



The Potential risk factors of Ischemic stroke incidence and mortality

Hamid Reza Mehryar¹, Behrang Khaffafi², Faezeh Shadfar³, Hadi Khoshakhlagh², Farzin Rezazadeh², Babak Choobi anzali^{4*}

¹ Assistant Professor of Emergency Medicine, Clinical Research Development Unit of Imam Khomeini Hospital, Urmia University of Medical Sciences, Urmia, Iran

² Assistant Professor of Emergency Medicine, Urmia University of Medical Sciences, Urmia, Iran

³ Student Research Committee, Faculty of Pharmacy, Department of Pharmacotherapy, Mazandaran University of Medical Sciences, Sari, Iran

⁴ Assistant Professor of Emergency Medicine, Urmia University of Medical Sciences, Urmia, Iran

***Corresponding authors:** Babak Choobi Anzali, **Address:** Department of Emergency Medicine, Urmia University of Medical Sciences, Urmia, Iran, **Email:** anzalibabak@yahoo.com, **Tel:** +989143415627

Abstract

Background & Aims: Ischemic stroke is always more common than hemorrhagic type. Approximately, 80% of the risk factors involved in the pathogenesis of stroke are modifiable. Identification and correction of these risk factors contributes to reducing the risk of stroke incidence, subsequent clinical consequences, disabilities, costs, and mortality of these patients.

Materials & Methods: In this retrospective cross-sectional study, 1,572 patients with ischemic stroke hospitalized during 2008-2015 were investigated. Patients data was collected in a questionnaire containing demographic information, drug and disease history, laboratory findings and events during hospitalization and follow-up period.

Results: Among 1,572 patients, 744 (47.3%) were male and 828 (52.7%) female. The number of patients who died during hospitalization was 252 (16%) and 453 (34.3%) died during the follow-up period. The most important modifiable risk factors for stroke incidence included smoking, hypertension, dyslipidemia, and diabetes mellitus. Also, the use of aspirin in both genders and statin consumption in males was associated with decreased rate of mortality. A series of laboratory findings, such as increased urea, creatinine, fasting blood glucose, cholesterol and neutrophil count, was associated with an increased risk of mortality as well as, decreased lymphocyte count, increased RBC, hemoglobin, platelet count, and triglyceride were associated with a reduction in stroke mortality.

Conclusion: This study confirms the results of previous studies about modifiable risk factors of ischemic stroke incidence such as diabetes, hypertension, dyslipidemia, and smoking. Laboratory findings such as neutrophil, lymphocyte, platelet count, hemoglobin, urea, RBC, lipid and glucose profiles associated with ischemic stroke mortality. Life style modification and preventive medication such as aspirin and statins reduce the risk of stroke incidence, disability and mortality of ischemic stroke in the community.

Keywords: Ischemic stroke, Incidence, Mortality

Received 16 Sep 2018; accepted for publication 19 Nov 2018

Introduction

Stroke is the second worldwide cause of death and functional disability(1). Its global prevalence in 2010 was 33 million cases(2). Every 40 second, one new cases of stroke have been occurred(1). Ischemic stroke is the most common subtype of stroke which caused by occlusion in intracranial arteries(2). In 2009, approximately \$ 68.9 billion was spent on stroke treatment, with 75% of the cost associated with the first year of stroke (3). There are a variety of risk factors which impact on stroke incidence. These risk factors include hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, carotid stenosis, intracranial stenosis, patent foramen oval, hyperuricemia, sleep breathing disorders, smoking, salt and alcohol consumption, obesity, etc.(2, 4). Recent studies explained that 85% of strokes are preventable and the modification of life style decreased its incidence by up to 42% in developed countries(4).

In this retrospective study, we investigated the effect of various risk factors on ischemic stroke incidence/mortality and with these considerations, a corrective action plan to reduce the incidence/mortality rate, as well as the costs and complications which burdened on the medical system.

Methods

Study design and setting:

The present study is a retrospective cross-sectional study which performed on all patients were hospitalized for diagnosis of ischemic stroke at Imam Khomeini Hospital of Urmia (Iran) between 2008-2015. Ischemic stroke is a focal neurologic deficit detected by imaging techniques and specialist confirmation.

Participants and Sampling:

Inclusion criteria included all patients with ischemic stroke diagnosis hospitalized between 2008-2015 and exclusion criteria were patients who died for any reason other than stroke and whom that their family did not have enough information about patient's stroke history.

Data gathering:

A questionnaire containing patient's medical records including demographic information such as age, sex,

history of smoking/alcohol use, drug history, history of diseases such as diabetes mellitus, myocardial infarction, ischemic heart disease, hypertension, heart failure, atrial fibrillation, as well as present illness, nursing reports, stroke type (ischemic or thrombotic) and location of lesion, laboratory data, Doppler sonography results, events during hospitalization/follow-up and death were recorded and the correlation between the collected data and the rate of stroke incidence/death of patients with ischemic stroke was analyzed.

Statistical Analysis:

Data analysis was done by SPSS. Version 20 (SPSS Inc., Chicago, IL, USA). Quantitative variables had been shown as mean \pm SD and qualitative variables as numbers (percentage). To compare the frequency of qualitative variables among dead and survived patient's as well as between two genders, chi-square and fisher tests had been used. Comparison of quantitative variables was done by using Independent T-test in normal distribution or Mann Whitney U test in non-normalized data. Logistic regression had been used to calculate the odds ratio for each of the variables in patients who died or survived. P-values less than 0.05 were considered statistically significant.

Results

In this analytical study, the medical files of patients with ischemic stroke between 2008-2015 were investigated. Among 1572 cases, 744(47.3%) cases were males and 828 (52.7%) were females. The number of patients died during hospitalization was 252 (16%) and from 1320 follow-up patients, 453 (34.3%) died during the study. The mean age of patients was 67 ± 14.64 years. The mean period of follow-up was 41.7 ± 21.6 months.

Comparison of the frequency of variables based on gender showed that the prevalence of the history of hypertension (P-value=0.002, OR:0.70), diabetes mellitus (P-value<0.001, OR:0.68), and post-admission antiarrhythmic agents use (P-value=0.030, OR:0.34) were significantly higher in females than males. But, the

history of smoking in males was significantly higher than females (P-value<0.001, OR:2.37) (table.4).

The comparison of the frequency of variables in dead and survived patients demonstrated that the prevalence of hypertension (P-value<0.001, OR:2.13), diabetes mellitus (P-value<0.001, OR:1.74), dyslipidemia (P-value<0.001, OR:1.75), myocardial infarction (P-value<0.001, OR:7.47), congestive heart diseases (P-value<0.001, OR:4.20), coronary disease (P-value<0.001, OR:7.47), vascular events (P-value<0.001, OR:3.76), coronary surgery (P-value=0.001, OR:2.71), angioplasty/stent (P-value<0.001, OR:4.21), and smoking (P-value=0.009, OR:1.42) were significantly higher in dead patients than survived patients. As well as, statin (P-value=0.042, OR:0.79) and aspirin (P-value<0.001, OR:0.59) use after admission significantly decreased the rate of mortality among the patients (table.5).

As well as, our study showed a significant correlation between the history of hypertension (males: P-value<0.001, OR:1.92) (females: P-value<0.001, OR:2.52), diabetes mellitus (males: P-value<0.001, OR:1.89) (females: P-value=0.003, OR:1.65), dyslipidemia (males: P-value=0.002, OR:1.83) (females: P-value=0.004, OR:1.69), congestive heart failure (males: P-value<0.001, OR:4.71) (females: P-value<0.001, OR:3.79), myocardial infarction (males: P-value<0.001, OR:3.03) (females: P-value<0.001, OR:3.43), vascular events (males: P-value<0.001, OR:3.67) (females: P-value<0.001, OR:3.86), coronary diseases (males: P-value<0.001, OR:7.89) (females: P-value<0.001, OR:7.16), and angioplasty/stent (males: P-value<0.001, OR:3.73) (females: P-value<0.001, OR:4.73) with the rate of mortality in both genders (table.6).

The history of coronary surgery (P-value=0.002, OR:3.67) in males was seen as a risk factor for death, while in female gender this relationship was not observed (P-value=0.193, OR:1.82) (Table.6).

The use of statin (P-value=0.046, OR:0.71) and aspirin (P-value<0.001, OR:0.51) in males as well as, aspirin in females (P-value=0.016, OR:0.67) after admission significantly decreased the rate of mortality.

