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Predictors of long-term mortality after first-ever stroke

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Abstract:

BACKGROUND AND OBJECTIVE: Data on the factors affecting long-term mortality following a stroke in Iran are scarce. The current research aimed at investigating the extent of 2-year mortality following a stroke and the factors affecting it in the northwest of Iran.

MATERIALS AND METHODS: This prospective cohort study was conducted in Tabriz, Northwest of Iran. Patients with computed tomography/magnetic resonance imaging confirmed the first-ever stroke were included in this study and followed up to 2 years. Clinical examinations, including the severity of the stroke using the modified National Institutes of Health Stroke Scale (mNIHSS), were conducted by a neurologist. The general characteristics, lifestyle factors, and laboratory tests were also completed. To estimate the survival, Kaplan–Meier analysis was used; and for group comparison, the log-rank method was applied. To identify the factors predicting 2-year mortality, semiparametric Cox regression analysis was used.

RESULTS: A total of 1036 first-ever stroke patients were included in the present study. The mortality rates of stroke in 6-month, 1-year, and 2-years follow-up periods were 31.6%, 34.5%, and 38%, respectively. The two-year mortality rate was 33.6% in ischemic and 58.7% in hemorrhagic stroke ($P < 0.001$). In the multivariate Cox model, variables age, type of stroke, diabetes, and severity of the stroke, according to the mNIHSS index, were identified as factors predicting 2-year mortality following the stroke.

CONCLUSION: The 2-year mortality following acute stroke was relatively high compared to that of in developed countries. Implementation of secondary prevention is recommended to better management of modifiable predictors of mortality.

Keywords:

Hemorrhagic stroke, ischemic stroke, mortality, survival

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Introduction

Stroke is the second leading cause of adults' death and disability in most Western countries.[1] In 2013, there were almost 25.7 million stroke survivors and 6.5 million deaths from stroke of whom 71% and 51% were with ischemic and hemorrhagic strokes, respectively. During the last two decades, in high-income countries, the incidence and mortality of both ischemic and hemorrhagic stroke decreased, in contrast, the incidence of hemorrhagic and ischemic stroke increased by 22% and 6% in low- and middle-income countries, respectively.[2]

According to the studies conducted throughout the world, the age-standardized ratio of stroke varies from 145.9 (130.3–162.8)/100,000 people in Japan,[3] 76 (59–94) in Australia,[4] and 57.9 (54–61.8) in France.[5] According to studies conducted in Iran, the overall crude incidence rate of first ever-stroke is 139 (128–149)/100,000 people; 144 in men (128–159) and 133 (111–148) in women. The incidence rate of stroke in Iran is significantly higher than that of Western countries, and regarding age, brain

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stroke occurs a decade earlier compared with Western countries.[6]

A study reported short-, intermediate-, and long-term mortality following stroke and factors affecting it in different parts of the world, including the WHO MONICA project,[7] European countries,[8-10] the USA,[11,12] and Australia.[13,14] Age, gender, type and severity of the stroke, history of previous stroke or transient ischemic attack (TIA), diabetes, and heart disease are among risk factors affecting mortality following a stroke that is reported in various studies.[8,15-18]

Studies have also been conducted in Iran on mortality following a stroke and its related factors.[19-22] In Mashhad study, factors associated with death within a year except for cases dying within the 1st week included age, type of stroke, NIHSS score, and a history of TIA.[23] In the study by Khosravi *et al*., age, a Glasgow Coma Scale Score of less than 13 and diabetes had a significant relationship with survival.[20] However, there is little knowledge of the extent of fatality and the factors affecting long-term mortality following a stroke in Iran, especially in the East Azerbaijan province. Many previous studies have been focused on ischemic stroke, whereas this study covers both ischemic and hemorrhagic types of stroke. The results of this study will enable clinicians to improve the management and clinical care of stroke patients. The current research was designed and implemented with the aim of investigating the extent of 2-year mortality following a stroke and the associated affecting factors.

Materials and Methods

This study was conducted using a prospective cohort study designed in Tabriz, Northwest of Iran. All hospitalized cases in Razi and Emam Reza (referral centers of Tabriz) from October 2013 to March 2015 were included and followed until 2 years after the onset of the stroke. Patients with first-ever ischemic stroke (embolic and thrombotic) and hemorrhagic stroke (intracerebral hemorrhage and subarachnoid hemorrhage), according to the International Classification of Diseases-10 system with definitive diagnosis based on computed tomography (CT) and magnetic resonance imaging (MRI) scans, were included in the study.

