The Cognitive Impairment At Acute Stage After Intracerebral Hemorrhage

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Abstract

**Background:** We determined the frequency and factors of cognitive impairment at acute stage and investigate the prognostic effect of the cognitive function at acute stage on the delayed cognitive impairment after acute intracerebral hemorrhage (ICH).

**Methods:** A total of 208 patients with acute ICH were enrolled from January 2017 to February 2019. Cognitive function was assessed during the acute stage and follow-up after ICH using Montreal Cognitive Assessment (MoCA) score. The significant acute stage and delayed cognitive impairment was defined as a MoCA score <20 within 1 week after hospital admission and during follow-up respectively.

**Results:** During a mean 20 (IQR 17-23) months follow-up, 185 patients with follow-up cognitive function data. There are 89 (42.8%) and 86 (46.5%) patients had acute stage and delayed significant cognitive impairment respectively. The older age, large baseline hematoma volume, more severe ICH, and low level of education were significant associated with significant cognitive impairment at acute stage (all P<0.009). In the multivariable logistic regression model, the low acute phase MoCA score (odds ratio [OR] 0.59; 95% confidence interval [CI] 0.48-0.71; P<0.001) was the only one independent factor associated with delayed significant cognitive impairment after ICH.

**Conclusions:** Near half of patients have significant cognitive impairment at acute stage after ICH, which is more frequent in the elderly, those with large baseline hematoma volume, and more severe initial neurological deficit. The acute phase MoCA score was independent increased the risk of delayed cognitive impairment.

Introduction

Intracerebral hemorrhage (ICH) is well recognized as a serious type of stroke with high risk of premature mortality and morbidity [1, 2]. Post-stroke cognitive impairment is common in the survivors and is reported to associated with poor prognosis [3-5].

The rate of cognitive impairment or dementia after ICH was higher than those with ischemic stroke [5-12]. A recently meta-analysis of 11 studies shown the prevalence of cognitive impairment ranged from 14 to 88% after ICH for different definition and follow-up period [10]. And most of these studies was focus on the long-term cognitive impairment after ICH. However, data on early cognitive impairment, especially at acute stage, after ICH is limited [11, 12]. A more recently study of 141 ICH patients indicated 75.2% patients had cognitive impairment during 2 weeks after ICH onset [11]. Meanwhile, the characteristics and the factors of cognitive impairment at acute stage after ICH were unclear. Additional, whether the cognitive function at acute stage will affecting the long-term cognitive impairment after ICH was not investigated.

Herein, in this study, we assess the frequency and factors of cognitive impairment at acute stage after ICH. Moreover, we investigate the predict effect of cognitive function at acute stage on the long-term
cognitive impairment after ICH.

Methods

Study participants

We prospectively identified acute ICH patients from the Second Affiliated Hospital of Soochow University in China from January 2017 to February 2019. Briefly, patients with computerized tomography (CT) confirmed ICH from onset to admission were potentially eligible for the study. After excluding patients with trauma, brain tumor, hemorrhagic transformation of ischemic stroke, and vascular cerebral malformations, a total of 372 potentially eligible participants were enrolled. Additional exclusion criteria were as follows: 1) time from onset to admission over 5 days (n=8); 2) Pre-existent cognitive impairment, defined with the short Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) ≥ 53 [13] (n=19); 3) Communication problem or limb paralysis and other reasons could not finish the cognitive function assessment (n=122); and 4) loss of follow-up (n=15) measurements. 208 patients with available data were finally included in this study. (Supplementary Figure 1)

Data Collection

Demographic characteristics, lifestyle risk factors, medical history, clinical laboratory tests were collected at the time of enrollment. Trained neurologists assessed the baseline stroke severity using the National Institutes of Health Stroke Scale (NIHSS). Baseline imaging data including hematoma volume, hematoma location, intraventricular extension was assessed by two neuroradiologists who were blinded to the clinical data according to baseline head CT scan. And the hematoma volume was assessed using the formula ABC/2 method [14]. Using a standard mercury sphygmomanometer, blood pressure (BP) measurements were performed in the supine position for admission. Blood samples were collected at hospital admission or within 24 hours after hospital admission.