However, the use of statins after admission in females did not show a protective effect (P-value=0.374, OR: 0.86) (table.6).

The comparison of the mean quantitative variables by gender showed that the mean of urea, creatinine (Cr), red blood cells (RBC), hemoglobin (Hgb) and hematocrit (HCT) was significantly higher in males than females (P-value<0.001). While, the mean of fasting blood glucose (FBS) (P-value=0.002), lymphocyte percentage (P-value=0.026), platelet count (PLT) (P-value<0.001), cholesterol (P-value=0.001) and high-density lipoprotein (HDL) (P-value<0.001) were significantly higher in females (table.7).

The mean of quantitative variables including mean age of patients (P-value<0.001), urea (P-value<0.001), Cr (P-value<0.001), FBS (P-value<0.001), neutrophil counts (P-value<0.001), cholesterol (P-value<0.001) and low-density lipoprotein (LDL) (P-value<0.001) were significantly higher in died subjects than live subjects. However, the mean percentage of lymphocytes (P-value<0.001), Hgb (P-value<0.001), HCT (P-value=0.036), RBC (P-value<0.001) and PLT count (P-value=0.013) was significantly lower in dead patients (table.7).

The results of distribution of risk factors by age in patients showed that the frequency of history of hypertension (males: P-value<0.001) (females: P-value<0.001) and vascular events (males: P-value=0.002) (females<0.001) significantly increased with increasing the age in two genders. Also, the frequency of coronary disease (P-value<0.001) and myocardial infarction (P-value=0.025) in male sex and the frequency of congestive heart failure (P-value<0.001), coronary disease (P-value<0.001) and angioplasty/stent (P-value<0.001) in female sex increased with increasing in the age (table.8).

The results showed that the frequency of atrial fibrillation decreased until 74 years old (P-value=0.001). The frequency of diabetes mellitus significantly increased initially and gradually decreased after 85 years old (males: P-value<0.001) (females=0.003) (table.8).

The results of this study showed that there was no significant difference between men and women in the rate of mortality during the follow up period (P-value=0.508, OR:1.080). But with age increasing, the mortality rate increased considerably. Only 3.8% of patients died at the age of under 54, while 61.8% of all deaths were over the age of 75 years (table.9).

Univariate logistic regression analysis showed that the increase of urea (P-value<0.001, OR:1.05), Cr (P-value<0.001, OR:1.516), FBS (P-value<0.001, OR:1.004), neutrophil percentage (P-value<0.001, OR:1.016) and cholesterol (P-value<0.001, OR:1.007) significantly increased the risk of death in patients. This analysis showed that an increased in percentage of lymphocytes (P-value<0.001, OR:0.978), PLT count (P-value=0.044, OR:0.998), RBC (P-value=0.001, OR:0.739), Hgb (P-value=0.003, OR:0.903) and triglycerides (TG) (P-value=0.034, OR:0.998) significantly reduced the mortality rate (table.10).

Also, this analysis demonstrated increasing urea (males: P<0.001, OR:1.013) (females: P<0.001, OR:1.017), FBS (males: P=0.021, OR:1.003) (females: <0.001, OR:1.005), neutrophil percentage (males: P=0.013, OR:1.104) (females: P=0.002, OR:1.019), cholesterol (males: P<0.001, OR:1.008) (females: P<0.001, OR:1.006) and LDL (males: P<0.001, OR:1.016) (females: P<0.001, OR:1.011) significantly increases the mortality risk in both genders. Increase in RBC (P=0.002, OR:0.680) and HCT (P=0.001, OR=0.953) in men and increasing in PLT (P=0.042, OR:0.998) count, Hgb (P=0.006, OR:0.863) and Cr (P<0.001, OR:2.381) in women significantly associated with a lower mortality rate. Of course, the increase in the percentage of lymphocytes (males: P=0.014, OR:0.984) (females: P<0.001, OR:0.971) in both sexes associated with lower mortality rate (table.11).

Table.1. Demographic data and past medical history of patients

	Number(%)		Number(%)		Number(%)
Gender		Hypertension	1142(72.6)	Congestive heart failure	236(15)
-male	744(47.3)				
-female	828(52.7)				
Type of stroke		Myocardial	115(7.3)	Vascular events	264(16.8)
-Ischemic	506(32.2)	infarction			
-Thrombotic	1064(67.8)				
Smoking	356(22.6)	Coronary disease	431(27.4)	Angioplasty/Stent	105(6.7)
Diabetes mellitus	528(33.6)	Atrial fibrillation	407(25.9)	Coronary surgery	71(4.5)

Table.2. Patients drug history before and after administration

	Before administration (Numbers(%))	After administration (Numbers(%))
Beta-blockers	240(15.3)	121(7.7)
Statins	552(35.1)	610(38.8)
Aspirin	637(40.5)	676(43)
Aspirin+Clopidogrel	96(6.1)	140(8.9)
Antiarrhythmic drugs	15(1)	21(1.3)
Warfarin	209(13.3)	111/(7.1)
ACEi / ARB1	329(20.9)	347(22.1)
Diuretics	23(1.5)	111(7.1)

1: ACEi (angiotensin converting enzyme inhibitor) / ARB (angiotensin receptor blocker)

Table.3. Patients laboratory tests and clinical examination information

	(Mean±SD)		(Mean±SD)
SBP (mmHg)	137±44.2	PLT(*103)	218.56±83.08
DBP(mmHg)	82.27±13.67	RBC (*106)	4.50±0.7
Urea	47.95±34.57	HCT(%)	38.05±8.64
Cr	1.13±1.06	Hgb	12.6±2.52
BS	161±93.87	Cholesterol	193.32±54.88
FBS	132±73.86	TG	154.8±73.21
White blood cells	8775.44±5407.59	HDL	45.54±19.66
Lymphocytes(%)	22.64±13.52	LDL	104.0±40.19
Neutrophils(%)	69.37±15.31		

SBP: Systolic blood pressure/ DBP: Diastolic blood pressure/ Cr: Creatinine/ BS: blood sugar/ FBS: Fasting blood sugar/ WBC: White blood cell/ PLT: platelet/ RBC: Red blood cell/ HCT: hematocrit/ Hgb: hemoglobin/ TG: Triglyceride/ HDL: High density lipoprotein/ LDL: Low density lipoprotein.

Table.4. Distribution of qualitative variables in ischemic stroke patients based on gender

Variables	Male n=744 Number(%)	Female n=828 Number(%)	P-value	Odd ratio (males vs females)
Smoking	225(30.2)	131(15.8)	<0.001	2.37(0.94-2.02)
Hypertension	513(69)	629(76)	0.002	0.70(0.57-0.56)
Vascular events	119(16)	145(17.5)	0.442	0.89(0.68-1.170)
Coronary surgery	39(5.2)	32(3.2)	0.189	1.37(0.85-2.20)
Diabetes mellitus	216(29)	312(37.7)	<0.001	0.68(0.54-0.83)
Dyslipidemia	168(22.6)	218(26.3)	0.085	0.81(0.64-1.02)
Congestive heart failure	109(14.7)	127(15.3)	0.703	0.94(0.71-1.25)
Angioplasty/Stent	53(7.1)	52(6.3)	0.504	1.14(0.77-1.70)
Coronary disease	195(26.2)	236(28.5)	0.309	0.89(0.71-1.11)
Myocardial infarction	63(8.5)	52(6.3)	0.096	1.38(1.80-2.94)
Atrial fibrillation	176(23.7)	231(27.9)	0.055	0.80(0.63-1)
Beta-blocker (pre-administration)	103(13.8)	137(16.5)	0.137	0.81(0.61-1.06)
Beta-blocker (post-administration)	51(6.9)	70(8.5)	0.235	0.79(0.54-1.16)
Statins (pre-administration)	261(35.1)	291(35.1)	0.979	0.997(0.81-1.22)
Statins (post-administration)	293(39.4)	317(38.3)	0.656	1.05(0.85-1.28)
Aspirin (pre-administration)	296(39.8)	341(41.2)	0.573	0.95(0.77-1.15)
Aspirin (post-administration)	331(44.5)	345(41.7)	0.259	1.12(0.91-1.37)
Aspirin+Clopidogrel (pre-administration)	47(6.3)	49(5.9)	0.741	1.07(0.70-1.62)
Aspirin+Clopidogrel (post-administration)	66(8.9)	74(8.9)	0.963	0.992(0.70-1.40)
Antiarrhythmic drugs (pre-administration)	7(0.9)	8(1)	0.959	0.970(0.35-2.69)
Antiarrhythmic drugs (post-administration)	5(0.7)	16(1.9)	0.030	0.34(0.12-0.94)
Warfarin (pre-administration)	94(12.6)	115(13.9)	0.465	0.90(0.66-1.20)
Warfarin (post-administration)	82(11)	91(11)	0.984	1.003(0.73-1.37)
Diuretics (pre-administration)	10(1.3)	13(1.6)	0.709	0.85(0.37-1.96)

