

PATENT FORAMEN OVALE (PFO) IN PATIENTS OF CRYPTOGENIC STROKE AND TRANSIENT ISCHEMIC 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]. 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[3-4]. 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[8]. 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)[9], 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[10]. 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[11]. 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[16]. 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.

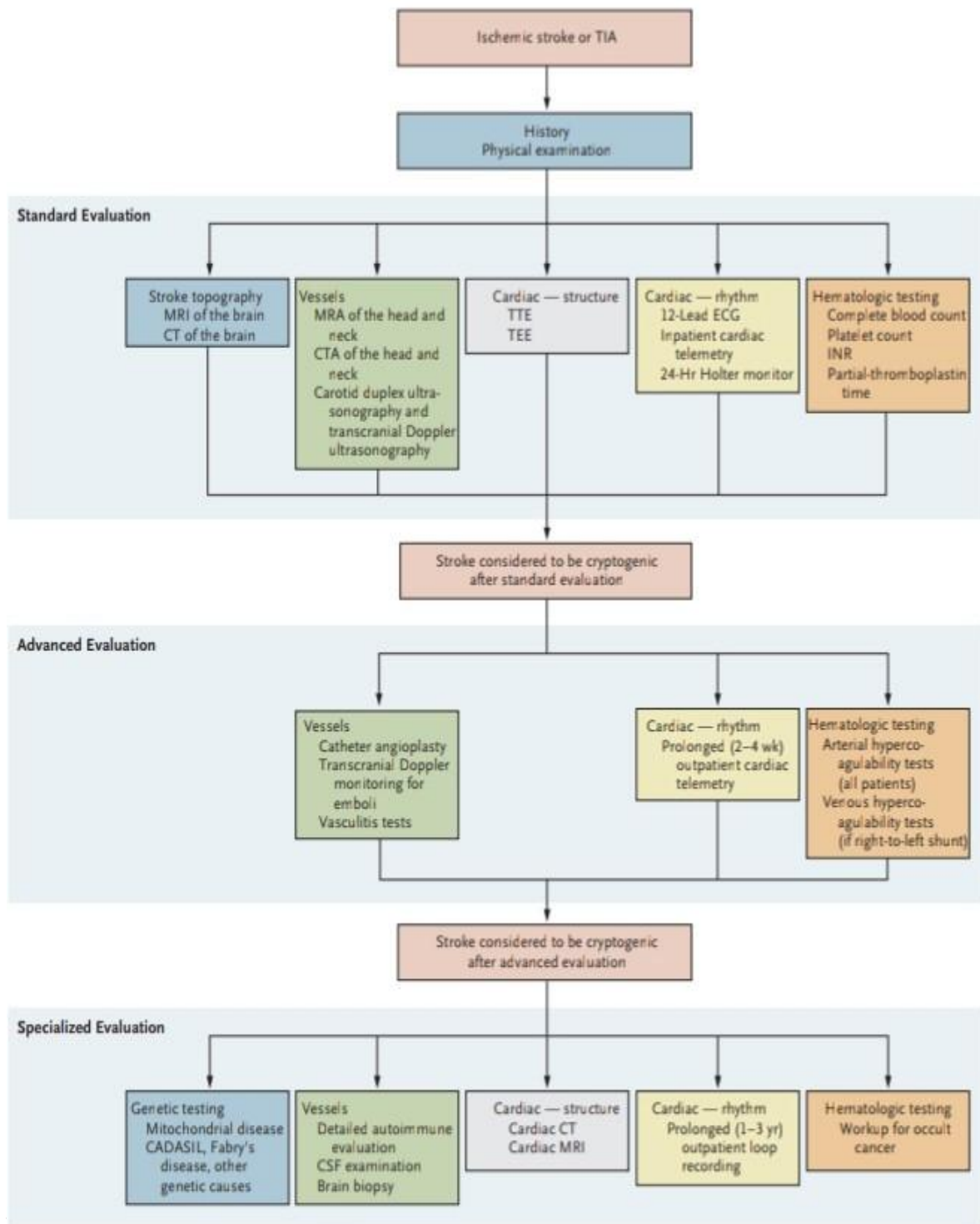


Chart 1 :Theabovepicturedepictsthealgorithmforidentificationanddiagnostic evaluationof patients with ischemic strokes or transient ischemic attack (TIA)²⁰

Material and method

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

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, neuroimaging (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 $P < 0.05$.

Ethical Consideration:

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

RESULTS

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:

The mean age of study participants was 44.80 ± 9.13 years (Range 29-59 Years).

Gender:

Table 1. Gender distribution of study participants

Gender	Number	Percentage
Male	16	64%
Female	9	36%
Total	25	100%

In the present study, there were 16 (64%) males and 9 (36%) females.

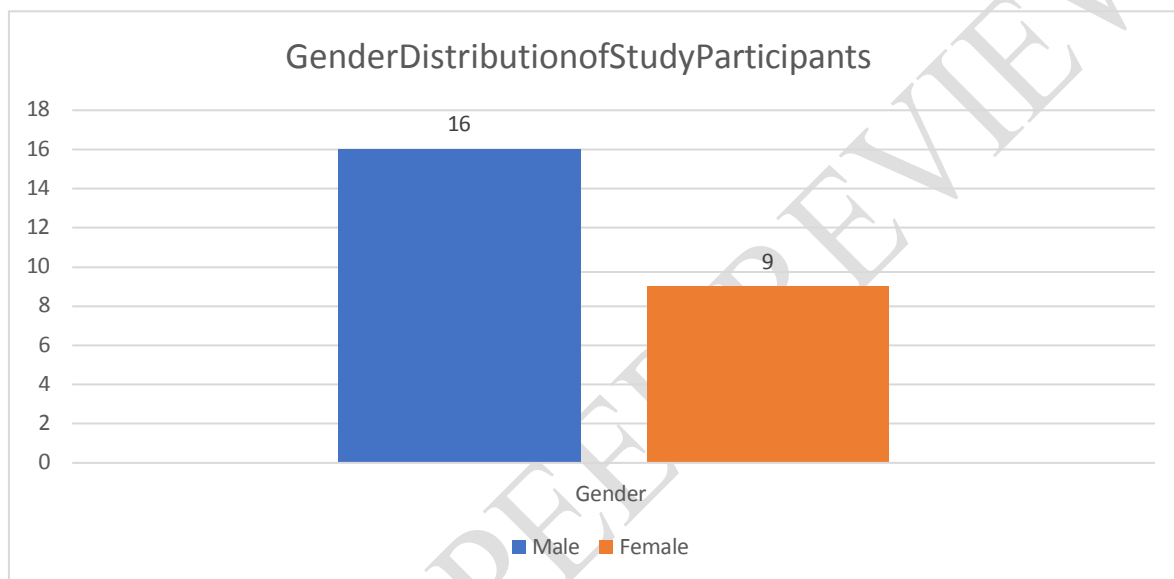


Figure 1. Gender distribution of study participants

Type of Stroke:

Table 2. Distribution of type of stroke among study participants

Type of Stroke	Number	Percentage
Ischaemic	18	72%
TIA	7	28%
Total	25	100%

In the present study, most of the participants reported with Ischaemic stroke (72%). There were 7 (28%) people with TIA.

