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Gender-related differences in clinical presentation, electrocardiography signs, laboratory markers and outcome in patients with acute pulmonary embolism

Polne razlike u kliničkoj prezentaciji, elektrokardiografskim znacima, laboratorijskim markerima i ishodu kod bolesnika sa akutnom embolijom pluća

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Abstract

Background/Aim. Acute pulmonary embolism (PE) is a potentially life threating event, but there are scarce data about gender-related differences in this condition. The aim of this study was to identify gender-specific differences in clinical presentation, the diagnosis and outcome between male and female patients with PE. **Methods.** We analysed the data of 144 consecutive patients with PE (50% women) and compared female and male patients regarding clinical presentation, electrocardiography (ECG) signs, basic laboratory markers and six-month outcome. All the patients confirmed PE by visualized thrombus on the multidetector computed tomography with pulmonary angiography (MDCT-PA), ECG and echocardiographic examination at admission. **Results.** Compared to the men, the women were older and a larger proportion of them was in the third tertile of age (66.0% *vs* 34.0%, $p = 0.008$). In univariate analysis the men more often had hemoptysis [OR (95% CI) 3.75 (1.16–12.11)], chest pain [OR (95% CI) 3.31 (1.57–7.00)] febrile state [OR (95% CI) 2.41 (1.12–5.22)] and pneumonia at PE presentation [OR (95% CI) 3.40 (1.25–9.22)] and less likely had heart decompensation early in the course of the disease [OR (95%CI) 0.48 (0.24–0.97)]. In the multivariate analysis a significant difference in the rate of pneumonia and acute heart failure between genders disappeared due to strong influence of age. There was no significant difference in the occurrence of typical ECG signs for PE between the genders. Women had higher level of admission glycaemia [7.7 mmol/L (5.5–8.2 mmol/L) *vs* 6.9 mmol/L (6.3–9.6 mmol/L), $p = 0.006$] and total number of leukocytes [10.5×10^9/L (8.8—12.7 $\times 10^9$/L *vs* 8.7 × 109/L (7.0–11.6 $\times 10^9$/L)), $p = 0.007$]. There was a trend toward higher plasma level of brain natriuretic peptide in women compared to men 127.1 pg/mL (55.0–484.0 pg/mL), $p = 0.092$] *vs* [90.3 pg/mL (39.2–308.5 pg/mL). The main 6-month outcomes, death and major bleeding, had similar frequencies in both sexes. **Conclusion.** There are several important differences between men and women in the clinical presentation of PE and basic laboratory findings which can influence the diagnosis and treatment of PE.

Key words:
pulmonary embolism; sex factors; risk factors; signs and symptoms; diagnostic techniques and procedures; electrocardiography; treatment outcome.

Apstrakt

Uvod/Cilj. Akutna plućna embolija (PE) potencijalno je životnougrožavajuće stanje. Podaci u razlikama među polovima u tom stanju oskudni su. Cilj rada bio je da se identifikuju razlike između polova u pogledu kliničke prezentacije, dijagnostičke specifičnosti i ishoda PE. **Metode.** Analizirali smo podatke o 144 uzastopna bolesnika sa PE (50% žene) i uporedili muškarce i žene s obzirom na kliničke prezentacije, elektrokardiografske (EKG) znakove, osnovne laboratorijske markere i šestomesečni ishod. Svi bolesnici su imali potvrđen PE na multislajsnoj kompjuterizovanoj tomografiji sa plućnom angiografijom (MSCT-PA), EKG-u i ehokardiografskoj dijagnostici na prijemu. **Rezultati.** U poređenju sa muškarcima, žene su bile starije i većinom u trećem tercilu životnog doba (66,0% *vs* 34,0%; $p = 0,008$). Univarijantna analiza pokazala je da su kod muškaraca na prijemu hemoptizije bile učestalije nego kod žena [OR (95% CI) 3,75 (1,16–12,11)], kao i bol u grudima [OR (95% CI) 3,31 (1,57–7,00)], febrilno stanje [OR (95% CI) 2,41 (1,12–5,22)] i pneumonija [OR (95% CI) 3,40 (1,25–9,22)], a manje verovatna bila je srčana dekompenzacija u ranoj fazi bolesti [OR (95% CI) 0.48 (0.24–0.97)]. Nije bilo značajnih razlika između polova u pojavi tipičnih EKG znakova za PE. Žene su imale viši nivo glikemije na prijemu [7.7 mmol/L (5.5–8.2 mmol/L) *vs* 6.9 mmol/L (6.3–9.6 mmol/L), $p =$

