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Utility of biochemical markers and RVD/LVD ratio in acute pulmonary embolism risk classification in Emergency Department

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Abstract. – OBJECTIVE: We aimed to determine the efficacy of troponin I, D-dimer, and lactate levels and right ventricular diameter (RVD)/left ventricular diameter (LVD) ratio on pulmonary computed tomography angiography (PCTA) in the risk classification of patients who were diagnosed with acute pulmonary embolism (APE) in Emergency Department (ED).

PATIENTS AND METHODS: Patients who were diagnosed as having APE by PCTA in ED were included in this retrospective study. Patients were grouped as high-risk (undergoing cardiopulmonary resuscitation or given thrombolytic therapy), moderate-risk (with non-high-risk and positive ECO findings) and low risk (others). Troponin I, D-dimer, and lactate levels of patients were determined. RVD, RVD/LVD ratio, and interventricular septum deviation were calculated from PCTA images.

RESULTS: A total of 121 patients were included (35 high, 36 moderate, 50 low risk). Lactate was different in the high-risk group from the other groups, whereas there was no difference between the moderate and low-risk groups. Troponin I levels were not different between the high-risk and moderate-risk groups. There were statistically significant differences between the high, moderate, and low-risk groups in terms of mean RVD/LVD ratios. ROC analyses performed in order to define high-risk group revealed a cut-off value of > 2.3 (AUC = 0.848, sensitivity = 70%, specificity = 90%, + Likelihood ratio (LR) = 7, -LR = 0.33, 95% CI = 0.752-0.943) for lactate and > 1.40 (AUC = 0.695 sensitivity = 71%, specificity = 80%, + LR = 3.6, -LR = 0.36, 95% CI = 0.668-0.822) for RVD/LVD ratio.

CONCLUSIONS: Lactate levels and RVD/LVD ratio were shown to be useful in distinguishing high-risk patients from other patient groups. Troponin I is important in terms of showing cardiac involvement, but it is inadequate in distinguishing between high and moderate-risk patients. Lactate, troponin I, and RVD/LVD ratio may be used together for a more accurate separation of patients with high, intermediate and low-risk.

Key Words:
Classification, Pulmonary computed tomography angiography, Pulmonary embolism, Right ventricular diameter, Lactate, Troponin I, RVD/LVD ratio.

Introduction

Acute pulmonary embolism (APE) is a potentially fatal condition which occurs due to the obstruction of the pulmonary arteries by the dislodging and embolization of thrombotic material coming in most cases from the deep veins of the leg, pelvis and arms[1,2]. For this reason, accurate diagnosis along with proper patient management is essential to reduce morbidity and mortality in the emergency department (ED). Recently, risk classification for patient management has been made. While patients with hypotension and shock were classified as having high risk, patients with only cardiac involvement were classified as having moderate risk and patients without any clinical findings as having low risk[3-5].

The presence of cardiovascular collapse and shock due to massive pulmonary thromboembolism induced acute right ventricular failure is directly related to the risk of premature death. Early hospital mortality is at least 15% in these high-risk cases. Right ventricular dysfunction is detected in 27-56% of normotensive patients with APE. The 30-day mortality risk and the recurrence of pulmonary thromboembolism are significantly increased in moderate-risk cases[5-7].

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Today, while thrombolytic therapy is suggested for high-risk patients, indication for thrombolytic therapy in moderate-risk patients is controversial. However, mortality ranges from 5 to 15% in this group[8]. Therefore, it is important to determine the risk classification of patients with APE in the emergency service and during clinical follow-up.

Various clinical, laboratory and imaging studies have been performed to determine the high risk in patients with APE. However, the parameters that distinguish high, medium and low risk patients from each other are not clearly defined.

In this study, it was aimed to determine the efficacy of troponin I, D-dimer, and lactate levels, right ventricular diameter (RVD), RVD/left ventricular diameter (LVD) ratio and interventricular septum deviation on pulmonary computed tomography angiography (PCTA) in the risk classification of the patients who were diagnosed with APE in ED.

Patients and Methods

This retrospective study was started after the approval of the local Ethics Committee. Patients over 18 years of age from both genders, who underwent PCTA in the Emergency Service and who were diagnosed with APE between September 2014 and September 2015, were included in this study. Patients without fully accessible study data and patients with excluded APE diagnosis were excluded from the study. The patients' file information was retrieved from the hospital automation system and the hospital's archive. A standard study form was created for the study. Age, gender, the reason for emergency service admission, medical history, vital signs, physical examination findings and laboratory results (arterial blood gas, lactate, troponin I, D-dimer) on admission, echocardiography (ECHO) and PCTA reports, applied treatments, hospitalized clinic and outcome information, were recorded in this form.

