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ABSTRACT

BACKGROUND AND PURPOSE: Direct oral anticoagulants (DOAC) have rapidly replaced warfarin. Intracerebral hemorrhage (ICH) is known to be one of the most severe side effects of anticoagulant drugs. The black hole (BH) sign is reportedly a valid radiologic sign for predicting hematoma expansion in acute ICH. Here, we hypothesized that the frequency of BH signs might differ between warfarin and DOAC treatment. We critically evaluated the clinical value of the BH sign in acute ICH under warfarin versus DOAC therapy.

MATERIALS AND METHODS: Patients with acute ICH under anticoagulant therapy were enrolled. Hematoma volumes were measured by ABC/2. Radiologists blinded to the clinical information determined the presence or absence of the BH sign on CT images. This study defined a more than 12.5 mL increase in hematoma volume as cases with "expanded hematoma."

RESULTS: We analyzed 111 patients with acute ICH under anticoagulant therapy. Among them, 21 patients were treated with antagonists in this cohort. Multivariate logistic regression analysis revealed that the presence of ventricular perforation ($P = .02$; adjusted OR: 3.51; 95% CI: 1.32–10.2) and the BH sign ($P < .01$; adjusted OR: 4.86; 95% CI: 1.73–14.3) were significantly different between expanded and nonexpanded hematoma cases. Comparison of hematoma volume and the presence of the BH sign between warfarin and DOAC cases indicated significant differences in maximum hematoma volume ($P = .03$) and presence of the BH sign ($P < .01$). The increase in hematoma volume was significantly greater when the BH sign was present under warfarin therapy ($P = .05$). In contrast, the increase in hematoma volume did not differ between cases with and without the BH sign in patients under DOAC therapy ($P = .14$).

CONCLUSIONS: The BH sign is a useful radiologic signature to predict the expansion of acute ICH under anticoagulant therapy. ICH under warfarin tended to present the BH sign more frequently than that under DOAC. The results also showed that the BH sign is more reliable under warfarin than under DOAC therapy in patients with ICH.

ABBREVIATIONS: APTT = activated partial thromboplastin time; BH = black hole; DOAC = direct oral anticoagulants; Hb = hemoglobin; ICH = intracerebral hemorrhage; IQR = interquartile range; PT-INR = prothrombin time-international normalized ratio

While warfarin was previously the primary choice for anticoagulant therapy, it has recently been rapidly replaced by direct oral anticoagulants (DOAC), such as dabigatran, rivaroxaban, apixaban, and edoxaban. This shift in the treatment paradigm is due to the superior safety and efficacy of DOAC for stroke prevention in patients with atrial fibrillation as compared with warfarin.[1] While intracerebral hemorrhage (ICH) is known to be one of the most severe side effects of anticoagulant drugs,[2] its severity is significantly milder with DOAC, resulting in lower mortality of ICH under DOAC treatment compared with that under warfarin.[3] On the other hand, if an ICH occurs, regardless of the circumstances, accurate prediction of expansion of the hemorrhage is crucial for appropriate ICH management since hematoma expansion is a significant negative prognostic factor for ICH.[4]

The black hole (BH) sign on noncontrast CT has been reported as a valid and easily detected radiologic sign for predicting hematoma expansion in acute ICH.[5] The sensitivity, specificity, positive predictive value, and negative predictive value of the BH sign for predicting hematoma expansion were previously reported as 31.9%,

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SUMMARY

PREVIOUS LITERATURE: The BH sign on noncontrast CT has been reported as a valid and easily detected radiologic sign for predicting hematoma expansion in acute ICH. A positive BH sign independently predicts poor outcomes in patients with ICH and reportedly exhibits the best predictive accuracy of hematoma expansion compared with other CT features in patients with ICH.

KEY FINDINGS: The increase in hematoma volume was significantly greater when the BH sign was present under warfarin therapy. In contrast, the increase in hematoma volume did not differ between cases with and without the BH sign in patients under DOAC therapy.

KNOWLEDGE ADVANCEMENT: The BH sign is a useful radiologic signature to predict the expansion of acute ICH under anticoagulant therapy. The results showed that the BH sign is more reliable under warfarin than under DOAC therapy in patients with ICH.

