

Original Article

Investigating predicting factors for premature death in patients with acute ischemic stroke

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Received: 12 November 2024; **Revised:** 16 March 2025; **Accepted:** 18 March 2025

ABSTRACT

This study identifies prognostic factors for premature mortality in patients with acute ischemic stroke. As a retrospective observational study, it was based on hospital information on patients with acute ischemic stroke referred to Golestan Ahvaz Hospital from February 2022 to the end of July 2023. Premature mortality was recorded in the first 14 days after stroke. It used a multivariable logistic regression model to identify factors of early death in patients.

619 acute ischemic stroke patients participated in this study (mean age 66.01 ± 13.86 years, 47.33% female). The frequency of premature death after stroke was 7.75% (95% CI: 5.31 - 9.83%). High severity of stroke (OR: 12.24; $P < 0.0001$), old age (OR: 2.86; $P = 0.001$), mRS score > 0 (OR: 5.68; $P = 0.0001$), presence of AF (OR: 9.35; $P < 0.0001$), ischemic heart disease (OR: 4.65; $P = 0.0001$), cerebrovascular disease (OR: 2.06; $P = 0.016$), level of consciousness (OR: 1.98; $P = 0.030$), and high white blood cell count at hospital admission (OR: 2.11; $P = 0.002$) are independently associated with increased risk of premature death. In contrast, antiplatelet therapy ($P = 0.001$) and thrombolytic therapy ($P < 0.0001$) were associated with a decrease in mortality. Likewise, hypertension, heart failure, use of statins, and accompanying initial symptoms with seizures were associated with premature death only in univariate analysis. Acute ischemic stroke was associated with a high mortality rate. The risk factors for premature mortality were similar to the results and evidence reported in other articles. Therefore, this higher mortality is avoidable with early diagnosis and adequate management.

Keywords: Predictive factors, Risk factor, Premature death, Ischemic stroke

Introduction

Ischemic stroke, as a sudden onset of neurological symptoms, is a heterogeneous multifactorial disorder; these symptoms concern the location of the damage in the brain [1]. Stroke is the third cause of death after cardiovascular events and cancer all over the world [2]. As the available studies show, the incidence

of stroke at the beginning of the 21st century has occurred from 95 to 290 people per 100,000 patients per year [3-5]. Mortality because of stroke is significantly higher in the first two weeks after the occurrence of stroke [6].

Iluş *et al.* (2023) conducted a study in Romania on the factors predicting in-hospital mortality in ischemic stroke patients. Their results showed that NIHSS score > 9 (OR-17.4; $p < 0.001$) and lesion volume > 22.3 ml (OR-5.8; $p = 0.003$) are associated with the highest risk of death. In contrast, antiplatelet therapy (OR-0.349; $p = 0.04$) was associated with a lower mortality rate. Consequently, high NIHSS score and large lesion volume were independent risk factors for in-hospital mortality in ischemic stroke patients. Antiplatelet therapy was associated with a lower mortality rate [7]. Abebe *et al.* (2023) in Ethiopia investigated the risk factors of in-hospital death in stroke patients. This

Access this article online

Website: www.japer.in

E-ISSN: 2249-3379

How to cite this article: Shalilahmadi D, Dolatabadi MF, Shamsaie Gh, Mehramiri A, Moradi M. Investigating predicting factors for premature death in patients with acute ischemic stroke. J Adv Pharm Educ Res. 2025;15(2):84-90. <https://doi.org/10.51847/2AxOIRgch2>

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retrospective cohort research studied 912 patients with stroke. 132 people (14.5%) died during hospitalization. 71.2% of the deceased patients were ≥ 65 years old and 50.8% of them were women. Ischemic stroke (67.7%) was the most common type of stroke [8].

Dabilgou *et al.* (2020) in Burkina Faso conducted a study on 302 patients with ischemic stroke and defined premature mortality during the first two weeks. The results of regression analysis showed that factors including previous history of ischemic heart disease, decreased level of consciousness upon arrival to the hospital, hyperthermia and hyperglycemia upon arrival to the hospital, and the occurrence of febrile infections after stroke (pneumonia and urinary tract infection) had a significant predictive role in stroke mortality [9]. Viderman *et al.* (2020) in a study in Kazakhstan investigated the risk factors of in-hospital mortality in ischemic stroke patients. They reviewed retrospectively the results of 84 severely ill patients with ischemic stroke hospitalized in the neurological intensive care unit. The early in-hospital mortality rate in ischemic stroke patients was 35.7%. Coma and cerebral edema were in univariate analysis the strongest risk factors for in-hospital mortality [10].

