

Retrospecting atrial fibrillation and stroke severity: impact onset time of acute ischemic stroke

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Irrespective of the duration of the therapeutic window, the prognosis for acute ischemic stroke is closely correlated with the time of treatment initiation. Time from symptom onset to hospital arrival, defined as the onset time, is the determining parameter. Besides the prehospital transport, whether relative factors of illness may have an impact on stroke onset time is uncertain, which were invested in this study through statistical analyses. Results show that relative factors of illness, such as history of atrial fibrillation and stroke severity, impact stroke onset time.

Keywords

Acute ischemic stroke; onset time; atrial fibrillation; vascular risk factors; statistical analyses

1. Introduction

The prognosis for acute ischemic stroke (AIS) is closely correlated with timely treatment (Hillen et al., 2017). Thrombolysis and endovascular treatment within the therapeutic window have been considered to provide the most effective treatment (Berkhemer et al., 2015; Campbell et al., 2015; Goyal et al., 2015; Hacke et al., 2008; Jovin et al., 2015; Saver et al., 2015; Stroke Study Group, 1995). Over recent decades the therapeutic window has been extended and may reach up to 24 hours in the future (Albers et al., 2018; Nogueira et al., 2018). Irrespective of its length, earlier treatment results in greater benefit. For this reason, onset time (the period from symptom onset to hospital arrival), should be given more attention.

There have been a series of magnetic resonance imaging (MRI) studies that estimate stroke onset time (Berthet et al., 2014; Jokivarsi et al., 2010; McGarry et al., 2017). However, with the exception of prehospital transport (Vuong et al., 2017), little has been reported about the onset time factors that affect prognosis and there is no evidence as to which relative factors of illness may have an impact on stroke onset time. As patients who experience stroke symptoms, and have knowledge of them, may be more motivated to attend hospital, this study focuses on such patients and any associated illness.

2. Methods

2.1 Subjects

Data was collected from hospitalized patients in the Department of Neurology at the Affiliated Drum Tower Hospital of Nanjing University Medical School from February 2008 to May 2012. The study was approved by an institutional committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School (No. 2011051). At admission, the exact time from symptom onset to hospital arrival was recorded, a plain CT scan of the head was taken to eliminate hemorrhage as a cause of symptoms and an MRI was performed during the hospital stay to identify any new infarction and the location of the lesion. Patients who were asymptomatic by CT scan or MRI were excluded from the study. Stroke subtypes of either anterior circulation infarction (ACI) or posterior circulation infarction (POCI) were defined on the basis of Bogousslavsky's classifications (Bogousslavsky and Regli, 1992). A neurologist assessed all patients on admission and obtained baseline clinical information including sex, age, and National Institutes of Health Stroke Scale (NIHSS) score.

2.2 Definition of vascular risk factors

Hypertension, diabetes mellitus (DM, just non-insulin-dependent diabetes were included) and atrial fibrillation (AF) were defined as participants with history of relative disease, while a new diagnosis of them after admitting were not included.

2.3 Data analysis

Statistical analyses were performed with SPSS 17.0 software. Results are expressed as a constituent ratio for categorical variables (χ^2 test) and as mean \pm standard deviation (SD) for continuous variables (*t*-test). Associations between stroke onset time less than six hours and relevant factors of illness were performed through logistic regression and results are expressed as an odds ratio (OR), with a 95% confidence interval (CI). For the multinomial logistic regression analysis, the lowest grade of variables was set as a reference group, for example, age ≤ 60 or NIHSS < 4 . Level of significance for statistical testing was $p < 0.05$.

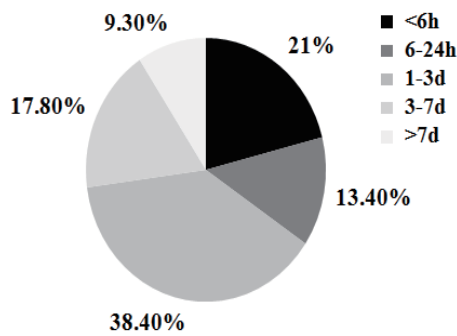


Figure 1. Percent of different levels of onset time in the AIS populations.

3. Results

3.1 Baseline characteristics

653 patients with AIS were included in the trial, 416 male and 237 female. Ages ranged from 15 to 92 years. Subjects were divided by age into four groups: ≤ 60 (210, 32.2%), 61–70 (148, 22.7%), 71–80 (204, 31.2%) and > 80 (91, 13.9%). There were 468 patients with hypertension, 213 with DM and 73 with AF. POCI was diagnosed for 182 subjects. The NIHSS mean score was 4.9 ± 5.0 . These scores were also divided into four levels: < 4 (358, 54.8%), 4–7 (149, 22.8%), 8–15 (111, 17.0 %) and ≥ 16 (35, 5.4 %) (Table 1).

