Pulmonary Embolism is an Important Cause of Death in Young Adults

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Background Population-based analysis shows that deaths from pulmonary embolism (PE) are increasing in the older age groups, but it is unclear to what degree PE contributes to death in different ages and gender.
Methods and Results Potential contribution factors for all PE and for critical PE (in which PE was the primary cause of death or the main diagnosis) were examined in 396,982 autopsy cases. For all PE, odds ratio (OR) in males was 0.61 (95% confidence interval (CI) 0.59–0.64, p<0.0001), compared with that in females. ORs were 1.10 (95% CI 1.05–1.14, p<0.0001) in 1991–1994 and 1.19 (95% CI 1.14–1.25, p<0.0001) in 1995–1998, compared with those in 1987–1990. ORs for ages 0–9 and 40+ were significantly low compared with that for ages 20–39. For critical PE, similar results were obtained. Pregnancy and/or delivery were found in 38.5% in cases of critical PE in females aged 20–39.
Conclusion Compared with other age groups, PE contributed more to deaths in those aged 20–39 years. In recent years, deaths from PE have been slightly but significantly increasing. The incidence of clinically diagnosed critical PE also has been increasing. (*Circ J* 2007; **71:** 1765 – 1770)

Key Words: Age; Delivery; Pregnancy; Pulmonary embolism

The number of deaths from pulmonary embolism (PE) has been increasing in Japan[1] and the incidence of PE in autopsy cases is also reported to have increased from 1958 to 1986[2,3] Population-based analysis shows that deaths from PE are increasing in older age groups but PE is often misdiagnosed[4,5]

There are no reports on the incidence of PE in autopsy cases after 1986 in Japan and the following remain to be solved: (1) to what degree does PE contribute to death in different ages and genders and (2) what factor(s) contributes to diagnosis of PE before death. Therefore, our aims in the present study were to examine the incidence of PE in autopsy cases after 1986, and to clarify these 2 unsolved questions.

Methods

The subjects of the present study included PE cases confirmed by autopsy in Japan between 1987 and 1998[6–17] We excluded cases of pulmonary microembolism with disseminated intravascular coagulation from our analysis. PE was defined as critical (critical PE) when it was the primary cause of death or the main diagnosis and it includes all types of PE. The term "all PE" was used to indicate the total number of thrombotic PEs, tumor PEs, bacterial PEs, mycotic PEs and other emboli (eg, fat, amniotic fluid, etc)[1,8] To make it possible to compare our data with those reported by Mieno et al[3] we analyzed our PE cases according to Mieno's criteria in which cases less than 1 year old and those with non-thrombotic PE were excluded.

Statistical Analysis

Statistical analysis was performed using SPSS 13.0 (SPSS Inc, Chicago, IL, USA). Non-ordinal categorical data using the chi-square test. The results of the logistic regression models and Poisson regression analysis[19] are presented as estimated odds ratios (ORs) with the corresponding 95% confidence intervals (CIs).

Table 1 Embolic Source (n=11,367)

	n (%)
Thrombus	*10,369 (91.2)*
Tumor	*503 (4.4)*
Bacterial or fungal	*247 (2.2)*
Bone marrow	*143 (1.3)*
Fat	*124 (1.1)*
Amnionic fluid	*49 (0.4)*
*Others**	*25 (0.2)*

Some cases had 2 or more sources.
**Air in 8 cases, cholesterin crystal in 6, contrast medium in 2, bone meal in 2 (both after bone fracture), foreign body in 2, and bile, amebic abscess, amyloid, ovum of paracsite, and compression from the aorta in 1 case each.*

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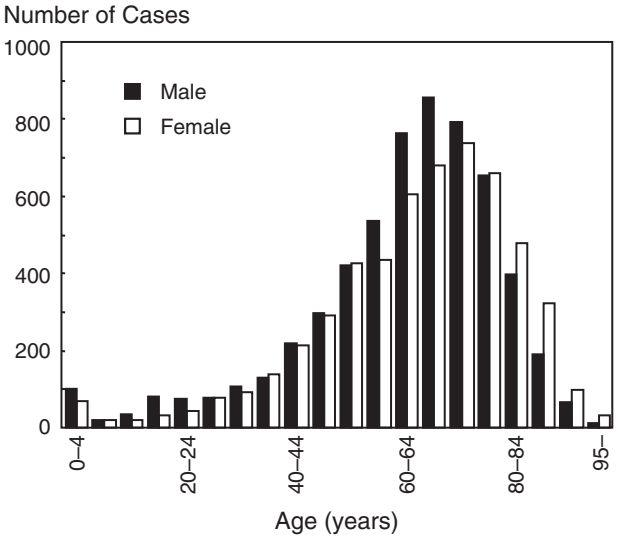

