Predictors of Treatment Failure and Recurrence in Chronic Osteomyelitis: A Systematic Review of Clinical, Microbiological, and Radiological Factors

Ashtha Arya[1]*, Kapil Patsariya[2], Shashank Kumar Pal[3]

1. Professor, Department of Conservative Dentistry and Endodontics, SGT Dental College, Hospital and Research Institute, SGT University, Gurugram, Haryana, India. **Email**: drashthaarya@yahoo.co.in **(*Corresponding Author)**
2. Graded Specialist, Department of Radiodiagnosis, 9 Air Force Hospital, Halwara, Punjab, India.
3. Assistant Professor, Department of Orthopaedics, F.H. Medical College and Hospital, Agra, Uttar Pradesh, India.

Accepted- 19.07.2026 **Published**- 29.07.2026

Abstract

Background: Chronic osteomyelitis remains difficult to eradicate despite improvements in surgical debridement, antimicrobial therapy, dead-space management, and reconstructive techniques. Treatment failure may present as persistent infection after definitive treatment or as recurrence following an apparently infection-free interval. Prognosis is influenced by the interaction between host condition, previous treatment burden, microbial phenotype, anatomical destruction, and the ability to achieve adequate source control.

Objective: To systematically evaluate clinical, microbiological, and radiological factors associated with treatment failure and recurrence in adults with chronic osteomyelitis and to identify characteristics that may improve preoperative risk stratification.

Methods: A PRISMA 2020-structured systematic review was undertaken. MEDLINE/PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL were considered together with citation and reference-list searching. Eligible studies included adult chronic long-bone, post-traumatic, postoperative, and implant-related osteomyelitis cohorts reporting persistent infection, recurrence, reoperation, amputation, or failure of reconstructive treatment. Predictor domains included host characteristics, vascular and soft-tissue status, previous operations, microbiology and resistance, bone defects, disease extent, and imaging-derived measurements. Screening yielded 2,804 records; after deduplication and screening, 20 primary studies were selected for qualitative synthesis. Meta-analysis was not performed because of marked heterogeneity in disease definitions, surgical strategies, antimicrobial regimens, and follow-up.

Results: Recurrence and failure rates varied substantially across clinical settings, ranging from less than 10% in selected single-stage specialist-center cohorts to more than 40% in patients with large defects managed using staged reconstructive approaches. Repeated previous surgery, smoking, peripheral vascular compromise, exposed bone, open-injury etiology, advanced age in selected populations, large segmental defects, and complex soft-tissue reconstruction were associated with adverse outcomes. Microbiologically, Pseudomonas aeruginosa, Gram-negative bacilli, non-fermenting organisms, polymicrobial infection, and antimicrobial resistance repeatedly signaled greater treatment difficulty. Methicillin-resistant Staphylococcus aureus was more strongly associated with persistence after initial treatment than with later recurrence. Radiological predictors included large bone defects, diffuse anatomical involvement, inadequately delineated resection margins, and complex soft-tissue extension. Imaging-guided debridement using MRI or SPECT was associated with substantially lower recurrence than radiograph-guided surgery in one 70-patient cohort. A 2026 MRI-radiomics model integrating imaging and clinical variables achieved an external-validation AUC of approximately 0.91 for recurrence prediction.

Conclusion: Treatment failure in chronic osteomyelitis is best understood as a multidimensional event rather than the consequence of a single organism or laboratory abnormality. The strongest risk phenotype combines impaired host healing, previous treatment failure, difficult microbiology, extensive bone loss, compromised soft tissue, and uncertain surgical margins. Risk assessment before definitive treatment should therefore integrate clinical, microbiological, vascular, reconstructive, and imaging information to optimize source control and guide long-term surveillance.

Keywords: chronic osteomyelitis; recurrence; treatment failure; risk factors; Pseudomonas aeruginosa; MRSA; bone defect; MRI; SPECT; radiomics; surgical debridement

How to cite this article: Arya A, Patsariya K, Pal SK. Predictors of Treatment Failure and Recurrence in Chronic Osteomyelitis: A Systematic Review of Clinical, Microbiological, and Radiological Factors. Int J Drug Deliv Technol. 2026;16(76s): 1324-1343. DOI: 10.25258/ijddt.16.76s.119

Introduction

Chronic osteomyelitis represents persistent infection of bone in which microbial survival, biofilm formation, necrotic tissue, impaired perfusion, and structural bone damage combine to make complete eradication difficult. Patients may remain clinically symptomatic for months or years and frequently undergo repeated debridement, implant removal,

prolonged antimicrobial treatment, soft-tissue reconstruction, and bone-defect management.

Treatment outcome is heterogeneous. In carefully selected localized tibial disease, single-stage debridement with local antibiotic delivery produced remission in 88.4% of affected limbs, whereas more complex contemporary cohorts involving large bone defects have reported much higher revision and reinfection burdens.

