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ORIGINAL ARTICLE

The Relationship between Interleukin 6 Level and Short Term Outcome in Atrial Fibrillation Subtypes a Case Control Study

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ABSTRACT

Background: Atrial fi brillation (AF) is the most common arrhythmia; at least more than two million individuals suffer from AF in the United States alone. AF is associated with high disease morbidity, mortality, a higher risk of stroke and thromboembolism. There are limited data on the role of Interleukin 6 (IL-6) as a prognostic factor in atrial fibrillation. So, we aimed to assess Interleukin 6(IL-6) level in AF subtypes and identify the relationship between IL 6 level, and short-term outcomes in AF. **Results:** Our results included three groups paroxysmal AF (19 cases), persistent AF (19 cases), and 19 in the control group; IL-6 level had the highest mean value in persistent AF at admission, after 24 h and after 7 days.13patients(68.4%) patients with paroxysmal AF experienced normal sinus rhythm and 6 patients (31.6%) developed ischemic stroke .4 cases(66.66%) from a total of 6 patients developed stroke after 24h while 2 cases (33.33%) developed stroke after 7 days. IL-6 level at admission was significantly related to the occurrence of stroke (RR: 2.571, CI: 0.5-1.1, p :0.002), and also at 24h (RR:2.267, CI: 2.267 (0.4-1.21), p: 0.0374). IL-6 equal to or more than 6.6 pg/ml was a statistically significant predictor of stroke occurrence with a sensitivity of 84.4%, and specificity of 66.7%P: 0.001. **Conclusions:** PlasmaIL-6 level was associated with the initiation and perpetuation of AF, and also was associated with the prognosis of AF. Admission of IL-6 at a cutoff value ≥ 6.6 pg/ml was a predictor of stroke occurrence in paroxysmal AF patients.

Keywords: Atrial fibrillation; Interleukin 6; Stroke

INTRODUCTION

AF is a common arrhythmia leading to marked morbidity and mortality [1**]**. AF can be divided into many subtypes depending on its presentation and duration, paroxysmal AF is defined as an intermittent attack that terminates spontaneously or within seven days of treatment [2]**.**

Systemic inflammation is a strong predictor of atrial fibrillation and Interleukins are inflammatory cytokines. IL-6 is a polypeptide secreted from a number of immune cells and also from some cardiac components; endothelial cells, vascular smooth muscle cells and fibroblasts [3]**.** The value of inflammatory cytokines in AF has been studied in recent years and yet the association between IL6 level and the short-term outcome is not well investigated. We aimed to assess the prevalence of interleukin 6 levels in AF subtypes and identify the relationship between IL 6 levels and short-term outcomes in AF.

METHODS

Our study population was fifty-seven patients, group 1 with paroxysmal AF (n=19), group 2 with persistent AF(n=19), and group 3 control group (n=19)who were admitted to the cardiology department, Zagazig University Hospitals and military medical academy. Case definition: Paroxysmal AF is defined as an attack of AF that terminates spontaneously or with intervention in less than seven days, while persistent AF is continuously sustained beyond 7 days. **[4]**For controls; individuals with sinus rhythm without a history of AF, which was confirmed in physical examination. All patients were evaluated for the complaint, the associated symptoms,risk factors: age, sex, hypertension, onset, the duration of the attack, drug history, and previous history of similar attacks. Patients and control groups were subjected to 12-lead electrocardiogram, and two-dimensional echocardiography using a commercially available echocardiography system