Fig 1. Distribution of autopsy cases with all pulmonary embolisms.

Fig 2. Ratio of autopsy cases of all pulmonary embolism by age (5-year groups) and gender.

Table 2 Number of Cases of PE in Autopsies by Years

Year	*No. autopsies*	*All PE, n (%)*	*Thrombotic PE, n (%)*	*Critical PE, n (%)*	*Clinically diagnosed critical PE, n (%)*
1987	*39,399*	*1,169 (2.97)*	*1,063 (2.70)*	*336 (0.85)*	*46 (13.69)*
1988	*39,333*	*1,028 (2.61)*	*939 (2.39)*	*318 (0.81)*	*48 (15.09)*
1989	*38,439*	*972 (2.53)*	*895 (2.33)*	*299 (0.78)*	*44 (14.72)*
1990	*38,288*	*980 (2.56)*	*885 (2.31)*	*347 (0.91)*	*55 (15.85)*
1991	*36,474*	*1,141 (3.13)*	*1,047 (2.87)*	*430 (1.18)*	*71 (16.51)*
1992	*34,071*	*889 (2.61)*	*797 (2.34)*	*356 (1.04)*	*76 (21.35)*
1993	*31,949*	*1,030 (3.22)*	*946 (2.96)*	*419 (1.31)*	*72 (17.18)*
1994	*28,563*	*726 (2.54)*	*657 (2.30)*	*310 (1.09)*	*43 (13.87)*
1995	*28,682*	*899 (3.13)*	*813 (2.83)*	*426 (1.49)*	*81 (19.01)*
1996	*27,774*	*796 (2.87)*	*743 (2.68)*	*353 (1.27)*	*71 (20.11)*
1997	*27,391*	*857 (3.13)*	*781 (2.85)*	*370 (1.35)*	*81 (21.89)*
1998	*26,619*	*880 (3.31)*	*803 (3.02)*	*399 (1.50)*	*88 (22.06)*

Numbers in parentheses show the percentage incidence in each year.
PE, pulmonary embolism.

Table 3 Univariate Analysis of Risk for PE in Autopsy Cases

Year	*All PE*		*Thrombotic PE*		*Critical PE*		*Clinacally diagnosed critical PE*	
	OR (95%CI)	*p value*	*OR (95%CI)*	*p value*	*OR (95%CI)*	*p value*	*OR (95%CI)*	*p value*
1987–1990	*1.00*		*1.00*		*1.00*		*1.00*	
1991–1994	*1.08 (1.04–1.13)*	*0.0004*	*1.08 (1.03–1.13)*	*0.001*	*1.38 (1.28–1.49)*	*<0.0001*	*1.16 (0.97–1.40)*	*0.11*
1995–1998	*1.16 (1.11–1.22)*	*<0.0001*	*1.17 (1.11–1.23)*	*<0.0001*	*1.68 (1.56–1.80)*	*<0.0001*	*1.40 (1.17–1.67)*	*0.0003*

OR, odds ratio; CI, confidence interval. Other abbreviation see in Table 2.

Results

A total of 11,367 PE cases (2.9%: 5,869 males, 5,474 females, and 24 cases without description of sex) were identified from 396,982 postmortem examinations (249,492 males, 146,484 females, and 1,006 cases without description of sex) between 1987 and 1998.[6–17] We excluded cases without confirmation of the diagnosis. There were 4,363 cases of critical PE (2,097 males, 2,258 females, and 8 without description of sex). Cases of thrombotic PE accounted for 91% of all PE (Table 1). The age distribution of cases with all PE had a peak between 60 s and 70 s for both sexes (Fig 1). The ratio of all PE in autopsy cases by age, however, had a peak in young adults in both sexes (Fig 2). All PE, thrombotic PE, critical PE, and also clinically diagnosed critical PE increased (Tables 2,3). Deep vein thrombosis (DVT) was reported in 1,044 (9.2%) cases among all PE.

