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The combination of warfarin use and the spot sign leads to detrimental outcomes in patients with intracerebral hematomas

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ABSTRACT

Objectives: While warfarin use and the presence of the spot sign on computed tomography angiography are associated with a high frequency of hematoma enlargement and high mortality among patients with intracerebral hematomas (ICHs), the effects of various combinations of warfarin use and/or the spot sign have never been clarified. The combinations of both or either of warfarin use and/or the spot sign were used to investigate their relationships with hematoma enlargement and mortality before the introduction of prothrombin complex concentrate (PCC) treatment.

Patients and Methods: Consecutive patients with ICHs admitted within 6 h of onset from 2009 to 2017 were investigated.

Results: Of 703 eligible patients, the combinations of warfarin use and spot sign-present and of warfarin use and spot sign-absent were seen in 23 (3.3%) and 35 patients (5.0%), respectively. The combination of warfarin use and spot sign-present was a predictor of hematoma enlargement ($p < 0.05$). In regard to mortality (13.5% for all patients), mortality with the combination of warfarin use and spot sign-present was 52.2%, which was significantly higher than in the 3 other groups. Multivariate analysis showed that the combination of warfarin use and spot sign-present was a significant predictor of mortality ($p < 0.05$).

Conclusion: Warfarin users with ICHs showing spot signs, who accounted for approximately 40% of ICH patients with warfarin use, showed a high frequency of hematoma enlargement and high mortality. This group was regarded as high-risk patients and should be considered candidates for prompt administration of PCC.

1. Introduction

Oral anticoagulation therapy with warfarin before the onset of intracerebral hematoma (ICH) has been reported to be associated with a larger hematoma volume [1], higher risk of hematoma enlargement [2–5], and higher mortality compared to non-warfarin ICH [3]. Similarly, the presence of spot signs on computed tomography angiography (CTA) has been regarded as a predictor of both hematoma enlargement and unfavorable outcomes [6–10]. On the other hand, a relationship between warfarin use and the presence of spot signs, and the effects of either or both of warfarin use and/or the presence of spot signs on hematoma enlargement and outcomes have not been clarified. Since November 2017, prothrombin complex concentrate (PCC) has been approved by the Japanese Ministry of Health, Labor and Welfare as a medication for patients with ICH who took warfarin before ICH onset [11–14]. Before evaluation to determine whether PCC could have efficacy, high-risk patients among warfarin users should be identified in combination with either the presence or absence of spot signs to clarify the therapeutic target that could show the worst outcomes and also should need prompt PCC treatment most.

The purposes of the study were to clarify the relationship between warfarin use and the presence of spot signs and to investigate the effects of various combinations of both or either of warfarin use and/or the presence spot signs on hematoma enlargement and outcomes, including mortality.

2. Patient and methods

2.1. Patient population

Consecutive patients with spontaneous ICH admitted to our hospital between January 2009 and November 2017 were retrospectively assessed. Patients admitted more than 6 h after onset were excluded. This series of patients did not include those with secondary ICH caused by a cerebral aneurysm, vascular malformation, moyamoya disease, sinus thrombosis, or trauma. Patients who did not undergo CTA on admission

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were excluded. Patients receiving direct oral anticoagulants (DOACs) were also excluded. Patients presenting with hemorrhagic stroke admitted to our neurosurgical unit routinely undergo their first noncontrast CT scan on arrival, followed by a CTA study, unless a history of renal dysfunction and/or allergy to contrast agent is obtained. Patients with hemorrhagic stroke have a second CT scan on the day after admission. This study was approved by the Ethics Committee of Tokai University School of Medicine (IRB No. 16R-264). The Ethics Committee board waived the need for patient consent in this retrospective study.

