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TITLE PAGE

COGNITIVE IMPAIRMENT PREDICTS POSTSTROKE DEATH IN LONG-TERM FOLLOW UP

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ABSTRACT

Background: Poststroke global cognitive decline and dementia have been related to poor long term survival. Whether deficits in specific cognitive domains are associated with long term survival in ischemic stroke patients is not known in detail. **Methods:** Consecutive acute stroke patients subjected to comprehensive neuropsychological evaluation were included in the study (N=409) and followed-up up to 12 years. **Results:** In Kaplan-Meier analysis, impairments in following cognitive domains predicted poor poststroke survival **(estimated years):** executive functions (48.2%) (5.8 vs. 10.1 years, $p<0.0001$), memory (59.9%) (6.8 vs. 9.3 years, $p=0.009$), language (28.9%) (5.3 vs. 8.6 years, $p=0.004$), and **visuospatial/constructional** abilities (55.2%) (5.6 vs. 10.1 years, $p<0.0001$). **Low** MMSE ≤ 25 (30.5%) (4.4 vs. 9.3 years, $p<0.0001$), low education (<6 years) (31.8%) (6.4 vs. 8.2 years, $p=0.003$) and poor modified Rankin score (39.9%) (**3.9 vs. 9.7 years**, $p<0.0001$) were also **related to poor** survival. In Cox regression proportional hazards analyses including age, sex **and** years of education as covariates, deficits in executive functions (HR 1.59, $p<0.0001$), memory (HR 1.31, $p=0.042$), language (HR 1.33, $p=0.036$) and **visuospatial/constructional** abilities (HR 1.82, $p<0.0001$), were significant predictors of poor poststroke survival. Of these, executive functions (HR 1.33, $p=0.040$) as well as **visuospatial/constructional** abilities (HR 1.53, $p=0.004$) remained as significant predictors after addition of MMSE ≤ 25 and poor modified Rankin score as covariates. **Furthermore, cognitive impairment no dementia (CIND) was also an independent predictor of poor poststroke survival (HR 1.63, $p=0.0123$).** **Conclusions:** In patients with ischemic stroke, cognitive impairment particularly in executive functions, and **visuospatial/constructional** abilities relate to poor survival.

INTRODUCTION

Poststroke cognitive impairment is frequent – up to 65 to 78% of patients demonstrate cognitive decline [1, 2] and 25 to 31% of patients demonstrate poststroke dementia [3-7]. Further ischemic stroke is an important factor predicting long-term survival [8].

Global measures of cognition e.g. Mini Mental Status Examination (MMSE) [9-12] and similar short mental status tests [13] have been related to a poor survival in poststroke follow-up studies. Similarly poststroke dementia has been related to a poor survival [4-7, 14].

Poststroke cognitive impairment consists of decline in various cognitive domains such as memory, language, visuospatial and constructional abilities [1, 15] and also in executive function [16, 17]. However, the role of these specific cognitive impairments on poststroke long-term survival has not been studied in detail. **Moreover, it is not known whether a milder cognitive impairment short of dementia is relevant for poststroke survival.**

The aim of our study was to detail the effect of **different cognitive deficits as well as cognitive impairment no dementia (CIND)** on poststroke survival controlling for main covariates in a large well defined ischemic stroke cohort followed up to 12 years. We hypothesized that cognitive impairment would be related to impaired poststroke survival.

METHODS

Patients

The Helsinki Stroke Aging Memory (SAM) cohort comprised a consecutive series of all Finnish (caucasian) patients with suspected stroke admitted to Helsinki University Central Hospital (n=1622) between 1 December 1993 and 30 March 1995, as described in detail previously [18-20]. Patients aged 55-85 years living in Helsinki were included. Patients without ischemic stroke (n=175), presenting with intracerebral (n=229) or subarachnoid hemorrhage (n=69) were excluded. A total of 642 patients fulfilled the inclusion criteria and were invited to a **baseline visit** 3 months later. Of these, 71 died (11.1%) before the 3-month follow-up, 82 refused (12.8%) and 3 were lost (0.5%) due to undefined causes. Finally, 486 (85.1%; 246 men, 240 women) of the living patients were included in the final cohort [21]. **Of these 409 (84.2%) participated in neuropsychological examination. Patients with severe aphasia and thus unable to participate neuropsychological examination were excluded together with those with severe sight or hearing disabilities, or reduced level of consciousness.**

