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ORIGINAL COMMUNICATION

Stroke-associated infection independently predicts 3-month poor functional outcome and mortality

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Abstract

Stroke-associated infection (SAI) is a common and serious complication of stroke. This study aimed to assess the effects of SAI on patient mortality and functional outcome at 3 months after stroke onset. We retrospectively analyzed 809 consecutive patients with acute stroke (517 men and 292 women; median age, 72 years) who were admitted to our department between September 2014 and June 2016. SAI was defined as an infection diagnosed during the hospitalization period. Poor outcome was defined as a modified Rankin Scale (mRS) score of 3–5 or death (mRS score of 6). The effect of SAI on functional outcome was evaluated using a multivariate logistic regression analysis. SAI occurred in 169 patients (20.9%); of these, 106 (62.7%) had pneumonia, 23 (13.6%) had a urinary-tract infection, and 40 (23.7%) had other types of infection. Patients with SAI were older, more likely to be female, had lower body mass indices, had higher stroke severity, and were more likely to have atrial fibrillation and a history of ischemic heart disease than patients without SAI. Poor functional outcome and mortality were more common in patients with SAI than in patients without SAI (poor functional outcome 41.8 vs. 4.8%, mortality 24.3 vs. 3.9%, respectively). After adjusting for age, sex, stroke severity, and various comorbidities, SAI was independently associated with poor functional outcome [odds ratio (OR) 6.88; 95% confidence interval (CI) 3.72–12.73] and mortality (OR 4.45, 95% CI 2.27–8.72) at 3 months after stroke onset. Our results suggest that SAI during the hospitalization period is independently associated with 3-month poor functional outcome and mortality.

Keywords Infection · Pneumonia · Prognosis · Stroke

Introduction

Stroke is a leading cause of mortality worldwide. Compared with cardiac events, stroke has a higher tendency to result in sequelae requiring long-term rehabilitation and care. Thus, stroke is associated with increased familial burden and medical costs. Individual stroke outcomes depend on age, sex, stroke severity, and comorbidity. Infection is a common complication of stroke that occurs in 5–65% of patients; yet, the previous studies of stroke-associated infection (SAI) have varied significantly in terms of length of the follow-up period, baseline risk factors, comorbidities, stroke severity, and clinical definitions [1]. Early studies showed that SAI was associated with increased mortality and prolonged hospital stays compared to those among patients without infection [2–4]. The proposed mechanisms for the relationship between infection and functional outcome include fever, hypoxia, hypotension, and leukocyte/platelet activation [3, 5]. Infection also leads to prolonged immobilization during hospitalization, which may delay rehabilitation and thereby influence functional outcome. In contrast, a recent study found no association between SAI and poor functional outcome at discharge [9]. Accordingly, the relationship between SAI and functional outcome remains unclear.

In the present study, we examined in detail the clinical characteristics of patients who develop SAI, the frequency of SAI occurrence, associated risk factors, and the influence of SAI on functional outcome and mortality at 3 months post-stroke.

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Methods

Subjects and evaluation

This study was approved by the ethics committee of Nippon Medical School and conformed to the tenets of the Declaration of Helsinki. All participants or participant family members provided written informed consent prior to study participation. We enrolled 809 consecutive patients with acute ischemic stroke or intracerebral hemorrhage who were admitted to our stroke unit within 7 days of symptom onset between September 2014 and June 2016. Data were retrospectively analyzed from a prospective registry. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) upon hospital admission. Functional outcome was assessed using the modified Rankin scale (mRS) at the time of discharge and at 3 months after stroke onset. A good outcome was defined as a mRS score of 0–2 and a poor outcome was defined as a mRS score of 3–5 or death (mRS score of 6).

