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Cardiovascular diseases and ischemic stroke: the importance of embolism and thrombosis

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Abstract

***Background & Aims*:** Congestive heart failure (CHF) is a risk factor for acute ischemic stroke (AIS) incidence. Currently, no specific biomarker exists to differentiate thrombotic and embolic strokes. Managing and treating AIS patients with CHF, particularly those with embolic or thrombotic causes, requires a nuanced understanding of CHF's role in AIS.

***Materials & Methods*:** In this study, we reevaluated the medical records of patients admitted to Urmia Imam Khomeini Hospital from 2006 to 2023. The data was entered into SPSS IBM 23 and evaluated statistically. The exclusion criterion was incomplete medical records.

***Results*:** Our results showed that the mean age of AIS patients with and without CHF was 71.18 ± 13.00 and 66.22 ± 14.76 years, respectively ($p = 0.001$). Hemoglobin levels, lymphocyte and neutrophil counts, and white blood cell counts showed a statistically significant difference between AIS patients with and without CHF. The frequency of thrombotic strokes was twice than that of embolic strokes, with the mean ages 68.75 ± 13.00 and 64.76 ± 16.38 years, respectively ($p < 0.001$). Patients with atrial fibrillation had an 8.27-fold increased risk of embolic ischemic stroke compared to those without atrial fibrillation ($p < 0.001$). Blood glucose, red blood cell count, total cholesterol, and LDLc cholesterol showed significant differences between embolic and thrombotic ischemic stroke patients.

***Conclusion*:** In conclusion, the findings show that CHF is a risk factor for AIS that acts independently of gender. Monitoring immunological processes may be more clinically significant than RBC count and HCT levels in AIS patients with CHF. Additionally, age, RBC count, anemia, cholesterol, lipoproteins, and blood glucose levels could be used in clinical settings for the differential diagnosis of thrombotic versus embolic ischemic stroke.

***Keywords*:** Congestive heart failure, Embolic, Ischemic stroke, Laboratory findings, Thrombotic

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Introduction

With 7.6 million new incidences, acute ischemic stroke (AIS) accounts for 62% of all strokes, with the rest categorized as hemorrhagic stroke (1). This pathological condition leads to patient mortality and morbidity (2). Cardiovascular diseases (CVDs) are among the most significant risk factors for AIS (3). CVDs range from endothelial dysfunction to congestive heart failure (CHF) (4). CHF is a chronic condition characterized by myocardial dysfunction and high blood pressure. Coronary artery disease and previous myocardial infarction are the main etiologies of CHF (5).

CHF and its associated underlying etiologies are considered risk factors for AIS incidence (6). The incidence of AIS in CHF patients is higher, and managing these patients is more complicated than managing AIS patients without CHF. For example, CHF increases the risk of stroke recurrence (7). Additionally, interactions between CHF medications and AIS drugs poses another challenging issue (8).

The underlying etiological mechanisms of AIS can be classified as thrombosis and embolism (9). Embolic strokes are caused by the degradation of thrombus, fat particles, and others materials located in the cardiac chambers, aortic, and arterial branches (10). Thrombosis in the brain circulation is the second subtype of AIS (11). Impaired fibrinolysis and inappropriate activation of coagulation factors, along with associated events, lead to the formation of localized plug or clot in a blood vessel, causing a blockage in the brain (12). A blockage of CNS circulation by embolism leads to a stroke, with its presentation depending on the affected cerebral region. The differential diagnosis of embolic from thrombotic AIS is a challenging task, and medical imaging is used for this purpose, with embolic strokes presenting with a non-lacunar pattern. Patient history, cognitive evaluation, and physical examination may help in understanding AIS subtypes. However, there is no biomarker panel for the differential diagnosis of embolic and thrombotic subtypes (13). A qualified biomarker is one that is easily measurable (14). It could be a molecule, metabolite, or variable involved in a disease's pathogenesis (15). Laboratory findings may be helpful in the differential diagnosis of AIS subtypes and in providing insight into the underlying mechanisms (16). We evaluated 12 years of retrospective data from West Azerbaijan Province to identify important findings in stroke patients with and without CHF and to differentiate patients with embolic and thrombotic etiologies admitted to Urmia Imam Khomeini Hospital.

