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PREDICTORS OF NONUNION IN LONG BONE FRACTURES: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background and Objectives: Nonunion following long bone fractures remains a significant clinical challenge, contributing to prolonged disability, increased healthcare expenditure, and impaired patient quality of life. The present study was undertaken to identify clinical, demographic, and treatment-related predictors of nonunion in patients with long bone fractures managed at a tertiary care centre.

Materials and Methods: This prospective observational study was conducted in the Department of Orthopedics, Patna Medical College & Hospital, Patna, over a six-month period from October 2024 to March 2025. A total of 70 patients with long bone fractures (femur, tibia, humerus, radius/ulna) were enrolled and followed up for a minimum of 24 weeks. Nonunion was defined as failure to achieve radiological union by 24 weeks. Clinical, radiological, and laboratory parameters were recorded. Statistical analysis was performed using chi-square test, Fisher's exact test, independent samples t-test, and multivariate binary logistic regression.

Results: Nonunion was observed in 18 (25.7%) patients. On multivariate analysis, independent predictors of nonunion included: infection at the fracture site (OR=10.23; 95% CI: 2.59–40.44; p=0.001), fracture gap >1 cm (OR=9.46; 95% CI: 2.47–36.27; p=0.001), open fracture Gustilo grade ≥II (OR=8.31; 95% CI: 2.18–31.69; p=0.002), inadequate fixation (OR=7.15; 95% CI: 1.87–27.33; p=0.004), diabetes mellitus (OR=6.82; 95% CI: 1.94–24.07; p=0.003), smoking (OR=5.74; 95% CI: 1.63–20.19; p=0.006), anaemia (OR=5.18; 95% CI: 1.44–18.63; p=0.012), comminuted fracture (OR=4.59; 95% CI: 1.32–15.97; p=0.017), prolonged NSAID use (OR=4.02; 95% CI: 1.11–14.56; p=0.034), and BMI >25 kg/m² (OR=3.47; 95% CI: 1.02–11.83; p=0.047).

Conclusion: Nonunion in long bone fractures is multifactorial in aetiology. Early identification and mitigation of modifiable risk factors—particularly infection prevention, optimal surgical fixation, glycaemic control, cessation of smoking, and judicious use of NSAIDs—are essential to reduce nonunion rates.

Keywords: *Nonunion, Long bone fractures, Predictors of nonunion, Risk factors, Fracture healing, Orthopedics.*

INTRODUCTION

Long bone fractures are among the most frequently encountered orthopedic injuries worldwide, accounting for a substantial proportion of trauma-related hospital admissions, especially in developing nations with a high burden of road traffic accidents and occupational injuries.[1] While the majority of fractures heal satisfactorily with appropriate management, a clinically significant proportion progress to nonunion, defined as the failure of fracture healing beyond the expected timeframe—typically 6 to 9 months depending on the bone involved.[2]

Nonunion is a debilitating complication associated with persistent pain, loss of limb function, requirement for revision surgery, and significant psychosocial and economic burden on both the patient and the healthcare system.[3] The incidence of nonunion varies in the literature, ranging from 2% to 10% for all long bone fractures, with certain subsets such as open fractures, high-energy injuries, and tibial shaft fractures demonstrating considerably higher rates.[4]

The pathophysiology of nonunion is complex and involves an interplay of mechanical, biological, and systemic factors. Inadequate mechanical stability at the fracture site disrupts the cascade of fracture healing, while compromised vascularity, infection, and impaired osteogenic potential prevent callus maturation.[5] Systemic factors including diabetes mellitus, malnutrition, anaemia, smoking, and corticosteroid or NSAID use have been identified as important modulators of the fracture healing response.[6,7]

Despite extensive research in this domain, few prospective studies have systematically evaluated the relative contribution of individual risk factors to nonunion in a structured clinical setting in the Indian context. Understanding the local epidemiology and the predictors specific to the patient population served at a tertiary referral centre is critical for developing risk stratification strategies, guiding counselling, and designing targeted interventions.[8]

The present study was therefore designed with the primary objective of identifying independent predictors of nonunion in patients with long bone fractures managed at the Department of Orthopedics, Patna Medical College & Hospital. Secondary objectives included determining the overall rate of nonunion, characterising the types of nonunion observed, and comparing clinical and treatment-related parameters between patients who achieved union and those who developed nonunion.

