

# Benefits and Risks of CT Angiography Immediately after Emergency Arrival for Patients with Intracerebral Hematoma

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## Abstract

Computed tomography angiography (CTA) immediately after diagnosis of intracerebral hematoma (ICH) on noncontrast CT in the emergency room has benefits, which consist of early diagnosis of secondary ICH and prediction of hematoma growth using the spot sign in primary ICH, but CTA also involves possible risks of acute kidney injury (AKI) and adverse reactions. The purpose of this study was to evaluate the benefits and risks of CTA. A total of 1423 consecutive adult patients diagnosed with ICH who were admitted within 3 days of onset between 2010 and 2017 were retrospectively analyzed. Of 1082 patients undergoing CTA, 162 patients (15.0%) showed secondary ICH, and the sensitivity of CTA for secondary ICH was 95.7%. Of 920 patients with primary ICH, a logistic regression model using the spot sign and four other previously reported risk factors (antiplatelet agents, anticoagulants, interval from onset to arrival, hematoma volume) with an area under the curve (AUC) of 0.787 significantly improved model performance to predict hematoma growth compared with a model using the same four factors without the spot sign (AUC: 0.697) (DeLong's test:  $P = 0.0002$ ). Rates of AKI occurrence were 9.0% and 9.8% in patients with and without CTA, respectively. The odds ratio of AKI in patients with CTA adjusted by reported risk factors was 1.16 (95% confidence interval: 0.72–1.95,  $P = 0.5548$ ). Emergency CTA following noncontrast CT in patients with ICH could be useful for early diagnosis of secondary ICH and prediction of hematoma growth using the spot sign in primary ICH with little risk.

Key words: acute kidney injury, computed tomography angiography, intracerebral hemorrhage, moyamoya disease

## Introduction

Intracerebral hematomas (ICHs) include secondary ICHs caused by various macroscopic pathological lesions that cannot be diagnosed using noncontrast computed tomography (CT). Early diagnosis of underlying vascular abnormalities can affect clinical management and predict prognosis in ICH patients. CT angiography (CTA) is highly sensitive and specific for detecting vascular abnormalities.<sup>1</sup> CTA can also identify patients at high risk of ICH expansion based on the presence of contrast within the hematoma, termed as the spot sign.<sup>1</sup> On the other hand, patients

with acute ICH have a high prevalence of acute kidney injury (AKI) possibly related to pre-existing hypertension and blood pressure-reduction therapy.<sup>2</sup> CTA also has a possible risk of AKI, while the relationship between AKI and CTA in patients with ICHs has never been reported in detail. We have in principle performed CTA immediately after diagnosis of ICH on precontrast CT in the emergency room.

The purpose of this study was to retrospectively evaluate the major benefits of emergency CTA, which are the diagnosis of secondary ICH and the prediction of hematoma growth using the spot sign. The frequencies and sensitivities of each pathological lesion causing secondary ICH were investigated. In primary ICH, improvement of hematoma growth prediction using a logistic regression model with the spot sign compared with a model without the spot sign was verified. Then, the main possible risks of

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emergency CTA, the occurrence of AKI and reactions to contrast media, were clarified.

## Materials and Methods

### Patient population

Consecutive patients with ICH admitted to our hospital between January 2010 and December 2017 were retrospectively assessed. Patients admitted later than 3 days after onset or patients <20 years of age were excluded. This series of patients did not include traumatic ICH cases. Patients with ICH with subarachnoid hemorrhage (SAH) on a CT scan were included, though only SAH without ICH, SAH with intrasylvian hematoma, or SAH with interhemispheric hematoma was excluded. Previously treated lesions were excluded. ICHs from tumors apparent on noncontrast CT scans were also excluded. This study was approved by the Ethics Committee of Tokai University School of Medicine (IRB No. 19R-01).

### Acute phase management of patients with ICHs

Patients presenting with hemorrhagic stroke admitted to our unit routinely underwent their first noncontrast CT scan on arrival, subsequently followed by a CTA study. Final determination about performing CTA was at the discretion of the primary physician. Especially when patients showed a history of renal dysfunction, CTA was not performed by the judgment of the primary physician. Magnetic resonance imaging (MRI) was routinely performed within 2 weeks after admission. Emergency cerebral angiography was performed at the discretion of the primary physician after initial CTA if necessary. After admission, the need for cerebral angiography was determined by a case study meeting. Patients with hemorrhagic stroke had a second CT scan on the day after admission. 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 and to subsequently maintain systolic blood pressure below 140 mmHg for 24 h in the intensive care unit.

