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Characteristics and outcomes of large artery occlusion-related stroke due to intracranial atherostenosis: An experience from a single center in Saudi Arabia

Azra S. Zafar, Rizwana Shahid, Aishah I. Albakr, Danah T. Aljaafari, Fahd A. Alkhamis, Erum M. Shariff, Majed M. Alabdali, Saima Nazish, Foziah J.G. Alshamrani, Abdullah S. Alamri, Kawther M. Hadhiah, Abdulla A. Alsulaiman, Norah A. Alkhaldi, Sari S. Al-Suhibani[1], Hosam M. Al-Jehani[2]

Departments of Neurology and [1]Radiology, College of Medicine and King Fahd Hospital of the University, Imam Abdulrahman Bin Faisal University, [2]Department of Neurosurgery, Critical Care Medicine and Interventional Radiology, King Fahd Hospital of the University, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Address for correspondence:
Dr. Azra S. Zafar, Department of Neurology, College of Medicine, King Fahd Hospital of the University, Imam Abdulrahman Bin Faisal University, Dammam 34212, Saudi Arabia.
E-mail: azafar@iau.edu.sa

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Abstract:

BACKGROUND: Literature on the frequency, response to treatment, and outcomes of acute ischemic stroke (AIS) due to intracranial atherostenosis (ICAS)-related intracranial large artery occlusion (ILAO) from Saudi Arabia is scarce. The aim of this study was to identify the percentage, describe the characteristics, and observe the treatment response in patients with AIS attributed to ICAS-related ILAO.

MATERIALS AND METHODS: This cross-sectional study included all adult patients from 2017-2021 who fulfilled the inclusion criteria for the diagnosis of ICAS-related AIS. Patients were dichotomized based on ILAO. Mortality and functional outcomes (FOCs) based on 90 days' dependence level were compared between the two groups. The association between ILAO and other variables was assessed using the Chi-squared test, odds ratios (OR), and 95% confidence interval (CI).

RESULTS: ILAO was found in 38.7% of patients with ICAS-related AIS. Men comprised three-fourths of the cohort and were more frequent in the ILAO group. Smoking was associated with increased ($P = 0.04$) likelihood of ILAO. Patients with ILAO had more severe strokes ($P \leq 0.001$) than patients without. Middle cerebral artery was the most common occluded vessel (52%). Functional dependence ($P = 0.003$, OR = 2.87, CI = 1.42–5.77), malignant transformation ($P = 0.001$, OR = 8.0, CI = 1.82–35.9), and mortality ($P \leq 0.001$, OR = 7.67, CI = 2.40–24.5) were significantly higher among ILAO group. Patients with ILAO with unfavorable FOC were older than those who achieved better FOC ($P \leq 0.001$). Thrombolysis ($P = 0.02$, OR = 2.50, CI = 1.15–5.41) and mechanical thrombectomy (MT) improved FOC in patients with ILAO ($P = 0.04$, OR = 2.33, CI = 1.10–4.92).

CONCLUSION: ILAO is common in patients with ICAS-related AIS. Timely hyperacute stroke treatment can help improve the FOC of otherwise disabling stroke due to ILAO. Raising awareness of the community about stroke is needed, so that a higher number of patients can arrive at hospital within the golden hours. Further data from the region are required to recognize the efficacy of MT in ICAS-related ILAO.

Keywords:

Acute ischemic stroke, endovascular treatment, intracranial atherosclerotic disease, intracranial large vessel occlusion, thrombolysis

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Introduction

Intracranial large artery occlusion (ILAO) is estimated to make up nearly half of the acute ischemic strokes (AISs).[1,2] Large artery occlusion affecting internal carotid artery (ICA), middle cerebral (MCA), and basilar artery (BA) is associated with higher mortality rates.[1] It has various etiologies, one of which is intracranial atherostenosis (ICAS) which is recognized as one of the most common stroke etiologies globally, particularly in Eastern and South Asian populations.[3] It is also considered one of the critical etiologies of ILAO, which is observed in populations of all ethnical origins, but particularly in the Asian populations.[4,5] The horizontal portion (M1 segment) of MCA is considered the most common site of occlusion.[2,6]