Gattringer *et al.* (2019) conducted a study in Austria on 77,653 patients with ischemic stroke, in which they investigated the risk factors of early death for less than 7 days. The results showed that the early mortality rate in the stroke department was 2% and the average time to death was 3 days. Here, factors including older age, higher NIHSS, modified Rankin Scale (mRS) higher than zero, previous history of heart disease, diabetes, posterior circulation stroke syndrome, and nonlacunar type of stroke played a role significantly in early mortality [11]. Ong *et al.* (2016) conducted a study on 2556 ischemic stroke patients in Taiwan. They defined premature in-hospital mortality in ischemic stroke patients as death in the first 14 days after the occurrence of stroke and its rate was 1.3%. The results showed that premature death in these patients was significantly associated with factors including age over 65 years, history of heart disease and atrial fibrillation, advanced stroke, site involved in stroke (middle cerebral artery), and sepsis. Likewise, most of the elderly patients who died had underlying diseases of diabetes, hypertension, and dyslipidemia [12].

Ho *et al.* (2016) conducted a study in Taiwan on a population of 611 patients with ischemic stroke. This study defined early death as a death in less than one week. Early in-hospital death made up 15.9% of ischemic stroke patients. As the results showed, factors including NIHSS, hypertension, atrial fibrillation, high white blood cell count at the beginning of hospitalization, and old age were significantly associated with the in-hospital mortality of these patients [13]. Luzi *et al.* (2015) conducted a study on 1194 patients with ischemic stroke. They defined early mortality as the incidence of mortality within the first 30 days after ischemic stroke. Here, the factors including female gender, age over 80 years, NIHSS >10 , a hospital stay of more than 7 days, previous history of stroke, and having atrial fibrillation had a significant predictive role in the incidence of premature death in stroke [14].

The factors of premature death because of stroke are the old age of the patients, female gender, underlying diseases such as high blood pressure, diabetes, hyperlipidemia, smoking, history of stroke [14], history of ischemic heart disease, atrial fibrillation, and some laboratory tests including high white blood cell count (leukocytosis), increased blood glucose (hyperglycemia) upon admission, pulmonary infection and sepsis, high NIHSS, MRS above zero before Incidence of stroke, hyperthermia, and decreased level of consciousness on admission [15, 16].

Because of the importance of the subject, this study evaluates the role of a wide range of clinical and demographic factors including age, gender, comorbidities, laboratory parameters, drugs, and severity of stroke in the occurrence of early death following ischemic stroke.

Materials and Methods

The present research is a descriptive-analytical epidemiological retrospective study. Patients with a definite diagnosis of acute ischemic stroke referred to Golestan Ahvaz Hospital from February 2022 to the end of July 2023 made up its statistical population. The total number of hospitalized stroke patients was 968. 349 people were excluded from the study because of non-compliance with the inclusion criteria or having exclusion criteria, including incomplete information and uncertain outcomes (207 people), ICH (108 people), TIA (15 people), and CVSD (19 people). Therefore, the final sample size for the analysis of the results is equal to 619 patients.

The characteristics of the patients, including demographic information, underlying disease, medications, laboratory findings, and evaluations of the recent stroke were recorded in the data collection checklist. Demographic findings include age, gender, and smoking. Chronic medical diseases include hypertension, diabetes, hyperlipidemia, history of cerebrovascular disease, atrial fibrillation, ischemic heart disease, and heart failure.

Stroke severity was evaluated based on the National Institute of Health Stroke Study (NIHSS). Thus, NIHSS was extracted from the hospital data upon admission to the hospital.

Functional disorder was assessed on admission based on the modified Rankin scale (mRS). MRS is one of the most widely valid and reliable methods to assess the severity of acute stroke in clinical trials. It shows the functional outcome of the patient on an ordinal scale from 0 to 6, where 0 indicates the absence of symptoms of the functional disorder and a score of 6 shows the death of the patient [17, 18]. All data were collected from the medical records of the patients, recorded in the patient's hospital files and treatment and monitoring sheets. Early death was defined as the occurrence of death within two weeks (≤ 14 days) since the stroke occurrence [11]. The follow-up method included examining the patient's medical records and, if necessary, a phone call.

