# Cortical bridging a union predictor: A prospective study after intramedullary nailing of the femoral shaft fractures

Arvin Najafi (1), Parmida Shahbazi (1), Salman Azarsina (1), Danoosh Zargar (1), Mohammad Saeed Kahrizi (1), Dorsa Hadavi (1), Reza Minaei-Noshahr (2)

*(1) Department of Orthopedic Surgery, Shahid Madani Hospital, Alborz University of Medical Sciences, Karaj, Iran; (2) Bone, Joint and Related Tissues Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*



***Abstract***

Early prediction of the union helps for timely intervention, reduction of hospitalization, treatment costs, and disability in cases of nonunion. With this in mind, we tried to find how long any cortical bridging predicts the union in femoral shaft fractures. A prospective study of 113 femoral shaft fractures treated with reamed, locked intramedullary nailing was performed. Radiographs were taken during months 2 to 4, 6, 9, and one-year follow-up. The cortical bridging (presence and number) was assessed by anterior-posterior and lateral views. The ROC curve provides the prediction of the union. The overall nonunion rate was 10.6% (12 of 113 fractures). Age and diabetes mellitus were statistically significant with nonunion (p value < 0.001). The final analysis demonstrated that any cortical bridging at four months postoperatively was the most accurate and earlier indicator (105 of 113, 92.9% accuracy), while it was 84.9% at six months in bicortical and 80.5% accuracy at nine months in tricortical bridging. Low-cost and simple radiographic imaging presents cortical bridging in any form 4 months after surgery that precisely predicts a union in femoral shaft fractures.

**Key Words**: Femoral fractures; fractures ununited; radiography; fracture fixation; intramedullary.

*Eur J Transl Myol 32 (4): 10835, 2022 doi: 10.4081/ejtm.2022.10835*

Midshaft femoral fractures, with an incidence of 10 in 100000 per year, are one of the most reasons for morbidity and mortality in lower extremity injuries. High-energy traumas, including falls, motor vehicle and motorcycle accidents, and high-velocity bullets in gunshots, are important causes of adult femoral shaft fractures. Another population suffering from these fractures are elderly females with a history of osteoporosis, experiencing low-energy traumas such as ground-level falls. Common crucial complications of femoral shaft fractures which could cause death include acute respiratory distress syndrome, fat embolism syndrome, and multi-organ failure.[1,2] Patients with femoral fractures complain about major physical impairments due to treatments such as fracture shortening or malalignment (resulting in limping and post-traumatic arthritis) and prolonged immobilization.[3] The most important goal of the treatments is that the patients start their regular physical activities as soon as possible.[4] While various treatment methods are available, interlocking intramedullary nailing is preferred for femoral shaft fracture fixation (successful union in 85-100%).[5-7] As the beneficial results of this technique are assessed in an enormous number of studies, open reduction and plating do not assume to be the proper treatment for these fractures.[8-12] One of the painful complications after the fixation surgery is nonunion, defined as proximal and distal segments' failure to unite after eight months or more than six months with no progression in the last three months.[13,14] It is worth noting that despite these timelines, some kinds of literature with more strict guidelines would suggest that we should consider the nonunion diagnosis as early as two months after the surgery.[15-19] Nonunion is a common problem for most surgeons as it requires much more time to recover and increases the costs of multiple hospitalizations and healthcare services.[20,21] A method used to assess the union is radiographic cortical bridging in the cortices of the femur, which by various studies has been considered a reliable source of information to predict the union better than measuring the callus area and its quality.[19] Although a healed fracture is described as the complete construction of all

***Table 1***. *Patients' characteristics and risk factors affecting the final healing outcomes.*

| Patient characteristics | | Union (n=101) | Nonunion (n=12) | p value |
|---|---|---|---|---|
| **Age (years) Mean±SD**** | | 38.6±13.8 | 54.0±12.4 | < 0.001* |
| **Fracture mechanism** | High energy (n=88) | 89.7% | 10.2% | 0.72 |
| | Low energy (n=25) | 88.0% | 12.0% | |
| **Fracture type** | Open (n=12) | 33.3% | 66.6% | < 0.001* |
| | Close (n=101) | 96.0% | 3.9% | |
| **Diabetes mellitus** | Yes (n=16) | 56.2% | 43.7% | < 0.001* |
| | No (n=97) | 94.8% | 5.1% | |
| **Smoking** | Yes (n=36) | 91.6% | 8.3% | 0.75 |
| | No (n=77) | 88.3% | 11.6% | |