### Image acquisition and analysis

The CT protocol was performed on a 40-slice CT (Brilliance; PHILIPS, Best, The Netherlands) or a 128-slice CT (Definition AS; Siemens, Erlangen, Germany). Axial reformats were 5 mm for non-contrast CT. Subsequently, CTA studies were acquired from C4 to the vertex in the helical mode. A non-ionic contrast agent (Iohexol, Omnipaque350, Daiichi Sankyo Co, Tokyo, Japan, or Iomeprol, Iomeron 350, Eisai Co. Tokyo, Japan) of 0.8 mL/kg to a maximum

of 70 mL was injected through an antecubital vein, and a 10-s delay scan was performed. CTA images were reconstituted as 3-mm-thick axial and coronal images and volume rendering (VR) images. Cerebral angiography was used as the reference standard for confirmation of vascular lesion presence when the diagnosis was in doubt or to confirm a diagnosis or before therapeutic intervention. All studies were separately evaluated by neurosurgeons for the presence or absence of abnormal enhanced lesions suggesting secondary ICH or spot signs by simultaneously visualizing noncontrast CT studies cross-linked with coronal and axial CTA reformatted and VR images. 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 accumulation was defined as more than twice the Hounsfield Unit (HU) value of the surrounding hematoma, or a value greater than 120 HU.<sup>3)</sup> A consensus reading by two neurosurgeons (AH, TS) with more than 20 years of experience in their specialties was conducted to resolve any ambiguous findings on CTA images. Hematoma volume was calculated by the ABC/2 method. A secondary ICH was defined as hemorrhage from a macroscopic pathological lesion, and a primary ICH as the others. Hematoma locations were classified as cortical hematoma, including lobar and subcortical hematomas, deep hematoma, including thalamic and putaminal hematomas, and posterior fossa hematoma, including brainstem and cerebellar hematomas. Hematoma enlargement was defined as an increased volume of  $\geq 6$  mL or  $\geq 33\%$ .<sup>3)</sup> Hematoma enlargement was basically determined by comparison of hematoma volume between an initial CT and a CT on the day after admission. Patients undergoing surgery, who deteriorated after admission and showed hematoma enlargement on a second CT within a day of admission, were also included in a hematoma enlargement group.

### Data collection

Clinical data were obtained by chart review. The following data were recorded: patient age and sex, diabetes mellitus (DM), antiplatelet agent use, anticoagulant use, time from symptom onset to emergency department arrival, serum creatinine at arrival, maximum subsequent serum creatinine within 3 days after admission, dialysis before and after admission, and reaction to contrast media. AKI was defined as a 0.5 mg/dL or 25% rise from baseline in serum creatinine within 72 h of CTA, the most frequently used criteria for contrast-induced nephropathy (CIN).<sup>4)</sup> With this definition, when the baseline creatinine was low, a value of a 25% increased creatinine was also within the normal limit,

which could not be interpreted as renal dysfunction. Therefore, the following additional definition was applied: that the maximum follow-up serum creatinine within 78 h was over the normal limit (1.2 mg/dL for males, 1.0 mg/dL for females). DM was defined as a history of previous treatment or HbA1c  $\geq 6.5\%$ . For evaluation of AKI, patients who underwent dialysis before admission, died within a day of admission, or showed early hypotension due to their critical condition were excluded. Reactions to contrast media included persistent vomiting, diffuse urticaria, facial edema, laryngeal edema, and shock.

### Statistical analysis

Univariate analysis was performed using chi-squared analysis for categorical variables and Student's *t*-test for continuous variables. For the prediction of hematoma growth, logistic regression analysis was used. The first prediction model used the five previously reported possible risk factors related to hematoma growth, which were antiplatelet use, anticoagulant use, interval from symptom onset to arrival at the emergency, hematoma volume, and the spot sign (analysis 1).<sup>5)</sup> Then, a second prediction model was developed using four predictors, excluding the spot sign (analysis 2). For verification of improvement in model performance using the spot sign, DeLong's test for two correlated receiver operating characteristic (ROC) curves was performed to show the increase in the area under the curve (AUC) as a method to quantify and test this improvement. To analyze the effect of CTA on renal function, logistic regression analysis was performed for the occurrence of AKI using previously reported possible risk factors related to CIN, which were age, sex, initial serum creatinine, presence of DM, and CTA.<sup>6)</sup> Numerical data are expressed as means  $\pm$  SD. Odds ratios (ORs) are expressed as OR [95% confidence interval (CI)]. Analyses resulting in *P*-values of  $<0.05$  were considered significant. Statistical analyses were performed using JMP 10 (SAS Institute Inc., Cary, NC, USA) for univariate and logistic regression analyses. DeLong's test was performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).<sup>7)</sup>

