Comparative analysis of echocardiographic and clinical characteristics among patients afflicted by embolic stroke of undetermined source and migraine, both accompanied by patent foramen ovale

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Abstract

Background: This study aimed to compare patients with migraine and embolic stroke of undetermined source (ESUS) with known patent foramen ovale (PFO) in terms of echocardiographic and clinical features. **Methods:** In this observational single-center study, we obtained 2-dimensional (2D) and color Doppler images using parasternal short axis (PSAX), apical 4-chamber (A4C), and subcostal 4-chamber (SC4C) transthoracic echocardiography (TTE) views for patients with Migraine and ESUS. In cases where a PFO was suspected, patients underwent transthoracic contrast echocardiography and transesophageal echocardiography (TEE). We compared the anatomical and functional high-risk characteristics of PFO, as assessed by TEE and the RoPe score, in both patient groups. **Results:** This research involved a cohort of 720 individuals with ages ranging from 18 to 60, and 73.2% of the participants were female. Among the participants, 43.5% had Migraine, and 56.5% had ESUS. The most common comorbidity was diabetes (26.1%). PFO characteristics were measured, and high-velocity shunting through the interatrial septum was observed in 35.5% of patients. ESUS patients had a higher median age, with a similar gender distribution. ESUS patients had higher rates of diabetes and hypertension, while active smoking was more common in Migraine patients. Basic echocardiographic parameters were similar, except for higher pulmonary artery systolic pressure in ESUS. In the ESUS group, as compared to the migraine group, there was a more substantial occurrence of large microbubble passage through the interatrial septum, and the PFO showed increased length, while the PFO width remained similar. The RoPe and High-risk PFO scores were similar between the groups. **Conclusions:** ESUS patients were older with higher rates of diabetes and hypertension, while Migraine patients had a higher prevalence of active smoking. ESUS patients showed elevated pulmonary artery pressure, increased large microbubble crossings through the interatrial septum, and longer PFO lengths.

Main Title

Comparative analysis of echocardiographic and clinical characteristics among patients afflicted by embolic stroke of undetermined source and migraine, both accompanied by patent foramen ovale

Short Title

Comparing echo & clinical characteristics in ESUS and migraine with PFO

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Ethical Approval

Local Ethics Committee approved the study.

Consent to Participate and Publish

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Conclusions: ESUS patients were older with higher rates of diabetes and hypertension, while Migraine patients had a higher prevalence of active smoking. ESUS patients showed elevated pulmonary artery pressure, increased large microbubble crossings through the interatrial septum, and longer PFO lengths.

Keywords: Patent foramen ovale (PFO), migraine, embolic stroke of undetermined source (ESUS), transthoracic echocardiography

INTRODUCTION

Patent foramen ovale (PFO) is a persistent fetal communication that is present in approximately 25% to 30% of the general population (1). The prevalence of PFO in the general population has raised interest in understanding its potential implications, and whether specific features of PFO are associated with a higher risk of adverse clinical outcomes. It is important to note that while most PFOs do not cause any clinical complications, there is a small percentage of cases where PFOs can lead to serious conditions such as paradoxical embolism, embolic stroke of undetermined source (ESUS), and migraine (2,3). Studies have shown a significant association between PFO and both ESUS and migraine (4,5).

Transthoracic echocardiography (TTE) is the initial diagnostic modality for PFO. Color Doppler imaging during TTE can detect a right-to-left color transition in the interatrial septum (IAS) following the Valsalva maneuver, indicating the presence of PFO. Transoesophageal echocardiography is often required to confirm the diagnosis of PFO in adults due to suboptimal transthoracic and subcostal echo windows. In 2D echocardiographic views, the central portion of the atrial septum, which is thin in normal cardiac anatomy, may not be clearly visualized (6). This "septal drop-out" phenomenon can lead to misinterpretation as PFO, especially in adults (7). Additionally, pulmonary vein flows projecting onto the IAS may be mistakenly perceived as color Doppler flow in the IAS, potentially resulting in misdiagnosis of PFO. Contrast echocardiography, utilizing the passage of microbubbles from the right atrium to the left atrium following peripheral venous injection of agitated saline during the strain phase of the Valsalva maneuver, can aid in establishing the diagnosis of PFO (8). The presence of a shunt is defined as the visualization of more than three contrast bubbles in the left atrium via contrast echocardiography (9). Transesophageal echocardiography (TEE) provides a definitive diagnosis and characterization of PFO.

