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ORIGINAL ARTICLE **ÖZGÜN ARAŞTIRMA**

INFLUENCE OF BLACK HOLE SIGN ON PROGNOSIS IN INTRACEREBRAL HEMORRHAGE AND ITS CORRELATION WITH CEREBRAL MICROBLEEDS

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ABSTRACT

INTRODUCTION: In this study, we aimed to evaluate the relationship between cranial computed tomography (CT) black hole sign (BHS) and cerebral microbleeds (CMB) detected on cranial magnetic resonance imaging (MRI), and the relationship between BHS and poor prognosis in patients with spontaneous intracerebral hemorrhage (ICH).
METHODS: Our study is designed as a prospective observational study. Patients admitted to our hospital between September 2018 and October 2019 were evaluated. Patients older than 18 years old and whose cranial CT were performed within 6 hours of onset were included. The patients divided into two groups according to BHS presence. After exclusion of the patients who underwent surgery, demographic, clinical, laboratory, and imaging characteristics were compared between the two groups. The effect of BHS on poor prognosis were evaluated using multivariable logistic regression analysis.
RESULTS: Sixty six of 88 patients admitted to our hospital were included. 47 of the patients (71.2%) were male, and mean age was 63.08 ± 14.33 years. BHS was found in 16 patients (24.2%). Anticoagulant use, hemorrhage volume on initial CT scan, presence of midline shift, and presence of pineal gland shift were significantly higher in BHS positive patients ($p<0.05$). While CMB presence was comparable between groups, CMB number was significantly lower in patients with BHS ($p=0.023$). In-hospital and 90-day mortality were significantly higher in BHS positive patients, but 90-day mRS scores were similar between two groups. BHS was not an independent predictor of poor prognosis in multivariable logistic regression ($p>0.05$).
DISCUSSION AND CONCLUSION: BHS was shown to be associated with in-hospital and 90-day mortality. Negative relationship between BHS and CMB number may support the microbleeding-macrobleeding concept in ICH patients.
Keywords: Intracerebral hemorrhage, black hole sign, cerebral microbleeds, prognosis.

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SPONTAN İNTRASEREBRAL HEMORAJİLERDE KARA DELİK BULGUSUNUN PROGNOZ ÜZERİNE ETKİSİ VE MİKROKANAMALAR İLE KORELASYONU

ÖZ

GİRİŞ ve AMAÇ: Bu çalışmada, spontan intraserebral hemoraji hastalarında (SİH) kranyal bilgisayarlı tomografide (BT) görülen kara delik bulgusunun (KDB), kranyal manyetik rezonans görüntülemelerde (MRG) saptanan serebral mikrokanamalarla (SMK) ilişkisini ve KDB'nin kötü prognozla olan ilişkisini değerlendirmeyi amaçladık.
YÖNTEM ve GEREÇLER: Çalışmamız prospektif gözlemsel bir çalışma olarak tasarlandı. Eylül 2018 ile Ekim 2019 tarihleri arasında hastanemizde yatan hastalar değerlendirildi. 18 yaşından büyük ve kranyal BT'si şikayetlerin başlangıcından itibaren 6 saat içinde çekilen hastalar dahil edildi. Hastalar KDB'nin varlığına göre iki gruba ayrıldı. Cerrahi uygulanan hastalar dışlandıktan sonra demografik, laboratuvar, klinik ve görüntüleme özellikleri iki grup arasında karşılaştırıldı. KDB'nin kötü sonlanım üzerine olan etkisi çok değişkenli lojistik regresyon analiziyle değerlendirildi.
BULGULAR: Hastanemize yatan 88 hastadan 66'sı çalışmaya alındı. Hastaların 47'si (%71,2) erkekti ve yaş ortalaması 63,08 ± 14,33 yıldı. KDB 16 hastada (%24,2) gözlendi. Antikoagülan ilaç kullanımı, ilk BT'deki hemoraji volümü, orta hat şifti varlığı ve pineal bez şifti varlığı KDB pozitif olan hastalarda anlamlı olarak daha yüksek bulundu ($p<0,05$). SMK varlığı gruplar arasında benzerken KDB olan hastalarda SMK sayısı anlamlı olarak daha düşüktü ($p<0,023$). Hastane içi ve 90. gün mortalite KDB pozitif hastalarda anlamlı olarak daha yüksekken 90. gün mRS skorları iki grup arasında benzerdi. KDB, çok değişkenli lojistik regresyon analizinde kötü sonlanımın bağımsız prediktörü olarak gösterilemedi ($p>0,05$).
TARTIŞMA ve SONUÇ: KDB varlığı, hastane içi ve 90. gün mortalite ile ilişkili bulundu. KDB ve SMK sayısı arasındaki negatif yönlü ilişki, İSH hastalarındaki mikrokanama-makrokanma konseptini destekleyebilir.
Anahtar Sözcükler: İntraserebral hemoraji, kara delik bulgusu, serebral mikrokanamalar, prognoz.

