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Sex-specific differences and risk factors for 30-day mortality in acute pulmonary embolism – results from the Serbian University Multicenter Pulmonary Embolism registry

Polno-specifične razlike i faktori rizika od 30-dnevne smrtnosti u akutnoj plućnoj emboliji – rezultati univerzitetskog multicentričnog registra za plućnu emboliju Srbije

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Abstract

Background/Aim. The prediction role of gender in early mortality in patients with acute pulmonary embolism (PE) is still debatable. The aim of the study was to examine sex-specific factors in all-cause 30-day mortality in patients suffering from acute PE. **Methods.** Acute PE subjects (n = 532), 49.6% men, were derived from a "real-life" observational multicenter study. We assessed independent risk factors as predictors for early (one-month) fatal outcome in men, women and total population using univariate Cox regression analysis. **Results.** Age, obesity, hypertension, renal dysfunction, anemia, community-acquired pneumonia, and smoking history presented statistically significant sex-specific differences. One-month mortality was 13.7%, without significant difference in survival based on sex (Log Rank test; $p = 0.324$). Tachycardia at admission [hazard ratio (HR) = 2.61, $p = 0.004$], coronary artery disease (HR = 2.30, $p = 0.047$), immobilization four weeks prior to a PE episode (HR = 2.31, $p = 0.018$) and older age (HR = 1.03, $p = 0.017$) in women, while chronic obstructive pulmonary disease (COPD) (HR = 4.03, $p < 0.001$) and leukocytosis (HR = 1.19, $p < 0.001$) in men significantly increased one-month mortality risk. **Conclusion.** Patient's sex did not prove to be the independent predictor for 30-day mortality in PE patients. We found that tachycardia at admission, older age, coronary artery disease and limb immobilization four weeks prior to PE in women, whereas COPD and elevated leukocyte count in men were associated with higher chance of all-cause early mortality.

Key words:
age factors; coronary disease; immobilization; mortality; pulmonary disease, chronic obstructive; pulmonary embolism; risk factors; sex factors; tachycardia.

Apstrakt

Uvod/Cilj. Uloga pola u predviđanju rizika od ranog smrtnog ishoda kod obolelih od akutne plućne embolije (PE) je nedovoljno razjašnjena. Cilj rada bio je da se utvrde polno-specifični činioci za 30-dnevnu smrtnost od svih uzroka ukupno kod obolelih od akutne PE. **Metode.** Studija po tipu "real-life" opservacionog multicentričnog istraživanja je obuhvatila 532 obolelih od akutne PE (49,6% muškaraca). Primenom univarijantne Cox regresione analize ispitali smo prediktivnu vrednost nezavisnih faktora rizika od ranog (jednomesečnog) smrtnog ishoda kod muškaraca, žena i svih bolesnika ukupno. **Rezultati.** Razlike specifične prema polu bolesnika pokazale su se u uzrastu, gojaznosti, arterijskoj hipertenziji, bubrežnoj slabosti, anemiji, vanbolničkoj pneumoniji i pušačkom statusu. Stopa smrtnosti u prvih mesec dana je iznosila 13,7%, bez značajne razlike u preživljavanju zavisno od pola bolesnika (Log Rank test, $p = 0,324$). Stepen rizika (*hazard ratio* – HR) od 30-dnevne smrtnosti bio je značajno povišen kod žena koje su imale tahikardiju na prijemu (HR=2,61; $p = 0,004$), koronarnu arterijsku bolest (HR = 2,30; $p = 0,047$), imobilizaciju unutar četiri nedelje pre epizode PE (HR = 2,31; $p = 0,018$) i stariji uzrast (HR = 1,03; $p = 0,017$), dok je povišen stepen rizika kod muškaraca bio udružen sa hroničnom op

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struktivnom bolešću pluća (HOBP) (HR = 4,03; $p < 0,001$) i leukocitozom (HR = 1,19; $p < 0,001$). **Zaključak.** Pol bolesnika se nije pokazao kao nezavisni prediktor 30-dnevne smrtnosti kod bolesnika sa PE. Utvrdili smo da su kod žena sa PE, tahikardija na prijemu, uzrast bolesnika, koronarna bolest i imobilizacija nogu četiri nedelje pre PE, a kod muškaraca sa PE, prisustvo HOBP i leukocitoze, povezani sa povećanim rizikom od ranog smrtnog ishoda.

Ključne reči:
životno doba, faktor; koronarna bolest; imobilizacija; mortalitet; pluća, opstruktivne bolesti, hronične; pluća, embolija; faktori rizika; pol, faktor; tahikardija.

