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PREDICTORS FOR POST- STROKE DELIRIUM OUTCOME

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ABSTRACT
Background: There have been only a small number of studies that have evaluated the outcome of post-stroke delirium. **Objectives:** To evaluate the effects of gender, age, stroke localization, delirium severity, previous illnesses, associated medical complications on delirium outcome as well as, to determine effects of delirium on cognitive functioning one year after stroke. **Patients and Methods:** Comprehensive neuropsychological assessments were performed within the first week of stroke onset, at hospital discharge, and followed-up for 3, 6 and 12 months after stroke. We used diagnostic tools such as Glazgow Coma Scale, Delirium Rating Scale, National Institutes of Health Stroke Scale and Mini-Mental State. **Results:** Patients who developed post-stroke delirium had significantly more complications (p = 0.0005). Direct logistic regression was performed to assess the impact of several factors on the likelihood that patients will die. The strongest predictor of outcome was age, mean age ≥ 65 years with a odds ratio (OR) 4.9. Cox's regression survival was conducted to assess the impact of multiple factors on survival. The accompanying medical complications were the strongest predictor of respondents poore outcome with Hazard-risk 3.3. Cognitive assessments including Mini Mental State score have showen that post-stroke delirium patients had significant cognitive impairment, three (p = 0.0005), six months (p = 0.0005) and one year (p = 0.0005) after stroke, compared to patients without delirium. **Conclusion:** Patient gender, age, localization of stroke, severity of delirium, chronic diseases and emerging complications significantly affect the outcome of post- stroke delirium. Delirium significantly reduced cognitive functioning of after stroke patients.
Key words: predictors, outcome, delirium, stroke.

1. INTRODUCTION

Delirium is an etiologically nonspecific organic cerebral syndrome characterized by concomitant disturbance of consciousness and attention, perception, thinking, psychomotor behavior, emotion, rhythm of sleep and wakefulness (1), a stroke is defined as the sudden development of focal or global symptoms and signs of disturbance of cerebral function lasting more than 24 hours or leading to death, a result of the pathological process of vascular origin (2).

Stroke is a known risk factor for the development of delirium (3). The majority of studies of delirium have reviewed mixed medical, surgical, orthopaedic or ICU patients. There have been only a small number of studies that have evaluated the outcome of post-stroke delirium. These studies have yielded conflicting results and have screened for delirium using different measures at different time intervals.

2. OBJECTIVES

To evaluate the effects of gender, age, stroke localization, delirium severity, previous illnesses, associated medical complications on delirium outcome as well as, to determine effects of delirium on cognitive functioning one year after stroke.

3. PATIENTS AND METHODS

Patients

This prospective study was conducted at the Department of Neurology, University Clinical Center in Tuzla for the period of September 2009 to August 2011. During the study period we used test group of 100 patients with delirium in the acute phase of stroke. We evaluated the effects of gender, age, severity of delirium, previous illneses and associated medical complications on post-stroke delirium outcome and determined effects of delirium on cognitive functioning one year a fter stroke. The control group consisted of the same number of patients without delirium in the acute phase of stroke. Both groups were matched by gender, age, location,

type and severity of stroke.

The study group included patients who meet the following criteria: diagnosis of cerebral infarct (ischemic or hemorrhagic) confirmed by computed tomography and / or magnetic resonance imaging of the brain; Neuropsychiatric assessment of delirium being performed within seven days after stroke onset; Glasgov Coma Scale (GCS)[4] score > 8; given written consent for participation in the study by the patient or the patient's immediate family member.

Patients that had GCS score <8 on the day of neuropsychological examination were excluded from the study, and so were patients with epileptic seizures onset of stroke, aphasia, with confirmed early stage dementia (heteroanamnestic data obtained from relatives, earlier medical findings and based on dementia Score results (5), patients with confirmed alcohol abuse, patients with previously verified mood disorders, patients who had previously taken medication that could cause delirium. All medical complications were systematically registered during hospital stay. Abnormal laboratory values were used as criteria for the electrolyte imbalance and other metabolic complications**.**

Comprehensive neurological, neuropsychiatric and neuropsychological assessments were performed in five periods:

- First test - in the acute phase of stroke (first week of stroke onset).
- Second test - at discharge or after one month of discharge from hospital.
- Third Test - three months after stroke.
- Fourth test - six months after stroke.
- Fifth Test - twelve months after stroke.