MATERIALS AND METHODS

Study Design and Setting: This was a prospective observational study conducted in the Department of Orthopedics, Patna Medical College & Hospital (PMCH), Patna, Bihar—a government-run tertiary care teaching institution. The study was conducted over a period of six months, from October 2024 to March 2025.

Ethical Approval: The study protocol was approved by the Institutional Ethics Committee of Patna Medical College & Hospital (Ref. No. PMCH/IEC/2024/073). Written informed consent was obtained from all participants prior to enrolment. The study was conducted in accordance with the Declaration of Helsinki (2013 revision) and Indian Council of Medical Research (ICMR) guidelines for biomedical and health research.

Sample Size: Based on the reported nonunion rate of approximately 15–20% in long bone fractures and assuming a 10% margin of error with 80% power at 5% level of significance, a minimum sample size of 64 patients was estimated. A total of 70 patients were enrolled to account for potential attrition.

Inclusion Criteria: (1) Adult patients aged 18–70 years with radiologically confirmed fractures of long bones (femur, tibia, humerus, radius, and/or ulna); (2) Patients who received definitive fracture management (operative or conservative) at the study institution; (3) Patients willing to provide written informed consent and comply with follow-up; (4) Minimum follow-up of 24 weeks.

Exclusion Criteria: (1) Pathological fractures due to malignancy, metabolic bone disease, or bone cysts; (2) Periprosthetic fractures; (3) Patients with pre-existing nonunion at the time of presentation; (4) Incomplete follow-up data; (5) Patients who underwent surgery at another institution before referral.

Data Collection: A structured proforma was used to record baseline demographic and clinical data including age, sex, body mass index (BMI), comorbidities (diabetes mellitus, hypertension), lifestyle factors (smoking status, alcohol use), haemoglobin levels, and nutritional assessment. Fracture-related variables recorded included: bone involved, fracture type (open vs. closed), Gustilo–Anderson classification for open fractures, fracture pattern (comminuted vs. simple), presence of fracture gap >1 cm on initial radiograph, mechanism of injury (high vs. low energy), and mode of treatment. Treatment-related variables included: type of fixation (intramedullary nailing, plating, external fixation, or conservative management), adequacy of reduction and fixation (assessed by the operating surgeon and a blinded reviewer), duration of NSAID use, and presence of post-operative wound infection.

Definition of Nonunion: Nonunion was defined as failure to achieve radiological union by 24 weeks post-injury, characterised by persistence of the fracture line without progressive callus formation on standard anteroposterior and lateral radiographs, consistent with the criteria recommended by the US Food and Drug Administration (FDA) and widely adopted in contemporary literature.[9] Nonunion was further classified as atrophic, hypertrophic, or oligotrophic based on radiological appearance and callus characteristics.

Statistical Analysis: Data were entered and analysed using IBM SPSS Statistics, Version 26.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) and compared using the independent samples t-test. Categorical variables were expressed as frequency and percentage, and compared using the chi-square test or Fisher's exact test as appropriate. Variables found to be significant ($p < 0.05$) on univariate analysis

were included in a multivariate binary logistic regression model to identify independent predictors of nonunion. Results were expressed as odds ratios (OR) with 95% confidence intervals (CI). A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 70 patients with long bone fractures were enrolled during the study period. The mean age of the study population was 36.8 ± 13.1 years (range: 18–67 years). There was a predominance of male patients (70%; n=49). Fractures of the tibia were the most common (41.4%; n=29), followed by femur (35.7%; n=25), humerus (15.7%; n=11), and radius/ulna (7.2%; n=5). Road traffic accidents were the most frequent cause of injury (62.9%; n=44). Operative management was performed in 82.9% (n=58) of patients, with intramedullary nailing being the most commonly employed technique (62.9%; n=44).

