# Prior antithrombotic therapy, particularly anticoagulant is associated with unfavorable outcomes in primary spontaneous intracerebral hemorrhage patients receiving craniotomy: A nationwide population-based cohort study

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**Abbreviations list**

Intracerebral hemorrhage (ICH)
National Health Insurance Research Database (NHIRD)
New oral anticoagulants (NOACs)
Propensity score matching (PSM)
Charlson comorbidity index (CCI)
Generalized estimating equation (GEE)
National Institute of Health Stroke Scale (NIHSS)

## Abstract

### Objective

The impact of antithrombotic agents on primary intracerebral hemorrhage (ICH) patients remains controversial, especially with patients that require emergent craniotomy. This study was to evaluate clinical outcomes in operated ICH patients with and without prior antithrombotic agents.

### Methods

This is a retrospective cohort study. Between January 2001 to December 2013, all ICH patients that received emergent craniotomy and is present in Taiwan's National Health Insurance Research Database were screened, and divided into prior antiplatelet therapy, anticoagulant therapy and non-antithrombotic therapy according to patient's healthcare claims data within 3 months of index admission. The primary endpoints included in-hospital mortality and complication, and short-term outcome.

### Results

Of 18,872 eligible patients, 16,251 (87.1%) patients did not receive any antithrombotic therapy, 2,267 patients had antiplatelet therapy and 354 patients had anticoagulation therapy. After propensity score matching, significantly higher amount of blood transfusion and number of craniectomy was identified in the patients with prior antithrombotic treatment compared with non-antithrombotic therapy. In comparison with the non-antithrombotic treatment cohort, patients under prior anticoagulant treatment had significantly higher in-hospital mortality rate (Odds ratio, 2.12; 95% confidence interval, 1.45–3.10). Furthermore, during the 6-month follow-up period, prior anticoagulant therapy was independently associated with a greater risk of all-cause mortality rates (P = 0.001). Interestingly, the in-hospital and 6-month all-cause mortality of patients with prior antiplatelet treatment was not significantly different to patients with non-antithrombotic treatment.

### Conclusion

These findings suggested an increased risk of in-hospital mortality and poor short-term outcome among operated ICH patients with prior antithrombotic therapy, particularly anticoagulant therapy, but not with antiplatelet therapy.

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## Introduction

Spontaneous intracerebral haemorrhage (ICH) accounts for 10 - 15% of all cerebrovascular accident, and exhibit a higher mortality rate than either ischaemic stroke or subarachnoid haemorrhage [1]. Recently, antithrombotic agents, including antiplatelet therapy such as aspirin and anticoagulants such as warfarin, have been widely prescribed for patients as secondary prevention of coronary heart- or thrombotic-related disease [2,3]. Therefore, it is more becoming common for patients prior to ICH to have previously been exposed to antithrombotic agents. It has been previously suggested that patients with exposure to antithrombotic agents prior ICH would have a higher risk of secondary hematoma expansion, and an increased risk of death, or poor functional outcome [4,5]. Therefore, one essential problem frequently encountered clinically is how to manage patients on antithrombotic agents following spontaneous ICH, especially those requiring craniotomy.

Craniotomy is a life-saving procedure regularly carried out in selected patients with spontaneous ICH, but the presence of antithrombotic agents may increase the possibility of postoperative haemorrhage, as well as complication and mortality following craniotomy[6]. Therefore, the dilemma in treating ICH patients on antithrombotic agents will be the risk of increasing blood loss during surgical intervention versus the risk of further secondary brain damage if the hematoma is not removed.

To date, the impact of antithrombotic effect on mortality and complicated rate after surgical intervention in spontaneous ICH has not been sufficiently accessed because of limited number of operated ICH patients. According to national cohort studies, there are only 6.9 - 7.9 % patients with ICH receiving hematoma evacuation [7,8]. Interestingly, since the incidence of ICH is much higher in Asian rather than non-Asian population [9]. Therefore, it provides us with an opportunity to evaluate the impact of antithrombotic agents on the clinical outcomes of Asian ICH patients requiring hematoma evacuation. In this study, we examined the hypothesis that antithrombotic agents provide unfavourable in-hospital and short-term outcomes for ICH

patients requiring craniotomy from the National Health Insurance Research Database (NHIRD) of Taiwan.

## Method

### Data source

This retrospective-collected and observational cohort study involved data obtained from Taiwan's National Health Insurance Research Database (NHIRD), which contains all healthcare claims data between Jan 1997 to December 2013, include demographic data, records of clinical visits, hospital admissions, prescriptions, and disease status for more than 99% of the Taiwanese population. Data were anonymized, encrypted and maintained by the National Health Research Institutes of Taiwan for research purposes. Diagnostic codes used in the database are based on the international classification of disease, ninth revision; clinical modification (*ICD-9-CM*) codes (Supplementary Table 1). Validation of the NHIRD data involving cerebrovascular accident have been demonstrated in several studies by NHI Bureau [10,11]. This study was exempt from approval requirements by the Institutional Review Board of Chang Gung Memorial Hospital in Taiwan (IRB number, 201601518B0) and without permission of patient's consent, given that it was an epidemiology study with no definable patient information.

### Subjects

Study patients were identified from the NHIRD as those admitted for first event of cerebrovascular accident from January 1, 2001 and December 31, 2013 (ICD-9 CM codes, 430–437) (Supplementary Table 1). Within these patients with cerebrovascular accident, those who were diagnosed as a spontaneous intracerebral haemorrhage were identified (ICH, ICD-9-CM code, 431). The date of the first admission for ICH was assigned as the index date. Patients younger than 20 years, and those diagnosed with cerebral vascular lesion, such as arteriovenous malformation, aneurysm were excluded (ICD-9-CM codes, 437.3, 747.81, 4470). We also excluded the comorbidities where the conditions can possibly interfere with

coagulation conditions, such as coagulopathy (ICD 9-CM codes, 286.0–286.9, 287.1, 287.3–287.5, 289.81–289.82), liver cirrhosis (ICD-9-CM codes, 571.2, 571.5, 571.6), malignancy (ICD-9 CM codes, 140.xx–208.xx) predating the index date. To ensure that ICH were not secondary to other events, we also excluded those who suffered head injury (ICD-9-CM codes, 800.xx–804.xx, 850.xx–854.xx), haemorrhage stroke (ICD-9-CM codes, 430.xx–432.xx), and brain surgery events within 6 months before the index date. Overall, patients which received craniotomy during the index ICH admission data were eligible for selection into our study.

