



Newly developed stroke in patients admitted to non-neurological intensive care units

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Abstract

Background Little is known about newly developed stroke in patients admitted to the intensive care unit (ICU).

Objective This study aimed to investigate characteristics and outcomes of newly developed stroke in patients admitted to the non-neurological intensive care units (ICU-onset stroke, IOS).

Methods A consecutive series of adult patients who were admitted to the non-neurological ICU were included in this study. We compared neurological profiles, risk factors, and mortality rates between patients with IOS and those without IOS.

Results Of 18,604 patients admitted to the ICU for non-neurological illness, 218 (1.2%) developed stroke (ischemic, $n = 182$; hemorrhagic, $n = 36$). The most common neurological presentation was altered mental status ($n = 149$), followed by hemiparesis ($n = 55$), and seizures ($n = 28$). The most common etiology of IOS was cardioembolism (50% [91/182]) for ischemic IOS and coagulopathy (67% [24/36]) for hemorrhagic IOS. In multivariable analysis, the Acute Physiology and Chronic Health Evaluation II (APACHE II) score (adjusted odds ratio [AOR] = 1.04, 95% CI = 1.03–1.06, $P < 0.001$), prothrombin time (AOR = 0.99, 95% CI = 0.98–0.99, $P = 0.013$), cardiovascular surgery (AOR = 1.84, 95% CI = 1.34–2.50, $P < 0.001$), mechanical ventilation (AOR = 6.75, 95% CI = 4.87–9.45, $P < 0.001$), and extracorporeal membrane oxygenation (AOR = 2.77, 95% CI = 1.62–4.55, $P < 0.001$) were related to the development of IOS. Stroke was associated with increased 3-month mortality after hospital discharge (AOR, 2.20; 95% CI, 1.58–3.05; $P < 0.001$), after adjustment for APACHE II and comorbidities.

Conclusions Patients who developed IOS had characteristics of initial critical illness and managements performed in the ICU as well as neurological presentations. The occurrence of IOS was related to high morbidity and mortality.

Keywords Critical care · Stroke · Cerebral infarction · Intracerebral hemorrhage · Coagulopathy

Introduction

In conjunction with high incidence, in-hospital stroke showed lower rates in reperfusion therapy and greater risk of mortality compared with community-onset stroke [1–3]. Patients admitted to intensive care unit (ICU) have distinct features such as unstable vital signs, coagulopathies, inflammation, as well as multiple comorbidities, and they often receive invasive procedures or surgical treatments. Thus,

there may be high risks of stroke as well as delays in the diagnosis of stroke during admission to the ICU, leading to suboptimal management of critically ill patients [4, 5].

Early detection of acute stroke is imperative for saving viable brain tissues and recovery of neurologic deficits [6]. Time saving measures are being implemented at every step from symptom recognition, imaging studies, and treatments. However, early detection of stroke symptoms in ICU-onset stroke (IOS) is challenging, not only due to comorbidities, but also due to immobilization, medical equipment, and use of sedative agents [7, 8]. Accordingly, there are substantial barriers to the conduct of neuroimaging studies to reveal IOS in the context of general critical care. Comprehensive studies regarding IOS are lacking, which limit the development of strategies for the prevention, early detection, and proper managements of IOS.

Here, we aimed to investigate the neurological and radiological profiles, risk factors, and clinical outcomes of IOS.

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Furthermore, we aimed to investigate differences of such characteristics between ischemic and hemorrhagic strokes.

Methods

Study population

This study was performed at Asan Medical Center, a 2700-bed tertiary hospital in Seoul, Republic of Korea. For this study, medical records of a consecutive series of ICU patients between November 1st, 2012 and March 31st, 2016 were retrospectively evaluated. We included patients who (1) were 18 years of age or older, (2) were admitted to clinical departments other than neurology and neurosurgery, and (3) did not have acute stroke before ICU admission. This study was approved by the institutional review board of Asan Medical Center, and the need for written informed consent was waived because of the retrospective design of the study.

Routine evaluations in the intensive care units

According to the routine practice of our ICUs, neurological evaluations, including the Glasgow Coma Scale, a pupillary size, light reflexes, and muscle strength (the Medical Research Council scale), were performed and documented by nurses every 1–2 h. When nurses detected abnormal neurological findings during their routine evaluations, they notified such findings to treating doctors perform computed tomography (CT) or magnetic resonance imaging (MRI) scans of the brain.

We reviewed electronic medical records for patients' baseline characteristics, laboratory findings, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score at the time of admission to the ICUs [9]. We investigated whether the patients underwent surgery (cardiovascular vs. non-cardiovascular surgery) and invasive cardiovascular interventions before the occurrence of stroke. Moreover, we assessed the application of life-support modalities such as inotropic agents, mechanical ventilation, continuous renal replacement therapy, or extracorporeal membrane oxygenation (ECMO). Systemic inflammatory response syndrome (SIRS) was defined in accordance with international guidelines [10].

Definition of intensive care unit-onset stroke

We defined IOS if (1) CT and/or MRI scans of the brain were performed during ICU admission and (2) CT and/or MRI images revealed findings compatible with acute infarcts, intracerebral hemorrhage (ICH), or subarachnoid hemorrhage (SAH). We dichotomized IOS into ischemic IOS (infarcts) and hemorrhagic IOS (ICH and SAH).

