

Effects of professional rehabilitation training on the recovery of neurological function in young stroke patients

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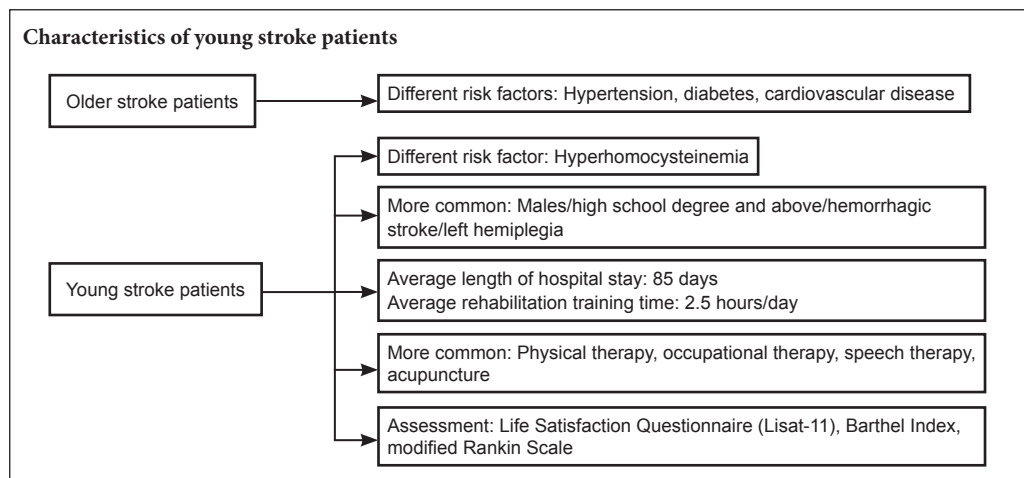
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Graphical Abstract



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Abstract

Young stroke patients have a strong desire to return to the society, but few studies have been conducted on their rehabilitation training items, intensity, and prognosis. We analyzed clinical data of young and middle-aged/older stroke patients hospitalized in the Department of Neurological Rehabilitation, China Rehabilitation Research Center, Capital Medical University, China from February 2014 to May 2015. Results demonstrated that hemorrhagic stroke (59.6%) was the primary stroke type found in the young group, while ischemic stroke (60.0%) was the main type detected in the middle-aged/older group. Compared with older stroke patients, education level and incidence of hyperhomocysteinemia were higher in younger stroke patients, whereas, incidences of hypertension, diabetes, and heart disease were lower. The average length of hospital stay was longer in the young group than in the middle-aged/older group. The main risk factors observed in the young stroke patients were hypertension, drinking, smoking, hyperlipidemia, hyperhomocysteinemia, diabetes, previous history of stroke, and heart disease. The most accepted rehabilitation program consisted of physiotherapy, occupational therapy, speech therapy, acupuncture and moxibustion. Average rehabilitation training time was 2.5 hours/day. Barthel Index and modified Rankin Scale scores were increased at discharge. Six months after discharge, the degree of occupational and economic satisfaction declined, and there were no changes in family life satisfaction. The degrees of other life satisfaction (such as friendship) improved. The degree of disability and functional status improved significantly in young stroke patients after professional rehabilitation, but the number of patients who returned to society within 6 months after stroke was still small.

Key Words: nerve regeneration; young stroke patients; risk factors; recovery of neurological function; prognosis; Life Satisfaction Questionnaire; Barthel Index; modified Rank Scale; neural regeneration

Introduction

Stroke with high incidence and high disability seriously threatens human life and health. Stroke onset in young patients between 18 and 44 years, is inclusive. Morbidity has been reported between 7 and 15 cases per 100,000 individuals (Griffiths and Sturm, 2011). Morbidity accounts for 5–15% of all strokes (Bi and Beijing Neurologist Club, 2003). In recent years, the incidence of stroke is rising. The etiology and risk factors for young stroke patients differ from those for middle-aged and older stroke patients, and are complicated in young patients with ischemic stroke (Béjot et al., 2013; Sultan and Elkind, 2013). Numerous studies have shown that the onset of stroke in young people is associated with hypertension, family history of stroke, smoking and hyperhomocysteinemia in developing countries (Hill et al., 1991; Lee et al., 2002; Feigin et al., 2003; Benninger et al., 2009; De Silva et al., 2009; Onwuchekwa et al., 2009; Griffiths and Sturm, 2011; Park et al., 2014). Moreover, the proportion of stroke without any clear cause increases year by year, and different risk factors are reported in different studies (Hill et al., 1991; Lee et al., 2002; Feigin et al., 2003; Benninger et al., 2009; De Silva et al., 2009; Onwuchekwa et al., 2009; Griffiths and Sturm, 2011; Park et al., 2014).

