The Egyptian Journal of Hospital Medicine (January 2025) Vol. 98, Page 615- 621

The Prognostic Value of C Reactive Protein and Interleukin 6 in Patients with Small Artery Cerebrovascular Stroke

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ABSTRACT

Background: Stroke is well acknowledged as a main contributor to both adult mortality & disability on a global scale.

Aim: The goal of this work was to identify laboratory markers that may relate to the severity and the prognosis of small artery cerebrovascular stroke.

Patients and methods: This prospective research has been performed out on 108 cases aged from 40 to 80 years old, both genders with stroke. All cases have been subjected to: Complete history taking, general examination [vital signs (blood pressure, respiration rate, heart rate, as well as, fibrillation and atrial temperature)], neurological examination [National Institutes of Health Stroke Scale (NIHSS) examination], investigational studies [Routine laboratory investigations (Complete blood cells, ESR, C reactive protein (CRP), ANA, and IL-6 by ELISA), and radiological investigation (electrocardiogram, echocardiography, duplex Ultrasound (by Toshiba Nemio 30 Ultrasound Machine), computed tomography brain), magnetic resonance imaging brain, and CT chest].

Results: A significant positive correlation was found between CRP, IL-6 concertation, and mRS and NIHSS scores on admission and at 3-month follow-up (P value less than 0.05). A receiver operating characteristic (ROC) analysis has been performed demonstrate the predictive value of CRP and IL-6 for poor prognosis on admission and at 3-months.

Conclusions: Inflammatory mediators have a pivotal role in ischemic stroke. IL-6 & CRP was found to have good prognostic value in cases with acute small artery ischemic stroke.

Keywords: C Reactive Protein, Interleukin 6, Small Artery, Cerebrovascular Stroke, Inflammatory Markers.

INTRODUCTION

Stroke is a major contributor to adult disability and death all around the world. Intravenous thrombolysis and recanalization have greatly improved stroke outcomes; nonetheless, many patients still experience impairments and disabilities after treatment [(1)].

Stroke, the most frequent form of cerebrovascular illness, is responsible for 47-67% of disability-adjusted life years and deaths throughout the world [(2)].

Stroke's natural progression helps to explain this, but it's also linked to neurological and medical problems. Even at the hyperacute stage of the disease, it is difficult to accurately predict prognosis and outcome [(3)].

Closure of a minor blood vessel (lacune), patients who have what are known as lacunar infarcts in other categorization systems are included in this group. There should be no sign of cerebral cortical malfunction, and the patient should be diagnosed with one of the classic clinical lacunar syndromes [(4)].

Persons who have suffered an ischemic stroke have been found to have elevated concentration of Interleukin 6 (IL-6) in the hours following the onset of symptoms [(5)] . IL-6 plays a vital function as a messenger molecule amongst the vascular endothelium, leucocytes, and parenchyma resident cells, making it an important inflammatory factor. A large rise in IL-6 concentration was stated in stroke cases quickly following the ischemic event. Based on the cellular environment, IL-6 may have opposing effects, for instance pro-proliferative, anti-apoptotic, growth-inhibitory, or differentiation-inducing. Early increases in circulating IL-6 concentration have been observed in stroke [(6)].

Biomarkers of the processes that are engaged in ischemic stroke were shown to increase predictive value to these basic statistical models, based on bedside clinical assessment. Inflammatory mediators like IL-6 have been linked to stroke progression and severity in a number of prior studies, but it has been shown that group data associations do not always fulfill better predictions of outcome in ischemic stroke patients unless they are very strong [(7)].

Microvascular disease is the root of lacunar stroke and leukoaraiosis. MRI scans of the elderly often show these abnormalities, which are associated to stroke, dementia, as well as depression [(8)].

