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Perioperative inflammatory biomarkers predicting complications in implant-based breast reconstruction: a systematic review

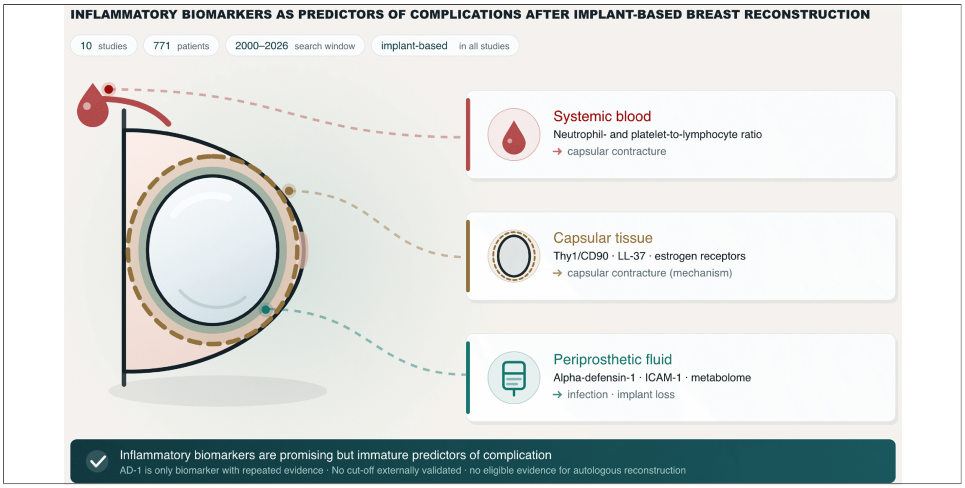
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Abstract

Aim: To review preoperative and perioperative inflammatory biomarkers as predictors of surgical complications after breast reconstruction and assess whether reproducible cut-off values exist.

Methods: PubMed/MEDLINE, Embase (Elsevier) and the Cochrane Library were searched (January 2000-April 2026) following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement. Two reviewers independently screened records using the population, intervention, comparator, and outcome (PICO) framework. Eligible studies quantified at least one systemic, fluid-based, or tissue-based inflammatory biomarker and reported its association with a defined surgical complication. Data were synthesized narratively due to heterogeneity.

Results: Ten studies (771 patients, 377 reported reconstructions, 959 specimens; 2014-2026) met the inclusion criteria, all concerned implant-based reconstruction, and no autologous study was eligible. Biomarkers measured in systemic blood (n = 1), local fluid (n = 6), and capsular tissue (n = 3) addressed breast implant-related infection (BIRI), capsular contracture, and implant loss. Alpha-defensin-1 (AD-1) in pocket fluid was the only

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biomarker replicated across multiple cohorts, achieving sensitivity and specificity 100% and area under the curve (AUC) of 1.00 for BIRI, with a graded relationship to severity. Preoperative neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) independently predicted Baker grade III-IV capsular contracture, particularly after radiotherapy. Drainage-fluid intercellular adhesion molecule-1 (ICAM-1) and untargeted seroma metabolomics allowed pre-clinical detection. Tissue markers converged on myofibroblast-driven and estrogen-modulated mechanisms. All cut-offs remain externally unvalidated.

Conclusion: Inflammatory biomarkers are promising but immature predictors of complications after breast reconstruction. AD-1 is the only biomarker with repeated evidence for BIRI; evidence for autologous reconstruction is absent. Future work should prioritize multi-center validation, harmonized outcome definitions, and biomarker-guided trials.

INTRODUCTION

Breast cancer has the highest incidence and prevalence of all diagnosed malignancies in women worldwide. According to GLOBOCAN 2022, an estimated 2.3 million new cases and 666,000 deaths occurred globally, making breast cancer the leading cause of cancer-related morbidity and the most common cause of cancer-related death in women[1]. The treatment of mammary carcinoma follows a multimodal concept including systemic therapies such as chemotherapy, endocrine therapy, HER2-directed agents, immune checkpoint inhibitors and radiotherapy[2]. Surgical resection remains the main pillar of multimodal treatment: More than 95% of patients with non-metastatic breast cancer undergo breast surgery as part of their oncological care[3]. Approximately 60%-70% of these patients are treated with breast-conserving surgery and 30%-35% with mastectomy[4], the latter performed today as simple (total), modified radical, skin-sparing or nipple-sparing mastectomy[5]. For these patients, breast reconstruction plays a central role not only in restoring breast contour but also in mitigating psychological distress and improving health-related quality of life[6,7].

Breast reconstruction is generally performed as implant-based or autologous. Implant-based reconstruction, using tissue expanders, direct-to-implant, or two-stage approaches, remains the most common modality, accounting for approximately 75%-86% of immediate reconstruction in the United States[8,9]. Autologous breast reconstruction includes free perforator flaps, most prominently the deep inferior epigastric perforator (DIEP) and the profunda artery perforator (PAP) flap, myocutaneous free flaps such as the transverse rectus abdominis myocutaneous (TRAM) and the transverse (upper) myocutaneous gracilis (TUG) flap, as well as the pedicled latissimus dorsi flap. These techniques achieve durable, natural-feeling reconstructions with the patient's own tissue, but they are technically demanding, require microsurgical expertise and entail longer operative times and additional donor-site morbidity[10,11]. Despite these techniques differing fundamentally, both modalities are associated with substantial complication burdens, especially in reconstructive cases.

Across autologous flap-based reconstructions, total flap loss is reported in approximately 1%-3% of cases, depending on the individual flap[12,13]. In a large DIEP series, partial flap loss occurred in 3.2%, hematoma in 3.6%; vascular complications such as venous congestion occurred in 3.4% or microvascular thrombosis in 1.3% of free flaps[14]. Fat necrosis occurs more frequently between 6.9% and 14.4% depending on flap type[15] and venous thromboembolism is reported in 2% of patients[16,17]. Donor-site morbidity varies markedly by flap choice and is particularly relevant for pedicled and free TRAM flaps (abdominal-wall hernia or bulging) as well as latissimus dorsi flaps (seroma, shoulder dysfunction)[18-20].

For implant-based reconstruction, pooled complication rates range between 26.6%-31.3%. In particular, skin necrosis is reported in approximately 10%, surgical-site infection (SSI) in 5%-7%, seroma in 7%, and reconstructive failure in 5% of cases; infection rates after prosthetic reconstruction reach 14% in some

series[21]. Capsular contracture is the most common complication of implant-based reconstruction. Reported rates of clinically relevant (Baker grade III-IV) contracture vary substantially with follow-up duration, implant characteristics, and adjuvant therapy, ranging from approximately 5%-15% in non-irradiated reconstructions to 20%-25% at two-year follow-up post-mastectomy[22,23]. Recently, biofilm-driven chronic inflammation has been considered a key driver of the underlying fibrotic process[24].

Despite refinements in surgical technique, perioperative protocols, and antibiotic prophylaxis, complication rates have not meaningfully declined and have even risen in recent large-cohort analyses[8]. Established clinical risk factors such as obesity, smoking, diabetes mellitus, prior radiotherapy, and prolonged operative time explain only a fraction of the variance in postoperative outcomes[25]. There is therefore a clear clinical need for objective, easily obtainable parameters that can identify patients at increased risk of complications before, during, or shortly after surgery.

Inflammatory biomarkers have emerged as promising candidates in this context. Surgical trauma triggers a stereotyped acute-phase response, and dysregulation of this response has been linked to postoperative morbidity across multiple surgical disciplines. Systemic markers such as C-reactive protein (CRP), the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and interleukin-6 (IL-6) are inexpensive, widely available, and have been associated with postoperative complications after abdominal and colorectal surgery[26-28], with postoperative infectious complications across surgical specialties[29] and with periprosthetic infection after joint arthroplasty[30].

Although individual studies in breast reconstruction have begun to evaluate systemic, local, or tissue-based inflammatory markers in relation to surgical complications, the available evidence has not yet been systematically synthesized[31-40]. Marker types, measurement matrices, timing, outcome definitions, and statistical approaches differ considerably between studies, and externally validated cut-off values for clinical decision-making in breast reconstruction are largely lacking.

