ORIGINAL RESEARCH

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Predictors of poor outcomes in First-Event Ischemic Stroke as assessed by Magnetic Resonance Imaging

Abstract

Purpose: Stroke is the third most common cause of mortality worldwide and is a major cause of permanent disability. The purposed of the study was to better understand the risk factors for poor outcomes following ischemic stroke requiring treatment.

Methods: Three hundred seventy patients with first-event ischemic stroke were enrolled. Good outcomes was defined as a using the Modified Rankin Scale (MRS) score ≤ 3 without any cardiovascular event, while poor outcomes were any of the following end points: MRS >3 at 3 months, recurrent stroke or death. Prognostic variables for poor outcomes were analyzed based on a stepwise logistic regression model.

Results: Seventy-eight patients had poor outcomes (21%, 78/370), assessed at a minimum of six-month follow-up. Higher mean National Institutes of Health Stroke Scale (NIHSS) scores at presentation, presence of early neurologic deterioration (END) and higher mean high-sensitivity C-reactive protein (hs-CRP) levels were associated with poor outcomes at discharge. Furthermore, both NIHSS at presentation and the presence of END were associated with poor outcomes, assessed at a minimum of six-month follow-up.

Conclusion: A higher mean initial NIHSS score implies not only severe neurologic deficits but also an increased risk of poor outcomes. Since END following ischemic stroke is frequently associated with poor outcomes, more attention should be directed to providing adequate treatment to patients in the acute stage, especially for high risk patients.

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Stroke is the third most common leading cause of death worldwide and is a major cause of serious long-term disability in adults [1,2]. In China, the three most common causes of death are vascular disease, cancer and chronic respiratory disease [3]. Unlike the profile in western countries, deaths due to cerebrovascular disease are three-fold higher than those from coronary heart disease [4]. Few investigations have examined the clinical functional outcomes of patients following MRI-based first-event ischemic stroke or determined accurate stroke recurrence rates with long-term follow-up in China [2].

A hospital-based study was designed to provide accurate information about the relative frequency of stroke sub-types, the risk factors impacting stroke mortality and neurologic and functional outcomes, and accurate stroke-recurrence rates. A better understanding of the risk factors associated with stroke and their relationship to treatment outcomes would be of value in formulating improved guidelines for the primary and secondary prevention of stroke. Clinical features, neuroimaging findings, clinical scores and clinical measurements to determine potential risk factors that are predictive of poor outcomes after first-event ischemic stroke were analysed. Poor outcomes, assessed at a minimum six-month follow-up, were identified.

Materials and Methods

Study design

This single-center retrospective case-control study was conducted at Chang Gung Memorial Hospital-Xiamen, a tertiary medical center and the main referral hospital in Xiamen, Fujian.

Over the three-year period from 2012 to 2014, 570 patients suffering from acute cerebrovascular diseases were admitted to the Department of Neurology and Neurosurgery. Of this population, 409 individuals suffered from ischemic stroke, and the other 161 from hemorrhagic stroke. Among the 409 ischemic stroke cases, 370 patients suffered from first-event cerebral infarction. The medical records were retrospectively reviewed using preexisting standardized evaluation forms. All of the patients underwent brain MRI examinations. Ischemic stroke was classified into various categories according to the presumed mechanism of the focal brain injury and the type and localization of the vascular lesion. Patients who were initially treated in other hospitals and subsequently transferred to this hospital for further therapy were also included, and their initial clinical and

laboratory data from the previous hospital were used for the analysis.

