Supplementary Materials

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

Nicolas Lehmenkötter, Justus P Beier, Lara Lingens

Department of Plastic Surgery, Hand Surgery - Burn Center, University Hospital RWTH Aachen, Aachen 52074, Germany.

Correspondence to: Dr. Nicolas Lehmenkötter, Department of Plastic Surgery, Hand Surgery - Burn Center, University Hospital RWTH Aachen, Aachen 52074, Germany. E-mail: nicolas.lehmenkoetter@rwth-aachen.de

Supplementary Table 1. Excluded records in Full-Text screening

Author	Title	*Exclusion criterion*
Adachi *et al*. (2020)	Effects of neoadjuvant chemotherapy on operative adverse events and chemotherapy and radiotherapy in patients undergoing immediate breast reconstruction	1 - No biomarker
Agresti *et al*. (2019)	Wound Healing Fluid Reflects the Inflammatory Nature and Aggressiveness of Breast Tumors	5 - Population not appropriate
Aurilio *et al*. (2014)	Does immediate breast reconstruction after mastectomy and neoadjuvant chemotherapy influence the outcome of patients with non-endocrine responsive breast cancer?	3 - Oncological outcome only
Axelsson *et al*. (2012)	Local injection of methylprednisolonacetat to prevent seroma formation after mastectomy	2 - No reconstruction
Azahaf *et al*. (2025)	Increased FGF-19 levels following explantation in women with breast implant illness	5 - Population not appropriate
Bachour *et al*. (2019)	Toll-Like Receptors (TLRs) Expression in Contracted Capsules Compared to Uncontracted Capsules	2 - No reconstruction
Backovic *et al*. (2007)	Simultaneous analysis of multiple serum proteins adhering to the surface of medical grade polydimethylsiloxane elastomers	2 - No reconstruction
Baker *et al*. (2020)	The impact of axillary node surgery on outcomes following immediate breast reconstruction	1 - No biomarker
Banuelos *et al*. (2019)	Infections following Immediate Implant-Based Breast Reconstruction: A Case-Control Study over 11 Years	1 - No biomarker
Borrelli *et al*. (2020)	Pro-Fibrotic CD26-Positive Fibroblasts Are Present in Greater Abundance in Breast Capsule Tissue of Irradiated Breasts	6 - Biomarker not quantified
Bouchard *et al*. (2016)	Postsurgical Depressive Symptoms and Proinflammatory Cytokine Elevations in Women Undergoing Primary Treatment for Breast Cancer	2 - No reconstruction
Brazin *et al*. (2014)	Mast cells in the periprosthetic breast capsule	2 - No reconstruction
Bui *et al*. (2015)	Histological characterization of human breast implant capsules	4 - Study design not appropriate
Cagli *et al*. (2023)	Histologic and Immunohistochemical Evaluation of Human Breast Capsules Formed around Five Different Expander Surfaces	4 - Study design not appropriate
Cheng *et al*. (2015)	Effects of the Zhikang capsule on healing of the flap after radical breast cancer surgery	2 - No reconstruction

Chow *et al*. (2003)	The study of cytokine dynamics at the operation site after mastectomy	2 - No reconstruction
Claroni *et al*. (2016)	Protective effect of sevoflurane preconditioning on ischemia-reperfusion injury in patients undergoing reconstructive plastic surgery with microsurgical flap, a randomized controlled trial	7 - Outcome not clearly defined
Cui *et al*. (2018)	Combination of preoperative D-dimer and mean platelet volume predicts postoperative deep venous thrombosis in breast cancer patients	2 - No reconstruction
Cullinane *et al*. (2024)	Perioperative systemic IL-6 and immune-adipose-metabolism transcription in tumour and tumour adjacent breast cancer	2 - No reconstruction
Curigliano *et al*. (2005)	Systemic effects of surgery: quantitative analysis of circulating basic fibroblast growth factor (bFGF), Vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-beta) in patients with breast cancer who underwent limited or extended surgery	7 - Outcome not clearly defined
D'Andrea *et al*. (2007)	Modification of cysteinyl leukotriene receptor expression in capsular contracture: Preliminary results	2 - No reconstruction
Davis *et al*. (2020)	Therapeutic Breast Reconstruction Using Gene Therapy-Delivered IFNγ Immunotherapy	4 - Study design not appropriate
Desai *et al*. (2025)	Presentation and Management of Silicone Lymphadenopathy: A Single Institutional Retrospective Cohort Study	1 - No biomarker
Frisell *et al*. (2023)	Capsular inflammation after immediate breast reconstruction - Gene expression patterns and inflammatory cell infiltration in irradiated and non-irradiated breasts	4 - Study design not appropriate
Galimberti *et al*. (2018)	Axillary dissection versus no axillary dissection in patients with breast cancer and sentinel-node micrometastases (IBCSG 23-01): 10-year follow-up of a randomised, controlled phase 3 trial	2 - No reconstruction
Gillard *et al*. (2004)	Matrix metalloproteinase activity and immunohistochemical profile of matrix metalloproteinase-2 and -9 and tissue inhibitor of metalloproteinase-1 during human dermal wound healing	2 - No reconstruction
Handschel *et al*. (2013)	Parameters predicting complications in flap surgery	5 - Population not appropriate
Hansson *et al*. (2020)	Comparison of inflammatory response and synovial metaplasia in immediate breast reconstruction with a	1 - No biomarker