INTRODUCTION

Intracerebral hemorrhage (ICH) accounts for approximately 9-27% of all strokes and has a high 30-day mortality rate ranging from 40% to 50% (1–3). Hematoma expansion is one of the main predictors of poor prognosis, along with age, level of consciousness, hemorrhage volume, and intraventricular extension (4). Various non-enhanced computed tomography (CT) signs described in the last decade, including the black hole sign (BHS) that was identified by Li et al. in 2016 (5). It was defined as a hypodense area encapsulated in the hyperdense hematoma and having a clear-cut border and no connections to the adjacent parenchyma (5). The ability of BHS to predict hematoma expansion and poor prognosis was proven in multiple studies, and it was also shown to be associated with higher initial hematoma volumes in various studies (5–12). Another finding that has been investigated regarding hematoma volumes is the cerebral microbleeds (CMB), which are described as small lesions with signal void and blooming artefacts in T2*-weighted images (13). Multiple studies evaluated the relationship between CMBs and initial hematoma volume. This relationship is controversial since there are studies that shows higher initial hematoma volumes or less initial hematoma volumes in patients with CMBs and studies that show no relationship at all (14–16). An interesting finding regarding the CMBs is that the spot sign, seen in contrast-enhanced CTs as a hyperdense area inside the hematoma, is seen more frequently in the absence of CMBs (17). To our knowledge, there are no studies evaluating the relationship between BHS and CMBs seen on magnetic resonance imaging (MRI) in patients with ICH in the literature. We aimed in our study to investigate the effects of BHS on functional prognosis and whether there is a relationship between BHS and CMBs.

METHODS

We prospectively enrolled patients with ICH who were admitted to both the neurology wards and the neurocritical care unit in our tertiary state hospital between September 2018 and October 2019. Patients older than 18 years old and who had a baseline CT scan within six hours of symptom onset were included in the present study. Hemorrhages due to secondary causes (i.e., tumor, trauma, vascular malformations) were excluded from this study. Patients who underwent surgery were not included in the control CT, MRI, and prognosis analyses.

All demographic and clinical characteristics, including age, sex, medical history, tobacco and alcohol use, and medications, were recorded upon

admission to the Neurological Emergency Department. Symptom onset, admission time to the Department of Neurology, vital signs, and neurological examination, including the National Institute of Health Stroke Scale (NIHSS) and Glasgow Coma Scale (GCS), were collected.

A baseline cranial CT scan was performed using a 2-mm slice thickness. The time from symptom onset to first cranial CT is calculated as onset-to-CT time. Localization and volume of the hemorrhage, presence of BHS, intraventricular extension, and presence of midline and pineal gland shift were analyzed. Hemorrhages were divided into non-lobar hemorrhage and lobar hemorrhage. The Volume of the hemorrhage was calculated using the ABC/2 method.

Unless there is a contraindication (e.g., heart valve and extremity prostheses, intubated patient), an MRI using either Siemens or General Electronic machines with a 1.5 Tesla field strength was performed. MRI protocol included axial T2-weighted, T1-weighted, and T2 fluid-attenuated inversion recovery (FLAIR) sequences, coronal and sagittal T2-weighted sequences, diffusion-weighted imaging, and apparent diffusion coefficient maps. As for cerebral microbleed evaluation, susceptibility-weighted imaging (SWI), susceptibility-weighted angiography (SWAN) or T2*-weighted gradient echo (GRE) sequences were used. The time from symptom onset to MRI procedure was calculated as days. CMB presence and numbers were interpreted from SWI, SWAN or GRE sequences. CMB locations were categorized as (1) deep and/or infratentorial, or (2) strictly lobar. The presence of cortical superficial siderosis and remote ischemic lesions were noted.

