PATENT FORAMEN OVALE (PFO) IN PATIENTS OF CRYPTOGENICSTROKEANDTRANSIENTISCHEMIC ATTACK (TIA) : A REAL WORLD EXPERIENCE

Abstract:

Background:
Stroke, a leading cause of brain tissue damage, presents a significant health concern globally. Cryptogenic stroke (CS), with an unclear origin, poses diagnostic challenges, with the patent foramen ovale (PFO) implicated in some cases. This study aims to investigate PFO prevalence in North India among patients with cryptogenic stroke, addressing current research gaps.

Objective:
To assess PFO occurrence in patients with cryptogenic stroke and Transient Ischemic Attack (TIA) using Echocardiography.

Methods & Results:
This preliminary study analyzed PFO prevalence in patients with CS and TIA from February 2020 to November 2021, involving 25 participants. Descriptive statistics and the Chi-square test were employed. Key findings include a mean age of 44.80±9.13 years, 64% men, and 36% women. Ischemic stroke accounted for 72% of cases, while TIA represented 28%. PFO prevalence was 44%, with no significant gender-PFO association. No correlations were found between stroke type and PFO presence, nor were comorbidities like hypertension and diabetes observed.

Conclusion:
The study highlights a clinically significant distribution of PFO presence but no notable association between stroke type and PFO presence. These findings contribute to understanding PFO's role in cryptogenic stroke and have implications for clinical practice.

Keyword: Cryptogenic stroke, Patent Foramen Ovale (PFO), Echocardiography, Cardioembolism

INTRODUCTION:

Stroke, characterized by a disruption in brain blood supply leading to tissue damage, represents a significant health challenge globally. While defined by the World Health Organization (WHO) as the sudden onset of focal neurological disturbance lasting over 24 hours[1], transient ischemic attacks (TIAs) denote brief episodes of neurological dysfunction without permanent cerebral infarction[2]. The age difference observed between the ischemic and hemorrhagic stroke groups was found to be statistically significant[3]. This underscores the necessity for implementing targeted public health interventions, particularly focused on the elderly population.In India, stroke prevalence is notably high, attributed to increased risk factors like hypertension and diabetes, ranking it as a leading cause of mortality and disability among non-communicable diseases[4-5]. Cryptogenic stroke (CS), characterized by an indeterminate cause, presents diagnostic

complexities despite extensive evaluation, as outlined by the trial of Org 10172 in acute stroke treatment[6]. Notably, patients with CS often manifest sudden-onset neurological deficits and embolic infarcts on imaging. The embryonic development of the atrial septum gives rise to the foramen ovale, which typically closes within infancy. Failure in this process leads to a patent foramen ovale (PFO)[7], associated with various conditions including cryptogenic stroke, migraine, and peripheral embolism. The historical link between PFO and stroke dates back to Cohnheim's description in 1877, sparking ongoing debates regarding its role in stroke pathogenesis[8]. While paradoxical embolism through PFO remains a debated mechanism, additional factors potentially related to PFO characteristics are under scrutiny, with accumulating evidence suggesting its involvement in thrombus formation[9]. Hypotheses suggest that embolic events in PFO may result from atrial tachyarrhythmias and/or paroxysmal atrial fibrillation (AF). Notably, young age serves as a significant marker of a non-incidental PFO in stroke patients[10]. Despite reports of high PFO prevalence in patients with cryptogenic stroke, studies on its occurrence in India, particularly in North India, remain scarce. This study aims to address this gap, contributing to the understanding of PFO prevalence and its implications in cryptogenic stroke among the Indian population.

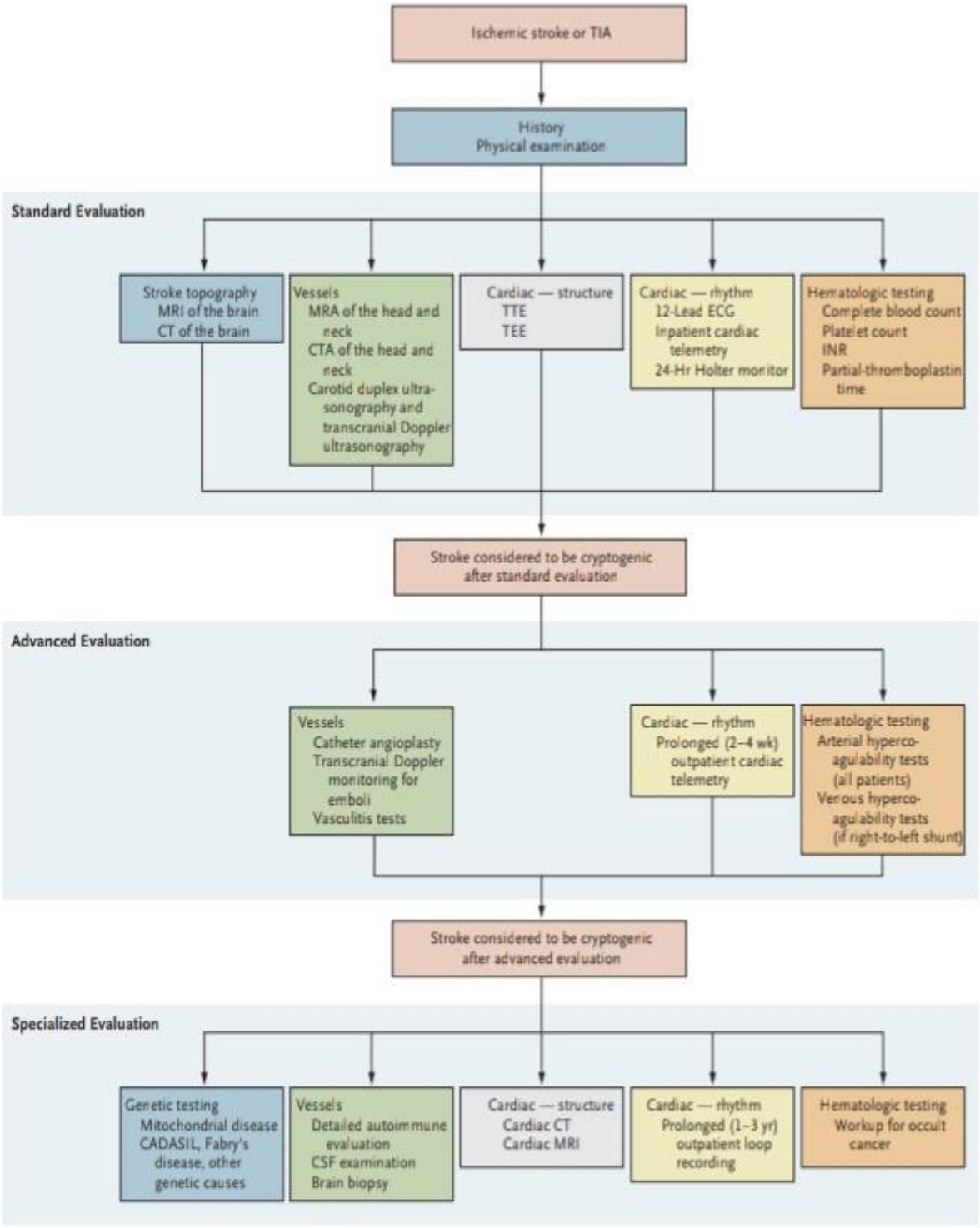


Chart 1: Thealgorithmforidentificationanddiagnosticevaluationof patients with ischemic strokes or transient ischemic attack (TIA)[20]

AIMS AND OBJECTIVES:

Study Population and Setting:
This study was conducted at Batra Hospital & Medical Research Center, New Delhi, within the Department of Neurology.

Study Design:
A prospective observational design was employed, carried out within the Neurology Department at Batra Hospital & Medical Research Center.

Study Duration:
The research took place from February 2020 to March 2022.

