The value of YKL-40 level in early thrombolytic treatment decision-making in patients with pulmonary thromboembolism

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Abstract

Introduction:

Pulmonary embolism (PE) often occurs secondary to deep vein thrombosis and is an important cause of mortality and morbidity. This study aimed to evaluate the relationship between YKL-40 level and clinical risk score in patients with PE.

Methods

The study included a total of 100 patients, 80 patients diagnosed with PE in the emergency department and 20 healthy controls. Patients with PE were divided into four groups: high-risk patients (n = 20), high-intermediate-risk patients (n = 20), low-intermediate-risk patients (n = 20), and low-risk patients (n = 20). Serum YKL-40 levels were measured by enzyme-linked immunosorbent assay. Pulmonary artery obstruction index (PAOI) was calculated from computed tomography angiography images.

Results

PAOI increased in correlation with PE risk and differed significantly between all patient groups ($p < 0.001$). Troponin-I levels were significantly higher in the high-risk and high-intermediate-risk groups compared to the other groups ($p < 0.001$), but did not differ significantly between high-risk and high-intermediate-risk patients ($p = 0.09$). YKL-40 level was significantly higher in the high-risk PE group than the high-intermediate-risk group ($p < 0.001$). In receiving operator characteristic curve analysis assessing the discriminatory value of YKL-40 for high-risk PE patients, a cut-off value of 227.2 ng/mL had sensitivity of 85% and specificity of 70%.

Discussion

YKL-40 may be an important biomarker in decisions regarding early thrombolytic treatment in patients with high-intermediate-risk PE. In addition, medical treatments targeting YKL-40 may also reduce thrombotic tendency in high-risk patient groups.

Highlights

- A cytokine called YKL-40 was found to be a stronger promoter of vascularization in endothelial cells than VEGF. Studies on the blockade of YKL-40 synthesis have shown that anti-YKL-40 antibody suppresses vascularization both in cell culture and a xenografted animal model. YKL-40 also plays an important role in the regulation of VEGF synthesis. For this reason, significant increases in YKL-40 have been observed in diseases associated with angiogenesis, inflammation, extracellular remodeling, and fibrosis.

- PE is an important disease associated with considerable morbidity and mortality, especially in high-risk patients, and this risk increases with delayed thrombolytic treatment. The decision for early thrombolytic therapy is made based on follow-up for patients at high-intermediate risk. YKL-40 may be a valuable biomarker that can guide thrombolytic therapy decisions in the early period for this patient group in particular. In addition, evaluated in light of previous reports, our results suggest that medical treatment targeting YKL-40 may also prevent thrombotic tendency in at-risk patient groups.

Introduction

Pulmonary embolism (PE) generally occurs as a complication of deep vein thrombosis (DVT). Occlusion of the pulmonary artery and/or its branches results from clots that dislodge from thrombi in the deep veins of the leg. Because of the frequent concurrence of PE and DVT, both events can be described using the general term venous thromboembolism (VTE) [1].

The commonly used biomarkers troponin, brain natriuretic peptide (BNP), and NT-proBNP are used to classify cases of submassive PTE as low- or high-risk [2]. Right ventricular dilation due to PE increases the myocardial oxygen demand of the right ventricle. Microinfarcts in the right ventricle caused by impaired circulation result in a localized increase in troponin release [3]. Meta-analyses revealed a strong association between complicated clinical course and mortality in patients with high troponin levels. This facilitated the differentiation of patients with submassive PE into low- and high-risk groups [1].

Right ventricular dilation also leads to the release of certain cytokines that contribute to oxygenation, neovascularization, and rapid thrombus organization. One of these is vascular endothelial growth factor (VEGF), which is an important mediator of neovascularization [4–6]. However, studies on the inhibition of tumor vascularization have shown that neovascularization involves multifactorial interactions. A cytokine called YKL-40 was found to be a stronger promoter of vascularization in endothelial cells than VEGF. Studies on the blockade of YKL-40 synthesis have shown that anti-YKL-40 antibody suppresses vascularization both in cell culture and a xenografted animal model [7]. In addition, a positive correlation between YKL-40 level and disease severity was observed in patients with coronary artery disease. It was also determined that YKL-40 is intensively synthesized by the macrophages involved in atheromatous plaque stabilization [8, 9].