	synthetic and a biological mesh: a randomized controlled clinical trial	
Hartman *et al*. (2020)	Bioinformatic Analysis of the Wound Peptidome Reveals Potential Biomarkers and Antimicrobial Peptides	2 - No reconstruction
Hill *et al*. (2012)	Preoperative anemia predicts thrombosis and free flap failure in microvascular reconstruction	5 - Population not appropriate
Hirche (2022)	[Autologous Breast Reconstruction in Conjuction with Lymphatic Microsurgery in Breast Cancer-Related Lymphedema]	4 - Study design not appropriate
Hu *et al*. (2023)	Diagnosis of breast implant associated anaplastic large cell lymphoma by analysis of cytokines in peri-implant seromas	2 - No reconstruction
Hu *et al*. (2024)	Comprehensive analysis of risk factors for postoperative wound infection following radical mastectomy in breast cancer patients	2 - No reconstruction
Jagasia *et al*. (2025)	Silicone breast implant-associated pathologies and T cell-mediated responses	4 - Study design not appropriate
Kadin *et al*. (2021)	Granzyme B Is a Biomarker for Suspicion of Malignant Seromas Around Breast Implants	3 - Oncological outcome only
Kamel *et al*. (2001)	The peri-implant breast capsule: an immunophenotypic study of capsules taken at explantation surgery	5 - Population not appropriate
Karamanos *et al*. (2021)	Impact of Blood Transfusion in Free Flap Breast Reconstruction Using Propensity Score Matching	No full text (PDF) available
Kim *et al*. (2018)	Inhibition Mechanism of Acellular Dermal Matrix on Capsule Formation in Expander-Implant Breast Reconstruction After Postmastectomy Radiotherapy	4 - Study design not appropriate
Kim *et al*. (2024)	Factors Predicting the Effect of a Complex Decongestive Therapy in Patients with Mild Lymphedema Following Mastectomy for Early Stage Breast Cancer	2 - No reconstruction
Kuehlmann *et al*. (2023)	Matrix Metalloproteinase-9 as a Potential Biomarker in 631 Human Implant-Induced Fibrotic Capsules: Analysis and Biomarker Study	5 - Population not appropriate
Kuhn *et al*. (2000)	Periprosthetic breast capsules contain the fibrogenic cytokines TGF-beta1 and TGF-beta2, suggesting possible new treatment approaches	6 - Biomarker not 5 - Population not appropriate
Kyle *et al*. (2013)	Identification of molecular phenotypic descriptors of breast capsular contracture formation using informatics analysis of the whole genome transcriptome	Not specified

Leong *et al*. (2015)	Further evidence that human acellular dermal matrix decreases inflammatory markers of capsule formation in implant-based breast reconstruction	4 - Study design not appropriate
Li *et al*. (2023)	Diagnostic value of inflammatory indicators for surgical site infection in patients with breast cancer	5 - Population not appropriate
Lisa *et al*. (2021)	Study of Inflammatory and Infection Markers in Periprosthetic Fluid: Correlation with Blood Analysis in Retrospective and Prospective Studies	1 - No biomarker
Liu *et al*. (2025)	Severe capsular contracture of breast implants may result from localized pathological changes: An intra-capsular comparative analysis	2 - No reconstruction
Loo *et al*. (2007)	Pro-inflammatory cytokine, matrix metalloproteinases and TIMP-1 are involved in wound healing after mastectomy in invasive breast cancer patients	2 - No reconstruction
Lucas *et al*. (2018)	Perceived Stress and Surgical Wound Cytokine Patterns	No full text (PDF) available
Mazzocchi *et al*. (2012)	Effects of zafirlukast on capsular contracture: long-term results	5 - Population not appropriate
McGuire *et al*. (2023)	Microbes, Histology, Blood Analysis, Enterotoxins, and Cytokines: Findings From the ASERF Systemic Symptoms in Women-Biospecimen Analysis Study: Part 3	2 - No reconstruction
Morris *et al*. (2000)	Are antioxidant levels measured immediately postoperatively an indicator of magnitude of injury?	2 - No reconstruction
Moyer *et al*. (2013)	Capsular contracture after breast reconstruction: collagen fiber orientation and organization	1 - No biomarker
Mukai *et al*. (2023)	An observational study of the impact of immediate breast reconstruction on perioperative inflammatory cytokines	4 - Study design not appropriate
Nakamoto *et al*. (2019)	Prediction of early C-reactive protein levels after non-cardiac surgery under general anesthesia	2 - No reconstruction
Nepon *et al*. (2024)	The cellular and molecular properties of capsule surrounding silicone implants in humans vary uniquely according to the tissue type adjacent to the implant	4 - Study design not appropriate
Nguyen *et al*. (2015)	An algorithmic approach to simultaneous vascularized lymph node transfer with microvascular breast reconstruction	1 - No biomarker
Panayi *et al*. (2024)	The combined risk predictive power of frailty and hypoalbuminemia in free tissue flap reconstruction: A cohort study of 34,571 patients from the NSQIP database	5 - Population not appropriate