Study Participants:
The study aimed to include a minimum of 25 patients admitted to the Neurology Department with ischemic stroke, meeting the criteria for cryptogenic stroke. Cryptogenic stroke is defined as brain infarction not attributed to definite cardio-embolism, large artery atherosclerosis, or small artery disease, despite an extensive evaluation of vascular, cardiac, and serological factors.

Statistical Analysis:
Presentation of quantitative data involved mean ±1 standard deviation, while qualitative parameters were expressed as numbers and percentages. Statistical comparisons between subgroups were carried out using the t-test for continuous variables and the chi-square test for categorical variables. The significance threshold was set at $P < 0.05$. Evaluation of diagnostic technique agreement was performed using the kappa test. Data management and statistical analysis were conducted using SPSS software.

Inclusion Criteria:

Patients with cryptogenic stroke/TIA
Age between 20 to 60 years
Exclusion Criteria:

Age less than 20 years
Age more than 60 years
Hemorrhagic stroke
Pregnant females
Presence of uncontrolled comorbidities: diabetes, hypertension, severe cardiac dysfunction, renal insufficiency
Coagulopathy
Methodology:
Recruitment focused on patients with a clinical history and examination indicative of

cerebrovascular accident (CVA), identified as ischemic after neuroimaging, and subsequently diagnosed as cryptogenic. This recruitment took place at Batra Hospital & Medical Research Centre's neurology department during the period from February 2020 to March 2022. Enrolled patients underwent a comprehensive evaluation, including clinical history, examination, neuro-imaging (NCCT/MRI brain), routine labs, ECG, coagulogram, 2D echo/TEE/contrast echo, 24-hour Holter monitoring, and carotid-doppler.

Data Analysis:
Recorded data were systematically tabulated and statistically analyzed using SPSS software. The chi-square test and Fisher's exact test were employed for comparing qualitative data, while the t-test was used for quantitative data. The significance level was set at $P < 0.05$.

RESULTS and DISCUSSION

STATISTICAL ANALYSIS

Statistical analysis was conducted using SPSS software (version 19, Armonk, NY: IBM Corp). Descriptive statistics were employed to compute mean and standard deviation for continuous variables (e.g., age) and numbers/percentages for categorical data. A comparison of study parameters was performed using the Chi-square test, with statistical significance set at a P value of less than 0.05.

This preliminary study, conducted at the Department of Neurology in Batra Hospital & Medical Research Center, New Delhi, aimed to investigate the prevalence of Patent Foramen Ovale (PFO) in patients with cryptogenic stroke and Transient Ischemic Attack (TIA) from February 2020 to November 2021. Cryptogenic stroke (CS) was defined according to the Trial of Org 10172 in Acute Stroke Treatment criteria, encompassing cerebral infarction without a definitive cause attributed to cardioembolism, large vessel atherosclerosis, or small vessel disease, despite extensive diagnostic evaluation.

The findings from our study revealed several key observations. However, it is imperative to distinguish between the clinical significance of PFO prevalence in our sample and the statistical significance of associations tested. While our study identified a notable prevalence of PFO in patients with cryptogenic stroke and TIA, further analysis indicated that this association did not reach statistical significance. These findings underscore the complexity of PFO's role in cryptogenic stroke etiology and highlight the need for additional research to elucidate the clinical implications of PFO prevalence in this patient population.

Age:

Themeanageofstudy participantswas44.80±9.13 years(Range29-59 Years).

Gender:

Table1. Genderdistributionofstudy participants

Gender	Number	Percentage

Male	16	64%
Female	9	36%
Total	25	100%

Inthepresent study,therewere16(64%)malesand 9 (36%)females.

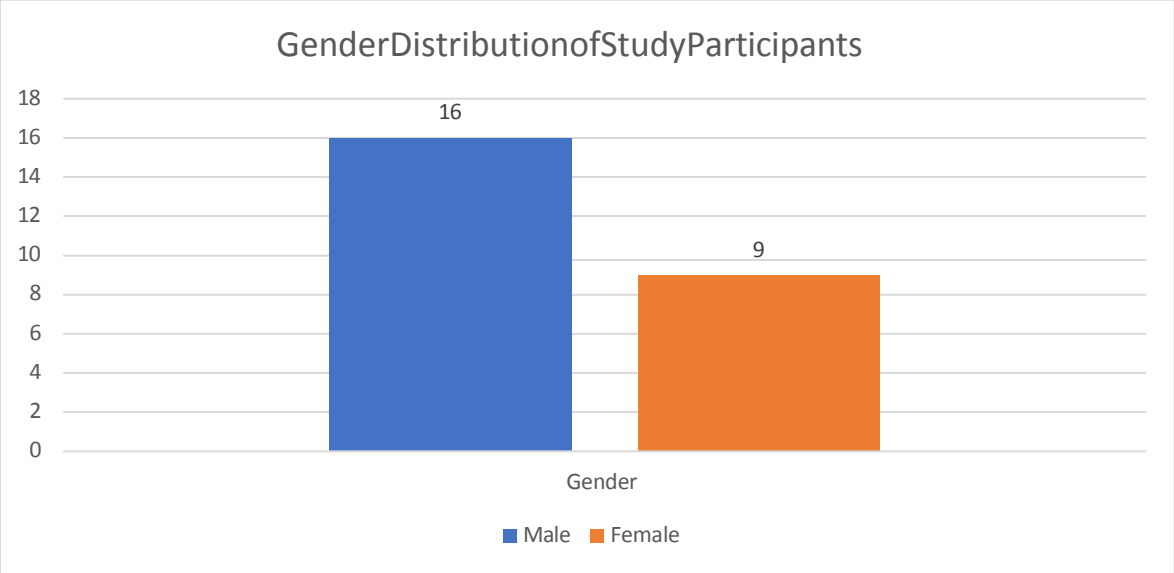


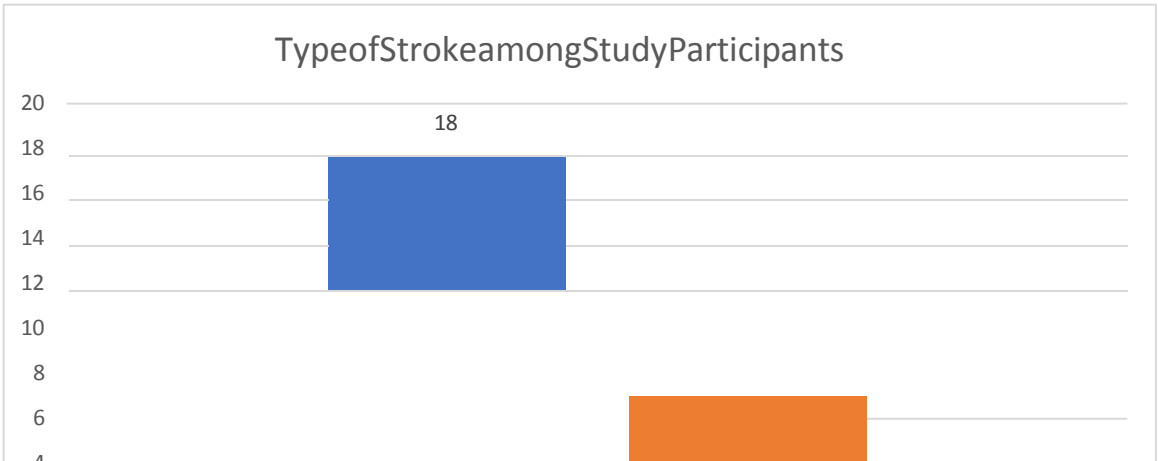
Figure1.Genderdistributionofstudyparticipants

TypeofStroke:

Table2.Distributionoftypeof strokeamongstudyparticipants

TypeofStroke	Number	Percentage
Ischaemic	18	72%
TIA	7	28%
Total	25	100%

Inthepresentstudy,mostoftheparticipantsreportedwithIschaemicstroke(72%). There were 7 (28%) people with TIA.