Cognitive function assessment and outcomes

The median follow-up was 20 (interquartile ranges [IQC] 17-23) months. The cognitive function was assessment using Montreal Cognitive Assessment (MoCA) score at acute phase (within 1 week after hospital admission) and follow-up by trained staff. The significant cognitive impairment at acute stage was defined as a MoCA score <20 within 1 week after hospital admission. And the delayed significant cognitive impairment was defined as a MoCA score <20 during the follow-up [15, 16].

Statistical analysis

Baseline characteristics of patients were summarized by means and SD for normally distributed variables, medians and interquartile ranges (IQR) for skewed continuous variable, and numbers (%) for categorical variables. Between-group comparisons were made using independent Student’s t test was performed for continuous variables with a normal distribution. Wilcoxon rank-sum test was used for those with skewed distributions and chi-square tests for categorical variables.
Crude and multivariable logistic regression was used to determine the factors association with acute stage and delayed significant cognitive impairment. All the variables with $p < 0.2$ in the univariate analysis were included in multivariable analyses. To assess the effect of cognitive function at acute stage on the delayed significant cognitive impairment, two multivariable logistic regression models were used, including and not including cognitive function at acute stage in the model. Data are reported as odds ratios (ORs) with 95% confidence interval (CIs). C-statistics (areas under receiver operating characteristic [ROC] curves) was used to assess the discriminatory ability of acute phase cognitive function on the delayed cognitive impairment. Pearson correlation was used to investigate the association between acute phase cognitive function and delayed function.

All $P$ values were 2-tailed, and a significance level of 0.05 was used. All analyses were conducted using the SPSS version 17.0 statistical software (SPSS Inc., Chicago, IL, USA).

**Results**

Complete data on cognitive function data were available for 208 acute ICH patients (148 men and 60 women). The mean age of the participants was $60.5 \pm 13.6$ years (range from 26 to 92 years). During a mean follow-up time point of 20 (interquartile ranges [IQC] 17-23) months, we identified 23 deaths from all causes and 185 patients with follow-up cognitive function data. There are 89 (42.8%) and 86 (46.5%) patients had acute stage and delayed significant cognitive impairment respectively, whose MoCA score $<20$. The table 1 shown the baseline characteristics of acute ICH patients with and without significant cognitive impairment at acute stage. Compare to patients without significant cognitive impairment at acute stage, those with acute stage significant cognitive impairment were more likely to be older and female, with low baseline diastolic BP. Patients with acute stage significant cognitive impairment were also had severity stroke (high NIHSS score) and large hematoma volume. Compare to patients without delayed significant cognitive impairment, those with delayed significant cognitive impairment were more likely to be older and female, with low baseline diastolic BP, higher baseline NIHSS score and large hematoma volume. Moreover, patients with delayed significant cognitive impairment have a higher odd of early cognitive impairment (Supplementary Table 1).

The table 2 shown the characteristics of cognitive impairment at acute stage based on seven cognitive domains in MoCA score. We noted all the ICH patients at acute stage at least with one cognitive domain impairment. Most impairment domains were memory recall (100%), visuospatial and executive function (95.2%), attention (75.5%) and orientation (69.7%).

The multivariable logistic regression shown older age (OR 1.05; 95% CI 1.02-1.08), large baseline hematoma volume (OR 1.07; 95% CI 1.02-1.13), high baseline NIHSS score (OR 1.16; 95% CI 1.04-1.30) and low level of education (OR 3.50; 95% CI 2.17-5.65) were associated with significant cognitive impairment at acute stage after ICH (table 3).

The multivariable logistic regression shown older age (OR 1.07; 95% CI 1.03-1.10), large baseline hematoma volume (OR 1.09; 95% CI 1.03-1.16), high baseline NIHSS score (OR 1.26; 95% CI 1.10-1.44),
labor location (OR 3.61; 95% CI 1.30-10.00) and low level of education (OR 2.98; 95% CI 1.78-4.99) were associated with delayed significant cognitive impairment after ICH (table 4). While after add acute phase MoCA score in the multivariable logistic regression model, we found only low acute phase MoCA score (OR 0.59; 95% CI 0.48-0.71) was significant associated with increased risk of delayed significant cognitive impairment after ICH (table 4).