Patients underwent a control CT scan 10 days after the initial CT scan. The time between the two scans was calculated as days. Hemorrhage resorption rate was calculated by subtracting the volume of the second scan from the volume of the first scan divided by the time between the two scans. Patients whose hematoma volumes increased when compared to initial hematoma volume were kept outside of this analysis.

Hospital length-of-stay was calculated as days. NIHSS score was recalculated on day 10, and the modified Rankin scale (mRS) score was evaluated. In-hospital mortalities were recorded. 90-day mRS was interpreted by making a phone call to either the patients or their relatives. mRS scores of 0-2 were considered as a good prognosis, whereas mRS scores of 3-6 was considered as a poor prognosis.

Statistical Analysis: All statistical analyses were performed using SPSS Statistics 25 for Mac. Descriptive statistics mean, median, standard deviation, interquartile range, and percentile were used as appropriate. Patients were divided into two groups according to the presence of BHS. Demographic and clinical features, radiological findings, and prognostic information were compared between the two groups. The chi-square test or Fisher's exact test was used for comparing categorical variables. Student t-test or Mann-Whitney U test was used for comparing continuous variables according to the normality of distribution. The correlation between CMB numbers and hemorrhage volumes was assessed using the Pearson correlation test. Sensitivity, specificity, positive predictive value, and negative predictive value of BHS for poor prognosis were calculated using receiver operator characteristics curve. Predictive values of variables for poor prognosis on day 90 were interpreted by logistic regression analysis. All the variables with a p level less than 0.1 in univariable analysis and anticoagulant use were included in the multivariable model. The forward selection was used for the multivariable model. A p-value less than 0.05 was used for inclusion, and a p-value greater than 0.1 was used for exclusion for every selection step. GCS showed a strong correlation with NIHSS and was not included in the multivariable model due to multicollinearity. A p-value less than 0.05 was considered statistically significant.

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. In order to perform the study, ethical approval was obtained from University of Health Sciences Bakirkoy Prof. Dr. Mazhar Osman Research and Training Hospital Ethical Committee (Number: 220, Date: 25.09.2018). Also, written informed consent was obtained from all the patients or their relatives for inclusion in the present study.

RESULTS

Of 88 patients admitted to the hospital with intracerebral hemorrhage, 66 of them were included in this study (Figure 1). The reasons for exclusion were onset-to-CT time longer than six hours in 21 patients and intra-axial tumor in one

patient. Forty-seven of the patients (71.2%) were male, and the mean age was 63.08±14.33 years. The demographic and clinical characteristics of all patients are presented in Table 1.

Table 1. Demographic and clinical characteristics of all patients.

	All patients n = 66
Age, years, mean (SD)	63.08 (14.33)
Male sex, n (%)	47 (71.2)
Medical history	
Hypertension, n (%)	53 (80.3)
Diabetes mellitus, n (%)	18 (27.3)
Prior cerebrovascular disease, n (%)	15 (22.7)
Chronic kidney disease, n (%)	9 (13.6)
Coronary artery disease, n (%)	7 (10.6)
Hyperlipidemia, n (%)	5 (7.6)
Smoking, n (%)	23 (34.8)
Alcohol use, n (%)	15 (22.7)
Medications	
Antiaggregant use, n (%)	13 (19.7)
Anticoagulant use, n (%)	13 (19.7)
Systolic blood pressure, mmHg, mean (SD)	190.63 (37.73)
Diastolic blood pressure, mmHg, median (IQR)	104 (92-126)
NIHSS on admission, median (IQR)	8.5 (4-16)
GCS on admission, median (IQR)	15 (10-15)
Initial cranial CT scan	
Presence of BHS, n (%)	16 (24.2%)
Onset-to-CT time, minutes, median (IQR)	102.5 (66-171.5)
Hemorrhage volume, ml, median (IQR)	10.35 (4.2-25.88)
Localization	
Basal ganglia, n (%)	25 (37.9)
Thalamus, n (%)	20 (30.3)
Cerebral lobes, n (%)	13 (19.7)
Cerebellum, n (%)	1 (1.5)
Brainstem, n (%)	3 (4.5)
Multiple, n (%)	4 (6.1)
Intraventricular extension, n (%)	24 (36.4)
Midline shift, n (%)	21 (31.8)
Pineal gland shift, n (%)	9 (13.6)

