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Long-Term Outcomes of Patients with Stroke Predicted by Clinicians to have no Chance of Meaningful Recovery: A Japanese Cohort Study

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Abstract

Background: Little is known about the natural history of comatose patients with brain injury, as in many countries most of these patients die in the context of withdrawal of life-sustaining therapies (WLSTs). The accuracy of predicting recovery that is used to guide goals-of-care decisions is uncertain. We examined long-term outcomes of patients with ischemic or hemorrhagic

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Author Contributions
SE, JA, and JC wrote the article. SE, SN, YF, SF, KM, AS, MO, YY, HA, SM, and HN were involved in data collection. QS performed data analysis. All authors contributed a critical and final revision of the article. The final manuscript was approved by all authors.

Ethical approval/informed consent
For this retrospective and prospective analysis, we sought approval from the ethics committee of the Toda Medical Group Asaka Medical Center (institutional review board [IRB]) to conduct this study (IRB 21–07). The IRB approved a waiver of participant consent for the retrospective review. For the prospective assessment of patient outcomes, we did obtain consent from the patient whenever possible and from the surrogate decision-maker if patients were unable to provide consent.

Supplementary Information
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Conflict of interest
There are no competing interests to report

stroke predicted by experienced clinicians to have no chance of meaningful recovery in Japan, where WLST in patients with isolated neurological disease is uncommon.

Methods: We retrospectively reviewed the medical records of all patients admitted with acute ischemic stroke, intracerebral hemorrhage, or nontraumatic subarachnoid hemorrhage between January 2018 and December 2020 to a neurocritical care unit at Toda Medical Group Asaka Medical Center in Saitama, Japan. We screened for patients who were predicted by the attending physician on postinjury day 1–4 to have no chance of meaningful recovery. Primary outcome measures were disposition at hospital discharge and the ability to follow commands and functional outcomes measured by the Glasgow Outcome Scale-Extended (GOS-E), which was assessed 6 months after injury.

Results: From 860 screened patients, we identified 40 patients (14 with acute ischemic stroke, 19 with intracerebral hemorrhage, and 7 with subarachnoid hemorrhage) who were predicted to have no chance of meaningful recovery. Median age was 77 years (interquartile range 64–85), 53% ($n = 21$) were women, and 80% ($n = 32$) had no functional deficits prior to hospitalization. Six months after injury, 17 patients were dead, 14 lived in a long-term care hospital, 3 lived at home, 2 lived in a rehabilitation center, and 2 lived in a nursing home. Three patients reliably followed commands, two were in a vegetative state (GOS-E 2), four fully depended on others and required constant assistance (GOS-E 3), one could be left alone independently for 8 h per day but remained dependent (GOS-E 4), and one was independent and able to return to work-like activities (GOS-E 5).

Conclusions: In the absence of WLST, almost half of the patients predicted shortly after the injury to have no chance of meaningful recovery were dead 6 months after the injury. A small minority of patients had good functional recovery, highlighting the need for more accurate neurological prognostication.

Keywords

Prognostication; Outcome; Withdrawal of life-sustaining therapy; Japan; Stroke

Introduction

Comatose patients with acute nontraumatic structural brain injury are common, and in the context of modern resuscitative strategies, they frequently survive the initial injury [1]. Neurologists are commonly asked to provide families and intensivists taking care of these patients with a prognosis to guide the goals of care, often early after admission. Prediction algorithms generated from observational case series [2–11] and data extrapolated from clinical trials [12–17] are used to provide estimates and are then applied to individual patients. However, prediction accuracy is uncertain [18], may be confounded by biases [19], and can result in a self-fulfilling prophecy by providing an extremely poor prognosis [20, 21].

In North America and most of Europe, early withdrawal of life-sustaining therapies (WLST) is common among patients who are thought to have a very poor prognosis [22] but has been called into question for patients with nontraumatic structural brain injury from cardiac arrest [20], intracerebral hemorrhage (ICH) [23], and traumatic brain injury [21]. This practice creates a major challenge in understanding the natural history and long-term outcomes of patients with acute coma. At many hospitals in Japan, however, although practice is beginning to change, WLST is still uncommonly offered by physicians for patients with isolated neurological disease and is even less commonly accepted by families [24–26]. A survey by the Japanese Society of Intensive Care Medicine found that withdrawal of mechanical ventilation in patients who are terminally ill was performed approximately 14.3% of the time [27]. This practice has to be seen in the context of highly publicized legal challenges in the 1990s involving the withdrawal of care, in which physicians were sentenced to multiple years in prison [26]. Additionally, there is a knowledge gap regarding WLST. In a survey of physicians in training in Japan, 27% were not aware of any guidelines around end-of-life care [26, 28]. Similarly, there is low public awareness regarding endof-life care, living wills, and advanced directives [26, 29]. Given the uncertain trajectory of these patients, we investigated the long-term outcomes of unconscious patients admitted with ischemic or hemorrhagic stroke to a neurocritical care unit (NCCU) in Japan who were predicted by the treating attending physician to have no chance for meaningful recovery.