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0.006] i veći ukupni broj leukocita [10.5 × 10^9/L (8.8–12.7 × 10^9/L) *vs* 8.7 × 10^9/L (7.0–11.6 × 10^9/L), p = 0.0 07] kao i trend ka višem nivou B-tip natriuretskog peptida u plazmi 127.1 pg/mL (55.0–484.0 pg/mL) *vs* [90.3 pg/mL (39.2–308.5 pg/ml), p = 0.092]. Krvarenje i smrt, najvažniji šestomesečni ishodi, bili su ravnopravno zastupljeni među polovima. **Zaključak.** Postoji nekoliko važnih razlika između muškaraca i žena u pogledu kliničke prezentacije i laboratorijskih nalaza karakterističnih za PE, koji mogu uticati na njenu dijagnostiku i lečenje PE.

Ključne reči:
pluća, embolija; pol, faktor; faktori rizika; znaci i simptomi; dijagnostičke tehnike i procedure; elektrokardiografija, lečenje, ishod.

Introduction

A lot of investigation was conducted to study difference in the distribution of risk factors, clinical presentation, recurrence risk and outcome for coronary artery disease among men and women [1]. However, there are only few such investigations of venous thromboembolism VTE [2–4]. The pathophysiology nature of acute myocardial infarction is arterial thrombosis on the ground of atherosclerosis and in the acute pulmonary embolism (PE) the underlying process is venous thrombosis which is quite different in relation to risk factors and the role of coagulation pathways involved. The annual incidence of VTE is 1–2 *per* 1,000, but it is probably underestimated because of a lot of undiagnosed patients [5]. Contrary to myocardial infarction, the incidence rate of PE is similar in men and women. However, the risk factors for VTE are quite different during lifetime between men and women [5]. In the younger age predominant risk factors in men are trauma and immobilization while in women oral contraceptive use, pregnancy and postpartum period [5]. In the older age various comorbidities and especially malignancy, are associated to VTE [6]. Are the efficacy of thrombolysis and bleeding risk similar in relation to gender is the matter of controversy [7, 8]. However, bleeding risk and the efficacy of oral anticoagulants are very similar in both sexes [9]. The recurrence rate of VTE is higher in men [10]. So, there are several important differences in the epidemiology and outcome of VTE associated to gender.

The aim of this study was to compare important clinical manifestations of PE and some biomarkers in relation to those manifestations between men and women.

Methods

The study included patients with PE treated in the Clinic of Emergency Medicine of the Military Medical Academy in Belgrade in the period from January, 2010 till July, 2015. Their data were collected from the database PE created in 2012 year. Due to this, some data were collected retrospectively and some of them prospectively. A total of 144 patients with visualized thrombus in multidetector computed tomography with pulmonary angiography (MDCT-PA) at admission were enrolled in this study. Anamnestic data about symptoms of PE were carefully registered from various doctors who were not involved in the preparing this paper. Pneumonia was defined as the febrile state with clear condensation of pulmonary tissue on MDCT-PA with necessity of parenteral antibiotics treatment for at least 7 days. Patients were considered to have acute heart failure if they had symptoms and signs of congestive heart failure after normalization of arterial blood pressure.

