Variation in Patient Backgrounds, Practice Patterns, and Outcomes of High-Risk Pulmonary Embolism in Japan: A Retrospective Cohort Study

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Summary

High-risk pulmonary embolism (PE) with hypotension, circulatory failure, or cardiac arrest is a rare, but life-threatening condition. Many guidelines recommend that thrombolytic therapy is the first-line therapy for this condition and surgical embolectomy is an alternative treatment. However, nationwide data have been lacking on patient characteristics and practice patterns for high-risk PE in a real-world clinical setting.

We defined high-risk PE patients as those who received noradrenaline and underwent surgical embolectomy or thrombolysis within one day after admission. Using a Japanese national inpatient database, we identified high-risk PE patients from July 2010 to March 2014, and divided them into patients with and without embolectomy and those with and without cardiopulmonary arrest (CPA) at admission. We examined variation in patient backgrounds, procedures, and outcomes in this population.

We identified 361 patients were eligible. Among those, including 266 received thrombolysis and 95 received embolectomy. The 30-day mortality was 41.4% in 266 patients with thrombolysis, and 14 patients died in 95 patients with embolectomy. Among the thrombolysis group, 30-day mortality was 35% in 187 patients without CPA thrombolysis and was 56% in 79 patients with CPA. Among the embolectomy group, 30-day mortality was 14% in 81 patients without CPA, and 21% patients died in 14 patients with CPA.

The present nationwide study showed that surgical embolectomy had a relatively low mortality. Further studies are needed to verify the comparative effectiveness of embolectomy.

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Key words: Cardiopulmonary arrest, Hypotension, Surgical embolectomy, Thrombolysis

High-risk pulmonary embolism (PE), or massive PE, is defined as PE with hypotension (< 90 mmHg of systolic blood pressure), circulatory failure, or cardiac arrest according to two major guidelines.1,2 The International Cooperative Pulmonary Embolism Registry (ICOPER) study reported that the 90-day mortality of high-risk PE was as high as 52.4%.3 Other studies showed that high-risk PE was associated with higher mortality than non-high-risk PE.4,5

Although there are several treatment options for high-risk PE, including thrombolysis, catheter embolectomy, venoarterial extracorporeal membrane oxygenation (VA-ECMO), open pulmonary embolectomy, and anticoagulation, it remains uncertain which treatment is most preferable for specific patient groups.6 The European Society of Cardiology (ESC) guideline on PE treatments recommended both thrombolysis and surgical embolectomy based on limited data.7,8 Surgical embolectomy was recommended for patients “with contraindication to thrombolysis and those in whom thrombolysis has failed to improve the hemodynamic status.”9,10

The outcomes of surgical embolectomy have been improving according to previous reports.9,10 However, because the occurrence of high-risk PE is rare, studies using large-scale data have been lacking on patient backgrounds and choices of treatment options in real-world clinical settings.

To address this lack of knowledge, the present study was conducted to verify the patient characteristics, clinical practice patterns, and short-term outcomes of patients hospitalized with a clinically recognized episode of high-risk PE, using a national inpatient database in Japan.

Methods

Study design and settings: This was a retrospective co-
A short study using data from the Diagnostic Procedure Combination database in Japan. The database is a nationwide administrative claims and discharge database including around half of all inpatient admissions to acute-care hospitals in Japan. The data covered around 92% of all tertiary-care emergency hospitals in Japan. The data collection period for the study was July 2010 to March 2014.

The DPC data include diagnoses, comorbidities at admission, and post-admission complications recorded in accordance with International Classification of Diseases 10th Revision (ICD-10) codes and text data in Japanese.

This study was based on a secondary analysis of the administrative data. The requirement for informed consent was waived because of the anonymous nature of the data. Study approval was obtained from the Institutional Review Board of The University of Tokyo.

**Patient selection:** The American Heart Association (AHA) defined massive PE as PE with sustained hypotension requiring inotropic support and no cause other than PE. The ESC defined high-risk PE as PE with hypotension (< 90 mmHg of systolic blood pressure), circulatory failure, or cardiac arrest.

