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ORIGINAL ARTICLE
Epidemiology

In-Hospital Pulmonary Thromboembolism Development by Disease at Admission

— A Nationwide, Retrospective, Observational Study Using Japanese Claims Data —

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Background: Prevention of death from in-hospital pulmonary thromboembolism (PE) is crucial, but research exploring the risk factors for this event remains limited.

Methods and Results: This retrospective analysis evaluated PE data among hospitalized patients, focusing on the diseases present on admission to hospital with the highest number of patients with in-hospital PE events, using the Medical Data Vision database (January 2017–December 2021). Endpoints included the incidence rate of in-hospital PE, patient characteristics, and PE prophylactic procedures. Overall, 4,684,659 patients (in-hospital PE cohort, n=5,007; non-PE cohort, n=4,679,952) were eligible: heart failure (n=208; n=87,160), femoral fracture (n=478; n=139,049), pneumonia (n=309; n=222,257), stroke (n=351; n=248,805), and cancer (n=934; n=764,413). The incidence rate of in-hospital PE in the overall population was 20.6/1,000 person-years: heart failure (34.6), femoral fracture (35.3), pneumonia (21.4), stroke (15.9), and cancer (25.6). History of venous thromboembolism (VTE) was a risk factor for in-hospital PE in >50% of patients in all subgroups. Prophylactic PE procedures were implemented in 33.8% of the overall population: femoral fracture (79.5%), cancer (49.7%), stroke (24.2%), heart failure (12.7%), and pneumonia (6.2%).

Conclusions: The incidence of in-hospital PE was not high overall but was higher in patients with a history of VTE and those with hospitalization due to heart failure or femoral fracture. Risk assessment for in-hospital PE, including medical history and diagnosis at admission, is preferred in hospitalized patients.

Key Words: Deep vein thrombosis; Inpatients; Patient safety; Pulmonary thromboembolism; Venous thromboembolism

Venous thromboembolism (VTE) is a collective term referring to deep vein thrombosis (DVT) and its sequelae, pulmonary thromboembolism (PE).[1] Approximately 90% of PE episodes occur due to obstruction of the pulmonary artery from an embolus often originating from the lower extremity.[2] Large emboli may lead to obstructive shock and sudden death in patients with low cardiorespiratory reserve.

In Japan, the death rate from an acute PE episode is as high as 11.9%, with early death generally reported after the development of a PE episode.[3] Therefore, early diagnosis followed by appropriate treatment or intervention is required; however, the absence of PE-specific symptoms, physical findings characteristic of PE, and specific diagnostic tests, together with numerous differential diagnoses, make the diagnosis of PE challenging.

The main factors contributing to thrombus formation are stagnation of blood flow, vascular endothelial damage, and hypercoagulability.[4] Approximately half of the risk factors of VTE are associated with stagnation of blood flow.[5] Prolonged hospitalization is a risk factor for VTE as it is often accompanied by decreased patient mobility and surgical procedures. In addition, nonsurgical hospitalized patients may have complications, or experience deterioration of their general condition, which may lead to the development of VTE.[6]

We previously conducted a nationwide, retrospective, database study using claims data and reported the incidence rate of in-hospital PE as 20.6/1,000 person-years among all-cause hospitalizations in Japan; the implementation proportion of PE prophylactic procedures was significantly different between surgical (59.2%) and nonsurgical (7.3%) patients during hospitalization.[7] This finding suggests that there are limited data on PE prevention in Japan, and

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defining appropriate PE prophylactic measures remains challenging, as it is based on protocols followed at each individual institution.[8,9]

This current analysis aimed to evaluate the characteristics of patients with in-hospital PE stratified by diagnosis at admission, focusing on 5 diagnoses that recorded the highest numbers of in-hospital PE cases.

Methods

Study Design

This retrospective, noninterventional, descriptive, database study evaluated in-hospital PE data[7] among hospitalized patients (other than for DVT or PE) using data extracted from the Medical Data Vision (Medical Data Vision Co., Ltd., Tokyo, Japan) administrative claims database.[10] Details of the study design have been previously published.[7] Patients were categorized into a hospitalized cohort (overall population) and subgroups of the 5 relatively common diagnoses at hospitalization with the highest number of patients with in-hospital PE events.

Baseline data were extracted from 6 months before hospitalization. Patient characteristics were evaluated as a surrogate for the risk of PE, and patients were followed up from the date of hospitalization to the date of discharge. The deidentified data evaluated in this study did not report the efficacy and safety of medicines or diseases. Therefore, informed consent from the patients and approval by an Institutional Review Board/Ethical Committee were not required.

Patients/Population

Patients aged ≥20 years who were hospitalized for diseases other than DVT or PE between January 1, 2017, and December 31, 2021, were enrolled. Patients with hospitalization due to heart failure (HF), femoral fracture, pneumonia, stroke, and cancer (using International Classification of Diseases, 10th Revision [ICD-10] diagnostic codes; **Supplementary Table 1**) were included and divided into subgroups because these diagnoses were the most frequently reported as hospitalization causes (diagnoses at admission) in our previous analysis.[7] The 5 subgroups were categorized by the name of the disease that triggered the hospitalization and listed in the descending order of the number of patients involved. Diagnoses other than the one that triggered hospitalization were treated as comorbidities at baseline. Details of the exclusion criteria are presented in **Figure 1** and have been previously published.[7] According to the rules for diagnoses at diagnosis procedure combination (DPC; a case-mix patient classification system designed in Japan that is linked with a lump-sum payment system for inpatients in acute care hospitals, so called DPC per-diem payment system) hospitals, if a patient is diagnosed with HF on admission and PE is found to be the cause for HF during hospitalization, the diagnosis at admission is updated and recorded as PE. Therefore, hospitalizations recorded as HF due to PE were not counted as in-hospital PE events in this study.