Professional rehabilitation relieves dysfunction in stroke patients, and promotes and maintains the recovery of cognition, language, movement, psychology, and social function. The demand to return to society and work is high in young stroke patients, but there are few studies that focus on rehabilitation training items, intensity, or prognosis for young stroke patients. Indeed, a multicenter study demonstrated a current lack of unified evaluation criteria for the effect of rehabilitation therapy in stroke patients (Engbers et al., 2005; Kuptniratsaikul et al., 2009). No studies regarding the rehabilitation, strength, or prognosis for young stroke patients have been performed in China.

We sought to analyze the clinical data of stroke patients hospitalized over the course of one year in the Department of Neurological Rehabilitation, China Rehabilitation Research Center, Capital Medical University, China. We compared general data and risk factors between young stroke patients and middle-aged/older stroke patients. We first analyzed rehabilitation and strength in young stroke patients by comparing the degree of disability and functional status between the time of admission and the time of discharge. We also collected information regarding the degree of disability, functional changes, life satisfaction, and return to society 6 months after discharge in young stroke patients. This was done to help patients have better access to rehabilitation services and to improve their quality of life.

Subjects and Methods

Ethics statement

We obtained written approval for all procedures from the Clinical Research Ethics Committee of Beijing Boai Hospital, China (approval No. 2012N15). Patients or their legal representatives signed an informed consent. This study was conducted in accordance with the *Declaration of Helsinki*, formulated by the World Medical Association.

Participants

We collected data from 324 stroke patients who were hospitalized in the Department of Neurological Rehabilitation, China Rehabilitation Research Center, Capital Medical University, China from February 2014 to May 2015. There were 135 young patients and 183 middle-aged/older patients. One hundred of these patients were randomly selected from each group. The specific method for random selection was as follows: (1) Number all the young patients and middle-aged/older patients separately, and generate two random number tables (data in **supplementary Tables 1 and 2 online**). (2) In the young group, patients were chosen by extracting every other number starting in row 1, column 1 of the table from left to right, proceeding to the last column of the last row. In the elderly group, the numbers were extracted from **supplementary Table 2 online**, and the method is the same as the young group.

Inclusion criteria: Young group: (1) met World Health Organization (WHO) diagnostic criteria for stroke (no authors listed, 1988); (2) verified by CT or MRI of the head (cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage); (3) age ≥ 18 years and ≤ 44 years; (4) vital signs stable, could complete instructions to keep sitting for longer than 30 minutes; (5) Mini-Mental State Examination score (Tombaugh and McIntyre, 1992) ≥ 17 , *i.e.*, normal cognitive function and mild to moderate cognitive impairment. Middle-aged/older group: (1) age ≥ 45 years; (2) other criteria were the same as the young group.

Exclusion criteria: (1) Brain tumor or brain injury; (2) other severe systemic diseases or death; (3) imperfect medical record data, unable to carry out the risk factor analysis.

Survey contents and methods

(1) General data

General data were obtained in the following respects. 1. General conditions: age, sex, type of stroke, side of hemiplegia, education level, and medical insurance; 2. Presence or absence of risk factors: hypertension, diabetes, heart disease, hyperlipidemia, hyperhomocysteinemia, previous stroke, history of smoking, and history of drinking.

Hypertension: In accordance with WHO diagnostic criteria, without taking any hypotensive medication, the average blood pressure was calculated after at least two measurements taken on different days. If systolic pressure was ≥ 140 mmHg or diastolic pressure was ≥ 90 mmHg, or if the patient had a history of hypertension, blood pressure was controlled with hypotensive medication to be below 140/90 mmHg (Chalmers, 1999).