Introduction

Pulmonary embolism (PE) is a partial or total occlusion of pulmonary arterial circulation usually by a clot migrating from deep veins resulting in various clinical scenarios – from asymptomatic state to hemodynamic instability, cardiogenic shock and death. PE and deep venous thrombosis (DVT) are referred as venous thromboembolism (VTE) with annual incidence 23-69/100,000 adults [1]. Mortality rate is high – around 30% when left untreated, while 10–15% of hospital-treated PE patients die in the first 1–3 months [1, 2]. Higher fatality rates are derived from registries than from randomized clinical trials [3]. Severity of clinical presentation, numerous patient and setting-related factors influence the outcome [4]. Therefore, according to the 2014 European Society of Cardiology Guidelines (2014 ESC) [4] model based on the simplified Pulmonary Embolic Severity Score (sPESI) [5], the presence of hypotension and right ventricular dysfunction (positive myocardial biomarkers and/or echocardiographic signs) in patients are stratified into four risk groups as having low, intermediate-low, intermediate-high or high risk for 30-day mortality. The respective all-cause mortality rates are 0.5%, 6.0%, 7.7% and 22% [6].

The essential patient assessment for anticoagulant therapy and/or thrombolysis starts with weighing bleeding and mortality risks. Many validated prediction rules have been used for this purpose and several have incorporated female/male gender in scoring, ie. the original PESI score for mortality risks and the VTE-bleed score for VTE patients on stable anticoagulation [7, 8]. However, there are controversies whether sex can impact the outcome following acute PE. One large research on ~280,000 acute PE hospitalizations in the United States found higher in-hospital mortality in females [9]. An opposite finding was derived from the U.S. National Center of Health Statistics which demonstrated that men consistently had a higher fatality rate in all racial and age strata following acute PE during 1979–1998 [10]. Also, a Japanese study on PE patients treated during 1951–2000 found that male mortality was higher [11].

The aim of this study was to determine possible sex-related risk factors influencing the outcome in acute PE patients and to evaluate if sex independently predicts 30-day mortality. The differences in clinical presentation of PE based on sex had previously been reported on a smaller sample of our patients [12].

Methods

This is an ongoing "real-life" observational multicenter study on PE patients initiated in 2012 as the *Serbian University Pulmonary Embolism Registry* (SUPER). These study data were collected retrospectively until 2018 from medical electronic records. The patients were detected by discharge code I26 of the standard International Classification of Diseases, the 10th edition. The authors gathered, maintained and extracted data to the SUPER. They were responsible for interpreting the data and composing the article.

The study population included 532 acute PE patients (49.6% men). Clinicians confirmed PE diagnosis mostly by positive computed-tomography pulmonary angiogram (CTPA), and in few patients by an intermediate-high probability nuclear pulmonary perfusion scintigraphy or by an autopsy finding of pulmonary thrombi. We studied only patients treated for PE. Vital parameters and levels of blood glucose, C-reactive protein (CRP), serum creatinine, leukocyte count and B-type natriuretic peptide (BNP) plasma concentration were recorded on the day of clinical suspicion for PE, i.e. admission, when the treatment decision was made. Creatinine clearance was calculated by Cockcroft-Gault equation [13]. Pneumonia was defined as the appearance of pulmonary infiltrates in the first 48h from admission requiring antibiotic treatment. Anemia was determined with hemoglobin upper limit of normal of 125 g/L and 115 g/L for men and women, respectively. Transthoracic echocardiography examinations had been performed at the bedside or in a specialized office before treatment decisions were made. Right ventricular systolic pressure (RVSP) was estimated using tricuspid regurgitation method [14].

Based on the sPESI (0 or more) presence of hypotension and right ventricular dysfunction (positive myocardial biomarkers and/or echocardiographic signs), all the patients were stratified into four risk groups as having high, intermediate-high, intermediate-low or low risk for one-month mortality [4, 5].

Depending on the risk-stratification group, the patients received treatment with weigh-adjusted subcutaneous low-molecular-weight heparin, unfractionated heparin intravenously or reperfusion. Reperfusion included conventional ESC fast and slow systemic thrombolysis protocols as well as local catheter thrombolysis [4]. Fast protocol used intravenous application of 100 mg alteplase in 2 hours or streptokinase (1,500,000 IJ in 2 h). The slow protocol presented 24 h-continuous intravenous infusion of alteplase 5 mg/h or streptokinase 100,000 IJ/h. In patients with intermediate-high risk PE with the increased risk of bleeding, we performed local catheter thrombolysis. We used ultrasound-assisted catheter thrombolysis (USACT) using the EKOS system (EKOS Corporation, BTG International Group Company) with 1–2 mg/h of alteplase with a dose range of 12–50 mg. We applied the higher doses in patients with a longer duration of PE symptoms, higher thrombus burden and younger age.

We grouped the patients according to sex and presented their characteristics as frequencies with mean values ± standard deviation (SD). Menopausal status was unknown and to avoid sex hormonal differences we analyzed two age-specific groups: < 55 years or older. The age was also assessed using age tertiles in men and women. We calculated statistical significance in difference between sex characteristics with the Pearson's, χ^2 or Student's *t*-test. The main outcome in the study population was all-cause 30-day mortality. We defined mortality as death from any cause within 30 days since the index date of hospital admission. Using univariate Cox regression analysis, we assessed the influence of each risk factor as an independent predictor for all-cause one-month mortality within the entire and gender-specific population. We calculated hazard ratios (HR) with 95% confidence intervals (CI). We applied multivariate Cox regression analysis to estimate HR adjusted for age, smoking status and body mass index (BMI). We looked at the four risk-groups as variable in the scale where the highest value had the highest risk (from 1 to 4). All these tests were two-sided and probability (*p*) value was of less than 0.05 determined statistical significance. We used Kaplan-Meier analysis with Log rank test to compare survival between genders. The analyses were performed with Statistical Package for Social Sciences, version 20.

