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Original Article

Exploring Laboratory Predictors of Early Mortality in Patients with Stroke Referred to the Emergency Department: A Case-Control Study

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Abstract

Background: Considering high mortality and morbidity in patients with stroke, identification of predictors of poor prognostic outcomes after stroke is vital for stroke management strategies. This study aimed to evaluate the clinical and laboratory characteristics of patients with stroke to determine the prognostic factors of early mortality within 72 *hrs* of admission.

Methods: This case-control study included patients with stroke attending the emergency department from March-June 2023. The patients were divided into two groups, who died early within 72 *hr* of admission (case group=135) and those who survived and/or expired lately after three days (control group=138).

Results: The mean age of the case group was significantly higher than the control group (68.53 *vs.* 64.78, p=0.04). No significant correlations were found between early death and gender distribution, marital status, and type of stroke (p>0.05). The overall rate of underlying diseases in case group (85.9%) was higher (71.74%, p=0.005, OR [95%CI]:2.4[1.3_4.428]). The mean levels of WBCs, ESR, RDW-SD, triglycerides, and blood sugar in case group were significantly higher (p<0.05). Moreover, adjusted models showed that underlying disease (p=0.035, OR[95%CI]:2.034[1.052-3.934]) and high levels of WBCs (p=0.025, OR[95%CI]:1.067 (1.008-1.129)]), RDW-SD (p=0.018, OR[95%CI]:1.11[1.018-1.21]) and triglycerides (p=0.045, OR[95%CI]:1.005 [1-1.01]) were independently associated with high risk of early lethal within 72 *hr*.

Conclusion: Older age and underlying diseases can be risk factors for stroke-related early death within 72 *hr*. Moreover, underlying disease and high levels of WBCs, RDW-SD, and triglycerides may independently be predictive of early in-hospital death in patients with stroke.

Keywords: Blood glucose, Emergency Service, Hospital, Hospital mortality, Humans, Morbidity, Prognosis, Risk Factors, Stroke

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Introduction

Stroke is a rapidly progressive local or widespread neurological disorder with cerebrovascular origin that lasts more than 24 *hr* or leads to death. In stroke, the brain cells in a specific area are destroyed due to insufficient or complete blockage of blood flow, and subsequently, the delivery of oxygen and nutrients to the brain is also stopped (1). Stroke is one of the most common types of chronic diseases with acute adverse events. Identification and control of risk factors of chronic diseases is the best way to reduce mortality (1,2). Depending on the area of the brain where the blood flow is blocked, the patient may face sudden death and/or long-term adverse outcomes, such as speech disorder, unilateral paralysis, and dementia. Therefore, treatment of stroke should be started within 3 to 6 *hrs* upon diagnosis; otherwise, it leads to serious complications (3).

There are two types of brain stroke: ischemic and hemorrhagic. Ischemic stroke accounts for 70-80% of stroke cases and occurs when a blood vessel in the brain is clogged. In comparison, the hemorrhagic type comprises only 10-30% of all cases. The hemorrhagic type is the deadliest and occurs with bleeding (4). Stroke is the second most common cause of death and the third most common cause of disability in the world. In developed countries, stroke is the third most common cause of death, after cardiovascular diseases and malignant tumors (5). A broad range of risk factors can increase the risk of stroke, such as older age, hypertension, obesity, high Low-Density Lipoprotein (LDL) cholesterol, high triglycerides, diabetes, smoking, and underlying cardiovascular diseases. High levels of LDL cholesterol and triglycerides increase the risk of atherosclerosis. Also, hypertension can induce stroke through an immense alteration in endothelium and smooth muscle in intracerebral arteries (6,7).

Identification of prognostic factors of early lethality of stroke is useful for better management of patients with stroke and for reducing the mortality rate (8). Accordingly, in the present study, the clinical and laboratory characteristics of patients with stroke were analyzed in order to determine the prognostic factors of early death within 72 *hr*.