2.2. Acute phase management of patients with ICHs

When ICH was diagnosed, the goal was to achieve a target systolic blood pressure below 140 mmHg with intravenous administration of nicardipine as soon as possible [15]. To maintain systolic blood pressure below 140 mmHg, most of the patients were subsequently controlled by continuous intravenous nicardipine for 24 h in intensive care units. To reverse increased prothrombin time-international normalized ratio (PT-INR) levels, defined as ≥1.5, patients were treated with vitamin K alone or in combination with fresh frozen plasma (FFP). The dosage of FFP was adjusted according to body weight, and the dosage of vitamin K was 5–20 mg [16]. Treatment decisions were made by the physician on duty. Emergency hematoma removal was performed in patients with severe consciousness disturbance due to a mass effect of the hematoma or with impending tentorial herniation due to the hematoma. Ventricular drainage was performed in patients with acute hydrocephalus on noncontrast CT. A CT scan for evaluation of hematoma enlargement could not be performed the following day in patients undergoing emergency hematoma removal and in patients who died on the day of admission.

2.3. Image acquisition and analysis

CTA was performed from the C4 level to the vertex. The CTA protocol was performed using the bolus tracking method in which a nonionic contrast agent is injected at 4 mL/sec through a peripheral vein via an indwelling 20-G angiocatheter. Precontrast images were reconstituted as axial, 5-mm-thick images. CTA images were reconstituted as axial and coronal 3-mm-thick images. All images were viewed on a computer terminal.

All studies were separately evaluated by neurosurgeons for the presence or absence of spot signs by simultaneously visualizing noncontrast CT studies cross-linked with coronal axial CTA reformats. The spot sign is defined as an enhancing focus more than 1 mm in diameter within a hematoma on a CTA source image. Its maximum attenuation was defined as more than twice the Hounsfield Unit (HU) value of the surrounding hematoma, or a value greater than 120 HU [8,9]. A consensus reading by 2 neurosurgeons (AH, TS) was conducted to resolve any ambiguous findings on CTA source images. Hematoma volume was calculated by the ABC/2 method [17]. Hematoma locations were classified as cortical and deep hematomas. Hematoma enlargement was defined as an increased volume of ≥12.5 mL or ≥33% [8.9].

2.4. Data collection

Clinical data were obtained by chart review. The following data were recorded: patient age and sex, level of consciousness (Glasgow coma scale [GCS] score) on admission, systolic blood pressure on admission, use of antiplatelet agents, use of anticoagulants, and time from ICH onset to admission. Hematoma locations were classified by the main hemorrhage topographies [18]. Clinical outcomes were assessed by the modified Rankin Scale (mRS) score at discharge. Favorable and unfavorable outcomes were defined as mRS scores of 0–2 and 3–6, respectively.

Based on the combination of warfarin use history and the presence of spot signs on CTA, the patients with an ICH were classified into the following 4 groups: warfarin use and spot sign-present; warfarin use and spot sign-absent; no warfarin use and spot sign-present; and no warfarin use and spot sign-absent. In the patients taking warfarin before admission, the changes in PT-INR were investigated after admission.

2.5. Statistical analysis

Univariate analysis was performed using chi-squared analysis and Fisher's exact probability test for categorical variables and using Student's *t*-test and one-way ANOVA for continuous variables. Numerical data are expressed as the means ± SD.

Multiple comparisons were controlled by the False discovery rate (FDR) Benjamini-Hochberg (BH) procedure. Each variable was analyzed by univariate analyses to find possible significant predictors; the variables found to be possibly significant at the $p < 0.05$ level were then included in multivariate analyses. Multiple logistic regression analysis was used for dichotomized independent factors, and multiple regression analysis was used for independent factors expressed as continuous values. All 3 combinations of both or either warfarin use and/or spot sign-present, and the other variables that had a $p < 0.05$ on univariate analysis were kept in the final model. Analyses resulting in p values of less than 0.05 were considered significant. All statistical analyses were performed using JMP 10 (SAS Institute Inc., Cary, NC, USA).