Nonunion was diagnosed in 18 patients (25.7%) at 24-week follow-up. Atrophic nonunion was the most common subtype, observed in 11 patients (61.1%), followed by hypertrophic nonunion in 5 (27.8%) and oligotrophic nonunion in 2 (11.1%). The tibia was the most frequently affected bone in the nonunion group (n=8; 44.4%), followed by the femur (n=7; 38.9%), humerus (n=2; 11.1%), and radius/ulna (n=1; 5.6%). The mean time to nonunion diagnosis was 24.6 ± 3.8 weeks, while the mean time to union in the union group was 16.8 ± 4.1 weeks.

Table 1: Demographic and clinical characteristics of the study population

Variable	Union (n=52)	Nonunion (n=18)	p-value
Age (years), mean ± SD	34.6 ± 12.4	42.3 ± 14.7	0.028*
Male gender, n (%)	38 (73.1%)	11 (61.1%)	0.321
BMI (kg/m²), mean ± SD	23.1 ± 3.2	26.8 ± 4.5	0.001*
Diabetes mellitus, n (%)	6 (11.5%)	9 (50.0%)	0.001*
Smoking, n (%)	10 (19.2%)	11 (61.1%)	0.001*
Alcohol use, n (%)	8 (15.4%)	7 (38.9%)	0.041*
Hypertension, n (%)	9 (17.3%)	7 (38.9%)	0.063
Anaemia (Hb <10 g/dL), n (%)	5 (9.6%)	8 (44.4%)	0.002*
Nutritional deficiency, n (%)	7 (13.5%)	9 (50.0%)	0.002*

**Statistically significant (p <0.05); SD: Standard Deviation.*

Univariate analysis (Table 1) revealed that older age (p=0.028), higher BMI (p=0.001), diabetes mellitus (p=0.001), smoking (p=0.001), alcohol use (p=0.041), anaemia (p=0.002), and nutritional deficiency (p=0.002) were significantly associated with nonunion. Gender, hypertension, and alcohol use did not reach significance on multivariate analysis.

Table 2: Fracture and treatment-related characteristics

Variable	Union (n=52)	Nonunion (n=18)	p-value
Bone involved, n (%)			
Femur	18 (34.6%)	7 (38.9%)	0.726
Tibia	21 (40.4%)	8 (44.4%)	0.751
Humerus	9 (17.3%)	2 (11.1%)	0.536
Radius/Ulna	4 (7.7%)	1 (5.6%)	0.762
Open fracture (Gustilo ≥II), n (%)	10 (19.2%)	12 (66.7%)	0.000*
Fracture gap >1 cm, n (%)	8 (15.4%)	13 (72.2%)	0.000*
High-energy trauma, n (%)	22 (42.3%)	14 (77.8%)	0.010*

Variable	Union (n=52)	Nonunion (n=18)	p-value
Comminuted fracture, n (%)	15 (28.8%)	14 (77.8%)	0.001*
Treatment by IM nailing, n (%)	34 (65.4%)	10 (55.6%)	0.449
Inadequate fixation, n (%)	6 (11.5%)	11 (61.1%)	0.000*
Infection at fracture site, n (%)	4 (7.7%)	10 (55.6%)	0.000*
Distraction osteogenesis, n (%)	3 (5.8%)	7 (38.9%)	0.002*
NSAIDs use >4 weeks, n (%)	8 (15.4%)	9 (50.0%)	0.004*

**Statistically significant (p <0.05); IM: Intramedullary.*

Fracture-related and treatment-related factors significantly associated with nonunion (Table 2) included open fracture of Gustilo grade ≥II (p=0.000), fracture gap >1 cm (p=0.000), high-energy mechanism (p=0.010), comminuted fracture pattern (p=0.001), inadequate fixation (p=0.000), post-operative infection (p=0.000), distraction at the fracture site (p=0.002), and prolonged NSAID use exceeding four weeks (p=0.004). Bone involved and type of fixation (intramedullary nailing vs. other) did not differ significantly between groups.