Every patient had signed an informed consent for proposed medical measures at the admission, as well as before each particular non-standard diagnostic or therapeutic procedure in accordance with national ethical standards and Helsinki declaration.

Results

The study population characteristics according to gender are summarized in Table 1. Arterial hypertension, anemia and creatinine clearance < 60 mL/min were more frequent in women, while pneumonia in the first 48 hours and smoking history proved more common in men. However, during their hospital stay, women were more often intubated and mechanically ventilated due to respiratory failure than men. Incidence rates of other comorbidities were not gender-specific. A BNP level of > 100 pg/mL was statistically more frequent in women than in men (72.4% vs. 57.7%, respectively; $p = 0.003$). Regarding therapy options, more than half of the patients treated with thrombolytic agents received slow systemic protocols, with

Table 1

Characteristics of the pulmonary embolism patients at the admission according to gender

Characteristic	Women (n = 268)	Men (n = 264)	*p*
Age (years), mean ± SD	65.06 ±16.557	58.18 ± 15.764	0.000
Age older than 55 years, n (%)	209 (78.3)	165 (62.5)	0.000
Obesity (BMI > 30 kg/m^2), n (%)	71 (30.5)	39 (16.6)	0.002
Arterial hypertension, n (%)	155 (57.8)	121 (45.8)	0.006
DVT at admission, n (%)	142 (55.7)	142 (56.6)	0.841
Previous DVT or PE, n (%)	34 (12.8)	42 (16.0)	0.137
COPD, n (%)	25 (9.3)	30 (11.4)	0.441
DM, n (%)	50 (18.7)	38 (14.4)	0.179
Malignancy, n (%)	39 (14.6)	27 (10.2)	0.130
Chronic heart failure, n (%)	39 (14.6)	27 (10.2)	0.130
Coronary disease, n (%)	24 (9.2)	28 (11.2)	0.454
Stroke, n (%)	21 (7.9)	18 (6.8)	0.635
Major surgery three weeks prior PE, n (%)	30 (11.6)	21 (8.4)	0.226
Immobilization four weeks prior PE, n (%)	40 (15.0)	30 (11.4)	0.218
Drug predisposing to bleeding, n (%)	78 (29.4)	85 (32.3)	0.473
Systolic blood pressure, n (%)	120.03 (26.92)	122.78 (24.65)	0.221
Heart rate, n (%)	101.38 (23.18)	101.15 (23.83)	0.912
Smoking, n (%)	22 (9.0)	64 (26.1)	0.000
Anemia, n (%)	100 (37.5)	61 (23.3)	0.000
Blood glucose (mmol/L), n (%)	8.25 (4.11)	7.90 (3.94)	0.325
Creatinine clearance < 60 mL/min, n (%)	88 (36.7)	56 (23.5)	0.002
Pneumonia in 48 hours from admission, n (%)	43 (16.1)	65 (24.6)	0.015
Leukocyte count, n (%)	11.95 (9.50)	10.81 (4.24)	0.081
C-reactive protein, n (%)	73.12 (79.24)	77.72 (78.80)	0.512
sPESI > 0, n (%)	180 (68.4)	201 (75.3)	0.080
RVSP > 40 mmHg, n (%)	169 (67.6)	149 (62.6)	0.247
BNP > 100 pg/mL, n (%)	139 (72.4)	112 (57.7)	0.003
Thrombolysis, n (%)			
fast systemic protocol	24 (29.3)	21 (23.1)	0.281
slow systemic protocol	47 (57.3)	48 (52.7)	
local catheter lysis	11 (13.4)	20 (22.0)	
Reanimation during hospital stay, n (%)	35 (13.9)	26 (10.4)	0.225
Mechanical ventilation during hospital stay, n (%)	34 (13.6)	20 (8.0)	0.044
Length of stay (days), mean ± SD	11.98 ± 8.00	10.91 ± 7.15	0.129

SD – standard deviation; BMI – body mass index; DVT – deep venous thrombosis; PE – pulmonary embolism; COPD – chronic pulmonary obstructive disease; sPESI – simplified Pulmonary Embolism Severity Index; RVSP – right ventricular systolic pressure; BNP – brain natriuretic peptide; DM – diabetes melitus.

no difference between gender for all four thrombolytic protocols. Mean length of stay (LOS) was 10.91 days for men and 11.98 days for women ($p = 0.129$). Mean LOS was similar in all four risk groups – low, intermediate-low, intermediate-high and high risk patients – 10.56 ± 6.05 days, 12.01 ± 7.39 days, 11.75 ± 7.90 days, and 11.16 ± 9.46 days, respectively.