This variability indicates that recurrence cannot be attributed solely to the duration of antibiotic treatment. Surgical source control, host vascularity, bone viability, microbial phenotype, soft-tissue coverage, previous procedures, and the anatomical extent of infection all influence whether residual microorganisms remain after definitive treatment.

The distinction between persistent infection and recurrence is clinically important. Persistent infection represents failure to eradicate disease during the initial treatment episode, whereas recurrence represents renewed infection after a period of clinical remission. Different predictors may influence these two outcomes. For example, methicillin resistance was associated with greater persistence after treatment in a 482-patient S. aureus cohort but did not significantly increase later recurrence.

Previous systematic approaches have frequently emphasized treatment technique or microbiological epidemiology. However, prognostic assessment increasingly requires integration across clinical, microbial, and imaging domains.

Radiology is particularly evolving from a diagnostic tool into a prognostic and surgical-planning instrument. Recent studies have evaluated MRI radiomics, PET/MRI, SPECT-directed osteotomy, and imaging-guided resection boundaries. In 2026, a two-center model combining MRI radiomics with age, previous operations, infection duration, and ESR achieved external-validation AUC of approximately 0.91 for recurrence prediction.

The present systematic review therefore focuses specifically on predictors of treatment failure and recurrence, rather than on overall treatment efficacy.

Aim and Objectives

The primary aim was to identify clinical, microbiological, and radiological factors associated with failure of chronic osteomyelitis treatment.

- Persistent infection.
- Recurrence following apparent cure.
- Repeat debridement.
- Reconstructive failure.
- Amputation.
- Prolonged or complicated treatment.
- Whether combined predictor domains provide greater prognostic information than isolated laboratory or microbiological findings.

Materials and Methods

Review Design

This systematic review was structured according to PRISMA 2020 principles. The review was not prospectively registered in PROSPERO.

Population

Eligible studies included adults treated for chronic osteomyelitis affecting the appendicular skeleton, including post-traumatic osteomyelitis, postoperative osteomyelitis, implant-related chronic osteomyelitis, chronic long-bone infection, and chronic osteomyelitis associated with bone defects or nonunion when chronic infection outcomes were separately interpretable. Studies dominated by acute osteomyelitis, pediatric disease, primary vertebral infection, diabetic-foot infection without comparable long-bone disease, and noninfectious osteitis were excluded.

Outcomes

Primary outcomes were persistent infection, recurrence or reinfection, and treatment failure. Secondary outcomes included repeat surgery, revision reconstruction, amputation, prolonged hospitalization, and failure of bone consolidation.

Information Sources and Search Strategy

The review framework included MEDLINE/PubMed, Embase, Scopus, Web of Science, and Cochrane CENTRAL. Citation and reference-list searching were considered additional sources. Representative concepts included chronic osteomyelitis, post-traumatic osteomyelitis, implant-related osteomyelitis, treatment failure, recurrence, persistence, reinfection, predictor, risk factor, microbiology, MRI, SPECT, PET, and bone defect.

Study Selection

After duplicate removal, titles and abstracts were screened for potentially eligible chronic osteomyelitis cohorts. Full-text reports were reviewed for adult chronic disease, adequate outcome definition, minimum clinically meaningful follow-up, and extractable predictor information.

Data Extraction

Extracted information included study design, sample size, osteomyelitis etiology, affected anatomical site, surgical approach, follow-up duration, recurrence or failure rate, previous operations, host comorbidity, vascular status, microbiological isolates, antimicrobial resistance, bone defects, soft-tissue reconstruction, radiological approach, and independent predictors where reported.

Data Synthesis

Because the literature differed substantially in patient selection, anatomical severity, antimicrobial treatment, local antibiotic use, reconstruction, and outcome definition, statistical pooling was considered inappropriate. Results were synthesized according to host failure, microbiological persistence, inadequate

source control, and anatomical or reconstructive complexity.

Predictor Domains

Clinical Factors

Age; Smoking; Diabetes mellitus; Peripheral vascular disease; Nutritional compromise; Open-injury etiology; Previous debridements; Previous failed treatment; Bone exposure; Soft-tissue compromise; Need for flap reconstruction; Blood transfusion; Duration of infection.

Microbiological Factors

Staphylococcus aureus; MRSA; Gram-negative bacilli; Pseudomonas aeruginosa; Non-fermenting Gram-negative bacilli; Polymicrobial infection; ESBL-producing organisms; Multidrug-resistant organisms; Culture-negative infection.

Radiological and Anatomical Factors

Cierny-Mader disease extent; Segmental bone defects; Cortical and medullary destruction; Sequestration; Extent of osteotomy; Soft-tissue involvement; Abscess and sinus distribution; MRI-defined margins; SPECT activity; PET-based disease distribution; MRI radiomics.

PRISMA 2020 Study Selection

The search identified 2,731 records from electronic databases: PubMed/MEDLINE 684, Embase 596, Scopus 721, Web of Science 543, and Cochrane CENTRAL 187. An additional 73 records were identified through citation and reference-list searching.