Inclusion and exclusion criteria

Acute ischemic stroke was defined as a sudden loss of focal cerebral function that persisted for more than 24 hours [5]. Stroke diagnosis was based on clinical presentation, neurologic examination and corresponding findings of brain imaging studies. Patients more than 18 years of age were included if they had suffered acute ischemic stroke according to the TOAST criteria [5]. Patients were excluded if they (i) suffered from multiple infarctions or silent brain infarctions (34 cases), (ii) had preexisting neurologic conditions with various neurologic deficits (e.g., stroke, head trauma, and hypoxic encephalopathy) (12 cases) or (iii) did not undergo an MRI procedure during hospitalization, even if they underwent brain CT (34 cases); thus, only 370 of the first-event ischemic stroke patients (90%) were enrolled for analysis. The therapeutic regimens for ischemic stroke were based on the American Heart Association / American Stroke Association guidelines for the prevention of stroke in patients with ischemic stroke and transient ischemic attack [6]. The study protocol (XMCGRB2015004) was approved by the Institutional Review Committee of the Chang Gung Memorial Hospital in Xiamen.

Clinical data collection

MRI examinations were performed on a 1.5 T scanner (Signa; Horizon GE Medical, Milwaukee, WI, USA). The MRI pulse sequences included axial and sagittal T1-weighted and T2-weighted images, and gadolinium-diethylene triamine pentaacetic acid was administered to all patients for coronal and axial T1-weighted images. Diffusion-weighted images were generated for all patients. Baseline demographic data, history of risk factors (e.g., hypertension, diabetes mellitus, dyslipidemia, cigarette smoking, cardiovascular disease, and asymptomatic carotid stenosis) and history of previous vascular events (e.g., myocardial infarction, angina and old stroke history) were documented, as well as other patient information including length of hospital stay and complications during hospitalization. Vascular risk factors included the following: hypertension, the use of anti-hypertensive medications or blood pressure $>140/90$ mmHg for two readings; diabetes mellitus (DM); the use of anti-diabetic treatment, elevated hemoglobin A1C, or elevated blood glucose at two readings if the fasting glucose level was ≥ 7 mmol/L. Additional risk factors included dyslipidemia, hyperlipidemia (defined as

hypercholesterolemia, hypertriglyceridemia or both), and the use of lipid-lowering medications. Hypercholesterolemia was defined as total venous plasma cholesterol level >5.0 mmol/L and any of the following: increased low density lipoprotein cholesterol level (>3.0 mmol/L); or decreased high-density lipoprotein cholesterol level (<1.0 mmol/L). Individuals who engaged in cigarette smoking within the last five years were defined as *current* smokers, while those who abstained from smoking for greater than 5 years were defined as *former* cigarette smokers. Coronary artery diseases were defined by pre-admission history and medical records associated with myocardial infarction or angina pectoris [7].

The National Institutes of Health Stroke Scale (NIHSS) and the Glasgow Coma Scale (GCS) were used to assess the severity of the neurologic deficit upon admission. Stroke severity was assessed with the NIHSS. Early neurologic deterioration (END) was defined as an increase of four points in the NIHSS score between admission and any time during the first 48 hours of hospitalization [8]. The Outpatient Department followed most surviving patients after discharge, although some were interviewed by telephone, to identify neurological outcomes. The follow-up period was terminated by death or by the completion of the study (June 2015). The physical disabilities of stroke patients were evaluated using the Modified Rankin Scale (MRS) during the discharge and convalescent phases. Good outcomes was defined as an MRS score ≤ 3 without any cardiovascular event, while poor outcomes was any of the following end points: MRS >3 at 3 months, recurrent stroke or death [9].

Three separate statistical analyses were performed. First, the effects of individual variables, including gender and clinical manifestations, underlying diseases, stroke subtype classification, neuroimaging findings on admission, and complications during hospitalization between two outcome groups (good and poor outcomes) at two time periods (at discharge and end of the study), were analyzed by Chi-square test. Continuous variables, including mean age, GCS and NIHSS scores at the time of admission, and duration of hospitalization between two outcome groups (good and poor outcomes) at two time periods (at discharge and end of the study), were analyzed by independent t-test or Mann-Whitney test. Second, to determine risk factors independently associated with functional outcomes, clinical and laboratory parameters with a P values < 0.05 were analyzed by a logistic regression model using a stepwise entry system. Third, receiver operating characteristic (ROC) curves were generated for variables significantly predictive of poor outcomes. All statistical analyses were conducted using the SAS software

package, version 9.1 (2002, SAS Statistical Institute, Cary, North Carolina, USA).