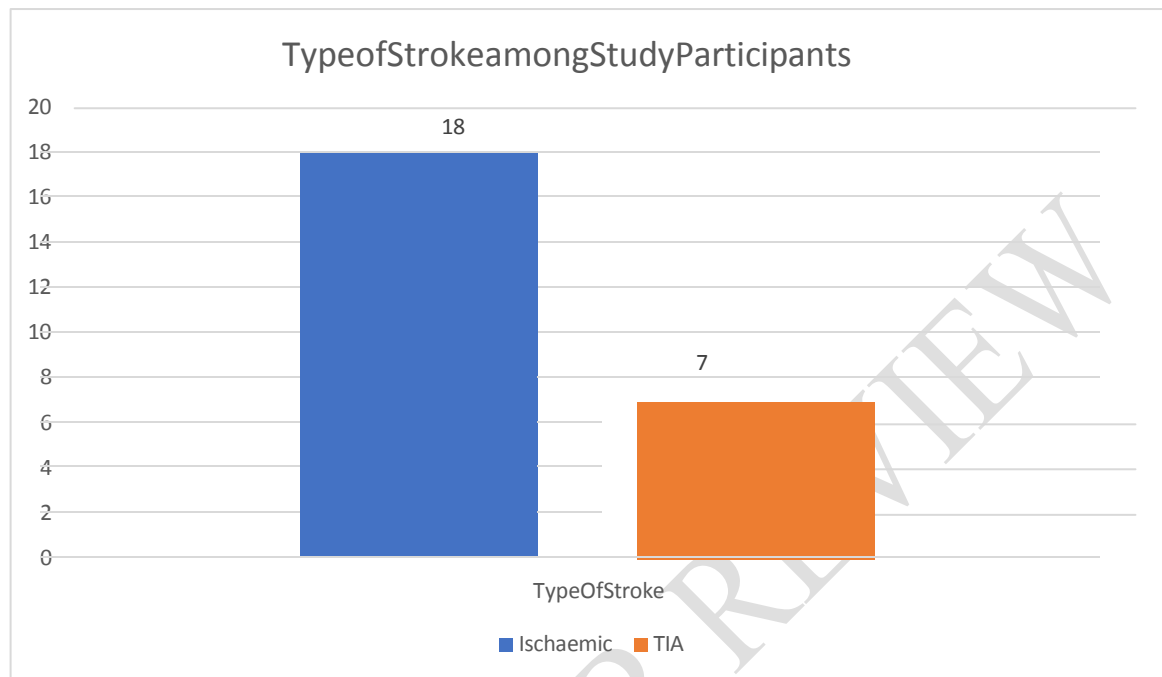


Figure 2. Distribution of type of stroke among study participants

PFO by TEE:

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

Table 3. Distribution of PFO among study participants

PFO by TEE	Number	Percentage
Yes	11	44%
No	14	56%
Total	25	100%

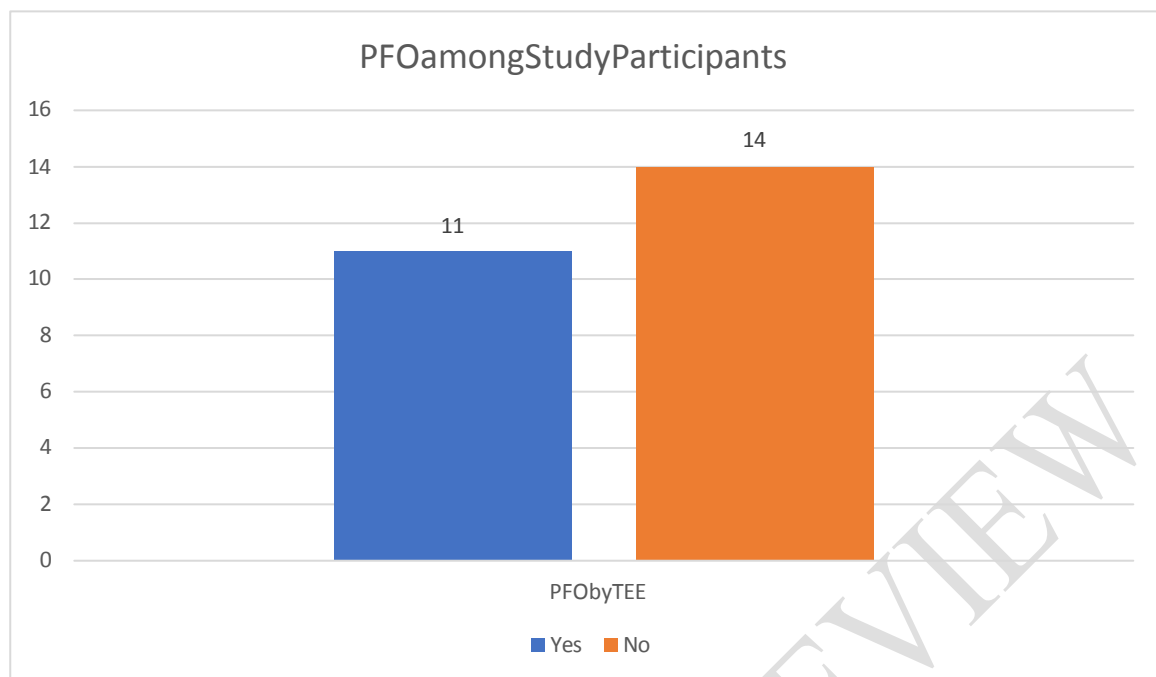


Figure3.DistributionofPFOamongstudyparticipants

Hypertension:

Table4.Hypertensionamongstudyparticipants

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

Inthepresent study,noneoftheparticipantshad hypertension.

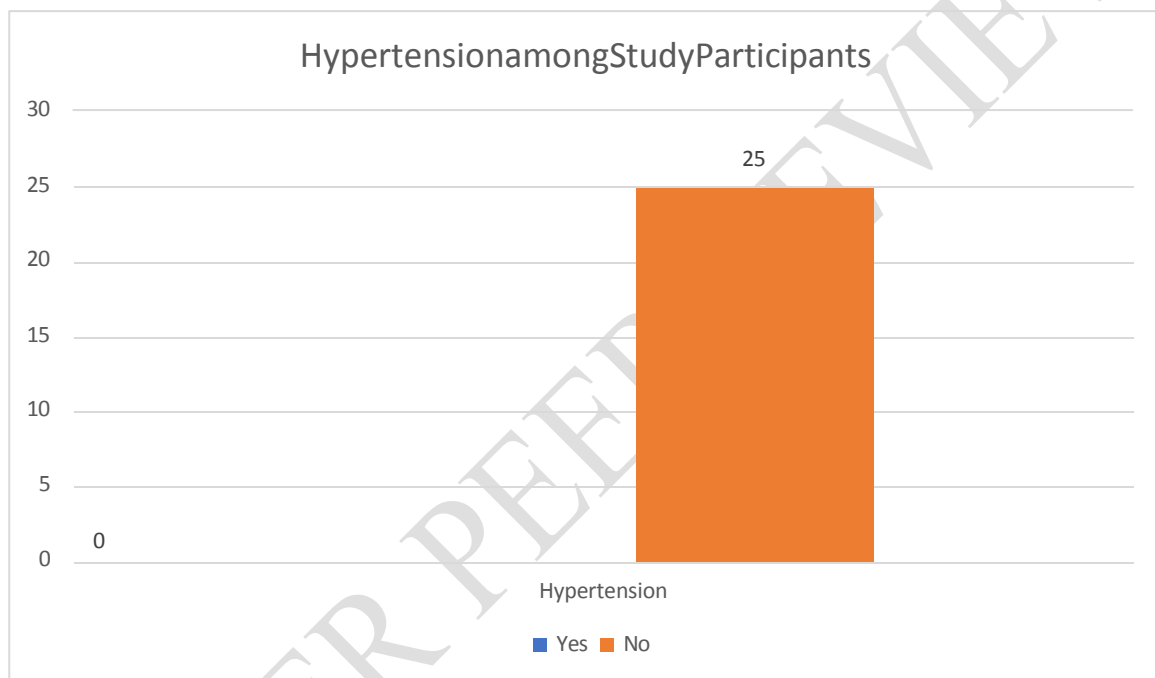


Figure4.Hypertensionamongstudyparticipants

DiabetesMellitus:

In the present study, none of the participants had Diabetes Mellitus.