As causes of critical PE according to patient age, heart diseases and major operations were prominent from birth to age 9, and almost all of the heart diseases were congenital. In this age group, there were no cases of critical PE diagnosed clinically. Cancer was a risk in many critical PE cases that were older than 10 years. In the 20 s and 30 s, pregnancy and/or delivery were associated with 38.5% of female cases with critical PE, whereas in males fractures and neuromuscular diseases were involved in 16% and 12.3% of cases, respectively (Table 4).

Both all PE and critical PE occurred at low OR in males, including those under the age of 10 years or older than 39 years (Table 5). In the 20–39 years age group, critical PE was found in 2.3% of autopsy cases. ORs of thrombotic PE were 1.08 (95% CI 1.03–1.13; p=0.001) between 1991 and 1994, and 1.17 (95% CI 1.11–1.23; p<0.0001) between 1995 and 1998, when using the data between 1987 and 1990 as the reference. By similar analysis, ORs of critical PE were 1.16 (95% CI 0.97–1.40; p=0.11) between 1991 and 1994, and 1.40 (95% CI 1.17–1.67; p=0.0003) between 1995 and 1998. Both all PE and critical PE according to Mieno's criteria increased year by year (Table 6).

Critical PE was diagnosed more frequently in the presence of DVT, recent major surgery, and more recent cases. On the other hand, it was less frequent in males and in the presence of cancer, heart diseases, chronic respiratory failure, neuromuscular diseases, and connective tissue diseases (Table 7).

Discussion

PE in Young Adults

Population-based analysis has shown that deaths from PE are increasing in older age groups[1] and the present study results supports this finding. But from the viewpoint of incidence in deaths, PE contributed more to deaths in patients between the ages of 20–39 years than in other age groups. The number of deaths was less in this age group than in older age, but PE was more important as the cause of death. As the cause of natural death in the forensic setting, PE comprised 5.0% of the leading causes of death for ages 18–40; that is, higher than in the 41–60-years age group (<2.7% for ages 41–60, and <2.4% for ages 61–80).[20]

One main reason why the ratio of deaths from PE is higher in the 20–39-years age group compared with other ages is that the overall number of deaths in that cohort is low. Another reason is that there are many cases of PE in females resulting from pregnancy/delivery, which are well-known risk factors for PE. The number of PE reported in the fields of gynecology and obstetrics increased 6.5-fold in 2000 compared with 1991.[21] In Japan, the incidence in obstetrics consists of 0.02% of total deliveries, 0.003% of vaginal deliveries, and 0.06% of cesarean deliveries between 1991 and 2000.[21] In the United States PE was attributed to 19.8% of maternal deaths between 1974 and 1978, and 23.4% between 1979 and 1986.[22,23] In forensic cases, 10 deaths were associated with pregnancy, and 3 of those resulted from PE.[24] Of the males in their 20s and 30s, 25% of deaths from PE were associated with a fracture or a neuromuscular disease, which is a higher rate than that in other age groups of males.

PE in Children Aged 0–9

Although pediatric cases of PE are rare, it is suggested that the risk of venous thromboembolism increases when central venous catheters are used.[25,26] The present study revealed that fatal PE was not diagnosed clinically in the 0–9 age group and the results indicate that even in children it is necessary to pay proper attention to the occurrence of PE associated with congenital heart diseases or major operations. Autopsy studies in Western countries have shown an incidence of PE ranging between 0.05% and 4.2% in childhood.[26] The Canadian Registry of Venous Thromboembolism (VTE) indicated that the incidence of VTE in children (ages 1 month to 18 years) was 5.3/10,000 hospital admis-