Table 1. Baseline characteristics (n = 653)

Factors	Value
Male	416 (63.7%)
≤ 60	210 (32.2%)
61–70	148 (22.7%)
71–80	204 (31.2%)
> 80	91 (13.9%)
Hypertension	468 (71.7%)
DM	213 (32.6%)
AF	73 (11.2%)
POCI	182 (27.9%)
NIHSS (mean \pm SD)	4.9 \pm 5.0
< 4	358 (54.8%)
4–7	149 (22.8%)
≥ 16	35 (5.4%)

3.2 Distribution of AIS populations with different level of onset time

Onset time was divided into five levels: < 6 h, 6–24 h [6 h, 24 h], 1–3 days (1 day, 3 days), 3–7 days (3 days, 7 days) and > 7 days. The exact distribution of these different levels is given in Fig. 1. Among them, 21% of patients arrived at the hospital within six hours, while the largest proportion of admissions occurred between one and three days.

3.3 Older subjects exhibited shorter onset time

A high percentage of shorter onset times was seen in the > 70 age group when compared to that of the ≤ 70 age group. The dis-

Table 2. AIS with onset time < 6 hours versus risk factors.

Variable	Beta estimate	Odds ratio	95% CI	p-value
Male	-0.247	0.782	0.531–1.149	0.210
Age	0.024	1.024	1.008–1.040	0.003
Hypertension	0.083	1.087	0.712–1.659	0.699
DM	-0.428	0.652	0.426–0.996	0.048
AF	1.529	4.614	2.781–7.658	0.000
POCI	-0.347	0.707	0.454–1.101	0.125
NIHSS	0.111	1.117	1.079–1.157	0.000
≤ 60	-	-	-	-
61–70	0.304	1.356	0.779–2.358	0.281
71–80	0.669	1.953	1.197–3.185	0.007
> 80	0.632	1.881	1.028–3.433	0.040
NIHSS (grade)	-	-	-	0.000
< 4	-	-	-	-
4–7	0.476	1.609	0.987–2.625	0.057
≥ 16	1.944	6.988	3.377–14.459	0.000
AF*	1.010	2.746	1.566–4.815	0.000
NIHSS [‡]	0.085	1.089	1.049–1.131	0.000
NIHSS (grade) [‡]	-	-	-	0.001
< 4	-	-	-	-
4–7	0.471	1.602	0.972–2.639	0.064
≥ 16	1.476	4.377	2.001–9.577	0.000

*Multivariable logistic regression, Adjusted for Age, DM, NIHSS;

[‡]Multivariable logistic regression, Adjusted for Age, DM, AF.

tribution for delayed levels of onset time was adverse ($p < 0.05$, Fig. 2A). There was no significant difference in onset time between males and females (Fig. 2B).

3.4 History of AF and DM shortened stroke onset time

A higher percentage of short onset times and a lower percentage of delayed onset times were seen in the AF group compared to that of the non-AF group (49% versus 17% of onset time < 6 h, respectively, $p < 0.05$, Fig. 3A), while hypertension had no significant effect on the distribution of onset times ($p > 0.05$, Fig. 3B). Only when the onset time was subdivided into two groups (< 6 hours and ≥ 6 hours) was there a significant difference between DM and non-DM subjects ($p < 0.05$, Fig. 3D), while this was not the case for onset time divided into five groups ($p > 0.05$, Fig. 3C).

3.5 Stroke severity and location linked to onset time

A higher percentage of rapid onset times and a lower percentage of delayed onset times were seen in the NIHSS ≥ 8 group compared to that of the NIHSS < 8 group, ($p < 0.05$, Fig. 4A). Alternatively, a significantly lower percentage of rapid onset times was seen for the POCI group compared to that of the ACI group ($p < 0.05$, Fig. 4B).

3.6 History of AF and stroke severity were correlated with an onset time less than six hours

Single factor logistic regression analysis showed that age, DM, AF, and NIHSS were correlated with an onset time of less than six hours, a greater age and NIHSS subjects showed a greater proportion of onset times less than six hours through multinomial logistic regression. Following relative risk factors adjustment, only AF

