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ORIGINAL COMMUNICATION

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Functional, cognitive and emotional long-term outcome of patients with ischemic stroke requiring mechanical ventilation

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Abstract Prognosis of patients with ischemic stroke requiring mechanical ventilation (MV) has been reported to be poor. However, long-term survival and functional outcome have scarcely been studied and nothing is known about the prevalence of cognitive impairment or depression in survivors and their quality of life (QoL).

We identified all patients treated for acute ischemic stroke on a Neurological Intensive Care Unit during 3.5 years who required MV for more than 24 hours. Early mortality rate at 2 months and survival rates at 1 and 2 years were determined. Survivors were examined for functional outcome (modified Rankin Scale (mRS), Barthel Index), cognitive impairment (Mini Mental State Examination (MMSE)), depression (Beck Depression Inventory, BDI) and QoL (Short Form-36). Clinical characteristics on admission were analyzed for prognostic significance. Of 101 consecutive patients, 44 % died within 60 days. Survival rates at 1 and 2 years were 40 % and 33 %, respectively. Age > 60 years ($p = 0.002$) and Glasgow Coma Scale score < 10 on admission ($p = 0.002$) were independent predictors of early and late mortality. History of myocardial infarction ($p = 0.007$) independently predicted late mortality at 2 years. Of 33 surviving patients, nine (27 %) had a good functional outcome (mRS 0–2). Of 27 survivors who could be interviewed, 17 (63 %) had no cognitive impairment (MMSE > 24) and 20 (74 %) did not suffer from relevant depression (BDI < 19).

In conclusion, longer-term survival of patients with ischemic stroke requiring MV was 33 % and every fourth survivor resumed an independent life without dementia or depression. Older patients comatose on admission and with concomitant cardiovascular disease had the lowest probability of a favorable outcome.

Key words cerebral infarction · respiration, artificial · dementia · depression · quality of life

Introduction

The prognosis of mechanically ventilated patients with ischemic stroke is generally considered to be poor, with reported hospital mortality rates of up to 91 % [11]. In most cases, intubation and mechanical ventilation (MV) are performed as life-saving interventions in patients with otherwise lethal respiratory failure or neurological deterioration. Thus, the decision to start or withhold MV in a patient with acute ischemic stroke is an ethical dilemma and must be based on the best estimate of the individual patient's clinical course.

Several studies examined the prognosis of mechani-

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cally ventilated stroke patients and tried to identify predictors of outcome. Yet, important differences in study design and results make it difficult to come to a general conclusion. Reported early mortality rates varied between 49 % and 91 % [3, 8, 11, 14, 15, 17, 18, 20, 27, 35], but different definitions of early mortality were used and several studies included patients with both ischemic and hemorrhagic stroke [7, 8, 15, 18, 20, 27]. Additional information on long-term survival and functional outcome is scarce, as follow-up after discharge from hospital was not done [3, 11, 15, 18, 35] or restricted to one year [7, 8, 14, 17, 25, 27]. Available results on functional outcome showed considerable differences, with percentages of independent or only slightly impaired survivors ranging from 2 % to 19 % [14, 17, 20, 25].

In addition to physical disability, cognitive and emotional impairment are common in patients with ischemic stroke and negatively influence functional recovery and quality of life (QoL) [4, 9, 22, 24]. Since post-stroke depression [2, 4] and dementia [10] are correlated with stroke severity and MV is often performed in the most severely affected patients [3, 17], an interrelation of these factors can be assumed. As yet, no information on cognitive and emotional outcome in surviving patients with stroke requiring MV have been published.

The aim of this study was to (1) assess the long-term survival and functional outcome of patients with ischemic stroke requiring MV, (2) identify predictors of mortality and poor functional outcome and (3) examine the prevalence of cognitive impairment and depression and the QoL in surviving patients.

