J Neurol (2012) 259:936–943
DOI 10.1007/s00415-011-6281-9

ORIGINAL COMMUNICATION

Hyperdensity on non-contrast CT immediately after intra-arterial revascularization

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Received: 5 September 2011 / Revised: 1 October 2011 / Accepted: 4 October 2011 / Published online: 21 October 2011

Abstract Non-contrast enhanced computed tomography (NCCT) is usually performed to estimate bleeding complications immediately after procedures. However, hyperdense areas on NCCT have not yet been understood; different interpretations have been reported in the literature. It remains unclear whether NCCT performed immediately after intra-arterial revascularization (IAR) could be useful for predicting hemorrhagic transformation (HT) or clinical outcomes. Therefore, we investigated the diagnostic values of hyperdense areas on NCCT images obtained immediately after IAR. This was a retrospective study of acute ischemic stroke patients who underwent IAR between October 2007 and December 2010. NCCT scans were routinely obtained immediately after IAR and additional follow-up imaging protocols included diffusion weighted imaging (DWI)/gradient echo imaging (GRE) 24 h after IAR. HT was assessed by means of GRE obtained 24 h after IAR. Hounsfield Unit (HU) of the hyperdensity was measured in the manually drawn regions of interest. A total of 68 patients were analyzed in this study. Twenty-nine patients (42.6%) developed HT on follow-up images. Thirty-eight patients had hyperdense areas on NCCT immediately after IAR. Hyperdensity on NCCT performed immediately after IAR revealed 23 (60.5%) of the 38 patients with six false negative areas. NCCT performed immediately after IAR showed a sensitivity of 79.3%, a specificity of 61.5%, a positive predictive value of 60.5% and a negative predictive value of 80% for HT. The HU value was a predictor of HT without statistical significance (area under curve of 0.629; 95% CI: 0.49–0.76; $p = 0.068$). In addition, an HU of >90 poorly predicted HT with a low sensitivity (23%) and a high specificity (94%). In conclusion, our results showed that although hyperdensity on NCCT images obtained immediately after IAR had a moderate predictive value for HT, there were limitations to the prediction of subsequent parenchymal hematoma and symptomatic intracranial hemorrhage, with a low specificity and a low positive predictive value.

Keywords Intra-arterial revascularization · Hyperdensity on NCCT · Extravasation of contrast · Hemorrhagic transformation · Non-contrast computed tomography · Gradient echo imaging

Electronic supplementary material The online version of this article (doi:10.1007/s00415-011-6281-9) contains supplementary material, which is available to authorized users.

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Introduction

Intra-arterial revascularization (IAR), including mechanical thrombectomy, has a high rate of successful recanalization. Patients who undergo successful recanalization by IAR have improved clinical outcomes and survival compared

with those who do not [11]. However, because of the possibility of direct endovascular injury to open vessels, procedure-related complications may sometimes occur, especially intracranial hemorrhage. Non-contrast enhanced computed tomography (NCCT) is usually performed in order to estimate bleeding complications immediately after procedures. Hyperdense areas may frequently be detected on NCCT after IAR, which are considered either hemorrhage or extravasation (or enhancement) of contrast medium. However, such hyperdense areas on NCCT have not yet been understood; different interpretations have been reported in the literature [7]. Yoon et al. [19] described that contrast extravasation is associated with parenchymal hematoma and unfavorable clinical outcomes. They defined contrast extravasation as a hyperdense lesion with a maximum Hounsfield Unit (HU) measurement of >90 that persisted on a 24-h follow-up computed tomography (CT) scan. Therefore, unlike NCCT performed immediately after IAR, only 24-h follow-up CT was able to differentiate among hemorrhage, contrast enhancement and contrast extravasation. It remains unclear whether NCCT performed immediately after IAR could be useful to predict hemorrhagic transformation (HT) or clinical outcomes.

Therefore, we sought to investigate the diagnostic values for prediction of HT of hyperdense areas on NCCT images obtained immediately after IAR. In addition, we investigated characteristics of hyperdensity on NCCT after IAR.