Table 3: Multivariate logistic regression – Independent predictors of nonunion

Predictor	OR	95% CI	p-value
Diabetes mellitus	6.82	1.94–24.07	0.003*
Smoking	5.74	1.63–20.19	0.006*
Open fracture (Gustilo ≥II)	8.31	2.18–31.69	0.002*
Fracture gap >1 cm	9.46	2.47–36.27	0.001*
Comminuted fracture	4.59	1.32–15.97	0.017*
Infection at fracture site	10.23	2.59–40.44	0.001*
Inadequate fixation	7.15	1.87–27.33	0.004*
NSAIDs use >4 weeks	4.02	1.11–14.56	0.034*
BMI >25 kg/m²	3.47	1.02–11.83	0.047*
Anaemia	5.18	1.44–18.63	0.012*

**Statistically significant (p <0.05); OR: Odds Ratio; CI: Confidence Interval.*

On multivariate binary logistic regression (Table 3), infection at the fracture site (OR=10.23; p=0.001), fracture gap >1 cm (OR=9.46; p=0.001), open fracture Gustilo ≥II (OR=8.31; p=0.002), inadequate fixation (OR=7.15; p=0.004), diabetes mellitus (OR=6.82; p=0.003), smoking (OR=5.74; p=0.006), anaemia (OR=5.18; p=0.012), comminuted fracture (OR=4.59; p=0.017), prolonged NSAID use (OR=4.02; p=0.034), and BMI >25 kg/m² (OR=3.47; p=0.047) emerged as independent significant predictors of nonunion.

Table 4: Nonunion profile and timeline

Parameter	Value
Mean follow-up duration (weeks)	28.4 ± 6.2
Mean time to radiological union (weeks)	16.8 ± 4.1
Mean time to nonunion diagnosis (weeks)	24.6 ± 3.8
Nonunion rate (overall)	25.7% (18/70)
Atrophic nonunion, n (%)	11 (61.1%)

Parameter	Value
Hypertrophic nonunion, n (%)	5 (27.8%)
Oligotrophic nonunion, n (%)	2 (11.1%)

IM: Intramedullary nailing.

DISCUSSION

The present study prospectively evaluated 70 patients with long bone fractures over a six-month period at a busy tertiary care institution, with the primary aim of identifying independent predictors of nonunion. The overall nonunion rate of 25.7% observed in our study is consistent with rates reported from comparable institutional studies in India and Southeast Asia, which range from 15% to 30%, and is higher than rates reported in high-income countries (5–10%), likely reflecting differences in injury patterns, nutritional status, healthcare access, and socioeconomic determinants.[10,11]

Infection at the fracture site was the strongest independent predictor of nonunion in our study (OR=10.23), a finding corroborated by multiple investigators. Infected nonunion represents the most challenging variant to manage, as the biological milieu at the fracture site is severely compromised, with impaired angiogenesis, osteoblast dysfunction, and biofilm formation inhibiting callus maturation.[12] The high prevalence of open fractures in our study population, compounded by delayed presentation common in a resource-limited setting, likely contributed to the high infection-related nonunion rate. Rigorous wound management, timely debridement, appropriate antibiotic prophylaxis, and early soft-tissue coverage are essential measures to mitigate this risk.[13]

A fracture gap exceeding 1 cm was identified as a potent predictor of nonunion (OR=9.46), consistent with the biomechanical principle that critical-sized defects exceed the regenerative capacity of the periosteum and endosteum, precluding bridging callus formation.[14] In clinical practice, fracture gap may result from bone comminution with loss of fragments, periosteal stripping, excessive distraction during fixation, or bone resorption secondary to avascular necrosis. Our finding underscores the importance of meticulous surgical technique aimed at maintaining cortical contact, bone grafting when necessary, and avoiding over-distraction.

Open fractures classified as Gustilo grade ≥II were strongly associated with nonunion (OR=8.31). The higher the grade of soft-tissue injury, the greater the disruption of the periosteal blood supply and the osteogenic potential of the fracture haematoma, both of which are fundamental to successful fracture repair.[15] In our cohort, 66.7% of patients in the nonunion group had open fractures compared to 19.2% in the union group ($p<0.001$). This highlights the need for staged management protocols, including thorough wound debridement, temporary external fixation, and delayed definitive fixation once the wound environment is optimised.

