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The impact of anticoagulant therapy on patients with hemorrhagic stroke: a retrospective observational study from eICU database

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Abstract: The timing and effectiveness of anticoagulant therapy (AT) are controversial in patients with hemorrhagic stroke (HS). We aim to evaluate the potential impact of AT on in-hospital mortality in HS, and how this impact is influenced by the Acute Physiological and Chronic Health Evaluation (APACHE) IV score. We identified individuals with hemorrhagic stroke as the primary diagnosis (n=1654) using individual patient data from a national multicenter cohort study (eICU database; n=200859). With in-hospital mortality as the primary outcome, hemorrhagic stroke patients were split into the anticoagulant therapy group and the other treatment (OT) group. First, univariate and multivariate logistic regression analyses were conducted to identify independent predictors of in-hospital mortality in patients receiving different forms of treatment. Next, the independent predictor's interaction with the AT status was evaluated.Resultly, 8.3%(n=137) of patients were in AT group. The survival rate in the AT group was significantly higher than that in the OT group (87.6% vs. 78.8%; P < 0.05). AT was an independent predictor of in-hospital mortality risk in the entire cohort [OR= 0.542, 95%CI(0.298-0.985), P<0.05], and APACHE IV score [OR= 1.055, 95%CI(1.048-1.061), P<0.05] score was an independent predictor of in-hospital mortality in the OT group in multivariate logistic regression (P< 0.05). The APACHE IV score was used to predict the risk for the entire cohort (the area under the receiver operator characteristic curve was 0.825 [(95% CI (0.799-0.851)]. Patients who started anticoagulant therapy seemed to benefit more when the predicted in-hospital mortality risk was more than 6.9%, and patients without anticoagulant therapy seemed to benefit more when the predicted in-hospital mortality risk was less than 6.9%. In conclusion, patients diagnosed with hemorrhagic stroke benefit from AT. APACHE IV score has a better ability to predict in-hospital mortality risk. Specifically, the higher the predicted risk of in-hospital mortality, the greater the benefits of anticoagulant therapy.

1. Introduction

Hemorrhagic stroke (HS) is a relatively common stroke syndrome including intracranial hemorrhage(ICH) and subarachnoid hemorrhage(SAH). Anticoagulant therapy (AT) after HS is a controversial topic. Recent reports have found that compared with the general population, survivors of ICH have a higher risk of ischemic stroke and myocardial infarction and a higher risk of all serious vascular events (approximately 8% per year) [1-3]. Especially in critically ill patients, new-onset atrial fibrillation is very high and has a high short and long-term risk. Another cohort comparison analysis suggests that low-dose intravenous heparin infusion may favorably influence the outcome of patients after aneurysm subarachnoid hemorrhage [4]. In addition, atrial fibrillation is present in 14%-42% of patients with HS (of any type) [5-9], and those who survive HS have a very high risk of ischemic stroke and mortality [10,11]. International guidelines state that early resumption of anticoagulant therapy may be necessary, but do not provide specific recommendations on effectiveness and timing [12-14]. Therefore, the available analysis and data quality do not appear sufficient to draw firm conclusions. APACHE IV score is widely used to evaluate the severity and prognosis of critically ill patients[15,16]， and there is a good assessment of acute brain injury and HS hospitalization and early mortality[17,18]. There are four versions of the APACHE score, APACHE IV score is the latest version. We evaluated the impact of AT on in-hospital mortality in patients with HS treated within the eICU database. The anticoagulation decision was made according to the effect of APACHE IV on the hospital mortality of HS.

2. Methods

2.1. Data Availability

Data were collected from the eICU Collaborative Research Database v2.0. The Collaborative Research Database of the eICU is a large public database created by Philips Healthcare in collaboration with the Laboratory of Computational Physiology of the Massachusetts Institute of Technology, covering routine data from 200,859 patients admitted to the intensive care unit in 208 hospitals in the United States in 2014 and 2015, The eICU database included hourly physiological readings from bedside monitors, demographic characteristics records, the severity of illness measures, diagnoses, treatment, and other clinical data collected during routine medical care[19,20]. The use of this database has been approved by the institutional review boards of the Massachusetts Institute of Technology (no. 0403000206) and with the 1964 Declaration of Helsinki and its later amendments. The author obtained access and was responsible for the data extraction (certification number: 41800801).