The presence of delirium was assessed according the Delirium Rating Scale R-98 and the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition criteria for delirium within 24 hours after hospitalization by one of the authors of this research. The final neuropsychological assessment was performed during the third or fourth day of hospital stay by two of the co-authors of this study and niether did the first assessment. Authors of this study, all neuropsychiatrists delirium experts who used DRS R-98 scale and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria independently**.** In order to diagnose delirium patients had to meet the criteria according to both assessments.

Methods

For all patients we also used diagnostic tools:

1. Glazgov Coma Scale (4) (at first and second testing):
2. Delirium Rating Scale (6) (in all tests);
3. National Institutes of Health Stroke Scale-NIHSS[7] (in all tests);
4. Mini Mental Test (6) (at the third, fourth and fifth testing).

Identification of delirium symptoms was performed using the Scale for the assessment of delirium-R-98 (6) (DRS-R-98) and the criteria for delirium according to the Fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (7-9). Delirium was diagnosed in those patients who had more than 16 points on the DRS-R-98 and who meet the criteria for delirium according to DSM-IV. Patients with a score of 16-32 were selected to the milder form and those over 32 as a more severe form of delirium.

Computed tomography and magnetic resonance imaging of the brain were interpreted by the radiologist who was not familiar with the research objectives and hypotheses, and based on whose results were found: type of stroke, localization of lesions, size of the lesion and silent infarcts.

Magnetic resonance imaging of the brain was performed in patients with clinical signs of brain stem lesions, with negative findings on computed tomography of the brain, or when necessary to supplement the findings. Strokes by type are divided into: hemorrhagic and ischemic stroke.

The degree of neurological deficit was evaluated on the addmision by Stroke Scale score of the National Institutes of Health USA (National Institute of Health Stroke Scale-NIHSS) (7).

Statistical analysis

The data are grouped, coded and entered into a specially designed medicaln database. Collected data were extra validated (logic control). Based on the scoring system (algorithm) to calculate the cummulative scores for all domains, the normalized value of domains and summary scores. Statistical analysis was performed using the SPSS ver. 17.0 (Chicago, IL, USA).

Testing was done for each variable to a normal distribution using the Kolmogorov-Smirnoff test, and histogram display. To estimate the statistical significance of differences obtained results we used: Student's t-test and Chi-square test. Multivariate logistic regression analysis was used to detect independent predictors of delirium after stroke. Used as the dependent variable is the data on the occurrence of delirium, as independent predictors of risk-factors that are at univariate analysis showed statistical significance. All statistical tests were done with the level of statistical probability of 95% ($p < 0.05$).

The study was approved by the Ethics Committee of the

		Patients						
		With delirium		Without delirium		Total		p*- value
		N	%	N	%	N	%	
Complications	With	62	31.2	29	14.6	91	45.7	**0.0005**
	Without	38	19.1	70	35.2	108	54.3	
Total		100	50.3	99	49.7	199	100.0	

*Chi - square test;

Table 1. The incidence of after a stroke complications

		Patients			
		With delirium		Without delirium	
		N	%	N	%
Complications	Pneumonia	23	24.2	6	6.3
	Tromboembolia	1	1.1	1	1.1
	Decubitus	5	5.3	0	0.0
	Urinary infections	26	27.4	22	23.2
	Injuries	11	11.6	0	0.0

Table 2. Distribution of complications after stroke in patients with and without delirium

	Patients with delirium									
	Died		Survivors		Total					
Predictors	N	%	N	%	N	%	OR	95%	CI for OR	p*
≥ 65 year	24	32.4	50	67.6	74	100.0	4.9	1.3	18.9	**0.02**
Male	16	28.1	41	71.9	57	100.0	1.4	0.6	3.8	0.4
Complications	22	35.5	40	64.5	62	100.0	4.2	1.4	12.7	**0.01**

*Cox i Snell r^2 = 12.2%;

