Efficacy and safety of patent foramen ovale closure for mitigating migraine: a systematic review and meta-analysis of randomized trials and observational studies

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Abstract

Background: Although often asymptomatic, patent foramen ovale (PFO) may cause disabling migraine symptoms. Evidence regarding PFO closure for prevention of migraine is still ambiguous and conflicting.

Objectives: This study aims to analyze the efficacy and safety of PFO closure for mitigating migraine symptoms.

Design: This is a systematic review and meta-analysis of randomized clinical trials (RCTs) and observational studies.

Data sources and methods: A comprehensive search was conducted on the Scopus, Medline, ClinicalTrials.gov, and Cochrane Library databases up until March 12, 2024. This review incorporates literature that examines the comparison between PFO closure and control with outcome data related to migraine. We employed random-effect models to analyze the standardized mean difference (SMD) and odds ratio (OR) for presentation of the outcomes.

Results: A total of five RCTs and six observational studies were incorporated. The results of our meta-analysis showed higher reduction of monthly migraine attacks from baseline (SMD −0.34; 95% CI: −0.51, −0.18, $p < 0.0001$, $I^2 = 19\%$) and monthly migraine days from baseline (SMD −0.30; 95% CI: −0.53, −0.08, $p = 0.009$, $I^2 = 0\%$) among PFO closure than control. However, the complete resolution of migraine (especially based on the evidence from RCTs; $p = 0.24$), HIT-6 score ($p = 0.08$), and MIDAS score ($p = 0.15$) did not differ significantly between two groups of intervention. The majority of adverse events reported were atrial fibrillation and access site infection/bleeding that only occurred in small proportions of patients (⩽5%).

Conclusion: This study suggests better efficacy of PFO closure in reducing monthly migraine attacks and days with similar safety profile when compared to control.

Registration: PROSPERO (CRD42023453635).

Background

Patent foramen ovale (PFO) is a congenital cardiac anomaly characterized by incomplete closure of the aperture situated between the right atrium and left atrium of the heart following birth.[1] During intrauterine development, the fetal heart exhibits a small aperture known as the foramen ovale, which is situated between the right and left cardiac chambers of the fetus.[1] The foramen ovale is essential for the fetus during its gestational period to facilitate the direct circulation of oxygenated blood from the placenta throughout

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the body, bypassing the fetus's non-functional lungs.[1] Typically, this aperture naturally seals upon the birth of the infant.[1] According to autopsy and transesophageal echocardiography research, the global prevalence of PFO is believed to be approximately 25% in the general population.[2,3] The frequency has declined to approximately 20% among those aged beyond 80 years.[3] The decline in the occurrence of PFO with advancing age can be attributed to two potential mechanisms: either the spontaneous closure of PFO in later stages of life (which is unlikely) or the phenomenon of selective mortality.[4]

Unfortunately, a significant number of individuals remain unaware of their PFO condition due to the absence of symptoms.[5] Despite the infrequent manifestation of symptoms, PFO has the potential to induce migraines and strokes in adult individuals, greatly diminishing their overall quality of life and reducing their survival.[4,5] The same holds true for myocardial infarction that can also occur in individuals with PFO through paradoxical embolism.[4] According to the systemic blood distribution, paradoxical embolism will cause about one myocardial infarction per three cerebral events.[4] This clearly indicates the significant burden that may arise from PFO.[4] Emerging research indicates a strong correlation between the existence of PFO and a heightened prevalence of migraine.[6,7] A community-based cross-sectional study conducted in China showed that the prevalence of migraine without aura in patients with PFO was 12.83%.[6] Their analysis also showed that the presence of a PFO increased the morbidity risk of migraine without aura.[6] The relationship between PFO and migraine has also been documented by a meta-analysis that summarized data from 18 studies.[7] The summary odds ratios (ORs) indicated a robust connection between the occurrence of PFO and migraine, with a value of 5.13 and a 95% confidence interval (CI) ranging from 4.67 to 5.59.[7]

The subsequent inquiry that emerges revolves around the potential impact of closing the PFO on the reduction of migraines in patients. Nevertheless, the available meta-analysis studies on this subject yield ambiguous and somewhat contradictory findings.[8,9] The findings of a meta-analysis conducted by Elbadawi et al.[8] indicate that while the closure of the PFO may have a notable impact on reducing migraine attacks and the number of migraine days, it did not demonstrate any significant improvement in the responder rate or complete resolution of migraines. These results raise concerns regarding the extent of clinical benefits associated with the closure of the PFO in the prevention of migraines.[8] Conversely, a separate meta-analysis conducted by Wang et al.[9] demonstrated that closing the PFO can substantially enhance the percentage of patients who get full relief of migraine. Furthermore, the safety evaluation of PFO closure for migraine prevention was not included in these two meta-analytic studies.[8,9] Given the presence of contradictory and insufficient evidence, it is necessary to do an updated meta-analysis that consolidates data from the most recent evidence. The objective of this study is to examine the efficacy as well as the safety of PFO closure as a preventive measure for migraines, drawing upon the most recent randomized clinical trials (RCTs) and observational research.