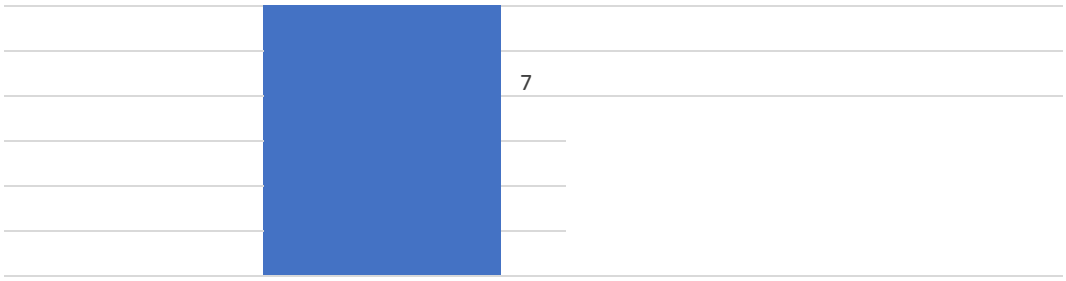


Figure2.Distribution oftypeofstrokeamongstudyparticipants

PFObyTEE:

There were 11 (44%) participants with patent foramen ovale while 14 (56%) did not have a patent foramen ovale.

Table 3.DistributionofPFO amongstudyparticipants

PFObyTEE	Number	Percentage
Yes	11	44%
No	14	56%
Total	25	100%

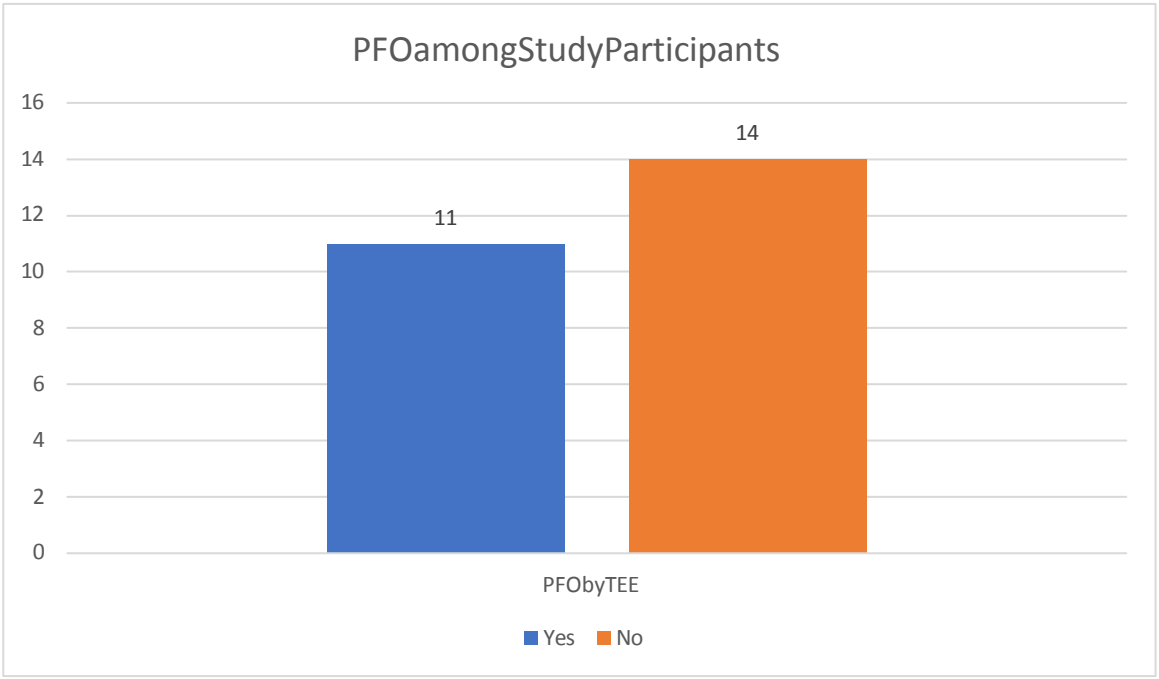


Figure3.DistributionofPFOamongstudyparticipants

Hypertension:

Table4.Hypertensionamongstudyparticipants

Hypertension	Number	Percentage
Yes	0	0%
No	25	100%
Total	25	100%

Inthepresent study,noneoftheparticipantshad hypertension.

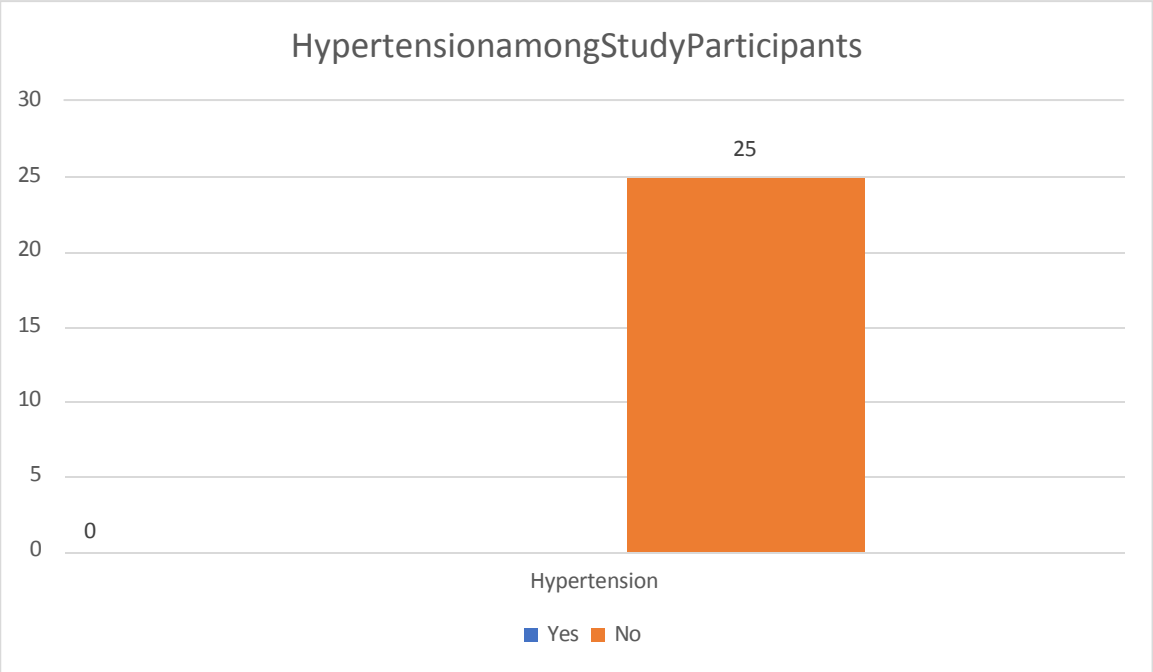


Figure4.Hypertensionamongstudyparticipants

DiabetesMellitus:

Inthepresentstudy,noneoftheparticipantshadDiabetes Mellitus.