Neurological and radiological assessments

For patients with a diagnosis of IOS, we categorized their symptoms (or signs) into categories such as altered mental status, seizures, pupillary changes (size and light reflexes), hemiparesis, and others. Time domains such as last-known-normal time, first-found-abnormal time, and time to initial neuroimaging studies were also reviewed. Clinical outcomes included length of ICU stay, length of hospital stay, mortality before ICU discharge, mortality before hospital discharge, mortality at 90 days after hospital discharge, and mortality at 90 days from ICU admission.

We evaluated for the presence of vascular stenosis (> 50% reduction of vascular diameter) or occlusion, if the patient underwent cerebral angiography. The subtypes of ischemic IOS were determined according to the classification of the Trial of Org 10,172 in Acute Stroke Treatment (TOAST) [11]. For patients with ICH, we measured the ICH score as well as the lesion location and volume [12]. We categorized the etiologies of ICH into hypertension, cerebral amyloid angiopathy, coagulopathy, medication (antiplatelet agents or anticoagulants), and unknown cause groups [13]. For patients with SAH, we reviewed CT brain scans to identify the presence of ruptured aneurysms and assessed SAH severity using the modified Fisher scale. Neuroimaging studies (CT, MRI, and angiographic studies) were reviewed jointly by two investigators and a third investigator was consulted in case of disagreements.

Clinical management

Treatment modalities for ischemic IOS included antiplatelet agents, anticoagulants, intravenous thrombolysis, intraarterial thrombectomy, and neurosurgery, and those for hemorrhagic IOS were categorized into either neurosurgical or medical treatments.

Statistical analysis

We compared baseline demographics, comorbidities, APACHE II score, the presence of SIRS, laboratory findings, and treatment modalities between patients with IOS and those without IOS using χ^2 tests, *t* tests, and Kruskal–Wallis tests, as appropriate. Variables with a *P* value of < 0.2 by univariate analysis were included as candidate variables in multivariable analysis. Backward stepwise selection was conducted to find factors associated with IOS in multivariable logistic regression models. We further performed all analyses using a forward selection procedure to confirm the final model. We also compared the aforementioned variables between patients with

ischemic IOS and those with hemorrhagic IOS. A Cox proportional hazards model was used to assess the hazard ratios of 90-day mortality from ICU admission according to the presence of stroke, with adjustments for demographics, comorbidities, and APACHE II scores. Kaplan–Meier survival curves were also plotted for mortality of patients with IOS and patients without IOS. Additionally, we evaluated the association between stroke and mortality, with adjustments for demographics, comorbidities, and APACHE II scores using multivariate logistic regression. All statistical analyses were performed using R, version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

A total of 27,679 patients were admitted to 8 adult ICUs during the study period. Of these, we excluded patients younger than 18 years of age ($n=514$), those who were admitted to neurological and neurosurgical departments ($n=8123$), and patients diagnosed with acute stroke before admission to the ICU ($n=438$). Thus, we finally included 18,604 patients. The median age of included patients was 63.0 years (IQR, 53.0–72.0 years) and 11,993 (64.5%) patients were male. Table 1 shows baseline characteristics of the finally included 18,604 patients.

Table 1 Baseline characteristics of the finally enrolled 18,604 study patients

	All patients ($n=18,604$)	IOS (+) ($n=218$)	IOS (–) ($n=18,386$)
Age, years, median (IQR)	63.0 (53.0–72.0)	66.0 (56.3–73.8)	63.0 (53.0–72.0)
Male, n (%)	11,993 (64.5)	136 (62.4)	11,857 (64.5)
Comorbidity, n (%)			
Hypertension	5104 (27.4)	67 (30.7)	5037 (27.4)
Diabetes mellitus	3030 (16.3)	32 (14.7)	2998 (16.3)
Atrial fibrillation	3590 (19.3)	45 (20.6)	3545 (19.3)
Smoking	6217 (33.4)	61 (28.0)	6156 (33.5)
Cancer	6846 (36.8)	88 (40.4)	6758 (36.8)
Findings on ICU admission			
Body mass index, kg/m^2 , mean (SD)	23.6 (3.7)	23.6 (3.5)	23.5 (3.7)
APACHE II score, median (IQR)	14 (9–20)	23 (17–31)	14 (8–20)
SIRS, n (%)	2334 (12.5)	62 (28.4)	2272 (12.4)
Temperature >38 °C or <36 °C	779 (4.2)	29 (13.3)	750 (4.1)
Heart rate >90 /min	683 (3.7)	11 (5.0)	672 (3.7)
Respiration >20 /min or $\text{PaCO}_2 <32$ mmHg	4579 (24.6)	95 (43.6)	4484 (24.4)
Leukocyte $>12,000/\mu\text{L}$ or $<4000/\mu\text{L}$	4857 (26.1)	78 (35.8)	4779 (26.0)
Laboratory tests, median (IQR)			
Hemoglobin, g/dl	12.1 (10.2–13.6)	10.9 (9.3–12.3)	12.1 (10.2–13.6)
Platelet, $10^3/\mu\text{L}$	192 (137–245)	160.5 (86.3–215)	192 (138–246)
Prothrombin time, %	84.0 (59.7–103.1)	63.6 (45.9–87.4)	84.3 (59.9–103.2)
Managements in the ICU			
Cardiovascular surgery, n (%)	3304 (17.8)	71 (32.6)	3239 (17.6)
Cardiovascular procedure, n (%)	658 (3.5)	4 (1.8)	648 (3.5)
Non-cardiovascular surgery, n (%)	8097 (43.5)	54 (24.8)	8043 (47.8)
Mechanical ventilation	3680 (19.8)	161 (73.9)	3519 (19.1)
CRRT	370 (2.0)	26 (11.9)	344 (2.0)
Inotropic agents	7931 (42.6)	174 (79.8)	7757 (42.2)
ECMO	174 (0.8)	21 (9.6)	126 (0.7)