The study was approved by the Ethics committee of the Department of Clinical Neurosciences, Helsinki University Central Hospital, Finland. The study was explained to the patients, and informed consent was obtained.

Clinical evaluation

A detailed medical and neurological history was taken [19]. **In the basic cohort of 486 patients, there were 388 (79.8%) patients with first-ever and 98 patients (20.2%) with recurrent stroke.** Exclusion of those with recurrent stroke did not have any effect on

study results and therefore the final study was conducted including recurrent stroke patients. Stroke severity was assessed using modified Rankin score at 3 months [22].

Neuropsychological analyses

A comprehensive neuropsychological assessment was administered three months after the index stroke as detailed before [23-25]. There were no statistically significant differences in gender, age, education, MMSE or modified Rankin score between these and the original 486 subjects.

In brief, **global cognitive function** was measured with the Mini-Mental State Examination [26]. Score ≤ 25 indicated cognitive impairment. **Executive functions** including attention were evaluated with the Trail making test [27], the Stroop color naming test [28] and the Digit span subtest of the Wechsler Memory Scale [29], the modified Wisconsin Card Sorting Test and the verbal fluency test [30]. Data was available in 365 and missing in 44 subjects (10.8%). The assessment of **memory functions** included the Logical memory and Visual reproduction subtests of the Wechsler Memory Scale-revised [31] as well as the Fuld Object Memory Evaluation [32]. Data was available in 379 and was missing in 30 subjects (7.3%). **Language** was evaluated with the short version of the Token test [33] the Boston naming test [34] and the verbal fluency test [30]. Moreover, overall evaluation of speech functions was based on the Boston Diagnostic Aphasia Examination [35]. Data was available in 395 and missing in 14 subjects (3.4%). **Visuospatial and constructional abilities** were assessed with the Block design subtest of the Wechsler Adult Intelligence Scale-revised [36], the clock test (recognizing and setting time), and by copying a triangle, a flag, a 3-dimensional cube, and a Greek cross [37]. Data was available in 391 and missing in 18 subjects (4.4%). Abnormality (impaired vs. not impaired) in each domain was

judged with the use of normative data from a random healthy Finnish population (2 SD or, if more than one test was used, 1 SD below the level of the norm on several tests indicated abnormality) [38]. The normal values were evaluated in different age groups.

Cognitive impairment without dementia, i.e. cognitive impairment no dementia (CIND) [39] was defined as cognitive impairment in any of the above mentioned domains after the exclusion of patients with dementia. Of the patients with MMSE≤25 (n=138), 94/138 (68.1%) had dementia at the 3 month follow-up. Further, of these 62/94 (66.0%) had had a prestroke cognitive decline. Assessment of prestroke cognitive decline involved interviews with the patient and a knowledgeable informant, using structured questions. Dementia was defined according to Diagnostic and Statistical Manual of Mental Disorders 3rd edition criteria. From the basic cohort of 486 patients, we first excluded those who had not been tested for dementia (n=35, 7.2%) and those who had dementia (n=115, 23.7%). Further we investigated whether patients had impairment in any of the assessed domains. 52 patients were excluded at this point because of missing values in the assessed domains, at the same time as none of the existing values indicated impairment. Finally, there were 212 patients with CIND and 72 patients with no cognitive impairment.

Survival data and causes of death

Long-term survival data and causes of death at 21 September 2006 were obtained from Statistics Finland. The mean (+SD) follow up time was 7.5 ± 4.0 years with a range between 0.3 and 12.8 years.

