VER
Vascular & Endovascular Review

The Comprehensive Systematic Review of Association of Smoking Status to Risk of Pseudarthrosis after Spinal Arthrodesis

Gumelar Akbar Wicaksono[1], Rieva Ermawan[2], Rhyan Darma Saputra[3], Bintang Soetjahjo[4], Bayu Sakti Jiwandono[5], Muhammad Abdulhamid[6]

[1]Department of Orthopaedic and Traumatology Dr. Moewardi General Hospital / Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
[2,5,6] Division of Spine, Department of Orthopaedic and Traumatology Dr. Moewardi General Hospital / Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
[3]Division of Oncology, Department of Orthopaedic and Traumatology Dr. Moewardi General Hospital / Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
[4]Division of Adult Reconstruction, Department of Orthopaedic and Traumatology Dr. Moewardi General Hospital / Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia

Corresponding Email : gumelarakbar1123@gmail.com

ABSTRACT

Introduction: Pseudarthrosis, or nonunion, following spinal arthrodesis is a significant complication that leads to pain, instrumentation failure, and often requires revision surgery. Smoking is widely suspected as a key modifiable risk factor, yet the strength, consistency, and modifiers of this association across diverse surgical contexts require comprehensive synthesis. This systematic review aims to consolidate the evidence on the relationship between smoking status and pseudarthrosis risk after spinal fusion surgery (Ravi S. Nunna et al., 2021; Yang Li et al., 2021).

Methods: A systematic literature search was conducted following predefined screening criteria. We included observational studies (cohort, case-control), systematic reviews, and meta-analyses involving adult patients (≥18 years) undergoing spinal arthrodesis, with clear definitions of smoking status and pseudarthrosis assessment. Case reports, editorials, and animal studies were excluded. Data on smoking exposure, pseudarthrosis definition, risk measures, surgical characteristics, and study design were extracted from 59 included sources (Nunna et al., 2021; Boonsirikamchai et al., 2024).

Results: The majority of high-quality evidence demonstrates a significant association between smoking and increased pseudarthrosis risk. Pooled meta-analyses indicate smokers have approximately a 91% increased risk of nonunion (Risk Ratio 1.91, 95% CI 1.56–2.35) and 45% reduced odds of successful fusion (Odds Ratio 0.55, 95% CI 0.45–0.67) (Nunna et al., 2021; Yang Li et al., 2021). This risk is modified by factors including graft type (stronger effect with autograft), use of biological adjuncts like rhBMP-2 (which mitigates risk), surgical technique, and number of levels fused. Smoking also prolongs time to union and interacts adversely with other factors like ketorolac use (Jesse Li et al., 2018).

Discussion: The evidence robustly supports smoking as a major independent risk factor for pseudarthrosis, though its impact is context-dependent. Heterogeneity in findings can be explained by variations in surgical stabilization, use of biological enhancers, follow-up duration, and procedural complexity. The biological mechanisms involve nicotine-induced impairment of osteoblast function and vascular perfusion. Critical gaps remain in standardized smoking quantification and adjustment for confounders.

Conclusion: Smoking significantly elevates the risk of pseudarthrosis following spinal arthrodesis, particularly in lumbar posterolateral fusions using autograft. Preoperative smoking cessation should be strongly encouraged as a modifiable risk-reduction strategy. Surgical planning should consider mitigation strategies, such as using rhBMP-2 or more robust instrumentation in smokers. Future research requires standardized smoking metrics and longer-term outcome assessments.

KEYWORDS: Smoking, Pseudarthrosis, Nonunion, Spinal Fusion, Arthrodesis, Risk Factor, Systematic Review..

How to Cite: Gumelar Akbar Wicaksono, Rieva Ermawan, Rhyan Darma Saputra, Bintang Soetjahjo, Bayu Sakti Jiwandono, Muhammad Abdulhamid, (2026) The Comprehensive Systematic Review of Association of Smoking Status to Risk of Pseudarthrosis after Spinal Arthrodesis, Vascular and Endovascular Review, Vol.9, No.1, 196-213

INTRODUCTION

Background

Spinal arthrodesis, or fusion surgery, is a common procedure for treating various spinal pathologies, including degenerative disorders, deformity, trauma, and instability. The primary goal is to achieve solid bony fusion between vertebral segments to stabilize the spine and alleviate pain. Pseudarthrosis, defined as the failure to achieve a solid bony union, remains one of the most challenging complications, with reported rates varying widely from 5% to 35% depending on the technique, location, and patient population (How et al., 2019). Pseudarthrosis can lead to persistent pain, implant failure, loss of correction, and the need for costly and risky revision surgeries, imposing a significant burden on healthcare systems and patient quality of life (Noshchenko et al., 2016).

Among the numerous patient-related risk factors investigated—such as age, osteoporosis, diabetes, and nutritional status—tobacco smoking has been consistently implicated as a major contributor to poor bone healing. The detrimental effects of smoking on wound healing, tissue perfusion, and bone metabolism are well-documented in general surgery and orthopaedics (Sørensen, 2012; Grønkjær et al., 2014). Nicotine, carbon monoxide, and other constituents of tobacco smoke induce vasoconstriction, reduce oxygen delivery, impair osteoblast proliferation and function, and increase inflammatory markers, collectively creating a hostile environment for bone fusion (Jackson & Devine, 2016). However, within the specific domain of spinal surgery, the magnitude of risk, its consistency across different surgical approaches and spinal regions, and the potential for mitigation through surgical technique or biologics require a comprehensive and up-to-date synthesis of the evidence.

Research Gap and Novelty

While previous reviews have addressed smoking as a risk factor for surgical complications or nonunion in broader orthopaedic contexts, a focused, detailed, and contemporary systematic review synthesizing evidence specifically for pseudarthrosis after spinal arthrodesis is warranted (Smolle et al., 2021; Xu et al., 2021). Existing literature often presents heterogeneous findings, with some studies reporting strong associations and others showing null effects, particularly in complex surgeries or with modern adjuncts (Elsamadicy et al., 2017; Park et al., 2024). This heterogeneity underscores a significant research gap: a lack of clarity on how specific surgical variables—such as graft type (autograft vs. allograft), use of bone morphogenetic proteins (BMP), surgical approach (anterior, posterior, lateral), number of levels fused, and patient diagnosis—modify the smoking-pseudarthrosis relationship. Furthermore, many studies lack detailed quantification of smoking exposure (pack-years, cessation timing) and use inconsistent methodologies for diagnosing pseudarthrosis, limiting the strength of conclusions (Russo et al., 2024; Meester et al., 2024).