The endothelial inflammatory response is characterized by an increase in C reactive protein (CRP). We postulated that increased CRP levels were more strongly linked to the onset and development of cerebrovascular illness in the elderly**.** Inflammation plays important role a pivotal role in ischemic stroke and can have both favourable and negative outcomes. Resident cell activation, including microglia, astrocytes, and

Received: 02/09/2024
Accepted: 03/11/2024

endothelial cells, has both protective and destructive effects on the brain. Protective effects include a reduction in neuronal cell death, cerebral edema, and haemorrhagic changes [9].

AIMS

The goal of this work is to identify the association between CRP and IL-6, as inflammatory markers. and the severity and prognosis in acute small artery cerebrovascular stroke, also to ascertain the connotation between level of serum inflammatory markers (CRP and IL-6) and prognosis of small artery cerebrovascular stroke.

PATIENTS AND METHODS

This prospective investigation has been performed out on 108 cases aged from 40 to 80 years old, both genders, with symptomatic small artery ischemic stroke through 1st twenty-four hours (26mm3 : 498mm3) (as defined by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria for ischemic stroke) [4].

Cases had symptomatic acute lacunar ischemic stroke (<15mm3), with symptomatic transient ischemic attacks (With regard to World Health Organization (WHO), this is characterized by the sudden onset of localized neurological symptoms of vascular origin that last more than 1 hour and are accompanied by indicators of acute infarction on diffusion-weighted MRI [10].

Time and settings:

The research was conducted at Neurology Departments and Clinics in Kobri El Kobba Medical Complex, other Military Hospitals, and El-Houssien Hospital. It has been conducted from February 2013 to July 2023.

Exclusion criteria:

The cases who had any type of stroke rather than small artery ischemic stroke (as defined by the TOAST criteria for ischemic stroke) [4], systemic disorders (inflammatory “confirmed by ANA and ESR” or Infectious disorders, haematological illnesses, rheumatologic illnesses, severe kidney or hepatic failure, who were receiving therapy with anti-inflammatory medications, immunosuppressive medications, or immunomodulatory medications, and stroke mimics excluded by normal MRI brain.

All cases have been subjected to: Complete history taking, general examination [vital signs (blood pressure respiration rate, heart rate, as well as temperature, and atrial fibrillation (AF))], neurological, examination [National Institutes of Health Stroke Scale examination], and investigational studies [Routine laboratory investigations (CBC, ESR, CRP, ANA, and IL-6 by ELISA), and radiological investigation (electrocardiogram (ECG), echocardiography, duplex Ultrasound (by Toshiba Nemio 30 Ultrasound Machine), computed tomography (CT) brain), magnetic resonance imaging (MRI) brain, and CT chest].

Procedures:

Assessment of subtype of stroke depending on The TOAST classification of ischemic stroke) [4]. IL-6 and CRP level was measured within 24 hours of ischemic stroke beginning and following three-months. The severity and prognosis of ischemic stroke were evaluated using the National Institutes of Health Stroke Scale (NIHSS) at the time of admission and at the three-month monitoring visit; a score above 21 indicated a poor prognosis, while a score below 5 indicated a favourable prognosis [11]. Modified Rankin Scale (mRS) at admission and after three-months. The cases have been examined using CT brain then magnetic resonance imaging of the brain (diffusion-weighted, flair, T1, T2, and T2* images) on admission only.

Additionally, MRA cerebral and carotid if needed. NIHSS was a standardized tool utilized to determine the severity of ischemic stroke on admission. It assessed various neurological functions and helped healthcare professionals assess the extent of neurological deficits caused by stroke. As the NIHSS score increased, the severity of the stroke increased [Mild Stroke: NIHSS score 1-5, moderate Stroke: NIHSS score 6-15, moderate to Severe Stroke: NIHSS score 16-20, severe Stroke: NIHSS score >20]. It is crucial to realize that the NIHSS score alone doesn't provide a comprehensive prognosis or predict the result of the stroke. The final result is additionally affected by other factors, involving the participant's overall health, the location and size of the stroke, and the timely administration of suitable therapy [12]. The mRS is utilized to assess the degree of disability in stroke cases, as described below;

0: Absence of symptom.
1: No significant disability despite symptoms, and able to perform all routine activities and duties.
2: Slight disability; incapable of performing all previous activities, but capable of managing personal affairs without help.
3: Moderate disability; capable of walking independently, but needing a little help.
4: Moderately severe disability; incapable of walking independently and incapable of attending to one's own physiological requirements without help.
5: Severe disability; bedridden, incontinent, and needing continuous nursing care and attention; and
6: Death [13].

