

# Malignant Tumor Is the Greatest Risk Factor for Pulmonary Embolism in Hospitalized Patients: A Single-Center Study

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## Research

**Keywords:** Venous thromboembolism, Pulmonary embolism, Gynecological cancer

**Posted Date:** December 29th, 2020

**DOI:** <https://doi.org/10.21203/rs.3.rs-134987/v1>

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# Abstract

## Background

This study aimed to investigate the background of patients who presented with pulmonary embolism (PE) on contrast-enhanced chest computed tomography (CT) and to explore the risk factors for PE.

## Methods

This study included a review of the medical records of all 50,621 patients who were admitted to one community hospital between January 1, 2013 and December 31, 2017. Data on sex, age, risk factors related to blood flow stagnation (obesity, long-term bed rest, cardiopulmonary disease, cast fixation, long-term sitting), risk factors related to vascular endothelial disorder (surgery, trauma/fracture, central venous catheterization, catheter tests/treatments, vasculitis, antiphospholipid antibody syndrome, history of venous thromboembolism (VTE)), and risk factors related to hypercoagulability (malignant tumor, use of oral contraceptives/low-dose estrogen progestin/steroids, infection, inflammatory enteric disease, polycythemia, protein C or protein S deficiency, dehydration) were evaluated.

## Results

Of all inpatients, 185 (0.37%) were diagnosed with PE after contrast-enhanced chest CT examination. The rate of discovering PE was significantly greater in women (0.48%, 93/19,409) than men (0.29%, 92/31,212) ( $P=0.0008$ ). Of the 185 patients with PE, 173 (94%) had some type of risk factor. For both men and women, the most frequent risk factor was a malignant tumor, followed by infection and obesity for men and long-term bed rest and obesity for women. The most common malignant tumor was lung cancer. Of the 12 patients whose clear PE-inducing factor could not be identified, but there is possible involvement of antipsychotic agent.

## Conclusions

The risk factors for PE were identified in this single-center, retrospective study.

## Background

The mortality of patients who develop acute pulmonary embolism (PE) is high, at 4.1–14.5% [1–3], indicating the seriousness of the condition. The mechanism of onset is as follows: first, the free-floating blood clots formed in the deep vein or right atrium rapidly occlude the pulmonary artery, and over 90% of the cases are caused by deep vein thrombosis (DVT) formed in the lower limbs or pelvis [4, 5]. Factors that cause venous thromboembolism (VTE), as proposed by Virchow in 1856 are (1) blood flow stagnation, (2) vascular endothelial disorder, and (3) hypercoagulability [6]. Numerous underlying conditions affect the onset of PE, and PE occurs in patients admitted to various departments. However, most reports of PE in Japan include cases from only a single department. This study aimed to investigate

the background of patients who presented with PE on contrast-enhanced chest computed tomography (CT) and to explore the risk factors for PE.

## Methods

This study included all 50,621 patients who were admitted to the Tsukuba Medical Center Hospital between January 1, 2013 and December 31, 2017. A retrospective examination of medical records was conducted to extract data on sex, age, risk factors related to blood flow stagnation (obesity, long-term bed rest, cardiopulmonary disease, cast fixation, long-term sitting), risk factors related to vascular endothelial disorder (surgery, trauma/fracture, central venous catheterization, catheter tests/treatments, vasculitis, antiphospholipid antibody syndrome, history of VTE), and risk factors related to hypercoagulability (malignant tumor, use of oral contraceptives/low-dose estrogen progestin/steroids, infection, inflammatory enteric disease, polycythemia, protein C or protein S deficiency, dehydration). Long-term bed rest and long-term sitting are not defined clearly, but the patients had more than 24 hours bed rest or 6 hours sitting in the present study. For patients with multiple risk factors, each factor was counted separately for the analysis. For patients with a malignant tumor, the frequency of PE was calculated by cancer type. The  $\chi^2$  test was used for analysis, and  $P < 0.05$  was considered significant.

Our hospital is a 453-bed community hospital primarily equipped to handle emergency medicine. Emergency admission to the cardiology and neurology departments is relatively common, and perinatal conditions are not handled. This study was approved by the institutional review board at Tsukuba Medical Center Hospital.

## Results

Of all inpatients, 185 (0.37%) were diagnosed with PE after contrast-enhanced chest CT examination. The rate of discovering PE was significantly greater in women (0.48%, 93/19,409) than men (0.29%, 92/31,212) ( $P = 0.0008$ ). Table 1 show the number of patients with PE by sex and age group.

