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Clinical outcomes of endovascular interventions for cerebral venous thrombosis in Japan: a nationwide retrospective study

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ABSTRACT

Introduction Cerebral venous thrombosis (CVT) is a rare but serious disease. Despite anticoagulation being the cornerstone therapy, some patients experience worsening disease, necessitating alternative treatment. Endovascular treatment is an anticipated option with an uncertain clinical relevance. The aim of this study was to assess the clinical effects and efficacy of endovascular therapy and identify patient populations that may benefit from treatment.

Patients and methods This retrospective study examined patient data from April 2014 to March 2022 that were extracted from a nationwide Japanese Diagnosis Procedure Combination database. The primary outcome was in-hospital mortality. The secondary outcomes included modified Rankin Scale (mRS) scores and post-hospitalisation complications of cerebral infarction and intracranial haemorrhage. Severity was adjusted using a generalised linear mixed model, and propensity-score matching was employed to compare outcomes between treatment groups.

Results The study included 2901 patients; 240 patients in the endovascular treatment group were matched with 240 patients in the standard treatment group. After adjusting for background factors, endovascular treatment did not improve in-hospital mortality (adjusted OR 1.45; 95% CI 0.74 to 2.16) or the mRS score (adjusted OR 0.89, 95% CI 0.56 to 1.23). No subpopulations that could benefit from endovascular treatment were identified. Post-hospitalisation cerebral infarction and intracranial haemorrhage did not increase with endovascular treatment (0.8% in the endovascular treatment group vs 1.2% in the standard treatment group).

Conclusion Endovascular treatment showed no significant benefit for patients with CVT, indicating that treatment guidelines need to be refined. Our findings can guide clinical decisions and suggest the necessity of further research on potential benefits in specific subpopulations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ While anticoagulation is the mainstay treatment for cerebral venous thrombosis (CVT), some patients experience worsening disease; therefore, alternative therapies are needed.

WHAT THIS STUDY ADDS

⇒ Endovascular treatment does not show any significant benefit for patients with CVT or for any subpopulations of patients with CVT.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Endovascular treatment guidelines for patients with CVT should be refined to assess its efficacy.

INTRODUCTION

Cerebral venous thrombosis (CVT), an uncommon cause of stroke, accounts for 0.5–3% of cerebrovascular diseases.[1–3] It is a critical condition, with death or dependence reported in 10–15% of patients, even after receiving intensive medical treatment.[2]

Anticoagulation is the cornerstone therapy for CVT,[4 5] but some patients experience deterioration despite treatment.[6–8] Endovascular treatments, including mechanical thrombectomy, thromboaspiration or balloon venoplasty with or without intrasinus thrombolysis, have been considered promising treatment options, supported by the findings of several case reports and systematic reviews.[7 9] Nonetheless, the importance of endovascular treatments in CVT has dampened in recent years following the inability to demonstrate their efficacy in a randomised controlled trial (TO-ACT).[10] However, abjuring endovascular treatments may be premature, considering the low sensitivity of this trial conjointly with the feasibility and safety of this treatment option.[11] Identifying subpopulations who may benefit from this treatment remains to be accomplished,[6] and consequently, well-grounded indication criteria for endovascular treatments are not explicitly advocated in the current guidelines.[2 7 12]

Here, we conducted a nationwide retrospective observational study to re-evaluate the treatment effect of endovascular therapy in patients with CVT with high sensitivity and identify the patient population that may benefit from these treatments.

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METHODS

Study design

In this retrospective study, we assessed the efficacy of endovascular treatments, including thrombectomy, angioplasty, fibrinolytic therapy and stent placement, in patients with CVT using data from the Japanese Diagnosis Procedure Combination (DPC) database. The DPC database, a nationwide case-mix patient classification system, lists over 1700 acute care hospitals, including all academic hospitals. The database not only contains assorted patient information, including age, sex, body weight and underlying disease information, but also includes information on all procedures performed and routinely administered drugs.[13] The diagnoses compiled in this database are in accordance with the International Classification of Diseases, Tenth Edition (ICD-10).[14]

This study was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Institutional Review Board of XXXX. As the study was retrospectively designed and deidentified data were used, the requirement to obtain informed consent was waived by the board.

Study population

The inclusion criteria for the study were as follows: patients who were diagnosed with CVT (ICD-10 code: G08 'Intracranial and intraspinal phlebitis and thrombophlebitis') and subsequently admitted to an intensive care unit during the designated study timeframe (April 2014–March 2022). The exclusion criteria were as follows: patients (1) with missing values for any of the variables used in the analysis, (2) aged <16 years or (3) discharged within 2 days of admission. The latter criterion was used to address immortal time bias, as patient severity adjustment was executed according to the treatment intensity rendered during this period.