The inclusion criteria were first-ever stroke, residence in East Azerbaijan Province, consciousness, and voluntary consent to participate in the study, and the exclusion criteria were TIA and patients with a previous history of stroke. Census sampling method was used, and all cases that met the criteria for the study and those willing to participate were included in the study.[24]

Clinical examinations were conducted by a neurologist, and the related measures were obtained for all hospitalized patients. Next, the blood pressure and anthropometric measurements were taken and recorded in the patient's file. As suggested by a neurologist, CT scan and MRI were requested so that the disease could be definitively diagnosed.

Following the definitive diagnosis of stroke and obtaining the informed consent of the patient, patients' data were recorded in a checklist through an interview or using their file by an instructed expert. The data were composed of two parts: general characteristics, including age, gender, marital status, education, weight, height, monthly income, address, as well as the section regarding main stroke risk factors such as TIA history, history of heart attacks and stroke, family history of heart disease and stroke, family history of diabetes and high blood pressure, history of hypertension, diabetes, hyperlipidemia, heart disease, smoking, hookah or taking drugs and history of having contraceptive pills in women, the patient's blood pressure while being hospitalized and laboratory tests (fasting blood sugar, cholesterol, hematocrit, triglyceride, high-density lipoprotein, and low-density lipoprotein [LDL]). In cases where the patients were not able to talk, their close relatives were interviewed as a proxy.

To measure the severity of the stroke, the modified National Institutes of Health Stroke Scale (mNIHSS) with high reliability and validity[25,26] was administered by a neurology resident at the hospital. At least two contact numbers were obtained from patients and their companions and were recorded in their files, and they were instructed on how to follow-up until 2 years after the occurrence of the stroke, and the patient's consent was obtained.

As the cases measured in this study were patient's death or survival during the follow-up period, the Modified Rankin Scale[27] was administered by an instructed expert until 2 years after the occurrence of the stroke. In case of the patient's death, the exact date and cause of death were asked and recorded. Cases who did not reply to several follow-ups and cases who had died due to reasons other than stroke were considered right censored in the survival analysis.

Hypertension was defined as systolic blood pressure >139 mmHg and/or diastolic blood pressure >89 mmHg.[28] People with hemoglobin $A_1C \geq 6.5$ and/or fasting plasma glucose level ≥126 mg/dl and/or 2-hour plasma glucose level ≥200 mg/dl during an oral glucose tolerance test/and/or random plasma glucose ≥200 mg/dl or those with medical treatments for diabetes were

considered diabetes.[28] Hyperlipidemia was defined as triglyceride ≥150 mg/dl or LDL ≥130 mg/dl or total cholesterol ≥240 mg/dl.[29]

Statistical analysis

Descriptive statistics were used to describe variables as frequency and percentage. The Chi-square test and if the observed frequency was limited, Fisher's exact test was used. To estimate the survival function, Kaplan–Meier analysis was used, and for between groups comparison, the Log-rank method was applied.

To identify the factors predicting 2-year mortality, semiparametric Cox regression analysis was used. Variables with $P < 0.1$ were included in the final, multivariable Cox analysis. The data were analyzed using the IBM SPSS software (version 24) and StataCorp STATA (version 14). $P < 0.05$ was considered the statistical significance level.

Results

A total of 1036 first-ever stroke patients were included in the study, among whom 394 (38%) died due to stroke within 2 years and 24 (2.3%) died of causes other than stroke. Most deaths occurred within the 1st month after the occurrence of the stroke (56.8%). Follow-up was not completed for 64 patients (6.2%). The mortality rate of stroke in 6-month, 1-year, and 2-year follow-up periods was 31.6%, 34.5%, and 38%, respectively. Eight hundred and fifty-two patients (82.2%) had ischemic stroke, and 184 patients (17.8%) had hemorrhagic stroke. The mean age of the patients was 69.09 years with a standard deviation of 12.79 years, and 54.6% of participants were male. Regarding comorbid condition, 85.8% of the patients suffered from hypertension, 47.8% from diabetes, 27.8% from cardiovascular diseases, and 46.9% from hyperlipidemia.

According to Table 1, as the age increases, mortality also increases in such a way that the age group >75 years (53.4%) had the highest mortality compared to other age groups. Mortality was significantly higher in illiterate patients than in literate ones ($P < 0.001$). Mortality was also higher in single patients ($P = 0.01$). No statistically significant difference was seen between the two groups regarding gender and place of living [Table 1].