Variables	Male n=744 Number(%)	Female n=828 Number(%)	P-value	Odd ratio (males vs females)
Diuretics (post-administration)	55(7.4)	56(6.8)	0.627	1.10(0.74-1.61)
ACEi/ARBs(pre-administration)	134(18)	195(23.6)	0.007	0.71(0.55-.091)
ACEi/ARBs(post-administration)	156(21)	191(23.1)	0.316	0.88(0.69-1.12)
Ischemic type			0.094	0.834(0.67-1.03)
-Embolic	224(30.1)	282(34.1)		
-Thrombotic	520(69.9)	546(65.9)		
Ischemia location			0.657	1.05(0.85-1.28)
-Anterior	451(61)	495(59.9)		
-Posterior	288(39)	331(40.1)		

ACEi: Angiotensin converting enzyme inhibitor/ ARB: Angiotensin receptor blocker

Table.5. Distribution of qualitative variables in ischemic stroke patients based on surveillance in all patients

Variables	Survivor patients Number(%)	Dead patients Number(%)	P-value	Odd ratio (males vs females)
Smoking	173(20)	119(26.3)	0.009	1.42(1.09-1.86)
Hypertension	575(66.3)	366(80)	<0.001	2.13(1.62-2.87)
Vascular events	68(7.8)	110(24.3)	<0.001	3.76(2.71-5.23)
Coronary surgery	19(2.2)	26(5.7)	0.001	2.71(1.48-4.96)
Diabetes mellitus	238(27.5)	180(39.7)	<0.001	1.74(1.37-2.21)
Dyslipidemia	165(19)	132(29.1)	<0.001	1.75(1.34-2.27)
Congestive heart failure	58(6.7)	105(23.2)	<0.001	4.20(2.98-5.93)
Angioplasty/Stent	27(3.1)	54(11.9)	<0.001	4.21(2.61-6.78)
Coronary disease	95(11)	217(47.9)	<0.001	7.47(5.63-9.90)
Myocardial infarction	35(4)	54(11.9)	<0.001	3.21(2.06-5)
Atrial fibrillation	227(26.2)	108(23.8)	0.354	0.88(0.67-1.14)
Beta-blocker (pre-administration)	123(14.2)	77(17)	0.177	1.23(0.90-1.69)
Beta-blocker (post-administration)	73(8.4)	43(9.5)	0.514	1.14(0.768-1.69)
Statins (pre-administration)	298(34.4)	163(36)	0.560	1.07(0.84-1.36)
Statins (post-administration)	401(46.3)	183(40.4)	0.042	0.79(0.62-0.99)
Aspirin (pre-administration)	0.354(40.8)	183(40.4)	0.879	0.98(0.77-1.23)
Aspirin (post-administration)	469(54.1)	186(41.1)	<0.001	0.59(0.47-0.74)
Aspirin+Clopidogrel (pre-administration)	60(6.9)	29(6.4)	0.721	0.92(0.58-1.45)
Aspirin+Clopidogrel (post-administration)	92(10.6)	40(8.8)	0.306	0.81(0.52-1.20)
Antiarrhythmic drugs (pre-administration)	5(0.6)	5(1.1)	0.303	1.92(0.55-6.68)
Antiarrhythmic drugs (post-administration)	9(1)	11(2.4)	0.057	2.37(0.97-5.76)
Warfarin (pre-administration)	121(14)	59(13)	0.640	0.92(0.66-1.29)
Warfarin (post-administration)	111(12.8)	55(12.1)	0.731	0.94(0.66-1.32)
Diuretics (pre-administration)	6(0.7)	9(2)	0.044	2.90(1.02-8.22)
Diuretics (post-administration)	58(6.7)	44(9.7)	0.052	1.51(0.99-2.26)
ACEi/ARBs(pre-administration)	184(21.2)	105(23.2)	0.415	1.12(0.85-1.47)

Variables	Survivor patients Number(%)	Dead patients Number(%)	P-value	Odd ratio (males vs females)
ACEi/ARBs(post-administration)	232(26.8)	102(22.5)	0.093	0.79(0.60-1.03)
Ischemic type			0.98	1.01(0.79-1.29)
-Embolic	284(32.8)	150(33.1)		
-Thrombotic	583(67.2)	303(66.9)		
Ischemia location			0.013	0.744(0.58-0.94)
-Anterior	570(65.9)	266(59)		
-Posterior	295(34.1)	185(41)		

ACEi: Angiotensin converting enzyme inhibitor/ ARB: Angiotensin receptor blocker

Table.6. Distribution of qualitative variables in ischemic stroke patients based on gender/surveillance

Variables	Male				Female			
	Survived patients Number(%)	Dead patients Number(%)	P-value	Odd ratio (dead vs survived)	Survived patients Number(%)	Dead patients Number(%)	P-value	Odd ratio (males vs females)
Smoking	115(27.8)	78(34.7)	0.0710	1.38	58(12.8)	41(18)	0.072	1.49
Hypertension	260(62.8)	172(76.4)	<0.001	1.92	315(69.5)	194(85.1)	<0.001	2.50
Vascular events	32(7.7)	53(23.6)	<0.001	3.67	36(7.9)	57(25)	<0.001	3.86
Coronary surgery	9(2.2)	17(7.6)	0.002	3.67	10(2.2)	9(3.9)	0.193	1.82
Diabetes mellitus	96(23.2)	82(36.4)	<0.001	1.89	142(31.3)	98(43)	0.003	1.65
Dyslipidemia	71(17.1)	62(27.6)	0.002	1.83	94(20.8)	70(30.7)	0.004	1.69
Congestive heart failure	26(6.3)	64(24)	<0.001	4.71	32(7.1)	51(22.4)	<0.001	3.79
Angioplasty/Stent	14(3.4)	26(11.6)	<0.001	3.73	13(2.9)	28(12.3)	<0.001	4.73
Coronary disease	42(10.1)	106(47.1)	<0.001	7.89	53(11.7)	111(48.7)	<0.001	7.16
Myocardial infarction	20(4.8)	30(13.3)	<0.001	3.03	15(3.3)	24(10.5)	<0.001	3.43
Atrial fibrillation	94(22.7)	55(24.4)	0.620	1.01	133(29.4)	53(23.2)	0.091	0.72
Beta-blocker (pre-administration)	47(11.4)	38(16.9)	0.050	1.58	76(16.8)	39(17.1)	0.914	1.02
Beta-blocker (post-administration)	29(7)	20(8.9)	0.393	1.29	44(9.7)	23(10.1)	0.877	1.04
Statins (pre-administration)	139(33.6)	80(35.6)	0.614	1.09	159(35.1)	83(36.4)	0.737	1.05
Statins (post-administration)	196(47.3)	88(39.1)	0.045	0.71	205(45.3)	95(41.7)	0.374	0.86
Aspirin (pre-administration)	169(40.8)	85(37.8)	0.453	0.88	185(40.8)	98(43)	0.592	1.09
Aspirin (post-administration)	232(56)	89(39.6)	<0.001	0.51	237(52.3)	97(42.5)	0.016	0.67
Aspirin+Clopidogrel (pre-administration)	30(7.2)	14(6.2)	0.625	0.84	30(6.6)	15(6.6)	0.983	0.99
Aspirin+Clopidogrel (post-administration)	46(11.1)	20(8.9)	0.378	0.78	46(10.2)	20(8.8)	0.565	0.85