Data collection

To examine patient severity, the following variables were collected: concurrent diagnoses on admission, post-admission complications including cerebral infarction and intracranial haemorrhage, age, sex, state of consciousness on admission and the Charlson Comorbidity Index. The Charlson Comorbidity Index is a widely used tool for assessing mortality risk in patients with multiple comorbidities. It provides estimates for 1-year and 10-year mortality rates and has been validated across various patient populations.[15] The following variables related to patient outcomes were also assessed: modified Rankin Scale (mRS) score, length of hospital stay, patient discharge status and post-admission complications. Medications administered within 2 days of admission, including warfarin and other anticoagulants, antiepileptics and antihypertensive drugs, were evaluated to gauge treatment intensity. Data on the year of admission and hospital identification number were also aggregated.

Outcomes

The endovascular treatment group included patients who underwent endovascular treatment within 2 days of admission. The primary outcome was in-hospital mortality, while the secondary outcomes included mRS score and post-hospitalisation complications (intracranial haemorrhage and cerebral infarction).

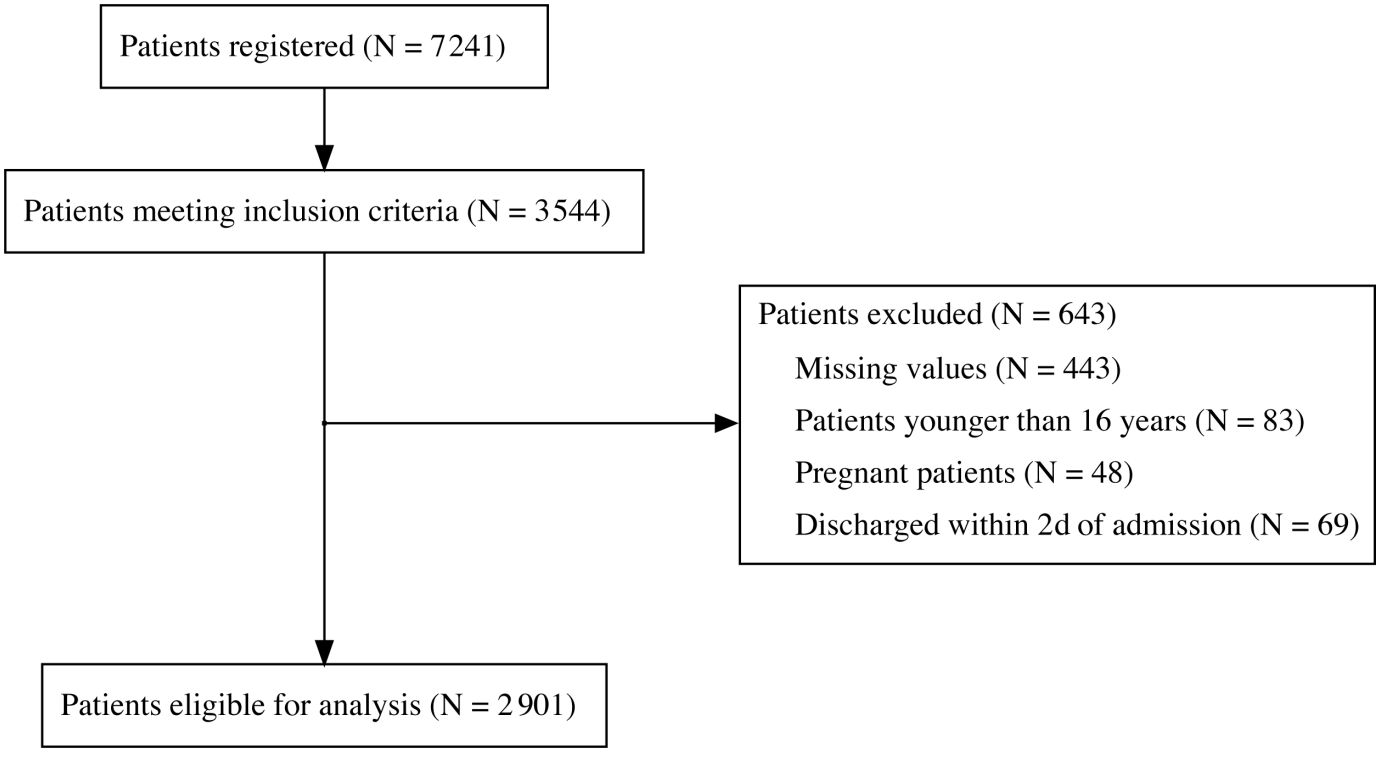

Figure 1 Flow diagram of the patient selection process.

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Statistical analysis

To adjust for severity among patients with CVT who received endovascular treatment and those who did not, a prediction model for predicting patient prognosis was constructed using a generalised linear mixed model (GLMM). The following explanatory variables were selected for the fixed effects of the model based on the findings of previous studies[6 9]: age, sex, consciousness, cerebral infarction, intracranial haemorrhage, acute renal failure, heart failure and use of drugs including warfarin, other anticoagulants, antiepileptics and antihypertensive drugs. Hospital identification numbers were used for the random effects of the model.

The prediction model was constructed using 80% of a randomly selected cohort, while its accuracy was assessed on the remaining cohort using the bootstrap method (N=1000). The accuracy was quantified by calculating the area under the receiver operating characteristic curve (AUROC).