**p value<0.05 is considered significant. **Standard deviation.*

three cortices of the femur, there is still a lack of information about the cortical bridging exact numbers in different postoperative intervals to evaluate and consider the healing process as a successful result in that proper timeline.[22]

The main purpose of this study was to collect precise data about the number of cortical bridgings in different intervals to obtain the accuracy of any cortical bridging callus as well as bicortical and tricortical bridging for the prediction of union or nonunion in the final results of healed fractures.

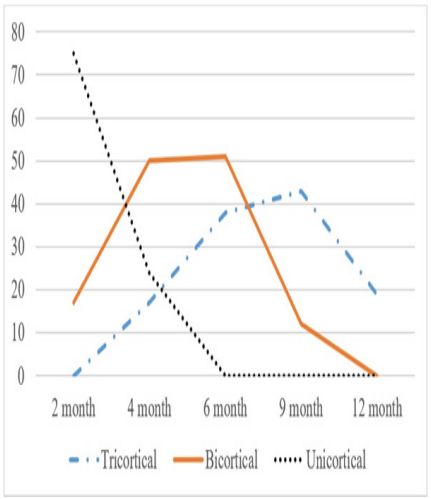


***Fig 1.*** *Number of fractures with three types of cortical bridging in different timelines*

## Materials and Methods

A prospective study conducted on 144 AO Foundation/Orthopaedic Trauma Association (AO /OTA) 32 A, B, C, femoral shaft fractures was performed in 18- to 80-year-old adults, treated with reamed, locked intramedullary nailing at Shahid Madani Hospital, a referral trauma center between February 20, 2019, and of August 21, 2021. A patient or a surrogate should have been able to give informed consent. A random computer-generated unique code identified all patients, and no personal data were revealed to any party during data extraction or analysis. The ethics committee has approved this study of the Alborz University of Medical Sciences under the code of IR.ABZUMS.REC.1399.173. Patients with open physis, fractures needing bone grafting due to segmental defect, and inadequate documentation or discontinuation of the follow-up visits were excluded. Demographic data and a complete history, including patients' sex, age, different mechanisms of injuries, smoking, presence of diabetes mellitus, and the fracture type (open or closed), and the information of the fully recovered patients, from the first to the last follow-up visits, was gathered from medical records, history taking, and physical examinations. Union was clinically defined as fully bearing weight on the limb with no pain or complication; stability and absence of swelling in the