The cardiac markers used in the clinical scoring and follow-up of PE are not always adequate for treatment planning. This study aimed to evaluate the relationship between YKL-40, which is believed to play an important role in neovascularization and inflammation, and the clinical course and prognosis of PE.

Methods

Study Population

The study included 80 patients who were diagnosed with PE in our emergency department between September 2021 and January 2022 and 20 healthy control subjects. All patients with clinical suspicion of PE (clinical signs, major risk factors) were assessed with chest x-ray, electrocardiography (ECG), and echocardiography (ECHO). For patients with high clinical suspicion, CT angiography was performed with a 16-slice multi-detector CT scanner to confirm the diagnosis.

Patients diagnosed as having PE were assessed using the Pulmonary Embolism Severity Index (PESI) in accordance with the 2019 European Society of Cardiology (ESC) guidelines for the management of PE, followed by scoring of acute PE severity and clinical risk of early mortality [1]. Clinical and laboratory evaluations, including physical examination, blood pressure, heart rate, complete blood count, and oxygen saturation, were performed before and after thrombolytic therapy. ECG examination and interpretation was performed only before thrombolytic therapy.

Twenty patients were evaluated as having high-risk PE, which was defined as sustained hypotension (systolic arterial pressure < 90 mmHg or ≥ 40 mmHg decrease in systolic arterial pressure for at least 15 min) and cardiogenic shock (with clinical signs such as altered consciousness, oliguria, or cool/clammy extremities). Twenty patients had high-intermediate-risk PE, defined as right ventricular dilation and troponin-I elevation without hypotension or signs of shock. Another 20 patients were classified as low-intermediate-risk PE, defined as right ventricular dilatation without troponin-I elevation.

Patients with high-risk PE received full-dose alteplase (10 mg bolus followed by 90 mg infusion over 2 hours) if under 65 years of age, and half-dose alteplase if over 65 years of age. Enoxaparin sodium at 12-hour intervals was initiated immediately after thrombolytic therapy. Patients with high-intermediate and low-intermediate-risk PE received only enoxaparin sodium therapy at 12-hour intervals. Two patients in the high-intermediate-risk PE group developed hypotension and shock in the first 72 hours and received thrombolytic therapy in accordance with the high-risk PE protocol.

Exclusion Criteria

Exclusion criteria were: diagnosis and/or treatment of myocardial infarction in the past 3 months, severe hypoxic respiratory failure, concomitant intracranial hemorrhage, diagnosed malignancy, lymphangioleiomyomatosis, and known history of right heart dilation.

Pulmonary Artery Obstruction Index

The pulmonary artery obstruction index (PAOI) is determined by dividing the pulmonary arteries in each lung into 10 segmental branches (3 upper lobe, 2 middle lobe and lingula, 5 lower lobe). A thrombus in the proximal pulmonary arteries (main, lobar) receives a score equal to the total number of segmental branches distal to the thrombus. In the absence of a proximal thrombus, isolated thrombi in the segmental arteries receive 1 point. Thrombi are also evaluated as causing partial obstruction (filling

defect, some contrast flow) or total obstruction (artery completely blocked, no contrast in distal pulmonary vessels). PAOI is calculated by multiplying the number of segmental arteries distal to the thrombus (range: 1–20) by the degree of obstruction (partial = 1, total = 2).

Statistical analysis

Analyses were performed using IBM SPSS Statistics version 20.0 software (IBM Corp, Armonk, NY). The data are presented as mean and standard deviation or number and percentage. Continuous variables were tested for normal distribution using the Shapiro-Wilk W test and Kolmogorov-Smirnov test. Comparisons of continuous variables between more than two independent groups were performed using analysis of variance (ANOVA) for normally distributed data and Kruskal-Wallis test for non-normally distributed data. After ANOVA, post-hoc analyses were performed using Tukey's test for data with homogeneous variances and Tamhane's T2 test for data with nonhomogeneous variances. After the Kruskal-Wallis test, post-hoc analysis was done using the Kruskal-Wallis one-way ANOVA (k samples) test. Relationships between two quantitative variables were analyzed using Pearson correlation analysis if they showed normal distribution and Spearman correlation analysis if they did not. Receiver operating characteristic (ROC) curve analysis was used to determine whether YKL-40 and troponin-I had diagnostic value, and optimal cut-off values were determined using Youden index. Results with p values < 0.05 were considered statistically significant.