Sensitivity analysis was conducted using propensity-score matching under the following conditions: nearest-neighbour matching without replacement and a calliper width of 0.2 times the SD of the logit-transformed propensity score. In addition to 1:1 propensity-score matching, 1:3 matching was conducted to cover a broader population of patients with CVT and enhance external validity. The standardised mean difference (SMD) was used to examine the balance between groups, and comparisons between the matched groups were performed using the χ^2 test.

For the main analysis, an antecedent GLMM and propensity-score matching were used. To identify the population of patients who may benefit from endovascular treatment, treatment effects were categorised by subgroups as follows: (1) patients stratified by disease severity, (2) patients stratified by the year of hospitalisation, (3) patients divided by age (<50 years vs ≥50 years) and (4) patients divided by sex. For the first analysis, the patients were stratified by disease severity using a prediction model, which divided the population into three groups—low, middle and high risk—based on the calculated severity scores, with an equal number of individuals in each group. Treatment effects were then estimated using propensity score matching. For the latter

Table 1 Patient characteristics

	Standard treatment	Endovascular treatment
N	2659	242
Age, years (mean (SD))	54.52 (18.47)	53.17 (18.33)
Female sex (%)	1322 (49.7)	121 (50.0)
Charlson Comorbidity Index (%)		
0	482 (62.0)	78 (70.9)
1	135 (17.4)	13 (11.8)
2	62 (8.0)	6 (5.5)
3	45 (5.8)	5 (4.5)
4	30 (3.9)	6 (5.5)
5	19 (2.4)	2 (1.8)
6	5 (0.6)	0 (0.0)
7	2 (0.1)	0 (0.0)
8	1 (0.0)	0 (0.0)
State of consciousness		
Alert (%)	1488 (56.0)	85 (35.1)
Coma (%)	174 (6.5)	35 (14.5)
Subarachnoid haemorrhage (%)	130 (4.9)	15 (6.2)
Intracranial haemorrhage (%)	4 (0.2)	0 (0.0)
Cerebral infarction (%)	8 (0.3)	2 (0.8)
Acute renal failure (%)	13 (0.5)	1 (0.4)
Heart failure (%)	66 (2.5)	4 (1.7)
Use of warfarin (%)	1481 (55.7)	118 (48.8)
Use of other anticoagulants (%)	528 (19.9)	72 (29.8)
Use of antiepileptic drugs (%)	815 (30.7)	143 (59.1)
Use of antihypertensive drugs (%)	607 (22.8)	154 (63.6)

SD, standard deviation.

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two analyses, treatment effects were evaluated using the GLMM.

R software, V.4.4.0 (R Foundation for Statistical Computing, Vienna, Austria), was used for performing all statistical analyses.

Patient and public involvement

No patients were involved in the study.

RESULTS

Figure 1 shows the patient selection process used in this study. During the study period (April 2014–March 2022), 7241 patients were diagnosed with CVT. Out of these, 3544 patients met the inclusion criteria, and 2901 patients ultimately included in the analysis. Patients were excluded (n=643) for the following reasons: missing values (n=443), aged <16 years (n=83), pregnancy (n=48) and discharge within 2 days of admission (n=69). The baseline patient characteristics are presented in table 1. The treatments conducted in the endovascular treatment group were as follows: thrombectomy (n=161); angioplasty (n=36); fibrinolytic therapy (n=24); thrombectomy and angioplasty (n=13); thrombectomy and fibrinolytic therapy (n=3); thrombectomy and stent placement (n=1); thrombectomy, angioplasty and fibrinolytic therapy (n=1); and angioplasty and fibrinolytic therapy (n=1). In the endovascular treatment group, the state of consciousness was poor, intracranial haemorrhage was frequently