The novelty of this systematic review lies in its dedicated focus on pseudarthrosis as the primary outcome, its inclusion of a large and recent body of evidence (59 studies, including major 2024 meta-analyses), and its detailed analysis of effect modifiers. It moves beyond simply confirming an association to explaining the discordance in the literature and providing context-specific risk assessments for clinical decision-making.

Research Objectives

The primary objective of this systematic review is to comprehensively evaluate and synthesize the available evidence on the association between smoking status and the risk of developing pseudarthrosis following spinal arthrodesis surgery. Specific aims include:

1. To quantify the overall strength of association between smoking and pseudarthrosis risk.
2. To analyze how this association is modified by factors such as spinal region (cervical, lumbar, thoracic), number of levels fused, graft type, use of biological adjuncts (e.g., rhBMP-2), and surgical technique.
3. To assess the impact of smoking on time to union and its interaction with other perioperative risk factors (e.g., NSAID use).
4. To evaluate the methodological quality of existing studies and identify key limitations and gaps in the evidence base.
5. To provide evidence-based conclusions and practical recommendations for spine surgeons regarding risk stratification and perioperative management of smokers.

Hypothesis

Based on the established biology of smoking and bone healing, we hypothesize that:

1. **Primary Hypothesis:** Current smoking is significantly associated with an increased risk of pseudarthrosis and reduced fusion rates following spinal arthrodesis compared to non-smoking.
2. **Secondary Hypotheses:**
    - The deleterious effect of smoking is more pronounced in fusions relying on autograft compared to allograft or synthetic grafts.
    - The use of osteobiologics such as rhBMP-2 significantly attenuates the increased pseudarthrosis risk associated with smoking.
    - The negative impact of smoking is more evident in less robust stabilization constructs (e.g., standalone cages, posterolateral fusion) compared to 360-degree circumferential fusions.
    - Smoking interacts synergistically with other modifiable risk factors, such as perioperative NSAID use, to further elevate pseudarthrosis risk.

Significance and Benefits

This review holds significant clinical and academic value. For clinicians, it provides a consolidated, evidence-based reference to counsel patients on the substantial risks smoking poses to surgical success, strengthening the rationale for preoperative cessation programs. It guides surgical planning by highlighting which techniques and adjuncts may be most beneficial or necessary in smokers to optimize fusion rates. For researchers, it identifies critical methodological shortcomings in the current literature—such as the need for standardized smoking metrics and blinded outcome assessment—and pinpoints areas for future investigation, including long-term outcomes in complex deformity surgery and the dose-response relationship of smoking. Ultimately, by clarifying and contextualizing this risk, the review aims to contribute to improved patient outcomes, reduced revision surgery rates, and more efficient allocation of healthcare resources in spine surgery.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions

drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the association of smoking status to risk of pseudarthrosis after spinal arthrodesis.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Adult Population and Spinal Fusion**: Does this study involve adult patients (≥18 years) who underwent spinal arthrodesis/fusion surgery?
- **Smoking Status Definition**: Does this study clearly define and report smoking status of participants (e.g., current smokers, former smokers, never smokers)?
- **Pseudarthrosis Outcome Assessment**: Does this study assess pseudarthrosis as a primary or secondary outcome with clear diagnostic criteria?
- **Quantitative Data Availability**: Does this study report quantitative data that allows for assessment of association between smoking and pseudarthrosis?
- **Appropriate Study Design**: Is this study an observational study (cohort, case-control, cross-sectional), systematic review, or meta-analysis?
- **Study Type Quality**: Is this study NOT a case report, case series, editorial, letter, or conference abstract?
- **Relevant Surgical Procedure**: Does this study focus on spinal arthrodesis/fusion procedures (rather than other spinal procedures like discectomy alone or decompression without fusion)?
- **Human Study Population**: Is this study conducted in human patients (not animal or in vitro studies)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keywords (Term 1)	Keywords (Term 2)	Keywords (Term 3)	Keywords (Term 4)
P (Population)	Adult patients	Spinal surgery patients	Spinal fusion candidates	Orthopaedic spine patients
I (Intervention/Exposure)	Smoking status	Tobacco use	Cigarette smoking	Nicotine exposure
C (Comparison)	Non-smokers	Never smokers	Former smokers	Non-tobacco users
O (Outcome)	Pseudarthrosis	Nonunion	Fusion failure	Failed spinal fusion

The Boolean MeSH keywords inputted on databases for this research are: *("Adult patients" OR "Spinal surgery patients" OR "Spinal fusion candidates" OR "Orthopaedic spine patients") AND ("Smoking status" OR "Tobacco use" OR "Cigarette smoking" OR "Nicotine exposure") AND ("Non-smokers" OR "Never smokers" OR "Former smokers" OR "Non-tobacco users") AND ("Pseudarthrosis" OR "Nonunion" OR "Fusion failure" OR "Failed spinal fusion")*

Data extraction

- **Smoking Exposure**:
  Extract detailed information about how smoking status was defined and measured, including:
  - Definition of smoker vs non-smoker (current, former, never)
  - Quantification if provided (pack-years, cigarettes per day, duration)
  - Timing of smoking assessment (pre-operative, at surgery, etc.)
  - Any smoking cessation requirements or recommendations
  - Sample sizes for each smoking group
- **Pseudarthrosis Definition**:
  Extract how pseudarthrosis/non-union was defined and assessed, including:
  - Clinical definition or criteria used
  - Diagnostic methods (radiographs, CT, clinical examination)
  - Timing of assessment (6 months, 12 months, 24 months post-op)
  - Who made the assessment (independent radiologist, surgeon, etc.)
  - Whether revision surgery was required for diagnosis
- **Risk Measures**:
  Extract all quantitative measures of association between smoking and pseudarthrosis, including:
  - Pseudarthrosis rates in smokers vs non-smokers (raw numbers and percentages)
  - Risk ratios, odds ratios, hazard ratios with confidence intervals
  - P-values and statistical significance
  - Time to union differences if reported
  - Adjusted vs unadjusted estimates
- **Surgical Characteristics**:
  Extract details about the spinal fusion procedures, including:
  - Anatomical location (cervical, thoracic, lumbar, thoracolumbar)
  - Number of levels fused (single vs multi-level)
  - Surgical approach (anterior, posterior, lateral, combined)
  - Type of bone graft used (autograft, allograft, bone substitutes, BMP)