Table 1  
Distribution of the number of patients by age and sex

Age(y)	Male(%)	Female(%)
10–19	1(1)	0(0)
20–29	1(1)	1(1)
30–39	8(9)	2(2)
40–49	14(15)	7(8)
50–59	15(16)	11(12)
60–69	18(20)	15(16)
70–79	18(20)	27(29)
80–89	13(14)	24(26)
90–99	4(4)	6(6)

In men, the number of patients increased gradually from the 30 s age group and reached a peak around the 60–70 s age group. In contrast, in women, the number increased from the 40 s age group, with a relatively steep peak at the 70–80 s age group. In men, the rate of discovering PE was not different between those under age 60 years (0.34%, 39/11,609) and those 60 years and older (0.27%, 53/19,603) ( $P= 0.33$ ). In contrast, in women, the rate was significantly greater in those 60 years and older (0.65%, 72/11,009) than in those under 60 years of age (0.25%, 21/8,400) ( $P < 0.0001$ ).

Of the 185 patients with PE, 173 (94%) had some type of risk factor (Table 2).

Table 2  
Patient's characteristics(n = 185)

<b>Sex(%)</b>	
Male	92(50)
Female	93(50)
Median(range)	
Age, years	69.5(17–99)
Body mass index (BMI), kg/m <sup>2</sup>	22.85(14.20-34.35)
n of patient's risk factor (%)	248
BMI ≥ 25 kg/m <sup>2</sup>	38(15)
Long-term bed rest	35(14)
Sitting for a long time	5(2)
Cardiopulmonary disease	9(4)
Trauma, Fracture, Cast fixed	19(8)
Central venous catheter	1(0)
Surgery	12(5)
Antiphospholipid antibody syndrome and collagen disease	9(4)
Past medical history of VTE	2(1)
Cancer	48(19)
OCs, LEP, Steroids	8(3)
Infection	35(14)
Inflammatory enteric disease	3(1)
Polycythemia	2(1)
Protein C or S deficiency	2(1)
Dehydration	8(3)
No risk factor	12(5)

Although there were no significant differences between men and women in the percentage of patients with each PE risk factor, long-term bed rest was more common in women, at 16%, compared with men, at 12%, and trauma/fracture/cast fixation was more common in men, at 10%, than in women, at 6%. A total of 35 (92%) obese patients had another risk factor. For both men and women, the most frequent risk

factor was a malignant tumor, followed by infection and trauma/fracture/cast fixation for men and long-term bed rest and infection for women. The risk factor for the development of PE could not be identified in 12 patients (Table 3).

Table 3  
The risk factors of patients diagnosed with PE

	<b>Risk factor</b>	<b>Male (%)</b>	<b>Female (%)</b>	<b>P-value</b>
Blood flow stagnation	Obesity	20(16)	18(14)	0.015
	Long-term bed rest	15(12)	20(16)	0.043
	Cardiopulmonary disease	3(2)	6(5)	0.042
	Trauma, Fracture, Cast fixed	12(10)	7(6)	0.063
	Central venous catheter	0(0)	1(1)	1.00
	Sitting for a long time	2(2)	3(2)	1.00
	Vascular endothelial disorder	Surgery	5(4)	7(6)
Antiphospholipid antibody syndrome and collagen disease		6(5)	3(2)	0.045
Past medical history of VTE		1(1)	1(1)	1.00
Hypercoagulability	Cancer	24(20)	24(20)	1,00
	OCs, LEP, Steroids	2(2)	6(5)	0.067
	Infection	19(15)	16(13)	0.026
	Inflammatory enteric disease	1(1)	2(2)	1.00
	Polycythemia	1(1)	1(1)	1.00
	Protein C or Protein S deficiency	2(2)	0(0)	1.00
	Dehydration	3(2)	5(4)	0.021
	No risk factor	7(6)	5(4)	0.021

Of the 48 patients with PE and a malignant tumor, patients with lung cancer were the most common, accounting for 35% of the 48 patients. The rate of discovering PE by cancer type was greatest in ovarian cancer, at 3.3%, followed by endometrial cancer, at 2.4% (Table 4). The rate of discovering PE in ovarian cancer was not significantly different from that of endometrial cancer, gallbladder cancer, and lung cancer, but it was significantly greater compared with that of colon cancer, stomach cancer, breast cancer, prostate cancer, kidney cancer, and cervical cancer ( $P = 0.0001$  to  $0.01$ ).