Patel *et al*. (2021)	Rotational Thromboelastometry Derivative Fibrinogen-Platelet Ratio Predicts Thrombosis in Microsurgery	No full text (PDF) available
Pelle *et al*. (2020)	Breast cancer surgery during the Covid-19 pandemic: a monocentre experience from the Regina Elena National Cancer Institute of Rome	4 - Study design not appropriate
Perfeito Abud *et al*. (2025)	Postoperative analgesia in breast cancer surgeries - anesthetic techniques and the role of cytokines	No full text (PDF) available
Pestana *et al*. (2013)	Factors affecting complications in radiated breast reconstruction	1 - No biomarker
Pochert *et al*. (2023)	Th2/Th17 cell associated cytokines found in seroma fluids after breast cancer surgery	2 - No reconstruction
Poh *et al*. (2018)	Non-linear optical microscopy and histological analysis of collagen, elastin and lysyl oxidase expression in breast capsular contracture	2 - No reconstruction
Prantl *et al*. (2005)	Serologic and histologic findings in patients with capsular contracture after breast augmentation with smooth silicone gel implants: is serum hyaluronan a potential predictor?	5 - Population not appropriate
Prantl *et al*. (2008)	Flow cytometric analysis of peripheral blood lymphocyte subsets in patients with silicone breast implants	5 - Population not appropriate
Rahman *et al*. (2024)	The Low-Abundance Plasma Proteome Reveals Differentially Abundant Proteins Associated with Breast Implant Capsular Contracture: A Pilot Study	2 - No reconstruction
Schneider *et al*. (2025)	Macrophage polarization is associated with postoperative seroma development in breast cancer in the SerMa pilot cohort	7 - Outcome not clearly defined
Schoberleitner *et al*. (2023)	Quantitative Proteomic Characterization of Foreign Body Response towards Silicone Breast Implants Identifies Chronological Disease-Relevant Biomarker Dynamics	4 - Study design not appropriate
Segreto *et al*. (2018)	The role of angiogenesis, inflammation and estrogen receptors in breast implant capsules development and remodeling	7 - Outcome not clearly defined
Shechter *et al*. (2018)	DIEP Flap Breast Reconstruction Complication Rate in Previously Irradiated Internal Mammary Nodes	No full text (PDF) available
Siggelkow *et al*. (2004)	Ki67, HSP70 and TUNEL for the specification of testing of silicone breast implants in vivo	5 - Population not appropriate
Silva *et al*. (2011)	Systemic inflammatory reaction after silicone breast implant	5 - Population not appropriate

Tan *et al*. (2011)	Hyaluronan, TSG-6, and inter-α-inhibitor in periprosthetic breast capsules: reduced levels of free hyaluronan and TSG-6 expression in contracted capsules	5 - Population not appropriate
Tang *et al*. (2022)	Prognostic significance of the skeletal muscle index and systemic inflammatory index in patients with lymph node-positive breast cancer after radical mastectomy	2 - No reconstruction
Ten Wolde *et al*. (2018)	Can Gentamicin-collagen Sponges Prevent Seroma Formation Following Mastectomy?	2 - No reconstruction
Ulrich *et al*. (2004)	Matrix metalloproteinases, tissue inhibitors of metalloproteinases, aminoterminal propeptide of procollagen type III, and hyaluronan in sera and tissue of patients with capsular contracture after augmentation with Trilucent breast implants	5 - Population not appropriate
Unger *et al*. (2021)	Potential Risk Factors Influencing the Formation of Postoperative Seroma After Breast Surgery - A Prospective Study	1 - No biomarker
van Bastelaar *et al*. (2019)	Analysis of TNF-α and interleukin-6 in seroma of patients undergoing mastectomy with or without flap fixation: is there a predictive value for seroma formation and its sequelae?	2 - No reconstruction
Vanni *et al*. (2021)	Breast Textured Implants Determine Early T-helper Impairment: BIAL2.20 Study	7 - Outcome not clearly defined
Veras-Castillo *et al*. (2013)	Controlled clinical trial with pirfenidone in the treatment of breast capsular contracture: association of TGF-β polymorphisms	5 - Population not appropriate
Wang *et al*. (2016)	The Impact of Radiation Therapy, Lymph Node Dissection, and Hormonal Therapy on Outcomes of Tissue Expander-Implant Exchange in Prosthetic Breast Reconstruction	1 - No biomarker
Wolfram *et al*. (2012)	T regulatory cells and TH17 cells in peri-silicone implant capsular fibrosis	5 - Population not appropriate
Yin *et al*. (2022)	Single-Institution Algorithm for Prevention and Management of Complications in Direct-to-Implant Breast Reconstruction	1 - No biomarker

