Title

Clinical predictors of short-term and long-term survival and functional outcome of ICU-admitted stroke patients

Short running title

Long-term survival & functional outcome after critical stroke

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Conflict of interests

The authors declare that they have no conflict of interest.

Trial registration

This study was registered at http://www.controlled-trials.com as ISRCTN13328713.

ABSTRACT

OBJECTIVES:

To determine the predictive value of commonly used clinical variables upon ICU admission for long-term all-cause mortality and functional outcome of adult stroke patients admitted to the ICU.

DESIGN:

Retrospective observational cohort study.

SETTING:

General and neurosurgical ICUs of the University College London Hospitals in North Central London.

PATIENTS:

All adult ICU patients with a clinical diagnosis of acute stroke admitted between February 2010 and May 2012.

INTERVENTIONS:

None.

MEASUREMENTS AND MAIN RESULTS:

Demographic and clinical data concerning the first 24 hours after ICU admission were obtained. Patients were followed until February 2016 to assess long-term survival. Functional outcome was determined using the modified Rankin Scale. We evaluated 131 critically ill stroke patients, with a median (interquartile range) age of 70 years (55-78 yr). One-year mortality rate was 52.7%. Surviving patients were followed up over a median (interquartile range) period of 4.3 years (4.0-4.8 yr). The multivariable model that best predicted long-term all-cause mortality indicated that mortality of critically ill stroke patients was predicted by high Acute Physiology and Chronic Health Evaluation II score, impaired consciousness (Glasgow Coma Scale score ≤ 8) as reason for ICU admission, low Glasgow Coma Scale sum score after 24 hours, and absence of brainstem reflexes. Long-term independent functional status occurred in 30.9% of surviving patients and was predicted by low Acute Physiology and Chronic Health Evaluation II score, high Glasgow Coma Scale sum score at ICU admission, and absence of mass effect on CT scan.

CONCLUSIONS:

Mortality in critically ill stroke patients is high and occurs most often shortly after the event. Less than one in three surviving patients is able to function independently after 1 year. This study has identified several clinical variables that predict long-term all-cause mortality and functional outcome among critically ill stroke patients and found that mainly acute physiologic disturbance and absolute values of neurologic clinical assessment are predictive.

Keywords: stroke; critical care; intensive care unit; mortality; survival; functional outcome

Stroke is a major healthcare issue worldwide despite the incidence of stroke and subsequent mortality declining over time [1]. Although global age-standardised death rates have fallen by 19.6% for ischaemic and 25.9% for haemorrhagic stroke from 1990 to 2013 [2], stroke is still the fourth leading cause of mortality in the United Kingdom with an age-standardized annual incidence of 85 and 30 per 100,000 person-years for respectively ischemic and hemorrhagic stroke (3)

Optimal in-hospital placement for acute stroke patients [4-8] and treatment decisions concerning (mainly acute ischaemic) stroke patients [9-15] have been widely discussed during the past decades. Patients with severe stroke may need to be treated in the intensive care unit (ICU) and these critical stroke patients can be seriously compromised with respect to vital organ function compared to other patients with neurologic problems [16]. Moreover, due to the increasing complexity of stroke treatment, the future of acute stroke care and the role of critical care will be increasingly intertwined [17]. Neurologic dysfunction is one of the most frequent reasons for initiating ICU admission for airway and respiratory monitoring or mechanical ventilation and may be the result of a variety of causes [18]. Of these, the structural brain lesions generally predict the worst prognosis and present the greatest challenge to clinicians [19].

The long-term consequences of ischaemic and intracerebral haemorrhagic stroke in terms of mortality and morbidity have been investigated thoroughly. Morbidity in terms of functional outcome is generally reported by the 7-level ordered categorical modified Rankin scale (mRS) [20, 21]. The mRS is widely applied and validated as a clinically relevant instrument for assessing recovery from stroke and a valuable endpoint in stroke studies [22]. However, stroke research concerning survival and functional outcome is often performed in a general population of stroke patients and before more invasive treatment modalities became standard [9-15]. Much less is known about post-stroke outcome in the subset of patients who need to be admitted to the ICU.

