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Incidence, clinical characteristics, and long-term prognosis of postoperative symptomatic venous thromboembolism: a retrospective cohort study

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ABSTRACT

Objectives: The purpose of this study was to evaluate the incidence, clinical characteristics, and prognosis of postoperative symptomatic VTE in Japan.

Design: Retrospective observational study. Two datasets, COMMAND VTE Registry and Japanese Society of Anesthesiologists (JSA) annual report, were used for current analyses.

Setting: Eighteen of 29 centres that participated in the COMMAND VTE Registry.

Participants: Acute symptomatic VTE patients who had undergone surgery 2 months prior to the diagnosis at 18 centres from January 2010 to December 2013 were identified in the COMMAND VTE Registry. From each centre's JSA annual report, the overall population that had received anaesthetic management during this period was retrieved.

Interventions: None.

Primary and secondary outcome measures: The primary outcome was the incidences and clinical characteristics of postoperative symptomatic VTE. The secondary outcomes were recurrent VTE, major bleeding, and all-cause death.

Results: We identified 137 patients with postoperative symptomatic VTE, including 57 patients with pulmonary embolism. The incidences of postoperative symptomatic VTE and pulmonary embolism were 0.067% and 0.028%, respectively, based on data from 203,943

patients who underwent surgery, managed by anaesthesiologists, during the study period. The incidences of postoperative symptomatic VTE varied widely, depending on surgical and anaesthetic characteristics. Postoperative symptomatic VTE occurred at a median of 8 days after surgery, with 58 patients (42%) diagnosed within 7 days. The cumulative incidence, 30 days after VTE, of recurrent VTE, major bleeding, and all-cause death was 3.0%, 5.2%, and 3.7%, respectively.

Conclusion: This study, combining the large real-world VTE and anaesthesiology databases in Japan revealed the incidence, clinical features, and prognosis of postoperative symptomatic VTE, providing useful insights for all healthcare providers involved in various surgeries.

Trial registration: Not applicable.

Key words: Venous thromboembolism; Pulmonary thromboembolism; Deep vein thrombosis; Postoperative; Prognosis

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- VTE is considered relatively rare in Asians, and the small number of cases makes epidemiological studies difficult to perform.
- This study combines data from the large real-world VTE database and anaesthetic database in Japan for information regarding the incidence, clinical features, and prognosis of postoperative symptomatic VTE.
- Another important feature of the current study was the comparison of the incidence of postoperative symptomatic VTE across surgical sites.
- This is a retrospective cohort study with inherent limitations based on the observational study design. Further, as a certain number of patients from ineligible centres were excluded, the incidence of postoperative symptomatic VTE may have been influenced.

INTRODUCTION

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a serious postoperative complication which can result in an in-hospital death.[1, 2] In perioperative management, it is crucial to prevent postoperative symptomatic VTE and to respond promptly, once it is recognized. Therefore, clinicians should be familiar with the clinical features of postoperative symptomatic VTE to optimize their management strategies.

Over the past 20 years, several guidelines have been recommended for the prophylaxis of postoperative VTE.[3-5] Despite the use of preventive measures, the incidence of postoperative VTE remains high and varies from 0.58% to 2.2%, according to reports from Western countries.[6-8] However, data on postoperative VTE from a cohort/registry-based study in Asian countries are scarce. A previous study reported a relatively low incidence (0.031%) of postoperative VTE throughout Japan.[9] However, it was a surveillance study of postoperative PE, conducted by mailing questionnaires to anaesthesiologists; therefore, the possibility of underreporting of events cannot be denied. Although the incidence of VTE in Asia has been considered to be lower than Western countries,[10] recent studies have

suggested an underestimation of VTE in Asia.[11-13] No large-scale study has systematically evaluated the incidence of postoperative symptomatic VTE in Japan.

Therefore, with a collaborative effort between cardiologists and anaesthesiologists, we investigated the incidence, clinical characteristics, and prognosis of postoperative symptomatic VTE, using a large, observational, real-world VTE database and an anaesthetic database of annual reports submitted to the Japanese Society of Anesthesiologists (JSA).

METHODS

Study design, setting, and population

In this study, two datasets were used for analyses. The first was Contemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism (COMMAND VTE) registry, a retrospective multicentre cohort study, which provided the data on patients with postoperative symptomatic VTE. The second was the JSA annual report, which provided cross-sectional data of all patients, who underwent surgical operations, managed by anaesthesiologists.

The design of the COMMAND VTE Registry has been reported in detail elsewhere.[14] Briefly, this physician-initiated registry was a large cohort of consecutive

patients with acute symptomatic VTE, who were objectively confirmed by the cardiologists at 29 centres in Japan, between January 2010 and August 2014. In this registry, the hospital databases were searched for clinical diagnoses and imaging examinations of patients with suspected VTE, and consecutive patients who met the definition of acute symptomatic VTE were enrolled. Baseline data were obtained from the hospital charts or hospital databases. Follow-up data on vital status, recurrent VTE, bleeding, and status of anticoagulation therapy, according to the prespecified definitions, were collected from the hospital charts, hospital databases, or by contacting patients, relatives, and/or referring to physicians through phone and/or mails.

As for the JSA annual reports, the training hospitals certified by JSA are required to submit the annual reports to JSA at the end of the year, which includes the total number of surgeries managed by anaesthesiologists, patient characteristics in detail, and surgical and anaesthetic information.

In this study, the JSA annual reports from January 2010 to December 2013 were collected from 18 centres that participated in the COMMAND VTE Registry. Furthermore, additional data of patients with postoperative symptomatic VTE, namely operative date,

operative procedure, surgical sites, surgical position, and types of anaesthesia on anaesthetic charts at each centre, were obtained.

In this study, the patients from the 18 centres registered in the COMMAND VTE Registry, for which the JSA annual report had been collected between January 2010 and December 2013, were enrolled (Figure 1). We could not enrol patients from the rest of the 11 centres of the COMMAND VTE Registry as their JSA annual reports and/or additional data on patients with postoperative symptomatic VTE were unavailable. We also could not register the patients between January 2014 and August 2014, since the JSA annual report was from January to December of each year. Further, within the COMMAND VTE Registry, the patients diagnosed with acute symptomatic VTE, who underwent surgery 2 months prior to the VTE diagnosis, were identified. The overall population that had received anaesthetic management, during the study period was retrieved from each centre's JSA annual report. Besides, additional data of patients with postoperative symptomatic VTE, namely operative date, operative procedure, surgical sites, surgical position, and types of anaesthesia on anaesthetic charts at each centre, were obtained.

Ethics

This retrospective observational study was conducted according to the 'STrengthening the Reporting of OBservational studies in Epidemiology' (STROBE) guidelines. This study was approved by the Ethics Committee of the Kyoto University Hospital, Kyoto, Japan (approval number: R1822, December 18th, 2018; Chairperson Prof Shinji Kosugi). Following Ethics Committee approval, additional data, including JSA annual reports, were collected from the centres listed in the Command VTE Registry, from March 2019 to September 2019. Written informed consent from each patient was waived, because we used clinical information obtained in routine clinical practices. This method is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare in Japan.

Patient and Public Involvement Statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Definition of postoperative symptomatic venous thromboembolism

In this study, postoperative symptomatic VTE was defined as the thromboembolic event that occurred within 2 months of the postoperative period.[15] The symptoms of VTE were defined as sudden onset dyspnoea, pleuritic and substernal chest pains, cough, fever, haemoptysis and syncope for PE; and erythema, warmth, pain, swelling, tenderness, and pain

upon dorsiflexion of the foot for DVT. Additionally, a sudden onset of abnormality in the vital signs, such as a decrease in arterial oxygen saturation and hypotension were considered as symptoms of PE.

Collection of baseline patient characteristics and clinical follow-up data

In the COMMAND VTE Registry, data for the patients' characteristics were collected from the hospital charts or hospital databases, according to the prespecified definitions, using an electronic case report form in a web-based database system. Physicians at each of the institutions were responsible for data entry, and data were automatically examined for missing or contradictory input and out-of-range values. Additional edits were performed at the general office of the registry.

Patients with postoperative symptomatic VTE, identified through the COMMAND VTE Registry, were further investigated at each centre using the anaesthetic charts created through the collaboration of cardiologists and the anaesthesiologists at each participating centre. Anaesthesia-associated data, such as surgical site, surgical position, and type of anaesthesia were extracted and incorporated into the data from the COMMAND VTE Registry.

The outcome measures assessed in this study were recurrent VTE, major bleeding, and all-cause death during the follow-up period, with a median of 1,507 days, in the surviving patients. Recurrent VTE was defined as symptomatic PE and/or DVT accompanied by confirmation of a new thrombus or exacerbation of the thrombus by objective imaging examinations or autopsy. Major bleeding was defined according to the International Society of Thrombosis and Haemostasis as a reduction in the haemoglobin level by at least 2 g/dL, transfusion of at least two units of blood, or symptomatic bleeding in a critical area or an organ.[16]

Statistical analysis

The incidence of postoperative symptomatic VTE was calculated using a combination of data from the COMMAND Registry and the JSA annual reports from the 18 centres. The numerator of the incidence was the number of cases of postoperative symptomatic VTE extracted from the COMMAND Registry; the denominator was the number of surgeries in the JSA annual report. The incidence of postoperative symptomatic VTE according to age, sex, surgical site, surgical position, and types of anaesthesia was calculated. The baseline and follow-up data were separately recorded for PE with or without DVT and DVT-only groups in patients with postoperative symptomatic VTE. No imputation was performed for missing

data. Categorical variables were calculated as numbers and percentages, and continuous variables were calculated as the means and standard deviations or the medians and interquartile ranges (IQR) based on their distributions. Additionally, the timing of the postoperative symptomatic VTE occurrences after the surgery were described. The Kaplan–Meier method was used to estimate the cumulative incidences of recurrent VTE, major bleeding, and all-cause death. The log-rank test was used to assess the differences in the cumulative incidences of the events between the PE- and DVT-only groups. Two-sided P-values of less than 0.05 were considered significant. All statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc; Cary, NC, USA) or JMP version 14.0.0 (SAS Institute Inc.; Cary, NC, USA).

RESULTS

Figure 1 represents the flow diagram of the study. We enrolled 3,027 consecutive patients with acute symptomatic VTE, after screening 19,634 consecutive patients with suspected VTE for eligibility, using the chart review by the physicians at each institution. After excluding 2,734 patients without a history of surgery within 2 months before VTE diagnosis,

293 patients were identified with postoperative symptomatic VTE during hospitalization among all 29 centres of the COMMAND VTE Registry. Furthermore, 135 patients outside the eligible period and 21 patients who underwent surgery without the management by anaesthesiologists, were excluded. Finally, the study population consisted of 137 patients diagnosed with VTE within 2 months after surgery, from 18 centres, between January 2010 and December 2013. The total number of surgical cases managed by anaesthesiologists during the study period in 18 centres was 203,943.

Incidence of postoperative symptomatic venous thromboembolism

The estimated incidence of postoperative symptomatic VTE was 0.067% (137/203,943) and VTE with PE was 0.028% (57/203,943) (Table 1). Of the 57 PE cases, 35 patients (0.017%) had hypoxic symptoms, nine patients (0.004%) presented with shock, and six patients (0.003%) had cardiac arrest. As for the surgical site, the incidence of postoperative symptomatic VTE was relatively high in surgeries involving the brain, hip, and upper/lower limbs. In terms of the types of anaesthesia, regional anaesthesia with or without general anaesthesia (0.100%) was associated with a higher incidence of VTE than general anaesthesia alone (0.045%) (Table 1 and Supplemental Table 1).

Table 1. Incidence of postoperative symptomatic VTE

	Total cases	VTE		PE		PE with hypoxia		PE with shock		PE with arrest	
Overall	203943	137	(0.067%)	57	(0.028%)	35	(0.017%)	9	(0.004%)	6	(0.003%)
Surgical Site											
Brain	9299	15	(0.161%)	8	(0.086%)	1	(0.011%)	0	(0.000%)	0	(0.000%)
Thorax	11100	4	(0.036%)	3	(0.027%)	2	(0.018%)	1	(0.009%)	1	(0.009%)
Cardiovascular	13637	6	(0.044%)	1	(0.007%)	1	(0.007%)	1	(0.007%)	1	(0.007%)
Thorax and abdomen	1656	2	(0.121%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Upper abdomen	27035	17	(0.063%)	11	(0.041%)	8	(0.030%)	1	(0.004%)	0	(0.000%)
Lower abdomen	42875	31	(0.072%)	16	(0.037%)	11	(0.026%)	3	(0.007%)	1	(0.002%)
Caesarean section	5056	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Head, pharynx, larynx	35414	4	(0.011%)	2	(0.006%)	2	(0.006%)	0	(0.000%)	0	(0.000%)
Chest, abdominal wall, perineum	22633	3	(0.013%)	2	(0.009%)	2	(0.009%)	0	(0.000%)	0	(0.000%)
Spine	7040	7	(0.099%)	3	(0.043%)	2	(0.028%)	1	(0.014%)	1	(0.014%)
Hip, upper/lower limbs	25160	48	(0.191%)	11	(0.044%)	6	(0.024%)	2	(0.008%)	2	(0.008%)
Other	2038	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)

All data were described as number and percentage.

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism

Baseline characteristics and timing of venous thromboembolism diagnosis

Table 2 shows the demographic and clinical characteristics of patients with postoperative symptomatic VTE. Figure 2 presents the duration from the surgery to the diagnosis of postoperative symptomatic VTE. The median inter-quartile duration was 8 days (4–15 days); and 58 patients (42%) were diagnosed within 7 days of surgery, while 79 patients (58%) were diagnosed 7 days after the surgery. The greatest number of patients were diagnosed with VTE on postoperative day 8.