The aim of this systematic review is therefore to summarize the current evidence on preoperative and perioperative inflammatory biomarkers as predictors of surgical complications after breast reconstruction. Specifically, we evaluate which biomarkers have been studied, in which reconstructive setting and patient population, against which complication outcomes, and whether reproducible cut-off values have been reported that could inform future risk-stratification strategies in plastic and reconstructive breast surgery.

METHODS

Reporting guideline

This systematic review was planned and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement (PRISMA 2020)[41]. A prospective registration was not performed. The methods were specified a priori and were not modified after the search was conducted.

Review question

The objective of this systematic review was to evaluate whether preoperative or perioperative inflammatory biomarkers are associated with surgical complications after breast reconstruction and whether validated biomarker cut-off values have been reported.

Information sources and search strategy

The electronic databases PubMed/MEDLINE, Embase (Elsevier) and Cochrane Library were searched for studies published from January 2000 to April 2026. The final search date was 13 April 2026.

Table 1. Identified records of each database per reviewer

Database	NL	LL
PubMed	834	789
Embase	430	517
Cochrane	30	117

NL: Nicolas Lehmenkötter; LL: Lara Lingens.

Two independent expert reviewers (NL, LL) created two search strategies with individual search terms for maximum coverage of possible eligible articles and heterogeneity in screening.

The search strategy combined terms for breast reconstruction, reconstructive modality, inflammatory biomarkers, and postoperative complications using the population, intervention, comparator, and outcome (PICO) framework. The complete database-specific search strings are reported in Supplementary Material M1. The identified number of articles per reviewer and Database is shown in Table 1.

Eligibility criteria

Eligibility was assessed according to the PICO framework. The population comprised adult women (≥ 18 years) undergoing breast reconstruction after mastectomy, including implant-based, tissue-expander, and autologous techniques (DIEP, TUG, PAP, TRAM, or latissimus dorsi flaps). Concurrent adjuvant chemotherapy or radiotherapy did not preclude inclusion. Eligible index biomarkers were grouped into fluid-based markers measured in serum, plasma, whole blood, or wound and drain fluid [e.g., CRP, NLR, PLR, albumin, prealbumin, IL-6, tumor necrosis factor-α (TNF-α), alpha-defensin-1 (AD-1), intercellular adhesion molecule-1 (ICAM-1)] and tissue-based markers (matrix metalloproteinase-2/-9 (MMP-2, MMP-9), transforming growth factor-β (TGF-β), tissue inhibitor of metalloproteinases (TIMP), Thy-1 cell-surface antigen (Thy1/CD90), cathelicidin antimicrobial peptide (LL-37), granzyme B), as well as related inflammatory or fibrotic mediators. Additional biomarkers outside this catalog were considered when otherwise eligible. The comparator was typically patients without the postoperative complication of interest, or patients with values outside the reported biomarker cut-offs, with the precise reference group dictated by the individual study design. Eligible outcomes were surgical complications following breast reconstruction, including Baker grade III/IV capsular contracture, SSI or breast implant-related infection (BIRI), implant loss or explantation, seroma, hematoma, wound dehiscence, flap necrosis or loss, donor-site complications, reoperation, and anastomotic failure.

Beyond these PICO criteria, included studies had to be original research published in English or German between 2000 and 2026, quantify at least one of the biomarker categories above, and report a statistical association between that biomarker and a clearly defined surgical complication. Records were excluded at title/abstract screening when they did not meet these criteria on the face of the title or abstract. At full-text screening, records were excluded using pre-defined exclusion criteria [Table 2].

Study selection

Each reviewer excluded duplicates between the databases beforehand using the Evidence Review Accelerator Online Tool. The records were imported into the online review software Rayyan and duplicates were removed once more. Screening was performed by the two independent reviewers. Title- and abstract- as well as full-text-screening were performed independently and blinded. Reasons for full-text exclusion were documented according to predefined exclusion categories. Disagreements were resolved by discussion. The study selection process is presented in Figure 1[41,42].

Table 2. Exclusion criteria with number of excluded articles in full-text screening per criterion

Code	Exclusion criterion	Rationale/Example	No.
E1	No inflammatory biomarker measured or reported	Study does not assess any inflammatory marker at any perioperative time point	12
E2	No breast reconstruction	e.g. mastectomy without reconstruction, breast-conserving surgery, lymphoedema management, axillary surgery, head-and-neck reconstruction	27
E3	Exclusively oncological outcomes; no perioperative complication endpoint	Overall survival, disease-free survival, tumor recurrence, or chemotherapy response reported without any surgical complication outcome	2
E4	Ineligible study design	Animal study; purely *in vitro* study without human validation; editorial, letter, or commentary; conference abstract without full text; case report or case series with $n < 10$	12
E5	Ineligible population	No breast cancer context; patients < 18 years; no prior mastectomy as primary indication (e.g. cosmetic augmentation only)	18
E6	Biomarker not quantified or not statistically analyzed	Biomarker mentioned but not measured; no statistically reported association between biomarker and surgical complication	2
E7	Outcome not clearly defined	No recognized classification system used (e.g. Baker grading for capsular contracture, CDC criteria for SSI, Clavien-Dindo for complications); patient-reported outcomes only	5
E8	Publication criteria not met	Not published in English or German; published before January 2000; full text not obtainable	0
E9	Duplicate cohort	Same patient population reported in multiple publications; most recent or most complete report retained	0

CDC: Centers for Disease Control and Prevention; SSI: surgical-site infection.

Data extraction

Data were extracted using a standardized extraction sheet, which was designed a priori. Extraction was performed by a single reviewer (NL) and verification was performed by the other (LL). Disagreements were resolved by discussion until consensus could be obtained. Extracted variables included first author, year of publication, country, study design, sample size, patient population, reconstruction type, biomarker type, timing and method of biomarker measurement, comparator group, outcome definition, complication type, effect measure, confidence interval (CI) or *P*-value, reported cut-off values, adjustment for confounders, follow-up duration, and study-level limitations.

Risk of bias assessment

Risk of bias had to be assessed using multiple tools because of the heterogeneous study types. The Newcastle Ottawa Scale (NOS) was used for all cohort studies. We used NOS as the closest available tool to rate the studies on the same scale. The NOS assessment was only conducted on the histological part. The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) Tool was used for all diagnostic accuracy studies. For the translational study, a narrative assessment was performed. Risk of bias was assessed blinded by two reviewers (NL, LL). Discrepancies were resolved by discussion. Traffic light and summary plots were created using the risk-of-bias visualization (robvis) tool[43].

Effect measures

Because of the expected heterogeneity and only narrative synthesis of results, various effect measures were considered. For binary complication outcomes (e.g., capsular contracture Baker III/IV, SSI/BIRI, implant loss, flap loss, reoperation), odds ratios (ORs), risk ratios, or hazard ratios with 95%CIs were extracted. Where studies compared continuous biomarker concentrations between patients with and without the outcome, mean differences or standardized mean differences with 95%CIs were extracted instead. For studies evaluating biomarker performance as a diagnostic test, sensitivity, specificity, positive and negative predictive values, area under the receiver operating characteristic (ROC) curve (AUC/ROC), and the corresponding cut-off values were recorded.