Materials and methods

Eligibility criteria
The PROSPERO international database was used to register the protocol for this study with the registration number CRD42023453635. The preparation of this systematic review and meta-analysis was based on standardized guidelines, known as the PRISMA statement.[10] For studies to be considered in this research, they must satisfy the inclusion criteria that have been established using the PICOS formula as outlined below:

(1) Population = individuals who are over the age of 18 and have been diagnosed with PFO based on an echocardiography examination.
(2) Intervention = received PFO closure procedure.
(3) Control = did not receive PFO closure, but receive other intervention that may be in the form of medical treatment only or sham procedure.
(4) Outcome = have data on the:

- Efficacy = complete resolution of migraine, change of monthly migraine attacks from baseline, change of monthly migraine days

from baseline, change of headache impact test-6 (HIT-6) score from baseline, and change of migraine disability assessment test (MIDAS) score from baseline;

- Safety = any documented adverse events (AEs) that occur during or after the procedure;

(5) Study Design = open-label, single-blind, or double-blind RCTs and observational studies (cohort or case-control).

Meanwhile, the following studies were excluded: (1) comparative research of populations with and without PFO; (2) do not include migraine-related outcomes; (3) insufficient data to enable calculation of the outcome of interest; (4) studies lacking no-PFO closure as the comparison group; (5) protocol, case-report, case-series, cross-sectional studies, and non-primary research; (6) scholarly articles that are not readily available in their complete text or researches that have not yet undergone the publication process.

Search strategy and study selection

Four international databases, namely Scopus, Medline, Cochrane Library, and ClinicalTrials.gov, were utilized by the two reviewers to conduct a comprehensive search of English language literature. A literature search was carried out until March 12, 2024, using the following keywords: "(patent foramen ovale OR persistent foramen ovale OR PFO) AND (closure OR occlusion OR repair) AND (migraine OR migraines OR migraine type headaches OR migrainous headache)." Supplemental Table 1 presents further details regarding the search methodology utilized for each database. The initial stage involved commencing the screening procedure by evaluating the compatibility between the titles and/or abstracts and our pre-established qualifying criteria. If any primary research publications that were cited in the systematic reviews or meta-analyses but were not initially detected during the search process were found to meet the planned inclusion and exclusion criteria, they would be included in the study. The redundant articles were removed. Following this, a comprehensive assessment of full-text articles was undertaken. Both reviewers separately performed all of these processes. If there was a disagreement throughout the

screening process, we sought resolution by seeking the views of a third reviewer.

Data extraction

The data collection process was carried out independently by two reviewers. The extracted data were provided in the following manner: the author of the study, the year of publication, the study design, the country of origin, the sample size, the type of migraine, the period of follow-up, the study arms, the mean age, the distribution of sexes, and the outcomes of interest.

Risk of bias assessment

Two independent reviewers utilized standardized assessment tools to evaluate potential bias in each study. The researchers utilized the Risk of Bias version 2 (RoB v2, Cochrane Collaborations) to evaluate the quality of each RCT study.[11] This scale encompasses assessments of the randomization of study participants, deviations from intended interventions, absence of outcome data, measurement of the outcome, and selection of the stated results of the studies.[11] The evaluations made by the authors were classified into three categories: "low risk," "high risk," or "some concerns" regarding bias.[11]

In order to assess the potential for bias in observational studies, we employed the Newcastle Ottawa Scale (NOS), which has three evaluation criteria: the deliberate selection of participants, the comparability between different groups of participants, and the accuracy of outcome measurements.[12] Studies that receive a score of 7 or higher were classified as high-quality studies according to this methodology.[12]

Statistical analysis

The standardized mean difference (SMD) and its matching 95% confidence interval (95% CI) were calculated using the Inverse-Variance approach across numerous studies related to a continuous outcome. We also utilized the Mantel–Haenszel computation to determine the average odds ratio (OR) and its associated 95% CI for binary outcome across multiple studies. The inclusion of a wide range of participant characteristics and the length of the follow-up period required the careful examination of a significant degree of variability. Random effect models were utilized to tackle

this issue. The I-squared (I^2) statistic was utilized to measure the degree of heterogeneity among research studies.[13] Values more than 50% were considered to indicate a significant or notable level of heterogeneity.[13] The median (IQR) or median (range) data was transformed into the mean (SD) using the formula provided by Wan et al.[14] The reliability of detecting publication bias through the use of funnel plots or statistical tests is diminished when the number of included research studies is less than 10, as opposed to when the number of included studies exceeds 10.[15] Hence, a funnel plot would be utilized to assess the existence of publication bias just when the meta-analysis encompasses more than 10 studies. The study only utilized Review Manager 5.4, a software tool created by the Cochrane Collaboration, for all the analysis.