Materials and Methods

Study design

This analytical and case-control study included patients with stroke attending the emergency department of Golestan Hospital in Ahvaz city of Iran from 21 March to 22 June 2023. All the procedures involving the human participants were in accordance with the ethical standards of the national research committee and with the 2008 Helsinki Declaration and its later comparable ethical standards. Also, all the procedures were approved by the Ethical Committee in the research deputy of Ahvaz Jundishapur University of Medical Sciences (Ethical Code: IR.AJUMS.HGOLESTAN.1401.075).

The inclusion criteria included patients over 18 years of age who had been referred to the emergency department with a final diagnosis of ischemic or hemorrhagic stroke. The patients with moderate to severe stroke based on the NIH Stroke Scale/Score (NIHSS) were evaluated. Head CT or MRI diagnosed strokes upon admission or during hospitalization. Exclusion criteria were considered as follows; patients with brain tumors, cerebral venous sinus thrombosis, brain abscess, and expired patients in prehospital emergency services.

Variables and measurements

All the demographic, clinical, and laboratory data of the patients were collected. Blood sampling was done within 24 *hr* after admission to measure the laboratory factors within 2 *hr* after blood sampling, including complete blood count, Erythrocyte Sedimentation Rate (ESR), Hematocrit (HCT), triglycerides, total cholesterol, (LDL) cholesterol, High-Density Lipoprotein (HDL) cholesterol, Lactate Dehydrogenase (LDH), and Blood Sugar (BS).

The patients were followed up to the date of discharge and/or death in the hospital by a nurse along with two investigators. Patients' demographic, clinical and laboratory characteristics were extracted from their medical records and recorded in data sheets for

Statistical analysis

After completing the minimum required sample size, the patients were divided into two groups, including patients who died early within 72 *hr* of admission and those who survived and/or died late after three days (control group). Then, their demographic, clinical, and laboratory factors measured upon admission were compared. The control group was matched with the

case group only regarding gender, since age was also one of the study factors.

Sample size

According to the study objectives, previous studies (9) and considering α=0.05, β=0.9, d=10 and S=23.11, the sample size was calculated using the following formula:

Z1-α/2=1.95 for 90% confidence interval

Zβ=1.28 for 90% of power

$N=2\times(Z1-\alpha/2+Z\beta)^2\ S^2/d^2=111$

Nevertheless, the maximum number of eligible patients were recruited to discover the exact relationship between the variables and outcomes.

Statistical analysis

Smirnov–Kolmogorov test was used to check the normality of the data. The variables were expressed as mean and Standard Deviation (SD) and/or frequency based on their statistical nature. Continuous variables were presented as mean±SD, and for data with non-normal distributions the median and IQR were used. The categorical variables were presented as frequency and percentage, and compared by Chi-square test. Both univariate and multivariate logistic regression models were applied to calculate Odds Ratios (ORs) and 95% confidence interval for occurrence of mortality in patients with stroke. A p-value less than 0.05 was considered significant. SPSS 26 statistical software (IBM Corp., Armonk, NY, USA) was used for statistical analysis.

Results

Baseline characteristics of the patients

In total, 273 patients, including 155 men with a mean age of 65.61±17.38 years and 118 women with a mean age of 67.95±11.7 years, were evaluated in this study. The average age of the patients who died early was significantly higher than those in control group (p=0.041). Out of 273 patients, 130 cases were diagnosed with ischemic stroke, and 143 cases had hemorrhagic stroke. There were no significant differences in gender distribution (p=0.264), marital status (p=0.142), and type of stroke (p=0.991) between the two studied groups. However, the overall rate of underlying diseases in patients who died early within 72 *hr* (85.9%) was higher than those in control group (71.74%, p=0.005, OR [95% CI]: 2.4 [1.3_4.428]) (Table 1).

Laboratory findings

The mean levels of White Blood Cells (WBCs) (p=011), ESR (p=0.023), Red Cell Distribution Width-Standard Deviation (RDW-SD) (p=0.007), triglycerides (p=0.011), and BS (p=0.001) in patients who died early within 72 *hr* were significantly higher than those in control group (Table 1).