Supplementary Material M1: Database Specific Search Strings

Pubmed

Reviewer NL:

```
(
   (
      "breast implant*" OR
      "implant-based reconstruction" OR
      "prosthetic breast reconstruction" OR
      "alloplastic reconstruction" OR
      "tissue expander*"
   )
   OR
   (
      (
         DIEP OR TRAM OR "MS-TRAM" OR "pedicled TRAM" OR
         "deep inferior epigastric perforator" OR
         "transverse rectus abdominis" OR
         PAP OR "profunda artery perforator" OR
         TMG OR "transverse myocutaneous gracilis" OR
         "latissimus dorsi" OR "LD flap"
      )
      AND (flap OR reconstruction)
   )
)
AND
(
   "capsular contracture" OR
   "capsular fibrosis" OR
   "implant infection" OR
   "periprosthetic infection" OR
   "surgical site infection" OR
   SSI OR
   seroma OR
   hematoma OR
   "implant loss" OR
   "reconstructive failure" OR
   complication* OR
   "flap failure" OR
   "reoperation" OR
   necrosis
)
AND
(
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biomarker* OR
marker* OR
"diagnostic marker*" OR
"prognostic marker*" OR
"alpha defensin" OR
defensin OR
"C-reactive protein" OR
CRP OR
procalcitonin OR
PCT OR
cytokine* OR
interleukin* OR
TNF OR
chemokine* OR
"gene expression" OR
proteomic* OR
metabolomic* OR
collagen OR
fibrosis OR
"periprosthetic fluid" OR
"implant fluid" OR
NLR[tiab] OR
PLR[tiab] OR
SII[tiab] OR
"TGF-beta"[tiab] OR
"TIMP-1"[tiab] OR
"TIMP-2"[tiab] OR
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"MMP-9"[tiab] OR
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"alpha defensin"[tiab]
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AND
("2000/01/01"[Date - Publication] : "3000"[Date - Publication])
AND
(english[Language] OR german[Language])
NOT
(review[Publication Type] OR systematic review[Publication Type])

Reviewer LL:
("Mammaplasty"[MeSH] OR "Breast Neoplasms/surgery"[MeSH] OR "Mastectomy"[MeSH] OR "Free Tissue Flaps"[MeSH] OR "Breast Implants"[MeSH] OR "Tissue Expanders"[MeSH] OR "breast reconstruction"[Title/Abstract] OR "DIEP flap"[Title/Abstract] OR "TRAM flap"[Title/Abstract] OR

"latissimus dorsi flap"[Title/Abstract] OR "implant-based reconstruction"[Title/Abstract] OR "tissue expander"[Title/Abstract] OR "postmastectomy reconstruction"[Title/Abstract])
AND
("C-Reactive Protein"[MeSH] OR "Interleukin-6"[MeSH] OR "Tumor Necrosis Factor-alpha"[MeSH] OR "Interleukin-10"[MeSH] OR "Interleukin-8"[MeSH] OR "Matrix Metalloproteinase 2"[MeSH] OR "Matrix Metalloproteinase 9"[MeSH] OR "Serum Albumin"[MeSH] OR "Procalcitonin"[MeSH] OR "Fibrinogen"[MeSH] OR "Biomarkers"[MeSH] OR "Inflammation/blood"[MeSH] OR "Immune System"[MeSH] OR "neutrophil-to-lymphocyte ratio"[Title/Abstract] OR "NLR"[Title/Abstract] OR "platelet-to-lymphocyte ratio"[Title/Abstract] OR "PLR"[Title/Abstract] OR "systemic immune-inflammation index"[Title/Abstract] OR "SII"[Title/Abstract] OR "inflammatory biomarker*"[Title/Abstract] OR "inflammatory marker*"[Title/Abstract] OR "systemic inflammation"[Title/Abstract] OR "perioperative inflammation"[Title/Abstract] OR "cytokine*"[Title/Abstract] OR "TGF-beta"[Title/Abstract] OR "TIMP-1"[Title/Abstract] OR "TIMP-2"[Title/Abstract] OR "MMP-2"[Title/Abstract] OR "MMP-9"[Title/Abstract] OR "sarcopenia"[Title/Abstract] OR "skeletal muscle index"[Title/Abstract] OR "hypoalbuminemia"[Title/Abstract] OR "hypoalbuminaemia"[Title/Abstract] OR "prealbumin"[Title/Abstract] OR "granzyme B"[Title/Abstract] OR "alpha defensin"[Title/Abstract]
AND
("Capsular Contracture, Implant"[MeSH] OR "Surgical Wound Infection"[MeSH] OR "Postoperative Complications"[MeSH] OR "Seroma"[MeSH] OR "Necrosis"[MeSH] OR "Reoperation"[MeSH] OR "Device Removal"[MeSH] OR "capsular contracture"[Title/Abstract] OR "flap failure"[Title/Abstract] OR "flap necrosis"[Title/Abstract] OR "wound dehiscence"[Title/Abstract] OR "wound complication*"[Title/Abstract] OR "implant loss"[Title/Abstract] OR "explantation"[Title/Abstract] OR "surgical site infection"[Title/Abstract] OR "wound healing"[Title/Abstract] OR "complication*"[Title/Abstract])

Filters: "humans" AND ("2000" - "2026") AND (English OR German)

Embase:
Reviewer NL:

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(
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    'implant-based reconstruction':ti,ab,kw OR
    'prosthetic breast reconstruction':ti,ab,kw OR
    'alloplastic reconstruction':ti,ab,kw OR
    'tissue expander*':ti,ab,kw
  )
  OR
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      'deep inferior epigastric perforator':ti,ab,kw OR
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      )
      AND (flap:ti,ab,kw OR reconstruction:ti,ab,kw)
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AND
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   'capsular fibrosis':ti,ab,kw OR