Biochemical Analysis

Troponin I was studied in Siemens IMMULITE 2000 Immunoassay System (Siemens Healthcare Diagnostics, Deerfield, IL, USA). D-dimer was studied in ACL TOP 700 device (Instrumentation Laboratory, Munich, Germany). Lactate was studied in ABL 80 flex device (Radiometer America Inc., Westlake, OH, USA). The reference values reported in healthy adults were as follows; 0.02 - 0.06 ng/ml for cardiac troponin I, 0-242 ng/ml for D-dimer and 0.3-1.3 mmol/L for lactate.

PCTA Imaging

PCTA images were obtained from the hospital automation system registry. A multislice computed tomography scanner (HITACHI ECLOS) was used for PCTA imaging in the emergency service. 8 ml intravenous contrast medium was administered via the antecubital vascular access for PCTA. Imaging was performed in the early arterial phase 10-15 s after power injection.

PCTA images were evaluated by the radiologist. Embolism on PCTA was grouped as subsegmental, segmental, and main pulmonary artery. The width of the heart cavities was measured from the end-diastolic images. The distance between the septum and the inner wall was measured just below the tricuspid valve for right ventricular diameter and just below the mitral valve for left ventricular diameter. For interventricular septum deviation, a longitudinal straight line was drawn at the level of apex, and a reference point was created by drawing a perpendicular line from the inner surface of the right ventricular septum. The measurement was made at this reference point in the presence of septum deviation. The measurements were made in mm.

Transthoracic Echocardiography

Cardiac involvement was agreed in the presence of the following right ventricular loading findings on ECHO: right ventricular dilatation, hypokinesia, paradoxical movement of the interventricular septum, increased end-diastolic diameter and tricuspid insufficiency, McConnell's sign and D-share findings.

Table I. Comparison of PCTA results with risk groups of acute pulmonary embolism.

Place of embolism	High-risk n (%)	Medium-risk n (%)	Low-risk n (%)
Subsegmenter	2 (6)	3 (8)	10 (20)
Segmenter	4 (11)	20 (55)	32 (64)
Main pulmonary artery	29 (83)	13 (37)	8 (16)
Total	35 (100)	36 (100)	50 (100)

Table II. Distribution of mean values of study parameters according to risk groups of acute pulmonary embolism.

	High-risk mean±SD min-max	Medium-risk min-max mean±SD	Low-risk mean±SD min-max
RVD	50.6±8.7	41.77±9.8	39.4±6.7
	35.5-62.7	23.0-58.4	27.2-53.0
RVD/LVD ratio	1.6±0.5	1.3±0.4	1.2±0.4
	0.8-2.8	0.8-2.2	0.6-2.2
Interventricular septum deviation	1.4±1.6	1.0±1.7	0.8±1.3
	0.0-4.5	0.0-5.8	0.0-4.0
Troponın I	0.3±0.3	0.3±0.3	0.02±0.02
	0.2-0.94	0.1-0.85	0.0-0.9
D-dimer	4959±3730	4587±3341	2479±2001
	499-13486	1090-10565	371-8135
Lactate	3.7±2.4	1.9±1.2	1.3±0.4
	1.2-10.0	1.0-5.9	0.6-2.1

LVD = Left ventricular diameter; RVD = Right ventricular diameter; SI = Shock index; RSI = Respiratory shock index.

Grouping of Patients

The patients were divided into 3 groups. Patients undergoing cardiopulmonary resuscitation or given thrombolytic therapy were included in the high-risk group. Patients with non-high-risk and positive ECO findings were included in the intermediate risk group. Other patients were taken at low risk group.

Statistical Analysis

SPSS 21.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis of the data. Categorical variables were expressed as number and percentage, and continuous variables were as mean and standard deviation (median and minimum – maximum, where necessary). x^2 test statistic was used to compare categorical variables. One-Way ANOVA and Student's *t*-test were used to compare continuous variables between groups. ROC analysis was performed to determine the cut-off value of the parameters. In all tests, values of $p < 0.05$ were regarded as statistically significant.

Results

A total of 121 patients, who were diagnosed with APE according to PCTA reports, were included in the study. 50 (41%) patients were male and 71 (59%) were female. The mean age of the female patients was 68 ± 16 years and the mean age of the male patients was 58 ± 16 years. 61 (50%) patients were older than 65 years. The most common reason for admission was shortness of breath. About patients, 42% had immobilization, 21% had history of surgery, 20% had malignancy, 17% had active DVT, 10% had heart failure and 2% had oral contraceptive usage.

High-risk groups included 35 (29%) patients. These patients were hospitalized in the intensive care unit (ICU). Cardiac involvement (moderate-risk) was detected in 36 (30%) of the patients except for patients included in high-risk group. While 26 patients with moderate risk were hospitalized in services, 10 were hospitalized in the ICU. Low-risk groups included 50 (41%) patients. While 10 (20%) patients with low-risk were discharged from the emergency service, 36 (72%) were hospitalized in the Chest Diseases Service and 4 (8%) were hospitalized in the ICU.