It is essential to identify ICAS as the underlying cause of ILAO because such patients are sometimes refractory to mechanical thrombectomy (MT) and have higher reocclusion rates than the ILAO of embolic origin.[7-9] A recent study identified ICAS as a predictor of poor outcomes in ILAO.[10] Nevertheless, various studies have reported MT as a safe measure and beneficial in attaining functional outcomes (FOCs) comparable to the patients with ILAO of embolic origin.[8,11] Furthermore, angiographic success and time metrics are also comparable with ILAO of embolic origin.[12,13] In addition, since recent landmark trials have proven the beneficial effect of endovascular treatment (EVT) in the extended therapeutic time windows, the chances of patients receiving such restorative treatment are now better.[14,15] The World Health Organization has reported stroke as the second contributor to mortality in Saudi Arabia, the largest country in the Middle East.[16] Although stroke is a huge contributor to economic and health burden in Saudi Arabia, not much is known about it. There are, therefore, barriers to the effective management of the acute condition.[17,18] A recent study from Saudi Arabia reported the prevalence of ILAO in anterior circulation among all AIS patients as 27.8%.[19]

In this study, we aimed to identify the percentage of ILAO in AIS due to ICAS from a single center in Saudi Arabia and determine its association with mortality and FOC. The observations from this study can help estimate the disease burden and disability as a result of ICAS-related ILAO in the region. By understanding the response to treatment in patients with ILAO due to ICAS, immediate management measures of the comprehensive stroke services already in place in the Eastern region of Saudi Arabia, can be improved.

Materials and Methods

This retrospective, observational study was carried out between 2017 and 2021. Ethical approval was obtained from the Institutional Review Board (IRB) vide Letter No. IRB-2017-01-206 dated 31/03/2019, with a waiver of informed consent since there was no direct relation with human subjects in this study.

Electronic charts of all adult patients admitted with a diagnosis of AIS attributed to ICAS as an underlying etiology were included in the final analysis. Patients with symptoms attributed to diagnoses other than AIS such as intracerebral hemorrhage, cerebral venous sinus thrombosis, brain tumors, demyelinating disease, and other illnesses were excluded.

ICAS was identified as an underlying etiology for AIS if ≥50% stenosis was detected by computed tomography angiogram (CTA), magnetic resonance angiogram (MRA), and/or digital subtraction conventional cerebral angiogram (DSA) in clinically symptomatic intracranial large arteries as mentioned previously.[20,21]

ILAO was defined as occlusion of the intracranial ICA, the horizontal portion of the MCA (M1), the insular portion of the MCA (M2), A1 segment of the anterior cerebral artery (ACA), BA, or the P1 segment of the posterior cerebral artery (PCA) and the intracranial segment of the vertebral artery.[2,22]

Data about demographics (such as age and sex), presence of vascular risk factors, and other relevant clinical information including thrombolysis and MT of patients meeting the inclusion criteria were retrieved from the electronic medical records. Patients were divided into two groups based on the presence of ILAO as ILAO and non-ILAO groups. Mortality and FOC of patients were noted. In-hospital mortality and FOC based on modified Rankin score (mRS)[23] after onset of stroke were the outcome parameters compared between the two groups. Patients with mRS 0–2 were defined as having favorable FOC, whereby ≥3 was unfavorable FOC. This study was a continuation of our project related to ICAS.[24]

Nearly all patients presenting with symptoms of AIS underwent computed tomography and CTA of the brain in the emergency department (ER) and received stroke-specific treatment when indicated within 24 h of therapeutic window.[14] The National Institute of Health Stroke Scale (NIHSS) was calculated for every patient to assess the severity of AIS.[25] Magnetic resonance imaging (MRI) of the brain and MRA were performed for some patients as required. DSA was performed by a neurointerventionist as determined by the neurovascular team. Infarctions were described as total MCA, partial MCA, ICA (ACA + MCA), ACA, border zone, and posterior circulation infarctions based on neuroimaging. The presence of malignant transformation was also noted.