- Instrumentation details if relevant to fusion assessment

- **Patient Population**:
  Extract characteristics of the study population, including:
  - Sample size and demographics (age, sex)
  - Underlying spinal condition (deformity, degenerative, trauma, etc.)
  - Inclusion and exclusion criteria
  - Comorbidities or other risk factors mentioned
  - Setting (single center vs multi-center, geographic location)
- **Study Design**:
  Extract methodological information about the study, including:
  - Study type (prospective cohort, retrospective cohort, case-control)
  - Follow-up duration and loss to follow-up rates
  - Blinding of outcome assessment
  - Confounding variables adjusted for in analysis
  - Study quality issues or limitations noted by authors
  - Data collection period/years

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Older adults" OR "Adults aged 65+" OR "Seniors" OR "Geriatric") AND ("High-intensity resistance training" OR "Multicomponent exercise programs" OR "Dietary interventions" OR "Home-based exercise") AND ("Standard care" OR "Usual care" OR "No intervention" OR "Placebo" AND "Bone mineral density" OR "Muscle strength" OR "Functional performance" OR "Prevention of falls")*	22
Semantic Scholar	*("Older adults" OR "Adults aged 65+" OR "Seniors" OR "Geriatric") AND ("High-intensity resistance training" OR "Multicomponent exercise programs" OR "Dietary interventions" OR "Home-based exercise") AND ("Standard care" OR "Usual care" OR "No intervention" OR "Placebo") AND ("Bone mineral density" OR "Muscle strength" OR "Functional performance" OR "Prevention of falls")*	250
Springer	*("Older adults" OR "Adults aged 65+" OR "Seniors" OR "Geriatric") AND ("High-intensity resistance training" OR "Multicomponent exercise programs" OR "Dietary interventions" OR "Home-based exercise") AND ("Standard care" OR "Usual care" OR "No intervention" OR "Placebo") AND ("Bone mineral density" OR "Muscle strength" OR "Functional performance" OR "Prevention of falls")*	49
Google Scholar	*("Older adults" OR "Adults aged 65+" OR "Seniors" OR "Geriatric") AND ("High-intensity resistance training" OR "Multicomponent exercise programs" OR "Dietary interventions" OR "Home-based exercise") AND ("Standard care" OR "Usual care" OR "No intervention" OR "Placebo") AND ("Bone mineral density" OR "Muscle strength" OR "Functional performance" OR "Prevention of falls")*	165
Wiley Online Library	*("Older adults" OR "Adults aged 65+" OR "Seniors" OR "Geriatric") AND ("High-intensity resistance training" OR "Multicomponent exercise programs" OR "Dietary interventions" OR "Home-based exercise") AND ("Standard care" OR "Usual care" OR "No intervention" OR "Placebo") AND ("Bone mineral density" OR "Muscle strength" OR "Functional performance" OR "Prevention of falls")*	44