Table 5. Diabetes Mellitus among study participants

Diabetes Mellitus	Number	Percentage
Yes	0	0%
No	25	100%
Total	25	100%

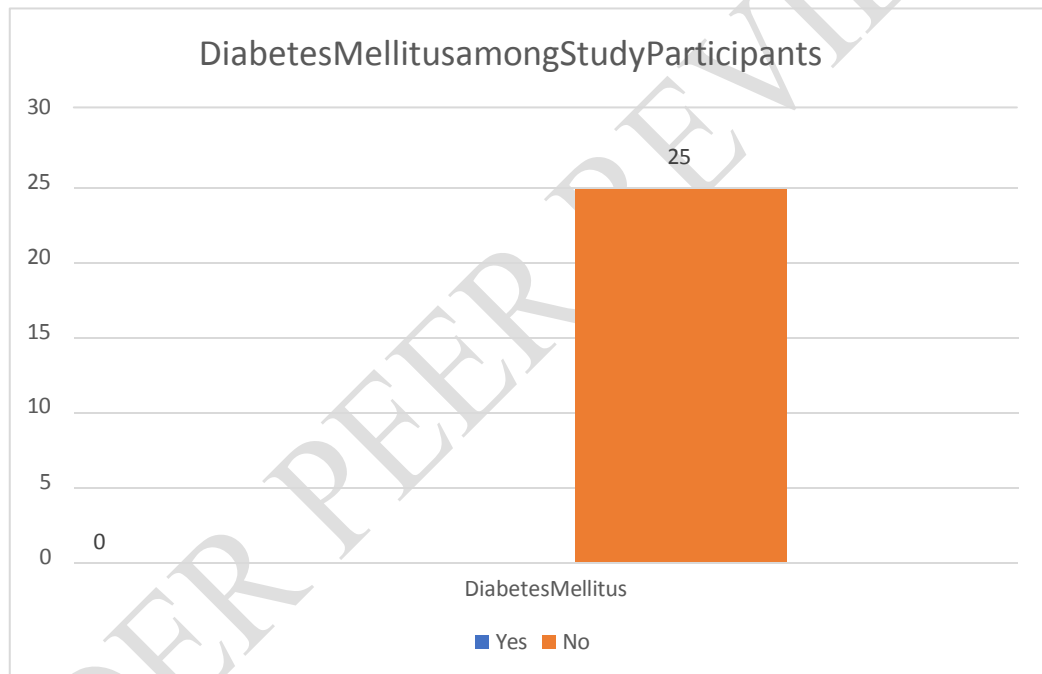


Figure 5. Diabetes Mellitus among study participants

Smoking:

Table6.Smokingstatusamongstudyparticipants

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

In the present study, none of the participants were smokers.

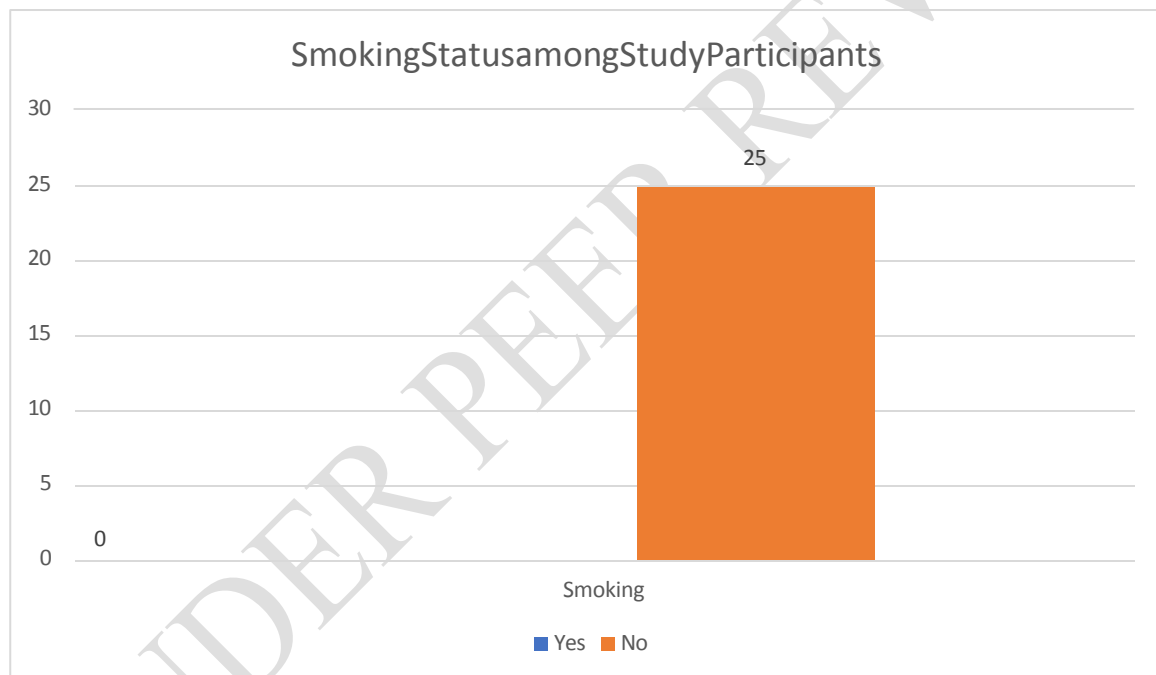


Figure6.Smokingstatusamongstudyparticipants

Dyslipidemia:

Table7.Dyslipidemiaamongstudy participants

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

In the present study, none of the participants had dyslipidemia.

