УДК: 616.71-001.5-089.2: 615.465 : 616-06-036.3 – 02 – 089.168/.17
*DOI: https://doi.org/10.37647/2786-7595-2025-127-4-28-36*

# Patient-Dependent Risk Factors for Nonunion of Long Bone Fractures After Metal Osteosynthesis

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***Summary. Background.*** *Delayed consolidation and nonunion after long bone fractures remain among the most severe complications in the surgical treatment of musculoskeletal injuries.* ***Objective.*** *The study aims to determine the impact of patient-dependent risk factors for nonunion of long bone fractures after metal osteosynthesis and to rank these factors depending on fracture location.* ***Materials and Methods.*** *A total of 165 patients who underwent metal osteosynthesis for long bone fractures (64 females and 101 males) and were treated for impaired reparative osteogenesis and nonunion were evaluated. The systematization of cases of nonunion of fractures was carried out according to the Weber-Cech classification. Patient-dependent factors (patient's age, gender, smoking, alcohol abuse, overweight, use of nonsteroidal anti-inflammatory drugs, comorbidity) were studied.* ***Results and Discussion.*** *The incidence of nonunion was higher in males than in females. The oligoplastic type of nonunion was more common than other types of impaired bone healing. A higher incidence of aplastic nonunion of humeral fractures was observed in females; for the lower extremities, oligoplastic nonunion most often occurred in males. Hyperplastic nonunion predominated exclusively in the group of segments of the lower extremities. Statistical analysis of risk factors for nonunion demonstrates a strong influence of smoking and the use of nonsteroidal anti-inflammatory drugs.* ***Conclusions.*** *Smoking and the use of nonsteroidal anti-inflammatory drugs are the key factors influencing nonunion formation in long bone fractures. The distribution of prognostic factors for the formation of a false joint by morphological features demonstrates a homogeneous trend of ranking in the following areas: nonsteroidal anti-inflammatory drugs, age, smoking, gender, comorbidity, and alcohol consumption. The identification and ranking of these factors will allow for accurate clinical profiling of patients with long bone nonunion and for assessing the prognostic impact of these factors in individual clinical cases.*

***Key words:*** *long bone fracture; fracture nonunion; osteosynthesis; patient-dependent risk factors.*

## Introduction

Delayed consolidation and nonunion formation after long bone fractures remain one of the complications of surgical treatment of musculoskeletal injuries, which has a significant social and economic impact on the healthcare system [1]. This is associated with prolonged treatment, including multiple surgical interventions. The outcomes of such repeated procedures may be unfavorable, leading to further patient disability and inability to restore work capacity. Healthcare costs for patients diagnosed with nonunion, according to numerous studies, are more than twice as high as those for patients with uncomplicated fracture union [2]. The overall risk of nonunion is up to 5%, whereas for certain fractures in older patients this risk may increase to 9% [3, 4]. In high-energy open fractures of long bones, the risk of nonunion increases significantly and may be up to 19 times higher compared with closed fractures [5]. Certain anatomical regions demonstrate a higher incidence of nonunion, particularly fractures of the humerus, femur, tibia, and forearm bones [6]. Recent studies have identified factors associated with impaired fracture healing, allowing for more targeted patient monitoring and treatment strategies [3–16]. Several reports indicate a number of factors associated with the incidence of long bone nonunion in the elderly [6]. Other presumed risk factors for nonunion include male gender, smoking, and diabetes; however, these factors have not been clearly quantified, as some studies lacked adequate control for the presence of comorbidities [17].

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Thus, the contradictory data regarding fracture union complications and the uncertainty surrounding the influence of factors affecting impaired regeneration and false joint formation reported in the literature highlight the relevance and need for further investigation. Timely diagnosis based on a standardized definition of long bone nonunion is crucial for early prognostic assessment at the stage of primary surgical intervention and for determining the optimal treatment strategy for patients with impaired fracture repair. Accordingly, the present study aims to identify patient-dependent predictors of impaired bone regeneration and nonunion after metal osteosynthesis (MOS), depending on the localization of long bone fractures.

**Objective.** This study aims to determine the impact of patient-dependent risk factors for nonunion of long bone fractures after MOS and their ranking depending on the localization of the injury.

## Materials and Methods

The study was conducted at the clinical bases of the Department of Traumatology and Orthopedics of Dnipro State Medical University from 2009 to 2022. A homogeneous cohort of 165 patients (64 females and 101 males) with long bone fractures treated by MOS was formed. The patients were admitted to the clinic within a period of three months to three years after the initial surgery due to complications associated with impaired reparative osteogenesis and nonunion formation.