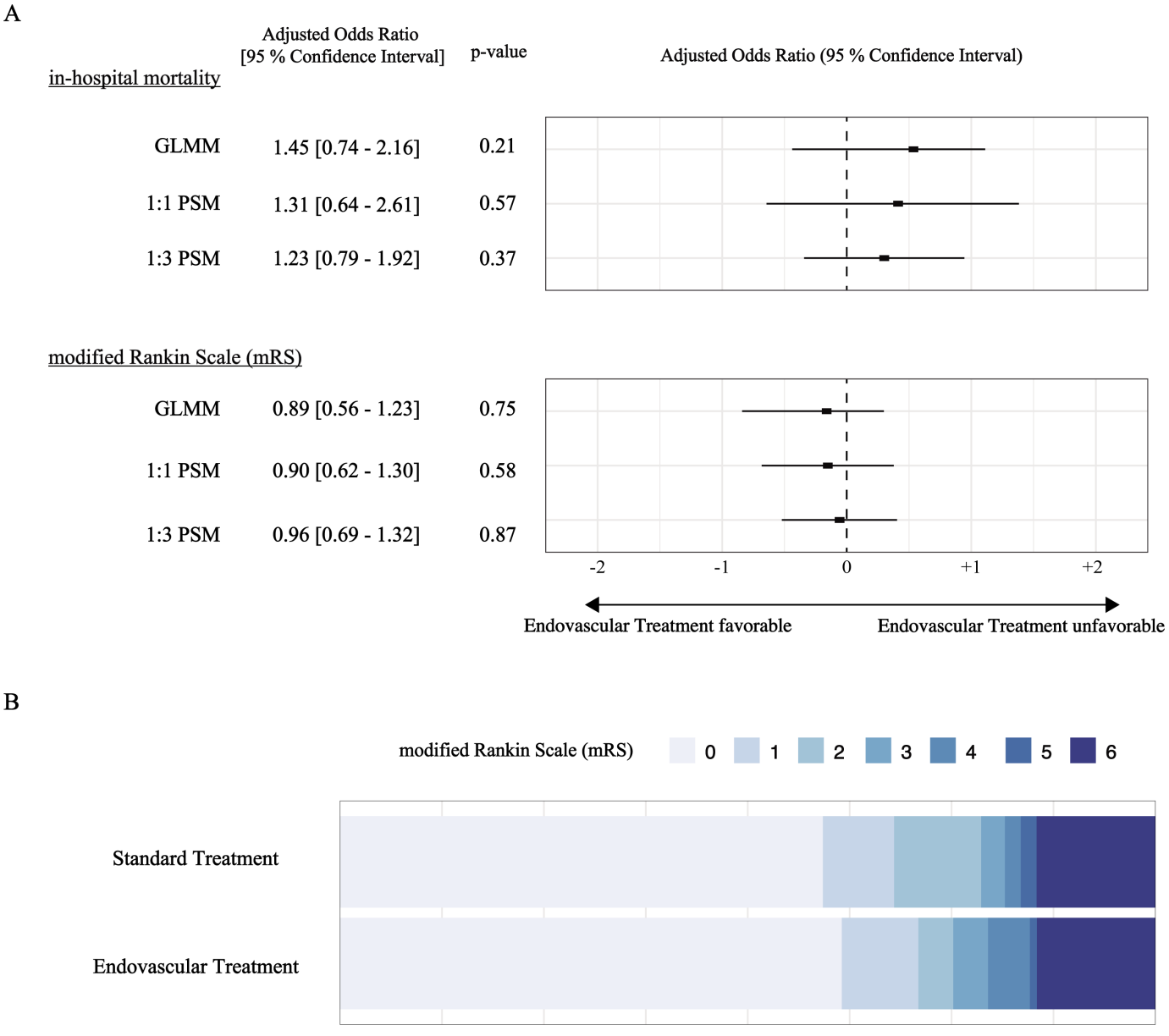

Figure 2 Comparison of outcomes between the endovascular and standard treatment groups. (A) Forest plot comparing in-hospital mortality and mRS score between the endovascular and standard treatment groups (X-axis is presented in log scale). (B) mRS score at the time of discharge. GLMM, generalised linear mixed model; mRS, modified Rankin Scale; PSM, propensity-score matching.

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observed, and antiepileptic and antihypertensive drugs were often administered.

The GLMM established in this study showed satisfying prediction accuracy with an AUROC of 0.877±0.037 (online supplemental figure 1). The results of the main analysis, in which the effect of endovascular treatment was estimated using this prediction model, are shown in figure 2A. The adjusted OR of in-hospital mortality was 1.45 (95% CI 0.74 to 2.16, p=0.21), showing no favourable outcome from this treatment. Regarding mRS score, the adjusted OR was 0.89 (95% CI 0.56 to 1.23, p=0.75), indicating no significant benefit of endovascular treatments for patients with CVT.

The baseline characteristics after 1:1 propensity-score matching are shown in table 2, while those after 1:3 propensity-score matching are presented in table 3. In-hospital mortality after propensity-score matching was 17/240 (7.1%) in the endovascular treatment group and 15/240 (6.2%) in the standard treatment group, consistent with the results estimated using the aforementioned GLMM (adjusted OR of 1.31 (95% CI 0.64 to 2.61, p=0.57) for in-hospital mortality and 0.90 (95% CI 0.62 to 1.30, p=1.30) for the mRS score) (figure 2A). The mRS scores for both the groups at the time of discharge are shown in figure 2B. The incidence of cerebral infarction and intracranial haemorrhage post-hospitalisation was 2/240 (0.8%) in the endovascular treatment group and 3/240 (1.2%) in the standard treatment group. No patients in either group experienced intracranial haemorrhage. Results from 1:3 propensity-score matching, conducted to cover a broader range of patient demographics, were consistent with those of 1:1 matching and the GLMM. The adjusted ORs were 1.23 (95% CI 0.79 to 1.92, p=0.37) for in-hospital mortality and 0.96 (95% CI 0.69 to 1.32, p=0.87) for the mRS score.