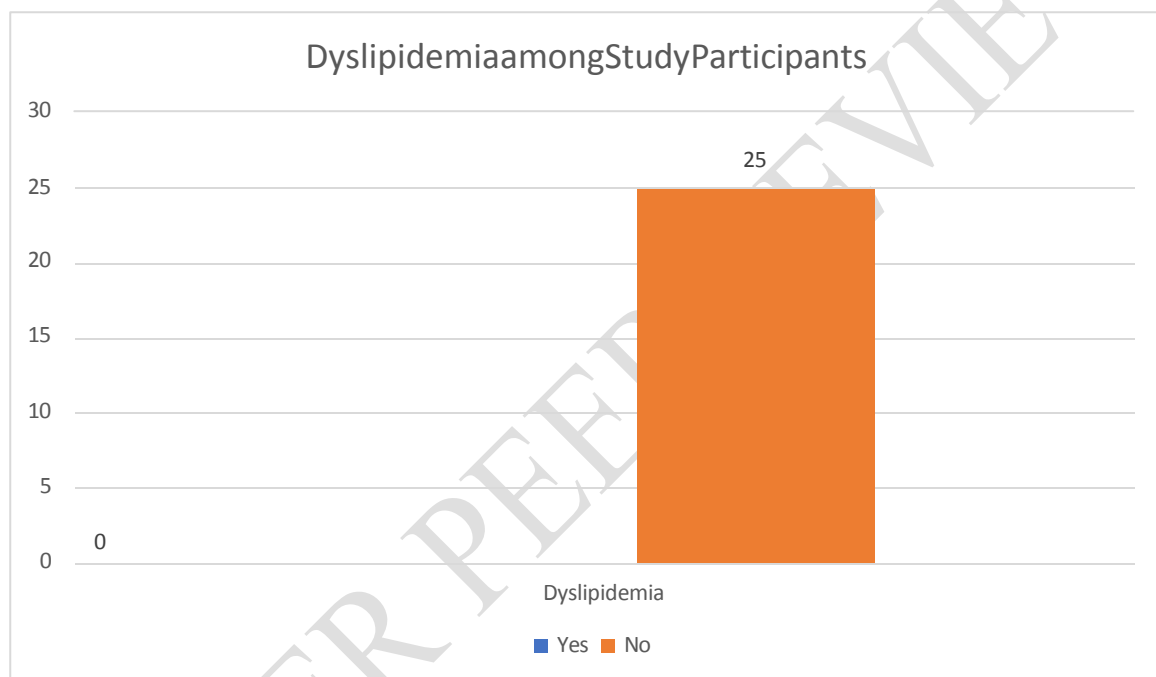


Figure7.Dyslipidemiaamongstudyparticipants

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.

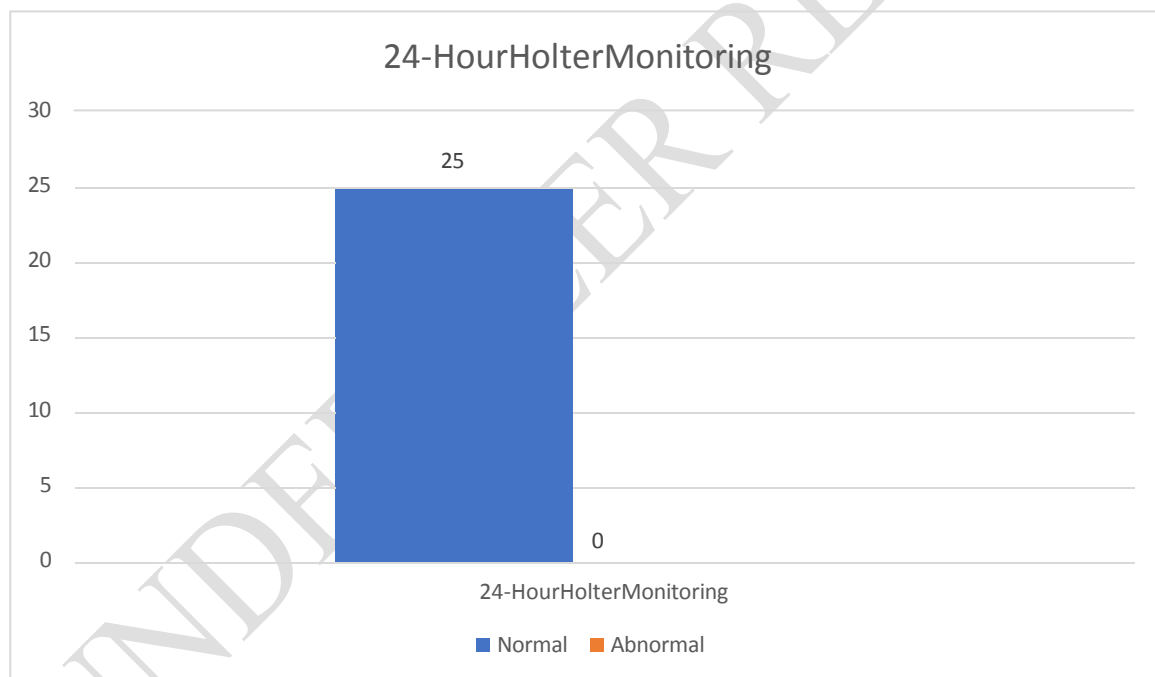


Figure8.24-HourHolterMonitoringamongstudyparticipants

CarotidDoppler:

Table9. Carotid Doppleramongstudyparticipants

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

Inthepresent study,alloftheparticipantshadnormal carotidDoppler.

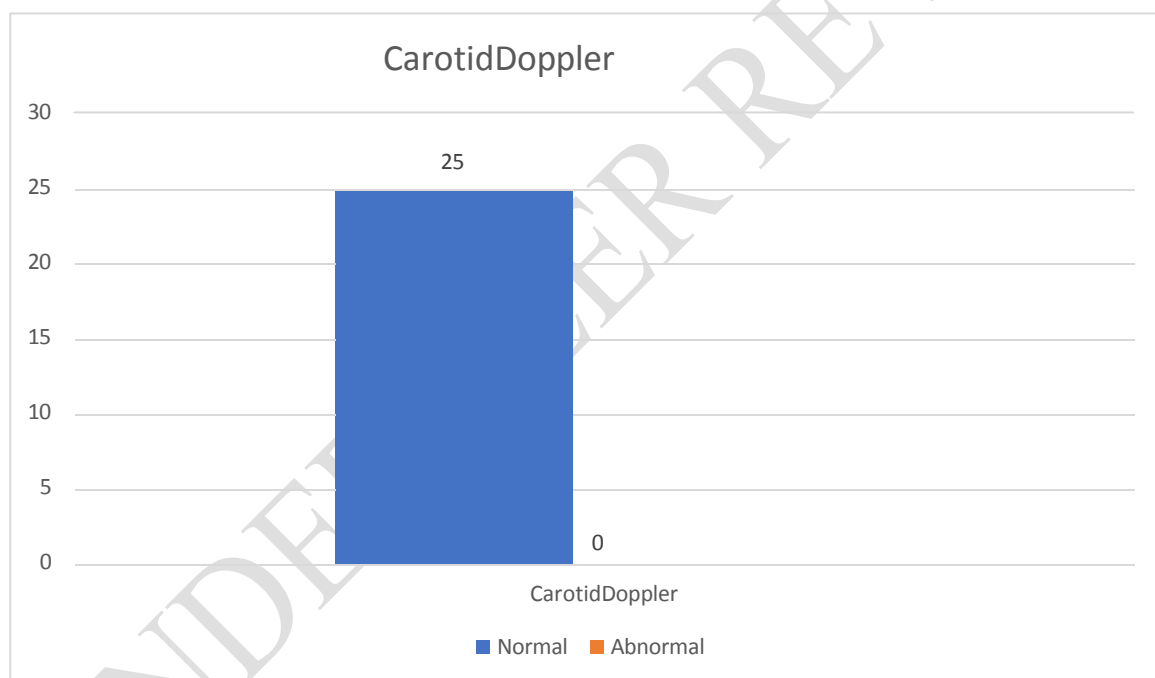


Figure 9.CarotidDoppleramongstudyparticipants

HYPERCOAGULABILITYPROFILE

Homocysteine:

Table10.Homocysteineamongstudyparticipants

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

Inthepresent study,alloftheparticipantshadnormal homocysteine.