Diabetes: In accordance with WHO criteria for diabetes (World Health Organization, 2006), diabetes was diagnosed if fasting blood glucose was ≥ 7.0 mM, 2-hour postprandial blood glucose was ≥ 11.1 mM, random blood sugar levels were ≥ 11.1 mM, or glycosylated hemoglobin was $\geq 6.5\%$.

Coronary atherosclerotic heart disease: including stable angina, non-ST-segment elevation acute coronary syndrome, ST-segment elevation acute myocardial infarction, and silent myocardial ischemia (Fraker et al., 2007; Rapezzi et al., 2008).

Heart disease was diagnosed if there was mitral stenosis,

prosthetic valve replacement, coronary atherosclerotic heart disease, left ventricular mural thrombus, left ventricular aneurysm, persistent or paroxysmal atrial fibrillation, sick sinus syndrome, dilated cardiomyopathy, endocarditis, intracardiac tumor, or patent foramen ovale.

Hyperlipidemia was diagnosed if there was an abnormally elevated level of plasma or serum cholesterol and (or) triglycerides induced by lipid metabolism disorders. This included serum cholesterol levels > 5.72 mM (220 mg/dL), plasma triglycerides levels > 1.7 mM (150 mg/dL) (Joint Committee for Developing Chinese guidelines on Prevention and Treatment of Dyslipidemia in Adults, 2007). Because the WHO classification from 1970 was complicated, this study used the following clinical classification: hypercholesterolemia, hypertriglyceridemia, low high-density lipoprotein hyperlipidemia, and mixed hyperlipidemia (Beaumont et al., 1970; Lisak et al., 2013).

Hyperhomocysteinemia was diagnosed if the range of total plasma homocysteinemia concentration was 5–15 μ M in an empty stomach. Abnormally high total homocysteinemia concentration is known as hyperhomocysteinemia (Petras et al., 2014).

Smoking: At least 1 cigarette every day for at least 1 year.

Drinking: At least twice every month for at least half the current year. Additionally, the amount of alcohol consumed was more than the standard amount of 120 mL wine, 360 mL beer, or 45 mL spirits.

(2) Evaluation criteria

1. Time from onset to arriving at the rehabilitation center and hospital stay; 2. Degree of disability, functional status in young stroke patients at admission, discharge, and 6 months after discharge. The Modified Rankin Scale was used to assess the degree of disability (score range: 0–6) (van Swieten et al., 1988). The Barthel Index was utilized to evaluate functional status of patients (Mahoney and Barthel, 1965; Muir et al., 2004) (independence: 95–100, slight dependence: 60–90, severe dependence: 0–55). 3. The Life Satisfaction Questionnaire (Lisat-11) (Röding et al., 2010; Bergström et al., 2011) was used to assess the degree of satisfaction with life at admission and 6 months after discharge. This included satisfaction in life on the whole, occupation, economy, entertainment, friendship, body, mind, and marital relationship. Score 0 represents nonapplication; scores 1–3 represent dissatisfied (1: very dissatisfied; 2: dissatisfied; 3: partially dissatisfied); scores 4–6 represent satisfied (4: partially satisfied; 5: satisfied; 6: very satisfied). 4. Rehabilitation items and intensity during hospitalization in young stroke patients.

Rehabilitation and intensity in young stroke patients

All patients in the young group received rehabilitation training, including physical therapy, occupational therapy, speech therapy, balance training, sports training, cognitive training, hyperbaric oxygen therapy, hydrotherapy, acupuncture, massage, suspension therapy, transcranial magnetic stimulation therapy, and biofeedback therapy. Physical therapy and occupational therapy were performed once or twice per day,

each for 45 minutes, five times a week. Speech therapy, balance training, sports training, cognitive training, hyperbaric oxygen therapy, hydrotherapy, acupuncture, massage, and suspension therapy were conducted once a day, each for 30 minutes, five times a week. Transcranial magnetic stimulation therapy and biofeedback therapy were carried out once a day, each for 10 minutes, five times a week.

