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ORIGINAL ARTICLE

# Frequency of Patent Foramen Ovale in Migraine Patient with Aura versus Migraine Patient without Aura in Outpatient Department of Tertiary Care Hospital

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## ABSTRACT

**Background:** Migraine is a highly prevalent neurological disorder and a leading cause of disability worldwide. Patent foramen ovale (PFO) has been implicated in the pathogenesis of migraine, particularly migraine with aura; however, evidence from Pakistan remains scarce. This study aimed to compare the frequency of PFO between patients with migraine with aura (MA) and those with migraine without aura (MOA) attending a tertiary care hospital.

**Methodology:** This comparative cross-sectional study was conducted at the Department of Neurology, Pak Emirates Military Hospital (PEMH) Rawalpindi, from Jan/2025 to June/2025, including 68 patients, classified into two groups according to migraine type: Group A (MA, n=36) and Group B (MOA, n=36). All participants underwent contrast-enhanced transthoracic echocardiography for assessment of PFO. Data was analyzed through SPSS-24. Chi-square / Fisher's Exact test was used, keeping p value<0.05 as significant.

**Results:** Mean age and headache duration were comparable between groups. The prevalence of PFO was significantly higher in the MA group than in the MOA group (41.7% vs. 11.1%; p=0.003). The distribution of PFO categories also differed significantly between the groups (p=0.013). No significant differences were observed between the groups regarding age distribution, gender, family history of migraine, or headache severity (all p>0.05). Additionally, PFO status was not significantly associated with age, gender, or headache severity.

**Conclusion:** Patients who had migraine with aura had significantly higher frequency of PFO compared to those without aura.

**Keywords:** Headache, Migraine, Patent foramen ovale

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## Introduction

Migraine is a severe disability that affects people under 50 and has a significant negative impact on social and personal well-being. It is a major global public health problem, with an estimated 593.8 million cases reported worldwide in 2021, representing a 39.5% increase since 1990 (1). It is more prevalent among females, with the highest burden observed in individuals aged 35–39 years (1). Although high socio-demographic index (SDI) regions report the greatest prevalence, migraine remains underdiagnosed in many low-SDI settings (2).

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The condition substantially impairs quality of life, contributes significantly to disability-adjusted life years (DALYs), and interferes with daily functioning (2). It is also associated with increased mental health problems, particularly among young adults, leading to greater social and economic burdens (2).

To lessen the impact of migraines and increase patient satisfaction, accurate diagnosis and suitable treatment are essential. Regretfully, migraine sufferers have historically received inadequate diagnosis and care (3). Numerous studies have indicated that a patent foramen ovale (PFO) could be the probable cause or risk factor for migraine in the context of long-term evaluations (4).

Migraine attacks can be brought on by vasoactive biochemicals, microembolism, or diluted blood that enters the brain directly from the systemic venous circulation, bypassing the pulmonary circulation and causing cortical spreading depression (5). Often referred to as a "back door to the brain," the PFO is the most common congenital intracardiac right-to-left shunt in adults and has been implicated in the development of many neurological conditions (6,7).

About 25–30% of migraine sufferers have migraine with aura (MA), which has a 4.4% incidence rate (8). Research has indicated a more robust correlation between PFO and MA. Compared to migraine without aura (MOA), MA has a higher prevalence of PFO. They are also approximately 4.5 times more likely to see a >50% decrease in migraine frequency following PFO closure (9). Although there is ongoing discussion on the relationship between PFO and MOA, guidelines recommend that people with MA undergo priority screening for PFO (10). In the past decade, hospital-based case-control studies have dominated related research, which may have added some admission bias. The results may dispel some skepticism and gain greater credibility if the study participants' sources are dispersed throughout the community (11).

Although international studies have consistently demonstrated a higher prevalence of patent foramen ovale (PFO) among patients with migraine with aura, evidence from South Asia remains limited, particularly from Pakistan, where standardized echocardiographic assessment has rarely been used to investigate this association. Ethnic, genetic, environmental, and healthcare-related factors may influence both the prevalence of PFO and its relationship with migraine, limiting the generalizability of findings from other populations. Therefore, locally generated evidence is needed to better understand this association and guide clinical decision-making. The present study aimed to determine the frequency of PFO in patients with migraine with aura compared with those without aura presenting to a tertiary care hospital. Identifying a higher frequency of PFO in a specific migraine subtype may help clinicians recognize patients who could benefit from further cardiac evaluation and individualized management, particularly those with refractory symptoms.