(GE Vivid 7 Pro, Horten, Norway).IL6 was withdrawn on admission, after 24 hours, and on the 8th day to assess a curve of IL 6 titter. Plasma concentrations of IL-6 were determined in venous blood samples taken in a heparin tube. The samples were immediately centrifuged, and the obtained plasma was frozen. Plasma levels of IL-6 were assessed using an ELISA kit (Elabscience Biotechnology Co, Ltd, China). All cases were followed after 7 days for the restoration of sinus rhythm as a primary outcome and for the occurrence of heart failure, recurrence of AF, stroke, or thromboembolic manifestations as a secondary outcome; stroke was defined as an acute onset of the focal neurologic lesion and categorized as ischemic, hemorrhagic and confirmed by imaging. Systemic embolism was defined as sudden vascular occlusion of an organ or extremity, which was confirmed by imaging. Excluded patients from the study were injuries or surgery within one month before the study, acute coronary syndrome, significant structural heart disease (more than mild valvular lesion), systolic heart failure (Ejection fraction was less than 50%), chronic inflammatory disease, malignancy or autoimmune disease and liver or kidney impairment.

Ethical standards:

Official permission was obtained by the local Institutional Review Board (Zagazig University, Egypt) NO. (ZU-IRB # 6805-18-3-2021). The included participants were informed about the study and written informed consent was taken from all participants before inclusion in our study.

Sample size and technique:

Finding that the mean IL6 among AF patients is 29.8 ±22.8 and that among the control group is 14.2 ±9.8 so the sample size is 57; 19 in each group calculated by open Epi program to be at 80% power and 95% CI

Statistical analysis

Analysis of data using Statistical Package for the Social Sciences (SPSS version 21.0). ANOVA (F) test was used for comparison among the three groups. Post-hoc Least Significant Difference (LSD) test was used to compare each 2 groups separately.

RESULTS

The demographic data and risk factors were presented in **Table 1**.

IL-6 level was always higher in persistent AF in comparison to paroxysmal AF and the control group. **Table 2**

In the paroxysmal AF group, 13 patients (68.4%) experienced normal sinus rhythm as a primary outcome and 6 cases (31.6%) developed ischemic stroke as a secondary outcome. **Table 3**

4 cases (66.66%) developed stroke after 24h from AF onset, and they were at a target INR while the remaining 2 cases (33.33%) developed stroke after 7 days from AF onset, and they weren't at a target INR. **Table 4**

The mean value of IL-6 levels at admission and at 24 hours was higher among patients with stroke compared to those without stroke. **Table 5**

High IL-6 level at admission was significantly related to stroke (RR: 2.571, CI: 0.5-1.1, p: 0.002), high level of IL6 at 24h was significantly related to the occurrence of stroke (RR: 2.267, CI: 0.4-1.2, p: 0.0374) .**Table 6**

A cutoff point of admission IL-6 equal to or more than 6.6 pg.\ml can significantly predict stroke with AUC=0.76 sensitivity = 84.4%, specificity = 44.4%, PVP =84.4%, PVN = 44.4%, p value <0.001. **Figure 1**

Table (1): Baseline characteristics among the studied groups:

Variable	Group1 (Paroxysmal AF) (n=19)		Group2 (Persistent AF) (n=19)		Group 3 (Control group) (n=19)		Test*	P	Post-hoc
Age: (years) *Mean ± SD*	61.2 ±9.1		65.5 ± 9.1		58 ±12		2.607	0.08	-
Body mass index :(Kg/m2) *Mean ± SD*	23.8 ±4.3		26.8 ± 3.9		27.4 ±5		**3.612**	**0.03**	**<0.05** [1] **<0.05** [2] >0.05 [3]
	No.	**%**	**No.**	**%**	**No.**	**%**	χ^2	**P**	
Sex: *Male:* *Female:*	10 9	52.6 47.4	10 9	52.6 47.4	11 8	57.9 42.1	0.141	0.931	
Smoking: No: Yes:	8 11	42.1 57.9	7 12	36.8 63.2	11 8	57.9 42.1	1.839	0.893	
Diabetes Mellitus									

Variable	Group1 (Paroxysmal AF) (n=19)		Group2 (Persistent AF) (n=19)		Group 3 (Control group) (n=19)		Test*	P	Post-hoc
: No Yes:	12 7	63.2 36.8	8 11	42.1 57.9	4 15	21.1 78.9	**6.90**	**0.03**	
Hypertension No: Yes:	8 11	42.1 57.9	7 12	36.8 63.2	5 14	26.3 73.7	1.078	0.583	