Understanding the prevalence and potential consequences of PFO is crucial for effective diagnosis, treatment, and management of patients at risk (10). Echocardiographic and clinical characteristics of patients with ESUS and migraine accompanied by PFO are important factors to consider in a comparative analysis. Comparing the echocardiographic and clinical characteristics of patients with embolic stroke of undetermined source and migraine, both accompanied by PFO, can provide valuable insights into the potential mechanisms underlying these conditions and assist in identifying appropriate management strategies.

It has also been shown that the size, length, and width (functional potential) of the PFO, play a critical role in the development of migraine and ischemic stroke. Additionally, presence of atrial septal aneurysm, hypermobile IAS, large right-to-left (RL) shunt, Eustachian valve or a Chiari's network, and a sharp ([?]10°) angle between the inferior vena cava and the PFO flap is associated with a high-risk PFO (11,12).

This study aims to investigate the characteristics of PFO and its potential link to clinical conditions, specifi-

cally migraine and ESUS, in a cohort of 720 patients aged between 18 and 60. In this context, we conducted a comprehensive assessment of the PFO characteristics, clinical demographics, and echocardiographic findings in a diverse patient population. Additionally, we compared the characteristics of PFO and the presence of high-risk criteria for paradoxical emboli in patients with migraine and ESUS. This investigation explores the potential differences in PFO morphology, as well as accompanying structural and functional criteria, in patients with migraine and ESUS. It also examines the association between PFO characteristics and the prevalence of microbubble passage through the IAS, a phenomenon linked to paradoxical emboli. The study further assesses the RoPe score, which identifies high-risk clinical features for stroke in ESUS patients, and the High-risk PFO score, used to determine high-risk PFO based on anatomic and functional criteria.

METHODS

For this observational single-center study, approval was obtained from the Local Ethics Committee before data collection began. Images of a total of 720 ESUS and migraine patients who complied with the study protocol between 2020 and 2022 were analyzed. For imaging purposes, two TTE devices and one TEE probe were used in the same center.

The study included patients presenting with migraine and ESUS, along with suspected PFO detection in color Doppler imaging within the interatrial region using at least one transthoracic echocardiographic window. We recorded parameters such as the basal right ventricular (RV) and mediolateral right atrial (RA) diameters, as well as estimated pulmonary artery (PA) systolic pressure for all patients. Additionally, detailed examinations were conducted to assess the presence of interatrial septal aneurysm, Chiari network, and Eustachian valve.

Transthoracic echocardiography was performed using various imaging windows, including parasternal long axis (PLAX), parasternal short axis (PSAX), apical four-chamber (A4C), apical three-chamber (A3C), apical two-chamber (A2C), and subcostal four-chamber (SC4C) views. PSAX, A4C, and SC4C windows were specifically used to detect Doppler blood flow in the IAS. To rule out abnormal pulmonary venous return, we visualized the entry of pulmonary veins into the left atrium using 2D and color Doppler imaging in one or more transthoracic echocardiographic windows. Identical color Doppler gain settings were applied to all patients. Estimated pulmonary artery systolic pressures (PASP) were calculated using the modified Bernoulli equation, considering the peak Doppler velocity of the tricuspid regurgitation jet and the end-diastolic velocity of the pulmonary regurgitation jet (PASP = $4V^2$ + right atrial pressure [mmHg]). Contrast echocardiography was performed via the transthoracic A4C window following 2D and Doppler TTE. Agitated saline was prepared by adding 9cc of saline to a 10cc syringe. A positive finding was defined as the presence of three or more microbubble transitions from the right atrium to the left atrium during the first five beats of the cardiac cycle following the Valsalva maneuver. TEE involved evaluating 2D and color Doppler images of the IAS at 30-50 degrees mid-esophageal and in the bicaval window. Defects in the fossa ovalis region were diagnosed clefts were identified as PFO.