Table5.DiabetesMellitusamong study participants

DiabetesMellitus	Number	Percentage
Yes	0	0%
No	25	100%
Total	25	100%

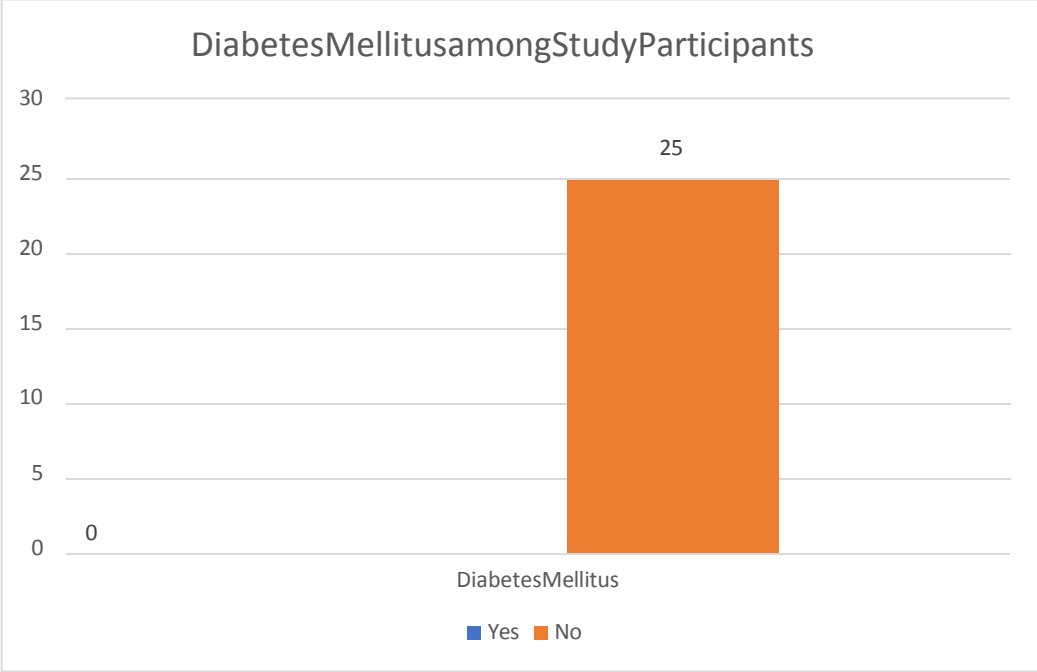


Figure5.DiabetesMellitusamongstudyparticipants

Smoking:

Table6.Smokingstatusamongstudyparticipants

Smoking	Number	Percentage
Yes	0	0%
No	25	100%
Total	25	100%

Inthepresent study,noneoftheparticipantsweresmokers.

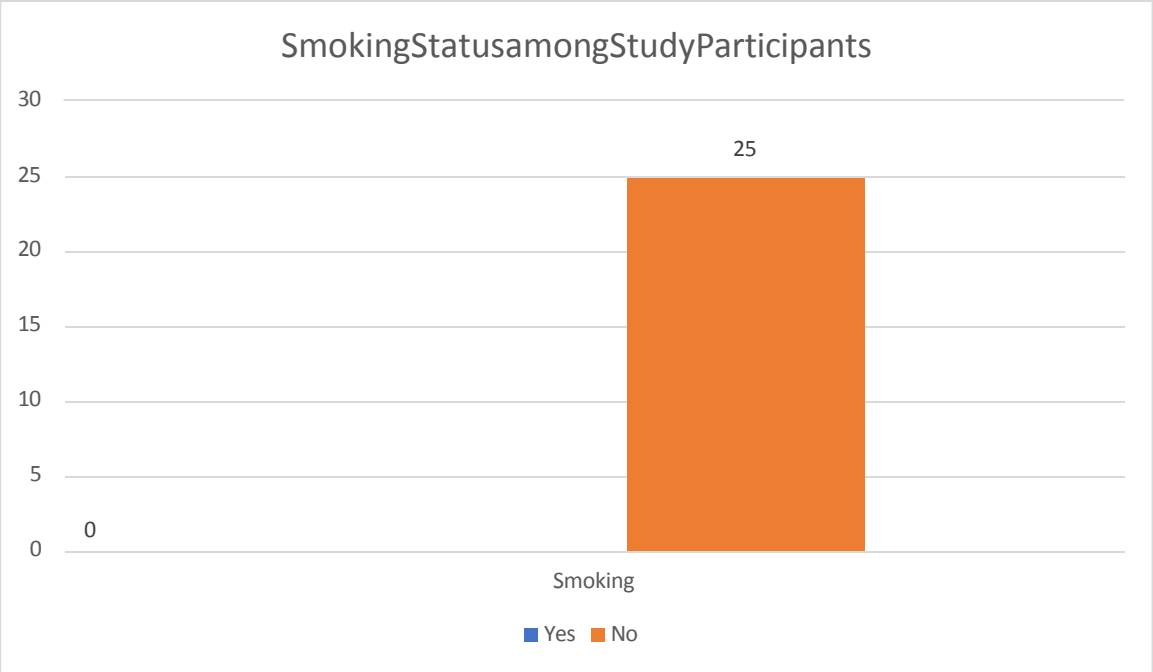


Figure6.Smokingstatusamongstudyparticipants

Dyslipidemia:

Table7.Dyslipidemiaamongstudy participants

Dyslipidemia	Number	Percentage
Yes	0	0%
No	25	100%
Total	25	100%

Inthepresent study,noneoftheparticipantshad dyslipidemia.

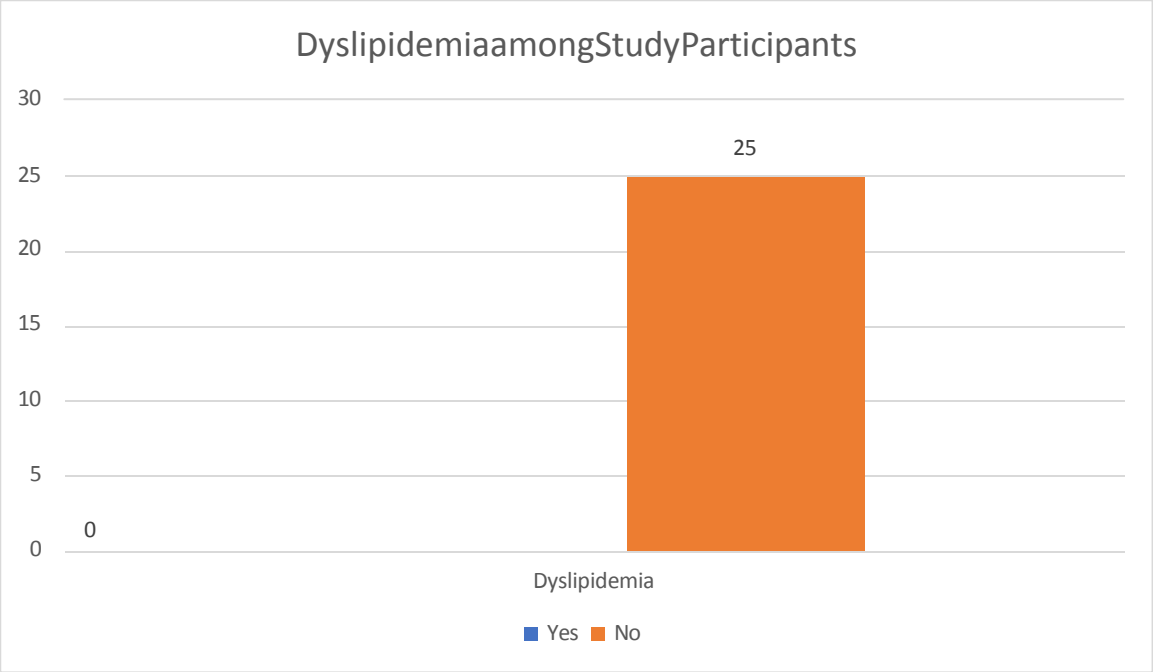


Figure7.Dyslipidemiaamongstudyparticipants

24-HourHolterMonitoring:

Table8. 24-HourHolterMonitoringamongstudy participants

24-HourHolter Monitoring	Number	Percentage
Normal	25	100%
Abnormal	0	0%
Total	25	100%

Inthepresent study,alloftheparticipantshadnormal 24-hourHoltermonitoring.