94.1%, 73.3%, and 73.2%, respectively.[5] A positive BH sign independently predicts poor outcomes in patients with ICH,[6] and reportedly exhibits the best predictive accuracy of hematoma expansion compared with other CT features in patients with ICH.[7] Though its simplicity renders the BH sign clinically useful, the value of the BH sign in patients with ICH under anticoagulant therapy is still debatable.

In this report, we hypothesized that the frequency of the BH sign might differ between patients taking warfarin and DOAC. Hence, we critically evaluated the clinical value of the BH sign in patients with acute ICH under warfarin versus DOAC therapy.

MATERIALS AND METHODS

Cohort Design

The local institutional review board approved the retrospective use of clinical data for this research (Japanese Kitami Red Cross Hospital: 2309, Asahikawa Medical University approval number: 23,082). The current study followed the STROBE guidelines; further information can be found in the Supplemental Data. Patients with acute ICH under anticoagulant therapy were enrolled from January 1, 2011, to March 31, 2023, at Japanese Kitami Red Cross Hospital and from February 1, 2015, to November 31, 2022, at Asahikawa Medical University Hospital. Cases with suspected trauma were excluded from this study. Cases with pure intraventricular hemorrhage were excluded from the analysis because most of the hematoma flowed from the central nervous system through the ventricular system. Cases that lacked follow-up CT, which precluded the measurement of maximum hematoma size over the clinical course, were excluded from the analysis.

Image Acquisition and Analysis

CT images with a slice thickness of less than 5 mm were used in all cases. The initial CT images, including those acquired at outside institutions, were used to determine the presence or absence of hematomas perforating into the ventricle. Hematoma volumes were measured by ABC/2.[8] This procedure was performed by 2 neurosurgeons (1 with 6 years of experience and another with 11 years of experience).

Interpretation of the Black Hole Sign

The BH sign was previously defined as an area of hypoattenuation completely encapsulated by an adjacent hyperattenuated area within a hematoma.[5] Specifically, it was described as a radiologic finding on CT with: 1) a relatively hypoattenuated area (BH) encapsulated within the hyperattenuated area of the hematoma, 2) a round, oval, or rod-like shape, but not connected with the adjacent brain tissue, 3) the relative hypoattenuated area having an identifiable border, and 4) the hematoma having at least a 28 Hounsfield units difference between the 2 attenuation regions. In this study, 2 radiologists, 1 with 10 years of experience and the other with more than 30 years of experience, both of whom were blinded to the clinical information, determined the presence or absence of the BH sign.

Clinical Variables

The patients' characteristics, including their histories of hypertension and diabetes mellitus, were obtained from their medical records. Patients who were habitual drinkers and smokers at the time of hospitalization were defined as being alcoholics and smokers. Data on blood pressure, hemoglobin (Hb, g/dL), serum Cr (mg/dL), prothrombin time-international normalized ratio (PT-INR), and activated partial thromboplastin time (APTT, sec) at admission were collected. Information on the prescription of antithrombotic drugs, including anticoagulants (warfarin or DOAC) and antiplatelet drugs, was also collected.

Statistical Analysis. Comparative 2-group analysis was performed by using GraphPad Prism 10 (GraphPad Software) statistical analysis software. Fisher exact test or Pearson $\chi 2$ statistical analysis was performed to assess the associations between categoric

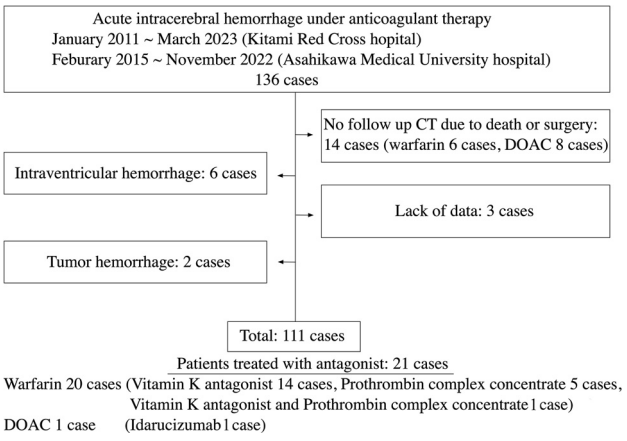

FIG 1. Patient cohort.

variables. The normality of data distribution for continuous variables was tested by using the Kolmogorov-Smirnov test. Distributed continuous variables were compared by using the Student *t* test and Mann-Whitney *U* test. Multivariate logistic regression analysis was performed by using factors with significant differences in univariate analysis. A *P* value of less than .05 was considered statistically significant.