Cardiopulmonary resuscitation was performed in 7 (6%) patients in Emergency Department. These patients were administered thrombolytic therapy in the Emergency Department. Of these patients, 6 died in the ICU. Of all included patients, 115 (95%) were discharged with healing.

When the PCTA images of the patients were examined, subsegmental embolism was detected in 15 (13%) patients, segmental embolism in 56 (46%) patients and main pulmonary artery embolism in 50 (41%) patients. Embolism was detected in the main pulmonary artery in 29 (85%) of patients in high-risk group (Table I).

Right ventricular diameter was greater than LVD in the measurements made on PCTA images of 101 (83%) patients (RVD/LVD>1). Right ventricular diameter was greater than LVD in 33 (94%) patients with high risk, 29 (83%) patients

Table III. Statistical comparison of study parameters according to risk groups of acute pulmonary embolism.

	p-value (mean difference) of risk groups		
	High-Medium	**High-Low**	**Medium-Low**
RVD	**0.008** (5.7)	**0.001** (9.5)	0.067 (3.8)
RVD/LVD ratio	**0.006** (0.3)	**0.001** (0.5)	**0.023** (0.2)
Interventricular septum deviation	0.204 (0.6)	**0.004** (1.0)	0.321 (0.4)
D-Dimer	0.820 (536)	0.25 (2093)	0.143 (1556)
Troponin I	0.989 (0.01)	**0.001** (0.3)	**0.001** (0.3)
Lactate	**0.002** (2.2)	**0.001** (2.9)	0.422 (0.8)

LVD = Left ventricular diameter; RVD = Right ventricular diameter; SI = Shock index; RSI = Respiratory shock index.

Table IV. Results of ROC analysis of the study parameters to determine hypotensive shock.

	AUC	Cutt-off value	Sensitivity %	Specificity %	+LR	-LR	PPV	NPV	95% CI
RVD	0.713	> 45.0	77	72	2.8	0.31	84	89	0.592-0.834
RVD/LVD ratio	0.695	> 1.40	71	80	3.6	0.36	60	87	0.668-0.822
Lactate	0.848	> 2.3	70	90	7.0	0.33	77	84	0.752-0.943

AUC = area under curve; +LR = + likelihood ratio; LR = likelihood ratio; PPV = positive predictive value; NPV = negative predictive value; CI = confidence interval; RVD = Right ventricular diameter; LVD = Left ventricular diameter.

with moderate risk and 38 (76%) patients with low risk. The high-risk group had the greatest RVD and RVD/LVD ratio. Interventricular septum deviation was observed in 19 (54%) of the high-risk patients, 14 (39%) of the moderate-risk patients and 13 (26%) of the low-risk patients (Table II).

Lactate levels of the high-risk patients were statistically higher than the other patients. There was no difference between the groups in terms of D-dimer levels (Table III).

The RVD of the high-risk patients was statistically higher than the other patients. RVD/LVD ratio was statistically different between the groups. Interventricular septum deviation was not statistically different between the groups. When the risk groups were compared among themselves, troponin I levels were found to be not different between the high-risk and moderate-risk groups. Lactate was different in the high-risk group from the other groups, whereas there was no difference between the moderate and low-risk groups (Table III). ROC analyses performed in order to define high-risk group revealed a cut-off value > 2.3 (AUC = 0.848, sensitivity = 70%, specificity = 90%, + Likelihood ratio (LR) = 7, -LR = 0.33, 95% CI = 0.752-0.943) for lactate and > 1.40 (AUC= 0.695 sensitivity = 71%, specificity = 80%, + LR = 3.6, -LR = 0.36, 95% CI = 0.668-0.822) for RVD/LVD ratio (Table IV).

Discussion

APE is the most important clinical presentation of venous thromboembolism[3]. Most APE patients have concurrent deep vein thrombosis (DVT). Risk factors for the development of venous thromboembolism are surgery, trauma, immobilization, pregnancy, oral contraceptive use or hormone replacement therapy and cancer. At the same time, cardiovascular diseases such as atherosclerotic heart diseases and heart failure pose a risk[5]. In our study, 43% of patients had immobilization and 17% had active DVT. Heart failure was found in 12% and ischemic heart disease was present in 12%.

It is very important to determine the risk classification when the acute pulmonary embolism is clinically suspected. A multimarker pannel approach performed by rapid and accurate assays could be useful for emergency physicians to promptly identify different causes of dyspnea such as APE thus managing to improve diagnosis, treatment and risk stratification[9]. Patients with hemodynamic instability along with shock or hypotension are at high risk and pharmacologic reperfusion therapy is administered primarily (or surgical or interventional, alternatively) in these patients when APE is confirmed (PCTA, ECHO, scintigraphy, pulmonary angiography, magnetic resonance angiography)[5].