Results

The patients with PE (all groups) had a mean age of 67.1 ± 1.9 years. The mean age in the healthy control group was 69.8 ± 5.6 years. There was no significant difference in age between the patient and control groups ($p = 0.46$). The patient subgroups also showed no significant difference in age ($p = 0.08$). The male-to-female ratio was 1:1 in both the patient and control groups.

A comparison of ECHO, PAOI, and laboratory values between the study groups are shown in Table 1. Mean pulmonary artery pressure (PAP) was significantly higher in patients with intermediate- and high-risk PE compared to the low-risk and control groups and in patients with high-risk PE compared to those with intermediate-risk PTE ($p < 0.001$ for all). Ejection fraction was significantly lower in high-risk and high-intermediate-risk PE patients compared to the low-intermediate-risk group ($p = 0.02$ and 0.006, respectively). PAOI increased in association with PE risk and differed significantly between all patient subgroups ($p < 0.001$). Troponin-I levels were significantly higher in the high-risk and high-intermediate-risk groups compared to the other groups ($p < 0.001$), but did not differ significantly between high-risk and high-intermediate-risk patients ($p = 0.09$). Similarly, YKL-40 levels were significantly higher in patients with intermediate-risk and high-risk PE compared to the low-risk PE and control groups ($p < 0.001$ for all). Although YKL-40 level did not differ significantly between the low-intermediate and high-intermediate risk groups ($p = 0.67$), it was significantly more elevated in the high-risk PE group than the high-intermediate-risk group ($p < 0.001$).

Table 1
Comparison of selected parameters between the pulmonary embolism (PE) patient and control groups

	Low-risk PE (n = 20) Mean ± SD	Low-intermediate-risk PE (n = 20) Mean ± SD	High-intermediate-risk PE (n = 20) Mean ± SD	High-risk PE (n = 20) Mean ± SD	Control (n = 20) Mean ± SD	p
Age (year)	70.4 ± 10.1	70.9 ± 13.3	71.1 ± 16.6	71.4 ± 12.5	69.8 ± 5.6	0.08
Mean PAP	30.8 ± 3.2	46.1 ± 5.7	46.1 ± 7.4	59.1 ± 10.1[a]	29.8 ± 5.4	**< 0.001**
PAOI	10.8 ± 2.4	25.9 ± 6.9	35.8 ± 10.3	53 ± 7.5[a]	-	**< 0.001**
Ejection fraction	56.9 ± 3.7	55.3 ± 4.4	52.9 ± 6.2	52.2 ± 6.1	59.4 ± 5.5	**0.01**
Troponin I (ng/L)	5.6 ± 1.4	8.9 ± 2.3	326.5 ± 120.5	271.9 ± 75.9	5.4 ± 2.1	**< 0.001**
YKL-40 (ng/ml)	89.1 ± 71.1	208.5 ± 94.9	194.8 ± 103.1	350.9 ± 125.1[a]	86.9 ± 27.2	**< 0.001**

PAOI: Pulmonary arterial obstruction index, PAP: Pulmonary artery pressure

In the comparison of continuous variables between more than two independent groups, analysis of variance (ANOVA) was used if normally distributed and Kruskal-Wallis test if non-normally distributed. Post-hoc tests after ANOVA were performed using Tukey's test when variances were homogeneous and Tamhane's T2 test when variances were not homogeneous. Post-hoc analysis after Kruskal-Wallis test was performed using the Kruskal-Wallis 1-way ANOVA (k samples) test. p[a]: High-risk vs. high-intermediate-risk group ($p < 0.001$)

In the ROC curve analysis of troponin-I and YKL-40 levels to differentiate high-risk PE patients, area under the curve (AUC) values were 0.796 for troponin-I and 0.858 for YKL-40. At a cut-off value of 227.2 ng/mL, YKL-40 had sensitivity and specificity values of 85% and 70%, respectively. For troponin-I, a cut-off value of 176.9 ng/L had 90% sensitivity and 68% specificity (Fig. 1).

The results of correlation analysis between YKL-40 and troponin-I levels, PAOI, ejection fraction, and mean PAP are shown in Table 2 and Fig. 2. YKL-40 was positively correlated with mean PAP ($r = 0.705$, $p = 0.01$), PAOI ($r = 0.618$, $p = 0.01$), and troponin-I ($r = 0.587$, $p = 0.01$) and negatively correlated with ejection fraction ($r=-0.334$, $p = 0.01$).

