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Outcome Predictors of Acute Stroke Patients in Need of Intensive Care Treatment

Angelika Alonso[a] Anne D. Ebert[a] Rolf Kern[a] Simone Rapp[b]
Michael G. Hennerici[a] Marc Fatar[a]

[a]Department of Neurology, and [b]First Department of Medicine, Universitätsmedizin Mannheim, University of Heidelberg, Mannheim, Germany

Key Words
Stroke · Intracerebral hemorrhage · Intensive care unit · Mechanical ventilation · Prognosis · Mortality

Abstract
Background: The prognosis of stroke patients admitted to intensive care units (ICU) is commonly regarded to be poor. However, only limited data regarding outcome predictors are available. ***Patients and Methods:*** Out of 4,958 consecutive patients admitted to our stroke unit with the diagnosis of acute stroke, after analysis we identified 347 patients (164 male) in need of ICU management. In-hospital and post-rehabilitation mortality as well as functional outcome at discharge and after rehabilitation were analyzed. ***Results:*** Ischemic stroke was diagnosed in 252 patients (72.6%) and intracerebral hemorrhage occurred in 95 patients (27.4%). The mean age in our cohort was considerably high (70.8 years). One hundred patients were comatose at admission. The median NIHSS score at admission in the remaining patients was 12. Apart from stroke-related disturbances of consciousness (47.1%), the most common reasons for ICU treatment were cardiac (23.4%) and respiratory (12.1%) complications or interventional procedures requiring mechanical ventilation (11%). In all, 231/347 patients (66.6%) were mechanically ventilated (mean 84 h). In-hospital mortality (143/347; 41.2%) was associated with old age, poor NIHSS score at admission, intracerebral hemorrhage and mechanical ventilation ($p < 0.001$ in all). Further, admission to ICU because of stroke-related impairment of consciousness increased in-hospital mortality ($p < 0.001$). Similarly, poor outcome after rehabilitation was associated with old age ($p = 0.029$) and mechanical ventilation ($p < 0.001$). In patients ≥80 years with either intracerebral hemorrhage or need of mechanical ventilation, outcome was unfavorable in nearly any case. However, the overall post-rehabilitation outcome did not differ between patients with intracerebral hemorrhage and ischemic stroke ($p = 0.275$). ***Conclusion:*** The stroke population in our study was associated with an increased early mortality; however, given the same conditions, it was old with a high percentage of patients requiring mechanical ventilation. This did not result in increased in-hospital mortality rates compared to younger and less severely affected cohorts. Thus, ICU management is a life-saving initiative even among the elderly. However, the functional outcome was poor in older patients, thus limiting the benefits of ICU care in these patients.

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Angelika Alonso, MD
Department of Neurology, Universitätsklinikum Mannheim
Theodor Kutzer Ufer 1–3
DE–68167 Mannheim (Germany)
E-Mail alonso@neuro.ma.uni-heidelberg.de

Introduction

Stroke remains the major cause of severe disability and the second most common cause of death despite several advances in prevention and treatment over the last two decades [1]. Management in a stroke care unit has been proven to be beneficial, with a significant reduction of both death and poor outcome [2]. However, the percentage of stroke patients being admitted to an intensive care unit (ICU) for monitoring and/or management of post-stroke complications is increasing [3]. The growing number of ICU-admitted stroke patient parallels the advances in intensive care management as well as a trend toward more aggressive and invasive treatments. An increasingly aging population with growing incidence of elderly patients suffering a stroke may also account for incremental rates of stroke patients treated in ICUs.

Despite the high socioeconomic impact, the actual benefit of ICU treatment of stroke patients remains a matter of discussion, not in the least due to the scarcity of reliable data. The reported mortality rates for stroke patients requiring ICU management vary widely, with a short-term mortality of more than 50% in some studies [4, 5]. Newer data of a multicenter retrospective cohort study, however, report on lower mortality rates both in the short- and long-term in older ICU patients with acute ischemic stroke [6]. The wide range of mortality rates is explained by several factors, including ICU admission criteria and percentage of patients with intracerebral hemorrhage in the respective cohorts. Regardless of this, some factors like comatose state at admission to ICU or mechanical ventilation have been shown to predict a poor prognosis in several studies [4, 7, 8]. How to determine suitability for ICU admission in acute stroke patients is a key question that still remains.