Methods

Case Ascertainment

This retrospective, cohort study was conducted at the Toda Medical Group (TMG) Asaka Medical Center, a 446-bed hospital in Saitama, Japan. We retrospectively identified all patients admitted between January 2018 and December 2020 to the NCCU from the electronic medical record that fulfilled the following inclusion criteria: age 18-years or older, and admission diagnosis of acute ischemic stroke (AIS), ICH, or nontraumatic subarachnoid hemorrhage (SAH). At TMG Asaka Medical Center, family meetings are generally held on admission to the NCCU to discuss patient status, long-term functional recovery, and goals of care, although WLST is rarely performed. Summaries of these discussions are documented by the physicians leading the discussion in the medical chart. Charts of all identified patients were reviewed for notes written on postinjury days 1 through 4, which documented an attending neurologist’s or neurosurgeon’s prediction that there was no chance of meaningful recovery. Specifically, we identified patients with notes predicting that the best outcome was death, coma, vegetative state, or bedridden without the ability to communicate. All patients with ambiguous notes and notes suggesting the possibility of meaningful recovery were excluded. Additionally, we identified patients with notes indicating that interventions would only result in survival but not lead to meaningful outcomes. Patient selection was conducted blinded to the clinical course and outcome measures.

Ethical approval was obtained from the ethics committee of the TMG Asaka Medical Center (institutional review board 21–07): the institutional review board approved a waiver of participant consent for the retrospective review. For the prospective assessment of patient outcomes, we did obtain consent from the patient whenever possible and from the surrogate decision-maker if patients were unable to provide consent.

Data Collection

For all included patients, we recorded demographics, baseline functional status with retrospective estimation (using the Glasgow Outcome Scale-Extended [GOS-E] [30] and modified Rankin Scale [mRS] [31]), and hospital treatment data based on chart review. We determined the severity of their overall illness by collecting Acute Physiology and Chronic Health Evaluation II [32] and Sequential Organ Failure Assessment [33] scores. Disease specific scores collected included National Institutes of Health Stroke Scale [34] for AIS, primary ICH score [4] for ICH, and Hunt-Hess score [11] for SAH. We also collected Glasgow Coma Scale scores of patients at the time of discussing prognosis with families.

Outcomes

The primary outcome measures included disposition at hospital discharge and the ability to follow commands and functional outcomes measured by the mRS and GOS-E [30, 35], both assessed at hospital discharge and at 6 months after injury. The GOS-E is a functional outcome scale mainly validated in traumatic brain injury research, but also widely used for other conditions including patients with stroke [36–38]. It ranges from 1 to 8, with a score of 1 indicating death, a score of 4 indicating the ability to be left alone independently for at least 8 h during the day, and a score of 8 indicating complete recovery. Additionally, patient-centered outcomes were obtained with all patients available to be interviewed using the Short Form 36 [39].

Discharge disposition was characterized as home, rehabilitation centers, nursing homes, and long-term care hospitals. Generally, in Japan, patients go to rehabilitation centers if they are expected to regain more functional recovery, go to nursing homes if they need only minimal care that could in theory be managed by the family, and go to long-term care hospitals if they are expected not to regain functional recovery with a “do not intubate” and “do not attempt resuscitation” status.

Patient disposition and functional outcomes were determined based on the electronic medical record at discharge and prospectively obtained by phone interviews at 6 months, as available. Phone assessments were conducted for study purposes only by physical therapists who were part of the study team and were trained to score GOS-E and Short Form 36. These outcomes assessors were blinded to the details of the medical information of the patients. Whenever possible, assessments were obtained directly from the patient and supplemented by caregivers if that was not possible (i.e., patients were noncommunicative or dead) or if the data were insufficient. For patients who were reached more than 1 month after the 6-month follow-up window, current functional status of the patient was assessed and the family was asked to quantify any changes in function noticed since the 6-month follow-up time point had passed.