To identify the subpopulation that may benefit from endovascular treatment, we stratified the study cohort into three groups according to disease severity. A slight tendency toward favourable outcomes following endovascular treatment was observed in the low-severity and medium-severity groups (figure 3), whereas unfavourable outcomes were reported in the high-severity group. However, none of these results were conclusive (low-severity group: in-hospital mortality 0.36 (95% CI 0.08 to 1.78, p=0.27), mRS score 0.31 (95% CI 0.09 to 1.09); medium-severity group: in-hospital mortality 0.30 (95% CI 0.04 to 2.36, p=0.61), mRS score 0.84 (95% CI 0.27 to 2.60, p=1.00); high-severity

Table 2 Patient characteristics after 1:1 propensity-score matching

	Standard treatment	Endovascular treatment	SMD
N	240	240	
Age, years (mean (SD))	53.88 (17.57)	53.27 (18.37)	0.034
Female sex (%)	123 (51.2)	120 (50.0)	0.025
Charlson Comorbidity Index (%)			0.187
0	76 (31.7)	71 (29.6)	
1	73 (30.4)	80 (33.3)	
2	51 (21.2)	53 (22.1)	
3	24 (10.0)	26 (10.8)	
4	10 (4.2)	7 (2.9)	
5	3 (1.2)	3 (1.2)	
6	3 (1.2)	0 (0.0)	
State of consciousness			
Alert (%)	84 (35.0)	85 (35.4)	0.009
Coma (%)	33 (13.8)	35 (14.6)	0.024
Subarachnoid haemorrhage (%)	24 (10.0)	15 (6.2)	0.138
Intracranial haemorrhage (%)	69 (28.7)	71 (29.6)	0.018
Cerebral infarction (%)	86 (35.8)	78 (32.5)	0.07
Acute renal failure (%)	1 (0.4)	1 (0.4)	<0.001
Heart failure (%)	7 (2.9)	4 (1.7)	0.084
Use of warfarin (%)	122 (50.8)	118 (49.2)	0.033
Use of other anticoagulants (%)	72 (30.0)	70 (29.2)	0.018
Use of antiepileptic drugs (%)	136 (56.7)	141 (58.8)	0.042
Use of antihypertensive drugs (%)	153 (63.7)	152 (63.3)	0.009

SMD, standardised mean difference.

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Table 3 Patient characteristics after 1:3 propensity-score matching

	Standard treatment	Endovascular treatment	SMD
N	240	720	
Age, years (mean (SD))	53.88 (17.57)	53.68 (18.51)	<0.001
Female sex (%)	123 (51.2)	368 (51.1)	0.018
Charlson Comorbidity Index (%)			0.156
0	76 (31.7)	223 (31.0)	
1	72 (39.9)	236 (32.8)	
2	51 (21.2)	158 (21.9)	
3	24 (10.0)	75 (10.4)	
4	10 (4.2)	20 (2.8)	
5	3 (1.2)	6 (0.8)	
6	3 (1.2)	2 (1.7)	
State of consciousness			
Alert (%)	84 (35.0)	268 (37.2)	0.019
Coma (%)	33 (13.8)	97 (13.5)	0.024
Subarachnoid haemorrhage (%)	24 (10.0)	81 (11.3)	0.012
Intracranial haemorrhage (%)	69 (28.7)	213 (29.6)	0.022
Cerebral infarction (%)	86 (35.8)	278 (38.6)	0.010
Acute renal failure (%)	1 (0.4)	3 (0.4)	<0.001
Heart failure (%)	7 (2.9)	12 (1.7)	0.087
Use of warfarin (%)	122 (50.8)	355 (49.3)	0.059
Use of other anticoagulants (%)	72 (30.0)	207 (28.8)	0.013
Use of antiepileptic drugs (%)	136 (56.7)	400 (55.6)	0.006
Use of antihypertensive drugs (%)	153 (63.7)	436 (60.6)	0.006

SD, standard deviation; SMD, standardised mean difference.

group: in-hospital mortality 5.56 (95% CI 0.81 to 37.19, p=0.20), mRS score 1.35 (95% CI 0.57 to 3.19, p=0.52)).

Figure 4 shows an additional analysis accounting for technological advancements, with subgroups stratified by the fiscal year of admission. The results of this subgroup analysis did not demonstrate any preference for endovascular treatment. Furthermore, because this study population skewed toward older patients, we conducted an analysis by dividing patients with CVT into two groups according to a cut-off age of 50 years. However, no evidence of favourable outcomes after endovascular treatment was found in either age group (<50 years: in-hospital mortality 2.32 (95% CI 0.73 to 19.30, p=0.11), mRS score 1.53 (95% CI 0.38 to 3.06, p=0.81); ≥50 years: in-hospital mortality 2.43 (95% CI 0.12 to 31.19, p=0.65), mRS score 1.36 (95% CI 0.53 to 2.28, p=0.74)) (figure 5A). Similarly, an analysis stratified by sex showed no difference in treatment response between male and female patients (female patients: in-hospital mortality 2.73 (95% CI 0.03 to 23.10, p=0.88), mRS score 1.40 (95% CI 0.51 to 2.51, p=0.71); male patients: in-hospital mortality 1.80 (95% CI 0.40 to 10.49, p=0.28), mRS score 1.43 (95% CI 0.36 to 2.01, p=0.79)).