Most surprisingly, the actual 'Guidelines for the Early Management of Patients With Acute Ischemic Stroke', released by the AHA/ASA in 2013, do not answer this question in detail [9], while the 'Guidelines for management of ischaemic stroke and transient ischaemic attack 2008' by the European Stroke Organisation (ESO) do not address this issue at all [10, 11]. The 'Guidelines for ICU Admission, Discharge, and Triage', published by the American College of Critical Care Medicine of the Society of Critical Care Medicine as far as 15 years ago [12], have been recalled, and a revision is still in preparation. Indisputable criteria for ICU management in acute stroke patients include decreased level of consciousness, need for mechanical ventilation and invasive monitoring and were taken as a basis for ICU treatment indication in our study. Recently, possible further indications for ICU admission have been recommended by Kirkman and colleagues, namely, large MCA infarct volume that predicts a malignant course, postoperatively following decompressive craniectomy or management of organ support [3]. Notably, a recent study by Cereda and colleagues suggested that stroke patients admitted to a semi-intensive stroke unit (SI-SU) showed a lower proportion of unfavourable outcome at three months compared to those admitted to an ICU with a mobile stroke team [13]. The authors suggest that the continuity of the primary neurology team, a harmonized neuro-rehabilitation program as well as comprehensive medical, nursing protocols and treatment algorithms on SI-SU might account for this finding. Patients with 'relative' indications for ICU treatment as defined by Kirkman and colleagues [3] might therefore rather profit from treatment in a stroke unit.

However, even in patients with indisputable indications for ICU treatment, criteria when ICU treatment does not provide reasonable chances for good functional outcome are still lacking.

Our study now aimed at defining factors in patients with acute hemorrhagic or ischemic stroke in need of ICU management that may allow a prognosis of the short-term outcome.

Methods

This study was approved by the local Institutional Review Board (Medizinische Ethikkommission II der Medizinischen Fakultät Mannheim, University of Heidelberg). Patient consent was not required due to the retrospective nature of the study and the lack of patient interaction.

From January 2007 to July 2011, 4,958 patients were admitted to the Department of Neurology with the diagnosis of ischemic stroke or intracerebral hemorrhage (ICH). The diagnosis was confirmed in all patients by cranial computed tomography (CT) or magnetic resonance tomography (MRT). Of these, 347 required treatment in an intensive care unit (ICU) and were included in the study.

All patients underwent stroke workup according to a standardized protocol including assessment of risk factors (history of hypertension, diabetes, dyslipidemia, smoking, coronary artery disease, atrial fibrillation and previous stroke), neurological status (National Institute of Health Stroke Scale Score, NIHSS; Richmond Agitation Sedation Scale, RASS, if applicable), extra-/transcranial ultrasound and continuous monitoring (ECG, blood pressure) on our Stroke Unit (SU) or ICU.

The reasons for ICU admission were classified into neurological (stroke-related disturbances of consciousness with reduced brain stem reflexes), cardiac (therapy refractory tachy- or bradycardia, acute cardiac insufficiency, acute myocardial infarction, resuscitation), respiratory (aspiration, pneumonia, pulmonary edema, decompensated chronic obstructive lung disease, pulmonary embolism) complications, infections (pulmonary, abdominal, CNS), interventional procedures requiring mechanical ventilation

and other reasons. Multiple assignments were allowed. Indication for mechanical ventilation was classified as coma, respiratory failure or procedure-related. The duration time of ventilation was assessed in terms of hours.

In order to assess the outcome after rehabilitation, the medical records of patients transferred to rehabilitation hospitals were evaluated. In-hospital and post-rehabilitation mortality as well as modified Rankin scale (mRS) at discharge and after rehabilitation were analysed as outcome parameters. A mRS score of ≤3 was defined as favorable functional outcome.

Statistical Analysis

In order to analyze possible predictors of mortality, we performed χ^2-test for categorical and t-test for metric variables. The Spearman-Rho rank correlation coefficient was used to calculate nonparametric correlations between age or duration of rehabilitation on the one hand and the outcome after rehabilitation (mRS) on the other hand. The impact of mechanical ventilation, stroke type and thrombolysis on the outcome after rehabilitation was calculated by the Mann-Whitney U test. A p value <0.05 was considered to indicate statistical significance. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 22.0.0.0 (IBM, USA).

