Signa Vitae

ORIGINAL RESEARCH

Effect of monocyte-to-high-density cholesterol ratio on mortality in patients with ischemic stroke and atrial fibrillation: preliminary findings

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Abstract

Acute ischemic stroke (AIS) is one of the most common neurological emergencies, especially in elderly patients with high morbidity and mortality. The objective of this study is to evaluate the use of monocyte and high-density lipoprotein cholesterol (HDL-C) values, which play important roles in the inflammatory process after ischemia, in the prediction of 30-day mortality in patients. This is a retrospective, cross-sectional, observational study on demographic characteristics, vital signs and laboratory parameters of adult patients who were diagnosed with AIS and had atrial fibrillation (AF) rhythm in their electrocardiograms (ECGs) were retrospectively abstracted from hospital registry. The relationship of the laboratory values (i.e., monocyte count, blood HDL-C level and monocyte HDL-cholesterol ratio (MHCR)) were analyzed. Among 92 patients enrolled in the study, 54 (58.7%) were male, 31 (33.7%) of the patients had a yellow triage code, 61 (66.3%) were recorded as red. Sixty-nine patients (75%), had a history of chronic disease. While 86 (93%) of the patients were hospitalized to the wards, 5 (6%) were admitted into the intensive care unit and one patient (1%) was referred to another institution. The minimum duration of signs and symptoms varied between 1 hour and 240 hours (median 12 hours). Length of stay in the emergency department varies between 1 hour and 26 hours (median 4 hours). Monocyte counts of the patients were in the range of 310 to 1510 $\times 10^9/\mu L$, (median 685 $\times 10^9/\mu L$). Blood HDL-C level is in the range of 12–84 mg/dL, (median 40 mg/dL). The MHCR was in the range of 5.95–89.1 (median 18.2 and mean 19.7 $\pm$ 10.6). MHCR is not effective in predicting 30-day mortality in ischemic stroke patients due to AF who presented to the emergency department. It would be more appropriate to design more comprehensive, multicenter and prospective studies on this subject.

Keywords

Acute ischemic stroke; Atrial fibrillation; High-density lipoprotein cholesterol; Monocyte-to-high-density lipoprotein cholesterol ratio

1. Introduction

Ischemic stroke is the third most common cause of death in the world and also ranks among the most prevalent causes of permanent disability [1]. Acute ischemic stroke (AIS) is defined as an infarction due to arterial occlusion [2]. It is one of the most common neurological emergencies especially in elderly patients with high morbidity and mortality [2, 3]. Large artery atherosclerosis and cardioembolic causes occupy a serious area in the etiology of AIS. Atrial fibrillation (AF) is one of the leading diseases which cause cardioembolic events [3].

Regardless of the etiology of AIS, there is increasing evidence that the inflammatory process plays an important role in the development and prognosis of the disease [4]. The fastest reaction to the vascular occlusive event begins with the response to ischemic damage in the tissue where the occlusion is located. Within this context, functions of monocytes/macrophages and T-lymphocytes are determinant factors in the pathogenesis and outcomes of stroke. They have roles that increase the production of inflammatory cytokines, infiltration and lipids and determine the clinic in patients with AIS, furthering the brain damage caused by ischemia [5].

Microglial cells, which exhibit the fastest response to ischemia, are responsible for this damage in the brain tissue. These cells are resident macrophages of the brain and play a major role in the brisk response [6]. In particular, post-ischemic microglial proliferation peaks 48–72 hours after focal cerebral ischemia and may last for several weeks after the onset of ischemic injury [7]. In addition, reactive microglia cells

are morphologically and functionally similar to blood-derived monocytes/macrophages.

Studies have pointed out the activation of microglial cells as the most important factor in proinflammatory damage after ischemia in brain tissue. The effect of macrophages, whose blood counts increase markedly in third-to-seventh days of ischemia on damage is an ongoing debate [8].