Subjects and methods

Study population

All patients who were treated for acute ischemic stroke on the Neurological Intensive Care Unit (NICU) at Charité University Hospital between January 1, 1996 and June 30, 1999 and required MV for more than 24 hours were identified by review of hospital charts. Diagnosis of ischemic stroke was confirmed by computed tomography (CT) or magnetic resonance imaging (MRI). General indications for intubation were severely or progressively decreased consciousness, impaired airway protection and respiratory failure. No specific protocol for starting MV was applied but decisions were based on general clinical criteria. Elective intubation for diagnostic procedures (e. g., angiography) or surgery were exclusion criteria unless complicating neurological or respiratory deterioration resulted in prolonged ventilation.

Data collection

Medical records were reviewed for demographic data, stroke characteristics, past medical history, comorbidities, Glasgow Coma Scale (GCS) score [30], National Institutes of Health Stroke Scale (NIH-SS) score [5], results of CT or MRI, specific therapies and clinical course, including indications for MV, hospital mortality and BI score [19] at discharge. Patient identification and collection of in-hospital data took place from July 1999 to June 2000. For all patients discharged alive, patients or caregivers were contacted by telephone to assess longer term survival and functional status one and two years after the stroke. After giving informed consent, all surviving patients were prospectively followed and visited in person at their home or nursing facility between June and December 2000 to assess neurological and functional outcome, emotional and cognitive state and quality of life and final telephone interviews were done in July 2001.

Follow-up investigations

Functional assessment at one and two years after the stroke was performed by using BI and the modified Rankin Scale (mRS) [31]. A favorable functional outcome was defined as mRS score ≤ 2 or BI score ≥ 65. The NIH-SS was used for estimating the neurological outcome. The emotional state was evaluated by using the Montgomery Asberg Depression Rating Scale (MADRS) [21] and the Beck Depression Inventory (BDI) [1]. A MADRS score of 7–19 and a BDI score of 10–18 were judged as mild depression, whereas MADRS and BDI scores ≥ 20 and ≥ 19, respectively, were judged as moderate depression or worse. Cognitive function was measured by using the Mini Mental State Examination (MMSE) [13], with a score of 20–24 indicating mild, 12–19 moderate and < 12 severe dementia. Health-related QoL was assessed with a German version of the Medical Outcome Study 36-item Short Form (SF-36), a patient-reported health rating scale containing 36 items of 8 domains (physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems, mental health) [6, 33]. SF-36 mean scores were compared with age-adjusted German population-based norms [12].

Statistical analysis

Demographic and clinical variables were tested for significant association with mortality at 2 months and with poor functional outcome (mRS > 2) at follow up in univariate analysis using the χ^2 test. For the purpose of analysis, dichotomized variables were used. Significant variables were entered into a multivariate Cox regression analysis to identify independent predictors of early and late mortality. Survival curves were obtained by the Kaplan-Meier method. Significance was judged at the $p < 0.05$ level. All statistical analyses were performed by use of SPSS 10.0.

Results

One hundred and one patients met the inclusion criteria of the study. Diagnosis of ischemic stroke was confirmed by head CT or MRI in all patients. Forty-two patients (42 %) were initially admitted to the NICU, whereas 59 patients (58 %) were referred from peripheral wards or surrounding hospitals after a mean ± SD interval of 2.9 ± 6.1 days. Fifty-two patients (51 %) were already mechanically ventilated on admission, while 49 patients (49 %) were intubated on NICU after a mean ± SD of 1.8 ± 3.2 days (range, 0.1 to 28 days). Patient characteristics at baseline are presented in Table 1.

Table 1 Patient characteristics (n = 101)

Age (years)	63.8 ± 12.4
Women	45 (44.6%)
Stroke localization	
Carotid	66 (65%)
Vertebrobasilar	26 (26%)
Both	9 (9%)
Stroke etiology	
Large artery arteriosclerosis	39 (39%)
Cardiac embolism	35 (35%)
Lacunar	1 (1%)
Unusual cause (dissection, etc.)	7 (7%)
Unknown	19 (19%)
Mean GCS score on admission	9.2 ± 3.3
Carotid stroke	9.6 ± 2.9
Vertebrobasilar stroke	9.4 ± 4
Both	6.6 ± 2.8
Cause of intubation	
Neurological deterioration	72 (71%)
Respiratory failure	18 (18%)
Impaired brainstem reflexes	7 (7%)
Seizures	3 (3%)
Myocardial infarction	1 (1%)
Specific therapies	
Decompressive craniectomy	21 (21%)
External ventricular drainage	13 (13%)
Intraarterial thrombolysis with urokinase	12 (12%)
Systemic thrombolysis with rtPA	6 (6%)
Acute endarterectomy	2 (2%)
Tracheostomy	38 (37%)
PEG feeding	23 (23%)