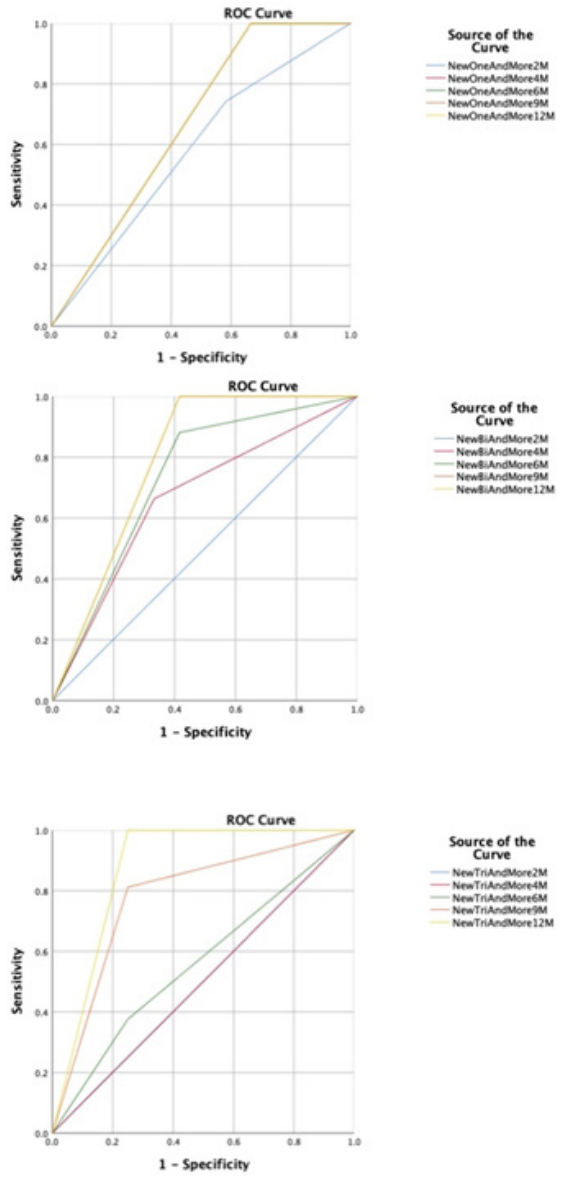


***Fig 2.*** *The ROC curve analysis of unicortical, bicortical, and tricortical bridgings in 2, 4, 6, 9, and 12 months respectively.*

limb aìwere also considered. The radiologic definition of healing was the presence of callus bridging in all three cortices (tricortical bridging) with no lucency in the fracture sites. Nonunion is defined as the absence of progressive bone healing, failure of bone construction, and painfulness or swelling in the fracture site. Cortical bridging is described as the formation of the callus continuously spanning between the proximal and distal segments of the fracture sites. All patients included in the study were treated with stainless steel intramedullary nails. All patients have undergone the fixation surgery in the interval of 1 to 6 days after the trauma. Surgeries have been conducted by two of our authors, which are orthopedic surgeons with more than five years of experience. The majority of patients were able to bear weight with the aid of crutches after the surgery. Weight-bearing was allowed for all patients for ten weeks postoperatively. Follow-up intervals were at the weeks 6 to 8, and months 3 to 4, 6, 9, and one year of the postoperative period. The final healing results (union or nonunion) were assessed by obtaining radiographs from the anterior-posterior and lateral views to examine all three cortices of the femur for callus formation by a specialized radiologist. All fractures were analyzed for the final results of union or nonunion; different types of cortical bridging and the time needed to form each class were also analyzed. The sample size was convenient and calculated based on previous studies.

*Statistical analysis*

Categorical variables were described as frequencies, and continuous variables were described using mean and Standard Deviation (SD). Proportions for categorical variables were compared using the chi-square test. A ROC curve model was designed to compare the final results of the bridging in different timelines by the windows-OS version of SPSS v.26. A p value less than 0.05 was considered statistically significant.

## Results

Of all patients with midshaft femoral fractures, 144 patients met the inclusion criteria to participate in the study. Unfortunately, patients with open physis (n =2), fractures needing bone grafting due to segmental defect (n=8), and 21 patients due to discontinuation of the follow-up visits and lack of information on final results of union or nonunion were excluded. Between the 113 Cases, 69 fractures were isolated, and the others were associated with other fractures. No patient had fractures in both femurs, and 72 cases were male (63.7%). The average age of the study population was 40.2±14.4 years, (38.8±14.0) among males and (42.7±14.8) for females. Most patients had experienced high-energy trauma (77.8%, n=88). Twelve patients (10.6%) presented with an open fracture. Thirty-six patients were documented as tobacco users (31.8%). Sixteen patients (14.15%) presented with a previous history of diabetes mellitus. At the end of the study, 12 of 113 patients (10.6%) were diagnosed with nonunion. Of 12 nonunion cases, construction failure in 4, progression failure in radiographic healing in 5, and secondary complications (infection) in 3 patients were the principal diagnoses of these patients. None of the patients with completely healed fractures needed secondary surgeries due to failure or reconstruction. The cumulative percentage of healed fractures (with no need for any interventions) was 82 (72.5%) at nine months and 101 (89.3%) at 12 months. Complete healing reached the mean time of 9.5±1.1 months. Nonunion occurred in 9 of 88 (10.2%) patients with high-energy trauma, in comparison with 3

