Journal of the Neurological Sciences 396 (2019) 219–224

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Hypodensities detected at 1.5–3 h after intracerebral hemorrhage better predicts secondary neurological deterioration

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ARTICLE INFO

Keywords:
Intracerebral hemorrhage
Secondary neurological deterioration
Time period
Hypodensities
Noncontrast computed tomography

ABSTRACT

Background: Secondary neurological deterioration in patients with spontaneous intracerebral hemorrhage (sICH) develops within the first 24 or 48 h after ICH onset and appears to portend a poor prognosis. We aimed to verify whether hypodensities within an acute ICH detected by noncontrast computed tomography (NCCT) were able to predict secondary neurological deterioration and investigate which monitoring window was of the highest predictive value.

Materials/methods: This study involved sICH patients from three clinical centers of Fudan University between October 1, 2016 and March 31, 2018. Logistic regression analysis was used to assess the association between hypodensities and secondary neurological deterioration. The receiver operating characteristic curve of the subjects was performed to evaluate the critical value of the detection time window of hypodensities that best predicted the secondary neurological injury. Then, we divided the detection time window of hypodensities into 0–1.5 h, 1.5–3 h, 3–4.5 h and 4.5–6 h, and calculated the sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and accuracy respectively.

Results: A total of 240 ICH patients met the inclusion criteria, 97 (40.42%) of whom were observed secondary neurological deterioration. Hypodensities were positive in 113 patients (47.08%), and more common in patients with secondary neurological deterioration (76.25%). The multivariate logistic regression analysis demonstrated that infratentorial hemorrhage ($P < .001$), the baseline hematoma volume ($P = .015$), and the presence of hypodensities on admission CT scan ($P < .001$) were independent predictors of secondary neurological deterioration. The sensitivity, specificity, PPV, and NPV of hypodensities in predicting secondary neurological deterioration were 76.3%, 72.7%, 65.5%, and 81.9%, respectively. When the time to the baseline NCCT was 114.5 min, the hypodensities were of the highest predictive value. Besides, the risk of secondary neurological deterioration predicted by hypodensities detected during 1.5–3.0 h was higher than other time periods.

Conclusions: Hypodensities within hematoma detected by an NCCT scan may predict secondary neurological deterioration, independent of other clinical and imaging predictors. Hypodensities detected at 1.5–3.0 h after ICH onset have better predictive efficacy.

1. Introduction

Spontaneous intracerebral hemorrhage (sICH) is a severe type of stroke with high morbidity and mortality throughout the world, which accounts for approximately 15% of all strokes worldwide [1–3]. Several studies have investigated early neurological deterioration in patients with ICH, which develops within the first 24 or 48 h after symptom onset, and appears to portend a poor prognosis [4].

Hematoma expansion, which often occurs within 6 h after ICH onset, is closely associated with early deterioration and poor outcomes [5]. The definition of hematoma expansion varies in different literature. Some studies define hematoma expansion as a proportional increase of 33% or an absolute increase of > 6 mL [6]. In addition, it is also defined as an increase of hematoma volume > 33% or absolute > 12.5 mL from initial CT scan in the large clinical trial such as INTERACT 1 and rFVIIa ICH trail [3,7]. The computed tomography angiography (CTA) spot sign is a well-established imaging marker that independently predicts secondary neurological deterioration in patients with sICH [8].

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https://doi.org/10.1016/j.jns.2018.11.032
Received 22 July 2018; Received in revised form 1 November 2018; Accepted 26 November 2018
Available online 28 November 2018
0022-510X/

However, early CTA examination requires contrast administration and is contraindicated in patients with several renal function impairment [9]. Therefore, the markers detected by noncontrast CT (NCCT) scan as possible imaging predictors for secondary neurological deterioration are identified. The swirl sign is described as region(s) of hypoattenuation or isoattenuation (compared to the attenuation of brain parenchyma) within the hyperattenuated ICH [10]. But actually, swirl sign is not well-defined in a global context, so it is hard to make a unified definition in different medical institutions. The blend sign on NCCT, which represents the blending of the hypoattenuating area and the hyperattenuating region with a clear margin, has been introduced as a predictor for hematoma expansion [11]. Blend sign can be used to predict secondary neurological deterioration as well [7]. Nevertheless, it also has drawbacks such as hyposensitivity. Meanwhile, the definition based on CT attenuation values (Hounsfield units, HU) makes it difficult to identify just from a single CT film. Hypodensities, which have been accepted as reliable tools for predicting hematoma expansion in ICH patients [12], are much easier to identify in NCCT. In addition, it has been hinted that hypodensities are associated with 90-day poor outcome in patients with sICH [13].