SAI was defined as any infection diagnosed during the hospitalization period. Infections were diagnosed on the basis of the modified Centers for Disease Control and Prevention (CDC) criteria by trained and experienced clinicians [6], and were divided into three groups: pneumonia, urinary-tract infection (UTI), and other infections. The definitions of pneumonia and UTI were similar to those used in previously published studies [7–9]. Briefly, pneumonia was defined on the basis of the presence of relevant clinical symptoms and/or signs (e.g., purulent cough, unilateral inspiratory crackles, and bronchial breath sounds) with at least one of the following: leukocytosis, fever, or a positive chest radiograph. UTI was defined based on the presence of relevant clinical symptoms and/or signs (e.g., dysuria and urinary frequency changes) with positive microbiological cultures, or negative cultures with leukocytosis, fever (temperature ≥ 38.0 °C), or both. Fever in combination with leukocytosis that did not fulfill the diagnosis criteria for pneumonia or UTI was classified into the "other infections" group [7, 10]. The nursing staff performed frequent noninvasive monitoring of blood pressure, temperature, and heart rate as well as pulse oximetry. Each patient's individual medical team determined whether it was appropriate to treat infections with oral or intravenous antibiotics, and whether it was appropriate to treat fever with oral or rectal non-steroidal anti-inflammatory drugs.

Clinical information

For each patient, we collected clinical background characteristics including sex, age, cardiovascular risk factors, and past medical history. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg persisting after the acute stage of ischemic stroke or on the basis of use of antihypertensive medication prior to admission. Atrial fibrillation was diagnosed using electrocardiography upon admission or on the basis of paroxysmal atrial fibrillation during hospitalization. Diabetes was defined by the use of antidiabetic medication or as a fasting blood glucose level ≥ 126 mg/dL, normal glucose level ≥ 200 mg/dL, or glycosylated hemoglobin ≥ 6.5% upon admission. Dyslipidemia was defined as a fasting plasma cholesterol level ≥ 220 mg/dL, fasting plasma triglyceride level ≥ 150 mg/dL, or on the basis of the use of lipid-lowering medication prior to admission. Prior ischemic heart disease was defined as a previous diagnosis and treatment of myocardial infarction and/or angina. Upon admission, body mass index (BMI) was calculated; BMI < 18.5 was regarded as underweight, according to guidelines from the World Health Organization.

Statistical analysis

We initially compared clinical characteristics between patients with and without SAI. Furthermore, we compared clinical characteristics of patients in accordance with 3-month stroke outcome. Intergroup differences were assessed using either Chi-square tests or the Wilcoxon rank-sum tests as appropriate. Variables with P values < 0.05 in the univariate analysis were entered into a multivariate logistic regression model to identify variables independently associated with poor functional outcome and mortality. Odds ratios (ORs) are presented with the corresponding 95% confidence intervals (CIs). Data are presented as the median [interquartile range (IQR)] or number (%). All analyses were performed using the JMP version 13 statistical software (SAS Institute Inc., Cary, NC, USA). P values < 0.05 were considered statistically significant.

Results

In total, 809 patients (median age 72 years, 517 men and 292 women, 624 patients with ischemic stroke and 185 patients with intracerebral hemorrhage) were enrolled; of these, 169 (20.9%) developed SAI. The most common infection was pneumonia (106 patients; 62.7%), followed by other infections (40 patients; 23.7%) and UTIs (23 patients; 13.6%).

Table 1 shows the baseline characteristics of patients with and those without SAI. Age ($P < 0.0001$), female sex ($P < 0.0001$), ischemic heart disease ($P = 0.0030$), atrial fibrillation ($P = 0.0100$), time from symptom onset to hospital arrival ($P < 0.0001$), pre-admission mRS score ($P < 0.0001$), NIHSS score at admission ($P < 0.0001$),

Table 1 Baseline characteristics of patients with and without stroke-associated infection