Materials & Methods

After approving and receiving the ethical code IR.UMSU.REC.1400.235, this retrospective study was conducted on the medical records of 1,572 patients who were admitted to Imam Khomeini Hospital of Urmia from 2006 to 2023. Incomplete medical records were excluded, and new data were entered into the database. Laboratory findings were collected from the records. The patients were classified into two groups: AIS patients with and without CHF. Additionally, the AIS patients were categorized into embolic and thrombotic groups.

The laboratory variables included fasting blood sugar (FBS), blood sugar (BS), lymphocytes (LYM), white blood cells (WBCs), neutrophils (NET), platelets (PLT), hemoglobin (HB), red blood cells (RBC), hematocrit (HCT), low-density lipoprotein cholesterol (LDLc), cholesterol (CHL), triglycerides (TG), high-density lipoprotein cholesterol (HDLc), urea, and creatinine. Statistical analysis was performed using the SPSS statistical package version 23.0, and the data were represented in tables and charts. The data were compared between the two groups, and a *P-value* of less than 0.05 was considered significant.

Results

Age and Gender in the Patients with and without CHF

In total, 15% (236) of the 1,572 stroke patients had CHF as a comorbidity. As shown in Table 1, there was no significant difference in the frequency of CHF between male and female patients ($p = 0.724$). The mean age of AIS patients with CHF was 71.18 ± 13 years,

compared to 66.22 ± 14.76 years in those without CHF, which was statistically significant ($p = 0.001$).

Table 1. The CHF and sex Crosstabulation

		sex		Total	Chi-Square Tests
		male	female		Exact Sig. (2-sided)
CHF	yes	109	127	236	
	no	635	701	1336	0.724
Total		744	828	1572	

Laboratory and Clinical Findings in Patients with and without CHF

There were no statistically significant differences in systolic and diastolic blood pressure, blood sugar, and fasting blood sugar, PLT, red blood cell count, HCT, TG, high- and low-density lipoproteins, creatinine, or and urea levels between the two groups. However, HB levels, LYM and NET counts, and white blood cell counts showed statistically significant differences between AIS patients with and without CHF. Table 2 and Figure 2 present the mean values and corresponding *P-values.*

Table 2. The variable with a significant difference or a near-significant in the AIS patient with and without CHF

Variables		Sig.	T at df 1571	Sig. (2-tailed)
Creatinine	Equal variances assumed	.000	3.246	.001
	Equal variances not assumed		1.567	.118
Urea	Equal variances assumed	.000	2.533	.011
	Equal variances not assumed		1.850	.065
WBC	Equal variances assumed	.009	3.032	.002
	Equal variances not assumed		3.339	.001
LYM	Equal variances assumed	.888	-3.523	.000
	Equal variances not assumed		-3.523	.000
NET	Equal variances assumed	.532	3.211	.001
	Equal variances not assumed		3.181	.002
Hb	Equal variances assumed	.137	2.254	.024
	Equal variances not assumed		1.930	.055

The Main Finding in the Embolic and Thrombotic Strokes

The frequency of embolic and thrombotic strokes was 32.2% (506), and 67.8% (1,066), respectively. As shown in Figure 3, the average age of embolic and thrombotic patients was 64.76 ± 16.38 and 68.75 ± 13.50 years, respectively. The difference in the average age of the two groups was statistically significant ($p = 0.001$). However, gender had no effect on embolic and/or thrombotic AIS incidence (see Table 1, $p < 0.053$). The mean age of males and females was not significantly different among patients with embolic stroke, and a similar observation was noted in the thrombotic group.

Atrial fibrillation was a more commonly observed in embolic patients. Table 3 and Figure 4 clearly show the prevalence of atrial fibrillation in embolic AIS patients. Patients with atrial fibrillation had an 8.27-fold higher

risk of embolic AIS compared to those without atrial fibrillation ($p < 0.001$).