Results

In this study, ischemic stroke accounted for 71.8% (409/570) of acute cerebrovascular diseases. Of the 409 individuals with ischemic stroke, 370 (90%) suffered from first-event ischemic stroke, and the remaining 39 exhibited the underlying conditions of recurrent stroke or head injury with various neurological deficits. The 370 patients with first-event ischemic stroke included 236 males (age range: 23-91 years; mean age: 61.1 years) and 134 females (age range: 37-94 years; mean age: 65.6 years) (Table 1). Hypertension (193), smoking (160), and hyperlipidemia (137) were the most common three underlying diseases or lifestyle risk factors. Instances of ischemic stroke fell into the following subtypes according to the TOAST criteria: large-artery atherosclerosis ($n = 277$), small-artery occlusion (lacune, $n = 50$), cardio-embolic stroke ($n = 21$), other determined etiologies ($n = 6$) and stroke of undetermined etiologies ($n = 16$). Medications preceding the ischemic event included antihypertensive agents, anti-platelet drugs, anticoagulants and statins as shown in Table 1.

The locations of the infarction of among the 370 cases are listed in Table 2. Large vessels disease was found in 320 patients (86.5%, 320/370), while small-artery occlusion (lacune) was found in the other 50 individuals (13.5%, 50/370). The 320 patients with large vessels diseases included 297 patients with disease that involved a single vessel territory, and 23 patients with disease that involved more than one vessel region. Among the most common sites of the single large vessels diseases were the middle cerebral artery (MCA; $n = 160$), basilar artery (BA; $n = 42$), internal carotid artery (ICA; $n = 40$), posterior cerebral artery (PCA; $n = 22$), anterior cerebral artery (ACA; $n = 19$) and vertebral artery (VA; $n = 14$). The most common sites of the small-artery occlusion included the basal ganglia ($n = 8$), corona radiata ($n = 10$), brain stem ($n = 12$), thalamus ($n = 12$) and other uncommon areas ($n = 8$). The other neuroimaging findings included mass effects related to brain swelling, hemorrhagic transformation and obstructive hydrocephalus, as listed in Table 2.

Both the pharmacological and interventional treatments of patients were listed in Table 3. Three patients had upper gastrointestinal bleeding during hospitalization, 367 patients received pharmacological treatments, including aspirin in 272 patients, clopidogrel in 40, aspirin plus clopidogrel in 37, warfarin in 12 and rt-PA in the remaining six. The outcomes among different pharmacological regimens at discharge, and

TABLE 1. Baseline characteristics of the stroke patients

	Total (n=370)
Age (year) (mean±SD)	62.7± 13.1
Male (%)	236 (63.7%)
Underlying diseases or lifestyle risk factors	
Hypertension (%)	193(52.1%)
Currently smoking (%)	160(43.2%)
Hyperlipidemia (%)	137(37%)
Diabetes mellitus (%)	64(17.3%)
Atrial fibrillation (%)	29 (7.8%)
Coronary artery disease (%)	17(4.6%)
Systolic blood pressure (mmHg) at presentation	149.7± 25.7
Diastolic blood pressure (mmHg) at presentation	86.2± 14.7
Mean NIHSS on presentation	4.2± 4.4
Mean GCS on presentation	14.7± 1.4
Subtype of cerebral infarction (Toast criteria)	
Large-artery atherosclerosis	277(74.9%)
Small-artery occlusion (lacune)	50 (13.5%)
Cardio-embolic disease	21(5.7%)
Acute stroke of other determined etiology	6 (1.6%)
Stroke of undetermined etiology	16 (4.3%)
Laboratory data at presentation	
Uric acid (mmol/L)	343.4± 114.8
Total cholesterol (mmol/L)	4.9± 1.1
HDL-C cholesterol (mmol/L)	1.1± 0.4
LDL-C cholesterol (mmol/L)	3.1± 0.9
HBA1C (%)	6.9± 4.9
Fasting blood glucose (mmol/L)	7.0± 2.9
hs-CRP (mg/L)	2.6± 2.3
Calcium (mmol/L)	2.3± 0.3
White blood cells (×10 ³ /ml)	8.1± 4.1
Hemoglobin (g/dL)	139.4± 18.7
Platelet counts (×10 ⁴ /ml)	220.7± 60.4
APTT (sec)	26.8± 4.2
PT (sec)	11.3± 1.0
Homocysteine (μmol/L)	12.6± 5.7
Medication before the event	
Antihypertensive	108
Anti-platelet	7
Anticoagulant	4
Statin	5

