Contrast Extravasation on Computed Tomography Angiography Predicts Clinical Outcome in Primary Intracerebral Hemorrhage
A Prospective Study of 139 Cases

Na Li, MD*; Yilong Wang, MD, PhD*; Wenjuan Wang, MD; Li Ma, MD; Jing Xue, MD; Karin Weissenborn, MD; Reinhard Dengler, MD; Hans Worthmann, MD; David Z. Wang, DO; Peiyi Gao, MD, PhD; Liping Liu, MD, PhD; Yongjun Wang, MD; Xingquan Zhao, MD, PhD

Background and Purpose—Several retrospective studies suggested that contrast extravasation on CT angiography predicts hematoma expansion, poor outcome, and mortality in primary intracerebral hemorrhage. We aimed to determine the predictive value of contrast extravasation on multidetector CT angiography for clinical outcome in a prospective study.

Methods—In 160 consecutive patients with spontaneous intracerebral hemorrhage admitted within 6 hours of symptom onset, noncontrast CT and multidetector CT angiography were performed on admission. A follow-up noncontrast CT was done at 24 hours. Multidetector CT angiography images were analyzed to identify the presence of contrast extravasation. Clinical outcome was assessed by modified Rankin Scale on discharge and at 90 days.

Results—A total of 139 patients with primary intracerebral hemorrhage were included in the final analysis. Contrast extravasation occurred in 30 (21.6%) patients. The presence of contrast extravasation was associated with increased hematoma expansion ($P<0.0001$), in-hospital mortality ($P=0.008$), prolonged hospital stay ($P=0.006$), poor outcome on discharge ($P=0.025$), increased 3-month mortality ($P=0.009$), and poor clinical outcome ($P<0.0001$). In multivariate analysis, contrast extravasation was a promising independent predictor (OR, 10.5; 95% CI, 3.2–34.7; $P<0.0001$) for 90-day poor clinical outcome followed by the presence of intraventricular hemorrhage (OR, 3.4; 95% CI, 1.5–7.7; $P=0.003$) and initial hematoma volume (OR, 1.0; 95% CI, 1.0–1.1; $P=0.013$).

Conclusions—The presence of contrast extravasation on multidetector CT angiography in patients with hyperacute-stage intracerebral hemorrhage is an independent and strong factor associated with poor outcome. Any patient with intracerebral hemorrhage with such sign on multidetector CT angiography should be monitored intensely and treated accordingly. (Stroke. 2011;42:00-00.)

Key Words: contrast extravasation ■ CT angiography ■ intracerebral hemorrhage ■ hematoma expansion ■ outcome ■ spot sign
Subjects and Methods

Patient Selection
All patients with ICH admitted to the Neurological Department of Beijing Tiantan Hospital from November 2007 to July 2010 were screened for this study. To be eligible for the study, patients with ICH need to meet the following inclusion criteria: (1) diagnosis of primary ICH; (2) age between 18 and 80 years; (3) presentation within 6 hours of symptom onset; and (4) informed consent by patients or relatives. The exclusion criteria were: (1) deep coma (Glasgow Coma Scale 3–5); (2) allergy to contrast medium; (3) a history of renal dysfunction or thyroid disorder; (4) a history of congenital or acquired coagulation disorders; and (5) incompletion of a standard CT protocol including noncontrast CT (NCCT) and MDCTA. The study has been approved by the local ethics board. Patients or relatives provided written informed consent.

Clinical Data
Clinical data of patients with ICH were collected by 2 neurologists blinded to the radiological data during patients’ hospitalization and at the 90-day follow-up. The collected demographic and clinical variables included gender, age, body mass index, alcohol and tobacco use, history of hypertension, diabetes, hyperlipidemia, stroke, coronary heart disease, and medications (antihypertensives, antiplatelet, and anticoagulation agents). The systolic and diastolic blood pressure of patients were recorded. Stroke severity on admission was evaluated by Glasgow Coma Scale and National Institutes of Health Stroke Scale. Laboratory tests on admission included white blood cell count, hemoglobin, platelet count, serum glucose, serum creatinine, fibrinogen, activated partial thromboplastin time, and prothrombin time as expressed by the international normalized ratio. Length of hospital stay was recorded. The patients’ clinical outcome was assessed by modified Rankin Scale on discharge and 90-day follow-up. Poor clinical outcome was defined as modified Rankin Scale >2.