Demographics, vascular risk factors' distribution, and radiological characteristics were compared between ILAO and non-ILAO groups. Relevant data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 22.0 (IBM Corp., Armonk, New York, USA). The results are presented as frequencies and percentages for categorical variables. The mean ± standard deviation, median, and interquartile range (IQR) were used to describe quantitative variables. Statistical significance of categorical variables including sex, risk factors, and FOC between the two groups was checked using Pearson's Chi-squared test. One-way analysis of variance and Mann–Whitney *U*-test were performed to identify the statistically significant differences in the mean values of quantitative variables such as age and NIHSS. The difference in the distribution of categorical variables was ascertained by estimating odds ratios (OR) and 95% confidence intervals (CI). In all cases, a two-sided $P < 0.05$ was considered statistically significant.

Results

In total, 150 out of the 852 patients with AIS admitted during the study period met the inclusion criteria, and their electronic charts enrolled for analysis. Fifty-eight (38.7%) of these patients were found to have ILAO. Baseline demographic characteristics, risk factors distribution, and other relevant clinical details are outlined in Table 1. The statistical power of the study using general linear model was 93%.

The median age (IQR) of the entire sample was 59 years (31–92), and the mean age was comparable in the two groups with no significant difference. Men comprised three-fourths of the cohort, and the male: female ratio was 4.2:1 in the ILAO group and 2.2:1 in non-ILAO group. Smokers were significantly more frequent in the ILAO group than in non-ILAO group ($P = 0.04$). Although the OR for diabetes mellitus (DM), coronary artery disease, dyslipidemia, and previous transient ischemic attack were higher in patients with ILAO than without, none of these could achieve statistically significant *P* value. Nevertheless, hypertension was significantly less prevalent in the ILAO group ($P = 0.008$). Patients with ILAO had more severe strokes than patients without ILAO, as reflected by significantly higher baseline NIHSS with a median (IQR) of 10 (1–24) versus 5 (1–21), respectively.

Notably, more patients with ILAO arrived at the ER within the therapeutic window than patients without ILAO ($P = 0.007$). The mean total cholesterol, low-density lipoprotein cholesterol, and triglycerides did not differ significantly between the two groups. A significantly higher number of patients in the ILAO group had thrombolysis and EVT than patients in non-ILAO group.

Table 1: Demographic and clinical characteristics of patients diagnosed with AIS attributed to ICAS by presence of intracranial large artery occlusion (ILAO)

Characteristics	Total (*n*=150) *N* (%)	ILAO (*n*=58) *N* (%)	No ILAO (*n*=92) *N* (%)	*P*-value	OR	95% CI
Demographic characteristics						
Age (mean±SD)	59.7±13.6	58±14.3	61±13.3	0.20*		54.26–61.84
Male	110 (73.3)	47 (81.0)	63 (68.5)	0.09	1.96	0.89–4.33
Vascular risk factors						
DM	114 (76.6)	44 (81.0)	70 (74.0)	0.66	1.20	0.52–2.72
HTN	122 (81.3)	41 (70.7)	81 (88.0)	0.008	0.32	0.14–0.76
CAD	32 (21.3)	15 (25.9)	17 (18.5)	0.28	1.53	0.69–3.38
DLP	86 (57.3)	35 (60.3)	51 (55.4)	0.55	1.22	0.62–2.38
Smoker	36 (24.0)	19 (32.8)	17 (18.5)	0.04	2.14	1.00–4.59
Previous stroke	45 (30.0)	15 (25.9)	30 (32.6)	0.38	0.72	0.34–1.49
Previous TIA	16 (10.6)	8 (13.8)	8 (8.7)	0.32	1.68	0.59–4.75
Clinical and other relevant characteristics						
NIHSS on presentation (mean±SD)	8.40±6.05	11.3±6.5	6.6±4.5	<0.001*	-	9.57–13.03
Arrival within therapeutic window	40 (26.7)	22 (37.9)	12 (13.0)	0.007	2.75	1.30–5.81
Anterior circulation	102 (68.0)	45 (77.6)	57 (62.0)	0.04	2.12	1.00–4.48
Alteplase given	28 (18.7)	17 (29.3)	11 (12.0)	0.008	3.05	1.31–7.11
EVT	17 (11.3)	11 (19.0)	6 (6.5)	0.01	3.35	1.16–9.64
Outcome parameters						
Malignant transformation	11 (7.3)	10 (17.2)	1 (1.1)	0.001	8.01	1.82–35.9
In hospital complications	28 (18.7)	16 (27.6)	12 (13.0)	0.02	2.72	1.15–6.43
Died	19 (12.7)	15 (25.9)	4 (4.3)	0.000	7.67	2.40–24.5
Unfavorable FOC	83 (55.3)	41 (70.7)	42 (45.7)	0.003	2.87	1.42–5.77