SD: standard deviation, IQR: interquartile range, NIHSS: National Institute of Health Stroke Scale, GCS: Glasgow Coma Scale, CT: computed tomography, BHS: black hole sign.

Black hole sign was present in 16 patients (24.2%) on initial CT scans. The median onset-to-CT time was 102.5 minutes (interquartile range [IQR] 66-171.5). The median hemorrhage volume of all patients was 10.35 milliliters (IQR 4.2-25.88). Intraventricular extension of hemorrhage, midline shift, and pineal gland shift were observed in 24 (36.4%), 21 (31.8%), and nine (13.6%) patients, respectively. Hemorrhage localization was basal ganglia in 25 (37.9%), thalamus in 20 (30.3%), cerebral lobes in 13 (19.7%), cerebellum in one (1.5%), brainstem in three (4.5%), and multiple in four (6.1%) patients. A detailed comparison of patients with and without BHS for demographic, clinical, laboratory, and CT imaging parameters was presented in Table 2. Demographic characteristics and medical history were comparable between patients with and without BHS. Patients with BHS were using anticoagulants more frequently when compared to patients without BHS (6/16 [37.5%] vs. 7/50 [14%], p=0.040). Vital signs and neurological examination were similar between groups. However, there was a trend for lower GCS scores for patients with BHS (10.5 [IQR 9.25-15] vs. 15 [IQR 10-15], p=0.096). When comparing initial CT scans, patients with BHS had significantly higher hemorrhage volumes (17.63 ml [IQR 5.66-71.5] vs. 8.44 ml [IQR 3.48-20.18], p=0.048), higher percentage of midline shift (9/16 [60%] vs. 12/50 [24%], p=0.013] and pineal gland shift (5/16 [33.3%] vs. 4/50 [8%], p=0.025).

Surgical operations were performed on seven patients (10.6%) and one of these patients had BHS on the initial CT scan. These seven patients were not included in the control CT scan, MRI, and prognostic evaluation. Of 59 non-surgical patients, 48 of them had a control CT scan on day 10. The reason for not having a control CT scan on day 10 was death in six patients and hemodynamic instability in five patients. Five of 48 patients had higher hemorrhage volume on the control CT scan. They were kept apart from control CT scan evaluation as well. Forty-three patients with control CT scans were evaluated. Patients with BHS had higher median hemorrhage resorption rate than patients without BHS (0.59 ml [IQR 0.28-0.79] vs. 0.26 [IQR 0.06-0.53], p=0.049).

MRI was performed in 51 of 59 non-surgical patients. Patients who did not have MRIs were all intubated during their hospital stay until they passed away. As for hemosequence, 37 patients had SWI, six patients had SWAN, and five patients had T2*-weighted GRE sequence. Two patients did not have hemosequence. CMB presence was not significantly different between patients with and without BHS (7/16 [63.6%] vs. 28/50 [70%], p=1) (Table 3). However, median CMB numbers were significantly lower in patients with BHS (2 [IQR 2-5] vs. 8 [IQR 4-18.25], p=0.023) (Table 3). CMB locations, presence of cortical superficial siderosis and remote ischemic lesions were similar between the two groups. Median number of CMBs were 5 (IQR 3-14) in all patients. There was no correlation between median CMB number on cranial MRI and hemorrhage volume on initial CT scan (r=-0.229,

Table 2. Comparison of demographic and clinical characteristics and initial CT scan between BHS positive and negative patients.