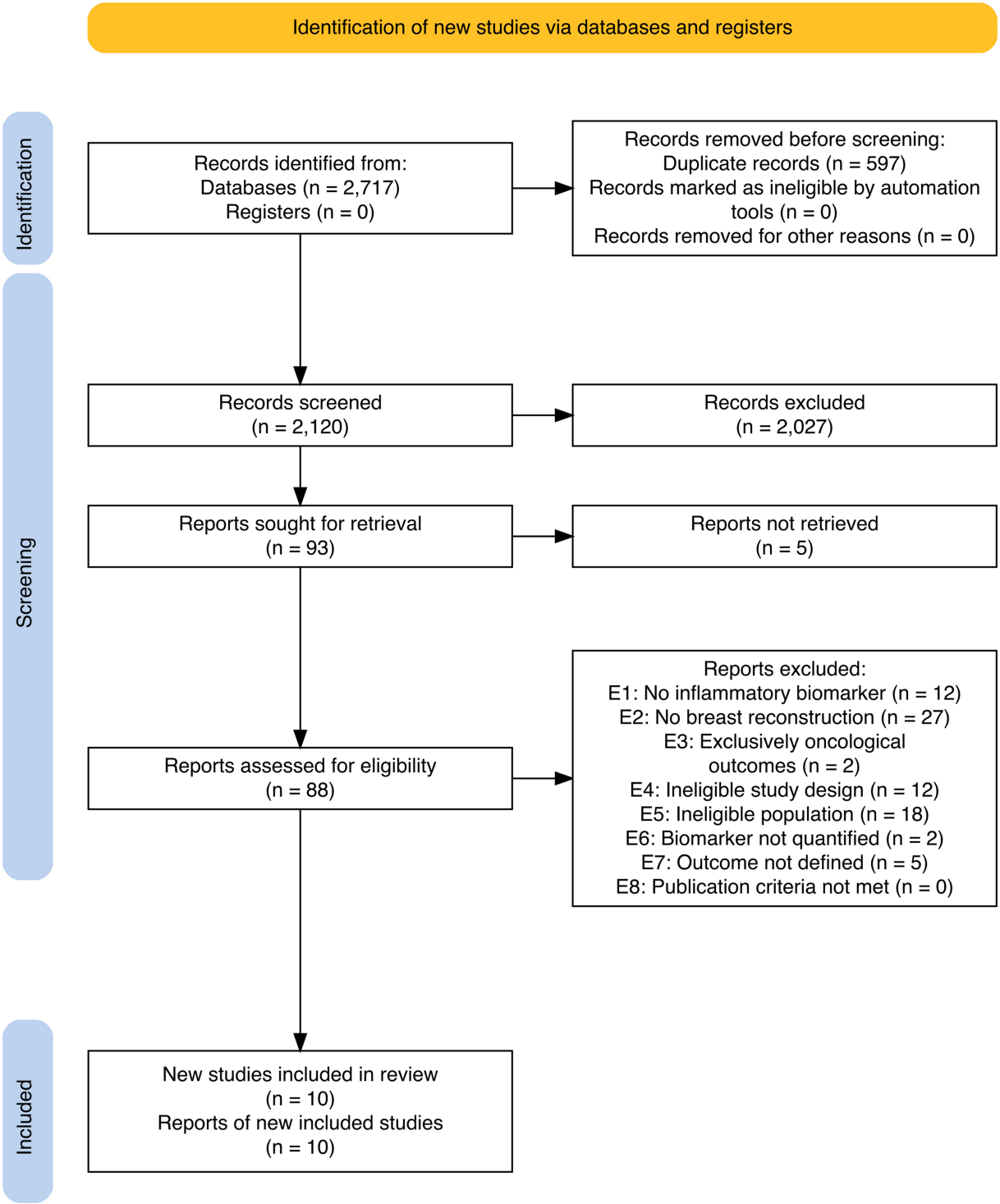


Figure 1. PRISMA 2020 diagram of the study selection process[41], generated with the PRISMA2020 R package[42]. Two independent search strategies retrieved 2,717 records from PubMed/Medline, Embase and the Cochrane Library. 597 duplicates were removed before screening. 2120 record were screened by title and abstract by two independent reviewers, 2027 were excluded. Of 93 reports sought for retrieval, 5 could not be retrieved. 88 full texts were assesses and 78 were excluded for the reasons listed (E1-E8). 10 studies were included in the qualitative synthesis. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Data synthesis

Because the included studies differed substantially in reconstruction type, biomarker source, biomarker timing, outcome definition, statistical approach, and reported effect measures, findings were synthesized narratively. Studies were grouped by reconstruction type, biomarker category, and complication type.

Due to substantial heterogeneity in biomarker type, measurement timing, outcome definitions, and reported effect measures, meta-analysis was not performed.

Reporting bias assessment

Across-study publication bias was discussed narratively, since no meta-analysis was performed. Funnel-plot methods were therefore not applicable.

Evaluation of strength of evidence

Because the included studies were exclusively small, predominantly single-center observational studies that differed substantially in biomarker choice, measurement matrix, sampling timepoint, and complication definition, no quantitative synthesis was possible and a formal rating such as the Grading of Recommendations, Assessment, Development and Evaluations (GRADE)[44] system per outcome was not undertaken. The certainty of evidence for any individual biomarker-complication association is therefore expected to be low to very low across the body of evidence. For each biomarker category, the strength and consistency of the available evidence are discussed narratively with reference to study design, sample size, risk of bias, and reproducibility of reported cut-off values.

RESULTS

Study selection

The study selection process is summarized in the PRISMA 2020 flow diagram [Figure 1].

The two independent search strategies retrieved 1,423 records (reviewer LL) and 1,294 records (reviewer NL) from PubMed/MEDLINE, Embase (Elsevier) and the Cochrane Library [Table 1]. Using the Evidence Review Accelerator Online Tool, reviewer NL excluded 287 duplicates and reviewer LL 159. After import into Rayyan, 151 duplicates were removed, leaving 2,120 unique records for title and abstract screening against the predefined PICO-based eligibility criteria. Ninety-Three records were judged potentially eligible and forwarded to full-text assessment. Eighty-eight full texts could be retrieved. After full-text review, 78 reports were excluded using the criteria illustrated in Table 2.

Ten studies, published between 2014 and 2026 and reporting on a total of 771 patients, 377 reported reconstructions and 959 specimens, met all eligibility criteria and were included in the qualitative synthesis[31-40]. The interrater reliability between the two reviewers was substantial, with a Cohen's kappa of $\kappa = 0.785$ and an observed agreement of 94.6%. No additional records were identified through citation searching of included studies. A list of full-text reports excluded at the eligibility step, together with reasons, is provided in Supplementary Table 1.

Characteristics of included studies

The ten included studies were heterogeneous with respect to design, biomarker source and complication of interest [Table 3]. Reconstruction modality was implant-based in all ten studies, with mixed expander/direct-to-implant cohorts and one study restricted to nipple-sparing mastectomy with direct-to-implant reconstruction (Kang *et al.*, 2026)[31]. No studies examining perioperative risks of autologous breast reconstruction were eligible for inclusion. Three studies were prospective: two diagnostic-accuracy studies (Basta *et al.*, 2019, $n = 13$ patients/15 reconstructions; Basta *et al.*, 2023, $n = 35/53$)[32,33] and one longitudinal cohort study with untargeted metabolomics (Wildenthal *et al.*, 2026, $n = 70$ patients/82 reconstructions)[37]. One was a cohort study (Segreto *et al.*, 2024, $n = 28$ patients/29 reconstructions and specimens) and one was a cross-sectional histological study (Persichetti *et al.*, 2014, $n = 70$ patients/80 capsules, complemented by a retrospective clinical analysis of 233 cases)[39,40]. Four were retrospective: three cohort studies (Sobti *et al.*, 2024, $n = 29$ patients/38 reconstructions and specimens; He *et al.*, 2026, $n = 106$ patients with 106 drainage

Table 3. Characteristics of the 10 studies included in the qualitative synthesis, grouped by biomarker compartment

Ref.	Design, country	Patients (*n*)	Recon-structions (*n*)	Specimens analyzed (*n*, type)	Reconstruction	Index biomarkers	Primary outcome
Systemic blood-based biomarkers							
Kang *et al.*, 2026[31]	Retrospective cohort, South Korea	376	nr	376 peripheral blood samples	NSM + immediate DTI	Pre-op NLR, PLR	Capsular contracture (Baker III-IV)
Fluid-based biomarkers (periprosthetic and drainage fluid)							
Basta *et al.*, 2019[33]	Prospective single-center pilot, diagnostic; USA	13	15	15 periprosthetic fluid	Implant or expander reconstruction	AD-1 (qualitative)	BIRI
Basta *et al.*, 2023[32]	Prospective multicenter case-control, diagnostic; USA	35	53	53 implant-pocket fluid	Implant or expander reconstruction	AD-1 (qualitative)	BIRI
Sobti *et al.*, 2024[34]	Retrospective cohort; USA	29	38	38 periprosthetic fluid	Mostly prepectoral expander/DTI with ADM	AD-1 (quantitative)	BIRI severity, explantation
Stewart *et al.*, 2020[35]	Retrospective single-center, diagnostic; USA	44	54	54 periprosthetic fluid	Mostly expander, ADM 85%	Cell count, PMN	BIRI; secondary capsular contracture
He *et al.*, 2026[36]	Retrospective cohort; China	106	nr	106 drainage fluid	DTI, mostly prepectoral	ICAM-1 (≥ 15.0 IU/mL)	Implant loss
Wildenthal *et al.*, 2026[37]	Prospective longitudinal, untargeted metabolomics; USA	70	82	82 seroma + 100 longitudinal drainage	Tissue-expander reconstruction	Untargeted LC-MS metabolome (16 robust features)	BIRI (CDC criteria), pre-clinical detection
Tissue-based biomarkers (capsular tissue)							
Hansen *et al.*, 2017[38]	Cross-sectional translational (tissue + cell culture); USA	nr	26	26 capsule specimens	Implant-based revision surgery	Thy1/CD90 (with αSMA, collagen I)	Radiation-induced capsular contracture
Segreto *et al.*, 2024[39]	observational (IHC); Italy	28	29	29 capsule specimens	Two-stage post-mastectomy reconstruction (textured)	LL-37; CD68, αSMA, collagen I/III, CD31	Capsular contracture
Persichetti *et al.*, 2014[40]	IHC + retrospective clinical analysis; Italy	70	80	80 capsule specimens	Post-mastectomy submuscular textured implants	ER-α, ER-β; αSMA	Capsular contracture; effect of anti-estrogen therapy
Total	**10 studies**	**771 patients**	**377 reconstructions**	**959 specimens**			