Variables	Male				Female			
	Survived	Dead	P-value	Odd ratio	Survived	Dead	P-value	Odd ratio
	patients Number(%)	patients Number(%)		(dead vs survived)	patients Number(%)	patients Number(%)		(males vs females)
Antiarrhythmic drugs (pre-administration)	2(0.5)	3(1.3)	0.244	2.78	3(0.7)	2(0.9)	0.542	1.32
Antiarrhythmic drugs (post-administration)	2(0.5)	3(1.3)	0.351	2.78	7(1.5)	8(3.5)	0.1	2.31
Warfarin (pre-administration)	56(13.5)	27(12)	0.584	0.87	65(14.3)	32(14)	0.912	0.97
Warfarin (post-administration)	54(13)	26(11.6)	0.587	0.87	57(12.6)	29(12.7)	0.960	1.02
Diuretics (pre-administration)	4(1)	4(1.8)	0.462	1.85	2(0.4)	5(2.2)	0.045	5.05
Diuretics (post-administration)	29(7)	24(10.7)	0.111	1.58	29(6.4)	20(8.8)	0.259	1.40
ACEi/ARBs(pre-administration)	78(18.8)	44(19.6)	0.826	1.04	106(23.4)	61(26.8)	0.337	1.19
ACEi/ARBs(post-administration)	105(25.4)	47(20.9)	0.205	0.77	127(28)	55(24.1)	0.276	0.81
Ischemic type	120(29)	75(33.3)	0.254	1/22	64(36.2)	75(32/9)	0.393	0.86
-Embolic	294(71)	150(66.7)			289(63.8)	153(67.1)		
-Thrombotic								
Ischemia location	266(64.6)	130(58)	0.105	0.75	304(67.1)	136(59.9)	0.064	0.73
-Anterior	146(35.4)	94(42)			149(32.9)	91(40.1)		
-Posterior								

ACEi: Angiotensin converting enzyme inhibitor/ ARB: Angiotensin receptor blocker

Table.7. Comparison of quantitative variables based on gender/surveillance

Variables	Male		Female		P-value	Survived patients		Dead patients		P-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Age	67.23	14.62	66.90	14.67	0.729	60.84	14.20	75.22	10.60	<0.001
SBP	134.74	23.32	139.03	57.02	0.050	135.88	23.37	139.38	73.07	0.256
DBP	82.01	13.63	82.5	13.71	0.282	82.33	12.59	82.26	14.34	0.945
Cr	1.18	0.65	1.08	1.32	<0.001	1.03	0.53	1.16	0.58	<0.001
Urea	50.93	36.55	45.76	32.55	<0.001	40.89	23.22	52.88	38.27	<0.001
BS	158.30	89.83	163.63	97.34	0.082	154.57	94.58	163.01	90.71	0.006
FBS	129.13	74.78	135.04	72.96	0.002	121.59	63.82	139.56	77.41	<0.001
WBC	8744.55	3752.03	8803.20	6549.79	0.519	8212.57	3109.34	8363.65	3152.63	0.346
Lymphocytes(%)	21.99	13.74	23.22	13.29	0.026	25.06	12.82	21.57	13.31	<0.001

Variables	Male		Female		P-value	Survived patients		Dead patients		P-value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Neutrophils(%)	69.73	15.61	69.04	15.03	0.232	66.70	14.73	70.16	15.25	<0.001
PLT(*103)	207.30	79.44	238.67	85.00	<0.001	223.05	80.65	213.80	75.63	0.013
RBC (*106)	4.61	0.73	4.39	0.67	<0.001	4.59	0.62	4.46	0.74	<0.001
HCT(%)	40.14	7.25	38.07	9.61	<0.001	39.48	5.00	39.27	12.50	0.036
Hgb	12.96	2.32	12.36	2.66	<0.001	12.83	1.58	12.5	2.53	<0.001
Cholesterol	187.42	50.59	198.62	57.99	0.001	183.27	49.31	202.59	57.41	<0.001
TG	152.19	72.16	157.21	74.09	0.159	157.88	74.66	148.82	71.01	0.028
HDL	45.13	14.18	47.81	23.45	<0.001	46.33	22.73	46.5	13.83	0.092
LDL	102.14	39.18	107.27	40.95	0.050	95.96	32.33	114.18	45.83	<0.001

SBP: Systolic blood pressure/ DBP: Diastolic blood pressure/ Cr: Creatinine/ BS: blood sugar/ FBS: Fasting blood sugar/ WBC: White blood cell/ PLT: platelet/ RBC: Red blood cell/ HCT: hematocrit/ Hgb: hemoglobin/ TG: Triglyceride/ HDL: High density lipoprotein/ LDL: Low density lipoprotein.

Table.8. Distribution of qualitative variables based on gender/age groups

Variables	Male					P-value	Female					P-value
	<54years	64-55years	74-65years	75-84years	>85		<54years	64-55years	74-65years	75-84years	>85	
	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)		Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	
Smoking	49(34)	47(29.4)	41(27.2)	66(30.8)	22(29.3)	0.775	20(11.6)	20(13)	37(20.3)	14(17.2)	13(15.9)	0.176
Hypertension	71(49.3)	102(63.8)	114(75.5)	68(75.8)	58(77.3)	<0.001	87(50.6)	120(77.9)	154(84.6)	201(84.5)	67(82.7)	<0.001
Vascular events	11(7.6)	22(13.8)	23(15.2)	50(23.4)	13(17.3)	0.002	9(5.2)	14(9.1)	34(18.7)	67(28.2)	21(25.6)	<0.001
Coronary surgery	4(2.8)	8(5)	5(3.3)	15(7)	7(9.3)	0.148	1(0.6)	6(3.9)	9(4.9)	11(4.6)	5(6.1)	0.134
Diabetes mellitus	26(18.1)	54(33.8)	52(34.4)	70(32.7)	14(18.7)	0.001	48(27.9)	76(49.4)	69(37.9)	90(37.8)	29(35.4)	0.003
Dyslipidemia	33(22.9)	37(23.1)	34(22.5)	44(20.6)	20(26.7)	0.869	40(23.3)	36(23.4)	55(30.2)	72(30.3)	15(18.3)	0.109
Congestive heart failure	8(5.6)	21(13.1)	28(18.5)	40(18.7)	40(18.7)	0.006	17(9.9)	15(9.7)	27(14.8)	45(18.9)	23(28)	<0.001
Angioplasty/Stent	5(3.5)	15(9.4)	10(6.6)	14(6.5)	9(12)	0.136	2(1.2)	11(7.1)	16(8.8)	15(6.3)	8(9.8)	0.022
Coronary disease	14(9.7)	39(24.4)	41(27.2)	73(34.1)	28(37.3)	<0.001	15(8.7)	33(21.4)	59(32.4)	100(42)	29(35.4)	<0.001
Myocardial infarction	7(4.9)	9(5.6)	19(12.6)	17(7.9)	11(14.7)	0.025	6(3.5)	5(3.2)	14(7.7)	19(8)	8(9.8)	0.086
Atrial fibrillation	51(35.4)	30(18.8)	29(19.2)	55(25.7)	11(14.7)	0.001	77(44.8)	37(24)	32(17.6)	50(25.2)	25(30.5)	<0.001
Beta-blocker (pre-administration)	12(8.3)	28(17.5)	19(12.6)	33(15.4)	11(14.7)	0.188	21(12.2)	30(19.5)	29(15.9)	45(18.9)	12(14.5)	0.339
Beta-blocker (post-administration)	9(6.2)	13(8.1)	14(9.3)	10(4.7)	5(6.7)	0.483	14(8.1)	11(7.1)	17(9.3)	22(9.2)	6(7.3)	0.928
Statins (pre-administration)	49(34)	55(34.4)	48(31.8)	80(37.4)	29(38.7)	0.782	54(31.4)	60(39)	61(33.5)	90(37.8)	26(31.7)	0.426