For the purpose of risk stratification all the patients were classified according to the simplified Pulmonary Embolic Severity Score (sPESI) [11] and hemodynamic status and right ventricle dysfunction in low, intermediate and high risk patients [12].

Electrocardiography (ECG) analysis was performed with admission ECG record. Typical ECG signs for pulmonary thromboembolism were registered (S1Q3T3 sign, right bundle branch block, negative T-waves in precordial leads, S-waves in aVL and paroxysmal atrial fibrillation).

Transthoracic echocardiography examination (VIVID 7 Pro, General Electric Medical Systems) was performed at admission in all patients and systolic pressure in the right ventricle was recorded using tricuspid regurgitation method [13].

Embolic burden score [14] was calculated at admission MDCT-PA (Aquilion 64-sliced multidetector computed tomography Toshiba) by the experienced radiologist.

The concentration of venous glycaemia (hexokinase assay, ADVIA 1200, Siemens) and leukocyte count (Advia 120, Siemens) at admission was available in all the patients. Brain natriuretic peptide (BNP) plasma concentration (immunoassay, ADVIA Centaur XP, Siemens) and C-reactive protein (CRP) serum concentrations (immunoturbidimetric assay, ADVIA 1200, Siemens) were measured 24 hours after admission and the results were available in 114 (57 women and 57 men) and 115 (59 women and 56 men) patients, respectively.

The patients had 1 month and 6 months follow-up visits and if they did not appear we contacted them by phone.

Statistics

The main characteristics of patients according to gender were presented as frequencies, mean values ± standard deviation (SD) or as median with interquartile. The percentages of women and men across the age tertiles were presented in stacked bars graph. The significance of differences particular characteristics between genders was calculated with χ2-test or Student's t-test or with Mann-Whitney test according to nature of data and their distribution. Odds ratios (OR) (with 95% confidence intervals (CI) for symptoms according to gender were calculated with binary regression analysis and in multivariate analysis results were adjusted to three confounding characteristics which were differently distributed in men and women (age, smoking status and body mass index). The difference between two main outcomes, death and major bleeding events, was calculated with Kaplan Meier method using log rank test. The significant differences of data according to gender were considered if p was less than 0.05.

Results

The main characteristics of patients are presented in Table 1. The women were significantly older, they had higher body mass index (BMI) and fewer smokers were among them. There was a significant difference between men and women in the distribution of patients according to tertiles of age (Figure 1). According to the clinical presentation, men had more frequently pleural or substernal chest pain (44.4% *vs* 19.4%, $p = 0.002$), hemopyisis (18.1% *vs* 5.6%, $p = 0.036$), fever (34.7% *vs* 18.1%, $p = 0.037$) and severe pneumonia (23.6% *vs* 8.3%, $p = 0.021$) with pulmonary condensation and need for the parenteral antibiotics (Table 2). There was the trend that symptoms of acute heart failure were presented more often in women than in men (27.1% *vs* 47.3%, $p = 0.053$). In multivariate binary regression, adjusted factors

Table 1

Characteristics of the pulmonary embolism (PE) patients at admission and the frequency of thrombolytic therapy according to gender