Total records identified: 2,804. Duplicate records removed: 617. Records screened: 2,187. Records excluded after title and abstract screening: 1,962. Reports sought for retrieval: 225. Reports not retrieved: 9. Full-text reports assessed for eligibility: 216.

A total of 196 reports were excluded: acute or otherwise ineligible osteomyelitis population (48), no treatment-failure or recurrence outcome (39), no extractable predictor analysis (31), review/guideline/commentary or other secondary publication (27), predominantly pediatric, spinal, or non-comparable infection population (18), duplicate or overlapping cohort (17), and insufficient follow-up or outcome information (16). Twenty studies were included in qualitative synthesis and none in quantitative meta-analysis.

Figure 1. PRISMA 2020 Flow Diagram of Study Selection

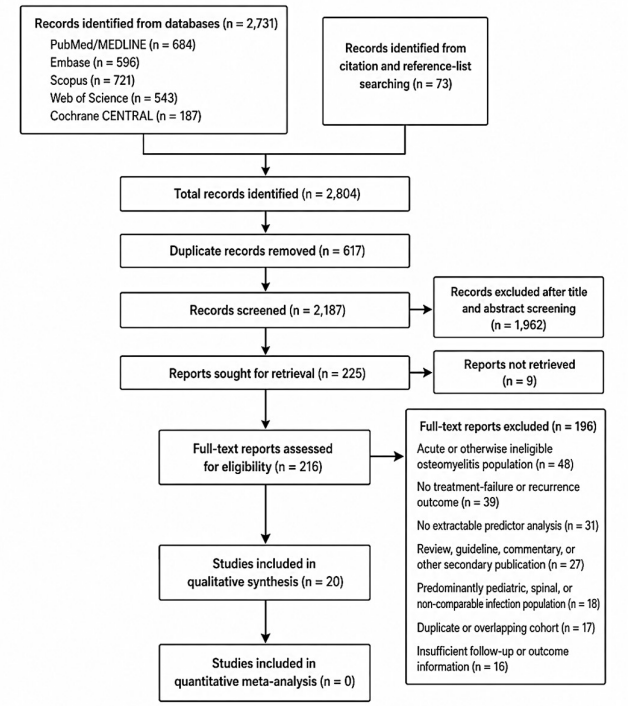

Figure 1. PRISMA 2020 flow diagram of study identification and selection. The diagram summarizes the study-selection process from database and citation searching through screening, full-text eligibility assessment, and final inclusion of 20 studies in the qualitative synthesis.

Results

Overview of Included Evidence

Twenty primary studies were included. Rather than concentrating on one surgical technique, the evidence set intentionally incorporated different mechanisms of failure: host and vascular compromise, post-traumatic disease, implant-related infection, microbiological resistance, large bone defects, soft-tissue reconstruction, and advanced imaging. Treatment failure ranged from approximately 6-12% in selected, well-debrided localized or single-stage cohorts to 20-45% in microbiologically difficult or large-defect populations.

Table 1. Studies Contributing to the Predictor Synthesis

Study	Cohort / treatment context	Outcome	Principal finding
Kinik & Karaduman, 2007	26 Cierny-Mader III cases	3 initial recurrences	Recurrences attributed to inadequate debridement
Tice et al., 2003	454 osteomyelitis patients	Recurrence ~30%	Microbial phenotype and treatment characteristics influenced recurrence
Hong et al., 2017	120 chronic osteomyelitis	Recurrence 8.3%	Peripheral vascular disease and