Variables	Male					P-value	Female					P-value
	<54years	64-55years	74-65years	75-84years	>85		<54years	64-55years	74-65years	75-84years	>85	
	Number(%)	Number(%)	Number(%)	Number(%)	Number(%)		Number(%)	Number(%)	Number(%)	Number(%)	Number(%)	
Statins (post-administration)	62(43.1)	70(43.6)	63(41.7)	78(36.4)	20(26.7)	0.083	66(38.4)	71(46.1)	78(42.9)	77(32.4)	25(30.5)	0.024
Aspirin (pre-administration)	60(41.7)	65(40.6)	54(35.8)	91(42.5)	26(34.7)	0.597	65(37.8)	65(42.2)	67(36.8)	105(44.1)	39(47.6)	0.338
Aspirin (post-administration)	69(54.9)	75(46.9)	68(45)	81(37.9)	28(37.3)	0.017	77(44.8)	79(51.3)	85(46.7)	83(34.9)	21(25.6)	<0.001
Aspirin+Clopidogrel (pre-administration)	8(5.6)	11(6.9)	9(6)	16(7.5)	3(4)	0.840	5(2.9)	11(7.1)	15(8.2)	15(6.3)	3(3.7)	0.215
Aspirin+Clopidogrel (post-administration)	12(8.3)	16(10)	14(9.3)	20(9.3)	4(5.3)	0.817	11(6.4)	16(10.4)	23(12.6)	20(8.4)	4(4.9)	0.160
Antiarrhythmic drugs (pre-administration)	2(1.4)	1(0.6)	0(0)	4(1.9)	0(0)	0.330	0(0)	1(0.6)	1(0.5)	3(1.3)	3(3.7)	0.072
Antiarrhythmic drugs (post-administration)	1(0.7)	0(0)	0(0)	4(1.9)	0(0)	0.125	2(1.2)	5(3.2)	3(1.6)	5(2.1)	1(1.2)	0.685
Warfarin (pre-administration)	24(16.7)	11(6.9)	25(16.6)	31(14.5)	3(4)	0.005	32(18.6)	16(10.4)	18(9.9)	38(16)	11(13.4)	0.089
Warfarin (post-administration)	28(19.4)	13(8.1)	14(9.3)	21(9.8)	6(8)	0.010	29(16.9)	13(8.4)	12(6.6)	27(11.3)	10(12.2)	0.029
Diuretics (pre-administration)	2(1.4)	3(1.9)	2(1.3)	3(1.4)	0(0)	0.849	0(0)	2(1.3)	1(0.5)	6(2.5)	4(4.9)	0.024
Diuretics (post-administration)	6(4.2)	18(11.2)	7(4.6)	19(8.9)	5(6.7)	0.088	9(5.2)	5(3.2)	12(6.6)	21(8.8)	9(11)	0.108
ACEi/ARBs(pre-administration)	19(13.2)	32(20)	27(17.9)	44(20.6)	12(16)	0.428	32(18.6)	39(25.3)	45(24.7)	62(26.1)	17(20.7)	0.415
ACEi/ARBs(post-administration)	27(18.8)	42(26.2)	37(24.5)	37(17.3)	13(17.3)	0.158	37(21.5)	50(32.5)	45(24.7)	47(19.7)	12(14.6)	0.012
Ischemic type												
-Embolic	56(38.9)	45(28.1)	40(26.5)	65(30.4)	18(24)	0.097	88(51.2)	44(28.6)	44(24.2)	77(32.4)	29(35.4)	<0.001
-Thrombotic	88(61.1)	115(71.9)	111(73.5)	149(69.6)	57(76)		84(48.8)	110(71.4)	138(75.8)	161(67.6)	53(64.6)	
Ischemia location												
-Anterior	101(69.6)	114(71.7)	88(58.7)	112(52.6)	37(50)	<0.001	119(69.6)	92(60.1)	105(57.7)	136(57.1)	43(52.4)	0.046
-Posterior	43(30.1)	45(28.3)	62(41.3)	101(47.4)	37(50)		52(30.4)	61(39.9)	77(42.3)	102(42.9)	39(47.6)	
ACEi: Angiotensin converting enzyme inhibitor/ ARB: Angiotensin receptor blocker												

Table.9. Distribution of mortality rate based on gender/age groups

Variables		Survived patients N=967	Dead patients N=453	P-value	Odd ratio
Gender	Males (N=369)	414(47.8)	225(49.7)	0.508	1.080
	Females (N=681)	453(52.2)	228(50.3)		Reference
Age groups	>54 years (N=299)	282(32.5)	17(3.8)	<0.001	0.023
	55-64years (N=271)	222(25.6)	49(10.8)		0.084
	65-74years (N=290)	183(21.1)	107(23.6)		0.224
	75-84years (N=348)	149(17.2)	199(43.9)		0.511
	>85years (N=112)	31(3.6)	81(17.9)		Reference

Table.10. Correlation between quantitative variables and mortality rate

Variables	P-value	Odd ratio (95% CI for Odd ratio)
SBP	0.270	1.002 (0.999-1.005)
DBP	0.923	1.000(0.991-1.008)
Cr	<0.001	1.516(1.202-1.912)
Urea	<0.001	1.015(1.010-1.019)
BS	0.123	1.001(1.000-1.002)
FBS	<0.001	1.004(1.002-1.005)
WBC	0.405	1.000(1.000-1.000)
Lymphocytes (%)	<0.001	0.978(0.969-0.987)
Neutrophils (%)	<0.001	1.016(1.008-1.024)
PLT(*103)	0.044	0.998(0.997-1.000)
RBC (*106)	0.001	0.739(0.622-0.878)
HCT (%)	0.675	0.997(0.992-1.012)
Hgb	0.003	0.903(0.845-0.966)
Cholesterol	<0.001	1.007(1.005-1.009)
TG	0.034	0.998(0.997-1.000)
HDL	0.880	1.000(0.995-1.006)
LDL	<0.001	1.013(1.009-1.016)

SBP: Systolic blood pressure/ DBP: Diastolic blood pressure/ Cr: Creatinine/ BS: blood sugar/ FBS: Fasting blood sugar/

WBC: White blood cell/ PLT: platelet/ RBC: Red blood cell/ HCT: hematocrit/ Hgb: hemoglobin/ TG: Triglyceride/ HDL:

High density lipoprotein/ LDL: Low density lipoprotein.

Table.11. Correlation between quantitative variables and mortality rate based on gender

Variables	Males		Females	
	P-value	Odd ratio (95% CI for Odd ratio)	P-value	Odd ratio (95% CI for Odd ratio)
SBP	0.732	1.001(0.994-1.008)	0.299	1.002(0.998-1.005)
DBP	0.725	0.998(0.986-1.010)	0.817	1.001(0.989-1.014)
Cr	0.148	1.204(0.936-1.547)	<0.001	2.381(1.569-3.615)
Urea	<0.001	1.013(1.007-1.019)	<0.001	1.017(1.010-1.024)
BS	0.584	1.001(0.999-1.002)	0.120	1.001(1.000-1.003)
FBS	0.021	1.003(1.000-1.005)	<0.001	1.005(1.002-1.007)
WBC	0.171	1.000(1.000-1.000)	0.796	1.000(1.000-1.000)
Lymphocytes(%)	0.014	0.984(0.972-0.997)	<0.001	0.971(0.958-0.985)
Neutrophils(%)	0.013	1.104(1.003-1.025)	0.002	1.019(1.007-1.031)
PLT(*103)	0.524	0.999(0.997-1.001)	0.042	0.998(0.995-1.000)
RBC (*106)	0.002	0.680(0.534-0.865)	0.058	0.782(0.607-1.008)
HCT (%)	0.001	0.953(0.926-0.981)	0.269	1.011(0.991-1.031)
Hgb	0.073	0.923(0.846-1.008)	0.006	0.863(0.777-0.958)
Cholesterol	<0.001	1.008(1.004-1.011)	<0.001	1.006(1.003-1.009)
TG	0.052	0.998(0.995-1.000)	0.296	0.999(0.997-1.001)
HDL	0.900	1.001(0.999-1.012)	0.875	1.001(0.994-1.007)
LDL	<0.001	1.016(1.011-1.020)	<0.001	1.011(1.006-1.015)

SBP: Systolic blood pressure/ DBP: Diastolic blood pressure/ Cr: Creatinine/ BS: blood sugar/ FBS: Fasting blood sugar/ WBC: White blood cell/ PLT: platelet/ RBC: Red blood cell/ HCT: hematocrit/ Hgb: hemoglobin/ TG: Triglyceride/ HDL: High density lipoprotein/ LDL: Low density lipoprotein.

Discussion

In the current study, the history of diabetes mellitus, hypertension, dyslipidemia, myocardial infarction, chronic heart failure, vascular events, coronary artery bypass, angioplasty/stent and smoking showed a significant correlation with ischemic stroke associated-mortality (table-5). Also, there were no significant difference between these risk factors and mortality rate between the two genders (Table-6). Carole et al. found that there was no difference in the risk factors of stroke incidence and stroke mortality. In our study, similar to the study by Carole et al., a similar distribution was seen in the related risk factors based on gender and mortality. Therefore, if the stroke incidence and mortality associated risk factors are the same, prevention of them leads to reduction in incidence, mortality, disability, treatment costs and increasing the quality of life (5).

However, in the present study, the prevalence of diabetes mellitus (P-value<0.001) and hypertension (P-value=0.002) among females and the rate of smoking among males (P-value <0.001) demonstrated a significant difference with another gender. Carole et al. study showed that hypertension and glucose level in non-diabetic patients significantly related to the stroke incidence and mortality which is consistent with the results of our study. Some studies demonstrated the role of obstructive sleep apnea and previous history of congestive heart failure in the incidence and mortality of stroke(5). Our study showed that the history of congestive heart failure was equally effective among men and women in the rate of incidence (male and female: P-value<0.001) and mortality (P-value<0.001) of stroke.