Table 2. Baseline patients' characteristics

	Total VTE N=137	PE with or without DVT (N=57)	DVT only (N=80)
Baseline characteristics			
Age (years)	66.2 ±15.5	67.7 ±12.6	65.1 ±17.2
Men	55 (40.1%)	22 (38.6%)	33 (41.3%)
Body weight (kg)	56.3 ±11.8	57.8 ±11.1	55.3 ±12.3
Body mass index (kg/m^2)	23.2 ±4.3	23.6 ±3.7	22.9 ±4.7
Surgical and anaesthesia characteristics			
ASA PS			
ASA PS 1	19 (13.9%)	10 (17.5%)	9 (11.3%)
ASA PS 2	91 (66.4%)	42 (73.7%)	49 (61.3%)
ASA PS 3	22 (16.1%)	4 (7.0%)	18 (22.5%)
ASA PS 4	5 (3.6%)	1 (1.8%)	4 (5.0%)
Emergent surgery	18 (13.1%)	11 (19.3%)	7 (8.8%)
Surgical site			
Hip and limb	48 (35.0%)	11 (19.3%)	37 (46.3%)
Brain	15 (10.9%)	8 (14.0%)	7 (8.8%)
Thorax and mediastinum	4 (2.9%)	3 (5.3%)	1 (1.3%)

Cardiovascular	6	(4.4%)	1	(1.8%)	5	(6.3%)
Thorax and abdomen	2	(1.5%)	0	(0.0%)	2	(2.5%)
Upper abdomen	17	(12.4%)	11	(19.3%)	6	(7.5%)
Lower abdomen	31	(22.6%)	16	(28.1%)	15	(18.8%)
Head and neck	4	(2.9%)	2	(3.5%)	2	(2.5%)
Chest abdominal wall and perineum	3	(2.2%)	2	(3.5%)	1	(1.3%)
Spine	7	(5.1%)	3	(5.3%)	4	(5.0%)
Type of Anaesthesia						
General anaesthesia	61	(44.5%)	26	(45.6%)	35	(43.8%)
General anaesthesia with regional anaesthesia	56	(40.9%)	24	(42.1%)	32	(40.0%)
Local anaesthesia	20	(14.6%)	7	(12.3%)	13	(16.3%)
Surgical position						
Supine position	100	(73.0%)	39	(68.4%)	61	(76.3%)
Prone position	6	(4.4%)	2	(3.5%)	4	(5.0%)
Lateral position	18	(13.1%)	7	(12.3%)	11	(13.8%)
Lithotomy position	11	(8.0%)	8	(14.0%)	3	(3.8%)
Other position	2	(1.5%)	1	(1.8%)	1	(1.3%)
Comorbidities						
Hypertension	43	(31.4%)	22	(38.6%)	21	(26.3%)
Diabetes mellitus	15	(10.9%)	7	(12.3%)	8	(10.0%)
Chronic kidney disease	24	(17.5%)	8	(14.0%)	16	(20.0%)
Dialysis	2	(1.5%)	0	(0.0%)	2	(2.5%)
History of chronic lung disease	13	(9.5%)	3	(5.3%)	10	(12.5%)
History of heart failure	6	(4.4%)	3	(5.3%)	3	(3.8%)
History of myocardial infarction	4	(2.9%)	0	(0.0%)	4	(5.0%)
History of stroke	9	(6.6%)	5	(8.8%)	4	(5.0%)
Atrial fibrillation	8	(5.8%)	7	(12.3%)	1	(1.3%)
Liver cirrhosis	3	(2.2%)	2	(3.5%)	1	(1.3%)
Connective tissue disease	5	(3.6%)	1	(1.8%)	4	(5.0%)
History of VTE	1	(0.7%)	1	(1.8%)	0	(0.0%)
History of major bleeding	17	(12.4%)	7	(12.3%)	10	(12.5%)
Active cancer	41	(29.9%)	24	(42.1%)	17	(21.3%)
Varicose vein	8	(5.8%)	3	(5.3%)	5	(6.3%)
Presentation						

PE with hypoxemia	-	-	35	(61.4%)	-	-
PE with Shock	-	-	9	(15.8%)	-	-
PE with cardiac arrest/collapse	-	-	6	(10.5%)	-	-
Proximal DVT	64	(46.7%)	21	(36.8%)	43	(53.8%)
Laboratory tests at diagnosis						
Anaemia	109	(82.6%)	45	(83.3%)	64	(82.1%)
Thrombocytopenia	6	(4.4%)	5	(8.8%)	1	(1.3%)
eGFR (mL/min/m^2)	78.3	(59.0-91.8)	72.7	(51.2-87.7)	80.4	(62.4-93.6)
eGFR <60mL/min/m^2	36	(26.3%)	17	(29.8%)	19	(23.8%)
D-dimer (μg/mL, n=122)	16.5	(8.6-31.5)	16.8	(8.6-39.3)	16.4	(7.9-27.3)
Thrombophilia	4	(2.9%)	3	(5.3%)	1	(1.3%)
Initial anticoagulation therapy	115	(83.9%)	53	(93.0%)	62	(77.5%)
Heparin	107	(78.1%)	52	(91.2%)	55	(68.8%)
Fondaparinux	11	(8.0%)	2	(3.5%)	9	(11.3%)
Thrombolysis	8	(5.8%)	5	(8.8%)	3	(3.8%)
Inferior vena cava filter use	26	(19.0%)	13	(22.8%)	13	(16.3%)
Ventilator support	6	(4.4%)	6	(10.5%)	0	(0.0%)
Percutaneous cardiopulmonary support	2	(1.5%)	2	(3.5%)	0	(0.0%)

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the mean and standard deviation or the median and interquartile range based on their distributions.

Chronic kidney disease was diagnosed if there was persistent proteinuria or if eGFR was <60 mL/min/1.73 m^2 for more than 3 months. The values of eGFR were calculated based on the equation reported by Japan Association of Chronic Kidney Disease Initiative [man: 194*Scr−1.094*age-0.287, woman: 194*Scr−1.094*age-0.287*0.739]. Anaemia was

diagnosed if the value of haemoglobin was <13 g/dL for men and <12 g/dL for women. Thrombophilia included protein C deficiency, protein S deficiency, antithrombin deficiency, and antiphospholipid syndrome.

Abbreviations: ASA PS, American society anaesthesiologists performance status; DVT, deep venous thrombosis; eGFR, estimated glomerular filtration rate; PE, pulmonary embolism; VTE, venous thromboembolism

Clinical outcomes after postoperative symptomatic venous thromboembolism

The cumulative incidence of recurrent VTE was 3.0% at 30-day follow-up, 5.3% at 90-day follow-up, and 5.3% at the 5-year follow-up after postoperative symptomatic VTE (Figure 3a). The cumulative incidence of major bleeding was 5.2% at 30-day follow-up, 6.7% at 90-day follow-up, and 12.6% at 5-year follow-up (Figure 3b). The cumulative incidence of all-cause death was 3.7% at 30-day follow-up, 5.1% at 90-day follow-up, and 27.4% at 5-year follow-up (Figure 3c). The details of clinical events within 90 days are given in Supplemental Table 2. VTE recurrence occurred in seven patients (4 patients were treated with anticoagulant therapy), all of which were early recurrences within 60 days of diagnosis.

Difference in the cumulative incidence of recurrent VTE, major bleeding, and all-cause death

was not significant between the PE- and DVT-only groups, although 30-day incidence of major bleeding and all-cause death was higher in the PE group than the DVT-only group (11.1% versus 1.3%, and 8.8% versus 0.0%, respectively) (Figure 4).

DISCUSSION

The main findings of this study are as follows: 1) the incidence of postoperative symptomatic VTE within 2 months after surgery was 0.067% and VTE with PE was 0.028%, representing 203,943 patients from 18 centres in Japan; 2) the incidences of postoperative symptomatic VTE varied widely, according to surgical and anaesthetic characteristics; and 3) nearly half of the patients were diagnosed within 7 days of the surgery, while the rest were diagnosed 7 days after surgery, with the highest number of patients diagnosed on postoperative day 8.

VTE is considered relatively rare in Asians and the small number of cases makes epidemiological studies difficult to perform.[10] Previously, two major studies from Japan had evaluated the incidence of the postoperative complication of VTE. The first study was based on the JSA initiated questionnaire annual survey, where the incidence of PE was 0.031% (3,667/ 11,786,489.[9] The second study used the diagnosis–procedure combination (DPC) database, and the VTE and PE incidences were 0.24% (2,485/1,016,496) and 0.05%

(538/1,016,496), respectively.[17] The incidence of postoperative symptomatic VTE in the current study was lower than that in the DPC study. In the DPC study, VTE was identified based on the International Classification of Diseases, 10th version (ICD-10) codes; and therefore, may have been misclassified and overrated. The incidences of postoperative VTE were reported to be 0.58%–2.2%, based on the clinical databases in the USA. Therefore, postoperative VTE incidence was suggested to be lower in Japan than in the United States and Europe. These differences could be explained by ethnic variations.[10] Western guidelines,[4, 5] due to racial disparities, are more likely to lead to over-triage in the Japanese population.

Another important feature of the current study was the comparison of the incidence of postoperative symptomatic VTE across surgical sites. As with the JSA initiated questionnaire study,[9] neurosurgeries and orthopaedic surgeries (hip, upper, and lower extremity) were associated with a higher incidence of postoperative symptomatic VTE. According to the Japanese guidelines, there is a high risk of postoperative symptomatic VTE in patients over 40 years of age undergoing major cancer surgery; however, in the present study, abdominal surgery was not identified with high risk. Therefore, risks should be stratified according to

the surgical sites and procedures, and the additional risks in each patient should be considered in the preventive strategies.

Additionally, in this study, the timing of the onset of postoperative symptomatic VTE was bimodal in nature. These results may suggest that postoperative symptomatic VTE occurs, not only in the very acute postoperative period, which is directly affected by surgical immobilization, but also approximately 10 days after surgery; the information can guide the healthcare providers involved in surgery, regarding the risk perception and diagnosis of postoperative symptomatic VTE.

The duration of anticoagulant therapy is generally divided into an initial treatment phase (up to 7 days), a maintenance treatment phase (~3 months after the initial treatment), and a prolonged treatment phase (beyond 3 months).[18] Surgery is a transient risk factor of VTE; prolonged treatment is usually not performed, as the possibility of recurrence is considered relatively low. In this study, VTE recurrence had occurred in all the affected seven patients within 3 months of the onset, and no recurrence was observed after 3 months, suggesting the importance of relatively early recurrence.

PE was apparently associated with a higher mortality, especially in the early phase of postoperative symptomatic VTE, although the difference between the PE- and DVT-only

groups was not significant. The difference may be explained by insufficient sample size. Notably, the initial mortality rate and recurrence rate was higher for acute PE than for DVT.[19, 20] Therefore, in comparison to DVT, postoperative PE should be more closely monitored and aggressively treated.[3]

Study limitations

First, two different databases were combined to estimate the incidence of postoperative symptomatic VTE. Although the COMMAND Registry included real consecutive patients with acute symptomatic VTE,[9, 17] for determining VTE incidence, we included only the cases in which intraoperative management was performed by an anaesthesiologist. Second, patients outside the eligible period in the COMMAND VTE Registry were also excluded, which may have influenced the results of this study. As a certain number of patients were excluded due to ineligible centres, the incidences of postoperative symptomatic VTE could have been greatly influenced, especially as the analysis targeted the low event rates. Third, this is a retrospective cohort study with inherent limitations based on the observational study design. In particular, the prophylactic and therapeutic management for postoperative symptomatic VTE were based on the discretion of the attending physicians, which may have influenced clinical outcomes. However, in the COMMAND Registry, the definitions of VTE

were specified in advance, and the follow-up after VTE was nearly complete. Finally, we also considered the postoperative date of onset, but the disease may have developed before the surgery or the diagnosis. Nevertheless, we do not expect a significant gap between the onset and diagnosis, because we included only symptomatic patients with postoperative VTE.

Conclusions

This study, combining the large real-world VTE database and anaesthetic database in Japan, revealed the incidence, clinical features, and prognosis of postoperative symptomatic VTE, providing useful information for all healthcare providers involved in various surgeries.

Declarations

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Competing interests

Dr. Yamashita received lecture fees from Daiichi-Sankyo, Bristol-Myers Squibb, Pfizer, and Bayer Healthcare. Dr. Morimoto received lecture fees from Mitsubishi Tanabe Pharma and Pfizer Japan and consultant fees from Asahi Kasei, Bristol-Myers Squibb, and Boston Scientific. Dr. Kawakami receives consulting fees from Kaken Pharmaceutical Co., Ltd.;

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Author Contributions

C.T. and Y.Y. contributed equally to this work and had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. C.T., Y.Y., M.T., and T. Mizota participated in study conception. C.T. and Y.Y. performed data analysis. C.T., Y.Y., M.T., H.Y. T. Morimoto, T.K., and T. Mizota drafted and revised the paper. All authors approved the final draft of the manuscript for publication.

Availability of data and materials

Data available on request from the authors. The data that support the findings of this study are available from Chikashi Takeda or Yugo Yamashita, upon reasonable request.

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Figure legends

Figure 1. Study flow diagram.

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; JSA, Japanese Society of Anesthesiologists; COMMAND VTE, contemporary management and outcomes in patients with venous thromboembolism.

Figure 2. The distribution of days of VTE diagnosis after surgery.

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Figure 3. The Kaplan–Meier curves for the clinical events after VTE diagnosis.

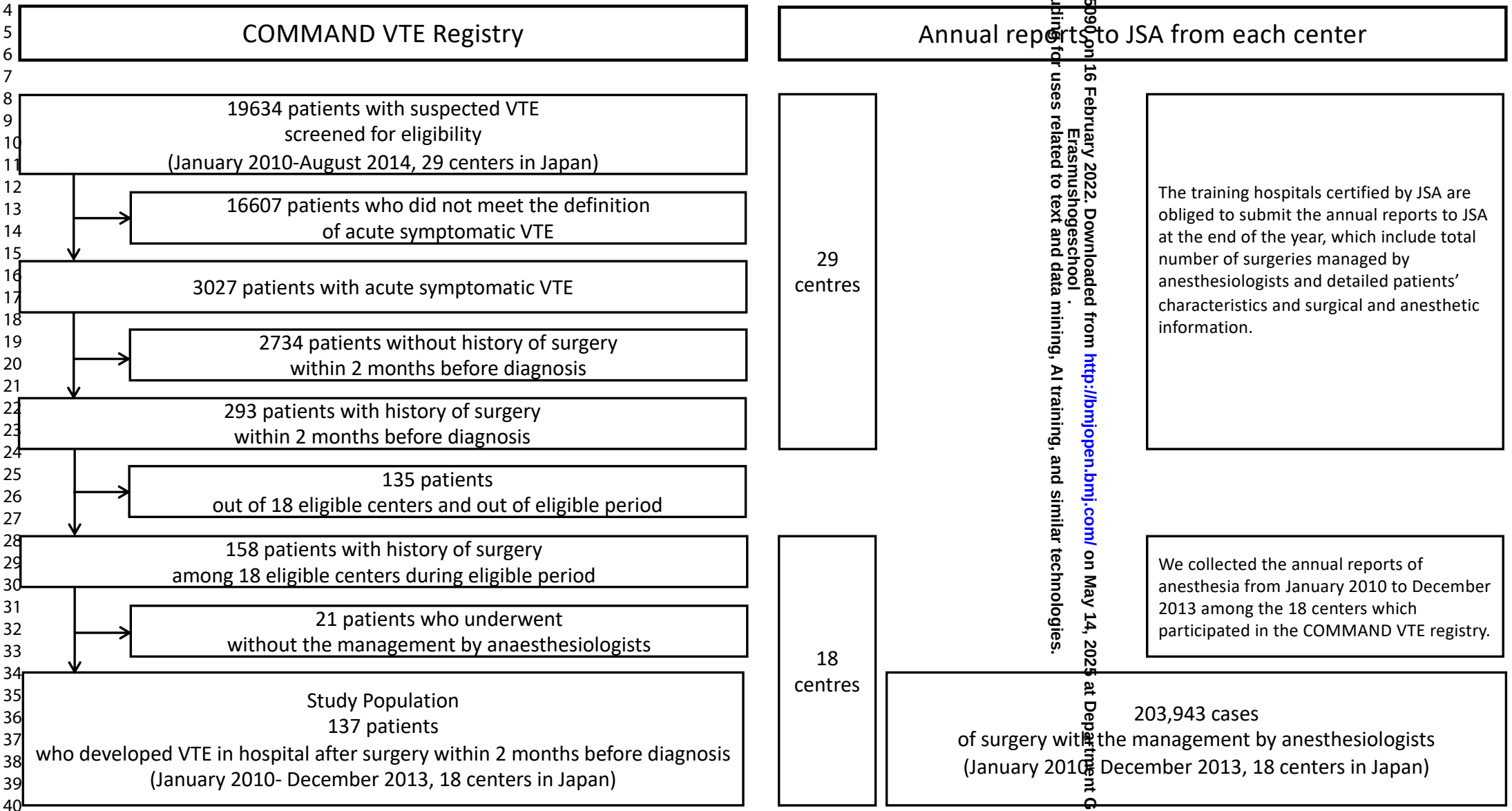
(a) Recurrent VTE, (b) Major bleeding, and (c) All-cause death.