Patients, reconstructions and biological specimens are reported as separate units and are not interchangeable; column totals are therefore not additive across columns. The patient total refers to the nine studies reporting a patient-level denominator; Hansen *et al*. analyzed 26 capsule specimens without reporting the number of contributing patients[38]. AD-1: Alpha-defensin-1; ADM: acellular dermal matrix; BIRI: breast implant-related infection; CDC: Centers for Disease Control and Prevention; CD31: cluster of differentiation 31; CD68: cluster of differentiation 68; DTI: direct-to-implant; ER-α/ER-β: estrogen receptors alpha/beta; ICAM-1: intercellular adhesion molecule-1; IHC: immunohistochemistry; LC-MS: liquid chromatography-mass spectrometry; LL-37: cathelicidin antimicrobial peptide; NLR: neutrophil-to-lymphocyte ratio; nr: not reported; NSM: nipple-sparing mastectomy; PLR: platelet-to-lymphocyte ratio; PMN: polymorphonuclear neutrophils; Pre-op: preoperative; αSMA: alpha-smooth muscle actin; Thy1/CD90: Thy-1 cell-surface antigen (cluster of differentiation 90); USA: United States of America.

samples; Kang *et al.*, 2026, $n = 376$ patients and samples) and one diagnostic-accuracy study (Stewart *et al.*, 2020, $n = 44$ patients/54 reconstructions and specimens)[31,34-36]. One study had a translational cross-sectional design on capsular tissue from revision surgery (Hansen *et al.*, 2017, $n = 26$ capsules)[38]. Studies were conducted in the United States ($n = 6$), Italy ($n = 2$), China and South Korea ($n = 1$ each). Mean or median patient age, where reported, ranged from 45.9 to 59.8 years.

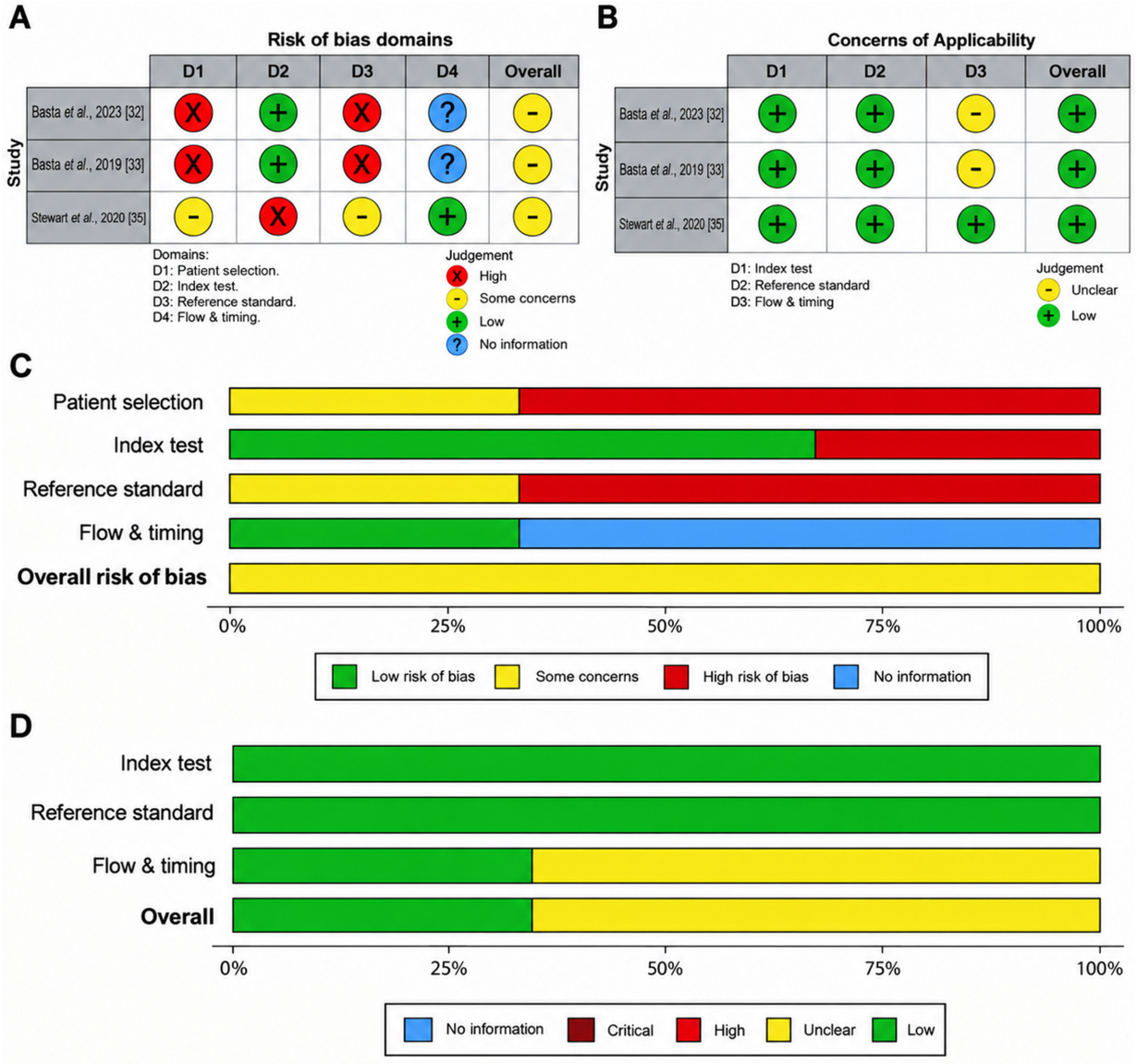


Figure 2. Traffic light (A and B) and summary plots (C and D) of QUADAS-2 assessment of risk-of-bias domains (A and C) and concerns of applicability (B and D). Figure created using the robvis tool[43]. QUADAS-2: Quality Assessment of Diagnostic Accuracy Studies-2; D1: patient selection; D2: index test; D3: reference standard; D4: flow and timing.

Across the 10 studies, the index biomarkers fell into three pre-specified categories: systemic blood-based markers (one study), local fluid-based markers from periprosthetic drainage or seroma fluid (six studies), and tissue-based markers measured in explanted capsules (three studies). The primary postoperative outcomes were periprosthetic BIRI (5 studies), capsular contracture (3 studies), and implant loss/explantation (two studies, with overlap to the infection-focused work). Detailed study-level characteristics are presented in Table 3.

Risk of bias within studies

Methodological quality varied across study designs and was assessed using different tools because of varying study types. The three diagnostic-accuracy studies were assessed with QUADAS-2 [Figure 2][43]. Risk of bias was judged high to medium in all studies. Applicability concerns were low to medium. Detailed assessment can be found in Supplementary Table 2.