During the first month of the treatment, 73 (13.7%) of patients died without any statistically significant difference between women and men (41 women, 32 men, $\chi^2 = 1.134$; $p = 0.287$). All of these fatal outcomes occurred during the in-hospital treatment. The majority of deceased patients (86.3%) were in the high and intermediate-high risk group. Mortality rate was the highest on the first hospital day (32.9%), out of which 70.8% patients were in high, 20.8% in intermediate-high, 8.3% in intermediate-low and 0.0% in low risk group. Total population mortality rate was 6.0%, 5.8%, 1.7% and 0.2% in high, intermediate-high, intermediate-low and low risk patients, respectively. Observing closely within the risk groups, death within 30 days occurred in 41.6% of high-risk patients, 15.3% of intermediate-high-risk patients, 7.1% of intermediate-low-risk patients and 0.8% of low-risk patients.

We assessed the influence of each independent predictor for all-cause 30-day mortality for three groups – all-patient population, separately for men and women, using univariate Cox regression analysis, and after adjusting for age, BMI and smoking status using multivariate Cox regression analysis (Table 2, A–C). Regardless of the group observed, a patient having any of the following factors – reanimation or mechanical

Table 2

Risk factors for 30-day mortality in all patients (A), men (B) and women (C) with acute pulmonary embolism (PE)

(A) All patients (n = 532)

Risk factor	*p*	Unadjusted-HR (95% CI)	*p*	Adjusted-HR* (95% CI)
Age	0.001	**1.026 (1.010-1.043)**		
Body mass index > 30 kg/m^2	0.393	0.760 (0.406–1.425)		
Smoking	0.432	0.784 (0.427–1.439)		
Arterial hypertension	0.470	1.186 (0.747–1.883)	0.256	1.561 (0.724-3.368)
DVT at presentation	**0.000**	**2.767 (1.580–4.846)**	**0.027**	**2.422 (1.107–5.300)**
Previous DVT	0.195	0.576 (0.250–1.328)	0.207	0.395 (0.093–1.674)
COPD	**0.022**	**2.015 (1.106–3.671)**	0.502	0.505 (0.069–3.717)
Chronic heart failure	**0.024**	**1.893 (1.087–3.295)**	0.114	1.942 (0.853–4.422)
Diabetes mellitus	**0.034**	**1.778 (1.044–3.028)**	**0.004**	**3.068 (1.426–6.601)**
Malignancy	0.073	1.704 (0.951–3.052)	0.135	1.858 (0.825–4.187)
Coronary artery disease	**0.007**	**2.317 (1.265–4.246)**	**0.010**	**3.031 (1.308–7.025)**
Stroke	**0.000**	**3.083 (1.658–5.734)**	0.057	2.472 (0.974–6.269)
Drugs	**0.001**	**2.235 (1.412–3.539)**	**0.005**	**2.821 (1.363–5.840)**
Heart rate > 100 bpm	**0.012**	**1.828 (1.141–2.931)**	**0.001**	**4.121 (1.776–9.561)**
Systolic BP < 100 mmHg	**0.000**	**4.886 (3.070–7.778)**	**0.003**	**2.994 (1.457–6.153)**
Anemia	0.388	1.238 (0. 762–2.011)	0.226	1.545 (0.764–3.125)
Glycaemia	**0.000**	**1.096 (1.053–1.140)**	**0.000**	**1.148 (1.084–1.215)**
Creatinine clearance (mL/min)				
> 60	**0.000**	**1.00[a]**	**0.008**	**1.00[a]**
< 60		**4.774 (2.864–7.960)**		**3.097 (1.336–7.180)**
Pneumonia	0.084	1.573 (0.940–2.631)	0.271	1.676 (0.668–4.210)
Leukocyte count	**0.012**	**1.021 (1.004–1.037)**	0.403	1.012 (0.984–1.089)
C–reactive protein	**0.000**	**1.006 (1.004–1.008)**	**0.001**	**1.006 (1.002–1.010)**
sPESI score				
0	**0.000**	**1.00[a]**	**0.011**	**1.00[a]**
> 0		**15.073 (3.697–61.455)**		**13.532 (1.815–100.864)**
RVSP > 40 mmHg	**0.000**	**4.352 (1.980–9.565)**	**0.004**	**8.592 (1.985–37.184)**
BNP > 100 pg/mL	**0.000**	**5.491 (2.182–13.822)**	**0.003**	**6.929 (1.975–24.315)**
Thrombolysis protocol				
fast systemic		**1.00[a]**		**1.00[a]**
slow systemic	**0.001**	**0.264 (0.123–0.564)**	**0.002**	**0.197 (0.069–0.559)**
local catheter	**0.011**	**0.073 (0.010–0.551)**	**0.040**	**0.111 (0.014–0.900)**
Reanimation	**0.000**	**17.647 (11.003–28.302)**	**0.000**	**37.811 (16.297–87.725)**
Mechanical ventilation	**0.000**	**20.893 (12.583–34.692)**	**0.000**	**77.120 (28.490–208.755)**
Surgery prior PE				
up to 3 weeks		1.00[a]		1.00[a]
3 weeks – 6 months	0.986	1.010 (0.308–3.311)	0.665	0.717 (0.160–3.223)
no	0.357	1.483 (0.641–3.428)	0.678	0.799 (0.277–2.304)
Immobilization four weeks prior PE	**0.004**	**2.197 (1.276–3.781)**	0.357	1.529 (0.619–3.780)
Risk groups for 30–day mortality				
low risk		**1.00[a]**		1.00[a]
intermediate–low	**0.033**	**9.520 (1.206–75.142)**	0.903	55,820.5 (0.000→∞)
intermediate–high	**0.003**	**20.701 (2.826–151.648)**	0.900	75,264.3 (0.000→∞)
high	**0.000**	**67.097 (9.164–491.271)**	0.891	22,8437.8 (0.000→∞)