Endpoints

Endpoints were evaluated in the overall population and 5 subgroups. These included the incidence proportion (%) and rate (number of events/1,000 person-years) of in-hospital PE; differences in patient characteristics between patients with and without in-hospital PE; activities of daily living (ADL) scores at hospitalization and discharge; cumulative incidence for in-hospital PE, death, and survival at discharge; implementation proportion of PE prophylactic procedures; time to PE development; time to discharge after PE onset; duration of hospitalization; and death rate during hospitalization.

Definitions

In-hospital PE was defined as a new PE event occurring during hospitalization for diseases other than DVT and/or PE; patients with and without a new PE event were categorized into in-hospital PE and non-PE cohorts, respectively. Patients who were hospitalized and discharged from the hospital but readmitted the same or next day with PE were included in the in-hospital PE cohort. A validated algorithm was used for examination, diagnosis, treatment, and follow-up of a PE event.[11] A new PE event during hospitalization was diagnosed using ICD-10 codes (I26.0, I26.9) and confirmed using imaging protocols such as scintigraphy (E100-00) and computed tomography (E200, E2001, E2002, and E2003); PE events listed as comorbidities at admission were excluded.[7,11]

The date of in-hospital PE development was defined as the date of treatment initiation for the PE. Due to the absence of diagnostic codes for asymptomatic and undiagnosed PE, these events could not be captured in this study. The date of in-hospital PE development among patients who developed PE during anticoagulation therapy for thrombus prevention was defined as the date on which the anticoagulant dosage or regimen was changed. Patients who underwent thromboembolectomy or received >5,000 units of heparin (unfractionated heparin), fondaparinux, oral anticoagulants, and thrombolytic agents (urokinase and tissue plasminogen activator) were considered to have been treated for a PE event. Ultrasonography, chest radiography, electrocardiography, and blood gas analysis to evaluate the need for oxygen administration and to monitor respiratory and heart rates within 7 days of treatment for PE were regarded as follow-up examinations for PE.

The New York Heart Association (NYHA) functional classification data used to assess the severity of HF were available only at discharge (not at hospitalization). Barthel Index (BI) data were used to assess physical performance in ADL at the time of hospitalization and discharge.

The implementation of cardiac rehabilitation in patients with HF was defined as the availability of a rehabilitation fee billed/claimed for cardiovascular diseases (H 000-00). Prophylactic procedures for PE were defined as the availability of a prophylactic procedure fee (N 001-6) claim for elastic stockings or an intermittent air compression device for PE prevention; prophylactic anticoagulants were not included. Only postoperative use of approved prophylactic anticoagulants for DVT and/or PE, such as edoxaban ≤30 mg/day (Japan only), recommended doses of enoxaparin or heparin (<5,000 units), and fondaparinux for ≤15 days, was considered as prophylactic interventions. The types of surgeries performed on patients during hospitalization were identified using standard medical procedure coding with "K-codes." Patients who underwent surgery were included as perioperative patients.

Statistical Analysis

All analyses were performed using SAS V.9.4 (SAS Institute Inc., Cary, NC, USA). For each subgroup, patient characteristics are presented as median and mean (standard devi-

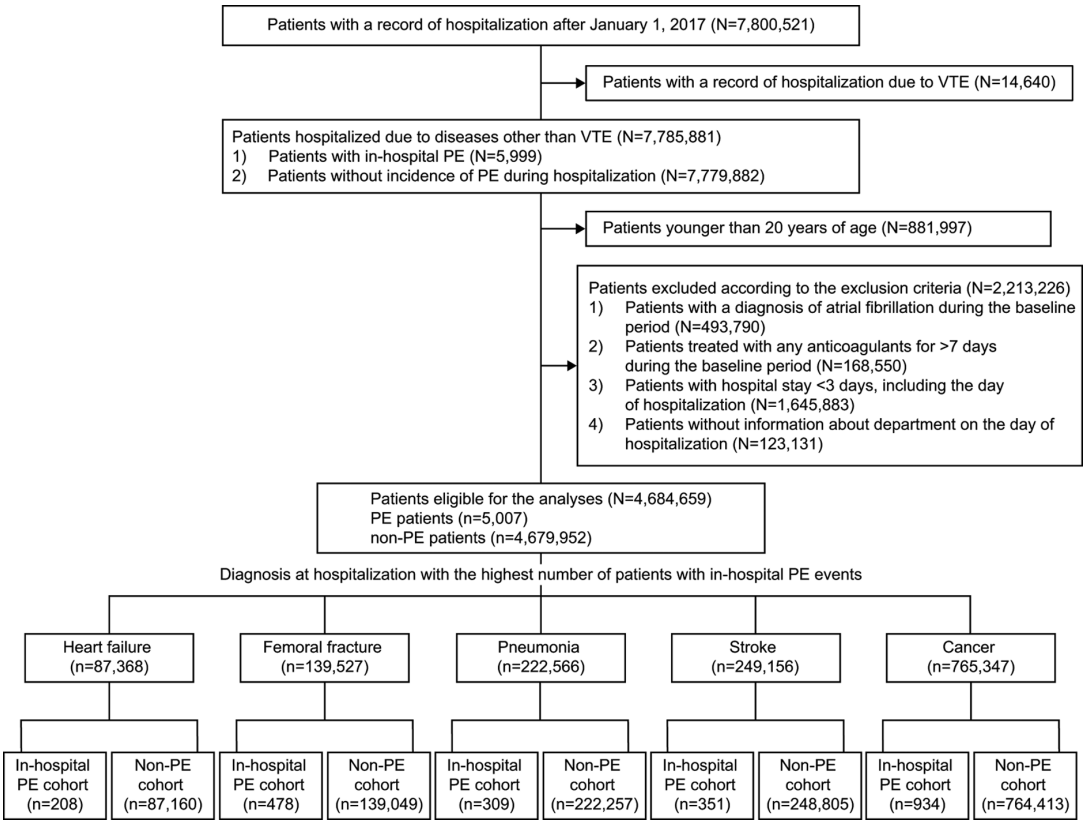

Figure 1. Patient disposition. PE, pulmonary thromboembolism; VTE, venous thromboembolism.

ation [SD]) for continuous variables and percentages (%) for categorical variables. Differences between patients with and without in-hospital PE were evaluated using the standardized difference (std.diff; difference in means or proportions divided by standard error), and imbalance was defined as an absolute value >0.10. The incidence of in-hospital PE was calculated as proportion (%) and rate (number of events/1,000 person-years). The cumulative incidence of in-hospital PE, deaths during hospitalization, and survival at discharge was examined using the cumulative incidence function (CIF). The observation period was defined as the hospitalization period, and the incidence of PE, death, and survival at discharge was counted as the events, whichever occurred first. Administrative censoring was applied only for patients who had hospitalization on day 365. The main purpose of this study was to evaluate the onset of PE during hospitalization. If survival at discharge is used as a censoring point in the Kaplan-Meier method, many patients will fall into censoring, which makes data interpretation difficult. For this reason, we used the CIF to analyze the outcomes of patients with hospitalization, with survival at discharge and death being each event.