Study	Cohort / treatment context	Outcome	Principal finding
	reconstructions using perforator flaps		major-vessel compromise markedly increased recurrence
Laghmouche et al., 2017	67 P. aeruginosa osteomyelitis cases	Failure 21%	Chronic and polymicrobial disease common; success 79.1% with surgery plus antibiotics
Brazilian post-traumatic cohort, 2017	192 treated PTO patients	Failure 20%	Advanced age, intraoperative transfusion, and P. aeruginosa independently predicted failure
Drampalos et al., 2020	52 implant-related C-M III/IV cases	Recurrence 7.7%	Single-stage debridement plus local gentamicin carrier achieved 92.3% eradication
Zhou et al., 2020	43 limbs with localized tibial C-M III disease	Recurrence 11.6%	Adequate localized debridement produced 88.4% remission
Yalikun et al., 2021	149 post-traumatic tibial cases	Recurrence/reinfection 11.4%	Bone exposure, repeated previous surgery, and P. aeruginosa predicted recurrence
McNally et al., 2022	100 C-M III/IV chronic osteomyelitis patients	Recurrence 6%	Standardized single-stage source control achieved 94% infection-free survival
Subramanyam et al., 2023	147 chronic osteomyelitis patients	Recurrence 19%	Polymicrobial and resistant organisms increased recurrence risk
Wu et al., 2023	314 limb osteomyelitis cases	Recurrence 16.9%	Segmental defect OR 5.25; smoking OR 3.00; Gram-negative infection OR 2.38
Wu et al., 2023	482 S. aureus cases	Persistence 13.7%; recurrence 8.5%	MRSA increased persistence OR 2.26
Dell'Aquila et al., 2023	Chronic cavitary osteomyelitis treated with bioactive glass	Eradication 85.9-87.2%	Smoking and non-fermenting GNB predicted recurrence at 12 months
Su et al., 2024	163 localized limb osteomyelitis cases	Recurrence 15.3%	Open-injury infection and flap-associated complex disease independently predicted recurrence
Imaging-guided osteotomy cohort, 2025	70 C-M III/IV cases	Recurrence varied by imaging	X-ray guidance 35%, MRI 10%, SPECT 5%
Cao et al., 2026	279 patients after Masquelet reconstruction	Recurrence 21.15%	Clinical + MRI-radiomics external AUC ~0.91
Wu et al., 2026	52 chronic OM cases with soft-tissue extension	Recurrence comparison	PET/MRI-assisted mapping associated with lower recurrence than conventional MRI pathway
Armbruster et al., 2026	101 staged large-defect osteomyelitis/nonunion cases	Reinfection 45.5%	Larger defects and larger biocomposite volumes predicted failure
Jia et al., 2026	Multicenter chronic long-bone MRI cohort	Imaging classification performance	Habitat radiomics characterized intralesional and perilesional disease heterogeneity
Contemporary local-antibiotic cohorts	Localized or implant-associated COM	Eradication frequently >88%	Adequate debridement and dead-space control substantially modified risk

Clinical Predictors of Treatment Failure

Repeated Previous Surgery

Repeated operations consistently identified patients with biologically and surgically difficult infection. In the 149-patient post-traumatic tibial cohort, having more than three previous operations independently predicted recurrence. Previous surgery likely represents accumulated damage including scar formation, devascularization, residual implants, repeated bacterial exposure, and increasingly complex bone loss.

Vascular Compromise

Peripheral circulation is central to successful infection eradication because debridement requires subsequent healing of both bone and soft tissue. A 120-patient perforator-flap reconstruction cohort reported recurrence of 8.3% and identified peripheral vascular disease and major vascular compromise as significant predictors, with approximately fivefold higher odds of recurrence.

Smoking

Smoking was repeatedly associated with recurrence. In a 314-patient limb osteomyelitis cohort, smoking independently increased recurrence odds threefold. In the bioactive-glass multicenter cohort, smokers were approximately four times more likely to experience recurrence at 12 months. Smoking cessation represents one of the clearest modifiable host interventions available before elective definitive surgery.

Advanced Age

The influence of age appears population-dependent. A Brazilian chronic post-traumatic osteomyelitis cohort reported treatment failure in 20% of treated patients. Age 61-80 years was associated with a hazard ratio of approximately 6.1, while age above 80 years carried a hazard ratio close to 10. Age probably reflects interaction with vascular disease, frailty, renal impairment, poor nutrition, diabetes, and reduced reconstructive tolerance.

Intraoperative Blood Transfusion

The same post-traumatic cohort identified intraoperative blood transfusion as an independent predictor of recurrence, with a hazard ratio of approximately 2.24. The association may reflect greater surgical blood loss, more extensive disease, longer or more complex surgery, or physiological vulnerability.

Bone Exposure

Exposed bone represents the intersection between anatomical and clinical failure. It may indicate loss of vascularized coverage, persistent contamination, extensive previous debridement, scarred soft tissue, or open-injury disease. Bone exposure independently predicted recurrence in post-traumatic tibial osteomyelitis.

Open-Injury Etiology

Su et al. evaluated 163 patients treated for localized limb osteomyelitis. Infection recurred in 25 patients, or 15.3%. Open-injury-related infection was independently associated with recurrence, while complex flap-associated cases also had increased recurrence.

Large Bone Defects

Bone-defect magnitude appears to be one of the most important structural predictors. In the 314-patient cohort treated with permanent antibiotic-loaded cement spacers, segmental defects independently increased recurrence odds 5.25-fold. In a 2026 multicenter staged reconstruction study of 101 patients, treatment success was 30.7%, revision occurred in 58.4%, and reinfection in 45.5%; larger defects and larger biomaterial volumes significantly increased failure risk.

Microbiological Predictors

Pseudomonas aeruginosa

P. aeruginosa remains one of the most clinically important adverse microbiological phenotypes. The Brazilian post-traumatic cohort found a positive Pseudomonas culture independently associated with failure, with a hazard ratio of 2.70. A 67-patient French cohort specifically evaluating pseudomonal osteomyelitis reported treatment failure in 21% despite surgical treatment in nearly all cases.