Methods

Subjects

This was a retrospective study of acute ischemic stroke patients who were consecutively admitted to the Cerebrovascular Center at the Chonnam National University Hospital, Gwangju, Korea, between October 2007 and December 2010. Patients were included if they (1) had an acute ischemic stroke within 6 h of symptom onset and (2) underwent emergency IAR. IAR methods included intra-arterial urokinase (IA-UK) administration, mechanical clot disruption (MCD), angioplasty and stenting. We excluded patients with neither follow-up NCCT performed immediately after IAR nor gradient echo (GRE) imaging performed 24 h after IAR. This study was approved by the Institutional Review Board of Chonnam National University Hospital.

Clinical assessment

We prospectively obtained collected demographic and clinical information from the stroke registry at our institution. The following stroke risk factors were identified: (1) hypertension (HTN), (2) diabetes mellitus (DM), (3) atrial fibrillation (AF), (4) dyslipidemia, (5) current smoking defined as cigarette smoking within the last 5 years, (6) a previous history of stroke or transient ischemic attack and (7) coronary artery disease. Stroke pathophysiology was stratified according to the trial of org 10172 in acute stroke treatment (TOAST) criteria after a complete diagnostic workup [2]. We also assessed neurological status at admission and on a daily basis using the National Institutes of Health Stroke Scale (NIHSS) scores. Clinical outcomes were assessed by modified Rankin scale (mRS). Favorable outcomes were defined as scores of 0–2 on the mRS at 90 days. Mortality was defined as death within 3 months of symptoms onset.

Eligible patients who met National Institute of Neurological Disorders and Stroke (NINDS) criteria for intravenous (IV)-recombinant tissue plasminogen activator (rtPA) were treated with 0.9 mg/kg of IV-rtPA [1]. IAR was considered within 1 h of IV-rtPA if patients had (1) no neurologic improvement as determined by an unchanged NIHSS score from baseline or worsening of neurologic deficits, (2) no hemorrhage or mass effect, (3) hyperintensities in less than one-third of the middle cerebral artery (MCA) territory or less than a half of the vertebra-basilar (VB) territories on diffusion-weighted imaging (DWI), (4) major arterial occlusion on magnetic resonance angiography (MRA) and (5) significant ischemic penumbra on perfusion-weighted imaging (PWI) [18]. IAR was performed by using a variety of treatment methods, including low-dose IA-UK, MCD, angioplasty and stent insertion. Some patients underwent all of these treatments simultaneously. Our institution has previously reported these IAR methods [18]. In brief, after demonstration of an arterial occlusion on diagnostic angiography, low-dose urokinase was infused for 3–5 min. In total, <500,000 U of IA-UK was administered over a period of 30–60 min. Mechanical clot disruption was undertaken immediately after 50,000–100,000 U of urokinase was administered. MCD was performed on some patients who were administered low-dose urokinase (<100,000 U). Percutaneous angioplasty with a coronary balloon catheter (Ryujin; Terumo, Tokyo, Japan) was carried out on patients with MCA or distal ICA occlusion. Stents were applied in some patients with carotid or vertebra-basilar occlusion. The duration of IAR was defined as the time lapse from starting time point of a femoral puncture to its completion time point. The duration of NCCT after IAR was defined as the time lapse from the completion time point of an endovascular procedure to the time point where NCCT was performed.

All patients or their relatives gave informed consent before cerebral angiography and IAR.

Imaging analysis

According to our stroke imaging protocol, patients were scheduled to undergo emergency magnetic resonance imaging (MRI) on admission. The MRI protocol included DWI, GRE, fluid-attenuated inversion recovery (FLAIR), PWI and time-of-flight (TOF) MRA. The MRI was acquired with the 1.5 T system (Sigma, GE Medical System, Milwaukee, WI, USA) with echo-planar capabilities. Brain NCCT scans were routinely obtained immediately after IAR and additional follow-up imaging protocols included DWI/GRE 24 h after IAR and DWI/GRE/MRA or CT angiography (CTA) 3–5 days after IAR. NCCT was performed with a 64-detector-row multi-slice spiral unit (Sensation Cardiac 64; Siemens, Erlangen, Germany) using 120 kV, 110 mA, and 5-mm slice thickness. If neurological deterioration occurred, brain CT or DWI/GRE was also performed. Time delay of NCCT immediately after IAR was obtained.