P1: Paroxysmal (G1) versus persistent AF (G2) groups.
P2: Paroxysmal AF (G1) versus control (G2) groups.
P3: Persistent AF(G2) versus control (G3) groups.
*****ANOVA test. LSD: least significant difference.
$\chi 2$: Chi-square test.
AF: Atrial fibrillation

Table (2): IL-6 levels among the studied groups:

Variable	Group1 Paroxysmal AF (n=19)	Group2 Persistent AF (n=19)	Group3 Control group (n=19)	Test #	P	Post hoc
At admission: (pg/ml) Mean ± SD *Intragroup t test*	4.9 ± 1.1 [a]p<0.05	6.1 ± 1.5 [b]p<0.05	3.6 ± 1 [c]p<0.05	19.90	<0.001 (HS)	<0.05 [1] <0.05 [2] <0.05 [3]
At 24 hours: (pg/ml) Mean ± SD *Intragroup t test*	6.8 ± 2.6* [a]p<0.05	7.9 ± 1.2* [b]p<0.05	3.6 ± 1* [c]p<0.05	15.30	<0.001 (HS)	<0.05 [1] <0.05 [2] <0.05 [3]
After 7 days: (pg/ml) Mean ± SD *Intragroup t test*	4.1 ± 1.9** [a]p<0.05	5.7 ± 1.5** [b]p<0.05	3.6 ± 0.9** [c]p<0.05	15.75	<0.001 (HS)	<0.05 [1] <0.05 [2] <0.05 [3]

#: One-way ANOVA test. HS: highly significant
*Intergroup comparison: Significant difference in comparison to admission reading.
**Intragroup comparison: Significant difference comparing at 24 hours reading to 7 days reading.
[a]p intragroup comparison of group 1
[b]p intragroup comparison of group 2
[c]p intragroup comparison of group 3

Table (3): Outcomes between the AF groups

Variable	Paroxysmal AF (n=19)	Persistent AF (n=19)	Test	P
Outcome: Sinus rhythm Ischemic Stroke Mortality Heart failure Recurrence of AF	13 (68.4%) 6 (31.6%) 0 0 0	0 (0%) 0 (0%) 0 0 0	**38.00**	**<0.001**

AF: atrial fibrillation

Table (4): Descriptive analysis time of stroke onset and state of anticoagulation

Stroke occurrence N= 6 from total 19 case of paroxysmal	
Time of occurrence After 24 h After 7 days	 4 cases (66.66%) 2 cases (33.33%)
Anticoagulated with target INR **Anticoagulated** without target INR	4cases (66.66%) 2 cases (33.33%)

INR: International normalized ratio.

Table (5): Relationship between mean value of IL-6 levels and occurrence of stroke:

Variable	Patients without stroke (n=32)	Patients with stroke (n=6)	Test #	P
At admission: (pg./ml) Mean ± SD	5.2 ± 1.6	7.2 ± 2.5	**-2.577**	**0.01**
At 24 hours: (pg./ml) Mean ± SD	6.9 ± 1.5	9.5 ± 3.2	**-3.092**	**0.005**
After 7 days: (pg./ml) Mean ± SD	4.7 ± 1.7	6.2 ± 2.3	-1.818	0.077

Table (6): Relationship between IL-6 low level and high level and occurrence of stroke:

Variable	Patients Without stroke (n=32)	Patients with stroke (n=6)	RR (95% CI)	P
At admission: Low level: High level:	18 (90%) 14 (77.8)	2 (10%) 4 (22.2%)	2.571 (0.51-1.1)	0.002
At 24 hours: Low level: High level:	17 (89.5%) 15 (87.9%)	2 (10.5%) 4 (21.1%)	2.267 (0.4-1.21)	0.0374

