The Effect of Age and Sex on Ischemıc Stroke: A Sıngle-Centred Neuro-Intensıve Care Unıt Experıence

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Abstract

Background: Age and sex are important determinants in the acute ischemic stroke (AIS). In this study, we examine the effects of age and sex on stroke survival and treatment in our clinic.

Methods: We reviewed 368 AIS patients' records between January 1, 2019, and January 1, 2020, and formed three groups of age; Group 1:18-64 years, Group 2:65-79 years, and Group 3:≥80 years. Then, we analyzed patients' data (sex, risk factors, hospital outcome, etc.), reperfusion therapy (RT) types (tissue plasminogen activator(tPA), endovascular therapy(EVT) and tPA+EVT), and reasons for none-RT (time mismatch, absolute and relative contraindications).

Results: The majority of patients were age<65 years (48.6%), and the proportion of women increased in the older (56.1%). The most common stroke risk factor was hypertension (44.7%), but for those<65 years, it was obesity (46.6%). The most common RT type was tPA (56.7%), and no patients≥80 years received tPA+EVT. The most common none-RT reason was time mismatch (65%). Being≥80 years and female over 80 years (p=0.001, and p=0.005) were associated with increased mortality risk. While the frequency of none-RT patients was 28.8% in general, it increased up to 62.8% for the ones age≥80 years. Also, the mortality rate was the highest in the none-RT(p<0.01).

Conclusions: RT practices differed according to patients' age and sex. The main determinant of the mortality rate was the lack of RT. However, the older patients and older women had less opportunity for RT.

Keywords: Acute ischemic stroke, reperfusion therapy, age, sex.

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INTRODUCTION

Acute stroke (AS) is the second most common cause of death worldwide. Furthermore, the most common cause of adult dependency that reduces the quality of life is also AS [1].

The incidence of AS increases with the aging of the population. In 2030, there may be about 10 million stroke survivors just in the United States [1,2].

Specifically for developed countries, approximately half of the AS patients are 80 years and older [3,4]. These patients may double in 2040 and more than double in

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2060 [5].

Morbidity and mortality rates increase in older AS patients [6]. Especially in women, the risk of stroke and stroke-related death increases with older age. Besides, the recovery phase is longer, and recovery-without-sequelae is fewer [7].

Acute ischemic stroke (AIS) has recently been treated more rapidly and effectively [8]. Although there is no age or sex limit in the guidelines, older patients, especially older women, receive less reperfusion therapy (RT). Bias for poor functional outcomes and higher mortality rates are the leading causes [9-11]. However, the effects of age and sex on stroke pathophysiology are still under investigation.

In the light of these, we aimed to find differences in stroke treatment and mortality rate according to age and sex in our clinic.

METHODS

Study Design

We retrospectively conducted this study between January 1, 2019, and January 1, 2020, in a 3rd-level stroke-center hospital (ethics committee approval no: 499). We analyzed the data of 368 patients admitted to the neurointensive care unit (NICU), respectively. We excluded a total of 160 patients. Reasons for exclusion of 122 of 160 patients were non-AIS diagnoses: hemorrhagic stroke, seizure, neuromuscular diseases, and dementia-related causes, respectively. The remaining 38 of 160 patients were excluded due to recurrent admission. As a result, 208 acute ischemic stroke patients were included in the study. We collected patients' data from the electronic database and archive files. Exclusion criteria were being under 18 years, pregnant and recurrent patient (number of admission>1 to neuro-intensive care unit for the last year).

Clinical and Demographic Data

We divided patients into three age groups; Group 1: 18-64 years, Group 2: 65-79 years, and Group 3: 80 years and over. We recorded demographic data, stroke risk factors (diabetes mellitus (DM: prior diagnosis, ongoing treatment or at least two measurements of capillary glucose > 200 mg/dl, 72 hours postictus), atrial fibrillation (AF: history of chronic or paroxysmal AF or demonstration through electrocardiogram during hospitalization), hypertension (HT: prior diagnosis, ongoing treatment, or at least two measurements greater than 140/90 mmHg 72 hours postictus), dyslipidemia (prior diagnosis, ongoing treatment or elevated total or low-density lipoprotein cholesterol levels, or low levels of high-density lipoprotein cholesterol), obesity (body mass index ≥30 kg/m^2), smoking, need for mechanical ventilation (MV), length of NICU stay the National Health Stroke Scale (NIHSS), the modified Rankin Scale (mRS), and the Acute Physiology and Chronic Health Assessment-II score (APACHE-II) at NICU admission.