Table 4 Characteristics inof Autopsy Cases With Critical PE

Age (years)	*0–9*		*10–19*		*20–39*		*40–59*		*60–70*		*80–*	
Gender	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*	*Male*	*Female*
Critical PE	*30*	*20*	*48*	*14*	*162*	*174*	*517*	*584*	*1,080*	*1,099*	*258*	*367*
Clinically diagnosed critical PE	*0 (0.0%)*	*0 (0.0%)*	*4 (3.4%)*	*2 (3.7%)*	*29 (7.4%)*	*49 (14.0%)*	*84 (5.7%)*	*138 (10.1%)*	*152 (5.0%)*	*225 (8.4%)*	*31 (4.5%)*	*62 (6.7%)*
Cancer	*3 (10.0%)*	*4 (20.0%)*	*25 (52.1%)*	*5 (35.7%)*	*41 (25.3%)*	*47 (27.0%)*	*260 (50.3%)*	*285 (48.8%)*	*585 (54.2%)*	*458 (41.7%)*	*114 (44.2%)*	*112 (30.5%)*
Major operation	*16 (53.3%)*	*10 (50.0%)*	*7 (14.6%)*	*4 (28.6%)*	*39 (24.1)*	*57 (32.8%)*	*133 (25.7%)*	*206 (35.3%)*	*297 (27.5%)*	*303 (27.6%)*	*42 (16.3%)*	*50 (13.6%)*
Heart disease	*19 (63.3%)*	*10 (50.0%)*	*6 (12.5%)*	*2 (14.3%)*	*18 (11.1%)*	*17 (9.8%)*	*58 (11.2%)*	*41 (7.0%)*	*170 (15.7%)*	*148 (13.5%)*	*54 (20.9%)*	*69 (18.8%)*
Neuromuscular disease	*1 (3.3%)*	*1 (5.0%)*	*5 (10.4%)*	*1 (7.1%)*	*20 (12.3%)*	*11 (6.3%)*	*50 (9.7%)*	*46 (7.9%)*	*118 (10.9%)*	*130 (11.8%)*	*26 (10.1%)*	*42 (11.4%)*
Fracture	*0 (0.0%)*	*0 (0.0%)*	*2 (4.2%)*	*2 (14.3%)*	*26 (16.0%)*	*6 (3.4%)*	*20 (3.9%)*	*19 (3.3%)*	*26 (2.4%)*	*49 (4.5%)*	*6 (2.3%)*	*19 (5.2%)*
Pregnancy and/or delivery	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*67 (38.5%)*	*0 (0.0%)*	*8 (1.4%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*
*Myocardial infarction**	*1 (5.3%)*	*1 (10.0%)*	*1 (16.7%)*	*0 (0.0%)*	*1 (5.6%)*	*6 (35.3%)*	*36 (62.1%)*	*15 (36.6%)*	*138 (81.2%)*	*100 (67.6%)*	*42 (77.8%)*	*51 (73.9%)*
*Cardiomyopathy**	*0 (0.0%)*	*0 (0.0%)*	*3 (50.0%)*	*0 (0.0%)*	*8 (44.4%)*	*3 (17.6%)*	*10 (17.2%)*	*5 (12.2%)*	*9 (5.3%)*	*9 (6.1%)*	*2 (3.7%)*	*2 (2.9%)*
*Valvular heart disease**	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*2 (11.1%)*	*1 (5.9%)*	*7 (12.1%)*	*7 (17.1%)*	*10 (5.9%)*	*29 (19.6%)*	*4 (7.4%)*	*12 (17.4%)*
*Congenital heart disease**	*18 (94.7%)*	*10 (100.0%)*	*2 (33.3%)*	*2 (100.0%)*	*4 (22.2%)*	*6 (35.3%)*	*2 (3.4%)*	*9 (22.0%)*	*3 (1.8%)*	*5 (3.4%)*	*2 (3.7%)*	*2 (2.9%)*
*Myocarditis**	*0 (0.0%)*	*1 (10.0%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (5.6%)*	*1 (5.9%)*	*0 (0.0%)*	*2 (4.9%)*	*2 (1.2%)*	*2 (1.4%)*	*1 (1.9%)*	*0 (0.0%)*
*Cerebral vascular disease***	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*10 (50.0%)*	*6 (54.5%)*	*36 (72.0%)*	*37 (80.4%)*	*96 (81.4%)*	*109 (83.8%)*	*24 (92.3%)*	*39 (92.9%)*
*Brain tumor***	*0 (0.0%)*	*1 (100.0%)*	*0 (0.0%)*	*1 (100.0%)*	*1 (5.0%)*	*1 (9.1%)*	*6 (12.0%)*	*3 (6.5%)*	*6 (5.1%)*	*6 (4.6%)*	*0 (0.0%)*	*2 (4.8%)*
*Degenerative disease***	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*2 (18.2%)*	*2 (4.0%)*	*1 (2.2%)*	*10 (8.5%)*	*9 (6.9%)*	*1 (3.8%)*	*2 (4.8%)*
*Traumatic brain injury***	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*4 (20.0%)*	*1 (9.1%)*	*3 (6.0%)*	*1 (2.2%)*	*3 (2.5%)*	*4 (3.1%)*	*1 (3.8%)*	*0 (0.0%)*
*Meningitis and/or encephalitis***	*1 (100.0%)*	*0 (0.0%)*	*1 (20.0%)*	*0 (0.0%)*	*1 (5.0%)*	*1 (9.1%)*	*0 (0.0%)*	*1 (2.2%)*	*2 (1.7%)*	*2 (1.5%)*	*0 (0.0%)*	*0 (0.0%)*
*Demyelinating disease***	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (2.0%)*	*0 (0.0%)*	*0 (0.0%)*	*2 (1.5%)*	*0 (0.0%)*	*0 (0.0%)*
*Progressive muscular dystrophy***	*0 (0.0%)*	*0 (0.0%)*	*2 (40.0%)*	*0 (0.0%)*	*2 (10.0%)*	*0 (0.0%)*	*2 (4.0%)*	*1 (2.2%)*	*0 (0.0%)*	*1 (0.8%)*	*0 (0.0%)*	*0 (0.0%)*