Results

Study selection and characteristics
After conducting a comprehensive literature search across four databases using predetermined keywords, a total of 908 studies were identified. Out of the total of 908 research, duplicates were eliminated and screening was conducted based on titles and abstracts. As a result, 841 papers had to be discarded. Out of the remaining 67 articles, a comprehensive evaluation of the full-text was conducted, resulting in the exclusion of 56 articles based on the following criteria: 30 lacked a control group, 16 were reviews, 5 were solely protocols, 4 lacked data on the desired outcome, and 1 article had incomplete data for calculations. Ultimately, the final analysis contained 11 papers,[16–26] with 840 individuals in the PFO closure group and 834 individuals in the control group (Figure 1). Out of the 11 papers examined, two comprised double-blind RCTs, three comprised open-label RCTs, one comprised a non-randomized clinical trial, and the remaining five consisted of case–control studies. Italy has contributed to four studies, China has contributed three studies, while the United States (US), United Kingdom (UK), France, and multi-countries (Canada, Germany, Switzerland, and UK) have each contributed one study. A significant proportion of the studies included in the analysis examined migraine accompanied by aura, with follow-up periods ranging from 3 months to 5 years. Three of the studies included in the

analysis employed a sham procedure as a means of comparison, whilst the remaining eight research utilized medical treatment as a control group. Table 1 provide a comprehensive overview of the characteristics of each study included in this analysis.

Quality of study assessment
Based on the RoB v2 evaluation method, it was observed that among the five RCTs examined, three of them were classified as exhibiting a "low" risk of bias across all assessment domains. The two remaining RCTs exhibited a "high" risk of bias. This was primarily attributed to the presence of unclear information regarding protocol deviations among participants and the lack of blinded outcome assessment, which was not compensated for in the analysis (Table 2). In accordance with the NOS tool, the observational studies used in the analysis were deemed to possess a high level of quality, as indicated by scores ranging from 8 to 9 (Table 3).

Efficacy outcomes
Complete resolution of migraine. Five RCTs and 5 observational studies reported data on the complete resolution of migraine among all of the participants. Meta-analysis from these studies showed higher number of participants who experienced complete resolution of migraine among those who received PFO closure than those in the control group (OR 2.92; 95% CI: 1.57, 5.43, $p = 0.0007$, $I^2 = 63\%$, random effect model; Figure 2).

However, when divided based on the study design, the result was only significant among the observational studies (OR 4.80; 95% CI: 2.06, 11.19, $p = 0.0003$, $I^2 = 62\%$, random effect model), while data from RCTs showed non-significant results (OR 1.55; 95% CI: 0.74, 3.26, $p = 0.24$, $I^2 = 35\%$, random effect model) in the complete resolution of migraine between PFO closure and the control group (Figure 2).

Changes in the monthly migraine attacks from baseline. The data for this outcome were only derived from RCTs without any observational studies. Meta-analysis from 5 RCTs showed that PFO closure was associated with higher reduction in the monthly migraine attacks from baseline when compared to the control group
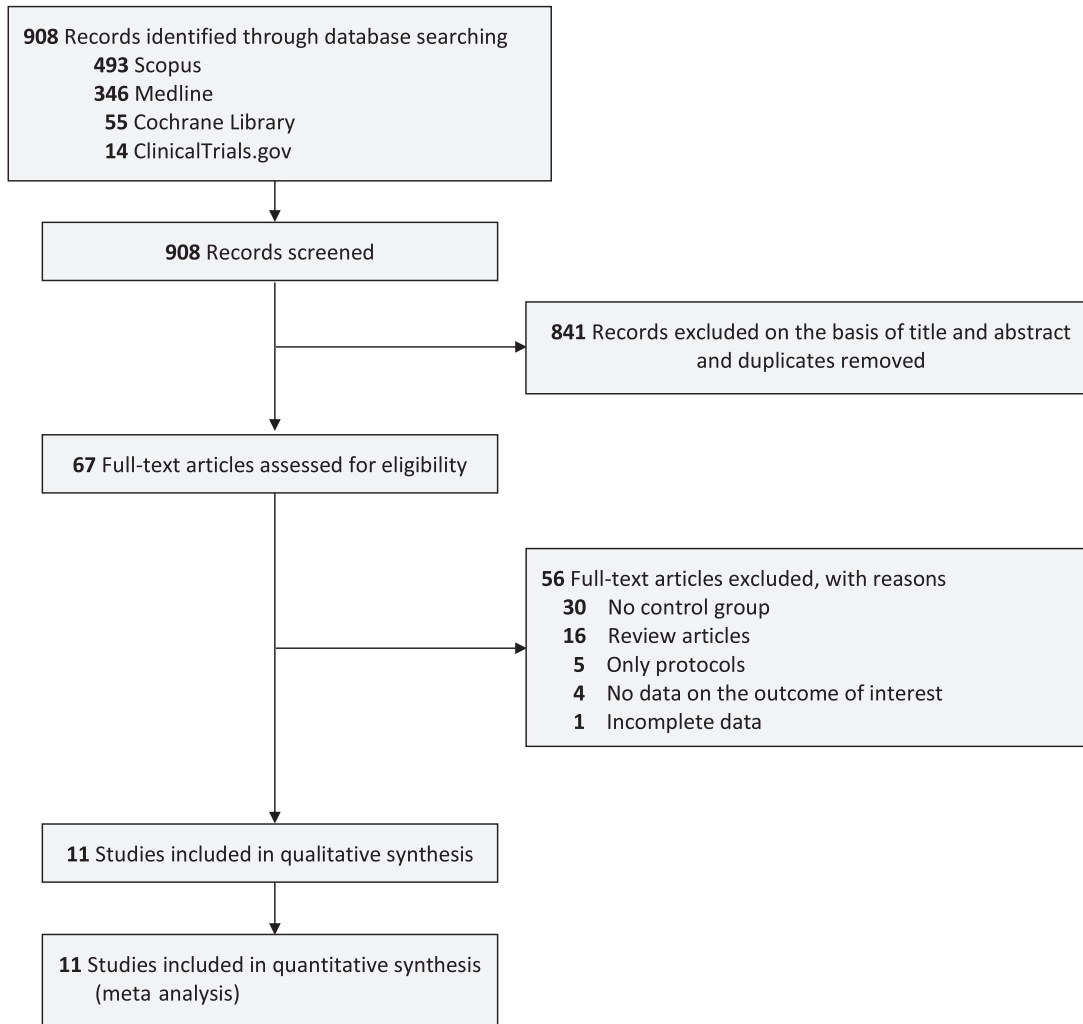
Figure 1. PRISMA diagram of the detailed process of selection of studies for inclusion in the systematic review and meta-analysis.
PRISMA, Preferred reporting items for systematic reviews and meta-analyses.