The RT types were; tissue plasminogen activator (tPA), endovascular therapy (EVT), and EVT with tPA (tPA+EVT). The reasons for not performing RT were; time mismatch, absolute contraindication, and relative contraindication.

Statistical Analysis

First, we checked the data according to descriptive statistics and distributions with IBM SPSS Statistics 25.0 software. Categorical variables were presented as percentage and frequency. Continuous variables were presented as mean, standard deviation, median, and quartiles (interquartile range= IQR). We then analyzed the relationship between demographic data (age, sex, etc.), RT status (applied-RT or none-RT), and mortality rate. Since the studied variables were categorical, bivariate chi-square (the chi-squared test χ^2) tests were used to compare. We accepted the maximum value of type-I error probability as 5%, p≤ .05 in the analyses. We also expressed the p values, considering the p<0.01 to increase sensitivity to minor errors.

RESULTS

We reviewed 368 patients' records for the study, and we included 208 patients. Demographic data (sex, stroke risk factors, etc.), MV need, NIHSS, mRS, and APACHE-II scores, and NICU length of stay results are in table 1. Group 1 had the highest number of patients (49.5%). There were more men for age<65 years (51.4%) and more women for age≥65 years (56.1%). HT was the most common risk factor in general (44.7%) and in patients≥65 years (55.2%). Differently, in patients<65 years, obesity (46.6%) was the most common risk factor. The NIHSS, mRS, and APACHE-II scores increased with age ($p<0.01$). MV-need (16.3%, $p<0.01$) and length of NICU stay were (14.23±10.75, $p<0.01$) also higher in Group 3.

The distribution of stroke subtypes was as follows: 33% large artery stroke, 18% cardioembolic stroke, 10% small artery stroke, 8% stroke of determined causes such as dissection, vasculopathy, etc., and 31% stroke of unknown causes [12].

Applied-RT types, reasons for none-RT, and the relation between RT type and survival rate are in table 2. The most frequent RT type was tPA (56.7%). There were no patients over 80 years who received tPA+EVT combined therapy. The most frequent reason for none-RT was time-mismatch (65%). The frequency of none-RT patients was 28.8% for all patients and primarily seen in Group 3 (62.8%). The mortality rate was higher in none-RT patients (25%, $p<0.01$).

The mortality rates were 9.13% for all patients, 2.7% for RT received patients, and 25% for none-RT patients. When we examined the deceased's info, 57.8% were women, all of whom were over 65 years (Group 2: 42.1% and Group 3: 57.9%).

The analysis results between age-sex-mortality rate are in Table-3. There was no difference in the mortality rate between women and men ($\chi^2=0.253$, $p=0.615$). However, when women and men were analyzed according

Table 1. Demographic characteristics of acute ischemic stroke patients

Parameters		All Groups (208)		Group 1(103)		Group 2(62)		Group 3(43)	
		n	%	n	%	n	%	n	%
Sex	Female	109	52,4	50	48,5	35	56,5	24	55,8
	Male	99	47,6	53	51,5	27	43,5	19	44,2
DM	Yes	72	34,6	29	28,2	27	43,5	16	37,2
	No	136	65,4	74	71,8	35	56,5	27	62,8
AF	Yes	22	10,6	5	4,9	8	12,9	9	20,9
	No	186	89,4	98	95,1	54	87,1	34	79,1
HT	Yes	93	44,7	35	34,0	34	54,8	24	55,8
	No	115	55,3	68	66,0	28	45,2	19	44,2
Dislipidemia	Yes	60	28,8	19	18,4	18	29,0	23	53,5
	No	148	71,2	84	81,6	44	71,0	20	46,5
Obesity	Yes	82	39,4	48	46,6	24	38,7	10	23,3
	No	126	60,6	55	53,4	38	61,3	33	76,7
Smoke	Yes	52	25,0	25	24,3	19	30,6	8	18,6
	No	156	75,0	78	75,7	43	69,4	35	81,4
MV Need	Yes	26	12,5	12	11,7	7	11,3	7	16,3
	No	182	87,5	91	88,3	55	88,7	36	83,7

Parameters	All Groups (208)		Group 1(103)		Group 2(62)		Group 3(43)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
NIHSS	13	6	12	4	14	5	17	4
mRS	2	2	1	2	2	1	3	0
APACHE	12	6	10	3	14	4	17	4
Length of NICU stay (day)	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**
	9,21	8,28	5,96	3,97	11,11	9,35	14,23	10,75