ICU intensive care unit, IOS ICU-onset stroke, APACHE II Acute Physiology and Chronic Health Evaluation II, CRRT continuous renal replacement therapy, ECMO extracorporeal membrane oxygenation, PaCO_2 partial arterial carbon dioxide, SIRS systemic inflammatory response syndrome (meeting 2 or more criteria regarding temperature, heart rate, respiratory rate, and leukocyte), IQR interquartile range, SD standard deviation

Intensive care unit-onset stroke assessments

The incidence of IOS in our study population was 1.2% (218/18,604). Of 18,604 patients, 4056 (21.8%) underwent CT/MRI brain scans (CT, $n=824$ [4.4%]; MRI, $n=2552$ [13.7%]; and CT + MRI, $n=680$ [3.7%]). Of the 4056 patients who underwent CT/MRI imaging, 218 had findings compatible with acute stroke; of these, 182 (83.5%) had ischemic IOS, and 36 (16.5%) had hemorrhagic IOS (ICH, $n=33$; and SAH, $n=3$).

Altered mental status ($n=149$) was the most common neurological manifestation of IOS (the reason to conduct neuroimaging studies), followed by hemiparesis ($n=55$), seizures ($n=28$), pupillary changes ($n=16$), and aphasia ($n=9$). Comatose state (52.8% vs. 13.7%; $p<0.001$) and pupillary changes (25.0% vs. 3.8%; $p<0.001$) were more common in patients with hemorrhagic IOS than those with ischemic IOS, while aphasia (4.9% vs. 0%; $p<0.001$) and hemiparesis (29.7% vs. 2.8%; $p<0.001$) were more common in patients with ischemic IOS than those with hemorrhagic IOS. (Table I in Data Supplement).

When we compared ischemic IOS with hemorrhagic IOS, there was no significant difference in the time interval for stroke recognition (9.1 h [IQR, 2.3–23.5 h] vs. 8.4 h [IQR, 4.1–29.9 h]; $p=0.482$). Of 218 patients with IOS, the median time interval from the first-found-abnormal time to the first neuroimaging studies (CT or MRI scans of the brain), *i.e.*, time interval for neuroimaging, was 5.4 h (IQR, 1.5–24.5 h); the median time interval for neuroimaging studies was significantly longer for patients with ischemic IOS

compared to patients with hemorrhagic IOS (182 patients with ischemic IOS, 6.7 h [IQR, 1.9–29.3 h]; 36 patients with hemorrhagic IOS, 1.8 h [IQR, 1.0–7.4 h]; $p=0.010$).

The main reasons for delays in stroke recognition included the use of sedative agents following surgery ($n=51$) or mechanical ventilation ($n=29$), presumed metabolic encephalopathy ($n=18$), and missed findings of neurological deficits during routine hourly evaluations ($n=4$) (as described for 102 patients who had such a time interval beyond the median time of 8.9 h). Patients with altered mental status as an initial stroke manifestation had time delays to the stroke recognition than patients without altered mental status ($p=0.027$), while patients with seizure as an initial stroke manifestation had shorter time intervals for the stroke recognition than patients without seizure ($p=0.047$). The main reasons for delays in neuroimaging study included unstable vital signs ($n=22$), the application of ECMO ($n=8$), poor cooperation of patients ($n=3$), and unknown reasons ($n=70$) (as described for 103 patients who had a time interval beyond the median time of 5.4 h). Patients with hemiparesis or pupillary changes as a stroke manifestation had shorter time intervals for neuroimaging studies than patients without those symptoms ($p=0.002$ and 0.006 , respectively) (Table 2).

