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Evaluation of demographic/clinical features and hemorrhagic complications in patients with ischemic stroke who underwent reperfusion therapy

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ABSTRACT

The relationship between demographic/clinical characteristics, clinical outcomes and the development of hemorrhagic complications in patients with ischemic stroke who underwent reperfusion therapy has not been studied sufficiently. We have aimed to compare genders and age groups in terms of clinical features and outcome; and types of reperfusion treatments and clinical features regarding the development of hemorrhagic complications in patients with ischemic stroke who underwent recombinant tissue plasminogen activator (rtPA) and/or thrombectomy. Patients with acute ischemic stroke undergoing rtPA and/or thrombectomy were divided into six age groups. Parameters including hemorrhagic complications, anticoagulant and antiaggregant use, hyperlipidemia, smoking status, biochemical parameters, and comorbidities were documented. National Institutes of Health Stroke Scale (NIHSS) scores, modified Rankin Score (mRS) and Glasgow Coma Scale scores were recorded. Etiological classification of stroke was done. These parameters were compared in terms of age groups, genders, and hemorrhagic complications. Significant differences were found between age groups concerning hypertension, coronary artery disease, smoking status, and antiaggregant use. Rate of hemorrhagic complications in rtPA group was significantly lower when compared with other treatment groups. Hemorrhagic complications developed mostly in the rtPA+thrombectomy group. Among the patients who developed hemorrhagic complications, NIHSS scores on admission were found to be significantly lower in men than women. Admission, discharge, and 3rd month mRS values in men were significantly lower than those of women. Knowing demographic and clinical features of patients that may have an impact on the clinical course of ischemic stroke managed with reperfusion therapy will be useful in predicting the hemorrhagic complications and clinical outcomes.

Keywords: acute ischemic stroke, rtPA, thrombectomy, clinical features, hemorrhagic complications

Abbreviations:
NIHSS: National Institutes of Health Stroke Scale
mRS: modified Rankin Scale
rtPA: recombinant tissue plasminogen activator
HT: hypertension
DM: diabetes mellitus
CAD: coronary artery disease

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TGL: triglyceride
ICH: intracranial hemorrhage
IVT: intravenous thrombolysis

INTRODUCTION

Intravenous (IV) recombinant tissue plasminogen activator (rtPA) therapy and/or thrombectomy have been shown to be effective in acute ischemic stroke as the first-line treatments in selected cases.[1-4] Sometimes rtPA therapy is also used as a bridge therapy before thrombectomy. Early recanalization of occluded vascular blood flow in patients with acute ischemic stroke is associated with a good clinical prognosis. IV rtPA can be given within 4.5 hours after the onset of symptoms to ensure reperfusion and improve the clinical course.[5] Thrombectomy can be performed within the first 6–24 hours after onset of symptoms in selected cases.[6-8]

National Institutes of Health Stroke Scale (NIHSS) is a standard test used to determine the severity of stroke. It is a scoring scale that has been proven effective in determining the severity of ischemic damage. NIHSS scores range from 0 to 42 with higher scores indicating a more severe deficit. The modified Rankin Scale (mRS) is a widely used tool to measure the degree of disability or dependence in daily activities of people with neurological and non-neurological disabilities.[9] The mRS value of zero signifies asymptomatic and an excellent health state, and a score of six indicates death.[3,9] Reperfusion therapy may cause hemorrhagic complications including intracerebral hemorrhage. The complications developing after IV rtPA therapy and thrombectomy are associated with high morbidity and mortality rates.[10] The rtPA therapy alone increases the rate of symptomatic intracerebral hemorrhage 3-10-fold when compared with patients who do not receive rtPA.[3] Clinical, laboratory, and demographic characteristics of patients may play a role in the development of hemorrhagic complications. The risk factors of intracranial hemorrhage after reperfusion therapy are not yet precisely defined, and the implicated risk factors do not yet reliably predict morbidity and mortality.[11-13] Hence, it is crucial to identify beforehand the patients at risk for intracerebral hemorrhage complicating reperfusion therapy. Many demographic/clinical factors including patients' age, gender, hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), smoking, blood lipid profiles, blood sugar and HbA1c levels, etiologic factors of stroke, cardioembolic stroke, and stroke of undetermined source (small vessel occlusion, large artery atherosclerosis), pre-stroke mRS, admission NIHSS scores, renal functions, pre-stroke use of antiaggregant or anticoagulant drugs play a role both in the success of rtPA therapy and/or thrombectomy in ischemic stroke and also in the development of hemorrhagic complications. Herein, we have aimed to compare genders and age groups of the patients in terms of their clinical features and NIHSS/mRS values; and also to compare types of reperfusion treatments and clinical features regarding the development of hemorrhagic complications in patients with ischemic stroke who underwent rtPA and/or thrombectomy.