Two-year mortality rate was 33.6% in ischemic stroke patients and 58.7% in hemorrhagic stroke patients ($P < 0.001$). Two-year mortality rate following the stroke was 42% in patients with diabetes and 31.7% in patients without diabetes ($P < 0.001$). Mortality of patients with a body mass index (BMI) <25 (42.3%) was significantly higher than patients with BMI > 25 ($P < 0.001$). According to mNIHSS scores, the mortality rate in severe strokes with an index of mNIHSS ≥ 20 was the highest (80%), and it had a statistically significant relationship with a 2-year mortality rate ($P < 0.001$). No statistically significant difference was observed between the two groups regarding factors such as smoking, history of heart disease, heart attack and TIA, hypertension, and use of contraceptives [Table 2].

Table 1: Sociodemographic characteristics of study participants

Variable	All case, *n* (%)	Death within 2-year of stroke		*P**
		No, *n* (%)	Yes, *n* (%)	
Age				
<55	136 (13.1)	117 (86)	19 (14)	<0.001
55-64	214 (20.7)	115 (72.4)	59 (27.6)	
65-74	290 (28)	186 (64.1)	104 (35.9)	
≥75	395 (38.2)	186 (46.6)	211 (53.4)	
Sex				
Male	566 (54.7)	363 (64.1)	203 (35.9)	0.12
Female	469 (45.3)	279 (59.5)	190 (40.5)	
Marital status				
Yes	845 (81.60)	538 (63.7)	307 (36.3)	0.01
No	191 (18.4)	104 (54.5)	87 (45.5)	
Education				
Illiterate	697 (67.3)	398 (57.1)	229 (42.9)	<0.001
Under diploma	241 (23.3)	171 (71)	70 (29)	
Diploma and university	98 (9.5)	73 (74.5)	25 (25.5)	
Location				
Rural	288 (28)	178 (6108)	110 (38.2)	0.85
Urban	740 (72)	462 (62.4)	278 (37.6)	

*The level of statistical significance $P<0.05$

Survival rate of patients based on all variables was compared using the Log-rank test and showing a statistically significant difference between the mean 2-year survival of patients in terms of age, education, marital status, type of stroke, family history of stroke, diabetes, hyperlipidemia, BMI, and severity of stroke [Figure 1].

In a univariate analysis, factors such as age, marital status, education, BMI, type of stroke, family history of stroke, diabetes, hyperlipidemia, and the mNIHSS had a statistically significant relationship with a 2-year mortality rate. Two-year mortality risk in hemorrhagic stroke was 2.37 times higher than patients with ischemic stroke. People with diabetes and hypertension had a 1.41 and 1.15 higher risk of mortality than those with no diabetes and hypertension. However, this difference for diabetes was statistically significant at $P = 0.001$ and not significant for hypertension ($P = 0.34$). Female sex and a history of heart attack increased mortality risk, though not statistically significant. Regarding marital status, patients without spouse had 1.27 mortality risk higher than married patients. Illiterate patients showed 1.95 higher risk of mortality than patients holding a diploma or a higher degree [Table 3].