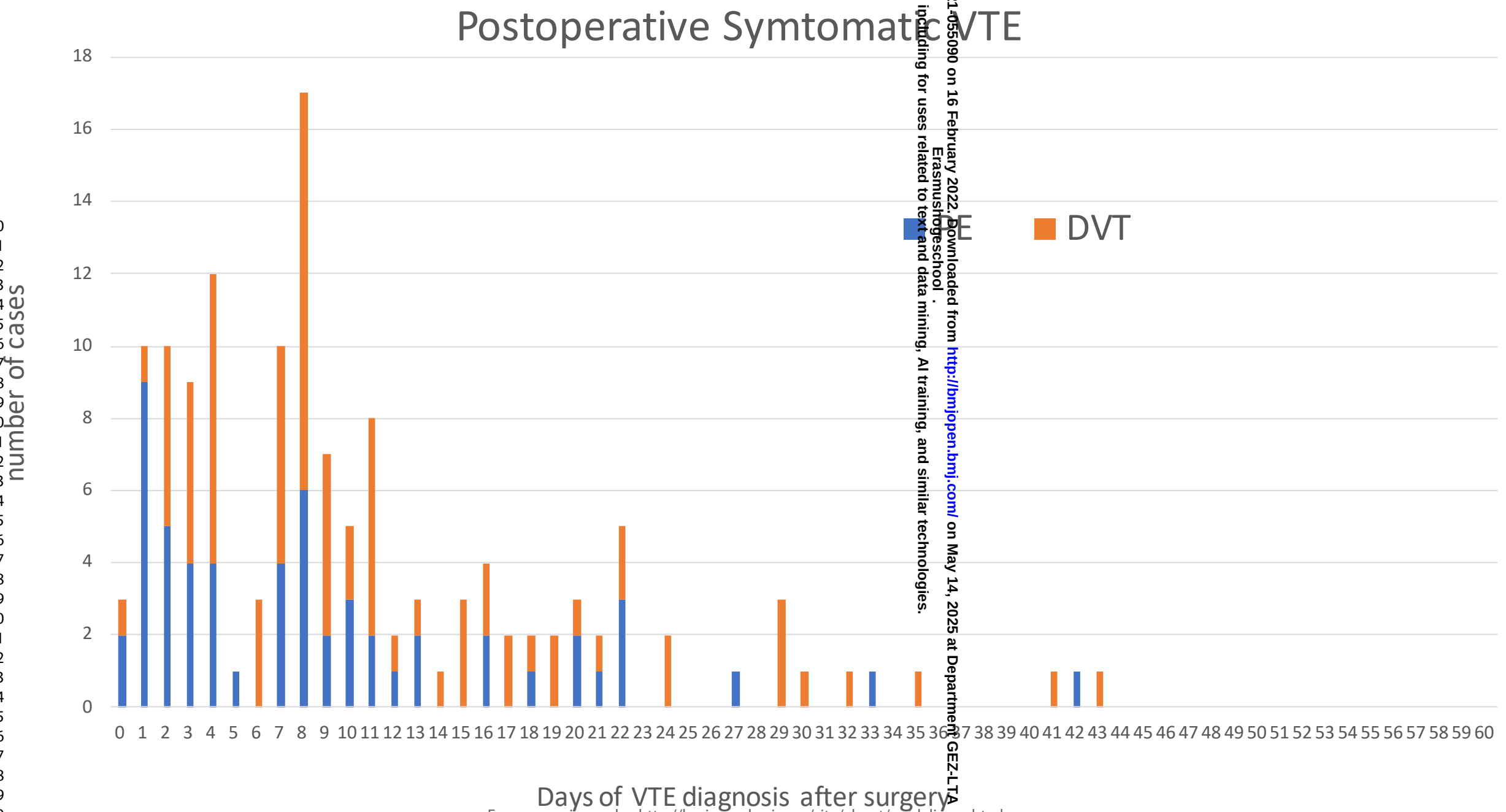
VTE, venous thromboembolism.

Figure 4. The Kaplan–Meier curves for the clinical events after VTE diagnosis comparing PE and DVT.

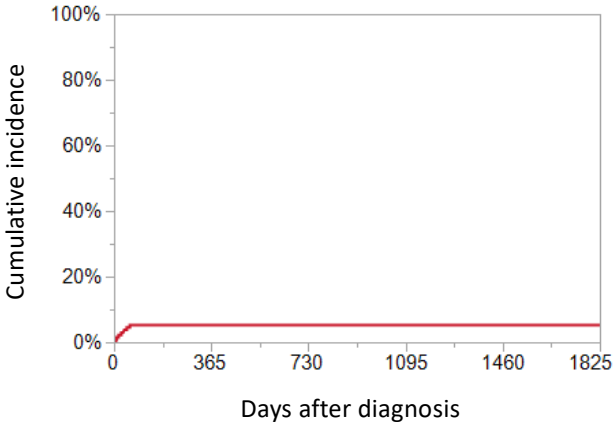
(a) Recurrent VTE, (b) Major bleeding, and (c) All-cause death.

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism



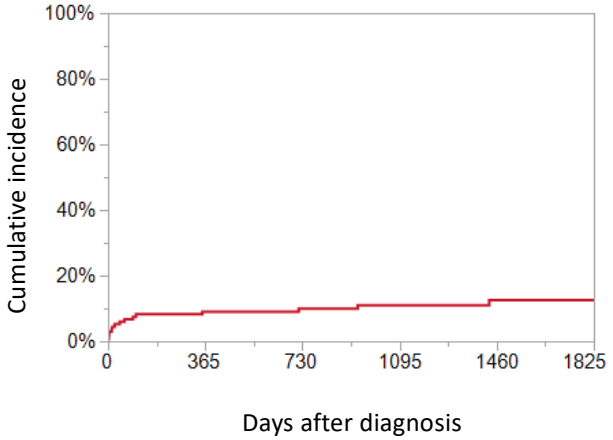


(a) Recurrent VTE



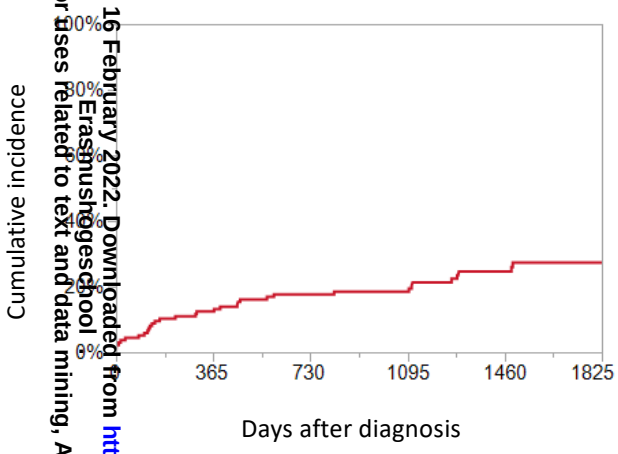
	0-day	7-day	30-day	90-day	1-year	5-year
N of patients with event		1	4	7	7	7
N of patients at risk	137	134	129	124	116	32
Cumulative incidence		0.8%	3.0%	5.3%	5.3%	5.3%

(b) Major bleeding



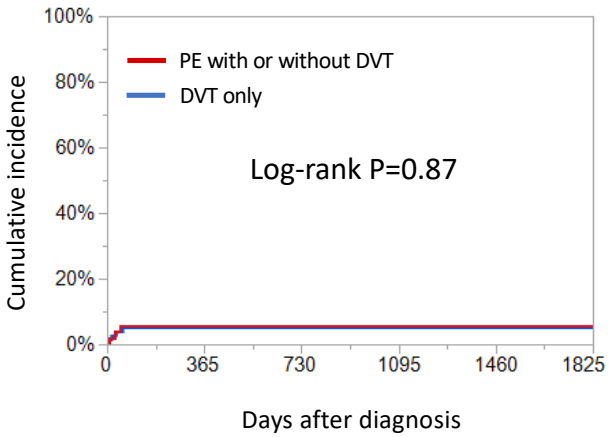
	0-day	7-day	30-day	90-day	1-year	5-year
N of patients with event		4	7	9	12	15
N of patients at risk	137	131	128	124	114	31
Cumulative incidence		3.0%	5.2%	6.7%	9.0%	12.6%

(c) All-cause death



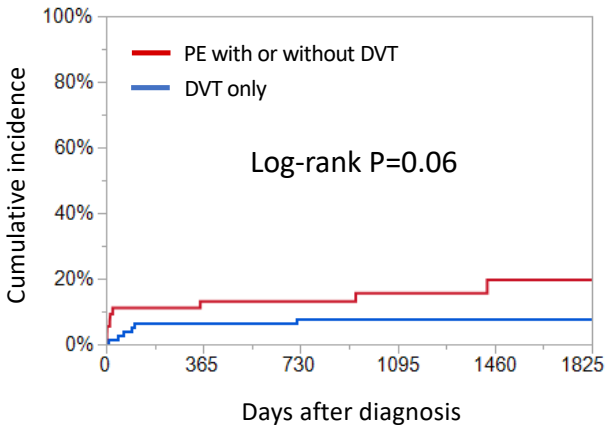
	0-day	7-day	30-day	90-day	1-year	5-year
N of patients with event		3	5	7	17	33
N of patients at risk	137	136	133	131	121	34
Cumulative incidence		2.2%	3.7%	5.1%	12.4%	27.4%

(a) Recurrent VTE



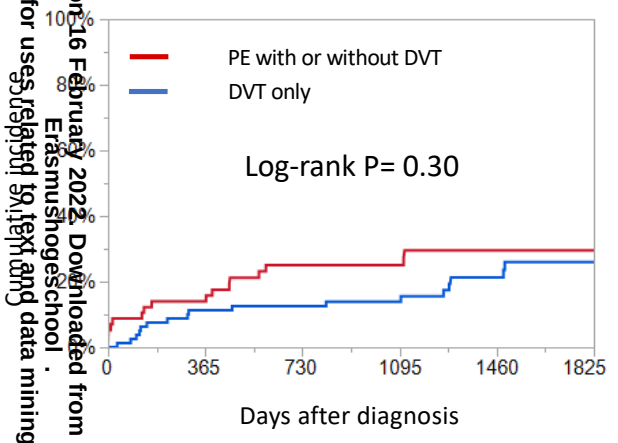
	0-day	7-day	30-day	90-day	1-year	5-year
PE with or without DVT						
N of patients with event		0	2	3	3	3
N of patients at risk	57	56	51	50	47	16
Cumulative incidence		0.0%	3.8%	5.7%	5.7%	5.7%
DVT only						
N of patients with event		1	2	4		
N of patients at risk	80	80	79	75	70	17
Cumulative incidence		1.3%	2.5%	5.0%	5.0%	5.0%

(b) Major bleeding



	0-day	7-day	30-day	90-day	1-year	5-year
PE with or without DVT						
N of patients with event		3	6	6	7	9
N of patients at risk	57	52	49	49	45	15
Cumulative incidence		5.5%	11.1%	11.1%	13.0%	19.6%
DVT only						
N of patients with event		1	1	3	5	6
N of patients at risk	80	80	80	76	70	17
Cumulative incidence		1.3%	1.3%	3.8%	6.4%	7.9%

(c) All-cause death



	0-day	7-day	30-day	90-day	1-year	5-year
PE with or without DVT						
N of patients with event		3	5	5	8	16
N of patients at risk	57	56	53	53	50	16
Cumulative incidence		5.3%	8.8%	8.8%	14.0%	29.5%
DVT only						
N of patients with event		0	0	2	9	17
N of patients at risk	80	80	80	79	72	19
Cumulative incidence		0.0%	0.0%	2.5%	11.3%	25.9%

Supplemental Table 1. Incidence of postoperative symptomatic VTE

	Total cases	VTE		PE		PE with hypoxia		PE with shock		PE with arrest	
Overall	203943	137	(0.067%)	57	(0.028%)	35	(0.017%)	9	(0.004%)	6	(0.003%)
Type of anaesthesia											
Inhalation general anaesthesia	110833	49	(0.044%)	23	(0.021%)	13	(0.012%)	3	(0.003%)	1	(0.001%)
Total venous general anaesthesia	25467	12	(0.047%)	3	(0.012%)	1	(0.004%)	1	(0.004%)	1	(0.004%)
Inhalation general anaesthesia combined with regional anaesthesia	34872	46	(0.132%)	19	(0.054%)	11	(0.032%)	2	(0.006%)	2	(0.006%)
Total venous general anaesthesia combined with regional anaesthesia	12863	10	(0.078%)	5	(0.039%)	4	(0.031%)	2	(0.016%)	1	(0.008%)
Combined spinal and epidural anaesthesia	4078	4	(0.098%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Epidural anaesthesia	623	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Spinal anaesthesia	13522	16	(0.118%)	7	(0.052%)	6	(0.044%)	1	(0.007%)	1	(0.007%)
Conduction anaesthesia	560	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Other	1125	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
ASA classification											
ASA PS class 1	56196	16	(0.028%)	7	(0.012%)	5	(0.009%)	1	(0.002%)	1	(0.002%)
ASA PS class 2	98410	85	(0.086%)	37	(0.038%)	22	(0.022%)	4	(0.004%)	2	(0.002%)

ASA PS class 3	25563	17	(0.067%)	2	(0.008%)	2	(0.008%)	1	(0.004%)	1	(0.004%)
ASA PS class 4	549	1	(0.182%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
ASA PS class 5	11	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
ASA PS class 6	1	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
ASA PS class 1E	5300	3	(0.057%)	3	(0.057%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
ASA PS class 2E	9575	6	(0.063%)	5	(0.052%)	4	(0.042%)	2	(0.021%)	1	(0.010%)
ASA PS class 3E	6514	5	(0.077%)	2	(0.031%)	1	(0.015%)	0	(0.000%)	0	(0.000%)
ASA PS class 4E	1446	4	(0.277%)	1	(0.069%)	1	(0.069%)	1	(0.069%)	1	(0.069%)
ASA PS class 5E	109	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
ASA PS class 6E	1	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Classification error	268	-	-	-	-	-		-	-	-	-
Surgical position											
Supine position	147838	100	(0.068%)	39	(0.026%)	22	(0.015%)	5	(0.003%)	3	(0.002%)
Prone position	10106	6	(0.059%)	2	(0.020%)	2	(0.020%)	1	(0.010%)	1	(0.010%)
Lateral position	20642	18	(0.087%)	7	(0.034%)	4	(0.019%)	2	(0.010%)	2	(0.010%)
Lithotomy position	22882	11	(0.048%)	8	(0.035%)	6	(0.026%)	1	(0.004%)	0	(0.000%)
Sitting position	1069	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Other	1406	2	(0.142%)	1	(0.071%)	1	(0.071%)	0	(0.000%)	0	(0.000%)
Age (years old)											
0-5	9518	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
6-18	10255	2	(0.020%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)

19-65	99283	47	(0.047%)	19	(0.019%)	11	(0.011%)	4	(0.004%)	3	(0.003%)
66-85	79796	82	(0.103%)	36	(0.045%)	22	(0.028%)	4	(0.005%)	2	(0.003%)
86-	5081	6	(0.118%)	2	(0.039%)	2	(0.039%)	1	(0.020%)	1	(0.020%)
Classification error	10	-	-	-	-	-		-	-	-	-
Sex											
Men	99712	45	(0.045%)	16	(0.016%)	10	(0.010%)	2	(0.002%)	1	(0.001%)
Women	104223	92	(0.088%)	41	(0.039%)	25	(0.024%)	7	(0.007%)	5	(0.005%)
Classification error	8	-	-	-	-	-		-	-	-	-

All data were described as number and percentage.