2.2. Patient selection

All patients recorded in the database with a primary diagnosis of hemorrhagic stroke of nervous system disease who were admitted to the ICU for the first time were eligible for inclusion in this study. Patients were excluded for the following reasons: (1) absence of data on patient in-hospital status(alive or expired) data; (2) missing patient APACHE IV score and APACHE IV score equal to -1. In the end, 1654 patients met the study requirements, including 137 who received anticoagulant therapy and 1517 who did not. See Figure 1 (flow chart) for details.

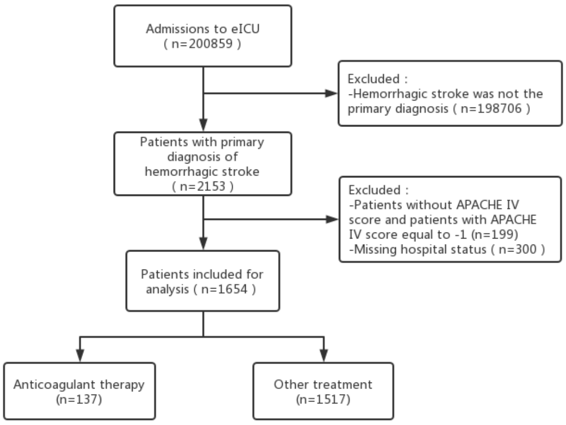

Figure 1: Flow chart of the subject of the study

2.3. Variables and endpoint definition

Patients were stratified according to treatment type. AT is defined as anticoagulant therapy including heparin, coumarins, bivalirudin, factor Xa inhibitors and thrombin inhibitors, and OT is defined as other treatment without anticoagulant therapy. The following data were extracted from the eICU database: gender, age, ethnicity, admission height, admission weight, APACHE IV score, anticoagulant therapy, comorbidities (atrial fibrillation, hypertension, diabetes mellitus, heart failure, pulmonary infection, gastrointestinal bleed, chronic renal insufficiency, coronary artery disease, chronic obstructive pulmonary disease, and in-hospital mortality). The APACHE IV system is a tool for risk-adjusted ICU patient performance benchmarks that provide valid patient mortality estimates based on ICU admission data within 24 hours. The specific score can be through an online website (https://intensivecarenetwork.com/Calculators/Files/APACHE 4. HTML). The endpoint of interest was in-hospital mortality.

2.4. Statistical analysis

First, the normality of the continuous variables is tested. Results were exhibited as median (interquartile range, IQR) for continuous variables while categorical variables were expressed as numbers (percentages). Secondly, to compare the In-hospital survivors' and In-hospital non-survivors' baseline characteristics, the Wilcoxon rank-sum test was used for continuous variables when appropriate; the chi-square test was used for categorical variables. The proportion of the missing values in the study was 3.9%. The missing values were substituted by multiple imputation methods. Finally, five complete datasets were obtained with the "mice" of R package, reducing bias and increasing statistical power. Multiple copies were created and the missing values were substituted with the mean of the datasets.

Statistical analysis consisted of two main steps to test the hypothesis that in-hospital mortality is associated with AT in patients with HS at diagnosis. Firstly, the standard univariate and multivariable logistic regression were analyzed to test the relationship between AT and in-hospital mortality. Robust standard errors were used for all logistic regression to provide accurate estimates. To assess the discrimination of the basic model, the area under Receiver Operating Characteristic Curve was calculated. Three-step approaches were used to evaluate the interaction between AT and in-hospital mortality risk: (1) univariate logistic regression and multivariable logistic regression to test the association between in-hospital mortality and covariates in the OT cohort. (2) The independent predictor of OT cohort to test the interaction between AT and in-hospital mortality risk,

(3) and interaction between AT and in-hospital mortality risk was graphed using binary logistic regression fitting of the generalized linear model.

