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The Epidemiology and Diagnostic Approach to Acute Pulmonary Embolism in the University Hospital

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A B S T R A C T

The aim of this retrospective study was to evaluate the demographics and clinical characteristics of patients with pulmonary embolism treated in medical intensive care unit (ICU) at the University Hospital during a six-year period, and to assess the impact of several risk factors on patients' survival. The study included 165 patients, mean age 69.3 ± 13.7 years, predominantly female (70.3%). Dominant symptom was dyspnea (97.0%), the most common sign tachypnea (69.6%). Pulmonary embolism was confirmed by high-probability ventilation/perfusion lung scan or multidetector computed tomography in 71.5% and was regarded as massive in 63 (38.2%), submassive in 23 (13.9%) and non massive in 79 patients (47.9%). Mean hospital stay was 5.7 ± 4.4 days for ICU, and 14.8 ± 9.1 days, overall. The ICU mortality was 26.7% and in-hospital mortality 30.9%. No statistical difference in mortality between male and female patients was observed (30.6% and 31.0%, respectively; p=0.965), but prolonged immobilization (p=0.002), recent operation (p=0.034) or malignancy (p=0.009) were shown to influence the outcome. Although a number of risk factors for developing pulmonary embolism have been identified and heparin prophylaxis along with early mobilization proposed to reduce the incidence, pulmonary embolism remains an important clinical problem with high mortality rate. The diagnostics should not wait and the therapy should start as soon as possible.

Key words: *pulmonary embolism, epidemiology, ventilation/perfusion lung scintigraphy, multidetector computed tomography of lungs, outcome*

Introduction

Pulmonary embolism is an acute obstruction of blood flow to pulmonary circulation usually by a blood clot. It is a common cardiovascular illness with an incidence of 1–2% in general population[1]. Although multidetector computed tomography (MDCT) and D-dimer test have revolutionized its diagnostics, the disease still remains undetected in a small number of cases. It is estimated that the incidence of pulmonary embolism among hospitalized patients varies between 12 and 20%[2]. Patients with pulmonary embolism present with a wide spectrum of illness that ranges from mild to severe, even death. The aim of our study was to evaluate the demographic data as well as clinical characteristics of patients treated for pulmonary embolism in medical intensive care unit (ICU) at the University Hospital. Also to assess the impact of several risk factors on survival. The findings might be useful in improving our efforts to timely recognize the disease, start treatment as soon as we can and work on prevention if possible.

Patients and Methods

This study was a retrospective analysis of all the charts of patients that were admitted to the ICU of the Department of Medicine, University Hospital 'Sestre milosrdnice', Zagreb, Croatia, with suspected diagnosis of acute pulmonary embolism between January 2000 and

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December 2005. Patients were examined in the Emergency Room (ER) and after the pulmonary embolism was suspected, the ER attending requested admission to the ICU. The diagnosis of pulmonary embolism was suspected in patients complaining of sudden shortness of breath – dyspnea, chest pain, dry cough or hemoptysis. Tachypnea (defined as more than 18 breaths per minute), hypotension (systolic blood pressure (BP) less than 90 mmHg), tachycardia (heart rate (HR) more than 100 beats per minute) or syncope were noted as signs that strengthened the diagnosis made by the ER physician even further. Patients were also being examined in the ER for the signs of right ventricular dysfunction (distended jugular veins, accentuated pulmonary component of the second heart tone, or tricuspid regurgitation murmur). To each patient an electrocardiogram (ECG) was recorded on admission and the chest X-ray performed for the exclusion of other lung pathology. Abnormal ECG findings suggestive of pulmonary embolism were recorded as follows: sinus or supraventricular tachycardia, complete or incomplete right bundle branch block, $S_1Q_3T_3$ pattern, or inverted T waves in right precordial leads.

Two hundred and fourteen charts from the ER were coded as pulmonary embolism. The exclusion process conducted by authors consisted of yet another clinical assessment made by the ICU specialist on the day of admission, ECG and chest X-ray findings or by high-probability ventilation/perfusion (V/Q) lung scan or MDCT (if available on the day of admission), Figure 1.