Abbreviations: ASA PS, American society anesthesiologists performance status; PE, pulmonary embolism; VTE, venous thromboembolism

Supplemental Table 2. Details of clinical events within 90 days after postoperative symptomatic VTE events

Case Number	Age	Sex	BMI	Time from index VTE to events (days)	Types of index VTE	Time from surgery to index VTE (days)	Surgical site	ASA classification	Type of anaesthesia	Surgical position	Preexisting Medical Conditions	History of VTE or major bleeding
Cases of recurrent VTE												
1	73	Woman	24.8	9	PE with DVT	5	Brain	2	GA(I)	Spinal position		
2	69	Woman	26.5	48	PE	4	Upper abdomen	2	GA(I) with RA	Spinal position	AC	
3	75	Man	21.3	27	PE with DVT	21	Lower abdomen	2	SA	Lithotomy position	HT, DM, CKD, AC	
4	53	Man	21.6	7	DVT	11	Brain	2	GA(I)	Spinal position	HT, CKD	
5	40	Woman	14.3	59	DVT	7	Lower abdomen	2	GA(I) with RA	Spinal position	CKD, AC	
6	60	Woman	25.8	38	DVT	6	Lower abdomen	1	TIVA	Spinal position	CKD	

7	75	Woman	17.7	17	DVT	4	Lower abdomen	2	GA(I) with RA	Spinal position	CKD (Dialysis), AC	Major bleeding
Cases of major bleeding												
1	73	Woman	24.8	25	PE with DVT	5	Brain	2	GA(I)	Spinal position		
5	40	Woman	14.3	44	DVT	7	Lower abdomen	2	GA(I) with RA	Spinal position	CKD, AC	
7	75	Woman	17.7	62	DVT	4	Lower abdomen	2	GA(I) with RA	Spinal position	CKD (Dialysis), AC	Major bleeding
8	62	Woman	22.3	3	PE	10	Brain	2	TIVA	Spinal position	AC	VTE, Major bleeding
9	49	Man	22.5	4	PE	1	Brain	2	GA(I)	Spinal position	HT, Af, AC	
10	59	Woman	22.4	16	PE with DVT	20	Brain	3E	GA(I)	Spinal position	HT, CKD,	Major bleeding

11	50	Man	23.5	14	PE with DVT	7	Head, pharynx, larynx	2E	GA(I)	Spinal position	AC	
12	93	Woman	15.5	1	PE	0	Hip, upper / lower limbs	2	SA	Lateral position	HT, CKD	
13	55	Woman	20.2	6	DVT	2	Hip, upper / lower limbs	3	SA	Spinal position	MI, CTD	
Cases of all-cause death												
7	75	Woman	17.7	85	DVT	4	Lower abdomen	2	GA(I) with RA	Spinal position	CKD (Dialysis), AC	Major bleeding
10	59	Woman	22.4	17	PE with DVT	20	Brain	3E	GA(I)	Spinal position	HT, CKD,	Major bleeding
12	93	Woman	15.5	10	PE	0	Hip, upper / lower limbs	2	SA	Lateral position	HT, CKD	

14	65	Man	23.0	1	PE	1	Thorax	3	GA(I) with RA	Lateral position	CLD, LC	
15	66	Woman	27.3	1	PE with DVT	8	Spine	2	TIVA	Prone position	HT, DM	
16	42	Woman	25.9	1	PE	20	Hip, upper / lower limbs	2E	TIVA with RA	Spinal position		
17	68	Man	24.4	34	DVT	29	Hip, upper / lower limbs	3	SA	Spinal position	DM, CKD, AC	Major bleeding

Abbreviations: BMI, body mass index; DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; GA(I), inhalation general anaesthesia; TIVA, total venous general anaesthesia; GA(I) with RA, inhalation general anaesthesia combined with regional anaesthesia; TIVA with RA, total venous general anaesthesia combined with regional anaesthesia; SA, Spinal anaesthesia, AC, active cancer; Af, atrial fibrillation; CKD, chronic kidney disease; CLD, chronic lung disease; CTD, connective tissue disease; DM, diabetes mellitus; HT, hypertension; LC, liver cirrhosis; MI, myocardial infarction

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3	"Incidence, clinical characteristics, and long-term prognosis of postoperative symptomatic venous thromboembolism: a retrospective cohort study" Design: Retrospective observational study. Two datasets, COMMAND VTE Registry and Japanese Society of Anesthesiologists (JSA) annual report, were used for current analyses."
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4	We identified 137 patients with postoperative symptomatic VTE, including 57 patients with pulmonary embolism. The incidences of postoperative symptomatic VTE and pulmonary embolism were 0.067% and 0.028%, respectively, based on data from 203,943 patients who underwent surgery, managed by anesthesiologists, during the study period. The incidences of postoperative symptomatic VTE varied widely, depending on surgical and anesthetic characteristics. Postoperative symptomatic VTE occurred at a median of 8 days after surgery, with 58 patients (42%) diagnosed within 7 days. The cumulative incidence, 30 days after VTE, of recurrent VTE, major bleeding, and all-cause death was 3.0%, 5.2%, and 3.7%, respectively."
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7	"Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a serious postoperative complication which can result in an in-hospital death.[1, 2] In perioperative management, it is crucial to prevent postoperative symptomatic VTE and to respond promptly, once it is recognized. Therefore, clinicians should be familiar with the clinical features of postoperative symptomatic VTE to optimize their management strategies.

				Over the past 20 years, several guidelines have been recommended for the prophylaxis of postoperative VTE.[3-5] Despite the use of preventive measures, the incidence of postoperative VTE remains high and varies from 0.8% to 2.2%, according to reports from Western countries.[6-8] However, data on postoperative VTE from a cohort/registry-based study in Asian countries are scarce. A previous study reported a relatively low incidence (0.31%) of postoperative VTE throughout Japan.[9] However, it was a surveillance study of postoperative PE, conducted by mailing questionnaires to anaesthesiologists; therefore, the possibility of underreporting of events cannot be denied. Although the incidence of VTE in Asia has been considered to be lower than Western countries,[10] recent studies have suggested an underestimation of VTE in Asia.[11-13] No large-scale study has systematically evaluated the incidence of postoperative symptomatic VTE in Japan."
Objectives	3	State specific objectives, including any prespecified hypotheses	7	"Therefore, with a collaborative effort between cardiologists and anaesthesiologists, we investigated the incidence, clinical characteristics, and prognosis of postoperative symptomatic VTE, using a large, observational, real-world VTE database and an anaesthetic database of annual reports submitted to the Japanese Society of Anesthesiologists (JSA)."
Methods				
Study design	4	Present key elements of study design early in the paper	7	"In this study, two datasets were used for analyses. The first was Contemporary MAnageMent AND outcomes in patients with Venous ThromboEmbolism (COMMAND VTE) registry, a retrospective multicentre cohort study, which provided the data on patients with postoperative symptomatic VTE. The second was the JSA annual report, which provided cross-sectional data of all patients, who underwent

				surgical operations, managed by anaesthesiologists."
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9	"In this study, the JSA annual reports from January 2010 to December 2013 were collected from 18 centres that participated in the COMMAND VTE Registry. Furthermore, additional data of patients with postoperative symptomatic VTE, namely operative date, operative procedure, surgical sites, surgical position, and types of anaesthesia on anaesthetic charts at each centre, were obtained. In this study, the patients from the 18 centres registered in the COMMAND VTE Registry, for which the JSA annual report had been collected between January 2010 and December 2013, were enrolled (Figure 1). We could not enrol patients from the rest of the 11 centres of the COMMAND VTE Registry as their JSA annual reports and/or additional data on patients with postoperative symptomatic VTE were unavailable."
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9	"In this study, the patients from the 18 centres registered in the COMMAND VTE Registry, for which the JSA annual report had been collected between January 2010 and December 2013, were enrolled (Figure 1). We could not enrol patients from the rest of the 11 centres of the COMMAND VTE Registry as their JSA annual reports and/or additional data on patients with postoperative symptomatic VTE were unavailable. We also could not register the patients between January 2014 and August 2014, since the JSA annual report was from January to December of each year. Further, within the COMMAND VTE Registry, the patients diagnosed with acute symptomatic VTE, who underwent surgery 2 months prior to the VTE diagnosis, were identified. The overall population that had received anaesthetic management during the study period was retrieved from each centre's JSA annual report. Besides, additional data of

				patients with postoperative symptomatic VTE, namely operative date, operative procedure, surgical sites, surgical position, and types of anaesthesia on anaesthetic charts at each centre, were obtained."
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		Not relevant text
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-12	In the COMMAND VTE Registry, data for the patients' characteristics were collected from the hospital charts or hospital databases, according to the prespecified definitions, using an electronic case report form in a web-based database system. Physicians at each of the institutions were responsible for data entry, and data were automatically examined for missing or contradictory input and out-of-range values. Additional edits were performed at the general office of the registry. Patients with postoperative symptomatic VTE, identified through the COMMAND VTE Registry, were further investigated at each centre using the anaesthetic charts created through the collaboration of cardiologists and the anaesthesiologists at each participating centre. Anaesthesia-associated data, such as surgical site, surgical position, and type of anaesthesia were extracted and incorporated into the data from the COMMAND VTE Registry. The outcome measures assessed in this study were recurrent VTE, major bleeding, and all-cause death during the follow-up period, with a median of 1,507 days, in the surviving patients. Recurrent VTE was defined as symptomatic PE and/or DVT accompanied by confirmation of a new thrombus or exacerbation of the thrombus by objective imaging examinations or autopsy. Major bleeding was defined according to the International Society of Thrombosis and

				Haemostasis as a reduction in the haemoglobin level by at least 2 g/dL, transfusion of at least two units of blood, or symptomatic bleeding in a critical area or an organ.[16]"
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		No relevant text
Bias	9	Describe any efforts to address potential sources of bias		No relevant text
Study size	10	Explain how the study size was arrived at		No relevant text
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		No relevant text
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12	"The incidence of postoperative symptomatic VTE was calculated using a combination of data from the COMMAND Registry and the JSA annual reports from the 18 centres. The numerator of the incidence was the number of cases of postoperative symptomatic VTE extracted from the COMMAND Registry; the denominator was the number of surgeries in the JSA annual report."
		(*b*) Describe any methods used to examine subgroups and interactions	12	"The incidence of postoperative symptomatic VTE according to age, sex, surgical site, surgical position, and types of anaesthesia was calculated. The baseline and follow-up data were separately recorded for PE with or without DVT and DVT-only groups in patients with postoperative symptomatic VTE."
		(*c*) Explain how missing data were addressed	12	"No imputation was performed for missing data."
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		No relevant text
		(*e*) Describe any sensitivity analyses		No relevant text
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13-14	"Figure 1 represents the flow diagram of the study. We enrolled 3,027 consecutive patients with acute symptomatic VTE, after screening 19,634

				consecutive patients with suspected VTE for eligibility, using the chart review by the physicians at each institution. After excluding 2,334 patients without a history of surgery within 2 months before VTE diagnosis, 293 patients were identified with postoperative symptomatic VTE during hospitalization among all 29 centres of the COMMAND VTE Registry. Furthermore, 135 patients outside the eligible period and 21 patients who underwent surgery without the management of anaesthesiologists, were excluded. Finally, the study population consisted of 137 patients diagnosed with VTE within 2 months after surgery, from 18 centres, between January 2010 and December 2013. The total number of surgical cases managed by anaesthesiologists during the study period in 18 centres was 203,943."
		(b) Give reasons for non-participation at each stage	Figure 1	Figure 1 gives reasons for non-participation at each stage.
		(c) Consider use of a flow diagram	Figure 1	"The study flow diagram is shown in Figure 1"
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table1 Supplemental Table1 Table2	"Table 1 shows the baseline patient characteristics of both groups."
		(b) Indicate number of participants with missing data for each variable of interest		No relevant text
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		No relevant text
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	14,16	"The estimated incidence of postoperative symptomatic VTE was 0.067% (137/203,943) and VTE with PE was 0.028% (57/203,943) (Table 1). Of the 57 PE cases, 35 patients (0.017%) had hypoxic symptoms, nine patients (0.004%) presented with shock, and six patients (0.003%) had cardiac arrest. As for the surgical site, the incidence of postoperative symptomatic VTE was relatively high in surgeries involving the brain, hip, and upper/lower limbs. In terms of the types of anaesthesia, regional anaesthesia with or without general anaesthesia (0.100%) was associated with a higher incidence of VTE than general anaesthesia alone (0.045%) (Table 1 and

				Supplemental Table 1)." "Table 2 shows the demographic and clinical characteristics of patients with postoperative symptomatic VTE. Figure 2 presents the duration from the surgery to the diagnosis of postoperative symptomatic VTE. The median inter-quartile duration was 8 days (4–15 days); and 58 patients (42%) were diagnosed within 7 days of surgery, while 79 patients (58%) were diagnosed 7 days after the surgery. The greatest number of patients were diagnosed with VTE on postoperative day
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14	"The estimated incidence of postoperative symptomatic VTE was 0.067% (137/203,943) and VTE with PE was 0.028% (57/203,943) (Table 1). Of the 57 PE cases, 35 patients (0.017%) had hypoxic symptoms, nine patients (0.004%) presented with shock, and six patients (0.003%) had cardiac arrest."
		(*b*) Report category boundaries when continuous variables were categorized		
		© If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		No relevant text
Discussion				
Key results	18	Summarise key results with reference to study objectives	20	"The main findings of this study are as follows: 1) the incidence of postoperative symptomatic VTE within 2 months after surgery was 0.067% and VTE with PE was 0.028%, representing 203,943 patients from 18 centres in Japan; 2) the incidences of postoperative symptomatic VTE varied widely, according to surgical and anaesthetic characteristics; and 3) nearly half of the patients were diagnosed within 7 days of the surgery, while the rest were diagnosed 7 days after surgery, with the highest number of patients

				diagnosed on postoperative day 8."
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23-24	"First, two different databases were combined to estimate the incidence of postoperative symptomatic VTE. Although the COMMAND Registry included real consecutive patients with acute symptomatic VTE,[9, 17] for determining VTE incidence, we included only the cases in which intraoperative management was performed by an anaesthesiologist. Second, patients outside the eligible period in the COMMAND VTE Registry were also excluded, which may have influenced the results of this study. As a certain number of patients were excluded due to ineligible centres, the incidences of postoperative symptomatic VTE could have been greatly influenced, especially as the analysis targeted the low event rates. Third, this is a retrospective cohort study with inherent limitations based on the observational study design. In particular, the prophylactic and therapeutic management for postoperative symptomatic VTE were based on the discretion of the attending physicians, which may have influenced clinical outcomes. However, in the COMMAND Registry, the definitions of VTE were specified in advance, and the follow-up after VTE was nearly complete. Finally, we also considered the postoperative date of onset, but the disease may have developed before the surgery or the diagnosis. Nevertheless, we do not expect a significant gap between the onset and diagnosis, because we included only symptomatic patients with postoperative VTE."
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	24	"This study, combining the large real-world VTE database and anaesthetic database in Japan, revealed the incidence, clinical features, and prognosis of postoperative symptomatic VTE, providing useful information for all healthcare providers involved in various surgeries."
Generalizability	21	Discuss the generalizability (external validity) of the study results	21	"First, two different databases were combined to estimate the incidence of postoperative symptomatic VTE. Although the COMMAND

				Registry included real consecutive patients with acute symptomatic VTE,[9, 17] for determining VTE incidence, we included only the cases in which intraoperative management was performed by an anaesthesiologist. Second, patients outside the eligible period in the COMMAND VTE Registry were also excluded, which may have influenced the results of this study. As a certain number of patients were excluded due to ineligible centres, the incidences of postoperative symptomatic VTE could have been greatly influenced, especially as the analysis targeted the low event rates."
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25	"This work was supported in part by the JSPS KAKENHI (grant number 20K09242; TM, principal investigator). The COMMAND VTE Registry is supported by the independent clinical research organization (Research Institute for Production Development, Kyoto, Japan) and research funding from Mitsubishi Tanabe Pharma Corporation. The research funding had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript."

