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ORIGINAL PAPER

Impact of Infection on Length of Intensive Care Unit Stay after Intracerebral Hemorrhage

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Abstract
Introduction The vast majority of patients with intracerebral hemorrhage (ICH) are admitted to an intensive care unit (ICU). Patients admitted to ICUs have a high risk of developing nosocomial infections, while complicating infection appears to be associated with a longer ICU stay. An increased length of ICU stay translates directly into increased costs. The aim of this study was to assess the impact of a complicating infection on the length of ICU stay in patients with ICH.
Methods We studied 148 consecutive patients who were admitted to the ICU and diagnosed with spontaneous ICH. Complicating infection was defined as when a patient was treated with antibiotics for the diagnosis of an infectious disease after admission. The impacts of clinical factors on the length of ICU stay were assessed, including complicating infection, sex, age, Glasgow Coma Scale (GCS) score at admission, and surgical intervention.
Results The median ICU stay was 8 days (interquartile range, 3–18 days). Complicating infection occurred in 75 patients (51%). A multiple regression model for predicting the length of ICU stay was performed. After controlling for sex, age, GCS score, and surgical intervention, complicating infection was significantly associated with a longer ICU stay ($P < 0.001$). Surgical intervention was also an independent predictor ($P < 0.001$). The length of the ICU stay was significantly longer for patients with GCS scores of 6–8, compared to those with GCS scores of 13–15 ($P = 0.01$).
Conclusions Complicating infection was an independent predictor of a prolonged ICU stay in patients with ICH.

Keywords Intracerebral hemorrhage · Intensive care units · Length of stay · Infection · Complication · Critical care

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Introduction

The vast majority of stroke patients with an intracerebral hemorrhage (ICH) are admitted to an intensive care unit (ICU) because of their impaired consciousness, elevated blood pressure, and frequent need for intubation and mechanical ventilation [1, 2]. Stroke hospitalizations are among the most expensive, with a mean hospital stay longer than for other hospitalizations. One of the largest cost drivers in the hospital setting is the ICU [3, 4]. An increased length of ICU stay translates directly into increased healthcare costs. To improve the efficiency of healthcare services, length of stay is a meaningful outcome. It is essential to identify what factors prolong the length of the ICU stay after an acute ICH.

Patients admitted to ICUs have a high risk of developing nosocomial infections [5, 6]. Clinical experience and clinical studies demonstrate a high incidence of infectious complications after stroke. Infections were diagnosed in 21 to 65% of stroke patients in previous studies that focused mainly on ischemic stroke [7–10]. Complicating infection appears to be associated with a longer ICU stay [11, 12]. In patients with ICH, as in other patients, complicating infection may also increase the length of an ICU stay.

Addressing this question requires careful consideration of other factors that influence the length of an ICU stay. Age and neurological severity are commonly thought to predict resource utilization. Patients undergoing surgery need to be hospitalized for a longer period. Although outcomes appear to be worse in febrile patients with ICH [13], little information is available on the impact of complicating infection on the length of the ICU stay after ICH.

We examined whether, after controlling for other predictive factors, complicating infection remained an important factor in determining the length of the ICU stay in patients with acute ICH.

Patients and Methods

Patient Population

We retrospectively assessed 170 consecutive patients who were admitted to the Trauma and Critical Care Unit of Teikyo University Hospital between April 1998 and March 2002 and diagnosed with spontaneous ICH. The Trauma and Critical Care Unit serves tertiary emergency cases, and neurosurgeons evaluate all patients with neurological symptoms. The diagnosis of ICH was based on computed tomography (CT) in all patients. In cases where ICH was suspected to be secondary, based on the patient's history and CT findings, cerebral angiography was also performed, and those with an underlying etiology (e.g., aneurysm, vascular malformation, or amyloid angiopathy) were excluded from the study ($n = 25$).

Other patients were excluded for (1) brain death shortly after admission ($n = 7$) and (2) length of ICU stay $\leq$ 1 day ($n = 14$). Most of the patients with length of ICU stay $\leq$1 day were severely affected (GCS score 3–5, 50%; GCS score 6–8, 21%) and nine patients died at discharge. One medical record was not available. Complete medical data were available for 148 patients.