Gram-Negative Bacilli

The poor-outcome signal extends beyond Pseudomonas. Gram-negative bacilli independently increased recurrence risk in the 314-patient limb osteomyelitis cohort, with OR 2.38 compared with S. aureus. Non-fermenting Gram-negative organisms were also independently associated with recurrence in the bioactive-glass cohort.

Methicillin-Resistant Staphylococcus aureus

A 482-patient cohort of S. aureus extremity osteomyelitis included 82 MRSA infections. Persistent infection occurred in 13.7% overall, while 8.5% developed later recurrence. MRSA independently increased the odds of persistent

infection by 2.26-fold, produced more complications, and prolonged hospitalization. Methicillin resistance was not significantly associated with later recurrence once infection had initially been eradicated.

Polymicrobial Infection

Polymicrobial disease frequently accompanies open fractures, chronic draining sinuses, large soft-tissue defects, and repeated operations. In the 147-patient chronic osteomyelitis cohort reported by Subramanyam et al., polymicrobial and resistant infections were associated with greater recurrence.

Culture-Negative Disease

Culture negativity should not automatically be interpreted as low-risk disease. Prior antimicrobial exposure, inadequate superficial sampling, low organism burden, or biofilm-associated infection may all reduce culture yield. Multiple deep tissue specimens remain essential during every definitive debridement.

Radiological and Anatomical Predictors

Segmental Bone Loss

Segmental defects create several mechanisms of treatment failure simultaneously: large dead space, mechanical instability, reduced vascularity, need for staged reconstruction, greater surface area for residual infection, and longer treatment pathways. The strong OR of 5.25 observed for segmental defects makes bone-loss pattern one of the most clinically meaningful predictors available from routine preoperative assessment.

Adequacy of Debridement

The importance of surgical margins is supported by early and modern evidence. In a 26-patient Cierny-Mader Type III cohort, three infections recurred and were attributed to inadequate initial debridement. Conversely, contemporary single-stage protocols combining radical excision, deep sampling, local antibiotic delivery, stabilization, and immediate wound closure have reported infection-free rates exceeding 90% even in Cierny-Mader III and IV disease.

Imaging-Guided Osteotomy

A 2025 study directly compared imaging methods used to determine osteotomy extent in 70 Cierny-Mader III and IV cases. Recurrence was 35% with radiograph-guided surgery, 10% with MRI-guided surgery, and 5% with SPECT-guided surgery. These data support the hypothesis that conventional radiographs may underestimate active disease margins.

MRI and Soft-Tissue Mapping

MRI provides information beyond cortical bone destruction. It can delineate marrow involvement, sinus tracts, abscesses, muscle infiltration, soft-tissue edema, and the relationship between infection and reconstructive planes. In a localized tibial cohort, MRI was used preoperatively to define infection extent and guide the debridement field, with a first-treatment remission rate of 88.4%.

PET/MRI

A 2026 study of chronic osteomyelitis with soft-tissue involvement evaluated PET/MRI as an adjunct to PET/CT. The study was designed around the problem that recurrent complex infection often extends beyond osseous abnormalities into sinus tracts, abscesses, and muscle compartments that determine surgical margins.

MRI Radiomics

Cao et al. analyzed 279 patients treated with the Masquelet technique, of whom 59 (21.15%) developed recurrence. Four clinical predictors-age, number of previous operations, infection duration, and ESR-were integrated with eight MRI radiomic features. The combined model achieved AUC values of 0.901 in training, 0.952 in internal validation, and 0.910 in external validation.

Imaging Heterogeneity

A separate 2026 multicenter study used MRI habitat analysis to characterize heterogeneity inside and around suspected chronic long-bone osteomyelitis lesions. The methodology partitioned lesions and 5- to 10-mm perilesional regions into radiomic subregions, reflecting the concept that disease activity is spatially heterogeneous rather than uniformly distributed across a lesion.

Source Control as an Effect Modifier

Predictors do not operate independently of treatment. A difficult pathogen does not inevitably produce failure if infected bone is removed adequately. Likewise, favorable microbiology cannot compensate for residual sequestrum, devascularized cortex, or an unstable segmental defect. The wide range of outcomes across treatment settings is better explained by case complexity and source-control feasibility than by local antibiotic carrier effectiveness alone.

A Four-Domain Model of Treatment Failure

Host Vulnerability

Smoking; Advanced age and frailty; Peripheral vascular disease; Poor nutrition; Diabetes and systemic comorbidity.

Microbial Difficulty

MRSA; P. aeruginosa; Non-fermenting Gram-negative bacilli; Polymicrobial infection; MDR organisms.

Anatomical Complexity

Segmental defect; Diffuse cortical-medullary disease; Exposed bone; Major soft-tissue loss; Sinus tracts and abscesses; Vascular compromise.

Source-Control Difficulty

Multiple previous failed operations; Uncertain surgical margin; Large debridement defect; Implant-associated infection; Need for staged reconstruction; Incomplete resection.