MATERIALS AND METHODS

Patients presenting with ischemic stroke who underwent reperfusion therapy (rtPA and/or thrombectomy) between January 2018 and March 2020 were retrospectively included in the study. Patients with acute ischemic stroke treated with rtPA or rtPA and endovascular thrombectomy within the first 4.5 hours of stroke, and those treated with endovascular thrombectomy within

the first 24 hours of stroke were included in the study. Among the patients receiving reperfusion therapy, those with bleeding foci evidenced in cerebral computed tomography or magnetic resonance imaging obtained after the first 24 hours of stroke were considered as the group with "hemorrhagic complications" (symptomatic or asymptomatic). This group included patients with hemorrhagic transformation of infarcted brain tissue, intracerebral hemorrhage within and beyond infarcted brain tissue, or intracranial extracerebral hemorrhage.

Medical information of all patients including the presence of hypertension, anticoagulant/antiaggregant drug use, hyperlipidemia (HL), and smoking history; biochemical test results (lipids, fasting blood glucose, HbA1c, creatinine) at hospital admission, comorbidities (CAD, DM), the etiology of stroke, NIHSS scores (at admission and 72nd hour), mRS values (at admission, discharge, and 3rd month), and Glasgow Coma Scale scores (at hospital admission) were documented. The criteria of Trial of ORG 10172 in Acute Stroke (TOAST)[14] were used for the etiological evaluation of patients' stroke. The TOAST classification has 5 categories: 1. Large artery atherosclerosis 2. Cardioembolism 3. Small vessel occlusion 4. Stroke from another known cause 5. Stroke of unknown cause. In our study, patients in groups 4 and 5 were considered as a single group.

To evaluate the effects of risk factors of ischemic stroke according to the age parameter in more detail, the patients were classified into six age groups as follows: ≤ 50, 51–60, 61–70, 71–80, 81–90, and > 90 years. The risk factors were compared according to the above-mentioned age groups and gender.

Patients with hematological diseases or malignancies and patients with traumatic hemorrhagic episodes were not included in the study.

Statistical analyses

Conformity of the parameters to normal distribution was investigated with Shapiro-Wilks test. Kruskal-Wallis test was used in the intergroup comparisons of descriptive statistical parameters (mean, standard deviation, frequency) and quantitative data that did not show normal distribution. Dunn's test was used to determine the group causing the intergroup difference. Comparisons of non-normally distributed parameters between the two groups were performed with Mann-Whitney U test. Additionally, chi-square test, Fisher-Freeman-Halton test, and Continuity (Yates) Correction test were used for the comparison of qualitative data. Statistical significance was accepted as $p<0.05$.

RESULTS

The study population with a median age of 73 years (range: 22–97 years) consisted of 226 (50.1%) male, and 225 (49.9%) female patients. The patients were hospitalized for a mean period of 10.14±11.14 days (range: 3–15 days). The mean (±SD) NIHSS scores were 11.41±5.31 (range 1–28) and 6.98±7.07 (range 0–28) on admission and at the 72nd hours of admission, respectively. The mean (±SD) Glasgow Coma Scale score of the patients at the time of admission to the hospital was 13.25±2.23 (range 3–15). The evaluated parameters of the patients (age groups, medical history, and etiology of ischemic stroke, type of reperfusion therapy, and rates of hemorrhagic complications) are listed in Table 1.

Table 1 Patients' age groups, medical conditions, etiologies of ischemic stroke, types of reperfusion therapy and hemorrhagic complication rates

		n	%
Age groups (years)	≤ 50	47	10.4
	51–60	58	12.9
	61–70	97	21.5
	71–80	114	25.3
	81–90	114	25.3
	> 90	21	4.7
Hypertensive patients		296	65.6
Patients with diabetes mellitus		143	31.7
Patients with coronary artery disease		144	31.9
Smokers		174	39.1
Hyperlipemic patients		50	11.1
Anticoagulant users		42	9.3
Antiaggregant users		179	39.7
Etiologies of ischemic stroke (TOAST)	Small vessel occlusion	36	8.2
	Large artery atherosclerosis	62	14.2
	Cardioembolism	210	47.9
	Other or undetermined etiology	130	29.7
Types of reperfusion treatment	rtPA	228	50.6
	Thrombectomy	129	28.6
	rtPA+Thrombectomy	94	20.8
Patients with hemorrhagic complications		119	27.0

rtPA: recombinant tissue plasminogen activator
TOAST: Trial of ORG 10172 in Acute Stroke

Comparison of demographic and some clinical parameters according to age groups

In all cases. When compared according to the age groups, significant differences were found concerning the history of HT, CAD, smoking, and antiaggregant use (Table 2).

In men. When compared according to age groups, significant differences were found regarding the history of CAD, smoking, and antiaggregant use (Table 3).

In women. When compared according to age groups, significant differences were found regarding the history of HT and smoking (Table 3).