The implementation proportion of PE prophylaxis, implementation proportion of cardiovascular rehabilitation, and deaths during hospitalization are presented as percentages. ADL scores at hospitalization and discharge are presented as median and mean (SD) and were compared using the Mann-Whitney U test. Statistical significance was set at $P<0.05$ (two-tailed test). The duration of hospitalization and days to in-hospital PE development are presented as median and mean.

Results

Patient Disposition

Of the 7,800,521 hospitalized patients captured in the primary analysis, 4,684,659 met the eligibility criteria for this analysis and were categorized into 5 groups (in-hospital PE cohort, non-PE cohort): HF (n=208, n=87,160), femoral fracture (n=478, n=139,049), pneumonia (n=309, n=222,257), stroke (n=351, n=248,805), and cancer (n=934, n=764,413; **Figure 1**).

Differences in Patient Characteristics by Subgroup

Heart Failure Among patients hospitalized for HF, characteristics considered different between the in-hospital PE and non-PE cohorts based on std.diff. values >0.1 were as follows: baseline mean (SD) body mass index (BMI), proportion of male and female patients, comorbidities (diabetes, hypertension, and liver disease), comorbidities with risk of PE (varicose veins, history of VTE (DVT, PE), fractures involving the lower extremities, and active cancer), and baseline medications (anticoagulants, nonsteroidal anti-inflammatory drugs (NSAIDs), and anticancer drugs; **Table 1**).

Based on ICD-10 codes, a majority of patients in the HF group had congestive HF, the causes of which could not be

Table 1. Patient Characteristics (Heart Failure Subgroup)

	All patients	Patients with in-hospital PE (in-hospital PE)	Patients without in-hospital PE (non-PE)	std.diff
N	87,368 (100.0)	208 (100.0)	87,160 (100.0)	
Sex				
Male	44,372 (50.8)	71 (34.1)	44,301 (50.8)	0.34
Female	42,996 (49.2)	137 (65.9)	42,859 (49.2)	0.34
Age, years				
Mean (SD)	79.1 (13.8)	78.2 (12.9)	79.1 (13.8)	0.07
Median	83.0	81.5	83.0	
≤65	13,561 (15.5)	32 (15.4)	13,529 (15.5)	0.00
>65–≤75	13,725 (15.7)	35 (16.8)	13,690 (15.7)	0.03
>75	60,082 (68.8)	141 (67.8)	59,941 (68.8)	0.02
BMI (kg/m²)				
N	77,965	188	77,777	
Mean (SD)	23.0 (4.8)	24.0 (5.0)	23.0 (4.8)	0.21
Median	22.3	23.8	22.3	
Comorbidity				
Stroke/TIA	7,257 (8.3)	18 (8.7)	7,239 (8.3)	0.01
Diabetes	31,987 (36.6)	56 (26.9)	31,931 (36.6)	0.21
Hyperlipidemia	31,660 (36.2)	77 (37.0)	31,583 (36.2)	0.02
Hypertension	61,827 (70.8)	130 (62.5)	61,697 (70.8)	0.18
Liver disease	6,421 (7.4)	22 (10.6)	6,399 (7.3)	0.11
Renal disease	3,303 (3.8)	8 (3.9)	3,295 (3.8)	0.00
Comorbidities with risk of PE				
Varicose veins	413 (0.5)	4 (1.9)	409 (0.5)	0.13
History of VTE	2,080 (2.4)	158 (76.0)	1,922 (2.2)	2.31
DVT	1,695 (1.9)	59 (28.4)	1,636 (1.9)	0.80
PE	385 (0.4)	99 (47.6)	286 (0.3)	1.33
Fractures involving the lower extremities	3,459 (4.0)	16 (7.7)	3,443 (4.0)	0.16
Peripheral vascular disease	3,060 (3.5)	9 (4.3)	3,051 (3.5)	0.04
Pregnancy	14 (0.02)	0 (0.0)	14 (0.02)	–
Coagulopathy	83 (0.1)	0 (0.0)	83 (0.1)	–
Active cancer	1,531 (1.8)	13 (6.3)	1,518 (1.7)	0.23
Medicines				
ACE inhibitors/ARBs	72,214 (82.7)	172 (82.7)	72,042 (82.7)	0.00
β-blockers	16,478 (18.9)	34 (16.4)	16,444 (18.9)	0.07
CCBs	20,488 (23.5)	46 (22.1)	20,442 (23.5)	0.03
Anticoagulants	2,894 (3.3)	18 (8.7)	2,876 (3.3)	0.23
Antiplatelet drugs	17,606 (20.2)	39 (18.8)	17,567 (20.2)	0.04
Estrogen hormone agents	60 (0.07)	0 (0.0)	60 (0.07)	–
NSAIDs	4,365 (5.0)	20 (9.6)	4,345 (5.0)	0.18
Statins	13,214 (15.1)	27 (13.0)	13,187 (15.1)	0.06
Anticancer drugs	3,950 (4.5)	31 (14.9)	3,919 (4.5)	0.36

Data are presented as n (%) unless otherwise specified. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; DVT, deep vein thrombosis; NSAID, nonsteroidal anti-inflammatory drug; PE, pulmonary thromboembolism; SD, standard deviation; std.diff, standardized difference; TIA, transient ischemic attack; VTE, venous thromboembolism.

extracted; however, approximately 6% of patients in the in-hospital PE cohort had ischemic HF (surrogate for percutaneous coronary intervention), and there were no records indicating right HF. Cardiac rehabilitation during hospitalization was provided to 34.6% (72/208) of patients with HF prior to in-hospital PE development, and 49.0% (102/208) of patients received cardiac rehabilitation before discharge. In the non-PE cohort, cardiac rehabilitation was provided to 51.9% (45,207/87,160) of patients during hospitalization.