(Std. Mean Difference −0.34; 95% CI: −0.51, −0.18, $p < 0.0001$, $I^2 = 19\%$, random effect model; Figure 3(a)).

Change in the monthly migraine days from baseline. The data for this outcome were only derived from RCTs without any observational studies. Meta-analysis from 2 RCTs showed that PFO closure was associated with higher reduction in the monthly migraine days from baseline when compared to the control group (Std. Mean Difference −0.30; 95% CI: −0.53, −0.08, $p = 0.009$, $I^2 = 0\%$, random effect model; Figure 3(b)).

Change in the HIT-6 score from baseline. One RCT and two observational studies reported the

change in the HIT-6 score from baseline among the overall population. Meta-analysis from these studies showed no significant difference in the HIT-6 score change from baseline between PFO closure group and the control group (Std. Mean Difference −0.44; 95% CI: −0.94, 0.06, $p = 0.08$, $I^2 = 88\%$, random effect model; Figure 3(c)).

However, when divided based on the study design, the result turned into statistically significant ones among observational studies (Std. Mean Difference −0.65; 95% CI: −1.12, −0.19, $p = 0.006$, $I^2 = 82\%$, random effect model), while RCT study still showed nonsignificant result (Std. Mean Difference 0.00; 95% CI: −0.33, 0.33, $p = 1.00$, random-effect model; Figure 3(c)).

Table 1. Baseline characteristics of the included studies.

Study	Country	Design	Migraine type	Study durations (months)	Comparator	Study arms	Number of participants	Age (years)	Male (%)	Outcome[a]
Anzola et al.[16] 2006	Italy	Case–control	- With aura: 70.1% - W/o aura: 29.9%	12	Medical treatment	PFO Closure Control	50 27	39.5 36	20% 14.8%	1
Biasco et al.[17] 2014	Italy	Case–control	- With aura: 68.7% - W/o aura: 31.3%	46.3 ± 32.7	Medical treatment	PFO Closure Control	89 128	46.4 47.1	24.7% 13.3%	1,5
Dowson et al.[18] 2008 (MIST)	UK	Double-blind RCT	- With aura: 100%	3	Sham procedure (skin incision in the groin)	PFO Closure Control	74 73	44.3 44.6	16.2% 15.1%	1,2,4,5
He et al.[19] 2019	China	Case–control	- With aura: 22.9% - W/o aura: 77.1%	60	Medical treatment	PFO Closure Control	91 101	37.1 39.2	25.3% 28.7%	1,4
Mas et al.[20] 2013 (CLOSE-MIG)	France	Open-label RCT	- With aura: 51.7% - W/o aura: 48.3%	60	Medical treatment	PFO Closure Control	67 78	41 42.6	32.8% 48.7%	1,2
Mattle et al.[21] 2016 (PRIMA)	Multi-countries	Open-label RCT	- With aura: 100%	12	Medical treatment	PFO Closure Control	53 54	44.1 42.7	15% 17%	1,2,3,5
Rigatelli et al.[22] 2010	Italy	Case–control	- With aura: 48.8% - W/o aura: 51.2%	29.2 ± 14.8	Medical treatment	PFO Closure Control	40 46	38.9 40	15% 24%	1,5
Tobis et al.[23] 2017 (PREMIUM)	US	Double-blind RCT	- With aura: 65.6% - W/o aura: 34.4%	12	Sham procedure	PFO Closure Control	123 107	42.8 43.7	10.6% 11.2%	1,2,3
Vigna et al.[24] 2009	Italy	Case–control	- With aura: 43.9% - W/o aura: 56.1%	16 ± 7	Medical treatment	PFO Closure Control	53 29	42 43	9% 10%	1
Xing et al.[25] 2016 (EASTFORM)	China	Non-randomized clinical trial	- With aura: 24.5% - W/o aura: 75.5%	12	Sham procedure (contrast only)	PFO Closure Control	125 116	39 38.3	26.4% 28.4%	4
Yan et al.[26] 2023	China	Open-label RCT	Not reported	3	Medical treatment	PFO Closure Control	75 75	52.3 52	54.6% 56%	1,2

aOutcome: 1 = complete resolution of migraine; 2 = change in the monthly migraine attacks from baseline; 3 = change in the monthly migraine days from baseline; 4 = change in the HIT-6 score from baseline; 5 = change in the MIDAS score from baseline.
PFO, patent foramen ovale.