3. Results

Between January 2009 and November 2017, 1330 consecutive patients diagnosed with spontaneous ICH were treated. Of these 1330 patients, 973 were admitted within 6 h after onset, including 255 who failed to undergo CTA on admission. Of the 718 remaining patients, 15 were receiving DOACs. A total of 703 patients met the inclusion criteria, with a mean age of 67.5 ± 13.3 years. There were 405 (57.6%) male patients and 298 (42.4%) female patients. Of the 703 eligible patients, 58 (8.3%) received warfarin, and 143 (20.3%) showed spot signs on CTA. The primary underlying diseases that required warfarin were nonvalvular atrial fibrillation in 36 patients, mitral or aortic valve replacement in 4, deep vein thrombosis in 3, dilated cardiomyopathy in 1, old myocardial infarction in 5, and peripheral arterial disease in 1. In the remaining 8 patients, underlying diseases were not clarified. In-hospital mortality rates classified by the hematoma locations were 10.3% (18 of 175 patients) in the thalamus, 10.6% (31 of 292 patients) in the capsulo-ganglion, 16.6% (23 of 139 patients) in the cortex, 9.4% (6 of 64 patients) in the cerebellum, 57.9% (11 of 19 patients) in the pons, and 42.9% (6 of 14 patients) in the multiple topographies.

3.1. Comparison between patients with and without warfarin use

Table 1 shows the comparisons between the patients with and without warfarin use. On univariate analyses, patients with warfarin use were older and had larger hematoma volume, more frequent spot signs, and more frequent hematoma enlargement ($p < 0.05$). As far as the outcomes were concerned, unfavorable outcomes, death and death primarily caused by neurological damage were more frequently found in patients on warfarin. In regard to hematoma volume, multiple regression analysis showed that warfarin use [$p = 0.0054$, Estimate (95% confident interval): 3.81 (1.13–6.49)], GCS score on admission [$p < 0.0001$, Estimate (95% CI): -2.57 (−2.93 to −2.20)], and cortical hematoma [$p < 0.0001$, Estimate (95% CI): 9.18 (7.33–11.02)] were predictors of hematoma volume. As for the presence of spot signs on CTA, warfarin use [$p = 0.0075$, OR (odds ratio): 2.28 (1.25–4.07)] and hematoma volume [$p < 0.0001$, Unit OR: 1.026 (1.017–1.036)] were predictors of spot signs on multiple logistic regression analysis.

Table 1
Comparison between patients using warfarin and the others in 703 patients with intracerebral hemorrhage.

Variable	Warfarin		P value Univariate analysis
	Use (n = 58)	The others (n = 645)	
Age (years)	74.6 ± 8.6	66.9 ± 13.4	< 0.0001
Male	39 (67.2%)	366 (56.7%)	0.1212
Interval from onset to arrival (minutes)	98.3 ± 84.9	98.4 ± 79.3	0.9964
Arrival Glasgow Coma Scale	10.4 ± 4.5	11.3 ± 4.0	0.1025
Arrival systolic blood pressure (mmHg)	177.7 ± 33.7	187.2 ± 38.5	0.0628
Deep hemorrhage (n = 563)	44 (75.9%)	519 (80.5%)	0.4005
Hematoma volume (ml)	65.6 ± 24.0	54.8 ± 23.5	0.0009
Spot sign (n = 143)	23 (39.7%)	120 (18.6%)	0.0001
Hematoma enlargement (n = 59)	11 (23.4%)	48 (8.4%)	0.0008
Unfavorable outcomes (*mRS ≥ 3, n = 591)	55 (94.8%)	536 (83.1%)	0.0194
Death (n = 95)	17 (29.3%)	78 (12.1%)	0.0002
Death caused by neurological damage	15 (26.8%)	59 (9.4%)	< 0.0001

*mRS : modified Rankin Scale; Underlines indicate *p*-value less than 0.05.

3.2. Evaluation using the 4 combinations of warfarin use and spot signs

The numbers of patients belonging to the 4 combinations were: warfarin use and spot sign-present, 23 patients (3.3%); warfarin use and spot sign-absent, 35 patients (5.0%); no warfarin use and spot sign-present, 120 patients (17.1%); and no warfarin use and spot sign-absent, 525 patients (74.7%). Hematoma enlargement was observed in 59 of the 703 patients (8.4%). Inter-group comparisons among the 4 combinations regarding hematoma enlargement are shown in Fig. 1. After conducting the FDR-BH procedure for multiple comparisons, the group of no warfarin use and spot sign-absent showed a significantly lower frequency of hematoma enlargement than the other 3 groups.

