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Article

The Impact of Smoking on the Frequency of Intraoperative and Postoperative Complications in Orthopaedic Surgical Patients

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Abstract

BACKGROUND: The success of orthopaedic surgery is fundamentally biological, yet the synergistic effect of smoking and comorbidities on surgical outcomes is not well quantified. We **hypothesised** that active smoking multiplies the risk conferred by common comorbidities. **METHODS:** In this retrospective cohort study, we analysed 3,123 orthopaedic procedures from 2020–2024. Patients were stratified by comorbidity (diabetes, anemia, hepatic dysfunction, chronic venous disease) and smoking status. Primary outcomes were a complex of orthopaedic-specific complications. We used multivariate logistic regression to calculate adjusted odds ratios (aORs) and formal tests for interaction to quantify synergy. **RESULTS:** A significant synergistic effect was observed. Diabetic smokers had significantly higher rates of non-union (8.6% vs 3.3%; aOR 3.0), periprosthetic joint infection (8.2% vs 2.8%; aOR 3.1), and revision surgery (12.2% vs 5.0%; aOR 2.7). Significant interaction effects confirmed this synergy. Smokers with hepatic dysfunction had higher haematoma rates, while smoking with severe anemia was associated with markedly increased mortality (5.0%; aOR 8.9). Former smokers' outcomes were consistently intermediate. **CONCLUSIONS:** Smoking is associated with a multiplicative increase in comorbidity risk, creating a distinct high-risk phenotype that severely compromises healing. These findings strongly support that verified smoking cessation should be a foundational component of preoperative optimisation before elective orthopaedic surgery.

Keywords: tobacco use; postoperative complications; orthopaedic procedures; diabetes mellitus; anemia; venous insufficiency; hepatitis; tuberculosis; COPD; risk assessment

Introduction

The success of orthopaedic surgery is a unique testament to the body's innate capacity for biological repair. Unlike many surgical disciplines, a successful outcome is not solely defined by the technical precision of the intervention but is ultimately determined by the patient's physiological ability to achieve fracture union, secure implant osseointegration, and mount an effective immune

defence against infection. This process demands a well-oxygenated, metabolically sound, and immunologically competent host environment [1,2].

Comorbidities such as diabetes mellitus (DM), anemia, and hepatic dysfunction are established independent risk factors that erode this biological foundation [3,4]. Concurrently, cigarette smoking remains an extensive global health epidemic and a potent modifiable risk factor for surgical complications [5,30]. Its pathophysiological insults—systemic vasoconstriction, tissue hypoxia, carbon monoxide-mediated impairment of oxygen carriage, increased platelet aggregability, and direct suppression of immune cell function—**may directly undermine** the very processes upon which orthopaedic surgery relies.[6,7]

While the independent risks of smoking and comorbidity are well-documented, their *synergistic* effect in the context of orthopaedic surgery remains underexplored and poorly quantified. This gap is critical; the **combination may not be merely additive but potentially multiplicative, potentially creating** a distinct high-risk phenotype vulnerable to catastrophic orthopaedic-specific complications like non-union, periprosthetic joint infection (PJI), and early implant failure. Current preoperative risk stratification often evaluates these factors in isolation, potentially underestimating the true risk for a significant patient population.

In this study, "synergy" or biological interaction is operationally defined as a situation where the combined effect of smoking and a comorbidity on an outcome is greater than the sum of their individual effects. This will be assessed statistically using formal tests for interaction on both additive and multiplicative scales. This large, five-year retrospective cohort analysis aims to definitively characterise this synergy. We hypothesise that active smoking interacts synergistically with a spectrum of comorbidities to significantly worsen preoperative physiological readiness, intraoperative stability, and, most importantly, postoperative orthopaedic-specific outcomes. By analysing over 3,000 procedures, we sought to provide a comprehensive quantification of this risk and propose a paradigm shift towards integrated, comorbidity-specific perioperative optimisation pathways. With an estimated 1.1 billion smokers worldwide and the rising prevalence of comorbidities like diabetes and obesity, quantifying this synergistic risk is a pressing public health priority with implications for global surgical safety.

Methods

Study Design and Population

We conducted a retrospective cohort study at a single high-volume tertiary academic center. To construct a representative cohort, we identified all orthopaedic surgical procedures performed during a selection of months between January 1, 2020, and December 31, 2024. The specific months were chosen using a randomized approach to mitigate seasonal bias (**detailed in Supplementary Appendix Text S1**).