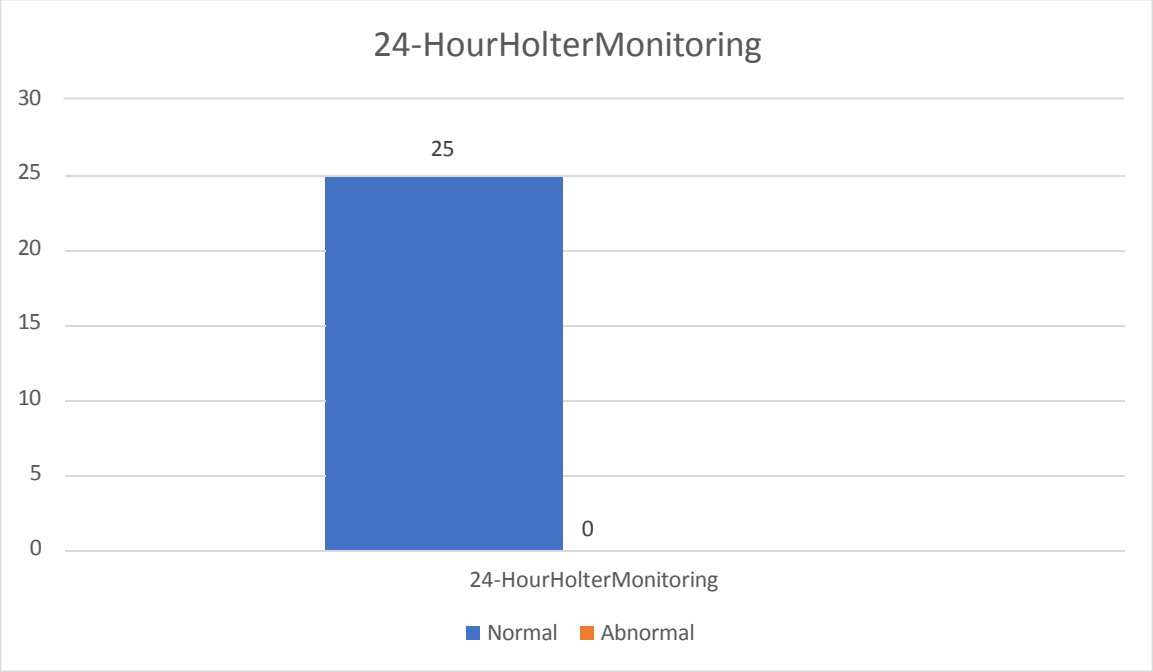


Figure8.24-HourHolterMonitoringamongstudyparticipants

CarotidDoppler:

Table9. Carotid Doppleramongstudyparticipants

CarotidDoppler	Number	Percentage
Normal	25	100%
Abnormal	0	0%
Total	25	100%

Inthepresent study,alloftheparticipantshadnormal carotidDoppler.

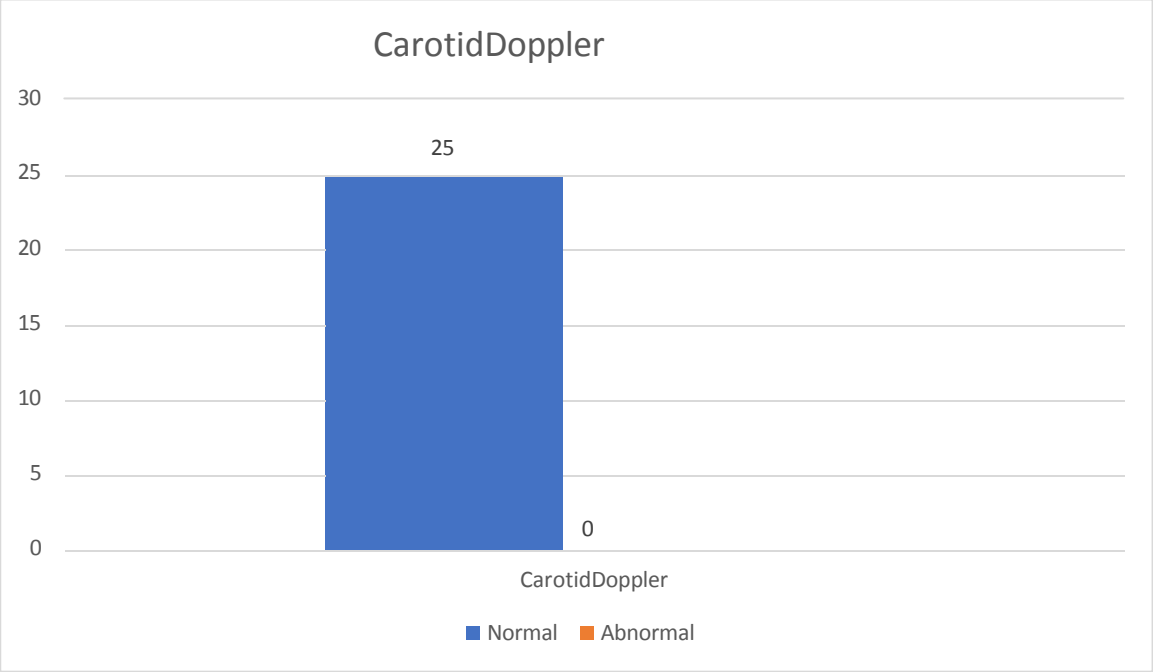


Figure 9.CarotidDoppleramongstudyparticipants

HYPERCOAGULABILITYPROFILE

Homocysteine:

Table10.Homocysteineamongstudyparticipants

Homocysteine	Number	Percentage
Normal	25	100%
Abnormal	0	0%
Total	25	100%

Inthepresent study,alloftheparticipantshadnormal homocysteine.

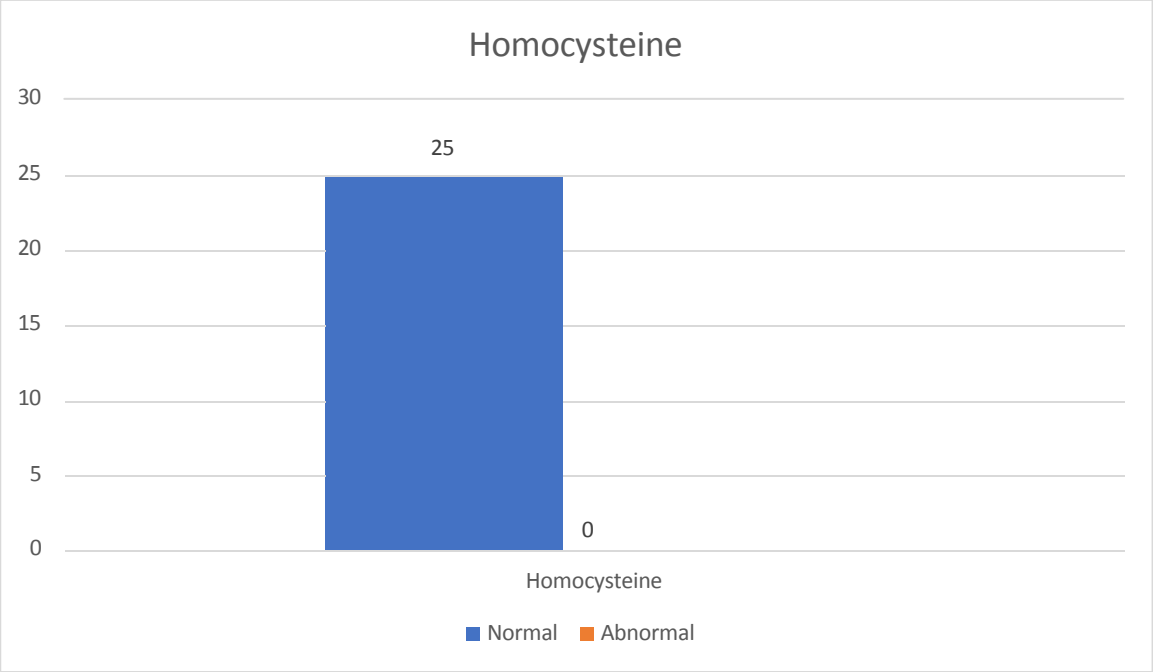


Figure10.Homocysteineamongstudyparticipants

ProteinC:

Table11.ProteinCamongstudyparticipants

ProteinC	Number	Percentage
Normal	25	100%
Abnormal	0	0%
Total	25	100%

Inthepresent study,allofthe participantshadnormal ProteinC.