To predict secondary neurological deterioration and offer the patients proper treatments in time, we aimed to investigate the relationship between hypodensities and secondary neurological deterioration. Moreover, we also made a comprehensive evaluation of the best predictive time period at which hypodensities were detected.

2. Materials and methods

This study involved sICH patients aged 18 years or older between October 1, 2016 and March 31, 2018 from three clinical centers of Fudan University: Huanshan Hospital, Zhongshan Hospital and Jinshan Hospital. In this prospective study, patients were eligible for the study providing the baseline NCCT scan was performed within 6 h after sICH onset. The exclusion criteria included secondary ICH (cerebral aneurysm, moyamoya syndrome, arteriovenous malformation, tumor, or hemorrhagic transformation from brain infarction), primary intraventricular hemorrhage (IVH), and baseline ICH volume < 1 ml. All patients or their next-of-kin gave their informed consent prior to inclusion in this study. This study was approved by the Ethics Committee of Fudan University. All study protocol and procedure were conducted in accordance with the Helsinki Declaration of 1975.

Hypodensities were defined as the hypodense regions within the hematoma, irrespective of their specific patterns [12]. There were mainly 4 types of hypodensities, empirically defined based on the distinctness of their margins and their relative density (Fig. 1). Hypodensities connected to the outer surface of the hematoma were excluded to avoid partial volume errors.

The demographic data, history of diabetes mellitus, hypertension, cigarette smoking, and alcohol consumption were recorded. The location of the hematoma, presence of IVH, hematoma volume (ABC/2 formula) [14], international normalized ratio (INR) and Glasgow Coma Scale (GCS) score, and time to the baseline NCCT were also documented. As to secondary neurological deterioration, we defined [1] early hemicraniectomy understandardized criteria according to our in-house guidelines or [2] secondary decrease of GCS of > 3 points, both within the first 48 h after symptom onset [8].

2.1. Statistical analysis

All statistical data were analyzed with SPSS 22.0. Data for continuous variables are presented as means (standard deviations [SDs]) or medians (interquartile ranges [IQRs]) when appropriate and compared with two-tailed Student *t*-test or Mann-Whitney *U* test. Categorical variables are expressed as a percentage and compared with χ [2] test or Fisher exact test (2-tailed). *P* values < .05 were indicative of statistical significance. Independent association between CT hypodensities and significant secondary neurological deterioration was evaluated by using multivariable logistic regression. We used Cohen κ interagreement test as agreement statistics (interrater and intrarater reliability) for judgment of the presence of NCCT hypodensities. The receiver operating characteristic (ROC) analysis was performed to determine the optimal time of hypodensities detection to the baseline NCCT for predicting secondary neurological deterioration. The data of groups differentiated by baseline CT time were also compared with area under the curve (AUC) by ROC analysis. The sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV) and accuracy of each time period in predicting secondary neurological deterioration were well calculated.

3. Results

3.1. Baseline characteristics

43 of 283 patients with primary ICH were excluded (time to baseline NCCT > 6 h: 7; inclusion disapproval: 13; secondary ICH: 6; primary IVH: 8; and baseline ICH volume < 1 ml: 9). A total of 240 patients (male: 179, female: 61) met the inclusion criteria, 97 (40.42%) of whom were found secondary neurological deterioration. The mean age of the patients was 62.9 ± 11.5 years (age range, 25–90 years). The median (IQR) of baseline hematoma volume was 22.25(4.43–27.78) ml. The median (IQR) of time to baseline CT scan was 163.37 (87.25–235.75) minutes from the onset of symptoms. The baseline hematoma was located in basal ganglia (73.3%), cerebral lobes (18.3%) and infratentorial brain (8.3%). IVH was found in 29.6% of the patients. The baseline clinical and radiological variables of patients with and without CT hypodensities were compared and listed in Table 1. No statistical differences between patients with CT hypodensities or not ($P > .1$) were observed in the following variables: age, sex, history of hypertension, diabetes mellitus, smoking history, alcohol consumption, INR, and time to the baseline NCCT.

