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SYSTEMATIC REVIEW

Immediate clip migration after breast biopsy: a meta-analysis for potential risk factors

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Objectives Immediate clip migration following breast biopsy is not a rare condition but its impact on future cancer management can be profound. However, there is limited knowledge on what causes the phenomenon and how to prevent it.
Methods A systematic search was performed to identify articles discussing factors associated with clip migration, and a meta-analysis for each risk factor was conducted to determine the risk ratio.
Results The most significant risk factor for immediate clip migration is globally fatty breast (RR = 2.00 [1.43-2.80], P<0.00001), while local heterogeneity has a moderate but insignificant protective effect (RR=0.68 [0.45-1.04], P=0.07). Clips with bioabsorbable carriers and biopsy along the superior/inferior breast axis do not change the rate of clip migration.
Conclusion Intrinsic breast composition is the most important determinant for accurate clip placement. Further research to identify potentially modifiable factors, such as clip design and biopsy techniques, is needed.
Advances in knowledge Fatty breast composition has the highest risk of clip migration. Research on potentially modifiable factors such as clip design and biopsy techniques is needed.

INTRODUCTION

Minimally invasive image-guided core biopsy for breast lesions has become a mainstay of clinical practice for non-surgical tissue sampling. It has been promoted to a standard process to place a clip at the end of the biopsy. The clips help localize the tumor if surgical excision is warranted subsequently and monitor treatment response to neoadjuvant chemotherapy. Biopsy clip was first approved by the US Food and Drug Administration in 1995.[1] With the advancement in core biopsy and neoadjuvant chemotherapy, complete removal or significant regression of small breast lesions are now possible before definite surgical resection, making accurate placement of tissue clips even more important for follow-up purposes.

However, the biopsy clips do not always remain at the precise location of biopsy after the procedure, especially for stereotactic and MRI-guided biopsy. Breast compression for immobilization is necessary for these procedures, resulting in a negative pressure gradient known as the accordion effect. Some other mechanisms of clip migration are also proposed, such as migration along the biopsy tracks, the effect of hematoma or air in biopsy cavities, and changes in the clip site after neoadjuvant chemotherapy.[2] A number of studies have been conducted to assess the frequency and possible associated factors of clip migration. These studies showed variable results, and so is the effort to design tissue clips that are more resistant to migration.[3,4]

The objective of this review, therefore, is to systematically review existing literature in the field to determine which factors may contribute to immediate biopsy clip migration after imaging-guided core biopsy.

METHODS AND MATERIALS

Data sources

The literature search was performed on 2021/11/08 in four medical databases—PubMED, Ovid/MEDLINE, Cochrane Library, and Embase with keywords and MeSH terms (Supplementary Table 1) determined jointly by the two authors. Additional studies were identified from the references and added to the review. This study was structured according to the guidance of PRISMA guidelines.[5]

Study selection

To identify eligible records, two authors independently screened the articles with predetermined criteria for inclusion and exclusion. A predetermined protocol was followed by all reviewing authors but it was not registered in protocol databases. Clinical trials and cohort studies on image-guided vacuum-assisted core biopsy with clip placement in English were included with no limitation to the publication date. Case reports, case series, and reviews were excluded. Studies on surgical biopsy, radioactive seed localization, and delayed clip migration were also excluded. All studies went through a title and abstract screening. Eligible studies were then subjected to full-text review. Disagreements were settled by consensus. Reasons for exclusion were recorded at every stage.

Data extraction

Two authors independently extracted data from the eligible articles to an excel sheet. The sheets were merged to find any inconsistency, which was settled by consensus. The primary endpoint was the percentage of clip migration, which was defined as displacement of clip>10 mm from the biopsy site on immediate re-check mammography. Globally fatty breasts are defined as BI-RADS type A; while heterogeneously dense breasts are BI-RADS type C.[6] Additional information was also extracted, which included the name of the first author, publication year, the total number of patients, age, imaging modality, biopsy technique, clip type, and indication for biopsy. The quality of the studies was appraised with the Risk of Bias tool, ROBINS-I, and the Newcastle-Ottawa Scale for randomized control trials, non-randomized controlled trials, and cohort studies, respectively.[7–9]

Missing data

Migration was defined as clip displacement of >10 mm from the lesion. In the study by Teichgraeber et al,[10] the outcome was divided into three groups: ≤5 mm, >5 mm and ≤20 mm, and >20 mm. We divided the number of patients in the second group and added each half to the first and the third group, respectively.