Values are n (%) or mean ± SD. GCS Glasgow Coma Scale

Early mortality and long-term survival

Early mortality at 2 months was 44% (n = 44), and 39 of those 44 patients (89%) died on NICU within a median interval of 8.6 days and after a median duration of MV of 5 days. Overall, 75% (n = 33) of deaths during the first 2 months had a neurological cause, whereas 18% (n = 8) were due to medical complications and 7% (n = 3) remained undetermined. The survival rates at 1 and 2 years were 40% (n = 40) and 33% (n = 33), respectively. Among the 24 patients who died after 60 days but within 2 years, the cause of death was recurrent stroke in 4 (17%), not neurological in 13 (54%) and undetermined in 7 (29%) patients.

Long-term outcome

Among 33 surviving patients, the median BI score at 2 years was 65 (0–100), with 16 patients (48%) having a score ≥ 65. The median mRS score was 3 (0–5), with 9 survivors (27%) being independent or only slightly disabled (mRS 0–2), accounting for 9% of the entire study population. Of 21 patients treated with craniectomy for space-occupying MCA infarction, twelve (57%) survived at 2 years and 2 (17%) of these had a mRS score ≤ 2. All 7 operated patients older than 50 years had an mRS score ≥ 4.

In all 33 survivors, cognitive and emotional impairment and QoL were assessed after a median ± SD interval of 34.7 ± 12 months after admission. In 32 patients, follow-up could be done by personal visit, while 1 patient was followed by telephone. Of these 32 patients, 27 (84%) could be interviewed, whereas 2 patients (6%) were in vegetative state and 3 (9%) suffered from severe aphasia.

Among 27 interviewed patients, mean ± SD MMSE score was 22.7 ± 9.8. Overall, 17 patients (63%) had no cognitive impairment (MMSE > 24), 3 (11%) suffered from mild dementia (MMSE 20–24) and 7 (26%) had MMSE scores indicative of moderate or severe dementia (MMSE ≤ 19). Aphasia ($p < 0.001$), functional impairment ($p < 0.005$), depression ($p < 0.01$) and complete MCA infarction ($p = 0.035$) significantly correlated with cognitive impairment.

Approximately two thirds of 27 interviewed patients (70% and 63%, respectively, as assessed with MADRS and BDI) suffered from emotional impairment of various degrees. Symptoms of moderate or severe depression (MADRS ≥ 20 or BDI ≥ 19) were found in 9 (33%) and 7 patients (26%), respectively. Ten patients (37%) had symptoms of mild depression (MADRS 7–19 or BDI 10–18), and 8 (30%) and 10 patients (37%), respectively, were tested free of relevant depression (MADRS < 7 or BDI < 10). Categorised results as assessed with MADRS and BDI were significantly correlated ($p < 0.01$). Aphasia ($p = 0.022$), functional impairment ($p = 0.003$), cognitive impairment ($p = 0.003$) and lack of family support ($p = 0.029$) significantly correlated with occurrence of depression.

All 9 patients with a good functional outcome (mRS 0–2) had MMST scores > 24. Two of them had had symptoms of mild depression before their stroke which remained unchanged over time.

Health-related quality of life

Mean SF-36 scores of survivors were lower for all domains compared with the age-adjusted German population-based norms, except for 'bodily pain' (Figure). The widest differences to population norms were found for 'physical functioning', 'role limitations due to physical problems' and 'role limitations due to emotional problems'. For these domains, significant differences between subgroups with good and poor functional outcome as assessed with mRS were found ($p = 0.012$, $p < 0.0001$ and $p = 0.047$, respectively). In patients with mRS scores ≤ 2, a relevantly lower mean SF-36 score as