DISCUSSION

This study examined the efficacy of endovascular therapy in patients with CVT and found no significant benefits in terms of survival or neurological outcomes. We explored a subpopulation that might potentially benefit from this treatment; however, none of the results suggested favourability. Notably, in the 1:1 propensity-score matching analysis, fewer patients in the endovascular treatment group presented with complications such as subarachnoid haemorrhage and cerebral infarction. These baseline differences may have led to an overestimation of the potential advantages of endovascular treatment. However, we confirmed the robustness of our findings using 1:3 propensity-score matching, which helped us compare the outcomes of the two groups without these baseline imbalances. Thus, our results, together with multiple estimation methods, did not suggest the efficacy of this treatment, ensuring robustness through multiple analyses.

Conflicting evidence exists regarding the use of endovascular treatments in patients with CVT, which was once welcomed with great enthusiasm and supported by positive evidence.[9 16] However, a nationwide retrospective study analysing 49 952 patients showed antagonistic results, indicating higher mortality in the endovascular

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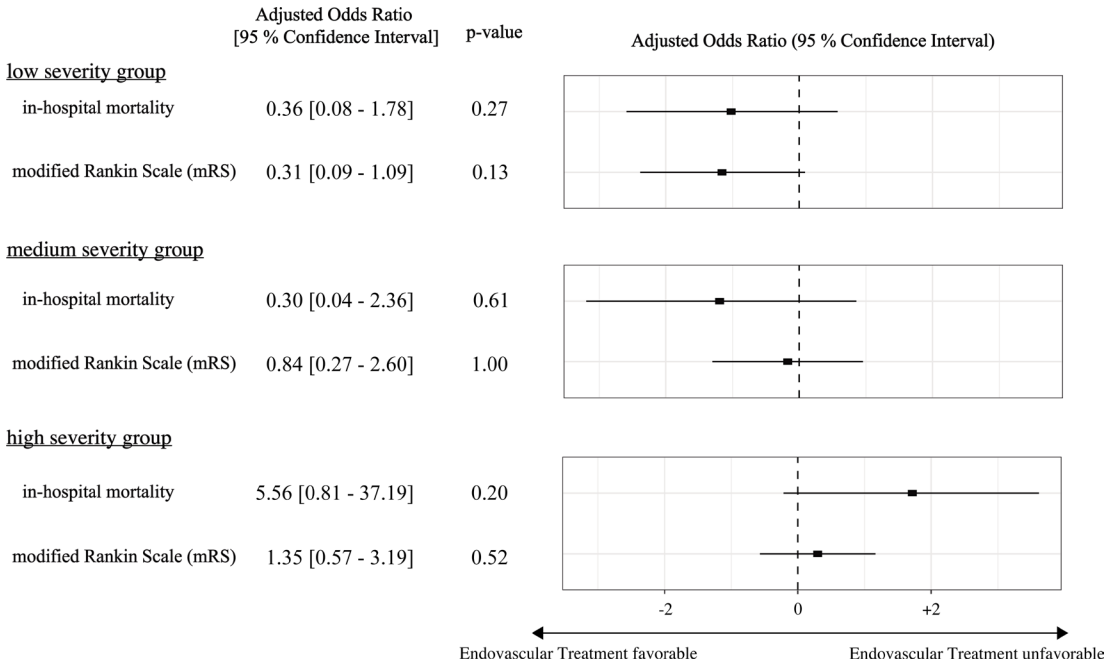

Figure 3 Comparison of outcome among groups classified by disease severity. Severity is stratified using the prediction model, while treatment effects are estimated using the propensity score matching. X-axis is presented in log scale. mRS, modified Rankin Scale.

treatment group.[17] Furthermore, a multicentre randomised controlled trial was prematurely terminated due to futility.[10] Nonetheless, these findings are insufficient for abandoning this treatment option. The prediction model in the aforementioned retrospective study was not sufficiently high (AUROC=0.75) and only few variables were adjusted, raising the suspicion that the negative results may have been caused by unadjusted confounders. However, the randomised controlled trial[8] was arranged from a sanguine perspective, aiming to detect no less than an absolute difference of 20%, resulting in enrolling only 34 patients in both arms. Considering the population size, a reliable subgroup analysis was impractical. The present study serves as a complement in this respect, as the study population included no less than 2901 patients, with patient severity being prudently adjusted, followed by a few subgroup analyses.