Contrary to the fact that the inflammatory response following ischemia both strengthens the atherosclerotic plaque structure and increases the brain damage due to inflammation; high-density lipoprotein cholesterol (HDL-C) exerts anti-inflammatory, antioxidant and antithrombotic effects by reversing cholesterol transport and preventing endothelial dysfunction [9].

Therefore, researchers pointed out that monocyte-to-high-density lipoprotein cholesterol ratio (MHCR) can be a new prognostic biomarker in cardiovascular diseases, ischemic stroke and acute intracerebral hemorrhage (ICH) [10–12].

AF is the most common cardiac rhythm disorder whose prevalence increases with age. Its prevalence in developed countries is 2% to 4% whilst a 2.3-fold rise is expected, owing to extended life expectancy in the general population and intensifying search for undiagnosed AF [13]. Classifications of AF exist, but are traditionally divided into five classes based on clinical duration and spontaneous termination. This classification includes *de novo* diagnosis, paroxysmal, persistent, long-standing persistent, and permanent. In patients experiencing both paroxysmal and persistent episodes of AF, it is recommended to use the one which had been recorded more frequently for classification.

In general, AF increases the risk of stroke fivefold when the nonhomogeneous effect of additional risk factors is included [13]. The type of AF also poses a risk at different rates for thromboembolism that will develop in the patient. For example, non-paroxysmal (i.e., persistent or permanent) AF poses a higher risk of thromboembolism than paroxysmal episodes [14]. Although the guidelines still recommend CHA2DS2-VASc scoring for calculating stroke probability and initiating treatment in patients with AF, there are no commonly used and recommended biomarkers to highlight the exact risk for stroke in a given patient. Cardiac troponin T and I, Natriuretic peptides, Cystatin C, Proteinuria, Creatinine Clearance (CrCl)/Estimated Glomerular Filtration Rate (eGFR), C-reactive protein (CRP), interleukin 6 (IL-6), Growth Differentiation Factor-15 (GDF-15), von Willebrand factor (vWF), D-dimer were also advocated in the evaluation of stroke risk in patients with AF in recent years although none of these biomarker-based classifications have been found to possess high predictivity for stroke risk and decision making on treatment [13].

Generally speaking, it is difficult to predict outcomes of diseases in medicine. The process of prediction of functional outcomes after stroke is more challenging given the complex interplay between stroke-related factors (e.g., the degree of severity and subtype of stroke) and associated comorbidities. There are several different risk scores currently in use (i.e., the iScore, the Astral *etc.*). However, the stroke subtype caused by AF is important in all ischemic stroke patients, because AF alone can lead to mortality in these patients. There are studies

on iScore evaluating similar predictive strength in terms of early mortality in this group, but MHCR have been rarely examined. Therefore, the aim of this study is to investigate the usefulness of MHCR, whose components are important biomarkers for atherosclerosis, in predicting the stroke risk of AF patients.

2. Materials and methods

2.1 Study design

The study has been conducted retrospectively in Istanbul Training and Research Hospital, a first-degree center with nearly 1000 beds and all specialties on duty.

2.2 Research Sample

Research Sample included all consecutive patients diagnosed with AIS associated with AF in six months' study period (between 01 June 2017 and 01 January 2018) presented to the hospital-based emergency department (ED) without the exclusion criteria.

2.3 Data Collection

Patients older than 18 years of age, diagnosed with AIS accompanied by an AF rhythm in ECG were recruited in the study. The datasheets of the patients included the patients' age, gender, duration of complaint until presentation, mode of referral to the ED, systolic and diastolic blood pressure, heart rate, Peripheral oxygen saturation (pulse oximetry, SpO_2), temperature, need for radiological examination, need for consultation, duration of stay in the ED, monocyte count, blood HDL cholesterol level, mortality in 30 days and mode of disposition (discharge, admission to wards or intensive care unit).