DM: Diabetes Mellitus, AF: Atrial Fibrillation, HT: Hypertension, MV: Mechanical Ventilation, mRS: Modified Rankin Scale, National Institute of Health Stroke Scale, APACHE-II: Acute Physiology and Chronic Health Evaluation-II score, NICU: Neuro-intensive Care Unit

Table 2. Applied RT types, reasons for none-RT, and the relation between RT type and mortality rate

RT (n=208)	All Groups		Group 1 (103)		Group 2 (62)		Group 3 (43)	
	n	%	n	%	n	%	n	%
tPA only	118	56,7	69	67	36	58,1	13	30,2
EVT only	17	8,2	8	7,8	6	9,7	3	7
tPA+EVT combined	13	6,3	5	4,9	8	12,9	--	--
Total RT	***148***	***71,2***	***82***	***79,6***	***40***	***80,6***	***16***	***37,2***
None-RT	***60***	***28,8***	***21***	***20,4***	***12***	***19,4***	***27***	***62,8***
Reasons for none-RT (n=60)	**All Groups**		**Group 1 (21)**		**Group 2 (12)**		**Group 3 (27)**	
	n	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Time mismatch	39	65	15	71,4	7	58,3	17	63
Absolute contrendication	10	16,6	2	9,5	3	25	5	18,5
Relative contrendication	11	18,3	4	19	2	16,7	5	18,5

RT type	Survivor (189)		Dead (19)		X^2	p
	n	%	n	%		
tPA only (118)	116	98,3	2	1,7	**26,313**	**.000***
EVT only (17)	16	94,1	1	5,9		
tPA+EVT (13)	12	92,3	1	7,7		
None-RT (60)	**45**	**75**	**15**	**25**		

RT: Reperfusion therapy, tPA: Tissue plasminogen activator (alteplase), EVT: Endovascular therapy
*p values are statistically significant.

Table 3. The evaluation of the mortality rates for age groups and sex

Groups			Survivor (98)	Dead (11)	X^2	p
Female (n=109)	Group 1 (50)	n	49	1	**13,322**[a]	**.001***
		%	98	2		
	Group 2 (35)	n	32	3		
		%	91,4	8,4		
	Group 3 (24)	n	17	7		
		%	70,8	29,2		
Groups			**Survivor (91)**	**Dead (8)**	**,253**[b]	**.615**
Male (n=99)	Group 1 (53)	n	50	3	**1,955**[c]	**.376**
		%	94,3	5,7		
	Group 2 (27)	n	25	2		
		%	92,6	7,4		
	Group 3 (19)	n	16	3		
		%	84,2	15,8		
Chi-Squared in all patients (Hospital Outcome X Age Groups)					**13,838**[d]	**.001***
Chi-Squared in all patients (Hospital Outcome X Age Groups X Sex)					**16,564**[e]	**.005**

Not: a= Hospital Outcome X Age Groups in female; b= Hospital Outcome X Sex; c= Hospital Outcome X Age Groups in male patients; d= Hospital Outcome X Age Groups, e= Hospital Outcome X Age Groups X Sex
*p values are statistically significant.

to the age groups, the mortality rate was higher in older women (χ^2 =13.322, p=0.001), and there was no difference in men (χ^2 =1,955, p=0.376). When we examined hospital outcomes (survivor and dead) for all patients according to age groups, the mortality rate was higher in older age (χ^2 =13.838, p=0.001). Again, when we examined hospital outcomes with the age groups and sex, the mortality rate was higher in older women (χ^2 =16.564, p=0.005).

DISCUSSION

Age

Older AIS patients (age≥80 years) receive less RT than the rest of the patients, and none-RT patients have a higher mortality rate than the RT performed patients. Eventually, the none-RT older patients have the highest mortality rate.

Aging changes the cerebrovascular system's physiology, morphology, and metabolic processes: neuroplasticity decreases, leucoaraiosis increases. Furthermore, the number of comorbidities and the pre-stroke dependency rate also rise. Consequently, the very old population becomes more prone to stroke (11,13-15). On the other hand, age is an unmodifiable risk factor for in-hospital mortality and poor functional outcome in stroke patients (16,17).

Although there is no age limit for RT in guidelines, older AIS patients had been excluded from some multicenter RT studies (9, 18-20). Even the guidelines emphasized that the patient should be evaluated not only for age itself but the infarct volume, collateral presence, the NIHSS value, and concomitant comorbidities. The survival odds and good-functional outcome should be considered multifactorial.