Table 1: Patient characteristics (*n* = 111)

Median age (years) (IQR)	76 (70–83)
Sex (female), *n* (%)	37 (33%)
Hypertension, *n* (%)	76 (68%)
Diabetes mellitus, *n* (%)	29 (26%)
Alcohol, *n* (%)	39 (35%)
Smoking, *n* (%)	19 (17%)
Antiplatelet drugs, *n* (%)	25 (23%)
Hemoglobin (mg/dL) (mean ± SD)	13.3 (± 2.1)
Creatinine (mg/dL) (IQR)	0.9 (0.7–1.1)
PT-INR (IQR)	1.3 (1.1–2.0)
APTT (sec) (IQR)	34.6 (30.6–40.9)
SBP (mm Hg) (mean ± SD)	164.0 (142.0–188.0)
DBP (mm Hg) (IQR)	91.0 (76.0–106.0)
Number of deaths	15 (14%)
Number of surgery cases	13 (12%)
Follow-up interval (hours) (IQR)	17.0 (10.0–22.0)
Ventricular perforation, *n* (%)	54 (49%)
Location, *n* (%)	
Subcortical	28 (25%)
Basal ganglia	66 (59%)
Infratentorial	17 (15%)
Initial hematoma volume (mL) (IQR)	17.3 (7.2–37.0)
Maximum hematoma volume (mL) (IQR)	21.9 (10.1–52.6)
Expanded hematoma volume (mL) (IQR)	2.9 (−0.1–13.1)
BH sign, *n* (%)	35 (32%)

Note:—DBP = diastolic blood pressure; SBP = systolic blood pressure.

Table 2: Predictors of expanded hematoma volume cases

	≥ 12.5 mL (*n* = 28)	< 12.5 mL (*n* = 83)	*P* Value
Median age (years) (IQR)	74.5 (66.0–81.8)	77.0 (70–83)	.37
Sex (female), *n* (%)	7 (25%)	30 (36%)	.36
Hypertension, *n* (%)	17 (61%)	59 (71%)	.35
Diabetes mellitus, *n* (%)	13 (33%)	16 (22%)	.27
Alcohol, *n* (%)	9 (23%)	31 (37%)	.50
Smoking, *n* (%)	4 (27%)	15 (18%)	.78
Antiplatelet drugs, *n* (%)	6 (21%)	19 (23%)	1
Anticoagulant drug (warfarin), *n* (%)	13 (46%)	27 (33%)	.26
Hemoglobin (mg/dL) (mean ± SD)	12.8 ± 2.4	13.5 ± 2.0	.14
Creatinine (mg/dL) (IQR)	0.9 (0.7–1.3)	0.9 (0.7–1.0)	.28
PT-INR (IQR)	1.4 (1.1–2.2)	1.2 (1.1–1.9)	.23
APTT (sec) (IQR)	37.0 (30.9–49.3)	34.0 (30.6–40.0)	.22
SBP (mm Hg) (mean ± SD)	157.5 (128.5–173.8)	168.0 (143.0–189.0)	.30
DBP (mm Hg) (IQR)	88.5 (74.0–103)	91.0 (77.0–106.0)	.47
Follow-up interval (hours) (IQR)	13.0 (5.3–23.8)	18.0 (12.0–21.0)	.08
Ventricular perforation, *n* (%)	20 (71%)	34 (41%)	.01[a]
Location, *n* (%)			.11
Subcortical	10 (36%)	18 (64%)	
Basal ganglia	12 (19%)	54 (84%)	
Infratentorial	6 (35%)	11 (65%)	
Initial hematoma volume (mL) (IQR)	32.8 (19.2–64.7)	12.3 (5.8–27.0)	<.01[a]
BH sign, *n* (%)	17 (61%)	18 (22%)	<.01[a]

[a] Variables with significant differences; DBP = diastolic blood pressure; SBP = systolic blood pressure.

Table 3: Multivariate analysis of factors corresponding to expanded hematoma (≧12.5 mL)

	OR	95% CI	*P* Value
Ventricular perforation	3.51	1.32–10.02	.02[a]
Initial hematoma volume	1.00	0.99–1.02	.41
Black hole sign	4.86	1.73–14.3	< .01[a]

[a] Variables with significant differences.