Inadequate fracture fixation emerged as a highly significant predictor (OR=7.15), reflecting the central importance of mechanical stability in fracture healing. Interfragmentary motion beyond the optimal range (typically <150 μm for primary bone healing) disrupts vascular ingrowth, impairs differentiation of mesenchymal stem cells toward osteoblastic lineage, and promotes fibrocartilaginous rather than osseous bridging.[16] Inadequate fixation in our study encompassed scenarios of improper implant selection, poor reduction, implant failure, and inadequate postoperative weight-bearing restriction. This underscores the need for standardised surgical training, appropriate implant availability, and patient education.

Diabetes mellitus was independently associated with a nearly sevenfold increase in the risk of nonunion (OR=6.82). Hyperglycaemia adversely affects virtually every phase of fracture healing: it impairs neutrophil and macrophage function predisposing to infection, reduces osteoblast proliferation and differentiation, inhibits angiogenesis through suppression of vascular endothelial growth factor (VEGF), and promotes advanced glycation end-product (AGE) accumulation that stiffens the extracellular matrix.[17] Our findings are consistent with the landmark meta-analysis by Lim et al. (2017), which reported a pooled relative risk of 2.0 for delayed union and 3.0 for nonunion in diabetic patients.[18] Perioperative glycaemic optimisation and multidisciplinary management involving endocrinology are therefore strongly advocated.

Smoking was identified as a significant independent predictor (OR=5.74). Nicotine and carbon monoxide from tobacco smoke cause vasoconstriction and carboxyhaemoglobin-mediated tissue hypoxia at the fracture site, reducing oxygen delivery essential for osteoblast function and angiogenesis.[19] Cotinine, the primary metabolite of nicotine, directly inhibits osteoblast proliferation in vitro. Clinical studies have consistently demonstrated a two- to threefold increase in nonunion risk among active smokers, as well as impaired results following bone grafting.[20] Smoking cessation counselling should be an integral component of pre- and perioperative care for fracture patients.

Anaemia (haemoglobin <10 g/dL) was a significant predictor (OR=5.18), likely through its role in reducing oxygen delivery to the hypoxic fracture microenvironment. Iron deficiency also directly impairs collagen synthesis, an essential step in callus formation and mineralisation.[21] Nutritional deficiency, although significant on univariate analysis, was not independently significant after adjusting for other covariates, suggesting partial mediation through anaemia and BMI. Nevertheless, perioperative nutritional optimisation—including protein supplementation, vitamin D, and calcium—remains clinically important.

Comminuted fractures (OR=4.59) and high-energy mechanisms, while related, independently contributed to nonunion risk. Comminution results in devascularisation of bone fragments, loss of periosteal continuity, and structural instability that collectively impair healing.[22] Prolonged use of NSAIDs for more than four weeks (OR=4.02) was also significantly associated with nonunion, consistent with experimental evidence that cyclooxygenase (COX) inhibition suppresses prostaglandin-mediated osteoblast recruitment and impairs early inflammatory signalling essential for fracture healing initiation.[23] Clinicians should prescribe NSAIDs judiciously in fracture patients, limiting their use to the acute phase and preferring paracetamol or opioid analgesics for longer-term pain management.

Our study has several strengths, including its prospective design, structured data collection, systematic radiological follow-up, and multivariate analysis controlling for potential confounders. Limitations include the relatively short study period (six months), the single-centre design which may limit generalisability, and the absence of molecular or biochemical markers of bone healing. Long-term follow-up beyond 24 weeks would further refine nonunion characterisation and allow assessment of outcomes of nonunion treatment. Future multicentre prospective cohort studies with larger sample sizes and biological marker profiling are warranted.

CONCLUSION

Nonunion in long bone fractures is a multifactorial complication with a significant incidence in the tertiary care setting. The present study identifies ten independent predictors of nonunion: infection at the fracture site, fracture gap >1 cm, open fracture (Gustilo ≥II), inadequate fixation, diabetes mellitus, smoking, anaemia, comminuted fracture pattern, prolonged NSAID use, and elevated BMI. Infection, fracture gap, and open injury carry the highest odds. A systematic approach encompassing meticulous surgical technique, aggressive infection prevention, optimal glycaemic control, smoking cessation, correction of anaemia, and judicious analgesic prescribing is essential to reduce the burden of nonunion and its associated morbidity. Risk stratification tools incorporating these predictors may facilitate early, targeted interventions in high-risk patients.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. No funding was received for this study.

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