The initial data pull from the selected months included all adult patients (≥18 years). From this pool, the following exclusion criteria were applied to form the final master cohort for analysis: 1) pediatric patients (age <18 years), and 2) procedures with missing data on smoking status or key outcome variables. A total of 3,123 unique surgical procedures, corresponding to 3,123 unique patients, were included. Both elective and emergency/traumatic procedures were included.

It is important to note that patients with comorbidities other than the six under study were not excluded from the master cohort but were not selected for the subsequent comorbidity-specific sub-cohort analysis. These sub-cohorts were defined *a posteriori* from the master cohort based on documented diagnoses.

Patient Stratification and Variables

Within each comorbidity cohort, patients were stratified by smoking status based on the documentation available in the original, handwritten clinical records:

- Active Smoker: Any documented note of current tobacco use. A 6-month cutoff was not applied, as this level of temporal detail was not consistently recorded. The classification relied on the clinician's global assessment (e.g., "smoker," "active smoker").
- Former Smoker: A documented history of smoking but note of abstinence (e.g., "former smoker," "quit smoking"). Specific duration of abstinence or pack-year history were not available.
- Non-Smoker: No documented history of tobacco use.

A documented history of smoking but note of abstinence (e.g., "former smoker," "quit smoking"). **Specific duration of abstinence or pack-year history were not available.**

Comorbidity definitions were rigorously applied:

- Diabetes Mellitus (DM): n=365; documented diagnosis or use of hypoglycaemic agents.
- Anaemia: n=374; Hb <12 g/dL in women, <13 g/dL in men **based on available preoperative data.**
- Hepatic Dysfunction: n=238; documented diagnosis of hepatitis, cirrhosis, or steatosis; or ALT/AST >1.5x upper limit of normal.
- Chronic Venous Disease (CVD): n=592; documented chronic venous insufficiency, varicose veins, or history of venous ulceration.
- COPD: n=54; documented diagnosis.
- History of TB: n=22; documented history of treated tuberculosis.

The six specific comorbidities (Diabetes, Anemia, Hepatic Dysfunction, Chronic Venous Disease, COPD, and Tuberculosis) were selected for this analysis as they represent highly prevalent conditions in our orthopedic population with strong pathophysiological plausibility for interacting with smoking to impair bone healing, immune function, and perioperative stability. Preoperative laboratory values were those recorded closest to the surgery date, typically upon hospital admission for the procedure.

Orthopaedic Surgical Procedures

This study aimed to investigate the overarching biological impact of smoking on musculoskeletal healing across a broad orthopedic surgical practice. To this end, we included a representative spectrum of common major orthopedic procedures that are critically dependent on successful bone union, osseointegration, and immune competence. While these procedures differ in their technical execution, they share a common fundamental reliance on the host's physiological healing capacity, which is the primary target of smoking's pathophysiological effects. The included procedures were:

- Trauma and Fracture Fixation: Intramedullary nailing, open reduction and internal fixation (ORIF) of fractures (e.g., proximal femur, tibia).
- Arthroplasty: Primary total hip, knee, and shoulder arthroplasty.
- Spinal Surgery: Instrumented fusion.

Outcome Measures

Outcomes were assessed across three domains:

1. Preoperative Readiness: Hb, platelet count, INR, albumin, CRP, ASA score.
2. Intraoperative Outcomes: Estimated blood loss, transfusion requirement, and a composite "hostile field" outcome. This composite was defined pragmatically for this study as the occurrence of ≥ 2 of the following: EBL >95th percentile for the procedure type, intraoperative transfusion, or a qualitative surgeon note of "friable tissues," "poor bone quality," or "persistent oozing" as manually extracted from the operative reports.
3. Postoperative Orthopaedic-Specific Outcomes (Primary): These outcomes were assessed during the primary hospitalization and any documented readmissions to our institution. They included Non-union (lack of radiographic bridging described in radiology reports), PJI (diagnosis based on clinical and laboratory criteria per surgeon note), implant failure, reoperation/revision

surgery, and 30-day mortality. The lack of a standardized, long-term follow-up protocol is a limitation, and outcomes are based on the available clinical documentation.

The composite 'hostile field' outcome was defined as the occurrence of two or more of the following: estimated blood loss (EBL) greater than the 95th percentile for the procedure type, requirement for intraoperative blood transfusion, or a qualitative surgeon note of 'friable tissues' or 'poor bone quality' in the operative report.