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   'periprosthetic infection':ti,ab,kw OR
   'surgical site infection':ti,ab,kw OR
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   seroma:ti,ab,kw OR
   hematoma:ti,ab,kw OR
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   'reconstructive failure':ti,ab,kw OR
   complication*:ti,ab,kw OR
   'flap failure':ti,ab,kw OR
   reoperation:ti,ab,kw OR
   necrosis:ti,ab,kw
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AND
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   interleukin*:ti,ab,kw OR
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   metabolomic*:ti,ab,kw OR
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   'periprosthetic fluid':ti,ab,kw OR
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   sii:ti,ab,kw OR
   'tgf-beta':ti,ab,kw OR
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   'granzyme b':ti,ab,kw
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)
AND ([english]/lim OR [german]/lim)
AND [2000-2026]/py
NOT ('review'/it OR 'systematic review'/it)
Reviewer LL:
('mammaplasty'/exp OR 'breast reconstruction'/exp OR 'mastectomy'/exp OR 'breast prosthesis'/exp OR 'tissue expander'/exp OR 'free tissue graft'/exp OR 'breast reconstruction':ti,ab,kw OR 'DIEP flap':ti,ab,kw OR 'TRAM flap':ti,ab,kw OR 'latissimus dorsi flap':ti,ab,kw OR 'implant-based reconstruction':ti,ab,kw OR 'tissue expander':ti,ab,kw OR 'postmastectomy reconstruction':ti,ab,kw)
AND
('C reactive protein'/exp OR 'interleukin 6'/exp OR 'tumor necrosis factor'/exp OR 'interleukin 10'/exp OR 'interleukin 8'/exp OR 'gelatinase A'/exp OR 'gelatinase B'/exp OR 'serum albumin'/exp OR 'procalcitonin'/exp OR 'fibrinogen'/exp OR 'neutrophil lymphocyte ratio':ti,ab,kw OR 'neutrophil-to-lymphocyte ratio':ti,ab,kw OR NLR:ti,ab,kw OR 'platelet lymphocyte ratio':ti,ab,kw OR 'platelet-to-lymphocyte ratio':ti,ab,kw OR PLR:ti,ab,kw OR 'systemic immune-inflammation index':ti,ab,kw OR SII:ti,ab,kw OR 'inflammatory biomarker':ti,ab,kw OR 'inflammatory biomarkers':ti,ab,kw OR 'inflammatory marker':ti,ab,kw OR 'inflammatory markers':ti,ab,kw OR 'systemic inflammation':ti,ab,kw OR 'perioperative inflammation':ti,ab,kw OR cytokine*:ti,ab,kw OR 'TGF-beta':ti,ab,kw OR 'TIMP-1':ti,ab,kw OR 'TIMP-2':ti,ab,kw OR 'MMP-2':ti,ab,kw OR 'MMP-9':ti,ab,kw OR sarcopenia:ti,ab,kw OR 'skeletal muscle index':ti,ab,kw OR hypoalbuminemia:ti,ab,kw OR hypoalbuminaemia:ti,ab,kw OR prealbumin:ti,ab,kw OR 'granzyme B':ti,ab,kw OR 'alpha defensin':ti,ab,kw)
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AND [humans]/lim
AND ([english]/lim OR [german]/lim)
AND [2000-2026]/py
NOT 'conference abstract'/it

Cochrane:

Reviewer NL:

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      TMG:ti,ab,kw OR "transverse myocutaneous gracilis":ti,ab,kw OR
      "latissimus dorsi":ti,ab,kw OR "LD flap":ti,ab,kw
    )
    AND (flap:ti,ab,kw OR reconstruction:ti,ab,kw)
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   )
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AND
(
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   SII:ti,ab,kw OR
   "TGF-beta":ti,ab,kw OR
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   "MMP-9":ti,ab,kw OR
   "granzyme B":ti,ab,kw
)
Reviewer LL:
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   "TRAM flap":ti,ab,kw OR
   "latissimus dorsi flap":ti,ab,kw OR
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   "tissue expander":ti,ab,kw OR
   "postmastectomy reconstruction":ti,ab,kw
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   [mh "Tumor Necrosis Factor-alpha"] OR
   [mh "Interleukin-10"] OR
   [mh "Interleukin-8"] OR
   [mh "Matrix Metalloproteinase 2"] OR
   [mh "Matrix Metalloproteinase 9"] OR
   [mh "Serum Albumin"] OR
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   "inflammatory marker*":ti,ab,kw OR
   "systemic inflammation":ti,ab,kw OR
   "perioperative inflammation":ti,ab,kw OR
   cytokine*:ti,ab,kw OR
   "TGF-beta":ti,ab,kw OR
   "TIMP-1":ti,ab,kw OR
   "TIMP-2":ti,ab,kw OR
   "MMP-2":ti,ab,kw OR
   "MMP-9":ti,ab,kw OR
   sarcopenia:ti,ab,kw OR
   "skeletal muscle index":ti,ab,kw OR
   hypoalbuminemia:ti,ab,kw OR
   hypoalbuminaemia:ti,ab,kw OR
   prealbumin:ti,ab,kw OR
   "granzyme B":ti,ab,kw OR
   "alpha defensin":ti,ab,kw
```

```
)
AND
(
   [mh "Capsular Contracture, Implant"] OR
   [mh "Surgical Wound Infection"] OR
   [mh "Postoperative Complications"] OR
   [mh Seroma] OR
   [mh Necrosis] OR
   [mh Reoperation] OR
   [mh "Device Removal"] OR
   "capsular contracture":ti,ab,kw OR
   "flap failure":ti,ab,kw OR
   "flap necrosis":ti,ab,kw OR
   "wound dehiscence":ti,ab,kw OR
   "wound complication*":ti,ab,kw OR
   "implant loss":ti,ab,kw OR
   explantation:ti,ab,kw OR
   "surgical site infection":ti,ab,kw OR
   "wound healing":ti,ab,kw OR
   complication*:ti,ab,kw
)
```