Results

Out of 4,958 consecutive patients admitted to our stroke unit with the diagnosis of acute stroke, 347 patients (164 male, 183 female, mean age 70.8, range 28–95 years) required ICU admission at any time point during their index hospitalization. Of these, 174 patients (50.5%) were initially admitted to ICU. Ischemic stroke was diagnosed in 252/347 (72.6%); ICH occurred in 95/347 (27.4%).

Out of 347 patients, 100 had been intubated and sedated in the prehospital setting and were comatose (Richmond Agitation Sedation Scale –5 in all) at admission. In the remaining 247 patients, the median NIHSS score at admission was 12 (interquartile range 5–18). Of the 252 patients with ischemic stroke, 97 patients (38.5%) underwent thrombolysis: intravenous thrombolysis with rtPA (85 patients), mechanical thrombectomy (5 patients) or a combination of both according to the 'bridging' concept (7 patients). The number of patients undergoing thrombolysis was significantly higher in this collective than in ischemic stroke patients not requiring ICU management over the same time period (23%, p = 0.041). Cardiac embolism due to newly detected or known atrial fibrillation was the most common stroke etiology and was documented in 140/347 patients (40.4%). Patients numbering 290 (83.6%) had a history of arterial hypertension requiring antihypertensive medication; diabetes was diagnosed in 125 patients (36.0%) and dyslipidemia in 114 patients (32.9%). Fifty-three patients (15.3%) were current smokers. Coronary artery disease was known in 79 patients (22.8%), and 62 patients (17.9%) had a history of previous stroke.

Table 1. Patient characteristics (n = 347)

Age, years, mean (range)	70.8 (28–95)
Sex, male/female	164/183
Diagnosis, %	
Ischemic stroke	252 (72.6)
Thrombolysis performed in	97/252 (38.5)
Intracerebral hemorrhage	95 (27.4)
Risk factors, %	
Atrial fibrillation	140 (40.4)
Arterial hypertension	290 (83.6)
Diabetes	125 (36.0)
Dyslipidemia	114 (32.9)
Current smoker	53 (15.3)
Coronary artery disease	79 (22.8)
Previous stroke	62 (17.9)
Neurological status at admission, %	
Comatose (RASS –5)	100 (28.8)
Non-comatose	247 (71.2)
NIHSS score at admission, mean, IQR	12 (5–18)
Indication for ICU management, %	
Neurological complications	162 (46.7)
Cardiac complications	81 (23.3)
Respiratory complications	42 (12.1)
Intervention requiring mechanical ventilation	39 (11.2)
Other	23 (6.6)
Mechanical ventilation, %	231 (66.6)
Duration, mean (range)	84 h (1 h to 56 days)

RASS = Richmond Agitation Sedation Scale; NIHSS = National Institute of Health Stroke Scale; ICU = intensive care unit; IQR = interquartile range.

The most common reasons for ICU treatment were neurological complications (46.7%), followed by cardiac (23.3%) and respiratory (12.1%) complications. An 11.2% of patients were admitted to ICU because of interventional procedures requiring mechanical ventilation. Patients numbering 231 (66.6%) were mechanically ventilated with a mean duration of ventilation of 84 h (range 1 h to 56 days). An overview of the patient characteristics is given in table 1.

One hundred and forty three patients (41.2%) died during hospitalization. Of these, 64 patients suffered from ICH (37 with additional intraventricular hemorrhage), and 79 patients had ischemic stroke, resulting in a significantly higher mortality in patients with ICH (p < 0.001). In-hospital mortality was further associated with old age (p < 0.001) and severity of neurological deficit at admission (p < 0.001). Moreover, admission to ICU be-

cause of stroke-related impairment of consciousness as well as the need for mechanical ventilation was related to in-hospital mortality ($p < 0.001$ for both). In-hospital mortality in mechanically ventilated patients was 57.1%.

Patients with atrial fibrillation (AF) were more likely to develop cardiac complications ($p < 0.001$) and to die from non-neurological reasons ($p = 0.044$); overall in-hospital mortality, however, was not increased in patients with AF ($p = 0.225$). In-hospital mortality due to non-neurological reasons was further associated with the occurrence of cardiac and respiratory complications, infection and resuscitation ($p < 0.001$). In contrast, patients who experienced neurological complications like recurrent stroke, secondary hemorrhage, brain edema or epileptic seizures were more likely to die as a consequence of the neurological disease ($p < 0.001$).