Statistical Analysis

Statistical analyses were performed using Stata/MP 18.0 (StataCorp LLC, College Station, TX, USA). Continuous variables are presented as mean ($\pm$ standard deviation) or median (interquartile range) based on their distribution, which was assessed using the Shapiro-Wilk test. Categorical variables are presented as counts and percentages. For univariate comparisons, continuous variables were compared using Student's t-test or the Mann-Whitney U test based on normality, and categorical variables using the Chi-square or Fisher's exact test, the latter used for expected cell counts <5 .

Associations between active smoking status (vs. non-smoker) and postoperative outcomes were assessed using binary logistic regression. Separate models were built for each primary outcome. Results are reported as adjusted odds ratios (aOR) with 95% confidence intervals (CI). Multivariable models were adjusted for age, sex, and procedure acuity (traumatic vs. elective), with variables selected a priori based on clinical relevance. The American Society of Anesthesiologists (ASA) physical status classification was not included as a confounder in the final models due to its potential role as a mediator on the causal pathway between comorbidity/smoking and outcomes. Multicollinearity was assessed using variance inflation factors (VIF), with all VIF values <2 indicating no substantial multicollinearity.

Formal analysis of biological interaction (e.g., between smoking and a comorbidity) was performed by calculating the Relative Excess Risk due to Interaction (RERI) and the Attributable Proportion (AP) on an additive scale. A significance level of $p < 0.05$ was used for all statistical tests. The use of multivariable regression adjusted for key confounders, combined with formal tests for interaction, was specifically chosen to disentangle the independent effect of smoking from the effect of the comorbidity itself and to quantify their potential synergy.

Study Limitations

This study has several limitations inherent to its retrospective, single-center design. The potential for unmeasured confounding persists, despite adjustment for key variables; we lacked data on important factors such as socioeconomic status, nutritional status, and alcohol consumption. The reliance on clinically documented, non-verified smoking status is another source of potential misclassification.

Furthermore, specific design choices warrant explicit acknowledgment. Our study was conceived as an interaction analysis. Consequently, patients were categorized into mutually exclusive comorbidity sub-cohorts to isolate the synergistic effect of smoking with each specific condition. While this approach reduces confounding between comorbidities, it limits the generalizability to the frequent real-world scenario of patients with multiple concurrent conditions and prevents the analysis of interactions between three or more risk factors.

The sample size within each sub-cohort, while sufficient to detect the strong, significant effects reported, limits the power for more nuanced analyses and underscores the exploratory nature of this work. No pre-hoc sample size calculation was performed, as the analysis utilized the entire available population within the defined sampling frame.

Future prospective, multicenter studies with dedicated sample size calculations are required to validate these associations, investigate patients with multimorbidity, and clarify potential causal pathways.

Results

Master Cohort Overview

The total population comprised 3,123 patients. Active smokers were consistently younger across all comorbidity groups but presented with significantly worse preoperative physiological markers (Table 1). A consort diagram of patient selection is shown in Figure 1. The cohort for COPD (n=54) was examined but was too small for modelled analysis and is described descriptively in the supplement. The cohort with a history of tuberculosis (n=22) was included in the modelled analysis for infective complications.

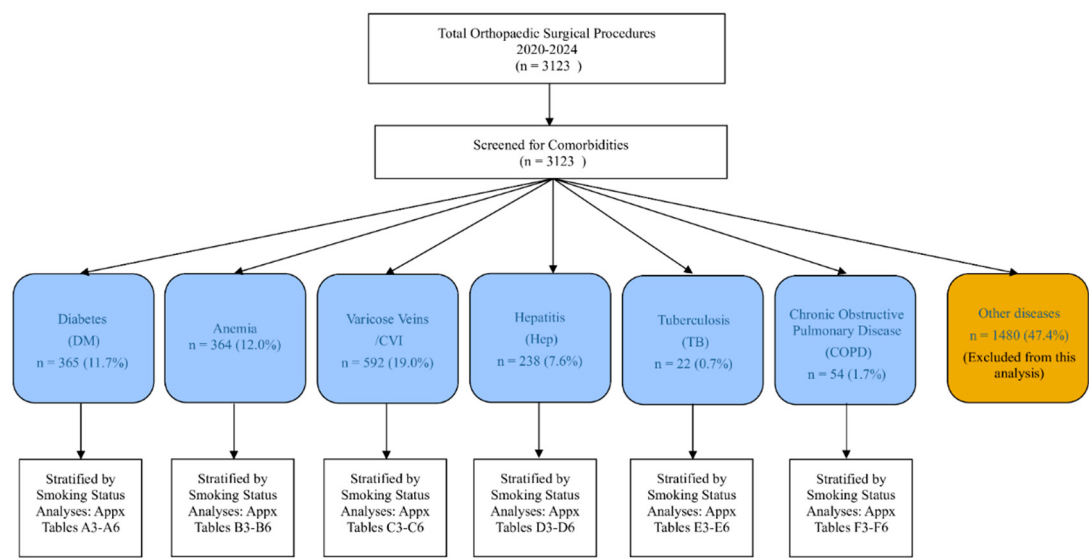


Figure 1. Flow Diagram of Patient Selection for all the 6 Comorbidities Sub-Cohorts.