Plasma D-Dimer levels increase in acute thrombotic events such as APE and DVT. Besides, the negative predictive value (NPV) of the D-dimer test is very high, and negative D-dimer test excludes the possibility of APE[5,9]. In a study with risk groups, the D-dimer level was found to be higher in moderate-risk patients than in low-risk patients[10]. In another study, D-dimer was found to be much higher than in the control group and it was shown that it could be used safely as an exclusion criterion[11]. In our study, plasma D-dimer levels were found to be high in all patients, but there was no statistical difference between the risk groups. For this reason, D-dimer was found to be not used to determine the risk group of patients with APE.

In clinical practice, lactate levels are often used to determine disease severity and to measure response to therapeutic interventions. Therefore, lactate levels have been studied in various patient groups[12]. However, the level of high lactate is uncertain and is not universally defined. However, in many studies, the cut-off value was defined as 2.0-2.5 mmol / L, and > 4 mmol/L was associated with poor results in undefined shock[13]. In a study investigating the prognostic value of lactate in APE, plasma lactate levels were associated with in-hospital mortality associated with all reasons and PE-related mortality[14]. In another study, plasma lactate levels of ≥ 2 mmol/L were associated with mortality associated with all reasons independent of hypotension/shock, right ventricular dysfunction, and elevated troponin levels[15]. In this study, it was seen that the lactate levels were higher in high-risk patients than the other patients. According to the ROC analysis, cut-off value of lactate was determined as > 2.3 mmol/L (sensitivity = 70%, specificity = 90%). Lactate may be useful as a marker to identify high-risk patients and to make a decision on thrombolytic therapy. There was no difference between moderate and low-risk patients. This result is important since lactate is inadequate to reveal cardiac effects unless circulatory failure develops.

Cardiac troponins (troponin I and T) are predictors of myocardial injury and poor prognosis. They are superior in sensitivity and specificity to the all other available biomarkers including markers indicative of myocardial ischemia, inflammation, dysfunction and plaque rupture[16]. Besides, the NPV of normal Troponin test, which has a high-sensitivity, in the determination of poor prognosis is 98% [17-20]. In our study, troponin I level was found to be higher in middle and high-risk patients than in low-risk patients. However, it was determined that troponin I was not different between high and moderate-risk groups. This result suggests that troponin I reflects cardiac damage, but it is not a good marker for shock development.

Recently, studies on the measurement of heart cavity diameters from PCTA images have been carried out and it has been concluded that the combined use of hs-cTnI and RVD/LVD ratio for determining the clinical outcome is more predictive in identification of patients at risk[21]. In current prognostic studies, ventricular dilatation and end-diastolic right ventricular/left ventricular ratio in PCTA were assessed and right ventricular dilatation was associated with 30-day mortality in all APE patients, including clinically stable patients. In addition, RVD/LVD ratio of ≥ 0.9-1 was associated with an increase in three-month mortality rates[22-28]. We determined that the ratio of RVD/LVD was different among all groups. The cut-off value of > 1.40 (AUC = 0.695 sensitivity = 71%, specificity = 80%, + LR = 3.6, -LR = 0.36, 95% CI= 0.668-0.822) for RVD/LVD ratio was determined in order to define high-risk group.

Using echocardiography (ECO) to assist diagnosis and risk stratification of APE is recommended in current guidelines. ECO can detect features of right ventricular strain from massive and sub-massive APE[29]. One of the important ECO findings to present cardiac involvement in APE is interventricular septum deviation. In our work, interventricular septum deviation was observed in 19 (54%) of the high-risk patients, 14 (39%) of the moderate-risk patients and 13 (26%) of the low-risk patients. Besides, there was no significant difference between groups in terms of interventricular septum deviation. However, it is important to determine the severity of the cardiac effect in the patient. This result suggests that interventricular septum deviation is insufficient in terms of showing the severity of cardiac involvement.

Conclusions

The ratio of RVD/LVD was found statistically significant in distinguishing between high, middle, and low-risk patients. This finding suggests that RVD/LVD is the most important parameter of determining the severity of cardiac involvement in pulmonary embolism. Troponin I is important in terms of showing cardiac involvement, but it is inadequate in distinguishing between high and moderate-risk patients. RVD/LVD ratio and lactate were shown to be useful in distinguishing high-risk patients from other patient groups. Lactate, troponin I, and RVD/LVD ratio, may be used together for a more accurate separation of patients with high, intermediate and low-risk of pulmonary embolism. There is a need for more extensive work to be done in this regard.

Conflict of interest

There is no potential financial and non-financial conflict of interest. Any part of this paper is not under consideration for publishing or published in anywhere else.

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