Table 4  
Numbers and incidence of patients with PE by each cancer type

Cancer type	Number of hospitalized patients	Number of patients with PE(%)
Ovarian cancer	152	5(3.3)
Endometrial cancer	122	3(2.4)
Gallbladder cancer	89	2(2.2)
Lung cancer	1.258	17(1.4)
Colon cancer	1.177	9(0.8)
Gastric cancer	693	3(0.4)
Breast cancer	1.109	5(0.5)
Prostate cancer	881	3(0.3)
Kidney cancer	816	1(0.1)
Cervical cancer	287	0(0)

Of the 12 patients whose clear PE-inducing factor could not be identified, one had a mental illness and was taking an antipsychotic agent.

## Discussion

Although there are conflicting reports that the incidence of PE is higher in men [7, 8] or is not different between men and women [9], the incidence is 1.5-fold higher in Japanese women than men, peaking in the 60–70 s age group [10]. The present results also showed that the discovery rate was greater in women and peaked around the 60–70 s, corroborating previous reports from Japan. PE is thought to more likely occur in older individuals than in younger individuals because the morbidity of underlying conditions, such as cerebrovascular disease/neurological disease, long-term bed rest from a lumbar compression fracture, malignant tumor, and bacterial infections including aspiration pneumonia/pyelonephritis, that are likely to cause VTE increases with increasing age. In particular, in postmenopausal women, events such as cardiovascular diseases and fractures increase rapidly, and this is considered to be the reason why PE is frequently observed in older women.

In PE patients with a malignant tumor, lung cancer was the most common tumor. This is because patients with lung cancer are the most common cancer inpatients at our hospital, and because smoking, a risk factor for lung cancer [11], is also a risk factor for VTE [12]. Thus, this was an expected outcome. Analysis of the PE discovery rate by cancer type showed that patients with ovarian cancer had the highest rate. Before treatment, PE was discovered in 8.8–13.3% of ovarian cancer [13, 14], 3.0–4.7% of endometrial cancer [13, 15], 1.1–1.4% of cervical cancer [13, 16], and 2.9% of advanced pancreatic cancer [17] cases. Moreover, whereas PE was not discovered in bladder cancer or stomach cancer cases, DVT

was found in 13.9% and 4.4% of the patients, respectively [18]. VTE is common in ovarian cancer due to vascular dehydration caused by ascites [19] and venous compression by a large tumor [20]. In clear cell carcinoma, Factor VII is activated via the extrinsic blood coagulation pathway, leading to the production of tissue factors that augment coagulation [21, 22], and this is thought to be one of the causes for high VTE rates.

Of the 12 patients whose general risk factors related to PE could not be identified, one had a mental illness and was taking atypical antipsychotics. Antipsychotics are known to induce pulmonary vasospasm and contraction, as well as platelet aggregation via the serotonin-like action of 5HT<sub>2</sub>/D<sub>2</sub> antagonists [23]. Taking antipsychotics for more than 24 months increases the risk for VTE by 32%, and by 73% with atypical antipsychotics [24]. In Japan, the Ministry of Health, Labour and Welfare in 2010 recommended the addition of PE and DVT as serious side effects to the package inserts of antipsychotics such as haloperidol, blonanserin, clozapine, and risperidone. The use of antipsychotics should perhaps be noted as a risk factor for VTE.

## Conclusions

In our hospital, the rate of discovering PE was high in women who were at least 60 years old. In 94% of the cases, some type of risk factor for onset was identified. The most frequently observed risk factor was a malignant tumor. Lung cancer was the most common by the number of patients, and ovarian cancer was the highest by frequency of discovery. Other risk factors were infection, obesity in men, and long-term bed rest and obesity in women. 92% of obese patients had another risk factor. Antipsychotic drugs may have been associated with PE in some patients whose risk factors could not be identified.

Though there are limitations with this single-center retrospective study, it demonstrated the risk factors for PE in patients who presented with PE.

## Abbreviations

PE
Pulmonary embolism
CT
Computed tomography
VTE
Venous thromboembolism
DVT
Deep vein thrombosis
BMI
Body mass index
OCs
Oral contraceptives

## Declarations

**Ethics approval and consent to participate:** This study was approved by the institutional review board at Tsukuba Medical Center Hospital.

**Consent for publication:** Not applicable

**Availability of data and materials:** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests.

**Funding:** This work was supported by JSPS KAKENHI Grant Number JP18K09218 Grant-in-aid for Scientific Research (C).

**Authors' contributions:** AN, KF and NK were involved in study design and data interpretation. AN, KF, NK and TS were involved in the data analysis. All authors read and approved the final manuscript.

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