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Predictors of Poor Outcome in Patients with Acute Cerebral Infarction

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Background and Purpose Plasma D-dimer levels are elevated during the acute phase of cerebral infarction (CI). We investigated whether the D-dimer level on admission and other clinical characteristics could be used to predict the poor outcome of patients with acute CI.

Methods The clinical characteristics and plasma D-dimer levels measured within 3 days of onset were compared according to outcome among patients with acute CI.

Results In total, 359 consecutive patients (mean age, 71.8 years) were examined, of which 174 had a poor outcome [score on the modified Rankin scale (mRS) ≥ 3] at 30 days after hospitalization. The mean mRS score was higher and a poor outcome was observed more frequently among women than among men ($p < 0.001$ for each). The proportions of women, cardioembolism, atrial fibrillation, advanced age (≥ 75 years), prior history of CI or transient ischemic attack, and elevated D-dimer level (≥ 1.0 $\mu\text{g/mL}$) were significantly higher among patients with a poor outcome than among those with a good outcome. A multivariate analysis showed that elevated D-dimer level (≥ 1.0 $\mu\text{g/mL}$; odds ratio (OR), 2.45; 95% confidence interval (95% CI), 1.52-3.89; $p < 0.01$], advanced age (OR, 1.93; 95% CI, 1.21-3.07; $p < 0.01$), and female gender (OR, 1.75; 95% CI, 1.08-2.83; $p = 0.02$) were independent predictors of a poor outcome.

Conclusions Certain clinical characteristics (gender and advanced age) and an elevated D-dimer level upon admission can be used to predict the outcome of patients with acute CI at 30 days after hospitalization.

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Key Words cerebral infarction, D-dimer, stroke, outcomes, atrial fibrillation, gender.

Introduction

Cerebral infarction (CI) accounts for 70-80% of all strokes in Japan.¹ Predicting the outcome after an acute CI is important for both clinicians and patients; however, such predictions remain difficult. Many factors are associated with the poor outcome of patients with acute CI, including gender, age, congestive heart failure, dementia, stroke severity, and diabetes mellitus.²⁻⁴ Although many studies have indicated that the outcome after an acute CI is worse among women than among men,⁵⁻¹¹ some other studies found no such difference.^{3,12}

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Several studies have investigated the relationship between levels of plasma hemostatic markers and acute CI subtypes. D-dimer is a marker of the fibrinolytic state, and the level of this marker is typically higher in cases with cardioembolism than in cases with other CI subtypes (i.e., atherothrombosis and lacunar infarction). We previously reported that an elevated D-dimer level was useful for distinguishing cardioembolic infarction from other CI subtypes in the emergency room.¹³ Some investigators have reported that the D-dimer level is an independent predictor of poor outcome among patients with acute CI.¹⁴⁻¹⁶ However, conflicting results have also been reported.¹⁷⁻²⁰ Therefore, in the present study we retrospectively investigated whether the D-dimer level upon admission and other clinical characteristics could be used to predict the poor outcome of patients with acute CI.

Methods

Study subjects

Consecutive patients with acute CI who were admitted to our university hospital between January 1, 2002, and December 31, 2006, were used as the study group. The following inclusion criteria were applied:

1) Neurological signs including paralysis, agnosia, apraxia, sensory disturbance, and cortical signs.

2) Lack of intracerebral hemorrhage, subarachnoid hemorrhage, and mass lesions on computed tomography (CT) or magnetic resonance imaging (MRI).

3) Admission within 24 hours after the onset of neurologic symptoms.

4) Determination of D-dimer levels within 3 days after admission.

Patients were excluded if they met one of the following criteria: epilepsy, systemic inflammatory or infectious diseases, the presence of diseases of the central nervous system other than CI on subsequent CT or MRI findings, or head injury. This retrospective study was performed in accordance with the Declaration of Helsinki.

Clinical characteristics

The presence of risk factors and co morbidities affecting thromboembolic events was determined. These factors included age, gender, hypertension, diabetes mellitus, congestive heart failure, underlying organic heart diseases, atrial fibrillation, and a prior history of CI or transient ischemic attack (TIA). The CHADS₂ (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or TIA) score was calculated to determine the levels of cardioembolic risk as follows:²¹ 1 point was given for the presence of each of advanced age (75 years or older), hypertension, congestive heart failure, and diabetes mellitus; while 2 points were given for the presence of a prior CI or TIA. The use of antithrombotic drugs, including warfarin and antiplatelet drugs, was also determined. For patients with repeated admission as a result of CI during the enrollment period, only the first admission was included in the present analyses.