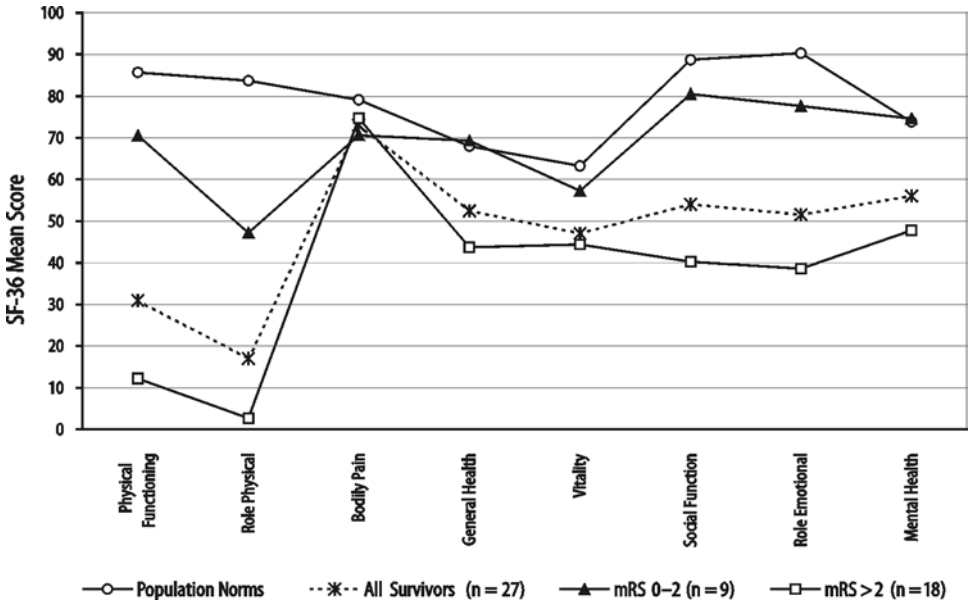

Fig. Health-related quality of life at follow-up: mean SF-36 scores in all survivors and in subgroups according to mRS score compared to age-adjusted population-based norms

compared to the population norm was only found for the domain 'role limitations due to physical problems'. Presence of depression significantly correlated with lower mean scores in the domains 'role limitations due to physical problems' ($p < 0.002$), 'vitality' ($p = 0.034$), 'role limitations due to emotional problems' ($p = 0.003$) and 'mental health' ($p = 0.034$).

Factors influencing early mortality and long-term outcome

Of 17 variables included in the univariate analysis (Table 2), age greater than 60 years ($p = 0.001$), GCS score on admission < 10 ($p = 0.001$), complete MCA territory infarction ($p = 0.022$), prior myocardial infarction ($p = 0.023$) and history of coronary artery disease ($p = 0.022$) were found to significantly influence the probability of death at 2 months. In the multivariate regression analysis, age greater than 60 years (relative risk (RR) 2.54, $p = 0.002$) and GCS score < 10 (RR 2.25, $p = 0.002$) were identified as independent predictors of mortality at 2 months and at 2 years. Additionally, history of myocardial infarction was independently predicting death at 2 years (RR 2.34, $p = 0.007$).

In the univariate analysis of variables associated with a poor functional outcome (mRS ≥ 3) at follow-up, only complete MCA territory infarction ($p = 0.013$) significantly correlated with functional dependency. The multivariate regression analysis yielded no independent predictor of a poor functional outcome.

Table 2 Univariate analysis of variables associated with early mortality at 2 months

	n	%	RR	CI	p
Age > 60 years	65	64.4	4.34	1.72–10.96	**0.001**
Female sex	45	44.6	1.25	0.56–2.77	0.573
History of					
Stroke	23	22.8	1.56	0.61–3.99	0.343
TIA	15	14.9	0.84	0.27–2.57	0.763
Myocardial infarction	14	13.9	3.89	1.13–13.42	**0.023**
Ischemic heart disease	40	39.6	2.57	1.13–5.85	**0.022**
Atrial fibrillation	50	49.5	1.43	0.64–3.15	0.373
Peripheral arterial disease	25	24.8	1.02	0.41–2.54	0.960
Arterial hypertension	65	64.4	0.94	0.41–2.14	0.894
Diabetes mellitus	28	27.7	1.17	0.48–2.81	0.719
GCS < 10 on admission	55	54.5	3.94	1.68–9.21	**0.001**
Complete MCA infarction	42	41.6	3.05	1.15–8.08	**0.022**
Infratentorial infarction	26	25.7	1.41	0.58–3.47	0.442
Basilar artery occlusion	15	14.9	0.62	1.39–5.35	0.625
Neurological deterioration	72	71.3	1.13	0.47–2.71	0.079
Respiratory failure	18	17.8	1.18	0.64–5.03	0.258
Impaired brainstem reflexes	7	6.9	5.8	0.44–0.64	5.8

