4.0)

When we divide the sample into two groups based on H-FABP levels, accepting 4000 pg/ml as the threshold value, we have found that having H-FABP values of 4000 pg/ml and above was related to a constellation of symptoms, accompanying venous thrombus, and atrial fibrillation in electrocardiography (ECG) (**Table 4**).

In this study, we have found significant positive correlations between H-FABP and PAP, pro-BNP, troponin T level, and oxygen saturation. The correlation of H-FABP with tropenin T was a slight correlation, with pro-BNP there was a mild correlation, and with PAP there was a strong correlation. With increases in PAP, pro-BNP, troponin T, and oxygen saturation levels, the H-FABP level was also increasing (**Figure 2**).

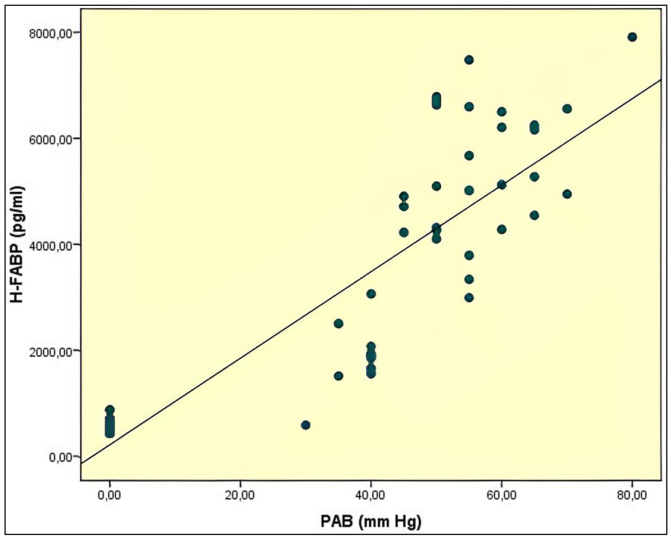

Figure 2. Correlation between H-FABP levels and PAP scores

DISCUSSION

In this study, we have found that the H-FABP level is a superior marker in determining prognosis compared to troponin T and pro-BNP because of H-FABP having a faster septicemia than other cardiac markers such as the aforementioned ones and having significant differences across all PTE sub-groups and having been influenced from PAP levels.

It is very important to determine the severity of the disease rapidly in order to decide treatment for patients diagnosed with PTE. In this way, we can make thrombolytic treatment decisions for required patients because it is scientifically proven that thrombolytic treatment reduces PTE related mortality and recurrence (10). In 2019, this document was revised and updated with the 2019 ESC Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism (4,11). In this guide, mortality risk of acute pulmunorythromboly was groupped into three categories: high risk, moderate risk, and low risk. The moderate mortality group was further divided into low risk and high-risk groups. In this new classification, thrombolytic treatment is recommended for the high-risk sub-group of the moderate mortality risk group. Thus, while acute pulmunorythromboly was considered in two groups and only those in the high mortality risk group was offered thrombolytic treatment, now the number of patients for whom thrombolytic treatment decision could be made has been expanded with the new classification of three risk groups.

It is recommended to use PESI, sPESI, right ventricular dysfunction indicators and cardiac markers in classifying patients. From cardiac markers, BNP and NT-proBNP are released from the ventricule muscles as soon as high

Table 4. Comparison of major parameters that are influential in selecting the patient group that could have worse prognosis condition for thrombolic treatment decision of acute PTE patients across two H-FABP Levels

	H-FABP <4000 pg/ml (n=32)	H-FABP<4000 pg/ml (n=26)	Significance
Existence of malignite	3 (9.4%)	10 (38.5%)	0.008
Shortage of breath	28 (87.5%)	26 (100.0%)	0.120
Chest pain1	12 (37.5%)	20 (76.9%)	0.003
Syncope	0	5 (19.2%)	0.014
Hemoptysis	4 (12.5%)	2 (7.7%)	0.681
Sputum	13 (40.6%)	3 (11.5%)	0.014
Flank pain	18 (56.3%)	8 (30.8%)	0.052
Hipertansion2 or shock	1 (3.1%)	14 (53.8%)	<0.001
Heartbeat per minute	109.3±13.3	127.0±11.1	<0.001
Respiratory rate per minute	19.8±4.4	30.7±3.8	<0.001
Oxygen-free saturation3(%)	93.6±3.1	82.5±4.5	<0.001
Existence of deep venous thrombosis	17 (53.1%)	24 (92.3%)	<0.001
Existence of atrial fibrillation in ECO (electrocardiography)	5 (15.6%)	13 (50.0%)	0.005
PAP (mm Hg)4	0 (0-55)	55 (45-80)	<0.001