Radiological findings and presumed etiologies of ischemic IOS and hemorrhagic IOS are shown in Table 3. Of the 182 patients with ischemic IOS, cardioembolism (50.0%) was the most common etiology of ischemic IOS, followed by undetermined etiology (39.6%), other determined etiology (6.0%), large-artery disease (2.7%), and small-vessel disease

Table 2 Time delays in recognition of stroke and performance of neuroimaging studies according to neurologic manifestations

	LKNT to FFAT Median (IQR)	<i>p</i> value	FFAT to neuroimaging Median (IQR)	<i>p</i> value
IOS	8.9 (2.6–23.5)	0.482	5.4 (1.5–24.5)	0.010
Ischemic IOS	9.1 (2.3–23.5)		6.7 (1.9–29.3)	
Hemorrhagic IOS	8.4 (4.1–29.9)		1.8 (1.0–7.4)	
Neurological manifestations				
Altered mental status				
Absent ($n=60$)	5.9 (1.8–15.0)	0.027	3.3 (1.4–16.3)	0.183
Present ($n=144$)	10.2 (3.5–32.3)		6.8 (1.5–29.3)	
Hemiparesis				
Absent ($n=149$)	9.2 (2.6–23.9)	0.811	7.3 (1.8–35.9)	0.002
Present ($n=55$)	8.0 (3.8–20.5)		2.8 (1.1–9.7)	
Seizure				
Absent ($n=176$)	9.6 (3.0–24.8)	0.047	5.4 (1.5–23.2)	0.118
Present ($n=28$)	4.4 (1.1–13.9)		5.5 (2.9–46.6)	
Pupillary change				
Absent ($n=189$)	9.2 (2.4–24.7)	0.718	6.1 (1.8–25.9)	0.006
Present ($n=15$)	7.6 (4.0–15.2)		1.1 (0.9–6.6)	

IQR interquartile range, IOS intensive care unit-onset stroke, FFAT first-found-abnormal time, LKNT last-known-normal time

Table 3 Radiological findings and stroke etiologies

Ischemic IOS (<i>n</i> = 182) ^a	
Vascular territory of acute infarcts, <i>n</i> (%)	
Single territory	60 (33.0)
Multiple territory	122 (67.0)
Angiographic findings, <i>n</i> (%)	
Large-artery occlusion	18 (9.9)
Large-artery stenosis > 50%	33 (18.1)
Etiology of acute infarcts, <i>n</i> (%)	
Large-artery disease	5 (2.7)
Small-vessel disease	3 (1.6)
Cardioembolism	91 (50.0)
Undetermined etiology	72 (39.6)
Two or more causes	26 (14.3)
Incomplete study	38 (20.9)
Negative study	8 (4.4)
Other determined etiology	11 (6.0)
Hemorrhagic IOS (<i>n</i> = 36)	
Intracerebral hemorrhage ^b	
Location of hemorrhage	
Supratentorial	26 (72.2)
Infratentorial	6 (18.2)
Supratentorial and infratentorial	1 (3.0)
Volume of hemorrhage, ml, median (IQR)	23.8 (13.6–67.5)
Intracerebral hemorrhage score, median (IQR)	3.5 (2.0–4.0)
Etiology	
Coagulopathy	24 (75.0)
Medication (antiplatelet agents or anticoagulants)	2 (6.3)
Hypertensive	1 (3.1)
Cerebral amyloid angiopathy	1 (3.1)
Unknown	5 (15.6)
Subarachnoid hemorrhage	3 (8.3)
Modified Fisher scale	
1	1 (33.3)
4	2 (66.7)
Etiology	
Ruptured aneurysm	1 (33.3)
Unknown	2 (66.6)

IOS intensive care unit-onset stroke, IQR interquartile range, MRI magnetic resonance imaging, CT computed tomography

^aIncluding 6 patients with hemorrhagic transformation: 3 patients with hemorrhagic infarction type I on the initial brain MRI; 1 patient with hemorrhagic infarction type II on the initial brain CT scan; and 2 patients with hemorrhagic infarction type II on the follow-up CT scan within the first week of the diagnosis of ischemic stroke [28]

^bIncluding 2 patients with cerebral infarct: 1 patient with right frontoparietal lobar hemorrhage showed multiple acute infarcts on the left cerebral hemisphere on the initial CT scan; and 1 patient with extensive bilateral lobar hemorrhage extending into subarachnoid space showed acute temporal cortical infarct on the follow-up CT scan 7 days after the diagnosis of hemorrhagic stroke

(1.6%). Other determined etiologies included cancer-related stroke (*n* = 5), cerebral air embolism (*n* = 3), and arterial dissection (*n* = 2), and meningitis-related stroke (*n* = 1). Of the 33 patients with ICH, the most common etiology of ICH was coagulopathy (*n* = 24), and the presumed causes of such coagulopathy were liver disease (*n* = 11), sepsis (*n* = 9), and hematologic malignancy (*n* = 4). Among 3 patients with SAH, modified Fisher scale was 4 in 2 patients and 1 in 1 patient, and only 1 patient had a ruptured aneurysm.

