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Thrombolysis treatment protected impairment of functional ability, quality of life and fatigue seven years after stroke

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ABSTRACT

Objectives: We studied quality of life, functional outcome, depression, and fatigue of ischemic stroke patients treated with or without thrombolysis seven years post-stroke.
Materials and methods: A total of 204 ischemic stroke patients treated with or without thrombolysis during 2013–2015. After seven years the 136 survivors were assessed with telephone interview, which included questions about subjective quality of life (European Quality of Life-5 Dimensions), depression, fatigue with Fatigue Severity Scale, functional ability assessed with Barthel Index and Modified Rankin Scale, living conditions, need of care, and medical aids.
Results: At admission patients with thrombolysis had higher National Institutes of Health Stroke Scale scores compared with those not treated with thrombolysis. At seven years post-stroke, 99% of alive patients answered the questionnaires. There were no group differences concerning functional outcome, quality of life, depression, fatigue, or insomnia. The Barthel Index was normal in both groups. The quality of life was good in both groups without group differences in any domains. Of all patients, 68% reported no problems in usual activities, and 61% were without pain. Anxiety or depression were experienced by 19% of all stroke patients, while fatigue was present in 32% of cases.
Conclusions: Seven years post-stroke the quality of life was good and functional outcome remained in good level in both study groups. One third experienced fatigue, while every fifth experienced depression. The thrombolysis treatment seems to protect from decreased quality of life, fatigue, and decreased mobility, self-care, and usual activities despite more severe stroke.

Introduction

Approximately fifteen million people experience stroke and at least 160000 experience recurrent ischemic stroke every year[1,2] Stroke is worldwide the second most common cause of mortality, and it is associated with long-term disability, morbidity, and healthcare costs[2–4] Within past years, treatment of acute stroke with intravenous thrombolysis and mechanical thrombectomy have improved the post-stroke outcomes and have decreased case-fatality up to 12 months after stroke (5–9).

Previous studies have pointed out that stroke patients with thrombolysis treatment are self-employed (Modified Rankin Scale, mRS scores

Abbreviations: EQ-5D, European quality of life-5 dimensions; FSS-9, fatigue severity scale; BI, barthel index (BI); mRS, modified rankin scale; NIHSs, national institutes of health stroke scale; GCS, glasgow coma scale; ADL, activities of daily living; ESS, epworth sleepiness scale; ISI, insomnia severity index; OSA, obstructive sleep apnea; OR, odds ratio.

We studied quality of life among ischemic stroke patients in Oulu University Hospital, Department of Neurology, Finland

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0–2) in 68% of the cases three months after stroke and are most likely to have better performance and survival in the future.[10,11] The studies evaluating ability to work after thrombolysis treated stroke are scarce Five years post-stroke the rate of return to work after reperfusion-treatment was equal to the general population of Sweden.[12] The re-employment in ischemic stroke patients undergoing mechanical thrombectomy after three months follow-up was better in those who were younger, males, had lower National Institutes of Health Stroke Scale (NIHSS) scores on admission, non-smokers, and non-diabetics.[13]

High pre-stroke mRS[3–5] 24h NIHSS score over 4, age over 75 years, hypertension, renal failure and atrial fibrillation are related to lower quality of life in ischemic stroke patients treated with acute revascularization therapy one year post-stroke.[14] Some studies have reported that intravenous thrombolysis has been associated with improved quality of life[12,15,16] However, a few studies have evaluated post-stroke long-term outcomes and quality of life over one year after stroke survivors who have been treated with thrombolysis.[15,17,18] Long-term post-stroke evaluation shows that every fifth of stroke patient's mobility status declines and predictors of mobility decline are inactivity, fatigue and depression[19] One year post-stroke quality of life correlates with Barthel Index and NIHSS scores in ischemic stroke patients with intravenous thrombolysis.[20]

After stroke the cumulative incidence of depression estimates range from 39 to 52% within five years, with the pooled prevalence of post-stroke depression is 29% and up to ten years in the recent review.[21] According to the literature, the predictors of post-stroke depression are pre-stroke disability and depression, stroke severity and anxiety[21,22] Previous studies have reported that independent outcomes of