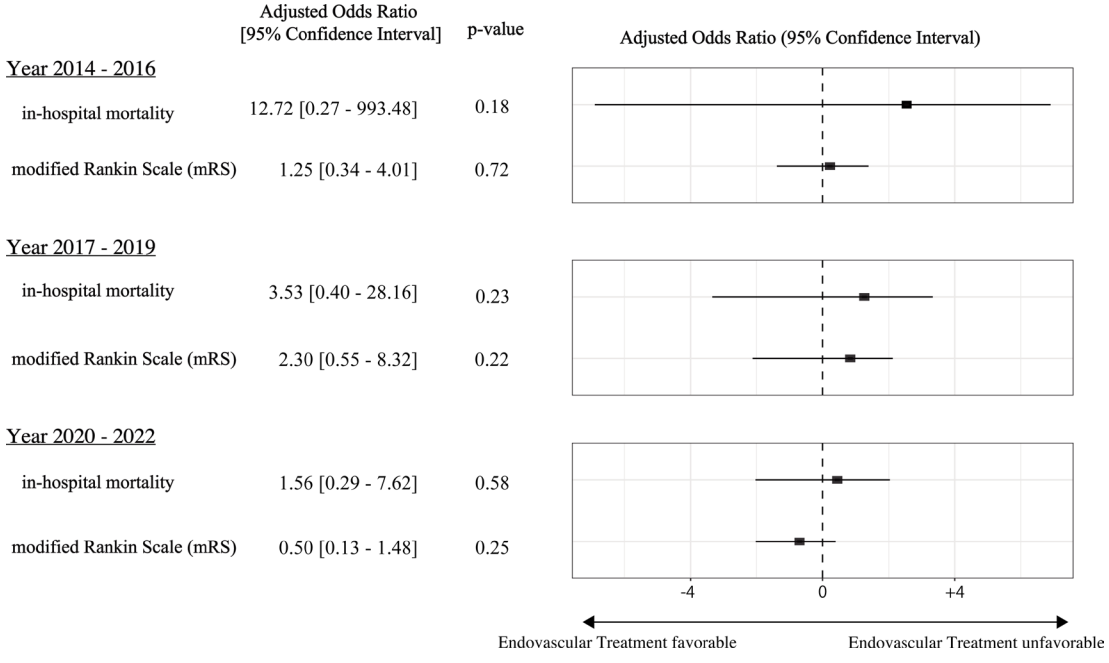

Figure 4 Comparison of outcome among groups categorised by year of admission. Treatment effects are estimated using a generalised linear mixed model. X-axis is presented in log scale. mRS, modified Rankin Scale.

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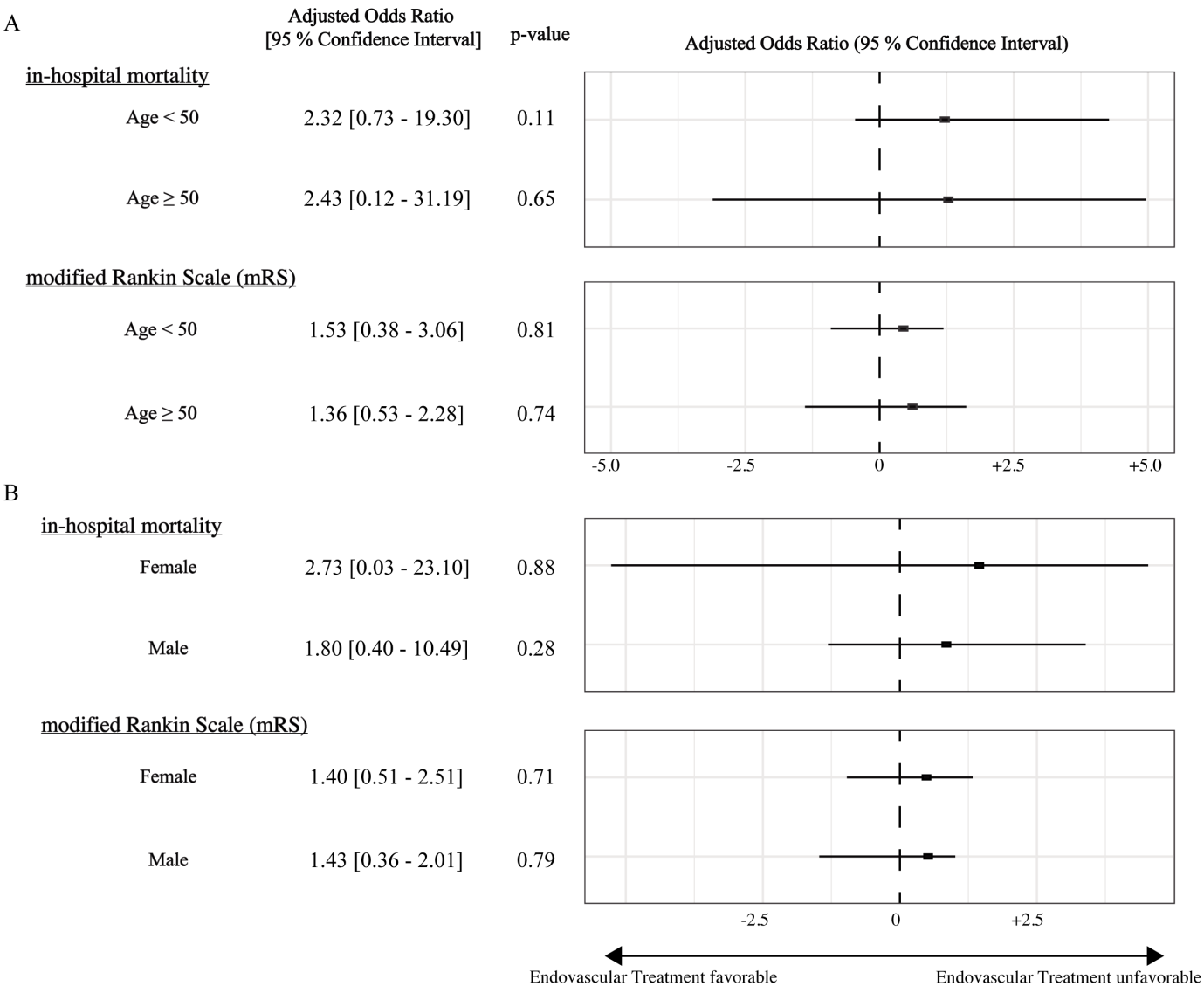