**Exposure of antithrombotic therapy and study design**

In order to compare the impact of antiplatelet and anticoagulant regiment on those receiving craniotomy, we retrieved the patient's healthcare claims data within 3 months of index admission. According to prescription record system, we exclude those under dual antiplatelet treatment. Eligible patients were further divided into three groups according to the antithrombotic agents exposure including; (1) no antithrombotic therapy, (2) antiplatelet therapy (e.g. aspirin, clopidogrel and ticlopidine), (3) anticoagulant therapy (e.g. warfarin and new oral anticoagulants (NOACs) including dabigatran and rivaroxaban). In order to balance all possible confounding factors between groups, propensity score matching (PSM) method with 1:1 matching between groups was performed prior analysis of clinical outcomes (Figure 1).

**Outcomes measures and comorbidities**

Baseline comorbidities, in-hospital complications and short-term outcomes were identified based on ICD-9-CM diagnosis codes recorded during hospitalization or clinic visit (Supplementary Table 1). The Charlson comorbidity index (CCI) was calculated to measure the patient’s underlying condition. Selected comorbidities were ascertained based on one in-

patient diagnosis or at least 2 outpatient diagnoses one year before index date. History of event (i.e. stroke, myocardial infarction) was verified using in-patient diagnosis before index date and tracked back to year 1997. In order to assess the severity of haemorrhagic stroke, estimated National Institute of Health Stroke Scale (NIHSS) based on weighted evaluation findings was applied, which was validation in a previous NHIRD study [12]. The primary outcome of this study was in-hospital mortality during the index admission. In-hospital treatment (including neurosurgical procedure and volume of blood transfusion) and postoperative conditions (including ischaemic stroke, pneumonia, septicaemia, surgical wound infection, pulmonary embolism, deep venous thrombosis, acute kidney injury, and massive blood transfusion) during the index admission were secondary outcomes. The short-term 6-month all-cause mortality were identified according to the withdrawal from the NHI system [13]. Data of patients were censored in the date of event occurrence, date of death or before 31 December, 2013.

**Ascertainment of ICH, comorbidities and Outcomes**

A majority of comorbidities based on ICD-9-CM have previously been validated [14,15]. The study patients with ICH were selected when their principal diagnosis of index hospitalization was ICH ([ICD-9-CM] code: 431). The high accuracy of the diagnosis of ICH based on ICD-9-CM coding in the NHIRD has been confirmed in a previous study [16]. Furthermore, a validation study was conducted in one centre by randomly sampling the records of 119 hospitalized patients in which their principal diagnosis of hospitalization was coded as ICD-9-CM: 431. A positive predictive value of 98% (117/119) was obtained when their medical records and images were independently reviewed by a physician (C-H Liu).

**Statistical analysis**

The distributions of demographic and clinical characteristics were compared between the

three study groups using chi-square test for categorical variable or one-way analysis of variance for continuous variable. Bonferroni adjustment was made as to the pairwise comparisons when the overall test was significant. Risk factors associated with in-hospital mortality were studied using multivariable logistic regression analysis. A propensity score matching (PSM) analysis was performed before comparing outcomes among the prior antiplatelet, anticoagulant, and non-antithrombotic groups, to ensure that the baseline characteristics among these three groups would be comparable (Supplementary Tables 2-4). The selected covariates used to calculate the propensity scores were gender, ages, hospital level where the operation was performed, coexisting diseases, history of event, CCI comorbidity, estimated NIHSS score and the index date. A 1:1 matching ratio was chosen in which greedy nearest neighbour algorithm was adopted and the caliper was set as 0.2 times the standard deviation of the logit of propensity score [17]. Comparison in blood transfusion volume between any two PSM groups was made using generalized estimating equation (GEE) type linear regression. Furthermore, comparison of risk of in-hospital treatment (neurosurgical procedures), in-hospital complication and mortality between any two PSM groups were made using GEE type logistic regression. The correlation of patients among the same match pair was adjusted in GEE model. The risk of time to all-cause mortality was compared within the three study groups before PSM using pairwise log-rank test. Likewise, the survival curves during the 6-month follow up were compared between any two PSM groups by using log-rank test stratified by match pair. Level of statistical significance were set as 0.05 and no adjustment of multiple testing (multiplicity) was made in this study. The data analysis were conducted using SAS software version 9.4 (SAS Institute, Cary, NC).

## Result

### Patient characteristics

From an initial sample of 699,291 patients with cerebrovascular accident events during the 13 year period between January 1, 2001 and December 31, 2013, there were 114,219 patients admitted for spontaneous ICH in Taiwan. After applying a series of excluding criteria, a total eligible 18,872 ICH adult patients were included, of which 2,267 (12 %) and 354 (1.9 %) received antiplatelet or anticoagulant treatment prior surgical intervention, respectively (Figure 1, Table 1). The mean age for the overall cohort was 59.7 years with a predominant male gender (66.5 %).

There were several significant differences in the baseline demographics and clinical characteristics of the study patients (Table 1). The mean age in the control group (58.6 years) was significantly younger compared to that in the antiplatelet (66.6 years) and anticoagulant (65.3 years) groups. Patients with anticoagulant therapy (54.5 %) were significantly more likely to receive craniotomy in teaching hospital than the antiplatelet (38.9 %) or control (36.9 %) groups. In general, patients underwent antithrombotic or anticoagulant regimens had a significantly higher prevalence of all major medical comorbidities (i.e., atrial fibrillation, hypertension, chronic kidney disease), and history of event (i.e., ischaemic stroke) compared to control patients. Noticeably, the prevalence of atrial fibrillation was significantly higher in the anticoagulant group (46.3 %) than that in the antiplatelet group (6.4 %).

