REGIONAL PATTERNS OF PATIENTS WITH ACUTE PULMONARY EMBOLISM AND THEIR IMPLICATIONS IN MANAGEMENT AND TREATMENT

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Abstract: *The purpose of our study was to identify regional patterns of patients with acute pulmonary embolism, admitted to our hospital. Patients were divided into four groups of mortality risk: high, intermediate-high, intermediate-low and low risk. Treatment strategy and early mortality rate was followed. The highest early mortality rate was recorded in the high-risk PE group (20%), followed by the intermediate-high-risk group (15%) and the intermediate-low-risk group (7%), with no deaths in the low-risk group. Some patients from the high and intermediate-high risk classes benefited from thrombolysis therapy. The number of PE patients that received VKA treatment was higher than that of the NOAC patients (59,33% vs 36%), but in the last years, we recorded a significant increase of NOAC use. Early mortality rate in PE remains high, especially in the high and intermediate-high risk classes. NOAC use in PE patients has become an option with a good efficacy/safety balance.*

INTRODUCTION

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most frequent cardiovascular disease, with an annual incidence of 100 –200 per 100 000 inhabitants.(1,2) Most DVT patients with proximal clots develop acute pulmonary embolism, whether they present clinical symptoms or not.(3)

Current treatment guidelines recommend initial risk stratification of all patients with PE using clinical symptoms (the presence of shock or hypotension), validated clinical prognostic scores (PESI - pulmonary embolism severity index or sPESI - its simplified version), signs of right ventricular dysfunction identified through imaging and laboratory cardiac biomarkers. Thus, patients are divided into low, intermediate or high risk classes for early adverse outcome or mortality (in-hospital or 30 day-PE related death).

The patients from the intermediate-risk class, who present both right ventricular dysfunction and elevated cardiac biomarkers, are considered at an intermediate-high-risk category and require close monitoring for early detection of hemodynamic decompensation. This classification may also decide the duration of hospitalization and the choice of therapeutic strategy used.(2)

PURPOSE

The purpose of our study was to identify regional patterns of patients with acute PE, their implication in treatment strategy and early mortality rate (in-hospital and 30 days PE-related death).

MATERIALS AND METHODS

We performed a prospective, observational study on consecutive patients with PE admitted to our hospital between 2012 and 2017. The diagnosis was confirmed by computer tomographic angiography, which identified one or more filling defects in the pulmonary arteries.

The study protocol was approved by the local ethics committee. Patients were included after signing the informed consent. The inclusion criteria were: consecutive adult patients with acute PE confirmed by computer tomographic angiography who gave their signed informed consent, thus a lack of patient agreement was the only exclusion criteria.

Information was recorded for all patients consisting of clinical data including sex, age, time of symptom onset, medical history, vital signs and an individual risk score sPESI was calculated. Electrocardiography (ECG) and common blood analysis were determined using standard techniques and validated equipment. Laboratory cardiac biomarkers like N-terminal pro-brain natriuretic peptide (NT-proBNP) and cardiac troponins were determined using a tabletop chemiluminescence immunoassay analyzer. In some patients, the serum levels of heart-type fatty acid-binding protein (H-FABP) were measured using a quantitative sandwich enzyme-linked immunoassay (Thermo Fisher Scientific, Frederick, MD, USA).

Echocardiographic examinations were performed using a Vivid E9 System and a 3,5 MHz probe (GE, Horten, Norway) in accordance with the latest recommendations (4). The right ventricular (RV) end-diastolic diameter was measured from the apical 4-chamber RV-focused view at the basal level, the left ventricle (LV) end-diastolic diameter was measured from the parasternal long-axis view, the RV/LV ratio was calculated and patients with an increased ratio of more than 0.9 were identified. The presence of McConnell's sign was assessed and the tricuspid annular plane systolic excursion (TAPSE) was determined, from the apical view.

The initial mortality risk assessment and the treatment strategy were decided by the attending physician, in accordance with the current PE management guideline recommendations of the European Society of Cardiology. Early in-hospital and 30-day PE-related mortality rates were recorded.

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The data collected was used for statistical analysis, which was performed using the dedicated software SPSS v20 (IBM, Armonk, NY, USA). All numerical data was analyzed in order to determine if it has normal distribution using the Kolmogorov-Smirnov test, and, according to the results, parametrical or non-parametrical tests were used. The Student's *t*-test and Mann-Whitney U test were used to compare means, and the chi-squared was used to compare discrete variables. A p value of less than 0.05 was considered significant for all tests.

RESULTS

Between 2012 and 2017, we enrolled in our study 154 patients with acute PE. The patients' baseline characteristics are presented in table no. 1.