The MRI/MRA and CTA results were assessed by two experienced stroke neurologists (J.-T. K. and M.-S. P.) who were blinded to clinical data. Disagreements of imaging analysis were resolved through a consensus conference. Recanalization status was based on the thrombolysis in myocardial infarction (TIMI) grading system [12]. Recanalization was defined as TIMI grade 2 or 3. HT was assessed by means of GRE obtained 24 h after IAR and GRE or CTA obtained 3–5 days after IAR. HTs were categorized into hemorrhagic infarction (type 1 and 2) and parenchymal hematoma (PH, type 1 and 2), as defined in a previous study [6]. We defined symptomatic intracranial hemorrhage (SICH) according to the definition in the ECASS II trial [6]. HU of the hyperdensity was measured in the manually drawn region of interests on the PACS system (Marotech, Seoul, South Korea). If there were several hyperdensities on NCCT, each HU was separately obtained in each area. The locations of each hyperdensity were also described.

Statistical analysis

Data are presented as mean ± SD or frequencies of categorical variables. The Chi-square test or Fisher's exact test was used to compare categorical variables and the Mann–Whitney *U* test was employed to assess continuous variables in univariate analysis. We reported the sensitivity, specificity, positive and negative predictive values for predicting HT, PH and SICH of the presence of hyperdensity on NCCT obtained immediately after IAR. Multiple logistic regression analysis was used to evaluate the independent predictors of HT using a stepwise logistic regression model, in which entry was set at a univariate association of $p < 0.2$ (supplemental table). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A p value of <0.05 was considered statistically significant. In addition, areas under the receiver operating characteristic (ROC) curve indicated the predictive value of the HU for HT. All statistical analyses were performed using SPSS for Windows (version 13.0, SPSS Inc., Chicago, IL).

Results

General characteristics

A total of 78 patients underwent IAR during the study period. Of those patients, 10 were excluded; four because of incomplete imaging acquisition and six because they underwent only carotid angioplasty and stenting due to severe carotid stenosis. Thus, 68 patients (38 men, 30 women) were analyzed in this study. The mean age of the patients was 64.9 ± 14.43 years; 38 patients had hyperdense areas on NCCT immediately after IAR. Favorable outcomes at 3 months were observed in 30 of the 68 patients.

General characteristics and clinical outcomes in patients with and without hyperdensity on NCCT images obtained immediately after IAR are summarized in Table 1. Baseline clinical variables, including risk factors, occluded arteries and IAR methods, did not differ between the two groups. Baseline NIHSS scores, the frequencies of use of urokinase over 100,000 U and the elapse time of IAR were higher and longer in patients with hyperdensity on NCCT images obtained immediately after IAR, than in those without. Patients who underwent combined IV and IAR more frequently had hyperdensity on NCCT images than those who underwent only IAR, with borderline statistical significance. However, at 3 months, clinical outcome, including mortality, SICH and favorable outcomes, were not significantly different between patients with IAR alone and those with combined IV and IAR.

Hemorrhagic transformation after IAR

Of the 68 patients, 29 (42.6%) developed HT and PH on follow-up images and 58 (85.3%) showed recanalization (TIMI 2 or 3). Of the 38 patients with hyperdensity on NCCT images obtained immediately after IAR, 23 (60.5%) had HT on follow-up images ($p = 0.001$). Sixteen of the 29 patients with HT had PH. Six of the 29 patients with HT had no hyperdensity on the first NCCT images obtained after IAR. Of these six patients, six had subsequent HT which required combined IAR ($p = 061$), five had MCA occlusion ($p = 0.175$), and four had cardioembolism ($p = 0.016$) (Table 2). In patients with no hypodensity on NCCT performed immediately after IAR, radiologic and

Table 1 Comparisons of hyperdensity versus no hyperdensity on NCCT performed immediately after IAR