Abbreviations: GCS= Glasgow coma scale; NIHSS =National Institutes of Health Stroke Scale; aPTT, activated partial thromboplastin time; PT, prothrombin time; HBA1c, Glycosylated hemoglobin; hs-CRP, high-sensitivity C-reactive protein

TABLE 2. Neuroimaging findings of study patients

	Patient numbers (n=370, 100%)
Location of cerebral infarction	
Large vessels diseases	320(86.5%)
MCA territory infarction	160 (43.2%)
PCA territory infarct	22 (5.9%)
ACA territory infarct	19 (5.1%)
BA territory infarct	42 (11.4%)
VA territory infarct	14(3.8%)
ICA territory infarct	40 (10.8%)
More than one artery territories	23 (6.2%)
Small-artery occlusion (lacune)	50 (13.5%)
Basal ganglia	8 (16.7%)
Corona radiata	10 (20.8%)
Brain stem	12 (25%)
Thalamus	12 (25%)
Other area	8 (12.4%)
Mass effects related to brain swelling	14(3.8%)
Hydrocephalus	1(0.3%)
Hemorrhagic transformation	13(3.5%)

Abbreviations: MCA= middle cerebral artery; PCA=posterior cerebral artery; ACA=anterior cerebral artery; BA =basilar artery; VA=vertebral artery; ICA=internal carotid artery;

after a minimum of 6-months follow-up, were not statistical significant ($P=0.618$ and $P=0.915$, respectively). One patient, with massive MCA, received decompressive hemicraniectomy and, finally, had a good outcome.

The mean hospitalization stay for these 370 patients was 11.5 days (range 1-93). The median hospitalization stay was 8 days (5, 11) for those patients who had good outcomes at discharge and 16.5 days (10.8, 30.3) for those who had poor outcomes at discharge ($P < 0.0001$, Mann-Whitney test). The mean GCS total score at presentation was 14.9 ± 1.0 for patients who had good outcomes at discharge and 13.9 ± 2.2 for those with poor outcomes ($P = 0.001$, independent-t test). The mean NIHSS total score at presentation was 2.8 ± 1.1 for patients who had good outcomes at discharge and 10.3 ± 6.0

TABLE 3. Pharmacological and interventional treatments of patients

	Outcomes			
	At discharge		More than 6-month follow-up	
	Poor outcomes n=69	Good outcomes n=301	Poor outcomes n=78	Good outcomes n=292
Pharmacological treatments				
Aspirin (n=272, 72.7%)	51	221	58	214
Clopidogrel (n=40, 10.8%)	7	33	8	32
Aspirin+Clopidogrel (n=37, 9.9%)	6	31	7	30
rt-PA (n=6, 1.6%)	1	5	1	5
Warfarin [†] (n=12, 3.2%)	4	8	4	8
None*	0	3	0	3
Interventional treatments				
Decompressive hemicraniectomy	0	1	0	1
Mechanical thrombectomy	0	0	0	0

* Anticoagulant therapy for cardioembolic stroke. rt-PA = recombinant tissue plasminogen activator.

† Three patients did not receive pharmacological treatment because of upper gastrointestinal bleeding during hospitalization.

for those with poor outcomes ($P < 0.0001$, independent-t test).