In this study, the TEE parameters used by Nakayama et al. to define the anatomical and functional high-risk features associated with PFO were used (13). A 'large' PFO is characterized by a height of [?] 2 mm, measured as the maximum separation between the septum primum and septum secundum in the end-systolic frame. Furthermore, a 'long' PFO tunnel is defined as having a length of [?] 10 mm, measured by the maximum overlap between the septum primum and septum secundum. High-risk PFO is further defined by the presence of an atrial septal aneurysm (ASA), which involves a septal excursion of [?] 10 mm from the midline into either the right or left atrium or a total excursion of [?] 15 mm between the right and left atrium. Another characteristic of high-risk PFO is a hypermobile IAS, described as a septum with an excursion of [?] 5 mm in every heartbeat. Additional determinants associated with an increased risk of cerebrovascular events through PFO include the presence of a large right-to-left (RL) shunt, identified by the presence of [?]20 microbubbles in the left atrium during rest and the Valsalva maneuver. Moreover, high-risk PFO is linked to anatomical factors such as the presence of a prominent Eustachian valve or a Chiari's network measuring [?] 10 mm in the right atrium. Additionally, a sharp ([?]10deg) angle between the inferior vena cava and the PFO flap is associated with a high-risk PFO.

Using the noted anatomical and functional features of PFO determined by TEE, Nakayama and colleagues developed a simple scoring system for identifying high-risk PFO (14) (Table 1). When ESUS-related factors were each scored as 1 point, a total score [?] 2 points was strongly associated with ESUS. A score of [?]2 points showed 91% sensitivity and 80% specificity for association with ESUS.

Risk criteria for stroke in patients with PFO can be categorized as clinical, anatomical, and functional criteria. The Risk of Paradoxical Embolism (RoPE) score is based on 12 data and is used to distinguish incidental PFO from clinically significant PFO in ESUS patients (15) (Table 2).

We excluded patients with interatrial septal defects outside the fossa ovalis region, and patients under 18 years and above 60 years of age from the study. The primary endpoints of the study are the comparison of atrial septum, PFO and accompanying anatomical variant of right atrial structures in migraine and ESUS patients. Secondary endpoints were comparison of RoPe and High-risk PFO scores in migraine and ESUS patients.

Statistical analysis

Statistical analysis was conducted to examine the data obtained from patient baseline characteristics. Categorical variables were compared using the $\chi 2$ test or Fisher exact test. The Independent Samples T-test was employed to compare data from two independent groups that exhibited normal distribution, while the Mann-Whitney U test was utilized for two independent groups with non-normally distributed data. Normality analysis was performed using the Kolmogorov-Smirnov test. The results were evaluated at a 95% confidence interval, and statistical significance was defined as $p < 0.05$. All statistical analyses were performed using the IBM SPSS-25 (Statistical Package for Social Sciences, Chicago, Illinois, USA) software package.

RESULT

The study involved 720 participants aged between 18 and 60, with a median age of 41 (with an interquartile range of 26-49), and 73.2% of them were females. Of these participants, 43.5% (135 individuals) were diagnosed with migraine, while 56.5% were diagnosed with ESUS. The most prevalent coexisting condition was diabetes, affecting 26.1% of the patients. All patients underwent assessment using 2D transthoracic echocardiography, contrast echocardiography, and transesophageal echocardiography. The average ejection fraction (EF%) was 59.3 (with a standard deviation of ± 2.36), and the PASP was 26.21 (± 7.06). Diastolic dysfunction was observed in 11.3% of the patients. While moderate or severe mitral and tricuspid regurgitation was infrequent (4.8% and 4.2%, respectively), 16.1% of the patients had moderate or severe tricuspid regurgitation.