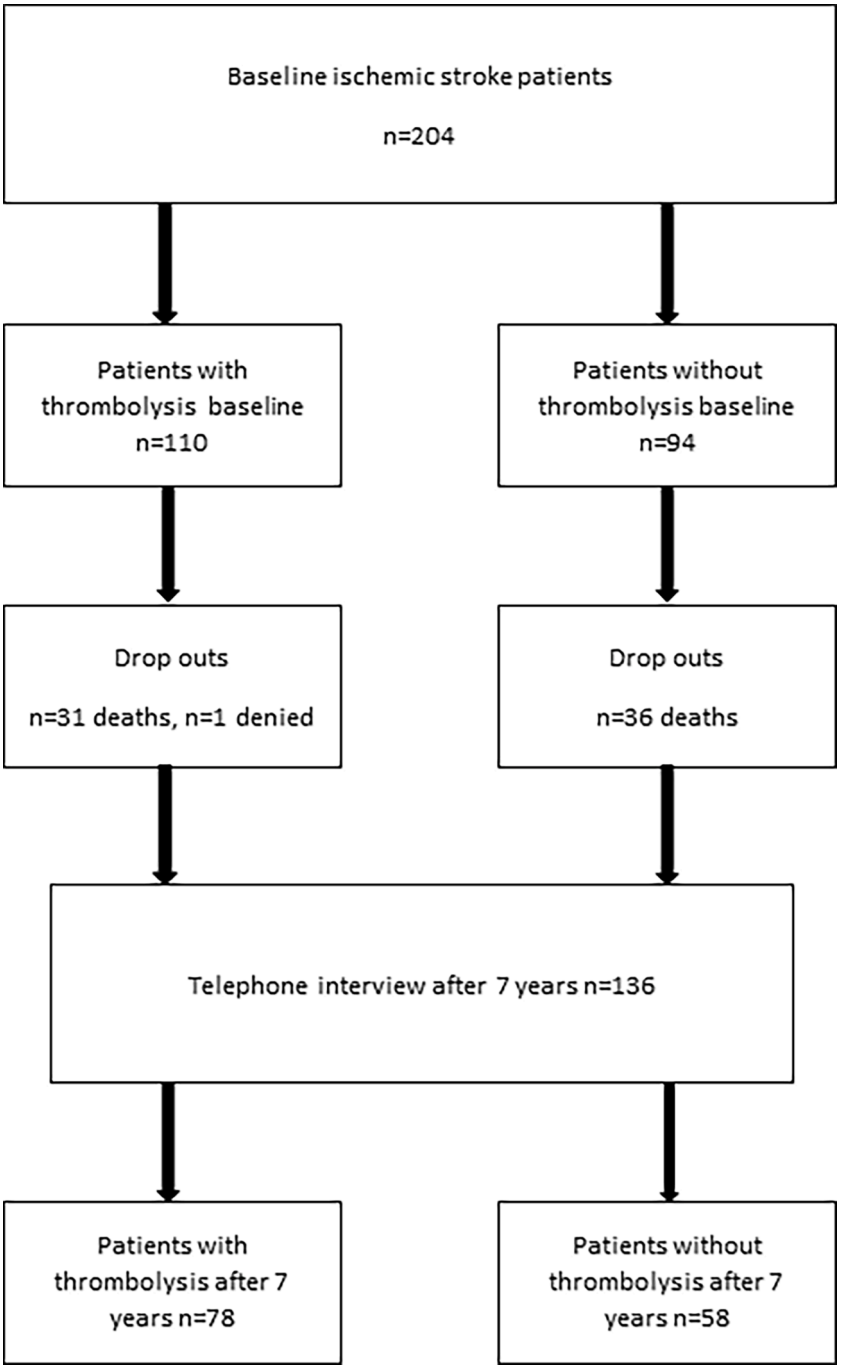

Fig. 1. The flowchart of study patients.

post-stroke depression are higher mortality after ten years, decreased quality of life and disability after one year.[23,24]

The prevalence of fatigue after ischemic stroke varies between 29 and 77%[25,26] Subjective fatigue is difficult to define and measure and one definition is that subjective fatigue is a feeling of exhaustion, weakness and unable to effort[27] Fatigue is a reversible loss of ability, feeling of physical and mental overwork, which makes it unable to do routine activities.[28] Post-stroke fatigue at six months associates with older age, higher mRS scores, depressive symptoms, hypercholesterolemia and decreased quality of life in ischemic stroke patients treated with intravenous thrombolysis.[29]

We performed an observational prospective study to investigate acute ischemic stroke patients, treated with or without thrombolysis, and their long-term functional recovery, quality of life, and fatigue seven years post-stroke.

Materials and methods

We performed an observational, prospective, single center study in 204 ischemic stroke patients over 18 years, who were admitted to the Stroke Unit at the Department of Neurology of the Oulu University Hospital from April 2013 to January 2015. Of those 110 received thrombolysis and the remaining 94 patients treated without thrombolysis. Participation was voluntary and non-cooperative patients excluded. We obtained written informed consent from all patients or from their relatives. The ethics committee of the Northern Ostrobothnia Hospital District approved the study protocol.

The patients were followed prospectively until 2021. The same investigator made a telephone-interview during April and November 2021 to every study patient. If the patient was unable to speak, caregivers answered to the specific questionnaire. The investigator sent postal questionnaires to ten patients, because they didnt answer to the numerous phone calls. Of those, only one sent the postal questionnaire back, nine patients phoned back, and the investigator interviewed them by telephone. One patient denied attending the study. The flowchart of study patients is shown in Fig. 1.