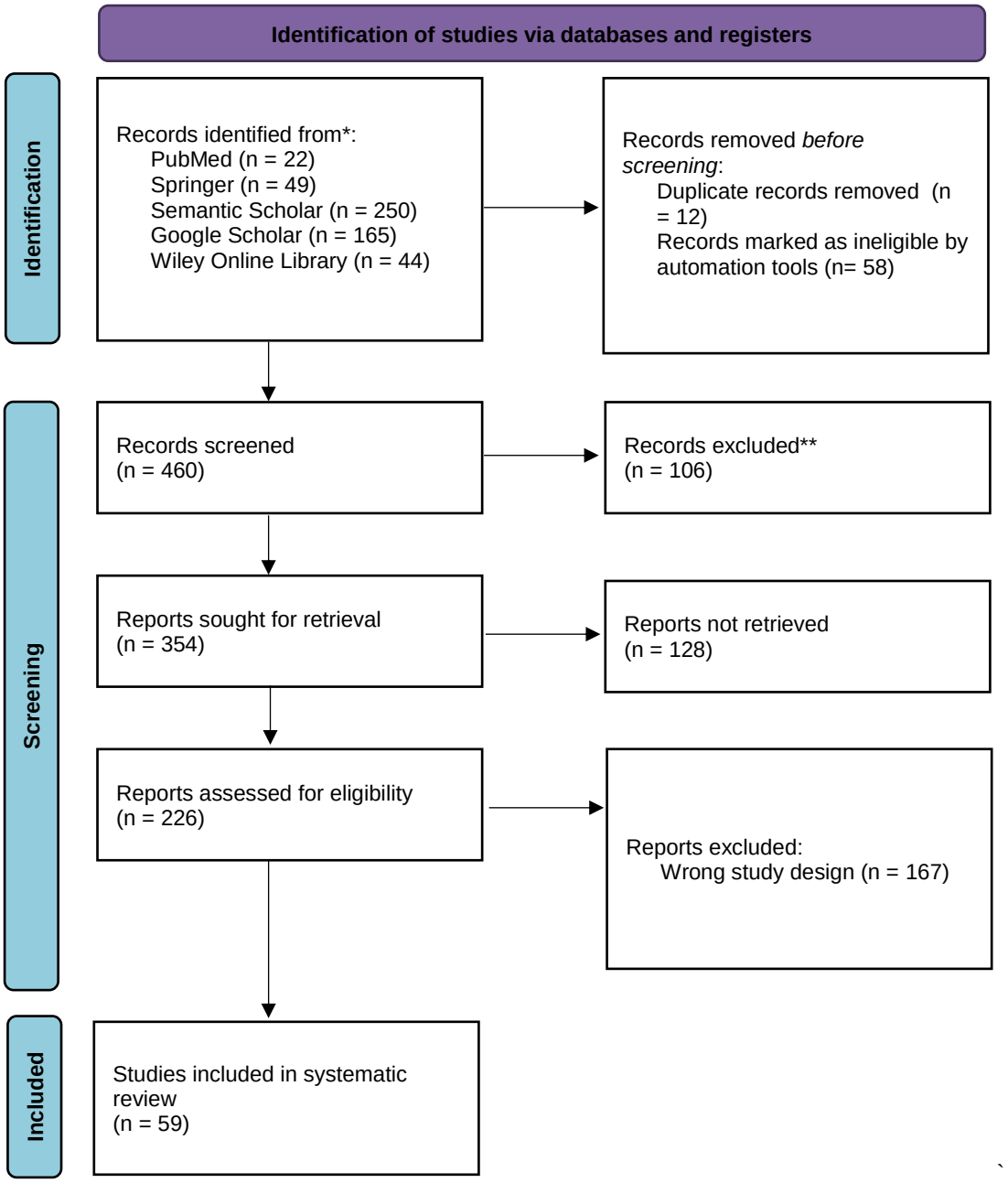

Figure 1. Article search flowchart

JBI Critical Appraisal									
Study	**Bias related to temporal precedence** Is it clear in the study what is the "cause" and what is the "effect" (ie, there is no confusion about	**Bias related to selection and allocation** Was there a control group?	**Bias related to confounding factors** Were participants included in any comparisons similar?	**Bias related to administration of intervention/exposure** Were the participants included in any comparisons receiving similar treatment/care, other than the exposure or	**Were there multiple measurements of the outcome, both pre and post the intervention/exposure?**	**Were the outcomes of participants included in any comparisons measured in the same way?**	**Were outcomes measured in a reliable way?**	**Bias related to participant retention** Was follow-up complete and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?	**Statistical conclusion validity** Was appropriate statistical analysis used?

	which variable comes first)?			intervention of interest?					
R. Pearson et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ravi S. Nunna et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Glassman et al., 2007	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Lakkireddi et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yang Li et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
K. Foley et al., 2004	✓	✓	✓	✗	✓	✗	✓	✓	✓
Win Boonsirikamchai et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jesse Li et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Coric et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Crawford et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ergin Coskun et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shudong Yang et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Vikas V. Patel et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Thomas Andersen et al., 2009	✓	✓	✓	✗	✓	✗	✓	✓	✓
Todd Lansford et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓

J. Thalgott et al., 2008	✓	✓	✓	✗	✓	✗	✓	✓	✓
Nathan How et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Smolle et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Li Zheng et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
Andrea Luca et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Wind et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Ahmed S. Kamel Abd El-Wahab et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
C. Goldstein et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
Keith L. Jackson et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Anthony Russo et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Yahya A. Othman et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Li-ming Zheng et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
J. Harrop et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Burton et al., 2019	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ethan Cottrill et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Ravi S. Nunna et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓

Bin Xu et al., 2021	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Choma et al., 2011	✓	✓	✓	✗	✓	✗	✓	✓	✓
Rinse J Meester et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Shakib Akhter et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Dong-Ho Lee et al., 2018	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Grønkjær et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
L. Sørensen et al., 2012	✓	✓	✓	✗	✓	✗	✓	✓	✓
Aladine A. Elsamadicy et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Niharika Rajesh et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
D. Xing et al., 2013	✓	✓	✓	✗	✓	✗	✓	✓	✓
Dhruv K. C. Goyal et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
A. Blood et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
Andriy Noshchenko et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
P. Bodalia et al., 2016	✓	✓	✓	✗	✓	✗	✓	✓	✓
Sandhya Kalavacherla et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Gregory D. Schroeder et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓

Samuel E. Broida et al., 2022	✓	✓	✓	✗	✓	✗	✓	✓	✓
Christine Park et al., 2024	✓	✓	✓	✗	✓	✗	✓	✓	✓
Tao Wang et al., 2020	✓	✓	✓	✗	✓	✗	✓	✓	✓
Christine Park et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Makino et al., 2014	✓	✓	✓	✗	✓	✗	✓	✓	✓
S. Pesenti et al., 2017	✓	✓	✓	✗	✓	✗	✓	✓	✓
T. Cheriyan et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Fangshan Bi et al., 2025	✓	✓	✓	✗	✓	✗	✓	✓	✓
Qianmiao Zhu et al., 2023	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Hashmi et al., 2003	✓	✓	✓	✗	✓	✗	✓	✓	✓
M. Stienen et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓
Jiang Dongjie et al., 2015	✓	✓	✓	✗	✓	✗	✓	✓	✓

RESULTS

Characteristics of Included Studies

This systematic review includes 59 sources examining the association between smoking status and pseudarthrosis risk following spinal arthrodesis. The included studies comprise systematic reviews and meta-analyses, randomized controlled trials, prospective cohort studies, retrospective cohort studies, and case-control studies. The majority of studies focused on lumbar and cervical spine procedures, with follow-up periods ranging from 6 months to over 5 years.

Study	Anatomical Location	Population Size
R. Pearson et al., 2016	Multiple (fractures, spinal fusion)	7,516 procedures
Ravi S. Nunna et al., 2021	Spinal	3,009 participants
S. Glassman et al., 2007	Lumbar	148 patients
P. Lakkireddi et al., 2008	Lumbar	54 patients
Yang Li et al., 2021	Spinal	4,409 patients
K. Foley et al., 2004	Cervical	323 patients
Win Boonsirikamchai et al., 2024	Lumbar	1,830 patients