Table 2 Comparison of the age groups with some demographic and clinical parameters in all cases

Age groups (years)	≤ 50 n (%)	51–60 n (%)	61–70 n (%)	71–80 n (%)	81–90 n (%)	> 90 n (%)	*p*-value
HT	18 (38.3)	29 (50.0)	61 (62.9)	85 (74.6)	85 (74.6)	18 (85.7)	0.000*
DM	7 (14.9)	17 (29.3)	40 (41.2)	37 (32.5)	36 (31.6)	6 (28.6)	0.063
CAD	5 (10.6)	14 (24.1)	38 (39.2)	35 (30.7)	48 (42.1)	4 (19.0)	0.001*
Smoking	31 (66.0)	36 (62.1)	54 (55.7)	34 (30.4)	19 (17.3)	0 (0.0)	0.000*
HL	2 (4.3)	7 (12.1)	13 (13.4)	16 (14.0)	12 (10.6)	0 (0.0)	0.265
ANTICO	3 (6.4)	0 (0.0)	14 (14.4)	12 (10.5)	10 (8.8)	3 (14.3)	0.067
ANTIAG	6 (12.8)	21 (36.2)	46 (47.4)	44 (38.6)	53 (46.5)	9 (42.9)	0.002*

HT: hypertension
DM: diabetes mellitus
CAD: coronary artery disease
HL: hyperlipidemia
ANTICO: anticoagulant users
ANTIAG: antiaggregant users
*$p<0.05$.

Table 3 Comparison of the age groups with some demographic and clinical parameters in men and women

	Age groups (years)	≤ 50 n (%)	51–60 n (%)	61–70 n (%)	71–80 n (%)	81–90 n (%)	> 90 n (%)	*p*-value
Men	**HT**	17 (47.2)	18 (42.9)	38 (62.3)	32 (62.7)	25 (75.8)	2 (66.7)	0.055[a]
	DM	7 (19.4)	12 (28.6)	24 (39.3)	11 (21.6)	9 (27.3)	1 (33.3)	0.283[a]
	CAD	5 (13.9)	9 (21.4)	27 (44.3)	16 (31.4)	18 (54.5)	2 (66.7)	0.001*[a]
	Smoking	26 (72.2)	30 (71.4)	45 (73.8)	28 (56.0)	12 (37.5)	0 (0.0)	0.001*[a]
	HL	2 (5.6)	6 (14.3)	9 (14.8)	7 (13.7)	3 (9.4)	0 (0.0)	0.766[b]
	ANTICO	3 (8.3)	0 (0.0)	9 (14.8)	2 (3.9)	3 (9.1)	0 (0.0)	0.074[b]
	ANTIAG	4 (11.1)	14 (33.3)	28 (45.9)	22 (43.1)	19 (57.6)	3 (100.0)	0.000*[a]
Women	**HT**	1 (9.1)	11 (68.8)	23 (63.9)	53 (84.1)	60 (74.1)	16 (88.9)	0.000*[a]
	DM	0 (0.0)	5 (31.3)	16 (44.4)	26 (41.3)	27 (33.3)	5 (27.8)	0.108[b]
	CAD	0 (0.0)	5 (31.3)	11 (30.6)	19 (30.2)	30 (37.0)	2 (11.1)	0.083[b]
	Smoking	5 (45.5)	6 (37.5)	9 (25.0)	6 (9.7)	7 (9.0)	0 (0.0)	0.000*[a]
	HL	0 (0.0)	1 (6.3)	4 (11.1)	9 (14.3)	9 (11.1)	0 (0.0)	0.569[a]
	ANTICO	0 (0.0)	0 (0.0)	5 (13.9)	10 (15.9)	7 (8.6)	3 (16.7)	0.313[a]
	ANTIAG	2 (18.2)	7 (43.8)	18 (50.0)	22 (34.9)	34 (42.0)	6 (33.3)	0.426[b]

HT: hypertension
DM: diabetes mellitus
CAD: coronary artery disease
HL: hyperlipidemia
ANTICO: anticoagulant users
ANTIAG: antiaggregant users
*$p<0.05$.
[a]Chi-square test.
[b]Fisher-Freeman-Halton test.

Comparison of triglyceride, low-density lipoprotein, and high-density lipoprotein values according to age groups

In all cases. When compared according to the age groups, significant intergroup differences were found concerning triglyceride (TGL) and high-density lipoprotein (HDL) values. TGL values were significantly lower in the 81–90 age group than in the age groups of ≤ 50, 51–60, 61–70, and 71–80 years (p=0.000; p=0.000; p=0.000, and p=0.014, respectively). In addition, TGL values were lower in the age group of > 90 years than those in the age groups of ≤ 50 and 51–60 years (p=0.037, and p=0.014, respectively). HDL values were significantly lower in the group aged ≤ 50 years than in the groups aged 81–90 and > 90 years (p=0.006, and p=0.024, respectively; Table 4).

