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Efficacy of Extremity Nonunion Prediction: State of the Art

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Abstract

Background: Nonunion remains a major orthopedic complication, occurring in 5–10% of fractures and drastically diminishing patients' quality of life. Traditional guidelines necessitate waiting up to nine months for a diagnosis, leading to therapeutic delays, prolonged disability, and substantial healthcare costs. This underscores the urgent need for early risk stratification.

Aim: This study aims to summarize and critically evaluate the efficacy of currently available and innovative tools for the early prediction of extremity nonunion.

Material and methods: A state-of-the-art narrative review was conducted. The analysis encompassed studies evaluating biological bone turnover markers, advanced imaging diagnostics, clinical scoring systems, machine learning (ML) algorithms, and smart implant technologies.

Results: The isolated use of single predictive tools has significant limitations. Systemic markers reflect early fracture biology but exhibit excessive inter-individual variability. Clinical heuristics effectively exclude complications (NPV up to 100%) but inadequately identify high-risk patients (PPV ~35.5%). While ML models provide superior analytics, their current PPV of ~55% indicates a continued challenge in accurately identifying patients for early intervention. Monitoring load transfer via smart implants represents a promising parallel alternative.

Conclusions: Predicting nonunion based on single modalities is insufficient. Effective prediction requires integrating multimodal diagnostics, combining comprehensive patient information with AI-driven analytics. This approach necessitates prospective, centralized databases for optimal and safe algorithm training.

Keywords: *fracture nonunion; fracture healing; biomarkers; risk assessment; machine learning*

1. Introduction

1.1. Definition

According to the FDA, nonunion is defined as the absence of a healed fracture 9 months after the injury, accompanied by a lack of signs of healing on radiographic examination for 3 months [1]. However, these are only certain time frames adopted to standardize terminology. They do not fully capture the definition and understanding of nonunion. Each bone has its own individual healing potential and associated healing time. Consequently, some authors define nonunion as the failure of a fracture to heal within the timeframe expected for that particular bone. This means that the term “nonunion” can be interpreted in various ways. What remains constant, however, is the fact that nonunion is a serious condition in which a fracture has not healed, typically requiring surgical intervention and modification of the patient's risk factors.

1.2. Epidemiology

Failure of bone union occurs in approximately 5–10% of all fractures [2]. This is one of the most serious complications of fracture treatment. The bones with the highest risk of nonunion are the scaphoid (15.5%), followed by the bones of the lower leg (14%) and the femur (13.9%). Nevertheless, given that the overall incidence of fractures is unevenly distributed, in practice we will most often encounter nonunion in the case of common injuries. For this reason, in absolute numbers, the highest number of cases will be observed following fractures of the forearm, the humerus, and, to a lesser extent, the lower leg [3].

1.3. Fracture Union Concept

The biological basis of bone union is best illustrated by the so-called “diamond concept.” This concept, in its classical form, is based on four pillars: the presence of osteogenic cells (mesenchymal stem cells (MSCs) capable of differentiating into osteoblasts), an osteoconductive scaffold (a matrix that allows cells to adhere and build new tissue), osteoinductive signals — primarily bone morphogenetic proteins (BMP-2, BMP-7) along with growth factors (TGF-β, VEGF) and mechanical stability [4].

Subsequent publications point to a need to expand this model to include additional key elements: vascularity and host factors. By focusing on deficiencies in these specific factors, we can more effectively identify fractures at risk of failing to heal within the standard timeframe and predict healing failure.

Predicting nonunion will therefore be based on an analysis of deficiencies in the aforementioned components of the "diamond concept".

1.4. Clinical presentation

The primary clinical symptoms of nonunion include pain and tenderness on palpation in the area of the fracture, worsening of symptoms when weight is placed on the limb, and, not infrequently, a complete inability to bear weight on it. The physical examination should include an assessment of abnormal mobility of bone fragments and any limb malalignment [5]. It is essential to assess the patient for possible local infection — including warmth, erythema, increased swelling, and, in extreme cases, active purulent fistulas [6]. The clinical evaluation of a patient with suspected nonunion should also include an assessment of the implant used, if a surgical treatment approach was chosen. Localized pain and tenderness over a subcutaneously palpable union may be an early clinical sign of implant loosening, migration, or mechanical damage. It is noteworthy that the chronic nature of the condition and prolonged immobilization lead to numerous secondary symptoms. These include progressive muscle atrophy, contractures, and secondary limitations of motion in the joints adjacent to the fracture, as well as regional disuse osteopenia.