### Events during index hospitalization

In addition to craniotomy, further neurosurgical intervention and in-hospital blood transfusion were studied (Table 2 and 3). There was a trend toward increasing number of craniectomy following craniotomy in patients receiving antiplatelet treatment when compared with no prior antithrombotic therapy. Patients under anticoagulant were significantly more likely to receive

craniectomy than those with prior antiplatelet treatment (odds ratio [OR], 2.21; 95% confidence interval [CI], 1.25 – 3.93) (Table 3). No significant difference was observed among the three groups with respect to other further surgical interventions (i.e. repeated brain surgery, extra-ventricular drainage) during the index admission. In contrast, greater amount of platelet during blood transfusion was required in the antiplatelet group than that in the control group (regression coefficient, 0.70 unit; 95% CI, 0.28 – 1.12) (Table 3). Furthermore, administration of fresh frozen plasma was significantly less in the antiplatelet than the other two groups. Interestingly, packed red blood cell usage was significantly higher in the anticoagulant than antiplatelet group, and that both groups were greater than non-antithrombotic (control) group. To understand the in-hospital complications, the complications after craniotomy were divided into the following categories: pulmonary, septicemia, wound infection, thromboembolic, postoperative haemorrhage, neurologic, and renal issues (Table 2 and 4). The order of greatest common complication (greatest number first with percentage of occurrence ≥ 4 %) was pneumonia, septicemia and ischaemic stroke. In comparison to the control group, there was no significant difference between surgical-related complications in the two antithrombotic groups. Interestingly, patients in the anticoagulant group were significantly more likely to suffer septicemia compared to those in the antiplatelet group (OR, 2.29; 95 % CI, 1.10 – 4.76) (Table 4). Furthermore, patients under anticoagulant treatment have significantly higher in-hospital mortality rate compared to the antiplatelet group (OR, 1.60; 95 % CI, 1.12 –2.30) and to the control group (OR, 2.12; 95 % CI, 1.45 – 3.10). However, the in-hospital mortality rate was not significantly different between the antiplatelet group and the control group.

Additional analysis was carried out to investigate risk factors of in-hospital mortality by using the whole cohort. The result identified the following variables as potential risk factors: male gender, age greater than 80 years (compared to 20-39 years), operation in non-teaching hospital, atrial fibrillation, epilepsy, hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease and history of ischaemic stroke (Figure 2).

**Outcomes during Follow-up**

Mortality rate of the three groups of patients during the 6 months follow-up period was studied in the whole cohort (Figures 3A). The all-cause mortality rates at 6 months follow up of control, antiplatelet, and anticoagulant patients were 9.9 %, 13.6 %, and 19.9 %, respectively. Large significant differences in the survival curves between all the three groups were observed (Figure 3A). Furthermore, the 6 months mortality rate was significantly higher toward the anticoagulant group compared to the control and the antiplatelet groups when using the PSM cohorts ($p = 0.001$, $p = 0.007$, respectively) (Figures 3B and C). However, the 6 month mortality rate was not significantly different between the antiplatelet and the control groups when using the PSM cohorts ($P = 0.773$, Figure 3D).

## Discussion

The use of antithrombotic agents in the general population is ever increasing due to their preventative use for a variety of disease such as cardiovascular disease. Therefore, it is important to understand their impact in emergency neurological surgery. In this study, we compared 18,872 patients that have received craniotomy after spontaneous ICH in a 13 year period with matched control group by using the Taiwan's health nationwide database. Our study showed the incidence of ICH receiving craniotomy was 16.5 %. To date, this is the largest cohort study of craniotomy for ICH. Furthermore, this study compares the admission events, in-hospital mortality and 6-months outcome of patients receiving prior antithrombotic therapy with those of a matched control group. We demonstrated significant increased in-hospital mortality in operated ICH patients receiving prior anti-coagulant treatment, but not in patients with prior anti-platelet treatment.

### Impact of antiplatelet therapy

Currently, the influence of prior antiplatelet therapy has on ICH expansion or neurologic outcome remains controversial [5,18,19]. A recent study revealed that a pre-hospital antiplatelet regimen could be associated with hematoma expansion, an increased mortality rate, and poor functional outcome in spontaneous ICH [5,8]. In contrast, other studies have failed to detect differences in outcome or hematoma growth [18,19]. The reason for this discrepancy is not clear, but this could be due to the heterogeneous clinical presentations of ICH, different treatment strategies and low incident rate.

A recent study demonstrated a significant higher risk of in-hospital mortality after hematoma evacuations in patients with prior antiplatelet treatment compared to patients without prior antiplatelet treatment [20]. From our real-world data, the in-hospital mortality and short-term outcome of patients with prior antiplatelet treatment was significantly increased compared to control group (Figure 3A). However, in-hospital and 6 months mortality revealed no significant

difference after matched control comparison (Figure 3D). This implies that the underlying condition of patients receiving antiplatelet plays a vital role in the clinical outcome.

**Impact of anticoagulation therapy**

It has been previously shown that the mortality and neurologic outcome were worse for anticoagulant associated ICH. This could be due to larger haemorrhage volumes [21,22], higher risk of hematoma expansion [4], and higher comorbidities among anticoagulated patients [23]. Interestingly, this worsening in neurological outcome may be associated with the patients' race, since a recent study demonstrated that haemorrhagic stroke rates were higher in Asians compared to non-Asians on warfarin [24]. In line with previous studies, our study observed pre-treatment with oral anticoagulant was a strong predictor of increased in-hospital mortality [25,26]. Furthermore, we found the rate of complication was significantly higher among patients receiving prior anticoagulant therapy compared to control and antiplatelet group. Interestingly, a recent study demonstrated that oral anticoagulants did not increase in-hospital mortality in ICH patients receiving hematoma evacuation because the international normalized ratio could be normalized before surgical intervention [27]. This discrepancy could be explained by the racial difference in warfarin pharmacokinetics. Asian population in particular have a higher risk for warfarin-related ICH [28]. The optimal range of international normalized ratio for Asians might be narrower than for non-Asians, which could lead to difficult control on anticoagulation quality [29]. Current data suggest that the NOACs are not associated with a higher risk of spontaneous ICH [30]. However, since this is a relative new therapy, the number of patients that have received NOACs in our study was too low for any meaningful statistical analysis.

**Surgical outcome of ICH with prior antithrombotic treatment**

The findings from our study demonstrated that patients taking prior antithrombotic treatment

required a greater number of decompression craniectomy. Our finding suggested the brain edema developed more frequently in the patients treated with antithrombotic. Another possible reason could be related to the significantly more blood transfusion performed in these patients. It should be noted that although complications of blood transfusion are rare, it can be life threatening because massive blood transfusions can result in abnormalities of coagulation status, vascular permeability, acid-base balance and temperature hemostasis [31]. Previous studies have demonstrated that the large quantity of blood transfusions can cause complications such as reversible posterior leukoencephalopathy syndrome [32-34]. Furthermore, blood transfusion may cause a rapid increase in total blood volume, which further leads to cerebral blood flow overload. It has been suggested that an abrupt or acute cerebral hyperperfusion exceeding the capacity of autoregulation of cerebral capillary perfusion pressure could result in vasogenic edema[34].