In men. When compared according to the age groups, a significant intergroup difference was found in terms of TGL values; however, low-density lipoprotein (LDL) and HDL values were not significantly different between age groups. TGL values were significantly lower in the 81–90 age group when compared with the age groups of ≤ 50 and 51–60 years (p=0.001, and p=0.002, respectively; Table 4).

In women. When compared according to the age groups, a significant intergroup difference was found concerning TGL and LDL values. TGL values in the 61–70 age group were significantly different than in the groups aged 81–90 and > 90 years (p=0.000, and p=0.028, respectively,). TGL values of the age group of 71–80 years were found to be higher than those in the 81–90 age group (p=0.026). LDL values were significantly higher in the 51–60 age group than those in the > 90 age group (p=0.019). HDL values were not significantly different among age groups (Table 4).

Table 4 Comparison of age groups with TGL, LDL and HDL parameters in all cases, men, and women

Age groups (years)		≤ 50 Mean±SD	51–60 Mean±SD	61–70 Mean±SD	71–80 Mean±SD	81–90 Mean±SD	> 90 Mean±SD	*p*-value[a]
All cases	TGL	142.27±70.62	151.91±97.33	142.01±89.04	119.64±55.18	96.60±43.26	97.20±43.72	0.000*
	LDL	115.28±33.42	134.39±62.84	124.47±34.06	119.96±33.60	121.83±36.40	108.31±37.21	0.142
	HDL	36.75±10.07	39.05±10.57	40.33±12.24	41.97±11.25	43.64±12.20	49.15±17.34	0.002*
Men	TGL	154.14±73.31	157.93±105.92	137.38±97.61	113.77±56.49	89.38±28.88	74.33±6.51	0.000*
	LDL	114.89±33.15	121.67±40.91	124.70±36.11	110.76±31.97	121.52±34.55	93.47±45.13	0.306
	HDL	34.71±8.48	37.05±8.76	39.20±11.49	38.79±9.52	41.14±11.80	37.00±10.54	0.175
Women	TGL	96.11±30.83	135.47±69.05	149.97±72.78	124.25±54.16	99.32±47.45	101.24±46.36	0.000*
	LDL	116.80±36.48	168.32±94.20	124.08±30.86	127.17±33.33	121.95±37.30	110.93±36.62	0.036*
	HDL	44.67±12.28	44.53±13.24	42.31±13.42	44.47±11.92	44.58±12.28	51.29±17.62	0.743

TGL: triglyceride
LDL: low-density lipoprotein
HDL: high-density lipoprotein
*$p<0.05$.
[a]Kruskal-Wallis test.

Comparisons between age groups and NIHSS scores

There was no significant difference between the age groups and the NIHSS scores on the day of admission and at the 72nd hour in all cases (p>0.05; Table 5).

Table 5 Comparison of age groups and NIHSS scores in men, women and in all cases

Age groups (years)		≤ 50 Mean ±SD	51–60 Mean ±SD	61–70 Mean ±SD	71–80 Mean ±SD	81–90 Mean ±SD	> 90 Mean ±SD	*p*-value[a]
Men	**Adm**	10.31±5.72	10.26±5.39	10.31±5.64	10.65±4.88	11.58±5.81	7.67±2.52	0.802
	72nd hour	5.74±7.27	6.88±6.81	5.82±7.02	6.76±7.47	8.34±6.87	3.33±0.58	0.298
Women	**Adm**	11.91±5.24	12.63±4.52	12.33±5.64	12.79±4.80	11.81±5.24	12.56±4.74	0.935
	72nd hour	7.18±6.95	6.06±8.09	6.61±7.57	7.17±7.16	8.15±7.03	7.94±5.66	0.509
All cases	**Adm**	10.70±5.59	10.91±5.24	11.06±5.69	11.83±4.93	11.75±5.38	11.86±4.78	0.621
	72nd hour	6.09±7.14	6.64±7.13	6.11±7.19	6.99±7.27	8.21±6.96	7.29±5.48	0.080

NIHSS: National Institutes of Health Stroke Scale
Adm: on admission
[a]Kruskal Wallis test.

Comparison between age groups and mRS values

When compared according to the age groups, significant differences were found in terms of mRS values in all cases.

In all cases. The mRS values at admission in the age group of > 90 years were significantly higher than those in the age groups of ≤ 50, 51–60, 61–70, and 71–80 years (p=0.000; p=0.000; p=0.000, and p=0.009, respectively). The admission mRS values in the age group of 81–90 years were significantly higher than those in the groups aged ≤ 50, 51–60, 61–70, and 71–80 years (p=0.000; p=0.000; p=0.000; p=0.018, respectively). The admission mRS values in the age group of 71–80 years were significantly higher than those in the groups aged ≤ 50 and 51–60 years (p=0.000). The admission mRS values in the 61–70 age group were significantly higher than those in the age group of ≤ 50 years (p=0.007; Table 6). The discharge mRS values of the 81–90 age group were significantly higher than the age groups of ≤ 50, 51–60, and 61–70 years (p=0.001; p=0.000; p=0.003, respectively; Table 6). The 3rd month mRS values of > 90 years age group were significantly higher than the groups aged ≤ 50 and 51–60 years (p=0.002). The 3rd month mRS values of the group aged 81–90 years were significantly higher than those of the age groups of ≤ 50, 51–60, and 61–70 years (p=0.000; p=0.000, and p=0.002, respectively; Table 6).