1.5. Quality of life and social impact

The absence of union is associated with a drastic decline in patients' quality of life. As demonstrated in a cohort study conducted on a Dutch population, the values of the Health Quality of Life (HRQoL) scores in these patients are significantly lower not only compared to the general healthy population, but also compared to patients with other, numerous chronic conditions, including musculoskeletal disorders [7]. Another method used to assess quality of life in this patient group is the Time Trade-Off (TTO) index. This method measures what is known as health utility, determining what part of the patient's expected remaining life they would be willing to sacrifice in exchange for immediate restoration of full health (for example, a willingness to give up 40% of a hypothetical 10-year life expectancy translates to a utility value of 0.60). In the analyzed cohort of patients with nonunion, the average utility value was only 0.68. This is a significantly lower result than for many severe systemic diseases, such as type 1 diabetes (0.88), post-stroke status (0.81), or AIDS (0.79) [8].

Nonunion also results in significant socioeconomic costs. The systemic costs associated with treating this complication exceed the costs of caring for a properly healing fracture by nearly 350% [9]. This amount consists of direct medical costs, including the cost of the surgical procedure, the implant used, hospitalization, extended outpatient care along with serial imaging, as well as necessary rehabilitation. It should be emphasized, however, that a significant portion of the total burden consists of indirect costs resulting from prolonged loss of occupational productivity. This is a consequence of the prolonged therapeutic process, which lasts an average of 45 weeks in patients with nonunion [10].

1.6. Aim

The main objective of this study is to provide a comprehensive analysis of the current prognostic predictors used in the early identification of the risk of nonunion.

2. Research materials and methods

The literature search and study selection for this narrative review were structured in accordance with the PICOS (Population, Intervention, Comparison, Outcomes, and Study design) framework. A comprehensive literature search was performed in PubMed/MEDLINE, Embase, and The Cochrane Library from database inception to April 2026. The search strategy combined keywords and Medical Subject Headings (MeSH) related to “nonunion”, “prediction”, and “predictive factors” within orthopedics and traumatology. Only studies published in English were included. Study selection was based on strict, predefined inclusion and exclusion criteria. According to the PICOS framework, the following inclusion criteria were applied: Population (P): adult patients (> 18 years of age) sustaining fractures of the upper and lower extremities; Intervention/Indicator (I): clinical assessment, biomarkers, imaging, or other tools used for fracture healing prediction; Comparison (C): normal fracture healing or standard diagnostic protocols; Outcomes (O): early diagnosis and prediction of nonunion; Study design (S): all clinical studies (both prospective and retrospective) involving human subjects.

The following were excluded from the analysis:

- Experimental studies on animal models and in vitro studies.
- Publications involving the pediatric population (patients < 18 years of age).
- Studies analyzing impaired bone healing within the axial skeleton (e.g., spine, pelvis, skull).
- Case reports, editorials, letters to the editor, and unpublished conference proceedings.

3. Results

3.1. Risk Factors

Early stratification of patient risk factors is crucial for predicting and preventing healing complications. The most significant modifiable risk factors include smoking, uncontrolled diabetes, vitamin D and calcium deficiencies, obesity, and long-term use of nonsteroidal anti-inflammatory drugs (NSAIDs) [11]. Active smoking significantly impairs microcirculation within the callus. This leads to more than a 2-fold increase in the risk of nonunion. For this reason, and given its prevalence and the potential for straightforward treatment, smoking appears to be one of the most important risk factors. Patient education on smoking cessation, behavioral and pharmacological treatments, as well as strict glycemic control in patients with diabetes, form the foundations of biological support for fractures during healing [12].

In contrast to the above, non-modifiable risk factors determine a patient's baseline risk profile, over which the physician has no direct influence. These primarily include: male gender, advanced age, as well as the characteristics of the injury itself — open, high-energy, and multifragmentary fractures. High-energy injuries are associated not only with bone destruction. They also lead to extensive damage to soft tissues and the periosteum. This reduces the potential for vascularization of the fracture site. Advanced age, in turn, correlates with osteoporotic changes and reduced proliferative capacity of progenitor cells [13].

An analysis of risk factors will not indicate precisely which patients will develop nonunion. However, this approach enables the identification of at-risk patients and careful monitoring of the treatment process. Consequently, it allows for the early implementation of an “extended monitoring protocol,” including more frequent radiographic follow-up (e.g., via the RUST scale). It is also important to identify modifiable risk factors as early as possible. This allows for the implementation of targeted therapeutic interventions aimed at optimizing the biological healing environment and partially preventing the development of complications.

