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Is Advanced Risk Stratification Unnecessary In Patients with Simplified Pulmonary Embolism Severity Index (sPESI) of 0?

Basitleştirilmiş Pulmoner Emboli Ağırlık İndeks (SPESI) Skoru 0 Olan Olgularda İleri Risk Sınıflaması Gereksiz Mi?

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Aim: The European Society Cardiology guidelines state that advanced risk stratification is unnecessary in patients with simplified pulmonary embolism severity index (sPESI) of 0 because it does not affect treatment decision. Also, these patients can be discharged early or treated as outpatients if feasible. There were three aims of the present study. The first was to determine the rate of patients with sPESI of 0 but classified into intermediate risk category with advanced risk stratification. is the second was to determine the clinical impact of this risk classification change. And the third was to define risk factors for this condition.

Patients and Methods: This is prospective single-center cohort study. All patients underwent advanced risk stratification at admission independent from the sPESI score. Patients with a sPESI score 0 were included.

Results: There were 33 patients with sPESI score of 0. With advanced risk stratification; 60.6% of patients were low risk, 30.3% were intermediate low risk and 9.1% were intermediate-high risk. In 2 (6.1%) patients, respiratory failure developed. One of these patients became hypotensive and required thrombolytic treatment. D-dimer value (p=0.017) and thrombus in main pulmonary arteries (p=0.000) were statistically significantly high in intermediate risk group.

Conclusions: Advanced risk stratification in sPESI 0 patients has an impact on management decisions. Early discharge or outpatient treatment decisions based on sPESI alone may cause the discharge of unstable patients especially in patients with main pulmonary artery thromboembolism or D-dimer level over 3600 ng/ml.

Key Words: ***Pulmonary Thromboembolism, Clinical Risk Score, Simplified Pulmonary Embolism Severity Index***

Amaç: Avrupa Kardiyoloji Derneği (ESC), risk sınıflama modeline göre, akut pulmoner tromboemboli (PTE) olgularında eğer basitleştirilmiş pulmoner emboli ağırlık indeksi (sPESI) 0 ise ileri risk sınıflaması gereksizdir. Bu olgular erken taburcu edilebilir veya uygun olanlar ayaktan tedavi edilebilir. Bu çalışmanın üç amacı vardı. Birincisi; sPESI 0 olduğu halde ileri risk sınıflaması ile orta riskli saptanan olguların oranı, ikincisi; bu durum için risk faktörlerinin saptanması ve üçüncüsü de risk sınıflaması değişikliğinin klinik üzerindeki etkilerinin saptanmasıdır.

Gereç ve Yöntem: Tek merkezde yapılan bu prospektif kuhort çalışmada olguların hepsine sPESI skorlarından bağımsız olarak başvuru anında eko ve kardiyak biomarkerlar ile ileri risk sınıflaması yapıldı. sPESI skoru 0 olan olgular çalışmaya dahil edildi.

Bulgular: PTE tanısı alan toplam 109 olgu vardı. Bunlardan 33'ünde sPESI skoru 0 idi. İleri risk sınıflaması ile bu 33 olgunun %60,6'sı düşük , %30,3'ü orta düşük ve %9,1'i orta yüksek riskti. Olguların hepsi yatarak tedavi edildi. Takipte İki (%6,1) olguda solunum yetmezliği gelişti ve bu olgulardan birisinde hipotansyon gelişmesi nedeniyle trombolitik uygulandı. D-dimer değeri (p=0.017) ve ana pulmoner arterlerde trombus olması (p=0.000) orta riskli grupta istatistiksel olarak anlamlı derecede daha yüksekti.

Sonuç: Sadece sPESI skoruna göre ayaktan tedavi veya erken taburculuk kararı verilmesi özellikle ana pulmoner arterlerde emboli olan veya D-dimer değeri 3600 ng/ml üzerinde olan ve aslında unstabil olan olguların taburculuğuna neden olabilir.