Statistical Analyses

Data are reported as frequencies or median and interquartile range (IQR), as appropriate. Statistical analyses were performed with R statistical software, Version 1.4.1717 (RStudio).

Results

From a consecutive series of 860 adult patients admitted with AIS (*n* = 500), ICH (*n* = 275), or SAH (*n* = 85), excluding ten ambiguous cases (Supplemental Fig. 1), we identified 40 patients for whom the treating physician documented in the chart that there was no chance of meaningful recovery (14 patients with AIS, 19 with ICH, and 7 with SAH; Fig. 1). The first note identified on chart review that documented a prediction of no chance for meaningful recovery was written on a median hospital admission day of 1 (range 1–4; IQR 1–1).

These 40 patients had a median age of 77 years (IQR 64–85), and 53% (*n* = 21) were women. A total of 80% (*n* = 32) of patients had no baseline functional deficits prior to hospitalization (Table 1). The median Glasgow Coma Scale score was 6 (IQR 5–9) on admission and 6 (IQR 5–8) at the time of discussing prognosis with families. On admission, the median Acute Physiology and Chronic Health Evaluation II score was 24 (IQR 22–28), and the median Sequential Organ Failure Assessment score was 6 (IQR 4–6). Among the 14 patients with AIS, the median National Institutes of Health Stroke Scale was 24 (IQR 21–27), endovascular thrombectomy was performed in 6 (the other 8 patients had large vessel occlusion but presented outside of the window for clot evacuation), and surgical decompression was performed in 2. Of the 19 patients with ICH, the median ICH score was 3 (IQR 3–3) and 11 underwent surgical intervention (clot evacuation in 9 patients, external ventricular drain in 6, and decompressive hemicraniectomy in 2). Of the seven patients with SAH, the median Hunt-Hess score was 5 (IQR 5–5) and four aneurysms were clipped and three were coiled. Median length of stay in the NCCU and the hospital was 11 (IQR 6–17) and 45 (IQR 25–70) days, respectively.

All included 40 patients had a documented prognosis of no chance for meaningful recovery and additionally specified a bedridden state without the ability to communicate (*n* = 24), coma (*n* = 7), death (*n* = 5), and vegetative state (*n* = 4) as the most optimistic outcome predictions. The treating physician documented in 17 of these patients that interventions including surgery would only allow the patient to survive but not achieve a meaningful outcome. Among the 40 patients predicted to have no chance of meaningful recovery, changing the goals of care to WLST was discussed by physicians caring for 5 of these patients but not accepted by any of the families.

On hospital discharge, 28% (*n* = 11) of the 40 included patients were dead (Fig. 2) and 35% (*n* = 14) were able to follow commands. Of 29 patients discharged alive, 76% (*n* = 22) were discharged to a long-term care hospital and 24% (*n* = 7) to a rehabilitation center (Fig. 2). Of hospital survivors, 79% (*n* = 23) were discharged with a GOS-E of 2–3 and 21% (*n* = 6) with a GOS-E of 4.

At 6 months, 21% (*n* = 6) of those discharged alive were dead and 72% (*n* = 21) were alive. Two patients were lost to follow-up. Among the 21 patients known to be alive 6 months after injury, 14 (67%) were living in a long-term care hospital, 3 (14%) were living at home, and 2 (10%) were living in a nursing home and rehabilitation center, respectively. Functional and patient-centered outcomes were available in eight patients at the 6-month followup: two had a GOS-E of 2, four had a GOS-E of 3, and the remaining two had a GOS-E of 4 and

5, respectively. Three of these patients were able to follow commands, and SF36 scores were obtained. Scores in these three patients ranged below Japanese population means in the domains of physical functioning, role limitation, and social functioning, but had comparable population norms for body pain, general health, vitality, and mental health (Supplemental Fig. 2).

Of the five patients for whom the treating physicians had discussed WLST with the families, at 6 months after the injury two were dead, one was in a vegetative state, one was severely disabled (GOS-E 3), and one was lost to follow-up. Among 17 patients who were predicted to have no chance of meaningful recovery even with aggressive surgical interventions, 8 were dead (one of them died after 6 months), 2 were in a vegetative state, 3 were severely disabled (GOS-E 3), one had recovery with a GOS-E of 5, and 3 were lost to follow-up. Of the 11 patients predicted at best to recover to a comatose or vegetative state, 3 were following commands by or before 6 months after injury.