3.2. Systemic and Local Biomarkers

3.2.1. Bone turnover markers

Biochemical markers of bone turnover (BTMs) are proteins or protein fragments released into the bloodstream during the process of bone remodeling. Their serum concentrations correlate with the processes of bone formation and resorption. A 2024 systematic review evaluated the utility of the most common markers, including markers of bone formation: bone alkaline phosphatase (BAP), C-terminal propeptide of type I collagen (CICP), N-terminal propeptide of type I procollagen (P1NP), and osteocalcin (OC). Among resorption markers, C-terminal telopeptide of type I collagen (CTx) and tartrate-resistant acid phosphatase 5b (TRACP5b) were analyzed, and among bone metabolism regulators — osteoprotegerin (OPG). Currently, there is insufficient evidence to recommend the use of a single BTM parameter for the early detection of nonunion. The ambiguity of the available data is likely due to methodological differences among the studies, as well as the diurnal variability of the markers and their dependence on the patients' age and sex [14]. A particular challenge in implementing BTM into routine clinical practice is posed by strict pre-analytical requirements, such as the need to collect samples in the morning on an empty stomach (especially in the case of CTx). Furthermore, a single measurement of concentration has low prognostic value; much greater clinical significance is attributed to the analysis of trends (dynamics of changes) in concentrations during the first weeks following injury. The introduction of BTM as a diagnostic standard therefore requires further standardization of laboratory procedures and the development of uniform cutoff thresholds for individual phases of healing.

The most popular and most commonly measured marker is alkaline phosphatase (ALP) — an enzyme found primarily in the liver, bones, kidneys, and intestines. It is highly expressed in the cells of mineralized tissues and plays a key role in bone formation. In clinical practice, it is used, e.g., in the diagnosis of Paget's disease, osteomalacia, osteosarcoma, and bone metastases. Some studies indicate that ALP levels remaining above reference values in the initial weeks following an injury are associated with a high risk of nonunion [15]. However, due to the low specificity of this enzyme, greater prognostic value is currently attributed to the analysis of trends in BAP. BAP is released into the bloodstream exclusively by active osteoblasts. Thanks to this high tissue specificity, measuring BAP levels allows for isolated and precise monitoring of the bone union mineralization process, eliminating the risk of false readings caused by disorders in other organs. This is of critical importance in patients with multiple organ injuries or comorbidities.

3.2.2. Growth factors and cytokines

Growth factors and cytokines are signaling molecules that coordinate the various phases of bone tissue regeneration. Proteins from the growth factor group, such as transforming growth factor beta (TGF-beta), bone morphogenetic proteins (BMP), and vascular endothelial growth factor (VEGF), exhibit osteoinductive and angiogenic effects, stimulating progenitor cells to form new bone tissue [16]. In turn, the early release of pro-inflammatory cytokines, including interleukins (such as IL-1 and IL-6) and tumor necrosis factor (TNF-alpha), is essential for initiating the repair cascade and recruiting inflammatory cells immediately after injury [17]. The correct sequence and precise location of action of these molecules are among the factors that determine proper bone healing.

TGF-beta is one of the key molecules involved in the fracture healing process. Its role involves promoting the proliferation and differentiation of MSCs, increasing the production of the extracellular matrix, and exerting a chemotactic effect on osteoblasts. In a prospective study of 103 patients, serum TGF-beta levels were measured following fracture. Patients who developed delayed union exhibited lower levels of the marker at 4 weeks post-injury compared to patients who achieved union. These differences persisted up to 12 weeks. Similar findings and trends have also been observed by other authors [18]. It was also noted that TGF-beta levels peaked later in patients with nonunion (3 weeks after injury) compared to patients with normal union [19]. However, this marker has significant limitations. Serum TGF-beta concentrations vary depending on smoking status, age, sex, diabetes, and chronic alcohol abuse at different time points. Because of these variations, it is difficult to consider it a reliable predictive marker when used independently and on a one-time basis [20]. Further research and the correlation of this marker with other predictors may make it a useful tool in clinical practice.