The baseline demographic data included age, gender body mass index, current smoking habits, daily alcohol consumption, employment status, comorbidities, vascular risk factors, current medication, stroke etiology and location. Stroke outcome was estimated by the modified Rankin scale (mRS; scale 0–5)[30] while Barthel Index (BI; scale 0–100)[31] was documented only after follow-up. At baseline we assessed the level of consciousness by the Glasgow Coma Scale (GCS;scale 3–15)[32] and stroke severity by the National Institutes of Health Stroke Scale (NIHSS, scale 0–35).[33]

The telephone interview and specific questionnaire included questions on functional independence (BI), degree of impairment in daily activities (mRS), health-related quality of life questionnaire: European Quality of Life-5 Dimensions (EQ-5D), fatigue questionnaire: Fatigue Severity Scale (FSS-9). We also made questions about daytime sleepiness and insomnia, employment status (retired or employed), disabilities, need of medical aids (wheel chair, wheel walker, walking stick) and a caregiver, smoking habits, and living condition. In case of death, the caregiver informed the cause of death or we collected the data from medical records. Diagnosis of depression was collected from medical records.

Activities of daily living (ADL) was measured by BI, which included 10 items of ADL; feeding, bathing, grooming, dressing, bowel and bladder care, toilet use, transfer to bed and chair, mobility and stair climbing. The BI scores 100 indicated full ability and score 0 showed full disability. The Barthel index has pointed out to be a reliable and valid measure of ADL in stroke patients.[34] We used (mRS to assess the dependence and stroke outcome.[30] The mRS score 0 meant full dependence, while 5 indicated full independence. Both the pre-stroke mRS values and mRS values after follow-up were recorded.

The study patients self-rated their quality of life by answering the EuroQol -questionnaire (EQ-5D), which contains five question domains about mobility, self-care, usual activities, pain/discomfort and anxiety or depression. This specific questionnaire has been applied and validated for stroke patient.[35,36] We used the modified standard five-dimensional format. The respondents, or their caregivers, described their own health state on five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The patients chose one of three levels for each five dimension: no problems, some problems or extreme problems with self-care or usual activities, pain, or anxiety. The EQ-5D showed good quality of life (5 points), moderate (10 points) or reduced (15 points) quality of life. Good quality of life means that there are no problems in none of the five items.

The fatigue severity scale (FSS-9) was used to assess fatigue after stroke.[37] We assessed fatigue with FSS-9 questionnaire only after follow-up. The FSS-9 contained nine questions and the patients rated each question by choosing appropriate number between 0 and 7. At first the total scores varies from 9 to 63 and then the score is divided by the number of responded questions and then the total scores range from 1 to 7. The FSS-9 points $\geq$4 means that the patient experience fatigue.[38]

We used Epworth Sleepiness Scale (ESS; scale 0–24) to indicate daytime sleepiness and ESS$\geq$10 indicated excessive daytime sleepiness.[39] We evaluated ESS both in the acute phase of stroke and after follow-up. The Insomnia Severity Index (ISI, scale 0–28) scores $\geq$8 meant that the patient has insomnia.[40]

Patients` demographic data was reported as means and standard deviations (SD) or as frequencies and percents. The modified Rankin Scale (mRS), the NIHSS and GCS scores were reported as medians. The variables measured at baseline were compared between the groups with and without thrombolysis using the Chi-square test or the Fischer exact test (categorical variables), the Student's t-test (normally distributed variables), or the Mann-Whitney U test (non-normally distributed) variables), separately for all the patients included and for those who were included in the follow-up data. Year-by-year mortality was analyzed with Kaplan-Meier survival curves. Logistic regression analyses were performed to determine odds ratios (OR) and 95% confidence intervals (CI) of variables that predict quality of life after stroke. The p value of < 0.05 was considered statistically significant. Statistical analyses were performed with IBM SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 29.0.1.0 Armonk, NY: IBM Corp.).

Results

The patients` baseline characteristics and clinical data are shown in Table 1. Of all patients, 62.7% were male, and the gender distribution did not differ between the groups. The thrombolysis patients were younger than the non-thrombolysis patients (mean age difference 4.2 years; $p = 0.027$). Daily alcohol consumption was more frequent in the thrombolysis group. Patients without thrombolysis had more atrial fibrillation than others. The median NIHSS score at admission was higher, and the median GCS score lower in the thrombolysis as compared to the non-thrombolysis group and the median pre-stroke Rankin Scale score were similar across the groups. Aphasia was more common at admission in the thrombolysis as compared to the non-thrombolysis group. The thrombolysis group had more middle cerebral artery and less lacunar infarctions than non-thrombolysis group.

Of the 204 treated patients, 137 (67.2%) survived, of whom 136 (99.3%) agreed to participate in the telephone interview seven years post-stroke. Those 136 patients (66.7%) were included in the final analyses (Fig. 1). The mean time from stroke onset to the telephone interview was 7.5 years, range 6.3–8.7 years. The patients` baseline characteristics and clinical data in alive patients after seven years are shown in Table 1, too. Of those 136 patients, 58.1% were male and 78 of patients had received thrombolysis. There was no longer age difference between the groups at the follow-up The daily alcohol consumption before stroke did not differ between the groups anymore. There were no between-group differences concerning the gender, BMI, smoking

Table 1
The baseline characteristics and clinical data measured at admission, separately for all the patients and for the patients who participated in the follow-up.