At discharge, NYHA classification data were available for 54 patients in the in-hospital PE cohort and 20,377 in the non-PE cohort. The NYHA classes in the in-hospital PE (I, 5.1%; II, 19.4%; III, 34.5%; IV, 41.0%) and non-PE (I, 5.1%; II, 19.3%; III, 34.6%; IV, 40.7%) cohorts were not significantly different (P=0.6248) at hospital discharge.

Femoral Fracture Among patients hospitalized for femoral fractures, 46.2% (64,421/139,527) had femoral neck fractures and 44.0% (61,341/139,527) had penetrating trochanteric fractures; surgery was performed in 87.2% of patients.

Among these patients, characteristics considered differ-

Table 2. ADL Scores at Hospitalization and Discharge (BI at Discharge)

		ADL scores at hospitalization				ADL scores at discharge			
		All patients	In-hospital PE	Non-PE	P value	All patients	In-hospital PE	Non-PE	P value
All diseases	N	4,629,271	4,986	4,624,285		4,450,930	4,447	4,446,483	
	Mean (SD)	71.5 (39.6)	46.5 (43.4)	71.5 (39.6)		83.8 (31.0)	63.6 (39.4)	83.8 (31.0)	
	Median	100.0	40.0	100.0	<0.0001	100.0	80.0	100.0	<0.0001
Heart failure	N	87,147	208	86,939		79,575	183	79,392	
	Mean (SD)	46.7 (41.2)	43.2 (41.0)	46.7 (41.2)		72.4 (35.2)	69.3 (35.4)	72.4 (35.2)	
	Median	45.0	37.5	45.0	0.1821	95.0	85.0	95.0	0.1015
Femoral fracture	N	139,312	477	138,835		136,700	452	136,248	
	Mean (SD)	18.6 (27.9)	14.8 (23.6)	18.6 (27.9)		49.3 (34.6)	41.7 (32.4)	49.3 (34.6)	
	Median	5.0	5.0	5.0	0.1427	50.0	40.0	50.0	<0.0001
Pneumonia	N	222,247	309	221,938		199,305	272	199,033	
	Mean (SD)	40.9 (42.1)	41.9 (43.1)	40.9 (42.1)		54.9 (42.9)	59.2 (41.8)	54.9 (42.9)	
	Median	25.0	20.0	25.0	0.5712	60.0	75.0	60.0	0.1346
Stroke	N	248,474	350	248,124		235,889	307	235,582	
	Mean (SD)	37.8 (39.6)	18.7 (33.3)	37.8 (39.6)		62.7 (40.2)	33.8 (37.8)	62.8 (40.2)	
	Median	25.0	0.0	25.0	<0.0001	80.0	15.0	80.0	<0.0001
Cancer	N	763,627	930	762,697		711,481	797	710,684	
	Mean (SD)	89.8 (25.5)	83.2 (30.5)	89.8 (25.5)		93.7 (20.0)	85.5 (28.9)	93.7 (20.0)	
	Median	100.0	100.0	100.0	<0.0001	100.0	100.0	100.0	<0.0001

P values represent comparison of medians using the Mann-Whitney U test (Wilcoxon's rank test). The 10 items evaluated as part of the BI are meals, transfer, preparation, toileting, bathing, walking (transfer), stair climbing, menopause, defecation, and urination. Each item was scored at 15, 10, 5, and 0 points according to the degree of independence shown by the patient. The total score reflects 100 points. Patients were considered independent if they scored ≥85 points, partially self-reliant at ≥60 points, requiring assistance at 40 points, and requiring complete assistance at 0 points. ADL, activities of daily living; BI, Barthel Index; PE, pulmonary thromboembolism; SD, standard deviation.

ent between the in-hospital PE and non-PE cohorts based on std.diff. values >0.1 were as follows: age ≤65 years, age >75 years, mean (SD) BMI, comorbidities (congestive HF, hypertension, and liver disease), comorbidities with risk of PE (history of VTE (DVT, PE), fractures involving the lower extremities, and active cancer), and baseline medications (angiotensin-converting enzyme (ACE) inhibitors/angiotensin 2 receptor blockers (ARBs), β-blockers, calcium channel blockers (CCBs), anticoagulants, antiplatelet drugs, and anticancer drugs; **Supplementary Table 2**).

Pneumonia Pneumonia requiring hospitalization was commonly triggered by aspiration pneumonitis caused by food inhalation or vomiting in 33.8% (75,158/222,566) of patients. Pneumonia (unspecified) was recorded in 22.7% (50,425/222,566) and bacterial pneumonia (unspecified) in 18.9% (41,943/222,566) of patients.

Among patients hospitalized for pneumonia, characteristics considered different between the in-hospital PE and non-PE cohorts based on std.diff. values >0.1 were as follows: mean (SD) age (age groups ≤65 years, >65 to ≤75 years, >75 years), mean (SD) BMI, and proportion of patients with comorbidities (congestive HF), comorbidities with risk of PE (varicose veins, history of VTE (DVT, PE), and active cancer), and baseline medications (ACE inhibitors/ARBs, β-blockers, CCBs, anticoagulants, NSAIDs, and anticancer drugs; **Supplementary Table 3**).