## Results

Between January 2010 and December 2017, 142 consecutive adult patients diagnosed with ICH and admitted within 3 days of onset were treated. The mean age of these patients was  $67.2 \pm 14.1$  years (median 68 years), 782 patients (55.0%) were male,

and 641 (45.0%) were female. CTA was performed in 1082 patients (76.0%). The mean age of the patients undergoing CTA was  $66.4 \pm 13.8$  years (median 67 years), and 595 patients (55.0%) were male. Clinical factors showing significant differences between the 1082 patients undergoing CTA and the other 341 patients were age ( $66.4 \pm 13.8$  and  $69.9 \pm 14.7$  years) ( $P < 0.0001$ ), interval between onset and arrival ( $5.3 \pm 10.3$  and  $10.2 \pm 15.3$  h) ( $P < 0.0001$ ), initial creatinine level ( $0.94 \pm 1.06$  and  $1.54 \pm 4.95$  mg/dL) ( $P = 0.0002$ ), cortical hematoma [317 (29.3%) and 80 patients (23.5%),  $P = 0.0361$ ], and hematoma volume ( $55.6 \pm 24.3$  and  $42.3 \pm 22.2$  mL,  $P < 0.0001$ ), respectively.

### Diagnosis of secondary ICH

Of the patients undergoing CTA, 162 (15.0%) showed secondary ICH. Table 1 shows the relationships between causes of ICH and the number of patients, interval from onset to arrival, and hematoma locations, as well as the sensitivity of CTA for diagnosis of causative lesions. Causes of secondary ICH with rates of patient numbers  $>1\%$  were cerebral aneurysm (10.0%), arteriovenous malformation (AVM) (1.9%), and moyamoya disease (1.7%). Causes of secondary ICH, which showed intervals from onset to arrival  $>6$  h more frequently, were sinus thrombosis (80%) and tumor (57.1%). Deep hematomas were frequently observed in moyamoya disease (61.1%) and primary ICH (63.5%). In the others, cortical hematomas were found most frequently.

Of the 162 patients with secondary ICH, causative lesions were diagnosed in 155 patients by CTA; therefore, the sensitivity of CTA for the diagnosis of secondary ICH was 95.7%. A small peripheral middle cerebral artery aneurysm was not diagnosed by CTA. In two patients with a small AVM, the nidus was not identified on CTA images, and cerebral angiography confirmed the AVM (Fig. 1A). Three patients with tumors, in whom the tumor was not diagnosed by CTA, showed enhanced lesions indicating the presence of tumors on contrast-enhanced MRI (Fig. 1B). On the other hand, in seven patients, an enhanced focus connecting with a linear enhancement, which led to suspicion of a vascular abnormality, resulted in the spot sign on cerebral angiography (Fig. 1C). Therefore, the specificity of CTA for the diagnosis of secondary ICH was 99.2%.

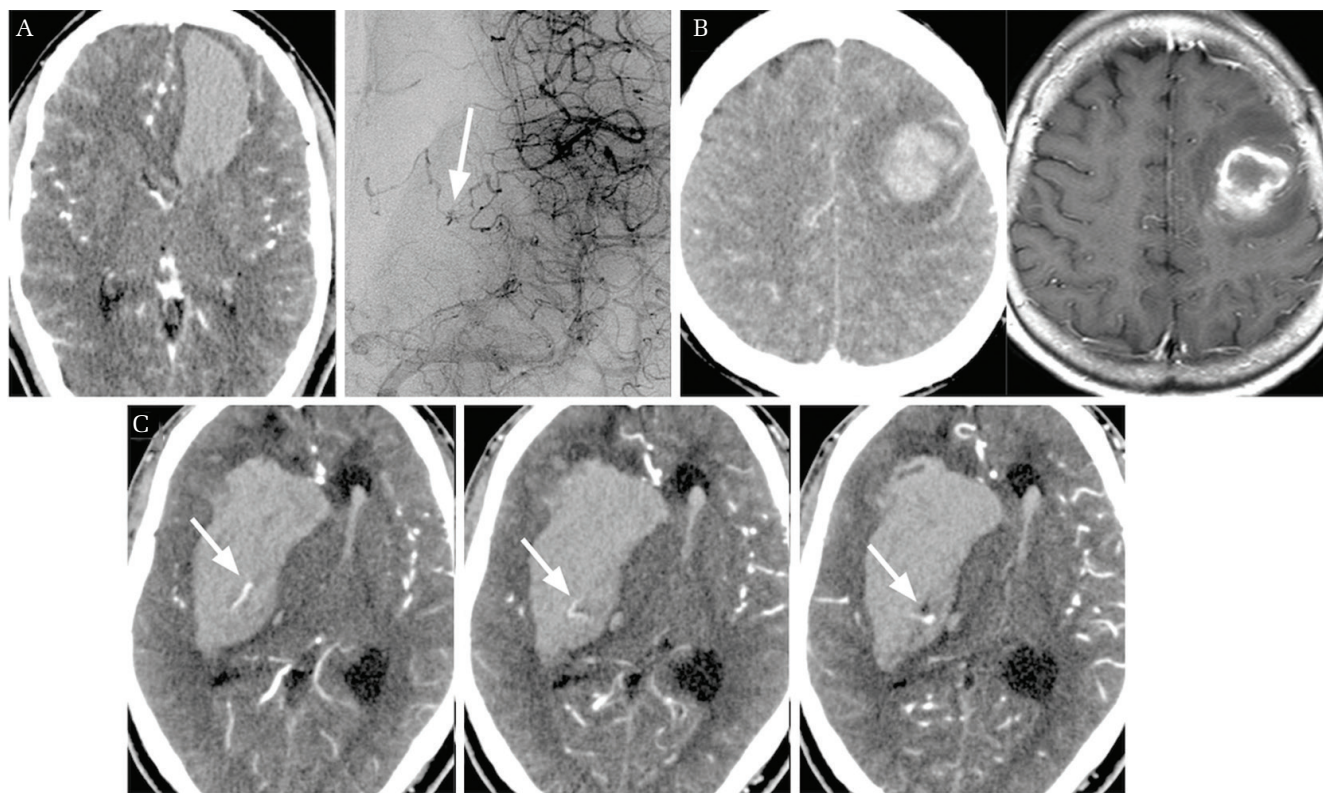
### Spot sign for prediction of hematoma growth in primary ICH