Discussion

In this cohort study, the majority of patients with ischemic or hemorrhagic stroke deemed by treating physicians within 4 days of hospital admission to have no chance of meaningful recovery were dead or in a vegetative state 6 months after the injury. However, long-term meaningful recovery was possible in a small minority of patients. At hospital discharge, one third of patients were following commands, and 15% had recovered to the point of being able to be left alone for at least 8 h in a day. Half a year after the brain injury, two patients were living in a rehabilitation center, two were living in a nursing home, and three were living at home. One of the patients living at home was fully independent, although judged by the family to be unlikely to return to work or social activities. These data highlight the potential for long-term improvements in patients with disorders of consciousness [40–44] that may apply to a few patients predicted to have no chance of meaningful recovery.

Long-term outcomes of patients with brain injury predicted to have no chance of meaningful recovery are uncertain in the context of modern critical care that includes early and aggressive resuscitative medical strategies and life-saving surgical treatments. Despite these impactful management strategies, patients with severe brain injury may not have a chance to recover, but much of the natural history of these patients relies on historical references. The uncertainty about their likely outcomes is largely due to the widespread practice of WLST in North America and most of Europe [21, 22, 45]. However, the relatively uncommon practice of of WLST in Japan made it possible to study the long-term trajectory of those patients who were predicted to have no chance of meaningful recovery and were managed with access to modern medical and surgical treatments [24–26].

Goals-of-care discussions that guide WLST are centered around aligning predicted outcomes with the patient's presumed wishes. This is an enormously challenging task, and prolonged suffering in patients who have no chance of meaningful recovery must also be taken into account. The accuracy of outcome predictions has been called into question [20], highlighting an ethical dilemma. Cautious prognostication based on the physician's clinical experience, available outcomes data, and predictive tools are widely practiced, but more individualized and precise prediction data are needed [1]. Novel approaches including the integration of advanced imaging modalities [46] and the diagnosis of cognitive motor dissociation may hold some promise [47, 48], but largescale studies are not available yet, and a multidimensionally defined, individual patient endotype–centered approach may be most promising [49]. Additionally, more work is needed to improve communication of prognoses with families, to provide decision support systems to help navigate the uncertainty of this process, and to ensure that shared decision making leads to decisions that are aligned with patient preferences and values [50, 51]. In the meantime, a practical way for clinicians to guide families in their decision making may be conceptualized around (1) an acknowledgment of the degree of uncertainty of available predictions and (2) a discussion with families about the range of outcomes along the axes of best-case, most likely case, and worst-case scenarios [50–54].

Prognostication for patients with severe neurological illness will likely always be an imperfect science. The case diversity is too great; large-scale, long-term outcome studies of these patients are extremely expensive; and rapid, ongoing changes in medical and surgical treatment strategies provide a constantly changing clinical landscape in which to center prognostic algorithms. Prognostications conceptualized around patient endotypes may allow more precise personalized predictions of outcomes in patients with acute disorders of consciousness [55].

Limitations

Findings of this retrospective study must be interpreted with great caution, as a number of limitations deserve mentioning. Firstly, because of the retrospective study design, a degree of uncertainty remains that documentation of the prognosis may not comprehensively reflect the physicians' impression, diverted from what was conveyed to the family, or the degree to which the family understood this information. However, the authors' collective experience practicing for many years at TMG Asaka Medical Center supports the notion that family meetings as a general practice are held on admission to the NCCU and are documented accurately in the chart study. To further minimize the impact of this limitation, all ambiguous cases and those with contradictory predictions were removed (Supplemental Fig. 1). Secondly, baseline GOS-E and mRS were retrospectively estimated based on review of the patient chart, taking into account notes from physicians, nurses, and physical therapists. To minimize missing or inaccurate data, future studies should collect this information prospectively using standardized data collection forms. Thirdly, generalizations about what constitutes "meaningful recovery" will always be challenging and will ultimately be a reflection of an individual's values and beliefs. This level of patient-centered assessment of meaningful recovery is clearly beyond the scope of this study and likely difficult to assess under any circumstances. The determination of "no chance for meaningful recovery" was based on physician documentation of the goals-of-care discussion in the medical record, as this was deemed to be the most accurate, available, comprehensive assessment for prognostication. At TMG Asaka Medical Center, prognostication is typically primarily based on the clinical impression by physicians taking prediction scores, among many other data points, into account. Importantly, prediction scores are rarely developed in a clinical context in which goals-of-care decision making is blinded to the data that later end up as predictors. This creates a risk of self-fulfilling prophecies. Fourthly, one could argue that the predictions made by the treating physicians were poorly informed. Although this is possible, we believe that this is unlikely, as only notes documenting the attending neurologist's, intensivist's, or neurosurgeon's predictions were considered. The sample size is too low to provide accurate population-based estimations of prediction accuracy, but, as outlined above, larger studies are challenging to obtain given the widespread practice of early WLST in many parts of the world. Here, we only considered early outcome predictions, specifically those documented within the first 4 days after injury. It is possible that predictions at later time points would be much more accurate, but in clinical practice families are often confronted with goals-of-care decisions based on predicted outcomes within days of the injury. Fifthly, 21% of patients who were discharged alive but were deceased 6 months later; we did not collect data on the cause of death after hospital discharge and are unable to comment on whether any of these patients died of WLST after discharge. Sixthly, future studies should include an assessment of explicit and implicit biases [19] that may cloud predictions communicated to the family and should be systematically quantified [56]. Seventhly, 7 of 40 patients were lost to follow-up for the long-term outcome assessment. To address these limitations, we are planning a larger prospective study to capture goals-of-care discussions and quantify prognosis with more objective and patient-centered instruments tracked over time.