Table 2 (continued)

(B) Men (n = 264)

Risk factor	*p*	HR (95% CI)
Age	0.058	1.023 (0.999–1.048)
Body mass index > 30 kg/m^2	0.196	0.387 (0.092–1.632)
Smoking	0.303	0.652 (0.289–1.472)
Arterial hypertension	0.660	1.168 (0.584–2.336)
DVT at presentation	**0.013**	**3.128 (1.274–7.684)**
Previous DVT	0.081	0.170 (0.023–1.246)
COPD	**0.000**	**4.031 (1.907–8.522)**
Chronic heart failure	0.083	2.028 (0.911–4.514)
Diabetes mellitus	0.142	1.875 (0.811–4.335)
Malignancy	0.117	2.033 (0.837–4.941)
Coronary artery disease	0.063	2.343 (0.954–4.062)
Stroke	**0.018**	**3.159 (1.215–8.211)**
Drugs	**0.027**	**2.187 (1.094–4.374)**
Heart rate > 100 bpm	0.563	1.227 (0.613–2.457)
Systolic BP < 100 mmHg	**0.000**	**8.365 (4.025–17.384)**
Anemia	0.108	1.819 (0.877–3.773)
Glycaemia	**0.003**	**1.098 (1.032–1.169)**
Creatinine clearance (mL/min)		
> 60	**0.000**	**1.00[a]**
< 60		**5.135 (2.426–10.868)**
Pneumonia	0.316	1.466 (0.694–3.095)
Leukocyte count	**0.000**	**1.186 (1.108–1.270)**
C–reactive protein	**0.000**	**1.007 (1.004–1.010)**
sPESI score		
0	**0.020**	**1.00[a]**
> 0		**38.550 (1.77–835.59)**
RVSP > 40 mmHg	**0.006**	**7.705 (1.821–32.610)**
BNP >100 pg/mL	**0.005**	**8.201 (1.916–35.094)**
Thrombolysis protocol		
fast systemic	**0.003**	**1.00[a]**
slow systemic		**0.168 (0.852–0.546)**
local catheter		**No male patients died with local catheter**
Reanimation	**0.000**	**19.138 (9.240–39.636)**
Mechanical ventilation	**0.000**	**25.689 (11.984–55.068)**
Surgery prior PE		
up to 3 weeks		1.00[a]
3 weeks–6 months	0.859	0.851 (0.142–5.091)
no	0.969	1.024 (0.311–3.375)
Immobilization four weeks prior to PE	0.142	1.947 (0.801–4.730)
Risk groups for 30–day mortality		
low risk		
intermediate–low		1.00[a]
intermediate–high	0.075	3.134 (0.893–10.999)
high	**0.000**	**13.070 (3.799–44.964)**

Table 2 (continued)

(C) Women (n = 268)

Risk factor	*p*	HR (95% CI)
Age	**0.017**	**1.029 (1.005–1.053)**
Body mass index > 30 kg/m^2	0.767	0.895 (0.432–1.857)
Smoking	0.647	1.115 (0.582–2.135)
Arterial hypertension	0.667	1.148 (0.613–2.149)
DVT at presentation	**0.010**	**2.576 (1.255–5.286)**
Previous DVT	0.791	1.135 (0.445–2.891)
COPD	0.635	0.752 (0.232–2.437)
Chronic heart failure	0.133	1.808 (0.835–3.915)
Diabetes mellitus	0.151	1.658 (0.831–3.310)
Malignancy	0.340	1.457 (0.673–3.154)
Coronary artery disease	**0.047**	**2.296 (1.011–5.214)**
Stroke	**0.009**	**2.955 (1.306–6.685)**
Drugs	**0.006**	**2.346 (1.270–4.336)**
Heart rate > 100 bpm	**0.004**	**2.609 (1.351–5.038)**
Systolic BP < 100 mmHg	**0.000**	**3.178 (1.721–5.865)**
Anemia	0.743	0.897 (0.468–1.718)
Glycaemia	**0.001**	**1.092 (1.037–1.150)**
Creatinine clearance (mL/min)		
> 60	**0.000**	**1.00[a]**
< 60		**4.459 (2.193–9.068)**
Pneumonia	0.101	1.815 (0.890–3.703)
Leukocyte count	0.505	1.008 (0.984–1.034)
C–reactive protein	**0.001**	**1.006 (1.001–1.009)**
sPESI score		
0	**0.008**	**1.00[a]**
> 0		**6.888 (1.663–28.529)**
RVSP > 40 mmHg	**0.024**	**2.966 (1.151–7.646)**
BNP >100 pg/mL	**0.035**	**3.616 (1.094–11.947)**
Thrombolysis protocol		
fast systemic		1.00[a]
slow systemic	0.064	0.383 (0.139–1.058)
local catheter	0.201	0.960 (0.032–2.061)
Reanimation	**0.000**	**16.153 (8.653–30.156)**
Mechanical ventilation	**0.000**	**17.753 (8.959–35.177)**
Surgery prior PE		
up to 3 weeks		1.00[a]
3 weeks – 6 months	0.842	1.176 (0.237–5.828)
no	0.227	2.439 (0.636–6.724)
Immobilization four weeks prior PE	**0.018**	**2.311 (1.158–4.613)**
Risk groups for 30–day mortality		
low risk		1.00[a]
intermediate–low	0.070	7.098 (0.855–58.961)
intermediate–high	**0.017**	**11.539 (1.540–86.444)**
high	**0.001**	**30.292 (4.015–228.559)**