In men. The mRS values in the age group of > 90 years were significantly higher than those of the groups aged ≤ 50 and 51–60 years (p=0.009 and p=0.020, respectively). The admission mRS values of the group aged 81–90 years were found to be significantly higher than the groups aged ≤ 50, 51–60, and 61–70 years (p=0.000; p=0.000; and p=0.001, respectively). The admission mRS values of the group aged 71–80 years were found to be significantly higher than those of the groups aged ≤ 50 and 51–60 years (p=0.000; and p=0.004, respectively). The admission mRS values in the 61–70 age group were found to be significantly higher than the age group of ≤ 50 years (p=0.041; Table 6). The mRS values in the 81–90 age group at discharge were found to be significantly higher than the group aged ≤ 50 years (p=0.021; Table 6). The 3rd month mRS values of the group aged 81–90 years were significantly higher than the groups aged ≤ 50 and 51–60 years (p=0.006 and p=0.008, respectively; Table 6).

In women. Admission mRS values in the group aged > 90 years were significantly higher than those aged ≤ 50, 51–60, and 61–70 years (p=0.000; p=0.007, and p=0.005, respectively). The admission mRS values of the 81–90 age group were significantly higher than those of the age groups of ≤ 50, 51–60, and 61–70 years (p=0.000; p=0.034; p=0.012, respectively). The admission mRS values of the 71–80 age group were significantly higher than those of the age groups of ≤ 50 years (p=0.019; Table 6). The discharge mRS values of the 81–90 age group were significantly higher relative to the age group of 51–60 years (p=0.032; Table 6). The 3rd

month mRS values of the age group of 81–90 years were significantly higher relative to the age group of 51–60 years (p=0.024; Table 6).

Table 6 Comparison of age groups with mRS values in all cases, men, and women

Age groups (years)		≤ 50 Mean± SD	51–60 Mean± SD	61–70 Mean± SD	71–80 Mean± SD	81–90 Mean± SD	> 90 Mean± SD	*p*-value[a]
All cases	**Adm**	0.15±0.36	0.37±0.67	0.69±0.95	1.00±0.92	1.43±1.00	1.90±1.04	0.000
	Disch	2.36±2.36	2.28±2.15	2.66±2.26	3.11±2.22	3.76±2.07	3.67±1.56	0.000
	3rd mo	2.36±2.68	2.37±2.65	3.15±2.97	3.61±2.90	4.65±2.92	5.15±2.80	0.000
Men	**Adm**	0.14±0.35	0.27±0.63	0.56±0.65	0.84±0.90	1.30±0.81	2.00±1.00	0.000
	Disch	2.31±2.27	2.39±2.07	2.51±2.16	3.04±2.22	3.94±2.33	4.33±3.22	0.012
	3rd mo	2.43±2.75	2.39±2.53	2.90±2.77	3.55±2.99	4.97±3.19	6.33±2.89	0.001
Women	**Adm**	0.18±0.41	0.63±0.72	0.92±1.30	1.13±0.92	1.48±1.07	1.89±1.08	0.000
	Disch	2.55±2.77	2.00±2.39	2.92±2.43	3.17±2.23	3.68±1.97	3.56±1.25	0.019
	3rd mo	2.10±2.56	2.31±3.03	3.58±3.27	3.65±2.85	4.52±2.81	4.94±2.82	0.002

mRS: modified Rankin Scale
Adm: on admission
Disch: at discharge
3rd mo: at 3rd month
[a]Kruskal Wallis test.

Comparison of demographic and some clinical parameters with the type of reperfusion therapy

There was no significant difference between the type of reperfusion therapy (rtPA, thrombectomy, or rtPA+thrombectomy) and age groups, presence of HT, DM, CAD, HL, smoking, antiaggregant use (p>0.05). However, a significant difference was found between the treatment groups and the history of anticoagulant use (p=0.000).

Comparison of hemorrhagic complications with demographic and some clinical parameters

There was no significant difference between the hemorrhagic complication rates and age groups, gender, and etiology of stroke (p>0.05). In addition, no significant difference was found between hemorrhagic complication rates and the history of HT, DM, CAD, HL, anticoagulant, and antiaggregant drug used (p>0.05; Table 7).

Hemorrhagic complication rates and the type of reperfusion therapy

Hemorrhagic complications developed in 27.1% of the patients. In all patients, the hemorrhagic complication rates in the rtPA treatment group were significantly lower than the other two treatment groups (p=0.001). However, there was no statistically significant difference between the groups that received only thrombectomy or rtPA+thrombectomy in terms of the hemorrhagic complication rates (p>0.05; Table 8).