Table 3. The atrial fibrillation and gender and the risk of embolic/thrombotic stroke

		Stroke type		Total
		embolic	**thrombotic**	
Sex	Male	224	520	744
	Female	282	546	828
Total(sex)		506	1066	1572
Atrial fibrillation	Yes	376	31	407
	No	130	1035	1165
Total(Atrial fibrillation)		506	1066	1572

The mean laboratory findings are shown in Table 4 and illustrated Figure 5. Blood glucose, red blood cell counts, total CHL, and LDLc showed significant differences between embolic and thrombotic AIS patients. Figure 4 depicts the differences.

Table 4. The mean statistical differences of laboratory findings between embolic and thrombotic stroke patients

	Stroke type	**N**	**Mean**	**Std. Deviation**	
Cr	Embolic	523	1.1575	1.60508	0.363
	Thrombotic	1222	1.1091	.61458	
urea	Embolic	523	46.7596	34.09673	0.340
	Thrombotic	1222	48.4613	34.17332	
BS	Embolic	523	154.7380	84.19717	**0.048**
	Thrombotic	1222	164.5295	98.86172	
FBS	Embolic	523	128.3423	71.92980	0.162
	Thrombotic	1222	133.7758	75.39588	
WBC	Embolic	523	9101.7289	7722.62111	0.067
	Thrombotic	1222	8599.4435	3729.08967	
LYM	Embolic	523	22.9960	13.62962	0.370
	Thrombotic	1222	22.3588	13.60379	
NET	Embolic	523	69.0073	15.96434	0.459
	Thrombotic	1222	69.5996	15.01962	
plt	Embolic	523	216.0268	69.29798	0.284
	Thrombotic	1222	220.6927	88.56710	
RBC	Embolic	523	4.5719	.70029	**0.003**
	Thrombotic	1222	4.4621	.71725	
Hct	Embolic	523	39.3438	5.54891	0.588
	Thrombotic	1222	39.0588	11.47203	
Hb	Embolic	523	12.8161	3.15737	0.164
	Thrombotic	1222	12.6264	2.33791	
Totol holesterol	Embolic	523	187.9962	53.87875	**0.003**

	Stroke type	N	Mean	Std. Deviation	
	Thrombotic	1222	196.4967	54.79193	
TG	Embolic	523	150.6673	75.59683	0.163
	Thrombotic	1222	155.9411	70.94922	
HDL	Embolic	523	46.4302	15.24162	0.866
	Thrombotic	1222	46.5728	20.53460	
LDLc	Embolic	523	101.0803	37.78647	**0.004**
	Thrombotic	1222	107.2281	41.27793	

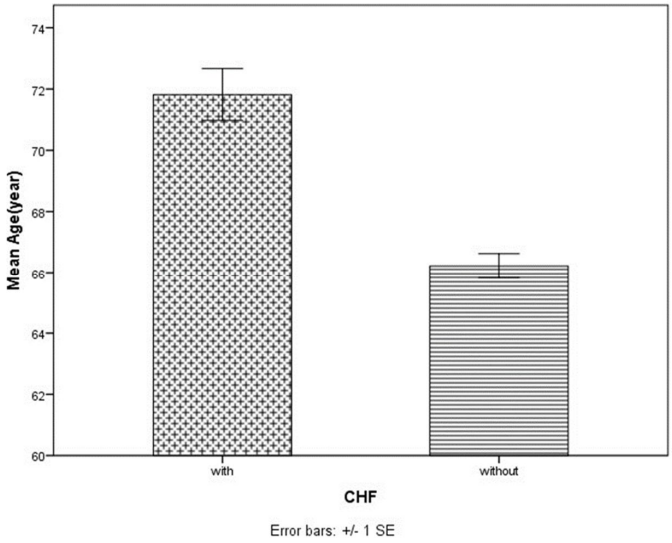

Fig.1. The mean age of AIS patients with and without CHF

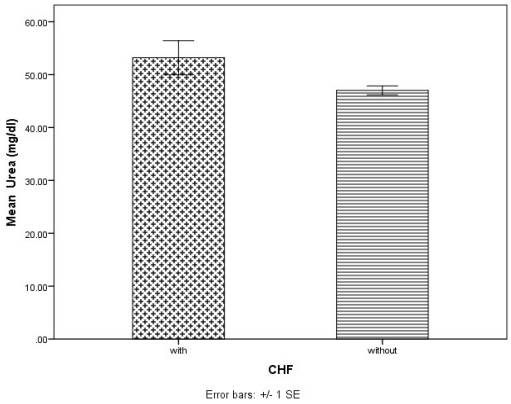

Fig. 2. The mean laboratory variables of AIS patient with and without CH, (A), urea

