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Risk of delirium and impaired neurological outcome associated with delay in neurorehabilitation after acquired brain injury

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ABSTRACT

INTRODUCTION Brain injury from haemorrhage, trauma, aneurysm and stroke is characterised by high mortality and impaired neurological outcome. In the OUTREACH study, the authors wanted to assess patient care from admission to intensive neuro rehabilitation to discharge. We hypothesised that early rehabilitation was beneficial to neurological outcome.

METHODS 180-day mortality and modified Rankin Scale (mRS) were primary end points. Secondary end points included length of stay, Glasgow Coma Scale (GCS) on admission, ventilator days, Simplified Acute Physiology Score (SAPS II/III) and serious adverse events.

RESULTS Sixty-seven patients were included. Mortality at 180 days was 17.91% and the median mRS score was four. Length of stay was 20.89 ± 12.33 days. GCS at admittance was 13 (3-15). The average SAPS II/III score was 55.72 ± 20.03. Twenty-eight patients suffered from serious adverse events. In all, 47 patients waited for transfer to another facility for an average of 7.77 ± 6.08 days. For mRS, the linear model indicated a negative effect of waiting time (effect = –0.056 (95% confidence interval (CI): –0.117-0.004); p = 0.07). Risk of delirium was significantly affected by waiting time; an additional day of waiting increased the risk of delirium by 13.4% (odds ratio = 1.134 (95% CI: 1.028-1.252); p = 0.01).

CONCLUSIONS In this study, mortality and neurological outcome were comparable with those reported in similar studies. Waiting for transfer to another facility due to capacity significantly impairs neurological outcome and increases delirium.

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The human brain is a delicate organ and intracerebral haemorrhage, traumatic brain injury, subarachnoid haemorrhage and stroke with subsequent malignant cerebral infarction are therefore devastating conditions characterised by high mortality [1] and severely impaired neurological outcome [2]. For survivors, life-long physical and psychological impairment is imminent. Studies have shown that early neurorehabilitation (NR) can improve neurological outcome [3, 4], supporting the need for a sufficient set-up for early NR.

The treatment possibilities for acute brain injury have improved drastically in the past decade, leading to increased survival rates in the acute phase [5, 6]. The need for NR has increased accordingly, leaving the

rehabilitation centres with an increased demand for in-patient NR.

In the OUTREACH study, the authors aimed to assess patient care from admission to intensive NR (I-NR) to discharge to another facility. We hypothesised that early neurorehabilitation is beneficial to neurological outcome and that waiting time from the intensive care unit to in-patient rehabilitation departments may have a negative effect on functional outcome and the development of serious adverse events (SAE).

PICOST statement

Eligible for this study were patients admitted to an I-NR unit for early neurorehabilitation at a regional hospital in Denmark. The intervention was early neurorehabilitation. Comparison between patients was conducted as per the descriptive data. The outcome measures were 180-day mortality and modified Rankin Scale (mRS) at discharge. The present study was a non-interventional, descriptive, retrospective study. The study period ran from 1 February 2017 to 1 July 2020.

ABBREVIATIONS

CI = confidence interval
GCS = Glasgow Coma Scale
I-NR = intensive neurorehabilitation
ICU = intensive care unit
LOS = length of stay
mRS = modified Rankin Scale
NR = neurorehabilitation
OR = odds ratio
SAE = serious adverse events
SAPS = Simplified Acute Physiology Score
SDU = step-down unit

METHODS

Research questions

Is early neurorehabilitation beneficial to neurological outcome and does waiting time affect the outcome?

Inclusion process

All consecutive patients admitted to I-NR were evaluated for inclusion by the investigators. The inclusion criteria were severe acute brain injury or neurological disease with a need for respiratory assistance in an intensive care unit. The exclusion criteria were progressive neurological disease, e.g. amyotrophic lateral sclerosis and patients in need of ventilator assistance due to non-neurological disease.

Authorisations and data handling

After authorisation from the Danish Patient Safety Authority, 18 August 2020, and from the Region of Southern Denmark (Record no /31596 and /34623), data were obtained from the management systems Cosmic and CIS

(Cambio Healthcare Systems, Denmark). Statistical analysis was performed using the STATA IC 16.0 software package software (STATA Corp., College Station, USA).