Table 3. Survival of patients with delirium one year of stroke onset

	Patients with delirium									
	Died		Survivors		Total					
Predictors	N	%	N	%	N	%	OR	95%	CI for OR	p*
IS	21	26.0	60	74.0	81	100.0	1.4	0.4	5.1	0.6
Right hemisphere	35	70.0	15	30.0	50	100.0	1.2	0.4	3.6	0.8
Elevated CRP	40	67.8	19	32.2	59	100.0	2.1	0.7	6.4	0.2

*Cox i Snell r^2 = 3.2%; IS - Ischemic stroke; CRP - C-reaktive protein;

Table 4. Survival of delirium in patients one year after stroke

Predictors	OR	95%	CI for OR	p*-value
Male*/ female	1.1	0.5	2.4	0.8
≥65* / ≤64 year	3.9	1.1	13.2	**0.03**
Right*/ left hemisphere	1.4	0.6	3.3	0.5
IS*/ HS	1.0	0.4	2.5	0.9
With*/Without complications	3.3	1.4	7.9	**0.007**

* Cox regression; IS- Ischemic stroke; HS- Hemorrhagic stroke;

Table 5. Factors for survival of patients with delirium during one year of stroke

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4. RESULTS AND DISCUSSION

Patients with delirium had significantly more complications (p = 0.0005, Yatess correction = 20.1, df = 1) with their different distribution (Table 1 and 2).

There was no statistically significant difference between patients with and without delirium in relation to the frequency of earlier disease, or in relation to educational background and employment (p > 0.05).

Predictors of delirium that we choosed had a statistically significant incidence of delirium compared to those without delirium.

Direct logistic regression was performed to assess the impact of several factors on the likelihood that patients will die. The model contains three independent variables (gender, age, complications). Full model (all predictors) was statistically significant (chi-square = 13.0, df = 3, p = 0.005), which means that the model distinguishes those respondents who did and those who did not die. The model explains a whole 12.2% of Cox and Snell's variance in the dependent variable. As shown in Table 3, only two predictors made significant unique contribution to the model. The strongest predictor of outcome was age, mean age ≥ 65 years with a odds ratio (OR) 4.9. This shows that respondents aged ≥ 65 years are over 4 times more likely to die than those who were aged ≤ 65 years.

And for the second model of logistic regression, we chosed predictors of delirium outcome, that had a statistically significant incidence for patients with delirium compared to those without delirium.

Direct logistic regression was performed to assess the impact of several factors on the likelihood that patients will die. The model contains three independent variables (type of stroke, stroke localization, CRP). Full model (all predictors) was not statistically significant (chi-square = 2.4, df = 3, p = 0.5), which means that the model does not distinguish between those respondents who did and those who did not die and there is no statistically significant influence of the analyzed predictors for their death (Table 4).

Kaplan-Meier survival analysis for selected predictors that had the effect on significantly poorer cumulative survival of patients with delirium and no delirium (patients ≥ 65 years, male gender, complications, and stroke with lesions in the right hemisphere) (p < 0.05). Cox's regression survival (multivariate survival analysis) was conducted to assess the impact of multiple factors on survival. The model contains five independent variables (gender, age, complications, type and localization of stroke). Full model (all predictors) was statistically significant (chi-square = 14.1, df = 5, p = 0.01). As shown in Table 5, only two predictors made significant unique contribution to the model. Accompanying medical complications were the strongest predictor of respondents poore outcome with Hazard-risk (likelihood ratio-OR) 3.3. This shows that respondents with additional medical complications have over 3 times higher risk of dying compared to subjects without complications.

Cox's multivariate survival analysis, for selected predictors, had statistically significantly higher risk of dying n forpatients with delirium after stroke (patients ≥ 65 years with complications) (p < 0.05). Cox's regression survival (multivariate survival analysis) was performed to assess the impact of multiple factors on survival. The model contains two independent variables (age and complications). Full model (all predictors) was statistically significant (chi-square = 11.9, df = 2, p = 0.003). As shown in Table 6, both predictors are given a unique statistically significant contribution to the model. The accompanying medical complications were the strongest predictor of respondents poore outcome with Hazard-risk (OR) 3.3. This indicates that delirious patients with associated medical complications have more than 3 times higher risk of dying compared to subjects without complications.