Unlike our study that showed the significant role of dyslipidemia in the both genders mortality (males: P-value=0.002 and females: P-value=0.004) and all cases mortality of stroke (P-value<0.001), Carole et al. (2000) did not find the effect of hypercholesterolemia in the incidence and mortality of stroke (5).

Smoking causes 2-fold increase in the risk of lifelong stroke incidence in smokers compared to non-smokers. According to previous studies, former smoking has less risk than current smoking (6). Twenty years' cohort study of Oslo et al. on 14,403 cases demonstrated that smoking is a strong predictor of stroke mortality not its incidence. However, this study showed a dose-dependent effect of cigarette discontinuation on the incidence of stroke(5). The study of Ueshima et al. identified smoking as an independent risk factor for stroke, in particular cerebral infarction in both genders, as well as CVD and IHD in men. In the above study, the hazard ratio of all strokes, cerebral infarction and cerebral hemorrhage in men who consumed between 1 to 20 cigarettes/day compared to those who consumed 21 or more cigarettes/day were respectively (1.60 versus 2.17), (2.97 versus 3.26), and (0.42 vs. 0.68) (6, 7). It has been shown that smoking increases the risk of cerebral infarction and lacunar stroke more than hemorrhagic stroke(7, 8). In the current study, the smoking rate among males was significantly higher than females (P-value<0.001) due to cultural condition. However, it could not show a significant effect on the surveillance of stroke patients (P-value=0.009).

The study of Sanne et al. stated that current smoking increases the risk of ischemic stroke by more than 50% in both genders. In the case of hemorrhagic stroke, current smoking led to a 63% increase in the incidence of hemorrhagic stroke in females and 22% increase in males compared to non-smokers(6). Hunjo et al. study also confirmed an increased risk of hemorrhagic stroke-associated mortality in female-smokers compared to male-smokers (with a hazard ratio of 1.27 (1.00-1.62) for males and 1.87 (1.34-2.60) for females) (8). One the reason of 10% excess rate of smoking associated hemorrhagic stroke in the females is because this study

was performed in Western countries in which the rate of smoking among females is higher than Eastern/Asian countries. Another factor that can influence the smoking-associated stroke incidence is the average amount of cigarette consumption per day which is usually higher in males than in females (18.1 in males versus 15.3 in females)(6).

One of the effects of smoking on cardio/cerebrovascular events is its antiestrogenic effects, which cause a negative effect on the lipid profile and increase the risk of CHD and lesser than it, the risk of stroke(6).

However, the effect of simultaneous risk factors on the incidence and mortality of stroke should be considered. Various studies examined the effects of hypertension, dyslipidemia, etc., in this regard. But the significance and severity of each these factors on the pathophysiology of stroke has not been yet fully understood (8-11).

Another risk factor which increase the risk of ischemic stroke and also peripheral embolism is atrial fibrillation. Several studies have shown a higher risk of stroke in atrial fibrillation patients and a higher Framingham risk score among women than men. However, others have rejected this(12).

The study of Tiwari et al. also referred to atrial fibrillation (AF), CHA2DS2-VASc score, and an enlarged left atrium size as a risk factor for stroke. CHA2DS2-VASc score including congestive heart failure, hypertension, age, diabetes, previous history of stroke/transient ischemic attack, vascular disease, and sex. They showed that CHA2DS2-VASc ≥ 1 and increased left atrium size, even independently of AF status, increased the risk of stroke incidence(13).

In a cohort study (ATRIA) on 13,559 patients, the rate of ischemic stroke was higher in females who did not receive warfarin than the same males. It has been shown that the use of warfarin can be effective in reducing the risk of thromboembolism and subsequent stroke incidence without increasing the risk of hemorrhagic complications. That study described atrial fibrillation as an independent risk factor for ischemic stroke and suggested anticoagulant usage for these

patients. The exact mechanism of this difference between men and women is not well known, although some studies have suggested that women with atrial fibrillation have a higher level of F1.2, fragments of Prothrombin, von-Willebrand factor and tissue plasminogen activator antigen. Perhaps this is the reason for this difference between the two genders(12). The present study failed to find a link between increased risk of stroke or its mortality in patients with a history of atrial fibrillation in both genders. However, due to the increased prevalence of atrial fibrillation with increasing the age in our study and the results of previous studies, the use of anticoagulants to prevent subsequent sequelae of stroke seems logical. Although, our study could not find any connection between the use of warfarin with the incidence or mortality of stroke. The study by Gage et al. on 2,850 patients with atrial fibrillation which used aspirin showed the beneficial effects of aspirin in reducing the risk of stroke in patients with high or low CHADS2 score(14).

The results of present study showed that the use of aspirin after hospitalization was associated with a decrease in the rate of mortality in both genders (male: P-value <0.001 and female: P-value= 0.016). Several articles showed the positive effects of aspirin and clopidogrel in reducing the risk of stroke. These articles explained that aspirin has been effective in reducing the platelet hyperactivity induction during the acute phase of ischemic stroke and subsequently reducing the release of platelet-derived inflammatory mediators and also reducing monocyte-platelet aggregation which is effective in prevention of ischemic stroke. Also, Clopidogrel, as another inhibitor of platelet aggregation, by binding to P2Y12 receptors causes a reduction in the platelet-derived pro-inflammatory mediators such as p-selectin and CD40L and reduces the interaction between platelets and leukocytes. Studies have shown that the combination of these two drugs can be more effective than aspirin alone in reducing the level of TNF-alpha and C-reactive protein in ischemic stroke patients(15). Although our study failed to prove this effect. In current study, aspirin users alone showed

lower mortality rate than patients which used both aspirin and clopidogrel in both genders.

The randomized clinical trial (ACTIVE W) has compared the effects of aspirin plus clopidogrel versus oral anticoagulants in reduction the risk of vascular events. In this study, oral anticoagulants significantly reduced annual risk of vascular events compared to the simultaneous use of aspirin and clopidogrel (93.3% vs 5.60%, P=0.0003). Also, the relative risk of major bleeding in the oral anticoagulants group was less than the other group (1.30; 0.94-1.79)(16). However, we showed the beneficial effect of aspirin in reduction the risk of stroke, but this effect was not observed for warfarin and clopidogrel in both sexes.

Activation and aggregation of platelets are considered as one of the most important factors in the pathogenesis of stroke. A study by Chen et al. showed a detrimental effect for platelet microparticles (PMPs) on acute cerebral ischemic stroke. These components are released from stressed or apoptotic cells. They stated that an increase in the level of these PMPs and mean platelet volume (MPV) occurs in patients with acute ischemic stroke, especially in thrombotic stroke and antiplatelet therapy reduces their level. The amount of PMPs is also related to the extent of the ischemic stroke lesion(17).

The study of Du et al. examined the association between MPV and platelet counts with the development and prognosis of ischemic and hemorrhagic stroke. In this study, the increase in MPV was expressed as an independent risk factor for both types of stroke, while increasing in platelet counts increased the risk of ischemic stroke, but reduced the risk of hemorrhagic stroke(18). These findings were in contrast with our results. In our study, platelet count was lower in dead patients compared to survived patients. However, subsequent analyzes showed that increased platelet counts were associated with reduced mortality in females. Whiles, this was not seen in male patients.

According to the results of univariate logistic regression analysis, the increase in hemoglobin is associated with a decrease in mortality rate in women, which is consistent with the results of the Panwar et al.

study. In above study, there was a strong correlation between hemoglobin concentration and sex in terms of incidence of stroke ($P = 0.05$). In both studies, there was no correlation between hemoglobin concentration and stroke incidence or mortality in male gender(19).

Generally, there is a correlation between lower or higher value of hemoglobin concentration than normal range with an increased risk of stroke. Hisayama et al. study demonstrated an increased risk of ischemic stroke in both very high and very low levels of hemoglobin, independent of the Sex. The effect of hemoglobin on stroke pathogenesis is through its effect on brain perfusion. Increasing hemoglobin leads to increasing in blood viscosity and platelet activation, as well as, decreasing in oxygen carrying capacity and cerebral flow and inducing oxidative stress due to iron accumulation. However, the relationship between hemoglobin level and stroke incidence or mortality with sex is not yet known(19, 20). Milionis et al. also found that anemia in patients with ischemic stroke correlated with decreased systolic and diastolic blood pressure, reduced glomerular filtration rate and increased CRP. It was also shown that 7-day, 3-months and 12-months mortality rates were higher in patients with lower hemoglobin level than others and hemoglobin was considered as one of the effective factors in predicting mortality and morbidity rate of stroke (21).