In daily practice, clinicians have to determine the validation of an ICU admission, start of therapy or withdrawal of treatment in critical stroke patients based on mostly empirical bases. To our knowledge, Computed Tomography (CT) results and change in neurologic status measured by the Glascow Coma Scale (GCS) are two of the most used parameters in these decisions. We question whether the clinical parameters we use on a day-to-day basis for these critical decisions are evidence based. An improved understanding of predictors of survival and functional outcome of critical stroke patients in and after the ICU setting would provide prognostic information useful for making treatment decisions that conform to a patient's preferences [23].

Therefore we conducted this long-term follow-up study to determine the clinical parameters measured at ICU admission that can predict long-term survival and functional outcome (measured by modified Rankin scale) of adult ischaemic and intracerebral haemorrhagic stroke patients admitted to the ICU.

MATERIALS AND METHODS

Study population

For this retrospective observational cohort study, all adult patients admitted via the Emergency Department (ED) to either the general or neurosurgical ICU of one of the University College London Hospitals (UCLH) in North Central London between February 2010 and May 2012 with a clinical diagnosis of acute ischaemic or intracerebral haemorrhagic stroke, confirmed by non-contrast cranial CT scan, were selected. This two-year time frame was particularly chosen, since it was after the introduction of the hyper-acute stroke unit (HASU) pathway, in which rapid administration of thrombolytic agents, when indicated, had been implemented. Consequently, patients were followed until February 2016.

Demographic and clinical data were obtained from the national, trust and hospital databases as part of an audit. Patients who met at least one of the following criteria were excluded from the study: subarachnoid or subdural bleedings, known intracerebral or intracerebellar tumour, in-hospital stroke and referral from another ICU for the same diagnosis.

Data collection

We tabularised patient's age, gender, time of admission, interval between stroke and admission to hospital, reason for ICU admission, prior illnesses and Acute Physiology and Chronic Health Evaluation II (APACHE II) with range of scores 0 to 71 [24]. Data according vital parameters (heart rate, mean arterial pressure, systolic blood pressure and temperature) and neurological examination (GCS on admission and after 24 hours, presence of brainstem reflexes and epileptic activity) were recorded, as well as laboratory results (haemoglobin, haematocrit, white blood cell count and CRP) and CT angiography results (mass effect, midline shift, presence of hydrocephalus and brain stem involvement). All collected data contained information concerning the first 24 hours after ICU admission.

Respiratory parameters were collected beyond the scope of the first 24 hours after ICU admission and included clinical diagnosis of pneumonia during ICU stay, whether patients were intubated during ICU stay and, if so, duration of ventilation and whether tracheostomy was performed.

Functional outcome assessed using mRS was obtained from the medical record draughted by the primary treating physician, mostly a neurologist or neurosurgeon, at hospital discharge and at one year follow-up check appointment.

Statistical Analyses

The primary outcome measure was stated as all-cause mortality after ischaemic or intracerebral haemorrhagic stroke. Surviving patients were censored on February 20, 2016. Cumulative risks were assessed by Kaplan-Meier analysis and prognostic factors for long-term all-cause post-stroke mortality were determined by univariable and multivariable Cox proportional hazards regression analysis with data presented as hazard ratio with 95% confidence intervals (CI). Log minus log plots were used to confirm proportionality of hazards assumption over time.

Secondary outcome measure was stated as good functional outcome (mRS 0-2; independent functional

status) versus poor functional outcome (mRS 3-6; dependent functional status or dead). Furthermore, transition in mRS was taken into account, defined as improved functional status (mRS even or increased between discharge and after one year) versus declined functional status (mRS decreased between discharge and after one year). Prognostic factors for good functional outcome and improved functional status were determined with binary logistic regression with data presented as odds ratio with 95% CI.

In both primary and secondary outcome analyses, all univariable predictor variables with a p-value <0.1 were entered into a multivariable regression model, as well as parameters expected unanimously by three investigators (MvV, SA & BG) to clinically influence respectively survival and functional outcome.