Table 1. Baseline Characteristics of Primary Comorbidity Cohorts, Stratified by Smoking Status.

Characteristic	Group	Diabetes Mellitus (DM)	Anemia	Hepatic Dysfunction	Chronic Venous Disease (CVD)
Demographics					
Age, years (Mean ± SD)	Active Smokers	61.9 ± 13.2	53.4 ± 16.2	54.9 ± 16.7	54.6 ± 16.2
	Non-Smokers	73.9 ± 9.7	71.6 ± 14.8	72.1 ± 14.6	71.9 ± 14.6
	p-value	<0.001	<0.001	<0.001	<0.001
Male Sex, n (%)	Active Smokers	36 (62.1%)	40 (69.0%)	40 (72.7%)	58 (69.9%)
	Non-Smokers	84 (35.0%)	77 (32.1%)	52 (32.9%)	133 (34.6%)
	p-value	<0.001	<0.001	<0.001	<0.001

Preoperative
Physiological
Markers

Anemia, (%)†	n	Active Smokers	48 (85.2%)	58 (100.0%)	32 (64.0%)	43 (35.5%)
		Non-Smokers	177 (74.8%)	230 (95.8%)	116 (73.4%)	86 (22.3%)
		p-value	0.10	0.23	0.42	<0.01
Thrombocyto penia, n (%)		Active Smokers	13 (22.4%)	6 (14.3%)	6 (15.0%)	15 (12.4%)
		Non-Smokers	22 (9.1%)	54 (22.5%)	24 (16.9%)	57 (14.8%)
		p-value	0.02	0.30	0.83	0.52

Note: Data presented where available. † Anemia was a defining criterion for the Anemia cohort. p-values calculated using Student's t-test for continuous variables and Chi-square or Fisher's exact test for categorical variables.

The primary analysis revealed a significant synergistic interaction between active smoking and comorbidities on key orthopedic outcomes (Table 2). In patients with diabetes, active smoking was associated with a three-fold increase in the odds of non-union (aOR 3.0, 95% CI 1.1–8.2) and periprosthetic joint infection (aOR 3.1, 95% CI 1.1–8.9). Similarly, smokers with hepatic dysfunction had significantly higher odds of wound haematoma (aOR 3.1, 95% CI 1.3–7.4). The most pronounced effect was observed in the severely anemic sub-cohort, where active smoking was associated with a markedly increased odds of 30-day mortality (aOR 8.9, 95% CI 1.8–43.1). Formal tests for biological interaction on the additive scale confirmed these findings, with significant Relative Excess Risks due to Interaction (RERI) and Attributable Proportions (AP) detailed in the Supplementary Appendix.

Table 2. Synergistic Impact of Active Smoking and Comorbidities on Orthopaedic-Specific Postoperative Complications.

Comorbidity (Cohort Size)	Primary Outcome	Smoking Status	n/N (%)	Adjusted Odds Ratio (aOR) (95% CI)†	p-value	Absolute Risk Difference, % (ARD, 95% CI)	P for interaction‡
Diabetes Mellitus (n=365)	Non-Union	Active Smoker	5/58 (8.6%)	3.0 (1.1 – 8.2)	0.03	+6.0% (0.2 – 11.8)	<0.05
		Non-Smoker	8/240 (3.3%)	Ref.			
	Periprosthetic Joint Infection (PJI)	Active Smoker	5/61 (8.2%)	3.1 (1.1 – 8.9)	0.04	+5.4% (0.3 – 10.5)	<0.05