***Table 2***. *Sensitivity versus specificity in different types of cortical bridging.*

| | Month of follow-up | AUC* | p value** | Sensitivity | Specificity | PPV+ | NPV³ |
|---|---|---|---|---|---|---|---|
| **Unicortical** | 2 | 0.580 | 0.368 | 74.2% | 41.6% | 91.4% | 16.1% |
| | 4 | 0.667 | 0.060 | 100% | 33.3% | 92.6% | 100% |
| | 6 | 0.667 | 0.060 | 100% | 33.3% | 92.6% | 100% |
| | 9 | 0.667 | 0.060 | 100% | 33.3% | 92.6% | 100% |
| | 12 | 0.667 | 0.060 | 100% | 33.3% | 92.6% | 100% |
| **Bicortical** | 2 | 0.501 | 0.993 | 16.8% | 83.3% | 89.4% | 10.6% |
| | 4 | 0.665 | 0.062 | 66.3% | 66.6% | 94.3% | 19.0% |
| | 6 | 0.732 | 0.009** | 88.1% | 58.3% | 94.6% | 36.8% |
| | 9 | 0.792 | 0.001** | 100% | 58.3% | 95.2% | 100% |
| | 12 | 0.792 | 0.001** | 100% | 58.3% | 95.2% | 100% |
| **Tricortical** | 2 | 0.500 | 1.000 | 0.0% | 100% | __ | 10.6% |
| | 4 | 0.501 | 0.993 | 16.8% | 83.3% | 89.4% | 10.6% |
| | 6 | 0.563 | 0.476 | 37.6% | 75.0% | 92.6% | 12.5% |
| | 9 | 0.781 | 0.002** | 81.1% | 75.0% | 96.4% | 32.1% |
| | 12 | 0.875 | 0.000** | 100% | 75.0% | 97.1% | 100% |

**AUC: Area Under the Curve, **p value<0.05 is considered significant.+Positive Predictive Value, ³Negative Predictive Value.*

of 25 (12%) patients with low-energy mechanisms (p value = 0.72). Of patients with a positive smoking history, 3 of 36 (8%) have been diagnosed with nonunion, while in 6 of 77 (7%) nonsmokers, nonunion was diagnosed (p value = 0.75). There was a statistically significant difference between the mean age in patients achieving union (38.6±13.8) and the patients with nonunion (54.0±12.4) (p value < 0.001). Open fractures with nonunion were 66.67% (8 of 12), and close fractures with nonunion were 3.96% (4 of 101) (p value < 0.001). Nonunion with diabetes mellitus was seen in 6 of 16 (37.5%) versus 6 of 97 (6.18%) in nondiabetic patients (p value < 0.001) (Table 1). The optimum postoperative time to evaluate radiographs was four months for any cortical bridging, as it was notable in 109 fractures (38 unicortical, 52 bicortical, and 19 tricortical) (Figure 1). Predicting the final results of healing was accurately done by a 4-month presence of any cortical bridging (accurate in 105 of 113 fractures, 92.9%) (p < 0.001). Among 109 fractures presented with cortical bridging, eight cases were diagnosed with nonunion (positive predictive value for union: 92.6%) according to poor progression to further bridging and unsatisfying clinical symptoms. The absence of cortical bridging at four months included four fractures in all cases, with final results of nonunion (negative predictive value: 100%). A ROC curve analysis revealed (Table 2, Figure 2) within six months. Bicortical bridging

***Table 3***. *Patients' characteristics and risk factors affecting time for reaching any degree of cortical bridging.*

| Patient characteristics | | Valid number | Month for any bridging Mean ± SD** | p value |
|---|---|---|---|---|
| **Fracture mechanism** | High energy | 79 | 2.67±0.85 | 0.03* |
| | Low energy | 22 | 3±1 | |
| **Fracture type** | Open | 4 | 3±0.98 | 0.04* |
| | Close | 97 | 2.52±0.88 | |
| **Diabetes mellitus** | Yes | 9 | 2.67±1 | 0.64 |
| | No | 92 | 2.67±0.9 | |
| **Smoking** | Yes | 33 | 3.39±0.93 | <0.001* |
| | No | 68 | 2.12±0.54 | |