Conclusions

In this study, we determined the short-term and long-term outcomes of 40 patients with AIS or hemorrhagic stroke managed in a Japanese NCCU who were predicted to have no chance of meaningful recovery. At 6 months after the injury, approximately half of the patients were alive. Among survivors, most lived in a full-time care facility providing high-level nursing care, but a small minority of patients lived at home, with one having good functional recovery. These findings should not be generalized, as prognostication practices and rates of WLST vary greatly, but at a minimum should motivate the community to work toward more precise predictions of long-term recovery in patients with acute brain injury.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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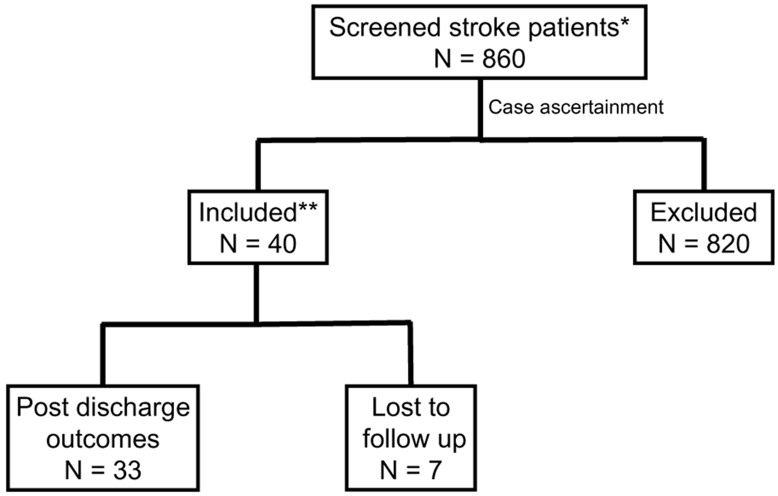

Fig. 1.

Study flowchart. Screened and included patients who were predicted to have no chance of meaningful recovery. *Acute ischemic stroke (AIS) ($n = 500$), intracranial hemorrhage (ICH) ($n = 275$), and nontraumatic subarachnoid hemorrhage (SAH) ($n = 85$); **AIS ($n = 14$), ICH ($n = 19$), and SAH ($n = 7$)