Primary end points synthesis

The primary end points were 180-day mortality and mRS at discharge. 180-day mortality is death within 180 days from ictus.

Secondary end points synthesis

Length of stay (LOS) in the intensive care unit (ICU); Glasgow Coma Scale (GCS) on admission to the ICU; ventilator days in the ICU; Simplified Acute Physiology Score II and III (SAPS II/III); SAE.

Descriptive data synthesis

For descriptive purposes, we recorded gender, age, diagnosis, time from ictus to transfer to I-NR, tracheostomies, time to decannulation of tracheostomy, gastrostomies, neurosurgery before admission to I-NR, final destination and time spent waiting for transfer to a relevant facility.

Statistical analysis

Non-normally distributed continuous data were given as median (interquartile range). Normally distributed continuous variables were reported as means ± standard deviations. Categorical variables were presented as numbers with percentages.

The primary outcomes were analysed using regression analyses. For 180-day mortality, a logistic regression was applied. For mRS, a linear regression (assuming normal distribution) was applied along with a nonparametric median regression without this assumption. As covariates, the following were included: age, gender, SAPS II/III, GCS, time from ictus to INR and waiting time.

The effect of waiting time on difference in mRS was analysed using regression analyses, both with difference in mRS as outcome and adjusted for covariates (age, gender, SAPS II/III, GCS and I-NR). Two regression analyses with waiting time (in days) and waiting time (yes/no) were conducted.

Differences in mRS change were analysed using an Anova analysis with difference in mRS as outcome and diagnosis groups (1-6) as classes. The Anova analysis was supplemented by a box plot of mRS difference by diagnosis groups.

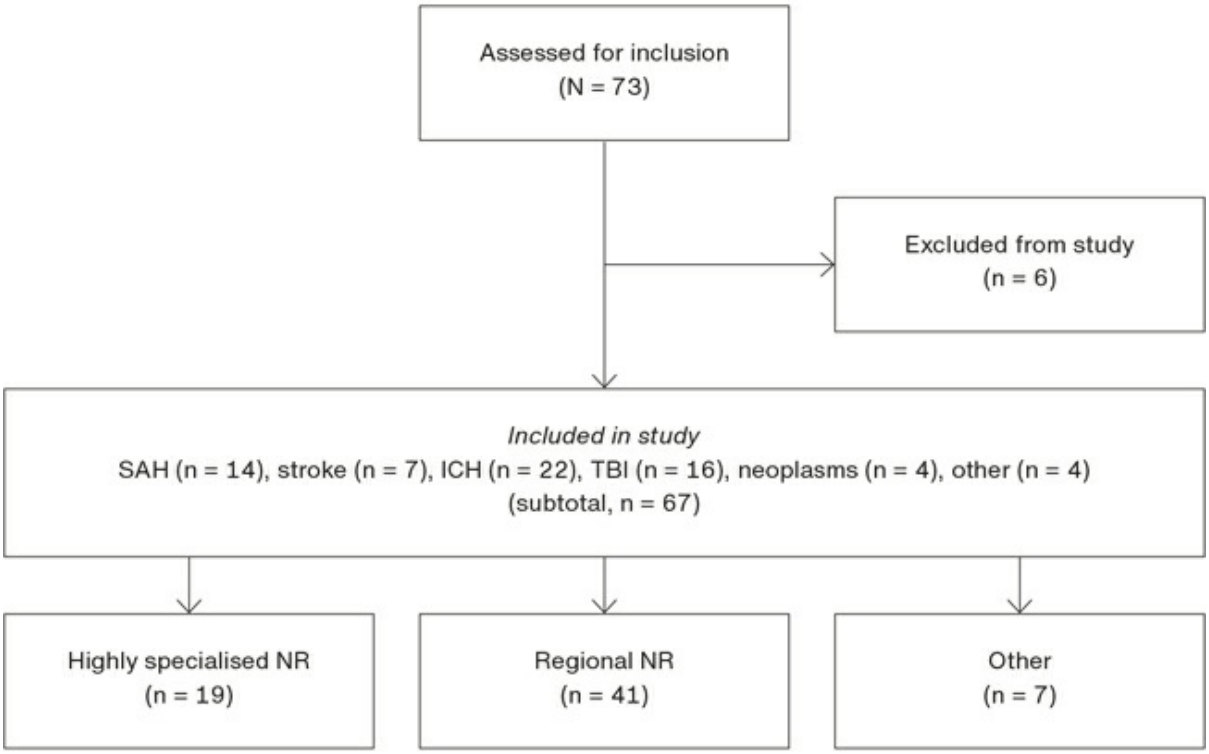
Trial registration: not relevant.