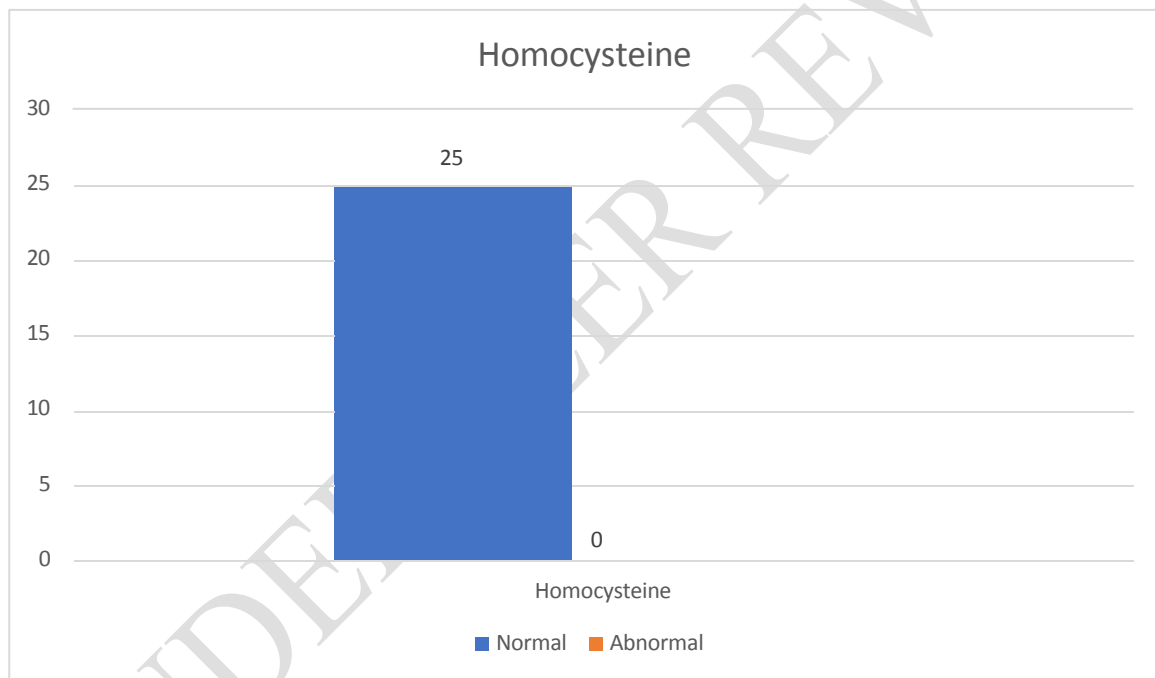


Figure10.Homocysteineamongstudyparticipants

ProteinC:

Table11. ProteinC among study participants

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

In the present study, all of the participants had normal ProteinC.

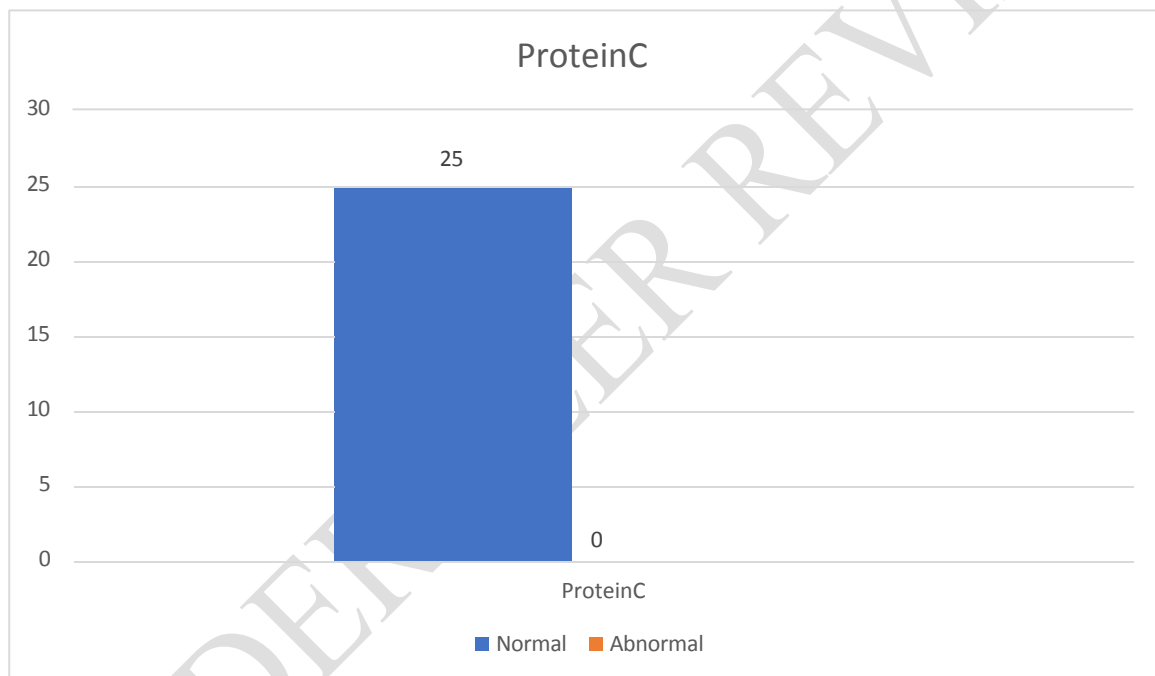


Figure11. ProteinC among study participants

ProteinS:

Table12. ProteinS among study participants

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

In the present study, all of the participants had normal ProteinS.

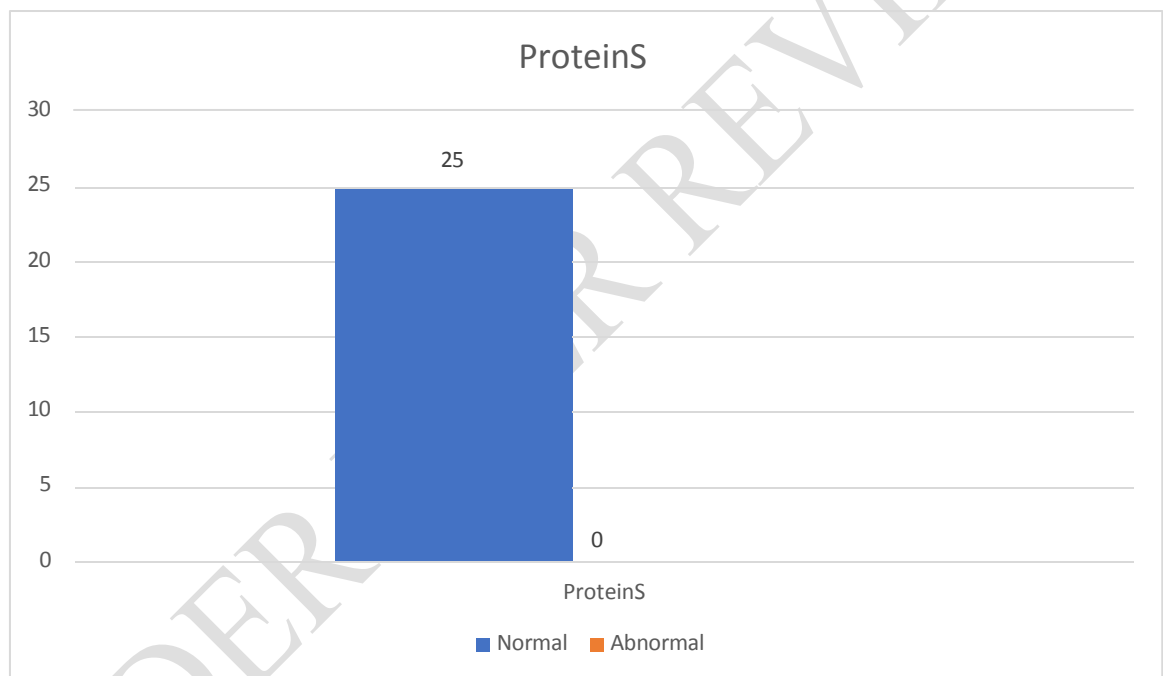


Figure12. ProteinS among study participants

Factor VLeidin Mutation:

Table13.FactorVLeidinMutationamongstudyparticipants

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

In the present study, all of the participants had normal Factor VLeidin Mutation.