	Total (n = 809)	Without infection (n = 640)	With infection (n = 169)	P value
Age, years (IQR)	72 (64–81)	71 (63–80)	78 (67–86)	< 0.0001
Male sex, n (%)	517 (62.7)	418 (65.3)	99 (58.6)	< 0.0001
Body mass index (IQR)	22.7 (20.3–24.7)	22.7 (20.5–24.9)	22.0 (19.5–24.0)	0.0057
Hypertension, n (%)	557 (68.9)	447 (69.8)	110 (65.1)	0.2351
Dyslipidemia, n (%)	275 (34.0)	227 (35.5)	48 (28.4)	0.0845
Diabetes mellitus, n (%)	188 (23.2)	150 (23.4)	38 (22.5)	0.7943
Smoking, n (%)	212 (26.3)	165 (25.8)	47 (27.8)	0.5936
Prior stroke, n (%)	170 (22.7)	134 (20.9)	36 (21.3)	0.9177
Ischemic heart disease, n (%)	84 (10.4)	56 (8.8)	28 (16.6)	0.0030
Atrial fibrillation, n (%)	142 (17.6)	101 (15.8)	41 (24.3)	0.0100
Time from symptom onset to hospital arrival, h (IQR)	6.2 (1.5–22.9)	6.8 (1.7–27.1)	3.8 (1.1–12.4)	0.0002
Pre-admission mRS (IQR)	0 (0–1)	0 (0–1)	0 (0–3)	< 0.0001
NIHSS score on admission (IQR)	3 (2–11)	3 (1–7)	17 (7–23)	< 0.0001
Thrombolytic therapy, n (%)	159 (19.7)	111 (17.3)	48 (28.4)	0.0013
mRS score at 3 months (IQR)	2 (1–4)	1 (0–3)	5 (4–5)	< 0.0001
Poor outcome at 3 months, n (%)	352 (43.5)	205 (32.0)	147 (87.0)	< 0.0001
Mortality at 3 months, n (%)	66 (8.2)	25 (3.9)	41 (24.3)	< 0.0001

IQR interquartile range, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale

thrombolytic therapy ($P = 0.0013$), mRS score at discharge ($P < 0.0001$), mRS score at 3 months after stroke onset ($P < 0.0001$), mortality during hospitalization ($P < 0.001$), and mortality at 3 months after stroke onset ($P < 0.0001$) were significantly higher or more frequent in patients with SAI than in those without SAI. While patients with SAI had a lower BMI than did patients without SAI ($P = 0.0067$), there were no significant differences in the frequency of dyslipidemia ($P = 0.0845$), diabetes mellitus ($P = 0.7943$), smoking ($P = 0.5936$), or prior stroke ($P = 0.9177$) between the SAI and non-SAI groups.

Table 2 shows associations between baseline characteristics related to SAI and 3-month functional outcome and mortality. There were significant differences in age ($P < 0.001$), sex ($P < 0.001$), smoking ($P = 0.0033$), atrial fibrillation ($P = 0.0003$), diabetes mellitus ($P = 0.0267$), ischemic heart disease ($P = 0.0151$), prior stroke ($P = 0.146$), pre-admission mRS score ($P < 0.001$), SAI ($P < 0.001$), body mass index ($P = 0.0067$), and NIHSS score at admission ($P < 0.001$) between the 3-month good and poor functional outcome groups. There were also significant differences in age ($P < 0.001$), sex ($P < 0.001$), atrial fibrillation ($P = 0.0003$), pre-admission mRS ($P = 0.0013$), SAI ($P < 0.001$), body mass index ($P = 0.0067$), and NIHSS score at admission ($P < 0.001$) between the 3-month non-mortality and mortality groups.

Figure 1 shows the distribution of mRS scores according to SAI classification. The distribution of mRS scores in the SAI group was as follows: 0, 3.0%; 1, 3.6%; 2, 6.5%; 3, 5.3%; 4, 24.8%; 5, 32.5%; and 6, 24.3%. The distribution of mRS scores in the non-SAI group was as follows: 0, 25.3%; 1, 24.8%; 2, 17.8%; 3, 9.4%; 4, 11.9%; 5, 6.9%; and 6, 3.9%. A multivariate logistic regression analysis revealed that SAI (OR 6.88, 95% CI 3.72–12.73), age (OR 1.62, 95% CI 1.34–2.00), dyslipidemia (OR 0.46, 95% CI 0.29–0.73), diabetes mellitus (OR 1.86, 95% CI 1.16–3.00), NIHSS (OR 1.14, 95% CI 1.10–1.18), pre-mRS (OR 1.85, 95% CI 1.51–2.29), and BMI (OR 2.29, 95% CI 1.13–4.62) were independently associated with a poor functional outcome (Table 3). Furthermore, SAI (OR 4.45, 95% CI 2.27–8.72), age (OR 1.39, 95% CI 1.03–1.91), atrial fibrillation (OR 1.97, 95% CI 1.03–3.78), and NIHSS (OR 2.38, 95% CI 1.19–4.79) were independently associated with mortality (Table 4).

Discussion

By analyzing data from a consecutive cohort of 809 patients with acute stroke, we found that SAI occurred in 21% of patients and was independently associated with poor functional outcome and mortality at 3 months after stroke onset, even after adjusting for the effects of stroke severity, various risk factors, and comorbidities.