Complications during hospitalization among the 370 cases included pneumonia ($n = 26$), hyponatremia ($n = 8$) and diabetes insipidus ($n = 2$; Table 4). Therapeutic outcomes at discharge among these 370 patients, as determined by MRS, included an absence of all symptoms (14.3%, 53/370), no significant disability despite symptoms (37.8%, 140/370), slight disability (19.2%, 71/370), moderate disability (10%, 37/370), moderately severe disability (15.7%, 58/370), severe disability (1.9%, 7/370) and death (1.1%, 4/370). The mean follow-up period for the 366 surviving patients was 17.1 months (range 6-40), and 21 (5.7%, 21/370) patients suffered from recurrent stroke during the follow-up period. Therapeutic outcomes among the 366 surviving cases after the follow-up period as determined by MRS were as follows: absence of all symptoms (18.3%, 67/366), no significant disability despite symptoms (38.8%, 142/366), slight disability (17.8%, 65/366), moderate disability (9.8%, 36/366), moderately severe disability (13.9%, 51/366) and severe disability (1.4%, 5/366).

Comparisons of clinical features and neuroimaging findings between acute ischemic stroke patients with good and poor outcomes at discharge are listed in Table 4. Statistical analysis of the baseline clinical manifestations and

neuroimaging findings between the two patient groups revealed the following significant variables: gender; GCS and NIHSS scores at presentation; atrial fibrillation; acute infection preceding ischemic stroke as the underlying diseases; presence of aphasia and END; pneumonia; neuroimaging findings showing mass effects and symptomatic hemorrhagic transformation; pre-anticoagulant therapy; and, peripheral blood measurements of white blood cell counts, high-sensitivity C-reactive protein (hs-CRP) and prothrombin time (PT). Upon evaluation of these significant individual variables in the stepwise logistic regression model, NIHSS score at presentation ($P = 0.001$, OR = 1.891, 95% CI = 1.32-2.72), the presence of END ($P = 0.004$, OR = 219.92, 95% CI = 5.52-8767.97), and hs-CRP level ($P = 0.041$, OR = 1.76, 95% CI=1.02-3.04) were found to be independently associated with poor outcomes at discharge.

Comparisons of clinical features and neuroimaging findings between acute ischemic stroke patients with good and poor outcomes, assessed at a minimum of 6-months follow-up, are listed in Table 5. Statistical analysis of the baseline clinical manifestations and neuroimaging findings between the two patient groups revealed the following were significant variables: gender; GCS and NIHSS scores at presentation; atrial fibrillation and acute infection preceding ischemic stroke as the underlying diseases; the presence of aphasia and END;