	BHS positive n = 16	BHS negative n = 50	p value
Age, years, mean (SD)	67.56 (13.95)	61.64 (14.28)	0.152
Male sex, n (%)	12 (75)	35 (70)	0.701
Medical history			
Hypertension, n (%)	13 (81.3)	40 (80)	1
Diabetes mellitus, n (%)	4 (25)	14 (28)	1
Prior cerebrovascular disease, n (%)	5 (31.3)	10 (20)	0.350
Chronic kidney disease, n (%)	4 (25)	5 (10)	0.204
Coronary artery disease, n (%)	1 (6.3)	6 (12)	1
Hyperlipidemia, n (%)	1 (6.3)	4 (8)	1
Smoking, n (%)	6 (40)	17 (37.8)	0.878
Alcohol use, n (%)	3 (20)	12 (26.7)	0.740
Medications			
Antiaggregant use, n (%)	3 (18.8)	10 (20)	0.913
Anticoagulant use, n (%)	6 (37.5)	7 (14)	**0.040**
Systolic blood pressure, mmHg, mean (SD)	192.5 (40.53)	190 (37.17)	0.821
Diastolic blood pressure, mmHg, median (IQR)	108 (95.25-125)	102 (91-126)	0.664
NIHSS on admission, median (IQR)	9 (5-16)	8 (4-15)	0.369
GCS on admission, median (IQR)	10.5 (9.25-15)	15 (10-15)	0.096
Initial cranial CT scan			
Onset-to-CT time, minutes, median (IQR)	100.5 (68.75-203)	102.5 (64.5-156.75)	0.740
Hemorrhage volume, ml, median (IQR)	17.63 (5.66-71.5)	8.44 (3.48-20.18)	**0.048**
Non-lobar hemorrhage	40 (80)	13 (81.3)	**1**
Intraventricular extension, n (%)	8 (50)	16 (32)	0.193
Midline shift, n (%)	9 (60)	12 (24)	**0.013**
Pineal gland shift, n (%)	5 (33.3)	4 (8)	**0.025**

SD: standard deviation, IQR: interquartile range, NIHSS: National Institute of Health Stroke Scale, GCS: Glasgow Coma Scale, CT: computed tomography, BHS: black hole sign.

Table 3. Comparison of cranial MRI findings in patients with and without BHS.

	BHS positive n = 11	BHS negative n = 40	p value
Onset-to-MRI, days, median (IQR)	2 (1-5)	2 (1-4)	0.543
Presence of CMBs, n (%)	7 (63.6)	28 (70)	1
CMB numbers (IQR)	2 (2-5)	8 (4-18.25)	**0.023**
Presence of deep or infratentorial localization, n (%)	6 (85.7)	25 (89.3)	0.511
Presence of cortical superficial siderosis, n (%)	2 (18.1)	5 (12.5)	0.625
Presence of remote ischemic lesions on diffusion-weighted imaging, n (%)	1 (9.1)	7 (17.5)	0.666

MRI: magnetic resonance imaging, BHS: black hole sign, IQR: interquartile range, CMB: cerebral microbleeds.

p=0.186). Median NIHSS and mRS scores on day 10 and hospital length-of-stay were not significantly different between groups (Table 4). In-hospital mortality was significantly higher in patients with BHS (6/16 [40%] vs. 6/50 [13.6%], p=0.028). Median mRS scores on day 90 were numerically higher in patients with BHS, but this association was not statistically significant (4 [IQR 3-6] vs. 3 [1-5], p=0.059).

As with median mRS scores, the percentage of patients with poor prognosis on day 90 was higher in patients with BHS but this also was not statistically significant (12/16 [80%] vs. 23/50 [52.3%], p=0.054).

Mortality on day 90 was significantly higher for [40%] vs. 6/50 [13.6%], p=0.028).For predicting poor prognosis, BHS had a 34.3% sensitivity, 87.5% specificity, 80% positive predictive value, and 47.7% negative predictive value. Univariable logistic regression analysis revealed that age, NIHSS on admission, GCS on admission, hemorrhage volume on initial CT scan, intraventricular extension, and midline shift were independent predictors of poor prognosis (Table 5). The multivariable model showed that only age and NIHSS on admission independently predict poor prognosis on day 90 (Table 6). Nagelkerke R square value for the model was 0.715.

Table 4. Comparison of prognostic parameters in patients with and without BHS.