Cases of long bone nonunion after MOS were systematized according to morphological characteristics using the Weber-Cech classification (1976) [18].

To analyze factors influencing long bone fracture nonunion, patient-dependent risk factors were assessed, including:

- patient age [19–21];
- patient gender [4, 6];
- smoking [4, 8, 19, 22, 23];
- alcohol abuse [19, 20, 23, 24];
- overweight [19, 20, 22, 24, 25];
- use of nonsteroidal anti-inflammatory drugs (NSAIDs) [4, 20, 24, 26];
- comorbidity [19, 27].

Statistical analysis was performed using a descriptive method. The total sample was initially divided by gender (females, n=64; males, n=101). Each gender sample was then divided into groups depending on the nature of the nonunion by localization. Results for each sample size were presented as minimum and maximum values, median, and mean values. The assessment of the presence of the nonunion criterion assumed an integer value.

## Discussion

It should be noted that the identification of such risk factors as patient gender, smoking, alcohol abuse, and overweight did not raise questions regarding the analysis in the study design. In contrast, the inclusion of factors such as age, use of NSAIDs, and comorbidity raised certain questions regarding the subsequent determination of the possibility of their inclusion in the further analysis.

The literature review on the issue of determining the risks of bone nonunion according to age-related thresholds did not provide a clear answer. Numerous studies have demonstrated the influence of age on delayed union or nonunion [28]. Age is considered a risk factor due to the presence of osteoporosis, metabolic changes, and reduced compliance of elderly patients with postoperative recommendations regarding timing and load-bearing of the operated limb [29]. According to the literature, bone nonunion, depending on the localization of the fracture and the age of the patients, was as follows: humerus – 30–60 years [30], forearm bones – 30–55 years [31, 32], femur – 31–60 years [33–36], and tibia – 30–55 [10,13,37]. Given the variability in defining age thresholds as a risk factor for nonunion, a cut-off value of 45 years and older was selected for all subgroups in the present study.

Consideration of NSAID administration as a risk factor also requires careful discussion. Numerous studies have reported the negative effects of NSAIDs on osteogenesis [47-51]. In particular, the literature discusses certain negative reactions to NSAIDs that are directly related to pain relief in bone fractures, such as an increased risk of fracture nonunion [38,39]. It is known that reparative regeneration of fractures is a complex process that includes elements of inflammation (particularly, the reaction of macrophages and osteoclasts) aimed at removing dead cells and destroyed intercellular matrix, stimulation of the production of growth factors, proliferation and differentiation of mesenchymal stem cells, synthesis of collagen and proteoglycans, and formation of newly formed bone and cartilage structures [40,41]. Cyclooxygenase-2 (COX-2) activity, which is intensively expressed at the injury site, plays a crucial role in effective repair, as prostaglandins E2 and I2 (prostacyclin) synthesized via this pathway regulate cellular proliferation and improve microcirculation. Prostaglandin E2, through interaction with EP2 and EP4 receptors, induces the synthesis of several growth factors, including bone morphogenetic proteins (BMPs), and accelerates bone remodeling and ossification of newly formed tissue [42]. By inhibiting COX-2 activity at the injury site, NSAIDs may suppress reparative

processes and negatively affect new bone formation in the fracture area. This effect has been confirmed in a number of experimental and laboratory studies using biological models [43]. For example, Pountos et al. (2021) demonstrated that NSAID-induced reduction of prostaglandin E2 concentration at the injury site may inhibit chondrogenesis and osteogenesis by decreasing the expression of genes responsible for the synthesis of growth factors TGF- 3 and FGF-1. Janssen et al. (2017) showed that NSAID administration inhibited chondrocyte differentiation and bone mineralization following experimental fracture. A meta-analysis of 47 studies evaluating the effects of NSAIDs on the consequences of experimental fractures in laboratory animals revealed a statistically significant reduction in biomechanical properties of repaired bone. However, a significant difference was observed in the effect of NSAIDs among different animal species (in particular, no negative effect of these drugs on the stiffness of newly formed bone in mice was noted), as well as between females and males, and across different injury localizations [46]. In addition to the negative biochemical impact on reparative regeneration, the duration and dosage of NSAID use are relevant. Thus, NSAID administration for up to two weeks has not been shown to significantly increase the risk of nonunion [47]. At the same time, some studies have determined a high risk of nonunion when using NSAIDs for more than 2 weeks; these terms are highly dependent on the localization of the fracture [49,50,52] and pharmacological properties of the NSAIDs themselves [51]. Accordingly, for patient selection in the present study, a risk group was defined for NSAID use for 30 days or longer.