Table 4. Methodological quality of included Cohort/histological (Newcastle-Ottawa Scale)

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total (max 9)	Quality
Segreto *et al.*, 2024[39]	4/4	1/2	2/3	7	good
Sobti *et al.*, 2024[34]	4/4	1/2	3/3	8	good
Wildenthal *et al.*, 2026[37]	4/4	1/2	2/3	7	good
He *et al.*, 2026[36]	3/4	1/2	2/3	6	fair
Kang *et al.*, 2026[31]	4/4	2/2	2/3	8	good
Persichetti *et al.*, 2014[40]	4/4	1/2	2/3	7	good

Assessment of quality based on eight items in three domains: Selection 0-4, Comparability 0-2, Outcome 0-3; Categorization using Agency for Healthcare Research and Quality indicators: ≥ 7: good; 4-6: fair; ≤ 3: poor.

The six studies were assessed with NOS [Table 4]. Five were rated as good quality and one as fair quality. Detailed reporting and comments on NOS assessment can be found in Supplementary Table 3.

The translational study (Hansen *et al.*, 2017)[38] was not applicable to a risk-of-bias tool and was evaluated narratively. It employed standardized molecular techniques but was limited by small, heterogeneous samples, absence of clinical outcome follow-up, and lack of multivariable adjustment for relevant covariates. Its findings should therefore be regarded as hypothesis-generating rather than directly applicable to clinical usage.

Results of individual studies

Because of substantial clinical and methodological heterogeneity in biomarker compartment, assay, sampling time point, outcome definition and reported effect measure, a quantitative meta-analysis was not appropriate. Results are therefore presented narratively, grouped by biomarker compartment (systemic blood-based, local fluid-based and tissue-based) and, within each group, by the postoperative complication of interest [Table 5].

Systemic blood-based biomarkers

Only one study evaluated routinely available systemic inflammatory indices. Kang *et al.* retrospectively analyzed 376 women who underwent nipple-sparing mastectomy with immediate direct-to-implant reconstruction at a single Korean center and tested the preoperative NLR and PLR as predictors of Baker grade III-IV capsular contracture during a mean follow-up of 38.6 months[31]. 43 patients (11.4%) developed Baker III-IV contracture.

Cut-offs identified by ROC analysis were NLR ≥ 1.835 and PLR ≥ 175.318. Both were significantly more frequent in the contracture group (NLR elevated 81.4% *vs.* 58.8%, $P = 0.004$; PLR elevated 51.2% *vs.* 29.7%, $P = 0.005$). On multivariable logistic regression, simultaneous elevation of NLR and PLR remained an independent predictor of contracture (OR: 5.29, 95%CI: 1.98-14.09; $P = 0.001$), alongside postmastectomy radiotherapy (OR: 11.20, 95%CI: 5.03-24.96; $P < 0.001$). Subgroup analysis suggested an effect that was confined to irradiated breasts (OR: 7.33, 95%CI: 2.09-25.78; $P = 0.002$), with no significant association in the non-irradiated stratum ($P = 0.144$)[31].

Local fluid-based biomarkers (periprosthetic, drainage and seroma fluid)

Six studies measured biomarkers directly in periprosthetic, drainage or seroma fluid. They can be grouped according to the analytes examined: antimicrobial peptides (e.g. AD-1), inflammatory cell differentials, the endothelial adhesion molecule ICAM-1 and untargeted small-molecule metabolomics.

Table 5. Biomarker-outcome associations and reported effect estimates from the 10 included studies, grouped by biomarker compartment and outcome

Biomarker group	Biomarker (study)	Outcome	Cutoff/Threshold	Effect estimate (95%CI; *P*)	Adjusted analysis
Systemic blood	NLR + PLR (Kang *et al.*, 2026)[31]	Capsular contracture, Baker III-IV	NLR ≥ 1.835 and PLR ≥ 175.318 (ROC, in cohort)	OR 5.29 (1.98-14.09); *P* = 0.001 for both elevated. RT subgroup: OR 7.33 (2.09-25.78); *P* = 0.002	Multivariable logistic regression
Periprosthetic fluid	AD-1 qualitative (Basta *et al.*, 2019)[33]	BIRI	Manufacturer cut-off (Synovasure)	Sens/Spec 100%; AUC 1.00 *vs.* Gram 0.55 (*P* < 0.001), culture 0.75 (*P* = 0.06)	No multivariable analysis
Periprosthetic fluid	AD-1 qualitative (Basta *et al.*, 2023)[32]	BIRI	Manufacturer cut-off (Synovasure)	Sens/Spec 100%; AUC 1.00 *vs.* culture 0.90 (*P* = 0.029), Gram 0.63 (*P* < 0.001)	Multivariable logistic regression for univariate-significant variables
Periprosthetic fluid	AD-1 quantitative (Sobti *et al.*, 2024)[34]	BIRI severity, explantation	No fixed cut-off; per-unit increase	Per unit: erythema OR 2.98 (1.53-5.82); explantation OR 2.48 (1.47-4.20). Median 3.97 *vs.* 0.12; *P* < 0.01	Ordinal logistic regression
Periprosthetic fluid	PMN and total cell count (Stewart *et al.*, 2020)[35]	BIRI; secondary capsular contracture	PMN ≥ 77%; cell count ≥ 1,777/μL (ROC, in-cohort)	PMN AUC 0.95 (89% sens/93% spec); capsular contracture in non-operative subgroup 100% *vs.* 11% (*P* = 0.006)	No multivariable analysis
Drainage fluid	ICAM-1 (He *et al.*, 2026)[36]	Implant loss	≥ 15.0 IU/mL at drain removal (ROC, in-cohort)	8/9 elevated → implant loss; *P* < 0.01	Multivariable analysis (forest plot); only ICAM-1 significant
Seroma & drainage fluid	Untargeted LC-MS metabolome (Wildenthal *et al.*, 2026)[37]	BIRI	No diagnostic threshold (feature selection by volcano plot and DCV score)	16 features robustly elevated; AUC 0.82-0.93 per analyte; subset elevated in drainage fluid before clinical diagnosis (*P* < 0.05)	Compositional multivariable analysis (SelEnergyPerm)
Capsular tissue	Thy1/CD90 (Hansen *et al.*, 2017)[38]	Radiation-induced capsular contracture	None	mRNA: irradiated *vs.* non-irradiated 3.7-fold; protein 2.8-fold (*P* < 0.05)	No multivariable analysis
Capsular tissue	LL-37 (Segreto *et al.*, 2024)[39]	Capsular contracture	None	Macrophage LL-37 ↔ Baker score: *P* = 0.04 (negative correlation); 100% positivity in infected capsules	No multivariable analysis
Capsular tissue	ER-α/ER-β (Persichetti *et al.*, 2014)[40]	Capsular contracture (Baker); anti-estrogen therapy effect	None	αSMA-ER-α *P* = 0.022; αSMA-ER-β *P* = 0.004. Baker III-IV with anti-estrogen: histo cohort *P* = 0.036; 233-case retrospective cohort *P* < 0.0001	Spearman/Fisher; no multivariable analysis

AD-1: Alpha-defensin-1; AUC: area under the curve; BIRI: breast implant-related infection; CI: confidence interval; DCV: differential compositional variation; ER-α/ER-β: estrogen receptors alpha/beta; FDR-adj: false discovery rate-adjusted; ICAM-1: intercellular adhesion molecule-1; LC-MS: liquid chromatography-mass spectrometry; LL-37: cathelicidin antimicrobial peptide; mRNA: messenger RNA; NLR: neutrophil-to-lymphocyte ratio; OR: odds ratio; PLR: platelet-to-lymphocyte ratio; PMN: polymorphonuclear neutrophils (percentage of the fluid cell differential); ROC: receiver operating characteristic; RT: radiotherapy; Sens/Spec: sensitivity/specificity; Thy1/CD90: Thy-1 cell-surface antigen (cluster of differentiation 90); αSMA: alpha-smooth muscle actin.