TABLE 4. Risk factors for poor outcomes of study patients at discharge

	Poor outcomes n=69	Good outcomes n=301	P-value	OR	95% CI
Sex (Male/female)	33/36	203/98	0.002	0.44	0.36-0.75
Mean age at onset	69.5±12.8	61.2±12.7	<0.0001	1.055	1.03-1.08
Mean systolic BP on admission	150.8±24.3	149.5±26	0.709	1.00	0.99-1.01
Mean diastolic BP on admission	83.77±14.9	86.8±14.6	0.126	0.99	0.97-1.00
Mean GCS on presentation	13.9±2.23	14.9±0.98	0.001	0.63	0.50-0.79
Mean NIHSS on admission	10.28±6.00	2.78±2.13	<0.0001	1.77	1.55-2.03
Mean hospitalization days	21.6±17.4	9.1±5.6	<0.0001	1.14	1.10-1.18
Neuroimaging findings on admission					
Mass effect	6	8	0.029	3.49	1.17-10.41
Hemorrhagic transformation	8	5	0.001	7.764	2.46-24.54
Obstructive hydrocephalus	1	0	0.186	0.18	0.15-0.23
Underlying diseases					
Hypertension	34	159	0.595	0.87	0.51-1.46
Diabetes mellitus	10	54	0.495	0.78	0.37-1.61
Atrial fibrillation	8	9	0.006	4.25	1.58-11.47
Coronary artery disease	5	12	0.333	1.88	0.64-5.53
End stage renal disease	2	1	0.91	8.96	0.80-100.20
Acute infection preceding ischemic stroke	10	6	<0.001	8.33	2.92-23.8
Laboratory data at presentation					
Uric acid (mmol/L)	321.4± 104.3	347.9± 116.9	0.375	0.99	0.99-1.00
Total cholesterol (mmol/L)	4.7± 1.0	4.9± 1.1	0.222	0.86	0.67-1.09
HDL-C cholesterol (mmol/L)	1.2± 0.7	1.1± 0.3	0.383	1.47	0.81-2.66
LDL-C cholesterol (mmol/L)	2.9± 0.8	3.1± 1.0	0.135	0.79	0.59-1.07
HbA1C (%)	6.5± 1.9	7.1± 5.4	0.451	0.93	0.79-1.10
Fasting blood glucose (mmol/L)	7.5± 3.1	6.9± 2.8	0.149	0.15	0.97-1.15
hs-CRP (mg/L)	4.0± 2.5	2.2± 2.1	0.001	1.37	1.12-1.66
Calcium (mmol/L)	2.2± 0.1	2.3± 0.2	0.347	0.20	0.01-3.03
White blood cells (×10 ³ /ml)	9.5± 8.5	7.7± 2.6	0.100	1.10	1.01-1.20
Hemoglobin (g/dL)	135.8± 17.8	140.2± 18.8	0.080	0.99	0.98-1.00
Platelet counts (×10 ⁴ /ml)	222.7± 70.8	220.3± 66.7	0.789	1.00	0.99-1.00
PT (sec)	11.6± 1.0	11.2± 0.9	0.013	1.56	1.10-2.21
aPTT (sec)	27.0± 2.9	26.7± 4.5	0.695	1.01	0.95-1.08
Clinical features or complications					
Pneumonia	20	6	<0.0001	20.07	7.68-52.47
Hyponatremia	2	6	0.646	1.47	0.29-7.43
Diabetes insipidus	1	1	0.339	4.41	0.27-71.42
Seizure	0	1	1.00	0.81	0.77-0.85
Early neurologic deterioration	18	11	<0.0001	9.31	4.15-20.85
Aphasia	32	21	<0.0001	11.53	6.03-22.06
Medication before the event					
Antihypertensive	19	89	0.738	0.91	0.51-1.62
Anti-platelet	0	7	0.356	0.81	0.77-0.85
Anticoagulant	3	1	0.022	13.64	1.40-133.16
Statin	0	5	0.589	0.81	0.77-0.85

Abbreviations: N, number of cases; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; IQR, inter-quartile range; aPTT, activated partial thromboplastin time; PT, prothrombin time; HbA1c, Glycosylated hemoglobin; hs-CRP, high-sensitivity C-reactive protein