Table 2
Correlation analysis between YKL-40 and selected variables

		YKL-40	PAOI	Ejection fraction	Troponin-I	Mean PAP
YKL-40	R	1.000				
	p	-				
	n	100				
PAOI	R	0.618	1.000			
	p	0.01	-			
	n	80	80			
Ejection fraction	R	-0.334	-0.262	1.000		
	p	0.01	0.01	-		
	n	100	80	100		
Troponin-I	R	0.587	0.62	-0.409	1.000	
	p	0.01	0.01	< 0.001	-	
	n	100	80	100	100	
Mean PAP	R	0.705	0.703	-0.265	0.591	1.000
	p	0.01	0.01	0.01	0.01	-
	n	100	80	100	100	100

PAOI: Pulmonary arterial obstruction index, PAP: Pulmonary artery pressure

Discussion

In this study, we observed that high-risk PE patients had significantly higher mean PAP, PAOI, and YKL-40 levels than other patients and healthy controls. In addition, in the comparison of the high-intermediate-risk group, whose thrombolytic treatment plan is decided according to follow-up, and the high-risk group, who receive early thrombolytic therapy, we observed that the high-risk group had significantly higher YKL-40 levels at diagnosis. Evaluation of the sensitivity and specificity of troponin-I and YKL-40 levels in the differentiation of high-risk and high-intermediate-risk patients showed that troponin-I was more sensitive while YKL-40 level had higher specificity. In addition, YKL-40 was more strongly correlated with mean PAP than troponin-I.

The classification of PE is based on clinical presentation as massive (high-risk), submassive (intermediate-risk), and nonmassive (low-risk) [10,11]. Transthoracic ECHO is the gold standard method for assessing right ventricular dysfunction in acute submassive PE using parameters such as dilation of the

right ventricle, hypokinesis of the right ventricular wall, paradoxical movement of the interventricular septum, tricuspid regurgitation, pulmonary artery dilation, and increased right-to-left ventricular end-diastolic diameter ratio [12, 13].

Cardiac troponin-T and troponin-I are cardiac muscle-specific enzymes. In acute right heart failure associated with massive PE, dilation of the right ventricle increases its oxygen demand. Assessment of troponin, BNP, and NT-proBNP may be useful as a prognostic evaluation to distinguish high- and intermediate-risk patients from low-risk patients, and can also be used to further stratify patients at intermediate risk into low-intermediate and high-intermediate risk groups. However, elevation of these markers may also be associated with conditions such as congestive heart failure, acute exacerbation of chronic obstructive pulmonary disease, acute kidney disease, sepsis, trauma, and rhabdomyolysis [1, 14]. Although cardiac biomarkers have an important place in clinical risk scoring, there is no definitive cut-off value to differentiate high-risk and high-intermediate-risk patients. Consequently, the decision to initiate thrombolytic therapy requires clinical observation in the high-intermediate-risk group. However, delaying treatment for clinical observation puts the patient at risk of sudden death due to hypoxic respiratory failure and hemodynamic collapse. Therefore, alternative biomarkers are needed for clinical scoring.

YKL-40 is an inflammatory biomarker produced by macrophages in atherosclerotic lesions, as well as by endothelial and vascular smooth muscle cells and possibly even activated hepatic stellate cells in a late stage of differentiation [15]. YKL-40 also plays an important role in the regulation of VEGF synthesis. For this reason, significant increases in YKL-40 have been observed in diseases associated with angiogenesis, inflammation, extracellular remodeling, and fibrosis [16, 17]. YKL-40 levels were also found to be significantly elevated in individuals with cardiovascular and liver disease compared to the healthy population [15, 16, 18]. Moreover, patients with high plasma YKL-40 levels were found to be twice as susceptible to ischemic stroke and VTE [9, 19]. Previous studies on PE have also shown that VEGF-D level increases in correlation with clinical risk score and emphasized that this parameter may guide early fibrinolytic treatment [4]. The present study on YKL-40, which is involved in VEGF synthesis, was planned in the same direction.