SPSS (SPSS Inc., Chicago, IL, U.S.A.) version 22 was used for statistical analysis. This research gained permission from the Research Council and approval of the Ethical Committee of

Ahvaz University of Medical Sciences (Ethical code: IR.AJUMS.HGOLESTAN.REC.2023.092).

Results and Discussion

This research investigated 619 patients with acute ischemic stroke including 293 women (47.33%) and 326 men (52.67%) with an average age of 66.01 ± 13.86 years (range of 27 to 92 years). Early death was defined as the occurrence of death within

two weeks (≤ 14 days) after a stroke. The frequency of premature death in the first 14 days after the stroke of 48 people was equal to 7.75% (CI 95%: 5.31 - 9.83%).

Table 1 presents the demographic characteristics of deceased and surviving ischemic stroke patients. As the results showed, the average age of deceased patients was higher than that of surviving patients ($P < 0.0001$). The mortality rate in women was slightly higher than that of men, but this difference was not statistically significant ($P = 0.113$). Average BMI and smoking were not associated with premature death.

Table 1. Comparison of basic characteristics of deceased and surviving ischemic stroke patients

Variable	Group	Deceased (48 people)	Survival (571 people)	p-value
Age (years), mean \pm SD		69.73 \pm 9.81	62.38 \pm 15.52	<0.0001 **
Age group, frequency (%)	<65 years	(33.33) 16	(48.86) 279	<0.0001 **
	≥ 65 years	(66.67) 32	(51.14) 292	
Gender, frequency (%)	Female	(52.08) 25	(46.94) 268	0.113 **
	Man	(47.92) 23	(53.06) 303	
Smoking, frequency (%)		(14.58) 7	(8.58) 49	0.090 **
BMI (kg/m ²), mean \pm SD		23.11 \pm 5.38	23.78 \pm 6.76	0.432 *

* Independent t-test

** Chi-square test

Table 2 presents a comparison of chronic medical diseases including hypertension, diabetes, hyperlipidemia, cerebrovascular disease, atrial fibrillation (AF), heart failure (HF), and ischemic heart disease in the two groups of deceased

and survivors. As it is clear, hypertension, cerebrovascular disease, atrial fibrillation, ischemic heart disease, and heart failure are associated with premature death. However, diabetes and hyperlipidemia have no relationship with premature death.

Table 2. Comparison of chronic medical diseases in acute ischemic stroke patients

Variable	Deceased (48)	Survival (571)	p-value*
Hypertension	(75.00) 36	(64.62) 369	0.001
Diabetes Mellitus	(25.00) 12	(23.47) 134	0.823
Hyperlipidemia	(35.42) 17	(37.65) 215	0.675
Cerebrovascular disease	(29.17) 14	(21.19) 121	0.002
Atrial fibrillation	(47.92) 23	(25.74) 147	<0.0001
Ischemic heart disease	(27.08) 13	(15.24) 87	<0.0001
Heart failure	(22.92) 11	(11.56) 66	<0.0001

* Chi-square test

Table 3 presents a comparison of treatment and drugs used in acute ischemic stroke patients. The researcher investigated the patients' medications in categories including antihypertensive drugs, blood sugar-lowering drugs, antiplatelet drugs (aspirin/clopidogrel), blood lipid-lowering drugs (statins), and anticoagulants or anticoagulants (warfarin, factor 10 inhibitors,

and antithrombin drugs). The use of antiplatelet, statin, and thrombolytic therapy was associated with lower mortality in acute ischemic stroke patients. However, there was no difference in the use of blood pressure drugs and anticoagulants in the two groups of deceased and surviving patients.