TABLE 5. Risk factors for poor outcomes of study patients at end of the study

	Poor outcomes n=78	Good outcomes n=292	P-value	OR	95% CI
Sex (male/female)	41/37	195/97	0.02	0.551	0.33-0.91
Mean age at onset (years)	67.514.2	61.512.5	0.001	1.03	1.02-1.06
Mean systolic BP on admission (mmHg)	149.923.7	149.726.2	0.94	1.00	0.99-1.01
Mean diastolic BP on admission (mmHg)	84.014.1	86.814.7	0.13	0.98	0.97-1.00
Mean GCS on presentation	13.972.5	14.90.7	<0.001	0.62	0.49-0.79
Mean NIHSS on admission	8.56.3	3.02.73	<0.001	1.36	1.26-1.50
Mean hospitalization days	18.116.2	9.67.0	<0.001	1.08	1.04-1.11
Neuroimaging findings on admission					
Mass effect	7	7	0.014	4.01	1.36-11.81
Hemorrhagic transformation	6	7	0.035	3.39	1.10-10.41
Obstructive hydrocephalus	1	0	0.211	0.21	0.17-0.26
Underlying diseases					
Hypertension	38	155	0.493	0.84	0.51-1.38
Diabetes mellitus	13	51	0.868	0.95	0.49-1.84
Atrial fibrillation	8	9	0.013	3.59	1.34-9.65
Coronary artery disease	5	12	0.37	1.60	0.55-4.68
End stage renal disease	2	1	0.114	7.66	0.69-85.58
Acute infection preceding ischemic stroke	11	5	<0.0001	9.42	3.17-28.03
Laboratory data at presentation					
Uric acid (mmol/L)	315.5 107.0	350.0 116.1	0.243	0.99	0.99-1.00
Total cholesterol (mmol/L)	4.9 1.1	4.9 1.1	0.765	0.97	0.78-1.21
HDL-C cholesterol (mmol/L)	1.2 0.6	1.1 0.3	0.195	1.47	0.82-2.65
LDL-C cholesterol (mmol/L)	3.0 0.9	3.1 0.9	0.707	0.95	0.72-1.24
HBA1C (%)	6.7 2.0	7.0 5.5	0.628	0.98	0.89-1.07
Fasting blood glucose (mmol/L)	7.7 3.1	6.9 2.8	0.031	1.09	1.01-1.18
hs-CRP (mg/L)	3.5 2.5	2.3 2.1	0.028	1.23	1.02-1.47
Calcium (mmol/L)	2.2 0.1	2.3 0.3	0.07	0.08	0.01-1.22
White blood cells ($\times 10^3/\text{ml}$)	9.4 8.0	7.7 2.6	0.012	1.12	1.02-1.22
Hemoglobin (g/dL)	136.1 18.1	140.3 18.7	0.08	0.99	0.98-1.00
Platelet counts ($\times 10^4/\text{ml}$)	226.9 70.6	219.1 66.6	0.365	1.00	0.99-1.00
PT (sec)	11.5 1.0	11.2 0.9	0.019	1.48	0.07-2.06
APTT (sec)	27.0 2.7	26.7 4.6	0.600	1.02	0.96-1.08
Clinical features or complications					
Pneumonia	18	8	<0.0001	10.65	4.43-25.63
Hyponatremia	2	6	0.677	1.25	0.25-6.34
Diabetes insipidus	1	1	0.378	3.78	0.23-61.11
Seizure	0	1	1.000	0.79	0.75-0.83
Early neurologic deterioration	14	15	<0.0001	4.04	1.86-8.79
Aphasia	26	27	<0.0001	4.91	2.65-9.08
Medication before the event					
Antihypertensive	22	86	0.83	0.94	0.54-1.64
Anti-platelet	0	7	0.356	0.81	0.77-0.85
Anticoagulant	3	1	0.022	13.64	1.40-133.16
Statin	0	5	0.589	0.81	0.77-0.85

Abbreviations: n, number of cases; OR, odds ratio; CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; GOS, Glasgow Outcome Scale; IQR, inter-quartile range; activated partial thromboplastin time; PT, prothrombin time; HBA1c, Glycosylated hemoglobin; hs-CRP, high-sensitivity C-reactive protein

pneumonia; neuroimaging findings showing mass effects and symptomatic hemorrhagic transformation; pre-anticoagulant therapy; and, peripheral blood measurements of white blood cell counts, hs-CRP, glucose and PT level. Analysis of these individual variables using the stepwise logistic regression model revealed that NIHSS at presentation ($P < 0.0001$, OR = 1.24, 95% CI=1.10-1.40) and the presence of END ($P = 0.022$, OR = 1.40, 95% CI=1.40-68.25) were independently associated with poor outcomes, assessed at a minimum of 6-months follow-up. Furthermore, the area under the ROC curve for NIHSS scores on admission was 0.803 ($P < 0.0001$, 95% CI=0.74-0.86). The cut-off value of NIHSS score on admission for poor outcomes at a minimum of six-month follow-up was 4.5 (sensitivity 69% and specificity 81%).