RESULTS

Primary end point results

Seventy-three patients were admitted to the I-NR unit in the study period from 1 February 2017 to 1 July 2020. Six patients were excluded for protocol violation, i.e. did not meet the inclusion criteria. Thus, 67 patients were included in the study (**Figure 1**). The 180-day mortality was 17.91% (12/67, nine males, three females, mean age 69.67 ± 14.52 years). The median mRS score at discharge was 4 (0-6). Nineteen patients (28.35%) were independent at discharge from hospital (mRS: 0-2). Thirteen patients (19.4%) required some help but were able to walk without assistance (mRS = 3). Twenty-eight patients (42%) required assistance with most bodily needs (mRS: 4-5).

FIGURE 1 OUTREACH study flow chart.



ICH = intracerebral haemorrhage; NR = neurorehabilitation; SAH = subarachnoid haemorrhage; TBI = traumatic brain injury.

Secondary end point results

LOS in ICU was 20.88 ± 12.33 days. Median GCS at admittance was 13 (3-15). Thirty patients (44.78%) were on mechanical ventilation for 7.97 ± 7.02 days. The SAPS II/III score was 55.72 ± 20.03. In all, 28 patients (41.79%) suffered from SAE, including delirium (64.29%), urine tract infection (21.42%), shunt dysfunction (7.14%), ventriculitis (3.57%) and adult respiratory distress syndrome (3.57%). Two patients died from SAE, i.e. cardiac arrest (3.57%) and sepsis (3.57%), respectively. Delirium was judged as an avoidable SAE; the remaining, as unavoidable. Three patients (4.48%) were readmitted to a university hospital for neurosurgical complications.

Descriptive data results

The gender distribution was 39 men (58.21%) versus 28 women (41.79%). Mean age at admission to I-NR was 62.9 ± 13.4 years. Time from ictus to transfer to I-NR was 21.42 ± 14.42 days. In all, 55 patients (82.09%) had a tracheostomy and 39 patients (58.21%) a gastrostomy. Fifty (74.63%) patients were decannulated at an average 11.0 ± 9.77 days after admission.

After I-NR, 19 patients (28.36%) were transferred to highly specialised NR, 41 patients (61.19%) to regional NR and seven patients (10.45%) were categorised as "other", i.e. three patients died during I-NR treatment, one was transferred to another regional NR facility and one was discharged directly home. One patient was transferred to a department of neurosurgery due to complications and died. Finally, one patient was transferred to a medical unit.

Forty-seven patients (70.15%) waited for transfer to another facility for 7.77 ± 6.08 days. The total number of days

spent waiting for transfer was 365 days. Patients accepted for highly specialised treatment spent 10.94 ± 7.11 days waiting for transfer, whereas those admitted to regional NR waited 6.39 ± 4.37 days.

The total results are displayed in **Table 1**. The distribution of diagnoses is presented in **Table 2**.

TABLE 1 OUTREACH results chart.