Statistical analysis

SPSS/WIN (version 12.0, SPSS Inc) software was used. Chi-Square test was used to test dichotomous variables and Student's t-test to test continuous variables. The effect of different neuropsychological domains (executive functions, memory, language and visuospatial/constructional abilities), **CIND** and **copredictors such** as global cognitive function i.e. MMSE (MMSE $\leq$ 25), education (low education <6 years), and poor modified Rankin score (3-5 vs. 0-2) on long-term survival were first analyzed using Kaplan-Meier log rank analysis. **The median estimated years of survival are presented.** The cumulative hazard function was also used and according to these analyses, the proportional hazards assumption was met for each parameter included in further models. In Cox-regression proportional hazards survival analysis, in the forced entry model (Model 1) **only** the demographic **background** variables were used as covariates (age, sex, years of education). Another model (Model 2) was constructed adding MMSE $\leq$ 25 and poor modified Rankin score (3-5 vs. 0-2) as **clinical** covariates. Statistical significance was set at $p<.05$.

RESULTS

Characteristics of the study sample

The basic demographics of the cohort are as follows: age 71.2 ± 7.7 years; female sex 49.4%; MMSE ≤ 25 28.6%; poor modified Rankin score 39.9%.

The demographics with respect to presence of deficits in cognitive domains are presented in table 1. Patients with executive, language or visuospatial/constructional deficit ($p < 0.0001$) were older than those without it. Women were overrepresented in patients with language ($p = 0.009$) or visuospatial/constructional deficits ($p = 0.004$). Low education was more prevalent in patients with deficits in executive functions ($p = 0.019$), memory ($p = 0.023$), language ($p = 0.017$) and visuospatial/constructional abilities ($p = 0.002$). Poor modified Rankin score was significantly more prevalent in those with any of the cognitive deficits ($p < 0.0001$) (Table 1). MMSE ≤ 25 was frequent in all patients with deficits in any of cognitive domains ($p < 0.0001$) (Table 1).

The cognitive deficits were highly interrelated: 77.3% of patients with executive deficit had also a deficit in visuospatial/constructional abilities, and 73.9% had a memory deficit. On the other hand, the least frequent combination was executive and language deficit (30.1%).

The effect of cognitive impairment on survival

In Kaplan-Meier log-rank analysis, deficits in executive functions ($n = 176$, **48.2%**) (5.8, CI 4.7-7.0 vs. 10.1, CI 8.7-11.4 years, $p < 0.0001$), memory ($n = 227$, **59.9%**) (6.8, CI 5.3-8.3 vs. 9.3, CI 7.9-10.7 years, $p = 0.009$), language ($n = 114$, **28.9%**) (5.3, CI 3.8-6.9 vs. 8.6, CI 7.7-

9.4 years, $p=0.004$) and visuospatial/constructional abilities ($n=216$, **55.2%**) (5.6, CI 4.6-6.7 vs. 10.1, CI 8.5-11.7 years, $p<0.0001$) predicted poor survival (Figure 1).

Furthermore, **low education (<6 years) ($n=151$, 31.8%) (6.4, CI 5.4-7.3 vs. 8.2, CI 7.1-9.1 years, $p=0.003$)**, MMSE ≤ 25 ($n=138$, 30.5%) (4.4, CI 3.7-5.1 vs. 9.3, CI 8.3-10.4 years, $p<0.0001$), and poor modified Rankin score ($n=194$, 39.9%) (3.9, CI 4.2-5.6 vs. 9.7, CI 8.5-10.9 years, $p<0.0001$) predicted poor poststroke survival (Figure 1).