Of 920 patients with primary ICH, 117 (12.7%) showed spot signs on CTA images. Of the 791 patients who underwent follow-up CT, 89 (11.3%) showed hematoma growth. In the 89 hematoma growth

**Table 1** Diagnosis of secondary intracerebral hematoma (ICH), interval from onset to arrival, location of hematoma, and diagnostic sensitivity in 1082 patients who underwent computed tomography angiography

	Number of patients (%)	Arrival ≤6 h from onset (%)	Hematoma location			Diagnosis of secondary ICH (Sensitivity)
			Deep (%)	Cortex (%)	Posterior (%)	
Primary ICH	920 (84.8)	775 (84.2)	584 (63.5)	198 (21.3)	138 (15.2)	n.a.
Aneurysm	108 (10.0)	89 (82.4)	10 (9.3)	93 (86.1)	5 (4.6)	107 (99.1%)
AVM	21 (1.9)	17 (81.0)	4 (19.0)	9 (42.9)	8 (38.1)	19 (90.4%)
Moyamoya disease	18 (1.7)	17 (94.4)	11 (61.1)	7 (38.9)	0	18 (100%)
Tumor	7 (0.6)	3 (42.9)	1 (14.3)	4 (57.1)	2 (28.6)	4 (57.1%)
Sinus thrombosis	5 (0.5)	1 (20)	0	5 (100)	0	5 (100%)
dAVF	3 (0.3)	3 (100)	1 (33.3)	1 (33.3)	1 (33.3)	3 (100%)
DVA	1 (0.1)	1 (100)	0	1 (100)	0	0 (0%)

AVM: arteriovenous malformation, dAVF: dural arteriovenous fistula, DVA: developmental venous anomaly.



**Fig. 1** Representative cases of failure to diagnose intracerebral hematoma (ICH) on computed tomography angiography (CTA). (A) Images of hemorrhage from an arteriovenous malformation (AVM). Left: An axial CTA image showing no apparent abnormal enhancement in a left frontal hematoma. Right: A cerebral angiogram (anterior-posterior view) demonstrating a small AVM (arrow). (B) Images of hemorrhage from a tumor. Left: An axial CTA image showing no abnormal enhancement in a left frontal hematoma. Right: A gadolinium-enhanced T1-weighted magnetic resonance image showing a tumor in the hematoma. (C) An axial computed tomography angiogram image demonstrating an enhanced focus continuing with a linear enhancement (arrows) in a primary ICH. Cerebral angiography (not demonstrated) showed no abnormal vessels, which resulted in this being considered a variety of the spot sign.

patients, 11 patients undergoing emergency hematoma removal, who deteriorated after admission and showed hematoma enlargement on a second CT within a day of admission, were included.