In the second main step, as sensitivity analysis, the propensity scores were calculated by multivariable logistic regression with a binary outcome variable (AT vs. OT) to eliminate differences among patients based on treatment selection. Propensity score matching (PSM) analysis[21] was conducted with the R package "MatchIt". All variables were used to calculate propensity scores. These were used to match patients treated with AT versus OT. R software (version 4.0.2, www.rproject.org) and SPSS 25.0 software package (www.spss.com) were used for statistical analysis, and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Demographic and Clinical Characteristics

Table 1: Baseline characteristics of hemorrhagic stroke patients of the entire cohort

Variables	In-hospital survivors (n=1315)	In-hospital non-survivors (n=339)	P value
Age,n(%)			0.001
<60	471(35.8)	81(23.9)	
60-75	459(34.9)	139(41.0)	
76-89	344(26.2)	106(31.3)	
>89	41(3.1)	13(3.8)	
Male,n(%)	674(51.3)	172(50.7)	0.865
Ethnicity,n(%）			0.677
Caucasian	945(71.9)	258(76.1)	
African American	164(12.5)	32(9.4)	
Other/unknown	82(6.2)	19(5.6)	
Hispanic	80(6.1)	19(5.6)	
Asian	34(2.6)	9(2.7)	
Native American	10(0.8)	2(0.6)	
Admissionheight, cm	167.9(160.1,177.8)	167.9(162.3,175.7)	0.743
Admissionheight, kg	78.2(65.2,93.0)	77.1(65.0,92.2)	0.490
APACHE IV score	45(34,58)	80(61,98)	<0.001
Anticoagulant therapy, n(%)	120(9.1)	17(5.0)	0.014
Comorbidities, n(%)			
Hypertension	430(32.7)	111(32.7)	0.988
Atrial fibrillation	96(7.3)	19(5.6)	0.274
Diabetes mellitus	61(4.6)	18(5.3)	0.606
Heart failure	19(1.4)	11(3.2)	0.027
Gastrointestinal bleed	11(0.8)	4(1.2)	0.552
Chronic obstructive pulmonary disease	16(1.2)	6(1.8)	0.428
Coronary artery disease	20(1.5)	10(2.9)	0.079
Chronic renal insufficiency	12(0.9)	5(1.5)	0.360
Pulmonary infection	59(4.5)	17(5.0)	0.679
Hemorrhagic stroke type,n(%)			0.162
intracranial hemorrhage	1000(76.0)	270(79.6)	
subarachnoid hemorrhage	315(24.0)	69(20.4)	

Note: Data are median [interquartile range] or number (percentages)IQR Interquartile range, APACHE acute physiology and chronic health evaluation

20.5% (n= 339) of HS patients died during hospitalization in the entire cohort. Table 1 shows the baseline characteristics. There was no significant difference in gender, ethnicity, admission height, admission weight, complications (diabetes, atrial fibrillation, chronic obstructive pulmonary disease, gastrointestinal bleeding, hypertension, pulmonary infection, chronic renal failure, coronary artery disease) and hemorrhagic stroke type between the two groups. However, the two groups had significant differences in age, APACHE IV score, and complications (heart failure). The missing data in the variable was displayed in Supplementary Table 1.

3.2. Logistic regression analysis for the entire cohort

The overall cohort survival rate was 79.5%, 86.7% in the AT group and 78.9% in the OT group. AT [OR= 0.542, 95%CI (0.298-0.985), P<0.05, Table 2] was a protective predictor of in-hospital mortality in multivariate logistic regression, suggesting that patients with hemorrhagic stroke could benefit from AT.

Table 2: Risk factors of in-hospital mortality in hemorrhagic stroke patients of the entire cohort

Variables	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
APACHE IV score	1.055(1.048,1.061)	<0.01	1.055(1.048,1.061)	<0.001
Heart failure	2.288(1.078,4.854)	0.031	1.022(0.412,2.530)	0.963
Anticoagulant therapy	0.526(0.312,0.887)	0.016	0.545(0.298,0.995)	0.048
Hemorrhagic stroke type				
Intracranial hemorrhage	Reference		Reference	
Subarachnoid hemorrhage	0.811(0.605,1.088)	0.162	0.814(0.570,1.163)	0.258
Age,years				
<60	Reference		Reference	
60-75	1.761(1.301,2.383)	<0.01	1.099(0.763,1.581)	0.613
76-89	1.792(1.300,2.470)	<0.01	0.983(0.669,1.444)	0.930
>89	1.844(0.946,3.592)	0.072	0.901(0.427,1.901)	0.785

Note: Odd ratios are adjusted for age, APACHE IV score, treatment, heart failure, hemorrhagic stroke type.

OR odd ratio, CI confidential interval, APACHE acute physiology and chronic health evaluation.