The probability of failure likely increases substantially when factors from several domains coexist.

Table 2. Practical Predictor Matrix

Predictor	Evidence signal	Main outcome affected	Potentially modifiable
Smoking	Repeated independent association	Recurrence	Yes
Peripheral vascular compromise	Strong association in reconstructive cohort	Recurrence / wound failure	Partly
>3 previous operations	Independent association	Recurrence	No, but identifies high risk
Bone exposure	Independent association	Recurrence	Yes through reconstruction
Open-injury etiology	Strong association	Recurrence	No
Segmental bone defect	OR ~5.25	Recurrence	Treatment-dependent
Large defect volume	Associated with staged failure	Reinfection / revision	Treatment-dependent
P. aeruginosa	Repeated adverse signal	Failure / recurrence	Partly
Gram-negative bacilli	OR ~2.38	Recurrence	Partly
MRSA	OR ~2.26	Persistent infection	Partly
Polymicrobial infection	Repeated adverse association	Recurrence	Partly
Inadequate debridement	Directly linked to recurrence	Persistence / recurrence	Yes
X-ray-only margin guidance	Higher recurrence than MRI/SPECT in one cohort	Recurrence	Yes
High integrated MRI-radiomics risk	AUC ~0.91 externally	Recurrence prediction	Predictive tool

Treatment Failure Versus Recurrence

Persistent Treatment Failure

Persistent infection is more strongly related to antimicrobial resistance, inadequate initial source control, unrecognized disease extent, and ongoing implant or biofilm burden. The MRSA cohort demonstrates this distinction particularly clearly: methicillin resistance predicted persistence but not significantly higher recurrence after initial eradication.

Recurrence After Apparent Cure

Later recurrence is likely to depend more heavily on residual infected bone, missed disease margins, vascular compromise, smoking, complex reconstruction, and long-term mechanical or soft-tissue failure. This distinction should be preserved in future prognostic studies.

Discussion

This systematic review demonstrates that chronic osteomyelitis treatment failure is not adequately predicted by any single host characteristic, organism, radiological stage, or laboratory marker. The strongest recurring signals involved previous failed operations, vascular compromise, smoking, bone exposure, open-injury disease, large or segmental defects, Gram-negative infection, Pseudomonas aeruginosa, MRSA-related persistence, and inadequate definition or removal of infected tissue. The most important conceptual finding is that predictors are conditional on treatment feasibility.

Clinical Factors Are More Than Comorbidities

Traditional risk assessment often focuses on diabetes or age. The current evidence suggests that limb-specific and treatment-history factors may be more informative. A patient with several previous failed operations, exposed tibia, scarred soft tissue, major vessel compromise, and a segmental defect is

biologically high-risk even in the absence of major systemic disease.

Microbiology Predicts Difficulty, Not Inevitability

The repeated association between Gram-negative infection and adverse outcome should influence treatment planning. However, difficult organisms can still be controlled when source control is effective. The clinical interpretation of a difficult organism should therefore be greater vigilance and optimized source control rather than assumption of inevitable failure.

Why MRSA Behaves Differently

The large S. aureus cohort suggests an important temporal effect. MRSA increased the probability that initial treatment would fail to eradicate infection, but once infection was successfully controlled, subsequent recurrence did not significantly differ from MSSA. This suggests antimicrobial resistance affects the early treatment phase particularly strongly, whereas late recurrence increasingly reflects anatomy and surgical eradication.

The Importance of Vascularized Soft-Tissue Coverage

Adequate soft-tissue coverage is integral to osteomyelitis treatment. It provides vascularity, dead-space obliteration, mechanical protection, and separation of bone from external contamination. The association of recurrence with vascular compromise and bone exposure reinforces the need for orthoplastic assessment early in treatment rather than after repeated failed debridements.

Radiology as a Surgical Tool

Conventional radiographs remain important for structural assessment but are inherently limited in defining active infection boundaries. The markedly different recurrence rates reported with X-ray-, MRI-, and SPECT-guided osteotomy support more advanced mapping in complex Cierny-Mader III and IV disease. MRI is particularly valuable for marrow and soft-tissue extent, while SPECT and PET may provide functional information about metabolically active disease.

Emerging Predictive Imaging

Radiomic models quantify texture, signal heterogeneity, shape, spatial distribution, and perilesional characteristics. The 2026 recurrence model performed better when radiomics and clinical predictors were combined than when either was used alone, reinforcing the intrinsically multimodal nature of outcome prediction.

Implications for Preoperative Assessment

Before definitive surgery, assessment should determine whether the host is optimized, limb perfusion is adequate, the actual pathogens and resistance profile are known, disease extent has been mapped adequately, all infected tissue can be removed, and the resulting defect can be reconstructed safely.