For this study, we identified data for patients aged > 18 years diagnosed with PE (ICD-10 codes, I26.0 and I26.9) at admission. Among them, we selected patients who received noradrenaline and surgical embolectomy or thrombolysis within 1 day after admission.

We collected patient characteristics, including age, sex, and ambulance usage. The patients were categorized as those with and without embolectomy, and patients with both thrombolysis and embolectomy were included in the embolectomy group. We then divided them into those with and without cardiopulmonary arrest (CPA) that occurred prior to admission, such as in a pre-hospital setting, ambulance, or emergency department.

We also examined several procedures performed during hospitalization, including artificial ventilation, VA-ECMO, and inferior vena cava (IVC) filter use and the recorded diagnosis of deep venous thrombosis (DVT). Outcomes included 30-day mortality and length of stay.

**Endpoints:** The primary endpoint was mortality within 30 days of admission. The secondary outcome was length of stay.

**Statistical analysis:** We compared the proportions of categorical variables between the groups using the chi-square test and the length of stay between the groups using the Mann-Whitney U-test and Kruskal-Wallis test. Values of $P < 0.05$ were considered statistically significant. All statistical analyses were performed using IBM SPSS version 22 (IBM Corp, Armonk, NY).

**Results**

During the 45-month study period, we identified 51,169 patients diagnosed with PE at admission. Among them, 1,374 patients received noradrenaline infusion within 1 day after admission. Of these, we identified 361 eligible patients who received thrombolysis ($n = 266$) or surgical embolectomy ($n = 95$) within 1 day after admission (Figure).

Table I shows the patient characteristics and procedures. The embolectomy group received artificial ventilation more frequently than the thrombolysis group. The proportions of ambulance service used and VA-ECMO did not differ significantly between the groups.

In contrast, patients who received IVC filter placement were significantly older. Although not significant, the IVC filter group had a relatively low proportion of receiving CPA prior to admission compared with the group without IVC.
was 35% in 187 patients without CPA thrombolysis and 56% in 79 patients with CPA. Among the embolectomy group, 30-day mortality was 14% in 81 patients without CPA and 21% in 14 patients with CPA.

Table II. Patient Characteristics Divided on the Basis of Artificial Ventilation

|                          | Artificial ventilation group (n = 273) | No artificial ventilation group (n = 88) | P   |
|--------------------------|--------------------------------------|----------------------------------------|-----|
| Age (years), mean (SD)   | 62.3 (16.1)                          | 67.7 (12.9)                            | <0.01|
| Male sex, n (%)          | 109 (39.9)                           | 27 (30.7)                              | 0.12|
| CPA prior to admission   | 87 (31.9)                            | 6 (6.8)                                | <0.01|

CPA indicates cardiopulmonary arrest; and SD, standard deviation.

Table III. Patient Characteristics Divided on the Basis of VA-ECMO

|                          | VA-ECMO group (n = 112) | No VA-ECMO group (n = 249) | P   |
|--------------------------|-------------------------|----------------------------|-----|
| Age (years), mean (SD)   | 58.5 (16.2)             | 65.9 (14.8)                | 0.048|
| Male sex, n (%)          | 42 (37.5)               | 94 (37.8)                  | 0.96 |
| CPA prior to admission   | 48 (42.9)               | 45 (18.1)                  | <0.01|

CPA indicates cardiopulmonary arrest; SD, standard deviation; and VA-ECMO, venoarterial extracorporeal membrane oxygenation.

Table IV. Patient Characteristics Divided on the Basis of IVC Filter

|                          | IVC filter group (n = 108) | No IVC filter group (n = 253) | P   |
|--------------------------|---------------------------|------------------------------|-----|
| Age (years), mean (SD)   | 67.2 (13.0)               | 62.1 (16.3)                  | <0.01|
| Male sex, n (%)          | 42 (38.9)                 | 94 (37.2)                    | 0.76 |
| CPA prior to admission   | 21 (19.4)                 | 72 (28.5)                    | 0.07 |

CPA indicates cardiopulmonary arrest; SD, standard deviation; and IVC, inferior vena cava.