Anahtar Sözcükler: ***Pulmoner Tromboemboli, Klinik Risk Skorları, Basitleştirilmiş Pulmoner Emboli Ağırlık İndeksi***

Pulmonary thromboembolism (PTE) is the third most common cardiovascular system disease after myocardial infarction and stroke, and it is also one of the leading causes of in-hospital deaths (1, 2). The European Society of Cardiology (ESC) recommends a two-step risk stratification in normotensive patients with PE to guide management. The first step is clinical risk stratification with pulmonary embolism severity index (PESI) or its simplified version (sPESI). In patients with PESI class, III-V or sPESI score ≥1 the second step is advanced risk stratification with echocardiography (echo) and cardiac biomarkers. It is stated that advanced risk stratification is unnecessary in

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patients with PESI class I-II or sPESI of 0 because it does not affect treatment decision. Also, these patients can be discharged early or treated outpatient if feasible (3). However, there are case reports of patients with sPESI of 0 but with right heart failure (4).

There are three aims of this study. The first is to determine the rate of patients with sPESI of 0 but classified into intermediate risk category with advanced risk stratification. The second is to determine the clinical impact of this risk classification change. And the third is to define risk factors for this condition.

1. Subjects and Methods

Patients who were diagnosed with PTE by computed tomography pulmonary angiography (CTPA) between January 2014 and June 2015 were followed prospectively in a single center. Presenting symptoms, the patients' history, heart rate, blood pressure, oxygen saturation were recorded at admission. Advanced risk stratification was performed in all patients with echo and cardiac biomarkers.

The study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. This study was approved by the institutional ethics committee

1.1. Inclusion criteria

Patients with sPESI score 0 were enrolled.

1.2. Exclusion criteria

The patients who had sPESI score 0 but didn't undergo advanced risk stratification with echo or cardiac biomarkers, were excluded from the study.

1.3. Risk stratification

The patients underwent risk stratification according to ESC guidelines (3). Troponin I and NT-pro-brain natriuretic peptide (proBNP) were measured. The upper limit of normal was accepted as 0.3 μg/L for Troponin I and 600 pg/mL for proBNP.

Right ventricular (RV) dysfunction was evaluated by real-time three-dimensional echo. RV dysfunction was diagnosed on echo according to the recommendations of 2014 ESC Guidelines.

1.4. Statistical methods

The data obtained in the study were entered into the database of the SPSS and statistical analyses were performed with the same program. The frequency and percentage of categorical variables were presented. Crosstables were formed between the independent groups and they were compared with the Chi-square test. Continuous variables are presented as mean, standard deviation, median, minimum and maximum values. The suitability of the normal distribution was investigated for the variables. While considering both graphical research and normality tests and data type, it was accepted that all of the variables did not meet the eligibility criteria of the normal distribution. Non-parametric methods were preferred in the comparison of these variables. The Mann-Whitney test was used in the comparison of the independent groups. In all statistical comparison tests, the margin of error (type 1) was determined as 0.05 and was tested bi-directionally. If P value was less than 0.05, the difference between groups was considered statistically significant.

2. Results

There were one hundred and ten patients diagnosed with PTE and 34 of these were with sPESI score 0. One patient was excluded because of the absence of cardiac biomarkers. The remaining 14 men and 19 women totaling 33 patients with a median age of 47 years were included. The most common symptom was dyspnea (87.8%). Fourteen (42.4%) patients had concomitant deep vein thrombosis (DVT) (Table-1). While 14 (42.4%) patients had unprovoked PTE, 19 (57.6%) patients had provoked PE. Sixteen (48.5%) patients had main pulmonary artery embolus. Of these, 10 patients had bilateral main pulmonary artery embolus (Table-2).

According to the ESC risk stratification, 20 (60.6%) patients were at low risk and 13 (39.4%) patients were at intermediate risk. From the intermediate-risk group, 10 (30.3%) patients were at intermediate low risk and 3 (9.1%) patients were at intermediate high risk (Table-1).