Comorbidity, as a risk factor for long bone nonunion, was assessed as a qualitative indicator. It should be noted that according to formal criteria, all patient-dependent factors of influence can be attributed to comorbidity; however, from the point of view of detailing and determining the influence and calculating the prediction of nonunion, this loses its meaning. Therefore, comorbidity in this study was considered as a present or absent criterion, which was added to the study design. Comorbidity was determined in the presence of the following diagnoses observed in patients: hypertension, heart disease, vascular diseases, diabetes, etc. [19, 27].

## Results

Data on the distribution of patients included in the study according to fracture localization, gender, and age are presented in Table 1. The main group was mostly comprised of males (101 patients, 61%); females were only 64 patients (39%). It should be noted that 146 out of 165 patients were of working age (Table 1).

According to the Weber-Cech classification (1976) [18], the studied cases of long bone nonunion after MOS were distributed by morphological factor as shown in Table 2 and Table 3.

The number of nonunion cases was higher in males than in females, and this trend was observed across all fracture localizations.

The main group of patients was further systematized into four clinical and radiological subgroups, the distribution of which was carried out taking into

*Table №1*

**Distribution of patients by fracture localization, gender, and age**

| Age / Gender | 18-20 | 21-30 | 31-40 | 41-50 | 51-60 | 61-70 | 71 + | Total | Average age |
|---|---|---|---|---|---|---|---|---|---|
| Humerus | | | | | | | | | |
| M | 0 | 5 | 6 | 2 | 1 | 1 | 1 | 16 | 39.3 |
| F | 0 | 1 | 5 | 6 | 5 | 4 | 2 | 23 | 48.9 |
| Generally | 0 | 6 | 11 | 8 | 6 | 5 | 3 | 39 | 44.1 |
| Forearm bones | | | | | | | | | |
| M | 0 | 3 | 9 | 4 | 2 | 0 | 0 | 18 | 37.4 |
| F | 0 | 4 | 2 | 1 | 1 | 0 | 0 | 8 | 36.8 |
| Generally | 0 | 7 | 11 | 5 | 3 | 0 | 0 | 26 | 37.1 |
| Femur | | | | | | | | | |
| M | 2 | 6 | 8 | 7 | 4 | 2 | 1 | 30 | 41.2 |
| F | 0 | 4 | 3 | 3 | 5 | 3 | 2 | 20 | 47.2 |
| Generally | 2 | 10 | 11 | 10 | 9 | 5 | 3 | 50 | 44.2 |
| Tibia | | | | | | | | | |
| M | 4 | 8 | 10 | 9 | 5 | 1 | 0 | 37 | 37.6 |
| F | 2 | 2 | 1 | 3 | 3 | 2 | 0 | 13 | 46 |
| Generally | 6 | 10 | 11 | 12 | 8 | 3 | 0 | 50 | 41.8 |

*Table №2*

**Distribution of nonunion cases by fracture localization, gender, and age**

| Type of nonunion / Gender | Slow consolidation | False joints | | | Total |
|---|---|---|---|---|---|
| | |  |  |  | |
| | | Hyperplastic | Oligoplastic | Aplastic | |
| Humerus | | | | | |
| M | 4 | - | 5 | 7 | 16 |
| F | - | | 9 | 14 | 23 |
| Generally | 4 | - | 14 | 21 | 39 |
| Forearm bones | | | | | |
| M | 4 | - | 8 | 6 | 18 |
| F | - | - | 3 | 5 | 8 |
| Generally | 4 | - | 11 | 11 | 26 |
| Femur | | | | | |
| M | 1 | 1 | 24 | 4 | 30 |
| F | 2 | 1 | 12 | 5 | 20 |
| Generally | 3 | 2 | 36 | 9 | 50 |
| Tibia | | | | | |
| M | 5 | 4 | 22 | 6 | 37 |
| F | 0 | 1 | 8 | 4 | 13 |
| Generally | 5 | 5 | 30 | 10 | 50 |

account the medical history, analysis of clinical data, radiological examination in the temporal aspect, and additional examination methods.