RESULTS

Patient Characteristics

Figure 1 summarizes the clinical characteristics of the study cohort. One hundred thirty-six patients presented with acute ICH under anticoagulant therapy. Among them, 14 patients were excluded because of lack of follow-up CT images due to death or surgery (warfarin: 6 cases, DOAC: 8 cases), 6 patients were excluded due to intraventricular hemorrhage, 3 patients because of lack of data, and 2 patients were excluded because of the presence of tumor hemorrhage. Consequently, we analyzed 111 patients with acute ICH under anticoagulant therapy. Among them, 21 patients were treated with antagonists in this cohort (warfarin: 20 cases [vitamin K antagonists 14 cases, prothrombin complex concentrate 5 cases, vitamin K antagonist and prothrombin complex concentrate 1 case], DOAC: [1 case, and idarucizumab 1 case]).

Table 1 summarizes the clinical characteristics of the 111 analyzed patients. Variables are expressed as means ± standard deviation (SD) or as the median (interquartile range [IQR] 25th–75th percentile). The follow-up interval for CT scans was 17.0 (10.0–22.0) hours. ICH with ventricular perforation occurred in 54 cases (49%). In terms of hematoma location, 28 cases (25%) were subcortical, 66 cases (59%) involved the basal ganglia, and 17 cases (15%) were infratentorial. The median values of initial hematoma volume, maximum hematoma volume, and hematoma expansion volume were 17.3 (7.2–37.0) mL, 21.9 (10.1–52.6) mL, and 2.9 (−0.1–13.1) mL, respectively. The BH sign was present in 35 cases (32%).

Predictors of Intracerebral Hematoma Expansion

First, we reevaluated the performance of the BH sign to predict intracerebral hematoma expansion in our cohort. While different thresholds, such as 3 mL, 6 mL, 12.5 mL, 26%, and 33%, have been reported as indicating clinically meaningful intracerebral hematoma expansion, an increase in hematoma volume by more than 12.5 mL previously showed the highest odds ratio for an mRS score of 2–6.[9] Thus, this study defined cases with a more than 12.5 mL increase in hematoma volume as having an "expanded hematoma." As the absolute volume rather than the rate of hematoma expansion is thought to be more clinically relevant, the main analysis was performed by using a threshold of 12.5 mL increase in hematoma volume for hematoma

Table 4: Comparison of cases receiving warfarin versus DOAC

	Warfarin ($n = 40$)	DOAC ($n = 71$)	*P* Value
Median age (years) (IQR)	75.5 (69–80)	77.0 (70–83)	.58
Sex (female), *n* (%)	12 (30%)	25 (35%)	.68
Hypertension, *n* (%)	28 (70%)	48 (68%)	.84
Diabetes mellitus, *n* (%)	13 (33%)	16 (23%)	.27
Alcohol, *n* (%)	9 (23%)	30 (42%)	.04[a]
Smoking, *n* (%)	6 (15%)	13 (18%)	.80
Antiplatelet drugs, *n* (%)	14 (35%)	11 (15%)	.03[a]
Hemoglobin (mg/dL) (mean ± SD)	12.9 ± 2.4	13.6 ± 2.0	.17
Creatinine (mg/dL) (IQR)	1.0 (0.8–1.4)	0.8 (0.6–1.0)	<.01[a]
PT-INR (IQR)	2.3 (1.8–3.1)	1.2 (1.1–1.3)	<.01[a]
APTT (sec) (IQR)	40.0 (33.9–49.0)	32.8 (29.5–37.6)	<.01[a]
SBP (mm Hg) (mean ± SD)	154.0 (134.5–187.0)	169.0 (147.0–189.0)	.27
DBP (mm Hg) (IQR)	81.5 (71.3–97.8)	96.5 (80.0–111.0)	<.01[a]
Number of deaths	9 (23%)	6 (8%)	.05[a]
Number of surgery cases	9 (23%)	4 (6%)	.01[a]
Follow-up interval (hours) (IQR)	14.0 (6.0–21.3)	18.0 (12.0–22.0)	.13
Ventricular perforation, *n* (%)	17 (43%)	37 (52%)	.43
Location, *n* (%)			.08
Subcortical	15 (54%)	13 (46%)	
Basal ganglia	19 (30%)	47 (73%)	
Infratentorial	6 (33%)	11 (61%)	
Initial hematoma volume (mL) (IQR)	20.5 (7.8–48.5)	14.8 (5.3–29.9)	.14
Maximum hematoma volume (mL) (IQR)	33.2 (10.8–65.5)	17.4 (8.5–50.9)	.03[a]
Expanded hematoma volume (mL) (IQR)	4.4 (0.35–24.5)	2.1 (−0.2–9.2)	.15
Black hole sign, *n* (%)	21 (53%)	14 (20%)	<.01[a]