Table 2: Major risk factor for study participants

Variable	All case, *n* (%)	Death within 2 years of stroke		*P**
		No, *n* (%)	Yes, *n* (%)	
BMI				
<25	482 (49.5)	278 (57.7)	204 (42.3)	<0.001
25-29/9	342 (35.1)	231 (67.5)	111 (32.5)	
≥30	150 (15.4)	110 (7303)	40 (26.7)	
Stroke type				
Ischemic	852 (82.2)	566 (66.4)	286 (33.6)	<0.001
Hemorrhagic	184 (17.8)	76 (41.3)	108 (58.7)	
History of heart attack				
No	982 (95.2)	612 (62.3)	370 (37.7)	0.74
Yes	50 (4.8)	30 (60)	20 (40)	
Previous TIA				
No	980 (96.7)	615 (62.8)	365 (37.2)	0.91
Yes	33 (3.3)	21 (63.6)	12 (36.4)	
History of heart disease				
No	744 (72.2)	456 (61.3)	288 (38.7)	0.34
Yes	287 (27.8)	185 (64.5)	102 (35.5)	
Family history of stroke				
No	819 (79.4)	487 (59.5)	332 (40.5)	<0.001
Yes	212 (20.6)	155 (73.1)	57 (26.9)	
Current smoker				
No	870 (85.1)	541 (62.2)	329 (37.8)	0.31
Yes	152 (14.9)	101 (66.4)	51 (33.6)	
Passive smoker				
No	897 (88.3)	564 (62.8)	334 (37.2)	0.89
Yes	119 (11.7)	74 (62.5)	45 (28.1)	
Opium consumer				
No	986 (97)	618 (62.7)	368 (73.3)	0.65
Yes	30 (3)	20 (66.7)	10 (33.3)	
Oral contraceptive				
No	369 (85)	222 (60.2)	147 (39.8)	0.10
Yes	65 (15)	46 (70.80)	19 (29.2)	
Diabetes mellitus				
No	511 (52.2)	349 (68.3)	162 (31.7)	<0.001
Yes	467 (47.8)	271 (58)	196 (42)	
Hypertension				
No	146 (14.20)	96 (65.8)	50 (34.2)	0.34
Yes	879 (85.80)	542 (61.7)	337 (38.3)	
Hyperlipidemia				
No	517 (53.1)	289 (55.9)	228 (44.1)	<0.001
Yes	456 (46.9)	323 (70.8)	133 (29.2)	
mNIHSS				
Minor ≤5	337 (36.3)	295 (89.1)	36 (10.9)	<0.001
Moderate 6-19	472 (51.7)	281 (59.5)	191 (40.5)	
Moderate to severe ≥20	110 (12)	22 (20)	88 (80)	

BMI=Body mass index, mNIHSS=modified National Institutes of Health Stroke Scale, TIA=Transient ischemic attack. *The level of statistical significance *P*<0.05

After adjusting age and gender, variables such as BMI, type of stroke, family history of stroke, diabetes, hyperlipidemia, and the mNIHSS score showed a statistically significant relationship with a 2-year mortality rate. Smoking, taking medication, and contraceptives and passive smoking increased the risk of 2-year mortality 1.12, 1.25, 1.04, and 1.05 times, respectively, although none of these variables had a significant relationship with 2-year mortality. In this model, illiterate patients showed 1.24 times higher risk of mortality than patients holding a diploma or a higher degree, though not statistically significant.

In the multivariate Cox model, variables such as age, type of stroke, diabetes, and severity of stroke, according to the mNIHSS, were identified as factors predicting 2-year mortality following the stroke. As the age increases, the risk of 2-year mortality also increases in a way that patients

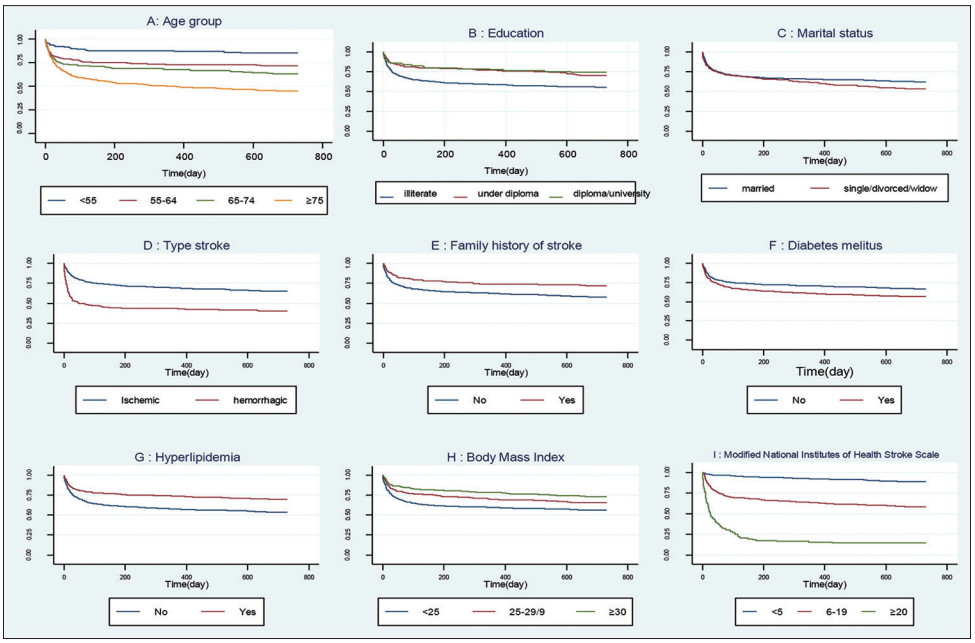

Figure 1: Kaplan–Meier survival estimates by age group in A (*P < 0.001); by education in B (*P < 0.001); by marital status in C (*P = 0.04); by stroke subtype in D (*P < 0.001); by family history of stroke in E (*P < 0.001); by diabetes mellitus in F (*P = 0.001); by hyperlipidemia in G (*P < 0.001); by body mass index in H (*P < 0.001); by stroke severity in I (*P < 0.001) *P value are based on Log Rank