RR: relative risk
CI: confidence interval

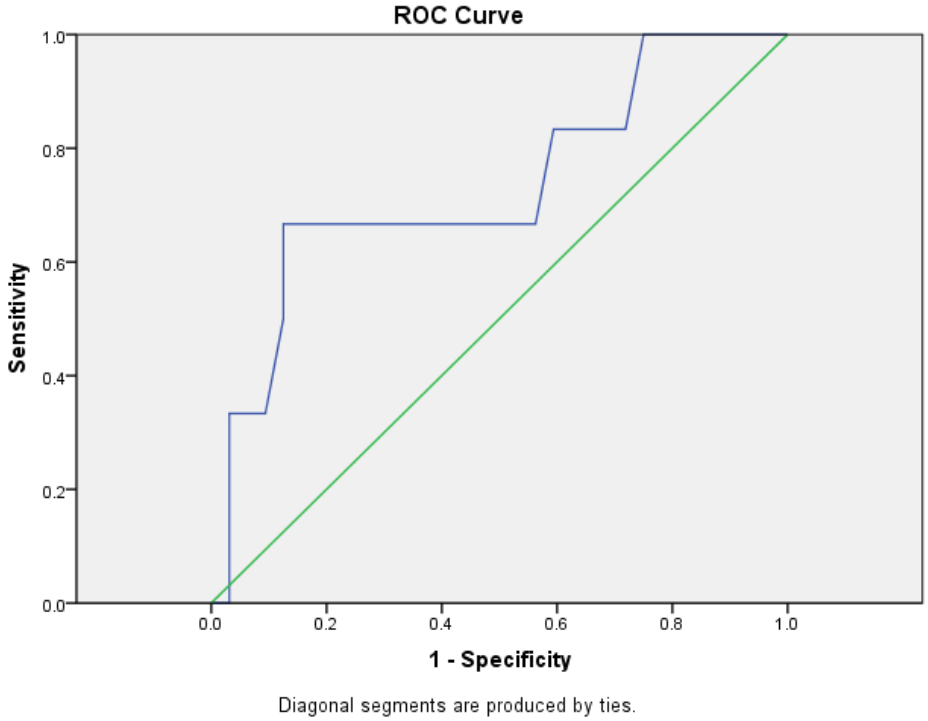

Figure (1): ROC curve of admission IL-6 cutoff as a predictor of stroke occurrence

DISCUSSION

AF is a common arrhythmia resulting in significant morbidity and mortality [1]. AF can be classified into many subtypes depending on its characteristics and duration, paroxysmal AF is defined as an intermittent attack that terminates spontaneously or within seven days of treatment [2]. Paroxysmal AF is estimated to constitute between 25% to 60% of all AF cases and its recurrences are associated with structural and electrical remodeling of the myocardium.[3]

The role of inflammatory cytokines in AF has been studied in recent years and yet the results are still inconclusive. Therefore**,** this study was conducted to estimate IL6 level changes in patients with paroxysmal AF, persistent AF, and control, and also to study the relation of IL6 levels with different outcomes.

Results of our study revealed a high statistically significant difference among the three studied groups regarding IL-6 levels at admission, after 24 hours, and after 7 days where the control group showed the lowest concentration. Interestingly statistically significantly higher IL6 was in persistent AF than paroxysmal at admission, 24 h, and after 7 days which denotes an important finding that IL6 has a role in the maintenance of AF being higher in persistent than paroxysmal. Also, we noticed that IL6 level was statistically significantly higher in paroxysmal than in control at admission, 24h, and after 7 days which denotes another important finding that IL6 has a role in the initiation and triggering AF being higher in paroxysmal than control. In agreement with Vílchez et a l [4] who concluded that IL-6 level was higher in AF cases than in normal (P <.001), and in persistent than in paroxysmal AF**.**

This was discordant with Stanciu et al [6] who reported that IL-6 level wasn't significant between recent AF and persistent AF and IL-6 seems related to triggering and not related to the perpetuation of AF**,** this discrepancy may be due to different sample size(85 in his study versus 57 in our study)