Median mRS after rehabilitation was mRS 4. The outcome after rehabilitation was associated with patient age, with younger patients achieving lower mRS scores than older patients ($p = 0.008$). However, patients attaining a good functional outcome (mRS ≤3) were not younger than patients with a less favorable outcome ($p = 0.16$). Improvement during rehabilitation was associated with duration of rehabilitation, with longer duration of stay predicting better recovery ($p = 0.022$). Nevertheless, absolute outcome defined as post-rehabilitation mRS was independent of the duration of rehabilitation. Thus, mechanical ventilation remained a major risk factor for poor outcome, even after rehabilitation ($p < 0.001$). Although in-hospital mortality was significantly associated with ICH, the outcome after rehabilitation did not differ between patients with ICH and ischemic stroke ($p = 0.275$). In patients with ischemic stroke, thrombolysis (performed vs. not performed) did not have an influence on the post-rehabilitation outcome mRS ($p = 0.921$) or on the risk of death ($p = 0.421$).

In patients ≥80 years, one additional risk factor for poor outcome resulted in an unfavourable outcome in nearly any case: of 65 patients ≥80 years requiring mechanical ventilation, 64 had a post-rehabilitation mRS of ≥4, with 47 fatalities. Likewise, 23/27 of the ≥80 year-old patients with ICH stroke did not survive the acute phase, the remaining 4 patients were severely disabled.

Discussion and Review of the Literature

There is plenty of evidence that management of both ischemic stroke and ICH patients on specialized stroke units is beneficial [14, 15]. However, the benefit of ICU treatment of severely affected stroke patients is yet uncertain. In our cohort of 347 acute stroke patients in need of ICU management, we could demonstrate that the overall in-hospital mortality was high, with 41.2% not surviving the acute phase. In-hospital mortality rates reported in the literature vary widely, highly depending on the patient characteristics.

A small Australian study (n = 58) including both ischemic stroke and ICH patients provided a slightly higher mortality rate of 47%; however, the analysed data dates back to the 1990s [5]. The Evascan project, a prospective observational study in 132 stroke patients admitted to the ICU, also as far back as in 1999, reported a lower mortality rate of 33% [4]. Newer studies with recruitment of patients after 12/1999 are scarce; an overview is given in table 2. Interestingly, the reported mortality rates in these studies vary substantially depending on the originating country, with rather low short-term mortality in Asian countries [16, 17] and markedly higher mortality rates up to 70% in studies originating from European countries [7] and the United States [18]. Two possible factors may account for this finding: first, although the incidence of ICH is known to be higher in Asians than in Caucasians, a recent study on racial/ethnic differences in the outcome of ICH patients found lower risk-adjusted, in-hospital mortality for Asian than white patients with ICH [19]. Second, ICU admission criteria in Asian countries may vary considerably from those in Europe/United States, not at least because of the limited access to tertiary care centers in many Asian countries [20]. Mortality rates should therefore be interpreted with caution and consider the patients' characteristics of the respective cohort.

We analysed several factors as possible outcome predictors and could identify the following negative outcome markers: age; coma at admission; severe neurological deficit at admission given by the NIHSS score, need for mechanical ventilation, and hemorrhagic stroke.

Age is a widely accepted predictor of poor outcome in stroke patients requiring ICU treatment [21]. Schielke and colleagues found a higher probability of death after 2 months and 2 years post-ischemic stroke in ischemic stroke patients >60 years [22]. In mechanically ventilated patients suffering from either ischemic or hemorrhagic stroke, an age of >65 years indicated a poor outcome [23]. Notably, both cut-off values are far below the mean age of patients in our cohort with 70.8 years. In their large multicenter retrospective cohort study in 31,301 ischemic stroke patients (26% of those in need of ICU admission), Golestanian and coworkers could demonstrate that age was associated with a gradually increasing risk of death,

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Table 2. Overview on studies addressing the prognosis and outcome of stroke patients admitted to intensive care units