The first group included 16 patients (10%) (Table 3) who had delayed consolidation of diaphyseal fractures of long bones in the period from 4 to 6 months after the injury and MOS. Radiographs of these patients clearly demonstrated a gap between the fragments with the absence of periosteal reaction or an indistinct gap between the fragments with the presence of a delicate periosteal callus. The second group included 91 patients (55%) with oligoplastic nonunion of long bones (Table 3). At 6 to 9 months after MOS, radiological examination of these patients demonstrated the absence of elements of fracture consolidation and formation of fibrous and/or cartilaginous tissue between the fragments, manifested by the presence of a gap between the fragments and the absence of bone callus elements. The third group consisted of 7 patients (4%) with hyperplastic nonunion of long bones (Table 3). According to X-ray examination, this group was characterized by the presence of significant expansion of the ends of the bone ("elephant foot" type) [18] or a less pronounced amount of reactive tissue at the ends of bone fragments ("horse hoof" type) [18]. The fourth group included 51 patients (31%) with aplastic nonunion of bones (Table 3). Radiologically, this group demonstrated the absence of bone callus formation, the presence of fragments with osteolysis, sharpening of fragment ends, closure of the bone medullary canals, and the development of osteosclerosis.

It is noteworthy that the oligoplastic type of nonunion was observed in almost half of the cases and, depending on the localization, exceeded other types of bone union disorders. In addition, aplastic nonunion in the humerus segment predominated in females, whereas in the lower extremities there was a tendency toward oligoplastic nonunion with a predominance in males. Hyperplastic nonunion predominated exclusively in the lower extremity segment group.

The data obtained during the collection of information on risk factors are presented in Table 4. For clarity of interpretation of the obtained and statistically processed data, petal diagrams were constructed (Fig. 1).

Where n* is the number of recorded cases.

Statistical analysis of the data demonstrates a strong impact of smoking and NSAID use in the overall group and in all localization-based subgroups, with pronounced peaks (Fig. 1). The gender factor traditionally demonstrates a male predominance, with the exception of false shoulder joints, where

*Table №3*

**Overall distribution of patients into subgroups according to the Weber-Cech classification (1976)**

| Groups of observation | Number (n) | Percent (%) | Type of nonunion |
|---|---|---|---|
| First group | 16 | 10 | Slow consolidation |
| Second group | 91 | 55 |  Oligoplastic |
| Third group | 7 | 4 |  Hyperplastic |
| Fourth group | 51 | 31 |  Aplastic |
| Total | 165 | 100 | |

female patients prevail. Comorbidity, despite the expected significant influence, showed no substantial effect, which is somewhat surprising in comparison with smoking, NSAID administration, and gender. When comparing the obtained data across localization-based subgroups, differences in nonunion risk factors for the humerus are noteworthy, particularly with respect to gender, smoking, and comorbidity.

Analysis of the relationship between the distribution of risk factors and the morphological type

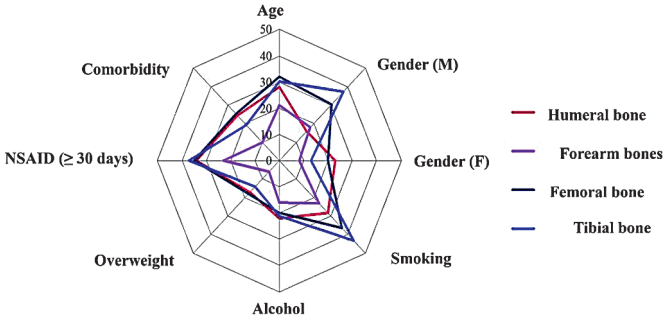


**Fig. 1.** Diagram of the generalized distribution of risk factors in the group of patients.

of nonunion is presented in Figures 1–3. Within the framework of prognostic modeling, a high degree of uncertainty was observed regarding the distribution of influencing factors in the subgroup of patients with delayed consolidation. Ranking of risk factors by their relative nature in this subgroup (Fig. 2) revealed the following order: age, gender, and the use of NSAIDs. Other analyzed factors did not demonstrate statistically significant influence. From the perspective of constructing a clinical model of a patient with long bone nonunion, delayed consolidation should be considered as a transitional state characterized by uncertainty in the direction of the reparative regeneration process toward the development of a type of nonunion. This conceptualization supports the paradigm of delayed consolidation as a potential predictor of nonunion, warranting further detailed study.