Characteristics	Men n = 72	Women n = 72	*p*
Age (years), $\bar{x} \pm SD$	56 ± 17	64 ± 15	0.005
Age older than 65 years, n (%)	25 (32.9)	39 (54.2)	0.013
Active smoking, n (%)	20 (29.0)	6 (8.5)	0.002
Obesity, n (%)	10 (13.9)	23 (31.9)	0.017
Positive familial history of venous thrombosis, n (%)	9 (12.5)	6 (8.8)	0.589
Previous DVT/PE, n (%)	14 (19.4)	10 (13.9)	0.503
Diabetes mellitus, n (%)	6 (8.3)	8 (11.1)	0.780
Spontaneous PE, n (%)	39 (54.2)	33 (45.8)	0.405
Surgery inside 6 months, n (%)	17 (23.6)	20 (27.8)	0.703
Surgery inside 3 weeks, n (%)	6 (8,3)	11 (15,3)	0.302
Active malignant disease, n (%)	5 (6.9)	11 (15.3)	0.184
Coronary disease, n (%)	10 (13.9)	3 (4.2)	0.078
Simplified PESI, n (%)			
0	29 (40.3)	19 (26.4)	0.109
1–2	33 (45.8)	35 (48.6)	
≥ 3	10 (13.9)	18 (25.0)	
Risk according to hypotension and righ ventricular (RV) dysfunction, n (%)			
high	10 (13.9)	14 (19.4)	0.647
intermediate	37 (51.4)	36 (50.0)	
low	22 (34.7)	22 (30.6)	
Systolic pressure in RV at admission (mmHg), $\bar{x} \pm SD$	49.3 ± 19.8	49.8 ± 18.6	0.865
Embolic burden score, median (IQR)	12.0 (7.0–18.0)	12.0 (6.0–18.0)	0.817
Thrombolysis, n (%)	42 (58.3)	44 (61.1)	0.865

DVT – deep vein thrombosis; PESI – Pulmonary Embolic Severity Score; IQR – interquartile range.

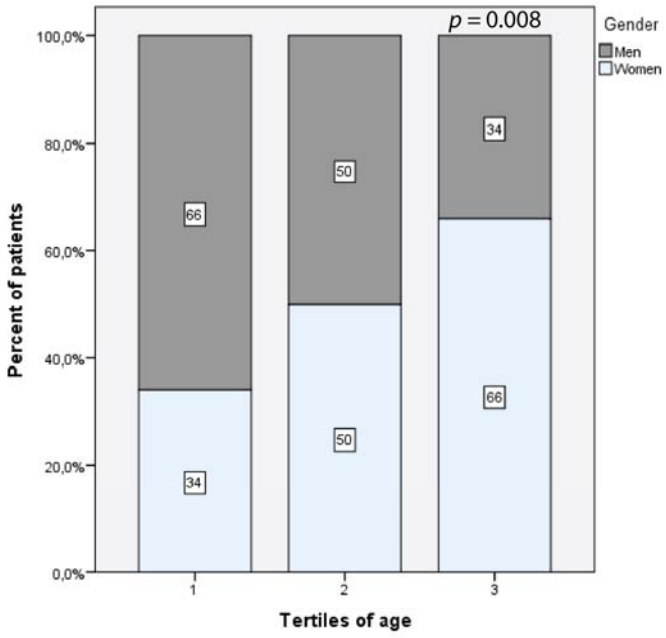

Fig. 1 – Gender distribution according to tertiles of age in the patients with pulmonary embolism.

for which we had found a significant difference in the distribution between the men and the women were included in analysis (Table 2). In such analysis, the difference between genders in the presence of severe pneumonia was lost due to the strong influence of age on the occurrence of pneumonia [non-adjusted HR and 95% CI were 3.40 (1.25–9.22) and was 2.27 (0.78–f6.64)]. There was a much higher number of male younger patients in our cohort and the presence of severe pneumonia was associated very significantly with younger age in PE patients.

There was no significant difference between the men and the women in the frequencies of typical ECG signs of PE at admission (Table 2).

Systolic blood pressure in right ventricle and embolic burden score were very similar in men and women (Table 1).

Admission glycaemia and total leukocyte count (Figures 2 and 3) were significantly higher in the women than in the men [7.7 mmol/L (5.5–8.2 mmol/L) *vs* 6.9 mmol/L (6.3–9.6 mmol/L), $p = 0.006$, and 10.5×10^9/L ($8.8–12.7 \times 10^9$/L) *vs* 8.7×10^9/L ($7.0–11.6 \times 10^9$/L), $p = 0.007$, respectively]. Maximum values of CRP (Figure 4) and BNP (Figure 5) during the first 2 days were not significantly different between the men and the women [52.0 mg/L (17.6–105.5 mg/L) *vs* 44.6 mg/L (26.2–84.9 ml/L), $p = 0.617$ and 90.3 pg/ml (39.2–308.5 pg/ml) *vs* 127.1 pg/ml (55.0-484.0 pg/ml), $p = 0.092$, respectively].