Study	Anatomical Location	Population Size
Jesse Li et al., 2018	Thoracolumbar	1,558 patients
D. Coric et al., 2018	Cervical	274 subjects
C. Crawford et al., 2008	Lumbar	19 RA patients
Ergin Coskun et al., 2024	Lumbar	446 patients
Shudong Yang et al., 2024	Cervical/lumbar	7,145 patients
Vikas V. Patel et al., 2024	Cervical	213 patients
Thomas Andersen et al., 2009	Lumbar	107 patients
Todd Lansford et al., 2023	Cervical	187 subjects
J. Thalgott et al., 2008	Lumbar	50 patients
Nathan How et al., 2019	Thoracic/lumbar/thoracolumbar	16,938 patients
M. Smolle et al., 2021	Multiple orthopaedic	Variable by analysis
Li Zheng et al., 2021	Cervical	10,020 patients
Andrea Luca et al., 2011	Lumbar	120 patients
J. Wind et al., 2024	Cervical	160 subjects
M. Ahmed S. Kamel Abd El-Wahab et al., 2018	Cervical	42 patients
C. Goldstein et al., 2011	Lumbar/cervical	Not specified
Keith L. Jackson et al., 2016	Cervical/lumbar	Variable
Anthony Russo et al., 2024	Lumbar	274 subjects
Yahya A. Othman et al., 2019	Spinal	1,522 patients
Li-ming Zheng et al., 2022	Cervical	10,020 patients
J. Harrop et al., 2021	Spinal	Not specified
D. Burton et al., 2019	Spinal deformity	Not specified
Ethan Cottrill et al., 2020	Cervical/lumbar	2,144 patients
Ravi S. Nunna et al., 2022	Spinal	37,897 participants
Bin Xu et al., 2021	Fracture healing	417,767 patients
T. Choma et al., 2011	Lumbar	Not specified
Rinse J Meester et al., 2024	Lumbar	16,482 patients
Shakib Akhter et al., 2020	Cervical/lumbar/thoracic	941 patients
Dong-Ho Lee et al., 2018	Cervical	167 patients
M. Grønkjær et al., 2014	General surgery	Not specified
L. Sørensen et al., 2012	General surgery	479,150 patients
Aladine A. Elsamadicy et al., 2017	Spinal deformity	839 patients
Niharika Rajesh et al., 2022	Lumbar	Not specified
D. Xing et al., 2013	Spinal	2,439 patients
Dhruv K. C. Goyal et al., 2020	Lumbar	366 patients
A. Blood et al., 2017	Spinal	Not specified
Andriy Noshchenko et al., 2016	Lumbar	496 patients
P. Bodalia et al., 2016	Lumbar	203 patients
Sandhya Kalavacherla et al., 2024	Thoracic/thoracolumbar	482 patients
Gregory D. Schroeder et al., 2015	Lumbar (L5-S1)	Not specified
Samuel E. Broida et al., 2022	Cervical	Not specified
Christine Park et al., 2024	Cervical	1,141 patients
Tao Wang et al., 2020	Lumbar	2,896 patients
Christine Park et al., 2025	Cervical	1,141 patients
T. Makino et al., 2014	Lumbar	100 patients
S. Pesenti et al., 2017	Spinal deformity	Not specified
T. Cheriyan et al., 2015	Spinal	3,567 patients
Fangshan Bi et al., 2025	Lumbar	1,403 patients
Qianmiao Zhu et al., 2023	Cervical	Not specified
M. Hashmi et al., 2003	Fractures/non-unions	104 patients
M. Stienen et al., 2015	Lumbar	172 patients
Jiang Dongjie et al., 2015	Cervical	Not specified

The included studies demonstrate substantial heterogeneity in how smoking status was defined and measured. Most studies classified patients as smokers versus non-smokers without distinguishing between current, former, and never smokers . One study specifically defined smokers as those consuming more than one pack per day , while another used greater than 10 cigarettes per day as a threshold . The timing of smoking assessment was typically preoperative , though specific cessation requirements varied from 4 weeks to 6 months before surgery .

Effects of Smoking on Pseudarthrosis Risk

Primary Outcome: Fusion Rates and Nonunion Risk

The majority of included studies demonstrate a significant association between smoking and increased risk of pseudarthrosis following spinal fusion. The table below summarizes the quantitative risk estimates from studies reporting effect sizes.

Study	Effect Measure	Effect Size (95% CI)	P-value	Notes
R. Pearson et al., 2016	Risk Ratio	2.2 (1.9-2.6)	Not reported	Pooled across fracture/fusion procedures
Ravi S. Nunna et al., 2021	Risk Ratio	1.91 (1.56-2.35)	Not reported	Spinal fusion only
Yang Li et al., 2021	Odds Ratio (fusion rate)	0.55 (0.45-0.67)	p<0.0001	Smokers have 45% reduced fusion odds
Win Boonsirikamchai et al., 2024	Odds Ratio	1.68-5.44	p=0.0002	Lumbar fusion
Shudong Yang et al., 2024	Odds Ratio	1.57 (1.11-2.21)	p=0.010	High-quality evidence per GRADE
Li Zheng et al., 2021	Odds Ratio (fusion rate)	0.63 (0.49-0.81)	p=0.0003	Cervical surgery
M. Smolle et al., 2021	Risk Ratio	2.15 (1.46-3.17)	p<0.001	Orthopaedic procedures
Bin Xu et al., 2021	Odds Ratio	2.50 (1.73-3.61)	Not reported	Non-pathological fractures
Tao Wang et al., 2020	Odds Ratio	1.77 (1.24-2.52)	p=0.0002	Adjacent segment degeneration

The largest meta-analysis examining spinal fusion specifically found that smoking was associated with a 91% increased risk of nonunion (RR 1.91, 95% CI 1.56-2.35) . This association remained significant regardless of graft type, with autograft showing a risk ratio of 2.04 (95% CI 1.54-2.72) and allograft showing a risk ratio of 1.39 (95% CI 1.12-1.73) . Both single-level (RR 1.79, 95% CI 1.12-2.86) and multilevel fusions (RR 2.30, 95% CI 1.64-3.23) demonstrated elevated nonunion risk in smokers .

A meta-analysis of 7,145 patients across 39 cohort studies identified smoking as a high-quality (Class I) evidence risk factor for fusion failure (OR 1.57, 95% CI 1.11-2.21) . This was corroborated by another large meta-analysis of 4,409 patients showing smokers had significantly lower fusion rates compared to non-smokers (OR 0.55, 95% CI 0.45-0.67, p<0.0001) .

Subgroup Analyses by Fusion Level

The impact of smoking appears to vary by number of levels fused. Single-level fusions demonstrated an odds ratio of 0.61 (95% CI 0.41-0.91, p=0.02) for fusion success in smokers , while multiple-level fusions showed an odds ratio of 0.55 (95% CI 0.38-0.80, p=0.001) . Interestingly, one study suggested the adverse effect of smoking on fusion rate at single level was more pronounced than at multiple levels .