2.4 Exclusion Criteria

Excluded from the study were those patients under the age of 18, with a previous ischemic history, diagnosed with hemorrhagic stroke, without AF on the ECG on presentation, those with infective findings in the evaluation (physical examination and history), or on blood biochemistry and/or imaging. In addition, patients who were hospitalized into the wards or intensive care unit (ICU) due to AIS were excluded from the study if an infectious condition occurred during their follow-up. This is also the rationale behind exclusion of C-reactive protein and white blood cell count in the analyses.

2.5 Statistical analysis

Statistical analysis was performed with SPSS (Statistical Package for the Social Sciences) version 24.0 (IBM Corp, Armonk, NY, USA). Findings of the study were analysed via descriptive statistical methods (mean, standard deviation, median, frequency, ratio, range) while independent sample t-test was conducted for comparisons between groups with normal distribution, and Mann-Whitney U test for those without normal distribution. Pearson's correlation analysis was used to highlight the relation of scales with each other and Pearson's Chi-Square test was performed to analyze qualitative data. Significance

T A B L E 1. Demographic data, vital signs on presentation, MHCR values of the patients.

	Mean ± SD	Range (Median)
Age (years)	71.4 ± 12.07	36–92 (73)
Time to admission (h)	1.70 ± 0.59	1–3 (2)
Duration of complaints (min)	37.63 ± 56.28	1–240 (12)
Systolic BP (mmHg)	155.13 ± 27.98	102–235 (154.5)
Diastolic BP (mmHg)	79.28 ± 13.88	47–124 (79)
Pulse rate (bpm)	90.03 ± 17.22	45–200 (90)
Respiratory rate (bpm)	14.23 ± 2.37	12–22 (14)
Temperature (°C)	36.38 ± 0.42	35.7–38 (36.3)
O_2 Saturation (%)	95.91 ± 2.29	90–100 (96)
Length of stay in the ED (h)	4.53 ± 3.77	1–26 (4)
Monocyte count (×10^6/mL)	0.71 ± 0.23	0.31–1.51 (0.69)
Blood HDL cholesterol level (mg/dL)	39.77 ± 10.98	12–84 (40)
Monocyte/HDL cholesterol ratio	0.02 ± 0.01	0.01–0.09 (0.02)

of the differences was evaluated with p levels below 0.01 and 0.05. Cut-off levels were calculated for sensitivity and specificity, to produce the highest true positive rate together with the lowest false positive rate, which are expressed with the concept of area under curve (AUC). The AUC levels are expected to be equal to or higher than 0.6 [14].

3. Results

Among 92 participants 41.3% (n = 38) were women and mean age was 71.4 ± 12.07 (range: 36–92). More than three-fourths were older than 65 years old (76.1%, n = 70).

The time to admission into the ED varies between 1 and 3 hours, with an average of 1.70 ± 0.59 hours. The duration of complaints of the participants ranged from 1 to 240 hours, (mean: 37.63 ± 56.28 hours). The triage codes were red in 66.3% of the patients (n = 61) and yellow in 33.7% (n = 31). Nearly half of the participants (47.8%, n = 44) were brought to the ED by ambulance, while the others presented with their families or friends. One-fourth of the sample (25.0%, n = 23) have no chronic disease, while the majority (75.0%, n = 69) had at least one comorbid conditions. All of the participants (n = 92) needed radiological examination and consultation. 6.5% (n = 6) were hospitalized in the wards and 93.5% (n = 86) were admitted in the ICU. One patient (1.1%) died during hospitalization and four (4.3%) died within 30 days (Table 1). Systolic blood pressure (BP) ranged from 102 to 235 mmHg with an average of 155.13 ± 27.98 mmHg, while diastolic blood pressure (BP) ranged from 47 and 124 mmHg with an average of 79.28 ± 13.88 mmHg.

The relationship of MHCR and systolic BP, diastolic BP, pulse rate, respiratory rate, temperature and O_2 saturation were not found statistically significant ($p > 0.05$, Table 2).