To account for potential confounders, and to estimate the predictive value of different factors, a multivariate Cox regression proportional hazards analysis utilizing two models (Table 2) was used. In Cox proportional hazards regression analysis (Model 1, including age, sex and years of education), deficits in executive functions (HR 1.65, CI 1.27-2.13, $p<.001$), memory (HR 1.31, CI 1.01-1.70, $p=0.042$), language (HR 1.33, CI 1.02-1.73, $p=0.036$) and visuospatial/constructional abilities (HR 1.82, CI 1.40-2.36, $p<0.0001$) were significant predictors of poor poststroke survival (Table 2). Deficits in executive functions (HR 1.38, CI 1.05-1.81, $p=0.021$) and visuospatial/constructional abilities (HR 1.53, CI 1.14-2.04, $p=0.004$) remained as significant predictors after addition of MMSE ≤ 25 and poor modified Rankin score as covariates (Model 2) (Table 2). MMSE ≤ 25 (HR 1.32-1.46) and poor modified Rankin score (HR 1.54-1.61) predicted poor survival in all the models.

To further explore the role of cognitive impairment we analyzed the effect of cognitive impairment no dementia (CIND) on poststroke survival. In this population ($n=284$), CIND ($n=212$, 74.6%) (7.9, CI 7.4-8.5 vs. 9.7, CI 8.8-10.6, $p=0.003$) was a predictor of poor poststroke survival (Figure 2) when compared to patients with no cognitive impairment in any of the assessed domains. In Cox proportional hazard

regression analysis with age, sex and years of education as covariates, CIND remained an independent predictor of survival (HR 1.63, CI 1.12-2.39, $p=0.012$).

The association of neuropsychological domains and causes of death

Of all the deaths ($n=347$), 30.5% were attributable to cardiac causes, 33.7% due to brain related causes (bleeding, infarct, dementia), 14.0% due to cancer, 4.3% due to infectious causes, 3.9% due to traumatic causes and 12.5% due to other causes.

According to Kaplan-Meier log rank test, the probability of dying due to cardiac causes alone showed no association with deficits in any of the cognitive domains. Death due to brain related causes on the other hand was more likely in those with deficits in executive functions ($p=0.019$), language ($p=0.001$), visuospatial/constructional abilities ($p<0.0001$). No associations between cognitive domains and infectious, traumatic or other causes of death were found.

DISCUSSION

The present study showed that poor poststroke survival relates to deficits in cognitive functions, i.e. executive, memory, visuospatial/constructional functions and language. Global cognitive impairment was also related to poor survival. Deficits in executive and visuospatial/constructional functions remained as independent predictors after controlling for global cognitive impairment and severity of stroke. Furthermore, cognitive impairment no dementia (CIND) was independently related to poor poststroke survival. These findings on CIND are in line with previous studies [39-41].

In the present study, proportion of patients with deficits in different cognitive domains varied between 29-60%, the lowest proportion found in language and the highest in memory. Studies on the effect of cognitive domains on poststroke survival are limited. Deficits in domains like verbal, visuomotor and memory performance and reaction time have previously been associated with shortened survival at general population level [42, 43].

Prestroke [6, 7], any poststroke [4-6] and new-onset poststroke [7] dementia has been consistently related to poor survival. This is in line with our finding of the association of global MMSE with survival. In a population based study 3 months after stroke [9], the proportion of cognitively impaired subjects (MMSE<25) was found to be 38% which is considerably higher than in the present study of hospitalized patients. However, similar prevalence was detected in a study of hospitalized patients [11]. We consider our cohort representative of hospitalized stroke patients. Our cohort with up to 12 year follow up showed significant effect of low MMSE on long-term survival. In line with our results,

cognitive impairment as measured by MMSE was associated with impaired survival up to 4 year follow-up [9-12]. However, two short 1 year studies demonstrate that MMSE is not an independent predictor of survival [44, 45]. A single study utilizing short 10 item mental status questionnaire showed that cognitive impairment is an independent predictor of 6 year survival [46]

In a previous study [47] severe aphasia was independently associated with poor survival which is in line with our finding of the association of deficit in language domain and survival. **In earlier studies, CIND has been related to impaired survival in studies of community based populations where stroke has not been regarded [39-41]. Our results of CIND, a potentially reversible condition, as an independent predictor of poor poststroke survival in a specified poststroke population is of clinical significance. Recognition of CIND might alert the clinicians to schedule more strict and accurate poststroke follow-up.**