Stroke Patients hospitalized for stroke were commonly diagnosed with cerebral infarction due to thrombosis of the cerebral arteries (29.5% [73,462/249,156]), intracerebral hemorrhage (19.6% [48,909/249,156]), miscellaneous cerebral infarction (15.4% [38,294/249,156]), cerebral infarction due to embolism of the cerebral arteries (7.1% [17,701/249,156]), and cerebral infarction (unspecified; 5.2% [12,988/249,156]).

Among patients hospitalized for stroke, characteristics considered different between the in-hospital and non-PE cohorts based on std.diff. values >0.1 were as follows: proportion of male and female patients, mean (SD) age, mean (SD) BMI, proportion of patients with comorbidities (diabetes), comorbidities with risk of PE (history of VTE (DVT, PE), coagulopathy, and active cancer), and baseline medications (ACE inhibitors/ARBs, CCBs, antiplatelet drugs, statins, and anticancer drugs; **Supplementary Table 4**).

Cancer In the in-hospital PE cohort (n=5,007), 176 patients had bronchial or pulmonary cancer, 139 had colorectal cancer, 117 had cancer of the female reproductive organs, 94 had gastric cancer, 73 had secondary cancers, 66 had pancreatic cancer, and 63 had liver, biliary tract, or gallbladder cancer. Using ICD-10 codes, the most common sites of malignant neoplasms were as follows: body of the stomach (5.5% [42,191/765,347]), rectum (4.6% [35,480/765,347]), breast (upper outer quadrant; 4.5% [34,632/765,347]), bronchus and lung (upper lobe, bronchus, or lung; 4.3% [32,580/765,347]), liver and intrahepatic bile ducts (3.9% [29,476/765,347]), bronchus and lung (lower lobe, bronchus, or lung; 3.2% [24,537/765,347]), sigmoid colon (3.2% [24,447/765,347]), and prostate (3.0% [22,974/765,347]).

Among patients hospitalized for cancer, characteristics considered different between the in-hospital PE and non-PE cohorts based on std.diff. values >0.1 were as follows: proportion of male and female patients, mean (SD) BMI, comorbidities (stroke/transient ischemic attack (TIA), congestive HF, hypertension, and liver disease), comorbidities with risk of PE (history of VTE (PE, DVT)), and baseline

Table 3. Incidence of PE by Disease at Hospitalization

Diagnosis at admission	N	PE, n (%)	Person-years up to event or censoring	Incidence rate (1,000 person-years)
All diseases	4,684,659	5,007 (0.11)	242,978.65	20.61
Heart failure	87,368	208 (0.24)	6,019.65	34.55
Femoral fracture	139,527	478 (0.34)	13,527.67	35.33
Pneumonia (including pneumonitis, pneumonia bacterial, and interstitial pneumonia)	222,566	309 (0.14)	14,420.78	21.43
Stroke (all including cerebral hemorrhage and cerebral infarction)	249,156	351 (0.14)	22,076.48	15.90
Cancer	765,347	934 (0.12)	36,427.89	25.64

PE, pulmonary thromboembolism.

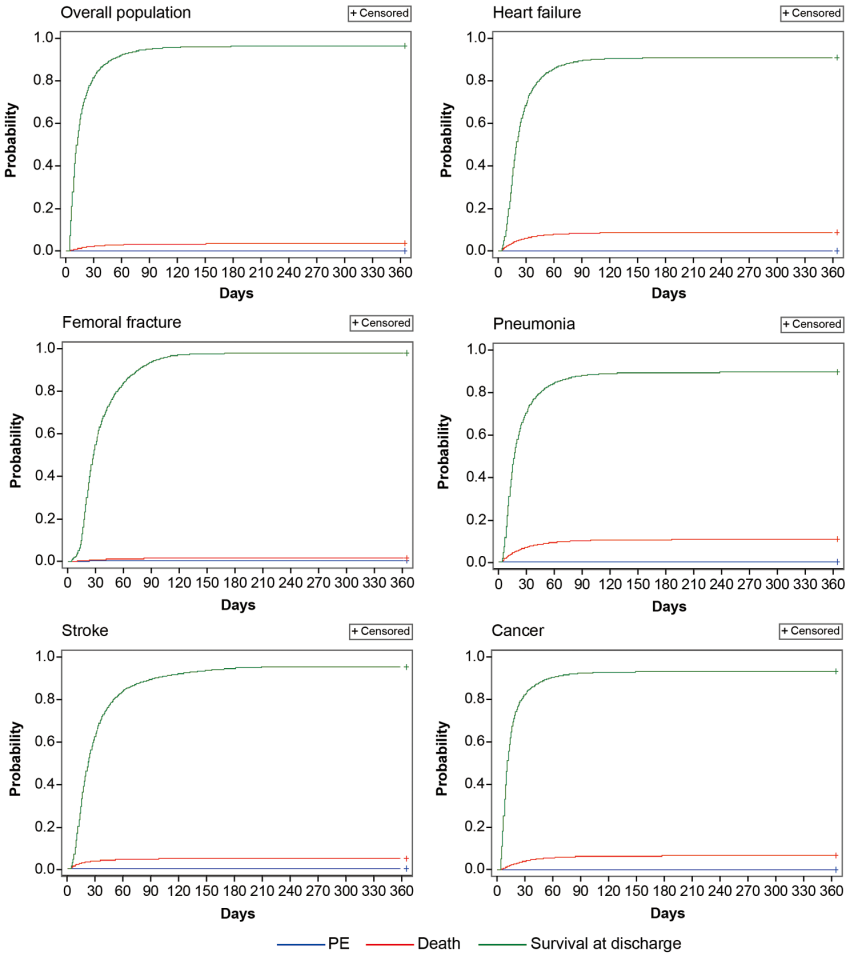

Figure 2. Cumulative incidence of in-hospital PE, discharge due to death, and survival at discharge (CIF method). CIF, cumulative incidence function; PE, pulmonary thromboembolism.

medications (ACE inhibitors/ARBs, CCBs, anticoagulants, NSAIDs, and anticancer drugs; **Supplementary Table 5**).