Table 2. Risk of bias assessment of included clinical trials.

Study ID	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
CLOSE-MIG (2021)	+	?	+	−	+	−
MIST (2008)	+	+	+	+	+	+
PREMIUM (2017)	+	+	+	+	+	+
PRIMA (2016)	+	+	+	+	+	+
Yan G (2023)	+	?	+	−	+	−

+ Low risk.
? Some concerns.
− High risk.

Table 3. Newcastle-Ottawa quality assessment of observational studies.

First author, year	Study design	Selection[a]	Comparability[b]	Outcome[c]	Total score	Result
Anzola et al.[16] 2006	Case-control	***	**	***	8	Good
Biasco et al.[17] 2014	Case-control	***	**	***	8	Good
He et al.[19] 2019	Case-control	***	**	***	8	Good
Rigatelli et al.[22] 2010	Case-control	***	**	***	8	Good
Vigna et al.[24] 2009	Case–control	***	**	***	8	Good
Xing et al.[25] 2016	Non-randomized study	****	**	***	9	Good

[a](1) Is the case definition adequate; (2) representativeness of the cases; (3) selection of controls; (4) definition of controls.
[b](1) Comparability of cases and controls on the basis of design or analysis, (maximum two stars).
[c](1) Ascertainment of exposure; (2) same method of ascertainment for cases and controls; (3) non-response rate.

Change in the MIDAS score from baseline. Two RCTs and two observational studies reported the change in the MIDAS score from baseline among the overall population. Meta-analysis from these studies showed no significant difference in the MIDAS score change from baseline between PFO closure group and the control group (Std. Mean Difference -0.61; 95%CI: -1.45, 0.23, $p = 0.15$, $I^2 = 95\%$, random effect model; Figure 3(d)).

This result remained non-significant when divided based on the study design: RCTs (Std. Mean Difference 0.01; 95%CI: -0.26, 0.27, $p = 0.96$, $I^2 = 0\%$, random-effect model) and
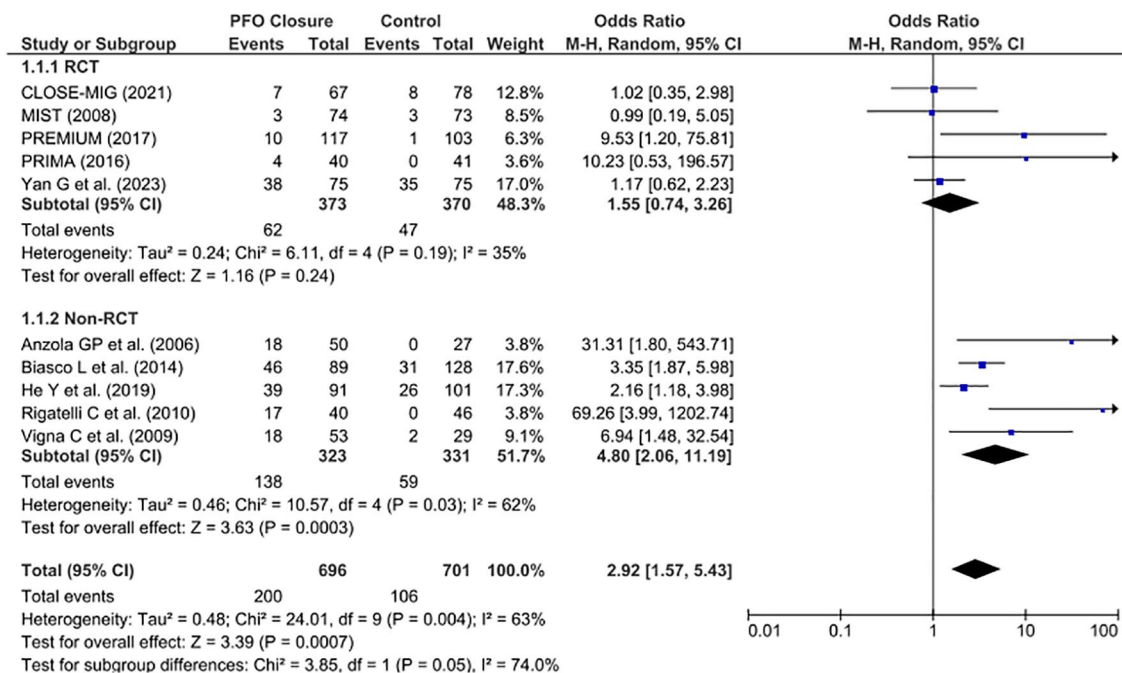
Figure 2. Forest plot that shows the complete resolution of migraine among patients in the PFO closure group and in the control group.
PFO, patent foramen ovale.

observational studies (Std. Mean Difference -1.24; 95%CI: -3.40, 0.92, $p = 0.26$, $I^2 = 98\%$, random-effect model; Figure 3(d)).