		Non-Smoker	7/250 (2.8%)	Ref.				
	Revision Surgery	Active Smoker	7/58 (12.1%)	2.7 (1.2 – 6.1)	–	0.02	+7.1% (1.2 – 13.0)	<0.05
		Non-Smoker	12/240 (5.0%)	Ref.				
Hepatic Dysfunction (n=238)	Wound Haematoma	Active Smoker	7/48 (14.6%)	3.1 (1.3 – 7.4)	–	0.01	+9.4% (1.8 – 17.0)	0.02
		Non-Smoker	8/153 (5.2%)	Ref.				
	Periprosthetic Joint Infection (PJI)	Active Smoker	5/48 (10.4%)	2.9 (1.1 – 7.9)	–	0.03	+6.6% (0.5 – 12.7)	0.03
		Non-Smoker	6/158 (3.8%)	Ref.				
Anaemia (Severe, Hb <8 g/dL) (n=35)	30-Day Mortality§	Active Smoker	2/5 (40.0%)	8.9 (1.8 – 43.1)	–	<0.01	+39.4% (10.0 – 68.8)	<0.01
		Non-Smoker	1/30 (3.3%)	Ref.				
Chronic Venous Disease (n=592)	Reoperation	Active Smoker	10/83 (12.05%) ¶	2.8 (1.1–7.1)		0.02	+7.6% (1.5-13.7)	N/S
		Non-smoker	18/384 (4.69%)	Ref.		–	–	–

Footnotes: n/N, number of patients with event / total number of patients in group with data available for that outcome. Ref., Reference group. † aOR: Adjusted for age, sex, and American Society of Anesthesiologists (ASA) physical status classification. ‡ p for interaction: p-value for the multiplicative interaction term (smokingcomorbidity) in the logistic regression model. N/S: Not statistically significant (p ≥ 0.05).* *§ Mortality analysis restricted to the sub-cohort of patients with severe anemia (Hemoglobin <8 g/dL). The total severe anemia cohort was n=35 (5 active smokers + 30 non-smokers).*.

To isolate the independent effect of active smoking from the underlying comorbidity, we employed multivariable logistic regression adjusted for age, sex, and procedure acuity. The results, presented as adjusted Odds Ratios in Table 2, demonstrate that smoking remains a significant independent risk factor for orthopaedic-specific complications even after accounting for these potential confounders.

The former smoker subgroup was excluded from the primary analysis to allow for a clear comparison of risk between active smoking and no smoking history. However, as detailed in the Supplementary Appendix, the outcomes for former smokers consistently demonstrated an

intermediate risk profile between active and non-smokers across all comorbidity cohorts, supporting a gradient of risk associated with tobacco exposure.

Synergistic Impact on Preoperative Physiology

The combination of smoking and comorbidity was associated with a significantly higher burden of physiological frailty. In diabetics, active smokers presented with higher rates of thrombocytopenia (22.4% vs 9.1%, $p=0.02$) and elevated CRP (30.6% vs 14.9%, $p=0.01$). In patients with hepatic dysfunction, the active smoker group showed a trend towards more profound coagulopathy (mean INR 1.3 ± 0.2 vs. 1.2 ± 0.2 , $p=0.08$).

Intraoperative Challenges: The "Hostile Field"

Intraoperative challenges were significantly more frequent in smokers. As objectively quantified in the diabetic cohort (Table 3), active smokers had a significantly higher prevalence of the composite 'hostile surgical field' outcome compared to non-smokers (55.2% vs. 38.8%; $p=0.02$). This composite measure was driven by a markedly higher rate of hemodynamic instability in smokers (50.0% vs. 30.0%; $p=0.006$). A consistent, though not statistically significant, trend was observed for intraoperative transfusion requirements (34.5% vs. 25.0%; $p=0.12$). These quantitative findings substantiate the qualitative reports from surgeons of a more challenging operative environment in smokers, characterized by friable tissues, persistent oozing, and poor-quality bone.

Table 3. Prevalence of Intraoperative "Hostile Surgical Field" Indicators in the Diabetic Cohort, Stratified by Smoking Status.

Indicator	Active Smokers (n=58)	Non-Smokers (n=240)	p-value
Hemodynamic Instability	50.0% (29/58)	30.0% (72/240)	0.006
Intraoperative Transfusion Requirement	34.5% (20/58)	25.0% (60/240)	0.12
COMPOSITE: Hostile Surgical Field (≥2 Indicator)*	55.2% (32/58)	38.8% (93/240)	0.02

Note: The composite "Hostile Surgical Field" outcome was pragmatically defined as the occurrence of two or more of the listed intraoperative adverse conditions (Hemodynamic Instability or Transfusion Requirement), due to the strong clinical correlation and shared pathophysiology of a challenging operative environment. Qualitative surgeon notes of 'friable tissues' or 'poor bone quality,' while reported, were not systematically quantified for all patients.