3.2. Prevalence and interobserver agreement of hypodensities

In this study, all of the hypodense regions within the hematoma were included as hypodensities, irrespective of their specific patterns (mainly be divided into 4 types). Of the total 240 patients who met the inclusion criteria, 127 were detected with no hypodensities. Hypodensities were positive in 113 patients (47.1%) and more common in patients with secondary neurological deterioration (76.3%). Interobserver agreement for identifying hypodensities was excellent between the 2 readers (κ = 0.875).

3.3. Univariate and multivariate analysis of the variables in secondary neurological deterioration prediction

The baseline clinical characteristics of patients with and without significant secondary neurological deterioration were listed in Table 2. Patients with secondary neurological deterioration had a lower median (IQR) GCS score [14.0 [12–15] vs 15.0 [13–15], $P = .015$], a larger percentage of IVH ($P = .020$), and a significantly larger median (IQR) baseline hematoma volume [36.3 (17.8–74.2) vs 12.7 (5.6–25.0), $P < .001$] than those without secondary neurological deterioration. In addition, hypodensities were more common in patients with secondary neurological deterioration (76.3% vs 27.3%).

By univariate logistic analysis, infratentorial hemorrhage, baseline hematoma volume, GCS score, presence of IVH, and hypodensities on admission CT scan were noticed a statistically association with secondary neurological deterioration. Infratentorial hemorrhage ($P < .001$), the baseline hematoma volume ($P = .015$), and the presence of hypodensities on admission CT scan ($P < .001$) remained statistically significant in multivariate model (Table 3).