3.3. Establishment and verification of prediction for hemorrhage stroke

The overall cohort survival rate was 79.5%, 86.7% in the AT group and 78.9% in the OT group. AT [OR= 0.542, 95%CI (0.298-0.985), P<0.05, Table 2] was a protective predictor of in-hospital mortality in multivariate logistic regression, suggesting that patients with hemorrhagic stroke could benefit from AT. In multivariate logistic regression focused on the OT group, the APACHE IV score [OR= 1.055, 95% CI (1.048-1.061), P<0.05, Supplementary Table 2] was an independent predictor of hospital mortality. The independent predictor (APACHE IV score) was then used to predict in-hospital mortality risk for the entire cohort. Then a nomogram was generated from the multivariate logistic regression analysis (shown in Supplementary Fig. 1), and the nomogram showed the risk of mortality of HS as a percentage. The discrimination of the model was 0.825 (95% CI 0.799–0.851, Fig. 2). The calibration plots with 1000 Bootstrap resamples were illustrated in Supplementary Figure 2, suggesting a nomogram with good discrimination, and the calibration curve of the nomogram showed good agreement between the predicted and actual probabilities in HS patients in this cohort. The risk calculator (provided online: http: //yangzn1027.shinyapps.io/Title/, Supplementary Fig. 3) was then used to predict in-hospital mortality risk for the entire cohort and plotted against observed in-hospital mortality. The lines for AT and OT cross at 6.9%, indicating that patients with a predicted in-hospital mortality risk <6.9 will not benefit from AT (Fig.4). The interaction between the APACHE IV score and AT was significant (OR 0.995, 95% CI 0.993–0.998, $p < 0.05$), which indicates that the benefit of AT is different based on the predicted mortality in the hospital. In the OT group, according to the cutoff point, the number of patients who benefited from anticoagulant therapy and those who did not benefit from anticoagulation therapy was evaluated in the study (Fig. 4). 70.6% of HS patients will benefit from the AT.

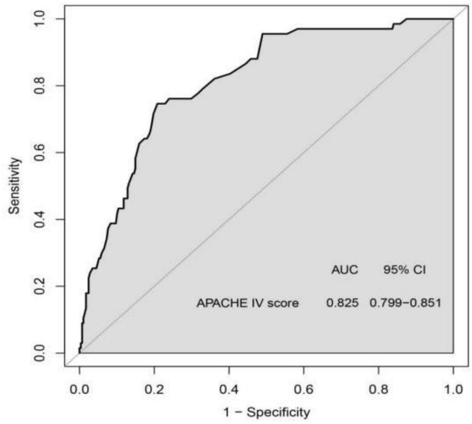

Figure 2: Receiver operator characteristic curve of APACHE IV score for predicting in-hospital mortality of hemorrhagic stroke

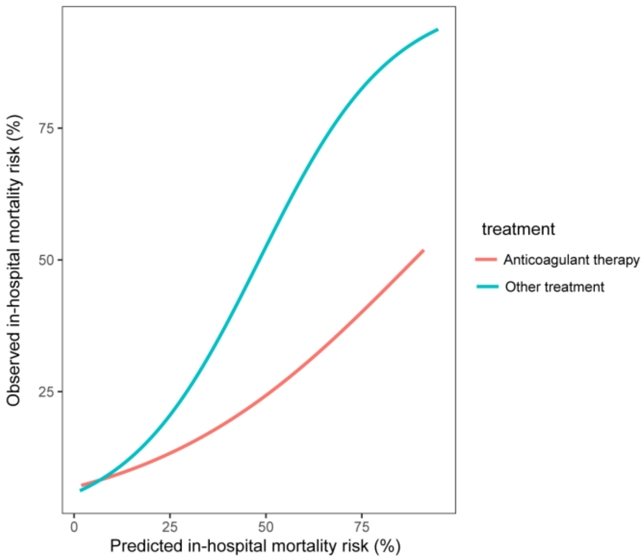

Figure 3: Predicted in-hospital motality risk plotted against observed in-hospital motality risk of hemorrhagic stroke