Safety outcomes

There were only six studies that reported the safety outcomes from PFO closure procedure. We did not perform meta-analysis on this outcome due to insufficient data and variety in the AEs reported by the included studies. The majority of AEs reported in the PFO closure group from the included studies were atrial fibrillation (AF) and access site infection or bleeding. However, these events were only occurred in small proportions of participants ($\leqslant 5\%$), temporary, and minor. Other AEs such as chest pain, tamponade, pericardial effusion, endocarditis, fatigue, syncope, and transient hypotension were also recorded, but only occurred in the minority of patients ($<3\%$). More details regarding the AEs both in the PFO closure and the control group documented by each of included studies can be seen in the Supplemental Table 2.

Publication bias

Funnel plot analysis was employed to assess publication bias. Relatively symmetrical inverted plot was seen for the complete resolution of migraine outcome, indicating no publication bias was evident (Supplemental Figure 1). However, for the remaining outcomes of interest, this study only included less than 10 studies, precluding the assessment of publication bias.[15,27]

Discussion

The findings of our meta-analysis indicate that the closure of the PFO was effective in reducing the frequency of monthly migraine attacks and the number of migraine days experienced per month, in comparison to medical treatment alone or a sham procedure. Nevertheless, the efficacy of PFO closure in attaining complete relief of migraine, particularly in light of the findings from RCTs, was shown to be limited. The included studies indicated that the majority of AEs associated with PFO closure were AF and infections or bleeding at the access site. The occurrence of
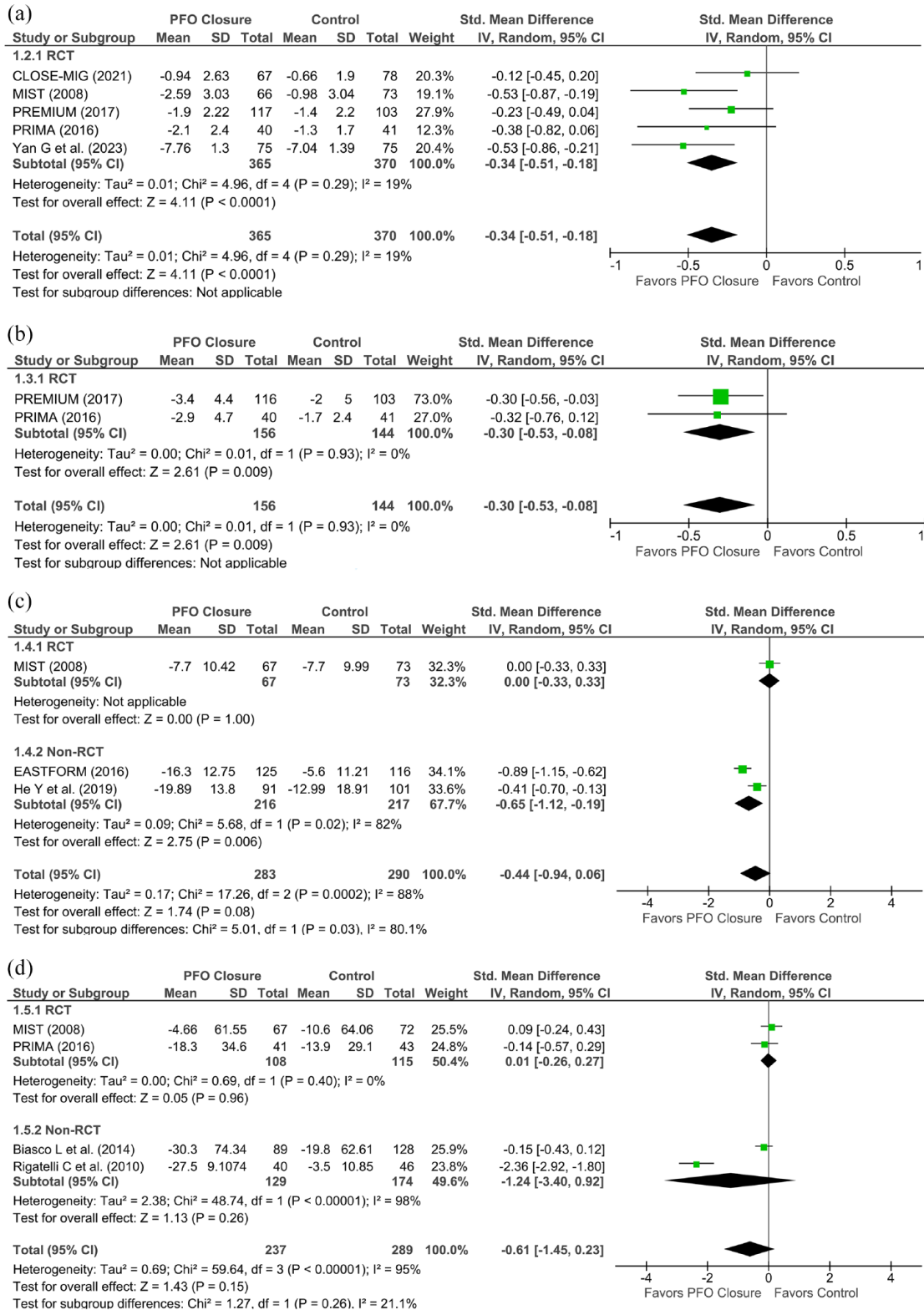
Figure 3. Forest plot that shows change in the monthly migraine attacks from baseline (a), change in the monthly migraine days from baseline (b), change in the HIT-6 score from baseline (c), and change in the MIDAS score from baseline (d) among patients in the PFO closure group and in the control group.
HIT-6, headache impact test-6; MIDAS, migraine disability assessment test; PFO, patent foramen ovale.

these AEs was limited to a small percentage of patients (<5%) and was temporary. Consequently, we can still infer that this procedure was relatively safe to carry out.