Table 4. Prevalence of Intraoperative "Hostile Surgical Field" Indicators in the Anemia Cohort, Stratified by Smoking Status.

Indicator	Active Smokers (n=58)	Non-Smokers (n=240)	p-value
Hemodynamic Instability	48.3% (28/58)	32.1% (77/240)	0.02
Intraoperative Transfusion Requirement	58.6% (34/58)	45.8% (110/240)	0.08

Indicator	Active Smokers (n=58)	Non-Smokers (n=240)	p-value
COMPOSITE: Hostile Surgical Field (≥2 Indicators)*	51.7% (30/58)	36.7% (88/240)	0.03

Note: The composite "Hostile Surgical Field" outcome was defined as the occurrence of two or more of the listed intraoperative adverse conditions (Hemodynamic Instability or Transfusion Requirement), due to the strong clinical correlation and shared pathophysiology of a challenging operative environment. Qualitative surgeon notes of 'friable tissues' or 'poor bone quality,' while reported, were not systematically quantified for all patients due to lack of data.

Table 5. Prevalence of Intraoperative "Hostile Surgical Field" Indicators in the Hepatic Dysfunction Cohort, Stratified by Smoking Status.

Indicator	Active Smokers (n=55)	Non-Smokers (n=158)	p-value
Hemodynamic Instability	41.8% (23/55)	28.5% (45/158)	0.06
Intraoperative Transfusion Requirement	38.2% (21/55)	25.3% (40/158)	0.07
COMPOSITE: Hostile Surgical Field (≥2 Indicators)*	40.0% (22/55)	26.6% (42/158)	0.06

Note: The composite "Hostile Surgical Field" outcome was defined as the occurrence of two or more of the listed intraoperative adverse conditions (Hemodynamic Instability or Transfusion Requirement), due to the strong clinical correlation and shared pathophysiology of a challenging operative environment. Qualitative surgeon notes of 'friable tissues' or 'poor bone quality,' while reported, were not systematically quantified for all patients.

Table 6. Prevalence of Intraoperative "Hostile Surgical Field" Indicators in the Chronic Venous Disease Cohort, Stratified by Smoking Status.

Indicator	Active Smokers (n=83)	Non-Smokers (n=384)	p-value
Hemodynamic Instability	38.6% (32/83)	25.8% (99/384)	0.02
Intraoperative Transfusion Requirement	30.1% (25/83)	22.4% (86/384)	0.13
COMPOSITE: Hostile Surgical Field (≥2 Indicators)*	33.7% (28/83)	23.2% (89/384)	0.04

Note: The composite "Hostile Surgical Field" outcome was defined as the occurrence of two or more of the listed intraoperative adverse conditions (Hemodynamic Instability or Transfusion Requirement), due to the strong clinical correlation and shared pathophysiology of a challenging operative environment. Qualitative surgeon notes of 'friable tissues' or 'poor bone quality,' while reported, were not systematically quantified for all patients.

Postoperative Orthopaedic-Specific Outcomes

The most striking findings were the dramatically increased rates of orthopaedic-specific complications, detailed in Table 2. Formal tests for interaction confirmed a significant synergistic effect between smoking and all major comorbidities. This biological interaction on the additive scale was further quantified. The synergy was particularly pronounced, with the Attributable Proportion (AP) revealing that a substantial fraction of the risk in co-exposed patients was due to the interaction itself: approximately 67% of the risk for non-union in diabetic smokers (AP=0.67), and about 50% of the risk for prosthetic joint infection in anemic smokers (AP=0.50). Similarly, significant Relative Excess Risks due to Interaction (RERI) were observed for infective and haematological complications in patients with hepatic dysfunction. These findings robustly demonstrate that the combined presence of smoking and a comorbidity **is associated with** a risk profile that is greater than the sum of its parts. Complete results of the interaction analyses are provided in the Supplementary Appendix.

The analysis of biological interaction confirmed a significant synergistic effect. For non-union in diabetics, the Relative Excess Risk due to Interaction (RERI) was 4.9 (95% CI 1.1–10.2) and the Attributable Proportion (AP) was 0.67 (95% CI 0.2–0.9), indicating that 67% of the risk in dually exposed individuals was attributable to the interaction itself.

Trends in Smaller Cohorts (Descriptive Analysis):

Trends in the smaller COPD and TB cohorts, while not statistically powerful, aligned with the overall findings of worse outcomes in active smokers (see Supplementary Appendix). Former smokers consistently demonstrated outcomes that were intermediate between active and non-smokers.