	Result
Primary end points	
180-day mortality, % (n/N)	17.91 (12/67)
mRS, median (IQR), score:	
On admission	5 (1-6)
At discharge	4 (1-6)
Secondary end points	
Length of stay at I-NR, mean ± SD, days	20.88 ± 12.32
GCS at admission to I-NR, median (IQR), score	13 (3-15)
Ventilator time, mean ± SD, days	7.97 ± 7.02
SAPS II/III, mean ± SD	55.72 ± 20.03
Serious adverse events, % (n/N)	41.79 (28/67)
Descriptive data	
Male/female patients, n (%)	39/28 (58.21/41.79)
Dead male/female patients, n (%)	9/3 (75.00/25.00)
Age at admission to I-NR, mean ± SD, yrs	62.9 ± 13.4
Time from ictus to admission to I-NR, mean ± SD, days	21.42 ± 14.42
Time from admission to I-NR to decannulation, mean ± SD, days	11.00 ± 9.77
Tracheostomy, % (n/N)	82.09 (55/67)
Gastrostomy, % (n/N)	58.21 (39/67)
Neurosurgery before admission to I-NR, % (n/N)	61.19 (41/67)
Waiting time data	
Total length of stay in I-NR, days (a)	1,399
Total waiting time for transfer, days (b)	365
Proportion waiting time for transfer, % (b/a)	26.09 (365/1,399)
Proportion of patients waiting for transfer, % (n/N)	89.47 (17/19)
Proportion of patients waiting for R-NR, % (n/N)	63.41 (26/41)
Proportion of patients waiting for other, % (n/N)	57.14 (4/7)
Average waiting time for HS-NR, mean ± SD, days	10.94 ± 7.11
Average waiting time for R-NR, mean ± SD, days	6.39 ± 4.37
Average waiting time for other, mean ± SD, days	3.25 ± 1.71

GCS = Glasgow Coma Scale; HS-NR = highly specialised neurorehabilitation; I-NR = intensive neurorehabilitation; IQR = interquartile range; mRS = modified Rankin Scale; R-NR = regional neurorehabilitation; SAPS II/III = Simplified Acute Physiology Score; SD = standard deviation.

TABLE 2 OUTREACH diagnosis groups.

Group no.	Diagnosis	n
1	Aneurysmal subarachnoid haemorrhage	14
2	Late effects of ischaemic stroke	7
3	Brain haemorrhage	22
4	Traumatic brain injury	16
5	Neoplasms of the brain or the central nervous system	4
6	Other[a]	4

a) Idiopathic intracranial hypertension, epilepsy, Guillain-Barré syndrome, aneurysm, non-ruptured.

Regression analyses results

For 180-day mortality, the odds ratio (OR) of 1.044 (95% confidence interval (CI): 0.979-1.114; p = 0.19) indicated that the risk of dying within 180 days increased by 4.8% per year. For males, an OR of 2.381 (95% CI: 0.540-10.50; p = 0.25) indicated that the risk of dying within 180 days was 126% higher for males than for females.

For 180-day mortality, an OR below one indicated that a longer waiting time reduced mortality (OR = 0.915 (95% CI: 0.792-1.057); p = 0.23). For mRS, the linear model (assuming normal distribution of mRS) indicated a negative effect of waiting time (effect = –0.056 (95% CI:–0.117-0.004); p = 0.07), i.e. an additional day of waiting reduced the expected mRS by 0.056 units. This result is not sensitive to the normality assumption as the median regression indicates a much similar effect (effect = –0.06 (95% CI:–0.130-0.009); one-sided p = 0.09).

For risk of delirium, an OR of 1.023 (95% CI: 0.970-1.079; p = 0.40) indicated that the risk of delirium increased by 2.3% per year of age. For males, an OR of 1.604 (95% CI: 0.472-5.477; p = 0.45) indicated that the risk of delirium was 60% higher for males than for females. The risk of delirium was significantly affected by waiting time; an additional day of waiting increased the risk of delirium by 13.4% (OR = 1.134 (95% CI: 1.028-1.252); p = 0.01).

The regression analyses showed that change in mRS was significantly reduced by waiting time, by 0.024 units per day (95% CI: –0.136-–0.011; p = 0.022), and that those waiting had a significant average reduction in mRS difference of 0.843 (95% CI: –1.686-0; p = 0.05).

The Anova analysis showed that mRS changes did not vary significantly by diagnosis groups (F = 2.13; p = 0.07) and the box plots for diagnosis groups overlapped considerably.

The regression analyses for primary outcomes are displayed in **Table 3.**

TABLE 3 OUTREACH regression analyses for primary outcomes.