All patients received the initial phase of their treatment at the hospital. Respiratory failure occurred during follow-up in 2 (6.1%) patients and oxygen supplement was administered. One of these patients also became hypotensive and required thrombolytic treatment. Both patients were at intermediate high risk and had embolus in their bilateral main pulmonary arteries.

The low-risk group was compared with the intermediate-risk group in terms of median age, gender, the median value of D-dimer, median body mass index (BMI), heart rate, blood pressure, saturation, the presence of main pulmonary artery embolus, DVT and the history of major surgery within the last 1 month. Heart rate ($p=0.021$), D-dimer value ($p=0.017$) and thrombus in main pulmonary arteries ($p=0.000$) were statistically significantly high in the intermediate group. There was no a statistically significant difference between the two groups in terms of gender, age, BMI, blood pressure, oxygen saturation, concomitant DVT and surgery (Table-3).

Hypotension and shock did not develop during follow-up in both groups. There was no mortality at hospital or during the 3-month follow-up.

Table-1. Baseline characteristics of patients

Gender	
Male	14 (42.4%)
Female	19 (57.6%)
Age (median min-max)	47 (21-79)
Symptoms	
Dyspnea	29 (87.9%)
Pleuretic pain	22 (66.7%)
Palpitation	16 (48.5%)
Dizziness	10 (30.3%)
Hemoptysis	8 (24.2%)
Retrosternal chest pain	4 (12.1%)
Etiology	
Provoked	19 (57.6%)
Unprovoked	14 (42.4%)
ESC risk classification	
Low risk	20 (60.6%)
İntermediate low risk	10 (30.3%)
Intermediate high risk	3 (9.1%)
Deep vein thrombosis	
Absent	19 (57.6%)
Present	14 (42.4%)

Table-2. Risk stratification according to presence or absence of main pulmonary artery thrombus

		Low risk	Intermediate Low risk	Intermediate High risk
Thrombus at main pulmonary arteries	Bilateral	1 (3%)	6 (18.2%)	3 (9.1%)
	Unilateral	3 (9.1%)	3 (9.1%)	0
	Absent	16 (48.5%)	1 (3%)	0

Table-3. Comparison of low risk and intermediate risk patients

		Low risk	Intermediate risk	P
Gender	Female	11	8	0.991
	Male	9	5	
BMI Median (min-max)		28 (20-43)	29 (23-40)	0.231
Age Median (min-max)		44 (21-69)	56 (27-79)	0.08
Heart rate (mean±SD)		90.74±9.237	98.00±7.390	0.021
SBP (mmHg) Median (min-max)		120 (110-140)	120 (110-160)	0.770
Oxygen saturation (%) Median (min-max)		96 (91-98)	96 (92-98)	0.172
D-dimer (ng/mL) Median (min-max)		1688 (502-6700)	3600 (760-10000)	0.017
Thrombus in the main pulmonary arteries		4	12	0.000
Concomitant acute DVT		8	6	0.854
Surgery		6	7	0.315

BMI: body mass index; SBP: systolic blood pressure; DVT: deep vein thrombosis.

Table-4. Simplified pulmonary embolism severity index (sPESI)

Age >80	1 point
Cancer	1 point
Chronic heart failure/ chronic respiratory disease	1 point
Heart rate ≥110 beats per minute	1 point
Systolic blood pressure <100 mmHg	1 point
Arterial oxyhemoglobin<%90	1 point

3. Discussion

In the present study, 39.4% of patients were intermediate risk despite sPESI score of 0. Two (6.1%) patients received oxygen supplementation due to hypoxemia and one of them required thrombolytic treatment due to development of hypotension. Mortality didn't increase in the intermediate risk group. However, contrary to ESC guidelines proposal, the treatment was changed.