Evaluation of the distribution of prognostic factors influencing delayed consolidation (Fig. 2) and morphologically defined nonunion types (Fig. 3) demonstrated a more homogeneous ranking pattern: NSAID use, age, smoking, gender, comorbidity, and alcohol consumption, with greater predominance observed in fractures of the femur and tibia. It should be noted that male predominance persisted in both oligoplastic and hyperplastic nonunion subgroups, except in shoulder localization. At the same time, hyperplastic nonunion demonstrated the highest prevalence in tibial fractures, with absolute values for all analyzed factors nearly twice as high compared with

*Table №4*

**Overall distribution of patient-related risk factors in the observation group**

| Localization of fracture | Age (n*) | Gender M/F (n) | Smoking (n) | Alcohol (n) | Excess weight (n) | NSAIDs (>30 days) (n) | Comorbidity |
|---|---|---|---|---|---|---|---|
| Humerus | 28 | 16/23 | 28 | 22 | 17 | 34 | 24 |
| Forearm bones | 21 | 18/8 | 23 | 16 | 6 | 23 | 10 |
| Femur | 32 | 30/20 | 36 | 20 | 18 | 35 | 25 |
| Tibia | 30 | 37/13 | 43 | 21 | 14 | 37 | 19 |
| Total | 111 | 101/64 | 130 | 79 | 55 | 129 | 78 |

Where n* is the number of recorded cases.