Table 2 shows the relationships between hematoma enlargement and clinical factors, including the combinations of both or either warfarin use and/or the spot sign. Multivariate analysis showed that the combination of warfarin use and spot sign-present [$p < 0.0001$, OR: 28.80 (8.39–99.63)] and the combination of no warfarin use and spot sign-present [$p < 0.0001$, OR: 2.62 (0.57–9.97)] were predictors of hematoma enlargement. In cases of the combination of warfarin use and spot sign-present, the hematoma enlargement occurred with the sensitivity of 11.9%, specificity of 98.0%, positive predictive value of 38.9%, negative predictive value of 91.3%, and diagnostic accuracy of 78.9%.

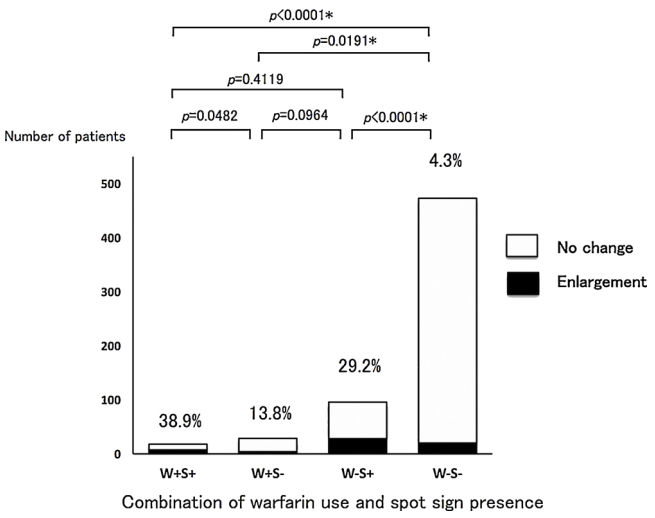

Fig. 1. Inter-group comparisons among the 4 groups with various combinations of warfarin use and spot signs with respect to hematoma enlargement. The combination of no warfarin use and spot sign-absent (W-S-) shows a significantly lower rate of hematoma enlargement than the other 3 groups. W + S +: combination of warfarin use and spot sign-present; W + S-: combination of warfarin use and spot sign-absent; W-S+: combination of no warfarin use and spot sign-present. Numbers above the bars are the rates of hematoma enlargement. * indicates a significant difference by the False discovery rate Benjamini-Hochberg procedure.

Death occurred in 95 of 703 patients (13.5%) during the hospital stay. Inter-group comparisons among the 4 combinations regarding mortality are shown in Fig. 2. After conducting the FDR-BH procedure for multiple comparisons, the group of warfarin use and spot sign-present showed significantly higher mortality (52.2%) than the other 3 groups. Table 3 shows the relationships between death and clinical factors, including the combinations of both or either warfarin use and/or the spot sign. Multivariate analysis showed that the combination of warfarin use and spot sign-present [$p = 0.0036$, OR: 5.70 (1.77–18.54)] was a predictor of death. In cases of the combination of warfarin use and spot sign-present, in-hospital death occurred with the sensitivity of 11.6%, specificity of 98.2%, positive predictive value of 52.2%, negative predictive value of 87.8%, and diagnostic accuracy of 86.6%. In 551 of 703 patients (78.4%), unfavorable outcomes were observed at discharge. Multivariate analysis showed that the combination of no warfarin use and spot sign-present [$p = 0.0174$, OR: 2.82 (1.19–7.92)], age [$p < 0.0001$, Unit OR: 1.055 (1.034–1.077)], GCS score on admission [$p < 0.0001$, Unit OR: 0.77 (0.68-0.85)], cortical hematoma [$p < 0.0001$, OR: 7.60 (3.82–15.54)], and hematoma volume [$p < 0.0001$, Unit OR: 1.064 (1.046–1.084)] were predictors of unfavorable outcomes. In cases of the combination of warfarin use and spot sign-present, unfavorable outcomes at discharge occurred with the sensitivity of 2.0%, specificity of 92.9%, positive predictive value of 61.1%, negative predictive value of 14.6%, and diagnostic accuracy of 14.7%.