[a] Variables with significant differences; DBP: diastolic blood pressure; SBP: systolic blood pressure.

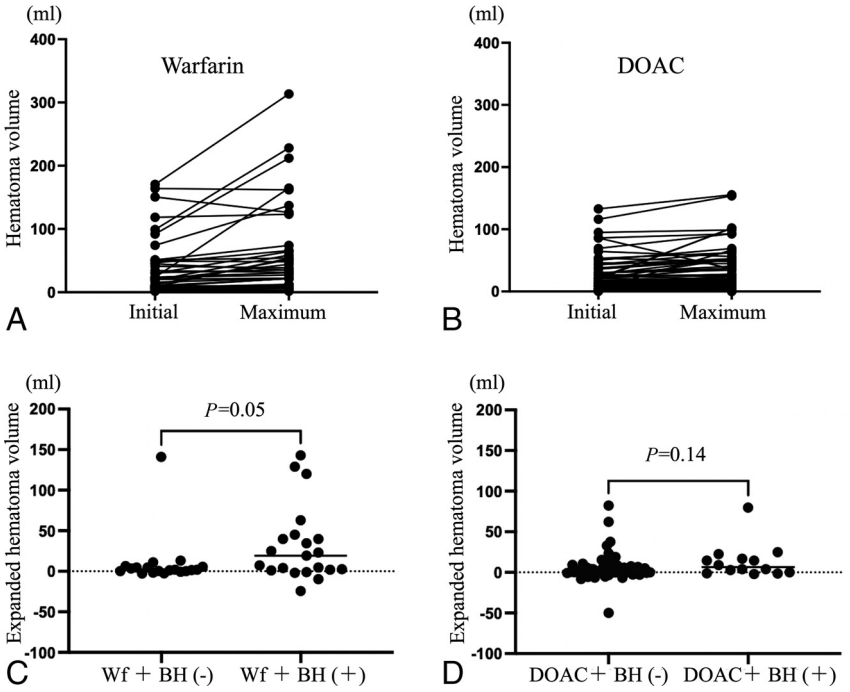

FIG 2. *A* and *B*, Change in hematoma volume with each anticoagulant drug. *C* and *D*, Expanded hematoma volume was compared between cases with and without the BH sign ([+] and [−]) among those treated with warfarin (*left panel*) versus direct oral anticoagulants (DOACs) (*right panel*). * indicates <0.05. Mann-Whitney *U* test was used to compare the hematoma volume.

expansion. A subanalysis using a 33% increase in hematoma volume as a threshold is provided in Supplementary Data.

Table 2 compares the clinical characteristics, hematoma volume, and presence or absence of the BH sign between expanded and nonexpanded hematoma cases. Significant differences were observed in the presence of ventricular perforation ($P = .01$), initial hematoma volume ($P < .01$), and presence of the BH sign ($P < .01$).

Subsequent multivariate logistic regression analysis revealed that the incidences of the presence of ventricular perforation ($P = .02$; adjusted odds ratio: 3.51; 95% CI: 1.32–10.2) and the BH sign ($P < .01$; adjusted odds ratio: 4.86; 95% CI: 1.73–14.3) were significantly different between expanded and nonexpanded hematoma cases (Table 3).

Comparison of Clinical Characteristics between Warfarin- and DOAC-Administered Cases

Table 4 shows a comparison of the clinical characteristics, hematoma volume, and presence or absence of the BH sign between warfarin- and DOAC-administered cases. Significant differences were observed in terms of excessive alcohol consumption ($P = .04$), use of antiplatelet drugs ($P = .03$), serum Cr ($P < .01$), PT-INR ($P < .01$), APTT ($P < .01$), diastolic blood pressure ($P < .01$), number of deaths ($P = .05$), number of surgery cases ($P = .01$), maximum hematoma volume ($P = .03$), and presence of the BH sign ($P < .01$) between the 2 drug groups. Fig 2*A*, *-B* shows the changes in hematoma volume for each anticoagulant.