Characteristic	At admission				After seven years post-stroke			
	Subjects with thrombolysis (n=110)	Subjects without thrombolysis (n=94)	Total (n=204)	P-value	Subjects with thrombolysis (n=78)	Subjects without thrombolysis (n=58)	Total (n=136)	P-value
Men,n (%)	72 (65.5)	56[59,6]	128 (62.7)	0.387	45 (57.7)	34 (58.6)	79 (58.1)	0.914
Mean Age, years (SD)	65.8 (14.6)	70.0 (11.5)	67.7 [13,4]	0.027	62.6 (14.0)	66.3 (10.8)	64.2 (12.8)	0.100
Mean BMI (SD)	27.5 (4.9)	27.1 (4.4)	27.3 (4.7)	0.474	27.6 (5.0)	27.6 (3.3)	27.6 (4.3)	0.983
Smoking n (%)	20 (18.2)	24[25,5]	44 (21.6)	0.234	43 (55.1)	38 (65.5)	81 (59.6)	0.360
Alcohol consumption daily n (%)	19 (17.3)	4 (4.3)	23 (11.3)	0.003	3 (3.8)	2 (3.4)	5 (3.7)	0.903
Mean ESS (SD)	4.7 (3.0)	4.7 (2.6)	4.7 (2.8)	0.880	4.8 (3.1)	4.5 (2.7)	4.7 (2.9)	0.639
Median prestroke Rankin Scale (SD)	0 (1.04)	0 (1.29)	0 (1.16)	0.083	0.0 (0.9)	0.0 (0.7)	0.0 (0.8)	0.782
Median NIHSS score (SD) (0-35)	5.5 (5.0)	2.0 (4.0)	4.0 (4.9)	<0.001	5.0 (4.6)	2.0 (2.4)	3.5 (4.4)	0.001
Aphasia n (%)	38 (34.5)	8[8,5]	46 (22.5)	<0.001	21 (26.9)	3 (5.2)	24 (17.6)	0.001
Median GCS score (SD)[3-15]	15.0 (1.3)	15.0 (1.3)	15.0 (1.3)	0.027	15.0 (1.1) 14.5	15.0 (0.6) 14.8	15.0 (1.0) 14.6	0.021
Hypertension n (%)	65 (59.1)	58 (61.7)	123 (60.3)	0.704	44 (56.4)	31 (53.4)	75 (55.1)	0.731
Hypercholesterolemia n (%)	46 (41.8)	47 (50.0)	93 (45.6)	0.242	27 (34.6)	27 (46.6)	54 (39.7)	0.159
Diabetes Mellitus n (%)	21 (19.1)	19 (20.2)	40 (19.6)	0.841	9 (11.5)	9 (15.5)	18 (13.2)	0.498
Coronary Artery Disease n (%)	22 (20.0)	27 (28.7)	49 (24.0)	0.146	11 (14.1)	13 (22.4)	24 (17.6)	0.209
Heart Failure n (%)	3 (2.7)	7 (7.4)	10 (4.9)	0.120	2 (2.6)	2 (3.4)	4 (2.9)	0.763
Atrial Fibrillation n (%)	5 (4.5)	27 (28.7)	32 (15.7)	<0.001	1 (1.3)	11 (19.0)	12 (8.8)	<0.001
PAD n (%)	3 (2.7)	4 (4.5)	7 (3.5)	0.501	1 (1.3)	3 (5.2)	4 (2.9)	0.312
Depression n (%)	0 (0.0)	3 (3.2)	3 (1.5)	0.059	0 (0.0)	3 (5.2)	3 (2.2)	0.075
Stroke Location: Middle cerebral artery infarction, n (%)	67 (60.9)	31 (33.0)	98 (48.0)	<0.001	46 (59.0)	14 (24.1)	60 (44.1)	<0.001
Stroke Location: Lacunar infarction, n (%)	19 (17.3)	34 (36.2)	53 (26.0)	0.002	16 (20.5)	22 (37.9)	38 (27.9)	0.025
Retired before stroke n (%)					48 (61.5)	37 (63.8)	85 (62.5)	0.788

BMI, body mass index; ESS, Epworth Sleepiness Scale; NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; PAD, peripheral artery disease

prevalence, daytime sleepiness, previously diagnosed depression, hypertension, hypercholesterolemia, diabetes mellitus, coronary artery disease, heart failure, or peripheral arterial disease at follow-up either. The median NIHSS score at admission was higher, and the median GCS score lower in the thrombolysis as compared to the non-thrombolysis group and the median pre-stroke Rankin Scale score was similar across groups. Aphasia was still more common and atrial fibrillation less common at follow-up in the thrombolysis as compared to the non-thrombolysis group. Furthermore, the thrombolysis group still had more middle cerebral artery and less lacunar infarctions than non-thrombolysis group. Before the stroke there were 48 (61.5%) retired patients in the thrombolysis group and 37 (63.8%) in the non-