The routine care of acute ICH patients in the critical care unit included endotracheal intubation for patients who were unable to maintain an adequate airway or had respiratory distress, and antihypertensive therapy with nicardipine or diltiazem.

Computed Tomography Findings

CT scans were performed using a 512 × 512-matrix with 5- to 10-mm slices. A neuroradiologist with 20 years experience, who was not informed of the aim of this study, reviewed the CT films. The CT images were then copied as computer files, concealing all personal identification. The hematomas in the initial CT scans were measured; in the slice with the largest area of ICH, the longest diameter (A) of the hematoma and the second diameter (B) on the perpendicular axis were measured. The height of the hematoma was calculated from the number of 10-mm interval slices in which the hematoma appeared, giving the third diameter (C). The three diameters were multiplied and then divided by 2 ($A \times B \times C/2$) to obtain the volume of the ICH [14]. The site of the hematoma was recorded as the putamen, thalamus, lobes, brain stem, cerebellum, or mixed (putamen and thalamus).

Data Collection

Complicating infection was defined as when a patient was treated with antibiotics for an infectious disease diagnosed after admission. The routine use of prophylactic antibiotics after surgical intervention was excluded.

The following clinical information was abstracted from the hospital records: sex, age, Glasgow Coma Scale (GCS) score at admission, surgical interventions, complicating infection, and length of ICU stay. In addition, the following inflammatory parameters were measured: fever duration, maximum body temperature, maximum white blood cell count (WBC), and maximum C-reactive protein (CRP) during the ICU stay. Fever duration was defined as the total number of days on which a patient had a body temperature ≥38.5°C. We used body temperature in the axilla as documented in the medical records. In most cases, body temperature recordings were made every 2 h. Blood tests were usually performed daily during the first week of admission. The study protocol was approved by the internal review board of Teikyo University School of Medicine.

Statistical Analysis

Age and hematoma volume were divided into two groups using the median of each variable. While the length of the ICU stay is shortened for patients with a very severe brain injury, because of early death, it is likely that the length of the ICU stay is shorter for patients with mild ICH. Therefore, GCS scores were categorized into four groups: 3–5, 6–8, 9–12, and 13–15. Since the length of ICU stay was not distributed normally, we used Wilcoxon's rank sum test or the Kruskal–Wallis test to examine the differences in all predictor variables. In addition to sex and age, factors with $P < 0.10$ were eligible for inclusion in the multiple regression analysis of predictive factors of the length of the ICU stay. The natural logarithm of the length of the ICU stay was used as the dependent variable for the multiple regression analysis. In addition, Wilcoxon's rank sum test was used to compare the inflammatory parameters, according to the existence of complicating infection. Values of $P < 0.05$ were considered significant. All analyses were performed using the Statistical Analysis System (SAS Institute).

Results

The study group consisted of 83 males (56%) and 65 females (44%). The ages of the patients ranged from 37 to 91 years, with a median of 63 years (missing data = 1). The locations of the hematomas were as follows: putamen in 30 patients (20%), thalamus in 24 (16%), lobes in 14 (9%), brain stem in 32 (22%), cerebellum in 13 (9%), and mixed in 35 (24%). The median GCS score at admission was 6.0. The median volume of the hematomas was 31 cm^3. Surgical intervention was performed in 49 patients (8 hematoma evacuations via craniotomy, 20 aspirations via burr hole, and 21 simple ventricular drainages). The median time from admission to surgical intervention was 4 h (interquartile range: 2.5 to 42). Only five patients were discharged directly to home and 61 were transferred to another ward within the same hospital.