*Mann–Whitney *U*-test was applied to check the statistical significance. Data are represented as means±SD or *n* (%). ILAO=Intracranial large artery occlusion, SD=Standard deviation, EVT=Endovascular treatment, TIA=Transient ischemic attack, FOC=Functional outcomes, OR=Odds ratio, CI=Confidence interval, DLP=Dyslipidemia, HTN=Hypertension, CAD=Coronary artery disease, DM=Diabetes mellitus, NIHSS=National Institute of Health Stroke Scale

Anterior circulation involvement was more frequent in the ILAO group than the non-ILAO group ($P = 0.04$, OR = 2.12, CI = 1.00–4.48). Frequencies of occluded vessels and infarct distribution are detailed in Table 2. Fifty-two percent of the cohort had ILAO in MCA. Partial MCA infraction was the most commonly observed infarct pattern. Only 5% of the patients had border-zone infarctions resulting from hypoperfusion. A significantly higher number of patients in the ILAO group had malignant transformation than patients in the non-ILAO group ($P = 0.001$).

In-hospital mortality and unfavorable FOC were significantly more prevalent in the ILAO group than the non-ILAO group. A significant association of ILAO with unfavorable FOC was persistent during logistic regression analysis ($P = 0.01$, OR = 2.78, CI = 1.25–6.18). The distribution of different variables according to the FOC in patients with ILAO is detailed in Table 3. Patients with unfavorable FOC in the ILAO group were significantly older than patients with favorable FOC ($P \leq 0.001$) and had more severe strokes ($P \leq 0.001$). FOC in patients with ILAO was also significantly dependent on the vessel occluded ($P = 0.03$) and infarction on neuroimaging ($P = 0.03$) as shown in Figure 1a and b, respectively. Patients with either ACA or PCA occlusion did not have unfavorable FOC. Patients who received thrombolysis had a significantly higher likelihood of favorable FOC than those who did not ($P = 0.02$, OR = 2.50, CI = 1.15–5.41). Patients undergoing MT were also found to have achieved favorable FOC more frequently than patients who did not have MT. Brain scans and angiographic images of two patients undergoing successful MT and endovascular stenting are shown in Figure 2.

Table 2: Distribution of Occluded vessels and infarction patterns in patients with intracranial large artery occlusion

Occluded vessel and infarction pattern	*N* (%)
Vessel occluded	
ICA	13 (22.4)
ICA and MCA	4 (6.9)
MCA	26 (44.8)
M1 segment of MCA	18 (69.2)
M2 segment of MCA	8 (30.8)
ACA	1 (1.7)
BA	8 (13.8)
VA	2 (3.4)
Basilar and VA	2 (3.4)
PCA	2 (3.4)
Distribution of infarction on neuroimaging	
Internal carotid artery infarction (ACA + MCA)	3 (5.2)
Total MCA infarction	12 (21.0)
Partial MCA infarction	24 (41.3)
Border zone infarction	3 (5.2)
ACA infarction	1 (1.7)
POCI	14 (24.1)
Mixed/unclear	1 (1.7)