TOAST criteria were a classification system that aimed to categorize ischemic strokes based on their underlying cause or etiology. The mechanism of the TOAST criteria

involved a systematic evaluation of various clinical features, imaging findings, and laboratory tests to determine the most likely stroke subtype.

IL-6 Human ELISA Kit:

A solid-phase sandwich ELISA for Human IL-6 may be utilized to determine the amount of target bound between a matched antibody pair. The target-specific antibody has already been applied to the wells of the microplate provided. The immobilized (capture) antibody was situated into the wells, and subsequently, samples, standards, or controls have been added. The second antibody (the detector) reacts with the enzyme-antibody-target combination to generate an observable signal upon its introduction to the sandwich. The strength of this signal is correlated with the quantity of target present in the starting material.

Steps:

Remove the desired number of segments and permit them to cool to room temperature. Once not in use, the desiccant and unused strips should be re-sealed in aluminum foil and stored among two and eight degrees Celsius. Set aside blank wells; these can be disregarded when dual-wavelength measurements are conducted. Proceed to introduce standards or samples into their respective wells, using 100µL per well. Kindly note that the 0pg/mL well ought to contain 100µL of the standard diluent. Apply the adhesive tape strip to the wells/plate, then incubate at 37°C for 90 minutes. 30 minutes prior to the event, prepare the necessary amount of biotinylated antibody. Wash ELISA plate 2 times. Transfer 100µL of the prepared biotinylated antibody to each well. Apply an adhesive tape strip to the reaction wells, then incubate at 37 degrees Celsius for sixty minutes. Make the necessary amount of enzyme conjugate 30 minutes beforehand. Wash ELISA plate 3 times. Transfer 100µl of the prepared enzyme conjugate to each well, excluding the blank wells. 30 minutes after sealing the wells with the adhesive tape strip, incubate at 37°C. Wash ELISA plate 5 times. Protection from light, incubate at 37°C with 100L of the prepared color reagent added to each well (involving the blank well). The process of incubation can be terminated when the coloration of the highest standards becomes darker, and a color gradient becomes apparent. 30 minutes should be allocated to regulate the chromogenic reaction. Proceed to add 100µL of Color Reagent C to each well, including the vacant well. Mix thoroughly. Obtain the OD at 450nm within ten minutes.

CRP:

The agglutination of latex was the basis for the CRP test. A notable agglutination reaction can happen within two minutes of the addition of latex particles complexed with human anti-CRP to cases serum that contains CRPs.

Procedure of CRP Test

Serum sample and reagents must be brought to room temperature prior to utilization, and the latex reagent should be gently mixed. You must not water down the controls or the serum. Separate reaction circles on a glass slide and add one drop of serum, the positive control, and the negative control to each circle. Following this, give a single drop of CRP latex reagent to each circle. Spread the fluid throughout the total surface of cell, then mix it with many mixing sticks. Under artificial lighting, slowly rock the slide back and forth for 2 minutes. Check for obvious agglutination.

Ethical considerations:

The study was conducted in accordance with Helsinki Standards. The whole study design was approved by the Research Ethics Committee, Neurology Department, Military Medical Academy, Armed Forces, Cairo, Egypt. Informed written consent has been obtained from the cases. Confidentiality and personal privacy were respected in all levels of the study, collected data will not be used for any other purpose.