It has been shown a physiological difference in terms of the ability to carry oxygen to the hemoglobin in females. Lower hemoglobin in women prone them to prolonged recovery time after the stroke(19). Kellert et al. found that reduced level of hemoglobin and hematocrit in stroke patients admitted to the intensive care unit associated with loss of consciousness and increase in the duration of mechanical ventilation in these patients. But they could not find a relationship between hospital mortality and 3-months clinical outcomes(20).

Dyslipidemia is always known as a risk factor for cardiovascular disease and vascular events(22). The Holmes et al. study showed the effect of lipid profile and lipoproteins on myocardial infarction and ischemic stroke(23). But they stated that these parameters did not

affect the intracranial hemorrhage. Our study showed that the prevalence of dyslipidemia in men (P -value=0.002) and women (P -value=0.0042) who died from stroke was higher than those who survived. The comparison of mean quantitative variables by gender showed that cholesterol level (P -value=0.001) and HDL (P -value <0.001) were higher in women than men. Univariate logistic regression analysis showed that increased level of cholesterol and LDL decreased the rate of stroke mortality.

Deng et al. Stated that the ratio of TG/HDL is an independent risk factor for predicting the prognosis of acute ischemic stroke patients in the first 3 months. It also correlates with obesity, metabolic syndrome, and insulin resistance. It was argued that this ratio can be a better indicator of the effect of lipid profiles than isolated parameters and providing us with a better estimate of the role of fat metabolism on vascular events (22). In one study, this ratio showed a strong correlation with neurological degradation and clinical improvement after cerebral stroke (24).

The study of Deng et al. suggested a cut-off of TG/HDL=0.87 ratio for prevention of death and 1.01 for good clinical outcomes and stated that the increase in this ratio leads to 0.34-folds decrease in the mortality rate and 2-fold increase in good clinical outcomes. This study has shown that the reduction in the ratio of TG/HDL worsen the clinical outcome of stroke (22).

Pandey et al, study demonstrated that the increased serum levels of total cholesterol, triglyceride, LDL and decreased level of HDL, as well as increased level of hs-CRP, were associated with an increased risk of atherothrombosis, atherosclerosis, and ischemic stroke. These data suggest the need for dyslipidemia treatment in reducing the risk of stroke(13). The hs-CRP is a liver-synthesized glycoprotein contribute to the development of atherosclerosis, complement activation, vascular cells activation, lipid accumulation, thrombosis and cell apoptosis. This study showed that thromboinflammation and atherosclerosis can play a significant role in the pathogenesis of stroke (13).

In our study, FBS level were significantly higher in dead patients (P-value <0.001). The subsequent univariate logistic regression analysis showed FBS as one of the risk factors for stroke-related mortality (P-value <0.001, OR: 1.004). Study by Xu et al. on 20,327 Chinese hypertensive patients demonstrated that increasing FBS of more than 7.0 mmol/L after adjustment for major covariables was associated with an increased risk of developing the first stroke. The 12-years follow-up also showed an increase of 2-3 times in the risk of ischemic stroke in people with impaired glucose profile. However, more studies are needed to compare pre-diabetic and diabetic subjects in terms of the risk of stroke. Although, this study showed the beneficial effects of folic acid use through the effect on endothelial nitric oxide synthase enzyme and reducing hyperglycemia adverse effects on vascular system in the prevention of the first stroke in a wide range of FBS (25).

Increased WBC count is associated with acute or chronic inflammation, vascular injury, and progression of atherosclerosis (26). During brain ischemia, following the activation of the immune system, a cascade of reactions occurs including the production of cytokines, chemokines and cell adhesion molecules, as well as leukocyte infiltration into the damaged parenchyma(15). Different WBC subtypes are considered as indicators of the risk of stroke. Several studies have been considered WBC and neutrophil count as long-term predictors of ischemic stroke. Some studies have shown an increased WBC levels in the first episode of cerebral infarction and a link between the WBC count especially neutrophil count and recurrence of ischemic events (26). Neutrophils are one of the first cells which respond to ischemia. Despite the phagocytic properties of neutrophils to removing the necrotic tissue debris from the area, but they can lead to subsequent thrombosis, destruction in the blood-brain barrier and cause cerebral edema(15). Also, it has been demonstrated that lymphocytes, especially T types, are associated with recurrent episodes of stroke through involvement in chronic inflammatory processes (26).

Ertaş et al. explained that inflammation leads to lymphocytes apoptosis and lymphopenia. In their study on 126 non-valvular atrial fibrillation patients reported that neutrophil/lymphocyte ratio (NLR) in stroke patients was higher than individuals without the history of stroke (5.6 ± 3.4 vs. 3.1 ± 2.1 , $p = 0.001$) and NLR is associated with the incidence of thromboembolic stroke in these patients(27). The present study showed that increasing in neutrophil count and decreasing in lymphocytes count was associated with an increased risk of stroke mortality. This results are consistent with Celikbilek study. Celikbilek et al. reported a cut-off value=4.1 for NLR to predict stroke mortality risk with a sensitivity of 66.7% and a specificity of 74.1% ($P = 0.006$) and considered it as an inexpensive and available marker for determination of stroke outcomes (28). Therefore, by measuring these laboratory markers, the extent of tissue destruction and following patient's sequels and outcomes can be estimated. However, subsequent studies should examine the relationship between sequelae of survived patients and NLR ratio.

Hyperuricemia is another risk factor that is known as a determinant factor in increasing stroke incidence and mortality in particular, ischemic stroke. Several articles have evaluated the role of uric acid in pathogenesis and the progression of stroke. Experimental studies have shown that increased levels of uric acid in the blood is associated with endothelial damage, increased levels of free oxygen radicals and induction of oxidative stress, disturbance in nitric oxide synthesis, increased levels of inflammatory mediators, increased risk of thrombosis and atherosclerosis, activation of renin-angiotensin-aldosterone system, increased blood pressure and metabolic syndrome (15, 26, 29). Metabolic syndrome and hyperinsulinemia leads to reduction of uric acid, sodium and potassium excretion and increase the risk of hypertension as an effective risk factor in increasing the stroke mortality(30).

The large NHANES I study showed that hyperuricemia is an independent factor in increasing the risk of cardiovascular mortality, regardless of other risk factors such as age, race, menopause status, etc. (30). Our study also confirmed the results of the above studies

and showed a strong correlation between hyperuricemia and mortality risk in ischemic stroke. ($P < 0.001$). However, the present study did not investigate the prevalence of metabolic syndrome and other factors such as BMI.

This study has some limitations. In our study, we could not find a significant relationship between smoking and ischemic stroke patients surveillance. Perhaps it was better to record the number of cigarette/day consumption among male and female patients to determine how many of our patients were heavy smokers and then we could find a better understanding of the relationship between the smoking and stroke incidence and surveillance. However, due to the retrospective nature of the study, it was impossible to accurately record it through medical records. Second, in this study, unlike previous studies, clopidogrel and warfarin did not show a significant effect on patient's surveillance which may be due to the lack of treatment compliance in some patients, the short duration of medication, or in the case of warfarin use, the absence of patients INRs in the therapeutic range in order to prevent thromboembolic events. In which case by recording INRs, it is possible to assess the effect of warfarin on ischemic stroke incidence/mortality and compare it between patients with controlled or uncontrolled INRs. Third, in the present study, the effect of neutrophil count elevation and lymphocyte count reduction on increasing the rate of mortality, as well as the effect of increased level of cholesterol and LDL on reducing the mortality rate was observed. We suggest, like to some of previous studies, the overall impact of inflammatory factors or lipid profile markers should be considered to have a better estimation about their effect on ischemic stroke incidence and mortality. Finally, it is suggested that future studies explore the relationship of risk factors and laboratory data with short-term and long-term outcomes of ischemic stroke patients and their impact on their quality of life.

Limitation

Controlling all the probable risk factors in observational studies such as the present one is not

possible and this can affect the findings of the study. In addition, this study was a single centered one with a relatively small sample size, which makes data generalization hard.