ICA=Internal carotid artery, BA=Basilar Artery, VA=Vertebral Artery, MCA=Middle cerebral artery, ACA=Anterior cerebral artery, PCA=Posterior cerebral artery, POCI=Posterior circulation infarction

Discussion

Stroke is one of the leading causes of mortality in Saudi Arabia; however, few hyperacute stroke units (HSUs) provide comprehensive stroke services, including EVT.[16] Knowledge of the disease burden and outcome of AIS due to ILAO in Saudi Arabia is important because outcomes depend on EVT, which can be provided in comprehensive stroke centers with hyperacute stroke treatment capabilities. To our knowledge, our study is the first in the literature to describe the clinicoradiological characteristics of patients with ILAO resulting from ICAS from Saudi Arabia. Of all the patients with AIS attributed to ICAS, ILAO accounted for 38.7%, which is in the range reported for ILAO in all patients with AIS. While some studies[1,2,6] have reported the prevalence of ILAO in patients with AIS of all causes and strokes affecting the anterior circulation only,[19] the prevalence of AIS attributed to ICAS solely is largely unavailable. Nevertheless, ICAS has been reported to be the cause of ILAO in 34% of Chinese[8] and 40% of the Asian population,[2,6] which is significant, and shows it as a

Table 3: Clinical variables and association with functional outcome in patients with intracranial large artery occlusion

Variables	Functionally independent (*n*=17)			Functionally dependent (*n*=41)			*P*-value
	N (%)	OR	95% CI	*N* (%)	OR	95% CI	
Age, means±SD	50.81±11.20	-	43.74–56.36	61.68±14.23	-	56.75–65.64	<0.001
NIHSS, median (IQR)	5.5 (1–20)	-	4.18–8.32	13 (2–24)	-	11.29–15.25	<0.001
DM	11 (64.7)	0.45	0.21–0.96	33 (83.0)	1.65	0.84–3.22	0.05
Arrival within therapeutic window	8 (47.0)	1.19	0.54–2.62	15 (36.6)	0.91	0.63–1.33	0.65
MT	6 (35.3)	2.33	1.10–4.92	5 (12.2)	0.59	0.30–1.15	0.04
Thrombolysis	9 (53.0)	2.50	1.15–5.41	9 (19.5)	0.62	0.38–1.01	0.02
Malignant transformation	-	-	-	11 (26.8)	1.56	1.26–1.94	0.01
In hospital complications	-			15 (36.6)	2.00	1.42–2.79	0.001

MT=Mechanical thrombectomy, SD=Standard deviation, IQR=Interquartile range, OR=Odds ratio, CI=Confidence interval, DM=Diabetes mellitus, NIHSS=National Institute of Health Stroke Scale