Statistical analysis

Analysis of binary predictors was performed on RevMan using Mantel-Haenszel test and a random effect model. For binary outcomes, risk ratios or proportions are reported, followed by a corresponding 95% CI interval. Single-arm analysis of binary outcomes and logistic regression models were performed in R studio. Heterogeneity within studies was evaluated by Cochrane's Q test and I^2. A *P*-value less than 0.05 was considered statistically significant. For publication bias, Egger's tests were performed and the results were visualized by funnel plots. In addition, the individual study's risk of bias was assessed using Newcastle-Ottawa Scale (NOS) for Cohort and Case-Control Studies, the Cochrane Risk of Bias 2 Tool (RoB2) for randomized control trials, and the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) for non-randomized trials.[7–9]

RESULTS

This study yielded 716 articles from the four above-mentioned databases and one more article from an additional source. After removing 414 duplicated records, title/abstract screening was conducted. 48 articles remained for full-text screening with predetermined criteria for inclusion and exclusion. Due to ineligibility for further analyses, 37 of the remained articles were excluded. The other nine articles (eight retrospective studies and one prospective study) proceeded to qualitative analysis, and among them, seven articles were included in the quantitative synthesis (Figure 1). Overall, the studies were of high quality (Table 1).

Characteristics of the included studies

This meta-analysis included 3,347 clips, breast biopsy clips, placed in patients from eight retrospective studies and one prospective study. According to available data, the mean age of patients was 55.72. All biopsies were performed with a vacuum-assisted device, and most of them were guided by mammography with only one study using magnetic resonance imaging (MRI)-guided technique. Indications for biopsy were mostly calcification (92.03%) followed by mass (3.93%). Detailed characteristics of the included studies were summarized (Table 2). The primary endpoint, the proportion of clip migration of over 10 mm, was 26.8% within the nine studies.

Effect of fatty breast tissue on clip migration

Compared with patients with dense breasts in five studies, patients with fatty breasts were at a significantly higher odds of clip migration ($p < 0.00001$). The pooled RR of clip migration was 2.00 [1.43–2.80], with a zero heterogeneity ($I^2 = 0\%$) (Figure 2). This suggests that BI-RADS type A is a risk factor for clip migration. On the other hand, patients with locally heterogeneous breasts have a moderately insignificant lower risk of clip displacement (RR = 0.68 [0.45–1.04], $p = 0.07$), with a moderate heterogeneity across studies ($I^2 = 56\%$) (Figure 3).

With meta-regression, it was further delineated that combining global fat as a major risk factor, and local heterogeneity as a protective factor, 88.64% of clip migration events can be explained. There was no significant confounding effect resulting from the interaction between global fat and local heterogeneity ($p = 0.9663$).