	No hyperdensity ($n = 30$)	Hyperdensity ($n = 38$)	
Age (years)	65.43 ± 14.49	64.55 ± 14.57	0.805
Male	18 (60.0)	20 (52.6)	0.626
Baseline NIHSS (med, IQR)	12.0 (7.25)	14.5 (6.00)	0.003
IAR methods			
Combined IV+IA	19 (63.3)	32 (84.2)	0.089
IA only	10 (33.3)	6 (15.8)	0.149
MCD	22 (73.3)	32 (84.2)	0.367
Angioplasty	10 (33.3)	14 (36.8)	0.803
Stent	6 (20.0)	7 (18.4)	>0.999
Elapse time to IAR	56.27 ± 14.11	69.24 ± 21.32	0.002
Elapse time to NCCT after IAR	15.20 ± 2.99	15.00 ± 2.99	0.547
Use of IA-urokinase	22 (73.3)	35 (92.1)	0.050
TOAST			0.320
LAD	14 (46.7)	6 (15.8)	
CE	7 (23.3)	21 (55.3)	
UD	9 (30.0)	11 (28.9)	
Risk factors			
HTN	14 (46.7)	18 (47.4)	>0.999
DM	3 (10.0)	8 (21.1)	0.323
Atrial fibrillation	9 (30.0)	19 (50.0)	0.137
Dyslipidemia	5 (16.7)	10 (26.3)	0.391
Smoking	10 (33.3)	16 (42.1)	0.616
Previous stroke	3 (10.0)	1 (2.6)	0.314
CAD	1 (3.3)	2 (5.3)	>0.999
Homocysteinemia	2 (6.7)	2 (5.3)	>0.999
Occluded arteries			
MCA	16 (53.3)	18 (52.9)	0.807
ICA_extracranial	9 (30.0)	11 (28.9)	>0.999
ICA_intracranial	2 (6.7)	5 (13.2)	0.452
Vertebro-basilar	5 (16.7)	7 (18.4)	>0.999
Radiologic outcomes			
Recanalization	24 (80.0)	34 (89.5)	0.318
Hemorrhagic transformation	6 (20.0)	23 (60.5)	0.001
Clinical outcomes			
Early mortality	1 (3.3)	3 (7.9)	0.624
SICH	1 (3.3)	5 (13.2)	0.218
Favorable outcomes at 3 months	11 (36.7)	19 (50.0)	0.330

IAR intra-arterial revascularization, *IV* intravenous, *IA* intra-arterial, *MCD* mechanical clot disruption, *LAD* large artery disease, *CE* cardioembolism, *UD* undetermined, *HTN* hypertension, *DM* diabetes mellitus, *CAD* coronary artery disease, *MCA* middle cerebral artery, *ICA* internal carotid artery, *SICH* symptomatic intracranial hemorrhage

clinical outcomes were not different between those with subsequent HT and those without. The presence of hyperdensity on NCCT performed immediately after IAR had a sensitivity of 79.3%, a specificity of 61.5%, a positive predictive value of 60.5% and a negative predictive value of 80% for HT (Table 2). In addition, it had higher sensitivity and negative predictive value but lower specificity and positive predictive value for PH and SICH (Table 2).

There were a total number of 60 hyperdense areas on NCCT images because some patients had several hyperdense areas on NCCT images. The locations of hyperdensity on NCCT images are summarized in Table 3. There were no significant differences in the location of hyperdensity on NCCT images between patients with HT and those without (Table 4). The mean HU value of hyperdensity on NCCT images was significantly higher in patients with HT on follow-up images than in those without (Fig. 1). However, the HU value was a predictor of HT without statistical significance (AUC of 0.629; 95% CI: 0.49-0.76; $p = 0.068$). In addition, an HU of >90 poorly

Table 2 Diagnostic values of hyperdenisty on NCCT performed immediately after IAR

	NCCT performed immediately after IAR				
	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
HT on FU GRE ($N = 29$)	79.3	61.5	60.5	80.0	69.1
PH-1 and 2 ($N = 16$)	87.5	53.8	36.8	93.3	61.8
SICH ($n = 6$)	83.3	46.8	13.2	96.7	50.0

HT hemorrhagic transformation, *PH* parenchymal hematoma, *SICH* symptomatic intracranial hemorrhage, *PPV* positive predictive value, *NPV* negative predictive value

Table 3 The characteristics of HT with no hyperdensity on NCCT obtained immediately after IAR