	BHS positive n = 15	BHS negative n = 44	p value
Hospital length-of-stay, days, median (IQR)	12 (8-23)	15.5 (11.75-18.25)	0.275
Day 10			
NIHSS, median (IQR)	5 (4-15.25)	5 (2-12)	0.467
mRS, median (IQR)	5 (2-5)	4 (1-5)	0.081
Day 90			
mRS, median (IQR)	4 (3-6)	3 (1-5)	0.059
Poor prognosis, n (%)	12 (80)	21 (47.7)	0.059
Mortality, n (%)	6 (40)	6 (13.6)	**0.028**

BHS: black hole sign, IQR: interquartile range, NIHSS: National Institute of Health Stroke Scale, mRS: modified Rankin Scale.

Table 5. Univariable logistic regression analyses for predicting poor prognosis on day 90.

	Odds Ratio	95% Confidence Interval	p value
Age	1.04	1.00-1.09	**0.030**
Anticoagulant use	0.30	0.05-1.59	0.160
SBP on admission	1.01	0.99-1.03	0.097
NIHSS on admission	1.40	1.16-1.70	**<0.001**
GCS on admission	0.64	0.47-0.87	**0.005**
Hemorrhage volume on initial CT scan	1.05	1.00-1.10	**0.044**
Intraventricular extension	10.38	2.11-51.05	**0.004**
Midline shift	20.44	2.47-169.02	**0.005**
Black hole sign	3.65	0.90-14.76	0.069
Hemorrhage resorption rate	2.69	0.68-10.55	0.156
CMB presence	0.81	0.22-2.90	0.746
CMB number	1.01	0.94-1.09	0.679

SBP: systolic blood pressure, NIHSS: National Institute of Health Stroke Scale, GCS: Glasgow coma scale, CT: computed tomography, CMB: cerebral microbleed.

Table 6. Multivariable logistic regression analyses for predicting poor prognosis on day 90.

	Odds Ratio	95% Confidence Interval	p value
Age	1.40	1.13-1.75	**0.012**
Presence of hypertension	*Not selected*		0.159
Anticoagulant use	*Not selected*		0.086
SBP on admission	*Not selected*		0.311
NIHSS on admission	1.53	1.17-1.99	**0.002**
Hemorrhage volume on initial CT scan	*Not selected*		0.240
Intraventricular extension	*Not selected*		0.391
Midline shift	*Not selected*		0.392
Black hole sign	*Not selected*		0.178
Presence of CMB	*Not selected*		0.120

SBP: systolic blood pressure, NIHSS: National Institute of Health Stroke Scale, CT: computed tomography, CMB: cerebral microbleed.

DISCUSSION AND CONCLUSION

Our study showed that BHS was associated with in-hospital mortality and 90-day mortality but not with 90-day poor prognosis. Age and NIHSS on admission were the only predictors of 90-day poor prognosis in multivariable logistic regression. A surprising finding was the inverse relationship between the presence of BHS and the median number of CMBs in cranial MRI. To our knowledge, our study is the first study to evaluate the relationship between MRI signs of small vessel disease markers, such as CMBs and BHS. However, we could not show any correlation between the hemorrhage volume and the number of CMBs in our study. There is only one study that evaluates the relationship between CMBs and hematoma expansion markers, and it shows that spot sign is found more often in patients without CMBs and CMB numbers were higher in patients without spot sign (17). One study by Suo et al. found that number of CMBs was significantly less in patients with hemorrhage expansion (18). As for the relationship between hemorrhage volume and CMBs, there are some conflicting results in the literature. Lee et al showed that the initial hemorrhage volume was higher in patients with CMBs while Ghelmez et al. found no association (14,15). Subgroup analysis of the ATACH-II (Antihypertensive Treatment of Acute Cerebral Hemorrhage II) trial did not show any association as well (19). Contrary to these studies, another

study reported that the absence of CMBs was associated with larger initial hemorrhage volumes in deep and lobar hemorrhage patients when controlling for sex, age, presence of spot sign, baseline ICH volume, and time to baseline CT (16).