AD-1

Two diagnostic-accuracy studies - a single-center pilot (Basta *et al.*, 2019, *n* = 13/15 breasts), and a following multicenter prospective case-control study (Basta *et al.*, 2023, *n* = 35/53) and a retrospective cohort with quantitative AD-1 (Sobti *et al.*, 2024, *n* = 29/38) addressed AD-1 in implant pocket fluid for the diagnosis of BIRI. In the pilot, the qualitative Synovasure® AD-1 assay correctly classified all 15 samples (sensitivity and

specificity 100%; AUC 1.00) and outperformed Gram stain (AUC 0.55, $P < 0.001$) while being numerically superior to culture (AUC 0.75, $P = 0.06$)[33]. In the replication study conducted by the same investigator group at Brown University and Vanderbilt University (37.7% BIRI prevalence), AD-1 again achieved sensitivity and specificity of 100% (AUC 1.00) and was significantly more accurate than culture (AUC 0.90, $P = 0.029$) and Gram stain (AUC 0.63, $P < 0.001$)[32]. The 2023 study is therefore more of a replication than an external validation. The 100% sens/spec and AUC 1.00 are observed in small cohorts. Sobti *et al.* moved beyond the binary readout and used a quantitative AD-1 signal, demonstrating that median AD-1 was 33-fold higher in infected *vs.* non-infected pockets (3.97 *vs.* 0.12, $P < 0.01$) and that, for every one-unit increase in AD-1, the odds of erythema, purulence, threatened or actual implant exposure, fever and explantation increased 1.8- to 3.0-fold (OR: 2.48, 95%CI: 1.47-4.20)[34]. Adjunctive serum markers measured in the pocket fluid (CRP, lactate, neutrophil-to-mononuclear ratio) were significantly elevated in BIRI cases in both qualitative studies (Basta *et al.*, 2019; Basta *et al.*, 2023) but did not match the diagnostic discrimination of pocket-fluid AD-1[32,33]. In the quantitative study (Sobti *et al.*, 2024), serum white blood cell count and lactate correlated with AD-1 levels[34]. AD-1 was therefore consistently identified as the most accurate single fluid-based diagnostic biomarker for BIRI across the three studies, with a graded association between concentration and infection severity. Confidence is tempered by small sample sizes, single- or two-center cohorts and near-universal preoperative antibiotic exposure.

Nucleated cell count and polymorphonuclear neutrophil (PMN) percentage

Stewart *et al.* retrospectively analyzed 54 periprosthetic fluid aspirates from 44 patients (50% with BIRI). Compared with non-infected samples, infected pockets had markedly higher total nucleated cell counts (25,141/μL *vs.* 1,468/μL, $P < 0.0001$) and a higher PMN percentage (84.2% *vs.* 19.3%, $P < 0.0001$). On ROC analysis, a PMN threshold of ≥ 77% gave a sensitivity of 89%, a specificity of 93% and an AUC of 0.95, while a total cell count of ≥ 1,777/μL achieved 81% sensitivity and 78% specificity. Patients with PMN above the threshold proceeded to operative management within 90 days in 96% of cases *vs.* 15% in those below it ($P < 0.0001$). In the subset managed non-operatively, PMN% > 77% was also associated with a markedly higher rate of subsequent capsular contracture (100% *vs.* 11%, $P = 0.006$), suggesting prognostic in addition to diagnostic value, although the absolute number of events was small[35].

ICAM-1

He *et al.* reported a two-stage Chinese cohort study. Firstly, a screening using a quantitative cytokine microarray of more than 400 analytes was performed on six patients. In a second step, ICAM-1 was measured at the time of drain removal in 106 patients undergoing immediate implant-based reconstruction. ICAM-1 was selected as the lead candidate based on a primary screening step followed by a validation in a second step. In the validation, an ICAM-1 concentration ≥ 15.0 IU/mL was strongly associated with implant loss. Among the 68 patients without intervention, eight experienced implant loss; nine had elevated ICAM-1 at drain removal, eight of whom subsequently lost the implant. Multivariable analysis showed ICAM-1 to be the only significant predictor ($P < 0.01$). In an exploratory interventional sub-study ($n = 38$), an intracavitary dexamethasone lavage at the time of drain removal lowered ICAM-1 levels and was associated with the absence of implant loss in all 38 treated patients ($P < 0.01$)[36]. The findings are substantial but rest on a small number of events from two centers and require external validation.

Untargeted small-molecule metabolomics

Wildenthal *et al.* performed untargeted small-molecule metabolomics on seroma fluid obtained at prosthesis removal in 70 patients [82 breasts; 43.9% infected according to criteria by the Centers for Disease Control and Prevention (CDC)] and on 100 longitudinal drainage samples from 44 breasts of 32 patients. Sixteen small-molecule features (including N1-acetylspermine and N1,N12-diacetylspermidine, defensins, glucosylsphingosine and bacterial exometabolites) were robustly elevated in infection (≥ 4-fold change, false

discovery rate-adjusted $P < 0.01$); individual analytes achieved diagnostic AUCs of 0.82-0.93. Critically, a subset of these metabolites was already significantly elevated in postoperative drainage fluid before clinical infection was diagnosed, and Pseudomonas aeruginosa-specific exometabolites preceded the corresponding culture-confirmed P. aeruginosa infection[37]. These data provide proof-of-concept that an untargeted metabolomic fingerprint could enable pre-clinical detection of BIRI, but the approach has not yet been translated into a deployable assay or a validated decision threshold.

Tissue-based biomarkers (capsular tissue)

Three studies analyzed biomarker expression in capsular tissue obtained at expander-implant exchange or revision surgery. All three addressed capsular contracture, either as a primary clinical outcome or as a histopathological correlate.

Myofibroblast and stromal markers [Thy1/CD90, alpha-smooth muscle actin (αSMA), collagen I/III]

Hansen *et al.* compared nine irradiated and 17 non-irradiated human implant capsules at the level of mRNA, protein and immunohistochemistry. Thy1/CD90 mRNA expression was 5.3-fold higher than in normal skin in non-irradiated capsules and 18.7-fold higher in irradiated capsules, with a 3.7-fold mRNA and 2.8-fold protein increase in irradiated *vs.* non-irradiated tissue (all $P < 0.05$). Short hairpin RNA (shRNA) knockdown of Thy1 in capsular fibroblasts reduced αSMA and collagen I expression, and pharmacological inhibition with salinomycin produced a comparable effect, supporting Thy1/CD90 as a candidate mechanistic biomarker of radiation-induced contracture rather than a clinically validated predictor[38].

LL-37

Segreto *et al.* examined 29 textured-implant capsules from 28 women followed for a mean of 5 ± 3 years after the second-stage exchange. LL-37 was detected immunohistochemically in 11 of 29 specimens (38%), localized to macrophages (10/29, 34%) and myofibroblasts (9/29, 31%). In clinically infected capsules, both cell populations were 100% LL-37-positive. Macrophage LL-37 expression correlated negatively with the Baker score at the definitive implant ($P = 0.04$), supporting a potentially protective role of innate antimicrobial peptide expression and identifying LL-37 as a candidate tissue-level prognostic marker for contracture severity[39].

Estrogen receptors alpha and beta (ER-α/ER-β)

Persichetti *et al.* examined estrogen receptor expression in 80 capsules from 70 women (44 capsules with Baker III-IV) and complemented the histological work with a retrospective analysis of 233 implant-based cases. αSMA expression correlated positively with ER-α ($P = 0.022$) and ER-β ($P = 0.004$), and ER-β correlated negatively with capsule thickness ($P = 0.019$). Clinically, the incidence of Baker III-IV contracture was significantly lower in women treated with anti-estrogen therapy (tamoxifen, aromatase inhibitor or gonadotropin-releasing hormone analog) in both the histological cohort ($P = 0.036$) and the retrospective cohort ($P < 0.0001$)[40]. The findings argue for an estrogen-driven myofibroblast contribution to contracture and suggest hormonal therapy as a potential modifier, but irradiated patients were excluded from this work, limiting generalizability to the high-risk reconstructive population.

Synthesis of results

A meta-analytic synthesis was not possible because no two studies evaluated the same biomarker, the same compartment, the same outcome definition and the same effect measure. We therefore performed a narrative synthesis structured by biomarker compartment [Tables 3 and 5]. Within the local fluid-based group, AD-1 was the only biomarker investigated in more than one study with a consistent diagnostic readout for BIRI, and the two diagnostic studies converged on an exceptional diagnostic accuracy (sensitivity and specificity 100%; AUC 1.00) and a dose-response relationship between AD-1 concentration and infection severity. For

capsular contracture, the available evidence comes from three methodologically heterogeneous tissue-level studies plus one large blood-based study. Despite different analytes, all four point to a shared pathophysiological theme of myofibroblast activation under pro-inflammatory and/or radiation-induced stress, modifiable by hormonal status[40] and detectable in the systemic immune-cell composition[31]. For implant loss, evidence is limited to two studies (He *et al.* 2026 for ICAM-1 in drainage fluid; Sobti *et al.* 2024 for AD-1 graded explantation risk), neither of which has been externally validated[34,36].