Figure 5 (A) Comparison of outcome in the subpopulation of patients aged <50 years and patients aged ≥50 years. (B) Comparison of outcomes between male and female patients. Treatment effects are estimated using a generalised linear mixed model. X-axis is presented in log scale. mRS, modified Rankin Scale.

A recent systematic review, which included 405 patients from a randomised controlled trial and 20 observational studies, concluded that routine incorporation of endovascular therapy is not recommended,[18] but with a reservation condition for severe cases. However, in the present study, favourable outcomes were observed neither in severe cases nor in the most recently presented cases.

Notably, CVT has been previously reported to be much more common in women than in men[6 19] and relatively rare in older patients.[20] However, this tendency was not observed in the present study. We deduced this difference to several conditions unique to the Japanese population: (1) an ageing population, (2) uncommon use of oral contraceptives[21] and (3) pregnant and puerperium patients being recorded differently in the database. To confirm the external validity of the present study, while accounting for these reasons, a subgroup analysis comparing the treatment effect between patients aged <50 years and those aged ≥50 years was conducted. The results indicated no beneficial effect in either age group, with a slight tendency toward an unfavourable effect on in-hospital mortality in younger patients. Similarly, no significant sex-based differences in the benefit of endovascular treatment were found. These results imply that endovascular treatments are unlikely to provide benefits when applied to previously reported 'general' populations of CVT.[6 19 20]

A previously reported meta-analysis did not detect any differences in outcomes between different treatment approaches.[22] In the current study, the small number of patients with CVT treated in individual hospitals made it difficult to assess differences among treatment techniques. However, to account for interhospital variability, a GLMM was employed, treating individual hospitals as random effects. This approach accounted for variability in techniques or expertise levels across hospitals, but it is

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possible that certain endovascular treatments that could truly benefit patients with CVT may have been overlooked. Therefore, further investigations are warranted.

Interpreting the results of the present study was arduous. Despite contradictory results regarding the benefits of endovascular treatments, no explicit cerebral infarction and intracranial haemorrhage were observed. As the safety of endovascular therapy has been repeatedly reported,[11 23] treatment abandonment may be premature. Hence, more detailed research is required to reach definitive conclusions.

This study has some limitations. First, the diagnosis in this study was based on the ICD-10 code recorded in the database, which may be considered less definitive compared with the diagnosis in prospective investigations. However, a preceding study ensured the accuracy of the DPC database, showing that its specificity is >96%.[24] Second, the analysis was performed only for patients who were hospitalised for more than 2 days. In total, 69 patients were discharged before this period, which is not likely to have affected the results of the study; however, the consequences of this bias have not been quantified. Third, the clinical efficiency of endovascular treatments in patients with CVT was measured, showing no observable improvement in terms of mortality and mRS score. However, other measures, such as occurrence of seizures and acute renal failure, were not evaluated. Fourth, the retrospective nature of the study introduces the possibility of potential biases and confounders that could significantly affect the results. Finally, due to of the nature of our dataset, longer term outcomes, which would have provided a more comprehensive understanding of the true impact of endovascular treatment on patients' functional recovery and quality of life, were not assessed.

Nevertheless, this study provided a higher level of evidence than that provided in previous studies, as it was conducted in a large population and the analysis minimised the effect of confounding factors.

CONCLUSION

This study found no clinical benefit of endovascular treatments for patients with CVT, highlighting the need for further research to explore potential benefits in specific subpopulations and refine treatment guidelines.

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Contributors AS and KF contributed to the acquisition of data. AS conceived of and designed this study. AS analysed and interpreted the data. HS confirmed the analysis. KM, HS and KF drafted the manuscript. All authors reviewed and discussed the manuscript. KM and KF revised the manuscript for important intellectual content. All authors read and approved the final manuscript. The guarantor of the manuscript is AS.

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Patient consent for publication Not applicable.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets generated and/or analysed during the current study are not publicly available due to privacy concerns but are available from the corresponding author on reasonable request.

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