



## Risk factors for long bone fracture non-union: a stratification approach based on the level of the existing scientific evidence

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### KEYWORDS

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long bones  
femur  
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### ABSTRACT

Non-union continues to be the most devastating complication after fracture fixation. Its treatment can be prolonged and often unpredictable. The burden to the patient, surgeon and health care system can be immense. Strategies to prevent it and or identify early its development are desirable in order to improve the clinical course of the affected patients and their outcomes.

We undertook a systematic review of the literature in order to identify the most common and important risk factors based on the hierarchy of level of evidence. Accordingly, a stratification scale was formed which highlighted 10 risk factors including; an open method of fracture reduction, open fracture, presence of post-surgical fracture gap, smoking, infection, wedge or comminuted types of fracture, high degree of initial fracture displacement, lack of adequate mechanical stability provided by the implant used, fracture location in the poor zone of vascularity of the affected bone, and the presence of the fracture in the tibia. Clinicians should take in to account these findings when managing patients with long bone fractures, particularly the femur and tibia in order to minimise the risk of non-union.

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### Introduction

Fracture non-union is a multifactorial disease and for its occurrence it is believed that the concomitant presence of different risk factors is essential. Multiple studies have been conducted to date, in order to analyse the numerous risk factors involved into the development of non-union [1–6]. Despite this, until now, none of these studies has analysed in a systematic approach the findings of the literature.

In order to identify the most important parameters, we undertook a literature review of the risk factors most frequently thought to contribute to an impaired bone healing response. Such factors were examined as age, alcohol intake, compartment syndrome, diabetes, fracture displacement, intake of drugs (antibiotics, anticoagulants, chemotherapeutics, NSAIDs, steroids), fracture gap, infection, the degree of mechanical stability, open reduction of fracture, open fracture, osteoporosis, peripheral vascular disease, chronic inflammatory diseases (rheumatoid arthritis, chronic obstructive pulmonary disease - COPD, systemic lupus erythematosus - SLE), smoking, type of fracture and

fracture location according to the inherent degree of vascularisation of the affected bone [2,3,6].

Other factors that have been discussed to have a potential role in the development of fracture non-union such as delayed weight bearing, anaemia, obesity, malnutrition, and multiple injuries, were not included in this review as it was felt that their impact would not have been present in a constant pattern [4,7–10].

In the herein study, our aim was to identify from all the discussed risk factors that affect negatively the fracture healing process, the ones which appear to be the most influential based on the hierarchy of level of evidence.

### Materials and methods

We conducted a research of the literature by electronically researching the PubMed Medline database from 1945 to present days. We searched for titles and abstracts using the mesh words 'fracture healing' OR 'bone healing' AND each identified parameter so 'age', 'alcohol', 'compartment syndrome', 'diabetes', 'fracture displacement', 'antibiotics', 'anticoagulants', 'chemotherapeutics', 'NSAIDs', 'steroids', 'fracture gap', 'infection', 'mechanical stability', 'open reduction', 'open fracture', 'osteoporosis', 'peripheral vascular disease', 'rheumatoid arthritis', 'smoking', 'type of fracture' and 'fracture location'. In total 21 searches were performed. The bibliographies of identified articles were manually reviewed in order to retrieve any further eligible articles.

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### Eligibility criteria

Studies selected were original articles that satisfied the following inclusion criteria: (1) articles referring to an impaired bone healing response following a fracture; (2) studies on diaphysis of femur and tibia; (3) articles demonstrating a significant impact on the development of an impaired bone repair response after a fracture; (4) full text of the article was available. Exclusion criteria were: (1) animal studies; (2) children studies; (3) in vitro studies; (4) biomechanical studies; (5) other than English language studies; (6) incomplete documentation of data or insufficient reporting of results.

### Extraction of data

The articles were independently reviewed in an un-blinded, standardised manner by the authors. Most citations excluded based on the information provided by their titles or abstracts. Any citation that met the inclusion criteria was obtained and the full text was carefully reviewed. Relevant information about journal name, publication year, author's name, type of study, patients' demographics, factors associated with an impair fracture healing response, level of evidence of the studies were carefully extracted for the final analysis.

### Results

The details of the electronic search are shown in Table 1. Although 199 articles found eligible for this review, as a number of them were relevant for each one of the 21 factors analysed, in total, excluding the duplicate number of manuscripts 83 formed the basis of this review [1-6, 9-85]. Each included manuscript retrieved was classified according to the level of evidence following the JBSJ guidelines [86]. For those papers in which the level of evidence was already stated, we followed the level already declared by the authors.

### Age

The literature research yielded eleven articles [1-6,10,25,39, 69,84]. The level of evidence of each article is shown in Table 2.

### Alcohol Intake

The literature research yielded five articles [2,3,5,6,24], all of which were level V studies, Table 3.

**Table 1**  
Summary of search strategy.

Identification	Screening			Eligibility		Inclusion					
	Pubmed	Other Sources	Total	Records After Duplicates Removed	Records Screened	Records Excluded	Included-Pubmed	Included-Other Sources	Full Text Assessed For Eligibility	Full Text Excluded With Reasons	Included
Age	7536	16	7552	5074	5074	5047	14	13	27	16	11
Alcohol	559	7	566	464	464	451	7	6	13	8	5
Compartment syndrome	306	10	316	206	206	192	7	7	14	8	6
Diabetes	938	8	946	765	765	740	18	7	25	12	13
Displacement	1915	8	1923	1260	1260	1244	8	8	16	10	6
Antibiotics	1519	4	1523	1208	1208	1204	0	4	4	0	4
Anticoagulants	258	4	262	232	232	226	2	4	6	3	3
Chemotherapeutics	4	5	9	9	9	4	0	5	5	3	2
NSAIDs	553	11	564	397	397	366	20	11	31	21	10
Steroids	759	6	765	592	592	589	0	3	3	1	2
Fracture gap	1193	15	1208	640	640	618	8	14	22	7	15
Infection	6970	9	6979	4993	4993	4966	19	8	27	12	15
Mechanical stability	727	16	743	483	483	464	3	16	19	8	11
Open reduction	3059	12	3071	1750	1750	1727	12	11	23	12	11
Open fracture	6311	15	6326	3640	3640	3602	24	14	38	15	23
Osteoporosis	2106	6	2112	1276	1276	1269	2	5	7	3	4
Peripheral vascular impairment	183	8	191	171	171	163	0	8	8	1	7
Chronic inflammatory disease	352	3	355	295	295	290	2	3	5	3	2
Smoking	455	12	467	353	353	305	40	8	48	24	24
Type of fracture	5292	20	5312	2964	2964	2935	10	19	29	15	14
Fracture site (vascularisation)	3791	22	3813	2101	2101	2077	4	19	24	13	11
TOTAL	44786	217	45003	28873	28873	28479	200	193	394	195	199

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