The in-hospital PE cohort included a higher proportion of women than the non-PE cohort among patients hospitalized for HF, stroke, and cancer. The mean age at admission was lower in the in-hospital PE cohort than in the non-PE cohort among patients hospitalized for pneumonia and stroke. The proportion of patients with a history of cancer and VTE was higher in the in-hospital PE cohort than in the non-PE cohort in all hospitalized subgroups; a history of VTE was reported in approximately ≥70% of patients with incident PE (**Table 1**; **Supplementary Tables 2–5**).

ADL

At baseline, the median BI was significantly lower in the in-hospital PE cohort than in the non-PE cohort in the overall population (median: 40 vs. 100, P<0.0001); no significant differences were observed in the HF (37.5 vs. 45), pneumonia (20 vs. 25), and femoral fracture (5 vs. 5) sub-

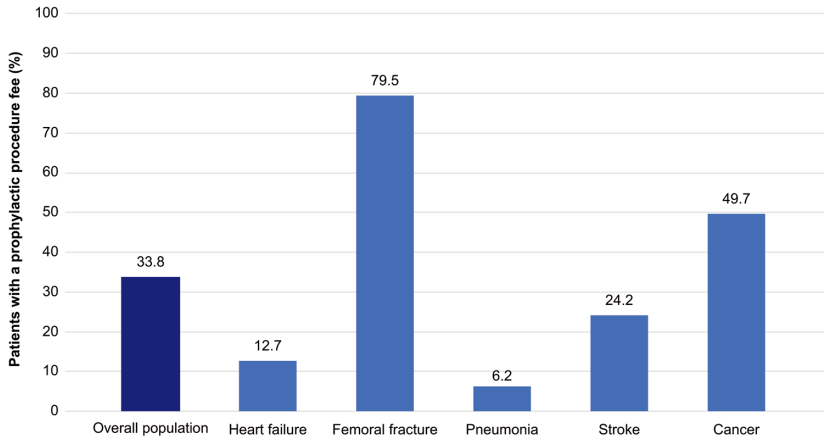

Figure 3. Patients with a prophylactic procedure fee in each subgroup. Pulmonary thromboembolism (PE) prophylaxis was administered when the PE prophylaxis fee (B001-6) was calculated prior to the onset of in-hospital PE.

Table 4. Time From Hospitalization to PE Development, Time to Discharge After PE Development, Duration of Hospitalization, and Proportion of Discharge Due to Death

Diagnosis at admission	PE	N	Time to PE development	After PE development	Duration of hospitalization (days)		Death, n (%)
			After hospitalization (median)	Time to discharge (median)	Mean	Median	
All diseases	All patient	4,684,659			19.0	11.0	165,339 (3.5)
	Yes	5,007	11.0	17.0	39.8	31.0	549 (11.0)
	No	4,679,652			18.9	11.0	164,790 (3.5)
Heart failure	All patient	87,368			25.2	18.0	7,746 (8.9)
	Yes	208	8.0	15.0	32.8	25.5	24 (11.5)
	No	87,160			25.2	18.0	7,722 (8.9)
Femoral fracture	All patient	139,527			35.5	27.0	2,392 (1.7)
	Yes	478	9.0	26.0	44.5	37.0	28 (5.9)
	No	139,049			35.5	27.0	2,364 (1.7)
Pneumonia	All patient	222,566			23.7	15.0	23,829 (10.7)
	Yes	309	10.0	15.0	34.6	26.0	41 (13.3)
	No	222,257			23.7	15.0	23,788 (10.7)
Stroke	All patient	249,156			32.4	21.0	12,293 (4.9)
	Yes	351	22.0	19.0	54.0	43.0	44 (12.5)
	No	248,805			32.3	21.0	12,249 (4.9)
Cancer	All patient	765,347			17.4	11.0	51,167 (6.7)
	Yes	934	10.0	14.0	37.4	27.0	134 (14.3)
	No	764,413			17.4	11.0	51,033 (6.7)

PE, pulmonary thromboembolism.

groups. In contrast, significant differences were observed in the stroke (0 vs. 25, P<0.0001) and cancer (100 vs. 100, P<0.0001) subgroups (**Table 2**).

Compared with baseline, the median BI improved in both the in-hospital PE and non-PE cohorts at discharge. The median BI at discharge, between the 2 cohorts, for the overall population (80 vs. 100, P<0.0001), HF (85 vs. 95), femoral fracture (40 vs. 50, P<0.0001), pneumonia (75 vs. 60), stroke (15 vs. 80, P<0.0001), and cancer (100 vs. 100, P<0.0001) subgroups was significantly different in most subgroups (**Table 2**).

Incidence Rate of In-Hospital PE

The incidence rate of in-hospital PE in the overall hospitalized population was 20.6/1,000 person-years (**Table 3**), being the highest in the femoral fracture subgroup (35.3/1,000 person-years), followed by the HF (34.6/1,000 person-years), cancer (25.6/1,000 person-years), pneumonia (21.4/1,000 person-years), and stroke (15.9/1,000 person-years) subgroups (**Table 3**). Most new PE events occurred during the first 30 days of hospitalization, and the overall incidence of PE was low. The cumulative incidence of in-hospital PE, deaths during hospitalization, and survival at discharge in all subgroups during follow-up are shown in **Figure 2** and **Supplementary Table 6**. The probability of PE occurrence by day 30 was 0.0009 (95% confidence interval [CI]: 0.0009, 0.0009), being the highest in the femoral fracture subgroup (0.003, 95% CI: 0.0028, 0.0033), followed by the HF

(0.0021, 95% CI: 0.0018, 0.0025), pneumonia (0.0012, 95% CI: 0.0011, 0.0014), stroke (0.001, 95% CI: 0.0009, 0.0011), and cancer (0.001, 95% CI: 0.0010, 0.0011) subgroups.

Implementation Proportion of PE Prophylactic Procedures

PE prophylactic procedures were implemented in 33.8% of the overall population; however, the implementation proportion varied widely by subgroup, being the highest among patients with femoral fractures (79.5%), followed by those with cancer (49.7%), stroke (24.2%), HF (12.7%), and pneumonia (6.2%) (**Figure 3**).