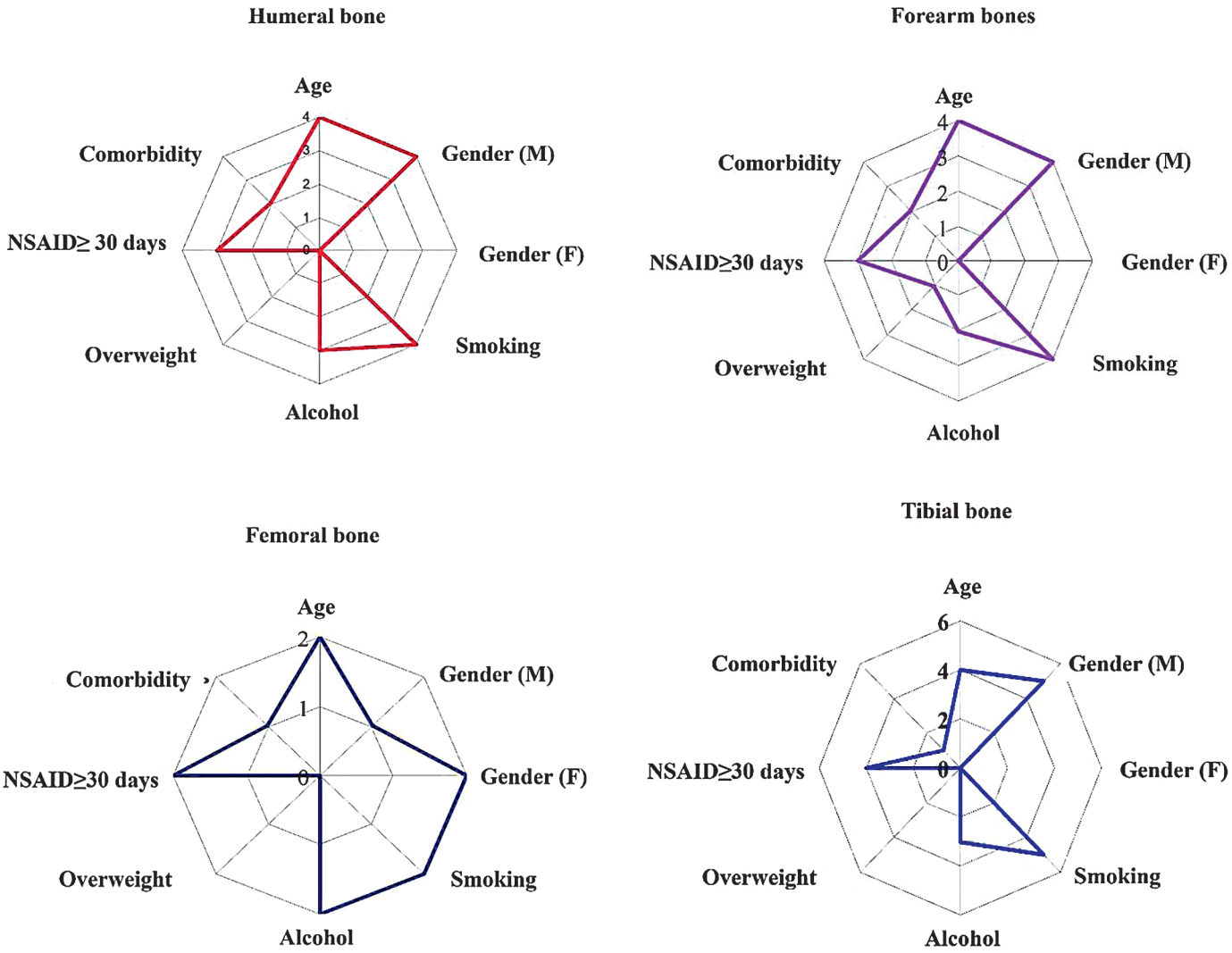


**Fig. 2.** Diagram of the distribution of risk factors in a subgroup of patients with slow consolidation

other localizations. In contrast, shoulder localization was predominantly associated with aplastic nonunion, with an advantage in females against the background of the predominant use of NSAIDs.

## Conclusions

Thus, the study of factors contributing to the formation of long bone nonunion remains relevant, since both quantitative and qualitative indicators of MOS continue to demonstrate a persistent rate of these complications despite the improvement of osteosynthesis methods. The relevance of this issue is further emphasized by the high incidence of nonunion complications among individuals of working age.

Smoking and the use of NSAIDs are the main sources of influence on the formation of long bone nonunion, which forces us to look for levers of influence on bad habits and optimization of drug treatment. In the pursuit of an "ideal" osteosynthesis technique, the patient is often overlooked; however, even with technically optimal fixation, an "ideal patient" does not exist. The role of comorbidity as a contributing factor to long bone nonunion requires continued investigation and more detailed evaluation. Data analysis demonstrates a strong influence of smoking factors and the use of NSAIDs in the general group and in all subgroups by localization with large peaks. The gender factor traditionally demonstrates male predominance, with the exception of shoulder nonunion, where female patients predominate.

The distribution of prognostic factors according to the morphological type of nonunion revealed a homogeneous trend of ranking in the following areas: the use of NSAIDs, age, smoking, gender, comorbidity, and alcohol consumption. Compliance with the definition and ranking of these factors will allow to form an accurate picture both for clinical modeling of a patient with long bone nonunion, and for determining their prognostic impact for a specific clinical case.