Effect of clip carriers and directions of biopsy on the rate of clip migration

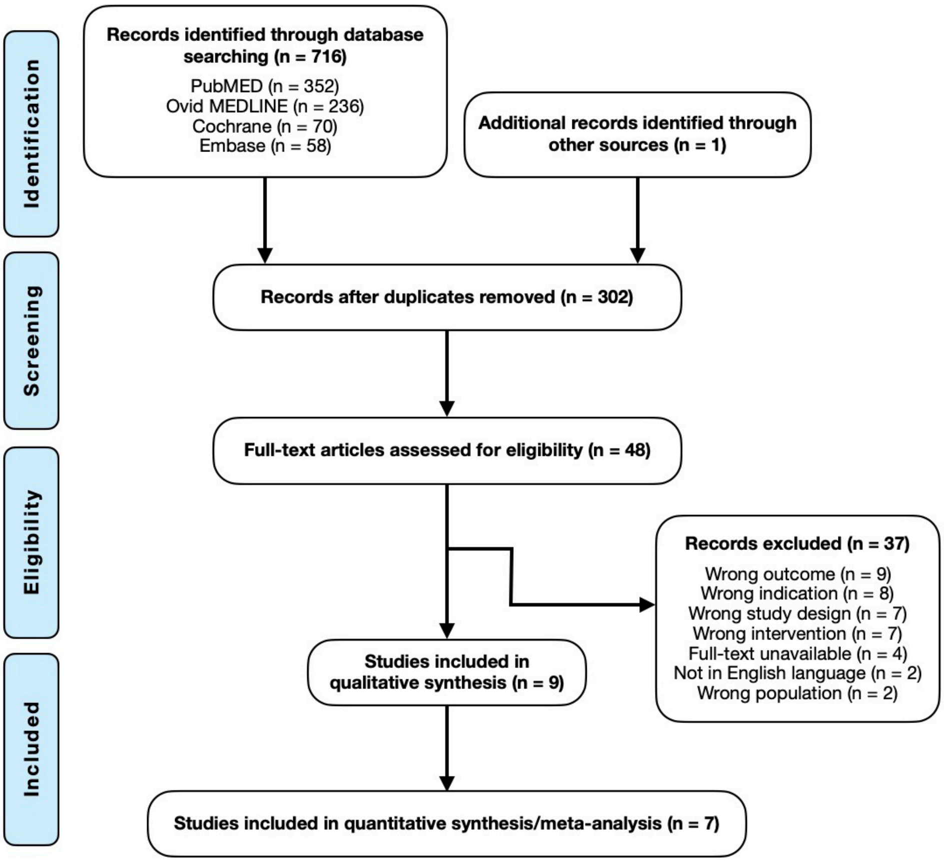
Whether or not carriers were used was not associated with different risks of clip migration. Patients with carriers were similarly favorable to clip placement compared with patients without carriers in three studies, with a pooled RR of 1.21 [0.75–1.93] ($p = 0.44$) and a moderate heterogeneity across studies ($I^2 = 72\%$) (Figure 4).

Likewise, superior/inferior direction of biopsies had similar impact on clip migration, as compared with medial/lateral direction of biopsies (RR = 0.79 [0.59–1.07], $p = 0.13$), with a zero heterogeneity across studies ($I^2 = 0\%$) (Figure 5). Thus, carriers and direction of biopsies had a neutral effect on clip migration.

Risk of bias assessment

For the analysis on global fat, the funnel plot is somewhat symmetric with only one study scattered at the lower left, suggesting a low risk of publication bias (Figure 2a). For the other analysis on breast heterogeneity, the plot appears less symmetric (Figure 2b). On the upper

Figure 1. PRISMA flowchart for study selection.



part, the studies lean toward the midline, while those on the lower part have a lower RR value. This finding could be a result of ascertainment bias in smaller studies. For the last two analyses on clip types and biopsy methods, the funnel plots are concentrated around the midline, which indicates a low risk of publication bias (Figure 2c and d). Nevertheless, it is hard to appreciate their symmetry due to the small number of studies.

DISCUSSIONS

Clip migration is not an uncommon phenomenon on immediate mammography follow-up after its placement. The incidence is about 26.8% (14.1–33.3%) in this current review. Clip displacement can affect the interpretation of follow-up images and localization for future surgery.[2] Reported risk factors include globally fatty breast tissue, inner and superficial location of the lesions, thinner breast, and bare clips; on the contrary, locally heterogeneous density and craniocaudal compression with a vertical biopsy approach is associated with less clip displacement.[10–12]

We found a significantly higher rate of clip migration in homogenously fatty breast (2.00 [1.43–2.80]) and a discernible but non-significantly favorable outcome in patients with local tissue heterogeneity (0.68 [0.45–1.04]). Some intrinsic clip factors likely affect technical success as well. Bare tissue clips were thought to be more suitable for smaller lesions given their smaller size, while clips associated with bioabsorbable carriers are designed to enhance ultrasound visibility, reduce bleeding complication, and prevent migration.[4] In the current review, we found an unremarkably higher migration rate in the bare clip subgroup (0.22 [0.17, 0.27]) compared to coated clips (0.13 [0.06, 0.28]), although there is no significant difference between them (p = 0.44). We were not able to stratify migration risk by lesion size and clip types due to limited information. To evaluate the impact of breast tissue density on clip displacement, we used multiple logistic regression models and find that models including global fat are superior to those without and the full model with both global fat and local heterogeneity has the best performance (p = 0.001). We divided breast density according to BI-RADS Atlas for breast density published in 2013.[6] Type A, B, C, and D describe breasts that are almost entirely fatty, composed of scattered areas of fibroglandular density, heterogeneously dense, or extremely dense, respectively. Using the classification of mostly fatty (BI-RADS A and B) and mostly dense (BI-RADS C and D) breasts, the regression coefficient for mostly fatty breasts is 0.8943 in the full model, which indicates an odds ratio of 2.10 compared to mostly dense breasts. When the four-grade reporting system is used for logistic regression, the odds ratio for a single level increase in global density is 0.83 (p = 0.05341). This is much higher than that reported by Teichgraeber et al[10] (odds ratio = 0.60). The discrepancy could be due to subjective classification of breast density by the reporting radiologists or cofounding effect from local breast density, which was not corrected for in the previous study. Nonetheless, our result was non-significant and included 0.60 in the 95% confidence interval. More studies are needed to determine the effect of global breast density on clip migration.