Multiple imputation was applied for the multivariable Cox PH analysis and multiple binary logistic regression analyses in case of missing covariates. The maximum amount of predictive variables considering the amount of events was taken into account. Model development was performed by applying the backward stepwise selection procedure on the multiple imputed dataset [25, 26] and estimates of the odds ratios from the analyses were pooled [27]. Variable exclusion in the backward stepwise selection procedures was set to the lowest p value in the model. A probability value of 0.05 or less was considered as significant. All statistical analyses were performed using SPSS Statistics for Macintosh version 22.0 (IBM Corp. Armonk, NY, USA).

RESULTS

Patient characteristics

During the study period, 131 acute stroke patients were admitted to the ICU with a mean (SD) age of 66.0 (15.4) and of which 76 (58.0%) were male. Seventy-five patients (57.3%) suffered an ischaemic stroke. One hundred two patients (77.9%) received adequate care within 6 hours after stroke onset and 64.9% arrived at the hospital during daytime. Main reason for ICU admission was a low GCS (52.7%) of which 61 patients (88.4%) needed mechanical ventilation during ICU stay. Mean length of stay (LOS) in ICU and in-hospital was respectively 8 and 25 days. Demographic and clinical patient characteristics are presented in Table 1.

Survival rates and distribution

Eighty-seven patients (66.4%) patients survived ICU stay, of which 72 were discharged from the hospital alive. One-year mortality rate was 52.7%. Seventy-seven critical stroke patients (58.8%) died during the follow-up period. Surviving patients (41.2%) were followed up over a median period of 4.3 years with a minimum and maximum follow-up period of respectively 3.8 and 6.0 years.
One in four patients who deceased during the study period, died within 2 days after the event. Thirty-nine patients (50.6% of the deceased patients) died within a week. Survival was charted by Kaplan-Meier method shown in Figure 1 with an 'inverse J-shaped' curve, displaying most deceased patients died shortly after the event.

Predictors of mortality

The univariable and consequent multivariable Cox PH regression analyses are shown in Table 2 and 3. The strongest predictors of long-term all-cause post-stroke mortality in the univariable analysis were age, APACHE II score, body temperature, GCS sum score on admission and after 24 hours, and presence of brainstem reflexes. Survivors and non-survivors did not differ in gender, type of stroke and time of admission. Prior illnesses, except atrial fibrillation and previous cerebrovascular incident (CVA), and all analysed laboratory results were neither predictive for mortality.
For every year older in age upon ICU admission, patients had 4.4% more chance to die. Lower APACHE II score and lower body temperature indicated higher changes of survival. For every point lower on the GCS sum score on ICU admission and after 24 hours, mortality probability increased by respectively 11.6% and 14.9%. A decline in GCS (from admission to 24 hours later) increased chances for death by 8.6%.

To investigate the context between predicting parameters, multivariable Cox regression analysis was performed (Table 3), in which multiple imputation with 50 repetitions has been applied for missing values of the covariates APACHE II and previous CVA in respectively 23 and 6 subjects. The multivariable model that best predicted long-term all-cause post-stroke mortality contained APACHE II score, GCS sum score lower than 8 as reason for ICU admission, GCS sum score after 24 hours and presence of brainstem reflexes. For every point higher on the APACHE II score, mortality probability increased by 11.9%. When a low GCS was the reason for admission, patients had a 3-fold chance to

die. For every point lower in GCS sum score 24 hours after ICU admission, mortality probability increased by 8.0%. When brainstem reflexes were absent on ICU admission, patients had a 2.35-fold chance to die.

Respiratory failure during ICU stay

Intubation was performed in 90 (68.7%) patients of whom 11 underwent tracheostomy. Mean duration on the ventilator (SD) was 7.9 (22.4) days. Pneumonias were diagnosed in 32 patients of whom 8 died during ICU stay. In the four year follow-up period, patients were 4 times more likely to die if intubation was performed during ICU stay (HR 3.98; 95% CI 2.14-7.39). Other parameters concerning respiratory failure during ICU stay showed no significant differences in univariable Cox PH regression analyses.