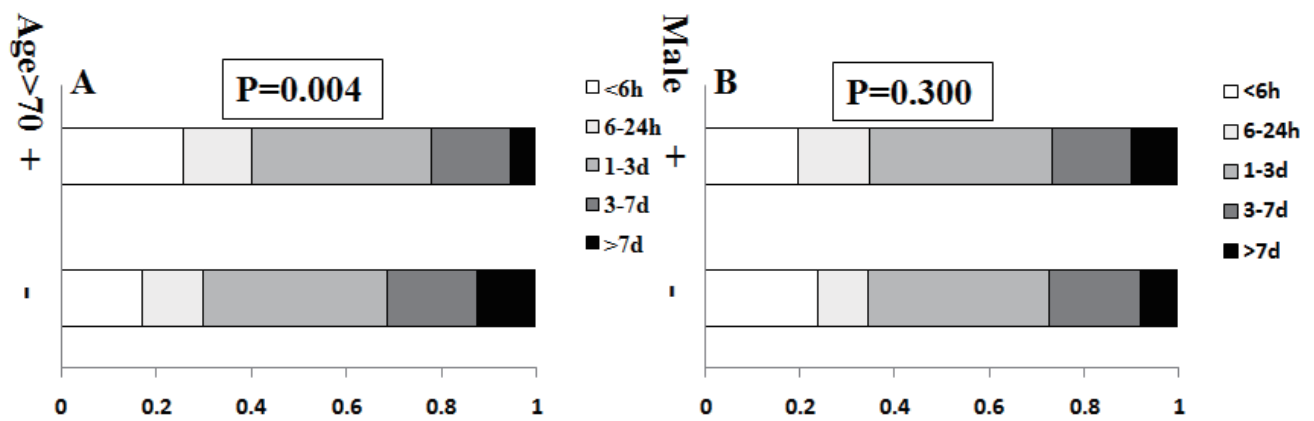


Figure 2. Onset time distribution for different groups based on age or sex (+ and – represent Yes and No; A: Constituent ratio of onset time between Age >70 and ≤70; B: Constituent ratio of onset time between Male and Female).

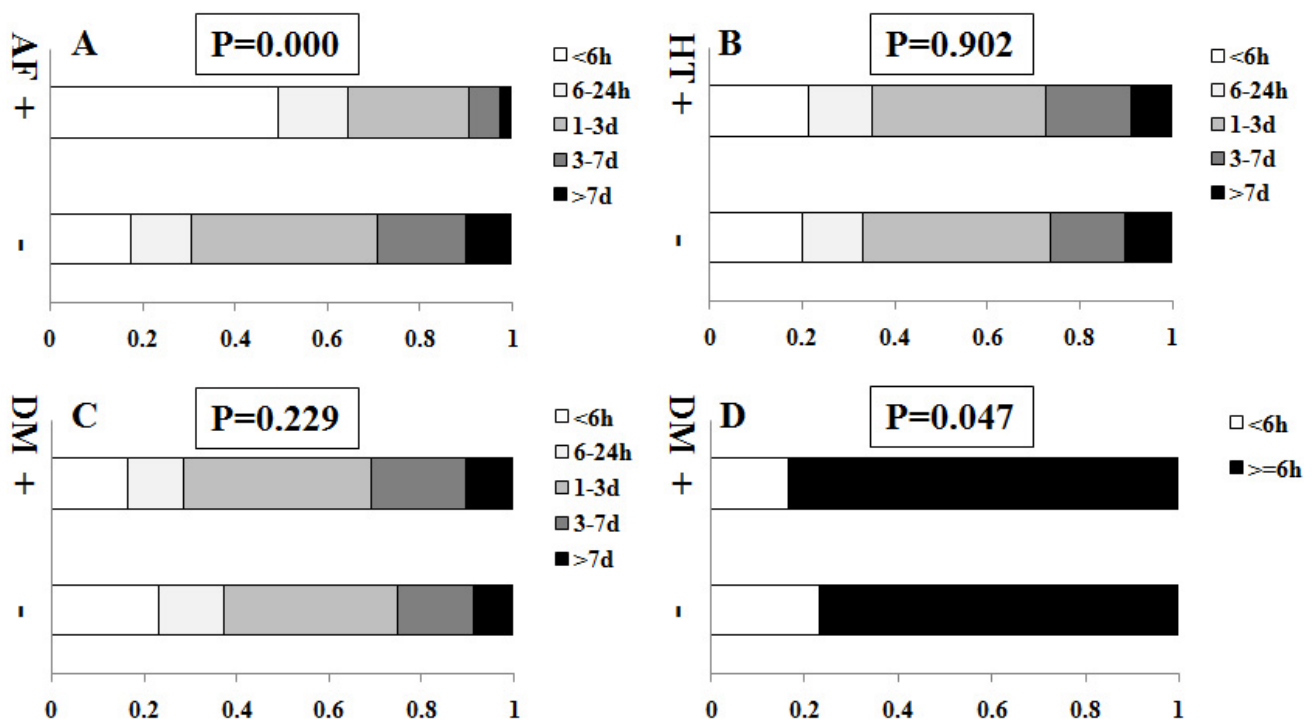


Figure 3. Onset time distribution for different groups based on AF or HT or DM (+ and – represent Yes and No; HT: Hypertension; A: Constituent ratio of onset time between AF and non-AF; B: Constituent ratio of onset time between HT and non-HT; C: Constituent ratio of onset time between DM and non-DM (multiple classification); D: Constituent ratio of onset time between DM and non-DM (binary classification).

and NIHSS were correlated with onset time less than six hours. Furthermore, multinomial logistic regression analysis based on different NIHSS levels gave an OR of 4.377 (95% CI, 2.001–9.577, p -value, 0.000) in the $\text{NIHSS} \geq 16$ group when compared with a reference group ($\text{NIHSS} < 4$), means 4.4-fold patients of onset time < 6 hours in the group of $\text{NIHSS} \geq 16$ compared to the group of $\text{NIHSS} < 4$ (Table 2).