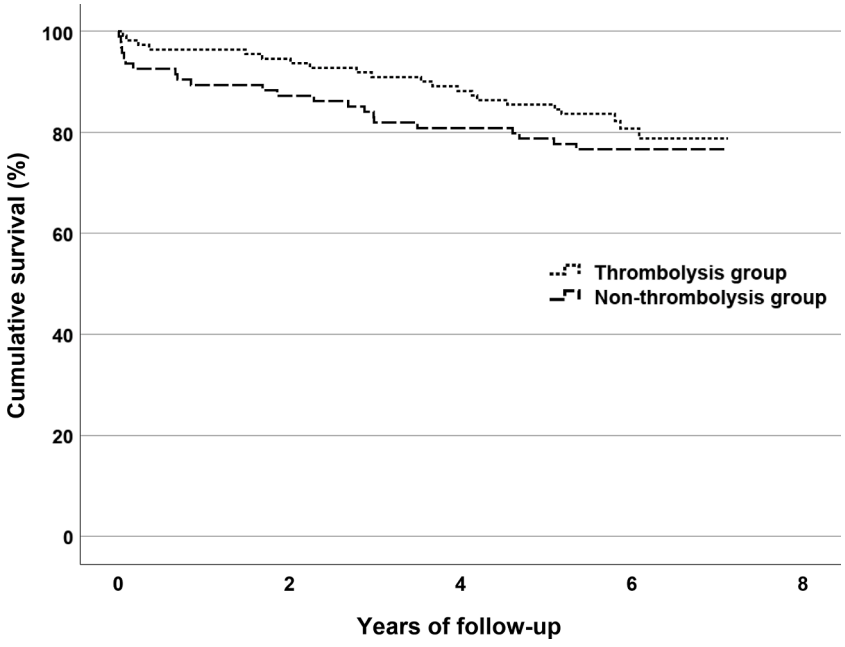

Fig. 2. Survival at seven years of Thrombolysis group and Non-thrombolysis group (log-rank p=0.449).

thrombolysis group. There was also no difference in terms of being at work.

Survival at seven years did not differ significantly between groups: 32 of 110 (29.1%) patients with alteplase treatment versus 36 of 94 (38.3%) without thrombolysis died (log-rank p=0.449; Fig. 2.)

Table 2 Presents the functional outcomes and quality of life seven years after the ischemic stroke. The overall mean BI was 90.74, the median mRS 1.00, and the mean EQ-5D 6.62, and did not differ between the groups. Fatigue was reported less frequently in thrombolysis group 26.9% vs. 39.7% but the difference was not significant (P=0.116). Of thrombolysis treated patients 7 (9.0%) and 6 (10.3%) of other patients were in the need of institutional care. After seven years, 83.3% of the patients were retired. There were significantly less retired patients in the thrombolysis group than others 78.2% vs. 91.4% (P=0.039). There were no between-group differences concerning neither the results of EQ-5D, FSS-9, ESS, ISI nor the rates of insomnia, depression and the need of care, and medical aids after follow- up time.

The exact data for EQ-5D and BI after 7 years of follow-up are presented in the Table 3. In the treatment group 31 (39.7%) had normal EQ-5D and 54 (69.2%) had normal BI while in others the corresponding numbers were 17 (29.3%) and 39 (67.2%). There were 27 (34.7%) patients suffering pain or discomfort in thrombolysis group and 26 (44.8%) in others. Two (2.6%) patients in thrombolysis group suffered from extreme pain or discomfort. In thrombolysis group there were 13 (16.7%) anxious or depressed patients and 13 (22.4%) among others. None of the patients was extremely anxious or depressed.

The logistic regression analysis for the influence of the severity of the stroke (NIHSS) and the thrombolysis treatment on the quality of life are presented in Table 4. We found out that the thrombolysis treatment decreases the risks of decreased BI (OR 0.340, 95% CI 1.132–0.875), need of care (OR 0.356, 95% CI 0.139-0.908), need of mobility aid (OR 0.310, 95% CI 0.126-0.760), decreased EQ-5D (OR 0.382, 95% CI 0.164-0.890), fatigue (OR 0.339, 95% CI 0.140-0.820), decreased mobility (OR 0.349, 95% CI 0.149-0.818), decreased selfcare (OR 0.326, 95% CI 0.119-0.887), and decreased usual activities (OR 0.345, 95% CI 0.135-0.886). On the other hand, the severity of the stroke increases the risks of decreased BI (OR 1.235 95% CI 1.107-1.379), need of care (OR 1.224, 95% CI 1.098-1.363), need of mobility aid (OR 1.118, 95% CI 1.015-1.232), decreased EQ-5D (OR 1.131, 95% CI 1.014-1.261), fatigue (OR 1.114, 95% CI 1.012-1.227), decreased mobility (OR 1.118, 95% CI 1.016-1.229), decreased selfcare (OR 1.196, 95% CI 1.076-1.330), and decreased usual activities (OR 1.231, 95% CI 1.104-1.374).

Table 2
Functional outcomes and quality of life seven years after stroke.