**Autopsy cases with critical PE and heart disease; **autopsy cases with critical PE and heart disease.*
Abbreviation see in Table 2.

Table 5 Multivariate Analysis of Risk for PE in Autopsy Cases

	All PE		Critical PE	
	OR (95%CI)	p value	OR (95%CI)	p value
Gender				
Female	1.00		1.00	
Male	0.61 (0.59–0.64)	<0.0001	0.53 (0.50–0.56)	<0.0001
Year				
1987–1990	1.00		1.00	
1991–1994	1.10 (1.05–1.14)	<0.0001	1.41 (1.30–1.51)	<0.0001
1995–1998	1.19 (1.14–1.25)	<0.0001	1.73 (1.60–1.86)	<0.0001
Age group				
0–9	0.14 (0.12–0.16)	<0.0001	0.07 (0.05–0.10)	<0.0001
10–19	0.90 (0.76–1.06)	0.22	0.73 (0.56–0.96)	0.02
20–39	1.00		1.00	
40–59	0.67 (0.62–0.73)	<0.0001	0.57 (0.51–0.65)	<0.0001
60–79	0.56 (0.52–0.60)	<0.0001	0.46 (0.41–0.52)	<0.0001
80–	0.51 (0.47–0.55)	<0.0001	0.41 (0.36–0.47)	<0.0001

Abbreviations see in Tables 2,3.

Table 6 Univariate Analysis of Risk for PE Using Mieno's Criteria

Year	Total PE*		Critical PE*	
	OR (95%CI)	p value	OR (95%CI)	p value
1967–1970	0.28 (0.25–0.30)	<0.0001	0.20 (0.16–0.24)	<0.0001
1971–1974	0.51 (0.47–0.54)	<0.0001	0.31 (0.26–0.36)	<0.0001
1975–1978	0.68 (0.64–0.72)	<0.0001	0.46 (0.40–0.52)	<0.0001
1979–1982	0.64 (0.61–0.68)	<0.0001	0.51 (0.46–0.56)	<0.0001
1983–1986	0.86 (0.82–0.91)	<0.0001	0.88 (0.81–0.96)	0.003
1987–1990	1.00		1.00	
1991–1994	1.07 (1.02–1.12)	0.006	1.39 (1.28–1.50)	<0.0001
1995–1998	1.15 (1.09–1.20)	<0.0001	1.68 (1.55–1.81)	<0.0001