**Surgical complication associated with antithrombotic treatment**

The three most common surgical complications in our study were pneumonia, septicaemia, and gastrointestinal bleeding. This was not surprising, since stroke patients have been demonstrated to be more susceptible to infection due to immune system suppression [35]. Pneumonia was the most common complication in our study, which is consistent with other studies on stroke patients [36]. Interestingly, pneumonia and septicaemia that required medical treatment were present more often in patients with prior anticoagulant treatment. Overall, patients receiving prior anticoagulant therapy have higher complication rate compared to either antiplatelet or non-antithrombotic therapy.

**Limitation of the study**

The presented data were analyzed from the Taiwan's national wide database and was not a randomized trial for operative treatment ICH patients. Therefore, there was no prospectively

document to suggest the reason why a craniotomy was necessary, so presumption was made that haemorrhage enlargement would led to a worse neurologic exam, such as a potential brain herniation. Additionally, the database does not include neurological or functional outcome, such as Glasgow Coma Scale, or modified Rankin Scale, respectively. However, the absence of such data does not lessen our data interpretation. Another consideration should be taken is that clinicians may not be blinded to antiplatelet or anticoagulant treatment prior to ICH development, so these data reflect an association between these medical treatments and the perceived need for craniotomy. The strengths of our study includes; 1) a large population-based follow-up study containing all adults living in Taiwan, 2) usage of estimated NIHSS which has already been well assessed to correlation of severity of ICH patients, and 3) the integrated details of prescription records prior to admission, complications, mortality and clinical following-up were well recorded. Furthermore, the analysis of propensity score matching was applied to eliminate the confounding factors among these patients.

## Conclusions

This study has provided a comprehensive national perspective on in-hospital complication and mortality in operative ICH patients in Taiwan. Prior antithrombotic agent treatment in ICH patients receiving craniotomy was associated with an increased risk of repeated brain surgery. Furthermore, our study also identified the significantly higher in-hospital mortality and six months all-cause mortality rate in patients with prior anticoagulant therapy, but not in patients with prior antiplatelet therapy. In summary, physicians should be more aware of the potential risk with prior antithrombotic therapy, especially anticoagulant treatment and their negative association with life-saving surgical intervention for spontaneous ICH. This is valuable information for surgeons faced with difficult decision in managing patients taking antithrombotic drugs, but requiring neurosurgical intervention.

**Contributors**

ZHL, YSL and NYC designed the research; PHT, CCC, YCW, PWH analyzed and interpreted the data, CHL validated the data, ZHL, YSL wrote the manuscript. , PKY critically revised of the manuscript.

**Figure legends**

**Figure 1** Flow chart illustrating the patient selection included in the study.

Flow chart illustrating the patient selection included in the study. (A) Spontaneous ICH patients receiving craniotomy were divided into three groups (control, antiplatelet, and anticoagulant) according to the prior antithrombotic therapy. Patients with cerebrovascular accident admitted for hemorrhage stroke were included after relevant exclusions. (B) Propensity score matching with a 1:1 ratio enable 3 groups of comparisons with their number of patients.

**Figure 2** Association of patient characteristics with risk of in hospital mortality.

This multivariable logistic regression analysis was adjusted for all variables listed in Table 1.

**Figure 3** Kaplan-Meier survival curves of all-cause mortality.

(A) The unadjusted Kaplan-Meier survival curves of all cause of mortality that estimated the mortality rate in ICH operative patients using real-world data. Log-Rank test demonstrated $p < 0.001$ for all antiplatelet vs control, anticoagulant vs control, anticoagulant vs antiplatelet, and antiplatelet vs control. (B-C) The matched control Kaplan-Meier survival curves of all cause of mortality estimated the mortality rate patients between different cohorts. Adjusted incidence curves were adjusted for all covariates listed in Table 1. P of log-Rank test demonstrated $p=0.001$ for anticoagulant vs control (B), $p = 0.007$ for anticoagulant vs antiplatelet (C), and $p =0.773$ for antiplatelet vs control (D).

**Table 1.** Baseline and clinical characteristics of the study patients before propensity score

matching

**Table 2.** Descriptive statistics of in-hospital treatment, complication and mortality of the study patients

**Table 3.** In-hospital treatment of the study patients

**Table 4.** In-hospital complication and mortality of the study patients

**Supplementary Table 1**. ICD-9-CM code used in the current study.

**Supplementary Table 2**. Baseline and clinical characteristics in the antiplatelet and control groups after propensity score matching.

**Supplementary Table 3**. Baseline and clinical characteristics in the anticoagulant and control groups after propensity score matching.

**Supplementary Table 4**. Baseline and clinical characteristics in the anticoagulant and antiplatelet groups after propensity score matching.