In all patients, the median PFO length was measured at 13 mm (with a range of 7-21 mm), and the median PFO height was 7 mm (with a range of 5-9 mm). High-velocity shunting from right to left through the interatrial septum (IAS) was observed in 35.5% of the patients, while 27.4% had Eustachian valve or Chiari network, 26.5% had atrial septal aneurysm, 40% had hypermobile IAS, and 14.5% had narrow-angle between the inferior vena cava and PFO flap ([?]10deg). The mean RoPe score for the study patients was 6.60 (with a standard deviation of +-1.31), and 104 patients (33.5%) were identified as having anatomic and functional high-risk PFO (Table 3).

Migraine and ESUS patients were compared based on their demographic, clinical, and echocardiographic characteristics. The median age was higher in ESUS patients (Migraine: 26 [IQR: 25-41]; ESUS: 45 [39-52], $p<0.001$). Gender and BMI features were similar between the groups. The prevalence of coronary artery disease was similar in both groups. However, diabetes and hypertension were more prevalent in ESUS patients ($p=0.003$ and $p=0.002$, respectively), while active smoking was more common among migraine patients ($p<0.001$). Echocardiographic evaluations showed that EF%, left and right heart dimensions, diastolic parameters, and moderate or severe valvular diseases were similar between the groups. Nevertheless, PASP was higher in ESUS patients (Migraine: 24.95+-5.95; ESUS: 27.19+-7.70, $p=0.004$) (Table 4).

The study groups were compared in terms of PFO characteristics and accompanying other structural and

functional high-risk criteria for paradoxical emboli. The presence of 20 or more microbubble crossings from right to left through the IAS during rest or Valsalva maneuver was more prevalent in ESUS patients compared to migraine patients (Migraine: 26.7%; ESUS: 42.3%, p=0.004). Findings such as the Eustachian valve or Chiari network, atrial septal aneurysm, hypermobile IAS, and an angle between the inferior vena cava and PFO flap [?] 10deg were similar between the groups.

PFO length was greater in ESUS patients compared to migraine patients (Migraine: 10 mm [IQR: 5-20]; ESUS: 15 mm [IQR: 7-24], p=0.001), while PFO width was similar between the groups (Figure 1).

The RoPe score, designed to identify high-risk clinical features for stroke in ESUS patients, had similar values in both groups (Migraine: 6.51+-1.38; ESUS: 6.66+-1.25, p=0.32). The High-risk PFO score, used to determine high-risk PFO based on anatomic and functional criteria, was higher in ESUS patients, but statistically similar in both groups (Migraine: 27.4%; ESUS: 38.3%, p=0.15) (Figure 2).

DISCUSSION

This study aimed to compare the clinical and echocardiographic characteristics of patients with migraine and ESUS who presented with a PFO. The findings of this research provide valuable insights into the potential relationships between these conditions, shedding light on their distinct cardiovascular characteristics and underlying mechanisms.

Transthoracic echocardiography is the initial non-invasive imaging technique used to assess cardiac structures. In cases where structural heart defects are suspected, 2D and color Doppler imaging provide crucial information, while contrast echocardiography and TEE may be necessary for a definitive diagnosis. Echogenicity issues encountered during TTE also contribute to false-positive evaluations. Therefore, obtaining 2D and color Doppler images from different windows and their complementary analysis are vital for an accurate diagnosis of PFO (16).

Patent Foramen Ovale is a common cardiac anomaly, present in a significant portion of the general population. Its diagnosis is of particular interest due to its potential implications for adverse clinical outcomes. While most PFOs remain asymptomatic, a fraction of cases are associated with paradoxical embolism, ESUS, and migraine. These associations have been previously established in the literature (17). The association between PFO and migraine remains uncertain, despite some studies suggesting a connection. Cao et al. conducted a study presenting neuroimaging evidence and novel insights into the correlation between PFO and migraine (18). Furthermore, an increased incidence of cerebrovascular events has been associated with a larger PFO size and a higher number of microbubbles passing through the shunt during echocardiography (19, 20).