RR relative risk; *CI* confidence interval; *TIA* transient ischemic attack; *GCS* Glasgow Coma Scale; *MCA* middle cerebral artery territory

Discussion

In this large hospital-based study on the prognosis of mechanically ventilated patients with ischemic stroke, early mortality at 60 days was 44 % and about one third of patients was still alive after two years. Of the survivors, 27 % resumed a functionally independent life

free of dementia or depression, accounting for 9 % of the study population.

The observed early mortality rate is in contrast to almost all previous studies of mechanically ventilated stroke patients. Three studies reported only slightly higher mortality rates (49–55 %) but had included patients with both ischemic and hemorrhagic stroke and ischemic stroke patients accounted for 31 % to 68 % of study populations [8, 15, 27]. Yet, with rates of 69 % to 91 %, early mortality was substantially higher in all previous series limited to ischemic stroke patients [3, 11, 14, 17, 25, 35]. In some small studies with mixed populations, though, ischemic stroke patients had a better outcome than those with hemorrhages [7, 20] and predictors of mortality also varied [15]. Methodical reasons are likely to be at least partly responsible for varying mortality rates. For instance, definitions of early mortality differed, including death rates at 1 [8, 20] or 2 months [3, 17] and general hospital mortality [11, 14, 15, 18, 27, 35] and most studies were limited by small populations [3, 8, 11, 14, 17, 18, 20, 35]. Apart from methodical differences, it could be suspected that an improved management of neurological complications and more aggressive treatment modalities on a dedicated NICU are to some extent responsible for the lower early mortality in our study. Supportive for this assumption would be the fact that the three studies with the lowest mortality rates previously reported also took place on specialized NICUs [8, 15, 27]. However, the superiority of any kind of specialized care in this setting remains speculative as only uncontrolled case series like ours are currently available. A meta-analysis of the Cochrane Collaboration on organized stroke care could not detect any significant differences between hyperacute neurological stroke units and general stroke unit care [28].

Information on the long-term outcome of patients with ischemic stroke requiring MV is scarce. The only other study so far which reported outcome at 2 years had studied only 20 patients and had found a survival rate of 20 % [14]. Two small studies reported 1-year survival rates of 28 to 31 % [17, 25]. In these three studies, 6–19 % of all patients were reported having a good functional outcome, as measured with the Barthel Index (BI). In our study, 16 % of patients had a BI score > 60, which is comparable to the 15 % [14] and 19 % [25] of patients in those two studies which used the same BI cut-off points. However, the value of the BI in assessing functioning and disability after stroke is limited due to a ceiling effect, thus overrating the percentage of patients with good outcome, and the preferred use of the mRS and of the SF-36 physical functioning index (PFI) has been advised [34]. In our study, 27 % of survivors had a mRS score ≤ 2, indicating a favorable functional outcome. At the same time, mRS and SF-36 PFI results were in good agreement. The mean SF-36 PFI score of patients with a mRS score ≤ 2 was not relevantly different to the respective population norm and well above the commonly applied cut-off point of 50 [34], as opposed to patients with a mRS score > 2 (Figure).