Association between the Black Hole Sign and Warfarin or DOAC Administration

Fig 2*C*, *-D* compares the increase in hematoma volume based on the presence or absence of the BH sign stratified by the type of anticoagulation therapy. The increase in hematoma volume was significantly larger when the BH sign was seen under warfarin therapy ($P = .05$). In contrast, the increase in hematoma volume did not differ with respect to the presence or absence of the BH sign among patients under DOAC therapy ($P = .14$).

DISCUSSION

The present study demonstrated that the BH sign is a useful prognostic sign on CT images in patients who develop ICH under anticoagulant therapy (Tables 2 and 3), and that acute ICH under

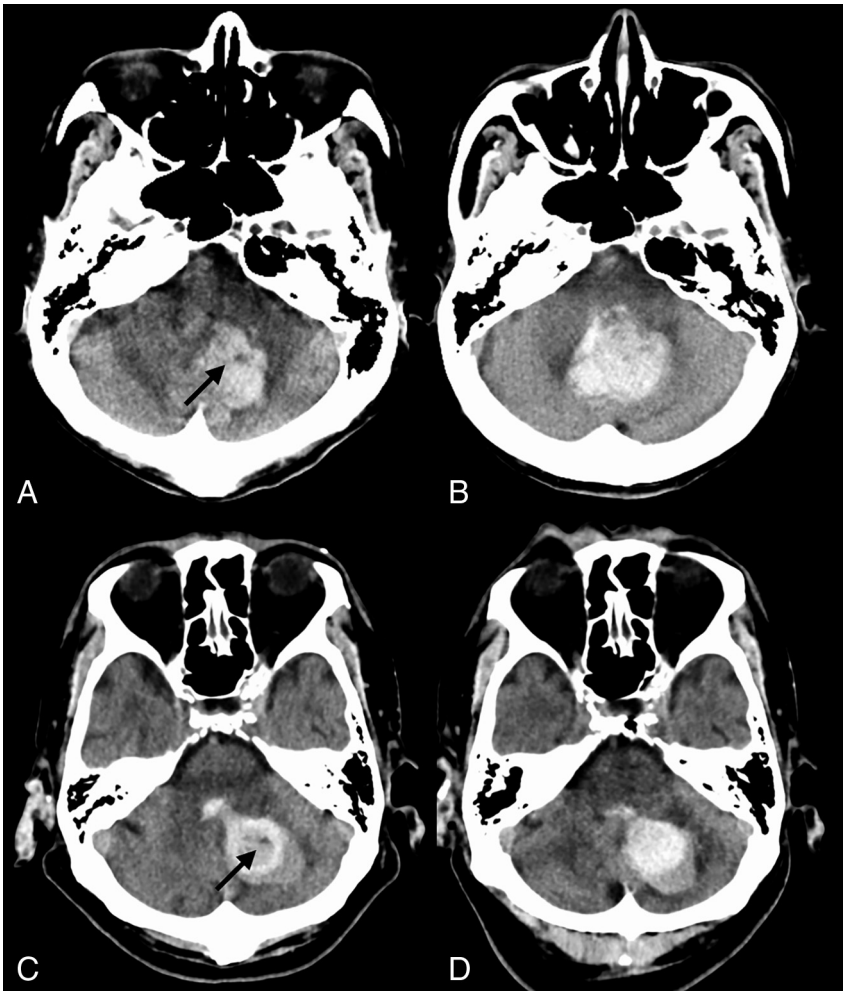

FIG 3. *A*, CT image of a case of ICH under warfarin treatment. The black arrow indicates the BH sign. *B*, Follow-up CT of the same patient showed expanded ICH. *C*, CT image of a case of ICH under DOAC treatment. The black arrow indicates the BH sign. *D*, Follow-up CT showed no hematoma expansion.

warfarin therapy tends to expand more frequently than that under DOAC therapy (Fig 2 and Table 4). In this study, the BH sign was encountered significantly more frequently under warfarin than DOAC therapy (Table 4). The results also showed that the BH sign was less reliable in predicting hematoma expansion in patients under DOAC than warfarin therapy (Figs 2 and 3).