Outcome	Patients with thrombolysis (n=78)	Patients without thrombolysis (n=58)	Total (n=136)	P-value
Mean Barthel Index (SD)	91.47 (18.76)	89.74 (20.91)	90.74 (19.65)	0.613
Median mRS (SD)	1.00 (1.57)	1.00 (1.49)	1.00 (1.53)	0.519
Mean EQ-5D (SD)	6.54 (1.86)	6.74 (2.02)	6.62 (1.92)	0.545
Mean Usual activities EQ-5D (SD)	1.37 (0.61)	1.41 (0.65)	1.39 (0.62)	0.699
Mean Mobility EQ-5D (SD)	1.35 (0.53)	1.34 (0.61)	1.32 (0.59)	0.199
Mean Self-care EQ-5D (SD)	1.29 (0.58)	1.34 (0.61)	1.32 (0.59)	0.629
Mean Pain or discomfort EQ-5D (SD)	1.37 (0.54)	1.45 (0.50)	1.40 (0.52)	0.400
Mean Anxiety or depression EQ-5D	1.17 (0.38)	1.22 (0.42)	1.19 (0.40)	0.403
Fatique n (%)	21 (26.9)	23 (39.7)	44 (32.4)	0.116
Mean FSS-9 (SD)	23.26 (16.21)	25.16 (16.47)	24.49 (16.32)	0.307
Mean ESS (SD)	4.21 (3.02)	3.66 (2.86)	3.97 (2.95)	0.284
Retired n (%)	61 (78.2)	53 (91.4)	144 (83.8)	0.039
Need of care n (%)	24 (30.8)	19 (32.8)	43 (31.6)	0.805
Medical aids n (%)	20 (25.6)	23 (39.7)	43 (31.6)	0.082
Institutional care n (%)	7 (9.0)	6 (10.3)	13 (9.6)	0.788
Mean Insomnia Severity Index (SD)	5.69 (4.09)	6.02 (4.07)	5.83 (4.07)	0.647
Insomnia n (%)	20 (25.6)	19 (32.8)	39 (28.7)	0.364
Depression n (%)	13 (16.7)	13 (22.4)	26 (19.1)	0.399

Table 3
EQ-5D and normal Barthel Index after seven years of follow-up.

	Patients with thrombolysis (n=78)	Patients without thrombolysis (n=58)	Total (n=136)	P-value
Normal EQ-5D (%)	31 (39.7)	17 (29.3)	48 (35.3)	0.208
Mobility Domain				
No problems walking (%)	53 (67.9)	32 (55.2)	85 (62.5)	0.128
Some problems walking (%)	23 (29.5)	25 (43.1)	48 (35.3)	0.100
Confined to bed (%)	2 (2.6)	1 (1.7)	3 (2.2)	0.610
Self-care Domain				
No problems with self-care (%)	60 (76.9)	42 (72.4)	102 (75.0)	0.548
Some problems washing or dressing (%)	13 (16.7)	12 (20.7)	25 (18.4)	0.549
Unable to wash or dress (%)	5 (6.4)	4 (6.9)	9 (6.6)	0.587
Usual activities Domain				
No problems with usual activities (%)	54 (69.2)	39 (67.2)	93 (68.4)	0.805
Some problems with usual activities (%)	19 (24.4)	14 (24.1)	33 (24.3)	0.976
Unable to do usual activities (%)	5 (6.4)	5 (8.6)	10 (7.4)	0.433
Pain or discomfort Domain				
No pain or discomfort (%)	51 (65.4)	32 (55.2)	83 (61.0)	0.227
Moderate pain or discomfort (%)	25 (32.1)	26 (44.8)	51 (37.5)	0.128
Extreme pain or discomfort (%)	2 (2.6)	0 (0.0)	2 (1.5)	0.327
Anxiety or depression Domain				
Not anxious or depressed (%)	65 (83.3)	45 (77.6)	110 (80.9)	0.399
Moderately anxious or depressed (%)	13 (16.7)	13 (22.4)	26 (19.1)	0.399
Extremely anxious or depressed (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Normal Barthel index (score=100) (%)	54 (69.2)	39 (67.2)	93 (68.4)	0.805

Discussion

Our prospective study showed that seven years post-stroke functional ability and quality of life in ischemic stroke patients treated with thrombolysis was as good as in those treated without thrombolytic treatment, although the first mentioned group had more severe strokes. Furthermore, we pointed out that most of our patients were not depressed or anxious, and only few experienced feelings of fatigue. Our study showed that seven out of ten of survived ischemic stroke patients treated with thrombolysis had normal functional ability and four out of ten had normal quality of life after seven years follow-up, despite more

Table 4
The effect of the severity of stroke and thrombolysis treatment on the quality of life after an ischemic stroke.

	NIHSS (severity of stroke)			Thrombolysis treatment		
	OR	95% CI	P-value	OR	95% CI	P-value
Barthel < 100	1.235	1.107-1.379	<0.001	0.340	0.132-0.875	0.025
Need of institutional care	1.071	0.935-1.226	0.321	0.619	0.161-2.383	0.486
Need of care	1.224	1.098-1.363	<0.001	0.356	0.139-0.908	0.031
Need of mobility aid	1.118	1.015-1.232	0.024	0.310	0.126-0.760	0.010
Decreased EQ-5D	1.131	1.014-1.261	0.027	0.382	0.164-0.890	0.026
Fatigue	1.114	1.012-1.227	0.028	0.339	0.140-0.820	0.016
Insomnia	0.998	0.903-1.102	0.962	0.715	0.303-1.687	0.444
OSA after 6 months	0.961	0.851-1.085	0.521	1.493	0.482-4.623	0.493
Decreased mobility	1.118	1.016-1.229	0.022	0.349	0.149-0.818	0.015
Decreased selfcare	1.196	1.076-1.330	0.001	0.326	0.119-0.887	0.028
Decreased usual activities	1.231	1.104-1.374	<0.001	0.345	0.135-0.886	0.027
Pain	1.019	0.930-1.116	0.688	0.601	0.270-1.340	0.214
Anxiety or depression	1.063	0.955-1.184	0.264	0.523	0.190-1.437	0.209