The median length of the ICU stay was 8 days (interquartile range: 3–18). Complicating infection occurred in 75 patients (51%). The types of the infections were as follows: chest infection in 51 patients (68%), urinary tract infection in 14 (19%), and other infections in 10 (13%). As shown in Table 1, the ICU stay was longer for patients with complicating infection, compared to those without complicating infection (18 vs. 5 days; $P < 0.001$). The ICU stay was longer for patients with chest infection (median, 19 days), compared to patients with urinary tract infection and other infections (median, 17 and 14 days, respectively), but the difference was not statistically significant ($P = 0.11$). In addition, the length of the ICU stay was significantly associated with the GCS score at admission ($P = 0.01$) and surgical intervention ($P < 0.001$). The ICU stay was the shortest for patients with GCS scores of 3–5, and was longer for patients with GCS scores of 6–8 and 9–12.

As shown in Table 2, complicating infection was significantly associated with maximum body temperature ($P = 0.02$), maximum WBC ($P = 0.01$), maximum CRP ($P < 0.001$), and fever duration ($P = 0.01$).

A multiple regression model for predicting the length of the ICU stay was constructed using sex, age, and the factors that had values of $P < 0.10$ (Table 3). Since the GCS score at admission had a non linear association with the length of the ICU stay, we used this factor as a dummy variable. After controlling for sex, age, GCS score, and surgical intervention, complicating infection was identified as an independent predictive factor of the length of the ICU stay ($P < 0.001$). Surgical intervention was also significantly

Table 1 Univariate analysis of ICU stay

Characteristics	No. (%)	Length of ICU stay, d[a]	P value
Sex			0.83
Male	83 (56)	8 (3–20)	
Female	65 (44)	9 (5–17)	
Age[b]			0.61
<63 year	72 (49)	8 (3–20)	
≥63 year	75 (51)	9 (4–18)	
GCS scores at admission			0.01
13–15	14 (9)	8 (3–13)	
9–12	14 (9)	15 (6–21)	
6–8	48 (32)	15 (7–22)	
3–5	72 (49)	6 (3–13)	
Surgical intervention			<0.001
Yes	49 (33)	21 (13–28)	
No	99 (67)	6 (3–10)	
Hematoma location			0.45
Supratentorial	103 (70)	9 (3–20)	
Subtentorial	45 (30)	8 (3–17)	
Hematoma volume			0.97
<31 cm^3	74 (50)	9 (4–18)	
≥31 cm^3	74 (50)	8 (3–20)	
Complicating infection			<0.001
Yes	75 (51)	18 (9–22)	
No	73 (49)	5 (3–8)	

ICU, intensive care unit; GCS, Glasgow Coma Scale

[a] Values are median (25th–75th percentile)

[b] Missing = 1

associated with the length of the ICU stay ($P < 0.001$). The ICU stay was significantly longer for patients with GCS scores of 6–8, compared to those with GCS scores of 13–15 ($P = 0.01$). This model explained 55% of the total variance of the length of the ICU stay.

Discussion

After controlling for other predictive factors, including age, neurological severity, and surgical intervention, we found that complicating infection was an independent predictor of prolonged ICU stay for patients with acute spontaneous ICH.

In a few studies undertaken previously, complicating infection was reported to be associated with a longer ICU stay [11, 12]. In addition, elevated body temperature was reported to be a significant predictor of a longer ICU stay [15, 16]. A preceding study found that fever was an independent predictor of poor outcome following ICH [13]. Elevated body temperature is common in critically ill patients with neurological diseases; it is not caused solely

Table 2 Differences in inflammatory parameters between patients with and without infectious disease

Parameters	Patients with infectious disease n = 75	Patients without infectious disease n = 73[a]	P value
Maximum body temperature, °C	38.8 (38.2–39.2)	38.4 (37.7–39.0)	0.02
Maximum WBC, $\times 10^3$	16.8 (13.7–19.5)	12.6 (10.7–17.5)	0.01
Maximum CRP, mg/dl	14.6 (7.8–22.8)	1.3 (0.2–8.3)	<0.001
Fever duration, d	1 (0–3)	0 (0–1)	0.01

Values are median (25th–75th percentile); WBC, white blood cell; CRP, C-reactive protein

[a] For two patients without infectious disease, data were missing

Table 3 Multiple regression analysis predicting ln(ICU stay) (R^2 = 0.553)