In a study, Kawabata et al. investigated the efficacy of EVT (21) in very old AIS patients (≥80 years). Naturally, pre-stroke dependency (mRS>1) was higher in the older group. However, pre-stroke dependence did not adversely affect the success of EVT (89.5% for patients over 80 years old and 67.5% for patients younger than 80 years old, p=0.11). The mortality rate was lower in the older, but there was no statistical difference (21.1% vs. 27.5%, respectively, p=1). Kawabata et al. defined the EVT efficacy as mRS≤2 or maintenance of current mRS. Another study emphasized that RT should ensure survival and protect the quality of life and cognitive functions. (22).

In an article by Goldhorn et al. (23), from the results of the MR-CLEAN study, 157 (11%) patients of 1441 patients were found pre-stroke dependent. But, this was not associated with less-favorable outcomes (OR adjusted: 0.90; 95% CI, 0.58-1.39). Besides, EVT treatment may decrease the mortality rate for AIS patients≥80 years (8,24).

In our opinion, the first purpose in stroke management should be to prevent stroke or at least decrease the stroke rate. If the stroke occurs, the preserved actual functional state might be accepted as a treatment success. So, age alone isn't a barrier to stroke management.

Sex

Being older and women is a risk factor for an increased mortality rate of AIS (p=0.001). We may explain this by women living longer than men, and stroke is more frequent in older age (25,26). However, it's not enough to explain it only with life expectancy.

Stroke is more frequent and severe in women than men (27-30). Besides, the stroke-related mortality rate is also higher in women than men, especially for those≥85 years old (31,32).

Sex itself is a determining risk factor for stroke and stroke-related mortality (33). In addition to sex chromosomes, social, economic, and behavioral differences affect the risk and outcome of stroke (34,35). Some studies showed that women received less RT than men for AIS. And they questioned the reasons for this inequality. It was multifactorial. For example, women living alone, having difficulty reaching the hospital, being late in admission, and having atypical symptoms (altered states in consciousness, generalized weakness, fatigue, etc.)-make the AIS diagnosis harder- more often than men (33, 36-41). Furthermore, unique conditions for women such as menopause, hormone replacement therapy, and oral contraceptive use may differ the frequency and outcome of stroke from men (33). In brief, stroke and sex have a multivariate relation. The deeper we understand the linkage between sex and stroke, the more we prevent and treat the stroke.

Other risk factors

The most common AIS risk factor for the general study population was HT (44.7%). But when we examined the patients over and under 65 years, we noticed that the results changed. HT was still the most common risk factor for the older, while obesity ranked first for the younger (46.6%).

Stroke prevalence in the young generation has been increasing [42]. This may be associated with the increasing number of obesity. Per unit increase in body mass index (BMI) was related to a 6% increase in stroke risk [43]. However, an increase in obesity does not mean an increase in stroke-related mortality. Because the mortality rate in obese-stroke patients was found less than non-obese stroke patients-"the obesity paradox" [42,44]. However, using only BMI to define obesity was not satisfactory. We need some other determinants of obesity as abdominal obesity or visceral obesity [45,46]. More studies are required to comprehend stroke-obesity interaction more precisely.

Limitations

We had some limitations in our study. First, we searched RT practice by age and sex in the acute stroke period. But prospective-longterm studies would be beneficial to observe if the differences among age and sex groups continue or not. E.g., will men and women have similar conditions for accessing rehabilitation services, or will functionality (maintained or elevated mRS) after rehabilitation vary by age or sex? Secondly, time-mismatch (delayed arrival to hospital) was the most frequent reason for the none-RT situation. Yet, what caused this time-mismatch was unsearched because it was beyond this study's scope. Nevertheless, if subsequent studies investigate the reason, more stroke patients may get the treatment without time delay.

Conclusions

The frequency and outcomes of RT vary by age and sex in AIS patients. Older patients, especially older women, had less RT chance and higher mortality rates. Although we do not know all the effects of age and sex on stroke pathophysiology, we know that on-time RT increases the survival rate for all stroke patients.

List of abbreviations

RT: Reperfusion therapy
AIS: Acute ischemic stroke
tPA: Tissue plasminogen activator
EVT: Endovascular therapy
AS: Acute stroke
NICU: Neurointensive care unit
DM: Diabetes mellitus
AF: Atrial fibrillation
HT: Hypertension
MV: Mechanical ventilation
NIHSS: The National Health Stroke Scale
mRS: The Modified Rankin Scale
APACHE-II: Acute Physiology and Chronic Health Evaluation II
IQR: Interquartile range
BMI: Body mass index

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