Radiological Data
The CT protocol included NCCT and MDCTA on a 16-slice CT scanner (Somatom Sensation 40; Siemens, Munich, Germany). Imaging was performed as follows: (1) initial and 24-hour follow-up NCCT scans were performed using 5-mm contiguous axial sections from skull base to vertex parallel to the inferior orbitomeatal line. Helical scan parameters were as follows: 120 kVp, 583 mAs, 15 mm collimation, 1 second/rotation, and a table speed of 5 mm/rotation; and (2) MDCTA was performed immediately after initial NCCT performance using a bolus-tracking method by injecting 90 mL of nonionic iodinated contrast (OPTIRAY 350) at 5 mL/s. The protocol for the circle of Willis was 120 kVp, 360 mAs, 0.5 second/rotation, 0.75 mm thick with a pitch of 0.65. Postprocessing procedure including multiplanar reconstruction was performed by a CT technologist at the CT operator’s discretion for assessment of contrast extravasation and exclusion of secondary ICH from etiologies such as aneurysms, vascular malformation, and venous sinus thrombosis. Coronal and sagittal multiplanar reconstructed images were created as 10.0-mm-thick images spaced by 3 mm. Axial reformed images were 4 mm thick with 2-mm spacing. Delayed CTA acquisitions were not performed in our study.

All images were prospectively viewed on PACS workstations independently by 1 neuroradiologist and 1 neurologist blinded to clinical data. The presence of contrast extravasation and spot sign score was determined according to the criteria from a prior study on MDCTA source or reconstructed images (Figure). Inter-rater agreement was evaluated and all differences in reviewer interpretation were resolved by consensus. Time from symptom onset to CTA, hematoma location (supratentorial deep gray matter versus others including lobar and infratentorial locations), and the presence of...
intraventricular hemorrhage (IVH) were recorded. ICH and IVH volumes were obtained by manually drawing a hematoma outline by measurement software made for a Siemens multidetector row scanner. An increase of hematoma volume >33% or >12.5 mL was considered as hematoma expansion.8,13,14

**Statistical Methods**

Statistical analyses were performed using the SPSS statistical package Version 13.0. Patients were classified according to survival versus fatality and good versus poor clinical outcome (modified Rankin Scale 0–2 versus 3–6) on discharge and at 90-day follow-up. The associations of contrast extravasation and spot sign score with clinical outcomes were examined by $\chi^2$ test for categorical variables or Student $t$ test for continuous variables. Univariate analyses were performed for association of demographic, clinical, laboratory, and imaging variables with respect to 90-day clinical outcome. Categorical variables were compared between groups with the $\chi^2$ test for significance. The Student $t$ test or Mann-Whitney $U$ test was used for continuous variables. Receiver operating characteristic curves were generated to assess the discriminative predictive capacity of contrast extravasation and spot sign score. The areas under the receiver operating characteristic curves were calculated and compared. Multivariable analyses with a backward stepwise logistic regression model were performed for determination of independent predictors. Variables were retained in the logistic regression model for $P$$\leq$$0.10$. A value of $P$$<$$0.05$ was considered significant.