Wang et al found a higher rate of clip migration for superficial lesions. They hypothesized that the closer the lesion is to the skin, the longer

Table 1. Risk of bias assessment of the included studies

Quality Assessment of Cohort Studies and Case–Control Studies – Newcastle-Ottawa Scale (NOS)

Cohort Studies	Representativess of Exposed Cohort	Selection of the Nonexposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest Was Not Present at Start of Study	Comparability of Cohorts on the Basis of the Design or Analysis	Assessment of Outcome	Was Follow-up Long Enough for Outcomes to Occur?	Adequacy of Follow-up of Cohorts	Total (/8)
Teichgraeber, 2019[10]	*	*	*	*	-	-	*	*	6
Jain, 2017[11]	*	*	*	*	*	-	*	*	7
Funaro, 2019[12]	*	*	*	*	*	-	*	*	7
Wang, 2020[13]	*	*	*	*	*	-	*	*	7
Kass, 2002[16]	*	*	*	*	-	*	*	*	7
Rosen, 2001[17]	*	*	*	*	*	-	*	*	7
Yen, 2018[19]	*	*	*	*	*	-	*	*	7

Quality Assessment of RCT—Cochrane Risk of Bias 2 Tool (RoB)

RCT	Random Sequence Generation (Selection Bias)	Allocation Concealment (Selection Bias)	Blinding of Participants and Personnel (Performance Bias)	Assessment (Detection Bias)	Blinding of Outcome	Incomplete Outcome Data Addressed (Attrition Bias)	Selective Reporting (Reporting Bias)	Overall
Le-Petross, 2017[20]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk

Quality Assessment of Non-RCT—Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I)

Non-RCT	Confounding	Selection	Intervention Classification	Deviation from Intervention	Missing Data	Measurement of Outcome	Selection of Report Result	Overall
Weinfurtner, 2020[18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Table 2. Characteristics of included studies

Study	Total # of patient	Study design	Age	Image guide	Technique	Clip type	Indication for biopsy (#)	Clip migration	
			Mean ± SD (range)					≤10 mm	>10 mm
Teichgraeber, 2019[10]	197	R	58 (30–85)	Mammo	VACB	SecurMark, TriMark	Calcification (161), mass (6), other (33)	148	49
Funaro, 2020[12]	298	R	55 (19–79)	MRI	VACB	Varies	-	256	42
Jain, 2017[11]	268	R	55.1 ± 10.6	Mammo	VACB	Varies	Calcification	233	35
Wang, 2020[13]	176	R	52.2 ± 8 (28-77)	Mammo	VACB	MicroMark II	Calcification	139	37
Kass, 2002[16]	93	R	58 ± 11.4	Mammo	VACB	MicroMark II	-	67	26
Rosen, 2001[17]	111	R	-	Mammo	VACB	MicroMark II	Calcification (79), mass (28), other (4)	93	18
Weinfurtner, 2021[18]	99	R	59 (29–87)	Mammo	VACB	-	Calcification	215	33
Yen, 2018[19]	2043	R	-	Mammo	VACB	Varies	-	1402	641
Le-Petross, 2017[20]	62	P	56 (30–78)	Mammo	VACB	Gel Mark	Calcification (60), mass (2)	46	16

[a]number; Mammo: mammography; R: retrospective; P: prospective; MRI: magnetic r*esonance imaging*; US: ultrasound; VACB: vacuum-assisted core biopsy.