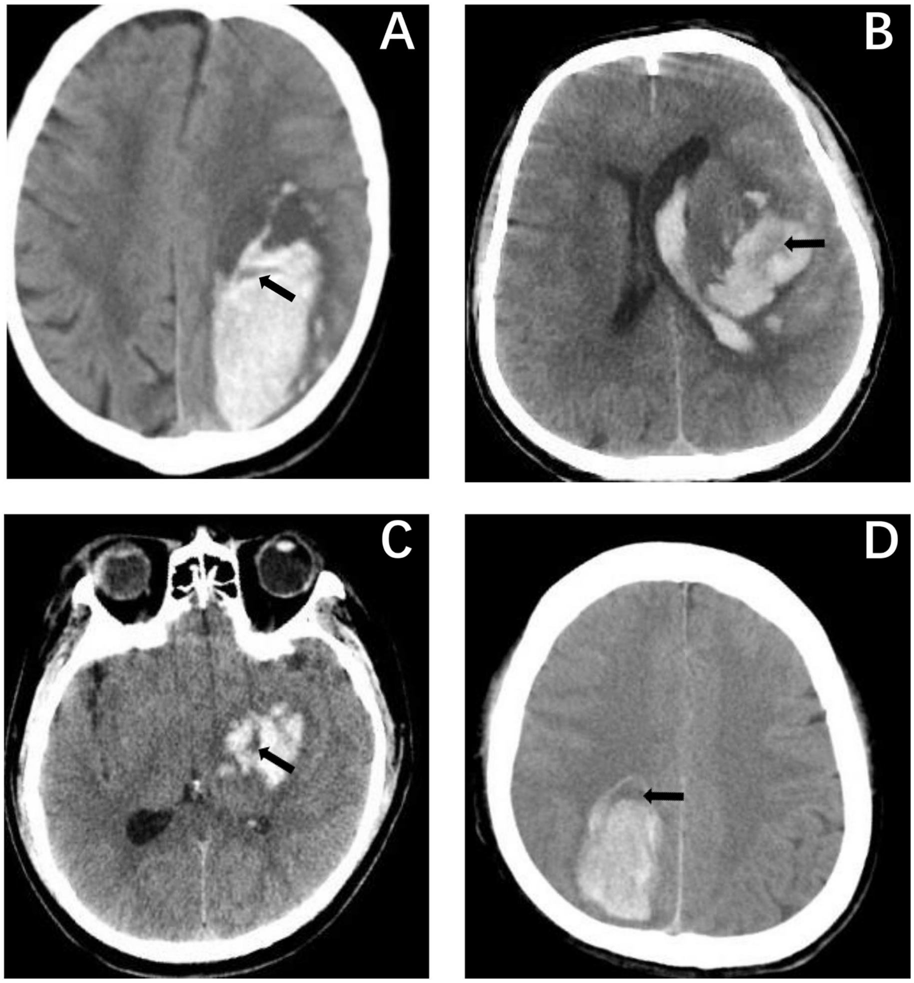

Fig. 1. Illustrative examples of hypodensities.

Table 1
The association between the occurrence of hypodensities and different clinical and radiological characteristics.

Characteristics	Hypodensities positive (n = 113)	Hypodensities negative (n = 127)	P value
Age, y, mean (SD)	62.7 (11.5)	62.9 (11.4)	0.890
Sex, male (%)	85 (75.2)	94 (74.0)	0.831
Hypertension (%)	76 (67.3)	86 (67.7)	0.940
Diabetes mellitus (%)	15 (13.3)	19 (14.9)	0.710
Smoking (%)	19 (16.8)	31 (24.4)	0.146
Alcohol consumption (%)	13 (11.5)	15 (11.8)	0.941
Time to the baseline NCCT, median (IQR)	137.0 (85.5–207.5)	138.0 (85.0–210.0)	0.897
Hematoma location			
Basal ganglia (%)	85 (75.2)	91 (71.7)	0.535
Cerebral lobes (%)	23 (20.3)	21 (16.5)	0.447
Infratentorial hemorrhage (%)	5 (4.4)	15 (11.8)	0.034
INR, median (IQR)	1.2 (1.0–2.3)	1.0 (1.0–2.0)	0.625
GCS, median (IQR)	14 (11–15)	15 (15–15)	< 0.001
IVH (%)	43 (38.1)	28 (22.1)	0.007
Baseline hematoma volume (ml), median (IQR)	26.0 (11.1–51.6)	4.9 (2.0–8.6)	< 0.001

Abbreviations: SD, standard deviation; IQR,interquartile range; NCCT, non-contrast computed tomography; GCS, Glasgow Coma Scale; INR, international normalized ratio; IVH, intraventricular hemorrhage.

Table 2
Comparison of baseline clinical and radiological characteristics between intracerebral hemorrhage patients with and without secondary deterioration.

Characteristics	Secondary deterioration (n = 97)	No deterioration (n = 143)	P value
Age, y, mean (SD)	61.3 (11.0)	63.9 (11.7)	0.081
Sex, male (%)	75 (77.3)	104 (72.7)	0.425
Hypertension (%)	64 (65.9)	98(65.7)	0.680
Diabetes mellitus (%)	16 (16.5)	18 (12.6)	0.396
Smoking (%)	21(21.7)	29 (20.2)	0.799
Alcohol consumption (%)	11 (11.3)	17 (11.9)	0.897
Time to the baseline NCCT (min), median (IQR)	139.0 (88.5–211.5)	128.0 (82.0–207.0)	0.311
Hematoma location			
Basal ganglia (%)	67 (69.1)	109 (76.2)	0.228
Cerebral lobes (%)	17 (17.5)	27 (18.9)	0.791
Infratentorial hemorrhage (%)	13 (13.4)	7 (4.9)	0.032
INR, median (IQR)	1.2 (1.0–2.2)	1.1 (1.0–2.0)	0.856
GCS, median (IQR)	14 (12–15)	15 (13–15)	0.015
IVH (%)	37 (35.1)	34 (25.9)	0.020
Baseline hematoma volume (ml), median (IQR)	36.3 (17.8–74.2)	12.7 (5.6–25.0)	< 0.001
Hypodensities (%)	74(76.3)	39(27.3)	< 0.001

Abbreviations: SD, standard deviation; IQR,interquartile range;NCCT, non-contrast computed tomography; GCS, Glasgow Coma Scale; INR, international normalized ratio; IVH, intraventricular hemorrhage.

Table 3
Multivariate analysis of the predictors for secondary deterioration.