Unadjusted and adjusted hazard ratios (HR) with 95% confidence interval (CI) were calculated using univariate and multivariate Cox regression model. *Adjusted for age, body mass index, and smoking. DVT – deep venous thrombosis; COPD – chronic obstructive pulmonary disease; BP – blood pressure; sPESI – simplified Pulmonary Embolism Severity Index; RVSP – right ventricular systolic pressure; BNP – brain natriuretic peptide; [a] – reference value.
Bolded values are statistically significant.

ventilation during hospitalization, systolic blood pressure < 100 mmHg, creatinine clearance < 60 mL/min, BNP level >100 pg/mL, RVSP > 40 mmHg, DVT at presentation, or using drugs predisposing to bleeding, had significantly increased chances of fatal outcome in the first month of the treatment. There was no difference in the all-cause mortality in men with admission heart rate > 100 beats/min comparing to men with heart rate < 101 beats/min (13.4% vs. 10.9%, respectively; $p = 0.576$). Still, women with the heart rate at admission > 100 beats/min had higher all-cause mortality rate within 30 days than women with lower heart rate (21.9% vs. 9.3%, respectively; $p = 0.006$) (Table 3). The same was for PE-cause mortality at 30 days. Elevated glycaemia and CRP level only slightly contributed to the 30-day mortality risk in each cohort. Simplified PESI score

> 0 appeared to be a strong predictor of fatality, especially in men, but with a wide confidence interval. PE presentation with previous stroke or elevated leukocyte count were found as mortality predictors, but lost the significance after adjusting for age, BMI and smoking. Tachycardia [in women HR 2.609 (1.351–5.038); $p = 0.004$] and coronary artery disease (CAD) [in women HR 2.296 (1.011–5.214); $p = 0.047$] influenced the outcome in all except the male group. The patients with chronic heart failure (CHF) and diabetes mellitus (DM) had 80% increase in mortality risk, but did not reach sex-specific statistical significance in predicting mortality due to their distribution between men and women. Age only slightly increased the chance of dying in the all-patient and female population. Extremity immobilizations within four weeks prior to PE appeared as independent predictors of early mortality in women [HR = 2.31 (1.16–4.61); $p = 0.018$]. Male patients with chronic obstructive pulmonary disease (COPD) ran the elevated risk of one-month mortality with HR of 4.03 (95% CI = 1.91–8.52; $p < 0.001$). Comparing with fast systemic thrombolysis, slow systemic protocols correlated with a reduction in 30-day mortality risk of up to 80% in men and all-patient cohort. We perceived a greater mortality risk reduction in patients treated with local catheter thrombolysis comparing to systemic protocols. Mortality risk in the all-patient group gradually decreased starting from the high, intermediate-high, and intermediate-low to the low-risk patients PE, but with wide confidence intervals. After adjusting for age, BMI and smoking, all confidence intervals reached zero value. Women classified in the intermediate-high or high-risk group bore significantly elevated mortality risk, whereas the increased chance of dying in men was found only in the high-risk group.

Table 3

All-cause death within 30 days in women and men according to heart rate at admission

Sex	Heart rate (bpm)		Total	Chi-square test (p)
	< 101	> 100		
Men	15/137	17/127	32/264	0.576
Women	13/140	28/128	41/268	0.006

bpm – beats per minute.

There was a statistically significant difference in the distribution of mortality rate in male patients according to tertiles of age ($\chi^2 = 9.104$; $p = 0.011$) (Figure 1). Men were dying more in their "third age" (67-88 years of age). Women who died in the third age tertiles (75 years or more) were more often high and intermediate-high-risk patients comparing to the age-matched men, but we could not perform a valid statistical analysis due to the small subgroup number of deceased patients. One-month survival within intermediate-risk group and high-risk group was not significantly different between men and women (Table 4).