Upon admission to the ICU some patients have had the echocardiography performed, and right ventricular dysfunction was being diagnosed in the presence of one of the following criteria: a) right ventricular dilation (diastolic diameter >30 mm), b) paradoxical motion of interventricular septum, c) hypokinesis of the free wall of the right ventricle, d) tricuspid valve regurgitation (jet velocity >2.5 m/s), e) pulmonary hypertension. If D-dimer test was done (Nyocard D-dimer Single Test, Axis-Shield PoC AS, Oslo, Norway), the value was recorded as well as the Duplex scan sonogram of the lower extremities that was used to confirm or exclude the presence of deep vein thrombosis.

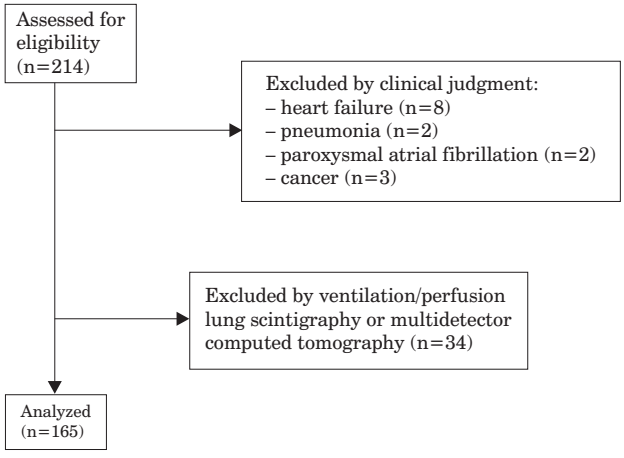

Fig. 1. Flow chart of the run-in period.

TABLE 1
CHARACTERISTICS OF 165 PATIENTS WITH PULMONARY EMBOLISM ADMITTED TO MEDICAL INTENSIVE CARE UNIT IN THE UNIVERSITY HOSPITAL

Characteristic	Number (%) of patients
Sex	
Male	49 (29.7)
Female	116 (70.3)
Age (mean ± SD)	
Male	66.5 ± 14.5
Female	70.5 ± 13.3
Season	
Spring	45 (27.3)
Summer	34 (20.6)
Autumn	50 (30.3)
Winter	36 (21.8)
Admission from	
Emergency room	109 (66.1)
Medical ward	23 (13.9)
Another clinic or hospital	33 (20.0)

Based on BP, clinical presentation and/or echocardiographic examination, patients were finally assessed as having: 1) non massive pulmonary embolism – in the absence of systemic hypotension and right ventricular dysfunction, 2) submassive pulmonary embolism – with right ventricular dysfunction but normal BP and 3) massive pulmonary embolism – those presenting with hypotension or cardiogenic shock and signs of right ventricular dysfunction. For final confirmation of the pulmonary arteries embolization either high-probability ventilation/perfusion (V/Q) lung scan or MDCT were used. Patients under the age of 75 years with symptoms of massive pulmonary embolism admitted within 24 hours and no risk for major bleeding (contraindications were followed according to the Guidelines on diagnosis and management of acute pulmonary embolism[3] from 2000) were treated with thrombolytics (streptokinase, loading dose: 250,000 IU over 30 minutes, followed by 100,000 IU/h over 24 hours). Others received unfractionated heparin (initial bolus of 5,000 IU followed by a continuous infusion of 1,000 IU/h – the dosage monitored by aPTT and adjusted by Raschke nomogram[4]) and later on warfarin tablets (Marivarin, Krka, Novo Mesto, Slovenia).

Statistical analysis

For descriptive purposes, all continuous variables were reported as mean ± standard deviation (SD), or median and corresponding range for variables with non-Normal distribution. Qualitative variables were presented as frequency tables, and differences tested using chi-square (χ^2) test while variables with inhomogeneous variances were tested by Kruskal-Wallis test. P values of <0.050

were considered significant. Statistical analysis was performed with the Statistical Package for Social Sciences, version 10.0 for Windows Release (SPSS, Chicago, IL, USA).

Results

Overall, authors went through hospital records of 214 patients admitted to the ICU with suspected diagnosis of acute pulmonary embolism. After the exclusion process, 165 records (77.1%) remained for final analysis, Figure 1. Demographic data regarding age, sex and data on hospital admissions for pulmonary embolism are numbered in Table 1.