## Methods

This comparative cross-sectional study was conducted from January/2025 to June/2025, at the Neurology Department of Pak Emirates Military Hospital (PEMH), Rawalpindi, Pakistan, after receiving approval from the Ethical Review Committee under Ref No:

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A/28/ERC/29/2025 dated: 13/3/2025. A sample of 36 patients in each group (total 72) was calculated keeping 95% confidence interval, 80% power of test, expected frequency of PFO in MA as 46.3% and in patients without aura as 16.2% (8). Non-probability consecutive sampling technique was used.

The inclusion criteria were patients of age 18-70 years, both genders, with an established diagnosis of migraine with or without aura. The study excluded patients with a history of severe head trauma, other abnormalities related to the heart (apart from PFO), acute vascular embolism or hypercoagulable state, insufficient cubital venous access, and severe heart or lung disease that prevented them from performing the Valsalva maneuver.

Migraine was defined according to the International Headache Society Criteria as 'two or more headache episodes with a completely reversible aura, presence of visual symptoms like fortification spectra or sensory symptoms like unilateral paresthesia or numbness are examples of aura symptoms and over the course of at least five minutes, the aura symptoms steadily spread'. MOA was define as 'at least five headache attacks that lasted 4–72 hours, the headache was moderate to severe, unilateral, and pulsating, physical exercise like walking or climbing stairs exacerbated the headache, the headache was linked to phonophobia, photophobia, nausea, and/or vomiting and another diagnosis did not provide a better explanation for the headache'.

Headache severity was assessed using a 10-cm Visual Analogue Scale (VAS), where 0 represented no pain and 10 represented the worst imaginable pain. Scores were categorized as mild (1-3), moderate (4–6), and severe (7–10).

PFO is the continuous openness of a foramen ovale, or congenital opening, in the interatrial septum, which typically shuts down after birth, which was confirmed by echocardiography by the blood moving between the upper heart chambers i.e. a right to left shunt at rest or during a Valsalva operation following an intravenous injection was indicative of PFO.

After obtaining written informed consent, all patients who met the inclusion criteria were added to the research. Demographic information, clinical history, and physical examination; of patients was recorded in a pre-design proforma. In addition to undergoing a thorough neurologic examination, patients were questioned about their usage of oral contraceptives (from females only) and current cigarette smoking. The average frequency, duration, and severity of headache attacks were noted in migraine patients. Aura-related symptoms, whether visual, sensory, or motor, were thoroughly examined. Eligible participants were classified into two groups according to the International Classification of Headache Disorders, 3rd edition (ICHD-3): migraine with aura (n = 34) and migraine without aura (n = 34). All participants underwent transthoracic echocardiography (TTE) using a standardized protocol performed by an experienced cardiologist/echocardiographer to identify evidence of a right-to-left shunt. ECG tracings were obtained concurrently with the acquisition of conventional Mmode, two-dimensional, pulsed wave, and color Doppler pictures. A right to left shunt at rest or during a Valsalva operation following an intravenous injection of contrast medium, consisting of a solution of mixed saline (9

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ml) plus air (1 ml), was considered to be indicative of the presence of PFO. PFO size was divided into two categories i.e. small or medium sized, based on confluent or solitary spikes observed following Valsalva strain; Large, if bubbles were discernible during regular breathing. This rating generally corresponds to PFO size, showing an increasing amount of blood that has been shunted. In order to prevent any potential bias in favor of a favorable result, the diagnosis was not visible to the Doppler operator. A pre-made proforma was used to record the findings, which were then statistically analyzed.

SPSS version 24.0 was utilized for data analysis. After determining that the data was normally distributed using the Shapiro-Wilk test, quantitative information such as age, headache frequency, and duration was displayed as mean ± standard deviation. Frequencies and percentages were used to display qualitative data, including gender, migraine severity, family history of migraine, and PFO category. The data was categorized according to migraine severity, age, and gender. To compare the difference between continues variable, independent sample t test was used. The Chi square test or Fisher's Exact test (where cell frequency <5) was used to compare the frequency of PFO in the two groups, and a p value of ≤0.05 was deemed significant.