Pearson correlation indicated significant positive association between acute phase MoCA score and follow-up MoCA score in Figure 1 (R=0.929). And the ROC curves and C-statistic demonstrated the acute phase MoCA (AUC=0.947, 95% CI 0.917-0.978) score was significant predict the delayed significant cognitive impairment after ICH in Figure 2.

Discussion

In present study of 208 ICH patients observed the cognitive impairment in the acute phase after ICH and its predictor effect on the long-term cognitive function. We found all the patients with one or more cognitive domains impairment and nearly 50% patients with significant cognitive impairment in the first week after hospital admission among ICH patients and the independent factors associated with cognitive impairment in acute phase was older age, large baseline hematoma volume, more severe ICH, and low level of education. Moreover, the cognitive function in the acute phase was strongly independent associated with delay cognitive impairment after ICH.

Previous studies [5–12] have indicated the frequency of cognitive impairment after ICH was high and a study from France of 20 patients with cerebral amyloid angiopathy (CAA) -related lobar ICH, 20 with deep ICH shown 87.5% patients with cognitive impairment during a median 4 months follow-up after ICH [7]. Most of these studies were focus on the long-term cognitive impairment after ICH. Data of cognitive impairment at acute phase after ICH were limited [11, 12, 17]. Recently, a study from China found 106 patients with cognitive impairment defined by MoCA score <26 in the first two weeks among 141 acute ICH patients [11]. Nakase, et al study demonstrated nearly 20% of patients with new cognitive impairment at hospital discharge among 306 ICH patients according to the criteria of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [17]. Another studies from UK of 187 ICH patients noted 84% and 65% patients with at least one or in two or more cognitive domain impairment at the 12 days after ICH [12]. In our studies, we found all the patients have one or more cognitive domain impairment and 42.8% patients with significant cognitive impairment defined with MoCA score <26 in the first week after hospital admission. Our finding was consisted with other studies that there was a high rate of cognitive impairment in the acute phase among ICH [11, 12, 17]. The different rate of cognitive impairment at acute phase may due to the criteria of cognitive impairment, the assess time of cognitive function, the race and sample size.

In our study, the memory recall, visuospatial and executive function, attention and orientation were the most common domain impairment at acute stage. Our finding was consisted with Banerjee, et al study that deficits in non-verbal IQ, information processing speed and executive functions were common in the
first two weeks after ICH [12]. The features of cognitive domain impairment at acute stage after ICH needs further studies with large patients to confirm.

The factors associated with cognitive impairment at acute phase were not well studied. The study by Nakase, et al shown the baseline white blood cell (WBC) count, C-reactive protein (CRP) and NIHSS score were higher among patients with cognitive impairment [17]. Another study from China indicated dominant-hemisphere hemorrhage, admission systolic BP, abnormal red blood cell (RBC), high mean corpuscular volume (MCV) was independent with the cognitive impairment at early stage [11]. In our study, we found older age, large baseline hematoma volume, more severe ICH, and low level of education were the factors associated with cognitive impairment. While, no significant association between the serum biomarkers and cognitive impairment were found in our study. The different findings partly relate to the difference in the important baseline characteristics such as hematoma volume, NIHSS score, the different confounders in the model.

Whether the cognitive function in the acute phase was affect the delayed cognitive impairment was uncertain. The data from a recently study indicated 64% patients have cognitive impairment in the first two weeks were still with cognitive impairment during 6 months follow-up [11]. In our study, we noted older age, large baseline hematoma volume, high baseline NIHSS score, labor location and low level of education were significant associated with delayed significant cognitive impairment after ICH if the acute phase MoCA score was not in the model, which was consisted with previous studies findings [5–9, 18]. After the acute phase MoCA score add in the model, we found the acute phase MoCA score was the only one independent factor predicts the delayed significant cognitive impairment after ICH. Moreover, the significant relationship between MoCA score at acute phase and during follow-up was seen suggest we should pay more addition to the cognitive impairment in the acute phase.