In our patient population dyspnea was the most prominent symptom (97.0%). Tachypnea was present in 69.6% and chest pain in 35.8% (Table 2). Patients were differently responsive to the symptoms. Fifty-two of them (31.5%) came to hospital within eight hours of the onset of symptoms but 58 (35.2%) came after three or more days though having symptoms. At the time of diagnosis heart rate was above 100 beats per minute in 52.7% of patients and systolic BP was below 90 mmHg in 24.2% of patients (Table 2). Clinical signs of right ventricular overload according to the aforementioned criteria are listed in Table 2.

Patients were analyzed according to chronic heart and lung disease. Fifty-eight percent had hypertension, 28.5% history of congestive heart failure, 11.5% coronary artery disease and 9% chronic obstructive pulmonary disease. Fifty two patients had more than one chronic condition.

To achieve the final diagnosis and confirm the pulmonary embolism several diagnostic tools were used (Table 3). Sinus tachycardia, $S_1Q_3T_3$ pattern and inversion of the T wave were the most frequently found signs on ECG while the most common abnormality found on chest X-ray were pleural effusion in 13.3%, elevated hemidiaphragm in 9.1% and infiltrate in 7.3%. D-dimer testing was done in 147 patients (89.1%), with a mean value 3.60 ± 3.89 mg/L. D-dimer levels were normal in 13,3% of patients.

TABLE 2
CLINICAL PRESENTATION OF PATIENTS WITH PULMONARY EMBOLISM ON ADMISSION

Signs and symptoms*	Number (%) of patients (n=165)
Dyspnea	160 (97.0)
Tachypnea (>18 breaths/min)	115 (69.6)
Chest pain	59 (35.8)
Cough	36 (21.8)
Syncope	31 (18.8)
Hemoptysis	4 (2.4)
Hypotension (systolic BP<90 mmHg)	40 (24.2)
Tachycardia (HR>100 beats/min)	87 (52.7)
Clinical signs of RV overload	
S3	13 (7.9)
Distended neck veins	25 (15.2)
Accentuated P2	8 (4.8)
Tricuspid regurgitation	16 (9.7)

* Abbreviations: BP – blood pressure, HR – heart rate, RV – right ventricle, S3 – third heart tone, P2 – pulmonary component of second heart tone

Duplex scan sonography of the lower extremities was performed in 70 patients (42.4%) and 20% had no evident deep vein thrombosis (Table 4). There was no significant difference in affection of either the left or right leg. Ventilation/perfusion lung scintigraphy was performed in 109 patients (66.1%) and pulmonary embolism found to be

TABLE 4
DUPLEX SCAN SONOGRAPHY OF VEIN CIRCULATION ON LOWER EXTREMITIES

Thrombosis	Number (%) of patients (n=70)
Lower leg	20 (28.6)
Upper leg	24 (34.3)
Pelvic	12 (17.1)
None	14 (20.0)

TABLE 3
DIAGNOSTIC INVESTIGATIONS USED TO DETECT THE LIKELIHOOD OF PULMONARY EMBOLISM

Diagnostic investigation*	Number of patients, n=165			
	Yes	No	Percentage obtained	mean ± SD†
ECG	165	0	100.0	–
Chest X-ray	162	3	98.2	–
Ventilation – perfusion lung scintigraphy	109	56	66.1	–
MDCT	9	156	5.4	–
D-dimer (mg/L)	147	18	89.1	3.6 ± 3.9
Duplex scan	70	95	42.4	–

* Abbreviations: ECG – electrocardiogram, MDCT – multidetector computed tomography
† when applicable

TABLE 5
RISK FACTORS FOR PULMONARY EMBOLISM ACCORDING TO OUTCOME (SURVIVAL)

Risk factor*	Patients number (%)			p†
	Total (n=165)	Survivors (n=114)	Non-survivors (n=51)	
Prolonged bed rest	49 (29.7)	25 (21.9)	24 (47.1)	0.002
Malignancy	45 (27.3)	24 (21.1)	21 (41.2)	0.009
Obesity	40 (24.2)	31 (27.2)	9 (17.7)	0.191
Operation (within 1 month)	36 (21.8)	30 (26.3)	6 (11.8)	0.034
History of DVT	30 (18.2)	27 (23.7)	3 (5.9)	0.004
History of PE	11 (6.7)	8 (7.0)	3 (5.9)	0.824
Coagulation disorder	5 (3.0)	5 (4.4)	–	–
Positive family history	5 (3.0)	5 (4.4)	–	–
Postpartal PE	2 (1.2)	2 (2.5)‡	–	–
OCT or HRT	1 (0.7)	1 (1.3)‡	–	–