Inflammatory markers such as CRP, IL-1β, TNF-alpha, and IL-6 are also noteworthy. It is well known that excessive or prolonged systemic inflammation is associated with impaired osteogenesis. Chronic, high concentrations of pro-inflammatory cytokines disrupt the differentiation of mesenchymal cells and the function of osteoblasts, hindering their recruitment and activity at the site of injury [21]. At the same time, chronic activation of the inflammatory response leads to dysregulation of angiogenesis and disruption of the reparative microenvironment. This promotes the dominance of resorptive processes by increasing osteoclast activity, which shifts the balance toward bone catabolism and increases the risk of nonunion [22]. Studies indicate significantly elevated baseline levels of CRP and IL-6 in patients who fail to achieve union. This association is confirmed by the latest prospective observations by Rathod et al., which showed that patients who developed nonunion had baseline C-reactive protein levels nearly twice as high as those in patients who achieved normal healing (12.8 vs. 6.3 mg/L) [23]. A similar trend was observed for IL-6, whose concentration immediately after injury was elevated in patients with complications, averaging 42.1 pg/mL, compared to 23.7 pg/mL in patients with normal healing.

Other growth factors and inflammatory cells involved in the healing process include: BMPs, VEGF, platelet derived growth factor (PDGF)-AB, placental growth factor (PlGF), cysteine rich angiogenic inducer 61 (CYR61), insulin-like growth factor (IGF)-1, interleukin 8 (IL-8), monocyte chemoattractant protein (MCP-1), macrophage colony stimulating factor (M-CSF), albumin, amino acids. Although each of the factors listed has been shown in scientific studies to have some correlation with the risk of nonunion, their use on their own in daily clinical practice has numerous limitations. One of the main challenges is the high level of inter-individual variability. Their levels are influenced by numerous systemic factors, including age and comorbidities (e.g., diabetes, autoimmune diseases). Furthermore, the dynamic nature of the fracture healing process causes cytokine and growth factor concentrations to change rapidly over time. Their interpretation depends on the timing of sample collection. Therefore, the trend in concentration should be the primary measure. Nevertheless, standardization is required regarding biomarker analysis methods and established threshold values. Additionally, most available studies are based on small patient cohorts. Thus, the ability to generalize the results is limited.

3.2.3. Immune cells and genetic factors

In recent years, the analysis of a patient's immunological and genetic profile has raised high expectations in predicting fracture healing disorders. Studies have examined, e.g., the TEMRA (terminally differentiated effector memory T cells re-expressing CD45RA) subpopulation of CD8+ T lymphocytes. It has been demonstrated that assessing the percentage of these cells with high CD11a antigen expression (CD11a++) two weeks after injury allows for the prediction of nonunion with a sensitivity of 85.5% and a specificity of 87.5%. Because the TEMRA population reflects the body's cumulative exposure to chronic antigenic stimulation, its level is measurable as early as the time of injury. This may make it an early indicator of a patient's individual susceptibility to the development of nonunion [24]. Other researchers analysed CD4+ regulatory T cells (Tregs), assessing their total number, differences in their expression profile, and functional capabilities. It was observed that patients with delayed bone union had significantly lower numbers of Treg cells, as well as significantly weaker reactivity. These studies offer promise for the dynamic development of this branch of diagnostics in the future [25].

Researchers are also paying ever greater attention to the analysis of specific gene expression. The measurement of free nucleic acids in the form of mRNA and miRNA in peripheral blood offers hope for the development of highly accurate markers of healing disorders. As demonstrated by McKinley et al., the use of a panel consisting of just 2 or 3 specific genes allowed for a positive predictive value (PPV) of up to 90% as early as the first 7 days after injury [26]. This type of advanced molecular diagnostics currently remains confined to the field of experimental research, partly due to the high cost of analysis (which requires techniques such as RT-PCR or next-generation sequencing). Nevertheless, genetics represents a promising avenue for the development of personalized traumatology.

It is also worth mentioning the target properties that a future, effective biomarker should strive to achieve in clinical trials. It should demonstrate both high sensitivity and specificity, be easily obtainable and minimally invasive. Furthermore, it must offer high predictability — serving as a reliable indicator of the condition/risk, disease progression, and treatment effect. Finally, it should be robust, meaning it is easy to perform, simple, and cost-effective [27].

3.3. Diagnostic Imaging

3.3.1. X-ray

X-rays are the most common imaging test used to monitor a fracture. Due to its widespread use and low cost, follow-up X-rays are typically taken at intervals of several weeks during the healing process. Comparing these images allows for the detection of healing progress or lack thereof. The most important features assessed include callus bridging and the fracture gap.