	Coefficient	Standard error	P value
Sex, male	–0.07	0.11	0.52
Age, per year	0.003	0.005	0.59
GCS at admission			
13–15	Reference		
9–12	0.26	0.25	0.29
6–8	0.50	0.20	0.01
3–5	0.09	0.19	0.63
Surgical intervention	0.87	0.12	<0.001
Complicating infection	0.75	0.11	<0.001

ICU, intensive care unit; GCS, Glasgow Coma Scale

by infectious fever, but also by endogenous pyrogens released by neuronal injury. The impact of elevated body temperature on the length of the ICU stay may be a consequence, at least in part, of worsening cerebral injuries that occur due to ongoing insults. Therefore, the association between elevated body temperature and the length of the ICU stay is complex. Our study tested the hypothesis that complicating infection is a predictor of a longer ICU stay in patients with ICH. Therefore, we did not assess the relationship between the length of the ICU stay and inflammatory parameters, such as body temperature and fever duration; the inflammatory parameters were used to confirm the reliability of the definition of complicating infection.

As expected, the ICU stay was shorter for patients with the most severe and mild ICH (GCS scores of 3–5 and 13–15). Among 72 patients with GCS scores of 3–5, 46 patients died at discharge (64%). Because of early death, the length of ICU stay seems to have been shortened for patients with GCS scores of 3–5. Stroke severity was reported to be a significant predictor of length of hospital stay in previous studies that focused mainly on ischemic stroke [17, 18]. Chang et al. reported that for patients with mild or moderate ischemic stroke, the hospital stay lengthened with increasing stroke severity, while for those who had severe strokes, it decreased with increasing stroke severity [18]. These findings are compatible with our results.

Surgical intervention was, as expected, a significant predictor of the length of the ICU stay. When there is surgical intervention, postoperative wound care is required. Since the patients thought to have a better chance of recovery may have been offered surgery, they would have received rehabilitation until their functional status improved to some extent. Although peri-operative antibiotic prophylaxis may have influenced the prevention of complicating infection, the effect of complicating infection remained significant after controlling for surgical intervention.

It is essential to identify the factors that prevent the occurrence of complicating infection. In a randomized, double-blind, placebo-controlled study, the prophylactic administration of levofloxacin is not better than optimal care for preventing infections in patients with acute stroke [19]. In our study, we did not specify a cause of the infection, which was beyond the scope of this article. Multiple factors may contribute to the high incidence of infection in patients with ICH. Therefore, we cannot suggest a specific plan. Early detection and appropriate treatment of infections seem the most judicious recommendations.

This study has several limitations. The discharge criteria were not clearly specified in advance. Given that an ICU must constantly accept patients in need of emergency care, the staff discharge patients as soon as possible. Hospital stays are much longer in Japan than in the United States and other Organization for Economic Co-operation and Development countries. However, the length of the ICU stay in our study was similar to that in other countries [20, 21]. In a preceding study that investigated 22 Japanese (including our unit) and 40 US hospitals, the risk-adjusted length of the ICU stay in Japan was not significantly longer than that in the US [22]. The decision-making process related to discharge might be influenced by factors other than the clinical factors that we assessed, including caregiver factors. However, only five patients were discharged directly to home in our study, and most of the patients admitted to the ICU are generally discharged to other than home. Therefore, it is unlikely that caregivers influenced the length of the ICU stay greatly. Further studies addressing the influence of different practices on the length of the ICU stay are necessary.

We did not use a universal definition of complicating infection. Standardized radiological and microbiological examinations were not performed. We did not consider related factors, such as symptoms, chest x-rays, and cultures. However, patients with complicating infection had a significantly higher maximum body temperature, maximum WBC, and maximum CRP, and had a significantly longer fever duration than did those without complicating infection.

In conclusion, given the increasing demand of health services owing to an aging population, it is crucial to identify the factors that hamper discharge in order to evaluate the most effective and acceptable methods of managing patients with acute ICH. For patients with acute ICH, after we controlled for sex, age, stroke severity, and surgical intervention, it was found that complicating infection was independently associated with a longer ICU stay. The results of our study may prove valuable for further analysis of cost-effectiveness.

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