The in-hospital mortality was 12.5% for the women and 5.6% in the men. During the 6-months follow-up 7 (9.7%) men and 10 (13.9%) women died ($p = 0.607$). In the same period, 10 (13.9%) men and 8 (11.1%) women had at least one episode of major bleeding ($p = 0.802$).

Table 2

Frequencies of the most important clinical symptoms and signs of pulmonary embolism (PE) at presentation according to gender. Unadjusted and adjusted odds ratios for symptoms occurrence in the men compared to the women

Symptoms or signs of PE	Men n = 72	Women n = 72	*p*	Unadjusted odds ratio (95% CI)	Adjusted odds ratio[1] (95% CI)
Dyspnea, n (%)	62 (86.1)	65 (90.3)	0.607	0.67 (0.24–1.84)	0.59 (0.20–1.74)
Pleural or chest pain, n (%)	32 (44.4)	14 (19.4)	0.002	3.31 (1.57–7.00)	2.88 (1.31–6.33)
Hemoptysis, n (%)	13 (18.1)	4 (5.6)	0.036	3.75 (1.16–12.11)	2.72 (0.79–9.32)
Fever, n (%)	25 (34.7)	13 (18.1)	0.037	2.41 (1.12–5.22)	2.72 (1.16–6.36)
Syncope, n (%)	11 (15.3)	13 (18.1)	0.823	0.67 (0.27–1.62)	0.80 (0.30–2.09)
Hypotension, n (%)	10 (13.9)	13 (18.3)	0.503	0.76 (0.36–1.61)	0.67 (0.25–1.82)
Tachycardia, n (%)	25 (34.7)	34 (47.2)	0.175	0.59 (0.30–1.16)	0.59 (0.28–1.23)
Severe, n (%)	17 (23.6)	6 (8.3)	0.021	3.40 (1.25–9.22)	2.27 (0.78–6.64)
Signs of DVT, n (%)	39 (54.2)	42 (58.3)	0.737	0.84 (0.44–1.63)	0.80 (0.38–1.66)
Acute heart failure, n (%)	19 (27.1)	31 (43.7)	0.053	0.48 (0.24–0.97)	0.47 (0.21–1.05)
ECG signs at admission, n (%)					
S1Q3T3	17 (23.6)	20 (27.8)	0.703	0.80 (0.38–1.70)	0.72 (0.31–1.66)
RBBB	15 (20.8)	20 (27.8)	0.437	0.68 (0.32–1.47)	0.62 (0.27–1.44)
negative T waves in precordial leads	30 (41.8)	35 (48.5)	0.503	0.75 (0.39–1.46)	1.03 (0.50–2.14)
significant S wave in aVL	35 (48.6)	32 (44.4)	0.738	1.18 (0.61–2.28)	1.24 (0.61–2.53)
paroxysmal AF	3 (4,5)	3 (4.4)	1.000	1.03 (0.20–5.30)	2.14 (0.32–14.54)

In the multivariate model confounding factors such as age, smoking status and body mass index were included.
DVT – deep vein thrombosis; RBBB – right bundle branch block; AF – atrial fibrillation; aVL – lead augmented vector left.

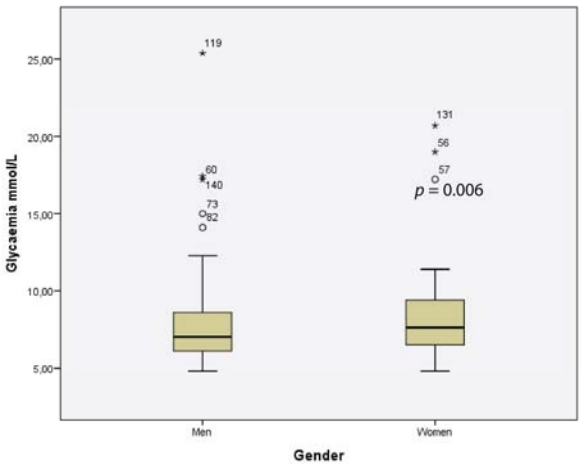

Fig. 2 – Glycaemia at admission in the men and the women with pulmonary embolism.