	NCCT (−) GRE (+) ($n = 6$)	NCCT (−) GRE (−) ($n = 23$)	*P*
Age in years (mean ± SD)	67.33 ± 10.01	64.95 ± 15.55	>0.999
Male (*n*, %)	2 (33.3)	16 (66.7)	0.184
IAR elapse time	60.83 ± 7.35	55.08 ± 15.30	0.212
NCCT elapse time	15.66 ± 1.96	15.08 ± 3.23	0.813
Baseline NIHSS score	13.0 (7.75)	12.0 (5.75)	0.494
Occluded arteries			
MCA	5 (83.3)	11 (45.8)	0.175
ICA			
Ex_ICA	1 (16.7)	8 (33.3)	0.637
IC_ICA	0	2 (8.3)	>0.999
VBA	0	5 (20.8)	0.553
Combined IAR	6 (100)	13 (54.2)	0.061
The use of UK	5 (83.3)	17 (70.8)	>0.999
TOAST classification			
LAD	2 (33.3)	12 (50.0)	0.657
CE	4 (66.7)	3 (12.5)	0.016
UD	0	9 (37.5)	0.141
Outcomes			
Recanalization	5 (83.3)	19 (79.2)	>0.999
SICH	1 (16.7)	0	0.200
Favorable outcomes	2 (33.3)	9 (37.5)	>0.999
Early mortality	0	1 (4.2)	>0.999

NCCT non-contrast computed tomography, *GRE* gradient echo imaging, *IAR* intra-arterial revascularization, *MCA* middle cerebral artery, *ICA* internal carotid artery, *VBA* vertebro-basilar artery, *UK* urokinase, *LAD* large artery disease, *CE* cardioembolism, *UD* undetermined, *SICH* symptomatic intracranial hemorrhage

predicted HT with a low sensitivity (23%) and high specificity (94%) (Fig. 2).

In univariate analysis, combined IV and IAR (OR 8.437), hyperdensity on NCCT images (OR 6.133), AF (OR 4.745) and cardioembolism (OR 3.606) were significantly associated with HT after IAR ($p < 0.05$). Factors included in multivariable analysis ($p < 0.2$) were hyperdensity on NCCT, combined IV and IAR, use of IA-UK, AF, large artery atherosclerosis, cardioembolism and ICA occlusion. Hyperdensity on NCCT images (OR 5.071; $p = 0.008$), combined IV and IAR (OR 5.597; $p = 0.022$) and AF (OR 3.493; $p = 0.039$) were independently associated with HT in multivariate logistic regression analysis (supplemental table).

Discussion

This study showed that hyperdensity on NCCT immediately after IAR had high sensitivity and negative predictive value but low specificity and positive predictive value for HT, PH and SICH. In addition, the range of HU values varied widely in patients with HT, and the AUC of the ROC curve could show that the HU value was a limited predictor of HT. A previous study has demonstrated that an HU of ≥90 detected on a 24-h follow-up CT scan may represent contrast extravasation and may be associated with PH and unfavorable clinical outcomes [19]. However, in our study, an HU of >90 poorly predicted HT with a low sensitivity (23%) and a high specificity (94%).

Table 4 Location of hyperdensity on NCCT

	Incidence (n, %)* ($N = 60$)	GRE (−) $n = 28$	GRE (+) $n = 32$
Basal ganglia (striatum including caudate)	30 (50.0)	13 (46.4)	17 (53.1)
Caudate only	6 (10.0)	3 (10.7)	3 (9.4)
Corona radiata	4 (6.7)	2 (7.1)	2 (6.3)
Cerebral cortex	14 (23.3)	6 (21.4)	8 (25.0)
Brainstem	6 (23.3)	4 (14.3)	2 (6.3)

* There were no significant differences in the location of hyperdensity on NCCT between patients with HT and those without (Chi-square test or Fisher's exact test were performed)