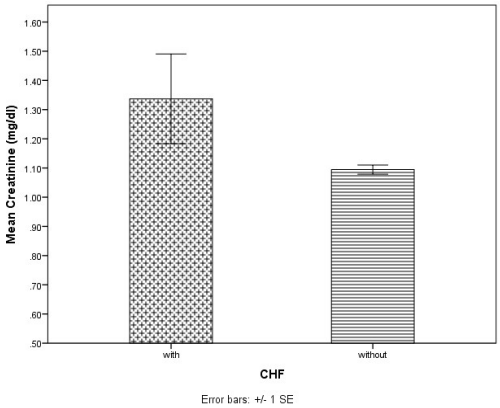

Fig. 2. (B) The mean creatinine

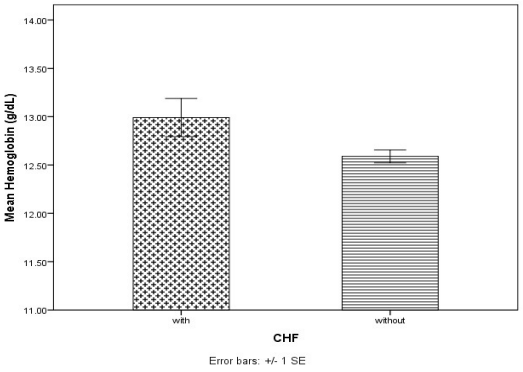

Fig. 2. (C). HB

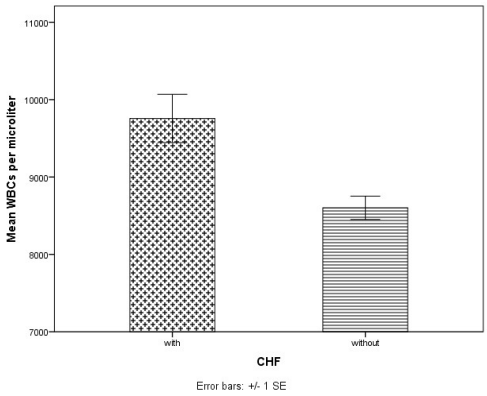

Fig.2. (D). WBC

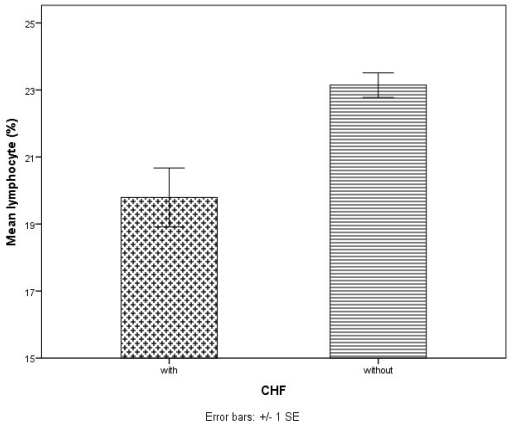

Fig. 2. (E) The mean lymphocyte

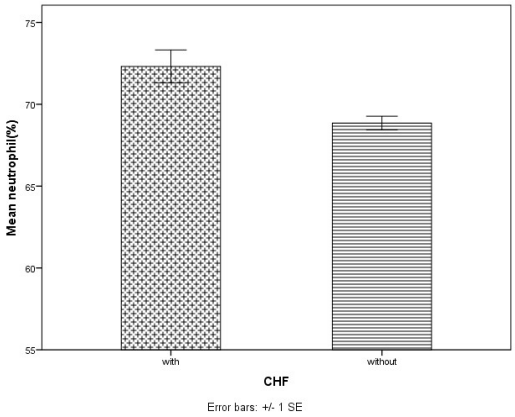

Fig. 2. The mean neutrophil (F)