PESI was designed to estimate mortality in patients with PTE (5). Validation studies revealed that PESI is a reliable clinical score for the decision of outpatient treatment and early discharge (6-8). Also, validation studies showed that sPESI has similar prognostic accuracy with PESI (9-11).

sPESI consists of 6 variables, each of which is allocated 1 point (Table-4). If there were none of these 6 variables, the patient gets 0 points. In 2014 ESC Guidelines, it is stated that advanced risk stratification is unnecessary in patients with a sPESI score of 0 because it does not have therapeutic implication and also this these patients may be a candidate for early discharge or outpatient treatment (3). However, in our study, contrary to the ESC Guidelines, treatment changed in 2 (6.1%) patients. Mortality was not increased but we think that this was due to hospitalization of all patients. Otherwise, these patients would have been discharged as a result, respiratory failure and hypotension wouldn't be recognized.

Guidelines classify patients according to right heart failure and treatment recommendations are made according to this risk classification (3, 12). However, hypoxemia is also an important problem in patients with PE and develops in various degrees of severity. Although hypoxemia usually improves spontaneously and/or with anticoagulation, sometimes it can be refractory and require thrombolytic treatment (13-15). sPESI has saturation variable (Table-4) and this can help to determine patients with respiratory

failure at admission. However, as our study revealed the development of respiratory failure may occur late on during the course. Also development of hypotension or shock is an important issue in patients with PTE. In the PEITHO study 5% of patients with intermediate-risk PE had hypotension despite anticoagulation (16). In our study one patient developed hypotension and required thrombolytic treatment.

In the present study, D-dimer level and the incidence of embolus in the main pulmonary arteries were statistically significantly higher in the patients with intermediate risk compared to the low-risk patients.

In the literature, there are conflicting results about the relationship between D-dimer level and mortality (17-19). D-dimer in combination with sPESI was shown to be more successful in predicting the prognosis (20). Also, it has been shown that D-dimer level was higher in patients with bilateral main pulmonary artery thromboembolism (21).

In our study, the D-dimer level was statistically significantly higher in patients with intermediate risk PTE group. However, there wasn't the relationship between elevated D-dimer level and mortality. The two groups were compared in terms of age, concomitant DVT and surgery which may lead to elevated D-dimer level but there wasn't a statistically significant difference between the two groups. These results suggest that D-dimer elevation in intermediate risk group was associated with increased embolic load and correlate with risk classification.

In the previous studies, conflicting results were found about the relationship between the main pulmonary artery thromboembolism and the mortality. While some studies showed the relationship between the main pulmonary artery thromboembolism and the mortality, this relationship could not be shown in other studies (22-25). In our study, the presence of main pulmonary artery thromboembolism did not increase mortality but these patients were at intermediate risk despite an sPESI score of 0. Also, patients who required oxygen supplementation and thrombolytic treatment had thrombus in main pulmonary arteries. Although the presence of main pulmonary thrombus is not included in risk scores, our study revealed that it may be important in management decision.

sPESI is one of the most extensively validated clinical risk scores. But as mentioned before early discharge or outpatient treatment decision which is based on sPESI alone may lead to the falsel discharge of unstable patients (4). Konstantinides et al. (26) suggested the addition of CT or echo imaging of RV to clinical score in order to maximize patient safety. We think that as mentioned above the presence of main pulmonary artery thrombus may also be one of these criteria. Also, other risk scores like BOVA (27) or Hestia (28) may be good alternatives to sPESI.

Despite the prospective design of the study, the small number of patients is an important limitation of our study. Further investigation with multicenter large cohorts is necessary.

In conclusion, early discharge or outpatient treatment decision based on sPESI alone may lead to the falsedischarge of unstable patients. Patients with main pulmonary artery thromboembolism or D-dimer level over 3600 ng/ml require further investigation before discharge even though the sPESI score is 0. In these patients, advanced risk stratification has an impact on the management decision.

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