Among patients with femoral fractures, 87.2% (121,644/139,527) underwent surgery during hospitalization, of whom 88.3% (107,417/121,644) received PE prophylactic procedures, including prophylactic anticoagulation (20.3% [21,803/107,417]) such as oral anticoagulant (OAC; 53.0%, 11,564/21,803), heparin (47.3%, 10,303/21,803), and fondaparinux (4.2%, 906/21,803). Among the 11.7% (14,227/121,644) of patients with femoral fractures who underwent surgery without the implementation of PE prophylactic procedures, 22.5% (3,207/14,227) received prophylactic anticoagulants such as OAC (56.7% [1,818/3,207]), heparin (44.3% [1,421/3,207]), and fondaparinux (3.1% [99/3,207]; **Supplementary Table 7**). Among patients in the overall population who underwent surgery during hospitalization (51% [2,390,642/4,684,659]), 59.2% (1,415,121/2,390,642) received PE prophylactic procedures, including prophylactic anticoagulants (27.1% [383,244/1,415,121]) such as heparin (91.2% [349,587/383,244]), OAC (9.8% [37,725/383,244]), and fondaparinux (0.7% [2,846/383,244]).

Among the 40.8% (975,521/2,390,642) of patients in the overall population who underwent surgery without the implementation of PE prophylactic procedures, 21.3% (208,077/975,521) received prophylactic anticoagulation such as heparin (97.4% [202,613/208,077]), OAC (3.4% [7,049/208,077]), and fondaparinux (0.1% [297/208,077]).

A total of 67.9% (1,623,198/2,390,642) of patients who underwent surgery received PE prophylactic procedures and/or prophylactic anticoagulation (**Supplementary Table 7**).

Time to Onset of In-Hospital PE

The median time to onset of in-hospital PE was 11.0 days in the overall population and similar among the subgroups, except among patients hospitalized for stroke, in whom the median time to onset of in-hospital PE was 22.0 days. The duration of hospitalization was longer in the overall population of the in-hospital PE cohort than in the non-PE cohort, with similar trends across the subgroups (**Table 4**).

Discussion

This retrospective analysis of a database study evaluated the characteristics of patients with and without in-hospital PE for relatively common diagnoses at hospitalization in Japan. The incidence rate of in-hospital PE was similar between patients hospitalized for femoral fracture (35.3/1,000 person-years) and HF (34.6/1,000 person-years), followed by those hospitalized for cancer (25.6/1,000 person-years), pneumonia (21.4/1,000 person-years), and stroke (15.9/1,000 person-years). Among the risk factors, a history of VTE was a risk factor for in-hospital PE in more than half of the patients across all subgroups. It is recommended that patients should be evaluated for a history of VTE and the diagnosis at admission if they are at risk of in-hospital PE.

Patients treated with anticoagulants, including parenteral anticoagulants, for >7 days during the baseline period were excluded from this study, suggesting that patients should be evaluated "on admission" for a past history of VTE, which requires caution to be exercised because these patients are being admitted in the post-anticoagulation follow-up phase. As risk assessment models (RAMs) have not been successfully validated in Japan,[12] a history of VTE has become an important surrogate marker for in-hospital PE in Japan.

Interestingly, the incidence rate of in-hospital PE in patients with HF was similar to that in patients with femoral fractures. Although a direct comparison could not be made, the implementation proportion of PE prophylaxis in patients with femoral fractures was high (79.5%; with anticoagulants, >90%) compared with the low implementation proportion among patients with HF (12.7%). In-hospital PE is frequently observed during the nonperioperative period, occurring in 50% of patients in Japan and in 70% in overseas countries.[1,7] In addition, patients with HF are at risk of VTE because of factors such as poor circulation. Among hospitalized patients with congestive HF, PE was diagnosed in 0.73% of patients and DVT in 1.03%;[13] however, those data were evaluated from 1979 to 2003 and may have included new in-hospital PE episodes due to other comorbidities. Although the in-hospital PE rate in this study was lower among patients with HF (0.24%), it represents the true rate of incidental/unexpected PE, as patients with comorbid PE at admission were excluded from the analysis. In addition, only patients diagnosed with new-onset PE were evaluated; patients with chronic PE were not.

Regarding the NYHA classification data available at discharge, most patients were in class III or IV, with no notable difference between the in-hospital PE and non-PE cohorts. Similarly, no differences were observed in the ADL scores (BI) at baseline/hospitalization between the in-hospital PE and non-PE cohorts among patients with HF. Therefore, hospitalized patients with HF may need to be diligently evaluated for PE risk assessment, as they are generally less active. A significantly increased risk of VTE has been reported in patients with ejection fraction <20%.[14] Japanese guidelines recommend measures such as elastic stockings, intermittent pneumatic compression (IPC), and prophylactic anticoagulation with drugs for high-risk patients after assessing the risk of hemorrhage.[1] However, the use of elastic stockings and IPC may lead to exacerbation of HF due to increased venous return. Therefore, PE prophylaxis in patients with HF should be applied in consultation with specialists, considering the individual patient's disease condition.

In our previous report, 59.2% of patients who underwent surgery received in-hospital PE prophylactic procedures, and 76.4% of those who underwent orthopedic surgery received in-hospital PE prophylactic procedures.[7] In addition, our results clarified that >90% of patients undergoing surgery for femoral fractures received in-hospital PE prophylaxis; 88.3% received prophylactic procedures, and of the remaining 11.7% of patients who did not receive prophylactic procedures, 22.5% received anticoagulants. However, despite the high implementation proportion of PE prophylaxis, the incidence rate of PE remained high (35.3/1,000 person-years) in the femoral fracture subgroup. Although the effectiveness of PE prophylaxis has been demonstrated, it needs to be verified whether it is being administered appropriately. To ensure PE prophy-

laxis is administered appropriately, the involvement of medical professionals with advanced knowledge and experience in compression therapy is essential. Despite the high incidence rate of in-hospital PE among patients with femoral fractures, a lower rate of in-hospital death was observed compared with other diseases. It may be possible that the response of healthcare personnel is likely to be prompt, owing to a high level of awareness of PE prevention in patients with femoral fractures.