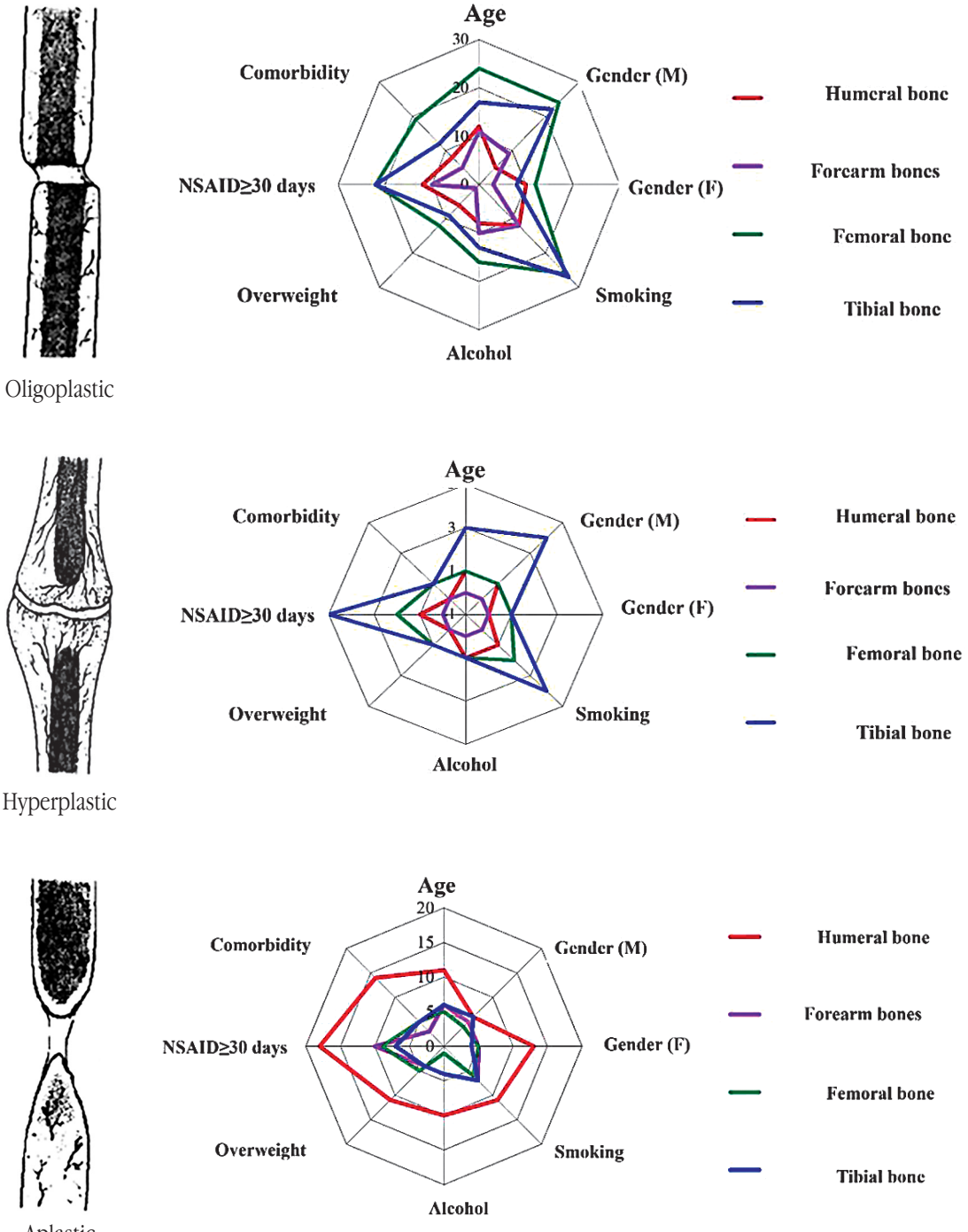


**Fig. 3.** Diagram of the distribution of risk factors in subgroups of patients with a false joint

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## Пацієнтозалежні фактори ризику незрощення переломів довгих кісток після металоостеосинтезу

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***Актуальність:*** *Затримка консолідації та формування незрощення після переломів довгих кісток залишається одним із важких ускладнень в хірургічному лікуванні травм опорно-рухової системи.* ***Мета дослідження:*** *Визначити вплив пацієнтозалежних факторів ризику незрощення переломів довгих кісток після металоостеосинтезу та їх ранжування в залежності від локалізації пошкодження.* ***Матеріали і методи:*** *Було досліджено групу з 165 пацієнтів після металоостеосинтезу переломів довгих кісток (64 жінки та 101 чоловік), які лікувалися з приводу порушень репаративного остеогенезу та формування несправжніх суглобів. Систематизація випадків незрощень переломів проводилась за класифікацією Weber-Cech. Досліджувались пацієнтозалежні фактори (вік хворого, стать, тютюнопаління, зловживання алкоголем, надмірна вага, застосування нестероїдних протизапальних засобів, коморбідність).* ***Результати та їх обговорення:*** *Кількість випадків незрощень у чоловіків переважало в порівнянні з жінками. Олігопластичний вид незрощення перевищував інші види порушень зрощення кісток. Відмічається перебільшення апластичного незрощення переломів плечової кістки у жінок, для нижніх кінцівок найчастіше відбувалося олігопластичне незрощення переважно у чоловіків. Гіперпластичне незрощення виключно переважає в групі сегментів нижніх кінцівок. Статистичний аналіз факторів ризику незрощення демонструє великий вплив факторів куріння та застосування нестероїдних протизапальних засобів. Висновки: Куріння та вживання нестероїдних протизапальних засобів є основним джерелом впливу на формування незрощення переломів довгих кісток. Розподіл прогностичних факторів на формування несправжнього суглоба за морфологічними ознаками вказує на однорідну тенденцію ранжування за наступними напрямками: нестероїдні протизапальні засоби, вік, куріння, стать, коморбідність, алкоголь. Визначення та ранжування цих факторів дозволить сформувати точне уявлення як для клінічного моделювання хворого з несправжнім суглобом довгих кісток, так і для визначення їх прогностичного впливу для конкретного клінічного випадка.*

***Ключові слова:*** *перелом довгих кісток, незрощення переломів, остеосинтез, пацієнтозалежні фактори ризику.*