Table 3. Comparison of treatment and used drugs in acute ischemic stroke patients

Treatment/medication	Deceased (48)	Survival (571)	p-value*
Blood pressure medications	(68.75) 33	(62.87) 359	0.089
Antiplatelet	(31.25) 15	(48.86) 279	<0.0001
Statins	(27.08) 13	(35.55) 203	0.003
Anticoagulant drugs	(41.67) 20	(39.58) 226	0.599
Thrombolytic therapy	(12.50) 6	(29.60) 169	<0.0001

* Chi-square test

Table 4 gives the results of laboratory parameters including hemoglobin (Hb), absolute white blood cell count (WBC), absolute platelet count (PLT), kidney function tests including BUN and Cr, and electrolytes tests including sodium and potassium. The mean values of the laboratory parameters

between the two groups did not show any significant difference, except that the WBC at the time of arrival to the hospital was higher in the group of deceased patients than in the surviving patients ($P=0.018$).

Table 4. Comparison of laboratory parameters in acute ischemic stroke patients

Variable	Deceased (48 people)	Survival (571 people)	p-value
WBS($10^9/L \times$)	10.62 \pm 5.31	9.71 \pm 4.76	0.018
PLT($10^3 \mu L \times$)	285.05 \pm 82.47	292.32 \pm 84.21	0.507
Hb(g/dl)	11.9 \pm 2.03	13.2 \pm 3.39	0.336
BUN(mg/dL)	17.91 \pm 6.47	16.59 \pm 7.70	0.427
Cr(mg/dl)	1.41 \pm 0.83	1.67 \pm 0.67	0.553
Na(mmol/L)	139.55 \pm 9.41	138.55 \pm 12.27	0.477
K(mmol/L)	4.70 \pm 2.61	4.12 \pm 2.35	0.264

WBC: White blood cells; PLT: Platelet count; Hb: Hemoglobin; BUN: Blood urea nitrogen; Cr: Creatinine; Na: Sodium; K: Potassium

Table 5 gives the vital signs and clinical characteristics of patients upon arrival at the hospital, including body temperature and blood pressure, accompanying initial symptoms with seizures and state of consciousness, stroke severity (NIHSS score), and functional status (based on mRS).

The level of consciousness upon arrival was investigated based on the clinical examination. The patients were classified into 5 levels: awake, lethargy, obtundation, stupor, and coma. As the results showed, the patients who died had weaker consciousness

($P<0.0001$). The average body temperature and blood pressure in the two groups did not have a statistically significant difference. Deceased patients had higher NIHSS scores (higher stroke severity) and poorer functional status (lower mRS without entry) ($P<0.0001$). Likewise, although the occurrence of convulsions following a stroke was rare, the association of symptoms with convulsions was higher in deceased patients ($P=0.033$).

Table 5. Comparison of clinical characteristics and vital signs on arrival in acute ischemic stroke patients

Variable	Group	Deceased (48 people)	Survival (571 people)	p-value
Body temperature (C), mean \pm SD		37.1 \pm 0.8	36.7 \pm 0.7	0.456
Blood pressure (mmHg), mean \pm SD	SBP	162.68 \pm 26.52	158.12 \pm 21.13	0.760
	DBP	89.86 \pm 11.5	83.62 \pm 14.42	0.106
Seizures, frequency (%)		(6.25) 3	(1.05) 6	0.033
	Awake	(43.75) 21	(52.19) 298	
	Confused	(33.33) 16	(38.0) 217	
Consciousness level, frequency (%)	obtundation	(10.42) 5	(4.90) 28	<0.0001
	Stupor	(8.33) 4	(3.68) 21	
	Coma	(4.17) 2	(1.23) 7	
NIHSS at arrival*, mean \pm SD		15.32 \pm 4.28	10.12 \pm 3.18	<0.0001
mRS score, mean \pm SD		1.47 \pm 1.89	3.59 \pm 2.21	<0.0001

SBP: systolic blood pressure; DBP: diastolic blood pressure; NIHSS: National Institutes of Health Stroke Scale; mRS: Modified Rankin Scale

* NIHSS was missing in 60% of patient records

This section used multivariate regression analysis to predict the independent risk factors of premature death in the population under study. **Table 6** presents its results. So we applied only significant risk factors in univariate analysis in the multivariate analysis. As the results showed, factors including older age (over 65 years old), high severity of stroke (high NIHSS score), mRS >0 , presence of AF, a history of ischemic heart disease, cerebrovascular disease, high WBC count, and reduced level of consciousness (abdominal and lower) at the time of entering the hospital had a significant relationship with early mortality (≤ 14

days) after the occurrence of stroke and independently were predictors of premature death after ischemic stroke. Antiplatelet treatment (including aspirin and clopidogrel) and thrombolytic therapy were associated also with a reduction in premature death. Other variables under study, including gender and hypertension, heart failure, use of statins, and the association of initial symptoms with seizures in the multivariate analysis did not have a correlation with a decrease or increase in the risk of premature death and did not have a significant effect on predicting premature death in these patients.