Of the remaining 129 patients without follow-up CT, 88 patients died within the day of admission, and 41 underwent surgery. Table 2 shows relationships between hematoma growth and

**Table 2 Hematoma growth in 920 patients with primary intracerebral hematoma who underwent computed tomography angiography**

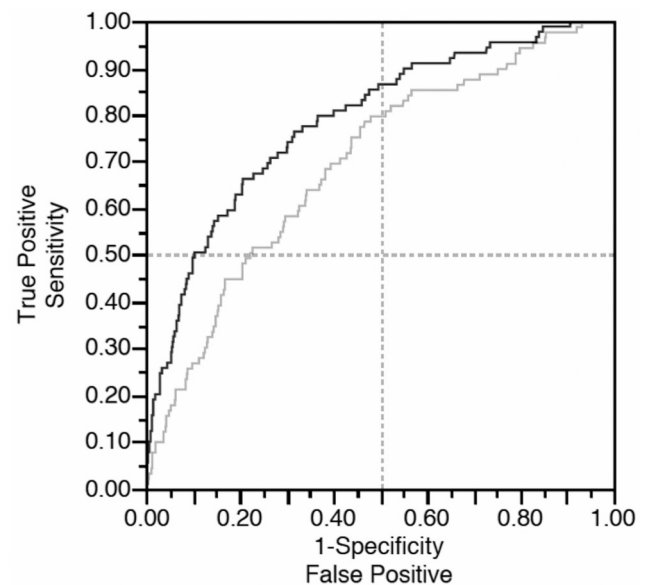
	Hematoma growth		Multivariate analysis 1 <sup>*</sup>		Multivariate analysis 2 <sup>†</sup>	
	Yes (n = 89)	No (n = 702)	P-value	OR (95% CI)	P-value	OR (95% CI)
Antiplatelets	20 (22.5%)	105 (15.0%)	0.2350	1.45 (0.78–2.61)	0.2488	1.40 (0.78–2.42)
Anticoagulants	20 (22.5%)	58 (8.3%)	0.0058	2.5 (1.32–4.76)	0.0004	3.08 (1.69–5.45)
Interval between onset and arrival (h)	2.4 ± 3.9	5.2 ± 9.9	0.0242	0.950* (0.88–0.99)	0.0007	0.93* (0.86–0.98)
Hematoma volume (mL)	59.7 ± 21.6	50.8 ± 22.3	0.1886	1.01* (0.99–1.02)	0.0013	1.02* (1.01–1.03)
Spot sign	45 (50.6%)	72 (10.3%)	<0.0001	6.97 (4.19–11.65)	n.a.	n.a.

<sup>\*</sup>Multivariate analysis 1: analysis using antiplatelets, anticoagulants, interval between onset and arrival, hematoma volume, and the spot sign as independent factors. <sup>†</sup>Multivariate analysis 2: analysis using antiplatelets, anticoagulants, interval between onset and arrival, and hematoma volume as independent factors. \*Unit OR. OR: odds ratio, CI: confidence interval.

antiplatelet use, anticoagulant use, interval from onset to arrival, hematoma volume, and the spot sign. The sensitivity and specificity of the spot sign for predicting hematoma growth were 50.6% and 89.7%, respectively. The results of logistic regression analysis 1, in which antiplatelet use, anticoagulant use, interval from onset to arrival, hematoma volume, and the spot sign were used as independent factors, and analysis 2 using antiplatelet use, anticoagulant use, interval from onset to arrival, and hematoma volume, but not the spot sign, as factors are shown in Table 2. In analysis 1, the OR of the spot sign was 6.97 (4.19–11.65). Figure 2 shows the ROCs curves of analyses 1 and 2. The AUCs of analyses 1 and 2 were 0.787 and 0.697, respectively. DeLong's test for two correlated ROC curves showed a significant increase in the AUC of analysis 1 compared with analysis 2 ( $P = 0.0002$ ).

### Renal function after CTA

Of the 1423 patients with ICHs, 25 patients undergoing dialysis before admission, 80 patients who died within the day of admission, 64 patients who showed early hypotension because of their critical condition, and 16 patients with no follow-up serum creatinine within 3 days of admission were excluded from the evaluation of the occurrence of AKI. Of the remaining 1238 patients, 114 (9.2%) met the definition of AKI. AKI occurred in 86 of 951 patients undergoing CTA (9.0%) and 28 of 287 patients without CTA (9.8%). None of the 114 patients with AKI underwent dialysis during their hospital stay. The results of logistic regression analysis for the occurrence of AKI are shown in Table 3. CTA was not a significant predictor for the development of AKI, with an OR of 1.16 (0.72–1.95,  $P = 0.5548$ ).



**Fig. 2** Receiver operating characteristic (ROC) curves of two logistic regression models in 920 patients with primary intracerebral hematomas (ICHs). Model 1 (*black curve*) uses five previously reported risk factors for hematoma growth: antiplatelet use, anticoagulant use, interval from symptom onset to emergency arrival, hematoma volume, and the spot sign [area under the curve (AUC): 0.787]. The four risk factors without the spot sign are used in model 2 (*gray curve*) (AUC: 0.697). DeLong's test for two correlated ROC curves shows a significant improvement in prediction for hematoma growth with model 1 including the spot sign as a predictor compared with model 2 ( $P = 0.0002$ ).