Assessment of callus bridging is the primary indicator of whether healing is progressing normally. It is not uncommon for it to appear only around 3 months after the fracture. As shown in the study by Lack et al., any cortical bridging within four months was an excellent predictor of final healing (accuracy = 99%, area under the curve [AUC] = 0.995, $p < 0.0001$) [28]. However, 4 months is a late timeframe. Therefore, there is a need for types of tests that can predict the failure of bone union in advance.

One of the well-known and thoroughly documented radiographic scales is the Radiographic Union Score for Tibial fractures (RUST). This system was developed to assess the healing status of tibial shaft fractures stabilized with intramedullary nailing [29]. The assessment is based on an evaluation of the four cortical layers (anterior, posterior, lateral, and medial) on AP and lateral radiographs. Each of the four cortical layers of the tibia was assigned a RUST score ranging from 1 to 3. A three-point scoring system was adopted, in which 1 point was assigned to a visible fracture line without signs of callus formation. Intermediate changes, with concomitant callus and a still-visible fracture line, were scored as 2 points. Full consolidation, scored as 3, was defined as the presence of bridging callus with complete obliteration of the fracture line. Thus, a RUST score of 4 or 5 will indicate that the fracture has definitely not united (none of the cortices scored 3) and a score of 11 or 12 indicates that it has definitely healed (3 or 4 of the cortices scored 3) [30].

Although the RUST Scale was introduced to standardize and objectify the radiological assessment of bone union, recent studies have demonstrated its effectiveness in predicting nonunion [31]. The primary objective of the researchers was to determine whether the RUST score at 3 months post-surgery is a significant prognostic factor for the occurrence of definitive nonunion assessed at 12 months in patients with tibial shaft fractures treated with intramedullary nailing. As the authors demonstrated, a RUST score of just 4 (compared to a score of 7) was associated with an absolute increase in the risk of nonunion of as much as 47%. A score of 5–6 corresponded to an absolute increase in this risk of 23% [32]. The RUST scale thus appears to be a validated, quantitative, and objective tool for predicting nonunion. Its limitation lies in the fact that it provides information about the potential risk of nonunion relatively late and has been studied only for a single anatomical region using a single treatment method. However, research is underway to apply its principles to the diagnosis of nonunion in other fractures and treatment methods, such as intramedullary nailing of the femur or conservative treatment of the humerus [33, 34].

3.3.2. Computed tomography

Computed tomography (CT) plays an important role in the diagnosis of bone union disorders, offering significantly higher sensitivity and precision than conventional X-rays. The primary advantage of CT is cross-sectional and three-dimensional imaging. It eliminates the problem of overlapping anatomical structures and shadows cast by massive implants. CT should be used as a second-line tool in patients with persistent clinical symptoms and no clear progression on X-ray. Computed tomography demonstrates very high sensitivity in detecting lack of clavicular union (100%), allowing for reliable exclusion of union as early as 3–6 months after injury. At the same time, its specificity remains limited (~82%), which stems from the difficulty in distinguishing delayed union from established nonunion, especially in the presence of hypertrophic callus. In contrast, the presence of features of atrophic nonunion on CT is characterized by a very high predictive value (100%) and constitutes a strong indicator of a lack of healing potential [35].

The CT scan also examined whether bone density measurements could serve as a predictor of nonunion. Patients with scaphoid neck fractures were studied. In the subacute phase (between 4 and 18 weeks after injury), three-dimensional (3D) bone density measurements were performed (relative to the density of the triquetrum). Significantly higher bone density was observed in the nonunion group. The mean density for the distal fragment in this group was 100.2% (vs. 85.7% for the union group), and for the proximal fragment, 126.6% (vs. 108.3% for the union group). The authors also determined cutoff values predicting nonunion at 90.8% for the distal fragment and 116.3% for the proximal fragment. Reaching either cutoff value (for one of the fragments) was associated with 100% sensitivity in detecting future nonunion [36].

Reschke et al. also focused on bone density [37]. However, they measured the bone density of undamaged radial bone segments in cases of distal radius fractures. In this case, the relationship was inverse. Patients with nonunion had significantly lower bone mineral density (median 68.1 mg/cm^3) compared to the group that achieved union (median 94.6 mg/cm^3). However, the study was performed using the less commonly available dual-energy CT (DECT).