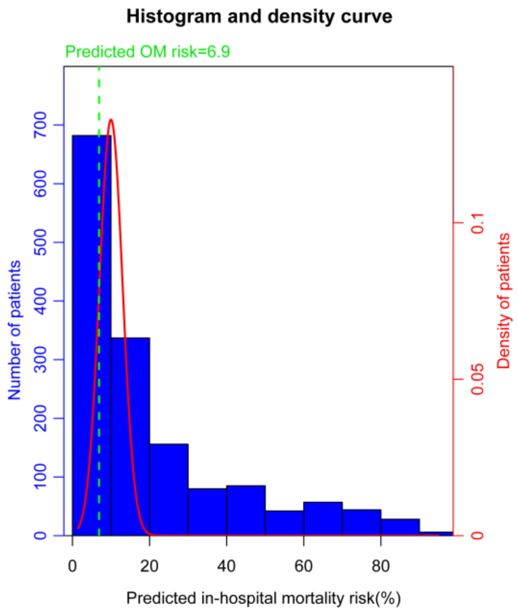

Figure 4: Number of patients needed to treat with anticoagulant therapy plotted against the predicted in-hospital motality risk. This analysis is focused on other treatment group

4. Discussion

The anticoagulant therapy strategy for patients with hemorrhagic stroke is an ongoing topic. In 2017, Alessandro Biffi et al. [22] conducted a meta-analysis on the long-term outcomes of oral anticoagulant therapy that resumed after a hemorrhagic stroke. The study included 1012 patients with warfarin-related hemorrhagic stroke from 3 original retrospective studies, including 379 lobular and 633 non-lobular hemorrhages. Studies have found that oral anticoagulant therapy reduces mortality and incidence of all-cause stroke in both lobar and non-lobar hemorrhage, and improves functional outcomes [23]. A national observational cohort study showed that oral anticoagulants significantly reduced the risk of ischemic stroke and all-cause mortality in patients with hemorrhagic stroke with atrial fibrillation [24] . In recent years, there are still different opinions on when to initiate anticoagulant therapy in HS. According to the European Heart Rhythm Association Practice Guidelines, oral anticoagulant therapy can start 4-8 weeks after hemorrhagic stroke when the risk of ischemic stroke is high and the risk of hemorrhagic stroke recurrence is relatively low [25]. This gives us a reference to the anticoagulant time. However, most previous studies have determined anticoagulant time based on post-onset complications, without complete acute-phase data of the HS patient data to assess.

The analysis revealed several significant findings. First, consistent with previous literature, HS patients who received AT had a higher survival rate than those who did not. More importantly, patients' APACHE IV scores highly influenced in-hospital mortality in patients with HS. An assessment of mortality in patients with HS treated with AT and OT based on the APACHE IV score found that patients of HS with a predicted mortality >6.9% benefited more from AT, which gives a decision on the timing of AT. APACHE IV score system included acute physiological scores (age, body temperature, mean arterial pressure, heart rate, respiratory rate, mechanical ventilation, inhaled oxygen concentration, partial pressure of blood oxygen, partial pressure of carbon dioxide, arterial blood PH, sodium concentration, 24-hour urine volume, creatinine, blood urea nitrogen, blood glucose level, albumin, bilirubin, hematocrit, white blood cell, Gesla score), chronic health conditions, admission information, and admission diagnosis information. APACHE IV score is widely used to evaluate the severity and prognosis of critically ill patients [26-28]. This study found that APACHE IV score also had good discrimination in predicting the prognosis of patients with HS.

The study has important clinical implications. Specifically, the risk calculator (https://yangzn1027.shinyapps.io/Title/) can help physicians and patients to achieve an informed clinical decision when evaluating the role of AT in the HS setting. The potential benefit of AT needs to be weighed against the drawbacks individually.

The study is not devoid of limitations, which are limited by the retrospective nature of the cohort. Despite propensity score matching analysis, residual treatment selection bias could still affect the study findings. Unfortunately, it is impossible to quantify the exact size of such bias. Secondly, the eICU database does not provide follow-up information on HS, which might make it impossible for us to get the patient's information after discharge. Thirdly, almost 30.2% of patients with a primary diagnosis of HS were excluded from the cohort with missing data. The exclusion was more frequent in the OT group, which might limit the results' generalizability.

5. Conclusion

Based on a large national hospital cohort, patients with hemorrhagic stroke in the ICU at diagnosis benefited from AT in terms of in-hospital mortality. The novel risk calculator can help determine which patients may benefit from AT. Specifically, those with predicted in-hospital mortality risk > 6.9% appeared to benefit most from AT. Of course, further evaluation and more studies are needed to validate what is likely a controversial conclusion. In addition, whether and when to restart anticoagulant therapy after HS should be combined with the risk of thrombosis and recurrent bleeding to make a more reasonable treatment plan.

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