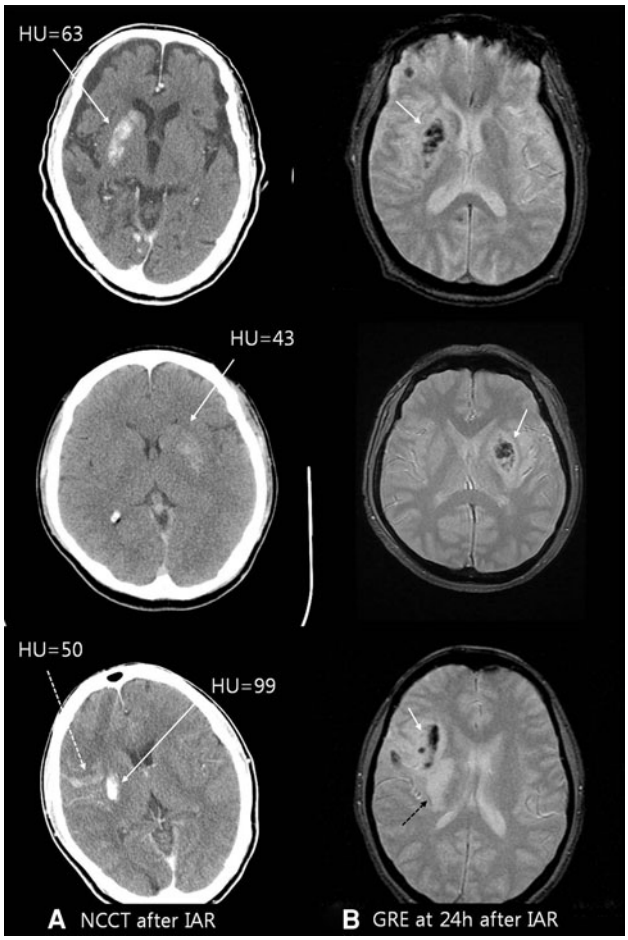

Fig. 1 Hyperdense areas on NCCT images obtained immediately after IAR (**a**) and follow-up GRE images (**b**). These figures show that the range of HU values varies widely in patients with hemorrhagic transformation

Hyperdensity on NCCT images obtained immediately after IAR may be attributed to either contrast extravasation, HT or contrast enhancement. The mechanism of hyperdensity on NCCT images obtained immediately after IAR could be simply speculated to be the result of extravasation of contrast media during angiography [10, 17]. The disruption of the blood–brain barrier (BBB) is considered a major possible explanation for hyperdensity on NCCT images [4, 5]. However, such different origins can only be differentiated through follow-up imaging studies, rather than NCCT images obtained immediately after IAR. The question posed is whether NCCT images obtained immediately after IAR could be used to predict hemorrhages or clinical outcomes after IAR. Hyperdensity on NCCT images obtained immediately after IAR may be independently associated with HT. However, the specificity and positive predictive value of NCCT preformed immediately after IAR were low for PH and SICH (53.8 and 46.8% for specificity; 26.8 and 13.2% for positive predictive value, respectively). These results suggest that patients without subsequent HT, PH and SICH may not be predicted by NCCT performed immediately after IAR. In addition, prediction of PH and SICH based on NCCT performed immediately after IAR may be inaccurate because of a low positive predictive value. Hyperdensity on NCCT performed immediately after IAR could be only helpful to predict HT, PH and SICH in patients with subsequent hemorrhages.

There were no significant differences in the location of hyperdensity on NCCT between patients with HT and those without. In our study, although hyperdensity on NCCT was an independent predictor of HT, it is still unclear whether hyperdensity on NCCT predicts HT, PH and SICH. Further studies are needed to find out better imaging tools for the accurate prediction of HT.

In addition, our study showed that HT and SICH occurred more frequently in patients treated with combined IV and IAR than those treated with IAR alone. Although similar results in patients with HT (or SICH) have been reported in previous studies [9, 13, 20], therapeutic modalities did not affect the functional outcomes in our study. IAR was performed according to the strict protocol of our institution. In particular, small DWI (less than one-third of the hemisphere or half of the posterior circulation) and PWI/DWI mismatch were considered important criteria for IAR. The size of the DWI lesion was previously considered an independent factor determining the risk for SICH [14]. These strict criteria for IAR may have made HT a negligible functional outcome. Therefore, strict indications for IAR might help perform a variety of IAR methods more safely. However, HT might be more related to pharmacological thrombolysis than mechanical thrombolysis. Previous studies have demonstrated that thrombolytic agents, including tPA, aggravate the disruption of BBB and cause HT [8, 16]. In addition, IAR with high doses of UK is associated with a high rate of SICH [3, 15]. In our center, because we performed IAR with low doses of UK [18], the doses of UK that had been administered were not different between patients with HT and those without. Unlike UK dose, combined IV and IAR increased the rate of HT.