Supplementary Table 2. Detailed Newcastle-Ottawa Scale (NOS) assessment for the included cohort studies (consensus values)

	Domain	Item	Score	Justification
Segreto 2024	Selection	Item 1: Representativeness of the exposed cohort	**1/1**	Consecutive patients with textured submuscular implants; population defined but selective (one implant type only).
	Selection	Item 2: Selection of the non-exposed cohort	**1/1**	Comparison group (no contracture) drawn from the same cohort, identical source population.
	Selection	Item 3: Ascertainment of exposure (biomarker measurement)	**1/1**	LL-37 expression assessed by immunohistochemistry (semiquantitative) and Western blot; methods adequately described.
	Selection	Item 4: Outcome of interest not present at start of study	**1/1**	Capsular contracture (Baker classification) diagnosed at re-operation; outcome not present at the time of implantation.
	Comparability	Item 5: Comparability of cohorts on the basis of design or analysis (0-2)	**1/2**	No multivariable adjustment reported; only descriptive and bivariate tests.
	Outcome	Item 6: Assessment of outcome	**1/1**	Baker score recorded clinically; IHC scored by blinded pathologist.

	Outcome	Item 7: Was follow-up long enough for outcomes to occur	**0/1**	Follow-up duration heterogeneous (interval between primary surgery and revision) and not uniformly defined.
	Outcome	Item 8: Adequacy of follow-up of cohorts	**1/1**	Losses to follow-up not reported in detail; however, all patients with capsule retrieval were included, suggesting plausible completeness.
Sobti 2024	Selection	Item 1: Representativeness of the exposed cohort	**1/1**	Consecutive patients with suspected periprosthetic infection (prospectively maintained database); representative of the at-risk population.
	Selection	Item 2: Selection of the non-exposed cohort	**1/1**	Test-negative cases drawn from the same cohort; identical source.
	Selection	Item 3: Ascertainment of exposure (biomarker measurement)	**1/1**	α-Defensin-1 measured with the standardized Synovasure assay (objective).
	Selection	Item 4: Outcome of interest not present at start of study	**1/1**	Outcome (infection / re-operation) not present at baseline.
	Comparability	Item 5: Comparability of cohorts on the basis of design or analysis (0-2)	**1/2**	Multivariable analysis with adjustment for antibiotics and clinical variables; a second class of confounders not clearly addressed.

	Outcome	Item 6: Assessment of outcome	**1/1**	Spear classification and microbiological outcome captured objectively.
	Outcome	Item 7: Was follow-up long enough for outcomes to occur	**1/1**	Follow-up sufficiently long to capture re-operation and implant loss.
	Outcome	Item 8: Adequacy of follow-up of cohorts	**1/1**	Completeness of follow-up documented; loss-to-follow-up not explicitly reported but no relevant issues evident.
Wildenthal 2026	Selection	Item 1: Representativeness of the exposed cohort	**1/1**	Prospective longitudinal cohort drawing from two cohorts, but enriched for high-risk patients (obesity, diabetes, smoking).
	Selection	Item 2: Selection of the non-exposed cohort	**1/1**	Non-infected controls from the same cohort with longitudinal sampling.
	Selection	Item 3: Ascertainment of exposure (biomarker measurement)	**1/1**	Untargeted LC-MS metabolomics in drainage fluid; objective, reproducible method, independent of outcome.
	Selection	Item 4: Outcome of interest not present at start of study	**1/1**	Infection develops postoperatively; outcome not present at baseline, no outcome-related bias.

	Comparability	Item 5: Comparability of cohorts on the basis of design or analysis (0-2)	**1/2**	Adjustment for clinical variables and antibiotic surrogate markers covers two classes of confounders, but no formal multivariable adjustment performed.
	Outcome	Item 6: Assessment of outcome	**1/1**	Outcome adjudicated by combined clinical diagnosis and microbiological findings.
	Outcome	Item 7: Was follow-up long enough for outcomes to occur	**1/1**	Follow-up sufficient to capture infection diagnosis; not a long follow-up overall, but adequate for the outcome of interest.
	Outcome	Item 8: Adequacy of follow-up of cohorts	**0/1**	Single-center setting but completeness of longitudinal samples well documented; 36 of 106 patients excluded.
He 2026	Selection	Item 1: Representativeness of the exposed cohort	**0/1**	Single-center selection with small validation cohort; representativeness limited.
	Selection	Item 2: Selection of the non-exposed cohort	**1/1**	Controls drawn from same cohort, without implant loss.
	Selection	Item 3: Ascertainment of exposure (biomarker measurement)	**1/1**	ICAM-1 measured in drainage fluid by microarray with subsequent validation; objective.

	Selection	Item 4: Outcome of interest not present at start of study	**1/1**	Implant loss occurs postoperatively; outcome not present at baseline.
	Comparability	Item 5: Comparability of cohorts on the basis of design or analysis (0-2)	**1/2**	Multivariable logistic regression reported; adjustment for antibiotics and comorbidities not unambiguous.
	Outcome	Item 6: Assessment of outcome	**1/1**	Outcome (implant loss) clearly captured clinically.
	Outcome	Item 7: Was follow-up long enough for outcomes to occur	**1/1**	Follow-up sufficient to capture implant loss.
	Outcome	Item 8: Adequacy of follow-up of cohorts	**0/1**	Few failure events (n=8); loss-to-follow-up not clearly quantified.
Kang 2026	Selection	Item 1: Representativeness of the exposed cohort	**1/1**	Consecutive patients, single center, acceptably representative.
	Selection	Item 2: Selection of the non-exposed cohort	**1/1**	Non-contracture group drawn from the same cohort.