The present study confirms and expands upon these associations, demonstrating that ESUS patients with PFO are older and more likely to have comorbidities such as diabetes and hypertension. In contrast, patients with Migraine and PFO exhibit a higher prevalence of active smoking. These differences in patient demographics suggest that distinct risk factors may be at play in the development of ESUS and Migraine in the presence of PFO.

The direction and magnitude of blood flow in patent foramen ovale (PFO) are influenced by factors such as defect size, compliance and pressures within the left and right atria and ventricles (21). The presence of the Eustachian valve is frequently observed in patients with PFO (22, 19) and is believed to increase the risk of paradoxical embolism by diverting blood from the inferior vena cava to the fossa ovalis region (23). In patients with PFO and right-to-left shunting, no changes in right atrial and ventricular volumes are expected. The echocardiographic evaluations performed in this study provide critical insights into the structural and functional characteristics of PFO in both patient groups. In ESUS patients, there was a higher prevalence of large microbubble passage through the interatrial septum, suggesting a more substantial right-to-left shunting of blood. This finding aligns with the increased risk of paradoxical embolism in ESUS patients. Additionally, ESUS patients exhibited longer PFO lengths, highlighting the potential role of PFO size in contributing to embolic events. These findings underscore the importance of assessing PFO morphology in the evaluation of patients with ESUS.

However, the PFO width was similar between the two patient groups, indicating that the width may not be a distinguishing factor in the development of ESUS or migraine. This highlights the importance of considering other structural and functional PFO characteristics, such as length and right-to-left shunt severity.

The study also assessed two scoring systems, the RoPe score and the High-risk PFO score, to identify high-risk PFO based on clinical and anatomical criteria. While the High-risk PFO score was higher in ESUS patients, it was statistically similar between the two groups. This suggests that the presence of high-risk criteria alone may not be sufficient to differentiate between ESUS and Migraine patients with PFO. The findings indicate the need for a comprehensive evaluation of PFO characteristics, including size, right-to-left shunt severity, and anatomical features, to better understand their role in clinical outcomes.

The results of this study have important clinical implications. Understanding the characteristics of PFO and its potential link to clinical conditions like migraine and ESUS is crucial for effective diagnosis and management. It also emphasizes the need for personalized treatment strategies based on the specific features of PFO in individual patients.

Future research in this field should continue to explore the mechanisms underlying PFO-related embolic events and migraines. Investigating the interplay between PFO characteristics and clinical outcomes will provide a foundation for developing targeted interventions and treatments. Moreover, large-scale, multicenter studies may help validate the findings of this single-center research, enhancing our understanding of these conditions.

In conclusion, this study contributes to our understanding of the relationship between PFO, Migraine, and ESUS by examining their clinical and echocardiographic characteristics. It underscores the need for a comprehensive evaluation of PFO morphology and its potential role in clinical outcomes, paving the way for more tailored approaches to patient management and treatment.

The present study has several limitations that should be considered when interpreting the findings. Firstly, this was an observational single-center study, which may limit the generalizability of the results to broader populations. Future multicenter studies are needed to validate and expand upon these findings. Additionally, the study population was relatively small, and the age range was limited to 18 to 60 years. This narrow age range may not fully capture the diversity of patients with PFO, Migraine, and ESUS, potentially excluding older or younger individuals who could also be affected. Moreover, this study primarily relied on echocardiographic assessments to evaluate PFO characteristics, and other diagnostic modalities were not employed, potentially limiting the comprehensiveness of the PFO characterization. The study also did not include long-term follow-up data to assess clinical outcomes related to PFO in Migraine and ESUS patients. A longer follow-up period would be valuable to determine the impact of PFO characteristics on the incidence of adverse clinical events. Lastly, the study's focus was on identifying differences and associations, and it did not delve into the underlying mechanisms driving the observed disparities in PFO features and clinical characteristics between Migraine and ESUS patients. Further research is warranted to explore the underlying pathophysiological processes involved in these conditions and their relationship to PFO characteristics.