Heterogeneity across studies was pronounced in patient selection (prophylactic *vs.* therapeutic mastectomy; mixed prepectoral and subpectoral planes; heterogeneous radiation and antibiotic exposure), in biomarker assay (qualitative Synovasure enzyme-linked immunosorbent assay (ELISA), quantitative AD-1 assay, cytokine microarray, liquid chromatography-mass spectrometry (LC-MS) metabolomics, quantitative reverse transcription polymerase chain reaction (qRT-PCR), immunohistochemistry), in cut-off derivation (manufacturer-fixed, ROC-derived in the same cohort, or none) and in outcome definition (intraoperative clinical BIRI, CDC criteria, Baker III-IV, Spear modified classification, implant loss). Sensitivity and subgroup analyses could therefore not be performed across studies and were carried out only within individual studies.

Reporting biases and certainty of the evidence

A formal small-study/funnel-plot evaluation of reporting bias was not feasible given the small number of studies per biomarker-outcome combination. However, several features raised concern: three studies received industry-related support (assay kits donated by the manufacturer in Basta *et al.*, 2019; commercial assay in Basta *et al.*, 2023 and Sobti *et al.*, 2024)[32-34]. An unrestricted educational grant was provided by Tepha/Galatea Surgical (Stewart *et al.*, 2020)[35], and a research gift was received from the implant manufacturer Sientra (Wildenthal *et al.*, 2026)[37]. Cut-offs were derived in the same cohort in which they were tested in three studies (Stewart *et al.*, 2020; He *et al.*, 2026; Kang *et al.*, 2026)[31,35,36]. In the exploratory studies by He *et al.* and Wildenthal *et al.*, the biomarker was modeled as a continuous variable or selected from the same dataset in which it was tested, so that these analyses are equally susceptible to in-cohort optimism. He *et al.* selected ICAM-1 from more than 400 analytes without correction for multiple testing. No threshold or model was validated in an independent cohort[31,34-37].

As mentioned in the Methods section, certainty of evidence was not assessed due to the heterogeneity and methodological limitations of the included studies. Nevertheless, evidence for systemic NLR/PLR, drainage-fluid ICAM-1, untargeted seroma metabolomics, and the tissue-level markers Thy1/CD90, LL-37 and ER-α/ER-β must be rated as low, given the single-study, single-center designs without external validation. While AD-1 is the only biomarker that has been reproduced in multiple studies, the certainty of the evidence is nevertheless low. The three studies were small (13, 35 and 29 patients), two were single-center, all three received industry-related assay support (in one of them the assay kits were donated by the manufacturer), and the threshold applied in the two qualitative studies was defined by the manufacturer for periprosthetic joint infection rather than for the breast pocket.

DISCUSSION

Summary of principal findings

This systematic review summarizes the currently available evidence on inflammatory biomarkers as predictors of operative complications after breast reconstruction. Ten heterogeneous studies, published between 2014 and 2026 and reporting on a total of 771 patients, met our PICO-based eligibility criteria. All studies reported on implant-based complications. Across these studies, biomarkers were measured in three distinct compartments: Systemic blood, local periprosthetic/drainage/seroma fluid, and capsular tissue. They were related to three principal complications: BIRI, capsular contracture and implant loss/explantation. The

most consistent and reproducible signal was generated by AD-1 in implant pocket fluid, which achieved exceptional diagnostic accuracy for BIRI (sensitivity and specificity 100%; AUC 1.00) in two prospective studies from the same group at two sites (Brown University and Vanderbilt University) and showed a graded, dose-dependent relationship with infection severity and explantation risk[32-34]. PMN reproduced this diagnostic-prognostic pattern in a single retrospective cohort[35]. For capsular contracture, a unified pathophysiological mechanism has been discovered: myofibroblasts are activated under pro-inflammatory and/or radiation-induced stress, modulated by estrogen signaling and reflected in the systemic immune-cell composition[38-40]. Drainage-fluid ICAM-1 and untargeted seroma small-molecule metabolomics provided proof-of-concept evidence that pre-clinical, molecular detection of impending infection or implant loss is technically feasible[36,37]. Despite these substantial findings, no biomarker has been externally validated in an independent cohort, and no two studies used identical analytes, sampling protocols or outcome definitions, precluding a quantitative meta-analysis.

Interpretation and comparison with the existing literature

Our findings position breast reconstruction approximately one decade behind the orthopedic literature in the context of biomarker-guided diagnosis of prosthetic infection. AD-1 has been evaluated in more than twenty primary studies and pooled in successive meta-analyses[45-47]. In these studies, similar results could be achieved for predicting BIRI with sensitivity of 0.86-0.96 and specificities of 0.95-0.98. AD-1 has also been incorporated into the 2018 International Consensus Meeting criteria for hip and knee infection[48]. The three breast-specific studies identified here (Basta *et al.*, 2019; Basta *et al.*, 2023; Sobti *et al.*, 2024) reproduce that diagnostic performance in a substantially smaller patient population and additionally demonstrate a graded relationship with infection severity, suggesting that the test behaves as a quantitative rather than a purely binary marker in the breast pocket[32-34].

Our results also confirm and extend a growing body of evidence implicating chronic, biofilm-associated low-grade inflammation in capsular contracture. The immunohistochemical findings (LL-37, Thy1/CD90) are convergent with the biofilm hypothesis articulated in the literature, and they offer a plausible explanation for the higher contracture rate observed after radiotherapy[38,39,49]. Irradiation appears to interfere with this inflammatory cascade at multiple levels. It upregulates Thy1/CD90 by approximately four-fold at the mRNA level[38] and is itself a strong amplifier of the NLR/PLR signal reported by Kang *et al.*[31]. The negative correlation between LL-37 expression and Baker score is biologically plausible, when comparing this antimicrobial peptide to the literature and following the biofilm hypothesis, as it was found to be involved in the inflammatory antimicrobial response[50]. The protective effect of anti-estrogen therapy described by Persichetti *et al.* raises the possibility that the same inflammatory pathway is susceptible to pharmacological modification[40]. These results are backed by a retrospective case-control study from 2025, where patients receiving Tamoxifen treatment at the time of implantation had lower odds of capsular contracture (OR: 0.30, 95%CI: 0.12-0.74; $P = 0.006$), whereas the association with aromatase inhibitors was not significant (OR: 0.46; $P = 0.058$)[51].

By contrast, the systemic biomarker evidence remains comparatively underdeveloped. While NLR has been associated with postoperative infectious complications across surgical specialties, with a median cut-off of 4.19[29], and NLR and PLR show fair accuracy for periprosthetic joint infection[30], only a single, retrospective study has tested them in implant-based breast reconstruction[31]. The reported cut-off (NLR ≥ 1.835) is substantially lower than in most non-breast surgical contexts, which may reflect either a true biological difference, a data-driven optimization in a single cohort, or the indirect influence of postmastectomy radiotherapy on the lymphocyte count. While CRP was also examined in the AD-1 studies[32-34], its inability to detect BIRI and the complete absence of IL-6, albumin and procalcitonin as primary predictors in our included studies is a striking gap, particularly given the routine availability and low cost of these tests in everyday surgical practice.

Finally, the metabolomic and cytokine-array work (Wildenthal *et al.*, 2026; He *et al.*, 2026) signals an emerging shift from single-analyte models towards multiplex, hypothesis-generating approaches. The detection of bacterial exometabolites and acetylated polyamines in drainage fluid days before clinical infection and the abrogation of implant loss after intracavitary dexamethasone application after demonstrating the association of ICAM-1 with implant loss, illustrate the translational potential of compartment-specific molecular profiling but also expose the logistical and regulatory hurdles that will need to be addressed before such assays can enter routine care[36,37].