The strengths of this study including a long-term follow-up and investigate the association between cognitive impairment at acute phase and in the long-term follow-up. However, the study has several limitations. Firstly, the number of patients was small and from one hospital. Secondly, a significant proportion of patients were excluded for loss of follow-up, which may also contribute to selection bias. Thirdly, the cerebral small-vessel disease (CSVD) on MRI scan was reported to associated with cognitive domain impairment after ICH [8], we were unable to evaluate the prognostic effect of CSVD on the cognitive impairment due to lack of relevant data.

Conclusions

In summary, our study has shown each patient had one or more cognitive domains impairment and half of the patients with significant cognitive impairment in the first week after hospital admission in patients with acute ICH. The cognitive function in the acute phase was significantly increased the risk of delay cognitive impairment after ICH. Our findings suggest should assess the cognitive function in the acute phase among ICH patients.
Declarations

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Authors’ contributions

SJY, HH, and YJC contributed to the concept and rationale for the study. SJY and CG were responsible for the first draft; SJY and JYW contributed statistical analyses. CG, WZ, JPX, and JL performed the data collection; HH and YJC for the first revision; All authors read and approved the final manuscript.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article. Some or all data or models generated or used during the study are available from the corresponding author by request.

Ethics approval and consent to participate

We obey the principles of the 1983 Declaration of Helsinki and this study was approved by the Ethics Committee of the Second Affiliated Hospital of Soochow University. Informed consent was obtained from all participants. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication

Not applicable

Competing interests

The authors declare no competing interests

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Tables

Table 1. Baseline characteristics of patients with and without significant cognitive impairment at acute stage after ICH
| Characteristics                     | MoCA≥20 (N= 119) | MoCA<20 (N=89) | P-value |
|------------------------------------|------------------|---------------|---------|
| Age, y                             | 57.2±14.0        | 64.8±11.9     | <0.001  |
| Female                             | 24 (20.2)        | 36 (40.4)     | 0.001   |
| Current smoking                    | 38 (31.9)        | 21 (23.6)     | 0.187   |
| Alcohol consumption                | 18 (15.1)        | 11 (12.4)     | 0.569   |
| Clinical features                  |                  |               |         |
| Time from onset to hospital, h     | 10.0 (4.0–22.5)  | 8.0 (4.0–12.0)| 0.095   |
| Baseline systolic BP, mm Hg        | 164.8±26.3       | 161.3±24.5    | 0.322   |
| Baseline diastolic BP, mm Hg       | 96.0±16.3        | 90.1±15.4     | 0.008   |
| Baseline NIHSS score               | 2.0 (0.0–4.0)    | 3.0 (1.0–8.0) | 0.010   |
| Medical history                    |                  |               |         |
| History of hypertension            | 89 (74.8)        | 64 (71.9)     | 0.641   |
| History of diabetes mellitus       | 10 (8.4)         | 9 (10.1)      | 0.672   |
| History of ICH                     | 8 (6.7)          | 7 (7.9)       | 0.753   |
| History of ischemic stroke         | 12 (10.1)        | 8 (9.0)       | 0.791   |
| Medication history                 |                  |               |         |
| Antihypertensive therapy           | 39 (32.8)        | 37 (41.6)     | 0.192   |
| CT findings                        |                  |               |         |
| Hematoma volume (mL)               | 5.0 (3.0–8.0)    | 10.0 (4.0–15.0)| <0.001  |
| Intraventricular extension         | 31 (21.6)        | 33 (37.1)     | 0.088   |
| Left side of hematoma              | 49 (41.2)        | 39 (43.8)     | 0.703   |
| Lobar hematoma location            | 30 (25.2)        | 31 (34.8)     | 0.132   |
| Laboratory test                    |                  |               |         |
| WBC, 10⁹/L                         | 7.7 (5.8–10.3)   | 8.1 (6.2–9.9) | 0.656   |
| Neutrophil, 10⁹/L                  | 5.9 (4.0–7.9)    | 6.3 (4.2–8.1) | 0.456   |
| Lymphocyte, 10⁹/L                  | 1.3 (0.9–1.7)    | 1.2 (0.9–1.6) | 0.164   |
| FPG, mmol/L                        | 5.4 (4.7–6.1)    | 5.4 (4.9–6.1) | 0.512   |
| CRP, mg/L                          | 5.5 (5.3–5.9)    | 5.6 (5.4–6.1) | 0.232   |
| Parameter   | Mean ± SD or Median (IQR) | p-value |
|-------------|---------------------------|---------|
| TC, mmol/L  | 4.7 (4.1–5.2)             | 4.5 (3.9–5.1) | 0.311 |
| LDL-C, mmol/L | 3.0 (2.3–3.4)         | 2.7 (2.2–3.3) | 0.392 |