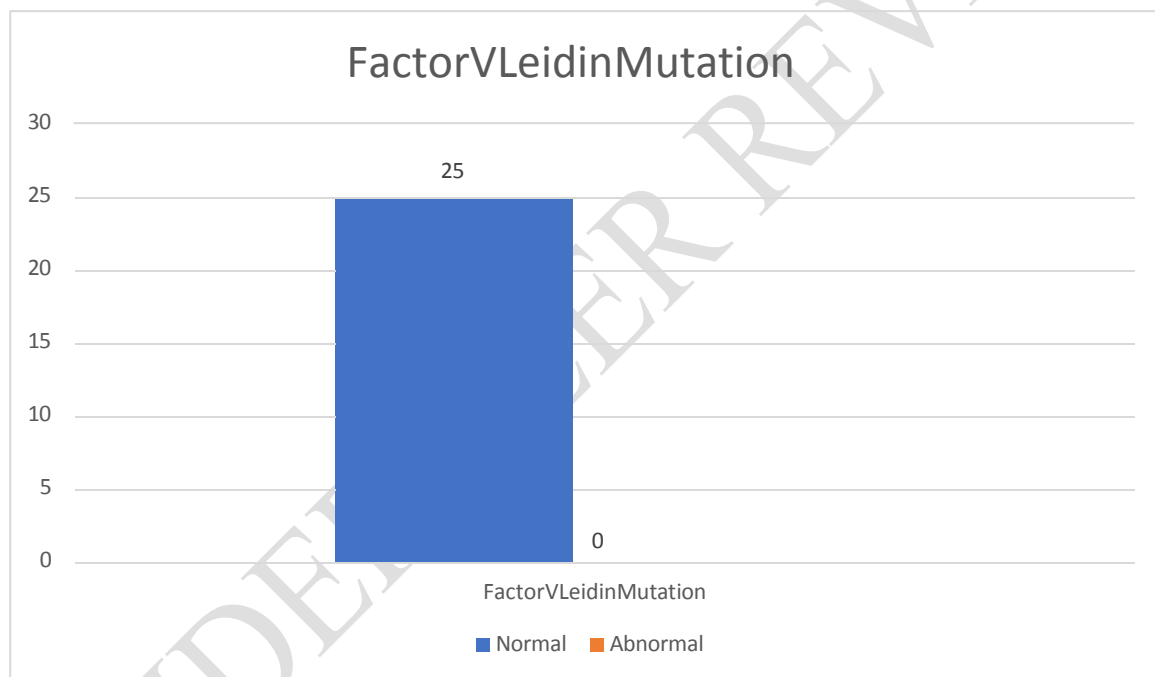


Figure13.FactorVLeidinMutationamongstudyparticipants

Antibody(APLA):

Table14.Antibody(APLA)amongstudyparticipants

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

In the present study, all of the participants had normal antibody (APLA)

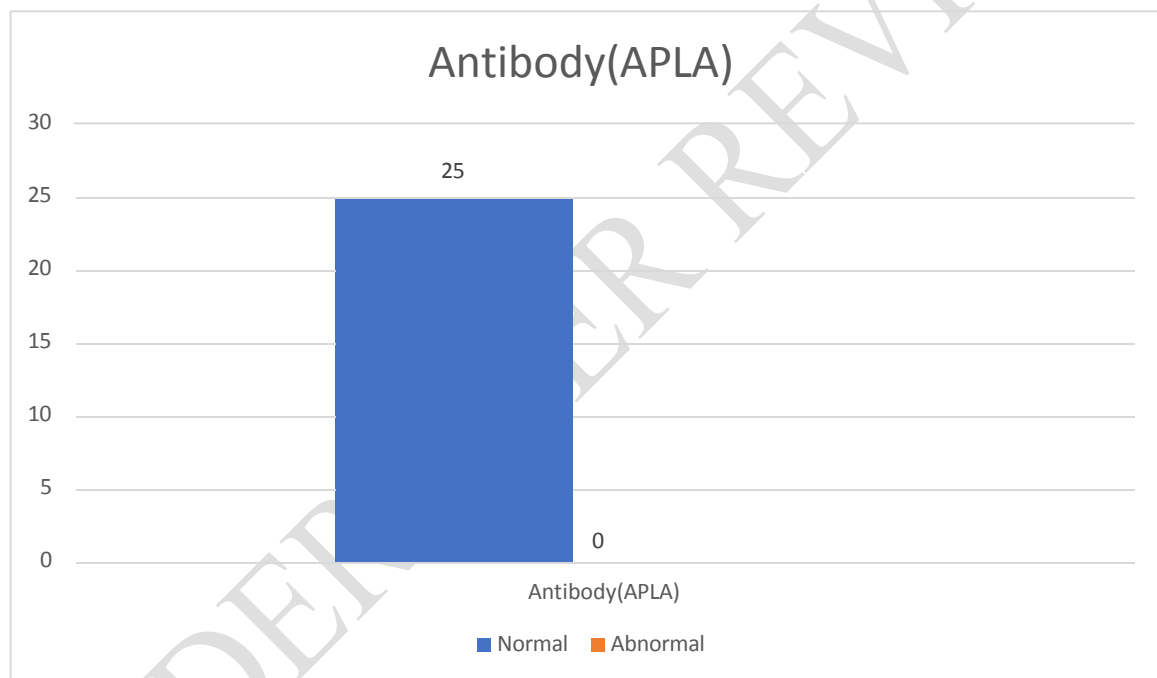


Figure14.Antibody(APLA)amongstudyparticipants

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.