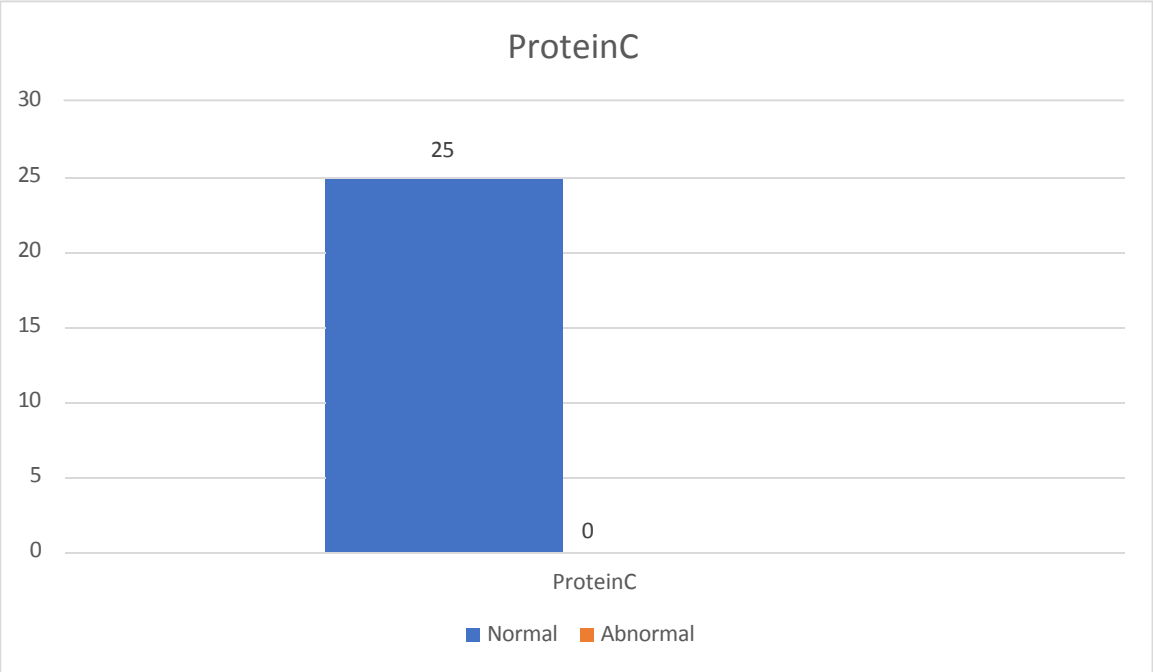


Figure11.ProteinCamongstudyparticipants

ProteinS:

Table12.ProteinSamong study participants

ProteinS	Number	Percentage
Normal	25	100%
Abnormal	0	0%
Total	25	100%

Inthepresent study,allofthe participantshadnormal ProteinS.

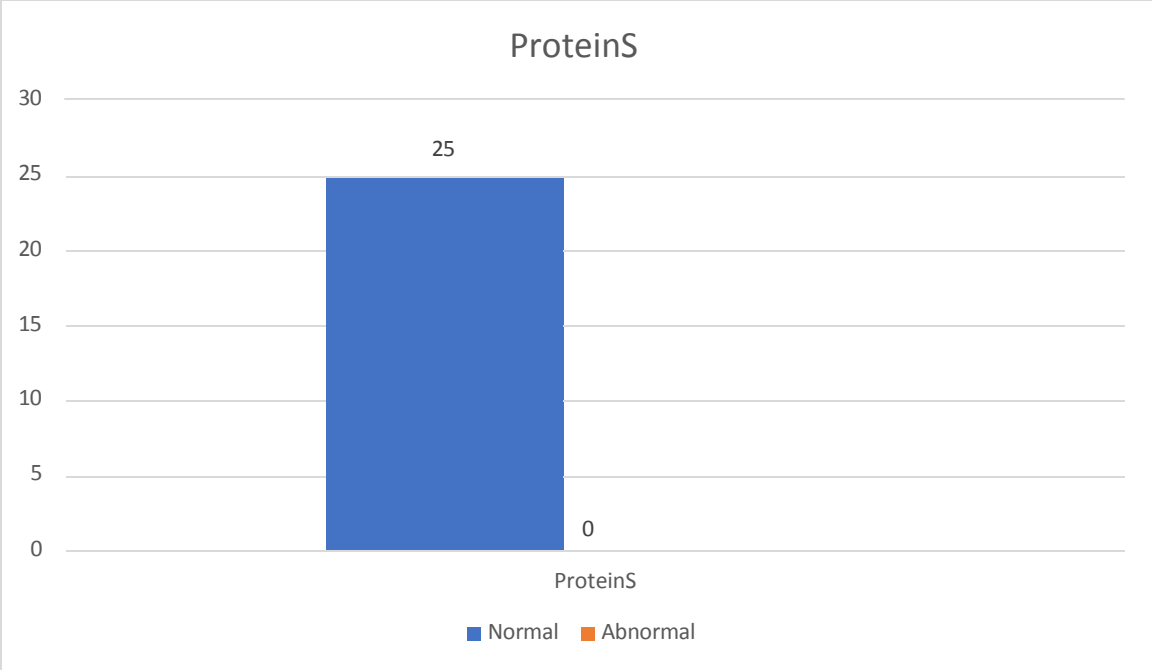


Figure12.ProteinSamongstudyparticipants

Factor VLeidin Mutation:

Table13.FactorVLeidinMutationamongstudyparticipants

Factor VLeidin Mutation	Number	Percentage
Normal	25	100%
Abnormal	0	0%
Total	25	100%

Inthepresent study,alloftheparticipantshadnormal FactorVLeidin Mutation.

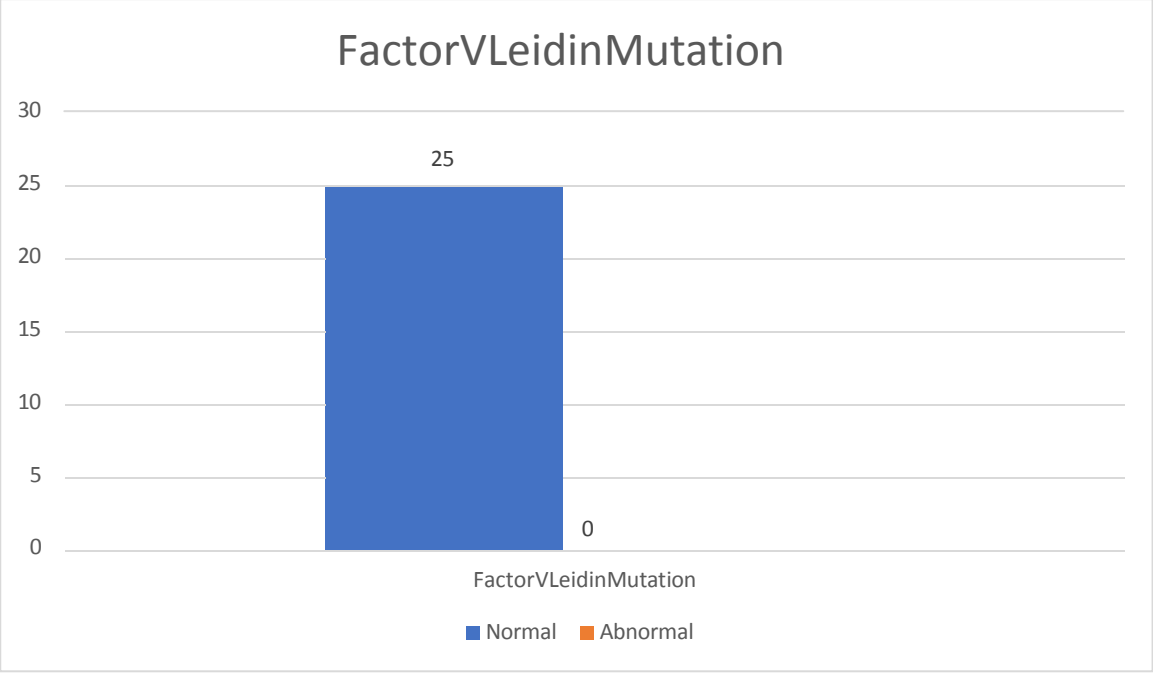


Figure13.FactorVLeidinMutationamongstudyparticipants

Antibody(APLA):