Table V shows the results of univariable analyses of patient characteristics, procedures, and outcomes between the embolectomy and thrombolysis groups. Patients who received artificial ventilation or VA-ECMO were significantly more likely to die within 30 days of admission. The embolectomy group had a significantly lower 30-day mortality. Patients who received IVC filter had significantly lower mortality and longer length of stay. Patients with DVT had a significantly lower mortality but had significantly longer length of stay than those without DVT.

Table VI shows the outcomes of patients with and without CPA in the thrombolysis and embolectomy groups. Among the thrombolysis group, 30-day mortality was 35% in 187 patients without CPA thrombolysis and 30-day mortality was 14% in 81 patients without CPA thrombolysis. Among the embolectomy group, 30-day mortality was 21% in 14 patients with CPA.

Discussion

The present study of 361 high-risk PE patients using a national inpatient database showed that embolectomy group had a relatively low 30-day mortality compared with the thrombolysis group, especially among younger patients without CPA. It may influence the treatment outcome that younger patients were likely to receive VA-ECMO and artificial ventilation. However, these results should be explained cautiously. In the present study, we
did not perform a multivariable analysis because there should be unmeasured confounders, which cannot be adjusted by multivariable regression models. It is noteworthy that the 30-day mortality of patients with embolectomy in the non-CPA group was 14% in the present study, being lower than that in a previous study in 2004 (> 30%). Although these figures cannot be directly compared, the difference in mortality suggests that current physicians may be more likely to select embolectomy candidates from relatively low-risk patients with young age and no CPA. The difference may also be explained by recent advances in surgery and postoperative management.

Because massive PE is very rare, data are lacking on the effectiveness of thrombolysis and embolectomy. The ESC, AHA, and Japanese guidelines recommend that systemic thrombolysis is the first-line treatment for patients with massive PE and that surgical embolectomy is an alternative treatment for patients who are not indicated for thrombolysis. However, these recommendations are based on limited data. The present study suggests that surgical embolectomy could be a feasible alternative for high-risk PE patients, especially for those with younger age and no CPA.

Univariable analysis showed that patients treated with

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| Table V. Univariable Analyses of Patient Characteristics, Procedures, and Outcomes |
|---------------------------------------------------------------|
| Age (years)                      | 30-day mortality (%) | P      | Length of stay [IQR] | P    |
|----------------------------------|----------------------|--------|----------------------|------|
| < 60                              | 40 (34.5)            | 0.53   | 20 [8-43]            | 0.80 |
| 60-79                             | 65 (32.7)            | 0.20   | 20 [5-37]            | 0.80 |
| ≥ 80                              | 19 (41.3)            | 1.00   | 17 [2-36]            | 1.00 |
| Sex                               |                      |        |                      |      |
| Male                              | 40 (29.4)            | 0.29   | 22 [15-37]           | 0.97 |
| Female                            | 84 (37.3)            | 0.13   | 19 [3-34]            | 0.12 |
| Artificial ventilation            |                      |        |                      |      |
| No                                | 13 (14.8)            | 0.01   | 20 [8-34]            | 0.97 |
| Yes                               | 111 (40.7)           | 0.98   | 18 [3-38]            | 0.98 |
| VA-ECMO                           |                      |        |                      |      |
| No                                | 72 (28.9)            | 0.01   | 20 [8-34]            | 0.97 |
| Yes                               | 52 (46.4)            | 0.99   | 20 [4-50]            | 0.99 |
| IVC filter                        |                      |        |                      |      |
| No                                | 114 (45.1)           | 0.01   | 15 [2-34]            | < 0.01|
| Yes                               | 10 (9.3)             | 0.99   | 29 [18-46]           | 0.99 |
| CPA prior to admission            |                      |        |                      |      |
| No                                | 107 (32.5)           | 0.02   | 20 [8-37]            | 0.33 |
| Yes                               | 17 (53.1)            | 0.17   | 16 [3-42]            | 0.17 |
| Deep vein thrombosis              |                      |        |                      |      |
| No                                | 105 (40.4)           | 0.01   | 17 [3-37]            | < 0.01|
| Yes                               | 19 (18.8)            | 0.03   | 25 [15-40]           | < 0.01|
| Treatment                         |                      |        |                      |      |
| Thrombolysis                      | 110 (41.4)           | < 0.01 | 18 [3-36]            | 0.15 |
| Embolectomy                       | 14 (14.7)            | < 0.01 | 24 [14-45]           | < 0.01|

CPA indicates cardiopulmonary arrest; VA-ECMO, venoarterial extracorporeal membrane oxygenation; IVC, inferior vena cava; and IQR, interquartile range.