*Continuous variables are expressed as mean ± standard deviation or as median (interquartile range). Categorical variables are expressed as frequency (percent).

Abbreviations: BP, blood pressure; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal Cognitive Assessment; ICH, intracerebral hemorrhage; CT, computed tomography; WBC, white blood cell; CRP, C-reactive protein.

**Table 2. The impairment of each cognitive domains according to MoCA score at acute stage after ICH.**

| Cognitive domains                      | Frequency (%) |
|----------------------------------------|---------------|
| Visuospatial and executive function || 198 (95.2%) |
| Naming                                 | 46 (22.1%)    |
| Attention                              | 157 (75.5%)   |
| Language                               | 81 (38.9%)    |
| Abstract reasoning                     | 99 (47.6%)    |
| Memory recall                          | 208 (100.0%)  |
| Orientation                            | 145 (69.7%)   |

Abbreviations: MoCA, Montreal Cognitive Assessment;

**Table 3. The factors associated with significant cognitive impairment at acute stage after ICH (MoCA<20)**
|                              | Univariable                      |                  | Multivariable                   |                  |
|------------------------------|----------------------------------|------------------|---------------------------------|------------------|
|                              | OR (95% CI)                      | P-value          | OR (95% CI)                      | P-value          |
| Age, y                       | 1.05 (1.02-1.07)                 | <0.001           | 1.05 (1.02-1.08)                | 0.003            |
| Female                       | 2.69 (1.45-4.98)                 | 0.002            | 1.96 (0.90-4.29)                | 0.092            |
| Time from onset to hospital, h| 0.99 (0.98-1.00)                 | 0.043            | 1.00 (0.98-1.01)                | 0.681            |
| History of hypertension     | 0.86 (0.46-1.61)                 | 0.641            |                                 |                  |
| History of diabetes mellitus | 1.23 (0.48-3.16)                 | 0.672            |                                 |                  |
| History of ischemic stroke   | 0.88 (0.34-2.26)                 | 0.791            |                                 |                  |
| History of ICH               | 1.18 (0.41-3.40)                 | 0.753            |                                 |                  |
| Baseline diastolic BP        | 0.98 (0.96-0.99)                 | 0.009            | 0.98 (0.96-1.01)                | 0.137            |
| Baseline hematoma volume     | 1.08 (1.04-1.13)                 | <0.001           | 1.07 (1.02-1.13)                | 0.009            |
| Intraventricular extension   | 1.67 (0.92-3.03)                 | 0.089            | 1.62 (0.72-3.64)                | 0.239            |
| Baseline NIHSS score         | 1.14 (1.05-1.23)                 | 0.001            | 1.16 (1.04-1.30)                | 0.009            |
| Lobar hematoma location      | 1.59 (0.87-2.89)                 | 0.133            | 2.20 (0.88-5.48)                | 0.092            |
| Right side of hematoma       | 0.90 (0.52-1.56)                 | 0.703            |                                 |                  |
| WBC, $10^9$/L                | 1.03 (0.94-1.13)                 | 0.538            |                                 |                  |
| CRP, mg/L                    | 1.02 (0.99-1.04)                 | 0.211            |                                 |                  |
| LDL-C, mmol/L                | 1.06 (0.80-1.42)                 | 0.677            |                                 |                  |
| Low level of education       | 3.48 (2.28-5.31)                 | <0.001           | 3.50 (2.17-5.65)                | <0.001           |

Abbreviations: BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal Cognitive Assessment; ICH, intracerebral hemorrhage; WBC, white blood cell; CRP, C-reactive protein; OR, odds ratio.