As far as we know, our study is thus far the largest poststroke cohort with a long follow up **and a** detailed neuropsychological examination. **It is also the only study controlling for main covariates including severity of stroke.** The present study showed that impairment in major cognitive domains relates to poor poststroke survival. **When** controlling for the effect of global cognitive decline ($MMSE \leq 25$) and severity of stroke only executive functions as well as visuospatial and constructional abilities remained as independent correlates of poor survival. Executive functions, including planning, initiation, sequencing and monitoring of complex goal-directed behaviour, heavily rely on the integrity of the prefrontal cortices and their connecting pathways with the subcortical structures [48]. **The frontal lobe functional system is also involved with visuospatial**

and constructional abilities which require intact attention and organisational skills together with the more posteriorly-mediated visuoperceptual functions.

Cerebral small vessel disease is reflected by white matter lesions seen in MRI [49, 50], which have also been related to recurrent stroke [51-55] and poor survival mostly due to cardiovascular causes [51, 53, 56]. White matter lesions on the other hand associate with general cognitive function and with **global functional decline** [50] and executive dysfunction related with frontal lobe system [50, 57-60]. **We have previously demonstrated the association of white matter lesions and cognitive deficits in the present cohort [61]. In addition, recently, we have demonstrated in the present cohort that of the patients 28% had mild, 18% had moderate and 54% had severe white matter lesions and that severe lesions predicted poor poststroke survival [62]. Together these results suggest that there may be a complex interplay of cerebral small vessel pathology and a related disruption of the frontal lobe functional system behind impaired poststroke survival.**

A potential weakness of our study is the possibility of selection bias, as the cohort was formed three months after the index stroke. This may limit generalization of the results. Therefore, we retrospectively obtained additional data on stroke-related deaths in Helsinki University Hospital district during the collection of the cohort from an independent organization (Statistics Finland). In this retrospective data, up to 64 percent of stroke related deaths occurred in women. While the proportions of both sexes in the present study were equal, this suggests that some women may have died before hospital assessment at 3 months. Due to exclusion of patients, the true survival rate may be underestimated. **In addition, since patients with severe aphasia could not be**

assessed with comprehensive neuropsychological examination, there is a possibility for survival bias since these patients are prone to impaired survival resulting in underestimation of the effect of language. Strengths of our study **are** that the cohort is a consecutive one, and that the neuropsychological and clinical characteristics of the patients were strictly evaluated, and also that the severity of stroke at admission was quantitated according to the modified Rankin score. Also, the survival data is comprehensive with negligible amount of unresolved deaths.

In summary, cognitive impairment already at less severe stages without dementia is related to poor long-term survival poststroke. Deficits in executive functions and visuospatial and constructional abilities, in particular, predict poor outcome independently of global cognitive decline and severity of stroke.

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Table 1. The association of cognitive deficits with demographic **and clinical** parameters (Stroke Aging Memory-cohort).

Variable	Executive			Memory			Language			Visuospatial		
	Yes	No	p	Yes	No	p	Yes	No	p	Yes	No	p
Age (SD)	71.7 (7.4)	69.1 (7.8)	<0.0001	70.8 (7.6)	70.0 (7.8)	0.311	72.2 (7.6)	68.6 (7.5)	<0.0001	72.2 (7.6)	68.6 (7.5)	<0.0001
Female sex (%)	90 (51.1)	92 (48.7)	0.639	109 (48.0)	82 (53.9)	0.258	46 (40.4)	154 (54.8)	0.009	123 (56.9)	74 (42.3)	0.004
Low education <6 yr (%)	61 (35.3)	44 (23.9)	0.019	74 (33.2)	33 (22.3)	0.023	44 (39.3)	74 (27.0)	0.017	76 (36.0)	37 (21.6)	0.002
MMSE≤25 (%)	74 (42.0)	23 (12.2)	<0.0001	87 (39.5)	18 (11.8)	<0.0001	48 (51.6)	58 (20.6)	<0.0001	94 (45.9)	14 (8.1)	<0.0001
Poor Rankin score (%)	86 (48.9)	29 (15.3)	<0.0001	95 (41.9)	35 (23.0)	<0.0001	67 (58.8)	76 (27.0)	<0.0001	109 (50.5)	28 (16.0)	<0.0001