The efficacy of PFO closure in mitigating migraine symptoms can be explained by at least three potential mechanisms.[7,28,29] Fist, the existence of a right-to-left shunt inside the PFO facilitates the passage of subclinical emboli and metabolites originating from the venous system, enabling their bypassing of the pulmonary circulation and subsequent entry into the systemic circulation.[7,28] This event leads to irritation of the trigeminal nerve and cerebral blood vessels, causing migraine symptoms to appear.[7,28] Through the closure of the PFO, the right-to-left shunt will no longer occurred, hence diminishing the likelihood of subclinical emboli or metabolites originating from the venous system to enter the systemic circulation.[7,29] By employing this approach, the trigeminal nerve and cerebral blood vessels will not experience any additional irritation.[7,29] Second, the occurrence of temporary hypoxemia resulting from the paradoxical shunting of blood through a PFO can lead to the formation of microinfarcts inside the brain; hence, inducing irritation and a propensity for migraines.[7,28] The absence of a right-to-left shunt from PFO closure can effectively avoid hypoxemia, thereby the formation of microinfarct in the brain with subsequent irritation can be effectively minimalized.[7,29] Finally, vasoactive chemicals such as 5-hydroxytryptamine and calcitonin-derived gene-related peptide can facilitate the transmission of pain signals in the central nervous system and have a role in the mechanism of migraines.[7,28] Typically, the monoamine oxidase in the pulmonary capillaries deactivates these vasoactive chemicals, preventing them from entering the arterial circulation.[7,28] Nevertheless, the presence of a PFO enables vasoactive substances to bypass the pulmonary circulation and enter the systemic circulation directly.[7,28] Consequently, these substances can reach the cerebral circulation in significant amounts and exert their effects on the trigeminal ganglion cells.[7,28] This process contributes to the dural neurogenic inflammatory response, ultimately leading to the onset of a migraine.[7,28] By sealing the PFO, the bypass pathway for these vasoactive substances to enter the systemic circulation, including the cerebral circulation, is eliminated.[7,29] Consequently, these substances will be broken down by monoamine oxidase in the pulmonary capillaries, leading to a reduction in neurogenic inflammation and migraine symptoms.[7,29]

It is important to note that the inclusion criteria for the 2 major RCTs comparing PFO closure to conventional migraine treatment (PRIMA[21] and PREMIUM[23]) were quite stringent. That led to patient cohorts with very difficult to treat migraines.[21,23] It is possible that a comparison among run-of-the-mill migraine patients, particularly such patients with typical aura, would have crystallized the advantage of PFO closure more conspicuously. A patient-level based meta-analysis that used data from both of these RCTs showed that PFO closure was superior to medical treatment in virtually all endpoints.[30] Thus, the findings of this meta-analysis, along with our own meta-analysis, indirectly suggest a notable additional benefit of PFO closure for migraines, which is particularly of relevance to neurologists. Patients with PFO closure, performed for whatever reason, are mechanically vaccinated for life against cerebral events (and myocardial infarctions) secondary to paradoxical embolism.[4] Neurologists should arrive at the conclusion that screening for PFO be an early integral part of migraine management and closure of PFOs that are found to be among the first steps in therapy.

The findings of our meta-analysis align with the prior meta-analysis conducted by Wang et al.[9] which similarly demonstrates a reduction in monthly migraine attacks and duration by implementing PFO closure. Nevertheless, notable distinctions exist between the prior meta-analysis conducted by Wang et al.[9] and the present meta-analysis.

First, prior meta-analysis conducted by Wang et al.[9] encompassed a total of 12 papers, comprising 3 RCTs and 9 observational studies. Out of the nine observational studies examined, it is noteworthy that three of the articles (see reference number 24, 25, and 26 in the prior meta-analysis by Wang et al.[9]) were written in the Chinese language and were not included in international databases such as Medline, Scopus, and even Google Scholar. The hyperlinks provided in the references section pertaining to the three aforementioned publications, which direct users to CrossRef or Scopus database, exhibit completely distinct articles upon opening.[9] This, naturally, gives rise to additional inquiries concerning

the level of quality of the research and the credibility of the data encompassed within the three studies.[9] Concurrently, our present meta-analysis encompassed a collective of 11 investigations, all of which were composed in the English language and included in internationally recognized databases, so facilitating the assessment of the studies' quality. Out of the 11 papers included, 5 are RCTs, and the remaining 6 are observational studies. Therefore, our current meta-analysis incorporates a greater number of RCT studies, which undoubtedly enhances the quality of the evidence generated.