Subtypes of cerebral infarction

The CI cases were classified into the following five groups using the Trial of Org 10172 in Acute Stroke Treatment criteria for acute CI²² and subsequent MRI and magnetic resonance angiography findings: cardioembolic diseases, large-artery atherothrombosis (atherothrombosis), small-vessel occlusion (lacunar infarction), unknown cause, and other (e.g., dissection of the cerebral artery or coagulation abnormalities). When two potential sources of CI were present

concomitantly, such as cardiac embolism and large-artery atherothrombosis, the CI subtype was defined as "unknown cause". Two neurologists who were unaware of the prognosis confirmed the final diagnosis of the CI subtype.

Outcome

Outcome was determined using the score on the modified Rankin scale (mRS; 0-6) at 30 days after hospitalization,²³ with an mRS score of 3-6 defined as a poor outcome.^{24,25}

Statistical analyses

Continuous variables are shown as mean \pm SD values, while categorical variables are shown as percentages. A chi-square test was used to compare categorical variables, while an unpaired *t*-test was used to compare continuous variables. A multivariate analysis was performed using the Cox proportional-hazards regression analysis to determine independent predictors of poor outcome. Explanatory variables were selected from the clinical characteristics that differed significantly between patients with a poor outcome and the remaining subjects. The data were analyzed using StatView, version J5.0 (SAS Institute, Berkeley, CA, USA). The level of statistical significance was set at $p < 0.05$.

Results

The study cohort comprised 359 patients (129 women and 230 men) aged 71.8 ± 11.7 years. The clinical characteristics are compared between the men and women in Table 1. Except for age, no significant differences were noted in the clinical characteristics between the genders, including the CHADS₂ score and antithrombotic drug usage. The distribution of the Trial of Org 10172 in Acute Stroke Treatment classification differed significantly between the men and women ($p=0.04$), with women being less likely to have large-artery atherothrombosis (24.8% vs. 37.4%) but more likely to have cardioembolism (39.5% vs. 25.7%)(Table 1). Three patients received intravenous tissue plasminogen activator (t-PA) treatment during the acute phase of CI after blood samples were obtained for the determination of D-dimer levels; these three patients were included in the subsequent analyses.

The plasma D-dimer level was determined in the emergency room on admission (day 1) in most of the patients (322 patients, 89.7%), on day 2 in 20 patients, and on day 3 in 17 patients. The D-dimer level tended to be higher among the women than among the men ($p=0.05$).

Outcome

The hospitalization period ranged from 2 to 216 days (median, 24 days). Seventeen patients (4.7%) died (mRS score=6)

and 70 patients (19.5%) were bedridden (mRS score=5) at 30 days after hospitalization. The mean mRS score was significantly higher among the women than among the men ($p<0.01$). Consequently, a poor outcome (mRS score ≥ 3) was observed more frequently among the women than among the men ($p<0.01$)(Table 1).

Risk factors of poor outcome

Table 2 compares the clinical characteristics and warfarin usage between patients with poor and good outcomes. The prevalences of female gender, cardioembolism, advanced age (≥ 75 years), prior history of CI or TIA, and elevated D-dimer level (≥ 1.0 $\mu\text{g/mL}$) were significantly higher among patients with a poor outcome (Table 2). The results of a multivariate analysis are summarized in Table 3. Elevated D-dimer level (≥ 1.0 $\mu\text{g/mL}$), advanced age, and female gender were independent predictors of poor outcome.

The predictive values of various combinations of independent predictors are summarized in Table 4. When all three predictors were combined, the negative predictive value was quite high but the positive predictive value was relatively low. Combining at least two predictors yielded modest positive and negative predictive values.

Discussion

Major findings

There are three major findings of the present study. First, compared with the men, the women with acute CI were older, suffered more frequently from cardioembolism and less frequently from atherothrombosis, and had a worse outcome at 30 days after hospitalization. Second, in a multivariate analysis, female gender, advanced age (≥ 75 years), and elevated D-dimer level (≥ 1.0 $\mu\text{g/mL}$) were independent predictors of a poor outcome (mRS score ≥ 3). Finally, combining at least two of these predictors yielded modest positive and negative predictive values.