* Abbreviations: DVT – deep vein thrombosis, PE – pulmonary embolism, OCT – oral contraceptive therapy, HRT – hormone replacement therapy
† χ^2 test – $p<0.050$ is considered statistically significant
‡ n=80 (female survivors)

highly probable in 88.9% of patients and of medium probability in 11.1%. Pulmonary embolism was confirmed by MDCT in only nine patients (5.4%) and solely in 2005 when this method was introduced to our hospital. The remaining 47 patients (28.5%) were treated for pulmonary embolism and included in the study although the diagnosis was not confirmed by the above mentioned techniques but was based on clinical presentation, ECG, and/or echocardiography and positive D-dimer testing.

In-hospital mortality was 30.9%. A post mortem was performed on 30 patients (58.8%) and the initial diagnosis of pulmonary embolism confirmed in 24 of these patients. There was no statistical difference in mortality between male and female patients (30.6%:31.0%), p=0.965. Reduced mobility, recent operation, history of deep vein thrombosis or malignoma, on the other hand, were shown to influence survival, Table 5.

Prolonged bed rest, malignancy and obesity (body mass index >30 kg/m^2), were the most common risk factors recorded among our patient population (Table 5). Thirty five women were considered obese as opposed to only five men (21.2% and 3.0%, respectively, p=0.005). Twenty percent (33 patients) had no evident predisposition for developing pulmonary embolism. Post-operative pulmonary embolism encountered in 21.8% of patients was seen particularly after abdominal operation or trauma. Out of 56 patients that were admitted from other medical wards or another Clinic or hospital, 33 of them (58.9%) received low molecular weight heparin (LMWH) prophylaxis.

Based on clinical judgment and echocardiography (if performed), pulmonary embolism was regarded as massive in 63 (38.2%), submassive in 23 (13.9%), and non massive in 79 patients (47.9%). The highest death rate (64.7%) was in the group with massive pulmonary embolism. Mortality in the two other groups was 19.6% and 15.7%, respectively.

Ninety-two percent of patients received heparin and only five (3%) were eligible for thrombolytic therapy with streptokinase. Three patients had minor bleeding as a complication (hematoma on puncture site). The average ICU stay of survived patients was 7.1 ± 4.4 days, (median 6, range 1–26 days). One hundred and ten survivors out of 114 (96.5%) were discharged with oral anticoagulant therapy. The average weakly dose of warfarin was 23.9 ± 11 mg.

Discussion

To the best of our knowledge, there is no national registry for pulmonary embolism in Croatia, nor has there been a study published, that would systematically describe main epidemiological characteristics of such patients. Therefore, by collecting data regarding demographic and clinical characteristics of patients with pulmonary embolism and analyzing this data we hoped to gain insights on the effect of certain predisposing factors on patients survival and our ability to make a timely diagnosis, to treat successfully and prevent it when possible.

Our results show that more female patients were hospitalized and treated for pulmonary embolism which is contrary to some findings already described by both Anderson et al.[5] and Silverstein et al.[6]. They found a slightly higher incidence of pulmonary embolism in men than in women. Our female patients were heavier but in order to say whether obesity was responsible for higher incidence of pulmonary embolism in women further studies should be conducted. Pregnancy or oral contraceptive use/hormone replacement therapy, were of no statistical significance in the incidence of this thromboembolic incident. Another thing we noticed was the statistically significant

difference between survivors and non survivors in connection to the risk factors recorded on admission (prolonged bed rest, malignancy, an embolic incident following surgery or the history of deep vein thrombosis), which is consistent with findings of White[7]. The presence of these risk factors should guide physicians to consider the possibility of PE before it actually occurs and initiate thromboprophylaxis. Seasonal variations that were described by Boulay et al.[8], with a higher incidence of fatal pulmonary embolism during winter, were not observed in our patients, probably due to the predisposing factors already mentioned.