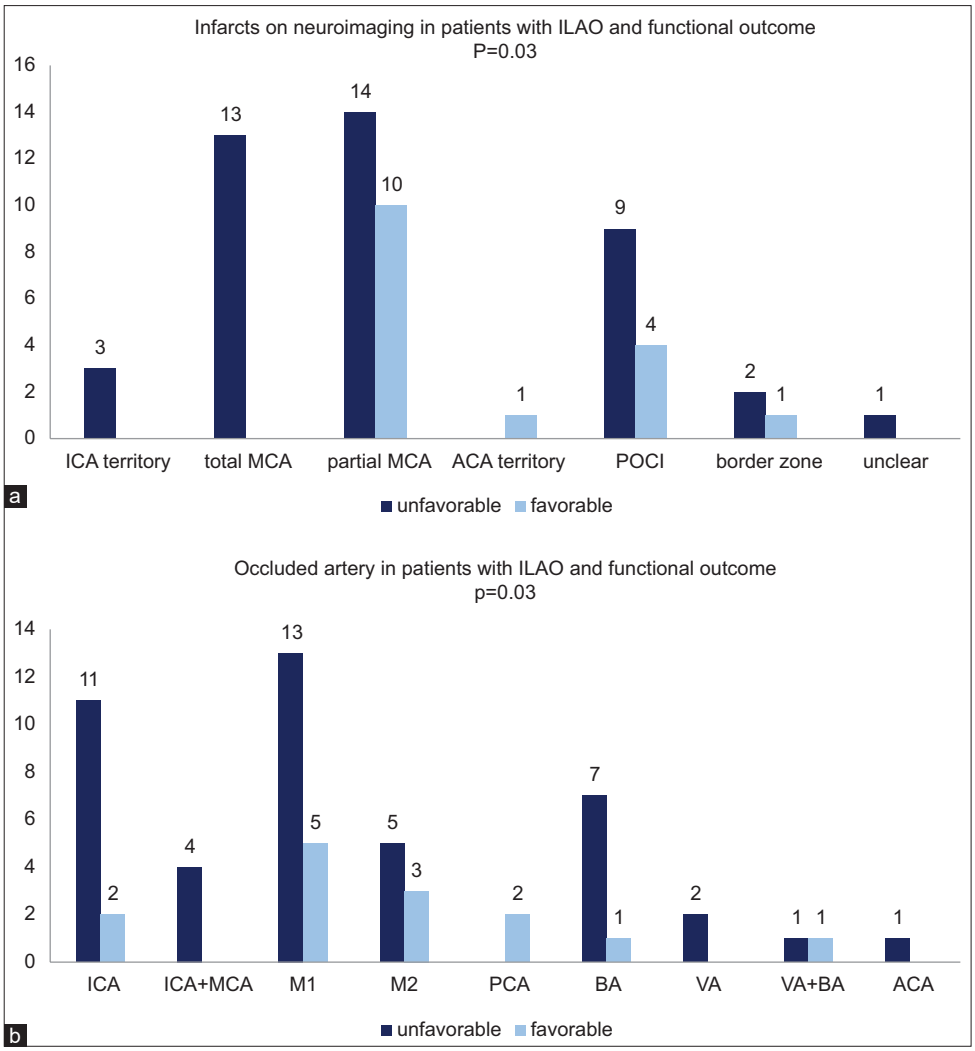

Figure 1: (a) Infarcts on neuroimaging in patients with intracranial large artery occlusion (ILAO) and functional outcome (data are represented in numbers). (b) Occluded artery in patients with ILAO and functional outcome (data are represented in numbers). ICA: Internal carotid artery, MCA: Middle cerebral artery, M1: The horizontal portion of the MCA, M2: The insular portion of the MCA, PCA: Posterior cerebral artery, BA: Basilar artery, VA: Vertebral artery, ACA: Anterior cerebral artery, POCI: Posterior circulation infarct

substantial contributor to the disease burden resulting from ILAO. The high prevalence of ILAO in patients with AIS observed during the last decade, the majority of which exceeds 30%, underscores the importance of addressing the underlying etiologies and developing a therapeutic paradigm to prevent resulting functional disability.[26]

The mean age of patients with ILAO in our study is comparable to that of patients with ILAO as a result of ICAS in other studies, which have reported that ILAO from ICAS occurs in younger populations than ILAO of embolic origin.[5,8] ILAO was observed more frequently in men than in women, which could partly be because of men's smoking habits, as smoking was significantly associated with ILAO in our cohort and all smokers were men ($P \leq 0.001$). Moreover, male sex and smoking are important risk factors for ICAS.[4] Smoking was significantly prevalent in ILAO due to ICAS in a study by Lee *et al*., as well.[5] In 2020, the rate of smoking in Saudi Arabia was reported as 14.3%, with a 0.1% recent rise.[27] Notably, smoking-related diseases cause more than 7 million deaths annually, 70,000 of which occur in Saudi Arabia, where the focus of the government, as a part of its 2030 vision, is significantly on preventive public healthcare measures including many planned initiatives to combat tobacco consumption. However, the impact of these initiatives should be evaluated.[28]