Second, Wang et al.[9] conducted a meta-analysis that integrated findings from RCTs with findings from observational studies. Adhering to the standards from the Cochrane Handbook of Systematic Reviews of Intervention,[31] we found this action to be inappropriate and not recommended. Observational studies are prone to many biases, including selection bias and information bias, which can potentially influence the outcomes of the research.[32,33] The presence of selection bias may result in disparities in the initial characteristics of the two participant groups, hence, exerting an influence on the outcomes of the analysis.[32,33] The presence of information bias has the potential to introduce inaccuracies into both the data and the final results of outcome measurement.[32,33] Furthermore, observational studies frequently lack the ability to predict the presence of additional confounding variables that might also influence research outcomes.[32,33] Concurrently, RCTs can mitigate the influence of confounding factors by employing a technique of participant randomization.[34,35] Allocation concealment and blinding strategies can effectively reduce bias, including selection bias and information bias, for both participants and outcome assessors.[34,35] Hence, it is recommended to differentiate between the findings derived from RCTs and those derived from observational studies. Our latest meta-analysis adheres to the Cochrane guidelines by segregating the findings from the RCTs and observational studies that can be found in all of our forest plots. We have found out a disparity between evidence derived from RCTs and evidence derived from observational research, particularly in relation to the complete resolution of migraine outcome. RCTs yield nonsignificant results, but observational studies yield significant results.

Third, the prior meta-analysis conducted by Wang et al.[9] lacks comprehensive information regarding the risk of bias assessment for each study that was included. They solely present the final conclusions or interpretations of the evaluation, so preventing readers from recognizing the specific aspects that are absent/lacking from each study that is presented. In addition, Wang et al.[9] employed Jadad scale to evaluate the likelihood of bias in RCTs. Despite its user-friendly nature, the Jadad scale exhibits certain limitations.[36,37] The Jadad scale fails to include certain crucial aspects that could potentially influence the accuracy of the results, including allocation concealment, industrial sponsorship, and conflict of interest.[36,37] In addition, the Jadad scale relies on a limited number of questions, lacking a clear framework for reference and specific questions.[36,37] As a result, it can produce ratings that are somewhat subjective, particularly when compared to more comprehensive tools like the Cochrane's RoB 2.[36,37] Hence, in our present meta-analysis, we employed Cochrane's RoB 2 to evaluate the risk for bias in the included RCTs, resulting in a more thorough and detailed assessment. The assessment aspects of the NOS and RoB 2 instruments for each included study are shown in detail in Tables 2 and 3, respectively.

Finally, the prior meta-analysis conducted by Wang et al.[9] solely focused on evaluating the effectiveness of PFO closure in the treatment of migraines, without incorporating a safety analysis. The consideration of intervention safety is a crucial issue in clinical practice, as a successful intervention should not only be beneficial but also possess a high level of safety to prevent harm to the patient.[38] In the present meta-analysis, we offer data pertaining to the safety evaluation of PFO closure for the purpose of migraine prevention. The findings indicate that the procedure exhibited an acceptable level of safety, with a limited occurrence of AEs observed in only a minority of patients.

The present investigation is not devoid of limitations. Most of the included RCTs had a relatively short follow-up period ranging from 3 to 12 months, while only one RCT had an extended follow-up period of up to 60 weeks. The long-term data are mostly obtained from observational studies, which are prone to various biases and confounding factors. Hence, the long-term effectiveness and safety of PFO closure in the context of migraine prophylaxis remains questionable. Second, it is crucial to

acknowledge that there is a lack of available data pertaining to the safety analysis of PFO closure for migraine prevention. Consequently, it cannot be analyzed further through meta-analysis. Finally, the present meta-analysis reveals substantial heterogeneity in several outcomes of interest, potentially attributable to variations in participant characteristics and follow-up duration. Nevertheless, we assert that the results obtained from our thorough review and meta-analysis can provide useful insights into improving the prevention and management of migraine. Multiple RCTs investigating the efficacy of PFO closure in migraine prevention are currently in the recruitment phase (NCT05561660, NCT04100135, NCT05546320). It is anticipated that these trials will be finished in the near future, providing valuable insights to corroborate the findings of our present investigation. In order to testify the prognostic values of PFO closure to improve migraine burden, more RCTs with larger sample sizes and longer duration of follow-up are still encouraged.

Conclusion

The systematic review and meta-analysis indicate the efficacy of PFO closure in reducing monthly migraine attacks and monthly migraine days. However, PFO closure was not effective in achieving complete resolution of migraine and improving HIT-6 or MIDAS score, especially based on the findings from RCTs. In terms of safety, PFO closure demonstrates a commendable safety profile, with AEs being documented in only a limited percentage of patients. Our study suggests that screening for the presence of a PFO should be included as an essential part of migraine management. If a PFO is detected, then PFO closure can be considered as the initial treatment option. Nevertheless, it is still recommended to conduct carefully designed RCTs with a substantial sample size and an extended period of follow-up in order to confirm the results of our study.

Declarations

Ethics approval and consent to participate
Not applicable for this study type (systematic review and meta-analysis study). The Faculty of Medicine, Krida Wacana University Research Ethics Committee has confirmed that no ethical approval is required.

Consent for publication
Not applicable.

Author contributions
Todung Donald Aposan Silalahi: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Competing interests
The authors declare that there is no conflict of interest.

Availability of data and materials
The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplemental materials.

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Supplemental material
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