4. Discussion

Timely medical treatment determines the prognosis of AIS, and better prognosis is closely related to a shorter time from the onset of symptoms to the reception of therapy (Hillen et al., 2017). Rather, it was the factors that impact during prehospital time, here

defined as the onset time, that were studied. Prehospital time was found to be only linked to prehospital transport, optimized by mobile stroke treatment units, or telemedicine or robotically assisted angiography, (Vuong et al., 2017) although few factors were investigated.

As is well known, more severe ischemic stroke results in more severe neurological defects. The symptoms are so obvious that they are easily recognized and linked to illness. This will motivate patients or family members to go to hospital. Motivation, the initiating step of going to hospital, determines the treatment, which has a clear impact on onset time. According to this viewpoint, stroke severity impacts the time of AIS onset, which itself orig-

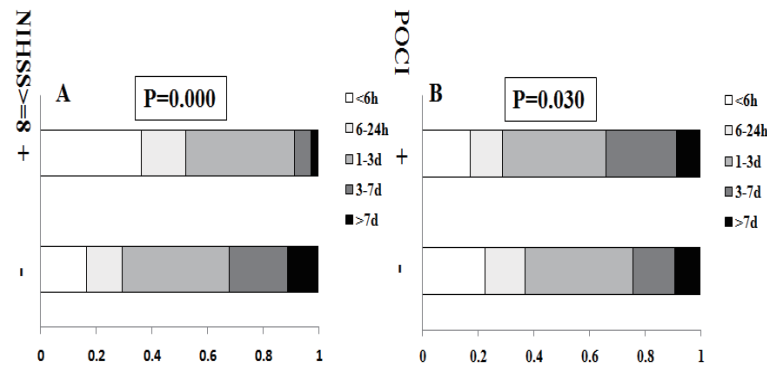


Figure 4. Onset time distribution for different groups based on NIHSS ≥ 8 or POCI (+ and - represent Yes and No; A: Constituent ratio of onset time for NIHSS ≥ 8 and < 8 ; B: Constituent ratio of onset time for POCI and ACI).

inates from recognition of stroke. Stroke severity is reflected by the symptoms, which can be simplified to the common mnemonic, BE-FAST (Balance, Eyes, Face, Arm, Speech, Time) which has been found useful in reducing the proportion of missed strokes (Aroor et al., 2017).

More serious stroke, characterized by greater infarct volume and more serious neurological defects, as seen in acute cardiogenic cerebral embolisms attributed to AF, (Arboix et al., 2000; Kimura et al., 2005; Lin et al., 1996) revealed that AF was correlated to stroke severity. In the current study, the history of AF also had a clear impact on the onset time. To remove the influence of stroke severity, multivariable logistic regression adjusting for NIHSS was used in the analyses reported here. It showed AF to be the independent factor that influenced onset time. Regardless of severity, relative symptoms of acute cardiogenic cerebral embolism due to AF usually peak quickly and the change of physical status is easily sensed. Also, AF is associated with a potentially high risk of arterial occlusive disease (cerebral embolism) at any time, including ischemic stroke (McIntyre and Healey, 2017; Wolf et al., 1991). Awareness of the existence of AF makes the risk of ischemic stroke more widely known, a situation which should benefit from advertizing and education about AF. Not only the high risk, but also the high mortality and disability of stroke that may result from AF has frequently been emphasized by neurologists and cardiologists. Patients with a history of AF are more likely to attend hospital based on recognition of the relationship between AIS and AF.

Some factors, such as age and DM, seemed to impact onset time, but multivariable logistic regression showed them not to be independent influence factors. Instead, there was a gradual correlation trend found between DM and onset time (data not given). It is likely that improvement of prehospital diagnosis of DM will contribute in part to a reduction in stroke onset time. Based on the variety or untypicality of POCI symptoms (Tao et al., 2012), in this study infarct location was divided between ACI and POCI. However, distinguishing between these two locations did not influence on onset time. This revealed that symptom variety or type had no impact on motivating hospital attendance.

5. Conclusion

Results were presented concerning the factors influencing patients and illness, that impact stroke onset. It is concluded that

retrospection of AF and stroke severity has a statistically significant impact on this measure.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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