Overall, the frequency of occluded vessel involvement in our cohort was similar to previous studies, in which the MCA was the most frequently occluded vessel followed by the ICA.[1,2] Importantly, significantly more patients with ILAO arrived within the therapeutic window and received thrombolysis and MT than the other group, which is consistent with previous studies.[19,29] This

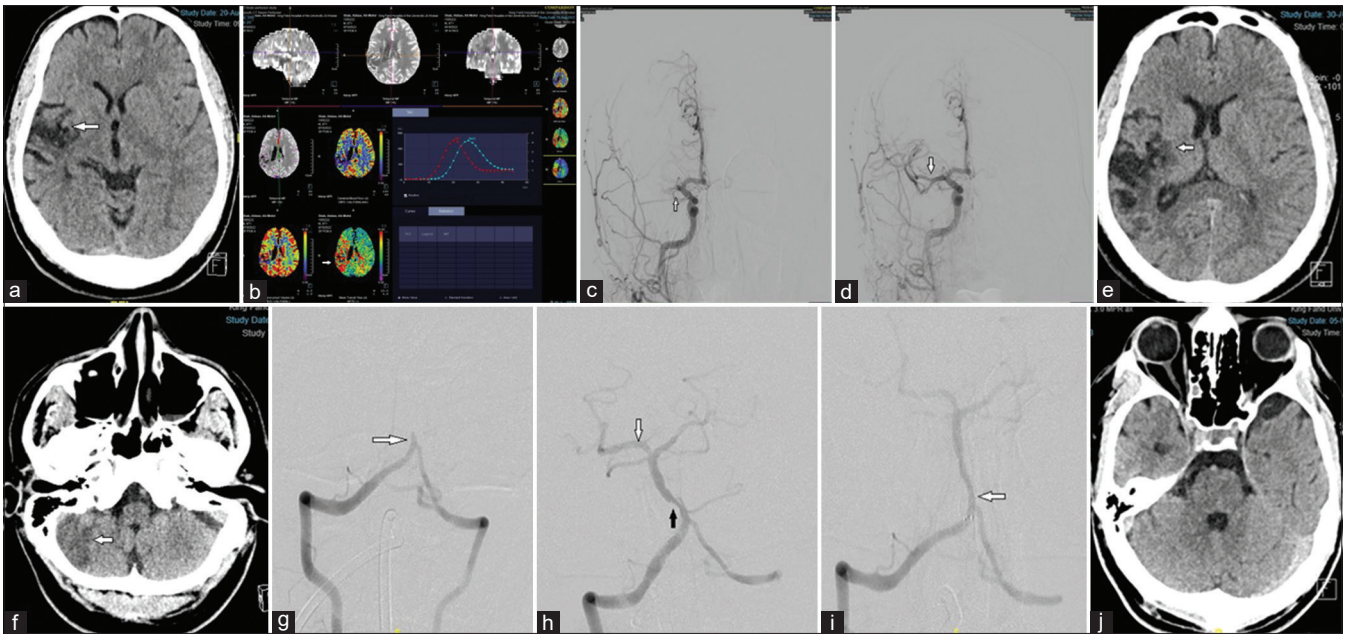

Figure 2: Neuroimaging of patients with successful mechanical thrombectomy (MT). (a e) Belong to the patient with middle cerebral artery focal stenosis with previous history of minor stroke with no residual deficit who presented with left mild hemiparesis. (a) Axial computed tomography (CT) scan upon arrival showing old infarction in middle cerebral artery (MCA) territory pointed by arrow, (b) CT brain perfusion (CTP) with salvageable penumbra pointed by arrow, (c) Digital subtraction angiogram (DSA) showing M1 segment occlusion of right middle cerebral artery pointed by arrow, (d) Successful recanalization with MT, arrow is indicating revascularization (e) Post MT axial CT scan brain with minimal new hypodensity pointed by arrow. (f j) Belong to the patient who presented with sudden onset headache, dysarthria, and lost consciousness. (f) Initial CT scan brain with hypodensity in right cerebellum pointed by arrow, (g) DSA showing basilar artery occlusion as indicated by loss of flow by arrow, (h) Successful recanalization with MT and stent placement, pointed by white arrow, underlying basilar artery stenosis pointed by black arrow.(i) DSA showing post stent placement flow by arrow. (j) CT scan brain axial cut before discharge. Both patients achieved favorable functional outcomes

could be explained by the fact that patients with ILAO have more severe strokes than those without ILAO, as reflected by higher NIHSS scores, which results in a rush to the hospital. In general, a higher percentage of patients in our cohort received stroke-specific treatment than reported previously from Saudi Arabia;[19,29] however, the number of participants in our study was smaller, and the methodology was different. Although only a few patients had MT in our cohort, successful recanalization was achieved in more than 50% of the patients, comparable to the studies that reported recanalization after MT.[30] Nearly half of the patients who underwent MT and more than half who had thrombolysis achieved functional independence, which underscores the significance of a timely and adequate hyperacute stroke treatment.