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Incidence, clinical characteristics, and long-term prognosis of postoperative symptomatic venous thromboembolism: a retrospective cohort study

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21

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ABSTRACT

Objectives: The purpose of this study was to evaluate the incidence, clinical characteristics, and prognosis of postoperative symptomatic VTE in Japan.

Design: Retrospective observational study. Two datasets, COMMAND VTE Registry and Japanese Society of Anesthesiologists (JSA) annual report, were used for current analyses.

Setting: Eighteen of 29 centres that participated in the COMMAND VTE Registry.

Participants: Acute symptomatic VTE patients who had undergone surgery 2 months prior to the diagnosis at 18 centres from January 2010 to December 2013 were identified in the COMMAND VTE Registry. From each centre's JSA annual report, the overall population that had received anaesthetic management during this period was retrieved.

Interventions: None.

Primary and secondary outcome measures: The primary outcome was the incidences and clinical characteristics of postoperative symptomatic VTE. The secondary outcomes were recurrent VTE, major bleeding, and all-cause death.

Results: We identified 137 patients with postoperative symptomatic VTE, including 57 patients with pulmonary embolism. The incidences of postoperative symptomatic VTE and pulmonary embolism were 0.067% and 0.028%, respectively, based on data from 203,943

patients who underwent surgery, managed by anaesthesiologists, during the study period. The incidences of postoperative symptomatic VTE varied widely, depending on surgical and anaesthetic characteristics. Postoperative symptomatic VTE occurred at a median of 8 days after surgery, with 58 patients (42%) diagnosed within 7 days. The cumulative incidence, 30 days after VTE, of recurrent VTE, major bleeding, and all-cause death was 3.0%, 5.2%, and 3.7%, respectively.

Conclusion: This study, combining the large real-world VTE and anaesthesiology databases in Japan revealed the incidence, clinical features, and prognosis of postoperative symptomatic VTE, providing useful insights for all healthcare providers involved in various surgeries.

Trial registration: Not applicable.

Key words: Venous thromboembolism; Pulmonary thromboembolism; Deep vein thrombosis; Postoperative; Prognosis

ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- VTE is considered relatively rare in Asian people, and the small number of cases makes epidemiological studies difficult to perform.
- This study combines data from the large real-world VTE database and anaesthetic database in Japan to provide information about the incidence, clinical features, and prognosis of postoperative symptomatic VTE.
- Another important feature of the current study was the comparison of the incidence of postoperative symptomatic VTE across surgical sites.
- This was a retrospective cohort study with inherent limitations based on its observational nature. Furthermore, as a certain number of patients from ineligible centres were excluded, the incidence of postoperative symptomatic VTE may have been influenced.

INTRODUCTION

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a serious postoperative complication which can result in an in-hospital death. [1, 2] In perioperative management, it is crucial to prevent postoperative symptomatic VTE and to respond promptly, once it is recognized. Therefore, clinicians should be familiar with the clinical features of postoperative symptomatic VTE to optimise their management strategies.

Over the past 20 years, several guidelines have been recommended for the prophylaxis of postoperative VTE.[3-5] Despite the use of preventive measures, the incidence of postoperative VTE remains high and varies from 0.58% to 2.2%, according to reports from Western countries.[6-8] Furthermore, the incidence rate of symptomatic VTE in patients after spinal surgery for metastases in the spine has been reported to be substantially higher (11%).[9] However, data on postoperative VTE from a cohort/registry-based study in Asian countries are scarce. A previous study reported a relatively low incidence (0.031%) of postoperative VTE throughout Japan.[10] However, it was a surveillance study of postoperative PE, conducted by mailing questionnaires to anaesthesiologists; therefore, the possibility of underreporting of events cannot be denied. Although the incidence of VTE in

Asia has been considered to be lower than Western countries,[11] recent studies have suggested an underestimation of VTE in Asia.[12-14] No large-scale study has systematically evaluated the incidence of postoperative symptomatic VTE in Japan.

Therefore, with a collaborative effort between cardiologists and anaesthesiologists, we investigated the incidence, clinical characteristics, and prognosis of postoperative symptomatic VTE, using a large, observational, real-world VTE database and an anaesthetic database of annual reports submitted to the Japanese Society of Anesthesiologists (JSA).

METHODS

Study design, setting, and population

In this study, two datasets were used for analyses. The first was Contemporary ManageMent AND outcomes in patients with Venous ThromboEmbolism (COMMAND VTE) registry, a retrospective multicentre cohort study, which provided the data on patients with postoperative symptomatic VTE. The second was the JSA annual report, which provided cross-sectional data of all patients, who underwent surgical operations, managed by anaesthesiologists.

The design of the COMMAND VTE Registry has been reported in detail elsewhere.[15] Briefly, this physician-initiated registry was a large cohort of consecutive patients with acute symptomatic VTE, who were objectively confirmed by the cardiologists at 29 centres in Japan, between January 2010 and August 2014. In this registry, the hospital databases were searched for clinical diagnoses and imaging examinations of patients with suspected VTE, and consecutive patients who met the definition of acute symptomatic VTE were enrolled. Baseline data were obtained from the hospital charts or hospital databases. Follow-up data on vital status, recurrent VTE, bleeding, and status of anticoagulation therapy, according to the prespecified definitions, were collected from the hospital charts, hospital databases, or by contacting patients, relatives, and/or referring to physicians through phone and/or mail.

As for the JSA annual reports, the training hospitals certified by the JSA are required to submit the annual reports to the JSA at the end of the year, which includes the total number of surgeries managed by anaesthesiologists, patient characteristics in detail, and surgical and anaesthetic information.

In this study, the JSA annual reports from January 2010 to December 2013 were collected from 18 centres that participated in the COMMAND VTE Registry. Furthermore,

additional data of patients with postoperative symptomatic VTE, namely operative date, operative procedure, surgical sites, surgical position, and types of anaesthesia on anaesthetic charts at each centre, were obtained.

In this study, patients from the 18 centres registered in the COMMAND VTE Registry, for which the JSA annual report was collected between January 2010 and December 2013, were enrolled (Figure 1). We could not enrol patients from the remaining 11 centres of the COMMAND VTE Registry as their JSA annual reports and/or additional data on patients with postoperative symptomatic VTE were unavailable. We also could not register the patients between January 2014 and August 2014, since the JSA annual report was from January to December of each year. Furthermore, within the COMMAND VTE Registry, cases of symptomatic postoperative VTE within 2 months [16] were identified. The overall population that had received anaesthetic management, during the study period was retrieved from each centre's JSA annual report. Besides, additional data of patients with postoperative symptomatic VTE, namely surgery date, surgical procedure, surgical site, surgical position, and type of anaesthesia on anaesthetic charts at each centre, were obtained.

Ethics

This retrospective observational study was conducted according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines. This study was approved by the Ethics Committee of the Kyoto University Hospital, Kyoto, Japan (approval number: R1822, December 18th, 2018; Chairperson Prof Shinji Kosugi). Following Ethics Committee approval, additional data, including the JSA annual reports, were collected from the centres listed in the Command VTE Registry, from March 2019 to September 2019. Written informed consent from each patient was waived, because we used clinical information obtained in routine clinical practice. This method is concordant with the guidelines for epidemiological studies issued by the Ministry of Health, Labor, and Welfare in Japan.

Patient and Public Involvement Statement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Definition of postoperative symptomatic venous thromboembolism

In this study, postoperative symptomatic VTE was defined as a thromboembolic event that occurred within 2 months of the postoperative period.[16] The symptoms of VTE were defined as sudden onset dyspnoea, pleuritic and substernal chest pain, cough, fever,

haemoptysis and syncope for PE; and erythema, warmth, pain, swelling, tenderness, and pain upon dorsiflexion of the foot for DVT. Additionally, a sudden onset of abnormality in the vital signs, such as a decrease in arterial oxygen saturation and hypotension were considered as symptoms of PE.

Collection of baseline patient characteristics and clinical follow-up data

In the COMMAND VTE Registry, data for the patients' characteristics were collected from the hospital charts or hospital databases, according to the prespecified definitions, using an electronic case report form in a web-based database system. Physicians at each of the institutions were responsible for data entry, and data were automatically examined for missing or contradictory input and out-of-range values. Additional edits were performed at the general office of the registry.

Patients with postoperative symptomatic VTE, identified through the COMMAND VTE Registry, were further investigated at each centre using the anaesthetic charts created through the collaboration of cardiologists and anaesthesiologists at each participating centre. Anaesthesia-associated data, such as surgical site, surgical position, and type of anaesthesia were extracted and incorporated into the data from the COMMAND VTE Registry.

The outcome measures assessed in this study were recurrent VTE, major bleeding, and all-cause death during the follow-up period, with a median of 1,507 days, in the surviving patients. Recurrent VTE was defined as symptomatic PE and/or DVT accompanied by confirmation of a new thrombus or exacerbation of the thrombus by objective imaging examinations or autopsy. Major bleeding was defined according to the International Society of Thrombosis and Hemostasis as a reduction in the haemoglobin level by at least 2 g/dL, transfusion of at least two units of blood, or symptomatic bleeding in a critical area or an organ.[17]

Statistical analysis

The incidence of postoperative symptomatic VTE was calculated using a combination of data from the COMMAND Registry and the JSA annual reports from the 18 centres. The numerator of the incidence was the number of cases of postoperative symptomatic VTE extracted from the COMMAND Registry; the denominator was the number of surgeries in the JSA annual report. The incidence of postoperative symptomatic VTE according to age, sex, surgical site, surgical position, and type of anaesthesia was calculated. The baseline and follow-up data were separately recorded for PE with or without DVT and DVT-only groups in patients with postoperative symptomatic VTE. No imputation was performed for missing

data. Categorical variables were calculated as numbers and percentages, and continuous variables were calculated as the means and standard deviations or the medians and interquartile ranges (IQR) based on their distributions. Additionally, the timing of the postoperative symptomatic VTE occurrence after the surgery was described. The Kaplan–Meier method was used to estimate the cumulative incidences of recurrent VTE, major bleeding, and all-cause death. The log-rank test was used to assess the differences in the cumulative incidences of the events between the PE- and DVT-only groups. In addition, we conducted an exploratory analysis to compare patients with and without active cancer. Two-sided P-values of less than 0.05 were considered significant. All statistical analyses were performed using SAS version 9.4 for Windows (SAS Institute Inc.; Cary, NC, USA) or JMP version 14.0.0 (SAS Institute Inc.; Cary, NC, USA).

RESULTS

Figure 1 represents the flow diagram of the study. We enrolled 3,027 consecutive patients with acute symptomatic VTE, after screening 19,634 consecutive patients with suspected VTE for eligibility, using the chart review by the physicians at each institution. After

199 excluding 2,734 patients without a history of surgery within 2 months before VTE diagnosis,
200 293 patients were identified with postoperative symptomatic VTE during hospitalisation
201 among all 29 centres of the COMMAND VTE Registry. Furthermore, 135 patients outside
202 the eligible period and 21 patients who underwent surgery without the management by
203 anaesthesiologists, were excluded. Finally, the study population consisted of 137 patients
204 diagnosed with VTE within 2 months after surgery, from 18 centres, between January 2010
205 and December 2013. The total number of surgical cases managed by anaesthesiologists
206 during the study period in 18 centres was 203,943.

207 **Incidence of postoperative symptomatic venous thromboembolism**

208 The estimated incidence of postoperative symptomatic VTE was 0.067% (137/203,943) and
209 VTE with PE was 0.028% (57/203,943) (Table 1). Of the 57 PE cases, 35 patients (61.4%)
210 had hypoxic symptoms, 9 patients (15.8%) presented with shock, and 6 patients (10.5%) had
211 cardiac arrest. As for the surgical site, the incidence of postoperative symptomatic VTE was
212 relatively high in surgeries involving the brain, hip, and upper/lower limbs. In terms of the
213 types of anaesthesia, regional anaesthesia with or without general anaesthesia (0.100%) was
214 associated with a higher incidence of VTE than general anaesthesia alone (0.045%) (Table 1
215 and Supplemental Table 1).