In the present study, SAI was associated with higher age and NIHSS score at admission, consistent with the previous studies [4, 5, 11]. Other research has suggested that infection after stroke is associated with increased mortality

Table 2 Associations between baseline characteristics and functional outcome and mortality at 3 months after stroke onset

	Total ($n = 809$)	Good outcome ($n = 457$)	Poor outcome ($n = 352$)	*P* value	Non-mortality ($n = 743$)	Mortality ($n = 66$)	*P* value
Age, years (IQR)	72 (64–81)	69 (59–77)	78 (69–85)	< 0.001	72 (64–80)	80 (69–87)	< 0.0001
Male sex, *n* (%)	326 (62.7)	325 (71.1)	192 (54.6)	< 0.001	325 (71.1)	192 (54.6)	< 0.0001
Body mass index (IQR)	22.7 (20.3–24.7)	22.7 (20.5–24.9)	22.0 (19.4–24.0)	0.0067	22.7 (20.4–24.8)	22.0 (18.5–23.7)	0.0036
Hypertension, *n* (%)	557 (68.9)	307 (67.2)	250 (71.0)	0.2416	511 (68.8)	46 (69.7)	0.8769
Dyslipidemia, *n* (%)	275 (34.0)	170 (37.2)	105 (29.8)	0.0282	257 (34.6)	18 (27.3)	0.2291
Diabetes mellitus, *n* (%)	188 (23.2)	93 (20.4)	95 (27.0)	0.0267	172 (23.2)	16 (24.2)	0.8403
Smoking, *n* (%)	212 (26.3)	138 (30.2)	74 (21.0)	0.0033	201 (27.1)	11 (16.7)	0.0659
Prior stroke, *n* (%)	118 (22.7)	82 (17.9)	88 (25.0)	0.0146	159 (21.4)	11 (16.7)	0.3657
Ischemic heart disease, *n* (%)	84 (10.4)	37 (8.1)	47 (13.4)	0.0151	74 (10.0)	10 (15.2)	0.1851
Atrial fibrillation, *n* (%)	142 (17.6)	61 (13.4)	81 (23.0)	0.0003	118 (15.9)	24 (36.4)	< 0.001
Pre-admission mRS score (IQR)	0 (0–1)	0 (0–0)	0 (0–3)	< 0.001	0 (0–1)	0 (0–3)	0.0013
NIHSS score on admission (IQR)	3 (2–11)	2 (1–4)	11 (4–20)	< 0.001	4 (2–10)	16 (6–23)	< 0.0001
Stroke-associated infection, *n* (%)	169 (25.8)	22 (4.8)	147 (41.8)	< 0.001	25 (3.9)	41 (24.3)	< 0.0001

IQR interquartile range, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *PVH* periventricular hyperintensity

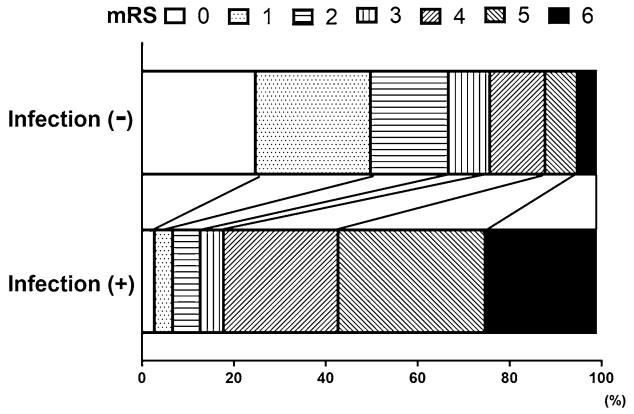

Fig. 1 Functional outcome at 3 months after stroke onset, assessed using the modified Rankin scale (mRS), in patients with or without stroke-associated infection

Table 3 Multiple logistic regression analysis of predictors for poor functional outcome