Four patients who died in 30 days after presentation had significantly higher pulse rates and lower O_2 saturation levels than those who survived ($p = 0.005$ and $p = 0.019$, respectively) (Table 3). On the contrary, measurements of systolic BP, diastolic BP, respiratory rate, and temperature were not found

T A B L E 2. The relation of monocyte/HDL cholesterol ratio (MHCR) with systolic BP, diastolic BP, pulse rate, respiratory rate, temperature and O_2 saturation.

	MHCR	
	r	p
Systolic BP (mmHg)	−0.064	0.545
Diastolic BP (mmHg)	−0.199	0.057
Pulse rate (bpm)	0.112	0.287
Respiratory rate (bpm)	0.146	0.165
Temperature (°C)	−0.106	0.316
O_2 saturation (%)	−0.019	0.855

r: Pearson correlation, p: Statistical significance.

to differ significantly with respect to 30-day mortality ($p > 0.05$). Since patients who died of infectious causes in the hospital were excluded from the study, four patients died in the study period were thought to have died due to cardioembolic causes. Although these deaths have not been confirmed by autopsy studies, there are confirmative radiological evidence.

MHCR did not differ significantly between patients older than 65 years and younger ones ($p > 0.05$). Likewise, MHCR was not found significantly different between sexes ($p = 0.861$), and between those with and without chronic diseases ($p = 0.510$). Cut-off point for the best predictive value of MHCR for 30-day mortality was found to be 0.021. This cut-off has shown a sensitivity of 75%, and specificity of 63.6% (Area under curve: 0.683, 95% CI 0.269–0.992) (Fig. 1).

4. Discussion

It is evident that the incidence of ischemic stroke increases globally every year, considering the analyzes published in recent decades [15]. Soaring incidence is explained with the "Dreaded-D's", that is, increases in chronic disability,

T A B L E 3. The relation of systolic BP, diastolic BP, pulse rate, respiratory rate, temperature and O_2 saturation with 30-day mortality.

	Survived (n = 88)		Died (n = 4)		
	Mean ± SD	Range (Median)	Mean ± SD	Range (Median)	[b]p
Systolic BP (mmHg)	154.09 ± 27.79	102–235 (154)	178 ± 24.94	143–202 (183.5)	0.073
Diastolic BP (mmHg)	78.94 ± 13.79	47–124 (78.5)	86.75 ± 15.88	64–101 (91)	0.243
Pulse rate (bpm)	89.3 ± 17.21	45–200 (89)	106.25 ± 5.85	99–113 (106.5)	0.005
Respiratory rate (bpm)	14.24 ± 2.37	12–22 (14)	14 ± 2.83	12–18 (13)	0.742
Temperature (°C)	36.39 ± 0.43	35.7–38 (36.3)	36.25 ± 0.21	36–36.5 (36.25)	0.648
O_2 saturation (%)	96.02 ± 2.28	90–100 (96)	93.5 ± 0.58	93–94 (93.5)	0.019

[b]: *Mann-Whitney U Test.*
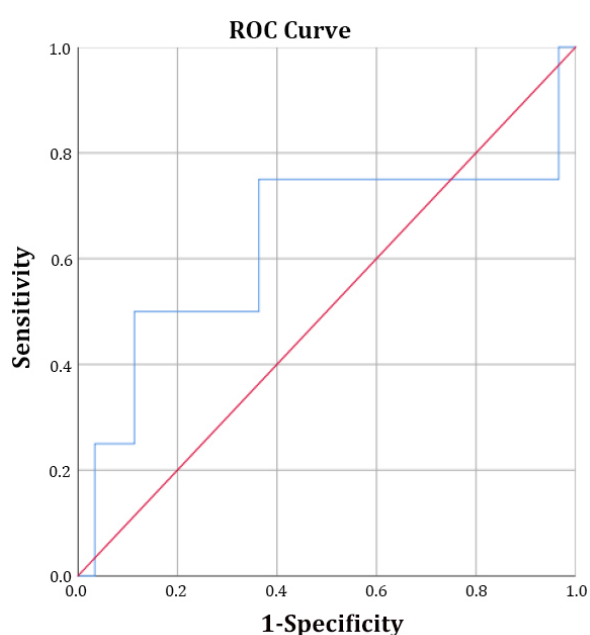
F I G U R E 1. Graphic depicting receiver operating characteristic (ROC)analysis of mortality with respect to monocyte HDL-cholesterol ratio (MHCR).