In the 58 patients with warfarin use, PT-INR on admission was 2.48 ± 1.22 (mean ± S.D.), ranging from 0.92 to 7.26. In 10 patients, the PT-INR values were less than 1.5 on admission. In 14 of the 48 patients with initial PT-INR ≥ 1.5, follow-up PT-INR was not measured because of the patients' critical conditions. In the remaining 34 patients, PT-INR < 1.5 was confirmed 9.2 ± 3.8 h (mean ± S.D.) after admission, ranging from 3.2 to 18 h.

4. Discussion

In the present study, warfarin use was a predictor of hematoma volume and the presence of spot signs, which was compatible with the result of the previous study [18]. To the best of our knowledge, this is the first reported study on the relationships between combinations of either or both warfarin use and/or the presence of spot signs and outcomes.

Table 2
Relationships between hematoma enlargement and clinical factors, including the combinations of warfarin and the spot sign.

Variable		Hematoma enlargement		P value Univariate analysis	OR (95% CI)	p value
		Positive (n = 59)	Negative (n = 557)		Multivariate analysis	
Combination of warfarin and spot sign	*WF + †Spot +	7 (11.9%)	11 (2.0%)	< 0.0001	28.80 (8.39-99.63)	< 0.0001
	WF + Spot-	4 (6.8%)	25 (4.5%)	0.4294	2.62 (0.57-8.87)	0.1940
	WF-Spot +	28 (27.5%)	68 (12.1%)	< 0.0001	14.03 (6.89-29.74)	< 0.0001
Systolic blood pressure (mmHg)		168.7 ± 26.7	185.6 ± 38.2	0.0015	(Unit OR) 1.016 (1.001-1.036)	0.0003
Cortical hemorrhage		18 (30.5%)	106 (19.0%)	0.0365	2.70 (1.24-5.83)	0.0125
Hematoma volume (ml)		80.9 ± 20.8	52.6 ± 22.4	< 0.0001	(Unit OR) 1.018 (1.001-1.036)	0.0327

*WF: warfarin use; †Spot: spot sign presence; The factors other than combinations of warfarin use and spot sign presence, in which p-value < 0.05 by univariate analysis, are presented. Underlines indicate $p < 0.05$.

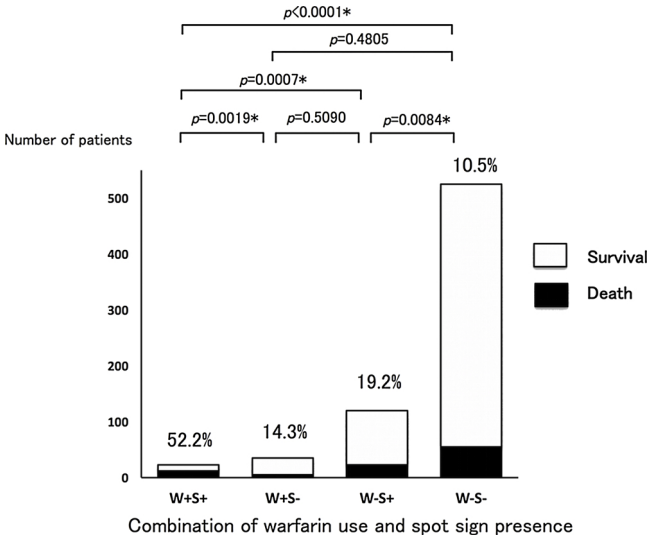

Fig. 2. Inter-group comparisons among the 4 groups with various combinations of warfarin use and spot signs with respect to mortality. The combination of warfarin use and spot sign-present (W + S+) shows a significantly higher mortality rate than the other 3 groups. W + S-: combination of warfarin use and spot sign-absent; W-S+: combination of no warfarin use and spot sign-present; W-S-: combination of no warfarin use and spot sign-absent. Numbers above the bars are mortality rates. * indicates a significant difference by the False discovery rate Benjamini-Hochberg procedure.