A previous study showed that the hematoma volume of ICH under DOAC therapy was significantly smaller than that under warfarin and had better functional outcomes.[10] Furthermore, some studies reported that patients with ICH under DOAC therapy had lower mortality,[11] smaller-sized hematomas,[10–12] and less hematoma expansion.[11,12] Additionally, it is known that hematoma expansion in ICH is a significant contributor to poor outcomes.[13] Neuropathological evidence suggests that expanded hematomas might partly entail a secondary rupture of surrounding vessels.[14] Thus, accurate risk prediction of hematoma expansion is as crucial as minimizing the initial ICH volume to achieve a favorable clinical outcome.

Several studies have linked heterogeneous hematoma with early hematoma growth. Barras et al[15] reported that large hematomas showed a more heterogeneous attenuation on CT and were more likely to expand than small hematomas, which was further validated by Takeda et al.[16] Various radiologic signs predictive of hematoma expansion have been identified,[17] such as the CT angiography spot sign representing active bleeding.[18] However, while the CT angiography spot sign is a valuable imaging signature, the need for contrast agent injection poses a problem for some patients, limiting its clinical utility. To address this problem, Li et al[5,6] reported the BH sign, which can be identified in noncontrast CT. The BH sign reportedly effectively predicted early hematoma growth in patients with ICH[5] and was an independent predictor for poor outcomes in them.[6] Furthermore, a meta-analysis reported the value of the BH sign in predicting hematoma expansion.[19]

However, the validity of the BH sign, regardless of the type of anticoagulant therapy, such as warfarin or DOACs, is unclear. In this study, we showed that the BH sign is indeed useful under warfarin therapy since its predictive value for hematoma expansion differed between warfarin and DOAC therapy. More specifically, the increase in acute ICH volume did not differ with respect to the presence or absence of the BH sign under DOAC therapy. At the same time, its predictive values seemed valid under warfarin therapy. This observation might question the value of the BH sign for acute ICH under DOAC therapy, which is now the preferred treatment following the change in treatment paradigm. Our results suggest that the clinical significance of the BH sign observed in patients with ICH under warfarin therapy is more significant than in those receiving DOAC.

Figure 3 illustrates representative cases of the argument mentioned above. Figure 3*A* shows a CT image of ICH with presence of the BH sign in a patient under warfarin. The ICH had expanded on follow-up CT, as shown in Fig 3*B*. Fig 3*C*, *-D* shows a case under DOAC therapy. Though the BH sign can be appreciated in Fig 3*C*, the ICH showed no expansion in the follow-up CT (Fig 3*D*). DOAC are excellent anticoagulants that are used in many clinical conditions. The pharmacological actions of DOAC differ from those of warfarin, meaning that previously reported imaging findings relevant to anticoagulant therapy may need to be reevaluated in terms of hematoma expansion.[20,21]

Limitations of the present study must be taken into consideration when interpreting the results. Patient background characteristics (such as administration frequencies of antiplatelet drugs, Cr, PT-INR, APTT, and diastolic blood pressure) differed

between warfarin and DOAC therapy. Among these characteristics, antiplatelet drugs have a significant impact on hematoma volumes. Another possible confounder is the reason for choosing a particular anticoagulant. Often, in the current DOAC first-choice era, only those patients who cannot take DOAC for clinical reasons are prescribed warfarin. Therefore, it is possible that the general condition of patients receiving warfarin was worse than that of those receiving DOAC. This concern is substantiated by the fact that pulse pressure and creatinine were higher in warfarin patients than in DOAC patients in this study. Second, interobserver discrepancy of the hematoma volume was not evaluated for this study. However, hematoma volumes measured by different methods, ie, the ABC/2 and the automated volumetric methods (ZIOSTATION2, Ziosoft), did not differ (Supplementary Data).

CONCLUSIONS

Our study showed that the BH sign is a useful radiologic signature to predict the expansion of acute ICH under anticoagulant therapy. Patients who presented with ICH under warfarin therapy tended to show the BH sign more frequently than those receiving DOAC. We also showed that the BH sign is more reliable under warfarin than under DOAC therapy.

Disclosure forms provided by the authors are available with the full text and PDF of this article at www.ajnr.org.

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