in the age group of 55–64 years showed 2.06 times, the age group of 65–74 years showed 2.06 times, and the age group ≥75 years showed 3.98 times risk of higher mortality than the age group of below 55 years. Having diabetes and hemorrhagic stroke increased the risk of 2-year mortality 1.40 and 1.44 times, respectively. Patients with a mNIHSS score of 6–19 and ≥20 had 3.62 and 12.92 times higher mortality, respectively, compared to people with mNIHSS ≤5 [Table 3].

Discussion

The current study aimed at investigating 2-year mortality following the first-ever stroke and identifying its predictors in the East Azerbaijan Province, Northwest of Iran. According to the results of this study, the rate of 2-year mortality was 38% (33.6% ischemic stroke and 58.7% hemorrhagic stroke), respectively. These results are almost in line with the study conducted in the Northeast of Iran.[23] Various studies have been conducted in different parts of the world to investigate the long-term mortality of stroke. In a study by Chang *et al*. carried in Taiwan, the mortality rate of ischemic stroke was 12.2%, 15.8%, 20.5%, and 25.6%, respectively, for 1–4 years after the occurrence of stroke.[30] In a study conducted in Denmark, mortality rates 1 year and 5 years following the occurrence of stroke were 41% and 60%, respectively.[31] In a study conducted in Brazil, cumulative mortality rates 1 year, 2 years, and 3 years after the stroke were 27.8%, 31.2%, and 33.4%, respectively.[32] Compared with the above-mentioned studies, the mortality rate in Iran was less than Taiwan and Brazil but more than Denmark. That might be because of the difference in patient's characteristics or health-care system.

In age- and sex-adjusted Cox analysis, BMI, type of stroke, family history of stroke, hyperlipidemia, diabetes, and severity of the stroke were associated with 2-year mortality. Patients with hyperlipidemia and those with higher BMI had a lower risk of mortality suggesting a protective role against mortality. Markaki *et al*. showed that the risk of long-term mortality increased in patients with low cholesterol that is in line with the results of the present study.[33] Recently, a prospective cohort study investigating the relationship among consuming fats, cardiovascular diseases, and stroke has shown that the use of various types of fat causes a reduction in mortality following a stroke.[34] Other studies also showed reduced mortality among patients with higher BMI.[35] The mechanism to explain how increased BMI might have a protective effect against stroke morality is not clear, further longitudinal studies are required to examine dietary habits after stroke, calorie intake, and the role of adipocytokines.[36] In our study, the risk of mortality in patients with a family history of stroke was lower that was different from the results of previous studies in Iran.[23]

In Cox multivariate analysis, age, type of stroke, the severity of stroke, and diabetes were main factors affecting 2-year mortality. As the age increased, mortality risk also increased in a way that ≥75-year-old patients had 3.98 times higher risk of mortality. In other studies

Table 3: Univariable and adjusted by sex, age group and multivariate survival analysis of suspected for death (Cox proportional hazards)