**Results**

Altogether, 1041 patients with ICH admitted into our neurological emergency room were screened. Three hundred eighty-eight were present beyond the 6-hour time window. Among the patients who presented within 6 hours after symptom onset, 254 were excluded because of Glasgow Coma Scale $<$$6$, 51 because of age $>$$80$ years or concomitant disorders as mentioned in exclusion criteria, and 188 because of refusal to join the study. A total of 160 patients with spontaneous ICH were enrolled. Fourteen patients were excluded from analysis because they had secondary ICH from aneurysm ($n$=3), vascular malformation ($n$=8), Moyamoya disease ($n$=1), or coagulopathy ($n$=2). Two patients were excluded after hematoma evacuation and 5 were lost to follow-up at 90 days. Therefore, 139 patients with primary ICH ($95$ male and $44$ female) underwent NCCT and MDCTA on admission within 6 hours after symptom onset and were entered into the final analysis. The mean age of the patients was 56 years (median, 55 years; range, 19–80 years). The mean time interval from symptom onset to CTA examination was 3.3 hours (median, 3.0 hours; range, 0.5–7.0 hours). Mean National Institutes of Health Stroke Scale score on admission was 11 (median, 12; range, 0–30). Median Glasgow Coma Scale on admission was 14 (range, 6–15). On the location of ICH, 118 (84.9%) were in deep gray matter, 12 (8.6%) were lobar, and 9 (6.5%) were in infratentorial location. Fifty-two patients (37.4%) had IVH. Median hematoma volume on baseline NCCT was 14.6 mL (range, 0.5–130.0 mL) and median IVH volume was 4.1 mL (range, 0.3–56.4 mL). Hematoma expansion was seen in 32 (23.2%) patients. The mean hospital stay was 22.5 days (median, 21.0 days; range, 1–75 days). Overall, 10 (7.2%) died during hospitalization and 16 (11.5%) at the 90-day follow-up. Poor outcome was seen in 103 (74.1%) patients on discharge and 72 (51.8%) at 90-day follow-up.

**Table 1. Comparison in Outcomes for Patients With ICH With and Without Contrast Extravasation**

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$P$$<$$0.05$ was considered significant.

ICH indicates intracerebral hemorrhage.

**Contrast Extravasation on MDCTA**

Contrast extravasation on MDCTA was observed in 30 (21.6%) patients. The interobserver agreement was congruent ($\kappa$$=0.767$). Patients with contrast extravasation had a shorter time interval from symptom onset to CTA examination (mean, 2.7 hours versus 3.4 hours; $P$$=0.009$). Among 75 patients who presented within 3 hours from stroke onset to MDCTA, 21 (28.0%) showed contrast extravasation. In contrast, the incidence of contrast extravasation was 14.1% in patients who received MDCTA within 3 to 6 hours from symptom onset ($P$$=0.046$). Median baseline hematoma volume was 17.2 mL (mean, 28.8 mL; range, 3.8–130.0 mL) and 13.2 mL (mean, 17.4 mL; range, 0.5–81.0 mL) in patients with and without extravasation ($P$$=0.048$). Contrast extravasation was unrelated to the location of the hematoma and the presence or volume of IVH.

**Contrast Extravasation and Clinical Outcome**

Patients with the presence of contrast extravasation on MDCTA had a significantly higher risk of hematoma expansion (76.7% versus 8.3%, $P$$<0.0001$), significant longer stay in the hospital than patients without contrast extravasation (25.0±17.9 versus 21.7±11.5 days, $P$$=0.006$), and showed a significantly higher mortality and worse clinical outcome (Table 1). Among patients who died during hospitalization, the patients with contrast extravasation lived shorter com-
The spot sign score also predicted hematoma expansion extravasation for clinical outcomes is demonstrated in Table 7.3. Hematoma expansion, no. 7 (10.4%) 25 (34.7%) 0.001*. Contrast extravasation, no. 4 (6.0%) 26 (36.1%) <0.0001*.

The predictive ability of contrast extravasation and spot sign score in relation to hematoma expansion was not significant (P>0.05).