Variables	Odds Ratio	95% Confidence Interval	P value
Infratentorial hemorrhage	8.050	2.682–24.162	< 0.001
GCS	0.908	0.758–1.087	0.291
IVH	1.146	0.570–2.306	0.702
Baseline hematoma volume	1.017	1.003–1.031	0.015
Hypodensities	7.883	3.665–16.954	< 0.001

Abbreviations: NCCT, noncontrast computed tomography; GCS, Glasgow Coma Scale; INR, international normalized ratio; IVH, intraventricular hemorrhage.

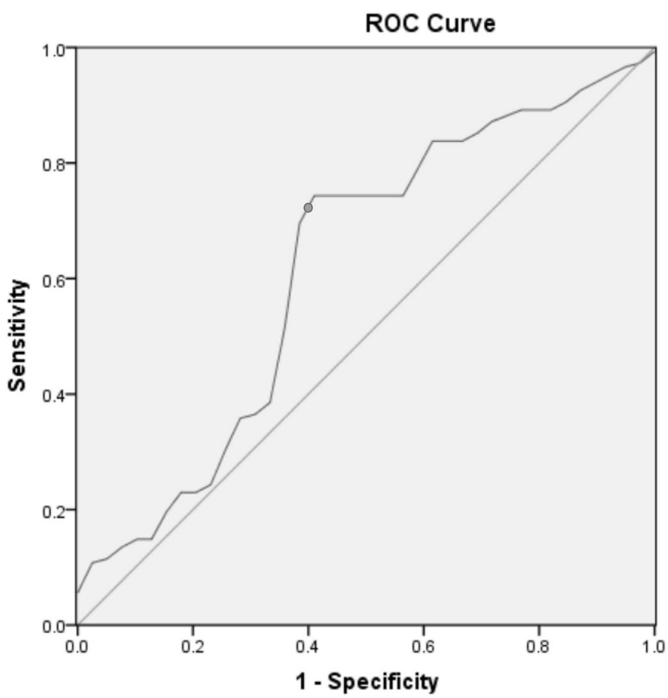

Fig. 2. Receiver operating characteristic curve. The cut-off point was marked as a black spot in the figure.

3.4. ROC Analysis for determining the Optimal Time to Baseline CT Scan

To determine the optimal cut-off time of hypodensities to baseline CT scan, we performed ROC analysis (Fig. 2). The AUC of ROC was 0.620 with *P* value of 0.036 and 95% confidence interval (CI) of 0.574–0.747. The optimal time to baseline CT scan for predicting secondary neurological deterioration was 114.5 min with the sensitivity, specificity and Youden index of 74.3%, 61.5% and 0.358, respectively. Therefore, the optimal baseline CT scan time of 114.5 min after ICH onset can best reflect the possibility of secondary neurological deterioration.

3.5. The sensitivity, specificity, PPV, NPV, and accuracy of hypodensities to predict secondary neurological deterioration

For further study, we divided the time periods into 0–1.5 h, 1.5–3 h, 3–4.5 h and 4.5–6 h, and well calculated the sensitivity, specificity, PPV, NPV, and accuracy to find out the optimal time period of hypodensities detection to predict secondary neurological deterioration. The sensitivity, specificity, PPV, NPV, and accuracy of hypodensities in predicting secondary neurological deterioration were 76.3%, 72.7%, 65.5%, 81.9%, 74.2%, respectively. After the calculation, we found hypodensities detection in 1.5–3 h displayed a higher sensitivity, specificity, PPV, NPV, and accuracy (81.6%, 75.0%, 70.5%, 84.8%, and 77.8%). We further demonstrated that the above diagnostic parameters were higher than other time periods (0–1.5 h and 3–4.5 h) (Table 4). Correspondingly, ROC analysis showed that AUC of 1.5–3 h (0.783, 95% CI: 0.637–0.882) was also larger than that of other periods (0.722, 95% CI: 0.684–0.806) (Fig. 3). Importantly, the cut-off of 114.5 min obtained by ROC curve was just in this time period, suggesting the consistency of the two analyses.

Table 4
Comparison of sensitivity, specificity, PPV, NPV, and accuracy among different time period of hypodensities in predicting secondary deterioration.