### Reactions to contrast media

Adverse reactions to the contrast media were found in four of 1085 patients undergoing CTA (0.4%). One patient (0.1%) developed hypotensive shock, which improved soon after administration of adrenalin, and the three others showed transient vomiting. There

**Table 3** Acute kidney injury (AKI) in 1238 patients with intracerebral hematomas

	AKI		Multivariate analysis	
	Yes (n = 114)	No (n = 1124)	P-value	OR (95% CI)
Age (years)	65.6 ± 15.8	67.0 ± 13.8	0.9208	0.99* (0.98–1.01)
Male	87 (76.3%)	577 (51.3%)	0.0006	2.24 (1.41–3.67)
Initial creatinine (mg/dL)	1.26 ± 0.88	0.79 ± 0.40	<0.0001	2.78* (1.96–4.19)
Diabetes mellitus	32 (28.3%)	145 (13.0%)	0.0004	2.41 (1.49–3.81)
CTA	86 (75.4%)	865 (77.0%)	0.5548	1.16 (0.72–1.95)

\*Unit OR. OR: odds ratio, CI: confidence interval, CTA: computed tomography angiography.

were no residual deficits caused by the reaction to the contrast media in all four patients.

## Discussion

In the present study, CTA was performed in more than three-quarters of 1423 consecutive patients with ICH. Reported risk factors for underlying vascular abnormalities in ICH patients are age <65 years, female sex, nonsmoker, lobar ICH, intraventricular extension, and absence of a history of hypertension or coagulopathy.<sup>1,8,9</sup> Previously reported CTA studies of ICH patients used various combinations of these risk factors as inclusion criteria for conducting CTA; therefore, the previously reported rates of CTA performance in the entire group of ICH patients were lower than in the present study.<sup>8–11</sup> The number of patients undergoing CTA, which was 1082 patients in the present study, was also larger than in previous studies, which varied from 96 to 623 patients.<sup>8,12,13</sup>

### Diagnosis of secondary ICH using CTA

Of the 1082 patients who underwent CTA, secondary ICH was found in 162 patients (15.0%), which was compatible with the previously reported secondary ICH rates in CTA series, varying from 13% to 31%.<sup>8,12,13</sup> When the previously mentioned criteria of screening risk factors for CTA are adopted, the rate of secondary ICH should increase, though secondary ICH, which does not meet the criteria, could be misdiagnosed. In the present series, the sensitivity and specificity of CTA for secondary ICH were 95.7% and 99.2%, respectively. A Cochrane review of 11 studies including 927 cases of ICH diagnosed using CTA reported sensitivity of 95% and specificity of 99%,<sup>14</sup> similar to the present results.

The variety and frequency of pathological lesions causing secondary ICH in the present series were similar to the previous reports, except for moyamoya disease, which was the third most common cause of secondary ICH in this Japanese population.<sup>8,12,13</sup> The present study included all ICHs associated with

SAH to avoid elimination of ICH with a small SAH. Therefore, the rate of cerebral aneurysms was 10%, which was higher than in the previous studies.<sup>8,12,13</sup> The sensitivity for the diagnosis of AVM was 90.4% in the present series. False-negative results on CTA have been reported in patients with a small AVM.<sup>15</sup> In regard to false-positive results on CTA, an enhanced focus continuing a linear enhancement in an ICH led to suspicion of a vascular abnormality, including an AVM. Subsequent cerebral angiography, which showed no pathological vessels, clarified that this enhanced lesion was a variety of the spot sign.<sup>16</sup>

### Prediction of hematoma growth in primary ICH using the spot sign

In 920 patients with primary ICH undergoing CTA, the sensitivity and specificity of the spot sign for hematoma growth were 50.6% and 89.7%, respectively, and the OR for hematoma growth in the presence of the spot sign was 6.97 (4.19–11.65). A meta-analysis of 18 studies reported that the presence of the spot sign showed sensitivity of 53%, specificity of 88%, and an OR of 4.70 for hematoma growth,<sup>17</sup> which were compatible with the present results. Another meta-analysis of 77 studies including 5435 cases showed that the spot sign was a predictor, with an OR of 4.46 adjusted by other predictors (antiplatelet use, anticoagulant use, time from onset to imaging, and hematoma volume).<sup>5</sup> In the present study, DeLong's test for two correlated ROC curves showed that a logistic regression model using the spot sign and four other factors, which had an AUC of 0.787, had significantly improved model performance to predict hematoma growth than a model using the same four factors but without the spot sign, with an AUC of 0.697. The spot sign on CTA images was verified to improve the prediction of hematoma growth.