The association of clinical, laboratory, and imaging variables with 90-day outcome is shown in Table 3. The predictors of poor clinical outcome at 90-day follow-up include male gender, Glasgow Coma Scale, platelet count on admission, baseline hematoma volume, baseline extension of IVH, the presence of contrast extravasation on MDCTA, and hematoma expansion. In addition to these predictors, age, baseline volume of IVH, and the time from symptom onset to MDCTA were examined in a multivariate analysis to determine independent variables. As a result, contrast extravasation on MDCTA, hematoma volume, and extension of IVH...
on baseline were independently associated with 90-day clinical outcome (Table 4). The spot sign score also independently predicted poor outcome at 90 days when it was entered into the multivariable analysis (OR, 5.4; 95% CI, 2.0–14.2; P=0.001). The presence of contrast extravasation was an independent indicator of poor clinical outcome at 90 days irrespective of the use of hematoma expansion as a dichotomizing (OR, 10.5; 95% CI, 3.2–34.7; P<0.0001) or a continuous variable (OR, 6.5; 95% CI, 1.8–23.1; P=0.004). Hematoma expansion proved significant predictive value as a continuous (OR, 1.0; 95% CI, 1.0–1.1; P=0.042), but not as a dichotomizing variable (OR, 1.2; 95% CI, 0.3–4.7; P=0.748).

### Discussion

In our prospective study, a standardized CT protocol including NCCT and MDCTA on admission and follow-up NCCT at 24 hours after symptom onset was performed. The sign of contrast extravasation was associated with hematoma expansion and poor clinical outcome represented by longer length of hospital stay, increased mortality, and disability (modified Rankin Scale >2) on discharge and 90-day follow-up. Our findings suggest that contrast extravasation on MDCTA in the hyperacute stage in patients with primary ICH is a crucial predictor of clinical outcome. Although initial hematoma volume and the extension of IVH were significantly related to poor outcome at 90 days, contrast extravasation has been proposed as a potential sign for predicting hematoma expansion, which is an important determinant of mortality and poor clinical outcome. However, the clinical meaning of hematoma expansion and its sufficiency to predict poor outcome and to identify effective hemostatic therapy has been questioned. It was proposed that contrast extravasation might be a feasible marker instead.

Our study examined contrast extravasation simultaneously with hematoma expansion as predictors for clinical outcome and provided the direct evidence that contrast extravasation was an independent predictor of hematoma expansion with poor outcome at 90 days (Table 4). Of note, the absolute growth of hematoma volume was an independent predictor for poor outcome when it was considered as a continuous variable. This reinforced the aforementioned argument.

Our study has some limitations. First, patients with Glasgow Coma Scale 3 to 5 were excluded. Although the rate of in-hospital mortality in this study was lower compared with the retrospective studies, the overall poor clinical outcome at 90-day follow-up was identical to the results of previous studies. Second, the number of cases is still relatively small, although this study had the largest series to date. A prospective study with larger number of cases is needed to confirm the association of contrast extravasation to poor clinical outcomes.

### Conclusions

The presence of contrast extravasation on MDCTA in patients with hyperacute stage ICH is an independent and strong predictor of poor outcome. NCCT and MDCTA in the hyperacute stage may be used as a tool for early stratification of patients with primary ICH into those at high risk of poor clinical outcome and therefore optimize their therapies early. Intensified monitoring and treatment should be provided to patients not only with larger hematoma or presence of IVH, but also those with signs of contrast extravasation.

### Sources of Funding

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### Disclosures

Yilong Wang is the recipient of the Beijing New Star Plan of Science and Technology (No. 2007B047).
References

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CT 혈관조영술에서의 조영제 유출이
일차성 뇌내혈의 임상적 예후를 예측한다

139명의 전향적 연구

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(Stroke. 2011;42:3441-3446.)