Predictors of early lethal in patients with stroke

Univariate and multivariable logistic regression models were adjusted by considering all the significant related factors to analyze the association between the variables and early lethality. The statistical results indicated that underlying disease (p=0.035, OR [95%CI]:2.034 [1.052-3.934]) and high levels of WBC (p=0.025, OR [95%CI]: 1.067 (1.008-1.129)]), RDW-SD (p=0.018, OR [95%CI]: 1.11 [1.018-1.21]) and triglycerides (p=0.045, OR [95%CI]: 1.005 [1-1.01]) were independently associated with high risk of early lethal within 72 *hr* in patients with stroke.

In further analysis, the prediction factors were compared between two types of strokes, hemorrhagic and ischemic. There were no significant differences between two types of strokes for sex (p=0.435), age (p=0.073), marital status (p=0.824), and underlying disorders (p=0.471) (Table 3).

The mean levels of Platelet count (PLT) (p=0.002), lymphocyte count (p<0.001), RDW-SD (p<0.001), RDW-CV (p<0.001), total cholesterol (p=0.042), and LDL (p=0.003) were significantly higher in patients with hemorrhagic stroke (Table 3). In contrast, ESR (p<0.001), and BS (p=0.037) were significantly higher in patients with ischemic stroke (Table 3).

Univariate and multivariable logistic regression models were adjusted by considering all the significant related factors to analyze the association between the variables and type of stroke. The multivariant results demonstrated that lymphocyte count (p<0.001, OR [95%CI]:0.998 [0.997-1.934]) and higher RDW-SD (p=0.011, OR [95%CI]: 1.236 (1.049-1.457)]), and RDW-CD (p=0.021, OR [95%CI]: 1.687 [1.083-2.627]) were independently associated with high risk of hemorrhagic stroke (Table 4).

Table 1. Comparison of demographics, clinical, and laboratory findings between the two groups of studied patients

Variables	Patients who died early within 72 *hr* (n=135)	Control group (n=138)	p-value
Gender, n(%)			
Male	68(50.4)	87(63)	0.264
Female	67(49.6)	51(37)	
Age (year), Mean±SD	68.53±12.25	64.78±17.42	0.041
Marital status, n(%)			
Married	70(51.85)	86(63.3)	0.142
Single	65(48.15)	52(36.7)	
Underlying diseases, n(%)	116(85.9)	99(71.74)	0.005
BPH	0	1	
DM	43	43	
CHF	1	0	
CVA	5	0	
HTN	55	58	
HF	4	4	
CKD	1	0	
HLP	4	6	
IHD	3	1	0.052 (Fisher exact)
MI	1	0	
RA	0	1	
Type of stroke, n(%)			
Ischemic stroke	64(47.4)	66(47.8)	0.991
Hemorrhagic stroke	71(52.6)	72(52.2)	
WBC ($10^3/\mu L$), Mean±SD	12.05±14.2	8.78±4.17	0.011
RBC ($10^3/\mu L$), Mean±SD	6.95±30.88	4.23±0.81	0.374
Hemoglobin (*g/L*), Mean±SD	12.16±2.71	12.41±2.53	0.436
Hematocrit (%), Mean±SD	35.96±6.12	36.52±5.94	0.441
PLT ($10^9/L$), Mean±SD	231.78±93.74	231.71±82.74	0.992
Lymphocytes count ($10^3/\mu L$), Mean±SD	13.69±8.17	14.51±7.94	0.403
Neutrophils count ($10^3/\mu L$), Mean±SD	81.04±9.35	79.28±10.09	0.133
RDW-SD, Mean±SD	44.61±4.82	43.27±3.1	0.007
RDW-CV, Mean±SD	13.64±1.92	13.55±3.45	0.784
ESR (*mm/hr*), Mean±SD	26.6±23.25	20.85±17.03	0.023
Triglycerides (*mg/dL*), Mean±SD	176.14±61.56	159.1±47.21	0.011
Total cholesterol (*mg/dL*), Mean±SD	171.57±55.82	168±40.28	0.548
HDL (*mg/dL*), Mean±SD	48.55±12.17	50.06±11.15	0.281
LDL (*mg/dL*), Mean±SD	87.75±50.79	86.09±33.79	0.756
LDH (*U/L*), Mean±SD	599.7±296.94	545.32±199.55	0.081
FBS (*mg/dL*), Mean±SD	189.6±119.49	148.88±85.9	0.001