CONCLUSION

ESUS patients were older and had a higher prevalence of diabetes and hypertension, while active smoking was more common among migraine patients. Echocardiographic assessments showed no significant differences in heart dimensions or valvular issues. However, ESUS patients had higher pulmonary artery systolic pressure (PASP). ESUS patients showed more microbubble crossings through the interatrial septum (IAS) and longer PFOs. While the RoPe score was similar, the High-risk PFO score was slightly higher in ESUS patients. This study highlights differences between migraine and ESUS patients in terms of some demographic, comorbid, and echocardiographic parameters.

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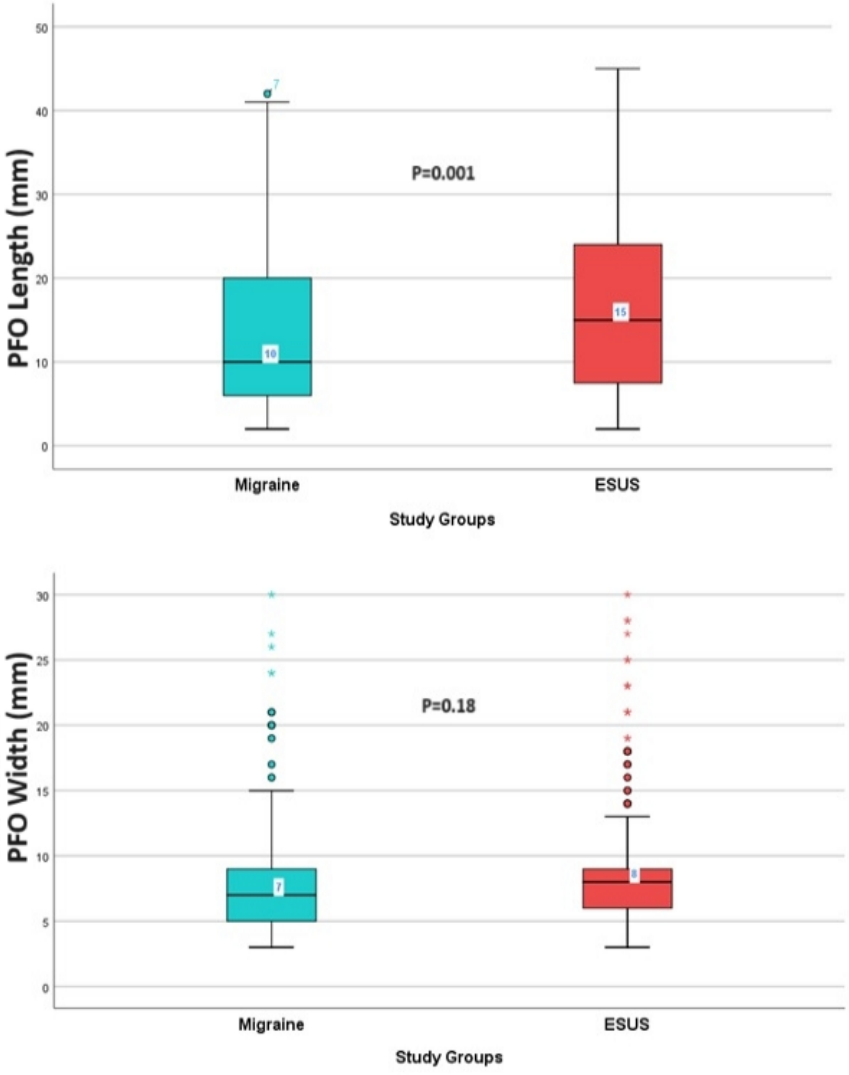
Table 1 Baseline clinical and echocardiographic characteristics of the study population