Table14.Antibody(APLA)amongstudyparticipants

Antibody(APLA)	Number	Percentage
Normal	25	100%
Abnormal	0	0%
Total	25	100%

Inthepresent study,alloftheparticipantshadnormal antibody(APLA)

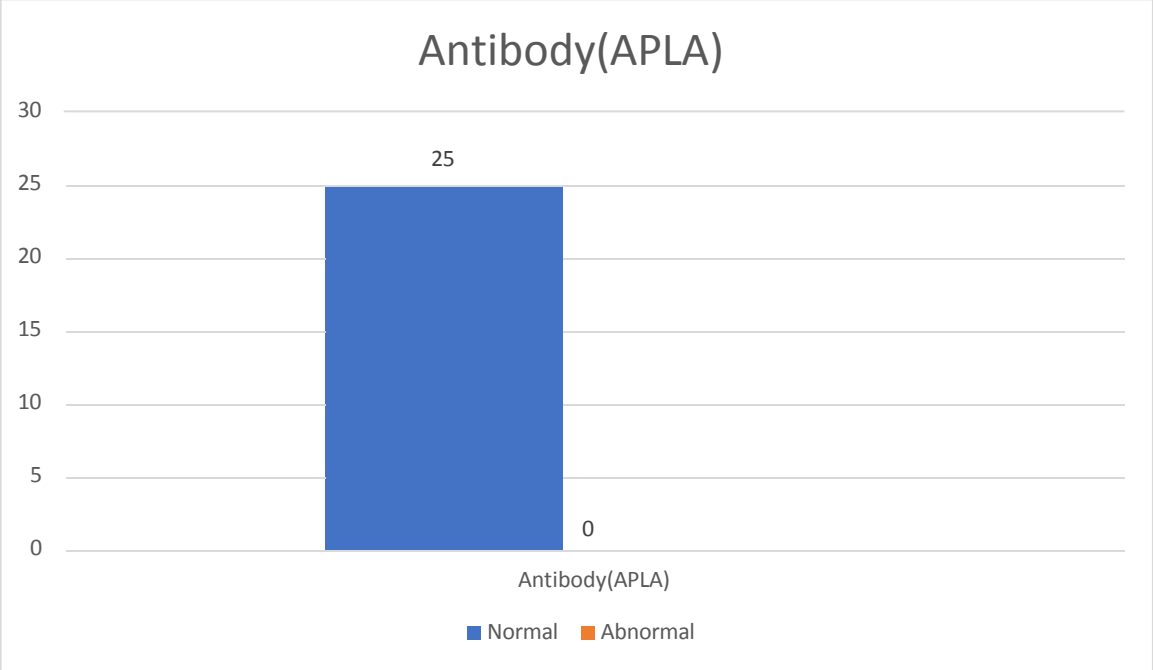


Figure14.Antibody(APLA)amongstudyparticipants

Anti-thrombin 3:

Table15. Anti-thrombin3amongstudyparticipants

Anti-thrombin3	Number	Percentage
Normal	25	100%
Abnormal	0	0%
Total	25	100%

Inthepresent study,alloftheparticipantshadnormal anti-thrombin 3.

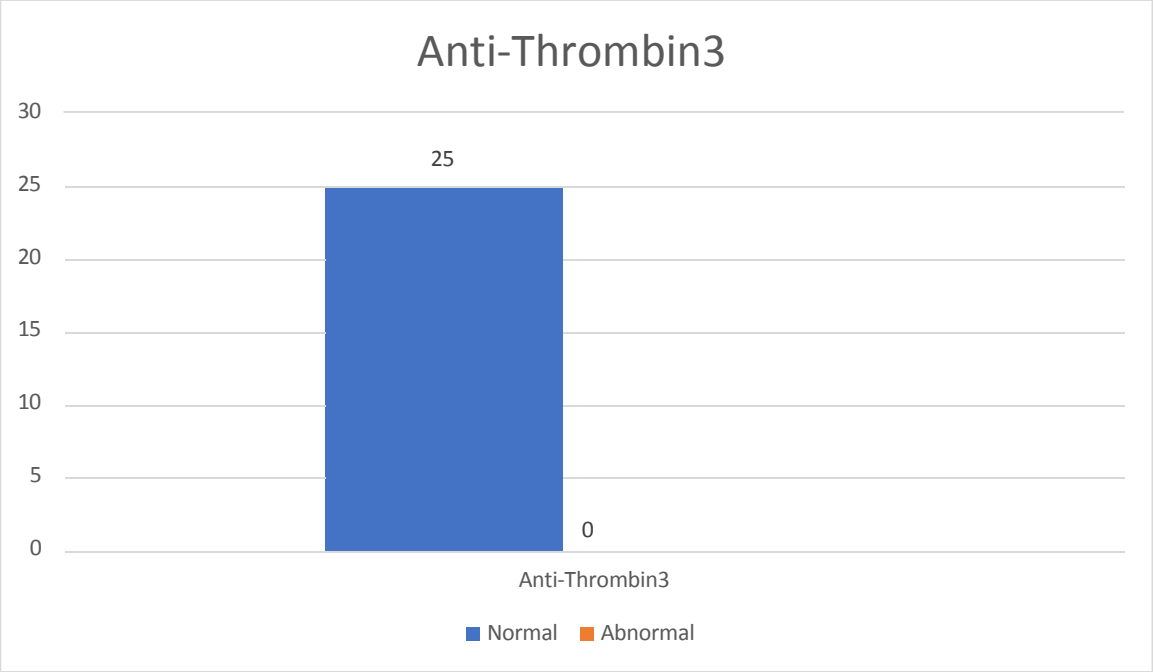


Figure15.Anti-thrombin3among studyparticipants

PFOand Gender:

Table16.AssociationbetweenPFOandGender

			Gender		
			Male	Female	Total
PFOby TEE	Yes	Count	7	4	11
		%	43.8%	44.4%	44.0%
	No	Count	9	5	14
		%	56.3%	55.6%	56.0%
Total		Count	16	9	25
		%	100.0%	100.0%	100.0%

Chi-square=0.001,P=1.000

There were 7 (43.8%) males and 4 (44.4%) females with patent foramen ovale. The analysis showed that there was no statistically significant association between gender and the presence of patent foramen ovale (Chi-square value = 0.001, P=1.000).