3.3.3. Ultrasound

Ultrasonography (USG) is an increasingly common tool in the early diagnosis of bone union disorders. Its advantage lies in the early assessment of soft bone tissue, bone bridges, and blood supply. One of the advantages of ultrasound over conventional radiography is its ability to visualize early, non-calcified soft callus. On standard X-rays, this callus remains invisible until it has calcified, which delays the assessment of healing dynamics by several weeks. Although a direct correlation between the form of soft callus and the occurrence of nonunion has not been proven, it provides insight into the healing process (a poor callus may indicate a complication) [38].

In the analysis of humeral fractures, early ultrasound assessment at 6 weeks showed that the complete absence of any callus allowed for the prediction of nonunion with a PPV of 100% and an negative predictive value (NPV) of 91%. In contrast, the use of another criterion — the absence of sonographic bridging callus — was characterized by a PPV of only 40%, with an NPV of 100%. Although the prospective nature of this pilot study was undoubtedly its strength, the very small study group (n=12) remains a significant limitation affecting the interpretation of predictive indices [39].

The failure to form a bridging callus within the first 3 months after injury is a significant predictor of nonunion, particularly in tibial fractures. In this context, ultrasound may allow for earlier identification of healing disorders compared to conventional radiography, which typically achieves predictive value only after approximately 3–4 months of follow-up. A characteristic finding accompanying the absence of bridging on ultrasound is the presence of an irregular gap within the fracture line, sometimes described as a “corkscrew” or “V”-shaped pattern. This phenomenon results from the absence of callus formation, causing the space between the cortical surfaces to remain unfilled with mineralized bone tissue and instead contain fluid or fibrous tissue. Under such conditions, ultrasound waves can penetrate deep into the fracture gap, revealing sharp, unremodeled bony margins, which is an image indirectly indicative of a disrupted osteogenesis process [40].

The use of the Power Doppler option also helps to monitor the vascularisation of the fracture site. It has been shown that vascular signals in the fractured bone segment gradually decrease as callus forms. Likewise, persistent hypervascularisation at the fracture site may indicate a delay in callus formation [41]. Strong vascularization was also observed in the absence of union [42].

3.3.4. MRI

Magnetic resonance imaging (MRI) is primarily used to diagnose infections at the fracture site — such as the presence of abscesses or fistulas — and to assess soft tissue damage. Therefore, MRI is not routinely used clinically for the early prediction of nonunion. However, new technologies such as dynamic contrast-enhanced MRI are emerging. This protocol allows for the assessment of vascularization following surgical treatment. Correlations with the absence of union were already observed as early as 6 weeks after surgery. Although vascularization was assessed only after surgical treatment of existing nonunion, this offers hope for the possibility of testing this method in fresh fractures [43].

3.4. Heuristic Evaluation

An important issue in everyday orthopedic practice is the accuracy of clinicians' assessments of the risk of nonunion. Based on an analysis of risk factors and radiological examinations, physicians often make predictions intuitively, using what is known as heuristic reasoning. In psychology, heuristics are defined as mental shortcuts that allow for decision-making with limited available data. In a study by Armbruster et al., the accuracy of this intuition was verified in perioperative settings by collecting clinicians' predictions based on patient risk factors, surgical data, and postoperative imaging (AP and lateral X-rays) [44]. It was demonstrated that this risk assessment for nonunion has a sensitivity of 50.4% and a specificity of 70.7%, indicating significant difficulties in accurately differentiating patients at the early stage of treatment. However, analysis of the predictive indices revealed a high NPV (87.7% postoperatively), meaning that clinicians are highly effective at reliably ruling out nonunion when they predict its absence. On the other hand, the low PPV (35.5% postoperatively) highlights the weakness of this method: physicians have difficulty correctly identifying patients who are actually at risk for this complication, often mistakenly predicting its occurrence or, conversely, failing to recognize it. These data confirm that, despite its ability to reliably rule out problems (high NPV), clinical judgment alone is insufficient for accurately identifying risks, which underscores the urgent need to implement more objective predictive algorithms.

In a similar study, Squyer et al. analyzed the effectiveness of early clinical predictions regarding the healing of long bone shaft fractures [45]. It was demonstrated that at 12 weeks post-surgery, physicians identified nonunion with 100% accuracy, reflecting an NPV of 100%. In practice, this means that every diagnosis of biological failure made at the 3-month follow-up was fully confirmed by the final treatment outcome. At the same time, the ability to accurately predict successful union (PPV) at the same time point was lower, at 70%. These data indicate that as time elapses from the moment of fracture stabilization, the accuracy of clinicians' predictions increases. The results presented here serve as an important reference point for the development of advanced decision-support systems, which are expected to offer greater predictive accuracy than traditional approaches. Although the cited studies suggest that clinicians have a measurable ability to predict the outcomes of fracture treatment, the relatively small size of the patient groups and the limited number of researchers necessitate great caution when extrapolating these findings. In this context, the pursuit of full objectivity in the diagnostic process appears to be a key and highly desirable direction for the development of modern orthopedics and traumatology.