It has been said that to diagnose pulmonary embolism one has to think of it first. That is why some cases remain unrecognized and are found on autopsy only. There is no doubt that early diagnosis reduces mortality[9]. Unfortunately the clinical presentation is not always typical as there is no pathognomonic sign that would unequivocally prove the diagnosis. Modern techniques such as MDCT may certainly help. We used Wells criteria for the likelihood of PE and if there was a high clinical suspicion (Wells score >4.0), D-dimer value guided the diagnostic and therapeutical decision[10]. The low rate of MDCT confirmed pulmonary embolism in our study was mainly due to the late implementation of this method at our hospital (in 2005) as well as to contraindications for the use of radiocontrast or significant renal impairment. The majority of our patients had a V/Q lung scan performed to obtain the correct diagnosis. PIOPED I study showed that high probability V/Q lung scan is a sufficient evidence to treat the patient for PE[11]. Only in case of hemodynamic instability or severe respiratory failure the V/Q lung scan was not performed. Continuous monitoring of these patients and their clinical improvement under therapy supported our judgment of pulmonary embolism and validated the initial treatment. Another finding that led us to the same conclusion was that one fifth of post mortem results in patients with pulmonary embolism confirmed *in vivo*, didn't show thrombi within the pulmonary circulation, which may have indicated either spontaneous or therapeutical resolution of thrombi.

The analysis of hospital records showed a small proportion of patients being clinically assessed for signs of right ventricular overload. It seems we mainly rely on technical aids instead of physical exam we have all been trained to do. Duplex scan sonography which may identify deep vein thrombosis has been underused, according to our hospital records, for the past five years. There are several reasons for this. The procedure was instituted at our hospital in year 2000 and some time was required to improve our skills. At present, there are only two specialists at our hospital who are able to perform the examination on both hospitalized and ambulatory patients and there is only one Duplex scan sonograph. A demand is huge but our possibilities are limiting. Therefore sometimes, when there is clinical evidence of deep vein throm-

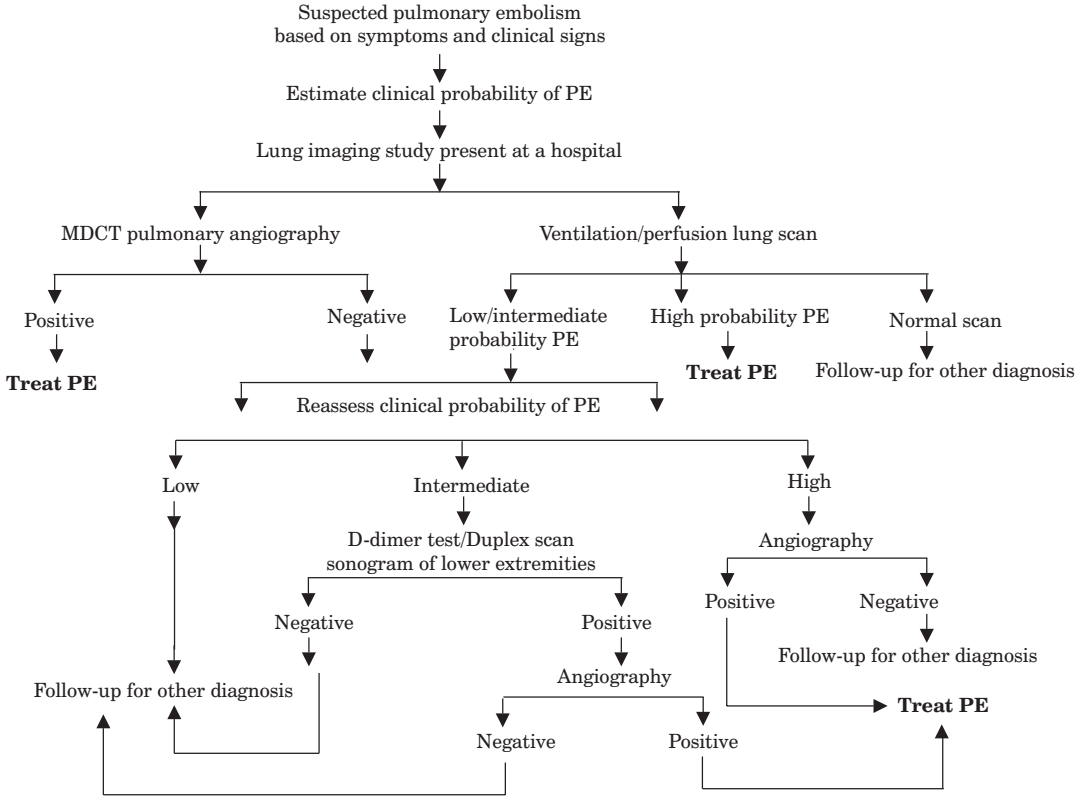

Fig. 2. A proposed algorithm of pulmonary embolism diagnostics in hospitals with or without multidetector computed tomography. PE – pulmonary embolism, MDCT – multidetector computed tomography.

bosis in the PE settings, duplex scan sonography is omitted from the usual workup.