Variables	OR	95% CI	*P* value
Age (per 10 years)	1.63	1.34–2.00	< 0.0001
Male sex	0.75	0.48–1.17	0.2043
Dyslipidemia	0.46	0.29–0.73	0.0010
Atrial fibrillation	1.33	0.76–2.34	0.3208
Diabetes mellitus	1.86	1.16–3.00	0.0103
Smoking	0.79	0.34–0.48	0.3430
Prior stroke	1.33	0.80–2.21	0.2742
Ischemic heart disease	1.33	0.66–2.66	0.4238
NIHSS score on admission (per 1 point)	1.14	1.10–1.18	< 0.0001
Body mass index < 18.5 (kg/m^2)	2.29	1.13–4.62	0.0203
Stroke-associated infection	6.88	3.72–12.73	< 0.0001
Pre-mRS score (per 1 point)	1.85	1.51–2.29	< 0.0001

CI confidence interval, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *OR* odds ratio

and poor functional outcome at hospital discharge [2, 12, 13]. In our study, we confirmed that SAI was associated with a poor long-term (3-month) outcome, and importantly, this association was independent of stroke severity, age, and pre-stroke independence level. In contrast, a previous prospective study reported that SAI was not an independent risk factor for poor outcome and mortality at discharge, but rather a marker of stroke severity [9]. The cohort size of this previous study was limited ($n = 229$) and follow-up was restricted to hospital discharge. Therefore, we consider a longer follow-up period (extended up to 3 months) and moderate cohort size to be important advantages of our study. Similarly, another study found that pneumonia and UTI were independently associated

Table 4 Multipe logistic regression analysis of predictors for mortality

Variables	OR	95% CI	*P* value
Age (per 10 years)	1.39	1.03–1.91	0.0382
Male sex	0.67	0.35–1.31	0.2435
Atrial fibrillation	1.97	1.03–3.78	0.0417
NIHSS score on admission (per 1 point)	2.38	1.19–4.79	0.0142
Body mass index < 18.5 (kg/m^2)	1.98	0.94–4.18	0.0735
Stroke-associated infection	4.45	2.27–8.72	< 0.0001
Pre-mRS score (per 1 point)	1.02	0.79–1.21	0.8588

CI confidence interval, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *OR* odds ratio

with poor outcome at 3 months after acute ischemic stroke [13].

Infections can affect stroke outcome in several ways. First, immobilization and general frailty associated with prolonged hospital stays can delay rehabilitation. Second, it is now well established that stroke produces a considerable inflammatory response with both peripheral and central production of pro-inflammatory cytokines, chemokines, and cell adhesion molecules [14–17]. Although some inflammation is necessary after injury, prolonged and excessive inflammation (e.g., related to SAI) can have deleterious effects on stroke recovery [18]. Patients with SAI were found to have higher plasma levels of interleukin-1, and polysaccharide infusion worsened functional outcomes in an animal model of stroke [19, 20]. Infection has also been reported to independently predict poor clinical outcome following brain injury such as traumatic brain injury or subarachnoid hemorrhage [21–23]. A large-scale retrospective study ($n = 7516$) demonstrated that hospital-acquired pneumonia was an independent predictor of poor global outcome in patients with severe traumatic brain injury up to 5 years after discharge [21]. Taken together, these findings suggest that SAI may play an important role in predisposing patients to poor prognoses following stroke.

The present study had several limitations. First, the generalizability of our findings is limited by a single-center retrospective study design. The incidence of SAI in our study was 21%, which is low compared to that in the previous studies [9, 13]. A low proportion of patients with SAI in our study may have been related to strict definitions for infection and a median NIHSS score at admission of 3 (IQR 2–11) in our general cohort [11]. Second, SAI was associated with older age, atrial fibrillation, prior ischemic heart disease, stroke severity, and pre-admission mRS score, such that multicollinearity may have inflated the variances of parameter estimates. Thus, associations of SAI with outcome measures in our multivariate analysis may have been overestimated. Third, we were unable to identify reasons for an association between SAI and mortality. Future prospective studies are needed to better elucidate the relationship between SAI and stroke prognosis.

In conclusion, SAI is a major clinical problem for hospitalized patients with acute stroke that has a strong independent effect on 3-month functional outcome and mortality. Further studies are required to improve our basic understanding about how and why systemic infections occur after stroke, and to develop new strategies to prevent or mitigate the deleterious effects of infection on recovery and outcome.

Compliance with ethical standards

Conflicts of interest The authors declare no financial or other conflicts of interest.

Ethical standards This study was approved by the ethics committee of Nippon Medical School and conformed to the tenets of the Declaration of Helsinki.

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