Abbreviations: BPH: Benign Prostatic Hyperplasia, DM: Diabetes Mellitus, CHF: Congestive Heart Failure, CVA: Cerebral Vascular Accident, HTN: Hypertension, HF: Heart Failure, CKD: Chronic Kidney Disease, HLP: Hyper Lipidemia, IHD: Ischemic Heart Disease, MI: Myocardial Infarction, RA: Rheumatoid Arthritis, PLT: Platelet Count, RDW-SD: Red cell Distribution Width-Standard Deviation, RDW-CV: Coefficient of Variation of Red Blood Cell Distribution Width, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, LDH: Lactate De Hydrogenase, FBS: Fasting Blood Sugar.

Table 2. Univariate and multivariable logistic regression models to predict early lethal by analyzing the association between the variables and the early lethal

Variables	Univariate					Multivariable				
	B	S.E.	Wald	p-value	OR (95% CI)	B	S.E.	Wald	p-value	OR (95% CI)
Age	0.017	0.008	4.1	0.043	1.017 (1.001-1.034)	0.013	0.009	1.975	0.16	1.013 (0.995-1.031)
Underlying disease	0.878	0.311	7.940	0.005	2.4 (1.306-4.428)	0.710	0.337	4.452	0.035	2.034 (1.052-3.934)
WBC	0.063	0.026	6.068	0.014	1.065 (1.013-1.121)	0.065	0.029	5.040	0.025	1.067 (1.008-1.129)
RDW-SD	0.094	0.037	6.327	0.012	1.099 (1.021-1.182)	0.105	0.044	5.637	0.018	1.11 (1.018-1.21)
ESR	0.014	0.006	5.131	0.024	1.014 (1.002-1.027)	0.010	0.007	2.440	0.118	1.011 (0.997-1.024)
Triglycerides	0.006	0.002	6.31	0.012	1.006 (1.001-1.01)	0.005	0.003	4.028	0.045	1.005 (1-1.01)
Fasting BS	0.004	0.001	9.464	0.002	1.004 (1.001-1.006)	0.002	0.001	2.280	0.131	1.002 (0.999-1.005)

Table 3. Comparison of demographics, clinical, and laboratory findings between patients with hemorrhagic and ischemic strokes

Variables	Hemorrhagic (n=143)	Ischemic (n=130)	p-value
Gender, n(%)			
Male	65(55.1)	78(50.3)	0.435
Female	53(44.9)	77(49.7)	
Age (year), Mean±SD	66.43±16.86	66.82±13.18	0.073
Marital status, n(%)			
Married	85(59.4)	69(53)	0.824
Single	58(40.6)	61(47)	
Underlying diseases, n(%)	111(51.6)	104(48.4)	0.471
BPH	0	1	0.325
DM	46	36	
CHF	2	2	
CVA	3	0	
HTN	48	55	
HF	4	2	
CKD	2	0	
HLP	3	4	
IHD	2	1	
MI	1	0	
RA	0	1	
WBC ($10^3/\mu L$), Mean±SD	9.71±6.46	11.14±13.66	0.246
RBC ($10^3/\mu L$), Mean±SD	4.25±0.86	4.27±0.88	0.819

Contd. table 3.