Figure 2. Effect of globally fatty breast tissue on clip migration. BI-RADS type A (global fat) breasts are associated with a higher clip migration risk ($p < 0.0001$).

Study or Subgroup	Fatty Events	Fatty Total	Dense Events	Dense Total	Weight	Risk Ratio M-H, Random, 95% CI
Funaro 2020	6	16	36	262	22.8%	2.73 [1.35, 5.50]
Jain 2017	9	34	26	234	25.2%	2.38 [1.22, 4.64]
Le-Petross 2017	1	1	17	61	14.0%	2.66 [1.09, 6.49]
Teichgraeber 2020	7	14	68	183	36.1%	1.35 [0.77, 2.35]
Wang 2020	0	1	37	175	1.9%	1.17 [0.10, 13.16]
Total (95% CI)		**66**		**915**	**100.0%**	**2.00 [1.43, 2.80]**
Total events	23		184			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 3.55$, df = 4 (P = 0.47); $I^2 = 0\%$
Test for overall effect: Z = 4.07 (P < 0.0001)

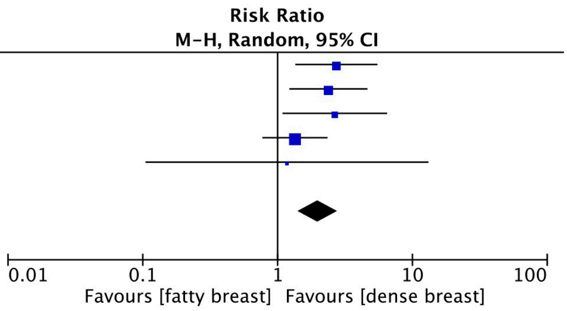


Figure 3. Effect of heterogeneous breast tissue on clip migration. Biopsy site local heterogeneity is associated with an insignificantly lower risk of clip migration ($p = 0.07$).

Study or Subgroup	Heterogenous Events	Heterogenous Total	Homogenous Events	Homogenous Total	Weight	Risk Ratio M-H, Random, 95% CI
Funaro 2020	21	125	21	153	22.6%	1.22 [0.70, 2.14]
Jain 2017	5	80	30	188	13.6%	0.39 [0.16, 0.97]
Le-Petross 2017	6	32	17	30	16.2%	0.33 [0.15, 0.73]
Teichgraeber 2020	35	105	40	92	29.5%	0.77 [0.54, 1.10]
Wang 2020	30	149	7	27	18.0%	0.78 [0.38, 1.58]
Total (95% CI)		**491**		**490**	**100.0%**	**0.68 [0.45, 1.04]**
Total events	97		115			

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 9.15$, df = 4 (P = 0.06); $I^2 = 56\%$
Test for overall effect: Z = 1.79 (P = 0.07)

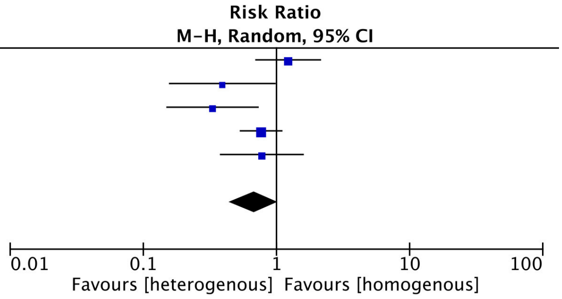
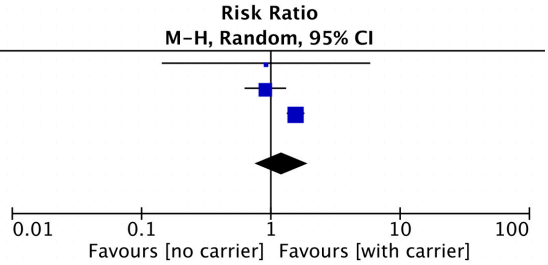


Figure 4. Effect of clip carriers on clip migration. The presence of clip carriers has no effect on clip migration ($p = 0.44$).