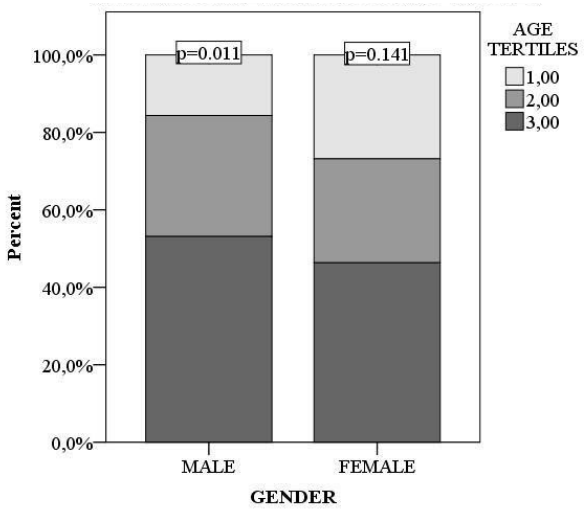

Fig. 1 – One-month mortality rate according to sex by age tertiles [(men: 1st tertile – 19–53 years; 2nd tertile – 54–66 years; 3rd tertile – 67–88 years); women: 1st tertile – 17-62 years; 2nd tertile – 63–74; 3rd tertile – 75–92 years)].

According to Kaplan Meier curve and Log rank test we recognised no significant sex-specific difference in survival time in the 30-day period (Log Rank test; $\chi^2 = 0.971$, $p = 0.324$) (Figure 2).

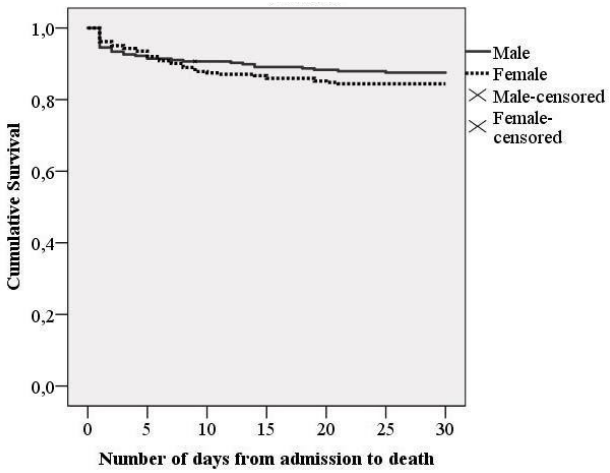

Fig. 2 – Kaplan-Meier one-month survival curve according to sex. Log rank test (Mantel-Cox) $\chi^2 = 0.971$, $p = 0.324$.

Table 4

One-month mortality based on the patient sex within intermediate-risk and high-risk groups

Death	Risk groups					
	intermediate-high			high		
	male	female	p	male	female	p
No	86 (86.9)	86 (82.7)	0.408	18 (52.9)	27 (62.8)	0.384
Yes	13 (13.1)	18 (17.3)		16 (47.1)	16 (37.2)	
Total	99 (100.0)	104 (100.0)		34 (100.0)	43 (100.0)	

Values are expressed as number (percentage).

Discussion

Management of acute PE patients depends primarily on the clinical presentation, based on the 2014 ESC model [4], but also on the patient and setting-related predisposing factors for thrombosis and bleeding. In this study, we assessed the sex-specific risk factors for all-cause 30-day mortality. Our total 30-day mortality rate was 13.7%, which corresponds to the previous bibliography data [1, 2]. Survival time in both patient sexes was almost identical (Log Rank test; $\chi^2 = 0.962$, $p = 0.327$). The first hospital day was fatal in one third of deceased patients, which additionally stresses the importance of prompt mortality risk stratification and appropriate treatment. The mean length of stay matched the mean LOS reported in one Italian real-life study [15].

According to the 2014 ESC model for 30-day mortality risk stratification [4], 77 (14.5%) of patients of our study population were classified as having high, 203 (38.1%) intermediate-high, 126 (23.7%) intermediate-low and 126 (23.7%) low risk, similar to the published research by Becattini et al. [6]. Interestingly enough, we discovered one-month mortality rate to be very high among high-risk (41.6%) and intermediate-high-risk patients (15.3%) in comparison with Becattini et al. [6] (22% and 7.7%, respectively). Comparing to women, we did not find the increased risk of dying in men of intermediate-high risk group, probably due to different sex-specific distribution in the low-risk group (no male patients died in the low-risk category). Some additional analysis of our population is necessary to discover the causes of higher death rate in these specific strata of patients.

We found that the heart rate of more than 100 beats/min increased the chance of death in the one-month period in women and in the total study population after adjusting for age, BMI and smoking status. Masotti et al.[15] reported that sPESI score had better predictive ability of all-cause in-hospital mortality in women than in men. In our study, no sex-specific differences were noticed in terms of sPESI score, even though it incorporates heart rate > 110 beats/min. Perhaps analyzing antiarrhythmic drug usage, ie. beta-blockers, would be of interest to assess its potential impact on the PE clinical presentation and prognosis. The increase in admission glycaemia level only slightly raised the chances of early death in our population. Scherz et al. [16] found that cumulative probability of 30-day mortality increased with the rise in blood glucose level at admission in PE patients without diabetes, but not in diabetic PE population. Nevertheless, we did not compare blood glucose level between diabetics and non-diabetics. We must note that the well-known risk factors for developing PE – surgery, previous DVT, malignancy, pneumonia, arterial hypertension and obesity – were not determined as mortality predictors in our study. In the International Cooperative Pulmonary Embolism Registry (ICOPER) study, malignancy was one of the best predictors of death both in men and women [3].