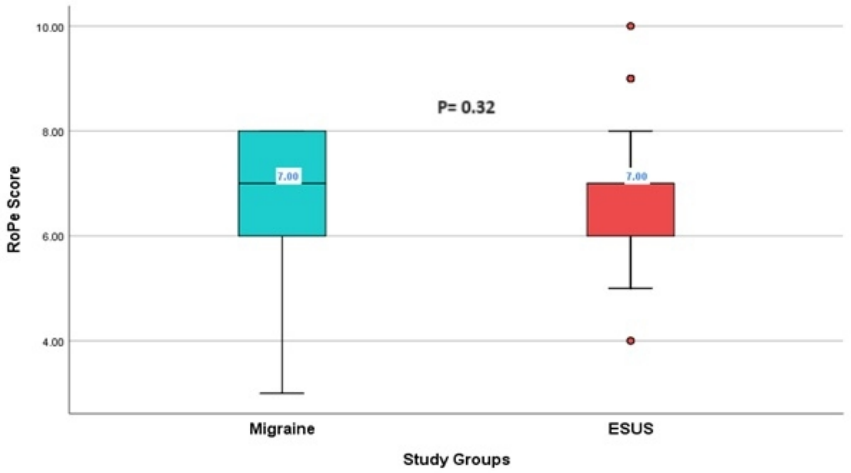
Table 2 Comparison of basal characteristics and echocardiographic features by study groups

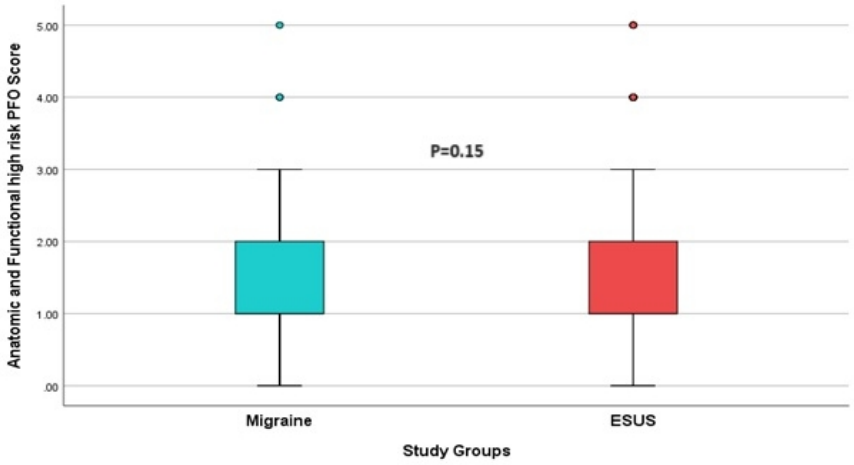
Figure 1 Comparison of PFO height and PFO length measurements in migraine and ESUS patients with Box Plot graph