Evaluation of NIHSS and mRS parameters according to gender in patients with hemorrhagic complications

The admission NIHSS scores of men were found to be significantly lower than those of women (Table 9). Admission, discharge, and 3rd month mRS values of men were significantly lower than those of women (Table 9).

Table 7 Comparison of hemorrhagic complications with some demographic and clinical parameters

		Hemorrhagic complications		*p*-value
		No - n (%)	**Yes - n (%)**	
Age groups (years)	≤ 50	35 (74.5)	12 (25.5)	0.470[a]
	51–60	36 (63.2)	21 (36.8)	
	61–70	75 (78.1)	21 (21.9)	
	71–80	78 (70.9)	32 (29.1)	
	81–90	81 (74.3)	28 (25.7)	
	> 90	16 (76.2)	5 (23.8)	
Gender	Male	158 (71.8)	62 (28.2)	0.592[a]
	Female	163 (74.1)	57 (25.9)	
Etiology of stroke (TOAST)	SVO	31 (86.1)	5 (13.9)	0.173[a]
	LAA	46 (75.4)	15 (24.6)	
	CE	153 (75.0)	51 (25.0)	
	Other or undetermined etiology	89 (68.5)	41 (31.5)	
Hypertension	No	111 (34.6)	43 (36.1)	0.761[a]
	Yes	210 (65.4)	76 (63.9)	
Diabetes mellitus	No	216 (67.3)	84 (70.6)	0.509[a]
	Yes	105 (32.7)	35 (29.4)	
CAD	No	223 (69.5)	78 (65.5)	0.432[a]
	Yes	98 (30.5)	41 (34.5)	
Smoking	No	196 (62.0)	68 (57.6)	0.404[a]
	Yes	120 (38.0)	50 (42.4)	
Hyperlipidemia	No	289 (90.3)	101 (84.9)	0.150[b]
	Yes	31 (9.7)	18 (15.1)	
Anticoagulant use	No	288 (89.7)	110 (92.4)	0.497[b]
	Yes	33 (10.3)	9 (7.6)	
Antiaggregant use	No	196 (61.1)	69 (58.0)	0.558[a]
	Yes	125 (38.9)	50 (42.0)	

TOAST: Trial of ORG 10172 in Acute Stroke
SVO: small vessel occlusion
LAA: large artery atherosclerosis
CE: cardioembolism.
CAD: coronary artery disease
[a]Chi-square test.
[b]Continuity (Yates) Correction.

Table 8 Hemorrhagic complications by type of reperfusion treatment

rtPA/ Thrombectomy		Hemorrhagic complications		**Total (N)**	***p*-value[a]**
		No	Yes		
rtPA	**N (%)**	191 (83.8)	37 (16.2)	228	
Thrombectomy	**N (%)**	83 (64.3)	46 (35.7)	129	0.001
rtPA + Thrombectomy	**N (%)**	58 (61.7)	36 (38.3)	94	
Total	**N**	332 (73.6)	119 (26.4)	451	

rtPA: recombinant tissue plasminogen activator
[a]Chi-square test.

Table 9 Comparison of the levels of NIHSS and mRS parameters according to gender in patients with hemorrhagic complications

		Men Mean±SD (median)	Women Mean±SD (median)	*p*-value[a]
NIHSS	On admission	10.53±5.41 (10)	12.29±5.06 (12)	0.000*
	72nd hour	6.53±7.04 (4)	7.43±7.08 (5)	0.106
mRS	On admission	0.63±0.81 (0)	1.20±1.09 (1)	0.000*
	At discharge	2.80±2.26 (3)	3.23±2.18 (3)	0.035*
	3rd month	3.22±2.95 (2)	3.88±2.98 (3)	0.009*

NIHSS: National Institutes of Health Stroke Scale
mRS: modified Rankin Scale
*$p<0.05$.
[a]Mann-Whitney U test.

DISCUSSION

We have investigated some demographic/clinical characteristics and hemorrhagic complications in patients with acute ischemic stroke who underwent rtPA therapy and/or thrombectomy. These parameters were investigated according to the gender and in six different age groups. In patients who developed hemorrhagic complications, the admission NIHSS scores of men were lower than those of women. In addition, mRS values of men on hospital admission, discharge, and 3rd months were found to be lower than those of women. The frequency of hemorrhagic complications in the group receiving rtPA treatment was significantly lower than the groups that received other treatments. Hemorrhagic complications developed mostly in the group that was treated with rtPA+thrombectomy.