Statistical analysis

Statistical analysis has been carried out by SPSS v26 (IBM Inc., Armonk, NY, United States of America). The mean and standard deviation (SD) of quantitative variables has been presented and compared among both groups using an unpaired Student's t-test. The Chi-square test or Fisher's exact test has been utilized to analyze qualitative variables, which have been presented as frequency and percentage (%) when appropriate.

The degree of correlation between two quantitative variables was estimated using Pearson correlation. The overall diagnostic performance of each test has been evaluated using Receiver Operating Characteristic (ROC) curve analysis. A curve that extends from the lower left corner to the upper left corner and then to the upper right corner is regarded as a perfect test. The overall test performance was assessed by the area under the curve (AUC), with an area under the curve above fifty percent indicating acceptable performance and an area at or near one hundred percent indicating the greatest performance for the test. Statistical significance has been defined as a two-tailed P value that was less than 0.05.

RESULTS

Table (1): Demographic, stroke, laboratory, and clinical data of the examined cases (n = 108)

Variables			Patients (n = 108)
Demographic data			
Gender	**Male**		83 (76.9%)
	Female		25 (23.1%)
Medical Comorbidities	**DM**		23 (21.3%)
	Hypertension		31 (28.7%)
	Dyslipidaemia		8 (7.4%)
	Atrial Fibrillation		6 (5.6%)
	Coronary Artery Disease		10 (9.3%)
	Previous Ischemic Stroke		17 (15.7%)
	Smoking		16 (14.8%)
Stroke data			
Volume of Infarct (ml^3)			248 ± 134
TOAST Classification	**Small Vessel Occlusion**		108 (100%)
Origin	**Anterior Cerebral Artery**		30 (27.8%)
	Middle Cerebral Artery		41 (38%)
	Posterior Cerebral Artery		15 (13.9%)
	Basilar Artery		13 (12%)
	Vertebral Artery		9 (8.3%)
Laboratory data			
Inflammatory Markers	**CRP mg/dl**	**At Admission**	10.86 ± 3.38
		At 3 months	9.74 ± 3.55
		P value	**0.013***
	IL-6 pg/ml	**At Admission**	9.93 ± 3.07
		At 3 months	8.66 ± 3.11
		P value	**0.001***
Clinical Data			
NIHSS	**At Admission**		13.69 ± 9.42
	At 3 months		9.64 ± 7.49
	P value		**0.001***
mRS	**At Admission**		2.27 ± 0.52
	At 3 months		1.95 ± 0.61
	P value		**0.021***

Data are presented as number (%) or mean ± SD. DM: diabetes mellites, TOAST: trial of org 10172 in acute stroke management, IL: interleukin, CRP: C reactive protein, mRS: modified Rankin scale, NIHSS: national institutes of health stroke scale, *: significant as P value below 0.05.