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**Figure 1**

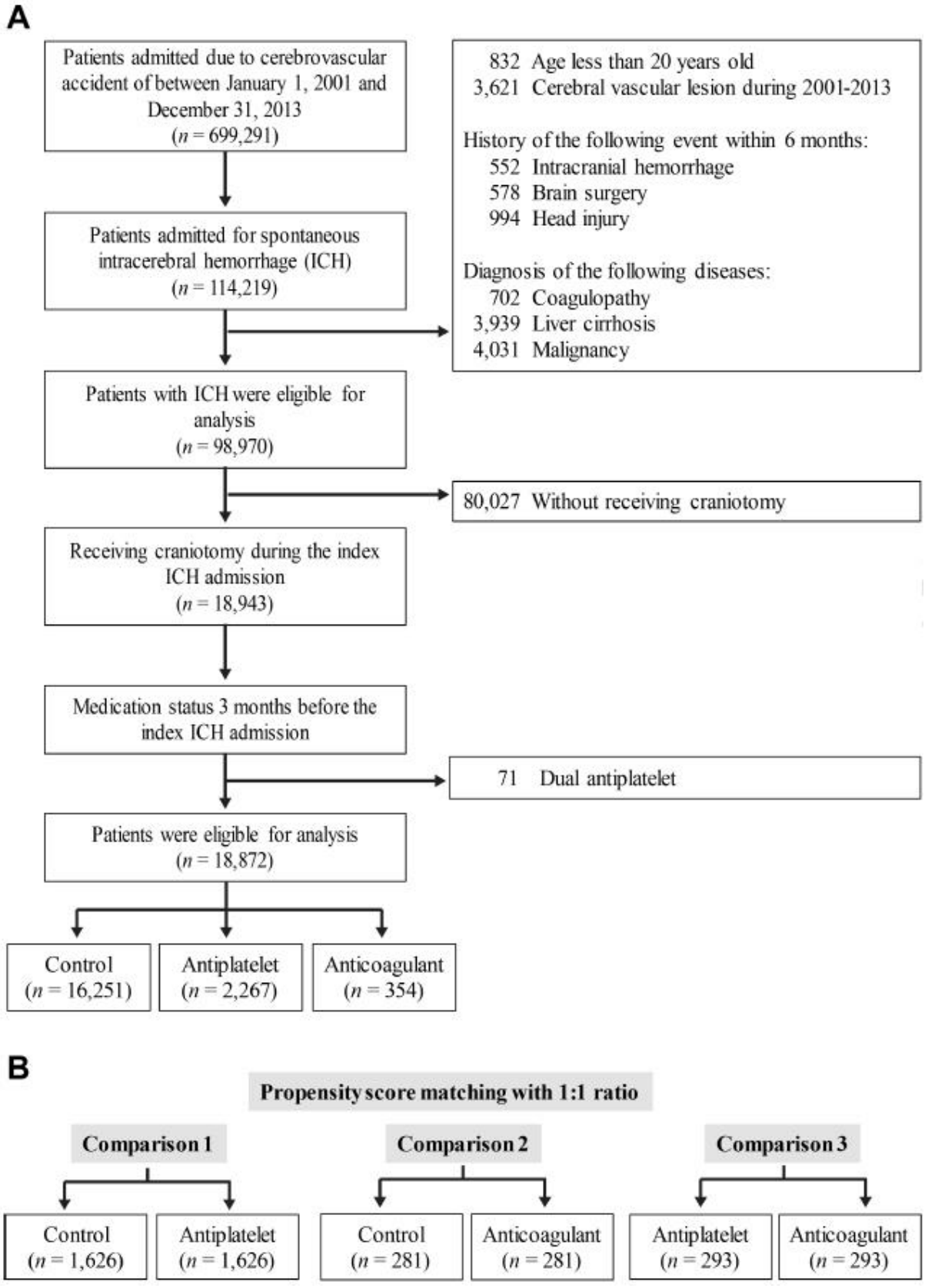
A
Patients admitted due to cerebrovascular accident of between January 1, 2001 and December 31, 2013 (n = 699,291)
Patients admitted for spontaneous intracerebral hemorrhage (ICH) (n = 114,219)
Patients with ICH were eligible for analysis (n = 98,970)
Receiving craniotomy during the index ICH admission (n = 18,943)
Medication status 3 months before the index ICH admission
Patients were eligible for analysis (n = 18,872)
Control (n = 16,251)
Antiplatelet (n = 2,267)
Anticoagulant (n = 354)
832 Age less than 20 years old
3,621 Cerebral vascular lesion during 2001-2013
History of the following event within 6 months:
552 Intracranial hemorrhage
578 Brain surgery
994 Head injury
Diagnosis of the following diseases:
702 Coagulopathy
3,939 Liver cirrhosis
4,031 Malignancy
80,027 Without receiving craniotomy
71 Dual antiplatelet
B
Propensity score matching with 1:1 ratio
Comparison 1
Comparison 2
Comparison 3
Control (n = 1,626)
Antiplatelet (n = 1,626)
Control (n = 281)
Anticoagulant (n = 281)
Antiplatelet (n = 293)
Anticoagulant (n = 293)

**Figure 2**

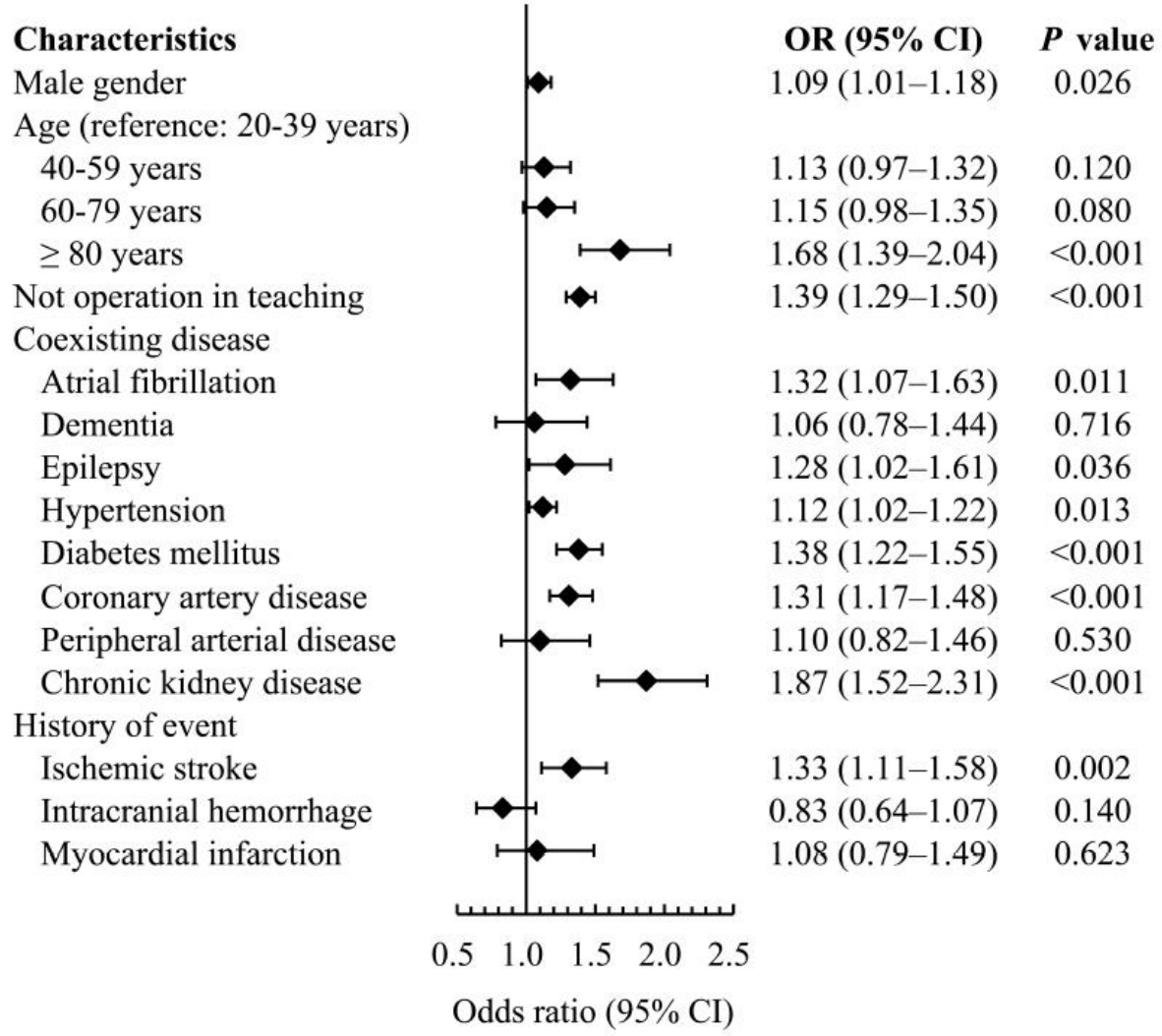
Characteristics
OR (95% CI)
P value
Male gender
1.09 (1.01–1.18)
0.026
Age (reference: 20-39 years)
40-59 years
1.13 (0.97–1.32)
0.120
60-79 years
1.15 (0.98–1.35)
0.080
≥ 80 years
1.68 (1.39–2.04)
<0.001
Not operation in teaching
1.39 (1.29–1.50)
<0.001
Coexisting disease
Atrial fibrillation
1.32 (1.07–1.63)
0.011
Dementia
1.06 (0.78–1.44)
0.716
Epilepsy
1.28 (1.02–1.61)
0.036
Hypertension
1.12 (1.02–1.22)
0.013
Diabetes mellitus
1.38 (1.22–1.55)
<0.001
Coronary artery disease
1.31 (1.17–1.48)
<0.001
Peripheral arterial disease
1.10 (0.82–1.46)
0.530
Chronic kidney disease
1.87 (1.52–2.31)
<0.001
History of event
Ischemic stroke
1.33 (1.11–1.58)
0.002
Intracranial hemorrhage
0.83 (0.64–1.07)
0.140
Myocardial infarction
1.08 (0.79–1.49)
0.623
0.5
1.0
1.5
2.0
2.5
Odds ratio (95% CI)