**p value<0.05 is considered significant. **Standard deviation.*

predicted union in 89 of 94 fractures (positive predictive value for union: 94.6%) and nonunion in 7 of 19 fractures with a negative predictive value of 36.8%, mispredicted 12 healing fractures as nonunion ($p < 0.001$). Tricortical bridging in 9 months, predicted union in 82 of 85 fractures (positive predictive value for union: 96.4%) and nonunion in 9 of 28 fractures (negative predictive value: 32.1%), incorrectly predicting 19 healing fractures as nonunion ($p < 0.001$). Further analysis on the accuracy of bicortical bridging in 6 months (accurate in 96 of 113, 84.9%) and nine months for tricortical bridging (91 of 113, 80.5%) were calculated. Among all fractures that resulted in the union, patients' characteristics and variables affecting the time for reaching any cortical bridging are presented in Table 3.

## Discussion

The overall rate of nonunion was reported at 10.6%. The nonunion rate is slightly higher than reported in the previous literature.[19,23] It may be due to the higher mean of age and diabetes in our study, which are diagnosed as risk factors for the nonunion.[24] Although a previous systematic review and meta-analysis show smokers have more risk of experiencing a nonunion fracture,[25] smoking status was not a significant prognostic indicator for nonunion. The low sample size may explain this result. Age, presence of diabetes mellitus, and injury characteristics (open versus closed fractures) were prognostic indicators for nonunion consistent with previous reviews.[25] The most remarkable result from the data is that any type of cortical bridging at four months postoperatively accurately predicts union for 92.9% of midshaft femoral fractures, as this criterion predicted the final results of the union in 105 of 113 fractures. (Figure 3), in agreement with previous findings.[19] Despite various risk factors for nonunion, including the presence of diabetes mellitus and open fractures,[17,25] this criterion seems to be accurately predictive. Surprisingly bicortical at six months and tricortical callus bridging at nine months accurately predicted the outcomes of the complete healing (union). As well, this study suggests that cortical bridging and callus formation four months after surgery could predict the complete healing in around 92.9% of the fractures, which is in line with previous studies.[19] Utilizing this criterion, 22 unnecessary surgical interventions have been avoided in our cases, and 14 cases of femur fractures that needed non-surgical interventions have been observed and completely healed. Tough strict decisions for 6-month bicortical bridging and 9-month tricortical bridging would significantly result in overtreatment, as utilizing the 6-month criterion and absence of bicortical callus bridging might result in treating 12 cases of true nonunion and 12 other cases of fractures which were healed with no need for further interventions. Using a nine-month time point and utilizing the criterion of tricortical callus bridging might lead to performing surgeries for 12 true cases of nonunion and 15 cases of fractures that were completely in union with no further interventions. There are limitations in our study due to excluding patients followed by discontinuation of the follow-up visits and lack of information on the final results of union or nonunion (21 patients). Although our results have demonstrated that the type of injury and

presence of diabetes mellitus is assumed to be prognostic indicators for the final nonunion results, this study was not originally designed for such assessments. To our knowledge, this is the second study with a large sample size to report cortical bridging prediction of the union in femoral shaft fractures with finding accuracy in bicortical and tricortical bridging.

In conclusion, the presence or absence of cortical bridging (unicortical, bicortical, or tricortical) four months after surgery would predict the probability of union and complete healing in the midshaft femoral fractures. The overtreatment of the nonunion in the femur shaft would occur by considering stricter criteria. This condition and all of the complications related to additional surgeries have been prevented by implementing radiographic imaging, a low-cost simple diagnostic assessment.

## List of acronyms

AO - Arbeitsgemeinschaft für Osteosynthesefragen
AO/OTA – AO/ Foundation/Orthopaedic Trauma Association
SD - standard deviation
A-P - anteroposterior
L - lateral

## Contributions of Authors

AN: supervision, interpretation of data, writing original draft, writing review and editing, final approval; PS: methodology, formal analysis, writing original draft, review and editing, final approval; SA: conceptualization, interpretation of data, writing original draft, writing review and editing, final approval; DZ: investigation, formal analysis, writing original draft, review and editing, final approval; MSK: investigation, formal analysis, writing original draft, review and editing, final approval; DH: investigation, interpretation of data, writing review and editing, final approval; RMN: methodology, formal analysis, writing original draft, review and editing, final approval.