Our results indicate that high-risk and high-intermediate-risk PE was more frequent in patients with low ejection fraction. This may be because patients with low ejection fraction have greater coagulopathic tendency or because immobilization is more likely in these patient groups. In addition, we observed that PAOI increased between the patient groups in correlation with their PE clinical score. Troponin-I is an important marker of right heart dilation and cardiac dysfunction, and its elevation in intermediate- and high-risk patients may be related to thrombus burden. In contrast, YKL-40 level was found to be lower in patients with high-intermediate-risk PE, for whom the decision to initiate thrombolytic therapy was based on hemodynamic instability during follow-up, compared to patients with high-risk PE. YKL-40 was also positively correlated with PAOI, troponin-I level, and mean PAP. Evaluated in the context of previous studies, these findings suggest that YKL-40 may be a biomarker indicating both increased thrombotic tendency and thrombus load. YKL-40, which also plays an important role in neovascularization, may be

elevated due to the increased need for vascularization in response to cardiac dilation. In the ROC curve analysis, YKL-40 had a larger AUC than troponin-I, suggesting it might be a more valuable biomarker for the differentiation of high-risk PE patients.

In this study, we excluded patients with comorbidities that may affect YKL-40 level as identified in previous studies. However, the fact that ejection fraction values were not homogeneous between the groups is an important limitation. Increased smooth muscle hypertrophy as a result of low ejection fraction may have caused an increase in YKL-40 level. Therefore, studies comparing patient groups with comparable ejection fraction may validate our findings.

In conclusion, PE is an important disease associated with considerable morbidity and mortality, especially in high-risk patients, and this risk increases with delayed thrombolytic treatment. The decision for early thrombolytic therapy is made based on follow-up for patients at high-intermediate risk. YKL-40 may be a valuable biomarker that can guide thrombolytic therapy decisions in the early period for this patient group in particular. In addition, evaluated in light of previous reports, our results suggest that medical treatment targeting YKL-40 may also prevent thrombotic tendency in at-risk patient groups.

Declarations

Compliance with Ethical Standards

Conflict of interest: The authors received no fnancial support for the research and/or authorship of this article. The authors declare that they have no confict of interest to the publication of this article.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent: Informed consent was obtained from all individual participants included in the study

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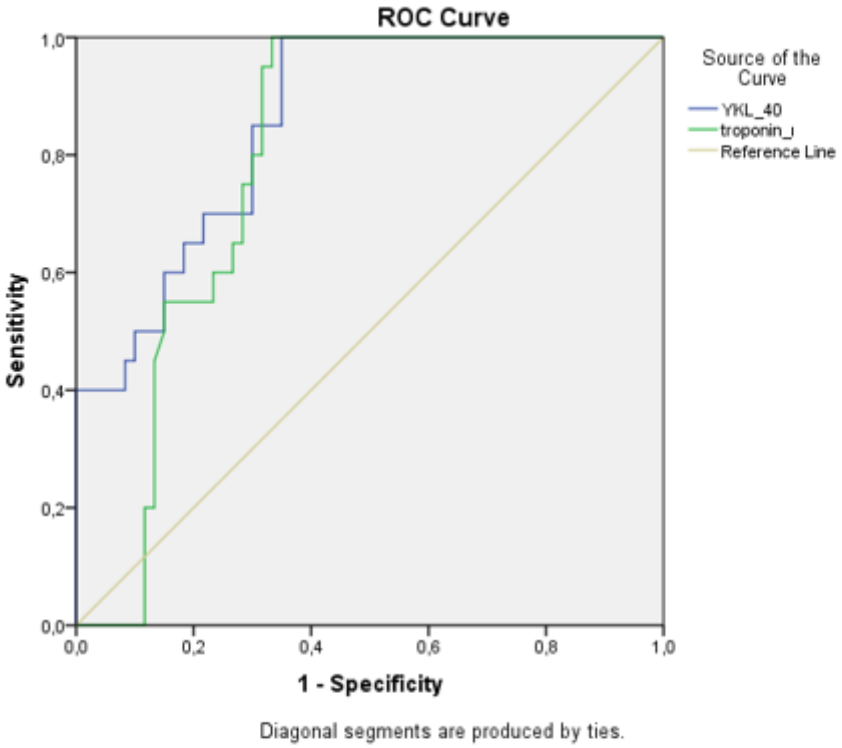
Figures