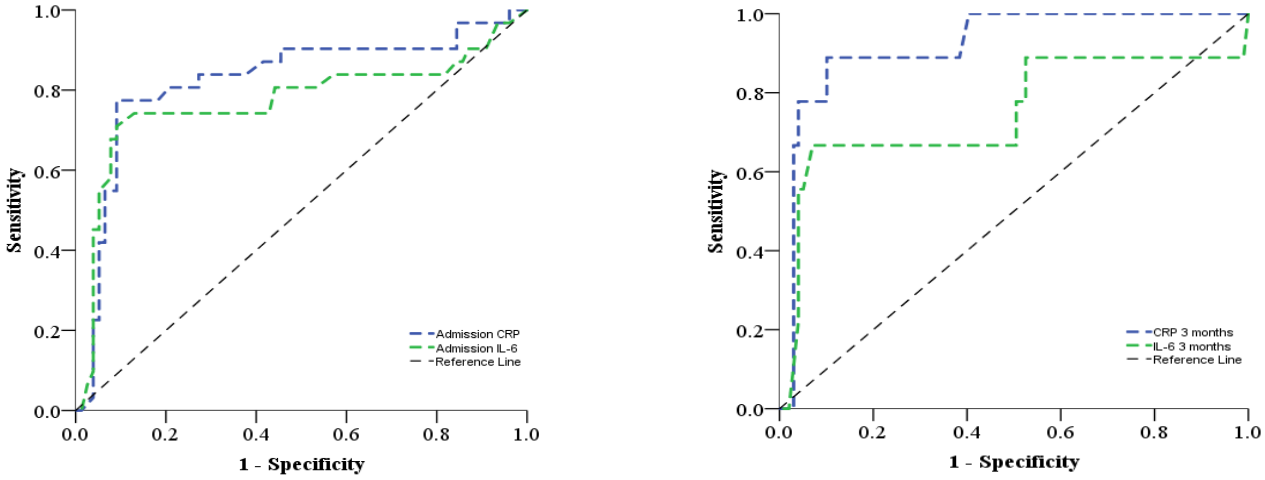
There were statistically significant variances with regard laboratory data [inflammatory markers (CRP, and IL 6)], clinical data [NIHSS, and mRS] in the studied group (P = 0.013, 0.001, 0.001, and 0.021). The data showed that 83 (76.9%) patients were males, 25 (23.1%) patients were females, 23 (21.3%) patients had DM, 31 (28.7%) had hypertension, 8 (7.4%) patients had dyslipidaemia, 6 (5.6%) had atrial fibrillation, 10 (9.3%) patients had coronary artery disease, 17 (15.7%) patients had previous ischemic stroke, 16 (14.8%) were smoking, volume of infarct was 248 ± 134 ml3, all patients had small vessel occlusion, the origin of the stroke was anterior cerebral artery in 30 (27.8%) patients, middle cerebral artery 41 (38%) patients, posterior cerebral artery 15 (13.9%) patients, basilar artery 13 (12%) patients, and vertebral artery 9 (8.3%) patients (Table 1).

Table (2): Correlation analysis (n= 108 patients)

Variables		r	P value
CRP			
On Admission	**NIHSS**	0.628	**0.001***
	mRS	0.583	**0.001***
At 3 months	**NIHSS**	0.796	**0.001***
	mRS	0.619	**0.001***
IL-6			
On Admission	**NIHSS**	0.501	**0.001***
	mRS	0.494	**0.001***
At 3 months	**NIHSS**	0.622	**0.001***
	mRS	0.594	**0.001***

r: correlation coefficient, *: significant as P value below 0.05.

A significant positive correlation was found between CRP & IL-6 concentration and NIHSS and mRS scores on admission and at 3-month follow-up (P < 0.05) (**Error! Reference source not found.**).



(A) **(B)**

Figure (1): ROC curve analysis (A) on admission and (B) at 3 months.

A receiver operating characteristic (ROC) curve analysis has been conducted to demonstrate the predictive value of CRP and IL-6 for poor prognosis on admission and at 3 months (

Figure).

DISCUSSION

An inflammatory response is crucial to the pathogenesis of acute ischemic stroke (AIS) [14]. Stroke cases, due to pathophysiological abnormalities, have been found to have a higher plasma level of different inflammatory markers compared to healthy people. Stroke can be classified into subtypes, each of which is thought to be associated with a unique pattern of immuno-inflammatory activity [1, 7].

In our study showed that hypertension was the most prevalent comorbidity in 31 (28.7%) patients followed by DM in 23 (21.3%) patients followed by previous stroke in 17 (15.7%) patients followed by smoking in 16 (14.8%) followed by coronary artery disease in 10 (9.3%) followed by dyslipidemia in eight (7.4%) patients, and followed by atrial fibrillation in six (5.6%) patients. Our result supported with **Hoshi *et al.*** [16] that showed that hypertension was the most prevalent comorbidity in 128 patients (66.0%). Our result disagrees with **Aref *et al.*** [15] which revealed that diabetes mellitus was the most common risk factor, affecting 59 individuals (65.6%), then hypertension (56 individuals, 62.2%), dyslipidemia (49 patients, 54.4%), smoking (32 people, 35.6%), ischemic heart disease (ISHD) (24 people, 26.7%), along with atrial fibrillation (AF) (19 people, 21.1%).