**Figure 3**

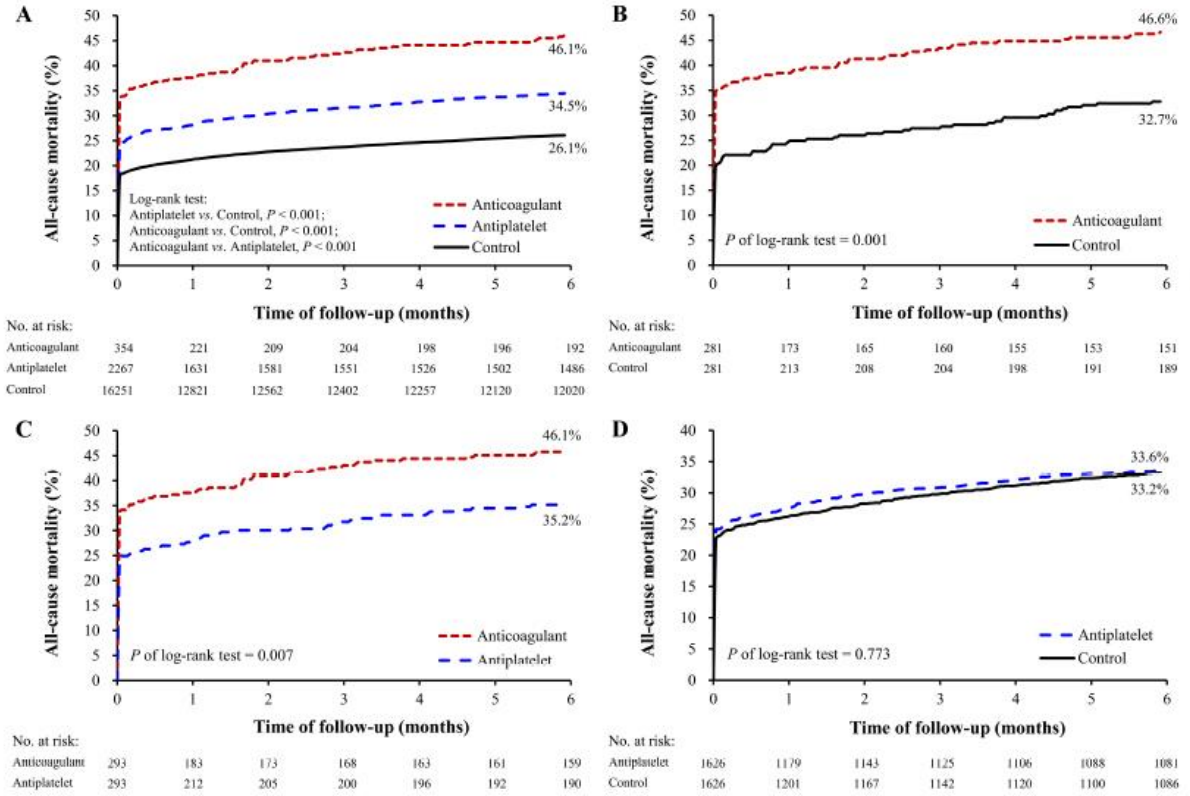
A
All-cause mortality (%)
Time of follow-up (months)
46.1%
34.5%
26.1%
Log-rank test:
Antiplatelet vs. Control, P < 0.001;
Anticoagulant vs. Control, P < 0.001;
Anticoagulant vs. Antiplatelet, P < 0.001
Anticoagulant
Antiplatelet
Control
No. at risk:
Anticoagulant 354 221 209 204 198 196 192
Antiplatelet 2267 1631 1581 1551 1526 1502 1486
Control 16251 12821 12562 12402 12257 12120 12020
B
All-cause mortality (%)
Time of follow-up (months)
46.6%
32.7%
P of log-rank test = 0.001
Anticoagulant
Control
No. at risk:
Anticoagulant 281 173 165 160 155 153 151
Control 281 213 208 204 198 191 189
C
All-cause mortality (%)
Time of follow-up (months)
46.1%
35.2%
P of log-rank test = 0.007
Anticoagulant
Antiplatelet
No. at risk:
Anticoagulant 293 183 173 168 163 161 159
Antiplatelet 293 212 205 200 196 192 190
D
All-cause mortality (%)
Time of follow-up (months)
33.6%
33.2%
P of log-rank test = 0.773
Antiplatelet
Control
No. at risk:
Antiplatelet 1626 1179 1143 1125 1106 1088 1081
Control 1626 1201 1167 1142 1120 1100 1086