### Adverse events of CTA

In the present study, AKI was found in 9.0% of 951 patients undergoing CTA and in 9.8% of 287 patients without CTA. The OR of AKI occurrence

with CTA adjusted by the four other reported risk factors was 1.16 (0.72–1.95). In a study of 157,140 scans of 53,439 patients with various diseases, the AKI risk was not significantly different between the contrast and noncontrast groups in any risk subgroup after propensity score adjustment using reported risk factors for CIN, with an OR of 0.92 (0.75–1.13,  $P = 0.46$ ).<sup>6)</sup> A meta-analysis of 14 studies including 5727 CTA/CT perfusion (CTP) and 981 noncontrast CT patients of AKI in acute ischemic stroke reported that the overall rate of AKI was 3% (95% CI: 2–4%).<sup>18)</sup> AKI was significantly less common in the CTA/CTP patients than in the noncontrast CT patients, with an OR of 0.47 (0.33–0.68,  $P < 0.01$ ). Hemodialysis rates among the patients with stroke receiving CTA/CTP were exceedingly low, at 0.07%.<sup>18)</sup> In a meta-analysis of AKI following acute stroke including ICH without regard for CTA, four studies of 615,623 ICH subjects showed that the pooled prevalence rate of AKI after ICH during hospital stay was 19.0% (95% CI: 8.3–29.7).<sup>2,19)</sup> The high prevalence of AKI in ICH may be related to the high prevalence of pre-existing arterial hypertension in patients with ICH, blood pressure-lowering treatment immediately after admission, and administration of various drugs after admission.<sup>2)</sup>

The rate of reaction to contrast media in the present study was 0.4%, consisting of hypotensive shock in one patient and transient vomiting in three. According to product information for the contrast media used in this study, rates of adverse reactions and hypotension were 2.2% and 0.2%, respectively. In a retrospective review of 298,491 low-osmolar iodinated intravascular doses, one death (0.0003%) in the study period occurred after administration of contrast media.<sup>20)</sup> In this series, mild symptoms of the adverse reaction occurred less frequently than listed in the product information, because most patients with ICH could not complain of subjective symptoms. Risks of CTA, including AKI and adverse reactions to contrast media, in patients with acute ICH were not high, though attention should be paid to the adverse effects of CTA.

### Limitations

The main limitation of the study is its retrospective nature, which makes it impossible to evaluate all of the variables accurately. In a moribund patient with increased intracranial pressure, vascular abnormalities could not be demonstrated on CTA because of poor cerebral perfusion of contrast medium, and subsequent angiography was seldom performed. Therefore, the rate of secondary ICH could be underestimated. The final decision about performing

CTA was at the discretion of the primary physician in this series. The patients, who did not undergo CTA, significantly showed older age, longer interval between onset and arrival, higher initial creatinine level, less frequent cortical hematoma, and smaller hematoma volume in comparison to the patients undergoing CTA ( $P < 0.05$ ). Thus, the CTA group had some selection biases. Among these clinical factors, age and initial creatinine level, which could affect renal function, were adjusted for evaluation of AKI occurrence. From an individual patient viewpoint, however, a patient, who showed an apparent history of renal dysfunction, did not undergo CTA by the judgment of the primary physician frequently. If CTA had been performed in all the patients with ICHs, a patient with a critical renal function could have developed severe renal failure. Avoidance of CTA might be a secure option in a patient with a history of renal dysfunction. Furthermore, the less frequency of cortical hematomas found in the patients without CTA compared with the patients with CTA possibly led to overrating the secondary ICH ratio in the CTA group.

### Conclusion

In 1082 patients undergoing CTA, approximately one-seventh of the patients showed secondary ICH, and the sensitivity of CTA for secondary ICH was 95.7%. In 920 patients with primary ICH, a logistic regression model using the spot sign and the four previously reported risk factors significantly improved model performance to predict hematoma growth compared with a model using the same four factors without the spot sign ( $P = 0.0002$ ). The OR of AKI in patients with CTA adjusted by the four other reported risk factors was 1.16 (0.72–1.95), with no significant difference in AKI rates between the groups with and without CTA ( $P = 0.5548$ ). Adverse reactions to contrast media, which improved rapidly, occurred in 0.4% of patients undergoing CTA. These results suggest that CTA following noncontrast CT in patients presenting with ICH could be useful for early diagnosis of secondary ICH and prediction of hematoma growth in primary ICH with little risk.

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### Conflicts of Interest Disclosure

All authors have no conflict of interest.