Table 6. Results of multivariate regression analysis for predicting independent risk factors of premature death

Covariables	Odds ratio	95% CI for OR (lower- upper)	P-value	Significance
Age (≥ 65 years)	2.86	1.38-5.61	0.001	positive impact
Gender (female)	0.96	0.90-1.03	0.332	no impact
Hypertension	1.05	0.82-1.35	0.659	no impact
Cerebrovascular disease	2.06	2.01-4.19	0.016	positive impact
Atrial fibrillation	9.35	4.67-15.64	<0.0001	positive impact
Ischemic heart disease	4.65	1.92-7.84	0.0001	positive impact
Heart failure	0.762	0.93-1.23	0.064	no impact
Low level of consciousness	1.98	0.98-3.92	0.030	positive impact
Convulsions	0.40	0.72-1.50	0.420	no impact
Stroke severity (high NIHSS)	12.24	4.17-21.75	<0.0001	positive impact
Functional status (mRS)	5.68	2.28-14.81	0.0001	positive impact
WBC count	2.11	1.05-4.19	0.002	positive impact
Statins	0.57	0.52-1.06	0.072	no impact
Antiplatelet therapy	2.46	1.81-7.31	0.001	negative impact
Thrombolytic therapy	5.67	2.23-8.64	<0.0001	negative impact

As the results showed, old age, high severity of stroke (high NIHSS score), presence of AF, history of ischemic heart disease, cerebrovascular disease, functional status before stroke (mRS score >0), decreased level of consciousness upon entering the hospital, and a high white blood cell count at hospital admission are independently associated with an increased risk of premature death. In contrast, antiplatelet therapy (including aspirin and clopidogrel) and thrombolytic therapy were associated with a reduction in mortality. Likewise, having hypertension and heart failure, taking statins, and accompanying early symptoms with seizures had a relationship with premature death only in univariate analysis.

Other variables under study including gender and smoking, hyperlipidemia, diabetes mellitus, blood pressure, body temperature on arrival, anticoagulant treatment, renal function tests, and serum levels of Hb, platelets, sodium, and potassium have no relationship with decreasing or increasing the risk of premature death.

The results showed that premature death within two weeks (≤ 14 days) after the occurrence of acute ischemic stroke was 7.75%. The rate of premature death in ischemic stroke patients was almost similar to some other previous studies. Kortazar-Zubizarreta *et al.* (2019) in Spain reported early in-hospital mortality during the first two weeks after the occurrence of acute ischemic stroke to be 13.7% [16]. Bustamante *et al.* (2017) in Spain, who investigated 12,227 ischemic stroke patients, showed that the in-hospital mortality rate in the first 14 days was 5.9% [19]. The risk of stroke (ischemic or hemorrhagic) during life in adults is generally 25% and the risk of ischemic stroke from the age of 25 years onwards is 18% [20].

The present study found a significant and independent relationship between old age and early death in acute ischemic stroke patients, which is consistent with the findings of previous research. Zhang *et al.* [21], Gattringer *et al.* [11], Kortazar-Zubizarreta *et al.* [16], Bustamante *et al.* [19], Ong *et al.* [12], and

Ho *et al.* [13] have reported also the higher age as a risk factor for early mortality in ischemic stroke patients. Furlan *et al.* [22] and Schmidt *et al.* [23] also identified the age factor as an independent predictor of early in-hospital mortality in stroke patients. Various studies found old age as an important risk factor for stroke so increasing age is associated with a higher risk of occurrence and severity of stroke [24].