Risk factors of intensive care unit-onset stroke

In the univariable analysis, risk factors associated with IOS were older age, APACHE II score, SIRS, cardiovascular surgery, non-cardiovascular surgery, use of mechanical ventilation, continuous renal replacement therapy, and use of ECMO. The following laboratory findings were also associated with IOS: hemoglobin level, platelet count, and prothrombin time (*p* < 0.001 for all variables). Multivariable analysis indicated that APACHE II score (adjusted odds ratio [AOR] = 1.04; 95% CI = 1.03–1.06; *p* < 0.001), prothrombin time (AOR = 0.99; 95% CI = 0.98–0.99; *p* = 0.013), cardiovascular surgery (AOR = 1.84; 95% CI = 1.34–2.50; *p* < 0.001), use of mechanical ventilation (AOR = 6.75; 95% CI = 4.87–9.45; *p* < 0.001), and use of ECMO (AOR = 2.77; 95% CI = 1.62–4.55; *p* < 0.001) were related to the occurrence of IOS. When patients with ischemic IOS were compared with patients without IOS, factors associated with ischemic IOS were APACHE II score (AOR = 1.05; 95% CI = 1.03–1.06; *p* < 0.001), cardiovascular surgery (AOR = 1.84; 95% CI = 1.34–2.50; *p* < 0.001), use of mechanical ventilation (AOR = 6.56; 95% CI = 4.64–9.40; *p* < 0.001), and use of ECMO (AOR = 2.72; 95% CI = 1.47–4.73; *p* = 0.001). When patients with hemorrhagic IOS were compared with patients without IOS, factors associated with hemorrhagic IOS were APACHE II score (AOR = 1.04; 95% CI = 1.01–1.07; *p* = 0.014), prothrombin time (AOR = 0.98; 95% CI = 0.97–0.99; *p* = 0.002), use of mechanical ventilation (AOR = 10.04; 95% CI = 4.16–28.10; *p* < 0.001), and use of ECMO (AOR = 3.71; 95% CI = 1.32–9.01; *p* = 0.007) (Table 4).

Managements for intensive care unit-onset stroke

Of the 182 patients with ischemic IOS, antithrombotic agents (antiplatelet agents and anticoagulants) were given to 164 patients. Antithrombotic agents were not given to 18 patients due to thrombocytopenia (*n* = 13), hemoptysis (*n* = 2), large infarct size (*n* = 2), and for uncertain reasons (*n* = 1). The reperfusion therapy rate for IOS was 7.1% (13/182; intravenous thrombolysis, *n* = 5; intraarterial thrombectomy, *n* = 8) in our study population. Intravenous thrombolysis (infusion of alteplase) was attempted in 5 patients. The reasons

Table 4 Risk factors for IOS

	IOS (<i>n</i> = 218)		Ischemic IOS (<i>n</i> = 182)		Hemorrhagic IOS (<i>n</i> = 36)	
	Univariate analysis OR (95% CI)	Multivariate analysis AOR (95% CI)	Univariate analy- sis OR (95% CI)	Multivariate analysis AOR (95% CI)	Univariate analy- sis OR (95% CI)	Multivariate analysis AOR (95% CI)
Age, years	1.02 (1.00–1.03)		1.02 (1.01–1.04)		0.98 (0.96–1.00)	
Sex, male	0.91 (0.70–1.21)		0.97 (0.72–1.32)		0.69 (0.36–1.35)	
Comorbidities						
Hypertension	1.36 (0.97–1.90)		1.58 (1.10–2.29)		0.67 (0.27–1.49)	
Diabetes mellitus	0.94 (0.62–1.38)		1.08 (0.70–1.63)		0.42 (0.10–1.20)	
Atrial fibrillation	1.09 (0.77–1.50)		1.22 (0.85–1.71)		0.52 (0.16–1.32)	
Smoking	0.80 (0.57–1.11)		0.75 (0.51–1.09)		1.05 (0.48–2.28)	
Cancer	1.17 (0.89–1.53)		1.08 (0.79–1.45)		1.72 (0.89–3.33)	
Findings on ICU admission						
APACHE II score	1.08 (1.07–1.09)	1.04 (1.03–1.06)	1.07 (1.06–1.09)	1.05 (1.03–1.06)	1.10 (1.07–1.13)	1.04 (1.01–1.07)
SIRS	2.82 (2.09–3.80)		2.33 (1.64–3.24)		6.35 (3.26–12.2)	
Hemoglobin, g/dl	0.85 (0.80–0.90)		0.88 (0.82–0.93)		0.72 (0.62–0.83)	
Platelet count, 10 ³ /μL	0.99 (0.99–0.99)		1.00 (0.99–1.00)		0.99 (0.98–0.99)	
Prothrombin time, %	0.98 (0.98–0.99)	0.99 (0.98–0.99)	0.99 (0.98–0.99)		0.97 (0.96–0.98)	0.98 (0.97–0.99)
Managements in the ICU ^a						
Cardiovascular surgery	2.26 (1.70–3.01)	1.84 (1.34–2.50)	2.48 (1.81–3.36)	1.84 (1.34–2.50)	1.34 (0.57–2.81)	
Non-cardiovascular surgery	0.42 (0.31–0.57)		0.37 (0.26–0.53)		0.73 (0.36–1.41)	
Mechanical ventilation	1.63 (1.24–2.13)	6.75 (4.87–9.45)	1.58 (1.17–2.11)	6.56 (4.64–9.40)	1.92 (0.99–3.71)	10.04 (4.16–28.10)
CRRT	3.71 (2.20–5.90)		3.17 (1.71–5.41)		6.66 (2.26–15.8)	
Inotropic agents	1.24 (0.95–1.62)		1.14 (0.85–1.52)		1.97 (1.01–3.99)	
ECMO	3.74 (1.96–6.49)	2.77 (1.62–4.55)	2.95 (1.32–5.67)	2.72 (1.47–4.73)	8.03 (2.38–20.4)	3.71 (1.32–9.01)