Key Words: contrast extravasation □ CT angiography □ intracerebral hemorrhage □ hematoma expansion □ outcome □ spot sign

배경과 목적
여러 후향적 연구들에서 CT 혈관조영술(angiography)에서의 조영제 유출이 일차성 뇌내혈(intracerebral hemorrhage) 환자에서 혈종의 확장, 뚜/Instruction 및 사망률을 예측하는 것으로 제시되었다. 저자들은 임상적 결과에 대한 MDCT (multidetector CT) 혈관조영술에서의 조영제 유출의 예측 가치를 알아보고자 전향적 연구를 진행하였다.

방법
중상 발현 6시간 이내에 내원한 일차성 뇌내혈 환자 160명에서 응급실 비조영 CT와 MDCT 혈관조영술을 시행하였다. 24시간 후 추적 비조영 CT를 시행하였다. 조영제 유출의 유무를 확인하기 위해 MDCT 혈관조영술 영상을 분석하였다. 임상적 결과는 응급실 입원 시와 90일째 mRS로 평가하였다.

결과
총 139명의 일차성 뇌내혈 환자가 최종 분석에 포함되었다. 조영제 유출은 30명(21.6%)에서 발생하였다. 조영제 유출은 혈종의 확장(P<0.0001), 원내 사망(P=0.008), 입원 기간 연장(P=0.006), 응급실에서 발생한 예후(P<0.025), 3개월째 사망률의 증가(P=0.009) 및 뚜/Instruction한 임상적 예후(P<0.0001)와 연관이 있었다. 다변량 분석에서 90일째 뚜/Instruction에 대한 독립적인 예측 인자로 조영제 유출이 가장 유의한 결과를 보였고 (OR, 10.5: 95% CI, 3.2~34.7; P<0.0001), 뇌실내혈(intraventricular hemorrhage) 유무(OR, 3.4: 95% CI, 1.5~7.7; P=0.003) 및 최초 혈종의 부피(OR, 1.0: 95% CI, 1.0~1.1; P=0.013)가 뒤를 이었다.

결론
조급성기 뇌내혈 환자에게 있어 MDCT 혈관조영술에서의 조영제 유출의 존재는 뚜/Instruction과 연관된 독립적이며 강력한 인자이다. MDCT 혈관조영술에서 조영제 유출을 보인 환자들에서는 더욱 집중적인 감시와 이에 따른 치료가 요구된다.
Table 1. Comparison in Outcomes for Patients With ICH With and Without Contrast Extravasation

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P<0.05 was considered significant.
ICH indicates intracerebral hemorrhage.

Table 4. Multivariable Analysis of Predictors of 90-Day Poor Clinical Outcome

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<th>Variables</th>
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<tr>
<td>Male gender</td>
<td>0.495 (0.196–1.253)</td>
<td>0.138</td>
</tr>
<tr>
<td>Age</td>
<td>1.019 (0.983–1.057)</td>
<td>0.296</td>
</tr>
<tr>
<td>GCS</td>
<td>0.876 (0.735–1.045)</td>
<td>0.142</td>
</tr>
<tr>
<td>Platelet count</td>
<td>1.005 (0.998–1.012)</td>
<td>0.166</td>
</tr>
<tr>
<td>Time from symptom onset to MDCTA</td>
<td>0.862 (0.659–1.129)</td>
<td>0.282</td>
</tr>
<tr>
<td>Hematoma expansion</td>
<td>1.244 (0.328–4.723)</td>
<td>0.748</td>
</tr>
<tr>
<td>Intraventricular hemorrhage volume</td>
<td>0.997 (0.944–1.053)</td>
<td>0.912</td>
</tr>
<tr>
<td>Hematoma volume</td>
<td>1.041 (1.009–1.075)</td>
<td>0.013</td>
</tr>
<tr>
<td>Extension of Intraventricular hemorrhage</td>
<td>3.423 (1.514–7.740)</td>
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GCS indicates Glasgow Coma Scale; MDCTA, multidetector CT angiography; OR, odds ratio; CI, confidence interval.
*Multivariable analysis was performed with a backward stepwise logistic regression model. Variables were retained in the logistic regression model for P<0.10, a value of P<0.05 was considered significant.