Predictors of outcome among patients with acute CI

Many clinical characteristics are known to be predictors of a poor outcome among patients suffering acute CI,²⁻⁴ including age, gender, severity of CI, cardiovascular comorbidities, diabetes mellitus, and prestroke functional status. Some blood markers are also associated with a poor outcome among patients with CI.^{18,26} Higher levels of C-reactive protein,^{15,18,19} D-dimer,¹⁴⁻¹⁶ plasminogen activator inhibitor-1,²⁰ and fibrinogen¹⁹ have been reported to predict a poor outcome; however, the previous results have not always been consistent.¹⁷ In the present study, advanced age (≥ 75 years), a female gender,

and an elevated D-dimer level were independent predictors of a poor outcome (mRS score ≥ 3). These findings are consistent with those of several previous studies.^{2,14-16} Importantly, combining all three predictors yielded a high negative predictive value (0.889).

Female gender as a predictor of poor outcome

Whether being female is an independent predictor of a poor outcome among patients with acute CI remains controversial. The Framingham Heart Study, Rotterdam Study, and European BIOMED Study found that the mortality rate did not differ between men and women who had suffered a stroke.^{3,12,27} However, the World Health Organization's MONICA (Multinational MONItoring of trends and determinants in Cardiovascular disease) study and the International Stroke Trial revealed that the mortality rate was significantly higher among women than among men.²⁸ Many other studies have indicated that the outcome after acute stroke is worse among women than among men.⁵⁻¹¹ In Japan, Fukuda et al.¹¹ reported the long-term outcome of patients with CI. Only age and female gender were found to be independent predictors of poor locomotive function. The mortality rate was also higher among the women than among the men.¹¹ The etiology of the poor functional outcome seen in women is likely to be multifactorial. A more advanced age,^{3,29,30} more risk factors,^{3,29,31} a higher prevalence of cardioembolism,^{29,31} a greater severity of CI upon admission,²⁹ and a weaker muscular strength³² are observed more frequently among women than among men who suffer from stroke. In the present study, we also found that the women were older and suffered from cardioembolism more frequently than the men. However, the severity of CI, muscle strength, and prestroke functional conditions were not determined in the present study.

D-dimer levels and poor prognosis

D-dimer levels are an index of fibrinolysis, and elevated values are associated with thrombogenesis in the cardiovascular system. Among the three subtypes of acute CI, cardioembolism is generally associated with the highest D-dimer level.^{33,34} The determination of D-dimer levels in patients with acute CI could provide valuable prognostic information. Feinberg et al.³⁵ reported that the D-dimer level was significantly higher among patients with cardioembolism than among those with other CI subtypes, and that it was a predictor of mortality. Montaner et al.³⁶ showed that a combination of high levels of brain natriuretic peptide and D-dimer could identify cardioembolic stroke in the acute phase. Berge et al.³⁷ showed that higher D-dimer levels were related to stroke severity on admission and a worse outcome. However, other investigators found no such correlations between D-dimer

levels and stroke severity and mortality.^{17,38} Plasminogen activator inhibitor-1,²⁰ fibrinopeptide A,³⁵ and fibrinogen¹⁹ have also been reported as independent predictors of outcome after acute CI. Furthermore, an elevated C-reactive protein level was found to be an independent predictor of poor out-

come after acute CI.^{15,18,19}

In the present study, the D-dimer level - which was the only hemostatic marker determined upon admission - was an independent predictor of a poor outcome determined at 30 days after hospitalization. This finding could reflect a corre-

Table 1. Clinical characteristics of the patients, stratified according to gender

	Men (n=230)	Women (n=129)	p
Age (years)	69.6±11.4	75.8±11.1	<0.01
Underlying diseases			
Hypertension	116 (50.4)	69 (53.5)	0.63
Diabetes mellitus	56 (24.3)	23 (17.8)	0.15
Congestive heart failure	12 (5.2)	8 (6.2)	0.70
Organic heart diseases	43 (18.7)	26 (20.2)	0.73
Atrial fibrillation	66 (28.7)	46 (35.7)	0.14
Prior cerebral infarction/TIA	46 (20.0)	16 (12.4)	0.07
CHADS ₂ score	1.6±1.2	1.7±1.1	0.64
Antithrombotic medication			
Warfarin	25 (9.8)	8 (6.2)	0.14
Antiplatelet drugs	52 (23.9)	25 (19.4)	0.48
Subtypes of cerebral infarction			0.04
Atherothrombotic	86 (37.4)	32 (24.8)	
Cardioembolic	59 (25.7)	51 (39.5)	
Lacunar	66 (28.7)	37 (28.7)	
Unknown cause	13 (5.6)	5 (3.9)	
Other	6 (2.6)	4 (3.1)	
D-dimer (µg/mL)	1.93±3.63	2.78±4.65	0.05
mRS score			
0-2	128 (55.7)	43 (38.0)	<0.01
3-5	91 (39.5)	80 (62.0)	<0.01
6 (death)	11 (4.8)	6 (4.7)	0.81
Mean	2.5±1.9	3.3±1.8	<0.01

Data are mean±SD values or the numbers (%) of patients.