ICU intensive care unit, IOS ICU-onset stroke, APACHE II the Acute Physiology, and Age, Chronic Health Evaluation II, FDP degradation products, CRRT continuous renal replacement therapy, ECMO extracorporeal membrane oxygenation, SIRS systemic inflammatory response syndrome, OR odds ratio, AOR adjusted odds ratio, CI confidence interval

^aEvents preceding stroke

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not to perform intravenous thrombolysis in the remaining 177 patients were as follows: neuroimaging studies were performed beyond 4.5 h from the last-known-normal time (*n* = 159), patients underwent recent major surgery (*n* = 9), had large hemispheric infarct (*n* = 1), prolonged activated partial thromboplastin time (*n* = 1), mild neurological deficits (*n* = 1), delays in decision-making (*n* = 2), and uncertain reasons (*n* = 4). Of 18 patients with large-artery occlusion, intraarterial thrombectomy was performed in 8 patients. Of the remaining 10 patients, intraarterial thrombectomy was not attempted due to reasons such as the patients having absence of diffusion-perfusion mismatch (*n* = 4), recent aortic surgeries (*n* = 3), rapidly resolving neurological

symptoms (*n* = 1), unstable vital signs (*n* = 1), or for uncertain reasons (*n* = 1). Two patients received decompressive craniectomy for large hemispheric infarcts. Of the 36 patients with hemorrhagic IOS, 5 (13.9%) underwent surgical treatments including decompressive hemicraniectomy (*n* = 3), decompressive hemicraniectomy with hematoma evacuation (*n* = 1), and bilateral frontotemporal decompressive craniectomy (*n* = 1).

Clinical outcomes of patients with ICU-onset stroke

The length of ICU stay was longer in patients with IOS compared with those without IOS (median days, 12.0 [IQR,

5.0–26.5] vs. 2.0 [IQR, 1.0–4.0]; $p < 0.001$). Accordingly, the length of hospital stay was longer in patients with IOS than those without IOS (median days, 29.0 [IQR, 13.8–58.0] vs. 12.0 [IQR, 7.0–24.0]; $p < 0.001$). Patients with IOS had higher mortality before ICU discharge (26.1% vs. 7.8%; $p < 0.001$), before hospital discharge (31.7% vs. 9.4%; $p < 0.001$), and during the first 90 days after hospital discharge (43.1% vs. 14.0%; $p < 0.001$), compared with those without IOS (Fig. 1). In the multivariable logistic regression analysis, patients with IOS had higher mortality before ICU discharge (AOR, 1.78; 95% CI, 1.23–2.57; $p = 0.002$), before hospital discharge (AOR, 1.87; 95% CI, 1.32–2.63;

$p < 0.001$), and at 90 days after hospital discharge (AOR, 2.20; 95% CI, 1.58–3.05; $p < 0.001$) than patients without IOS, after adjustments for APACHE II score and comorbidities. The Cox proportional hazard model showed that patients with IOS had a hazard ratio of 1.31 in terms of mortality at 90 days after hospital admission (95% CI, 1.04–1.64; $p = 0.002$) after adjusting for APACHE II score and comorbidities (Fig. 2).

Discussion

This is one of the largest studies reported to date on the rate of newly developed stroke during ICU care in patients with non-neurological disease. We found the incidence of IOS among adult patients admitted to ICU with non-neurological critical illnesses was 1.2% (218/18,604). The proportions of patients with ischemic and hemorrhagic IOS were 83% and 17%, respectively. Cardiovascular surgery was associated with ischemic IOS, and prothrombin time prolongation was associated with hemorrhagic IOS; higher APACHE II scores, mechanical ventilator and ECMO were associated with both ischemic and hemorrhagic IOS. Patients with IOS had high mortality rates before hospital discharge (32%) and at 90 days after hospital discharge (43%), which were approximately twice as high as the mortality rates of patients without IOS. Furthermore, the occurrence of IOS was independently associated with 2.2-fold increased risk of mortality at 90 days from hospital discharge.