## Results

This study includes 72 patients, 36 in each group, i.e.; MA (Group A, n = 34) and MOA (Group B, n = 34). The mean age of patients in Group A was 41.06 ± 10.92 years, while in Group B it was slightly higher at 43.29 ± 10.70 years, but difference was not significant. Regarding the duration of headache, patients with MOA experienced slightly longer attacks (21.82 ± 11.89 hours) compared to those with aura (19.76 ± 12.21 hours), but the difference was not significant. However, the frequency of headache episodes was notably higher in Group B (6.82 ± 1.36) compared to Group A (3.53 ± 0.99), with significant difference of (<0.001) table I.

**Table I: Baseline and Headache Characteristics of the Patients (n = 72)**

| Variable | Group A (n=36) Migraine with Aura | Group B (n=36) Migraine without Aura | p-value[1] |
|---|---|---|---|
| Age (years) | 41.06 ± 10.924 | 43.29 ± 10.697 | 0.385 |
| Duration of headache (hours) | 19.76 ± 12.213 | 21.82 ± 11.895 | 0.471 |
| Frequency of headache | 3.53 ± 0.992 | 6.82 ± 1.359 | <0.001 |

**[1]Independent-samples t-test was applied. p < 0.05 was considered statistically significant.**

There were no significant differences between the migraine with aura and migraine without aura groups in terms of age distribution (p = 0.410), gender (p = 0.080), family history of migraine (p = 0.620), or headache severity (p = 0.840). However, patent foramen ovale (PFO) was significantly more prevalent in patients with migraine with aura than in those without aura (41.7% vs. 11.1%, p = 0.003). Furthermore, the distribution of PFO categories differed significantly between the groups (p = 0.013), with small/medium and large PFO occurring more frequently among patients with migraine with aura (table II).

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**Table II: Frequency of Clinical Characteristics and Outcome in Both Groups (n = 72)**

| Variable | | Group A (n=36) Migraine with Aura | Group B (n=36) Migraine without Aura | OR (95% CI) | p-value |
|---|---|---|---|---|---|
| Age | 18–30 years | 8 (22.2%) | 4 (11.1%) | -- | 0.410[1] |
| | 31–50 years | 20 (55.6%) | 24 (66.7%) | | |
| | 51–70 years | 8 (22.2%) | 8 (22.2%) | | |
| Gender | Male | 13 (36.1%) | 21 (58.3%) | 0.40 (0.15–1.06) | 0.080[2] |
| | Female | 23 (63.9%) | 15 (41.7%) | | |
| Family History of Migraine | Yes | 13 (36.1%) | 11 (30.6%) | 1.28 (0.47–3.46) | 0.620[1] |
| | No | 23 (63.9%) | 25 (69.4%) | | |
| Severity of Headache | Mild | 4 (11.1%) | 4 (11.1%) | -- | 0.840[2] |
| | Moderate | 21 (58.3%) | 19 (52.8%) | | |
| | Severe | 11 (30.6%) | 13 (36.1%) | | |
| Patent Foramen Ovale (PFO) | Yes | 15 (41.7%) | 4 (11.1%) | 5.71 (1.67–19.54) | 0.003[1] |
| | No | 21 (58.3%) | 32 (88.9%) | | |
| Category of PFO | None | 21 (58.3%) | 32 (88.9%) | -- | 0.013[1] |
| | Small/Medium | 11 (30.6%) | 2 (5.6%) | | |
| | Large | 4 (11.1%) | 2 (5.6%) | | |

**[1]Fisher Exact test, [2]Chi-square test was applied to calculate p value. P value<0.05 is significant**

No significant associations were found between the presence of patent foramen ovale (PFO) and age group (p = 0.838), gender (p = 0.261), or headache severity (p = 0.080). Although patients with PFO more frequently had moderate headache severity, these differences were not statistically significant.