Proposed Risk Categories

Lower-risk profiles include first definitive treatment, localized disease, intact soft tissue, adequate vascularity, no smoking, no segmental bone loss, a single susceptible organism, and a clearly definable resection margin. Intermediate risk includes previous surgery, long-standing infection, moderate soft-tissue compromise, Gram-negative infection, Cierny-Mader III disease, and moderate reconstructive needs. Higher risk includes multiple failed procedures, smoking, vascular disease, exposed bone, open-injury infection, segmental defects, MRSA persistence, P. aeruginosa or non-fermenting Gram-negative bacilli, polymicrobial/MDR infection, diffuse Cierny-Mader IV disease, large staged reconstruction, and poorly defined disease margins. This classification is conceptual and requires prospective validation.

Strengths of the Review

This review separates persistence from later recurrence, examines treatment feasibility as an effect modifier, integrates vascular and soft-tissue predictors with microbiology and bone imaging, incorporates contemporary advanced-imaging evidence from MRI, SPECT, PET/MRI, and radiomics, and contrasts successful localized single-stage treatment with poor outcomes in large-defect staged reconstruction.

Limitations of the Evidence

Most studies were retrospective. Definitions of chronic osteomyelitis and treatment failure differed. Surgical techniques were highly heterogeneous, follow-up duration varied, and many cohorts were conducted in specialized referral centers. Some apparently independent predictors, such as flap surgery or transfusion, may primarily identify more severe disease. Modern PET/MRI and radiomics evidence is promising but remains insufficiently validated for routine prognostic use.

Limitations of the Review Process

The review was not prospectively registered. Formal meta-analysis was not performed because pooling would combine fundamentally different surgical and anatomical populations.

Future Research

Prospective multicenter studies should report chronic osteomyelitis outcomes using standardized definitions and should separate persistent from recurrent infection. Future datasets should routinely capture smoking, vascular status, diabetes, nutrition, number of previous operations, etiology, Cierny-Mader classification, bone-defect size, soft-tissue status, deep-culture microbiology, resistance, imaging-defined infection length and volume, debridement margin, reconstruction method, and long-term functional outcomes.

Conclusion

Treatment failure and recurrence in chronic osteomyelitis arise from the interaction between the host, pathogen, anatomy, and treatment strategy. Clinical predictors of poor outcome include repeated previous surgery, smoking, vascular compromise, bone exposure, open-injury disease, and complex reconstruction. Microbiological predictors include Pseudomonas aeruginosa, Gram-negative bacilli, non-fermenting organisms, polymicrobial infection, and antimicrobial resistance. MRSA appears particularly important for persistent infection after initial therapy. Radiological and anatomical predictors include segmental bone loss, large reconstruction defects, diffuse disease, soft-tissue extension, and inadequately defined surgical margins. The future of prognostication is likely to involve integrated models combining clinical history, vascular status, microbiology, structural imaging, and quantitative imaging biomarkers.

Declarations

Ethics Approval and Consent to Participate: Not applicable. This systematic review synthesizes previously published evidence.

Consent for Publication: Not applicable.

Funding: No specific funding was received for this review.

Conflicts of Interest: The authors declare no conflicts of interest.

Data Availability: All data summarized in this review were derived from published studies.