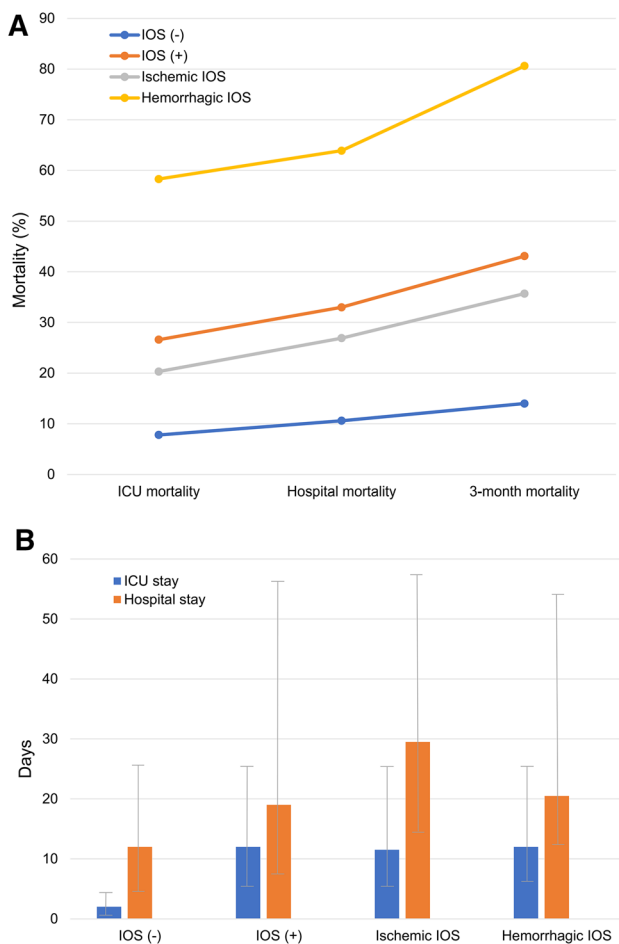


Fig. 1 Mortality and length of stay according to the occurrence of IOS. **a** Patients with stroke had significantly higher mortality at all three time points compared with those without IOS ($p < 0.001$ in all time points). Patients with hemorrhagic stroke had higher mortality than those with ischemic IOS ($p < 0.001$ in all time points). **b** The length of stay in both the ICU and hospital were longer in patients with stroke compared to those without IOS ($p < 0.001$ in all time points). The length of stay in the ICU and hospital were not significantly different between patients with ischemic IOS and patients with hemorrhagic IOS. All values are presented as median. Error bars indicate interquartile ranges. ICU intensive care unit, IOS ICU-onset stroke

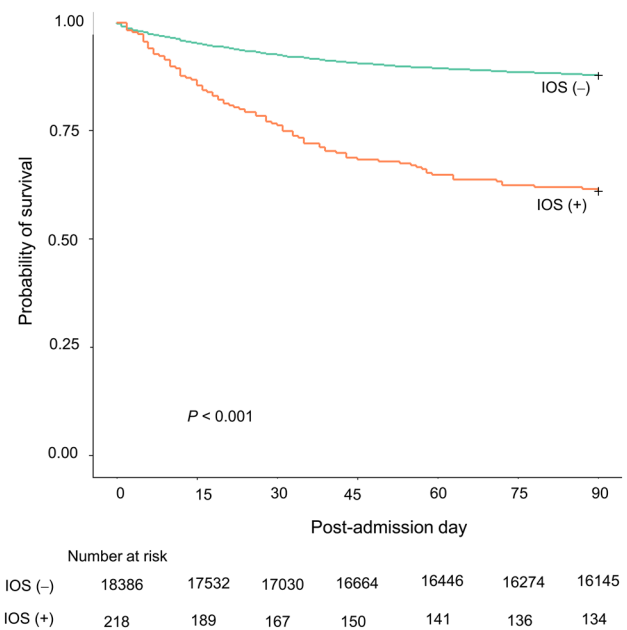


Fig. 2 Survival status according to the presence of IOS. The mortality 90 days after admission to the intensive care unit in both groups was compared. IOS intensive care unit-onset stroke

The incidence of IOS was higher than expected. During a median 4.0 days of their ICU admission, 1.2 of 100 patients developed IOS, which was much more common compared with general population in Korea (stroke incidence, 232 per 100,000 person-years) [14]. Moreover, risk factors for IOS in the current study were very different from well-known risk factors for community-onset stroke: critical conditions (e.g., APACHE II score, cardiovascular surgery, mechanical ventilation, and ECMO), but not the premorbid conditions (e.g., old age, hypertension, diabetes mellitus, and atrial fibrillation), were related to IOS. Cardiovascular surgery was also a risk factor for in-hospital stroke [4]. Prothrombin time prolongation, which suggests increased bleeding tendency, was associated with hemorrhagic IOS. This is in line with the most common etiology of ICH; coagulopathy from sepsis, liver failure, and hematologic malignancy. We also found that the application of mechanical ventilation and ECMO was related to both ischemic and hemorrhagic IOS. Positive pressure ventilation may provoke thromboembolism by inducing hypercoagulable state, opening unrecognized patent foramen ovale, and new-onset atrial fibrillation [15–19]. In addition, weaning from mechanical ventilation may induce hemodynamic changes and cardiac failure [20]. Exposure of blood to the ECMO circuit may result in the formation and embolization of thrombi. ECMO may also lead to platelet dysfunction and coagulopathy, and the use of anticoagulants may contribute to the occurrence of ICH [21]. These conditions might invoke or trigger both ischemic and hemorrhagic IOSs in vulnerable patients who were admitted to the ICU.

The current study showed that neurological manifestations may differ between ischemic and hemorrhagic IOS. Aphasia and hemiparesis were more common in patients with ischemic IOS than in patients with hemorrhagic IOS, while altered mental status and pupillary changes were more common in patients with hemorrhagic IOS than in patients with ischemic IOS. The diagnosis of stroke based on clinical findings is important in IOS, because there are high risks in transporting patients to the outside of the ICU for neuroimaging studies [22, 23].