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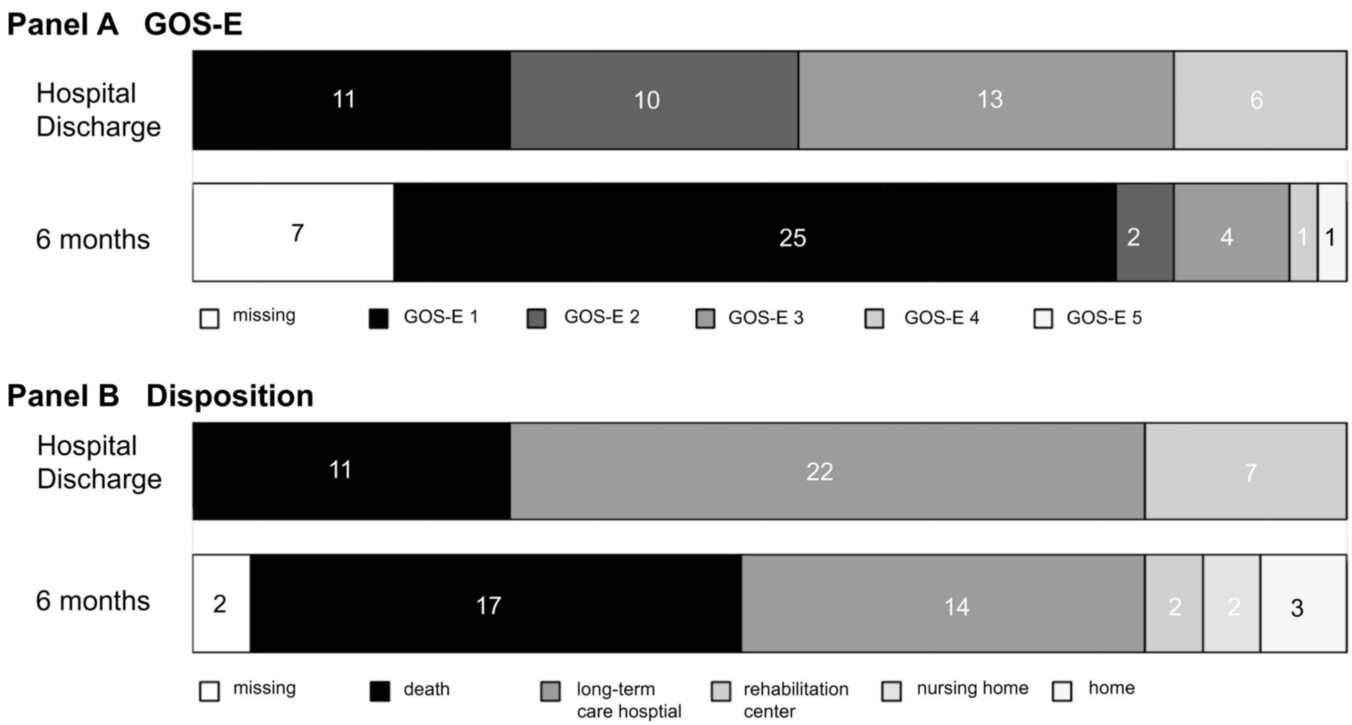

Fig. 2.
Outcomes of patients predicted to have no chance of meaningful recovery. Functional outcomes represented by the GOS-E score (**a**) and disposition (**b**) are reported at the time of hospital discharge and at 6-months after the injury. GOS-E 1, death; GOS-E 2, vegetative state; GOS-E 3, dependent; GOS-E 4, can be left alone for 8 h; and GOS-E 5, independent, although rarely able to work. GOS-E, Glasgow Outcome Scale-Extended

Table 1

Patient demographics

Demographics	Patients (*N* = 40)
Age (year)	77 (64–85)
Female sex	21 (53)
Baseline function	
Charlson Comorbidity Index	4 (3–5)
Modified Rankin Scale score	
0 (no symptoms at all)	32 (80)
1 (no significant disability despite symptoms)	1 (2)
2 (slight disability)	0 (0)
3 (moderate disability)	2 (5)
4 (moderately severe disability)	3 (8)
5 (severe disability)	2 (5)
Admission findings	
Global measures	
APACHE II	24 (22–28)
SOFA	6 (4–6)
GCS	6 (5–9)
Disease specific measures	
AIS (*n* = 14; 35% of patients)	
NIHSS	24 (21–27)
Endovascular treatment	6 (43)
Surgical decompression	2 (14)
ICH (*n* = 19; 48% of patients)	
ICH score	3 (3–3)
Surgical treatment	11 (58)
SAH (*n* = 7; 18% of patients)	
Hunt-Hess score	5 (5–5)
WFNS	5 (5–5)
Treatment of aneurysm	7 (100)
Behavioral exam at the time of discussing prognosis	
GCS	6 (5–8)
Length of stay	
NCCU (d)	11 (6–17)
Hospital (d)	45 (25–70)

Data are reported as *n* (%) or as median (IQR), as appropriate

AIS acute ischemic stroke, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *GCS* Glasgow Coma Scale, *ICH* intracerebral hemorrhage, *IQR* interquartile range, *NCCU* neurocritical care unit, *NIHSS* National Institute of Health Stroke Scale, *SAH* nontraumatic subarachnoid hemorrhage, *SOFA* Sequential Organ Failure Assessment, *WFNS* World Federation of Neurological Surgeons