For autologous reconstruction, two articles analyzing perioperative blood loss (not included as biomarker) showed that blood transfusion recipients had an increased risk and greater odds of experiencing any postoperative complication (relative risk: 2.3; OR: 3.4)[52] and that patients with higher perioperative blood loss have a higher risk for mild complications (seroma, infection requiring antibiotic therapy, redness, discoloration, hematoma, wound dehiscence, and thrombosis not requiring surgical intervention; $P = 0.01$)[53]. This could show that the factors critical for oxygenation of flaps have a higher impact on surgical complications than inflammatory markers.

Limitations

This systematic review followed PRISMA 2020, used two independent reviewers throughout screening and data extraction and assessed risk of bias with QUADAS-2 and NOS. To our knowledge, this is the first systematic review reporting on biomarkers of complications of breast reconstruction. However, several limitations must be acknowledged. Our review was planned to cover both autologous as well as implant-based reconstructions. Unfortunately, only records reporting about biomarkers of implant-based reconstructions could be retrieved. Consequently, the role of inflammatory biomarkers in flap-specific complications such as (partial) flap loss, venous congestion and donor-site morbidity remains an open question. Complications after implant-based reconstruction are dominated by a foreign-body and biofilm-driven response that evolves over weeks to months, whereas the early complications of free-flap reconstruction follow a different biology on a much shorter time scale.

Furthermore, the small number of included studies and the substantial clinical and methodological heterogeneity precluded a quantitative meta-analysis. All effect estimates could therefore only be presented narratively, and pooled diagnostic accuracy or pooled ORs are not available. Eight of the ten studies were single-center and several recruited fewer than 50 patients or fewer than 15 outcome events, which limits statistical power and external validity. Only five studies reported cut-off values. For NLR/PLR, PMN and ICAM-1, cut-off values were derived by ROC analysis within the same cohort. None have been validated externally[31,35,36]. The two AD-1 studies did not derive a threshold but used the binary positive/negative result of the Synovasure® assays, also receiving industry-related support, including donated assay kits, which raises the possibility of reporting bias[32,33]. Markers found by histological analysis in tissue are biomarkers by definition. Their clinical relevance for predicting capsular contracture is limited, as this diagnostic tool is only available in limited cases, e.g., when two-staged breast reconstruction is performed. The moment of prediction differs between biomarker compartments. Only the systemic markers were measured before surgery; the fluid-based markers were sampled at drain removal or at the time of suspected infection and related to the subsequent course, including implant loss, and the tissue-based markers were obtained at expander exchange and related to contracture recorded thereafter. The evidence reviewed here therefore concerns prediction at perioperative decision points rather than preoperative risk stratification, for which only a single study is currently available (Kang *et al.*, 2026)[31].

Our search was restricted to PubMed/MEDLINE, Embase (Elsevier) and the Cochrane Library and to studies in English and German. We cannot exclude that further small studies remain undetected in regional non-German or English databases. All included studies were observational, and the absence of randomized,

biomarker-guided interventional trials means that no causal claim about biomarker-directed management can yet be made.

Implications for clinical practice

The current body of evidence does not yet support routine biomarker-guided risk stratification in unselected patients undergoing breast reconstruction. Nevertheless, some pragmatic messages can be derived. First, in patients with clinical suspicion of BIRI in whom culture and Gram stain are confounded by prior antibiotic exposure, AD-1 in pocket fluid offers a rapid, antibiotic-resistant adjunct with diagnostic accuracy that is at least comparable to and often superior to existing tests. Where the assay is locally available, it may shorten the time to definitive operative management or antibiotic treatment, as early antibiotic treatment is crucial for possible salvage of an infected implant[54]. As a hands-on example, in our university hospital AD-1 cannot be tested in its central laboratory by default and would have to be established first for regular testing. Furthermore, in patients undergoing (nipple-sparing) mastectomy with planned postmastectomy radiotherapy, an elevated preoperative NLR and PLR may identify a high-risk subgroup for severe capsular contracture. This information could inform shared decision-making about implant choice, plane and timing of radiotherapy, although it should not yet drive a change in surgical strategy. Third, the protective signal associated with anti-estrogen therapy, although derived from a single team, deserves consideration in counseling oncology patients who are already prescribed endocrine treatment for their underlying disease. As mentioned before, the biomarkers analyzed histologically in capsular tissue have limited diagnostic relevance, since capsular tissue becomes available only at expander exchange or revision surgery; their value lies instead in identifying the myofibroblast pathway as a target that can be addressed pharmacologically, as the signal associated with anti-estrogen therapy illustrates.

Implications for future research

The methodological gaps identified above translate directly into a research agenda.

First of all, the research gap, that is, the absence of literature on perioperative biomarkers in autologous breast reconstruction, has to be addressed. Here, the full spectrum of research must be established, beginning with retrospective analyses, followed by early intervention studies and randomized controlled trials.

To further strengthen the positive results of AD-1 testing for BIRI, multi-center prospective validation of AD-1 in implant pocket fluid using pre-specified standardized BIRI criteria, with blinded assay reading and standardized antibiotic-stewardship protocols, has to be performed.

The routinely available, low-cost systemic markers (CRP, IL-6, NLR, PLR, albumin and procalcitonin) measured both preoperatively and on postoperative days 2-5, in adequately powered cohorts that include both implant-based and autologous reconstruction with associated complications have to be evaluated, as these could easily be integrated into pre- and perioperative diagnostics.

Research on small molecule metabolomics is just beginning. Here, further research on additional molecules must be performed. Identified molecules, such as ICAM-1, have to be examined further in larger cohorts and require validation cohorts and pre-registered cut-offs for diagnostic purposes.

Across all of these efforts, harmonization of outcome definitions (BIRI criteria, Baker grade for contracture, explantation as a hard endpoint), of sampling protocols (timing, volume, processing), and of reporting standards for the clinical context in which a biomarker is measured (irradiation, implant plane, antibiotic exposure) will be essential to enable the future meta-analysis that the variation across the present studies made impossible.

Conclusions

Inflammatory biomarkers represent a promising but still immature tool for the prediction and diagnosis of operative complications after breast reconstruction. AD-1 in peri-implant fluid is the only biomarker whose diagnostic performance has been reproduced in two prospective studies from the same group at two sites (Brown University and Vanderbilt University); the evidence remains of low certainty and industry-supported, and AD-1 should therefore be regarded as the most promising candidate for multicenter, investigator-initiated validation rather than as a test ready for clinical adoption. Tissue-level data point to a coherent, myofibroblast-driven mechanism of capsular contracture that is amplified by radiation and potentially modifiable by hormonal status, while emerging multiplex techniques signal a shift towards molecular fingerprinting of the periprosthetic milieu. The overall certainty of the evidence is, however, low to very low, and no biomarker has been externally validated, prospectively integrated into a clinical decision pathway, or tested in a randomized interventional trial, inflammatory biomarkers for autologous breast reconstruction have not been reported at all. Future work should focus on multi-center validation, standardization of sampling and outcome definitions, and biomarker-guided intervention trials that move the field from descriptive association towards actionable, personalized perioperative care in breast reconstruction.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study: Lehmenkötter N, Lingens L
Developed the search strategy and performed the literature search: Lehmenkötter N, Lingens L
Performed independent study selection (title/abstract and full-text screening) and resolved disagreements by consensus: Lehmenkötter N, Lingens L
Performed data extraction and cross-checking: Lehmenkötter N, Lingens L
Performed risk-of-bias/quality assessment: Lehmenkötter N, Lingens L
Performed data synthesis, statistical analysis, and interpretation of results: Lehmenkötter N
Drafted the manuscript: Lehmenkötter N
Revised the manuscript critically for important intellectual content: Lingens L, Beier JP
Provided administrative, technical, and material support and supervised the project: Beier JP
All authors read and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Availability of data and materials

All data analyzed in this review derive from the published studies cited in the reference list. The search strategies, the list of excluded full texts with reasons and the complete risk-of-bias assessments are provided as Supplementary Materials [Supplementary Tables 1-3]; the data-extraction sheet is available from the corresponding author upon reasonable request.

AI and AI-assisted tools statement

During the preparation of this manuscript, Rayyan was used for the screening process, and the AI tool Claude Opus (version 5.5, released 2026-09-22) was used to optimize manuscript readability and language quality. These tools did not influence the study design, data collection, analysis, interpretation, or the scientific content of the work. All authors take full responsibility for the accuracy, integrity, and final content of the manuscript.

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All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Supplementary Materials

Supplementary Materials

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