All authors have read and approved the final edited typescript.

## Acknowledgments

The authors would like to thank the Shahid Madani hospital's clinical research development unit for supporting all research processes. We thank Dr. Behrouz Banivaheb for his assistance with methodology and analyticalcomments that significantly improved the manuscript.

## Funding

The authors received no specific funding for this work.

## Conflict of Interest

The authors declare no financial, personal, or other conflicts of interest.

## Ethical Publication Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## Corresponding Author

Reza Minaei-Noshahr, M.D., Assistant Professor of orthopedic surgery, Bone, Joint and Related Tissues Research Center, Shahid Beheshti University of Medical Sciences, Velenjak St., Shahid Chamran Highway Tehran, Iran. Phone: +98912 857 6268.
ORCID iD: *0000-0002-7851-842X*
E-mail: reza.minaie@gmail.com

*E-mails and ORCID iD of co-authors*

*Arvin Najafi: Arvin.najafi@gmail.com*
*ORCID iD: 0000-0002-1762-7876*
*Parmida Shahbazi: Parmida.shabazi@gmail.com*
*ORCID iD: 0000-0002-3153-6153*
*Salman Azarsina: salmanazarsina@yahoo.com*
*ORCID iD: 0000-0001-6167-5499*
*Danoosh Zargar: danooshzargar@gmail.com*
*ORCID iD: 0000-0002-8230-8396*
*Mohammad Saeed Kahrizi: Miladkahrizi1994@gmail.com*
*ORCID iD: 0000-0002-8076-2413*
*Dorsa Hadavi: Hadavidorsa@gmail.com*
*ORCID iD: 0000-0002-1068-5790*

## References

1. Asplund CA, Mezzanotte TJ. Midshaft femur fractures in adults. UpToDate, Medilib, 2021. https://www.medilib.ir/uptodate/show/228
2. Rahman AF. The burden of road traffic injuries in South Asia: a commentary. J Coll Physicians Surg Pak. 2004;14(12):707-8. doi: 12.2004/jcpsp. 707708
3. Khan IA, Ahmad S, Shah MA, Ahmed S, Shafiq M, Shafaq SA. Static versus dynamic interlocking intramedullary nailing in fractures shaft of femur. Gomal Journal of Medical Sciences. 2015;13(2).
4. Omerovic D, Lazovic F, Hadzimehmedagic A. Static or dynamic intramedullary nailing of femur and tibia. Med Arch. 2015 Apr;69(2):110-3. doi: 10.5455/medarh.2015.69.110-113. Epub 2015 Apr 6.
5. Karadimas EJ, Papadimitriou G, Theodoratos G, Papanikolaou A, Maris J. The effectiveness of the antegrade reamed technique: the experience and complications from 415 traumatic femoral shaft fractures. Strategies Trauma Limb Reconstr. 2009 Dec;4(3):113-21. doi: 10.1007/s11751-009-0071-2. Epub 2009 Nov 21.
6. Basumallick MN, Bandopadhyay A. Effect of dynamization in open interlocking nailing of femoral fractures. A prospective randomized comparative study of 50 cases with a 2-year