Study or Subgroup	No carrier Events	No carrier Total	With carrier Events	With carrier Total	Weight	Risk Ratio M-H, Random, 95% CI
Funaro 2020	1	8	38	279	5.8%	0.92 [0.14, 5.88]
Teichgraeber 2020	49	133	26	64	41.6%	0.91 [0.63, 1.31]
Yen 2018	134	317	344	1265	52.6%	1.55 [1.33, 1.82]
Total (95% CI)		**458**		**1608**	**100.0%**	**1.21 [0.75, 1.93]**
Total events	184		408			

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 7.12$, df = 2 (P = 0.03); $I^2 = 72\%$
Test for overall effect: Z = 0.78 (P = 0.44)



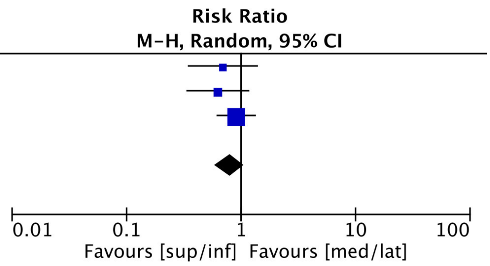
the distance for posterior displacement; and that the center of the sample notch of the biopsy probe is usually placed deeper to the target lesion to ensure sufficient vacuum force, creating a longer biopsy tract for potential clip migration.[13] Based on our finding on global fat, we suspect that subcutaneous fat, which is most abundant in the superficial region, may also contribute. For locally heterogeneous breast density, the risk ratio of clip migration is 0.68 but non-significant ($p = 0.07$). Apart from Jain et al[11] no other studies had found an association between local breast density and clip migration.[10,12]

We also found no significant difference between superior/inferior and medial/lateral biopsy techniques. A recent study published in 2021 discussed the rate of clip migration with the lateral arm technique and found no difference from the conventional technique.[14]

Figure 5. Effect of the biopsy direction on clip migration. Different biopsy directions have similar clip migration rates ($p = 0.13$).

Study or Subgroup	Superior/Inferior Events	Superior/Inferior Total	Medial/Lateral Events	Medial/Lateral Total	Weight	Risk Ratio M-H, Random, 95% CI
Jain 2017	10	98	25	170	18.1%	0.69 [0.35, 1.38]
Rosen 2001	13	61	17	50	22.6%	0.63 [0.34, 1.16]
Teichgraeber 2020	25	70	50	127	59.3%	0.91 [0.62, 1.33]
Total (95% CI)		**229**		**347**	**100.0%**	**0.79 [0.59, 1.07]**
Total events	48		92			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.19$, df = 2 (P = 0.55); $I^2 = 0\%$
Test for overall effect: Z = 1.53 (P = 0.13)



In this current meta-analysis, all reviewed studies used the conventional technique so a comparison cannot be made. The lateral arm technique was initially developed to decrease clip migration since it prevents obscuring of the lesion by the biopsy needle, and decreases the accordion effect when the breast is decompressed.[15] They reported a migration rate of 15% (in 292 patients) and 10% (in 97 patient) for the conventional and lateral arm approach, respectively. If the result were added to our data pool, the risk ratio for clip migration of conventional and lateral arm approach would increase to 2.51 ($p < 0.05$). This pooled result may support the theoretical superiority of the lateral arm technique to the conventional approach, albeit more research is needed to confirm this hypothesis.

There are some limitations to this study. First, the view of follow-up mammography can affect migration detection.[13] Displacement is usually largest on the z-axis, which is the direction of the needle tract, due to the accordion effect. Thus, migration is best evaluated from the plane orthogonal to the direction of compression.[2] However, only a few studies provided information on their follow-up technique. Second, there were variations in clip placement protocols, types of needles and clips used, and physician familiarity with the procedure. Besides, Teichgraeber et al used a different definition of clip migration and an *ad hoc* analysis was performed for the purpose of this study.[10] Third, the small number of studies included in each endpoint may introduce publication bias, which could not be confidently assessed by funnel plots and Egger's tests. Lastly, the retrospective nature of most referenced studies can only suggest association but not definitely causality.

CONCLUSIONS

In this systematic review and meta-analysis, breast biopsy clips show migration from the biopsy location at a frequency of around 26.8%, with the highest rate seen in females with globally fatty breasts. The lateral arm technique demonstrates positive preliminary results. Although some extrinsic factors such as clip types, and biopsy direction showed no definite influence, it is worthwhile to try other designs, materials, and methods as clip migration may complicate further management of breast pathologies.

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COMPETING INTERESTS

The authors have no competing interest to declare

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