In the present study showed that according to TOAST classification, all enrolled patients sustained a small vessel occlusion resulting in mean infarction volume of 248 ± 134 ml, ranging from 26 to 498 ml, including 18

(16.6%) infarctions less than 100 ml the occluded small vessel originated from MCA in 41 (38%) patients, ACA in 30 (27.8%) patients PCA in 15 (13.9%) patients, basilar artery in 13 (12%) patients, and vertebral artery in nine (8.3%) patients. Our results contradict those of **Aref *et al.*** [15] who demonstrated that stroke subtypes were categorized into three categories (as per the TOAST classification). There were thirty-eight cases of small vessel occlusion (SVO) (42.22 percent), twenty-seven cases of cardio embolic strokes (30 percent), and twenty-five cases of large artery atherosclerosis (LAA) (26.78 percent). Sixty-four ischemic strokes have been situated anteriorly in the distribution of the anterior cerebral artery or middle cerebral artery (71.1 percent), while twenty-six ischemic strokes have been situated posteriorly in the distribution of the vertebral, basilar, or posterior cerebral artery (28.1percent). Additionally, our studies are inconsistent with those of **Adams *et al.*** [4] who sought to classify the subtypes of AIS. They illustrated that the TOAST classification indicates five subtypes of ischemic stroke: (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-vessel occlusion, (4) stroke of other determined etiology, and (5) stroke of undetermined cause. The physicians demonstrated a high degree of agreement when utilizing this scoring technique. Only one of the two doctors had a different opinion regarding the patient. They were both successful in arriving at an accurate etiologic diagnosis for 11 of the individuals, but for nine of the people, the cause of the stroke could not be established.

In current study showed that the mean CRP level at admission was 10.86 ± 3.38 milligram per deciliters, ranging from 1.3 to 20 milligram per deciliters. At three-month monitoring the mean CRP level reduced to 9.74 ± 3.55 milligram per deciliters, varying from 0.3 to 19.5 milligram per deciliters. There was a significant reduction was observed in CRP level at 90 days follow-up following the stroke (Paired sample t test, P = 0.013). However, CRP level was persistently elevated throughout the study period. The findings of our research were consistent with those found by **Yang *et al.*** [17] carried out research with the intention of determining the association between high-sensitivity CRP and post-stroke depression (PSD). Two hundred twenty-six people who had suffered ischemic strokes participated in their study. They found that elevated hs-CRP serum concentration at the time of admission have been correlated with depression 6 months following a stroke, and they reported this finding.

Our study showed that the mean IL-6 level was 9.93 3.07 pg/ml, ranging from 5 to 15 pg/ml. At three-month monitoring, the mean IL-6 level reduced to 8.66 3.11 pg/ml, varying from 3 to 14.2 pg.ml, there was a statistically significant reduction was observed in IL-6 level at 3-month follow-up following the stroke (Paired sample t test, P = 0.001). However, IL-6 level was persistently elevated throughout the study period.

The mean value of IL-6 was 6.39 ± 4.68 picograms per milliliter, which is in line with the findings of **Aref *et al.*** [15], the mean value of IL-6 was 4.64 picograms per milliliter in individuals with cardio embolic stroke, 5.11 picograms per milliliter in individuals with LAA, and 8.47 picograms per milliliter in individuals with SVO. This indicates a statistically significant increase in the mean value of IL-6 in SVO (P value equal 0.005). In contrast to the outcomes of **Smith *et al.*** [18], which revealed that only 77% of the patients presented an elevation in plasma IL-6 following the admission sample (with a median elevation that was 148% of the value at admission), our results showed no such increase.