	Selection	Item 3: Ascertainment of exposure (biomarker measurement)	**1/1**	NLR/PLR derived from standardized routine laboratory testing.
	Selection	Item 4: Outcome of interest not present at start of study	**1/1**	Capsular contracture develops postoperatively; outcome not present at baseline, no outcome-related bias.
	Comparability	Item 5: Comparability of cohorts on the basis of design or analysis (0-2)	**2/2**	Multivariable Cox / logistic regression adjusting for age, BMI, radiation, and implant type.
	Outcome	Item 6: Assessment of outcome	**1/1**	Outcome (Baker score) ascertained retrospectively from records and photographs.
	Outcome	Item 7: Was follow-up long enough for outcomes to occur	**1/1**	Median follow-up sufficient for contracture manifestation.
	Outcome	Item 8: Adequacy of follow-up of cohorts	**0/1**	Retrospective chart review; loss-to-follow-up not adequately documented.
Persichetti 2014	Selection	Item 1: Representativeness of the exposed cohort	**1/1**	Heterogeneous cohort (prospective biopsies plus retrospective analysis of 233 cases) with clearly defined inclusion criteria; irradiated patients excluded but the cohort remains representative.

	Selection	Item 2: Selection of the non-exposed cohort	**1/1**	Controls (no contracture) from the same source.
	Selection	Item 3: Ascertainment of exposure (biomarker measurement)	**1/1**	ER-α/β immunohistochemistry standardized with validated antibodies and two independent observers.
	Selection	Item 4: Outcome of interest not present at start of study	**1/1**	Capsular contracture develops postoperatively.
	Comparability	Item 5: Comparability of cohorts on the basis of design or analysis (0-2)	**1/2**	Univariate analyses without multivariable adjustment; anti-oestrogen therapy analyzed as the principal confounder, time since implantation considered in a subgroup analysis.
	Outcome	Item 6: Assessment of outcome	**1/1**	Baker score recorded clinically; IHC blinded and standardized.
	Outcome	Item 7: Was follow-up long enough for outcomes to occur	**1/1**	Cross-sectional design with biomarker measurement and outcome ascertainment at the same time point.
	Outcome	Item 8: Adequacy of follow-up of cohorts	**0/1**	Completeness not clearly documented; potential gaps in the retrospective part and no information on drop-out.

Scores are 0-1 for items 1-4 and 6-8, and 0-2 for item 5 (Comparability). Maximum total score = 9. Quality categories (Agency for Healthcare Research and Quality, AHRQ): ≥7 = good, 4-6 =

fair, ≤3 = poor.

Supplementary Table S3. Detailed QUADAS-2 assessment for the included diagnostic accuracy studies (consensus values).

Study	Domain	Signaling question / Judgment	Answer	Justification
Basta 2023	Domain 1: Patient Selection	SQ1.1: Was a consecutive or random sample of patients enrolled?	Yes	Consecutive patients with clinical suspicion of periprosthetic infection at multiple centers.
	Domain 1: Patient Selection	SQ1.2: Was a case-control design avoided?	No	The study is explicitly designed as a case-control comparison (infected vs. non-infected with routine aspirate), increasing risk of bias.
	Domain 1: Patient Selection	SQ1.3: Did the study avoid inappropriate exclusions?	Yes	Exclusion criteria are described, but the completeness of consecutive sampling is not detailed.
	Domain 1: Patient Selection	**Risk of Bias (domain-level judgment)**	**High**	Case-control design for a diagnostic accuracy study; systematically elevated risk of bias.
	Domain 1: Patient Selection	**Applicability concern (domain-level judgment)**	**Low**	Population matches the review question (implant-based surgery with suspected complication).
	Domain 2: Index Test	SQ2.1: Were the index test results interpreted without knowledge of the reference standard?	Unclear	The Synovasure α-defensin assay is standardized; blinding to the reference standard is not explicitly described.
	Domain 2: Index Test	SQ2.2: If a threshold was used, was it pre-specified?	Yes	Manufacturer-defined cut-off (commercial assay); pre-specified.
	Domain 2: Index Test	**Risk of Bias (domain-level judgment)**	**Low**	Standardized commercial assay with pre-specified cut-off.
	Domain 2: Index Test	**Applicability concern (domain-level judgment)**	**Low**	α-Defensin-1 is a clinically relevant inflammatory marker.
	Domain 3: Reference Standard	SQ3.1: Is the reference standard likely to correctly classify the target condition?	Unclear	Clinical BIRI definition used as reference standard; no universal gold standard; combination of clinical signs, microbiology, and clinical course.
	Domain 3: Reference Standard	SQ3.2: Were the reference standard results interpreted without knowledge of the index test?	Unclear	Blinding of reference standard adjudication to the index test result not unambiguously described.