Time period		Sensitivity	Specificity	PPV	NPV	Accuracy
1.5–3.0 h (*n* = 90)		81.6%	75.0%	70.5%	84.8%	77.8%
Other time periods	0–1.5 h (*n* = 66)	69.2%	70.0%	60.0%	77.8%	69.7%
	3.0–4.5 h (*n* = 63)	80.9%	73.8%	60.7%	88.5%	76.2%
	4.5–6.0 h (*n* = 21)	66.7%	66.7%	72.7%	60.0%	66.7%
	Sum (*n* = 150)	72.9%	71.4%	62.3%	80.2%	72.0%
Total (*n* = 240)		76.3%	72.7%	65.5%	81.9%	74.2%

Abbreviations: PPV indicates positive predictive value; NPV, negative predictive value.

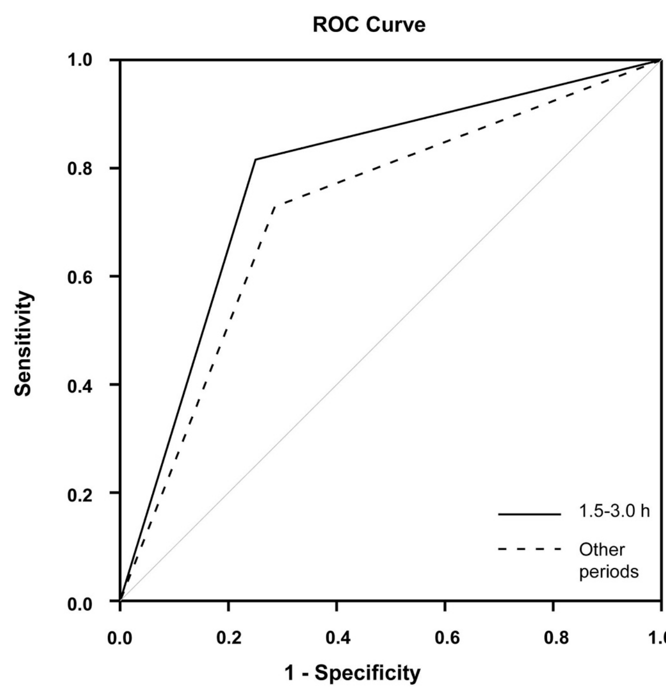

Fig. 3. Receiver operating characteristic curve. It was showed that AUC of 1.5–3 h (0.783, 95% CI: 0.637–0.882) was larger than that of other periods (0.722, 95% CI: 0.684–0.806).

4. Discussion

sICH remains a serious condition with a 30-day mortality of approximately 40%, half of which occurs within the first 48 h [15]. Patients with sICH may have any level of neurological deficit at the time of hematoma formation, ranging from none through to complete motor and sensory paraplegia. As to secondary neurological deterioration, we defined [1] early hemi-craniectomy under standardized criteria according to our in-house guidelines or [2] secondary decrease of GCS of > 3 points, both within the first 48 h after symptom onset [8]. Secondary neurological deterioration is usually bound up with poor prognosis of ICH patients, therefore early prediction and aggressive care is crucial in order to enhance the survival rate and survival quality of the patients.

Previous studies have suggested that many factors are associated with secondary neurological deterioration, including hematoma expansion, IVH extension, fever, elevated white blood cell count, and higher blood pressure [16-19]. In addition, many imaging features detected by CTA or NCCT are also regarded as prediction tools of secondary neurological deterioration, such as spot sign [8], blend sign [8], and swirl sign [20]. However, these signs have limitations in predicting secondary neurological deterioration. Early CTA examination requires contrast administration and is contraindicated in patients with severe renal function impairment. Meanwhile, CTA is not so popularized in the emergency rooms especially in the basic medical institutions of developing countries [9]. In addition, swirl sign has not been well-defined in a global context. The definition of blend sign based on CT attenuation values (HU) makes it difficult to identify just by a single CT film from other hospital.

Hypodensities are strictly defined and easy to identify compared with the above signs, which have been used in predicting hematoma expansion and 90-day prognosis in previous study [12,13]. However, no study has explored the relationship between hypodensities and secondary neurological deterioration till now. We performed this study to develop a new clinical prediction tool of secondary neurological deterioration using only NCCT image and simply measurable variables. Fortunately, we found hypodensities within an acute ICH detected by an NCCT scan may well predict secondary neurological deterioration, and has obvious advantages compared with the previous imaging prediction tools. Our data indicated hypodensities are not only easy to obtain and identify, but also with a higher sensitivity (76.3%).