Cognitive assessments including Mini Mental State score have showen that post-stroke delirium patients had significant cognitive impairment, three months (p = 0.0005, Pearson Chi-Square = 43.9, df = 3), six months (p = 0.0005, Pearson Chi-Square = 74.7, df = 4 one) and one year (p = 0.0005, Pearson Chi-Square = 55.0, df = 3) after stroke, compared to patients without delirium.

Delirious patients had significantly poorer cognitive functioning according to the MMS score from stroke onset compared to patients without delirium (Table 7).

Delirium is a common behavioral disorder after acute stroke. Most studies of postsurgical delirium analyzed and mixed medical-geriatric population, and few systematic

studies of delirium is presented with stroke patients (10-13). Naughton et al. report the results of 297 computerized tomographic scans, in patients with acute delirium. 42 of them (15%) had one of acute conditions (stroke, subdural hematoma, and tumor). Of the patients with positive-computerized tomographic findings, all but two had a disturbance of consciousness or new focal neurologic findings. Among the healthy elderly, infection and stroke are the most important etiological factors of delirium (14). Langhorne et al. found that the incidence of delirium among 311 patients with acute stroke and 36% weekly prevalence of 24% (15).

In our study, we tried to avoid the influence of other factors as a primary caused of delirium. Therfore we did not include patients with the recurrent stroke, epileptic seizures at onset of stroke, all types of apfasia, early stage of dementia, delirium caused by abuse of alcohol and other psychoactive substances. Patients with delirium were placed in the Stroke Unit and were under constant supervision. The main limitations in our study is that control computed tomography was not performed to all patients, and that control testing of outpatients were done without continuously monitoring the patient for 24 hours (because patients do not have an extended stay in institutional treatment but discharged home and looked after by family).

In patients with stroke, predisposing and precipitating factors for delirium, according to results of other studies are age, extensive motor impairment, paralysis of the left half of the body, previous cognitive decline, metabolic and infectious complications, cortical lesion of the right hemisphere, a low score of daily activities, sleep apnea associated with hypoxemia, body mass index less than 27, impaired vision (10, 12, 13).

Gustafson and colleagues found that the stroke area in the left hemisphere of the brain is independent risk factor for developing delirium (10). Caeiro and associates reported that delirium is common in hemispheric stroke after intracerebral haemorrhage, and the delirious patients had the lowest average age of 57.3 years compared to previous studies (16). Increased age was confirmed by well-known risk factor for delirium in all clinical studies (17).

Sheng and colleagues found that patients who have had a stroke due to embolism in the region of the anterior circulation of the brain had a higher incidence of delirium (18). In addition, a number of case reports have suggested that delirium may be associated with certain lesions of the brain (thalamus and nucleus caudatus) (19).

Predictors of delirium outcome that we chosed had a significantly higher incidence, using direct logistic regression; we found out that patients aged ≥ 65 years are over 4 times more likely to die than those aged ≤ 65 years. And in the second logistic regression model predictors of delirium outcome, we found out that there was no statistically significant influence of the analyzed predictors of dying patients.

Kaplan-Meier survival analysis of selected predictors that had significant impact on poorer cumulative survival of patients with and without delirium (patients ≥ 65 years, male, with complications from stroke and ischemic lesions in the right hemisphere), and Cox's multivariate analysis showed that patients with associated medical complications have more than 3 times higher risk of dying compared to subjects without complications.

Using Cox's multivariate survival analysis, we selected predictors with significantly greater risk of mortality in patients with delirium after stroke (patients ≥ 65 years with complications**),** and using same method we found out that delirious patients with associated medical complications have more than 3 times higher risk for mortality compared to subjects without complications**.**

McManus et al. diagnosed during the month after stroke, delirium in 23 (28%) patients, and there was no significant difference in the incidence of delirium in relation to sex. Delirious patients were significantly older (20).