3.5. Scoring systems

To improve the accuracy of predictions, researchers are striving to incorporate all available patient data and readily accessible studies. By synthesizing this information and applying it on the appropriate scoring systems, we can obtain the answers we seek more quickly. This also enhances the objectivity of treatment decisions. One such scale is the Leeds-Genoa Non-Union Index (LEG NUI), a prognostic tool developed to identify, at an early stage, patients at increased risk of nonunion following surgical stabilization of long bone fractures. It has been validated primarily for the assessment of tibial and femoral shaft fractures. The goal of its use is to identify a group of patients who will benefit from early revision surgery, eliminating the need for months of ineffective radiographic follow-up. The assessment is performed up to 12 weeks after the initial fixation, although in practice it is often performed in the immediate postoperative period. It consists of 8 risk factors — 4 clinical and 4 radiological — such as the post-surgical fracture gap, presence of infection, suboptimal mechanical stability of the fixation, initial fracture displacement (greater than 75% of the shaft width), the fracture site (the tibia carries a higher risk than the femur, scoring one point), significant soft tissue damage (open fractures or closed fractures with degloving), the use of an open reduction surgical technique, and the type of fracture (wedge or complex patterns) [46]. The PPV for detecting nonunion was 100% in each case, while the NPV was 90%. Other scales, such as FRACTURE and NURD, have PPVs of 80% and 40%, respectively, and NPVs of 60% and 90% [47].

Nicholson et al., in turn, assessed the predictability of union in completely displaced clavicle shaft fractures [48]. In their study, they analyzed parameters such as the QuickDASH score, the absence of callus on follow-up X-rays, and fragment mobility on physical examination at 6 weeks post-injury. Although the PPV was relatively low at 35.1%, the sensitivity and specificity were higher, at 77.8% and 79.2%, respectively. Although these tools enable us to achieve better treatment outcomes, a limitation is the need for access to extensive patient data, as well as the fact that the scales have been validated only for specific fractures and a small number of patients.

3.6. Machine Learning

Traditionally, medicine has relied on linear rating scales. Although these are widely used and clinically useful, they have a limited ability to capture complex relationships between variables. In recent years, methods based on machine learning (ML) have gained increasing importance, enabling the development of advanced predictive models. These methods utilize deep neural networks and sophisticated decision tree algorithms capable of analyzing large, multidimensional datasets. A key advantage of these approaches is the ability to integrate detailed features derived from imaging studies with a patient's clinical and demographic data. As a result, ML algorithms are able to identify hidden patterns (e.g., subtle features of bone morphology) and complex, nonlinear relationships that may be difficult to capture using classical statistical methods. In the future, this could translate into potentially higher prediction accuracy and a more personalized approach to treatment.

In a recent study, the authors used ML algorithms to predict nonunion (assessed 3 months after surgery) in patients who underwent surgery for unstable distal clavicle fractures. The analysis examined a wide range of predictors available as early as the immediate postoperative period, including demographic variables, biochemical blood parameters, surgical data (e.g., type of approach and implant used), and radiological measurements. Among the tested algorithms, the CatBoost model achieved the highest predictive performance. It was characterized by an area under the ROC curve (AUROC) of 0.863 (95% CI: 0.762–0.964), an accuracy of 74.7%, and a PPV of 55.3%. Three main risk factors were identified: increased carotid-clavicular distance, elevated HDL levels, and greater blood loss during surgery. The use of regional nerve blocks (e.g., brachial plexus) in perioperative care was found to be a risk-reducing factor [49].

However, due caution should be exercised when implementing such tools into daily practice. Although the use of artificial intelligence appears promising, the overall accuracy of

74.7% and the relatively low PPV of 55.3% indicate that the model still generates a significant margin of error. These results are lower than those achieved with standard prediction methods (e.g., X-ray). From a clinical perspective, a PPV of 55% means that nearly half of the patients classified by the algorithm as being at high risk for nonunion would ultimately achieve proper healing (a high rate of false positives). Therefore, basing medical decisions, such as surgical intervention, solely on the predictions of a machine learning model could lead to unjustified overtreatment. At the current stage of development, ML algorithms should be treated only as an auxiliary tool, with significant potential for future development.