Although a number of risk factors have been described, occasionally the clinician is unable to identify the underlying cause for pulmonary embolism. Calf vein thrombosis poses a risk, though a lower one[12]. Our study showed that deep vein thrombosis often results in pulmonary embolism with no regard to the localization in the lower or upper leg. As seen in the study, only 58.9% of patients after major surgery (such as hip fracture or hip replacement), which immobilizes a patient for a longer period, received heparin prophylaxis. Surgeons' knowledge and attitude towards the significance of thromboembolic incidents is partially responsible, so one of our goals is to emphasize the importance of perioperative thromboprophylaxis and help improve prevention and recognition of thromboembolic incidents on other wards.

Despite modern methods of diagnosis and treatment pulmonary embolism continues to have an unacceptably high mortality[13]. This may be partly because of the advanced age as well as co-morbidity in such patients or high number of malignant diseases in terminal phase. It is of utmost importance to identify patients at high-risk for an unfavorable outcome and treat them more aggressively, if appropriate. It is essential to point out the fact that in Croatia alteplase is not registered medication for treatment of pulmonary embolism. Following the contraindications for the use of thrombolytics strictly and bearing in mind that the population studied was an elderly one (mean age 69 years), the number of patients eligible for the thrombolytic therapy was rather small and that may explain high death rate in massive pulmonary embolism of 64.7%. Though similar rates, 65% (patients in need of CPR), and 58.3%, were reported by Kasper S. et al.[14] and by Goldhaber et al.[13], respectively. The overall in-hospital mortality of 30.9% does not differ a lot from the data published so far (21–32%)[5,8,15].

Pulmonary embolism is not rare and can be fatal. Understanding the epidemiology of the disease might help us improve our care regarding the early diagnosis and deciding on the appropriate treatment for the benefit of our patients. According to the data of this study we propose a diagnostic algorithm of PE for hospitals with or without MDCT availability (Figure 2).

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EPIDEMIOLOŠKI POKAZATELJI I DIJAGNOSTIČKI PRISTUP BOLESNIKU S AKUTNOM PLUĆNOM EMBOLIJOM U KLINIČKOJ BOLNICI

SAŽETAK

Cilj ove retrospektivne studije bio je procijeniti demografske i kliničke karakteristike bolesnika s plućnom embolijom liječenih u internističkoj jedinici intenzivnog liječenja (JIL) u Kliničkoj bolnici tijekom šestogodišnjeg perioda, s procjenom značaja pojedinih rizičnih čimbenika na njihovo preživljenje. U studiju je uključeno 165 bolesnika, prosječne dobi 69,3 ± 13,7 godina, 70,3% ispitivane populacije su činile žene. Kao najčešći simptom zabilježena je dispneja (97,0%), a kao najčešći klinički znak tahipneja (69,6%). Plućna je embolija dokazana ventilacijsko-perfuzijskom scintigrafijom pluća ili multidetektorskom kompjuteriziranom tomografijom u 71,5% bolesnika, stratificiranih u skupine s masivnom plućnom embolijom (63 bolesnika – 38,2%), submasivnom (23 bolesnika – 13,9%) i ne masivnom plućnom embolijom

(79 bolesnika – 47,9%). Prosječno trajanje liječenja u JIL iznosilo je 5,7 ± 4,4 dana, a ukupno 14,8 ± 9,1 dana. Smrtnost u JIL iznosila je 26,7%, a cjelokupna bolnička smrtnost 30,9%. Nije nađeno statistički značajne razlike u smrtnosti bolesnika po spolu (30,6%:31,0%, p=0,965), dokazan je statistički značajan utjecaj dugotrajne imobilizacije (p=0,002), nedavnog operativnog zahvata (p=0,034) i maligne bolesti (p=0,009) na ishod liječenja. Iako su definirani različiti rizični čimbenici za nastanak plućne embolije, te je uz ranu mobilizaciju bolesnika predložena i profilaksa heparinom u cilju smanjenja incidencije, ova bolest je i dalje značajan klinički i epidemiološki problem s visokom smrtnošću. Dijagnostički postupak ne smije odlagati početak liječenja.