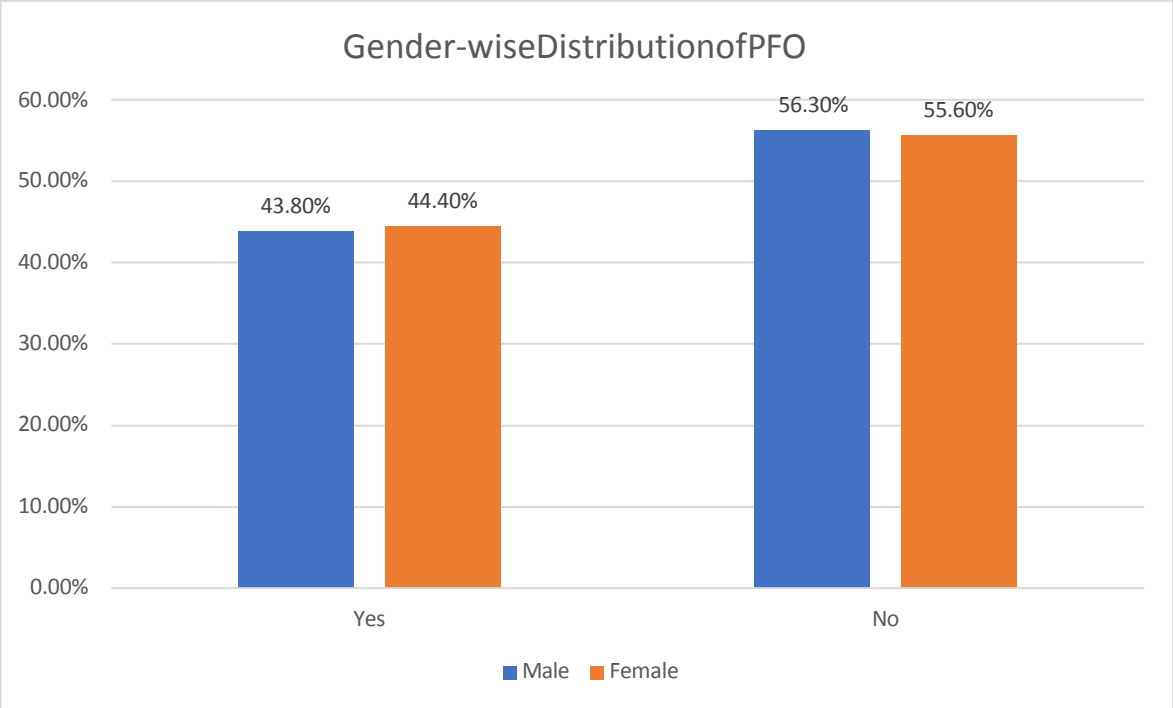


Figure16.Association betweenPFOandGender

PFOandTypeofStroke:

Table17.Associationbetween TypeofStrokeand Gender

			Typeof Stroke		
			Ischaemic	TIA	Total
PFOby TEE	Yes	Count	6	5	11
		%	33.3%	71.4%	44.0%
	No	Count	12	2	14
		%	66.7%	28.6%	56.0%
Total		Count	18	7	25
		%	100.0%	100.0%	100.0%

Chi-square=2.986,P=0.085

There were 6(33.3%) participants with Ischaemic stroke and 5 (71.4%) participants withTIAwhohadpatentforamenovale.Thedistributionwasclinicallysignificantbut the analysis did not find a statistically significant association between the type of stroke and the presence of patent foramen ovale (Chi-square value = 2.986, P=0.085).

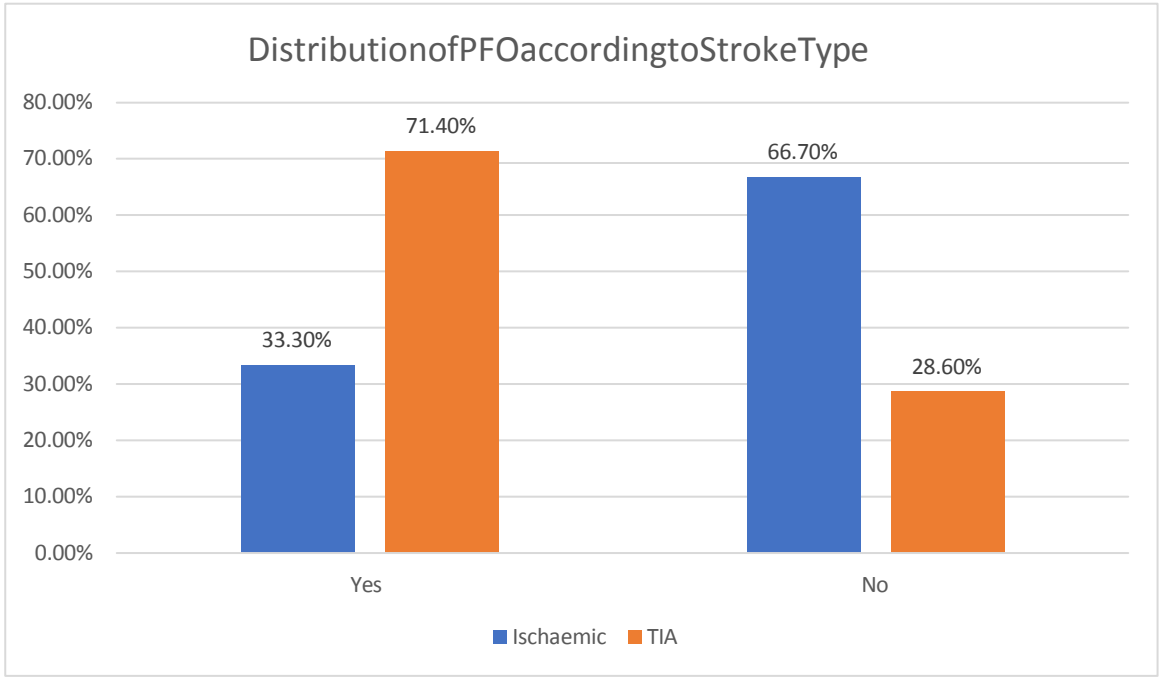


Figure17.AssociationbetweenTypeofStrokeandGender

Stroke stands as the third leading cause of death in developed nations, with resulting disabilities emphasizing its significance. The data gathered in this study underwent thorough assessment, analysis, and comparison with existing studies, leading to comprehensive evaluations. The current study's participant demographic revealed a mean age of 44.80±9.13 years (Range 29-59 Years), consisting of 16 (64%) men and 9 (36%) women. A comparable study by Marino Brian et al. [11] reported a mean age of 66.7 years (range, 50–91 years), with 42.5% female and 57.5% male participants**.** The majority of participants in the present study reported ischemic stroke (72%), with 7 (28%) experiencing TIA. In a related study by Li et al. [12], participants reporting Transient Ischemic stroke or Ischemic stroke were 668 (36.9%), and 187 (28.0%) had cryptogenic stroke. Furthermore, the current study identified 11 (44%) participants with patent foramen ovale, aligning with Mesa et al.'s findings [13], indicating that nearly half of young patients with ischemic stroke of unknown origin have a patent foramen ovale. Lechat et al. [6] discovered a significantly higher prevalence of patent foramen ovale in stroke patients (40%) compared to the control group (10%).Remarkably, none of the participants in the present study had hypertension or diabetes Mellitus, and none were smokers. This aligns with DC Fisher et al.'s study [14], which found patent foramen ovale in patients of all age groups with cerebrovascular accidents (CVAs) and transient ischemic attacks (TIAs) but noted no association between patent foramen ovale and stroke. The analysis in the present study revealed no statistically significant association between gender and the presence of patent foramen ovale (Chi-square value = 0.001, P=1.000), consistent with the findings of DC Fisher et al. [15].Regarding the type of stroke, 6 (33.3%) participants with Ischemic stroke and 5 (71.4%) participants with TIA had patent foramen ovale in the present study. While the distribution was clinically significant, the analysis did not find a statistically significant association between the type of stroke and the presence of patent foramen ovale (Chi-square value = 2.986, P=0.085). This result mirrors the findings of Lechat et al. [6], who observed a significantly higher prevalence of patent foramen ovale in stroke patients compared to the control group.These collective results reinforce the notion that patent foramen ovale is a risk factor for cryptogenic stroke, supported by Di Tullio et al. [16], Decastro et al. [17], Wu LA et al. [18], and Handke et al. [19]. Importantly, this study goes beyond cryptogenic stroke by including TIA patients, addressing a gap in previous research.

CONCLUSION:

Thepresentstudyconcludesthedistributionwasclinicallysignificantbutthereisnosignificant association between the type of stroke and the presence of patent foramen ovale.

Consent

Prior to participation, patients were provided with detailed information about the study, and written informed consent was obtained.

Ethical Approval:

Approval of the study protocol was obtained from the scientific research and ethical review committee of the hospital.

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ABBREVIATIONS

PFO	Patent foramenovale
ASD	Atrial Septaldefect
TIA	TransientIschemicAttack
TEE	TransEsophageal Echo-cardiography
TTE	TransthoracicEcho-cardiography
MRI	MagneticResonanceImaging
NCCT	Non-contrastcomputerizedtomography
USG	Ultra-sonography
ECG	Electrocardiography
CBC	Completebloodcount
KFT	Kidneyfunctiontest
LFT	Liverfunctiontest
CNS	CentralNervousSystem