dementia and death, which escalate the pressure of economic, psychological and health problems on the society [16].

Age is among the essential factors affecting the prevalence of AIS. The incidence of the disease increases rapidly with age and doubles every ten years after the age of 55 [17]. The incidence of stroke among adults aged 35 to 44 years is 30 to 120 per 100,000 per year, while it soars up to 670 to 970 in those aged between 65 and 74 years [18]. As age progresses, a parabolic increase in AIS rather than a linear one emerges. Epidemiological stroke studies in Turkey demonstrated that the age range is 35–95 years and the mean age is 64 ± 14.8 years [19].

The age range of the participants in the present study is 36 to 92, with an average of 71.4 ± 12.07 years. The higher mean age of patients with stroke in the same city population in the present study can be explained by the recruitment of patients with stroke associated with AF, which represents a more complex profile. The prevalence of AF increases with age, reaching rates of almost 6% to 8% in 75-year-old patients

[20, 21]. The age range of the present study corresponds to the elderly population who had a steadily increasing incidence of AF worldwide.

Another factor which has an impact on the outcomes in stroke patients is "early diagnosis-early treatment". A major cause of long prehospital times is delay in seeking medical attention by the patient or by lay bystanders who have witnessed a stroke [22].

In this study, patients presented to the ED within one to three hours following the onset of their symptoms and this time period falls within the window in which traditional neuroprotective treatment strategies can be pursued [23].

While almost half of the participants of the study presented to the ED as outpatients, half of them were admitted through the emergency health services or ambulances (112-911).

Most of the patients in the study have undergone radiological examination, have been consulted in the early period, and admitted to ICU for treatment and follow-up. The stroke teams were available for the patients with suspected stroke and the guidelines and procedures to be performed in the suspected patients were predetermined. Studies in the literature highlighted that most of the patients who presented to the ED within 3 hours after the onset of stroke symptoms received tissue plasminogen activator (tPA) unacceptably late, which was attributed to the procedures in the hospital [24]. Although some training activities focusing on the early prehospital diagnosis of stroke have been launched in Turkey, most supportive and specific treatment of these patients are administered in the EDs. An interesting point raised in the findings of the study is a majority of the patients (93.5%) was admitted to ICU which is in line with the main rationale of the study encompassing patients with stroke due to AF. Stroke associated with AF carries a substantially higher rates of mortality and morbidity, longer stay in hospital and lower rates of discharge from the hospital when compared to those unaccompanied by AF [25].

The coexistence of AF and stroke in a given patient results in a worse outcome and higher rate of mortality, which gave rise to a research area related to the follow-up of clinical course of these patients in the prehospital field, hospital, stroke units, and ICUs. One of the outstanding research areas involves the value of MHCR in prediction of the patients' outcomes. The similar phenomena have been studied in many studies related to the predictive role of MHCR. Use of this ratio has proved to be successful in predicting mortality and morbidity of stroke

patients [26]. However, there are scarce data focusing on value of MHCR in prediction of outcome of stroke patients associated with AF.

Cardioembolic stroke is a serious condition that accounts for 14–30% of ischemic strokes. Cardioembolic stroke patients are prone to stroke recurrence in the early period, although recurrences can be prevented with appropriate treatment and close follow-up during the acute phase [27].