In our clinical practice, there are some severe sICH patients who undergo several CT scans within the first 6 h after ICH onset. An interesting phenomenon is observed that sometimes hypodensities are not detected by NCCT in the super-early stage after admission, but may be detected in later time (1.5–3 h). Meanwhile, sometimes hypodensities detected in 1.5–3 h may disappear in 4.5–6.0 h. This phenomenon inspired us that the emergence and disappearance of hypodensities had certain time phase property. As reported previously, different emerging time of CTA spot sign may lead to different efficacy in predicting hematoma expansion, eg. delayed CTA scan and multiphase CTA spot sign [21,22]. Meanwhile, the CT attention value of hematoma always changes dynamically in early stage of ICH [23]. Paralleled with the above findings, we speculated that the time phase property of hypodensities was closely related with hematoma expansion and secondary deterioration. However, in routine treatment, a sICH patient usually undergoes one CT scan with the first 6 h, which restricted us to obtain the exact time point that the hypodensities emerge and how long the hypodensities persist. We then considered how to change the way of thinking to study the monitoring window of hypodensities. Thus we performed ROC analysis to examine the relation between the detection time of hypodensities and the presence of secondary deterioration (Fig. 2). The AUC of ROC was 0.620 with P value of 0.036, which indicated that it was of certain accuracy to predict secondary deterioration using the detection time of hypodensities. As the detection time of hypodensities is easily available, we considered using it to represent the time phase property of hypodensities. For further study, we divided the time periods into 0–1.5 h, 1.5–3 h, 3–4.5 h and 4.5–6 h, and found that hypodensities detected at 1.5–3.0 h after ICH onset had better predictive efficacy. Meanwhile, the cut-off point of 114.5 min obtained by ROC just fell in this period. In order to analyze this issue deeply, we compared hypodensities detected in 1.5–3 h with 0–1.5 h and 3–4.5 h, and discovered that the former showed a higher sensitivity and specificity. ROC curve showed that AUC of 1.5–3 h (0.783, 95% CI: 0.637–0.882) was also larger than that of other periods (0.722, 95% CI: 0.684–0.806). Although there is no relevant research at present, we speculate the mechanism may involve the pathophysiology of hematoma formation. At this stage, anyhow, these data suggest that there is a trend in the 240 ICH patients we studied, that is, detection of hypodensities during 1.5–3.0 h can better predict secondary deterioration. It is necessary to enlarge the sample size to confirm the rationality of the phenomenon and further study also required for explore the involved mechanisms.

So far, there has been no study working on the optimal detecting time of a certain NCCT imaging feature. Predicting secondary neurological deterioration by the time course of hypodensities in ICH patients ought to be of clinical value as an predictive index for poor prognosis, which may lead to effective treatment for ICH at the most appropriate time. Hypodensities detected at 1.5–3 h after ICH onset should be given heightened alertness by the clinicians to avoid secondary neurological deterioration developing in patients. In the previous studies, most clinical scientists found no evidence that patients with NCCT markers including hypodensities specifically benefit from intensive blood pressure reduction [24]. The results of our study indicate that patients may benefit from intensive blood pressure reduction providing that hypodensities are detected at 1.5–3 h.

The study has several limitations. The sample size is relatively small. Meanwhile, although the optimal time 1.5–3 h in our work led to the optimized sensitivity, specificity, PPV, NPV and accuracy, the cut-off time may be changed supposing the increase of sample size. Moreover, correlation of hypodensities with the CTA spot sign has not been analyzed.

5. Conclusions

Hypodensities within hematoma detected by an NCCT scan may predict secondary neurological deterioration, independent of other clinical and imaging predictors. Hypodensities detected at 1.5–3.0 h after ICH onset have better predictive efficacy.

Funding

This research was supported by grants from the National Natural Science Foundation of China (grant number 81500998); and Science and Technology Commission of Shanghai Municipality (grant number 16140903200).

Competing interests

None declared.

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