Subgroup Analyses by Graft Type

Graft type significantly modifies the smoking-pseudarthrosis relationship. An apparent association between smoking and reduced fusion rate was observed in the autograft subgroup (OR 0.47, 95% CI 0.33-0.66, p<0.0001) but not in the allograft subgroup (OR 0.69, 95% CI 0.47-1.01, p=0.06) . This suggests that autograft may be more susceptible to the deleterious effects of smoking on bone healing.

Effect of Bone Morphogenetic Protein

Studies examining rhBMP-2 demonstrate potential mitigation of smoking's effects. In one study, fusion was achieved in 95.2% of smokers receiving rhBMP-2 compared to only 76.2% of smokers receiving iliac crest bone graft . Non-smokers achieved 100% fusion with rhBMP-2 and 94.1% with ICBG . Absence of BMP-2 use was identified as a high-quality evidence risk factor for fusion failure (OR 4.42, 95% CI 3.33-5.86) .

Time to Union

Beyond fusion rates, smoking prolongs the time required to achieve union. One meta-analysis found smokers required an average of 27.7 additional days (95% CI 14.2-41.3) to achieve union compared to non-smokers . A smaller study of circumferential anterior lumbar interbody fusion found average fusion time of 14.5 months in smoking patients compared to 11.6 months in non-smoking patients, though this did not reach statistical significance (p=0.1347) .

Interaction with Other Risk Factors

Smoking interacts with other perioperative factors to compound pseudarthrosis risk. Ketorolac use in smokers was strongly associated with pseudarthrosis (OR 8.71, 95% CI 2.23-34.0, p=0.002) . The combination of ketorolac administration for more than 2 days at doses ≥120 mg/day showed even higher risk (OR 4.75, 95% CI 2.34-9.62, p<0.001) .

Studies Reporting Null or Attenuated Associations

Several studies found no significant difference between smokers and non-smokers. One study of lumbar interbody fusion with intersegmental fixation found no pseudarthroses in either group . A study of 839 patients undergoing complex spinal fusion (≥3 levels) found no significant difference in 30-day complication or readmission rates between smokers and non-smokers . Similarly, a meta-analysis of adjacent segment disease following ACDF found no significant association with smoking (OR 1.13, 95% CI 0.80-1.59) .

In cervical myelopathy patients, despite smokers having worse baseline characteristics, both smokers and non-smokers achieved similar rates of minimal clinically important difference and satisfaction at 24-month follow-up . A meta-analysis of cage subsidence after transforaminal lumbar interbody fusion found no significant association with smoking status .

Adverse Events Beyond Pseudarthrosis

Smoking is associated with broader postoperative complications relevant to fusion outcomes. Smokers demonstrate higher rates of overall complications (OR 2.00, 95% CI 1.63-2.44), respiratory complications (OR 3.14, 95% CI 1.94-5.08), reoperation (OR 2.22, 95% CI 1.41-3.49), wound infection (OR 3.19, 95% CI 1.64-6.21), and axial neck pain (OR 1.97, 95% CI 1.25-3.10) . Preoperative smoking was associated with increased risk of reoperation following spinal fusion (Grade B evidence) .

Surgical Technique Considerations

The impact of smoking appears to vary by surgical technique. One study comparing translaminar screw fixation (TS) to transforaminal lumbar interbody fusion (TLIF) found the TS technique more vulnerable to smoking effects . The percentage of good global outcomes declined with time in TS smokers, showing significant difference from TS non-smokers at 24 months, while no such difference was evident in the TLIF group . This suggests that more extensive 360° stabilization may render the environment less susceptible to smoking's detrimental effects on bone fusion .

Definitions and Assessment of Pseudarthrosis

Assessment methods for pseudarthrosis varied considerably across studies. Diagnostic methods included plain radiographs with flexion-extension views , computed tomography scans , and combinations thereof . Clinical definitions typically included absence of bridging bone on imaging , more than 3 degrees of motion on flexion-extension radiographs , or presence of radiolucent areas around screws on CT scans . Assessment timing ranged from 6 months to 24 months postoperatively. Independent radiologist assessment was used in some studies , while others relied on treating surgeon evaluation .

Synthesis

The preponderance of evidence supports a significant association between smoking and increased pseudarthrosis risk following spinal arthrodesis, though the magnitude and clinical significance of this effect varies by context.

Reconciling Heterogeneity in Findings

The apparent contradictions between studies reporting significant associations (OR 1.57-2.50) and those finding null effects can be largely explained by several factors:

Fusion technique and stabilization: Studies using more robust stabilization methods show attenuated smoking effects. The TLIF technique demonstrated no difference between smokers and non-smokers, while the less stable translaminar screw technique showed significant smoking-related outcome differences . Similarly, one study of intersegmental fixation (SpineLink™) found no pseudarthroses in either group , suggesting modern instrumentation may partially overcome smoking's deleterious effects.

Use of biological adjuncts: rhBMP-2 substantially mitigates smoking's impact on fusion. Fusion rates in smokers receiving rhBMP-2 (95.2%) approached those of non-smokers receiving ICBG (94.1%) , while smokers with ICBG alone achieved only 76.2% fusion . The absence of BMP-2 is itself a strong predictor of fusion failure (OR 4.42) .

Follow-up duration: Short-term outcomes may not capture smoking's full impact. Studies with 30-day outcomes showed no smoking effect on complications or readmissions , while studies with 12-24 month follow-up consistently demonstrated elevated pseudarthrosis risk .

Complexity of procedure: The association between smoking and adverse events appears stronger in simpler procedures. A meta-analysis found smoking significantly associated with major adverse events in ≤2 level fusions (RR 2.46, 95% CI 1.18-5.12) but not in ≥3 level fusions (RR 0.87, 95% CI 0.70-1.08) . This counterintuitive finding may reflect more aggressive perioperative optimization and closer monitoring in complex cases.

Graft source: Autograft is more susceptible to smoking's effects (OR 0.47) compared to allograft (OR 0.69, non-significant) . This may relate to the systemic effects of smoking on the patient's own bone healing capacity.

Population-Specific Conclusions

Based on the quality hierarchy of included evidence:

For patients undergoing **lumbar posterolateral fusion** without biological adjuncts, smoking approximately doubles the risk of nonunion (RR 1.91-2.2) , with the effect more pronounced when using autograft .

For patients undergoing **cervical fusion** , smoking is associated with significantly reduced fusion rates (OR 0.63) , though effects may be partially mitigated by PEMF stimulation in high-risk patients .