Since patients who died of infectious causes in the hospital were excluded from analysis, all 4 patients included in the study were thought to be due to cardioembolic causes. Cardioembolic stroke and early recurrent embolization are among the most important determinants of in-hospital mortality.

There is no clearly determined value as a cut-off point for mortality estimates of MHCR. In studies investigating the success of MHCR in estimating mortality, different cut-off values such as 0.28 and 0.51 were identified [26, 28]. In the present study, this ratio was determined as 0.02 with similar sensitivity and specificity values. Researchers investigated this rate in stroke patients in similar geographic populations regardless of the cause of stroke [11]. Analysis of the data unveiled that stroke patients with AF are distinguished from strokes with other etiologies with respect to expectations of mortality and morbidity. This study has shown that the MHCR value, which is frequently studied in the literature, may fail to predict mortality, especially in patients who have had a stroke due to AF.

The study focused on mortality over the 30-day mortality of MHCR in ischemic stroke patients, and although this value failed as a predictive tool in this sample, further studies are needed on the potential association of this ratio with silent microvascular abnormalities and cognitive impairment. Because silent lacunar infarctions have been associated with cognitive impairment in the early stage of cerebral microvascular disease [16, 18].

The present study has some important limitations. Single-center design with a limited sample size may prevent extrapolation of the results to the whole population. Likewise, exclusion of patients with hemorrhagic stroke and those who had no AF on the ECG on presentation prevent us from generalization of the findings.

5. Conclusion

MHCR does not appear to be effective in predicting 30-day mortality in patients with AIS due to AF who presented to the hospital ED. More comprehensive, population-based, multi-center and prospective studies on this subject will be needed to draw sound conclusions.

AUTHOR CONTRIBUTIONS

OA and OK designed the research study. SY and OA performed the research. OA, SY and OK analyzed the data. OA and SY wrote the manuscript. All authors read and approved the final manuscript.

REFERENCES

[1] Boursin P, Paternotte S, Dercy B, Sabben C, Maïer B. Semantics, epidemiology and semiology of stroke. Soins. 2018; 63: 24–27. (In French)

[2] Balkan S. Cerebrovascular diseases. 3rd edn. Gazi Bookstore: Ankara. 2002.

[3] Johnson RT, Griffin JW, McArthur JC. Current therapy in neurologic disease. 7th edn. Mosby: St. Louis. 2005.

[4] Fassbender K, Rossol S, Kammer T, Daffertshofer M, Wirth S, Dollman M, et al. Proinflammatory cytokines in serum of patients with acute cerebral ischemia: Kinetics of secretion and relation to the extent of brain damage and outcome of disease. Journal of Neurology Science. 1994; 122:135–139.

[5] Chiba T, Umegaki K. Pivotal roles of monocytes/macrophages in stroke. Mediators of Inflammation. 2013; 2013: 759103.

[6] Aloisi F. Immune function of microglia. Glia. 2002; 36: 165–179.

[7] Lalancette-Hébert M, Gowing G, Simard A, Weng YC, Kriz J. Selective ablation of proliferating microglial cells exacerbates ischemic injury in the brain. The Journal of Neuroscience. 2007; 27: 2596–2605.

[8] Schilling M, Besselmann M, Müller M, Strecker JK, Ringelstein EB, Kiefer R. Predominant phagocytic activity of resident microglia over hematogenous macrophages following transient focal cerebral ischemia: an investigation using green fluorescent protein transgenic bone marrow chimeric mice. Experimental Neurology. 2005; 196: 290-297.

[9] Nagao M, Nakajima H, Toh R, Hirata K, Ishida T. Cardioprotective effects of high-density lipoprotein beyond its anti-atherogenic action. Journal of Atherosclerosis and Thrombosis. 2018; 25: 985–993.

[10] Ganjali S, Gotto AM Jr, Ruscica M, Atkin SL, Butler AE, Banach M, et al. Monocyte-to-HDL-cholesterol ratio as a prognostic marker in cardiovascular diseases. Journal of Cellular Physiology. 2018; 233: 9237–9246.