More than half of patients with paroxysmal AF experienced normal sinus rhythm (68.4%) and the remaining developed stroke (31.6%). We noticed that 4 cases (66.66%) developed ischemic stroke at 24 h from AF onset and 2 cases (33.33%) after 7 days, this comes with IL6 level in the paroxysmal group which reached its highest level at 24h and then decreased after 7 days but still higher than the control group which denotes that elevated inflammatory cytokines levels value have a prognostic value in AF. This agrees with the fact that different changes in systemic inflammation have been associated with the prothrombotic state in AF, suggesting that inflammation stimulates the prothrombotic condition in AF [7]. IL6 being an inflammatory cytokine can stimulate a prothrombotic condition by enhancing the expression of fibrinogen, tissue factor, factor VIII, and von Willebrand factor, endothelial cells activation, and enhancing platelet production [8]. IL6 level decreases the natural inhibitors of hemostasis such as thrombomodulin antithrombin, and protein S. High level of IL-6 is related to an increased coagulation state and decreasing the anticoagulation function to enhance a prothrombotic condition [9]; this fact could explain a finding in our study that; although 4 patients from total 6 were in target INR they developed stroke.

High IL-6 level at admission was related to the occurrence of stroke (RR=2.571, 95% CI 0.5-1.1, p =0.002), high level of IL6 at 24h was significantly related to the occurrence of stroke (RR=2.267, 95% CI 2.267 (0.4-1.21), p =0.0374)**.** This was concordant with *Song et al* [10] who reported that high plasma IL-6 could significantly predict stroke [hazard ratio (HR)=3.81; 95% confidence interval (CI), 1.11–13.05; p=0.033]**.** On the contrary, Jia et al [11] conducted on a well-anticoagulated AF (permanent and paroxysmal) high IL6 had an odds of 1.46 (95% CI 0.73–2.90), P= 0.276 for stroke occurrence**,** this discrepancy with our study may be due to that all patients were fully anticoagulated in his study.

In our study, a cutoff point of admission IL-6 equal to or more than 6.6 that can significantly predict stroke with AUC of 0.76, a sensitivity of 84.4%, specificity of 44.4%, PVP of 84.4% and PVN of 44.4%, p-value 0.001, this was concordant with Jia et al [11] who conducted a large cohort study for two years aimed to evaluate the clinical usefulness of IL6 for predicting thrombotic and adverse cardiac events of AF (permanent and paroxysmal)found that the IL-6 value 3.35 pg./ml, with sensitivity 70%, specificity 50% can predict stroke**.**

CONCLUSIONS

Plasma IL-6 level was associated with the Initiation and perpetuation of AF. PlasmaIL-6 level was a pro-coagulant factor associated with the prognosis of AF. Admission of IL-6 at a cutoff value ≥6.6 pg./ml was a predictor of stroke occurrence in paroxysmal AF patients.

RECOMMENDATIONS

Large multi-center drug trials are recommended to study the role of anti-inflammatory drugs

introduction at the onset of AF as statins, and colchicine as we found high IL-6 levels at admission, after 24 hours, and then decrease after 7 days. This indicates that IL-6 levels in the early hours of AF manifestations were elevated which can support evidence of an increased inflammatory activity which opens up new thoughts in the therapeutic approach. A future long-term follow-up study is recommended to confirm our result.

List of Abbreviations

AF: Atrial fibrillation, **IL6:** Interleukin 6, **BMI:** Body mass index, **INR:** International normalizing ratio, **AUC:** Area under the curve, **PVP:** Predictive value positive, **PVN:** Predictive value negative.

Declarations

Ethical approval and consent to participate:

All methods were carried out in accordance with relevant guidelines and regulations.

Written informed consent was taken from all participants.

Consent for publication

Not applicable

Availability of data and materials:

The data used and \or analyzed during the current study are available from the corresponding author on a reasonable request (data analyzed for this study are not publicly available due to the presence of patients identifying information).

Competing interest

The authors declare that they have no competing interest in this section.

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