Genetic, demographic, and many other clinical risk factors play a role in the pathophysiology of stroke. Stroke is more common in women than men.[15,16] Hormonal activities that induce hypercoagulability are different in women, which may affect predisposition to stroke.[17-19] Decrease in the amount of estrogen, which has a neuroprotective effect in advanced age, may play a role in stroke. Cardioembolic stroke is more common in women.[20,21] In addition, factors such as age,[22-25] comorbidities, pre-stroke functional status,[23,24] and severity of stroke[20,26] may play a role regarding the differences between men and women regarding the incidence of stroke. Genetic variations in fibrinolysis inhibitors and time of arrival at the hospital after the onset of stroke symptoms[22,23] may also play a role in the different incidence rates of stroke observed between male and female patients.[26] In a meta-analysis examining gender differences in reperfusion therapy, the rate of rtPA administration in female patients was found to be 30% lower than male patients due to higher pre-stroke incidence of hypertension in women.[27] Previously, different age-related prognoses of men and women after IV rtPA therapy in acute ischemic stroke have been reported.[28] Although a better clinical response to rtPA therapy has been reportedly obtained in middle-aged women than men, the reverse is true in advanced age.[29] Additionally, no difference in clinical course has been reported between male and female patients who received thrombolytic therapy.[30,31] Some studies have shown a worse functional outcome in untreated women than men.[32] In our study, there was no significant difference between the treatment groups in terms of age groups, genders; history of HT, DM, CAD, HL, smoking, and antiaggregant use. However, a significant difference was observed between treatment groups regarding rates of anticoagulant use. IV-rtPA therapy is not applied to patients with acute ischemic stroke receiving anticoagulants; however,

these patients may benefit from mechanical thrombectomy.[33]

The clinical course after treatment with rtPA is rather favorable in men and women whose HT can be controlled.[34] In our study, although the rate of HT in women presenting with ischemic stroke was higher in advanced age groups, our older patients had better blood pressure control and met the criteria for rtPA therapy, accordingly rtPA application rate in these hypertensive women was higher than in some other studies.[18,35,36]

Some comments were made suggesting that women did not come to the hospital in case of mild clinical findings or came late, most elderly women lived alone, and could not receive rtPA therapy for their uncontrolled hypertension.[28] On the contrary, in our study group, almost equal number of men and female patients were treated with rtPA and/or thrombectomy. In our country, elderly women who lost their spouses generally live in extended families or in nursing homes, and in case of stroke they are brought to the hospital within a short time by their relatives.

In our study, the rate of smoking, which is one of the important risk factors for stroke was higher in younger age groups. Smoking is directly related to recanalization and reperfusion, and smokers with stroke respond better to rtPA therapy than non-smokers (smoking paradox theory).[37-39] The underlying mechanism involved is not fully understood.

The rtPA treatments were evaluated in a group of male and female patients with dyslipidemic stroke.[18] Dyslipidemia is closely associated with age and clinical factors such as carotid artery stenosis and stroke. Blum et al commented that effective use of lipid-lowering therapy in elderly dyslipidemic patients will favorably affect the prognosis of stroke after rtPA therapy.[18] The importance of gender and age as risk factors for stroke in dyslipidemia cannot be ignored. Our findings have also emphasized that dietary regulation and treatment for dyslipidemia should be planned according to age group and gender of the patients.

Intracranial hemorrhage (ICH) developed in 14% of the patients treated with intravenous thrombolysis (IVT) and 41% of those patients treated with endovascular therapy with or without IVT.[40] IVT applied before mechanical thrombectomy was reported as an independent risk factor for ICH. In those receiving endovascular treatment, DM, treatment with mechanical thrombectomy, and higher baseline NIHSS scores were found to be independent predictors of ICH.[12] Whether the application of IVT before mechanical thrombectomy increases the risk of ICH is still a controversial issue.[13] In a study, IVT applied before mechanical thrombectomy was stated as the most important predictor of ICH,[40] and IVT alone was independently associated with a lower risk of parenchymal hemorrhage.[40] In our study, hemorrhagic complication rates were significantly different according to the treatment type received (rtPA: 16.2%; thrombectomy: 35.7%, and rtPA+thrombectomy: 38.3%). Hence, the frequency of hemorrhagic complications in the group receiving rtPA therapy was found to be significantly lower than the other two treatment groups.

It has been shown that advanced age (age>75), high blood pressure, severe stroke, antithrombotic therapy received before reperfusion treatment, history of hypertension and hyperlipidemia are important risk factors for symptomatic intracerebral hemorrhage following rtPA therapy.[41] In our study, there was no significant correlation between hemorrhagic complications and predisposing factors for ICH including HT, DM, HL, smoking status, CAD, anticoagulant/antiaggregant use in all patient groups. Besides any significant difference was not found between the hemorrhagic complication rates in terms of age, gender, and etiologic subtypes of ischemic stroke.