Follow-up

All patients in the young group were followed up at 6 months after discharge, and data were collected again for the Barthel Index, modified Rankin Scale scores, and Life Satisfaction Questionnaire.

Statistical analysis

All data were analyzed using SPSS 13.0 (SPSS, Chicago, IL, USA). Measurement data are expressed as the mean \pm SD. The difference in Barthel Index for the young group at different time points was compared using a paired *t*-test. Modified Rankin Scale scores were analyzed with paired rank sum test. The age between the two groups was analyzed using an independent samples *t*-test. Other general data and risk factors were analyzed with chi-square test. Using *t*-tests to compare time from stroke to arrival at a rehabilitation center/hospital in two groups. Using a two-samples independent *t*-test to compare the difference in the amount the score changed between admission and discharge and between discharge and 6 months after discharge. A $P \leq 0.05$ was considered statistically significant using a two-sided test.

Results

General data

Of the 324 stroke patients who were hospitalized in the Department of Neurological Rehabilitation during the same period, 135 (41.7%) were young. From these, we randomly chose 100 for further analysis. The number of male patients was significantly greater than that of female patients ($\chi^2 = 3.889$, $P = 0.049$). Young patients mainly suffered from hemorrhagic stroke (59.0%), but older patients were mainly affected by ischemic stroke (60.0%), showing significant differences between the two groups ($P = 0.016$). No significant difference in the hemiplegic side was detected between the two groups ($P = 0.082$). Education level was higher in the young group than in the middle-aged/older group ($P = 0.013$). The proportion of patients with medical insurance was similar between the two groups ($P = 0.352$). The main risk factors observed in young stroke patients were hypertension, drinking, smoking, hyperlipidemia, hyperhomocysteinemia, diabetes, previous history of stroke, and heart disease. The incidence of hyperhomocysteinemia was higher in the young group than in the middle-aged/older group ($P < 0.05$). The incidences of hypertension, diabetes, and heart disease were higher in the middle-aged/older group than in the young group ($P < 0.01$; **Table 1**).

Rehabilitation

The course of diseases was similar between the two groups ($P > 0.05$), but mean hospital stay was longer in the young

Table 1 General data of included stroke patients

	Young (n = 100)	Middle-aged/older (n = 100)	χ^2 value	P value
Age (mean \pm SD, year)	36.42 \pm 7.24	58.76 \pm 10.26		0.329
Male (%)	78	64	3.889	0.049
Ischemic stroke (%)	41	60	5.781	0.016
Hemiplegic side (n)			6.706	0.082
Left	39	48		
Right	47	48		
Bilateral	13	4		
No	1	0		
Education level (n)			8.733	0.013
Primary school and below	6	10		
High school (including junior college)	47	64		
University and above	47	26		
Insurance (yes/no)	80/20	85/15	0.866	0.352
Risk factor (n)				
Hypertension	49	70	9.15	0.002
Diabetes	22	42	9.191	0.002
Hyperlipidemia	35	42	1.035	0.309
History of smoking	38	42	0.333	0.564
History of drinking	46	36	2.067	0.151
Heart disease	3	26	21.335	0.0001
Previous history of stroke	5	12	3.150	0.076
Hyperhomocysteinemia	23	11	5.103	0.024

Each group contained 100 patients. The age between the two groups was analyzed by using an independent samples *t*-test. Other general data and risk factors were analyzed with chi-square test.

Table 2 Time from stroke to arrival at a rehabilitation center/hospital in young and middle-aged/older stroke patients

	Young	Middle-aged/older	<i>t</i> value	P value
Time from onset to rehabilitation center (day)	75.14 \pm 90.20	53.56 \pm 73.76	1.852	0.066
Hospital stay (day)	85.29 \pm 65.95	59.59 \pm 43.61	3.250	0.001

Data are expressed as the mean \pm SD. Each group contained 100 patients. Intergroup comparisons were done using *t*-tests.