Author	Country		Age, y, mean	Stroke subtype, %	Thrombolysis, %	NIHSS admission	MV, %	In-hospital mortality, %	Predictors for in-hospital mortality	Predictors for poor outcome
Alonso et al., 2015	Germany	347	70.8	IS 252 (72.6) ICH 95 (27.4)	97 (38.5)	median 12	231 (66.6)	IS 79 (31.3) ICH 64 (67.4)	age, MV, ICH, NIHSS	age, MV
Lahiri et al., 2014 [18]	USA	99,782	67.2	IS 50,871 (51) ICH 32,967 (33)	n.a.	n.a.	99,782 (100)	IS 46.8 ICH 61.0	n.a.	n.a.
Moon et al., 2015 [25]	Korea	498	56	IS 198 (39.8) ICH 300 (60.2)	n.a.	mean 21.63	n.a.	131 (26.3)	NIHSS, GCS, APACHE II, SAPS II	n.a.
Riachy et al., 2008 [21]	Lebanon	62	65.8	IS 45 (62.6) ICH 17 (27.4)	10 (16.1)	n.a.	23 (37)	16 (25.8)	age, APACHE II, GCS, MV (a.o.)	n.a.
Jeng et al., 2008 [16]	Taiwan	850	65.3	IS 508 (59.8) ICH 342 (40.2)	70 (13.8)	median 17	278 (32.7)	139 (16.3)	n.a. (3-m-mortality: NIHSS, MV)	age, MV, NIHSS (a.o.)
Handschu et al., 2005 [26]	Germany	90	64.3	IS 41 (45.6) ICH 49 (54.4)	n.a.	n.a.	90 (100)	n.a. (10-d-mortality: 29 (32.2))	n.a. (10-d-mortality: GCS, SAPS I/II)	n.a.
Golestanian et al., 2009 [6]	USA	8,185	80.2	IS 8,185 (100)	n.a.	n.a.	876 (10.7)	n.a. (30-d-mortality: 1,748 (21.4))	n.a. (30-d-mortality: age, MV)	n.a.
Lan et al., 2006 [17]	Taiwan	231	68 (survivors), 71 (deceased), n.s.	IS 231 (100)	n.a.	n.a.	n.a.	34 (14.7)	impaired consciousness	n.a.
Milhaud et al., 2004 [7]	France	50	58.7	IS 50 (100)	n.a.	mean 19.9 (survivors) to 21.8 (deceased), n.s.	50 (100)	35 (70)	n.a. (1-y-survival: absence of complete MCA infarction)	n.a.

Only studies with patient recruitment after 12/1999 were considered.

Y = Years; NIHSS = National Institute of Health Stroke Scale; MV = mechanical ventilation; IS = ischemic stroke; ICH = intracerebral hemorrhage; n.a. = not available; APACHE = Acute Physiology and Chronic Health Evaluation (score); GCS = Glasgow Coma Scale; m = months; a.o. = and others; MCA = middle cerebral artery; d = days; SAPS = Simplified Acute Physiology Score.

resulting in a three-fold increase in mortality hazard for patients >85 years [6]. This is quite in line with our results, showing that patients >80 years with additional negative outcome markers either do not survive the acute phase or are left in a completely dependent state. The markedly higher mean age of our patients compared to the most previous studies reflects the actual epidemiological changes with an aging population. With an overall life-expectancy of about 80 years for US citizens and even slightly more for inhabitants of European states (WHO, 2012), we will have to face an increasing number of aged patients with multiple comorbidities suffering a stroke. Of importance, mortality rates for ischemic stroke patients in our study did not differ substantially from those reported in younger stroke populations [4, 24]. However, the functional outcome after rehabilitation in the acute stroke survivors was mainly influenced by the patients' age.

Impaired consciousness at admission is probably the most accepted negative outcome predictor in stroke patients needing ICU management. In our study, coma at admission was a strong predictor of in-hospital mortality. In line with this finding, several studies demonstrated a correlation of initial GCS and short-term mortality [21, 25, 26]. However, only two studies including >100 patients – both originating from Asian countries – evaluated the NIHSS score in their patient collectives as a stroke-specific severity marker [16, 25]. Consistent with our results, NIHSS was found to predict both in-hospital mortality as well as functional outcome. In contrast, the two large US studies with inclusion of 8,185 and 99,782 stroke patients treated on ICU, respectively, could only draw on administrative data and therefore lacked specific information on stroke severity or stroke treatment [6, 18].