Pharmacological thrombolysis, atrial fibrillation, and high NIHSS scores were reported as independent risk factors for parenchymal hemorrhage emerging after endovascular therapy[12]; In another study, delayed treatment, lower Alberta Stroke Program Early CT Scores (ASPECTS), and wake-up stroke were found as risk factors for the development of hemorrhagic complications.[6] In our study, there was no significant difference between men, women, and age groups in terms of the NIHSS scores at admission and 72nd hours. In the group that developed hemorrhagic

complications, the NIHSS scores of men were found to be significantly lower than those of women. This supports the information in the literature that the symptoms of stroke in men are milder than in women.[18,19] However, in our patient group with hemorrhagic complications, the lower admission NIHSS scores in men suggest that the risk of bleeding may be higher in men, even if they had experienced milder clinical symptoms.

The impact of reperfusion therapy on prognosis in the treatment of stroke in patients with high mRS values before reperfusion treatment is also a controversial issue.[9] In our study, mRS values in the total group differed according to age groups in men and women. Our results have shown that admission mRS values were higher in the elderly group compared to younger age groups which persisted at discharge and 3 months later. Compatible with the literature, our results have shown that the elevated mRS values before reperfusion therapy persisted at discharge and in the 3rd month of treatment in elderly men and women with ischemic stroke.

In our study, mRS values of patients with hemorrhagic complications detected on admission, discharge, and 3 months after reperfusion therapy were significantly lower in men than women. These findings show that although admission mRS values are lower in men with hemorrhagic complications, hemorrhagic complications more frequently develop after reperfusion therapy. Despite this fact, in our study, unfavorable impact of these complications in men on clinical course of the disease were not observed after discharge and in the 3rd month.

NIHSS scores of men with ischemic stroke and their hemorrhagic complications were seen at a significantly lower rate when compared with those of women.

The success of rtPA and/or thrombectomy treatment in ischemic stroke may be influenced by several factors such as patients' age, gender, clinical history (HT, DM, HL, smoking status, pre-stroke antiaggregant or anticoagulant use), biochemical, and functional parameters (blood lipid profiles, renal functions, blood sugar, HbA1c levels), the etiology of stroke (small vessel occlusion, large artery atherosclerosis, cardioembolic stroke, strokes related to other or undetermined etiologies), pre-stroke mRS, and admission NIHSS scores. These factors may also play a role in the development of hemorrhagic complications after treatment. We have also found differences in the rates of these factors depending on the age groups and genders of the patients presenting with ischemic stroke and undergoing reperfusion therapy. When the group that received reperfusion therapy and developed hemorrhagic complications was examined, we have found differences in terms of admission NIHSS and mRS values. We have shown that the evaluation of risk factors for ischemic stroke according to age groups and genders of patients is important in terms of providing detailed information helpful in predicting treatment complications and clinical course. In the literature, there is scarce data on rtPA and/or thrombectomy treatment in patients aged over 90 years. Our study contributes data to the literature in terms of demographic and clinical factors effecting reperfusion treatment and development of hemorrhagic complications in this age group.

The limitations of our study are the lack of assessment of ASPECTS, mortality rates, measurements of posttreatment blood pressures, and blood glucose values.

CONCLUSIONS

Significant differences were found between different age groups concerning the history of HT and CAD, smoking, and antiaggregant use. Among patients with ischemic stroke who were treated with rtPA and/or thrombectomy and developed hemorrhagic complications, the admision NIHSS scores of male patients were found to be lower than those of female cases. The mRS values of male patients on hospital admission, at discharge, and at 3rd month were found to be lower than those of female cases. These findings show that men with stroke present with

milder clinical findings, and even if hemorrhagic complications develop after reperfusion treatment, the favorable clinical course persists. The frequency of hemorrhagic complications in the group receiving rtPA treatment was significantly lower relative to the other treatment groups. Hemorrhagic complications developed mostly in the group that received combined treatment with rtPA and thrombectomy. Investigating the effects of demographic and clinical features on clinical course of ischemic stroke in patients undergoing reperfusion treatment will be useful in predicting hemorrhagic complications and clinical outcome. In addition, since the frequency of hemorrhagic complications after rtPA and/or thrombectomy in ischemic stroke patients differs widely, our findings will be useful in determining the type of reperfusion therapy to be applied in consideration of the risk factors of the patient.

There is a need for the conduction of further and larger-scale prospective studies investigating the effects of clinical and demographic parameters on prognosis and hemorrhagic complications.

ETHICAL APPROVAL

This retrospective study was performed in accordance with the ethical principles stated in the 1964 Declaration of Helsinki and its later amendments and approved by Clinical Trials Ethics Committee of Fatih Sultan Mehmet Training and Research Hospital (approval issue 2020/132, date 09.10. 2020).

CONSENT TO PARTICIPATE

This study was evaluated by the Scientific Evaluation Commission of Fatih Sultan Mehmet Training and Research Hospital and decided in its 5th meeting held on 06.22.2021 that there is no objection in using archival data of the patients.

CONFLICTS OF INTEREST

The authors have no conflict of interest to declare.

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