It is important to recognize altered mental status as a potential clinical presentation of IOS. The recognition of stroke is probably the first step to perform urgent brain and vascular imaging and allow rapid treatments. In patients admitted to the ICU, however, altered mental status related to sedative agents are likely difficult to be differentiated from altered mental status as the presenting symptom of IOS. The most common reason for delays in stroke recognition in our patients was the use of sedative agents following surgery and mechanical ventilation. Unfortunately, altered mental status was also the most common neurological manifestation of IOS. Thus, delays in symptom recognition were substantial in our patients with altered mental status. To reduce delays

in the stroke recognition for patients requiring sedative agents, targeting light sedation, interrupting sedative agents daily, and administering sedative agents with short context-sensitive half-time may be helpful [24, 25]. Patients with hemiparesis and pupillary changes had significantly shorter time intervals from the recognition of stroke symptoms to the performance of neuroimaging studies. Such differences of time intervals according to neurological symptoms may be in part due to the physician's confidence of the occurrence of IOS. Otherwise, coexisting medical conditions such as unstable vital signs and applications of medical equipment could have interfered with the performance of neuroimaging studies.

Time delays in diagnosing stroke may contribute to low rates of reperfusion therapy, which may result in worse outcomes. Reperfusion therapy was performed in only 7.1% in patients with ischemic IOS (intravenous thrombolysis, 2.7%; intraarterial thrombectomy, 4.4%), which is much lower than the reperfusion therapy rate in our previous study of emergency room treatment of community-onset stroke (intravenous thrombolysis and/or intraarterial thrombectomy, 15.8%; intravenous thrombolysis, 11.4%; intraarterial thrombectomy, 6.4%) as well as that in Korean nation-wide statistics for patients with community-onset stroke (intravenous thrombolysis, 10.7%; and intraarterial thrombectomy, 3.6%) [14, 26]. Notably, in 87% (159/182) of patients with ischemic IOS, the reason to not conduct intravenous thrombolysis was delays in identifying stroke beyond 4.5 h from the last-known-normal time. These patients could have received thrombolytic therapy if their strokes were detected earlier, and such therapy could have improved their outcomes. These findings suggest that special attention is necessary to expedite assessments and therapies for patients with IOS.

The mortality rate at any stage from ICU discharge to 90 days after discharge was significantly higher in patients with IOS than those without IOS. We evaluated increased risk of mortality by stroke both at 90 days after hospital discharge and 90 days after admission, because stroke onset time was wide-ranging. The mortality rate at 90 days after hospital discharge in patients with IOS was 43%, which is approximately three times higher compared with mortality rate in patients without IOS (14%) and mortality rate in patients with community-onset stroke (13%) [14]. It is uncertain whether the high mortality rate of patients with IOS resulted from IOS per se or if the high rate resulted from an underlying medical illness or an interaction between an underlying illness and IOS. However, the occurrence of IOS was associated with mortality, even after adjustments for APACHE II scores and comorbid conditions. These findings underline the importance of early detection and proper management of stroke in patients admitted to the ICU with non-neurological critical illness. As most patients with IOS are taken care of

by general physicians and intensivists who do not specialize in stroke management, the activation of stroke code and specialized teams may be needed for patients with stroke symptoms [27].

Our study has limitations. First, this is a single-center retrospective study; thus, our findings should be interpreted cautiously for patients in other centers. Second, the incidence of IOS might be underestimated in our study. We defined stroke according to the findings on CT and/or MRI images of the brain, but only 22% of ICU patients underwent such neuroimaging studies, so patients who developed stroke but did not undergo neuroimaging studies, due to very unstable vital signs and early death soon after admission to the ICU, may not have been identified as having IOS. Moreover, among patients who underwent brain scans for this study, as many as 20.3% underwent CT scans without MRI. It is possible that CT scans could have missed acute infarcts, because the sensitivity of CT for detecting acute infarct is lower than MRI (diffusion-weighted imaging). Third, neurological outcomes as evaluated with validated scales, such as the modified Rankin Scale, were not available for this retrospective study. The mortality and length of stay at ICU and at hospital may be insufficient to evaluate clinical outcomes of stroke victims.

Conclusions

Patients with initially severe illness, cardiovascular surgery, prothrombin time prolongation, and application of mechanical ventilation and ECMO had high risks for developing acute stroke during their admission to the ICU. Substantial time delays ensued in the evaluation and management of IOS. IOS was associated with increased morbidity and mortality. These results call for strategies for prevention, early detection, and proper managements for IOS.

Author contributions SJ, JYC, and S-BJ contributed to the concept and design of the study. SJ, JYC, SJ, S-BJ contributed to the acquisition and analysis of the data. SJ and S-BJ contributed to drafting the text, which was reviewed and revised by all co-authors.

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Data availability All deidentified data that support the findings of this study are available upon reasonable request to the corresponding author from other researchers if ethical approval is granted.

Compliance with ethical standards

Conflicts of interest The authors have no conflicts of interest to declare.

Ethical standards This study was approved by the institutional review board of Asan Medical Center.

Ethics approval and consent to participate This study was approved by the institutional review board of Asan Medical Center, and the need for written informed consent was waived because of the retrospective design of the study.

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