[11] Bolayir A, Gokce SF, Cigdem B, Bolayir HA, Yildiz OK, Bolayir E, et al. Monocyte/high-density lipoprotein ratio predicts the mortality in ischemic stroke patients. Neurologia i Neurochirurgia Polska. 2018; 52: 150–155.

[12] You S, Zhong C, Zheng D, Xu J, Zhang X, Liu H, et al. Monocyte to HDL

cholesterol ratio is associated with discharge and 3-month outcome in patients with acute intracerebral hemorrhage. Journal of the Neurological Sciences. 2017; 372: 157–161.

[13] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, *et al*. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. European Heart Journal. 2021; 42: 373–398.

[14] Tomak L, Bek Y. Process Characteristic Curve Analysis and Comparison of Areas Under the Curve. Journal of Experimental and Clinical Medicine. 2010; 27: 58–65. (In Turkish)

[15] Virani SS, Alonso A, Aparicio HJ, Benjamin EJ, Bittencourt MS, Callaway CW, *et al*. Heart disease and stroke statistics—2021 update: a report from the American Heart Association. Circulation. 2021; 143: e254–e743.

[16] Ovbiagele B, Nguyen-Huynh MN. Stroke epidemiology: advancing our understanding of disease mechanism and therapy. Neurotherapeutics. 2011; 8: 319–329.

[17] Chong JY, Sacco RL. Risk factors for stroke, assessıng risk, and the mass and high-risk approaches for stroke prevention. CONTINUUM: Lifelong Learning in Neurology. 2005; 11: 18–34.

[18] Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, *et al*. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. Circulation. 2011; 123: e18–e209.

[19] Türk Börü Ü, Kulualp AŞ, Tarhan ÖF, Bölük C, Duman A, Zeytin Demiral G, *et al*. Stroke prevalence among the Turkish population in a rural area of Istanbul: a community-based study. SAGE Open Medicine. 2018; 6: 1–6.

[20] Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, *et al*. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA. 2001; 285: 2370–2375.

[21] Oldgren J, Healey JS, Ezekowitz M, Commerford P, Avezum A, Pais P, *et al*. Variations in cause and management of atrial fibrillation in a prospective registry of 15400 emergency department patients in 46 countries. Circulation. 2014; 129: 1568–1576.

[22] Lecouturier J, Rodgers H, Murtagh MJ, White M, Ford GA, Thomson RG. Systematic review of mass media interventions designed to improve public recognition of stroke symptoms, emergency response and early treatment. BMC Public Health. 2010; 10: 784.

[23] Audebert HJ, Saver JL, Starkman S, Lees KR, Endres M. Prehospital stroke care: new prospects for treatment and clinical research. Neurology. 2013; 81: 501–508.

[24] Wahlgren N, Ahmed N, Dávalos A, Hacke W, Millán M, Muir K, *et al*. Thrombolysis with alteplase 3–4.5 h after acute ischaemic stroke (SITS-ISTR): an observational study. The Lancet. 2008; 372: 1303–1309.

[25] Lip GYH, Lane DA. Stroke prevention in atrial fibrillation: a systematic review. JAMA. 2015; 313: 1950–1962.

[26] Liu H, Zhan F, Wang Y. Evaluation of monocyte-to-high-density lipoprotein cholesterol ratio and monocyte-to-lymphocyte ratio in ischemic stroke. Journal of International Medical Research. 2020; 48: 1–12.

[27] Arboix A, Alió J. Cardioembolic stroke: clinical features, specific cardiac disorders and prognosis. Current Cardiology Reviews. 2010; 6: 150–161.

[28] Liu H, Liu K, Pei L, Gao Y, Zhao L, Sun S, *et al*. Monocyte-to-High-Density Lipoprotein Ratio Predicts the Outcome of Acute Ischemic Stroke. Journal of Atherosclerosis and Thrombosis. 2020; 27: 959–968.