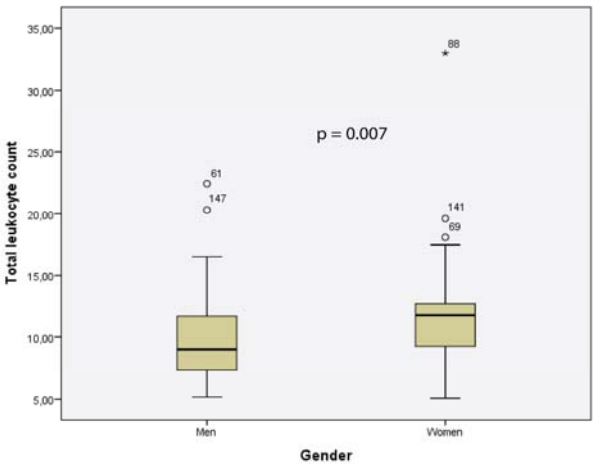

Fig. 3 – Total blood leukocyte count at admission in the men and the women with pulmonary embolism.

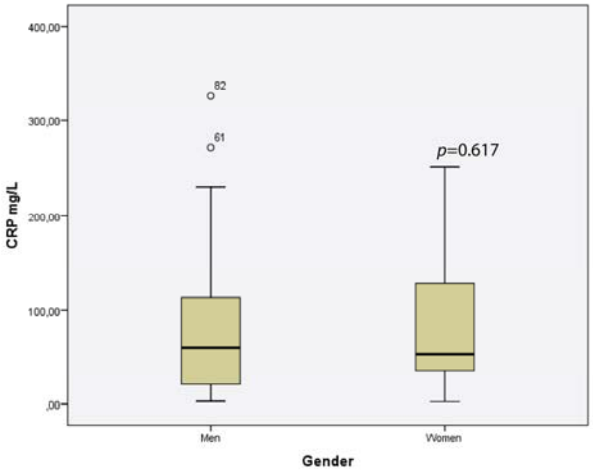

Fig. 4 – C-reactive protein (CRP) serum concentration 24–48 hours after admission in the men and the women with pulmonary embolism.

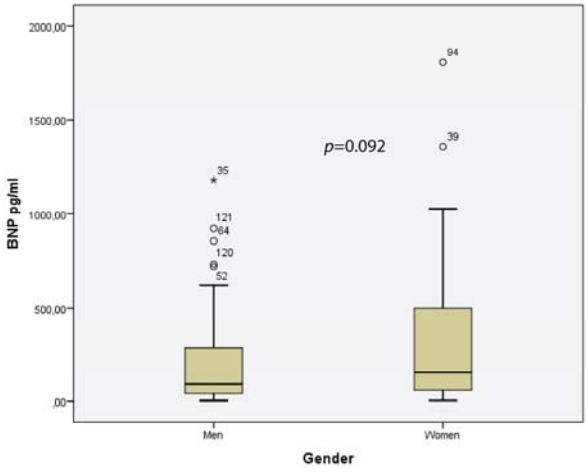

Fig. 5 – Plasma concentration of brain natriuretic peptide (BNP) 24–48 hours after admission in the men and the women with pulmonary embolism.