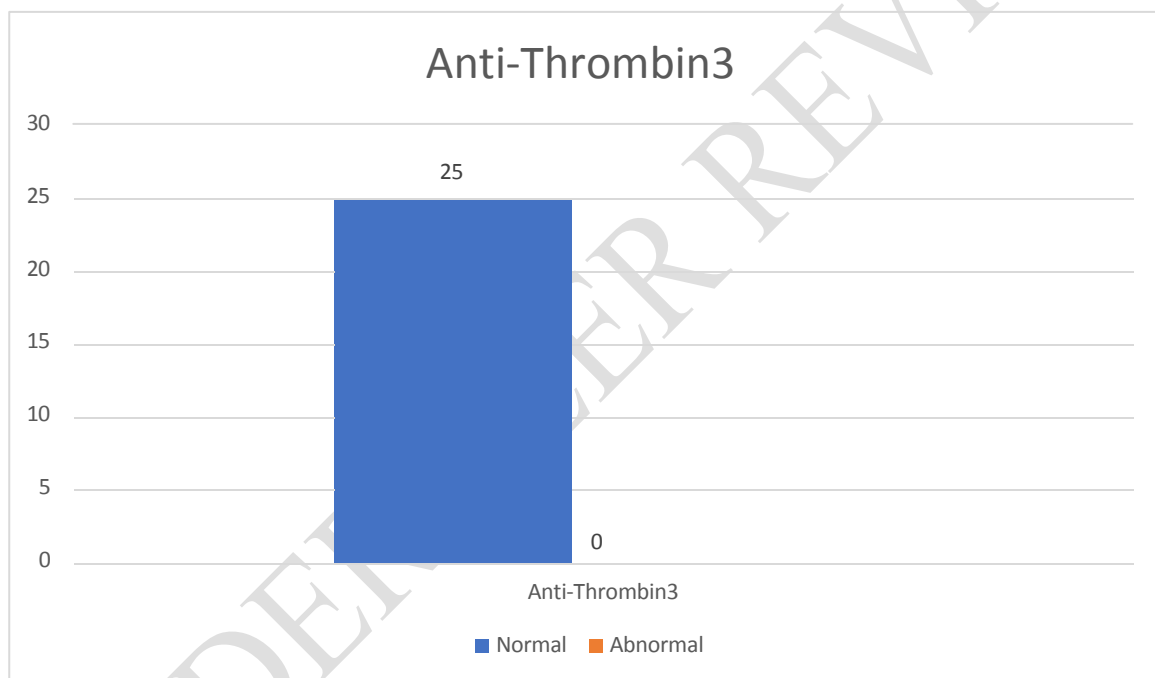


Figure15.Anti-thrombin3among studyparticipants

PFOand Gender:

Table16.AssociationbetweenPFOandGender

			Gender		Total
			Male	Female	
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).

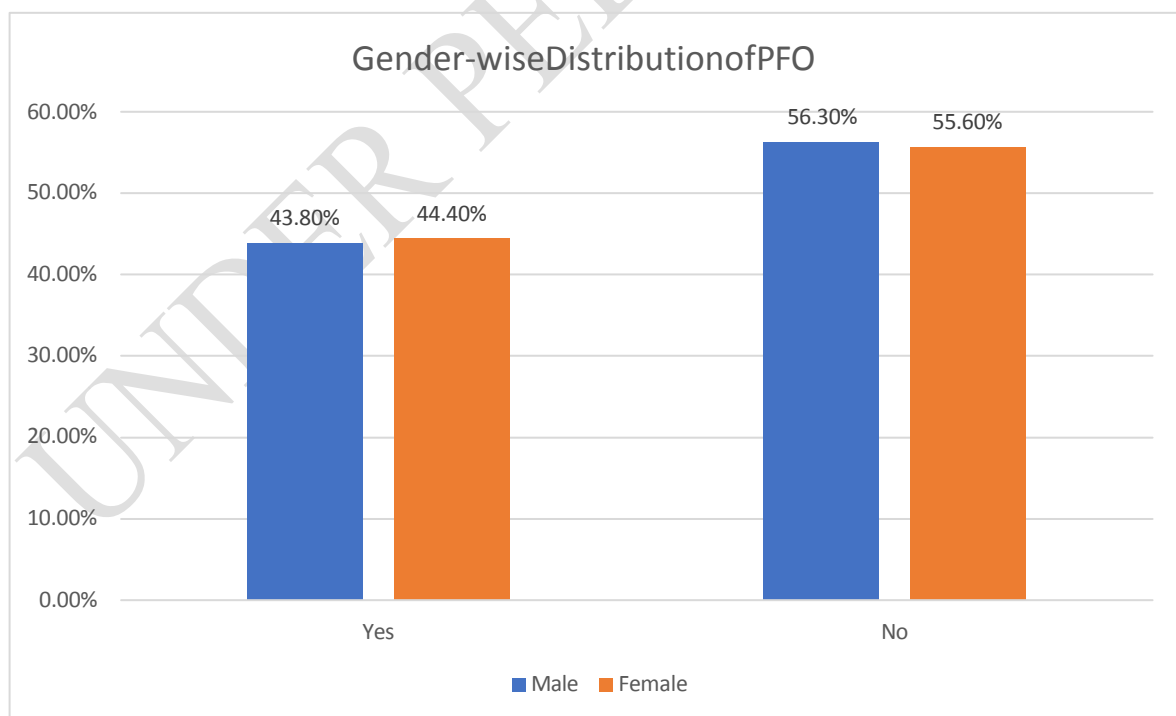


Figure16.Association betweenPFOandGender

PFOandTypeofStroke:

Table17.Associationbetween TypeofStrokeand Gender

			Typeof Stroke		Total
			Ischaemic	TIA	
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.The distributionwasclinicallysignificantbut 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).

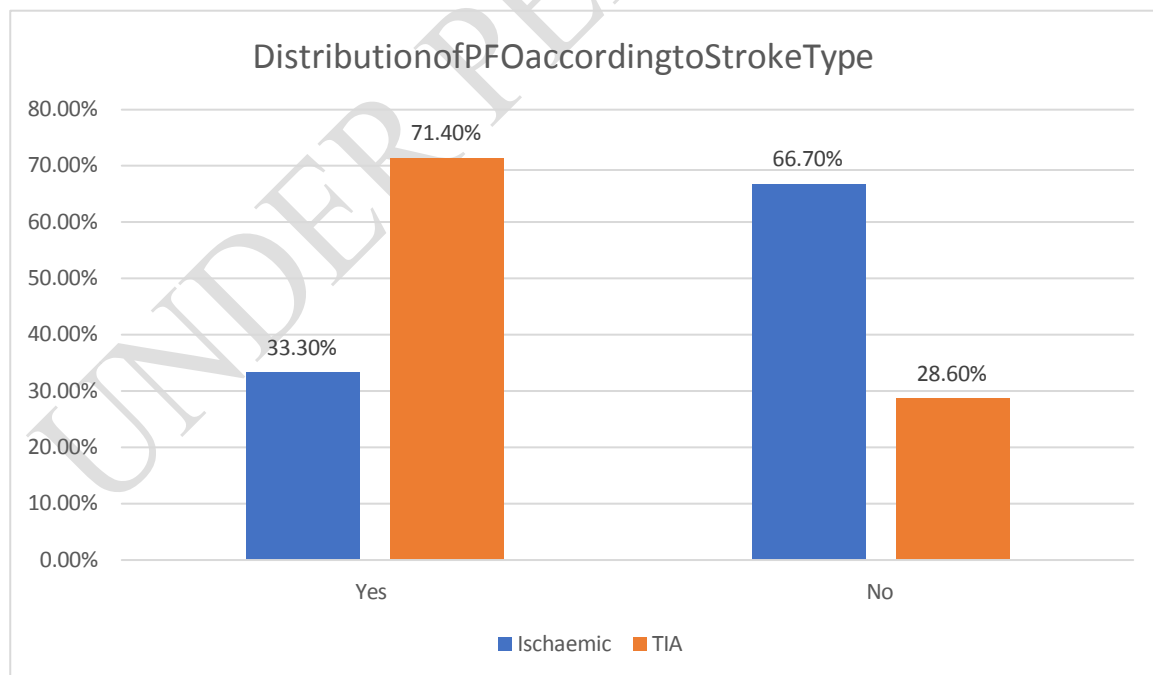


Figure17.AssociationbetweenTypeofStrokeandGender

DISCUSSION:

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. [25] 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. [26], 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 [27], indicating that nearly half of young patients with ischemic stroke of unknown origin have a patent foramen ovale. Lechat et al. [8] 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 [29], 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. [29]. 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. [8], 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. [7], Decastro et al. [31], Wu LA et al. [32], and Handke et al. [33]. Importantly, this study goes beyond cryptogenic stroke by including TIA patients, addressing a gap in previous research.