Table 5 Life satisfaction at admission and 6 months after discharge in young stroke patients

Life Satisfaction Questionnaire	Dissatisfied (scores 1–3)	Satisfied (scores 4–6)	Non-applicable (score 0)
Overall quality of life	11/10(36.70/33.33)	19/20(63.40/66.67)	–
Occupation	3/9(10/30)	21/20(70/66.67)	6/1(20/3.33)
Economy	4/9(13.33/30)	24/21(80/70)	2/0(6.67/0)
Entertainment	12/6(40/20)	18/24(60/80)	–
Friendship	1/1(3.30/3.30)	28/29(93.33/96.67)	–
Sex life	5/7 (16.70/23.33)	17/19(56.67/63.33)	8/4(26.67/13.30)
Self-care ability	9/6(30/20)	21/24 (70/80.00)	–
Family life	2/2(6.70/6.70)	28/28(93.33/93.33)	–
Marital status	2/1(6.67/3.33)	21/23(70.00/76.66)	7/6(23.33/20)
Physical health	17/13(56.67/43.33)	13/17(43.30/56.67)	–
Mental health	10/8(33.33/26.67)	20/22(66.67/73.33)	–

Numbers of patients are given as: at discharge/6 months after discharge (% at discharge/% 6 months after discharge).

group than in the middle-aged/older group ($P < 0.05$; Table 2). Mean rehabilitation time was 2.5 hours per day in the young group, excluding family assistance and self-training. The most accepted training in the young group included physical therapy, occupational therapy, speech therapy and acupuncture (Table 3).

The degree of disability and functional status in young stroke patients

Barthel Index scores in the young group were significantly higher immediately after discharge than at admission ($P < 0.05$). Immediately after discharge, 13% of patients had achieved independence in daily life, 50% were slightly dependent, and

Table 3 Rehabilitation training items for young stroke patients

	Hemorrhagic (n = 59)	Ischemic (n = 41)	Total (n = 100)
Physical therapy	55(93.22)	36(87.80)	91(91)
Occupational therapy	54(91.52)	36(87.80)	90(90)
Speech therapy	23(38.98)	20(48.78)	43(43)
Balance	5(8.47)	8(19.51)	13(13)
Sports	2(3.39)	3(7.3)	5(5)
Cognition	9 (15.25)	4(9.75)	12(12)
Hyperbaric oxygen	17(28.81)	7(17.07)	24(24)
Hydrotherapy	12(20.33)	8(19.51)	20(20)
Acupuncture	20(33.90)	13(31.70)	33(33)
Massage	9(15.25)	4(9.75)	13(13)
Suspension	2(3.39)	2(4.88)	4(4)
Others	27(45.76)	22(53.66)	49(49)

Data are expressed as the number of patients (*n*) and the numbers in the parentheses indicate the relative percentage of each item included in a total.

37% were severely dependent. Barthel Index scores were higher 6 months after discharge than immediately after discharge ($P < 0.05$). At 6 months after discharge, 30% of patients had achieved independence in daily life, 53% were slightly dependent, and 17% were severely dependent (Table 4).

In the young group, comparison of conditions at discharge with those at admission showed that the functional status had improved in 47 patients, had not changed in 52 patients, and had worsened in 1 case ($Z = -6.432$, $P = 0.000$). Comparison of conditions 6 months after discharge with those immediately after discharge showed that stroke had improved in 41 patients, had not changed in 58 cases, and had become aggravated in 1 case ($Z = -5.881$, $P = 0.000$; Table 4).

We performed an analysis to determine how conditions after stroke changed over time. We calculated the change in Barthel Index between admission and discharge, and between discharge and 6 months after discharge. A paired *t*-test showed that the amount of change in Barthel Index scores was significantly different ($t = 4.006$, $P = 0.000$) depending on the time period.

Changes in life satisfaction in young stroke patients

One hundred patients in the young group accepted a telephone follow-up 6 months after discharge. Excluding young patients with cognitive impairment, aphasia, or dysarthria, 30 patients finished the Life Satisfaction Questionnaire (Lisat-11). Results showed that compared with conditions at discharge, satisfaction in overall life, entertainment, friendship, sex life, self-care ability, spouse, physical health, and mental health had improved by 6 months after discharge, but that satisfaction in occupational and economic situations had decreased. Satisfaction in family life did not change (Table 5).