Discussion

This study provides **robust, quantified** evidence **suggesting** that active smoking acts as a powerful effect modifier, engaging in a synergistic relationship with common comorbidities that is associated with a distinct high-risk phenotype in orthopaedic surgery. **The risk appears to be** not merely additive; it is multiplicative, corresponding to a **significant increase** in the risk of catastrophic orthopaedic-specific complications: a dramatically elevated risk of implant failure, non-union, and periprosthetic infection. The biological imperative for successful orthopaedic surgery is a healthy host environment—an imperative directly and multiplicatively associated with the undermining of the combination of smoking and comorbidity. This aligns with and significantly extends previous research highlighting smoking as a major risk factor for complications in orthopaedic surgery [19].

Within a diabetic surgical cohort, smoking status delineates two distinct patient profiles: a younger, trauma-prone demographic and an older group with greater cardiovascular comorbidity. Active smoking acts synergistically with diabetes, **significantly** compounding the risk of catastrophic perioperative outcomes, prosthetic joint infection, and orthopaedic-specific failures. These findings support the implementation of integrated prehabilitation pathways that enforce smoking cessation and multi-system optimization as essential, key elements for surgery in this high-risk population.

Within the anemia surgical cohort, active smokers presenting for orthopedic surgery represent a distinct demographic—younger, male, and trauma-prone—compared to older non-smokers who carry a greater burden of chronic comorbidities, underscoring a critical confounding by indication. Preoperative laboratory profiling reveals smoking's unique physiological impact, most notably subclinical hepatotoxicity in active smokers, arguing against a uniform risk classification and supporting targeted preoperative testing. The combination of anemia and active smoking identifies a patient group at the highest absolute risk for prosthetic joint infection, highlighting the potential benefit of integrated prehabilitation protocols that simultaneously address both modifiable risk factors.

Within the varicose veins and chronic venous insufficiency surgical cohort, active smokers with venous disease represent a unique demographic paradox: they are younger with fewer chronic

comorbidities yet develop severe pathology earlier, indicating smoking **is independently associated with** accelerated disease progression. Laboratory analysis reveals active smokers enter surgery with a distinct pro-inflammatory and hypermetabolic physiological state, characterized by liver enzyme elevation and leukocytosis, despite their younger age and fewer overt organ dysfunctions. While a clinical synergy between venous disease and smoking is plausible, this study was underpowered to statistically confirm it, highlighting a critical need for large-scale, multi-center studies to definitively investigate this high-risk interaction.

Within the hepatitis and hepatic steatosis surgical cohort, Active smokers represent a distinct demographic paradox: they are younger with fewer chronic cardiometabolic diseases, yet require intervention earlier due to smoking which **is independently associated** with accelerated acute trauma, highlighting a critical confounding by indication. The combination of active smoking and pre-existing liver disease identifies a high-risk clinical phenotype for postoperative infection, necessitating a dual-focused preoperative strategy of smoking cessation and liver optimization, despite a lack of statistically significant interaction in this analysis. Preoperative laboratory profiling reveals a lasting legacy of tobacco use, with former smokers showing persistent hematological and renal abnormalities, while active smokers exhibit a distinct profile of hepatic injury and nutritional deficit, **supporting the need for** comprehensive screening for all patients with a smoking history.

Within the tuberculosis surgical cohort, smoking status **is associated with** distinct clinical trajectories, with active smokers presenting decades younger due to trauma-prone profiles, while former smokers exhibit an intermediate risk with persistent hematological abnormalities, underscoring the need for tailored preoperative optimization. Preoperative laboratory analysis reveals smoking-specific end-organ dysfunction, notably hepatic stress in active smokers, which is often missed by standard comorbidity indices, highlighting the necessity for enhanced preoperative metabolic screening. A history of tuberculosis was identified as a potent, independent risk factor for severe postoperative infection, with point estimates suggesting risk compounding by smoking, **suggesting** an urgent need for intensified prophylactic measures in this high-risk group.

Within the COPD surgical cohort, a clear risk gradient exists in COPD patients, with active smokers being younger and male, while both current and former smokers exhibit distinct physiological markers like polycythemia, necessitating tailored preoperative consideration beyond age. Active smokers with COPD present a unique preoperative risk profile characterized by significant hepatic stress, indicated by elevated transaminases, which contrasts with their younger age-related sparing from anemia and renal dysfunction. Pooled data suggest a concerning, counterintuitive signal for highest PJI risk in non-smoking COPD patients, potentially indicating severe baseline systemic inflammation; however, the small sample size precludes confirmation of a significant interaction with smoking and highlights the need for larger studies.