Hemoglobin(*g/L*), Mean±SD	12.20±2.63	12.38±2.61	0.628
Hematocrit(%), Mean±SD	36.37±6.15	36.09 ±5.90	0.495
PLT(10^9/*L*), Mean±SD	247.52±96.46	214.41±74.68	0.002
Lymphocytes count(10^3/*μL*), Mean±SD	17.10±5.20	10.69±9.27	<0.001
Neutrophils count (10^3/*μL*), Mean±SD	78.83±6.03	71.26 ±14.41	0.302
RDW-SD, Mean±SD	42.61±0.81	45.41±5.53	<0.001
RDW-CV, Mean±SD	12.94±0.33	14.31±3.92	<0.001
ESR (*mm/hr*), Mean±SD	20.69±19.81	26.99±20.82	<0.001
Triglycerides (*mg/dL*), Mean±SD	167.93±43.75	167.09±65.95	0.431
Total cholesterol (*mg/dL*), Mean±SD	171.45±31.04	167.92±62.44	0.042
HDL (*mg/dL*), Mean±SD	49.42±8.91	49.20±14.14	0.271
LDL (*mg/dL*), Mean±SD	88.38±23.39	85.29±57.32	0.003
LDH (*U/L*), Mean±SD	568.66±239.14	576.12±269.19	0.445
FBS (*mg/dL*), Mean±SD	166.18±111.37	172.14±99.44	0.037

Abbreviations: BPH: Benign Prostatic Hyperplasia, DM: Diabetes Mellitus, CHF: Congestive Heart Failure, CVA: Cerebral Vascular Accident, HTN: Hypertension, HF: Heart Failure, CKD: Chronic Kidney Disease, HLP: Hyper Li Pidemia, IHD: Ischemic Heart Disease, MI: Myocardial Infarction, RA: Rheumatoid Arthritis, PLT: Platelet Count, RDW-SD: Red Cell Distribution Width-Standard Deviation, RDW-CV: Coefficient of Variation of Red Blood Cell Distribution Width, HDL: High-Density Lipoprotein, LDL: Low-Density Lipoprotein, LDH: Lactate De Hydrogenase, FBS: Fasting Blood Sugar.

Table 4. Univariate and multivariable logistic regression models to predict early lethal by analyzing the association between the variables and the type of stroke

Variables	Univariate					Multivariable				
	B	S.E.	Wald	p-value	OR (95% CI)	B	S.E.	Wald	p-value	OR (95% CI)
PLT	-0.005	0.001	9.208	0.002	0.995 (0.993-0.998)	-0.003	0.002	2.521	0.112	0.997 (0.994-1.001)
Lymphocyte count	-0.001	0.002	37.739	<0.001	0.999 (0.998-0.999)	-0.002	0.000	19.103	<0.001	0.998 (0.997-1.934)
RDW-SD	0.343	0.067	26.45	<0.001	1.409 (1.236-1.605)	0.212	0.084	6.414	0.011	1.236 (1.049-1.457)
RDW-CV	1.078	0.2	29.106	<0.001	2.939 (1.987-4.348)	0.523	0.226	5.356	0.021	1.687 (1.083-2.627)
ESR	0.016	0.006	6.102	0.014	1.016 (1.003-1.029)	0.008	0.007	1.362	0.243	1.008 (0.994-1.023)
LDL	-0.002	0.003	0.349	0.555	0.998 (0.993-1.004)	-0.004	0.003	1.732	0.188	0.996 (0.989-1.002)
FBS	0.001	0.001	0.217	0.642	1.001 (0.998-1.003)	0.002	0.001	2.635	0.105	1.002 (1-1.005)

Discussion

Prediction of prognosis in patients with stroke is critical due to its high mortality and morbidity. Also, the information related to survival and improvement of patient function after acute stroke is vital in applying appropriate treatment management strategies (10). The findings of the present study showed that the average age of patients who died early within 72 *hrs* of admission was significantly higher than those who survived and/or died later after three days. Overall, in Western countries, stroke often occurs in younger

adults, while in other countries like China and Iran, stroke often occurs in older ages (11). In this regard, Gattringer *et al* in 2019 in Austria indicated that the average age in 1567 patients who died early because of acute ischemic stroke was 81.9 years, and majority of the deceased patients (43.1%) were in the age group of 80-89, while the average age in 76086 survived patients was 73.8 years (12).