follow-up. Acta Orthop Belg. 2002 Feb;68(1):42-8.
7. Shroeder JE, Mosheiff R, Khoury A, Liebergall M, Weil YA. The outcome of closed, intramedullary exchange nailing with reamed insertion in the treatment of femoral shaft nonunions. J Orthop Trauma. 2009 Oct;23(9):653-7. doi: 10.1097/BOT.0b013e3181a2a337.
8. Fisher W, Hamblen D. Problems and pitfalls of compression fixation of long bone fractures: a review of results and complications. Injury. 1979;10(2):99-107. doi: 10.1016/s0020-1383(79)80069-8.
9. DeCoster TA, Miller RA. Closed locked intramedullary nailing of femoral shaft fractures in the elderly. Iowa Orthop J. 2003;23:43-5.
10. Devnani AS. Open reamed femoral intramedullary nailing–revisited. Eastern J Med. 2003;8(1):7-11.
11. Meena R, Kundnani V, Hussain Z. Fracture of the shaft of the femur: Close vs open interlocking nailing. Indian J Orthop. 2006;40(4):243.
12. Bashir A, Mir B, Halwai M, Qayum A. First experience with locked intramedullary nailing of femur in Kashmir. Internet J Orthop Surg. 2008;8:1.
13. Nicoll E. Fractures of the tibial shaft. J Bone Joint Surg Br. 1964 Aug;46:373-87.
14. Müller ME, Perren S, Allgöwer M, Müller ME, Schneider R, Willenegger H. Manual of internal fixation: techniques recommended by the AO-ASIF group: Springer Science & Business Media; 1991.
15. Bishop JA, Palanca AA, Bellino MJ, Lowenberg DW. Assessment of compromised fracture healing. J Am Acad Orthop Surg. 2012 May;20(5):273-82. doi: 10.5435/JAAOS-20-05-273.
16. Canale ST, Beaty JH. Campbell's operative orthopaedics e-book: Elsevier Health Sciences; 2012.
17. Tay WH, de Steiger R, Richardson M, Gruen R, Balogh ZJ. Health outcomes of delayed union and nonunion of femoral and tibial shaft fractures. Injury. 2014 Oct;45(10):1653-8. doi: 10.1016/j.injury.2014.06.025. Epub 2014 Jul 7.
18. Hierholzer C, Glowalla C, Herrler M, von Rüden C, Hungerer S, Bühren V, Friederichs J. Reamed intramedullary exchange nailing: treatment of choice of aseptic femoral shaft nonunion. J Orthop Surg Res. 2014 Oct 10;9:88. doi: 10.1186/s13018-014-0088-1.
19. DiSilvio Jr F, Foyil S, Schiffman B, Bernstein M, Summers H, Lack WD. Long bone union accurately predicted by cortical bridging within 4 months. JBJS Open Access. 2018;3(4). doi: 10.2106/JBJS.OA.18.00012.
20. Giannoudis PV, MacDonald DA, Matthews SJ, Smith RM, Furlong AJ, De Boer P. Nonunion of the femoral diaphysis. The influence of reaming and non-steroidal anti-inflammatory drugs. J Bone Joint Surg Br. 2000 Jul;82(5):655-8. doi: 10.1302/0301-620x.82b5.9899.
21. Malik MH, Harwood P, Diggle P, Khan SA. Factors affecting rates of infection and nonunion in intramedullary nailing. J Bone Joint Surg Br. 2004 May;86(4):556-60.
22. Strotman PK, Karunakar MA, Seymour R, Lack WD. Any Cortical Bridging Predicts Healing of Supracondylar Femur Fractures After Treatment With Locked Plating. J Orthop Trauma. 2017 Oct;31(10):538-544. doi: 10.1097/BOT.0000000000000887.
23. Ma YG, Hu GL, Hu W, Liang F. Surgical factors contributing to nonunion in femoral shaft fracture following intramedullary nailing. Chin J Traumatol. 2016 Apr 1;19(2):109-12. doi: 10.1016/j.cjtee.2016.01.012.
24. Zura R, Mehta S, Della Rocca GJ, Steen RG. Biological Risk Factors for Nonunion of Bone Fracture. JBJS Rev. 2016 Jan 5;4(1):e5. doi: 10.2106/JBJS.RVW.O.00008.
25. Pearson RG, Clement RGE, Edwards KL, Scammell BE. Do smokers have greater risk of delayed and non-union after fracture, osteotomy and arthrodesis? A systematic review with meta-analysis. BMJ Open. 2016;6(11):e010303. doi: 10.1136/bmjopen-2015-010303.

## Disclaimer

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article or claim that may be made by its manufacturer is not guaranteed or endorsed by the publisher.

Submission: Sept 3, 2022
Revision received: October 12, 2022
Accepted for publication: October 12, 2022