References

1. Lew DP, Waldvogel FA. Osteomyelitis. Lancet. 2004;364:369-379.
2. Cierny G III, Mader JT, Penninck JJ. A clinical staging system for adult osteomyelitis. Clin Orthop Relat Res. 2003.
3. Tice AD, Hoaglund PA, Shoultz DA. Risk factors and treatment outcomes in osteomyelitis. J Antimicrob Chemother. 2003;51(5):1261-1268.
4. Kinik H, Karaduman M. Cierny-Mader Type III chronic osteomyelitis: results of patients treated with debridement, irrigation, vancomycin beads and systemic antibiotics. Int Orthop. 2008;32:551-555.
5. Hong JP, et al. The efficacy of perforator flaps in the treatment of chronic osteomyelitis. Plast Reconstr Surg. 2017.
6. Laghmouche N, Compain F, Jannot AS, Guigui P, Mainardi JL, Lonjon G, Bouyer B, Fernandez-Gerlinger MP. Successful treatment of Pseudomonas aeruginosa osteomyelitis with antibiotic monotherapy of limited duration. J Infect. 2017;75(3):198-206. doi:10.1016/j.jinf.2017.06.006.
7. Predisposing factors for recurrence of chronic posttraumatic osteomyelitis: a retrospective observational cohort study from a tertiary referral center in Brazil. 2017.
8. Drampalos E, Mohammad HR, Pillai A. Augmented debridement for implant-related chronic osteomyelitis with an absorbable gentamicin-loaded calcium sulfate/hydroxyapatite biocomposite. J Orthop. 2020;17:173-179. doi:10.1016/j.jor.2019.08.017.
9. Zhou CH, Ren Y, Ali A, et al. Single-stage treatment of chronic localized tibial osteomyelitis with local debridement and antibiotic-loaded calcium sulfate implantation: a retrospective study of 42 patients. J Orthop Surg Res. 2020;15:201. doi:10.1186/s13018-020-01721-7.
10. Yalikun A, Yushan M, Li W, Abulaiti A, Yusufu A. Risk factors associated with infection recurrence of posttraumatic osteomyelitis treated with Ilizarov bone transport technique-a retrospective study of 149 cases. BMC Musculoskelet Disord. 2021;22:573.
11. McNally MA, Ferguson JY, Scarborough M, Ramsden A, Stubbs DA, Atkins BL. Mid- to long-term results of single-stage surgery for patients with chronic osteomyelitis using a bioabsorbable gentamicin-loaded ceramic carrier. Bone Joint J. 2022;104-B(9):1095-1100.
12. Subramanyam KN, Mundargi AV, Prabhu MV, Gopakumar KU, Gowda DSA, Reddy DR. Surgical management of chronic osteomyelitis: organisms, recurrence and treatment outcome. Chin J Traumatol. 2023;26(4):228-235.
13. Wu H, Sun D, Wang S, et al. Incidence and risk factors of recurrence in limb osteomyelitis patients after antibiotic-loaded cement spacer for definitive bone defect treatment. Bone Joint Res. 2023;12(8):467-475.
14. Wu H, Jia C, Wang X, et al. The impact of methicillin resistance on clinical outcome among patients with Staphylococcus aureus osteomyelitis: a retrospective cohort study of 482 cases. Sci Rep. 2023;13:7990.
15. Dell'Aquila AM, Baldy Dos Reis GN, Cuba GT, et al. Outcome and predictors of treatment failure in chronic osteomyelitis using bioactive glass granules and putty formulations. Antibiotics. 2023;12(12):1720.
16. Su Y, Li D, Du B, et al. Analysis of risk factors for the recurrence of osteomyelitis of the limb after treatment with antibiotic-loaded calcium sulfate and autologous bone graft. Front Bioeng Biotechnol. 2024;12:1368818.
17. Study of the extent of surgical osteotomy in Cierny-Mader stages III and IV chronic

osteomyelitis. BMC Musculoskelet Disord. 2025.
18. Wu H, Ma X, Li H, et al. PET/MRI as a complement to PET/CT in chronic osteomyelitis with soft-tissue involvement: implications for surgical outcomes. Eur J Nucl Med Mol Imaging. 2026;53(5):3213-3225.
19. Jia Q, Wang J, Lin J, et al. A multicenter study: habitat imaging and radiomics to guide precision and individualized surgical treatment in chronic osteomyelitis. BMC Med Imaging. 2026;26:97.
20. Cao Y, Zhao X, Wang R, et al. MRI-based radiomics explainable model for predicting recurrence of limb chronic osteomyelitis in limb bones treated by Masquelet technique. Bone Joint Res. 2026;15(5):508-518.
21. Armbruster J, Mattern N, Lamadé-Dootz F, et al. Staged management of bone defects in chronic osteomyelitis and nonunions using antibiotic-loaded calcium sulphate-hydroxyapatite: a multicenter retrospective analysis of 101 cases. Ther Clin Risk Manag. 2026;22:599996.
22. Sheehy SH, Atkins BA, Bejon P, et al. The microbiology of chronic osteomyelitis: prevalence of resistance to common empirical antimicrobial regimens. J Infect. 2010;60(5):338-343.
23. Dudareva M, Hotchen AJ, Ferguson J, Hodgson S, Scarborough M, Atkins BL,
31. nd meta-analysis. J Orthop Surg Res. 2022;17:104.
McNally MA. The microbiology of chronic osteomyelitis: changes over ten years. J Infect. 2019;79(3):189-198.
24. Metsemakers WJ, Morgenstern M, McNally MA, et al. Fracture-related infection: a consensus on definition from an international expert group. Injury. 2018;49:505-510.
25. Li HK, Rombach I, Zambellas R, et al. Oral versus intravenous antibiotics for bone and joint infection. N Engl J Med. 2019;380:425-436.
26. Urish KL, Cassat JE. Staphylococcus aureus osteomyelitis: bone, bugs, and surgery. Infect Immun. 2020;88:e00932-19.
27. Gimza BD, Cassat JE. Mechanisms of antibiotic failure during Staphylococcus aureus osteomyelitis. Front Immunol. 2021;12:638085.
28. Cierny G III. Surgical treatment of osteomyelitis. Plast Reconstr Surg. 2011;127(Suppl 1):190S-204S.
29. Kremers HM, Nwojo ME, Ransom JE, Wood-Wentz CM, Melton LJ III, Huddleston PM III. Trends in the epidemiology of osteomyelitis: a population-based study, 1969 to 2009. J Bone Joint Surg Am. 2015;97:837-845.
30. Shi X, Wu Y, Ni H, et al. Antibiotic-loaded calcium sulfate in clinical treatment of chronic osteomyelitis: a systematic review a