In this study population, most of the patients who died early had hemorrhagic stroke (n=71) and were in an age range (28-92 years) lower than those who died of ischemic stroke (n=64, 46-99 years). This implies that the type of stroke may also play a key role in predicting the age range related to early death in these patients. This finding confirmed WM *et al*'s report (13). Also, according to a recent study by Szlachetka *et al*, older age is considered an independent predictor of patient death, especially after ischemic stroke (14).

In the present study, no significant correlation was found between gender and early mortality, since the control group was matched with the case group in terms of gender distribution. However, based on a meta-analysis study conducted by Abdel-Fattah *et al* in 2022, the stroke-related death rate was higher in women than in men, which may be due to the higher rate of pre-existing co-morbidities in female patients. Moreover, adjusted models revealed that the in-hospital mortality rate in women with hemorrhagic stroke was higher than that in men with hemorrhagic stroke. Conversely, in-hospital mortality was lower in women with ischemic stroke than in men with ischemic stroke. However, no significant gender difference was observed after hospital discharge (15).

In the study population, the number of married patients in both groups was higher than that of unmarried patients, though no significant correlation was found between marital status and early death. By contrast, Dupre *et al* reported that the risk of death associated with divorce and widowhood was respectively 23 and 25 times higher than those with a stable marriage (16). Such discrepancies in findings may be due to our study's much smaller sample size than other studies, which limits coming to an accurate conclusion.

Furthermore, present findings showed that the levels of WBCs, ESR, RDW-SD, triglycerides, and blood sugar in patients who died early within 72 *hrs* were significantly higher than those who died lately and/or survived (control group). Also, adjusted models indicated that only underlying disease and high levels of WBCs, RDW-SD and triglycerides were independently associated with a high risk of early in-hospital death in patients with stroke. The findings regarding the strong association between underlying diseases and in-hospital death caused by stroke confirm the reports of previous studies (6,17,18). Also, Ani *et al* reported that a higher RDW level (<13.90% *vs.* ≥12.75%) among patients with stroke was independently predictive of mortality (HR=2). An increase in RDW often occurs due to impaired production of red blood cells, which indicates a poor prognosis and ability to recover from illness (19). Anemia can induce a reduction in cerebral microcirculation below ischemic thresholds and leads to impaired blood circulation and increased brain damage (20,21). Wang *et al* conducted a comprehensive large-scale study on 1,558 patients with stroke. Their results revealed that higher RDW and lower hemoglobin levels could influence long-term mortality in patients with stroke (22).

The results regarding the independent and strong association of high levels of triglycerides with a high risk of early in-hospital death in patients with stroke confirmed the reports of the previous studies (23-25). Hypertriglyceridemia may increase the risk of stroke and death by promoting thrombosis, atherosclerosis, and hyper viscosity (26).

Study strengths and weaknesses

The present study is one of the rare studies in the southwest of Iran that assessed the clinical and laboratory characteristics of patients with stroke to determine the prognostic factors of in-hospital early death within 72 *hr* of admission. Also, this study provides an initial database on early mortality in patients with stroke, which can be useful for stroke management strategies in hospitals. However, this study has some limitations. First, its retrospective nature made the results prone to bias. Second, the study's small sample size limited the coming of a definitive conclusion. Furthermore, the single-center design of the study limited the generalizability of the results to the entire population of a region. Finally, comparing the various degree of strokes based on

the NIHSS gave us insightful data, which was not evaluated in the present investigation.

Conclusion

Findings of the present study demonstrated that older age and underlying diseases can be risk factors for early death within 72 *hr* in patients with stroke. Also, the type of stroke may play a key role in predicting the age range related to early death in these patients. High levels of WBCs, ESR, RDW-SD, triglycerides, and blood sugar were associated with early death in these patients. Moreover, adjusted models indicated that only underlying disease and high levels of WBCs, RDW-SD, and triglycerides may independently be predictive of early in-hospital death in patients with stroke.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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