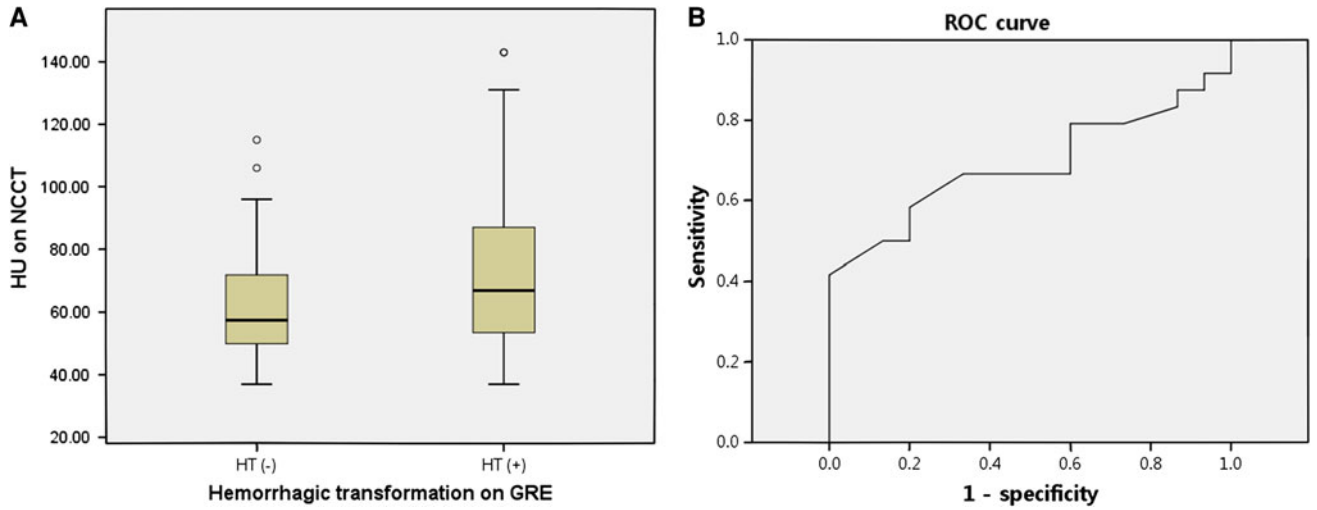

Fig. 2 **a** Hounsfield Unit (HU) of hyperdense area on NCCT images in patients with hemorrhagic transformation and those without ($p = 0.014$). **b** Receiver operating characteristic curves for the predictive value of the HU for HT. The HU value was a predictor of HT without statistical significance (area under curve of 0.629; 95% CI: 0.49–0.76; $p = 0.068$)

The results of this study are subjected to some limitations. First, this is a retrospective study with a small sample size at a single center. Further studies with a larger sample size are needed to confirm our results. Second, HT was defined based on GRE findings obtained at follow-ups, but not immediately after IAR. It seemed likely that same time sequences of GRE and NCCT results obtained at the same time points could predict HT precisely. Furthermore, some patients without hyperdensity on NCCT obtained immediately after IAR developed HT on follow-up images. Third, patients were treated with a variety of IAR methods, including IA-UK and different types of endovascular therapy, so we could only compare the risk for HT between individual combined treatments methods when IVT was concurrently performed.

In conclusion, our results showed that although hyperdensity on NCCT images obtained immediately after IAR had high sensitivity and positive predictive value for HT, PH and SICH, there were limitations to their accurate prediction, with low to moderate specificity and positive predictive value.

Acknowledgments This study was supported by a grant of the Korea Healthcare technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A102065).

Conflict of interest None.