**Table 4. The factors associated with delayed significant cognitive impairment after ICH (MoCA<20).**
|                                | Univariable |                                         | Multivariable (Not including acute phase MoCA) | Multivariable (Including acute phase MoCA) |
|--------------------------------|-------------|------------------------------------------|-----------------------------------------------|--------------------------------------------|
|                                | OR (95% CI) | P-value                                  | OR (95% CI)                                   | OR (95% CI)                                |
| Age, y                         | 1.06 (1.03-1.08) | <0.001                                   | 1.07 (1.03-1.10)                             | 1.03 (0.98-1.08)                           |
| Female                         | 2.62 (1.35-5.09) | 0.004                                    | 1.63 (0.68-3.91)                             | 1.49 (0.49-4.59)                           |
| Time from onset to hospital, h | 0.99 (0.98-1.00) | 0.122                                    | 1.00 (0.99-1.02)                             | 1.00 (0.98-1.02)                           |
| History of hypertension        | 0.98 (0.51-1.88) | 0.941                                    |                                              |                                            |
| History of diabetes mellitus   | 1.17 (0.42-3.25) | 0.768                                    |                                              |                                            |
| History of ischemic stroke     | 1.17 (0.46-2.96) | 0.739                                    |                                              |                                            |
| History of ICH                 | 1.17 (0.39-3.46) | 0.784                                    |                                              |                                            |
| Baseline diastolic BP          | 0.98 (0.96-1.00) | 0.012                                    | 0.99 (0.97-1.02)                             | 0.99 (0.96-1.03)                           |
| Baseline hematoma volume       | 1.07 (1.03-1.12) | 0.001                                    | 1.09 (1.03-1.16)                             | 1.03 (0.95-1.11)                           |
| Intraventricular extension     | 1.43 (0.76-2.69) | 0.269                                    |                                              |                                            |
| Baseline NIHSS score           | 1.15 (1.06-1.26) | 0.001                                    | 1.26 (1.10-1.44)                             | 1.15 (0.98-1.36)                           |
| Lobar hematoma location        | 1.85 (0.98-3.49) | 0.057                                    | 3.61 (1.30-10.00)                            | 2.81 (0.73-10.81)                          |
| Right side of hematoma         | 0.65 (0.36-1.17) | 0.153                                    | 0.53 (0.24-1.19)                             | 0.66 (0.23-1.85)                           |

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|                      | WBC, $10^9$/L | CRP, mg/L | LDL-C, mmol/L | Low level of education | Acute phase MoCA score |
|----------------------|--------------|-----------|--------------|------------------------|------------------------|
|                      | 1.02 (0.92- 1.12) | 1.02 (0.99- 1.06) | 1.09 (0.81- 1.47) | 2.67 (1.81- 3.95) | 0.54 (0.45- 0.65) |
|                      | 0.751        | 0.145     | 0.555        | <0.001                 | <0.001                 |
|                      |              | 1.04 (0.98- 1.10) |              | 2.98 (1.78- 4.99) | 0.59 (0.48- 0.71) |
|                      |              | 0.179     |              | <0.001                 | <0.001                 |
|                      |              | 1.04 (0.97- 1.10) |              | 1.56 (0.80- 3.01) |                |
|                      |              | 0.254     |              |                        |                        |

Abbreviations: BP, blood pressure; LDL-C, low-density lipoprotein cholesterol; NIHSS, National Institutes of Health Stroke Scale; MoCA, Montreal Cognitive Assessment; ICH, intracerebral hemorrhage; WBC, white blood cell; CRP, C-reactive protein; OR, odds ratio.

**Figures**

**Figure 1**

The correlation between acute phase MoCA score and follow-up MoCA score after ICH.
Figure 2

ROC curve of acute phase MoCA score on delayed significant cognitive impairment after ICH.

Supplementary Files

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- Supplementary1228.doc