Discussion

Several interesting findings were obtained in this study. The clinical presentation of PE was quite different between the men and the women despite of similar characteristics of the patients. There was a different distribution of gender across the tertiles of age, with the predominance of the men in the first tertile and the predominance of the women in the third tertile. In the the International Cooperative Pulmonary Embolism Registry (ICOPER) including 2,454 patients with PE from 52 hospitals similar distribution of gender across the age was noticed with significantly higher number of women at the age more than 70 years [2]. In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study [15] the proportion of men was much higher under 50 years. The higher percentige of patients with PE in elderly women is probably related to higher proportion of obesity and hypomobility in women and higher proportion of men among younger patients due to higher rate of traumatic immobilization. Symptoms at presentation were significantly different between genders. In our study the men more often had hemoptysis, chest pain, febrile state and pneumonia, and the women were more often decompensated in the early course of PE. Chest pain and hemoptysis were also more frequently presented in the men in ICOPER study [2] and also in the large study of Robert-Ebadi et al. [4] with 1,205 patients with PE [4]. Chest pain and hemoptysis are the consequence of pleural inflammation, pulmonary infarction and myocardial ischemia. Concomitant coronary disease was more often presented in men and it might be the reason for chest pain in some patients [16]. But the majority of patients with chest pain have actually pleural affection and pulmonary infarction and is not clear why it is more often existing in men. In our study men developed more often pneumonia with pulmonary parenchyma condensation and febrile state than women. In the ICOPER study men had more often atelectasis than women on the chest radiography; however febrile state was equally presented in both genders [2]. MDCT-PA was used for the diagnosis of PE in our study and we always carefully examined other structures of chest to diagnosed concomitant pathologies like pneumonias and malignancies. However, in the ICOPER study [2] MDCT of chest it was not available. Congestive heart failure was presented more often in the women in our cohort of PE patients and the same result was recorded in the ICOPER study. The level of BNP was higher in our female patients which supported the clinical diagnosis.

The appearance of ECG typical signs of PE was not different between men and women. The main parameters of PE severity on echocardiography – systolic pressure in right ventricle and on MDCT-PA – embolic burden score, were almost the same in men and women. It is interesting that women had higher level of admission glycaemia and total leukocyte count at presentation which is probably related to older age and higher stress influence in women than in men. Both parameters are prognostically useful in PE patients [17, 18]. CRP levels were almost the same in both genders.

For the outcome of patients according to gender we compared 6-month mortality and major bleeding events. The number of patients precluded analysis of recurrence of disease because of small number of such events. There was no significant difference in the mortality and major bleeding complications in our cohort of patients. In the recently published Italian registry of 1,716 PE patients, female sex was important risk factor for in-hospital death and hemodynamic instability [19]. However, in the recently published study of 815 PE patients followed-up 5 years, male gender was associated with increased risk of post-discharge mortality probably due to increased contribution of other cardiovascular morbidities which were more often presented in men [16]. In our study, the intrahospital mortality was non-significantly higher in women but the small number of patients was very probably the reason for such result. We

also did not find a difference in major bleeding events between the men and the women, although almost 60% of both sexes were treated with thrombolysis. The efficacy of thrombolysis and the risk of bleeding in relation to gender are the matter of controversy [7, 8]. In the summary of 5 prospective multicenter studies of thrombolytic therapy in PE, thrombolysis had equal benefit and safety for both genders [7]. However, in the large Management Strategy and Prognosis of Pulmonary Embolism Registry (MAPPET) women had significantly less benefit with thrombolysis with higher bleeding risk [8]. We developed a strategy of estimation of bleeding risk before introducing the thrombolytic therapy and it may reduce bleeding in both sexes.

Conclusion

To the best of our knowledge this is the first comparison of pulmonary embolism presentation with analysis of symptoms, ECG signs, echocardiography and MDCT-PA parameters between men and women in the era of MDCT with pulmonary angiography. Our results show a significant difference in the presentation of pulmonary embolism between genders across the age. Clinical symptoms and signs were strongly influenced by gender. ECG signs typical for pulmonary embolism were equally presented in both genders. Some biomarkers had significantly diverse blood concentrations. Finally, there was no difference in the mortality and bleeding rate between men and women.

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