## References

- 1) Hemphill JC, Greenberg SM, Anderson CS, et al.: Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for health-care professionals from the American Heart Association/American Stroke Association. *Stroke* 46: 2032–2060, 2015
- 2) Zorrilla-Vaca A, Ziai W, Connolly ES, Geocadin R, Thompson R, Rivera-Lara L: Acute kidney injury following acute ischemic stroke and intracerebral hemorrhage: a meta-analysis of prevalence rate and mortality risk. *Cerebrovasc Dis* 45: 1–9, 2018
- 3) Demchuk AM, Dowlatshahi D, Rodriguez-Luna D, et al.: 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: 307–314, 2012
- 4) Morcos SK, Thomsen HS, Webb JA: Contrast-media-induced nephrotoxicity: a consensus report. Contrast Media Safety Committee, European Society of Urogenital Radiology (ESUR). *Eur Radiol* 9: 1602–1613, 1999
- 5) Al-Shahi Salman R, Frantzas J, Lee RJ, et al.: Absolute risk and predictors of the growth of acute spontaneous intracerebral haemorrhage: a systematic review and meta-analysis of individual patient data. *Lancet Neurol* 17: 885–894, 2018
- 6) McDonald RJ, McDonald JS, Bida JP, et al.: Intravenous contrast material-induced nephropathy: causal or coincident phenomenon? *Radiology* 267: 106–118, 2013
- 7) Kanda Y: Investigation of the freely available easy-to-use software 'EZ' for medical statistics. *Bone Marrow Transplant* 48: 452–458, 2013
- 8) Bekelis K, Desai A, Zhao W, et al.: Computed tomography angiography: improving diagnostic yield and cost effectiveness in the initial evaluation of spontaneous nonsubarachnoid intracerebral hemorrhage. *J Neurosurg* 117: 761–766, 2012
- 9) Delgado Almandoz JE, Schaefer PW, Forero NP, Falla JR, Gonzalez RG, Romero JM: Diagnostic accuracy and yield of multidetector CT angiography in the evaluation of spontaneous intraparenchymal cerebral hemorrhage. *AJNR Am J Neuroradiol* 30: 1213–1221, 2009
- 10) Yoon DY, Chang SK, Choi CS, Kim WK, Lee JH: Multidetector row CT angiography in spontaneous lobar intracerebral hemorrhage: a prospective comparison with conventional angiography. *AJNR Am J Neuroradiol* 30: 962–967, 2009
- 11) Romero JM, Artunduaga M, Forero NP, et al.: Accuracy of CT angiography for the diagnosis of vascular abnormalities causing intraparenchymal hemorrhage in young patients. *Emerg Radiol* 16: 195–201, 2009
- 12) van Asch CJ, Velthuis BK, Rinkel GJ, et al.: Diagnostic yield and accuracy of CT angiography, MR angiography, and digital subtraction angiography for detection of macrovascular causes of intracerebral haemorrhage: prospective, multicentre cohort study. *BMJ* 351: h5762, 2015
- 13) Hilkens NA, van Asch CJJ, Werring DJ, et al.: Predicting the presence of macrovascular causes in non-traumatic intracerebral haemorrhage: the DIAGRAM prediction score. *J Neurol Neurosurg Psychiatry* 89: 674–679, 2018
- 14) Josephson CB, White PM, Krishan A, Al-Shahi Salman R: Computed tomography angiography or magnetic resonance angiography for detection of intracranial vascular malformations in patients with intracerebral haemorrhage. *Cochrane Database Syst Rev* CD009372, 2014
- 15) Gazzola S, Aviv RI, Gladstone DJ, et al.: Vascular and nonvascular mimics of the CT angiography “spot sign” in patients with secondary intracerebral hemorrhage. *Stroke* 39: 1177–1183, 2008
- 16) Sorimachi T, Osada T, Baba T, et al.: The striate artery, hematoma, and spot sign on coronal images of computed tomography angiography in putaminal intracerebral hemorrhage. *Stroke* 44: 1830–1832, 2013
- 17) Du FZ, Jiang R, Gu M, He C, Guan J: The accuracy of spot sign in predicting hematoma expansion after intracerebral hemorrhage: a systematic review and meta-analysis. *PLoS One* 9: e115777, 2014
- 18) Brinjikji W, Demchuk AM, Murad MH, et al.: Neurons over nephrons: systematic review and meta-analysis of contrast-induced nephropathy in patients with acute stroke. *Stroke* 48: 1862–1868, 2017
- 19) Ansaritoroghi M, Nagaraju SP, Nair RP, et al.: Study on acute kidney injury in patients with spontaneous intracerebral hemorrhage: an overview from a Tertiary Care Hospital in South India. *World Neurosurg* 123: e740–e746, 2019
- 20) Hunt CH, Hartman RP, Hesley GK: Frequency and severity of adverse effects of iodinated and gadolinium contrast materials: retrospective review of 456,930 doses. *AJR Am J Roentgenol* 193: 1124–1127, 2009

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