Variable	Univariable		Adjusted for sex, age group		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (ref <55)						
55-64	2.15 (1.28-3.62)	0.004			2.06 (1.08-3.91)	0.02
65-74	2.92 (1.79-4.76)	<0.001			2.75 (1.47-5.15)	0.001
≥75	4.80 (3.00-7.67)	<0.001			3.98 (2.17-7.29)	<0.001
Sex (female)	1.19 (0.97-1.45)	0.07			1.04 (0.79-1.37)	0.77
Marital status (single/divorced/widow)	1.27 (1.00-1.61)	0.04	1.01 (0.79-1.31)	0.88	0.94 (0.68-1.30)	0.74
Education (ref diploma and university)						
Under diploma	1.13 (0.72-1.79)	0.57	0.91 (0.57-1.45)	0.71	1.37 (0.73-2.57)	0.31
Illiterate	1.95 (1.29-2.93)	0.001	1.24 (0.8-1.90)	0.32	1.44 (0.79-2.61)	0.23
BMI (ref <25)						
25-29/9	0.69 (0.55-0.87)	0.002	0.76 (0.60-0.96)	0.02	0.96 (0.73-1.26)	0.79
≥30	0.52 (0.37-0.73)	<0.001	0.55 (0.39-0.78)	0.001	0.85 (0.57-1.24)	0.40
Location (Urban)	0.97 (0.78-1.21)	0.80	0.96 (0.77-1.19)	0.72		
Stroke type (hemorrhagic)	2.37 (1.90-2.96)	<0.001	2.64 (2.11-3.30)	<0.001	1.44 (1.06-1.97)	0.01
Hitory of heart attack	1.11 (0.70-1.74)	0.64	1.18 (0.75-1.85)	0.46		
Pervious TIA	0.85 (0.48-1.51)	0.58	0.84 (0.47-1.50)	0.57		
History of heart disease	0.87 (0.69-1.09)	0.24	0.84 (0.67-1.05)	0.14		
Family history of stroke	0.59 (0.44-0.78)	<0.001	0.67 (0.50-0.88)	0.006	0.77 (0.55-1.07)	0.12
Current smoker	0.83 (0.62-1.11)	0.22	1.12 (0.82-1.52)	0.46		
Passive smoker	1.00 (0.73-1.36)	0.98	1.05 (0.76-1.45)	0.73		
Opium consumer	0.87 (0.46-1.64)	0.68	1.25 (0.66-2.37)	0.48		
Oral contraceptive user	0.72 (0.44-1.16)	0.18	1.04 (0.63-1.70)	0.87		
Diabetes mellitus	1.41 (1.14-1.73)	0.001	1.47 (1.19-1.82)	<0.001	1.40 (1.09-1.81)	0.009
Hypertension	1.15 (0.85-1.55)	0.34	0.93 (0.68-1.26)	0.65		
Hyperlipidemia	0.57 (0.43-0.70)	<0.001	0.61 (0.48-0.76)	<0.001	0.94 (0.72-1.22)	0.67
mNIHSS (ref minor ≤5)						
Moderate to severe 6-19	4.62 (3.23-6.60)	<0.001	3.90 (2.72-5.59)	<0.001	3.62 (2.46-5.33)	<0.001
Severe ≥20	17.63 (11.90-26.11)	<0.001	15.06 (10.08-22.50)	<0.001	12.92 (8.20-20.35)	<0.001

HR=Hazard ratio, CI=Confidence interval, BMI=Body mass index, mNIHSS=modified National Institutes of Health Stroke Scale, TIA=Transient ischemic attack.
*The level of statistical significance *P*<0.05

done in Iran, age has been recognized as a factor affecting mortality.[20,23] This is also confirmed in studies carried out in other parts of the world.[30,36-38]

In the present study, the risk of 2-year mortality following hemorrhagic stroke was 1.44 times higher than ischemic stroke. The relationship between long-term mortality following a stroke has been confirmed by various studies conducted in Iran and other parts of the world. In other studies, hemorrhagic stroke with HR = 1.86[23] and HR = 1.56[39] was factors affecting mortality from stroke.

In this study, diabetes increased the risk of 2-year mortality following stroke 1.40 times. This has been shown in many studies, for example, Goulart *et al*. showed having diabetes increased the risk of 2-year mortality 1.45 times.[36] In a study by Wang *et al*., diabetes mellitus with HR = 1.20 had a significant relationship with stroke mortality.[40]

The severity of stroke at admission is a crucial factor that predicts mortality. In this study, patients with a mNIHSS score of 6–19 had 3.62 times and patients with mNIHSS ≥20 and 12.92 times higher risk of mortality than patients with mNIHSS ≤5. The severity of stroke in various studies has been identified as a factor predicting mortality. For example, a study in Iran, the NIHSS with HR = 1.13 had a significant association with 1-year mortality.[23] In other studies that have been carried out in other parts of the world,[16,18] the association between the severity of stroke and mortality was shown.

Conclusion

The present study is the first long-term study conducted in the East Azerbaijan Province, Northwest of Iran. It provides useful information about an epidemiologic picture of this disease and factors affecting mortality from stroke in the region. Being a hospital-based study is a limitation of this research that makes it difficult to generalize the findings to the population. Therefore, it is suggested that the results be interpreted with caution. Further population-based longitudinal studies are recommended.

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Conflicts of interest

There are no conflicts of interest.

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