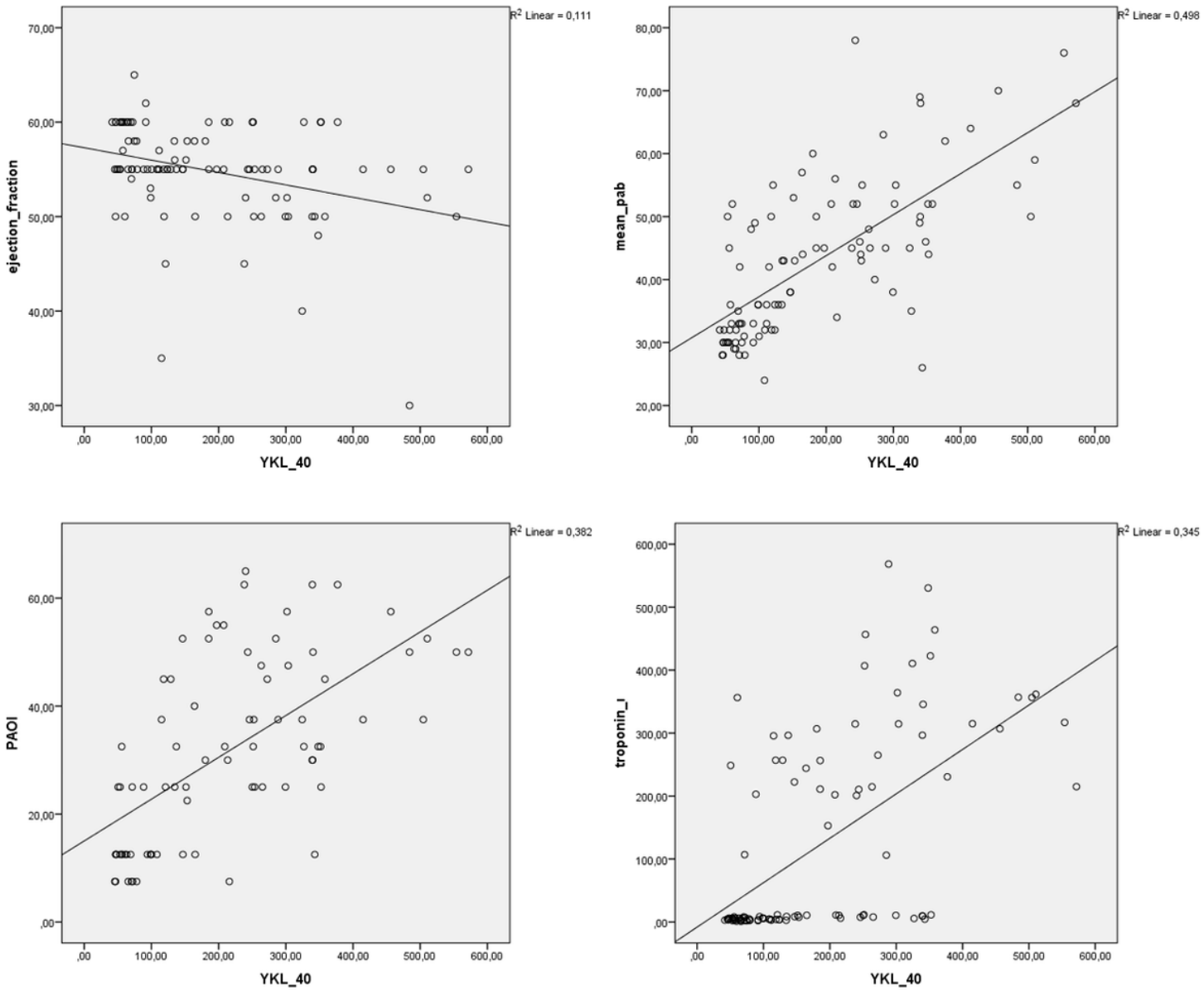


Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
YKL-40	.858	.042	.000	.776	.940
Troponin-I	.796	.048	.000	.702	.891

Figure 1

Receiver operating characteristic curve analysis of YKL-40 and troponin-I in patients with and without high-risk PE



PAOI: Pulmonary arterial obstruction index, PAP: Pulmonary arter pressure

Figure 2

Correlation analysis of YKL-40 level and ejection fraction, PAOI, mean PAP, and troponin-I