For patients undergoing **complex spinal deformity surgery** (≥3 levels), short-term outcomes appear similar between smokers and non-smokers , though long-term pseudarthrosis rates require further study.

For patients with **cervical myelopathy** , despite worse baseline function, smokers achieve similar improvements and satisfaction as non-smokers , suggesting the benefits of surgery outweigh smoking-related risks in this population.

Mechanistic Considerations

The biological mechanisms underlying smoking's effect on fusion are well-characterized. Nicotine impairs osteoblast function, reduces bone matrix synthesis, and compromises microvascular perfusion to the fusion site . These effects are reversible with smoking cessation, with recommendations ranging from 4 weeks preoperatively to 6 months postoperatively .

Study Quality Considerations

Several methodological limitations affect the certainty of conclusions. Many studies failed to distinguish between current, former, and never smokers . Quantification of exposure (pack-years, cigarettes per day) was rarely reported . Confounding adjustment was inconsistent, with potential confounders including age, diabetes, BMI, and use of biological adjuncts not uniformly controlled . Assessment of fusion status was often unblinded and used variable definitions and imaging modalities .

Despite these limitations, the consistency of findings across multiple large meta-analyses, the biological plausibility of the association, and the dose-response relationship observed in some studies (18.2% nonunion with >10 cigarettes/day vs. 9.8% with lower consumption) provide strong support for a causal relationship between smoking and pseudarthrosis risk.

DISCUSSION

This comprehensive systematic review of 59 studies provides robust evidence that smoking is a major independent risk factor for pseudarthrosis following spinal arthrodesis. The preponderance of data, particularly from large-scale meta-analyses, confirms a significant and clinically meaningful association, though the magnitude and clinical manifestation of this risk are nuanced and modified by several key factors (Nunna et al., 2021; Yang et al., 2024).

Reconciling Heterogeneity in the Evidence

A critical finding of this review is the apparent contradiction between studies reporting strong, significant associations and those reporting null or attenuated effects. This heterogeneity is not indicative of a lack of true effect but rather reflects the complex interplay between smoking and specific surgical and patient variables. Our synthesis identifies several key modifiers that explain these discrepancies:

1. **Surgical Technique and Construct Rigidity:** The stability provided by the surgical construct appears to be a major buffer against smoking's detrimental effects. For instance, Luca et al. (2011) found that smokers undergoing translaminar screw fixation (a less rigid construct) had significantly worse long-term outcomes compared to non-smokers, whereas no such difference was observed with the more stable transforaminal lumbar interbody fusion (TLIF). Similarly, the use of intersegmental fixation has been reported to result in zero pseudarthrosis cases regardless of smoking status, suggesting modern, rigid instrumentation can partially overcome the biological impediments caused by smoking (Thalgott et al., 2008). This underscores the principle that achieving immediate, rigid mechanical stability is paramount in high-risk patients.

2. **Use of Osteobiologic Adjuncts:** The role of biologic enhancers, particularly recombinant human bone morphogenetic protein-2 (rhBMP-2), is pivotal. Glassman et al. (2007) demonstrated that rhBMP-2 could elevate fusion rates in smokers to near-equivalent levels seen in non-smokers using iliac crest bone graft (ICBG). This powerful mitigating effect is further highlighted by Shudong Yang et al. (2024), who identified the *absence* of BMP use as a high-quality evidence risk factor for fusion failure (OR 4.42). This suggests that in smokers, the anabolic stimulus provided by rhBMP-2 may be sufficient to counteract the catabolic and anti-angiogenic effects of smoking, making it a valuable consideration in surgical planning for this population, albeit with careful attention to its cost and potential complications (Bodalia et al., 2016).

3. **Graft Source:** The interaction between smoking and graft type reveals important biological insights. The negative impact of smoking is significantly stronger when autograft is used (OR 0.47) compared to allograft (OR 0.69, often non-

significant) (Yang Li et al., 2021). This likely reflects the dual insult of smoking: it not only impairs the host bed's ability to support healing but also may directly affect the viability and osteogenic potential of the patient's own harvested bone cells within the autograft. Allograft, being non-viable and acting primarily as a scaffold, may be less sensitive to these systemic metabolic effects.

4. **Procedure Complexity and Follow-up Duration:** Counterintuitively, some evidence suggests the smoking effect might be less pronounced in highly complex procedures (≥3 levels) in the short term. Elsamadicy et al. (2017) found no difference in 30-day complications or readmissions between smokers and non-smokers after complex adult spinal deformity surgery. This may be attributed to more aggressive perioperative optimization, higher surgical skill, or closer monitoring in these complex cases. However, this does not preclude a significant effect on long-term fusion rates, which require follow-up beyond one or two years to manifest (How et al., 2019). Studies with short-term endpoints may therefore underestimate the true risk of pseudarthrosis related to smoking.

5. **Spinal Region and Specific Pathology:** The risk profile varies by anatomical location. In the cervical spine, smoking is consistently associated with reduced fusion rates (Li Zheng et al., 2021), yet interestingly, patients with cervical myelopathy who smoke achieve similar levels of patient-reported satisfaction and clinical improvement as non-smokers at 24 months, indicating that the net benefit of surgery remains substantial in this symptomatic population (Park et al., 2024, 2025). In the lumbar spine, the evidence is most robust for posterolateral fusions, showing a near-doubling of nonunion risk (Nunna et al., 2021; Pearson et al., 2016).

Mechanistic Considerations and Clinical Implications

The biological plausibility for our findings is strong. Smoking induces vasoconstriction, reducing blood flow and oxygen delivery to the fusion site, which is critical for bone formation (Jackson & Devine, 2016). Nicotine directly inhibits osteoblast function and proliferation, while other components like carbon monoxide hamper cellular respiration. These mechanisms explain not only the increased rate of nonunion but also the observed prolongation of time to union by nearly a month in smokers (Boonsirikamchai et al., 2024). Furthermore, the dangerous interaction between smoking and postoperative ketorolac use—resulting in an odds ratio for pseudarthrosis as high as 8.71—highlights how multiple inhibitory factors can act synergistically to devastate fusion potential (Jesse Li et al., 2018). This underscores the need for comprehensive perioperative risk management, including judicious use of NSAIDs in smokers.