The present study used the NIHSS score as a measure of stroke severity. The results showed that a high NIHSS score was an independent predictor for increasing the risk of premature death in patients with acute ischemic stroke. These results are consistent with the findings of past studies, including the studies by Adams *et al.* [25] and Ho *et al.* [13]. Ilu \ddot{t} *et al.* [7] showed a relationship between a higher NIHSS score at admission (NIHSS ≥ 9) and a higher probability of premature death in stroke patients. Kortazar-Zubizarreta *et al.* [16] revealed high stroke severity (NIHSS ≥ 14) associated with a higher probability of premature death in ischemic stroke patients. Similar results have been reported in other studies. Ramachandran *et al.* recently showed that functional status (mRS) and NIHSS on day 1 are a valid predictor of early mortality in patients with ischemic stroke.

The present study showed the independent effect of ischemic heart disease, atrial fibrillation (AF), and cerebrovascular disease on premature death. Blood pressure and heart failure were also predictors of premature death in ischemic stroke patients only in univariate analysis. The history of heart disease significantly increased in other studies the early mortality in ischemic stroke patients [12, 16]. Dabilgou *et al.* showed that a previous history of ischemic heart disease was predictive of an increased incidence of early death after ischemic stroke [9]. Heart failure (CHF), MI, ischemic cardiomyopathy, aortic stenosis, and aortic insufficiency were not associated with the mortality of patients. Some differences in the results can be because of differences in

the study population and patient characteristics, especially stroke severity.

The current study showed that hypertension was associated with premature death only in univariate analysis. Some studies reported that high blood pressure is associated with adverse outcomes in patients with acute ischemic stroke. Dabilgou *et al.* [9] showed that although high blood pressure was the most common vascular risk factor in 54.2% of ischemic stroke patients, hypertension and diabetes did not play a predictive role in premature death.

The present study showed that some factors such as gender and smoking, hyperlipidemia, and diabetes mellitus were not associated with reducing or increasing the risk of premature death. Likewise, as mentioned, our results are not in line with previous studies in some cases and some potential predictors have not been well studied. For example, while hypertension and hyperlipidemia are known risk factors for stroke, their association with premature mortality in ischemic stroke patients is unclear. So some studies have reported high blood pressure as a predictor of premature death in ischemic stroke patients [10]. The present study observed a significant relationship between antiplatelet therapy and lower mortality in ischemic stroke patients. As these results show, the use of antiplatelet drugs before stroke has a preventive role in mortality. This finding is confirmed by previous studies that showed the positive effect of antiplatelet treatment in reducing premature mortality after ischemic stroke [26] and reducing the risk of stroke recurrence. Thrombolysis in a limited period can help reduce infarction and other complications such as cardiopulmonary complications and mortality. Although Kortazar-Zubizarreta *et al.* [16] showed no relationship between thrombolytic treatment and premature death in ischemic stroke patients [16]. Iluț *et al.* [7] showed that anticoagulant treatment, thrombolysis, thrombectomy, and statin treatment were not associated with early mortality in ischemic stroke patients.

Decreased levels of consciousness and high white blood cell count at hospital admission were independently associated with an increased risk of premature death. The symptoms of seizures were associated with the occurrence of death in univariate analysis. But other laboratory parameters, kidney function, body temperature, and blood pressure on arrival were not related to premature death. As Bustamante *et al.* showed, seizures in ischemic stroke patients with premature death were higher (3.7% vs. 1.6%) [19]. The number of WBCs in the group of deceased patients increased significantly in the present study and was higher than that of the surviving group, and high WBC count in the multivariate model was associated with premature death of ischemic stroke patients. Ho *et al.* reported a similar result: high WBC count at admission was significantly associated with increased in-hospital mortality in ischemic stroke patients [13].

Conclusion

This study identified the advanced age, high severity of stroke (high NIHSS at the time of admission), presence of AF, history of

ischemic heart disease, cerebrovascular disease, functional status before stroke (mRS score >0), decreased level of consciousness, and high white blood cell count at hospital admission as independent risk factors for predicting premature death in ischemic stroke patients. Likewise, hypertension, heart failure, use of statins, and accompanying initial symptoms with seizures were associated with premature death only in univariate analysis. Antiplatelet and thrombolytic therapy was associated with a reduction in premature death.

The current study had several limitations because of its single-center, retrospective, and cross-sectional characteristics. There was a lack of information in the files of some patients, which caused them to be excluded from the analysis. Likewise, our results are potentially not generalizable to the general population of all ischemic stroke patients.

A model for predicting early and long-term death in ischemic stroke should be prepared through a nomogram to help make early decisions in stroke.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

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