severe strokes on admission compared to those treated without thrombolysis. Only one third of our patients experienced fatigue. Only two out of ten of our patients experienced depression and anxiety.

At baseline our ischemic stroke patients treated with thrombolysis had more severe strokes, because they had significantly higher NIHSS scores and more aphasia compared to patients treated without thrombolysis. Despite the above mentioned, there was no significant difference in daily activities, quality of life and fatigue between the two study groups post-stroke.

Our finding, that the quality of life was not impaired compared to the others despite that thrombolysis treated patients had severe stroke as assessed by NIHSS scores is in line with previous studies.[12,41,42] Contrary to our study previous study pointed out that poor post-stroke quality of life was independently related to NIHSS score >4 one year after stroke.[14] The functional level pre-and post-stroke was good in both our study groups and overall quality of life scores were not influenced by mRS scores, which is in line with the study by Cortez et al.[41] According to former studies mRS >2 was related to lower post-stroke quality of life.[14] In this study, seven years post-stroke approximately 69% of patients were independent in daily activities, with the Barthel index score of 100, and our results are comparable to the results from one previous study by Muhr 2017 et al.[12] as well as to the other study which showed that 85% had no or mild disability one year after thrombolytic treatment.[20] Previous studies have reported rates of favorable outcome in stroke patients treated with thrombolytic therapy at 3 months as 65%, at 6 months 45%[43] at 12 months 88%[42] and at 18 months 53%.[15] The good post-stroke outcome could be defined as mRS scores 0–2, and we showed that both our study groups´ pre-stroke functional ability was good (mRS 0) and the ability to act maintained in good level after seven years follow-up (mRS 1) in these groups. In this study only 5% of patients pre-stroke and 30% post-stroke had moderate or severe disability (mRS 3-5), while previous studies pointed out that more than half of patients presented with mRS score 3-5.[14] Our mean Barthel Index was 91 out of 100 scores without differences between thrombolysis treated and those treated without thrombolytic treatment. One third of our patients needed care, as assessed by BI below 100, and this is in line with the study from Sweden.[12] Kainz et al.[44] showed that the need of care was only 19% one-year post-stroke, while 18-month post-stroke IST-3 study[15] reported the need of care to be as high as 43%.[15] Nine out of ten were living at home post- stroke in this study and our results are comparable to the results from the previous studies.[12,42] Only 10% of our patients needed institutional care, which is a remarkably lower rate than in previous study with 22% rate of institutional care.[45] This can partly be due to the different healthcare systems.

In this study up to one third of stroke patients had insomnia, which is in line with previous studies, which reported that insomnia affected 12-37% of stroke survivors.[46,47] In our study, every fifth had the diagnosis of depression at seven years post-stroke, which is in line with the previous study by Ayerbe.[48] Higher rates of depression compared to ours were reported in the Swedish study where almost half of patients were depressed.[12]

In this study one third of all our stroke survivors needed medical aids contrary to one previous study, which showed that only one out five needed mobility aids.[49] We observed that thrombolysis treated patients need of medical aids was lower than in the non-thrombolysis group (26% vs 40%) and likewise we, another study showed that one fourth of thrombolysis treated stroke patients needed medical aids.[44]

We pointed out, that seven years post-stroke the quality of life was good and without group difference, which is in line with the former studies.[12] Our result concerning all five domains in EQ-5D questionnaire were in good level without group differences, contrary to the IST-3 study which pointed out that the patients with thrombolysis treatment had significantly better results in four out of five domains.[15] Our result, that 68% of the thrombolysis patients had no problems with walking, is comparable to the result from the previous study by Muhr et al.[12] Contrary to our study, the IST-3 study showed that only 40% in the thrombolysis group had no problems with walking.[15] Our thrombolysis treated stroke patients´ self-care was normal in 77% of cases and our results are comparable to the results from the study by Muhr et al.[12] while the self-care was normal only in 54% of thrombolysis treated patients in the IST-3 study. In this study, one third of those with thrombolysis had problems with usual activities, which is lower than that of the IST-3 study. The above-mentioned result, that seven out of ten had not problems in usual activities is in line with former study by Muhr et al.[12] Pain or discomfort rate was 35% in our stroke patients who underwent thrombolysis, which is lower than the rate of 50% in the two previous study.[12] We reported anxiety or depression only in 20% of cases, which is substantially lower rate than in previous studies.[12,15]