Table no. 1. Patient characteristics

Characteristic, unit	Value
Age, years	68.6 ± 12.4
Sex, pts. (% of total)	
Male	73 (47%)
Female	81 (53%)
Time from symptom onset, hours	60 (15 – 120)
Symptoms, pts. (% of total)	
Dyspnea	132 (86%)
Syncope	34 (22%)
Hemoptysis	7 (5%)
Concomitant deep vein thrombosis	98 (64%
Systolic Blood Pressure, mmHg	128 ± 27
Heart Rate, bpm	95 ± 20
Peripheral O_2 Saturation, %	93 (87 – 96)
H-FABP, ng/mL	4.873 (3.130 – 8.404)
Troponin I, ng/mL	0.033 (0.005 – 0.127)
NT-proBNP, pg/mL	2778 (605 – 8754)
Creatinine, mg/dL	1.05 (0.81 – 1.30)
Hemoglobin, g/dL	13.6 ± 2
Platelets, number/mm^3	226 954 ± 99 983
Risk factors, pts. (% of total)	
Previous immobilization	53 (34%)
Active cancer	21 (14%)
Atrial fibrillation	33 (21%)
Cardiomyopathy	35 (23%)
COPD history	23 (15%)
HF history	53 (34%)
sPESI 0 points, pts. (% of total)	41 (26%)
1 points	55 (36%)
2 points	32 (21%)
3 points	20 (13%)
4 points	5 (3%)
5-6 points	1 (1%)
End-diastolic RV Diameter, mm	36 (31 – 41)
McConnell's sign present, pts (% of total)	38 (25%)
RV/LV ratio >0.9, pts (% of total)	42 (27%)
TAPSE, mm	18 (15 – 20)
Right heart thrombi, pts (% of total)	9 (6%)
Death, pts. (% of total)	13 (8 %)

Values are expressed as number of patients (percent), mean ± SD for normal distribution or median (25th-75th percentile) for non-normal distribution. H-FABP heart-type fatty acid-binding protein, NT-proBNP N-terminal pro-brain natriuretic peptide, COPD chronic obstructive pulmonary disease, HF heart failure, sPESI simplified pulmonary embolism severity index, RV right ventricle, LV left ventricle, TAPSE tricuspid annular plane systolic excursion.

Patients were mostly females (55%), elderly (mean age 69 years), and presented on average with a normal blood pressure, peripheral oxygen saturation an elevated heart rate (95 bpm). The most frequent risk factors identified were previous immobilization and heart failure and 64% of PE patients presented concomitant deep vein thrombosis. At hospital admission, the mean time from symptoms onset was 60 hours, and the most frequent symptoms were dyspnea, followed by syncope. Laboratory analysis showed on average positive cardiac biomarkers and most patients had a mortality risk score sPESI over 1 point.

Echocardiography identified a slightly enlarged RV end-diastolic diameter (36 mm) with an abnormal RV/LV ratio >0.9 in some patients (27%), on average an abnormal TAPSE of 18 mm, and the presence of McConnell's sign in one quarter of the subjects. Right heart thrombi have been diagnosed only in nine patients (6%).

Subjects were divided into four groups of mortality risk: high-risk (10%), intermediate-high risk (21%), intermediate-low risk (50%) and low risk (19%) and early mortality rate was recorded. In our study, early mortality rate (in hospital and 30 day-PE related death) for all PE patients was 8%, with half of these patients dying during hospitalization. As expected the highest early mortality rate was recorded in high-risk PE group (20%), followed by intermediate-high-risk group (15%) and intermediate–low-risk (7%), with no deaths registered in the low-risk PE group (table no. 2).

Table no. 2. PE risk classes' characteristics

PE risk class	High risk	Intermediate-high risk	Intermediate-low risk	Low risk
Number of pts.	15	33	77	29
% of total	10	21	50	19
Early mortality rate (%)	20	15	7	0
Systemic thrombolysis (% of total)	53	6	0	0
VKA treatment (pts.)	6	20	49	14
NOAC treatment (pts.)	6	11	24	15

PE pulmonary embolism, NOAC non-vitamin K oral anticoagulants, VKA vitamin K antagonist.

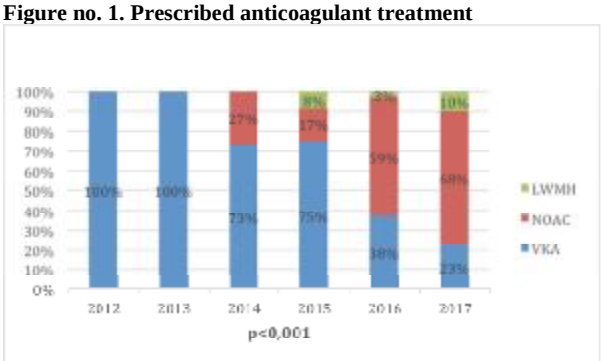
The attending physician, in accordance with current guideline recommendations, decided the treatment strategy. Ten patients benefited from reperfusion therapy through systemic thrombolysis, with recombinant tissue plasminogen activator (rtPA) 100mg/2 hours, eight of them from the high-risk class and two patients from the intermediate-high risk class. Two patients who received thrombolysis died in-hospital, both from the high-risk class.

The rest of the patients were treated with initial parenteral anticoagulation with aPTT dose-adjusted unfractionated heparin or weight dose-adjusted low molecular weight heparin, followed by oral anticoagulation, either with INR dose-adjusted vitamin K antagonist (VKA 59%) or non-vitamin K oral anticoagulants (NOAC 36 %).