Young stroke patients returning to society 6 months after discharge

Among the 30 patients who completed the Life Satisfaction Questionnaire, eight had returned to work. Four had full-time jobs, one was working 50% of a normal work load, one was doing 75%, and two were doing 10–20%. Another seven were planning to return to work at 12 months after discharge.

Table 4 Self-care ability and disability in young stroke patients

	Admission	Discharge	6 months after discharge
Barthel Index (mean±SD)	44.90±23.77	63.00±24.90	73.40±23.71
Self-care ability (%)			
Independence (scores 95–100)	3	13	30
Slight dependence (scores 60–90)	31	50	53
Severe dependence (scores 0–55)	66	37	17
Modified Rankin Scale score			
0	0	0	0
1	2	4	18
2	4	22	25
3	25	32	28
4	61	35	24
5	8	7	5
6	0	0	0

Significant differences in average Barthel Index scores in young patients at different time points compared using a paired *t*-test were detected ($P = 0.000$). The difference in the amount the score changed between admission and discharge and between discharge and 6 months after discharge was compared with a two-samples independent *t*-test. Modified Rankin Scale scores are expressed as the number of patients and analyzed with a paired rank-sum test. Modified Rankin Scale scores: 0, no symptom; 1, no obvious dysfunction; 2, mild dysfunction; 3, moderate dysfunction, can walk; 4, moderate dysfunction, cannot walk; 5, severe dysfunction; 6, death.

Discussion

Among 100 young stroke patients in each group, 59% experienced hemorrhagic stroke. An epidemiological survey has reported that ischemic stroke was the primary stroke type detected in young stroke patients (Lee et al., 2002; Feigin et al., 2003). Inconsistent results may be related to an increased incidence of hypertension and heavy disability after intracerebral hemorrhage.

The risk factors for young stroke patients are complicated, and differ in developed and developing countries (Kwon et al., 2000; Cerrato et al., 2004; Dash et al., 2014). The onset of ischemic stroke was reported to be associated with hypertension, family history of stroke, and smoking in young patients of developing countries (Hill et al., 1991; Onwuchekwa et al., 2009). Our study demonstrated that hypertension is a high risk factor for young, middle-aged, and older stroke patients, and that the incidences of diabetes and heart disease were higher in the middle-aged/older group than in the young group, which was consistent with previous studies (Bevan et al., 1990; Tuomilehto et al., 1991; Carolei et al., 1993; Warlow, 1998; Chraa et al., 2014). The incidence of hyperhomocysteinemia was higher in the young group than in the middle-aged and elderly group, which was consistent with a previous study (Benninger et al., 2009). The number of drinkers was higher in the young group than in the middle-aged/older group. Recently, life pressure has increased for urban youth, and they stay out late at night, have anxiety, abuse drugs, and are more obese (Renna et al., 2014). Poor lifestyle and sleep apnea may also lead to an increased

incidence of stroke in young people, and risk factors have a long-term impact on the prognosis of young stroke patients (Ellekjaer et al., 2001; Kiyohara et al., 2003; Hardie et al., 2004; Waje-Andreassen et al., 2013).

Presently, few studies have been conducted on the short-term and long-term prognosis of young stroke patients. For long-term follow-up, the Barthel Index can be used as a supplement for classifying the recovery of dysfunction using a modified Rankin Scale. The maximum sensitivity of the modified Rankin Scale is achieved 6 months after stroke (Ciconcoloni et al., 2012). In this study, 13% of patients achieved independence in daily life, and 87% of patients had dysfunction at discharge. Six months after discharge, 70% of patients had dysfunction, and 57% with only moderate dysfunction (modified Rankin Scale score > 2), which was similar to what has been reported in other studies (Luengo-Fernandez et al., 2013; Synhaeve et al., 2014; Meyer et al., 2015).