CONCLUSION:

The present study concluded the distribution was clinically significant but there is no significant association between the type of stroke and the presence of patent foramen ovale.

REFERENCES:

1. JeyarajDuraiPandianet.alStrokeEpidemiologyandStrokeCareServicesinIndia.J Stroke. 2013 Sep; 15(3): 128–134.
2. LópezAD. WHOdiesof what?Acomparativeanalysisof mortalityconditionsin developed countries around 1987. World Health Stat Q 1990; 43:105-14.
3. TomasAbadalL,PuigT,BalaguerVintróI.Accidentevascularcerebral:incidencia, mortalidad yfactoresde riesgoen 28 añosde seguimiento.Estudio de Manresa. Rev Esp Cardiol 2000;53: 15-20.
4. ManningWJ.Roleoftransesophagealechocardiographyinthemanagementof thromboembolic stroke. Am J Cardiol 1997;80: D19-28.
5. AutoreC,CartoniD,PiccininnoM.MultiplaneTransesophagealEchocardiography and Stroke. Am J Cardiol 1998;8: G79-81.
6. HusainAM,AlterM.Transesophagealechocardiographyindiagnosing cardioembolic stroke. Clin Cardiol 1995; 12:705-8.
7. DiTullioM,SaccoRL, GopalA,Mohr JP, HommaS.Patentforamenovaleasarisk factor for cryptogenic stroke. Ann Intern Med 1992; 117:461-5.
8. MasJL,LascaultG,LoronP,TheardM,KlimczacM,etal.Prevalenceofpatent foramen ovale in patients with stroke. N Engl J Med 1988;318: 1148-52.
9. Alsheikh-AliAA,ThalerDE,KentDM.Patentforamenovaleincryptogenicstroke: incidental or pathogenic. Epub 2009 May 14.40:2349–55.
10. Mojadidi MK, Elgendy AY, Elgendy IY, et al. Transcatheter patent foramen ovale closureaftercryptogenicstroke:anupdatedmeta-analysisofrandomizedtrials.JACC Cardiovasc Interv 2017; 10:2228–30. 10.1016/j.jcin.2017.09.002.
11. MojadidiMK,WinokerJS,RobertsSC,etal.Accuracyofconventionaltransthoracic echocardiographyforthediagnosisofintracardiacright-to-leftshunt:ameta-analysis of prospective studies. Echocardiography Epub 2014 Apr 2; 31:1036–48.
12. OzdemirAO,TamayoA,MunozC,etal.Cryptogenicstrokeandpatentforamen ovale: clinical clues to paradoxical embolism. J Neurol Sci 2008; 275:121–7.
13. MasJL, Arquizan C,Lamy C, etal. Recurrentcerebrovascular eventsassociated with patentforamenovale,atrialseptalaneurysm,orboth.NEnglJMed2001;345:1740–6.
14. TheNewEnglandJournalofMedicine, May2016.NEnglJMed374:21May26, 2016.
15. DeCastro,October2000.Morphologicalandfunctionalcharacteristicsofpatent foramen ovale and their embolic implications. Stroke 2000; 31:2407–2413.
16. WuLA2004. Patentforamenovaleincryptogenicstroke:currentunderstandingand management options. Arch Intern Med 2004 May 10;164(9):950-6.
17. DMKent, 2013.Anindextoidentifystroke-relatedvsincidentalpatentforamenovale in cryptogenic stroke. Epub 2013 Jul 17; 81(7): 619–625.
18. DomenicoConsoli2015.PrevalenceofPatentForamenOvaleinIschemicStrokein Italy: Results of SISIFO Study. Epub 2015 Feb 26.
19. MaryZBechis2017.ImagingAssessmentoftheInteratrialSeptumforTranscatheter Atrial Septal Defect and PFO Closure. InterventCardiol Clin 6 (2017).
20. MathewJ.Price,MD.Transcatheter closureofPFO. InterventCardiolClin6(2017).
21. NgPY,NgAK2018.AssociationofPreoperativelyDiagnosedPatentForamenOvaleWith Perioperative Ischemic Stroke. JAMA (Journal of the American Medical Association).

2018 Feb 6;319(5).

22. Vaduganathan M, Qamar A, Gupta A, et al. Patent foramen ovale closure for secondary prevention of cryptogenic stroke: updated meta-analysis of randomized clinical trials. *Am J Med* 2018;131. 10.1016/j.amjmed.2017.11.027
23. Mojadidi MK, Winoker JS, Roberts SC, et al. Accuracy of conventional transthoracic echocardiography for the diagnosis of intracardiac right-to-left shunt: a meta-analysis of prospective studies. *Echocardiography* Epub 2014 Apr 2; 31:1036–48.
24. Ozdemir AO, Tamayo A, Munoz C, et al. Cryptogenic stroke and patent foramen ovale: clinical clues to paradoxical embolism. *J Neurol Sci* 2008; 275:121–7.
25. Marino Brian, Abhishek Jaiswal, Seth Goldberg, Gary L. Berardini, (2016). Impact of transesophageal echocardiography on clinical management of patients over age 50 with cryptogenic stroke and normal transthoracic echocardiogram. *J. Hosp. Med.*;11(2):95-98 | 10.1002/jhm.2484.
26. Li, L., Schulz, U.G., Kuker, W., Rothwell, P.M., & Oxford Vascular Study (2015). Age-specific association of migraine with cryptogenic TIA and stroke: Population-based study. *Neurology*, 85(17), 1444–1451. <https://doi.org/10.1212/WNL.0000000000002059>.
27. Dolores Mesa. Prevalence of Patent Foramen Ovale in Young Patients with Cryptogenic Stroke, *Revista Española de Cardiología* 2003;66:662-668 (Julio 2003).
28. Homma S, Di Tullio MR. Characteristics of patent foramen ovale associated with cryptogenic stroke. *Abiplanar transesophageal echocardiographic study. Stroke* 1994 Mar;25(3):582-6.
29. DC Fisher, EA Fisher, JH Budd, SE Rosen, ME Goldman. (1995). The incidence of patent foramen ovale in 1,000 consecutive patients. A contrast transesophageal echocardiography study. *Chest.* ;107(6):1504-9. doi: 10.1378/chest.107.6.1504.
30. Herwig WS, Schuchlenz. The association between the diameter of a patent foramen ovale and the risk of embolic cerebrovascular events. *Am J Med.* 2000 Oct 15;109(6):456-62.
31. De Castro, October 2000. Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke* 2000; 31:2407–2413.
32. Wu LA. 2004. Patent foramen ovale in cryptogenic stroke: current understanding and management options. *Arch Intern Med* 2004 May 10;164(9):950-6.
33. Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. *N Eng J Med.* (2007) 357:2262–8. doi: 10.1056/NEJMoa071422.

ABBREVIATIONS

PFO	Patent foramen ovale
ASD	Atrial Septal defect
TIA	Transient Ischemic Attack
TEE	Trans Esophageal Echo-cardiography
TTE	Transthoracic Echo-cardiography
MRI	Magnetic Resonance Imaging

NCCT	Non-contrast computerized tomography
USG	Ultra-sonography
ECG	Electrocardiography
CBC	Complete blood count
KFT	Kidney function test
LFT	Liver function test
CNS	Central Nervous System

UNDER PEER REVIEW