4.1. Combination of warfarin use and spot sign-present

Among the 58 warfarin users, 23 patients (39.7%) belonged to this group. The outcome of more than half of the patients with warfarin use and the presence of spot signs was death at discharge. On multiple comparisons, mortality was significantly higher in this group than in the other 3 groups. The frequency of hematoma enlargement was also higher in this group compared to the combination of no warfarin use and spot sign-absent. Multivariate comparison showed that the combination of warfarin use and spot sign-present was a common predictor of both hematoma enlargement (OR: 28.8) and death at discharge (OR: 5.7). The patients who used warfarin and also showed spot signs on CTA were regarded as a high-risk group. An ICH patient with warfarin use and spot sign-present treated by PCC administration, who showed no hematoma enlargement and disappearance of the spot sign on follow-up CTA performed 3 h after the first CTA, has been reported [19]. Warfarin users also showing spot signs should be treated promptly by appropriate medication, including PCC administration [20,21].

4.2. Combination of warfarin use and spot sign-absent

This group consisted of 35 (60.3%) of the 58 warfarin users. The patients receiving warfarin showing no spot signs on CTA had no significant difference in mortality compared to the patients with the combination of no warfarin use and spot sign-absent on univariate analysis. This combination was not a predictor of hematoma enlargement, unfavorable outcomes, or death on multivariate analysis. Therefore, the combination of warfarin use and spot sign-absent could be regarded as a relatively benign entity among warfarin users with ICHs. However, hematoma enlargement was found in 13.8% of the patients with warfarin use and spot sign-absent, which was significantly higher than among patients with no warfarin use and spot sign-absent, in whom hematoma enlargement was found in 4.2% on univariate analysis. The possible room for improvement of hematoma enlargement in this group might suggest that administration of PCC ameliorates the hematoma enlargement rate.

4.3. Combination of no warfarin use and spot sign-present

Even in the absence of a history of warfarin use, the presence of spot signs was a predictor of both hematoma enlargement and unfavorable outcomes. Of the 703 eligible patients with ICH, 120 patients (7.1%) belonged to this group. Risk reduction for this group should be a forthcoming challenge. A retrospective study of ICH in patients showing spot signs on CTA without a history of warfarin use showed that administration of PCC reduced the number with hematoma enlargement

Table 3
Relationships between death and clinical factors, including combinations of warfarin use and the spot sign.

Variable		Outcome		P value Univariate analysis	OR (95% CI)	p value
		Survival (n = 606)	Death (n = 95)		Multivariate analysis	
Combination of warfarin and spot sign	*WF + †Spot +	11 (1.81%)	12 (12.6%)	< 0.0001	5.70 (1.77-18.54)	0.0036
	WF + Spot-	30 (4.9%)	5 (5.3%)	0.8910	1.053 (0.29-3.38)	0.9343
	WF-Spot +	97 (16.0%)	23 (24.2%)	0.0467	1.65 (0.87-3.07)	0.1260
Age (years)		66.7 ± 13.0	72.5 ± 13.9	< 0.0001	(Unit OR) 1.038 (1.017-1.060)	0.0002
Glasgow Coma Scale		12.0 ± 3.6	6.4 ± 3.6	< 0.0001	(Unit OR) 0.71 (0.66-0.76)	< 0.0001
Hematoma volume (ml)		52.8 ± 22.0	74.1 ± 26.3	< 0.0001	(Unit OR) 1.012 (1.001-1.023)	0.0318

*WF: warfarin use; †Spot: spot sign presence; The factors other than combinations of warfarin use and spot sign presence, in which p-value < 0.05 by univariate analysis, are presented. Underlines indicate $p < 0.05$.

[22]. This might be a clue to the resolution of this problem in this group.