In our population, age > 60 years and GCS score < 10 on admission independently predicted early and late mortality. Taken together, the evidence from our study and those of others indicates that a low GCS score is the strongest predictor of mortality among ventilated stroke patients [7, 8, 20, 25, 27] and age was found to be of significant influence in two other studies [8, 27]. As in the study by Santoli et al., concomitant ischemic heart disease independently influenced long-term survival but not early mortality [25]. Ischemic heart disease was present in about 40 % of our population and had a similar prevalence in previous studies [15, 17, 25]. Yet, other studies might have missed the importance of this comorbidity due to their shorter follow-up. Predictors of functional outcome had not been reported before. In our study, the occurrence of a complete MCA territory infarction was significantly correlated with a poor functional outcome (mRS ≥ 3) in the univariate analysis. However, neither a complete MCA infarction, nor any of the other 16 variables tested were independent predictors of outcome in the multivariate regression analysis. Notably the reason for intubation had no influence on the functional long-term outcome. Patients who were intubated for respiratory failure, e. g. pneumonia had no better functional outcome, as one could have expected. At the same time, there was no significantly worse outcome if neurological deterioration, e. g. following a complete MCA territory infarction, led to mechanical ventilation.

An improved survival has been reported for patients treated with hemicraniectomy for large space-occupying MCA infarction [26]. Consistent with published data, about 60 % of operated patients in our study were alive at 2 years. However, age markedly influenced long-term outcome in these patients. While patients younger than 50 years had a mean mRS score of 2.4 at follow-up, those older than 50 years all had scores of 4 or 5. These data extend our previous findings of poor functional outcome in elderly patients after decompressive surgery [16] and are in accordance with results of another study [32] which reported a significantly better outcome after 14 months in patients younger than 45 years (BI 75.7 ± 20.7) compared to older ones (BI 42 ± 22.7). Thus, there is growing evidence that advanced age is the main predictor of poor functional outcome after decompressive surgery whereas side of infarction, timing of hemicraniectomy and initial NIH-SS score seem to be less important [16, 26, 32].

Depressive disorders have been estimated to occur in 25–55 % of patients with stroke [2, 4] and with reported prevalences of 20–40 % cognitive impairment is just as likely to be found after ischemic stroke [10, 23, 29]. Both factors are generally considered to negatively influence

functional recovery and QoL [2, 4, 9, 22, 23]. Since both post-stroke depression and dementia are correlated with stroke severity [10, 23, 29] and MV is mainly performed in the most severely affected patients [3, 17], a particularly high prevalence of these sequelae could be assumed in ventilated stroke patients. However, rates of relevant depression and dementia at follow-up in our study are consistent with rates in general stroke populations. Nevertheless, significant interrelations were found between both factors and between each of them and severe functional impairment. In fact, none of the functionally independent survivors (mRS ≤ 2) suffered from cognitive impairment or relevant depression. In general, QoL as assessed with the SF-36 was lower than the population norms for all domains except bodily pain and particularly so for physical functioning and role limitations due to physical problems. However, QoL in patients with a mRS ≤ 2 did not differ relevantly from the population norm except for a slight decrease in role limitations due to physical problems.

Several limitations apply to our study. First, the analysis of factors associated with good or poor functional outcome is limited by the small numbers of survivors. For example, the reason for intubation could still have an effect on functional outcome that was missed in our population due to a type II error. Second, the study was carried out at a highly specialized unit in a single tertiary centre which may have caused a referral bias so that the results may not be generalizable to other centers. No specific criteria for referral to the unit were applied and patients were admitted from peripheral wards and the emergency department within the hospital as well as from other hospitals in Berlin. Third, although the outcome of all survivors was prospectively followed, the identification of patients and the assessment of data on the acute in-hospital stage were performed retrospectively and no standardized protocol as to general treatment and mechanical ventilation was applied. Fourth, data were collected from patients admitted up to 8 years ago which may challenge the relevance of the data for current practice. Nevertheless, management of the critically ill stroke patient remained essentially unchanged during the last years and promising new treatment options like hypothermia have not been adopted into general clinical practice yet.

In conclusion, patients with ischemic stroke requiring MV had a longer term survival of 33 % and about one fourth of survivors resumed an independent life without cognitive or emotional impairment and with an acceptable quality of life. Older patients comatose on admission and with concomitant ischemic heart disease had the lowest probability of a favorable long-term outcome. These patients potentially constitute a group for which maximal life support and NICU treatment may better be restricted. A validation of these and further predictive factors by prospective studies is needed.

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