Functional outcome at discharge and after one year

Eight (6.1%) patients scored a good functional outcome at hospital discharge. After one year mRS was obtained in 124 patients, of which 17 patients (13.7% or 30.9% of survivors) scored a good functional outcome. More detailed results are shown in Figure 2. Transition in mRS from hospital discharge upon follow-up after one year was analysed in 65 of the 72 hospital survivors, of which 36 patients decreased in mRS, 16 patients increased in mRS and 13 patients remained stable in their functional status in the first year after the event.

To investigate the context between predicting parameters for good functional outcome, multiple binary logistic regression analysis was performed on the multiple imputated database. The multivariable model that best predicted good functional outcome after one year contained APACHE II score, GCS sum score on admission and presence of mass effect on CT scan (Table 3). For every point higher on the APACHE II score, chances for good functional outcome decreased by 17.7%. For every point higher in GCS sum score on ICU admission, chances for good functional outcome increased by 27.9%. If mass effect was shown on CT scan, patients had a 8.55-fold chance to have a mRS score higher than 2 after one year.

The multiple binary logistic regression that best predicted improvement in functional outcome from hospital discharge upon follow-up after one year contained only APACHEII score as predicting variable (OR 0.87; 95% CI 0.78-0.97).

DISCUSSION

We have studied a cohort of 131 ICU-admitted stroke patients for a period of more than four years aiming to aid in the identification of critical stroke patients who are at increased risk of death or poor functional outcome in order to carry out a first step towards a decision support algorithm. Our results show that mortality in critical stroke patients is high and most deceased patients die shortly after the event. Long-term all-cause mortality of ICU-admitted stroke patients is predicted by APACHE II score, GCS sum score lower than 8 as reason for ICU admission, GCS sum score after 24 hours and presence of brainstem reflexes. Independent functional status occurs in less than 1 in 3 (30.9%) surviving critical stroke patients one year after the event and is predicted by APACHE II score, GCS sum score on ICU admission and presence of mass effect on CT scan. We are surprised to learn that a parameter that we use frequently to assess prognosis, like the change in GCS in the first days of admission, cannot actually help us.

Our hospital and 1-year mortality rates of respectively 45.0% and 52.7% lie well within the widely varying range reported in earlier studies [16, 28-34]. However, earlier literature does not elaborate post-stroke survival probabilities beyond one year after onset. Due to the extensive follow-up period, our study shows that one-year mortality rates cannot be extrapolated to the years afterwards. Conversely, mortality rates of critical stroke survivors after the first year of onset are rather low with an average annual mortality rate of 3.4% in our study cohort, which is comparable to ICU-admitted patients due to subarachnoid haemorrhage one year after onset or even a general population representative group [35].

The average age of our study group of 66 years corresponds to earlier study cohorts [16, 28-34]. General ICU laboratory results do not predict post-stroke mortality, though we have not included renal failure indicators like creatinin and albumin, both have been shown earlier to predict post-stroke mortality [36]. However, the incidence of a medical history of renal dysfunction in our ICU stroke population do not differ between survivors and non-survivors. Type of stroke does not predict mortality, which is inconsistent to earlier literature [16, 28]. These studies had different distributions of type of stroke within their populations and were conducted before the introduction of specialised care units for stroke, rapid intravenous thrombolysis and intra-arterial thrombosuction for ischaemic stroke patients. These treatment possibilities may cause a pleiotropic effect on the current distribution and mortality rates of critical stroke patients, due to patient selection for these treatments but also their possible complications. Furthermore, cultural, logistic and demographic differences in patient selection for treatment as well as admission at the ED and ICU may play a role. Type of stroke is, in accordance to earlier literature [16, 34], neither predictive for functional outcome.