In our study showed that the mean admission NIHSS was 13.69 ± 9.42 ranging from 1 to 30. At the 3-month follow-up, a statistically improvement was observed in the mean NIHSS to 9.64 ± 7.49 ranging from 1 to 24, regarding stroke prognosis on admission, 27 (25%) patients had good prognosis, 50 (46.3%) patients had fair prognosis and 31 (28.7%) patients had poor prognosis. At three-month monitoring, 40 (37%) cases had good prognosis, 59 (54.6%) patients had fair prognosis and nine (8.3%) patients had poor prognosis. The NIHSS greatly improved the predictive value of all other scores. Also, individuals with anterior circulation strokes had a median first NIHSS score of 7, whereas those suffering from posterior circulation strokes had a median initial NIHSs score of 2. This outcome is line with the evaluation conducted by **Inoa *et al.*** [19] who discovered that in order to precisely predict a positive prognosis in posterior circulation stroke, reduced NIH stroke scale scores are needed. Individuals with PC stroke was more probable to have low NIHSS ratings at the start (71%), as well as those with low scores, fifteen percent had a poor prognosis at three-months. According to ROC analysis, the optimum NIHSs cutoff for prediction of the outcome following AC infarction was 8, whereas the optimum NIHSS cutoff following PC infarction was 4. The NIHSs cutoff for detecting individuals that would have adverse results was 4 for AC infarctions and 2 for PC infarctions.

The present study showed that the mean admission mRS was 2.27 ± 0.52, ranging from 0 to 5. At three-month monitoring, a statistically significant improvement was observed in the mean mRS to 1.95 ± 0.61, ranging from 0 to 6, regarding stroke prognosis on admission, 61 (56.5%) patients had good prognosis, and 47 (43.5%) patients had poor prognosis. At 3-month follow-up, 70 (64.8%) patients had good prognosis, and 38 (35.2%) patients had poor prognosis. Our result supported with **Quinn *et al.*** [20] who used a large, independent, clinical trials dataset to examine the predictive accuracy of different acute stroke prognostic scales found a significant disparity in the modified Rankin

Scale among the Acute Stroke Registry as well as Analysis of Lausanne and all other scales.

A statistically significant positive association was discovered among CRP as well as IL-6 levels & NIHSS along with mRS scores both on admission & at the three-month monitoring (Pearson test, P 0.05). This was shown by our findings, which indicated that there was such a correlation. Our results contradict those of **Aref *et al.*** [15] who discovered an insignificant positive correlation between IL-6 and the NIHSS at admission (P value equal 0.2) (r = 0.135), but a significant positive association between IL-6 & the NIHSS following three-months (P value equal 0.009) (r = 0.28). Additionally, they detected a non-significant positive correlation between the mRS and IL-6 at the time of admittance (P value less than 0.0001) (r = 0.42).

The results of our study, which were based on the receiver operating characteristic curve as well as the area under the curve, revealed that CRP possesses a high predictive value at the time of admission and a great prognostic value after three-months. On the other hand, the prognostic value of IL-6 is regarded as being about average, both at the time of admission and throughout the 3-month follow-up after the patient has been discharged from the hospital.

Aref *et al.* [15] initiate that the area under the curve had a value of 0.9, indicating that the test had both high specificity and sensitivity in expecting recurrence with a P value of under 0.0001. Our study was consistent with their findings. At a value of 7.75 picograms per milliliter l for IL-6, the test has a sensitivity of 0.93 and a specificity of 0.75, hence this value has been chosen as the threshold at which recurrence is considered likely.

CONCLUSION

Inflammatory mediators have a pivotal role in ischemic stroke. IL-6 and CRP were found to have good prognostic value in cases with acute small artery ischemic stroke. Additionally, future research should involve a younger age group and other types of inflammatory markers. Our recommendation is to involve a representative sample of cases and comparable ages, gender, and disease severity as a control group. To accurately evaluate long-term results, additional investigations should have a longer monitoring duration, and the sample size must be large to represent more cases in the Egyptian society.

DECLARATIONS

- **Funding:** No fund.
- **Conflicts of interest:** None.

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