Notably, ILAO is an independent predictor of poor FOC and mortality.[30] However, several recent randomized controlled trials have proven the benefits of MT combined with the best medical therapy in improving the FOC and reducing 3-month mortality.[31] Our study agrees with previous studies that show a significantly higher mortality rate and functional dependence observed in patients with ILAO than in those without.[1,32] Predictors of unfavorable outcomes in patients with ILAO included age, DM, higher NIHSS at presentation, malignant transformation, and in-hospital complications. There are conflicting data on the safety and efficacy of EVT in ILAO of ICAS origin.[7-9] Nevertheless, various studies have reported EVT as a safe valuable treatment in ILAO resulting from ICAS.[8,11-13,33] In addition, we found that patients with MT were more likely to have a favorable FOC than those without. Furthermore, EVT has become the standard care treatment for ILAO.[34] Based on the findings of our study, we strongly support the need to establish more HSUs, as suggested by Al-Senani *et al*., to prevent disability because of the lack of acute treatment in rural and remote areas of SA.[16] Importantly, the Saudi Government has already planned major initiatives to raise awareness and has developed strategic programs for hyperacute stroke treatment by the Ministry of Health as part of vision 2030.[35] Raising awareness of the golden hours for treatment at the community and primary healthcare level is crucial in preventing functional disability.

This study has several limitations. The diagnosis of ICAS was based on available vascular imaging, and not all patients had DSA. The data were collected retrospectively only from a single center in the Eastern Province of Saudi Arabia, which limits the generalizability of these results and emphasize the need of future multicenter study. The number of patients who met the inclusion criteria in our study, the majority of whom were men, was small, and only a few had MT. However, the high statistical power of this study indicates its effectiveness. Finally, long-term follow-ups, which could help assess the long-term prognosis, were not included. Nevertheless,

this study describes the details regarding ILAO-related strokes in patients with ICAS, which has not been reported previously. Moreover, the study highlights the impact of ILAO-related strokes on mortality and FOC. In addition, we investigated the effects of MT and thrombolysis on AIS caused by ICAS-related ILAO, which is an area that has been understudied in this region.

Conclusion

ILAO was found in more than one-third of patients with ICAS-related AIS in our study. There was higher mortality of patients with ILAO and a less likelihood of achieving functional independence than those without. Thrombolysis and MT were effective in improving FOC in patients with ILAO.

We recommend that the general population should be made aware that the chances of significant functional disability and mortality as a result of ILAO-related AIS are high and emphasize the fact that it was crucial for patients who have alarming symptoms to arrive at the HSUs within the therapeutic window.

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Conflicts of interest

There are no conflicts of interest.

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