The strengths of our study lie in the extensive follow-up of almost 5 years and the small time frame (first 24 hours upon ICU admission) in which all incorporated parameters have been measured to enable a practical and therefore clinically relevant survival prediction model useful directly after or even in decision to ICU admission. Together with the incorporated model predicting long-term

functional outcome, this study can be helpful to identify the critical stroke patients who are at increased risk of death as well as the predictability of their healthy lifespan. Our findings may help clinicians in daily practice to inform patients and their family caregivers about patterns and survival probabilities after ICU admission due to an ischaemic or intracerebral haemorrhagic stroke.
A limitation of this study is its modest sample size and its retrospective design with all known disadvantages, including the issues concerning possibility of misclassification and missing data, that we solved by using multiple imputation in two covariates. In order to keep our survival prediction model as precise and distinct as possible with a small time frame of only the first 24 hours after ICU admission, necessity and duration of mechanical ventilation during ICU stay, both well-known predictors for mortality in critical stroke patients [6, 19, 37, 38], were not incorporated in our multivariable analyses. These parameters were analysed separately. In the functional outcome analyses, 7 patients were lost to follow up after one year and we did not incorporate the admittance and possible impact of rehabilitation on functional outcome. Furthermore, this study is limited to the UK health care system and therefore our study group is a selection of patients admitted to one type of organisation of stroke services, albeit with a very high standard of care.

Functional outcome was analysed in this study using dichotomisation of the mRS, which is still the prevailing choice of analysis of an ordinal scale in stroke trials published in the last decade [39]. The cut-off value of mRS 2 has been commonly used in earlier critical stroke studies [16, 31] and was defined as more favourable than dichotomisation at higher grades [22]. Incorporation of the transition across the mRS grade spectrum has been proposed as a comprehensive measure reflecting simultaneously risks and benefit of treatments or interventions [22] and can reveal clinically meaningful improvement in ADL and higher levels of physical and social functioning [40]. In this analysis we only incorporated hospital survivors, since prediction of the transition of patients with mRS score of 6 is useless. This led however to lower numbers to analyse these outcome parameters and therefore a less extensive prediction model.

The main result of this study is the conducted multivariable model that best predicted long-term all-cause post-stroke mortality, in which mainly acute physiological disturbance and absolute values of neurological clinical assessment are shown to be predictive for long-term mortality in critical stroke patients. Acute correctable physiological disturbance measured within 24 hours after ICU admission, aggregated into the APACHE II score, does not only predict hospital mortality [24], but also long-term all-cause post-stroke mortality and functional status. It seems to be that physiological disturbance of the whole body is both evident and predictive when stroke hits a patient so severely that ICU admission is required.
Neurological clinical assessments by registration of GCS during ICU stay are very informative for clinicians. Moreover, the absolute values are more important than the change in GCS over time for both mortality and morbidity. As expected based on pathophysiological and clinical knowledge, absence of brainstem reflexes is as well a very strong prognostic indicator for unfavourable outcome.

Results from CT scans are not predictive for long-term mortality. An aggregated score could have been predictive, as is APACHE II score for vital parameters during the first 24 hours after ICU admission.

Stroke incidence and subsequent post-stroke mortality have declined in recent years attributable to improved risk factor management and treatment options. However, still half of all critical stroke patients do not survive the first year after the event. This study has identified several clinical parameters that predict long-term all-cause mortality and functional outcome among ICU-admitted adult ischaemic and intracerebral haemorrhagic stroke patients. These results may be helpful for predicting outcomes for clinicians in daily practice or to aid in decision-making in critical stroke patients. This can be the first step towards a decision support algorithm in order to realize a clinically relevant survival prediction model. However, the design of this study does not allow to completely fulfil this intent nor does it help to distinguish the variables with a direct pathophysiological role in post-stroke mortality. These issues require assessment and validation in a larger and prospective multicentre study.

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Ethical statement

Data for this study were collected for quality audit purposes. This study is a publication of the results of this trust-audit.

Conflict of interests

The authors declare that they have no conflict of interest.