When all these findings are considered all together, the findings suggest that there may be an inverse relationship between CMBs and hemorrhage expansion markers. Since BHS is associated with larger initial hemorrhage volumes and hemorrhage expansion, patients with BHS may be classified as macrohemorrhage patients, while patients without BHS and with a higher number of CMBs may be classified microhemorrhage patients. This macro vs. microhemorrhage concept was questioned in the literature in the past. Atrophy in the vascular smooth muscle cells and increased matrix metalloproteinase activity related to aging and lipohyalinosis are thought to be related to CMB formation (20). Changes in the extracellular matrix and vascular smooth muscle cells and arterial stiffening were accused of a role in the development of CMBs (20,21). Greenberg et al proposed with their findings that macrobleeding and microbleeding were two separate entities owing to the bimodal distribution of hemorrhage volumes as well (21). However, regarding the relationship between CMBs and hemorrhage volume, it is not clear whether there is a difference between patients with hypertensive angiopathy or cerebral amyloid angiopathy. In the study by Boulouis et al., the absence of CMBs was related to higher hemorrhage volumes both in lobar and deep ICHs (16). We could not comment on the etiological differences in our study due to small number of patients. Although our study supports the microhemorrhage-macrohemorrhage concept, confirmatory studies are needed because of the small sample size.

The percentage of patients with BHS in our study was 24.2%. Overall, our study had a higher BHS frequency compared to previous studies with similar onset-to-CT times and 5-mm slice thickness (5,6). We used 2-mm slice thickness for acquiring CT scans and using a smaller thickness enabled the evaluation of smaller hemorrhages for BHS with less partial volume effect.

Patients with BHS had higher use of anticoagulants when compared to patients without BHS (37.5% vs 14%, respectively). There are a limited number of studies that included patients with anticoagulant use in BHS literature (5,8,9,11). To our knowledge, there is no report on these studies for comparing anticoagulant use between patients with and without BHS. BHS was proposed to show extravasated fresh plasma on CT scans as a hypoattenuation in the original study (5). Since anticoagulants impair hemostasis, it is reasonable to think that anticoagulant use may be associated with ongoing bleeding at the time of CT scan, hence the higher percentage of BHS.

We could not show a relationship between BHS and poor prognosis in our study. Previous studies showed that BHS is associated with poor prognosis (6,8,22). Small sample size may be the reason for not showing these relationship as in the literature. Our study also showed that BHS is associated with in-hospital mortality and 90-day mortality. These findings were in accordance with the previous study by Li et al.(6).

As for predictors of poor prognosis, we could not show that BHS is an independent predictor of poor prognosis. While two studies pointed out that BHS is an independent predictor of poor prognosis, other studies failed to show this relationship (6,8,9,22,23). Both studies with positive results included Asian patients, and racial disparity may be accused of the different results regarding the prediction of prognosis by BHS. A pooled analysis of the studies with patients from different origins is needed to verify this finding.

The most important aspect of our study is exploring the relationship between BHS and CMBs with MRI. We believe that adding the MRI to the research of hemorrhage expansion markers could shed light on the complex clinical and pathophysiological relationships between these findings. Using 2-mm slice thickness for CT scans was another strength of our study.

Our study had several important limitations. First, the sample size was relatively small. In addition, not all the patients had MRIs to evaluate CMBs, preventing clear conclusions regarding the relationship between BHS and CMBs. Second, we did not have a protocol-based control CT scan in our study. Having a control CT scan at 24 or 48 hours to evaluate hemorrhage expansion could lead to further assessments for CMBs, hemorrhage expansion, and BHS. Another limitation is the excluding patients who underwent surgery from prognosis analysis, which may add selection bias. Finally, pathophysiological mechanisms underlying macrohemorrhages and

microhemorrhages, which were not a part of our study, may be investigated in a further study to gain more insight into this intriguing concept.

In conclusion, our study showed that BHS is associated with higher in-hospital mortality and 90-day mortality consistent with the literature. We should note that CMB numbers were higher in patients without BHS. This result supports the macrohemorrhage vs microhemorrhage concept.

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Ethics

Ethics Committee Approval: The study was approved by University of Health Sciences Bakirkoy Prof. Dr. Mazhar Osman Research and Training Hospital Ethical Committee (Number: 220, Date: 25.09.2018).

Informed Consent: The authors declared that informed consent was obtained from all patients or their relatives for inclusion in the present study.

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