	Logistic regression for 180-day mortality		Linear regression for mRS		Median regression for mRS	
	OR (95% CI)	p-value[a]	effect (95% CI)	p-value	effect (95% CI)	p-value
Age	1.044 (0.979-1.114)	0.19	0.021 (–0.010-0.052)	0.18	0.026 (–0.024-0.075)	0.30
Male	2.381 (0.540-10.50)	0.25	0.312 (–0.387-1.010)	0.38	0.318 (–0.683-1.318)	0.53
SAPS II/III	1.005 (0.965-1.046)	0.82	0.017 (–0.003-0.037)	0.09	0.007 (–0.020-0.034)	0.59
GCS	0.926 (0.757-1.132)	0.45	–0.106 (–0.211- –0.001)	0.05	–0.093 (–0.252-0.067)	0.25
Ictus → I-NR	1.007 (0.956-1.061)	0.79	0.004 (–0.021-0.029)	0.77	0.012 (–0.036-0.060)	0.61
Waiting time	0.915 (0.792-1.057)	0.23	–0.056 (–0.117-0.004)	0.07	–0.060 (–0.130-0.009)	0.09[a]

CI = confidence interval; GCS = Glasgow Coma Scale; I-NR = intensive neurorehabilitation; mRS = modified Rankin Scale; OR = odds ratio; SAPS II/III = Simplified Acute Physiology Score.
a) 1-sided p-value.

DISCUSSION

A favourable outcome in 28% of the patients is considered acceptable. In the majority of our patients, the brain injury was caused by a cerebrovascular event and our data are comparable with those of studies including stroke patients [7, 8]. Thirty-two patients achieved some form of independency despite their poor starting point, supporting the hypothesis that early neurorehabilitation was beneficial. Therefore, even severely affected patients had benefit from neurorehabilitation regardless of aetiology or age.

A 180-day mortality rate of 17.91% is low compared with results from other studies [9]. An outcome study [8] described that one in four patients died within the first two days after stroke. We are aware that our data may potentially be biased towards a falsely low mortality due to the fact that our study also included non-stroke patients and that our stroke patients had already survived the first critical days immediately after their insult.

In our study, the magnitude of SAE was 42%, which is higher than reported in another study [10]. Delirium was the major SAE and is judged as avoidable. Since unnecessary waiting time significantly increased the risk of delirium, we believe that by reducing this unnecessary period, delirium may be avoided or at least reduced. We strongly believe that, without waiting, the level of SAE would be comparable to that of the previous study.

More than 80% of our patients had a tracheostomy and were decannulated within eleven days, which - to our belief - is a high fraction, depicting the magnitude of severe brain damage at admission. No evidence-based guidelines exist for optimal timing of tracheotomy [11], only institutional protocol and practice. The majority of patients had a tracheostomy performed prior to arrival in our department, reducing time to ventilator weaning and decannulation, which is essential for mobilisation and partaking in daily training activities. Finally, as we have demonstrated, early decannullation will reduce LOS in the ICU and thus limit the risk of delirium.

In our patients, waiting time had a significant negative effect on the overall outcome and the risk of delirium. Delirium is a serious condition associated with cognitive impairment, increased mortality and morbidity [12]. In our facility, along with a multitude of iatrogenic causes, the time spent in the challenging environment of an ICU may in itself produce delirium, as described by Kamdar et al. [13]. Delirium prevents the patient from partaking in the physiotherapy and cognitive training that are paramount in NR. Early detection [14] is one way of counteracting and treating delirium.

The waiting time for transfer to another facility also hindered the admittance of other patients with a need of early NR in combination with intensive care. A total waiting time of 365 days distributed on 67 individual cases must be taken into consideration when evaluating our concept. With a mean length of stay of some 21 days, approximately 17 additional patients could have been treated in the study period.

To avoid unnecessary waiting time, a demand exists for adequate rehabilitation settings with resources to

provide the right care for the right number of patients in the right amount of time. Until these demands are met, inherent risk exists of unnecessary delays in the rehabilitation process along with a significant risk of a poorer functional outcome.

One solution to waiting for transfer is a step-down unit (SDU). The feasibility and safety of the SDU concept was previously described [15, 16] and would definitely reduce LOS in the ICU and therefore potentially reduce SAE, especially delirium and, not least, improve neurological outcome as we have demonstrated in this study. Medical governance and a meticulous selection of SDU candidates by the treating physicians is of paramount importance. The SDU should work closely together with neurologists and intensivist on call and use protocols [17] to ensure a safe transfer from the ICU in order to streamline the patient pathway and optimise ICU use.

The flow of stroke patients for neuro rehabilitation is not linear and that alone represents a challenge. For the management of stroke patients from onset through emergency treatment and rehabilitation to discharge, Bussel et al. [18] described a solution that emphasises multidisciplinary involvement and variance management as key factors in optimising the patient pathway from ictus to discharge after rehabilitation.