Dichotomous variables: Pearson Chi-Square test

Continuous variables: Student's t-test

Table 2. Cox regression analysis on the association of multiple risk factors and cognitive deficits with poor long-term survival (all cause death endpoint) among patients with ischemic stroke (Stroke Aging Memory cohort). **Model 1 includes the demographic background variables. In model 2, the clinical co-predictors are added.**

	Model 1 (Forced entry)			Model 2 (Forced entry)				Model 1 (Forced entry)			Model 2 (Forced entry)			
Variable	HR	95% CI	p	HR	95% CI	p		HR	95% CI	p	HR	95% CI	p	
Age	1.08	1.06-1.10	<0.0001	1.06	1.04-1.08	<0.0001		Age	1.07	1.05-1.09	<0.000	1.06	1.04-1.08	<0.0001
Female sex	0.70	0.54-0.91	0.007	0.73	0.56-0.95	0.018		Female sex	0.71	0.54-0.92	0.010	0.71	0.55-0.93	0.014
Education	0.96	0.93-0.99	0.013	0.98	0.95-1.01	0.271		Education	0.97	0.93-1.00	0.027	0.98	0.95-1.01	0.188
MMSE≤25	not included			1.45	1.07-1.96	0.017		MMSE≤25	not included			1.44	1.06-1.94	0.019
Poor Rankin	not included			1.71	1.29-2.27	0.017		Poor Rankin	not included			1.56	1.17-2.08	0.003
Memory	1.31	1.01-1.70	0.042	1.20	0.92-1.57	0.182		Executive	1.59	1.23-2.06	<0.0001	1.33	1.01-1.74	0.040
Age	1.07	1.06-1.09	<0.0001	1.06	1.04-1.08	<0.0001		Age	1.07	1.05-1.09	<0.0001	1.06	1.04-1.08	<0.0001
Female sex	0.73	0.57-0.95	0.018	0.75	0.57-0.98	0.036		Female sex	0.64	0.49-0.82	0.001	0.68	0.52-0.89	0.005
Education	0.96	0.93-0.99	0.012	0.98	0.95-1.01	0.175		Education	0.97	0.94-1.00	0.041	0.98	0.95-1.01	0.227
MMSE≤25	not included			1.46	1.09-1.97	0.012		MMSE≤25	not included			1.28	0.94-1.75	0.116
Poor Rankin	not included			1.60	1.21-2.12	0.001		Poor Rankin	not included			1.55	1.17-2.06	0.002
Language	1.33	1.02-1.73	0.036	1.11	0.82-1.48	0.509		Visuospatial	1.82	1.40-2.36	<0.0001	1.53	1.14-2.04	0.004

FIGURE LEGENDS

Figure 1. The effect of different cognitive deficits (groups with given deficits are marked with + -sign), Mini-Mental State Examination (MMSE), and cognitive impairment not dementia (CIND) on overall poststroke survival (endpoint: all cause death) in Stroke Aging Memory cohort. Kaplan-Meier log rank analysis.

Figure 1.

Executive+	169	139	94	69	49	8
Executive-	191	174	148	125	90	11

Memory+	152	188	142	108	81	13
Memory-	227	135	109	90	69	9

Visuospat+	216	172	119	85	61	9
Visuospat-	175	162	136	114	89	13

Language+	114	88	61	44	32	3
Language-	281	250	196	156	116	15

MMSE < 25	216	103	59	36	21	2
MMSE > 25	315	279	233	192	147	22

CIND+	212	184	143	112	88	16
CIND-	72	66	59	53	42	4