**Table 1**

| Variable | Total (*n* = 18,872) | Control (*n* = 16,251) | Antiplatelet (*n* = 2,267) | Anticoagulant (*n* = 354) |
|---|---|---|---|---|
| Gender | | | | |
| Male | 12,548 (66.5) | 10,939 (67.3) | 1,413 (62.3)[a] | 196 (55.4)[ab] |
| Female | 6,324 (33.5) | 5,312 (32.7) | 854 (37.7)[a] | 158 (44.6)[ab] |
| Age (years) | 59.7±13.8 | 58.6±13.8 | 66.6±11.7[a] | 65.3±13.5[a] |
| Age group | | | | |
| 20-39 years | 1,404 (7.4) | 1,349 (8.3) | 35 (1.5)[a] | 20 (5.6)[b] |
| 40-59 years | 8,430 (44.7) | 7,721 (47.5) | 613 (27.0)[a] | 96 (27.1)[a] |
| 60-79 years | 7,670 (40.6) | 6,123 (37.7) | 1,354 (59.7)[a] | 193 (54.5)[a] |
| ≥ 80 years | 1,368 (7.2) | 1,058 (6.5) | 265 (11.7)[a] | 45 (12.7)[a] |
| Operation in teaching hospital | | | | |
| No | 11,796 (62.5) | 10,249 (63.1) | 1,386 (61.1) | 161 (45.5)[ab] |
| Yes | 7,076 (37.5) | 6,002 (36.9) | 881 (38.9) | 193 (54.5)[ab] |
| Coexisting disease | | | | |
| Atrial fibrillation | 470 (2.5) | 161 (1.0) | 145 (6.4)[a] | 164 (46.3)[ab] |
| Dementia | 242 (1.3) | 164 (1.0) | 70 (3.1)[a] | 8 (2.3) |
| Epilepsy | 425 (2.3) | 334 (2.1) | 84 (3.7)[a] | 7 (2.0) |
| Hypertension | 5,939 (31.5) | 3,945 (24.3) | 1,731 (76.4)[a] | 263 (74.3)[a] |
| Diabetes mellitus | 1,907 (10.1) | 1,159 (7.1) | 669 (29.5)[a] | 79 (22.3)[ab] |
| Coronary artery disease | 1,915 (10.1) | 947 (5.8) | 844 (37.2)[a] | 124 (35.0)[a] |
| Peripheral arterial disease | 269 (1.4) | 131 (0.8) | 111 (4.9)[a] | 27 (7.6)[a] |
| Dialysis | 476 (2.5) | 382 (2.4) | 80 (3.5)[a] | 14 (4.0) |
| Chronic kidney | 898 (4.8) | 680 (4.2) | 184 (8.1)[a] | 34 (9.6)[a] |

| | | | | |
|---|---|---|---|---|
| disease | | | | |
| History of event | | | | |
| Ischemic stroke | 750 (4.0) | 466 (2.9) | 244 (10.8)[a] | 40 (11.3)[a] |
| Intracranial hemorrhage | 427 (2.3) | 340 (2.1) | 79 (3.5)[a] | 8 (2.3) |
| Myocardial infarction | 206 (1.1) | 98 (0.6) | 94 (4.1)[a] | 14 (4.0)[a] |
| Charlson Comorbidity Index | 2.0 ± 1.3 | 1.9 ± 1.2 | 2.5 ± 1.5[a] | 2.7 ± 1.7[ab] |
| Estimated NIHSS | 22.5 ± 3.5 | 22.4 ± 3.5 | 22.9 ± 3.5[a] | 22.8 ± 3.4 |

**Table 1**. Baseline and clinical characteristics of the study patients before propensity score matching

Data are presented as frequency with percentage in brackets, or mean ± standard deviation. NIHSS, National Institute of Health Stroke Scale; The characters “a” and “b” denote a significant post hoc comparison versus control and antiplatelet, respectively.

**Table 2**. In-hospital treatment, complication and mortality of the study patients during index date hospitalization

| | Propensity score matched cohort | | | | | |
|---|---|---|---|---|---|---|
| | Antiplatelet *vs*. Control (*n* = 1,626 for each cohort) | | Anticoagulant *vs.* Control (*n* = 281 for each cohort) | | Anticoagulant *vs*. Antiplatelet (*n* = 293 for each cohort) | |
| Outcome | Anti-platelet | Control | Anti-coagulant | Control | Anti-coagulant | Anti-platelet |
| Neurosurgical procedure | | | | | | |
| Craniectomy | 148 (9.1) | 121 (7.4) | 34 (12.1) | 27 (9.6) | 39 (13.3) | 19 (6.5) |
| Repeated brain surgery | 165 (10.1) | 132 (8.1) | 36 (12.8) | 27 (9.6) | 41 (14.0) | 22 (7.5) |
| EVD | 290 (17.8) | 299 (18.4) | 55 (19.6) | 54 (19.2) | 61 (20.8) | 57 (19.5) |
| V-P shunt | 56 (3.4) | 56 (3.4) | 6 (2.1) | 11 (3.9) | 6 (2.0) | 8 (2.7) |
| Blood transfusion, U | | | | | | |
| Platelet | 1.8 ± 7.1 | 1.1 ± 4.9 | 2.1 ± 6.0 | 2.1 ± 7.8 | 2.2 ± 6.4 | 2.8 ± 9.1 |
| Fresh frozen plasma | 2.5 ± 6.8 | 2.0 ± 4.7 | 5.6 ± 6.2 | 2.3 ± 4.9 | 5.5 ± 6.1 | 3.0 ± 9.1 |
| PRBC | 1.6 ± 2.5 | 1.4 ± 2.2 | 2.1 ± 2.7 | 1.9 ± 3.2 | 2.2 ± 2.8 | 1.9 ± 3.0 |
| Complications | | | | | | |
| Ischemic stroke | 78 (4.8) | 64 (3.9) | 18 (6.4) | 10 (3.6) | 19 (6.5) | 25 (8.5) |
| Pneumonia | 398 (24.5) | 412 (25.3) | 82 (29.2) | 68 (24.2) | 84 (28.7) | 69 (23.5) |
| Septicemia | 80 (4.9) | 78 (4.8) | 22 (7.8) | 14 (5.0) | 24 (8.2) | 11 (3.8) |
| Wound infection | 11 (0.7) | 20 (1.2) | 4 (1.4) | 3 (1.1) | 5 (1.7) | 1 (0.3) |
| Pulmonary embolism | 4 (0.2) | 2 (0.1) | 1 (0.4) | 0 (0.0) | 1 (0.3) | 0 (0.0) |
| Deep vein thrombosis | 5 (0.3) | 5 (0.3) | 3 (1.1) | 1 (0.4) | 3 (1.0) | 0 (0.0) |
| Acute kidney injury | 62 (3.8) | 66 (4.1) | 10 (3.6) | 11 (3.9) | 11 (3.8) | 11 (3.8) |