**Mieno's criteria (see details in text).*
Abbreviations see in Tables 2,3.

Table 7 Factors Affecting Clinical Diagnosis of Critical PE

	OR (95%CI)	p value
Age (10-year increments)	1.02 (0.98–1.08)	0.35
Male	0.76 (0.64–0.90)	0.002
Deep vein thrombosis	1.40 (1.11–1.77)	0.004
Major operation	1.31 (1.08–1.59)	0.006
Cancer	0.26 (0.21–0.31)	<0.0001
Heart disease	0.36 (0.27–0.48)	<0.0001
Chronic respiratory failure	0.52 (0.42–0.64)	<0.0001
Neuromuscular disease	0.49 (0.37–0.66)	<0.0001
Connective tissue disease	0.18 (0.07–0.46)	0.0003
Fracture	0.70 (0.48–1.02)	0.07
Pregnancy and/or delivery	1.65 (0.97–2.81)	0.07
Coagulopathy	2.46 (0.85–7.09)	0.09
Year (10-year increments)	1.72 (1.35–2.18)	<0.0001

OR less than 1.00 means more difficult to diagnose clinically.
Abbreviations see in Tables 2,3.

sions or 0.07/10,000 children[27] Thereafter, the Canadian Childhood Thrombophilia Registry showed that 2.2% of children with VTE that was directly associated with deaths, and was central venous line-associated thrombosis.[28]

Incidence of PE

The present study showed that deaths from PE confirmed in autopsy have slightly but significantly increased in Japan, which is consistent with the results from death certificates[1] and in clinical settings.[29–31] Improvement in diagnostic techniques, incremental increase of the geriatric population, and westernization of life style are suggested as factors causing the increase of PE in Japan.[29–31]

The changes in the incidence of autopsy-proven PE by year differ among countries. An autopsy study from Hong Kong documented a rising trend of PE from 1975 to 1989.[32,33] Conversely, the incidence of PE in autopsies reduced in the United States from 1966 to 1980;[34] and in the United Kingdom from 1965 to 2000;[35,36] but a Swedish study indicated that the incidence of PE was unchanged from 1957 to 1987.[37] These differences may be related to differences in clinically diagnostic accuracy, in population structure, in prophylaxis and management of DVT/PE, and in life style.

Rate of Diagnosis of PE

We indicate that the incidence of clinically diagnosed critical PE is increasing, but it was only 22% in 1998. Walden et al showed that, in 425 autopsy cases with PE, 14% was diagnosed before death, 30% was written first on the death certificate, and 56% was revealed in autopsy.[4] Another report indicated that, in 92 cases confirmed as PE by autopsy, 49% was considered as PE before autopsy and the remaining 51% was diagnosed by autopsy. Moreover, PE was assigned as the cause of death on the death certificate or in the medical report in 32% of 92 cases.[5] In recent reports, only approximately 20% of PE confirmed by autopsy was diagnosed clinically.[38,39] On the other hand, there was improvement in the diagnosis of PE in a Swedish study.[40] Taken together, all the results shown indicate that fatal PE is difficult to diagnose before death.

PE was diagnosed before death more accurately in the presence of DVT, recent major operation, and more recent cases, but was difficult to diagnose in association with collagen diseases, cancer, heart diseases, neuromuscular diseases, chronic respiratory failure, and in males. This finding partly confirms the finding that diagnosis of PE delayed in clinical cases, as we previously reported, when cardiac disease or pulmonary diseases exist.[41]

Study Limitations

We could not sufficiently analyze the incidence of DVT in cases with PE. Generally, DVT is found in many cases of PE. DVT was detected in 165 legs (95%) among 174 legs from 87 autopsy cases with PE in a medical examiner's office.[42] Clinically, DVT was found in 84.6% and 87.5% of cases of acute PE on the day it was diagnosed or the next day, respectively.[41] However, in the present study, DVT was found in only 9.2% of cases with PE. The discrepancy between the previous reports and the present study may be related to insufficient examination for DVT in routine autopsy.

Conclusion

Compared with other ages, PE contributed more to deaths in those aged 20–39 years. In recent years, deaths from PE have been slightly but significantly increasing in Japan. The incidence of clinically diagnosed critical PE has also been increasing.

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