Table 1. Incidence of postoperative symptomatic VTE

	Total cases	VTE		PE		PE with hypoxia		PE with shock		PE with arrest	
Overall	203943	137	(0.067%)	57	(0.028%)	35	(0.017%)	9	(0.004%)	6	(0.003%)
Surgical Site		**P<0.001**		**P<0.001**		**P<0.001**		**P<0.001**		**P<0.001**	
Brain	9299	15	(0.161%)	8	(0.086%)	1	(0.011%)	0	(0.000%)	0	(0.000%)
Thorax	11100	4	(0.036%)	3	(0.027%)	2	(0.018%)	1	(0.009%)	1	(0.009%)
Cardiovascular	13637	6	(0.044%)	1	(0.007%)	1	(0.007%)	1	(0.007%)	1	(0.007%)
Thorax and abdomen	1656	2	(0.121%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Upper abdomen	27035	17	(0.063%)	11	(0.041%)	8	(0.030%)	1	(0.004%)	0	(0.000%)
Lower abdomen	42875	31	(0.072%)	16	(0.037%)	11	(0.026%)	3	(0.007%)	1	(0.002%)
Caesarean section	5056	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Head, pharynx, larynx	35414	4	(0.011%)	2	(0.006%)	2	(0.006%)	0	(0.000%)	0	(0.000%)
Chest, abdominal wall, perineum	22633	3	(0.013%)	2	(0.009%)	2	(0.009%)	0	(0.000%)	0	(0.000%)
Spine	7040	7	(0.099%)	3	(0.043%)	2	(0.028%)	1	(0.014%)	1	(0.014%)
Hip, upper/lower limbs	25160	48	(0.191%)	11	(0.044%)	6	(0.024%)	2	(0.008%)	2	(0.008%)
Other	2038	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)

All data are described as numbers and percentages. The proportions of cases at each surgical site were compared using the chi-squared test.

Abbreviations: PE, pulmonary embolism; VTE, venous thromboembolism

Baseline characteristics and timing of venous thromboembolism diagnosis

Table 2 shows the demographic and clinical characteristics of patients with postoperative symptomatic VTE. Figure 2 presents the duration from the surgery to the diagnosis of postoperative symptomatic VTE. The median inter-quartile duration was 8 days (4–15 days); and 58 patients (42%) were diagnosed within 7 days of surgery, while 79 patients (58%) were diagnosed 7 days after the surgery. The greatest number of patients were diagnosed with VTE on postoperative day 8.

Table 2. Baseline patients' characteristics

	Total VTE N=137	PE with or without DVT (N=57)	DVT only (N=80)
Baseline characteristics			
Age (years)	66.2 ±15.5	67.7 ±12.6	65.1 ±17.2
Men	55 (40.1%)	22 (38.6%)	33 (41.3%)
Body weight (kg)	56.3 ±11.8	57.8 ±11.1	55.3 ±12.3
Body mass index (kg/m^2)	23.2 ±4.3	23.6 ±3.7	22.9 ±4.7
Surgical and anaesthesia characteristics			
ASA PS			
ASA PS 1	19 (13.9%)	10 (17.5%)	9 (11.3%)
ASA PS 2	91 (66.4%)	42 (73.7%)	49 (61.3%)
ASA PS 3	22 (16.1%)	4 (7.0%)	18 (22.5%)
ASA PS 4	5 (3.6%)	1 (1.8%)	4 (5.0%)
Emergent surgery	18 (13.1%)	11 (19.3%)	7 (8.8%)
Surgical site			
Hip and limb	48 (35.0%)	11 (19.3%)	37 (46.3%)
Brain	15 (10.9%)	8 (14.0%)	7 (8.8%)
Thorax and mediastinum	4 (2.9%)	3 (5.3%)	1 (1.3%)

Cardiovascular	6	(4.4%)	1	(1.8%)	5	(6.3%)
Thorax and abdomen	2	(1.5%)	0	(0.0%)	2	(2.5%)
Upper abdomen	17	(12.4%)	11	(19.3%)	6	(7.5%)
Lower abdomen	31	(22.6%)	16	(28.1%)	15	(18.8%)
Head and neck	4	(2.9%)	2	(3.5%)	2	(2.5%)
Chest abdominal wall and perineum	3	(2.2%)	2	(3.5%)	1	(1.3%)
Spine	7	(5.1%)	3	(5.3%)	4	(5.0%)
Type of Anaesthesia						
General anaesthesia	61	(44.5%)	26	(45.6%)	35	(43.8%)
General anaesthesia with regional anaesthesia	56	(40.9%)	24	(42.1%)	32	(40.0%)
Local anaesthesia	20	(14.6%)	7	(12.3%)	13	(16.3%)
Surgical position						
Supine position	100	(73.0%)	39	(68.4%)	61	(76.3%)
Prone position	6	(4.4%)	2	(3.5%)	4	(5.0%)
Lateral position	18	(13.1%)	7	(12.3%)	11	(13.8%)
Lithotomy position	11	(8.0%)	8	(14.0%)	3	(3.8%)
Other position	2	(1.5%)	1	(1.8%)	1	(1.3%)
Comorbidities						
Hypertension	43	(31.4%)	22	(38.6%)	21	(26.3%)
Diabetes mellitus	15	(10.9%)	7	(12.3%)	8	(10.0%)
Chronic kidney disease	24	(17.5%)	8	(14.0%)	16	(20.0%)
Dialysis	2	(1.5%)	0	(0.0%)	2	(2.5%)
History of chronic lung disease	13	(9.5%)	3	(5.3%)	10	(12.5%)
History of heart failure	6	(4.4%)	3	(5.3%)	3	(3.8%)
History of myocardial infarction	4	(2.9%)	0	(0.0%)	4	(5.0%)
History of stroke	9	(6.6%)	5	(8.8%)	4	(5.0%)
Atrial fibrillation	8	(5.8%)	7	(12.3%)	1	(1.3%)
Liver cirrhosis	3	(2.2%)	2	(3.5%)	1	(1.3%)
Connective tissue disease	5	(3.6%)	1	(1.8%)	4	(5.0%)
History of VTE	1	(0.7%)	1	(1.8%)	0	(0.0%)
History of major bleeding	17	(12.4%)	7	(12.3%)	10	(12.5%)
Active cancer	41	(29.9%)	24	(42.1%)	17	(21.3%)
Varicose vein	8	(5.8%)	3	(5.3%)	5	(6.3%)
Anticoagulants at VTE diagnosis	14	(10.2%)	6	(10.5%)	8	(10.0%)

Heparin	6	(4.4%)	3	(5.3%)	3	(3.8%)
Warfarin	3	(2.2%)	2	(3.5%)	1	(1.3%)
Direct oral anticoagulant	5	(3.6%)	1	(1.8%)	4	(5.0%)
Presentation						
PE with hypoxemia	-	-	35	(61.4%)	-	-
PE with Shock	-	-	9	(15.8%)	-	-
PE with cardiac arrest/collapse	-	-	6	(10.5%)	-	-
Proximal DVT	64	(46.7%)	21	(36.8%)	43	(53.8%)
Laboratory tests at diagnosis						
Anaemia	109	(82.6%)	45	(83.3%)	64	(82.1%)
Thrombocytopenia	6	(4.4%)	5	(8.8%)	1	(1.3%)
eGFR (mL/min/m^2)	78.3	(59.0-91.8)	72.7	(51.2-87.7)	80.4	(62.4-93.6)
eGFR <60mL/min/m^2	36	(26.3%)	17	(29.8%)	19	(23.8%)
D-dimer (μg/mL, n=122)	16.5	(8.6-31.5)	16.8	(8.6-39.3)	16.4	(7.9-27.3)
Thrombophilia	4	(2.9%)	3	(5.3%)	1	(1.3%)
Initial anticoagulation therapy	115	(83.9%)	53	(93.0%)	62	(77.5%)
Heparin	107	(78.1%)	52	(91.2%)	55	(68.8%)
Fondaparinux	11	(8.0%)	2	(3.5%)	9	(11.3%)
Thrombolysis	8	(5.8%)	5	(8.8%)	3	(3.8%)
Inferior vena cava filter use	26	(19.0%)	13	(22.8%)	13	(16.3%)
Ventilator support	6	(4.4%)	6	(10.5%)	0	(0.0%)
Percutaneous cardiopulmonary support	2	(1.5%)	2	(3.5%)	0	(0.0%)

Categorical variables are presented as numbers and percentages, and continuous variables are presented as the means and standard deviations or the medians and interquartile ranges based on their distributions. Chronic kidney disease was diagnosed if there was persistent proteinuria or if eGFR was <60 mL/min/1.73 m^2 for more than 3 months. The values of eGFR were calculated based on the equation reported by the Japan Association of Chronic Kidney Disease Initiative [man: 194*Scr−1.094*age-0.287, woman: 194*Scr−1.094*age-0.287*0.739]. Anaemia was diagnosed if the value of haemoglobin was <13 g/dL for men and <12 g/dL for women. Thrombophilia includes protein C deficiency, protein S deficiency, antithrombin deficiency, and antiphospholipid syndrome.

Abbreviations: ASA PS, American society anesthesiologists Performance Status; DVT, deep venous thrombosis; eGFR, estimated glomerular filtration rate; PE, pulmonary embolism; VTE, venous thromboembolism

Clinical outcomes after postoperative symptomatic venous thromboembolism

The cumulative incidence of recurrent VTE was 3.0% at the 30-day follow-up, 5.3% at the 90-day follow-up, and 5.3% at the 5-year follow-up after postoperative symptomatic VTE (Figure 3a). The cumulative incidence of major bleeding was 5.2% at 30-day follow-up, 6.7% at the 90-day follow-up, and 12.6% at the 5-year follow-up (Figure 3b). The cumulative incidence of all-cause death was 3.7% at the 30-day follow-up, 5.1% at the 90-day follow-up, and 27.4% at the 5-year follow-up (Figure 3c). The details of clinical events within 90 days are given in Supplemental Table 2. VTE recurrence occurred in seven patients (4 patients were treated with anticoagulant therapy), all of which were early recurrences within 60 days of diagnosis. The difference in the cumulative incidence of recurrent VTE, major bleeding, and all-cause death was not significant between the PE- and DVT-only groups, although the 30-day incidence of major bleeding and all-cause death was higher in the PE group than in the DVT-only group (11.1% versus 1.3%, and 8.8% versus 0.0%, respectively) (Figure 4). The cumulative 5-year incidence of recurrent VTE was not significantly different between patients with and without active cancer (9.9% versus 3.3%, Log-rank P=0.13) (Figure 5). In

contrast, the cumulative 5-year incidences of major bleeding and all-cause death were significantly higher in patients with active cancer than in those without active cancer (major bleeding: 21.3% versus 8.8%, Log-rank P=0.046, all-cause death: 45.5% versus 19.8%, Log-rank P=0.001) (Figure5).

DISCUSSION

The main findings of this study are as follows: 1) the incidence of postoperative symptomatic VTE within 2 months after surgery was 0.067% and VTE with PE was 0.028%, representing 203,943 patients from 18 centres in Japan; 2) the incidence of postoperative symptomatic VTE varied widely, according to surgical and anaesthetic characteristics; and 3) nearly half of the patients were diagnosed within 7 days of the surgery, while the rest were diagnosed 7 days after surgery, with the highest number of patients diagnosed on postoperative day 8.

The strength of the present study is that the diagnosis of symptomatic VTE was accurately diagnosed by cardiologists (specialists for VTE in Japan), and the detailed information about this post-operative complication and its long-term prognosis could be evaluated, in contrast to previous studies on the subject.

VTE is considered relatively rare in Asian people and the small number of cases makes epidemiological studies difficult to perform.[11] Previously, three major studies from Japan had evaluated the incidence of the postoperative complication of VTE.[10,18,19] The first study was based on the JSA initiated questionnaire annual survey, where the incidence of PE was 0.031% (3,667/ 11,786,489).[10] The second study used the diagnosis–procedure combination (DPC) database, and the incidence of VTE and PE was 0.24% (2,485/1,016,496) and 0.05% (538/1,016,496), respectively.[18] The third study used the National Clinical Database (NCD), a nationwide project linked to the surgical board certification system. The incidence of DVT and PE was 0.26% (984/382,124) and 0.14% (553/382,124), respectively.[19] The incidence of postoperative symptomatic VTE in the current study was lower than that in the DPC study. In the DPC study, VTE was identified based on the International Classification of Diseases, 10th version (ICD-10) codes; and therefore, it may have been misclassified and overrated. In this study, we used data on symptomatic VTE confirmed by cardiologists. This may explain the lower incidence compared with the NCD study, which included asymptomatic VTE. The incidence of postoperative VTE was reported to be 0.58%–2.2%, based on the clinical databases in the USA. Therefore, postoperative VTE incidence was suggested to be lower in Japan than in the United States and Europe. These

differences could be explained by ethnic variations.[11] Western guidelines, [4, 5] due to racial disparities, are more likely to lead to over-triage in the Japanese population.

Another important feature of the current study was the comparison of the incidence of postoperative symptomatic VTE across surgical sites. Similar to the JSA initiated questionnaire study,[10] neurosurgeries and orthopaedic surgeries (hip, upper, and lower extremity) were associated with a higher incidence of postoperative symptomatic VTE. According to the Japanese guidelines, there is a high risk of postoperative symptomatic VTE in patients over 40 years of age undergoing major cancer surgery; however, in the present study, abdominal surgery was not identified with high risk. Therefore, risks should be stratified according to the surgical sites and procedures, and the additional risks in each patient should be considered in the preventive strategies.

Additionally, in this study, the timing of the onset of postoperative symptomatic VTE was bimodal. These results may suggest that postoperative symptomatic VTE occurs, not only in the very acute postoperative period, which is directly affected by surgical immobilisation, but also approximately 10 days after surgery; the information can guide the healthcare providers involved in surgery, regarding the risk perception and diagnosis of postoperative symptomatic VTE.

The duration of anticoagulant therapy is generally divided into an initial treatment phase (up to 7 days), a maintenance treatment phase (~3 months after the initial treatment), and prolonged treatment phase (beyond 3 months).[20] Surgery is a transient risk factor for VTE; prolonged treatment is usually not performed, as the possibility of recurrence is considered relatively low. In this study, VTE recurrence had occurred in all seven affected patients within 3 months of the onset, and no recurrence was observed after 3 months, suggesting the importance of relatively early recurrence.

PE was apparently associated with a higher mortality, especially in the early phase of postoperative symptomatic VTE, although the difference between the PE- and DVT-only groups was not significant. This difference may be explained by the insufficient sample size. Notably, the initial mortality rate and recurrence rate was higher for acute PE than for DVT.[21, 22] Therefore, in comparison to DVT, postoperative PE should be more closely monitored and aggressively treated.[3]

Study limitations

First, two different databases were combined to estimate the incidence of postoperative symptomatic VTE. Although the COMMAND Registry included real consecutive patients with acute symptomatic VTE,[10, 18] for determining VTE incidence, we included only the

cases in which intraoperative management was performed by an anaesthesiologist. Second, patients outside the eligible period in the COMMAND VTE Registry were also excluded, which may have influenced the results of this study. As a certain number of patients were excluded due to ineligible centres, the incidence of postoperative symptomatic VTE could have been greatly influenced, especially as the analysis targeted low event rates. Third, this was a retrospective cohort study with inherent limitations based on the observational study design. In particular, the prophylactic and therapeutic management for postoperative symptomatic VTE were based on the discretion of the attending physicians, which may have influenced the clinical outcomes. However, in the COMMAND Registry, the definitions of VTE were specified in advance, and the follow-up after VTE was nearly complete. Fourth, the incidence of postoperative symptomatic VTE may depend on the status of VTE prophylaxis. However, the JSA annual report does not include data on prophylaxis status, and we could not determine this status for the entire study population. Fifth, the JSA annual report does not include data on the status of malignancy either, and we could not determine it for the entire study population. Finally, we also considered the postoperative date of onset, but the disease may have developed before the surgery or the diagnosis. Nevertheless, we do

not expect a significant gap between the onset and diagnosis, because we included only symptomatic patients with postoperative VTE.