CONSLUSIONS

Sixty-seven patients admitted to the I-NR were included in this retrospective outcome study. All 67 patients required respiratory assistance at some point during their hospital stay and all patients had a mRS of five at admission to the I-NR. Furthermore, 28% had a good outcome and were independent at their discharge from hospital.

We have shown that the mortality and neurological outcome in this study were comparable to those of similar studies. The lack of significance of covariates to the primary outcomes confirms the heterogeneity of the brain injury population. Waiting for transfer to another facility due to capacity issues significantly impairs neurological outcome and increases delirium.

Strengths and limitations

The availability of ample documentation and the solidity of patient data with no loss to follow-up constitute the strengths of this study. The generalisability of the findings to similar organisations is advantageous. This study also has several limitations. The retrospective cohort design prompts an inferior level of evidence compared with prospective studies and is prone to recall bias or misclassification bias. Selection bias in retrospective studies is imminent and likely to have occurred in this study.

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REFERENCES

1. Poon MT, Fonville AF, Al-Shahi Salman R. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. J Neurol Neurosurg Psychiatry 2014;85:660-7.
2. Stabel HH, Pedersen AR, Johnsen SP et al. Functional independence: a comparison of the changes during neurorehabilitation

between patients with nontraumatic subarachnoid hemorrhage and patients with intracerebral hemorrhage or acute ischemic stroke. Arch Phys Med Rehabil 2017;98:759-65.

3. Saulle MF, Schambra HM. Recovery and rehabilitation after intracerebral hemorrhage. Semin Neurol 2016;36:306-12.
4. AVERT Trial Collaboration group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. Lancet 2015;386:46-55. Erratum in: Lancet 2015;386:30. Erratum in: Lancet 2017;389:1884.
5. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581-7.
6. Hacke W, Kaste M, Bluhmki et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med 2008;359:1317-29.
7. Golestanian E, Liou JI, Smith MA. Long-term survival in older critically ill patients with acute ischemic stroke. Crit Care Med. 2009;37:3107-13.
8. van Valburg MK, Arbous MS, Georgieva M et al. Clinical predictors of survival and functional outcome of stroke patients admitted to critical care. Crit Care Med 2018;46:1085-92.
9. Jeng JS, Huang SJ, Tang SC et al. Predictors of survival and functional outcome in acute stroke patients admitted to the stroke intensive care unit. J Neurol Sci 2008;270:60-6.
10. Rothschild JM, Landrigan CP, Cronin JW et al. The critical care safety study: the incidence and nature of adverse events and serious medical errors in intensive care. Crit Care Med 2005;33:1694-700.
11. Rashid A O, Islam S. Percutaneous tracheostomy: a comprehensive review. J Thorac Dis 2017;9(suppl 10):S1128-S1138.
12. Zaal IJ, Devlin JW, Peelen LM et al. A systematic review of risk factors for delirium in the ICU. Crit Care Med 2015;43:40-7.
13. Kamdar BB, Niessen T, Colantuoni E et al. Delirium transitions in the medical ICU: exploring the role of sleep quality and other factors. Crit Care Med 2015;43:135-41.
14. Oh-Park M, Chen P, Romel-Nichols V et al. Delirium screening and management in inpatient rehabilitation facilities. Am J Phys Med Rehabil 2018;97:754-62.
15. Laws L, Lee F, Kumar A et al. Admitting low-risk patients with intracerebral hemorrhage to a neurological step-down unit is safe, results in shorter length of stay, and reduces intensive care utilization: a retrospective controlled cohort study. Neurohospitalist 2020;10:272-6.
16. Hafeez S, Behrouz R. The safety and feasibility of admitting patients with intracerebral hemorrhage to the step-down unit. J Intens Care Med 2016;31:409-11.
17. Chartrain AG, Awad AJ, Sarkiss CA et al. A step-down unit transfer protocol for low-risk aneurysmal subarachnoid hemorrhage. Neurosurg Focus 2017;43:E15.
18. van Bussel EF, Jeerakathil T, Schrijvers AJ. The process flow and structure of an integrated stroke strategy. Int J Integr Care 2013;13:e025.