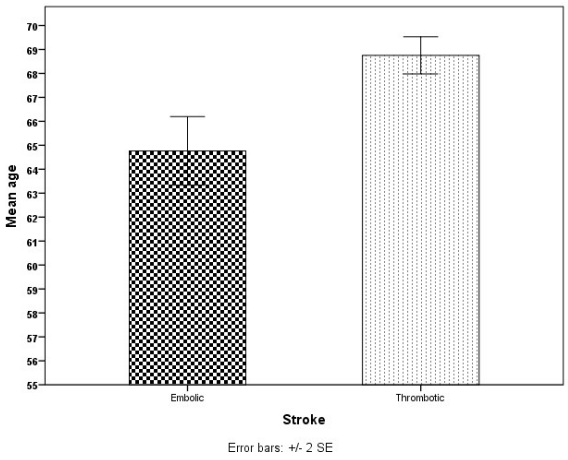

Fig. 3. The mean age of embolic and thrombotic stroke patients

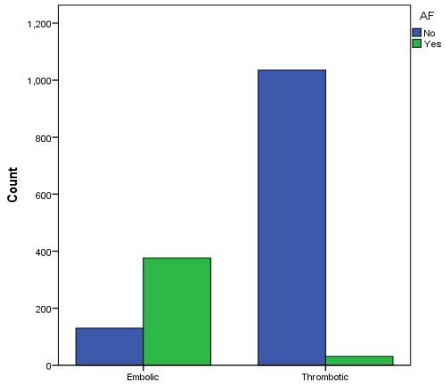

Fig. 4. The atrial fibrillation and risk or embolic and thrombotic stroke

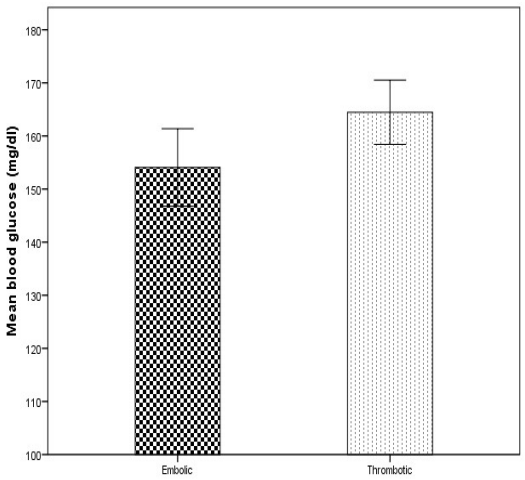

Fig. 5. (A) the laboratory findings and the difference between embolic and thrombotic stroke patients