Approximately one-third of our ischemic stroke patients reported post-stroke fatigue, the results being comparable to the recent systematic review, which reported the prevalence of post stroke fatigue 34% at one year after ischemic stroke in stroke survivors.[50–52] One study from China reported that the prevalence of fatigue was 24% at 24 months after stroke.[53] Some former studies pointed out higher post-stroke fatigue rates than ours, between 51 and 77%.[54–56] The feeling of fatigue after stroke causes impaired quality of life and depressive symptoms.[29]

One out of five of our patients had depression, which is in line with the study by Ayerbe.[48] The previous review reported the prevalence of depression was 29% and the prevalence remained stable up to 10 years after stroke.[21] Post-stroke depression is associated with concomitant fatigue.[28] The previous study from Sweden showed that, one year post-stroke presence of depression increased the OR for fatigue 3.2.[57] The post-stroke depression increased mortality in two previous studies with follow-up periods between 17 months and 11 years.[23,24,50]

We showed that patients treated with thrombolysis retired seldom than patients without thrombolysis (78% vs. 91%). This is partly explained by the fact that in the latter group patients were older. We did not evaluate if the retirement was due to stroke. The study patients´ post-stroke mRS was 0–2 in 70% of cases and only 22% of thrombolysis treated patients were still working after seven years follow-up. Only 1% post-stroke working rate was reported by Muhr et al.[12] after five years

follow-up. Three months post-stroke former studies reported high a working rate of 68% in thrombolysis treated patients with mRS score 0–2.[10,11]

Seven years post-stroke, 137 of the original 204 study patients had survived, of whom only one denied participating in the follow-up study. The final sample size in this study was 136, which is higher than in most former studies[12,20,29] although one randomized controlled trial had higher sample size than ours.[15] The participation rate (99%) in our study was higher than in the other long-term follow-up studies.[12,15] One third of our patients died during seven years follow-up, which is in line with the previous studies.[12,15,58] In this study, the thrombolysis patients` survival was first slightly better, but after seven years follow-up the survival curves did not differ significantly between the two groups. The thrombolysis treatment did not affect post-stroke survival after 18 months follow-up in the randomized controlled trial either, which showed 37% mortality rates for thrombolysis patients and control group.[15] Lower mortality rate than ours was pointed out in one previous study with smaller sample size.[20]

This study showed that the thrombolysis treatment protected from being dependent, need of care, need of mobility aid, decreased quality of life, fatigue, and decreased mobility, self-care and unable to do usual activities. In line with our study, the IST-3 study reported that thrombolysis for acute ischemic stroke patients with intravenous alteplase improved several measures of function and quality of life 18 months after treatment.[15] This study showed, that the severe the stroke according to baseline NIHSS scores, the more reduced were BI, mobility, self-care, usual activities, the quality of life and increased need of care, mobility aid and rate of fatigue. In agreement with our study, the previous studies reported that the initial stroke severity significantly predicted functional outcomes and quality of life at 3 to 12 months following thrombolytic treatment.[20,59]

After the subacute treatment, starting secundar prevention and individualized rehabilitation plan, a person from the cerebrovascular support network contacted all the patients and offered them possibility to participate in the stroke initial information day. The objective of this initial information day is among other information to support independent self-care and to prevent social isolation, anxiety and depression. These stroke initial information and the support of the network of cerebrovascular support persons might partly explain the better quality of life in the area on Northern Osthrobotnia compared with some other studies.

Our study has several strengths. First, our real life one-center, prospective, observational study had one of the largest sample size of studies addressing long-term outcome of stroke patients. Second, 99.3% of study patients alive participated after seven years follow up study while only one patient denied attending and none was lost to follow-up. The response rate in other studies has been lower and the drop off higher than ours.[12,41] Third, only few studies have followed thrombolysis treated stroke patients' ability to act, quality of life and fatigue over five years.[12,60] Fourth, the same investigator interviewed all study patients and only one patient posted the questionnaire.

However, our study has limitations. Unfortunately we did not evaluate our patients` EQ-5D, FSS-9 and BI in the acute phase of ischemic stroke, and therefore we were not able to evaluate the change in pre- and post-stroke quality of life, BI and fatigue. The data did not provide information on whether a patient`s retirement was due to stroke, disability or age. Our results may represent only situation in Finland.

Conclusions

Our main finding was that thrombolysis treatment seems to protect from reduced quality of life despite more severe stroke. The functional ability was better than expected after the thrombolysis treatment compared to the others with less severe stroke. There were less patients suffering pain or discomfort in our study group than in the previous studies. In the District of the Northern Ostrobothnia there is a health care provider system with a network of cerebrovascular support persons. That might partly explain the better quality of life in our study than in some other studies. In the future we suggest utilizing the questionnaires of quality of life and use them to improve the quality of life of the stroke patients.

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CRediT authorship contribution statement

Jaana K. Huhtakangas: Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Conceptualization, Data curation, Formal analysis, Funding acquisition. **Tarja Saaresranta:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – review & editing. **Moona Huhtakangas:** Data curation, Formal analysis, Visualization, Writing – review & editing. **Marianne Haapea:** Formal analysis, Writing – review & editing. **Juha Huhtakangas:** Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

Disclosures

None.

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