Only seven patients (5%) received at discharge dose-adjusted low molecular weight heparin because of concomitant active cancer.

Even if the number of PE patients that received VKA treatment was higher than that of the NOAC patients (59% vs. 36%), since 2014 we recorded a progressive and significant increase of NOACs use (p<0.001). Thereby, in the last two years, NOACs use exceeded VKA use in PE patients in our research population (figure no. 1).

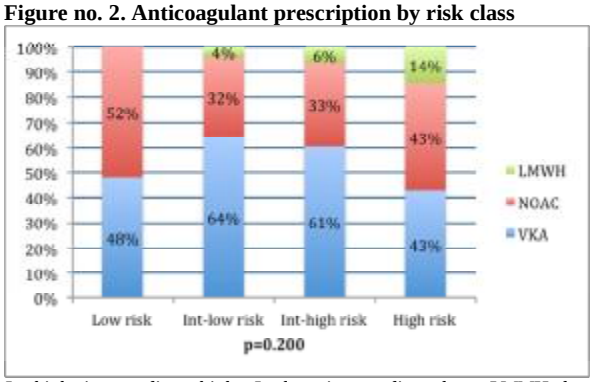
Figure no. 1. Prescribed anticoagulant treatment



LWMH low molecular weight heparin, NOAC non-vitamin K oral anticoagulants, VKA vitamin K antagonist.

However, the statistical analysis regarding use of NOACs according to PE risk classes did not find significant differences, with a p value of 0,200 (figure no. 2).

Figure no. 2. Anticoagulant prescription by risk class



Int-high intermediate high, Int-low intermediate low, LWMH low molecular weight heparin, NOAC non-vitamin K oral anticoagulants, VKA vitamin K antagonist.

DISCUSSIONS

The prognosis of PE depends mainly on the hemodynamic impact of the disease.(5) The patients who present a systolic blood pressure of less than 90 mmHg, a persistent 40 mmHg drop for at least 15 minutes or other signs of cardiogenic shock are considered at high risk and need reperfusion therapy.(2) In our study the high-risk group represented 10% of all PE patients, this percentage being higher than that reported by a group of researchers (3,4%) using a large, recent administrative database from the United States.(6) Data from registries shows 30-day all-cause mortality rates between 9% and 11%, for unselected patients with PE or VTE (7,8). Torbicki et al. reported in-hospital mortality rate of 25-50% for massive PE, 3-15% for submassive PE and 5 % or less for non-submassive PE, while recent data showed lower early mortality rates: 17.3% in the high-risk class, 4,6% in the intermediate-high-risk class, 4,4% in the intermediate–low-risk class and 0% in the low-risk PE class.(2,9,10) In our research early mortality rate for all PE patient was 8%, but we have recorded a higher mortality rate in all risk group except for the low risk group.

For patients with high-risk PE presenting with shock or hypotension, reperfusion therapy is indicated, preferably using systemic thrombolysis, with major benefits during the first 48 hours of symptoms onset.(2,11,12) Surgical embolectomy or percutaneous catheter-directed treatment should be considered in patients with contraindications or failed thrombolysis, if appropriate resources and expertise are available.(13-15) In our trial only 53% from patients with high-risk PE (8/15 patients) received reperfusion therapy through systemic thrombolysis, with the causes identified being late presentation and a high bleeding risk. Also, the early mortality rate was greater in patients with high-risk PE and reperfusion therapy versus high-risk PE without reperfusion (25% vs. 14%), albeit having a small number of patients in each group (2/8 vs. 1/7).

For patients belonging to the intermediate-high-risk group, systemic thrombolysis can prevent hemodynamic decompensation at the price of an additional increase of major bleeding.(16,17) From the 33 subjects with an intermediate-high-risk PE, only 2 patients benefited from reperfusion therapy (6%), both of them presenting a good clinical courses without complications. Bearing in mind that within this group, the mortality rate was higher, it suggests that probably a more aggressive treatment would have been more appropriate.

Even if VKAs have been the predominant anticoagulants prescribed for PE, for more than fifty years, NOACs have proven themselves as a new alternative, as a results of the faze III clinical trials with dabigatran (RE-COVER and RE-COVER II), rivaroxaban (EINSTEIN-DVT and EINSTEIN-PE), apixaban (AMPLIFY) and edoxaban (Hokusai – VTE), who indicate that these agents are non-inferior (in terms of efficacy) and possibly safer than the standard heparin/VKA regimen.(18-24) In our hospital NOACs use in PE patients started since 2014, increased progressively and exceeded VKAs use in the last two years, without a statistically significant difference between the four patient groups.

CONCLUSIONS

Early mortality rate in PE remains high, especially in the high-risk and intermediate-high risk classes. Reperfusion therapy is indicated for patients in the high-risk class and must be carefully considered in intermediate-high risk PE patients for improving mortality rate. NOAC use in PE patients has become an option at the physician's disposal with a good efficacy/safety balance.

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