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TABLES

Table 1. Demographics and patients characteristics of adult ischaemic and intracerebral haemorrhagic stroke patients admitted to the ICU.

	All ICU stroke patients (N = 131)
Age (Mean (SD))	66.0 (15.4)
Gender (Male)	76 (58.0)
Type of stroke (Ischaemic)	75 (57.3)
Apache II (Mean (SD))	20.4 (8.0)
Reason for admission	
• Low GCS (≤8)	69 (52.7)
• Post-neurosurgical or radiological intervention	33 (25.2)
• Haemodynamic instability	12 (9.2)
• Neuromonitoring	17 (13.0)
Time of admission (Day time 8-20u)	85 (64.9)
Interval between stroke and admission (< 6 hours)	102 (77.9)
ICU duration in days (Mean (SD))	8.1 (22.5)
Hospital length of stay in days (Mean (SD))	25.0 (44.3)
ICU mortality	44 (33.6)
In-hospital mortality	59 (45.0)
One-year mortality	69 (52.7)
Long-term all-cause mortality	77 (58.8)

Data are presented with references between parentheses as numbers and percentages, unless Mean (SD) is stated.

Table 2. Cox proportional hazard univariable regression analysis analysing prognostic factors for all-cause long-term post-stroke mortality.

Variable	**Univariable analysis**		
	HR	95%CI	p-value
Age	1.044	1.026-1.062	<0.0005*
Gender (male)	1.272	0.811-1.995	0.295
Type of stroke (haemorrhagic)	0.875	0.557-1.375	0.564
Time of admission (daytime)	0.800	0.505-1.270	0.344
Interval stroke (less than 6h)	1.587	0.967-2.604	0.067*
APACHE 2 score	1.142	1.107-1.178	<0.0005*
Reason for admission (neuromonitoring)	reference		
- Low GCS	5.031	2.005-12.623	0.001*
- Post-neurosurgical or radiological intervention	1.031	0.352-3.017	0.956
- Haemodynamic instability	1.989	0.607-6.517	0.256
PRIOR ILLNESSES			
Hypertension	1.207	0.758-1.922	0.427
Atrial fibrillation	1.821	1.128-2.941	0.014*
Hypothyroidism	1.505	0.653-3.464	0.337
Diabetes Mellitus	1.136	0.655-1.971	0.650
Hypercholesterolemia	1.017	0.593-1.742	0.952
Ischemic heart disease	1.531	0.882-2.659	0.130
Lung emphysema	0.898	0.328-2.458	0.834
Renal Dysfunction	2.183	0.684-6.962	0.187
Clotting disorder	0.368	0.090-1.498	0.163
Previous CVA	1.740	1.046-2.895	0.033*
Smoking	0.930	0.428-2.023	0.855
Alcohol abuse	0.792	0.320-1.963	0.615
VITAL PARAMETERS ON ADMISSION			
Temperature	0.788	0.660-0.940	0.008*
Heart rate	1.000	0.988-1.012	0.955
Mean arterial pressure	1.004	0.995-1.013	0.424
Systolic blood pressure	1.005	0.999-1.012	0.119
NEUROLOGICAL EXAMINATION			
GCS sum score on admission	0.884	0.837-0.933	<0.0005*
GCS sum score after 24 hours	0.851	0.807-0.897	<0.0005*
Difference GCS day 1 – GCS admission (no difference)	reference		
- decreased GCS after 24h	2.228	1.269-3.912	0.005*
- increased GCS after 24h	1.107	0.489-2.506	0.808
Brainstem reflexes (Absent)	0.169	0.079-0.359	<0.0005*
Epileptic Activity (Absent)	0.830	0.381-1.806	0.638
LABORATORY RESULTS ON ADMISSION			
Glucose level	1.009	0.977-1.043	0.568
Haemoglobin in g/L	0.950	0.851-1.061	0.366
Haematocrit	0.066	0.002-2.692	0.151
White blood cell count	1.018	0.962-1.078	0.531
C-reactive protein in mg/L	1.000	0.994-1.007	0.958
COMPUTED TOMOGRAPHY ANGIOGRAPHY RESULTS			
Mass Effect (No)	11.522	0.956-2.423	0.077*
Midline Shift(No)	1.344	0.807-2.238	0.256
Hydrocephalus (No)	1.621	0.908-2.896	0.103
Brain stem involvement (No)	2.594	1.119-6.010	0.026*