The population of advanced age were more frequently women, especially those older than 55 years, as previously reported [12], contrary to the ICOPER study where the elders were more often men [3]. Women had higher incidence of arterial hypertension related to age. Natural aging process results in atherosclerosis progression and development of multiple cardiovascular diseases. Paradoxically, women's death rate was not significantly rising with age, as we would expect and as we found in the men of the "third age". So, what protected women from PE in younger age? A hypothetical explanation could be linked to female hormonal protective mechanisms in reproductive period [17], but human trials did not investigate the impact of endogenous estrogen levels on venous thrombosis risk. Some findings suggest that lower endogenous estradiol levels in perimenopausal women were associated with higher levels of plasminogen activator inhibitor-I (PAI-I) and tissue plasminogen activator and higher cardiovascular risk [18]. Correspondingly, as established in thromboelastographic studies, the whole blood coagulability trend increases from men, from non-pregnant to pregnant women [19]. On the other hand, what contributed to fatal outcome in younger women remains uncertain. This requires certain further analyses of all factors based on the age groups in the future.

We found higher BMI in women, as expected [12], which may be coupled with lower physical activity and consequent VTE. Adiposity produces significantly higher levels of estrogen, fibrinogen, prothrombin, CRP, plasminogen activator inhibitor-I (PAI-I) and microparticles which all in part assist in the clot formation [20, 21]. Nonetheless, venous thrombosis risk can not be estimated only basing it on the BMI since metabolic profile substantially differs in people having identical BMI depending on adipose tissue distribution [20]. Unfortunately, we could not provide more information on the socioeconomic state and lifestyle. As previously mentioned, obesity was not connected with increased mortality rate in our population.

Interestingly enough, COPD increased the chance of fatal outcome in men fourfold ($p < 0.001$). Borrero et al. [22] also found chronic lung disease associated with higher mortality rate in men. Leukocyte count at admission and CRP levels did not differ considerably. Opposite to the fact that the female population more often required mechanical ventilation, men were more frequently smokers and had pneumonia in the first two days from admission. Community-acquired pneumonia did not influence mortality rate, but could have aggravated the clinical course of COPD patients. Considering that we could not extract the indications for mechanical ventilation from the Registry, we may only hypothesize that the underlying condition was heart failure as women presented more often with elevated BNP. Yet, higher levels of BNP could partly be a result of the lower estimated creatinine clearance measured in women. Naturally, women being older already had renal dysfunction as creatinine clearance declines over lifetime [13]. All these parameters: mechanical ventilation, elevated BNP level and creatinine clearance < 60 mL/min, were found to predict one-month fatality in both sexes. Women had lower admission hemoglobin level, as expected according to the anemia global prevalence sex distribution [23], but that did not increase their mortality risk. Other publications on the acute PE

patients also listed women to be more aged, with lower creatinine clearance and hemoglobin level [9, 15].

The patients treated with slow systemic thrombolysis protocols and local catheter-directed thrombolysis had better survival rate comparing to those receiving fast systemic protocols. This could be explained by the disease severity (i.e. cardiogenic shock) when the fast protocol as a salvage therapy is mandatory. However, we did not assess these protocols by patient risk-stratification groups.

Apart from the aforementioned and retrospective nature of the study, there are several more limitations in the analysis. Weighing mortality risk demanded some additional severity stratification of some conditions, such as COPD, chronic heart failure and malignancy stage. Echocardiographic parameters of right ventricular function were not always fully available (ie. tricuspid annular plane systolic excursion, pulmonary valve acceleration time, right atrium area, etc.) and we limited statistical analysis to the RVSP value alone. Equally important, the database currently could not supply more facts about the left ventricular heart function, i.e. left ventricular diastolic function. Echocardiography is of special interest in intermediate risk groups as these patients require closer monitoring and timely recognition of potential hemodynamic compromise with prompt and repetitious assessment for introducing thrombolysis in treatment [4]. Furthermore, we did not compare patients by medications and their dosage, ie. thrombolytic agents and anticoagulation (unfractioned heparin, low-molecular-weight heparin and direct oral anticoagulants).

Conclusion

We found that significant differences in sex-specific characteristics of the PE population were advanced age, presence of comorbidities – obesity, arterial hypertension, renal insufficiency, anemia, pneumonia and smoking history. Tachycardia, age, coronary artery disease and limb immobilization four weeks prior to PE in women, whereas COPD and elevated leukocyte count in men were associated with higher chance of all-cause 30-day mortality. Nevertheless, patient's sex alone did not predict the outcome. More research on mortality risk factors should help improve recognition and management of PE patients, especially those in high and intermediate-high risk of early mortality.

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