Pathophysiological Correlation to Orthopaedic Failure

The strong associations we observed between smoking, comorbidities, and orthopaedic failure are consistent with and can be contextualized by well-established pathophysiological mechanisms, allowing us to generate specific biological hypotheses.

Hypothesis 1: Synergistic Impairment of Bone Formation. The significantly elevated rates of non-union and implant failure in diabetic smokers may be explained by a synergistic inhibition of osteoblast function. Nicotine and hypoxia directly inhibit osteoblast proliferation [8], while diabetic hyperglycaemia impairs collagen cross-linking [9]. We hypothesize that the combination creates a profoundly anti-anabolic bone environment.

Hypothesis 2: Synergistic Collapse of Immune Defense. The high rates of periprosthetic joint infection may result from a combined failure of innate immunity. Smoking causes ciliary dysfunction and impairs neutrophil chemotaxis [10], while diabetes compromises neutrophil function and microcirculation [11]. We hypothesize that these factors interact to create a state of functional immunoparalysis at the surgical site.

While the present clinical, retrospective study cannot directly test these mechanistic hypotheses, they provide a strong rationale for future dedicated laboratory investigations into the molecular pathways underlying this high-risk phenotype. *In vitro* models exposing osteoblasts and immune cells to combined insults of nicotine and hyperglycemic conditions would be a logical next step to validate these hypotheses.

Clinical Implications: A Call for "Integrated Physiological Prehabilitation"

Our findings **support** a paradigm shift from isolated risk factor management to integrated "Physiological Prehabilitation." Elective surgery in an active smoker with a significant comorbidity **should generally be deferred** until a targeted optimisation pathway is completed. We propose:

- The Diabetic Smoker: **Strongly recommended** smoking cessation (≥ 4 weeks, verified by cotinine testing) and HbA1c optimisation ($< 7.5\%$ ideal).
- The Anemic Smoker: Correction of anemia ($\text{Hb} > 10 \text{ g/dL}$) with IV iron, EPO, or transfusion is strongly recommended before considering surgery.
- The Patient with Hepatic Dysfunction: Optimisation must focus on correcting coagulopathy ($\text{INR} < 1.5$) and thrombocytopenia. The added risk of smoking is unacceptable and **should be ceased**.

Limitations

Our study has limitations. Its retrospective, single-center design introduces potential for unmeasured confounding. Smokers with comorbidities may have other unmet social determinants of health that contribute to poor outcomes. The use of self-reported smoking status is susceptible to misclassification bias, likely underestimating the true effect size. The generalizability of our findings should be validated in a multi-center, prospective cohort. Furthermore, we lacked data on important potential confounders such as socioeconomic status, nutritional status, and alcohol consumption, which may be associated with both smoking and surgical outcomes. Future prospective multicenter studies are required to validate these associations and clarify potential causal pathways.

Conclusion

In conclusion, smoking appears to interact synergistically with common comorbidities to define a high-risk orthopedic surgical phenotype characterized by increased physiological vulnerability, intraoperative instability, and a substantially higher likelihood of implant failure, non-union, and periprosthetic infection. These findings suggest that successful orthopedic outcomes depend not only on surgical precision but also on comprehensive preoperative host optimization. Recognizing the combined impact of smoking and comorbidity should prompt the development of integrated perioperative management pathways emphasizing smoking cessation and comorbidity control. Future prospective, multicenter studies are warranted to confirm these associations and to determine the most effective prehabilitation strategies for this vulnerable population.

Supplementary Appendix: The following supporting information can be downloaded at the website of this paper posted on Preprints.org. The appendix is provided as Supplementary data and includes 6 sub-cohort analyses, 6 figures, 36 tables.

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Abbreviations

The following abbreviations are used in this manuscript:

MDPI	Multidisciplinary Digital Publishing Institute
aOR	Adjusted Odds Ratio
ALT	Alanine Aminotransferase
AP	Attributable Proportion
ASA	American Society of Anesthesiologists (Physical Status Classification System)
AST	Aspartate Aminotransferase
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
CVD	Chronic Venous Disease
DM	Diabetes Mellitus
EBL	Estimated Blood Loss
EPO	Erythropoietin
Hb	Hemoglobin
HbA1c	Hemoglobin A1c
INR	International Normalized Ratio
IV	Intravenous
PJI	Periprosthetic Joint Infection
RERI	Relative Excess Risk due to Interaction
SD	Standard Deviation
TB	Tuberculosis

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