Data are presented as hazard ratio with 95% CIs. The reference variables are stated between parentheses behind nominal covariates. Reference variables for comorbidities were absence of the disease. (* p-value < 0.1)

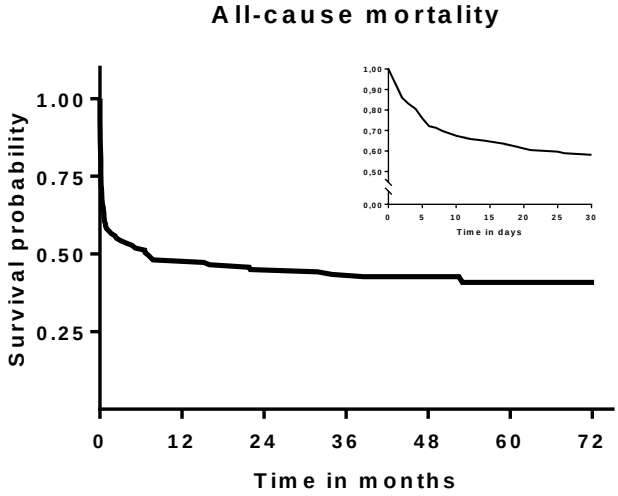
Table 3. Multivariable analyses analysing prognostic factors for all-cause long-term post-stroke mortality and functional outcome.

Variable	**Cox Proportional Hazard Regression**		
	HR	95%CI	p-value
APACHE 2 score	1.119	1.073-1.168	<0.0005*
Reason for admission (neuromonitoring) - Low GCS - Post-neurosurgical or radiological intervention - Haemodynamic instability	 3.054 1.841 3.480	 1.076-8.664 0.580-5.845 0.973-12.448	 0.036* 0.301 0.055
GCS sum score after 24 hours	0.920	0.851-0.995	0.037*
Brainstem reflexes (Absent)	0.425	0.185-9.77	0.044*
Variable	**Multiple Binary Logistic Regression**		
	OR	95%CI	p-value
APACHE 2 score	0,823	0,728-0,931	0,002*
GCS sum score on admission	1,279	0,976-1,675	0,074
Mass Effect (No)	8,547	1,010-71,428	0,049*

Data are presented as hazard ratio and odds ratio with 95% CIs. The reference variables are stated between parentheses behind nominal covariates. (* p-value < 0.05)

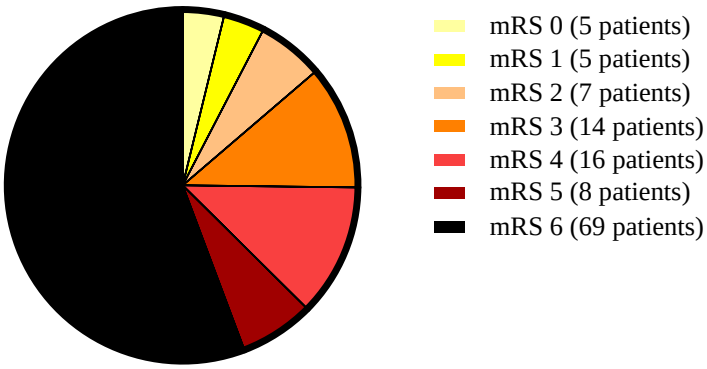
FIGURES

Figure 1. Kaplan-Meier survival curve of all-cause long-term post-stroke mortality



The inset shows the same data on an expanded y axis with time in days on the x axis.

Figure 2. Functional status after one year measured by modified Rankin Scale



All figures in the manuscript have been created using GraphPad Prism for Macintosh version 7.02 (GraphPad Software, Inc. La Jolla, CA, USA).