**Table III: Demographic Stratification of PFO (n = 72)**

| Variable | | PFO Yes (n=19) | PFO No (n=53) | p-value |
|---|---|---|---|---|
| Age Group | 18–30 years | 4 (21.1%) | 8 (15.1%) | 0.838[1] |
| | 31–50 years | 11 (57.9%) | 33 (62.3%) | |
| | 51–70 years | 4 (21.1%) | 12 (22.6%) | |
| Gender | Male | 11 (57.9%) | 23 (43.4%) | 0.261[2] |
| | Female | 8 (42.1%) | 30 (56.6%) | |
| Severity of Headache | Mild | 4 (21.1%) | 4 (7.5%) | 0.080[1] |
| | Moderate | 13 (68.4%) | 27 (50.9%) | |
| | Severe | 2 (10.5%) | 22 (41.5%) | |

***[1]Fisher Exact test, [2]Chi-square test was applied to calculate p value. P value<0.05 is significant***

## Discussion

Our study findings revealed that the frequency of PFO was significantly higher in the patients who had MA compared to those without it. Majority of the participants in our study were of the age group 31 to 50 years and there was no gender predominance. The presence of PFO was not linked with age, gender and severity of migraine.

With a range of 9.3% to 14.4%, migraine prevalence is considerable (12). To lessen the impact of migraines and increase patient satisfaction, accurate diagnosis and suitable treatment are essential (13). Regretfully, migraine sufferers have historically received inadequate diagnosis and care (14). For patients whose medical therapy is resistant or extremely unsatisfactory, internists and researchers are still searching for novel remedies (15). Numerous studies have indicated that a PFO could be the probable cause or risk factor for migraine in the context of long-term evaluations (16). Because of a PFO, certain chemicals and hormones, like

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serotonin, can flow through the blood-brain barrier and trigger migraines by avoiding the pulmonary circulation, where they would typically be processed (17). The PFO allows tiny emboli, debris and clots, to move from the venous to the arterial systems. Small regions of the brain may experience reduced blood flow and, consequently, low oxygenation if these emboli reach the central nervous system (18,19). This could lead to a migraine attack (with aura), a condition known as cortical spreading depression. PFO may cause hypoxia and decreased blood oxygen saturation as a result of the aberrant blood flow, which may have detrimental effects on the brain (20). Reduced blood flow to the brain can cause cortical spreading depression, which can lead to migraine (21). Without one affecting the other, genetic factors may cause both diseases to emerge at the same time. Despite having numerous hypotheses regarding the possible role of PFO in migraine patients, little is known about this association in our local setting. Keeping this in view, the current study was carried out to assess the frequency of PFO in patients of migraine with or without aura.

Our results showed that in patients of MA, PFO was seen in 41.7% patients compared to 11.1% in patients who had MO and this difference was of statistical significance (p=0.05). In a study, it was revealed that PFO was seen in 66.7% patients of MA compared to 47.4% MO (7). In another study it was revealed that in migraine patients without aura, the incidence of PFO is 16.2% to 34.9% and 46.3% to 88% in individuals with MA (7). Reisman and Cindy revealed that the frequency of PFO in MA ranged between 41% to 89% and in patients with MO it ranged between 7% to 34% (9). These findings are consistent with our study findings that PFO is more frequently encountered in patients who have MA compared to those with MO.

Patients with migraine, especially with aura, must be regularly screened for PFO in order to rule out this pathology and establish proper management plan for such patients in order to improve their quality of life.

## Study Limitations

This study has several limitations. First, it was conducted at a single center with a relatively small sample size, which may limit the generalizability of the findings. Second, because of its cross-sectional design, causal relationships between migraine and patent foramen ovale cannot be established. Third, contrast-enhanced transthoracic echo-cardiography was used for PFO detection. Although it is a non-invasive and widely available diagnostic modality, it has lower sensitivity than transesophageal echocardiography and contrast transcranial Doppler, particularly for detecting small right-to-left shunts. Consequently, some small PFOs may have been missed, potentially leading to an underestimation of the true prevalence of PFO in the study population.

## Conclusions

The present study demonstrated that the frequency of patent foramen ovale (PFO) was significantly higher among patients with migraine with aura compared with those without aura. These findings suggest that further cardiac evaluationshould be done in selected patients, particularly those with refractory migraine when clinically indicated. However, larger multicenter prospective studies are needed to confirm these findings and determine whether targeted screening for PFO improves clinical outcomes in this patient population.

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| CONTRIBUTION OF AUTHORS | |
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| **AUTHOR** | **CONTRIBUTION** |
| Conception/Design | AG |
| Data acquisition, analysis and interpretation | AG,AH |
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| All the authors agree to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed. | |