1: Existence of chest pain that cause tightness underneath sternum
2: 40mm Hg decrease in daily average arterial tension or having an arterial tension of ≤90/60 mm Hg
3: Figures include means and standard deviations
4: Figures include median and minimum-maximum in parentheses.

ventricule pressure is reached. Therefore, the level of BNP that is reased to the serum might increase when there is tension with the RV muscle fibresand when myocardial hypoxemia takes place (12). In a study conducted by Cavallazzi and his colleagues, it was found that high levels of BNP and NT-proBNP are associated with mortality and right ventricular dysfunction (13). In a study by Kostrubiec and his colleagues, while none of the patients with NT-proBNP <600 pg/ml levels had mortality or any complications, it was found that the mortality was increased by 6.7 times when the patients had NT-proBNP >7600 pg/ml levels (14). In our current study, pro-BNP increased significantly with pulmunory thrombolism and this increase was significantly the highest in the high mortality risk group and the lowest in the low mortality risk group. These findings are in line with other studies in the literature. Further, have found a positive milde correlation between H-FABP and pro-BNP. With an increase in pro-BNP the H-FABP levels was increasing.

Troponin I and T and a new marker, H-FABP are used as myocard injury markers. In Management Strategies and Prognosis of Pulmonary Embolism (MAPETT 2) study, a significant relationship between high troponin levels and mortality was found and because of this finding the authors proposed troponin as an indicator in predicting right ventricular microinfarctus. Increased serum troponin level is evidence for RV dysfunction (15). In a study conducted by Golpe and his colleagues, the authors report that high troponin I levels among hemodynamically stable PTE patients are associated with the seriousness of the disease (16). In another study by Sanchez and his colleagues, increased troponin levels were found to increase mortality 5.2 times in normotensive PTE patients (17). In our study, we found that troponin T level in low mortality risk group was significantly lower than moderate and high mortality risk groups. However, there was not a significant difference in troponin T levels between high and moderate mortality risk groups. Likewise, there was not any significant difference between Group 1 and Group 2 of the moderate mortality risk group. We have found a weak positive correlation between H-FABP and troponin T levels. As the troponin T levels increased, so did the H-FABP levels.

Recent studies in the literature show that H-FABP is a superior marker for acute PTE cases compared to troponin T and pro-BNP (18-20). Dellas and his colleagues' study on a sample of PTE patients found that, as one of the important markers of right ventricular dysfunction, H-FABP has 89% sensitivity, 82% specifity, 99% negative predictive value. In the same study, the authors also mention the value of utilizing H-FABP with tachycardiain prognosis (18). However, in another study by Jenab and his colleagues, patients and in the presence of NT-proBNP association was not with the short-term adverse events and long-term mortality in terms of H-FABP. The authors explained these contradictions with relatively low number of cases or the different inclusion criteria for their study (21).

We found significantly higher H-FABP values in Group 1 (PAP ≥45 mmHg) than Group 2 (PAP <45 mmHg). Otherwise, we could not find any significant differences between Group 1 and 2 in terms of troponin T and proBNP levels. There is enough research evidence on H-FABP to be a superior marker in PTE cases. Having higher values of H-FABP among patients with high pulmunory artery pressure led us to think that a high PAP value is one of the influential parameters on prognosis, but its value might be unnoticed when used together with other cardiac markers.

Moreover, in our research we have found a very strong positive correlation between PAP and H-FABP. H-FABP was increasing in parallel with the increase in PAP values. Particularly, having significantly high H-FABP values when PAP was equal to or higher than 45mm Hg values can be interpreted as an indicator of microinfarction and right ventricular infarction with the patients.

When the markers for right ventricular dysfunction are defined in 2019 ESC Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism, we do not see any prognostic evaluation regarding PAP. In our study, we have proved that high PAP should be considered as a bad prognostic parameter in addition to the right ventricular dysfunctions in ECO. In a study conducted by Qian and his colleagues, significantly higher PAP values were found in high mortality risk group than other groups (9).