TIA: transient ischemic attack, CHADS₂: congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA, mRS: modified Rankin scale.

Table 2. Univariate analyses of variables associated with outcome at 30 days after hospitalization

	Outcome		p
	Poor (n=179)	Good (n=180)	
Women	81 (45.3)	48 (26.7)	<0.01
Cardioembolism	67 (37.4)	43 (23.9)	<0.01
Congestive heart failure	13 (7.3)	7 (3.9)	0.16
Hypertension	88 (49.2)	98 (54.4)	0.32
Age ≥75 years	111 (63.1)	68 (37.8)	<0.01
Diabetes mellitus	40 (22.3)	39 (21.7)	0.88
Prior cerebral infarction/TIA	38 (21.2)	24 (13.3)	0.05
Organic heart diseases	31 (17.3)	38 (21.1)	0.36
Warfarin	16 (8.9)	17 (9.4)	0.87
Antiplatelet drugs	39 (21.8)	38 (21.1)	0.88
Elevated D-dimer level (≥1.0 µg/mL)	126 (70.4)	74 (41.1)	<0.01

Outcome was defined as poor when the score on the mRS was ≥3 and as good when the score was ≤2.

Values are the numbers (%) of patients.

mRS: modified Rankin scale, TIA: transient ischemic attack.

Table 3. Multivariate analysis for a poor outcome (mRS score ≥ 3) at 30 days after hospitalization

	OR	95% CI	p
Female gender	1.75	1.08-2.83	0.02
Cardioembolism	1.39	0.85-2.29	0.19
Age ≥ 75 years	1.93	1.21-3.07	<0.01
Prior cerebral infarction/TIA	1.70	0.94-3.11	0.08
Elevated D-dimer level (≥ 1.0 $\mu\text{g/mL}$)	2.45	1.52-3.89	<0.01

OR: odds ratio, 95% CI: 95% confidence interval, mRS: modified Rankin scale, TIA: transient ischemic attack.

Table 4. Efficacy of combining age ≥ 75 years, female gender, and elevated D-dimer level for predicting a poor outcome (mRS score ≥ 3)

	Sensitivity	Specificity	PPV	NPV
All three factors	0.688	0.542	0.246	0.889
At least two factors	0.672	0.664	0.653	0.683
At least one factor	0.585	0.770	0.889	0.372

PPV: positive predictive value, NPV: negative predictive value, mRS: modified Rankin scale.

lation between cardioembolism and an elevated D-dimer level. Cardioembolism is generally more severe and is associated with a higher mortality rate and higher levels of D-dimer than other CI subtypes.^{13,33,38} However, some investigators have reported conflicting data regarding the relationship between the D-dimer level and CI subtypes.^{39,40} In the present study, cardioembolism was not an independent predictor of a poor outcome (Table 3).

Systemic diseases, including malignancy and infection, are associated with elevated D-dimer levels; this observation might explain the relationship between an elevated D-dimer level and a poor outcome in the present study. However, only three patients had a concomitant malignancy, and patients with systemic inflammatory or infectious diseases were excluded from this study. Treatment with warfarin can decrease the D-dimer level, possibly modifying the present results. The severity of CI in patients receiving warfarin treatment might be less than that among those who are not receiving warfarin treatment.^{41,42} However, warfarin usage on admission did not differ between patients with poor and good outcomes.

Limitations

The present study was subject to several limitations. First, stroke severity (e.g., as assessed on the National Institutes of Health Stroke Scale) upon admission and functional status before admission were not determined in the present study, since the data were analyzed retrospectively. Second, the D-dimer levels were not determined serially and were only determined upon admission in approximately 90% of the patients. The serial determination of D-dimer levels might have modified the present results. Finally, thrombolytic therapy with t-PA was performed only in three patients. The D-dimer level increases significantly after fibrinolytic therapy.⁴³ Thus, the more widespread use of t-PA among our cohort may have

influenced the obtained results.

Conclusion

Despite the aforementioned limitations, the present study has revealed that certain clinical characteristics - such as female gender, advanced age, and elevated D-dimer levels upon admission - may be used to predict the outcome after acute CI.

Conflicts of Interest

The authors have no financial conflicts of interest.

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