References

1. (1995) Tissue plasminogen activator for acute ischemic stroke. The national institute of neurological disorders and stroke rt-PA stroke study group. N Engl J Med 333:1581–1587
2. Adams HP Jr, Woolson RF, Clarke WR, Davis PH, Bendixen BH, Love BB, Wasek PA, Grimsman KJ (1997) Design of the trial of org 10172 in acute stroke treatment (TOAST). Control Clin Trials 18:358–377
3. Brekenfeld C, Remonda L, Nedeltchev K, Arnold M, Mattle HP, Fischer U, Kappeler L, Schroth G (2007) Symptomatic intracranial haemorrhage after intra-arterial thrombolysis in acute ischaemic stroke: assessment of 294 patients treated with urokinase. J Neurol Neurosurg Psychiatry 78:280–285
4. del Zoppo GJ, Mabuchi T (2003) Cerebral microvessel responses to focal ischemia. J Cereb Blood Flow Metab 23:879–894
5. Dijkhuizen RM, Asahi M, Wu O, Rosen BR, Lo EH (2002) Rapid breakdown of microvascular barriers and subsequent hemorrhagic transformation after delayed recombinant tissue plasminogen activator treatment in a rat embolic stroke model. Stroke 33:2100–2104
6. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, Schneider D, Diez-Tejedor E, Trouillas P (1998) Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian acute stroke study investigators. Lancet 352:1245–1251
7. Jang YM, Lee DH, Kim HS, Ryu CW, Lee JH, Choi CG, Kim SJ, Suh DC (2006) The fate of high-density lesions on the non-contrast CT obtained immediately after intra-arterial thrombolysis in ischemic stroke patients. Korean J Radiol 7:221–228
8. Kastrup A, Groschel K, Ringer TM, Redecker C, Cordesmeyer R, Witte OW, Terborg C (2008) Early disruption of the blood-brain barrier after thrombolytic therapy predicts hemorrhage in patients with acute stroke. Stroke 39:2385–2387
9. Kim JT, Yoon W, Park MS, Nam TS, Choi SM, Lee SH, Kim BC, Kim MK, Cho KH (2009) Early outcome of combined thrombolysis based on the mismatch on perfusion CT. Cerebrovasc Dis 28:259–265
10. Komiyama M, Nishijima Y, Nishio A, Khosla VK (1993) Extravasation of contrast medium from the lenticulostriate artery following local intracarotid fibrinolysis. Surg Neurol 39:315–319
11. Nogueira RG, Liebeskind DS, Sung G, Duckwiler G, Smith WS (2009) Predictors of good clinical outcomes, mortality, and successful revascularization in patients with acute ischemic stroke undergoing thrombectomy: pooled analysis of the mechanical

embolus removal in cerebral ischemia (MERCI) and multi MERCI trials. Stroke 40:3777–3783
12. Sheehan FH, Braunwald E, Canner P, Dodge HT, Gore J, Van Natta P, Passamani ER, Williams DO, Zaret B (1987) The effect of intravenous thrombolytic therapy on left ventricular function: a report on tissue-type plasminogen activator and streptokinase from the thrombolysis in myocardial infarction (TIMI Phase I) trial. Circulation 75:817–829
13. Singer OC, Berkefeld J, Lorenz MW, Fiehler J, Albers GW, Lansberg MG, Kastrup A, Rovira A, Liebeskind DS, Gass A, Rosso C, Derex L, Kim JS, Neumann-Haefelin T (2009) Risk of symptomatic intracerebral hemorrhage in patients treated with intra-arterial thrombolysis. Cerebrovasc Dis 27:368–374
14. Singer OC, Humpich MC, Fiehler J, Albers GW, Lansberg MG, Kastrup A, Rovira A, Liebeskind DS, Gass A, Rosso C, Derex L, Kim JS, Neumann-Haefelin T (2008) Risk for symptomatic intracerebral hemorrhage after thrombolysis assessed by diffusion-weighted magnetic resonance imaging. Ann Neurol 63:52–60
15. Vora NA, Gupta R, Thomas AJ, Horowitz MB, Tayal AH, Hammer MD, Uchino K, Wechsler LR, Jovin TG (2007) Factors predicting hemorrhagic complications after multimodal reperfusion therapy for acute ischemic stroke. AJNR Am J Neuroradiol 28:1391–1394
16. Wang X, Tsuji K, Lee SR, Ning M, Furie KL, Buchan AM, Lo EH (2004) Mechanisms of hemorrhagic transformation after tissue plasminogen activator reperfusion therapy for ischemic stroke. Stroke 35:2726–2730
17. Wildenhain SL, Jungreis CA, Barr J, Mathis J, Wechsler L, Horton JA (1994) CT after intracranial intraarterial thrombolysis for acute stroke. AJNR Am J Neuroradiol 15:487–492
18. Yoon W, Park MS, Cho KH (2010) Low-dose intra-arterial urokinase and aggressive mechanical clot disruption for acute ischemic stroke after failure of intravenous thrombolysis. AJNR Am J Neuroradiol 31:161–164
19. Yoon W, Seo JJ, Kim JK, Cho KH, Park JG, Kang HK (2004) Contrast enhancement and contrast extravasation on computed tomography after intra-arterial thrombolysis in patients with acute ischemic stroke. Stroke 35:876–881
20. Zaidat OO, Suarez JI, Santillan C, Sunshine JL, Tarr RW, Paras VH, Selman WR, Landis DM (2002) Response to intra-arterial and combined intravenous and intra-arterial thrombolytic therapy in patients with distal internal carotid artery occlusion. Stroke 33:1821–1826