4.4. Limitations

This study has the limitations associated with a retrospective study. The treatment strategy for reversal of warfarin was not standardized. The frequency of warfarin use was so low that patients' data were collected over a time span of 9 years. Although the basic management strategy of ICH during that time period was consistent, a small modification of treatment by each primary physician might have affected the results of this study. In the present study, the rate of hematoma enlargement in the control group (no warfarin use and spot sign-absent) was 4.2%, which was relatively low among the previously reported rates [6,7,10]. This low rate of hematoma enlargement could be achieved by the intensive blood pressure reduction therapy during the early stages that was performed in our institute during the entire study period. This low hematoma enlargement rate might affect the results of this study. In the multivariate analysis, the outcomes related to patients age. Arboix A. et al reported that patients aged 85 and older with intracerebral hemorrhage showed poorer outcome, including higher in-hospital mortality and moderate or severe neurological deficit at hospital discharge, than younger patients [23]. Approximately 10% of the patients in this study belonged to the oldest old patient group, which could have been separated from the younger patients for the analysis.

5. Conclusions

Combinations of warfarin use and spot signs were used to identify high-risk patients with ICHs before the introduction of PCC treatment. The mortality of the combination of warfarin use and spot sign-present was 52.2%, which was significantly higher than of the other 3 combinations. Multivariate analysis demonstrated that the combination of warfarin use and spot sign-present was a predictor of both hematoma enlargement and death at discharge. This group was regarded as high-risk patients who should be treated promptly by appropriate therapies, including PCC administration.

The combination of warfarin use and spot sign-absent was not a predictor of either hematoma enlargement or death, and it could be regarded as a relatively benign entity among ICH patients on warfarin. Considering that the frequency of hematoma enlargement in this group was 13.8%, which was significantly higher than that of the combination of no warfarin use and spot sign-absent (4.3%), PCC administration might be useful to prevent hematoma enlargement.

References

[1] M.L. Flaherty, H. Tao, M. Haverbusch, P. Sekar, D. Kleindorfer, B. Kissela, et al., Warfarin use leads to larger intracerebral hematomas, Neurology 71 (2008) 1084–1089.

[2] H.B. Brouwers, Y. Chang, G.J. Falcone, X. Cai, A.M. Ayres, T.W. Battey, et al., Predicting hematoma expansion after primary intracerebral hemorrhage, JAMA Neurol. 71 (2014) 158–164.

[3] B. Cucchiara, S. Messe, L. Sansing, S. Kasner, P. Lyden, For the CHANT Investigators. Hematoma growth in oral anticoagulant related intracerebral hemorrhage, Stroke 39 (2008) 2993–2996.

[4] X. Wang, H. Arima, R. Al-Shahi Salman, M. Woodward, E. Heeley, C. Stapf, et al., INTERACT Investigators. Clinical prediction algorithm (BRAIN) to determine risk of hematoma growth in acute intracerebral hemorrhage, Stroke 46 (2) Febuary) (2015) 376–381.

[5] T.J. Huynh, R.I. Aviv, D. Dowlatshahi, D.J. Gladstone, A. Laupacis, A. Kiss, et al., PREDICT/Sunnybrook CTA investigators. Validation of the 9-Point and 24-Point hematoma expansion prediction scores and derivation of the PREDICT A/B scores, Stroke 46 (2015) 3105–3110.

[6] J.E. Delgado Almandoz, A.J. Yoo, M.J. Stone, P.W. Schaefer, J.N. Goldstein, J. Rosand, et al., Systematic characterization of the computed tomography angiography spot sign in primary intracerebral hemorrhage identifies patients at highest risk for hematoma expansion: the spot sign score, Stroke 40 (2009) 2994–3000.

[7] A.M. Demchuk, D. Dowlatshahi, D. Rodriguez-Luna, C.A. Molina, Y.S. Blas, Dzialowski I, et al; PREDICT/Sunnybrook ICH CTA study group Prediction of haematoma growth and outcome in patients with intracerebral haemorrhage using the CT-angiography spot sign (PREDICT): a prospective observational study, Lancet Neurol. 11 (2012) 307–314.

[8] K. Hotta, T. Sorimachi, T. Osada, T. Baba, G. Inoue, H. Atsumi, et al., Risks and benefits of CT angiography in spontaneous intracerebral hemorrhage, Acta Neurochir (Wien). 156 (2014) 911-017.