In another study on PTE cases, 6000 pg/ml was found as the cut-off threshold value for H-FABP level (18). In our study, we have considered this threshold value to be around 4000 pg/ml. With patients whose H-FABP value was 4000 pg/ml and above, we found senkop, hypertension, atrial fibrillation frequency values as significantly high. Additionally, we found significantly higher pulmunory artery pressure among patients whose H-FABP value was 4000 pg/ml or above. Findings of a study by Langer and his colleagues supports the hypothesis that H-FABP can be a promising prognostic marker of short-term mortality among low-risk PTE patients (19).

In addition to the findings above, we have also found strong negative correlation between H-FABP and oxygen saturation, which is one of the parameters in pulmunory embolism seriousness index. As the oxygen saturation decreased, the H-FABP levels increased. This finding shows that hypoxia should be considered as a bad prognostic marker.

The relationship between malignite and venous thromboembolism (VTE) is well known. Lee and his colleagues found VTE in 4-28% of the cancer patients (22). Similar to the Lee et al study, we found active malignite in 22.4% of the patients in our study. The earlier study showed 6-month VTE risk for cancer patients is currently 12-fold higher than in the general population (23). Parallel with other studies in literature on distribution of risk factors across PTE groups, we have also found significantly higher amounts of malignite and atrial fibrillation in high mortality risk group than the low-risk group. Therefore, we have come to conclude that atrial fibrillation is an important factor in developing pulmonary thromboembolism both in terms of its etiology and in the prognosis of these patients.

In this study, we have found that H-FABP level is a superior marker over other cardiac markers. There was not a significant difference in troponin T levels between high mortality risk group and moderate mortality risk groupH-FABP is a superior marker in determinin progranosis over pro-BNP and troponin because of its fast diffusion into blood stream and its significant variation across all PTE sub-groups, and its sensitivity for high PAP levels.

The H-FABP level was significantly higher with patients who had bilateral main pulmunory artery thrombus than it was with patients who had segmentary and sub-segmentary pulmunory artery thrombus. In one of our recent studies, cases with central thrombus had significantly higher troponin levels and frequent signs of Right ventricular dilatationon echocardiography, compared to cases with distal thrombus (24).

It is worth noting that our study has s ome limitations due to some factors such as collecting data in one hospital, having relatively low numbers of patients, and a lack of long-term follow up of patients.

In conclusion, diagnostic and treatment of PTE cases is an urgent matter. Therefore, in order to make proper treatment decisions, swift analyses must be made on PTE patients by evaluating clinical findings, markers of right ventricular dysfunction, cardiac markers and radiological findings. There is a much more sensitive approach regarding the classification of PTE patients in 2019 ESC Guidelines on the Diagnosis and Management of Acute Pulmonary Embolism (4). Nevertheless, this classification does not include any prognostic evaluations of PAP. We believe that having high PAP values should be considered as a prognostic parameter. Medium mortality risk group is a heterogenous group. The cardiac markers that are used for prognostic purposes must provide fast diagnosis capability, they must be sensitive and specific. In this regard, we have considered H-FABP as a superior marker over alter alternatives.

In risk classification of the disease, cardiac markers, right ventuculary dysfunctional findings, and pulmunory embolism seriousness index have begun to be used. In this connection, the clinical, physical and laboratory findings are evaluated altogether.

Limitations

Our study has some limitations such as being a single-centre study and having a limited number of patients.

CONCLUSION

According to the findings of our study, when cardiac markers are evaluated across PTE sub-groups:

- H-FABP is an important prognostic marker across all acute PTE groups.
- H-FABP is a superior marker over troponin T ve pro-BNP in determining prognosis.
- H-FABP levels in low mortality risk group was very close to H-FABP levels in healthy control group. This finding was interpreted as PTE group with low mortality risk to have good prognosis.

Strong positive correlation between H-FABP and PAP, and strong negative correlation between H-FABP and oxygen saturation led us to conclude that all three indicators are aggravating factors.

Making a decision for thrombolic treatment only after clinical, laboratory, and radiological evaluation will be in the best interest of normotensive patients as well. We need the more research to find out the risk coefficients factors of the aggravating factors and additional factors mentioned above.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Yıldırım Beyazıt University Non-interventional Clinical Researches Ethics Committee (Date: 18/06/2014; Decision No: 19).

Informed Consent: Written informed consent was obtained from all participants who participated in this study

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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