Results from the Life Satisfaction Questionnaire (Lisat-11) in this study showed that satisfaction in overall life, entertainment, friendship, sex life, self-care ability, spouse, physical health, and mental health increased over time in young patients after discharge, but that satisfaction in occupational and economic situations decreased. A Swedish study found that independence in daily life markedly affected life satisfaction in young patients 1–2 years after stroke onset. However, even if daily life can be independent, some patients are still unable to work because they have difficulty maintaining attention or cannot drive to work, which decreases overall life satisfaction (Röding et al., 2010). Varona et al. (2004) reported that among 90% of young stroke patients with independent daily lives, only half returned to work, which impacts patients and family economics. Return to work positively affects life satisfaction (Vestling et al., 2005; Waje-Andreassen et al., 2013). The young patients with mild dysfunction, high education levels, and no risk factors are the most likely to return to work (Otero Palleiro and Barbagelata López, 2007; Trygged et al., 2011; Dash et al., 2014; Kawle et al., 2015). For patients who are mildly dependent in daily life, cognitive impairment, emotional disorders and aphasia impact their return to work. As a result, their degree of life satisfaction decreases. In the current study, among 100 young stroke patients, only 8 returned to work, and an additional 7 planned to work by 12 months after discharge. Even counting the additional 7, the proportion of patients returning to work was still low. The degree of life satisfaction was higher than that in previous studies, but could be attributed to the short discharge time, cultural differences, and family structure.

Currently, patients with acute stroke can be treated in a comprehensive or specialized hospital (Weaver and Liu, 2015). Nevertheless, there are few studies on rehabilitation programs and the costs for young stroke patients. Some patients with complications need specialized rehabilitation. Because rehabilitation hospitals are relatively few, only a small proportion of patients are treated. Our results confirmed that the average time from stroke onset to entering a rehabilitation center was 75.13 days. The average hospital stay was 85.29 days and the average time of rehabilitation training was

2.5 hours per day. These findings suggest that patients wait a long time for professional rehabilitation, and that the time of actual effective rehabilitation training is short. Patients outside Beijing primarily only receive physical therapy and occupational therapy, such as Chinese massage, acupuncture, and moxibustion. This might be related to advantages of traditional Chinese medicine and development of different rehabilitation medicine in different regions. This study has some limitations: (1) a small sample size; the patients in the middle-aged/older group were randomly selected. There may have been selection bias in the telephone follow-up. (2) Lack of imaging data might affect the statistical results and analysis. (3) Compulsory treatment, robot training, music therapy, and motor imagery were not analyzed, but these items may have effects on functional status (Rabadi, 2011).

We will continue to focus on the situation of rehabilitation training, medication, returning to society or not, working problems, family living conditions, specialized rehabilitation nursing and factors influencing life satisfaction.

Declaration of patient consent: *The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.*

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Conflicts of interest: *None declared.*

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Supplementary table 1 Random number table of patients in the young group

8	128	98	65	74	112	134	65	26	53
91	33	35	112	58	17	134	126	74	59
24	100	22	19	70	33	10	15	50	50
32	20	1	131	85	84	106	133	45	75
129	116	73	58	122	37	55	5	128	66
60	99	113	96	130	50	43	81	12	103
98	134	89	18	18	93	52	43	119	93
104	118	99	66	86	26	69	66	4	41
21	21	124	91	26	38	93	120	128	43
68	8	87	50	93	19	75	87	68	6
61	111	28	45	2	65	42	55	86	122
47	22	68	7	33	14	5	133	65	18
107	31	90	1	84	26	125	92	132	104
27	117	9	61	99					

Supplementary table 2 Random number table of patients in the middle-aged and elderly group

109	20	127	99	78	10	57	182	80	64
102	19	97	145	25	71	101	117	128	65
5	17	113	30	32	31	170	7	24	36
146	148	160	175	12	29	79	4	131	26
22	181	44	116	123	165	8	52	124	2
47	167	129	15	122	60	119	75	39	73
62	143	92	172	103	126	33	136	114	96
69	173	59	121	179	66	154	55	9	132
54	118	46	180	72	41	87	104	162	100
84	93	85	130	23	67	40	171	168	11
83	13	153	28	174	76	164	3	105	88
58	56	147	107	178	34	155	94	134	177
111	81	42	108	141	82	161	1	45	115
89	138	176	149	163	6	21	35	27	158
14	18	95	90	51	169	144	135	91	152
183	140	98	49	156	133	70	125	86	77
112	151	68	159	53	43	48	142	139	166
38	150	74	63	110	120	37	61	157	137
106	16	50							