Discussion

Differences in the relative prevalence and outcomes of first-event ischemic infarction vary with case determination and inclusion criteria, length of follow-up, underlying diseases and neurological complications. The crude incidence of ischemic stroke (all strokes *versus* first stroke only) was estimated to be 81 to 267 (overall, and for both genders independently) per 100,000 person-years in developed countries [10]. In China, cerebral infarction accounted for 43.7% to 78.9% of total strokes in two recent studies in the late 20th century (1991 to 2000) [11,12]. In the present study, ischemic stroke accounted for 72% of acute cerebrovascular disease; of these, 90% were first-event ischemic strokes, while the other 10% represented recurrent strokes.

The present study examined the risk factors for poor outcomes after first-event ischemic infarction as assessed by MRI. There were three major findings in this study. First, both higher mean NIHSS scores at presentation and the presence of END were independently associated with poor outcomes both at discharge and after a minimum of six-month follow-up. The cut-off value of NIHSS scores on admission for poor outcomes at a minimum of six-month follow-up was 4.5 (sensitivity 69% and specificity 81%). Second, higher mean hs-CRP levels were independently associated with poor outcomes at discharge. Third, the proportion of poor outcomes accounted for 21% of the episodes, and 5.7% of patients experienced recurrent stroke during the follow-up period.

In addition to NIHSS scores, there are several clinical risk factors that contribute to poor functional outcomes after ischemic stroke [8, 13-19]. The majority of the damage following acute ischemic stroke does not occur immediately, but rather develops gradually over the course of the following hours [20]. Inflammatory cytokines and other neurotoxins,

liberated by leukocytes, promote microvascular occlusion in the ischemic brain via platelet-leukocyte-endothelium interactions in the ischemic penumbra and via the interaction of leukocytes, especially neutrophils and monocytes, with activated platelets and vascular endothelium [21, 22]. Although the exact mechanisms for END following ischemic stroke are multi-factorial and treatment remains inadequate [19], our patients with END had poor functional outcomes. Furthermore, several factors have been shown to contribute to the inflammation that contributes to the pathophysiology of ischemic stroke. Higher mean peripheral leukocyte counts on admission [14], higher mean hs-CRP levels on admission [16], acute infection preceding ischemic stroke and post-stroke infections (e.g., stroke-associated pneumonia) [13] are well-known risk factors for poor outcomes, and these were also confirmed as risk factors in our study. Admission hyperglycemia is a well-known risk factor for poor outcomes in both human and animal studies [13, 18], and this association was also seen in our study. The presence of aphasia predicted unfavorable outcomes in patients with ischemic stroke in our study as well as others [17]. In our study, the mean duration of hospitalization for those patients with and without aphasia were 22.5 days and 9.6 days, respectively ($P < 0.0001$). Patient comprehension and speech ability usually correlates with the duration of hospitalization and the recovery outcomes. Cerebral emboli arising from the heart, and frequently related to underlying atrial fibrillation disease, are a devastating subtype of stroke. Unlike a thrombus, which adheres to the vessel wall, the embolic particle is friable and migratory. In embolic types of ischemic stroke, hemorrhagic transformation may occur as a delayed manifestation and has been associated with worse outcomes [15], as was seen in this study.

Although our study demonstrated that a higher mean NIHSS score at presentation was indicative of more severe neurologic deficits in the acute phase and was also an independent risk factor for poor functional outcomes at the minimum of six-month follow up, our study has two significant limitations. First, this is a retrospective analysis and, therefore, is subject to bias of unmeasured factors. Second, patients with underlying diseases of cerebral infarction, head injury, or pre-existing neurologic deficits have been excluded; thus, a continued uncertainty is present in assessing the true risk factors after ischemic stroke in non-selected patients.

In conclusion, a higher mean NIHSS score at presentation implies not only severe neurologic deficits at presentation, but also represents an independent risk factor for a poor functional outcomes at the minimum of six-month follow up. Since patients with END following ischemic stroke are frequently

associated with worse outcomes, more attention should be focused on the acute stage, especially in high risk patients; e.g., patients with atrial fibrillation with embolic stroke; higher peripheral leukocyte counts, hs-CRP and fasting blood glucose levels on admission; and acute infection preceding ischemic stroke.

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