| | Propensity score matched cohort | | | | | |
|---|---|---|---|---|---|---|
| | Antiplatelet *vs*. Control (*n* = 1,626 for each cohort) | | Anticoagulant *vs.* Control (*n* = 281 for each cohort) | | Anticoagulant *vs*. Antiplatelet (*n* = 293 for each cohort) | |
| Outcome | Anti-platelet | Control | Anti-coagulant | Control | Anti-coagulant | Anti-platelet |
| Massive blood transfusion (PRBC > 10 U) | 22 (1.4) | 14 (0.9) | 5 (1.8) | 9 (3.2) | 5 (1.7) | 4 (1.4) |
| Any complications | 630 (38.7) | 629 (38.7) | 127 (45.2) | 112 (39.9) | 136 (46.4) | 113 (38.6) |
| In-hospital mortality | 384 (23.6) | 372 (22.9) | 97 (34.5) | 56 (19.9) | 98 (33.4) | 70 (23.9) |

Data are presented as frequency with percentage in brackets, or mean ± standard deviation. EVD, extra-ventricular drainage; V-P, ventriculoperitoneal; PRBC, packed red blood cell.

**Table 3**. In-hospital neurosurgical and blood transfusion procedures in the study patients

| | Odds ratio or regression coefficient and 95% CI | | | | | |
|---|---|---|---|---|---|---|
| | Antiplatelet *vs*. Control (*n* = 1,626 for each cohort) | | Anticoagulant *vs*. Control (*n* = 281 for each cohort) | | Anticoagulant *vs*. Antiplatelet (*n* = 293 for each cohort) | |
| Outcome | OR / *B* (95% CI) | *P value* | OR / *B* (95% CI) | *P value* | OR / *B* (95% CI) | *P value* |
| Neurosurgical procedure | | | | | | |
| Craniectomy | 1.25 (0.97–1.60) | 0.086 | 1.30 (0.76–2.21) | 0.344 | 2.21 (1.25–3.93) | 0.007 |
| Repeated brain surgery | 1.28 (1.01 – 1.63) | 0.045 | 1.38 (0.81 – 2.35) | 0.230 | 2.00 (1.16 – 3.46) | 0.013 |
| EVD | 0.96 (0.81–1.15) | 0.682 | 1.02 (0.67–1.55) | 0.915 | 1.09 (0.73–1.63) | 0.680 |
| V-P shunt | 1.00 (0.69–1.46) | 1.000 | 0.54 (0.20–1.47) | 0.225 | 0.75 (0.26–2.17) | 0.590 |
| Blood transfusion, U | | | | | | |
| Platelet | 0.70 (0.28–1.12) | 0.001 | -0.04 (-1.20– 1.12) | 0.945 | -0.55 (-1.82– 0.72) | 0.393 |
| Fresh frozen plasma | 0.51 (0.10–0.91) | 0.014 | 3.30 (2.38–4.22) | <0.001 | 2.59 (1.33–3.85) | <0.001 |
| PRBC | 0.23 (0.07–0.39) | 0.006 | 0.23 (-0.26– 0.71) | 0.358 | 0.32 (-0.15– 0.78) | 0.185 |

OR, odds ratio; *B*, regression coefficient; CI, confidence interval; EVD, extra-ventricular drainage; V-P, ventriculoperitoneal; PRBC, packed red blood cell.

**Table 4**. In-hospital complication and mortality of the study patients

| | Odds ratio and 95% CI | | | | | |
|---|---|---|---|---|---|---|
| | Antiplatelet *vs*. Control (*n* = 1,626 for each cohort) | | Anticoagulant *vs.* Control (*n* = 281 for each cohort) | | Anticoagulant *vs*. Antiplatelet (*n* = 293 for each cohort) | |
| Outcome | OR (95% CI) | *P value* | OR (95% CI) | *P value* | OR (95% CI) | *P value* |
| Complications | | | | | | |
| Ischemic stroke | 1.23 (0.88–1.72) | 0.230 | 1.86 (0.84–4.09) | 0.126 | 0.74 (0.40–1.38) | 0.348 |
| Pneumonia | 0.96 (0.82–1.12) | 0.570 | 1.29 (0.89–1.88) | 0.182 | 1.31 (0.90–1.89) | 0.159 |
| Septicemia | 1.03 (0.75–1.41) | 0.870 | 1.62 (0.81–3.24) | 0.172 | 2.29 (1.10–4.76) | 0.027 |
| Wound infection | 0.55 (0.26–1.15) | 0.110 | 1.34 (0.30–6.03) | 0.705 | 5.07 (0.59–43.66) | 0.140 |
| Pulmonary embolism | 2.00 (0.37–10.95) | 0.423 | NA | NA | NA | NA |
| Deep vein thrombosis | 1.00 (0.29–3.46) | 1.000 | 3.02 (0.31–29.22) | 0.340 | NA | NA |
| Acute kidney injury | 0.94 (0.66–1.34) | 0.718 | 0.91 (0.38–2.17) | 0.824 | 1.00 (0.43–2.34) | 1.000 |
| Massive blood transfusion (PRBC > 10 U) | 1.58 (0.81–3.10) | 0.184 | 0.55 (0.18–1.66) | 0.286 | 1.25 (0.33–4.72) | 0.737 |
| Any complications | 1.00 (0.87–1.16) | 0.971 | 1.24 (0.89–1.74) | 0.201 | 1.38 (0.99–1.92) | 0.055 |
| In-hospital mortality | 1.04 (0.89–1.23) | 0.618 | 2.12 (1.45–3.10) | <0.001 | 1.60 (1.12–2.30) | 0.011 |

OR, odds ratio; CI, confidence interval; PRBC, packed red blood cell; NA, not applicable.