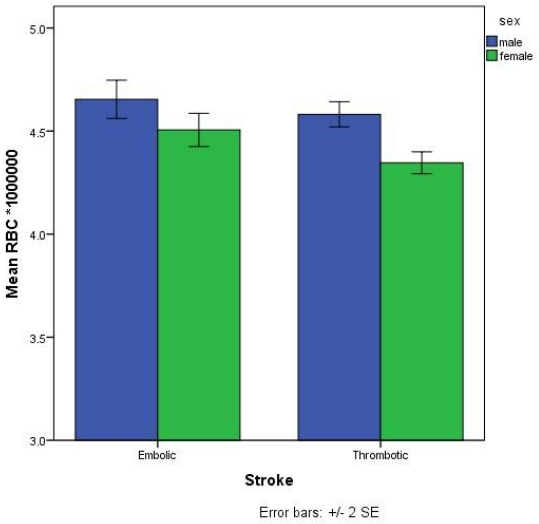

Fig. 5. (B) RBC count

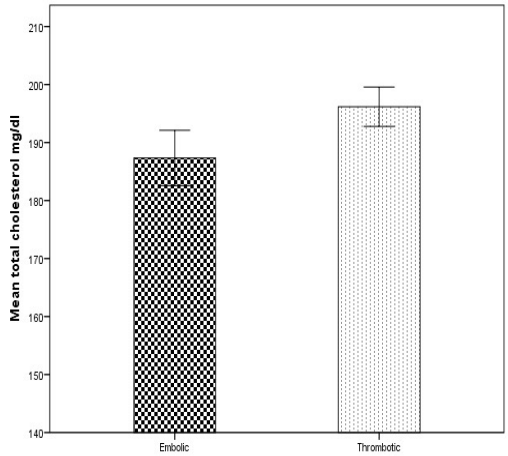

Fig. 5. (C) Total CHL

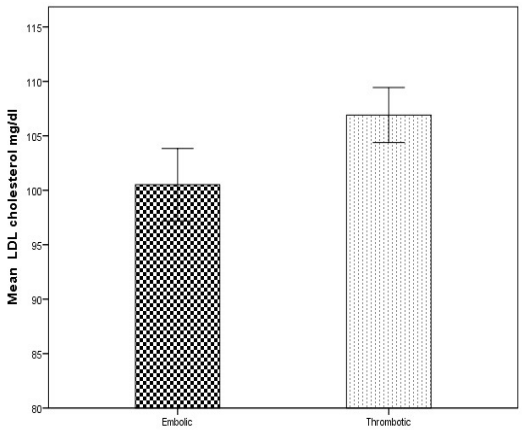

Fig. 5. (D) LDLc

Discussion

In spite of a large body of research on AIS, post-stroke mortality and morbidity remain a challenge for healthcare practitioners. A complete understanding of the underlying mechanisms will help us achieve effective diagnosis and treatment. The results of this study showed that the mean age of AIS patients with CHF was higher than that of non-CHF patients. HB levels and immunologic cell counts showed differences between AIS patients with and without CHF. Thrombotic strokes occurred more frequently and in older patients compared to embolic strokes. The incidence of embolic and/or thrombotic stroke was not associated with the gender of AIS patients. Atrial fibrillation increases the risk of embolic ischemic strokes. The blood glucose, red blood cell counts, total CHL, and LDLc levels showed significant differences between embolic and thrombotic ischemic stroke patients.

Previous studies have shown that 10–24% of AIS patients suffer from CHF, which is a major cause of AIS incidence. However, CHF development could also be a consequence of AIS (17). CHF is an age-related

disorder, which supports our finding that CHF patients were older than non-CHF patients (18).

The mean systolic and diastolic blood pressures showed no significant difference between the two groups. Therefore, variables other than hypertension are likly critical in CHF pathogenesis for AIS patients, including ischemic disease, dilated cardiomyopathy, and valvular heart disease (19).

The risk of congestion in heart failure is higher in women than in men, and female patients show poorer outcomes (20, 21). We found no significant difference in the prevalence of CHF in the studied AIS population. This finding can be interpret from different perspectives. The risk of AIS is equal among CHF patients and follows a gender-independent pattern. This interpretation aligns with a study by Ravandi et al., which found no association between gender and CHF in AIS patients (22). Despite this fact, male subjects are more susceptible to CVDs. However, we conclude that a person suffering from CHF is at risk of AIS, regardless of gender.

Blood sugar, fasting blood sugar, TG, high-density lipoprotein, and low-density lipoprotein levels are not statistically different between the two groups. However, previous studies have shown that carbohydrate and lipid metabolism disorders are associated with the incidence of CHF (23). Thus, we can conclude that these metabolic variables play a role in AIS, regardless of the predisposition to CHF.

The RBC count and HCT values differed between the two groups. However, CHF induces polycythemia in some patients, which is consistent with our study (24). Conversely, low HB levels and hemodilution significantly impact AIS outcomes and should be closely monitored in patients (25, 26). For example, Desai et al. showed that anemia is associated with worse outcomes (27). Taken together, RBC, HCT, and HB levels act as a double-edged sword: higher levels could induce AIS, while lower levels are associated with poor prognosis.

PLT levels showed no difference between the groups. As shown in previous studies, an elevated PLT count is a risk factor for ischemic stroke but reduces the risk of hemorrhagic stroke (28).

Among the studied variables, creatinine and urea levels did not show significant differences if we consider the variance. Creatinine is not a sensitive biomarker for kidney disease and only rises when kidney function is significantly reduced (29). Therefore, evaluating a more sensitive kidney biomarker may reveal a significant relationship.