Conclusions

This study, combining the large real-world VTE database and anaesthetic database in Japan, revealed the incidence, clinical features, and prognosis of postoperative symptomatic VTE, providing useful information for all healthcare providers involved in various surgeries.

Declarations

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Competing interests

Dr. Yamashita received lecture fees from Daiichi-Sankyo, Bristol-Myers Squibb, Pfizer, and Bayer Healthcare. Dr. Morimoto received lecture fees from Mitsubishi Tanabe Pharma and Pfizer Japan and consultant fees from Asahi Kasei, Bristol-Myers Squibb, and Boston Scientific. Dr. Kawakami received consulting fees from Kaken Pharmaceutical Co., Ltd.; research funds from Sumitomo Dainippon Pharma Co., Ltd., Bayer Yakuhin Ltd., Stella Pharma Corporation, CMIC Co., Ltd., and Pfizer Japan Inc.; honorarium from Daiichi-

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Author Contributions

Chikashi Takeda, MD, PhD: This author had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. This author helped design and conduct the study, analyse the data, and write and revise the manuscript.

Yugo Yamashita, MD, PhD: This author also had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. This author helped design and conduct the study, analyse the data, and write and revise the manuscript.

Masato Takeuchi, MD, PhD, MPH: This author helped analyse the data and write and revise the manuscript.

Hiroshi Yonekura, MD MPH: This author helped analyse the data and write and revise the manuscript.

Li Dong, MD: This author helped analyse the data and write the manuscript.

Miho Hamada, MD: This author helped analyse the data and write and revise the manuscript.

Akiko Hirotsu, MD, PhD: This author helped analyse the data and write and revise the manuscript.

Koh Ono, MD, PhD: This author helped analyse the data and write and revise the manuscript.

Koji Kawakami, MD, PhD: This author helped analyse the data and write and revise the manuscript.

Kazuhiko Fukuda, MD, PhD: This author helped design and conduct the study and write the manuscript.

Takeshi Morimoto, MD, PhD, MPH: This author helped design and conduct the study, analyse the data, and write and revise the manuscript.

Takeshi Kimura, MD, PhD: This author helped conduct the study, analyse the data, and write and revise the manuscript.

Toshiyuki Mizota, MD, PhD: This author helped design and conduct the study, analyse the data, and write and revise the manuscript.

Availability of data and materials

Data available on request from the authors. The data that support the findings of this study are available from Chikashi Takeda or Yugo Yamashita, upon reasonable request.

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Figure legends

Figure 1. Study flow diagram.

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; JSA, Japanese Society of Anesthesiologists; COMMAND VTE, Contemporary management and outcomes in patients with venous thromboembolism.

Figure 2. The distribution of days of VTE diagnosis after surgery.

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

Figure 3. The Kaplan–Meier curves for the clinical events after VTE diagnosis.

(a) Recurrent VTE, (b) Major bleeding, and (c) All-cause death.

VTE, venous thromboembolism.

Figure 4. The Kaplan–Meier curves for the clinical events after VTE diagnosis comparing PE and DVT.

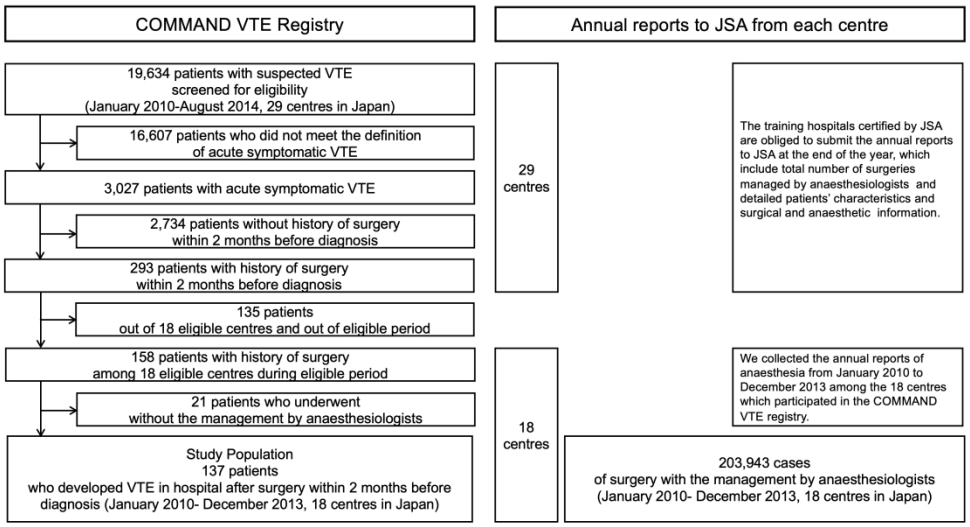
(a) Recurrent VTE, (b) Major bleeding, and (c) All-cause death.

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism

Figure 5. The Kaplan–Meier curves for clinical events after VTE diagnosis with and without active cancer.

(a) Recurrent VTE, (b) Major bleeding, and (c) All-cause death.

DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism



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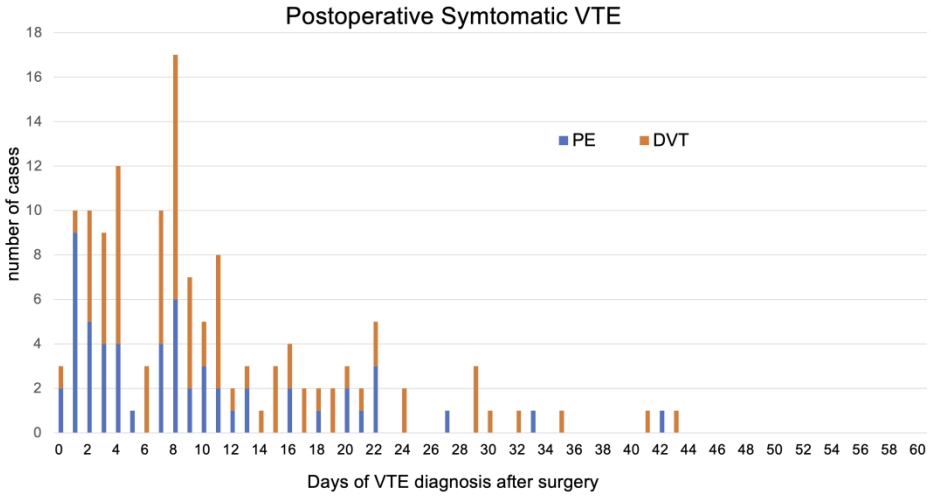

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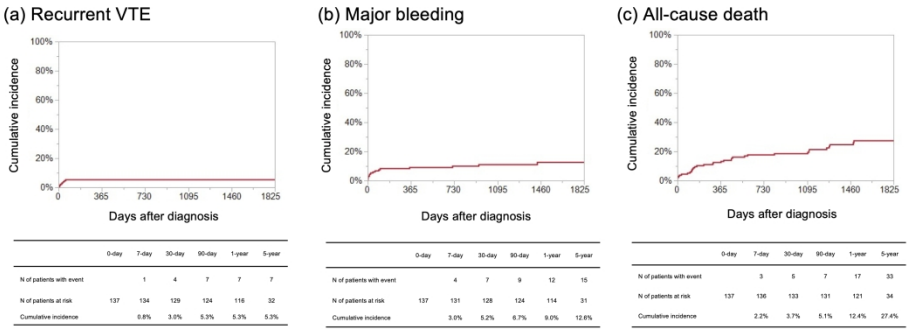

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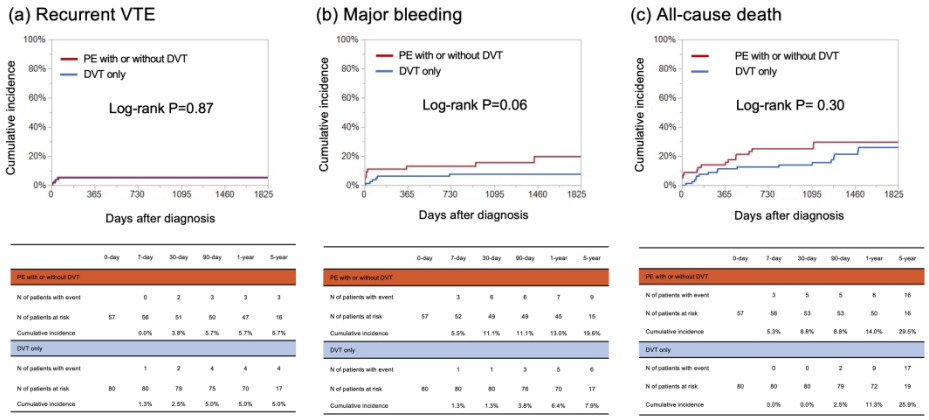

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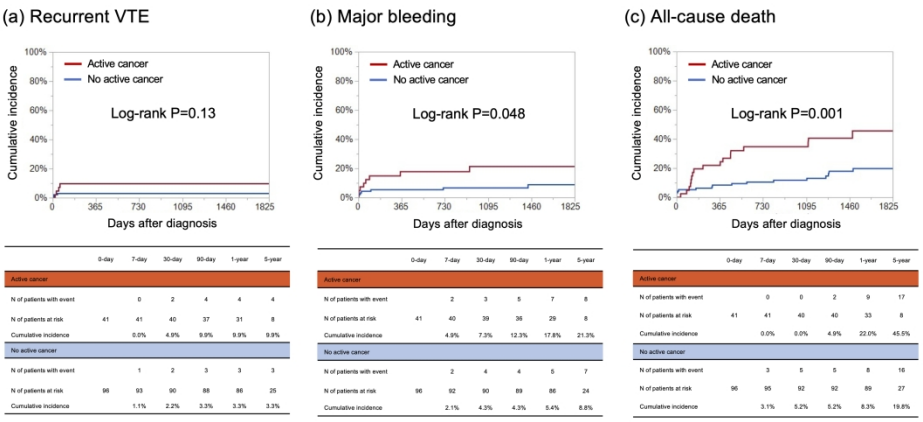

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Supplemental Table 1. Incidence of postoperative symptomatic VTE

	Total cases	VTE		PE		PE with hypoxia		PE with shock		PE with arrest	
Overall	203943	137	(0.067%)	57	(0.028%)	35	(0.017%)	9	(0.004%)	6	(0.003%)
Type of anaesthesia											
Inhalation general anaesthesia	110833	49	(0.044%)	23	(0.021%)	13	(0.012%)	3	(0.003%)	1	(0.001%)
Total venous general anaesthesia	25467	12	(0.047%)	3	(0.012%)	1	(0.004%)	1	(0.004%)	1	(0.004%)
Inhalation general anaesthesia combined with regional anaesthesia	34872	46	(0.132%)	19	(0.054%)	11	(0.032%)	2	(0.006%)	2	(0.006%)
Total venous general anaesthesia combined with regional anaesthesia	12863	10	(0.078%)	5	(0.039%)	4	(0.031%)	2	(0.016%)	1	(0.008%)
Combined spinal and epidural anaesthesia	4078	4	(0.098%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Epidural anaesthesia	623	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Spinal anaesthesia	13522	16	(0.118%)	7	(0.052%)	6	(0.044%)	1	(0.007%)	1	(0.007%)
Conduction anaesthesia	560	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Other	1125	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
ASA classification											
ASA PS class 1	56196	16	(0.028%)	7	(0.012%)	5	(0.009%)	1	(0.002%)	1	(0.002%)
ASA PS class 2	98410	85	(0.086%)	37	(0.038%)	22	(0.022%)	4	(0.004%)	2	(0.002%)

ASA PS class 3	25563	17	(0.067%)	2	(0.008%)	2	(0.008%)	1	(0.004%)	1	(0.004%)
ASA PS class 4	549	1	(0.182%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
ASA PS class 5	11	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
ASA PS class 6	1	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
ASA PS class 1E	5300	3	(0.057%)	3	(0.057%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
ASA PS class 2E	9575	6	(0.063%)	5	(0.052%)	4	(0.042%)	2	(0.021%)	1	(0.010%)
ASA PS class 3E	6514	5	(0.077%)	2	(0.031%)	1	(0.015%)	0	(0.000%)	0	(0.000%)
ASA PS class 4E	1446	4	(0.277%)	1	(0.069%)	1	(0.069%)	1	(0.069%)	1	(0.069%)
ASA PS class 5E	109	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
ASA PS class 6E	1	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Classification error	268	-	-	-	-	-	-	-	-	-	-
Surgical position											
Supine position	147838	100	(0.068%)	39	(0.026%)	22	(0.015%)	5	(0.003%)	3	(0.002%)
Prone position	10106	6	(0.059%)	2	(0.020%)	2	(0.020%)	1	(0.010%)	1	(0.010%)
Lateral position	20642	18	(0.087%)	7	(0.034%)	4	(0.019%)	2	(0.010%)	2	(0.010%)
Lithotomy position	22882	11	(0.048%)	8	(0.035%)	6	(0.026%)	1	(0.004%)	0	(0.000%)
Sitting position	1069	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
Other	1406	2	(0.142%)	1	(0.071%)	1	(0.071%)	0	(0.000%)	0	(0.000%)
Age (years old)											
0-5	9518	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)
6-18	10255	2	(0.020%)	0	(0.000%)	0	(0.000%)	0	(0.000%)	0	(0.000%)

19-65	99283	47	(0.047%)	19	(0.019%)	11	(0.011%)	4	(0.004%)	3	(0.003%)
66-85	79796	82	(0.103%)	36	(0.045%)	22	(0.028%)	4	(0.005%)	2	(0.003%)
86-	5081	6	(0.118%)	2	(0.039%)	2	(0.039%)	1	(0.020%)	1	(0.020%)
Classification error	10	-	-	-	-	-		-	-	-	-
Sex											
Men	99712	45	(0.045%)	16	(0.016%)	10	(0.010%)	2	(0.002%)	1	(0.001%)
Women	104223	92	(0.088%)	41	(0.039%)	25	(0.024%)	7	(0.007%)	5	(0.005%)
Classification error	8	-	-	-	-	-		-	-	-	-

All data were described as number and percentage.