3.7. Smart Implants

The use of implants to monitor bone union dates back to the 1970s, when strain gauges were first used to measure deformation in external fixation systems [50]. Currently, implantable devices are being developed that enable precise, repeatable measurement of mechanical loads. In 2025, the results of a study evaluating the long-term use of smart implants equipped with telemetric sensors in patients with femoral nonunion were published. The system was based on periodic measurement of the loads transmitted by the osteosynthetic plate. The measurements indicate that the decrease in recorded forces correlates with the progress of union and the transfer of loads to the regenerating bone tissue [51].

At the same time, solutions such as the Fracture Monitor system developed by the AO Research Institute are being developed; this system consists of a sensor module mounted on standard osteosynthetic plates. The device enables continuous load measurement and wireless data transmission to the physician. A prospective clinical trial initiated in 2025 by Braun et al. aims to evaluate the safety and efficacy of this system in patients undergoing primary stabilization of femoral fractures [52]. The study protocol calls for close monitoring of patients during the first few months following surgery. The study results may therefore provide information on what level of load correlates with the development of nonunion. In the future, such information could serve as a warning sign during patient treatment. The validation of this technology could represent a significant step toward objectifying and personalizing the real-time monitoring of the fracture healing process. However, it should be emphasized that this is still an early stage of clinical implementation, and data on safety, potential adverse effects, and long-term tolerance of the implant — as an additional foreign body introduced into the body — are of critical importance.

4. Discussion

Predicting bone nonunion remains one of the major challenges in modern musculoskeletal traumatology. The traditional definition of nonunion requires waiting up to 9 months after injury, which, given the decline in patients' Time Trade-Off index to 0.68 and rising systemic costs, is far from optimal. A review of the literature indicates an urgent need to implement tools enabling early risk stratification. This allows us to focus more quickly and with greater attention on optimizing the biological and mechanical environment.

Studies on systemic and local biomarkers, such as BAP, TGF-beta, and markers of inflammation (CRP, IL-6), provide evidence that the healing cascade becomes dysregulated long before radiographic manifestations appear. Unfortunately, their implementation into daily clinical practice is hindered by high interindividual variability, the influence of modifiable factors (e.g., smoking), and standardization challenges. Although analyses of the immunological profile (e.g., TEMRA-type T-lymphocyte subpopulations) and genetic profile (specific genes encoded in mRNA) show promising results, they remain in the sphere of experimental research. This means that a single marker, evaluated on a point-based scale, lacks sufficient predictive power.

Conventional radiography has evolved thanks to the introduction of standardized systems, such as the RUST scale, which allow for an objective assessment of healing dynamics. However, its predictive value becomes apparent relatively late. In this context, early ultrasound appears promising, as it allows for the visualization of the absence of callus formation and increased hypervascularization of the fracture gap in cases of nonunion.

The problem with the current diagnostic approach is the imperfection of the heuristic assessment performed by physicians. While clinicians are very good at correctly ruling out complications (high NPV ranging from 87.7% to 100%), they have significant difficulty accurately identifying patients in whom fusion disorders will actually occur (low PPV of 35.5%). For this reason, high hopes are associated with scoring scales and ML algorithms. Current ML models still exhibit suboptimal positive predictive value (approx. 55%), which is associated with a high rate of false-positive diagnoses. A parallel direction in the development of diagnostics, based on biomechanical parameters, involves smart implant technologies. These allow for real-time assessment of load transfer through the fracture zone; however, their widespread implementation still requires further evaluation regarding clinical utility.

5. Conclusions

I. The assessment of the risk of nonunion based on single factors (whether imaging, biological, or clinical) and currently available predictive models remains insufficient. The ability of these tools to accurately predict ultimate failure within the first quarter following injury remains moderate, resulting in a high margin of error and a high rate of false-positive results, which carries the direct risk of unjustified therapeutic interventions, including surgical ones (overtreatment).

II. The future of effective prediction lies in the close integration of multiparametric diagnostics. The target clinical model should synthesize diverse, multidimensional patient data with advanced statistical analysis supported by machine learning algorithms.

III. It is essential to establish centralized, standardized, and prospective databases of trauma patients. Only multidimensional, large-scale datasets will enable the proper training of predictive models and minimize diagnostic errors.

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