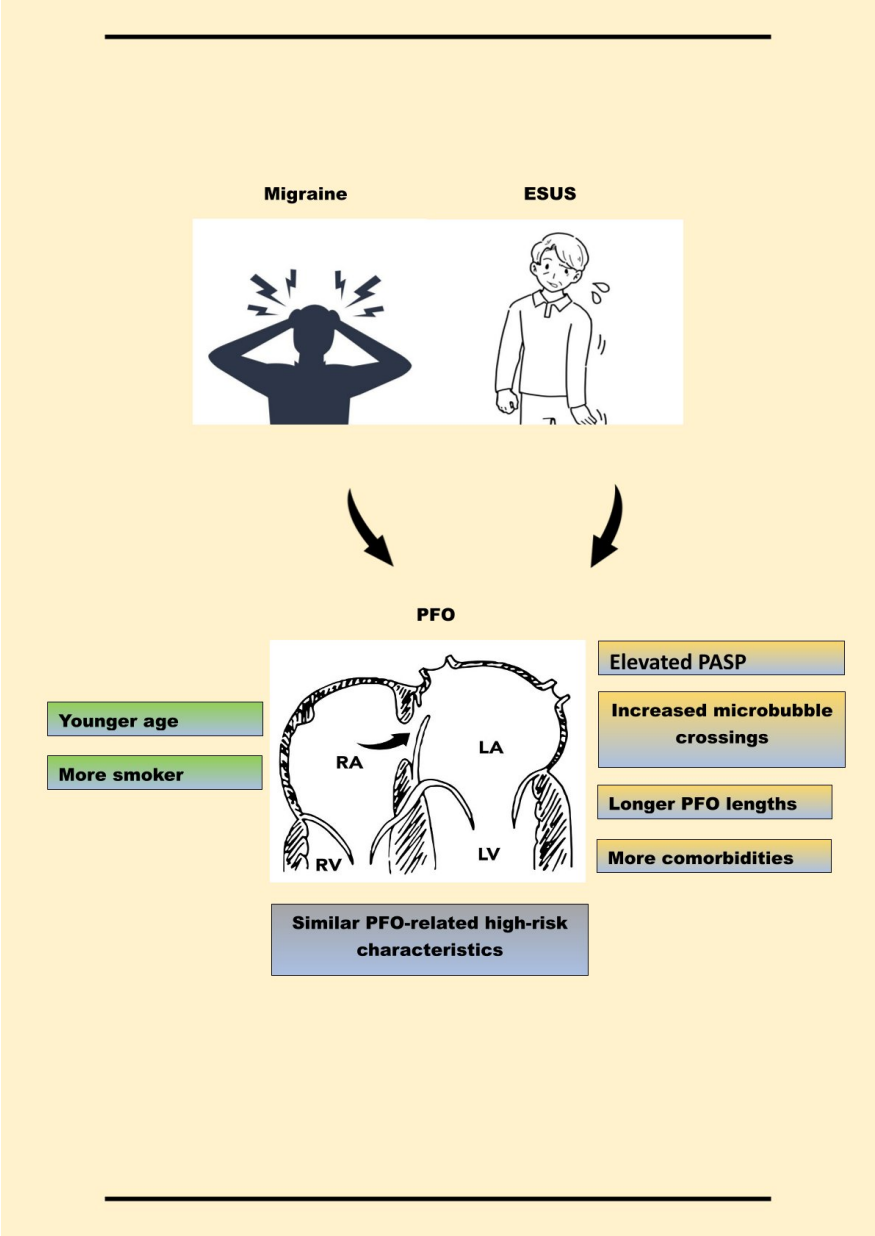
Figure 2 Comparison of RoPe score and anatomical and functional high-risk PFO score in migraine and ESUS patients with Box Plot graph

2.









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Graphical Abstract Test.docx available at https://authorea.com/users/697912/articles/685861-comparative-analysis-of-echocardiographic-and-clinical-characteristics-among-patients-afflicted-by-embolic-stroke-of-undetermined-source-and-migraine-both-accompanied-by-patent-foramen-ovale

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Table 1 High-risk PFO score.docx available at https://authorea.com/users/697912/articles/685861-comparative-analysis-of-echocardiographic-and-clinical-characteristics-among-patients-afflicted-by-embolic-stroke-of-undetermined-source-and-migraine-both-accompanied-by-patent-foramen-ovale

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Table 2 RoPe score.docx available at https://authorea.com/users/697912/articles/685861-comparative-analysis-of-echocardiographic-and-clinical-characteristics-among-patients-afflicted-by-embolic-stroke-of-undetermined-source-and-migraine-both-accompanied-by-patent-foramen-ovale

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Table 3 Baseline clinical and echocardiographic characteristics of the study population.docx available at https://authorea.com/users/697912/articles/685861-comparative-analysis-of-echocardiographic-and-clinical-characteristics-among-patients-afflicted-by-embolic-stroke-of-undetermined-source-and-migraine-both-accompanied-by-patent-foramen-ovale

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Table 4 Comparison of basal characteristics and echocardiographic features by study groups.docx available at https://authorea.com/users/697912/articles/685861-comparative-analysis-of-echocardiographic-and-clinical-characteristics-among-patients-afflicted-by-embolic-stroke-of-undetermined-source-and-migraine-both-accompanied-by-patent-foramen-ovale