Abbreviations: ASA PS, American society anesthesiologists performance status; PE, pulmonary embolism; VTE, venous thromboembolism

Supplemental Table 2. Details of clinical events within 90 days after postoperative symptomatic VTE events

Case Number	Age	Sex	BMI	Time from index VTE to events (days)	Types of index VTE	Time from surgery to index VTE (days)	Surgical site	ASA classification	Type of anaesthesia	Surgical position	Preexisting Medical Conditions	History of VTE or major bleeding
Cases of recurrent VTE												
1	73	Woman	24.8	9	PE with DVT	5	Brain	2	GA(I)	Spinal position		
2	69	Woman	26.5	48	PE	4	Upper abdomen	2	GA(I) with RA	Spinal position	AC	
3	75	Man	21.3	27	PE with DVT	21	Lower abdomen	2	SA	Lithotomy position	HT, DM, CKD, AC	
4	53	Man	21.6	7	DVT	11	Brain	2	GA(I)	Spinal position	HT, CKD	
5	40	Woman	14.3	59	DVT	7	Lower abdomen	2	GA(I) with RA	Spinal position	CKD, AC	
6	60	Woman	25.8	38	DVT	6	Lower abdomen	1	TIVA	Spinal position	CKD	

7	75	Woman	17.7	17	DVT	4	Lower abdomen	2	GA(I) with RA	Spinal position	CKD (Dialysis), AC	Major bleeding
Cases of major bleeding												
1	73	Woman	24.8	25	PE with DVT	5	Brain	2	GA(I)	Spinal position		
5	40	Woman	14.3	44	DVT	7	Lower abdomen	2	GA(I) with RA	Spinal position	CKD, AC	
7	75	Woman	17.7	62	DVT	4	Lower abdomen	2	GA(I) with RA	Spinal position	CKD (Dialysis), AC	Major bleeding
8	62	Woman	22.3	3	PE	10	Brain	2	TIVA	Spinal position	AC	VTE, Major bleeding
9	49	Man	22.5	4	PE	1	Brain	2	GA(I)	Spinal position	HT, Af, AC	
10	59	Woman	22.4	16	PE with DVT	20	Brain	3E	GA(I)	Spinal position	HT, CKD,	Major bleeding

11	50	Man	23.5	14	PE with DVT	7	Head, pharynx, larynx	2E	GA(I)	Spinal position	AC	
12	93	Woman	15.5	1	PE	0	Hip, upper / lower limbs	2	SA	Lateral position	HT, CKD	
13	55	Woman	20.2	6	DVT	2	Hip, upper / lower limbs	3	SA	Spinal position	MI, CTD	
Cases of all-cause death												
7	75	Woman	17.7	85	DVT	4	Lower abdomen	2	GA(I) with RA	Spinal position	CKD (Dialysis), AC	Major bleeding
10	59	Woman	22.4	17	PE with DVT	20	Brain	3E	GA(I)	Spinal position	HT, CKD,	Major bleeding
12	93	Woman	15.5	10	PE	0	Hip, upper / lower limbs	2	SA	Lateral position	HT, CKD	

14	65	Man	23.0	1	PE	1	Thorax	3	GA(I) with RA	Lateral position	CLD, LC	
15	66	Woman	27.3	1	PE with DVT	8	Spine	2	TIVA	Prone position	HT, DM	
16	42	Woman	25.9	1	PE	20	Hip, upper / lower limbs	2E	TIVA with RA	Spinal position		
17	68	Man	24.4	34	DVT	29	Hip, upper / lower limbs	3	SA	Spinal position	DM, CKD, AC	Major bleeding

Abbreviations: BMI, body mass index; DVT, deep venous thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; GA(I), inhalation general anaesthesia; TIVA, total venous general anaesthesia; GA(I) with RA, inhalation general anaesthesia combined with regional anaesthesia; TIVA with RA, total venous general anaesthesia combined with regional anaesthesia; SA, Spinal anaesthesia, AC, active cancer; Af, atrial fibrillation; CKD, chronic kidney disease; CLD, chronic lung disease; CTD, connective tissue disease; DM, diabetes mellitus; HT, hypertension; LC, liver cirrhosis; MI, myocardial infarction

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1,3	"Incidence, clinical characteristics, and long-term prognosis of postoperative symptomatic venous thromboembolism: a retrospective cohort study" "Design: Retrospective observational study. Two datasets, COMMAND VTE Registry and Japanese Society of Anesthesiologists (JSA) annual report, were used for current analyses."
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4	"We identified 137 patients with postoperative symptomatic VTE, including 57 patients with pulmonary embolism. The incidences of postoperative symptomatic VTE and pulmonary embolism were 0.067% and 0.028%, respectively, based on data from 203,943 patients who underwent surgery, managed by anesthesiologists, during the study period. The incidences of postoperative symptomatic VTE varied widely, depending on surgical and anesthetic characteristics. Postoperative symptomatic VTE occurred at a median of 8 days after surgery, with 58 patients (42%) diagnosed within 7 days. The cumulative incidence, 30 days after VTE, of recurrent VTE, major bleeding, and all-cause death was 3.0%, 5.2%, and 3.7%, respectively."
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7	"Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a serious postoperative complication which can result in an in-hospital death.[1, 2] In perioperative management, it is crucial to prevent postoperative symptomatic VTE and to respond promptly, once it is recognized. Therefore, clinicians should be familiar with the clinical features of postoperative symptomatic VTE to optimize their management strategies."

				Over the past 20 years, several guidelines have been recommended for the prophylaxis of postoperative VTE.[3-5] Despite the use of preventive measures, the incidence of postoperative VTE remains high and varies from 0.8% to 2.2%, according to reports from Western countries.[6-8] However, data on postoperative VTE from a cohort/registry-based study in Asian countries are scarce. A previous study reported a relatively low incidence (0.31%) of postoperative VTE throughout Japan.[9] However, it was a surveillance study of postoperative PE, conducted by mailing questionnaires to anaesthesiologists; therefore, the possibility of underreporting of events cannot be denied. Although the incidence of VTE in Asia has been considered to be lower than Western countries,[10] recent studies have suggested an underestimation of VTE in Asia.[11-13] No large-scale study has systematically evaluated the incidence of postoperative symptomatic VTE in Japan."
Objectives	3	State specific objectives, including any prespecified hypotheses	7	"Therefore, with a collaborative effort between cardiologists and anaesthesiologists, we investigated the incidence, clinical characteristics, and prognosis of postoperative symptomatic VTE, using a large, observational, real-world VTE database and an anaesthetic database of annual reports submitted to the Japanese Society of Anesthesiologists (JSA)."
Methods				
Study design	4	Present key elements of study design early in the paper	7	"In this study, two datasets were used for analyses. The first was Contemporary MAnageMent AND outcomes in patients with Venous ThromboEmbolism (COMMAND VTE) registry, a retrospective multicentre cohort study, which provided the data on patients with postoperative symptomatic VTE. The second was the JSA annual report, which provided cross-sectional data of all patients, who underwent

				surgical operations, managed by anaesthesiologists."
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	8-9	"In this study, the JSA annual reports from January 2010 to December 2013 were collected from 18 centres that participated in the COMMAND VTE Registry. Furthermore, additional data of patients with postoperative symptomatic VTE, namely operative date, operative procedure, surgical sites, surgical position, and types of anaesthesia on anaesthetic charts at each centre, were obtained. In this study, the patients from the 18 centres registered in the COMMAND VTE Registry, for which the JSA annual report had been collected between January 2010 and December 2013, were enrolled (Figure 1). We could not enrol patients from the rest of the 11 centres of the COMMAND VTE Registry as their JSA annual reports and/or additional data on patients with postoperative symptomatic VTE were unavailable."
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	9	"In this study, the patients from the 18 centres registered in the COMMAND VTE Registry, for which the JSA annual report had been collected between January 2010 and December 2013, were enrolled (Figure 1). We could not enrol patients from the rest of the 11 centres of the COMMAND VTE Registry as their JSA annual reports and/or additional data on patients with postoperative symptomatic VTE were unavailable. We also could not register the patients between January 2014 and August 2014, since the JSA annual report was from January to December of each year. Further, within the COMMAND VTE Registry, the patients diagnosed with acute symptomatic VTE, who underwent surgery 2 months prior to the VTE diagnosis, were identified. The overall population that had received anaesthetic management, during the study period was retrieved from each centre's JSA annual report. Besides, additional data of

				patients with postoperative symptomatic VTE, namely operative date, operative procedure, surgical sites, surgical position, and types of anaesthesia on anaesthetic charts at each centre, were obtained."
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		Not relevant text
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	11-12	In the COMMAND VTE Registry, data for the patients' characteristics were collected from the hospital charts or hospital databases, according to the prespecified definitions, using an electronic case report form in a web-based database system. Physicians at each of the institutions were responsible for data entry, and data were automatically examined for missing or contradictory input and out-of-range values. Additional edits were performed at the general office of the registry. Patients with postoperative symptomatic VTE, identified through the COMMAND VTE Registry, were further investigated at each centre using the anaesthetic charts created through the collaboration of cardiologists and the anaesthesiologists at each participating centre. Anaesthesia-associated data, such as surgical site, surgical position, and type of anaesthesia were extracted and incorporated into the data from the COMMAND VTE Registry. The outcome measures assessed in this study were recurrent VTE, major bleeding, and all-cause death during the follow-up period, with a median of 1,507 days, in the surviving patients. Recurrent VTE was defined as symptomatic PE and/or DVT accompanied by confirmation of a new thrombus or exacerbation of the thrombus by objective imaging examinations or autopsy. Major bleeding was defined according to the International Society of Thrombosis and

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				Haemostasis as a reduction in the haemoglobin level by at least 2 g/dL, transfusion of at least two units of blood, or symptomatic bleeding in a critical area or an organ.[16]"
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group		No relevant text
Bias	9	Describe any efforts to address potential sources of bias		No relevant text
Study size	10	Explain how the study size was arrived at		No relevant text
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why		No relevant text
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12	"The incidence of postoperative symptomatic VTE was calculated using a combination of data from the COMMAND Registry and the JSA annual reports from the 18 centres. The numerator of the incidence was the number of cases of postoperative symptomatic VTE extracted from the COMMAND Registry; the denominator was the number of surgeries in the JSA annual report."
		(*b*) Describe any methods used to examine subgroups and interactions	12	"The incidence of postoperative symptomatic VTE according to age, sex, surgical site, surgical position, and types of anaesthesia was calculated. The baseline and follow-up data were separately recorded for PE with or without DVT and DVT-only groups in patients with postoperative symptomatic VTE."
		(*c*) Explain how missing data were addressed	12	"No imputation was performed for missing data."
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		No relevant text
		(*e*) Describe any sensitivity analyses		No relevant text
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	13-14	"Figure 1 represents the flow diagram of the study. We enrolled 3,027 consecutive patients with acute symptomatic VTE, after screening 19,634

				consecutive patients with suspected VTE for eligibility, using the chart review by the physicians at each institution. After excluding 2,334 patients without a history of surgery within 2 months before VTE diagnosis, 293 patients were identified with postoperative symptomatic VTE during hospitalization among all 29 centres of the COMMAND VTE Registry. Furthermore, 135 patients outside the eligible period and 21 patients who underwent surgery without the management by anaesthesiologists, were excluded. Finally, the study population consisted of 137 patients diagnosed with VTE within 2 months after surgery, from 18 centres, between January 2010 and December 2013. The total number of surgical cases managed by anaesthesiologists during the study period in 18 centres was 203,943."
		(b) Give reasons for non-participation at each stage	Figure 1	Figure 1 gives reasons for non-participation at each stage.
		(c) Consider use of a flow diagram	Figure 1	"The study flow diagram is shown in Figure 1"
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table1 Supplemental Table1 Table2	"Table 1 shows the baseline patient characteristics of both groups."
		(b) Indicate number of participants with missing data for each variable of interest		No relevant text
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		No relevant text
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	14,16	"The estimated incidence of postoperative symptomatic VTE was 0.067% (137/203,943) and VTE with PE was 0.028% (57/203,943) (Table 1). Of the 57 PE cases, 35 patients (0.017%) had hypoxic symptoms, nine patients (0.004%) presented with shock, and six patients (0.003%) had cardiac arrest. As for the surgical site, the incidence of postoperative symptomatic VTE was relatively high in surgeries involving the brain, hip, and upper/lower limbs. In terms of the types of anaesthesia, regional anaesthesia with or without general anaesthesia (0.100%) was associated with a higher incidence of VTE than general anaesthesia alone (0.045%) (Table 1 and

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				Supplemental Table 1)." "Table 2 shows the demographic and clinical characteristics of patients with postoperative symptomatic VTE. Figure 2 presents the duration from the surgery to the diagnosis of postoperative symptomatic VTE. The median inter-quartile duration was 8 days (4–15 days); and 58 patients (42%) were diagnosed within 7 days of surgery, while 79 patients (58%) were diagnosed 7 days after the surgery. The greatest number of patients were diagnosed with VTE on postoperative day
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures		
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14	"The estimated incidence of postoperative symptomatic VTE was 0.067% (137/203,943) and VTE with PE was 0.028% (57/203,943) (Table 1). Of the 57 PE cases, 35 patients (0.017%) had hypoxic symptoms, nine patients (0.004%) presented with shock, and six patients (0.003%) had cardiac arrest."
		(*b*) Report category boundaries when continuous variables were categorized		
		© If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period		
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses		No relevant text
Discussion				
Key results	18	Summarise key results with reference to study objectives	20	"The main findings of this study are as follows: 1) the incidence of postoperative symptomatic VTE within 2 months after surgery was 0.067% and VTE with PE was 0.028%, representing 203,943 patients from 18 centres in Japan; 2) the incidences of postoperative symptomatic VTE varied widely, according to surgical and anaesthetic characteristics; and 3) nearly half of the patients were diagnosed within 7 days of the surgery, while the rest were diagnosed 7 days after surgery, with the highest number of patients

				diagnosed on postoperative day 8."
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	23-24	"First, two different databases were combined to estimate the incidence of postoperative symptomatic VTE. Although the COMMAND Registry included real consecutive patients with acute symptomatic VTE,[9, 17] for determining VTE incidence, we included only the cases in which intraoperative management was performed by an anaesthesiologist. Second, patients outside the eligible period in the COMMAND VTE Registry were also excluded, which may have influenced the results of this study. As a certain number of patients were excluded due to ineligible centres, the incidences of postoperative symptomatic VTE could have been greatly influenced, especially as the analysis targeted the low event rates. Third, this is a retrospective cohort study with inherent limitations based on the observational study design. In particular, the prophylactic and therapeutic management for postoperative symptomatic VTE were based on the discretion of the attending physicians, which may have influenced clinical outcomes. However, in the COMMAND Registry, the definitions of VTE were specified in advance, and the follow-up after VTE was nearly complete. Finally, we also considered the postoperative date of onset, but the disease may have developed before the surgery or the diagnosis. Nevertheless, we do not expect a significant gap between the onset and diagnosis, because we included only symptomatic patients with postoperative VTE."
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	24	"This study, combining the large real-world VTE database and anaesthetic database in Japan, revealed the incidence, clinical features, and prognosis of postoperative symptomatic VTE, providing useful information for all healthcare providers involved in various surgeries."
Generalizability	21	Discuss the generalizability (external validity) of the study results	21	"First, two different databases were combined to estimate the incidence of postoperative symptomatic VTE. Although the COMMAND

				Registry included real consecutive patients with acute symptomatic VTE,[9, 17] for determining VTE incidence, we included only the cases in which intraoperative management was performed by an anaesthesiologist. Second, patients outside the eligible period in the COMMAND VTE Registry were also excluded, which may have influenced the results of this study. As a certain number of patients were excluded due to ineligible centres, the incidences of postoperative symptomatic VTE could have been greatly influenced, especially as the analysis targeted the low event rates."
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	25	"This work was supported in part by the JSPS KAKENHI (grant number 20K09242; TM, principal investigator). The COMMAND VTE Registry is supported by the independent clinical research organization (Research Institute for Production Development, Kyoto, Japan) and research funding from Mitsubishi Tanabe Pharma Corporation. The research funding had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript."

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.