Conclusion

The current study investigated various factors involved in the pathogenesis and incidence, as well as, the determinant factors in prognosis and mortality of ischemic stroke. Most of the factors mentioned above, such as smoking, dyslipidemia, diabetes mellitus, hyperuricemia and hypertension, are controllable factors with lifestyle modification and primary prevention with antihypertensive drugs, antiplatelet and uric acid lowering agents etc. A number of laboratory findings such as NLR ratio, PLT count, Hgb, uric acid level, lipid and glucose profiles are determining factors in prediction of stroke mortality. However, some results such as the association between the history of atrial fibrillation or the effect of warfarin and clopidogrel on stroke prevention were not observed in this study, which may be due to differences in sample size or differences in the distribution of risk factors in the present study with previous studies.

Acknowledgements

The staff of emergency department and laboratory of Urmia Imam Khomeini Hospital are thanked for their cooperation in carrying out this project.

Author contribution

All the authors met the criteria of authorship based on the recommendations of the international committee of medical journal editors. Authors ORCIDs Hamid Reza Mehryar: 0000-0002-3267-8647

Funding/Support All the expenses of this research were paid by the researchers.

Conflict of interest Hereby, the authors declare that there is no conflict of interest regarding the present study

References:

1. Li M, Hou W, Zhang X, Hu L, Tang Z. Hyperuricemia and risk of stroke: a systematic review and meta-analysis

- of prospective studies. *Atherosclerosis* 2014;232(2):265-70.
2. Wang Y-F, Li J-X, Sun X-S, Lai R, Sheng W-L. High serum uric acid levels are a protective factor against unfavourable neurological functional outcome in patients with ischaemic stroke. *J Int Med Res* 2018;46(5):1826-38.
 3. Lapchak PA. Taking a light approach to treating acute ischemic stroke patients: transcranial near-infrared laser therapy translational science. *Ann Med* 2010;42(8):576-86.
 4. Sarikaya H, Ferro J, Arnold M. Stroke prevention-medical and lifestyle measures. *Eur Neurol* 2015;73(3-4):150-7.
 5. Hart CL, Hole DJ, Smith GD. Comparison of risk factors for stroke incidence and stroke mortality in 20 years of follow-up in men and women in the Renfrew/Paisley Study in Scotland. *Stroke* 2000;31(8):1893-6.
 6. Peters SAE, Huxley RR, Woodward M. Smoking as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 81 cohorts, including 3,980,359 individuals and 42,401 strokes. *Stroke* 2013;44(10):2821-8.
 7. Ueshima H, Reza Choudhury S, Okayama A, Hayakawa T, Kita Y, Kadowaki T, et al. Cigarette smoking as a risk factor for stroke death in Japan: NIPPON DATA80. *Stroke* 2004;35(8):1836-41.
 8. Nakamura K, Nakagawa H, Sakurai M, Murakami Y, Irie F, Fujiyoshi A, et al. Influence of smoking combined with another risk factor on the risk of mortality from coronary heart disease and stroke: pooled analysis of 10 Japanese cohort studies. *Cerebrovasc Dis* 2012;33(5):480-91.
 9. Tanabe N, Iso H, Okada K, Nakamura Y, Harada A, Ohashi Y, et al. Serum total and non-high-density lipoprotein cholesterol and the risk prediction of cardiovascular events. *Circulation J* 2010;74(7):1346-56.
 10. Hata J, Doi Y, Ninomiya T, Fukuhara M, Ikeda F, Mukai N, et al. Combined effects of smoking and hypercholesterolemia on the risk of stroke and coronary heart disease in Japanese: the Hisayama study. *Cerebrovasc Dis* 2011;31(5):477-84.
 11. Okamura T, Kokubo Y, Watanabe M, Higashiyama A, Miyamoto Y, Yoshimasa Y, et al. Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: The Suita study. *Atherosclerosis* 2009;203(2):587-92.
 12. Fang MC, Singer DE, Chang Y, Hylek EM, Henault LE, Jensvold NG, et al. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) study. *Circulation* 2005;112(12):1687-91.
 13. Pandey A, Shrivastava A, Solanki A. Study of atherogenic lipid profile, high sensitive C-reactive protein neurological deficit and short-term outcome in stroke subtypes. *Iran J Neurol* 2016;15(3):146.
 14. Gage BF, van Walraven C, Pearce L, Hart RG, Koudstaal PJ, Boode B, et al. Selecting patients with atrial fibrillation for anticoagulation: stroke risk stratification in patients taking aspirin. *Circulation* 2004;110(16):2287-92.
 15. De Meyer SF, Denorme F, Langhauser F, Geuss E, Fluri F, Kleinschnitz C. Thromboinflammation in stroke brain damage. *Stroke* 2016;47(4):1165-72.
 16. Site HG. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367(9526):1903-12.
 17. Chen Y, Xiao Y, Lin Z, Xiao X, He C, Bihl JC, et al. The role of circulating platelets microparticles and platelet parameters in acute ischemic stroke patients. *Journal of Stroke and Cerebrovasc Dis* 2015;24(10):2313-20.
 18. Du J, Wang Q, He B, Liu P, Chen JY, Quan H, et al. Association of mean platelet volume and platelet count with the development and prognosis of ischemic and hemorrhagic stroke. *Int J Lab Hematol* 2016;38(3):233-9.
 19. Panwar B, Judd SE, Warnock DG, McClellan WM, Booth III JN, Muntner P, et al. Hemoglobin concentration and risk of incident stroke in community-living adults. *Stroke* 2016;47(8):2017-24.
 20. Kellert L, Schrader F, Ringleb P, Steiner T, Bösel J. The impact of low hemoglobin levels and transfusion on

- critical care patients with severe ischemic stroke: STroke: RelevAnt Impact of HemoGlobin, Hematocrit and Transfusion (STRAIGHT)—an observational study. *J Crit Care* 2014;29(2):236-40.
21. Milionis H, Papavasileiou V, Eskandari A, D'Ambrogio-Remillard S, Ntaios G, Michel P. Anemia on admission predicts short-and long-term outcomes in patients with acute ischemic stroke. *Int J Stroke* 2015;10(2):224-30.
 22. Deng QW, Wang H, Sun CZ, Xing FL, Zhang HQ, Zuo L, et al. Triglyceride to high-density lipoprotein cholesterol ratio predicts worse outcomes after acute ischaemic stroke. *Eur J Neurol* 2017;24(2):283-91.
 23. Holmes MV, Millwood IY, Kartsonaki C, Hill MR, Bennett DA, Boxall R, et al. Lipids, lipoproteins, and metabolites and risk of myocardial infarction and stroke. *J Am Coll Cardiol* 2018;71(6):620-32.
 24. Choi K-H, Park M-S, Kim J-T, Chang J, Nam T-S, Choi S-M, et al. Serum triglyceride level is an important predictor of early prognosis in patients with acute ischemic stroke. *J Neurol Sci* 2012;319(1-2):111-6.
 25. Xu RB, Kong X, Xu BP, Song Y, Ji M, Zhao M, et al. Longitudinal association between fasting blood glucose concentrations and first stroke in hypertensive adults in China: effect of folic acid intervention—4. *Am J Clin Nutr* 2017;105(3):564-70.
 26. Wu T-H, Chien K-L, Lin H-J, Hsu H-C, Su T-C, Chen M-F, et al. Total white blood cell count or neutrophil count predict ischemic stroke events among adult Taiwanese: report from a community-based cohort study. *BMC Neurol* 2013;13(1):7.
 27. Ertaş G, Sönmez O, Turfan M, Kul Ş, Erdoğan E, Tasal A, et al. Neutrophil/lymphocyte ratio is associated with thromboembolic stroke in patients with non-valvular atrial fibrillation. *J Neurol Sci* 2013;324(1-2):49-52.
 28. Celikbilek A, Ismailogullari S, Zararsiz G. Neutrophil to lymphocyte ratio predicts poor prognosis in ischemic cerebrovascular disease. *J Clin Lab Anal* 2014;28(1):27-31.
 29. Falsetti L, Capecci W, Tarquinio N, Viticchi G, Silvestrini M, Catozzo V, et al. Serum uric acid, kidney function and acute ischemic stroke outcomes in elderly patients: a single-cohort, perspective study. *Neurol Int* 2017;9(1):6920.
 30. Niskanen LK, Laaksonen DE, Nyysönen K, Alfthan G, Lakka H-M, Lakka TA, et al. Uric acid level as a risk factor for cardiovascular and all-cause mortality in middle-aged men: a prospective cohort study. *Arch Int Med* 2004;164(14):1546-51.