Table VI. Patient Characteristics, Procedures, and Outcomes in the Non-CPA and CPA Groups

| Age (years), n (%) | Non-CPA group (n = 268) | CPA group (n = 93) |
|--------------------|-------------------------|-------------------|
| < 60               | 53 (28.4)               | 32 (40.5)         | 5 (35.7) |
| 60-79              | 101 (54.0)              | 48 (59.3)         | 42 (53.2) | 8 (57.1) |
| ≥ 80               | 33 (17.6)               | 7 (8.6)           | 5 (6.3)   | 1 (7.1) |
| Male sex, n (%)    | 63 (33.7)               | 37 (45.7)         | 30 (38.0) | 6 (42.9) |
| Artificial ventilation, n (%) | 117 (62.6) | 69 (85.2) | 74 (93.7) | 13 (92.9) |
| VA-ECMO, n (%)     | 45 (24.1)               | 19 (23.5)         | 38 (48.1) | 10 (71.4) |
| IVC filter, n (%)  | 58 (31.0)               | 29 (35.8)         | 15 (19.0) | 6 (42.9) |
| Deep venous thrombosis, n (%) | 55 (29.4) | 29 (35.8) | 15 (19.0) | 2 (14.3) |
| Length of stay (days), median [IQR] | 19 [12-26] | 24 [14-44] | 10 [3-41] | 25 [12-43] |
| 30-day mortality, n (%) | 65 (35.3) | 11 (13.6) | 44 (55.7) | 3 (21.4) |

CPA indicates cardiopulmonary arrest; VA-ECMO, venoarterial extracorporeal membrane oxygenation; IVC, inferior vena cava; and IQR, interquartile range.
IVC filter had lower mortality. The IVC filter group had a relatively low proportion of receiving CPA prior to admission. This suggests that IVC filters may have been placed for less severe patients. Thus, the effectiveness of IVC filter placement is not conclusive in our study.

A previous study showed that prevalence of DVT in patients with PE was about 50% and there was no association between concomitant DVT among PE patients and all-cause mortality. The present study showed the proportion of DVT was 28% among patients with massive PE. The reason for this relatively small proportion may be that confirmation of DVT at admission may have been difficult for patients with massive PE. In our study, patients with DVT had a significantly lower mortality than those without. We speculate that the diagnoses of DVT may have been underreported in dead patients.

However, the present study cannot be conclusive about which treatment is related to better outcomes because there were many unmeasured confounding variables. For example, deteriorated patients who could not withstand surgical embolectomy were allocated to thrombolysis. Although a randomized trial is needed to provide the best evidence and could be a conclusive study, it is difficult to perform a randomized trial for such a life-threatening condition as high-risk PE. Further observational studies with many more patients are necessary to clarify the comparative effectiveness of embolectomy.

The present study has several limitations. First, detailed data were not available, including CT findings, vital signs, and cardiac function. Second, some CPA patients may not have had return of spontaneous circulation, resulting in death before hospital arrival or in the emergency room. Because such patients were not included, the present study may have underestimated the overall mortality. Third, our definition of high-risk PE may have resulted in underestimation because it only included noradrenaline use along with embolectomy or thrombolysis. Fourth, not all hospital can perform emergency embolectomy, and this may have resulted in selection bias.

Conclusions

This large nationwide study suggested that surgical embolectomy had a relatively low mortality compared with previously reported rates. Further studies are warranted to confirm the advantage of embolectomy in reducing mortality.

Disclosures

Ethics approval and consent to participate: This study was based on a secondary analysis of the administrative data. The requirement for informed consent was waived because of the anonymous nature of the data. Study approval was obtained from the Institutional Review Board of The University of Tokyo.

Consent for publication: Not applicable

Availability of data and material: The datasets analyzed during the current study available from the corresponding author on reasonable request.

Conflicts of interest: The authors declare that they have no competing interests.

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