	Domain 3: Reference Standard	**Risk of Bias (domain-level judgment)**	**High**	Composite clinical diagnosis; no alternative gold standard available.
	Domain 3: Reference Standard	**Applicability concern (domain-level judgment)**	**Unclear**	The BIRI definition addresses a clinically relevant complication but is not universally accepted.
	Domain 4: Flow and Timing	SQ4.1: Was there an appropriate interval between index test and reference standard?	Yes	α-Defensin measurement and clinical diagnosis performed in close temporal proximity.
	Domain 4: Flow and Timing	SQ4.2: Did all patients receive the same reference standard?	Yes	All patients underwent the same clinical BIRI adjudication.
	Domain 4: Flow and Timing	SQ4.3: Were all patients included in the analysis?	Unclear	Completeness of the analyzed sample not reported in detail.
	Domain 4: Flow and Timing	**Risk of Bias (domain-level judgment)**	**Unclear**	Flow and timing partly unclear (drop-outs, completeness).
Basta 2019	Domain 1: Patient Selection	SQ1.1: Was a consecutive or random sample of patients enrolled?	Yes	Consecutive patients with suspected periprosthetic infection at a single center.
	Domain 1: Patient Selection	SQ1.2: Was a case-control design avoided?	Yes	Single-cohort design.
	Domain 1: Patient Selection	SQ1.3: Did the study avoid inappropriate exclusions?	Yes	Very small sample (n=15); exclusion criteria only briefly described.
	Domain 1: Patient Selection	**Risk of Bias (domain-level judgment)**	**High**	Very small sample size; selection bias cannot be excluded.
	Domain 1: Patient Selection	**Applicability concern (domain-level judgment)**	**Low**	Reconstruction population matches the review question.
	Domain 2: Index Test	SQ2.1: Were the index test results interpreted without knowledge of the reference standard?	Unclear	Blinding to the reference standard not described.
	Domain 2: Index Test	SQ2.2: If a threshold was used, was it pre-specified?	Yes	Manufacturer-defined Synovasure cut-off used.
	Domain 2: Index Test	**Risk of Bias (domain-level judgment)**	**Low**	Commercial assay with pre-specified cut-off; blinding unclear.
	Domain 2: Index Test	**Applicability concern (domain-level judgment)**	**Low**	Index test matches the review question.
	Domain 3: Reference Standard	SQ3.1: Is the reference standard likely to correctly classify the target condition?	Yes	Clinical diagnosis used as reference standard.
	Domain 3: Reference Standard	SQ3.2: Were the reference standard results interpreted without knowledge of the index test?	Unclear	Blinding not described.

	Domain 3: Reference Standard	**Risk of Bias (domain-level judgment)**	**High**	Composite clinical diagnosis; blinding unclear.
	Domain 3: Reference Standard	**Applicability concern (domain-level judgment)**	**Unclear**	Reference standard clinically relevant but not universally adopted.
	Domain 4: Flow and Timing	SQ4.1: Was there an appropriate interval between index test and reference standard?	Yes	Tests performed in close temporal proximity to clinical diagnosis.
	Domain 4: Flow and Timing	SQ4.2: Did all patients receive the same reference standard?	Yes	All patients underwent the same reference diagnostic process.
	Domain 4: Flow and Timing	SQ4.3: Were all patients included in the analysis?	Yes	All n=15 patients included in the analysis.
	Domain 4: Flow and Timing	**Risk of Bias (domain-level judgment)**	**Unclear**	Flow and timing partly unclear (drop-outs, completeness).
Stewart 2020	Domain 1: Patient Selection	SQ1.1: Was a consecutive or random sample of patients enrolled?	Yes	Retrospective consecutive enrollment of all patients undergoing periprosthetic aspiration.
	Domain 1: Patient Selection	SQ1.2: Was a case-control design avoided?	Yes	Single-cohort design.
	Domain 1: Patient Selection	SQ1.3: Did the study avoid inappropriate exclusions?	Unclear	Not described in detail.
	Domain 1: Patient Selection	**Risk of Bias (domain-level judgment)**	**Some Concerns**	Consecutive enrollment argues against selection bias; antibiotic exposure uncertain but this represents the actual clinical question.
	Domain 1: Patient Selection	**Applicability concern (domain-level judgment)**	**Low**	Population matches the review question.
	Domain 2: Index Test	SQ2.1: Were the index test results interpreted without knowledge of the reference standard?	Unclear	Blinding of cell count and differential interpretation to subsequent clinical diagnosis is unclear.
	Domain 2: Index Test	SQ2.2: If a threshold was used, was it pre-specified?	No	Cut-off derived post hoc by ROC analysis; not pre-specified.
	Domain 2: Index Test	**Risk of Bias (domain-level judgment)**	**High**	Retrospectively derived cut-off; risk of optimism bias.
	Domain 2: Index Test	**Applicability concern (domain-level judgment)**	**Low**	Cell differential is an inflammatorily relevant index test.
	Domain 3: Reference Standard	SQ3.1: Is the reference standard likely to correctly classify the target condition?	Yes	Reference standard = positive culture OR intra-operative findings; not fully objective but represents the accepted clinical gold standard.
	Domain 3: Reference Standard	SQ3.2: Were the reference standard results interpreted without knowledge of the index test?	Unclear	Blinding not described.
	Domain 3: Reference Standard	**Risk of Bias (domain-level judgment)**	**Some**	Best available means of ascertainment.

			Concerns	
	Domain 3: Reference Standard	**Applicability concern (domain-level judgment)**	**Unclear**	Heterogeneously defined but clinically relevant.
	Domain 4: Flow and Timing	SQ4.1: Was there an appropriate interval between index test and reference standard?	Yes	Aspiration and diagnosis performed in close temporal proximity.
	Domain 4: Flow and Timing	SQ4.2: Did all patients receive the same reference standard?	No	Not all patients received the same reference standard; some had clinical adjudication only, others microbiological culture.
	Domain 4: Flow and Timing	SQ4.3: Were all patients included in the analysis?	Unclear	Patient flow not reported in detail.
	Domain 4: Flow and Timing	**Risk of Bias (domain-level judgment)**	**Low**	Simultaneous aspiration and diagnosis; clinical flow adequate.

Signaling questions answered as Yes / No / Unclear; domain-level judgments (Risk of Bias and Applicability) rated as Low / High / Unclear/ Some concerns, following the QUADAS-2 guidance (Whiting et al., 2011). Domain 4 (Flow and Timing) does not include an Applicability rating.