The broader adverse event profile associated with smoking—including significantly higher risks of surgical site infection, respiratory complications, wound healing problems, and reoperation—creates a compounded negative impact on the surgical journey, increasing morbidity, cost, and patient suffering (Li-ming Zheng et al., 2022; Xing et al., 2013; Blood et al., 2017).

Limitations of the Existing Evidence and Future Directions

Despite the overall consistency, this review exposes important methodological limitations in the literature. A major weakness is the inconsistent and often crude definition of smoking exposure. Most studies dichotomize patients as "smokers" vs. "non-smokers," failing to distinguish between current, former, and never smokers, and rarely quantifying exposure via pack-years or duration of cessation (Russo et al., 2024; Meester et al., 2024). This obscures potential dose-response relationships and the benefits of cessation. The timing of required preoperative cessation varied widely (4 weeks to 6 months) and was often not reported. Furthermore, assessment of the primary outcome, pseudarthrosis, was frequently unblinded and utilized heterogeneous diagnostic criteria (e.g., plain radiographs vs. CT scan) and timepoints, introducing potential detection bias (Cheriyan et al., 2015; Makino et al., 2014). Confounding adjustment was also inconsistent; while some studies controlled for age, BMI, and diabetes, others did not, and few adequately accounted for the use of biologics or specific instrumentation in their analyses.

Future high-quality research should employ standardized, quantitative measures of smoking (current status, pack-years, cessation duration). Outcome assessment should be blinded, preferably by independent radiologists using agreed-upon CT-based criteria at standardized postoperative intervals (e.g., 12 and 24 months). Prospective studies are needed to clarify the optimal duration of preoperative smoking cessation required to normalize risk and to evaluate the long-term fusion rates in smokers undergoing complex deformity surgery with modern techniques and adjuncts. Research into other mitigating strategies, such as pulsed electromagnetic field (PEMF) stimulation, which has shown promise in high-risk cervical fusions, also warrants further investigation (Coric et al., 2018; Wind et al., 2024; Cottrill et al., 2020).

The discussion affirms that smoking is a potent, modifiable risk factor for pseudarthrosis. Its effect is not absolute but is dynamically modified by surgical choices. This knowledge empowers surgeons to engage in detailed risk-benefit discussions with patients, strongly advocate for and facilitate smoking cessation, and tailor their surgical strategy—opting for more robust constructs and considering biologic augmentation—when operating on patients who smoke.

CONCLUSION AND RECOMMENDATIONS

Conclusion

This comprehensive systematic review synthesizes high-quality evidence from 59 studies to conclusively demonstrate that smoking significantly increases the risk of pseudarthrosis following spinal arthrodesis. The aggregated data indicate that smokers face approximately a 91% higher risk of nonunion and have 45% lower odds of achieving successful fusion compared to non-smokers (Nunna et al., 2021; Yang Li et al., 2021). This detrimental effect is biologically plausible, mediated by nicotine-induced

impairment of osteoblast function and bone vascularity. However, the clinical impact is not uniform; it is significantly modified by surgical factors. The risk is most pronounced in procedures using autograft and less robust stabilization techniques, while it can be substantially mitigated by the use of biological adjuncts like rhBMP-2 and by employing rigid circumferential fusion constructs (Glassman et al., 2007; Luca et al., 2011). Smoking also prolongs time to union and acts synergistically with other risk factors, such as ketorolac use, to dramatically elevate failure rates. Despite some null findings in specific contexts—like short-term outcomes in complex deformity surgery—the overall body of evidence supports smoking as a major, independent, and modifiable determinant of fusion failure.

Recommendations

Based on the findings of this review, the following recommendations are proposed for clinical practice and future research:

For Clinical Practice:

1. **Preoperative Counseling and Cessation:** Spine surgeons should unequivocally counsel all smoking patients about the significantly elevated risk of pseudarthrosis, revision surgery, and other complications. Referral to structured smoking cessation programs should be a standard component of preoperative optimization. While the ideal cessation duration preoperatively remains to be precisely defined, a period of at least 4-8 weeks is commonly recommended, with longer cessation likely providing greater benefit (Jackson & Devine, 2016).

2. **Risk-Stratified Surgical Planning:** In patients who continue to smoke or have recently quit, surgical strategy should be adjusted to mitigate risk. This may include:
   - **Favoring Rigid Constructs:** Choosing 360-degree circumferential fusion (e.g., TLIF, ALIF with posterior instrumentation) over posterolateral-only or less rigid fixations when clinically appropriate.
   - **Consideration of Osteobiologics:** Strongly considering the use of rhBMP-2 or other evidence-based bone graft enhancers, especially in multi-level fusions or when using allograft, after weighing the benefits against potential risks and costs.
   - **Graft Selection:** Acknowledging that autograft may be particularly vulnerable in smokers; thus, the choice of graft should be made with this in mind.

3. **Postoperative Caution:** Avoid the concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs), particularly ketorolac, in patients who smoke, due to the dramatically heightened risk of nonunion (Jesse Li et al., 2018).

4. **Patient-Centered Decision Making:** For symptomatic patients with clear surgical indications (e.g., cervical myelopathy), surgery should not be universally withheld from smokers, as they can still achieve significant clinical improvement and satisfaction (Park et al., 2024). However, the informed consent process must transparently communicate the increased risk of pseudarthrosis.

For Future Research:

1. **Standardized Methodology:** Future studies must adopt standardized definitions for smoking exposure (current/former/never, pack-years, cessation timing) and for diagnosing pseudarthrosis (using CT-based criteria at standardized timepoints with blinded assessment).
2. **Dose-Response and Cessation Studies:** Prospective research is needed to establish a clearer dose-response relationship between smoking intensity/duration and pseudarthrosis risk, and to definitively determine the minimum preoperative cessation period required to normalize risk.
3. **Long-Term Outcomes in Complex Surgery:** More long-term follow-up studies are required to assess the true rate of pseudarthrosis in smokers undergoing complex spinal deformity surgery, beyond short-term complication metrics.
4. **Evaluation of Mitigation Strategies:** Further high-quality trials are needed to compare the cost-effectiveness and outcomes of different mitigation strategies (e.g., rhBMP-2 vs. cellular bone allografts vs. PEMF stimulation) specifically in smoking populations.

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