Among patients hospitalized for pneumonia, the incidence rate of in-hospital PE was comparable to that in the overall hospitalized population. Infection is a known potential risk factor for VTE because it promotes blood coagulation.[5] For example, patients infected with certain strains of COVID-19 are reported to be at risk of VTE;[15] however, for this evaluation, we focused on general pneumonia other than COVID-19. RAM (e.g., Padua prediction score) does consider acute infection as a 1-point risk, and individuals with respiratory failure and severe infection are considered to be at intermediate risk; therefore, implementation of PE prophylactic procedures, such as elastic stockings or IPC, is recommended when prolonged recumbency is anticipated.[1] Although we could not gather data on the severity of pneumonia, it can be stated that the implementation proportion of PE prophylaxis was as low as 6.2% for pneumonia.

The incidence rate of in-hospital PE was lower in patients with stroke than in those with other diseases. We observed that in-hospital PE occurred at a median of 11 days after hospitalization in the overall population and at 22 days in patients with stroke, suggesting that long-term bed rest may influence the development of in-hospital PE. Although PE prophylaxis was implemented in 24.2% of patients with stroke, PE risk re-assessment may be crucial for patients with stroke when prolonged hospitalization is required.

The cancer subgroup, which is prone to hypercoagulation associated with metastasis of neoplastic cells, is also at an increased risk of VTE, as these patients undergo intensive procedures such as surgery, chemotherapy, radiotherapy, and central venous catheterization. VTE episodes have been reported in approximately 10–30% of patients with cancer,[5,16,17] and the incidence of VTE is higher in patients with cancer than in those without.[18] Hospitalization is a known risk factor for VTE in patients with cancer.[8,19] In this study, although cancer was the most common reason for hospitalization, the observed incidence rate of PE was comparable with that in the overall hospitalized population. It has been reported that the risk of VTE varies by cancer type and stage;[20] therefore, more detailed evaluations giving considerations to cancer-specific factors associated with the development of PE are required for hospitalized patients with cancer.

The "Guidelines for diagnosis, treatment and prevention of pulmonary thromboembolism and deep vein thrombosis" issued by the Japan Circulation Society (JCS) recommend elastic stockings and IPC when there are factors that increase the risk of VTE, such as chemotherapy during hospitalization.[1] Similarly, the National Comprehensive Cancer Network (NCCN) guidelines recommend prophylactic anticoagulation therapy for hospitalized patients with cancer unless anticoagulation is contraindicated.[20] High-risk populations, such as those with active cancer, are considered to be at a 3-point risk in the Padua score and 2-point risk in the IMPROVE score. As the risk of VTE in patients with cancer depends on the stage and type of cancer, the use of the Khorana score[21] may be helpful in performing a more optimal risk assessment. This suggests that we can evaluate the risk of VTE using RAMs; however, it is also important to differentiate the application of RAMs in high- and low-risk patient populations. Although higher scores in high-risk populations are anticipated and easily validated, a larger patient population is required to validate the usefulness of RAMs in low-risk populations.[12]

Taken together, the diseases and factors that increase the risk of in-hospital PE are diverse and occur in patients with various backgrounds; therefore, adequate assessment of the risk factors for in-hospital PE and implementation of appropriate preventive measures are required, despite the incidental safety concerns it poses to all clinical departments. For example, recommendations for the prevention of recurrence of medical accidents (Issue 2) prepared by the Japan Medical Safety Research Organization provide a reference for preventing PE in hospitalized patients.[22]

Although PE is a serious event, it is rarely encountered during hospitalization; therefore, healthcare professionals and patients are less aware of the need to prevent it. Similarly, in this study, most hospitalized patients were alive when discharged from the hospital, and only a small proportion of patients developed PE during hospitalization. Moreover, most cases of in-hospital PE occurred during the first 30 days, and its incidence was higher in patients with a history of VTE and those with hospitalization due to HF or femoral fracture. Therefore, assessing the risk of in-hospital PE, including the disease at admission, is preferable for patients with hospitalization.

Study Limitations

As in-hospital PE events progress rapidly, a diagnosis of PE may not have been established in some patients who died during hospitalization, thereby underestimating the incidence of in-hospital PE. This study used insurance claims databases and diagnostic algorithms to identify patients with in-hospital PE. To assess surgical procedures, patients were categorized into surgical and nonsurgical groups using K-codes. Because patients hospitalized for <3 days, including the admission day, were excluded, those who were hospitalized for minor surgery were not included in this study; however, minor surgical procedures, such as wound care performed during hospitalization for ≥3 days, were included in the surgical groups. The JCS guidelines define major surgery as all abdominal surgeries or operational procedures that require ≥45 min.[1] For further clarity, a more detailed analysis using the JCS definition of major surgery (≥45 min) is warranted. Numerous confounding factors influence in-hospital PE development, and PE prophylaxis may have been predominantly implemented in high-risk patients. Heart failure is a heterogeneous disease and may require detailed stratification and assessment of causes leading to hospitalization. The relationship between PE prevention and in-hospital PE development was not investigated in this study. More detailed examinations are required to determine how the implementation of PE prophylaxis affects in-hospital PE development. Although this was a database study, we did not investigate the severity of in-hospital PE. Therefore, future studies should aim to clarify the severity of in-hospital PE, including the percentage of patients transferred to the intensive care unit and the incidence and prophylactic procedures for PE in patients admitted to the intensive care unit.

Conclusions

The incidence rate of in-hospital PE varied according to the disease diagnosed at admission, and the incidence rate in patients hospitalized for HF was as high as that in those hospitalized for femoral fracture. Our results indicate a need to assess the risk of in-hospital PE, including medical history and diagnosis at admission, in patients being hospitalized.

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Contributors

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Data Availability

All data generated or analyzed during this study are included in the previous published article or as supplementary information files.

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Supplementary Files

Please find supplementary file(s);
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