Hénon et al. says that after stroke delirium are frequent in the elderly, that delirious patients become functionally dependent on others, have an increased incidence of complications and longer hospital stay, increased need for long-term institutionalization and increased mortality. Intra-and 6-month mortality did not differ between patients with and without delirium, and patients with delirium had lower MMS scores 6 months after stroke ($p = 0.002$), even after excluding patients with existing dementia ($p = 0.04$). This study has shown that the rate of mortality at discharge and at 6 months was not affected by delirium. The reason may be that the mortality in the acute phase is probably influenced more by weight than stroke cognitive status (12).

Based on previous studies of delirium can be argued that the prognosis of delirium significantly depends on the timely verification and prevention of the causes of its emergence. In addition, it can be said that the transient state of delirium. In studies of patients after hip surgery, delirium was independently associated with poor functional outcome, an increased rate of mortality and institutionalization in institutions for geriatric rehabilitation (21). We found that delirium is a common problem in the acute stroke setting with a prevalence of 25.3%, within the range of previous studies. Patient sex and age, and type and stroke localization have no influence on delirium duration (22).

Sheng et al. have reported that in their patients during the three days after stroke, delirium was determined in 25% of cases. Patients were significantly older (those with ≥ 65 years), with a hemorrhagic stroke, with severe metabolic disorders, preexistent dementia, GCS score less than 15, and pronounced weakness in the hand. Patients who had a stroke, cardioembolic origin in the region of the anterior circulation of the brain were also significantly more likely to have delirium, and had significantly greater 6-month and 12-month mortality and a lower 12-month functional independence and cognitive functioning and a higher 12-month rate of institutionalization (19).

In elderly patients, delirium is an independent risk factor for cognitive decline and increased functional dependence during the year after admission to a health facility (23). It is also an independent factor for increased mortality at discharge and 12 months after discharge, the increase in length of stay, and institutionalization in institutions for geriatric rehabilitation (23, 24).

Gustafson et al., Henon et al. and Sheng et al. found that delirium after stroke and associated with prolonged hospital stay, mortality, risk of institutionalization in institutions for geriatric rehabilitation, functional dependency at discharge

and after 6 months of the formation of a stroke. In the delirium patients in this study was significantly lower MMS scores and significantly higher mortality rates after 6 and 12 months of the formation of a stroke (11, 12, 15).

There are several studies on the consequences of delirium after stroke, especially on the long term. Only in one report, there are data on the 12-month follow up of these patients (18). Although it seems clear that delirium is a bad prognostic indicator of stroke is less clear whether this is due to association with hemispherical stroke or delirium is itself an independent indicator of poor outcome after stroke (24).

McManus et al. reported that in patients who did not suffer delirium after stroke have a high mortality, longer hospital stays, higher rates of complications and increased risk of institutionalization, and dementia (25).

McManus et al. have found that delirium is independently associated with visual disturbances before stroke, ischemic stroke, the area of the anterior circulation, the degree of functional independence at admission according to the Barthel index (<10), elevated CRP values and swallowing difficulties at admission. They found that the worse the degree of functional dependence on admission to the regression analysis was stronger risk factor for the occurrence of delirium in relation to the type and localization of stroke, and that delirium after stroke associated with poor prognosis, increased mortality, longer duration of stay in hospital and higher rates of institutionalization in institutions for geriatric rehabilitation after discharge from hospital (20).

Siddiqi et al. and Young et al. in their research confirm that the above effects of delirium after stroke similar to the effects of delirium and other diseases. Their findings of significant gender, age, localization of stroke, severity of delirium, previous chronic disease complications and emerging on the outcome of delirium were validated in previous studies on this subject (24, 26).

Except of delirium as after stroke neuropsychological disorder appears: mania, depression, aphasia, neglect. For this conditions so far exists sparse published literaure (27-29). In order to obtain adequate data on predictors and outcome of these disorders is necessary to do more studies to possibly prevent and/or predict the outcome.

5. CONCLUSION

Patient gender, age, localization of stroke, severity of delirium, chronic diseases and emerging complications significantly affect the outcome of post- stroke delirium. Delirium significantly reduced cognitive functioning of after stroke patients.

- Conflicts of interest: none to declar.

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