The significant differences in immunologic variables, including WBC, LYM, and NET count, indicates that the root of CHF and its effects on AIS are probably mediated by immunologic processes. The immunologic nature of CHF is well documented, as endothelial dysfunction, cardiomyopathy, and hypertension have an immunologic basis. Thus, immunomodulation should be considered a treatment option for AIS with CHF.

In this effort, we also evaluated the importance of embolism and thrombosis. The results showed that about three out of four patients with embolic stroke had atrial fibrillation, which increases stroke risk 3–5-fold. On the other hand, the prevalence of atrial fibrillation is only 1% to 2% of the population (30). In contrast, the risk factors for thrombotic stroke are more prevalent, including hypertension, dyslipidemia, diabetes mellitus, and tobacco smoking. Therefore, it is expected that thrombotic stroke is more prevalent than embolic stroke, which aligns with our findings.

Aging and associated processes are an important risk factor for developing embolic and thrombotic stroke. As these risk factors accelerate, it is acceptable that the mean age of both subtypes was higher than 60 years old, as confirmed by other studies.

Blood glucose levels differed between the two groups, with thrombotic stroke patients having higher glucose levels. About 30–50% of AIS patients exhibited hyperglycemia. Therefore, it is suggested to scrutinize the importance of hyperglycemia in thrombotic stroke, as a literature review shows reports regarding the relationship between hyperglycemia and thrombosis (31).

The RBC count shows that both genders had lower levels of RBC in the thrombotic group compared to the embolic group. The levels tend to be lower than the upper cutoff point of the normal range. Therefore, it is recommended to evaluate the importance of anemia in AIS, particularly in the thrombotic subtype. Previous studies showed that anemia is a poor prognostic factor for AIS patients, and this study indicates that RBC and anemia are more critical in thrombotic AIS (32).

LDL cholesterol (LDLc) and total cholesterol (CHL) are well-documented risk factors for hemorrhagic AIS and cardiovascular diseases. Wu et al. showed that LDLc concentrations ≤ 40 mg/dL and ≤ 55–70 mg/dL are associated with an increased risk of AIS and hemorrhagic stroke, respectively (33). Therefore, LDLc plays a more critical role in ischemic than in hemorrhagic stroke. Here, our results lead to the conclusion that LDLc and total CHL levels are higher in thrombotic AIS than in embolic AIS. The role of LDLc in the pathogenesis of vascular events has various aspects, including inflammation and oxidative stress (34). Inflammation is associated with the immunologic response, and we showed that the immunologic process is affected in AIS patients with CHF. Thus, we conclude that immunomodulation could be considered a treatment and prevention strategy.

Conclusion

In conclusion, the findings show that CHF is a risk factor for AIS that acts independently of gender. Glucose and lipid metabolism are important for the predisposition to CHF and AIS, but they are not effective in CHF-associated AIS-induced catastrophic events. PLTs are more important in hemorrhagic strokes than in AIS. Monitoring the immunologic process is more critical than red blood cell and HCT levels for AIS patients with CHF. Thrombotic and embolic ischemic strokes have different pathophysiologies, and laboratory findings show distinct profiles. Among demographic variables, patient age is more important than sex. Laboratory variable analysis indicates that RBC, anemia, CHL, lipoproteins, and blood glucose—but not fasting blood glucose—could be used in clinical settings. The most important limitation of this study is its retrospective nature. It is recommended that prospective research be conducted under controlled conditions to reevaluate these findings. Additionally, we suggest extending laboratory tests to include more specific and molecular analyses rather than routine laboratory tests.

Acknowledgments

None.

Ethical statement

We followed all ethical recommendation and rules provided by ethics committee (ethical code IR.UMSU.REC.1400.235).

Data availability

Data is available upon request.

Conflict of interest

The authors declare that there is no conflict of interest.

Funding/support

None.

Author contributions

Dr. Mohammad Reza Amiri Nikpour, MD, contributed to the study design and supervision. Dr. Ali Zolfi-Gol and Arash Mosarrezaii consulted on the project. Surena Nazarbaghi contributed to data analysis. Dr. Zafar Gholinejad was involved in data analysis, interpreted the results, and drafted the manuscript. Fatemeh Hamzeh revised the first version.

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