[9] T. Sorimachi, T. Osada, T. Baba, G. Inoue, H. Atsumi, H. Ishizaka, et al., The striate artery, hematoma, and spot sign on coronal images of computed tomography angiography in putaminal intracerebral hemorrhage, Stroke 44 (2013) 1830–1832.

[10] N. Li, Y. Wang, W. Wang, L. Ma, J. Xue, K. Weissenborn, et al., Contrast extravasation on computed tomography angiography predicts clinical outcome in primary intracerebral hemorrhage: a prospective study of 139 cases, Stroke 42 (2011) 3441–3446.

[11] T. Steiner, S. Poli, M. Griebe, J. Hüsing, J. Hajda, A. Freiberger, et al., Fresh frozen plasma versus prothrombin complex concentrate in patients with intracranial haemorrhage related to vitamin K antagonists (INCH): a randomised trial, Lancet Neurol. 15 (2016) 566–573.

[12] R. Sarode, T.J. Milling Jr, M.A. Refaai, A. Mangione, A. Schneider, B.L. Durn, et al., Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study, Circulation 128 (2013) 1234–1243.

[13] J.N. Goldstein, M.A. Refaai, T.J. Milling Jr, B. Lewis, R. Goldberg-Alberts, B.A. Hug, et al., Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomized trial, Lancet 385 (2015) 2077–2087.

[14] K. Kuwashiro, M. Yasaka, R. Itabashi, H. Nakagaki, F. Miyashita, H. Naritomi, et al., Effect of prothrombin complex concentrate on hematoma enlargement and clinical outcome in patients with anticoagulant-associated intracerebral hemorrhage, Cerebrovasc. Dis. 31 (2011) 170–176.

[15] C.S. Anderson, E. Heeley, Y. Huang, J. Wang, C. Stapf, C. Delcourt, et al., INTERACT2 Investigators. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage, N. Engl. J. Med. 20 (368) (2013) 2355–2365.

[16] T. Steiner, J. Rosand, M. Diringer, Intracerebral hemorrhage associated with oral anticoagulant therapy: current practices and unresolved questions, Stroke 37 (2006) 256–262.

[17] R.U. Kothari, T. Brott, J.P. Broderick, W.G. Barsan, L.R. Sauerbeck, M. Zuccarello, et al., The ABCs of measuring intracerebral hemorrhage volumes, Stroke J Cereb Circ 27 (1996) 1304–1305.

[18] A. Arboix, E. Comes, L. García-Eroles, J. Massons, M. Oliveres, M. Balcells, et al., Site of bleeding and early outcome in primary intracerebral hemorrhage, Acta Neurol. Scand. 105 (2002) 282–288.

[19] F. Radmanesh, G.J. Falcone, C.D. Anderson, T.W. Battey, A.M. Ayres, A. Vashkevich, et al., Risk factors for computed tomography angiography spot sign in deep and lobar intracerebral hemorrhage are shared, Stroke 45 (2014) 1833–1835.

[20] S. Chakraborty, G. Stotts, C. Rush, M.J. Hogan, D. Dowlatshahi, Dynamic' Spot sign' resolution following INR correction in a patient with warfarin-associated intracerebral hemorrhage, Case Rep. Neurol. 3 (2011) 154–159.

[21] D. Dowlatshahi, K.S. Butcher, N. Asdaghi, S. Nahirniak, M.L. Bernbaum, A. Giulivi, et al., Canadian PCC Registry (CanPro) Investigators. Poor prognosis in warfarin-associated intracranial hemorrhage despite anticoagulation reversal, Stroke 43 (2012) 1812–1817.

[22] R. Rehmani, A. Han, J. Hassan, J. Farkas, Role of prothrombin complex concentrate (PCC) in AcuteIntracerebral Hemorrhage with Positive CTA spot sign: an institutional experience at a regional and state designated stroke center, Emerg. Radiol. 24 (2017) 241–247.

[23] A. Arboix, A. Vall-Llosera, L. García-Eroles, J. Massons, M. Oliveres, C. Targa, Clinical features and functional outcome of intracerebral hemorrhage in patients aged 85 and older, J. Am. Geriatr. Soc. 50 (2002) 449–454.