Whether to initiate mechanical ventilation in severely affected stroke patients is still a matter of debate, and, to date, trials that verify the utility of mechanical ventilation in severe stroke are still lacking [3]. Undisputedly, the need for mechanical ventilation is a potent predictor of mortality and poor outcome [16] and leads to a five-fold increase in mortality hazard in the short-term [6]. The restraint of many stroke physicians is based on large studies conducted in the 1990s showing catastrophic fatality rates of about 90% in acute stroke patients requiring mechanical ventilation [27, 28]. More recent studies report somewhat lower rates, however, still reaching about 70% mortality after 1 year [7, 8, 18]. In a small prospective study including 58 patients with ischemic stroke in need of mechanical ventilation, the presence of stupor or coma was an independent predictor of mortality [8], consistent with our own results. In our cohort, the in-hospital mortality of mechanically ventilated patients was 57.1%, which is quite in line with previously published data [18, 23]. Strikingly, the percentage of mechanically ventilated patients in our study was exceptionally high (66.6%) as compared to previous studies [6, 8]. This finding might be attributable to the multidisciplinary competencies on our stroke unit in the management of severe stroke and its complications, thus reducing the need for ICU transferrals in non-ventilated patients.

We further found that ICH was a predictor for in-hospital mortality, while the functional outcome after rehabilitation did not differ between ischemic and hemorrhagic stroke patients. A higher short-term mortality for ICH patients treated on specialized stroke units has already been shown by Chambers and coworkers in 1987 [29]; in stroke patients requiring ICU management, the data are more conflicting. Most studies agree with our results regarding an increased risk of mortality in ICH patients [4, 5]. After correction for age and APACHE III score, patients with ICH had a mortality that was 4.1 times higher than that of ischemic stroke patients in a Spanish prospective observational study [4]. However, several studies also linked the presence of intracerebral hemorrhage to a worse functional outcome [5]. The lack of association in our study might be attributable to two factors: first, severely affected ischemic stroke patients with high NIHSS at admission and only reduced potential for improvement might be overrepresented in our study. Second, hemorrhagic stroke patients have been shown to experience even more significant recovery than ischemic stroke patients [30]. This observation might be attributable to an improvement of the initial neurological deficit due to brain compression after the resolution of the hematoma [31].

Notably, the proportion of ischemic stroke patients receiving thrombolytic therapy was very high (38.5%), possibly raising the concern that thrombolytic therapy itself might be an additional risk for ICU admission. However, whether thrombolysis was performed or not did not affect the mortality rate or functional outcome. We believe that, apart from early admission to our stroke unit, the overrepresentation of severely affected stroke patients in our cohort may explain the high thrombolysis rates. Supporting this theory, Faigle and colleagues demonstrated that high NIHSS score at admission predicts ICU needs following tPA for acute ischemic stroke [32]. This finding should not discourage stroke physicians to perform thrombolysis even in severely affected and older stroke patients [33]. Although octogenarians undergoing throm-

bolytic treatment may exhibit a higher mortality rate compared with patients <80 years [34], recent data from the third international stroke trial (IST-3) demonstrated that patients >80 years achieved similar benefit when compared to younger patients [35]. Likewise, the study identified significant trends towards larger effects of treatment in patients with more severe strokes [35] despite an increasing risk of hemorrhagic complications.

In summary, we analysed the short-term outcome and outcome predictors in acute stroke patients in need of ICU treatment. In comparison to previously analysed cohorts, the stroke population in our study was remarkably older with a very high percentage of patients requiring mechanical ventilation. Although patient age and MV are main predictors of negative outcome, in-hospital mortality rates in our study were not significantly higher than in younger and less severely affected cohorts. This finding may reflect the recent advances in intensive care management. However, functional outcome was poor especially in older patients with either hemorrhagic stroke or need of MV, leaving barely all survivors in a dependent state. Several studies have shown that retrospective consent to neurointensive care depends on the functional outcome [36, 37]. In a cohort of 704 patients admitted to a neurocritical care unit, only 19% of patients with an outcome mRS of 4 or 5 retrospectively consented to ICU management [36]. Further decisions about when to admit stroke patients to ICU will thus have to focus on the potential functional outcome, taking account of accepted predictors of poor outcome. Consideration of the putative patient's will or patient's advance directives will become increasingly important [38], and efforts to improve end-of-life care should be made [39].

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