eISSN (Online): 2598-0580

Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

Comparison of Interleukin-1β Levels In Open and Closed Fracture Patients of The Long Bone In Padang

Iqbal Arnif[1]*, Roni Eka Sahputra[2], Hendra Maska[2]

[1]Resident of General Surgery Department, Faculty of Medicine, Andalas University / DR. M. Djamil Hospital, Padang, Indonesia

[2]Department of General Surgery, Faculty of Medicine, Andalas University / DR. M. Djamil Hospital, Padang, Indonesia

ARTICLE INFO

Keywords:

Fractures

Long bones

IL-1

Cytokines

***Corresponding author:**

Iqbal Arnif

E-mail address:

Iqbalarnif@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.32539/bsm.v5i4.383

ABSTRACT

Background: Trauma is a significant burden on causes of death, disability, and financing in least developed or "third world" countries. Fracture healing, especially in wounds and tissues, begins with a hemostatic and inflammatory phase triggered by inflammatory mediators such as cytokines, particularly IL-1β and TNF-. The purpose of this study was to determine the difference in levels of interleukin-1β in open and closed fractures of long bones in Padang **Methods:** This type of research is analytic observational with cross sectional design with primary data. The data were taken from the examination of IL-1β levels in long bone fracture patients at RSUP Dr. M. Djamil, RSKB Ropanasuro and RST Reksodiwiryo Padang for 4 months starting from March 2021 to July 2021. The sampling technique in this study used non-probability sampling with the consecutive sampling method. The analysis was carried out using the Independent sample T-Test to see the difference in mean IL-1 which would be calculated for open fractures and closed fractures of long bones. **Results:** The results showed that most (92.9%) of the patients were male, 50% had open fractures, and 50% closed fractures. The mean value of the patient's age was 34 years and the mean level of IL-1β was 555,951 pq/L. Most of the fracture sites in patients were tibia and fibula (35.7%) and femur (35.7%) and 28.6% were radius and ulna. The results showed that there was a significant difference in the mean levels of IL-1β in patients with open and closed fractures of long bones (p-value = 0.007). **Conclusion:** There are differences in the levels of interleukin-1β in open and closed fractures of long bones in Padang. This research is expected to provide consideration to support examinations in health services, in this case in fracture patients.

1. Introduction

Trauma is one of the epidemics that continues to increase worldwide today. Much of the literature on trauma comes from more developed countries and with more established trauma care systems. Trauma is a significant burden on the causes of death, disability, and financing in less developed or “third-world” countries. Traffic accidents alone are estimated to be the third largest contributor to the global burden of disease by 2030. These injuries occur frequently in parts of the developing world, where traffic systems are poorly organized, overcrowded, and the number of passengers in one vehicle is significantly high.[1]

Limb injuries associated with traffic accidents and various traumas are a major health problem in developed countries, resulting in long-term treatment with substantial socioeconomic effects. These injuries also have a major impact in less developed countries where secondary complications often lead to major disability.[2] Long bone fractures are difficult and slow to heal and may take months for consolidation to complete. Long hospital stays are not only associated with significant lost workdays with economic effects on patients and society.[2]

Fracture healing can be classified into primary

healing and secondary healing. Primary healing of a fracture, or intramembrane ossification, refers to healing that occurs without the formation of an intermediate cartilage callus. Hematoma forms at the fracture site accompanied by an inflammatory response immediately after the fracture. Platelets and macrophages enter the fracture site and begin to secrete inflammatory cytokines, such as interleukin 1β (IL-1β) and IL-6, tumor necrosis factor-alpha (TNF-α) and PGE2. into osteoblasts, endothelial cells, and osteoclasts. [3]

Secondary fracture healing or enchondral ossification refers to the healing that occurs through the cartilage callus. The inflammatory phase initiates fracture healing secondary to trauma, as well as primary healing. New bone does not bridge the fracture directly, but through the formation of cartilage callus which is gradually replaced by hard bone. Platelets and macrophages enter the fracture site which then secrete inflammatory cytokines, such as IL-1β and IL-6, TNF, and PGE. 3,4 Most fractures heal by both intramembranous and enchondral ossification processes.[3]

Healing of wounds and tissues begins with a phase of hemostasis and inflammation in which macrophages will immediately go to the injured area which then releases inflammatory mediators in the form of cytokines, especially IL-1β and TNF-α. These inflammatory mediators will initiate epithelialization by increasing the expression of the Keratinocyte Growth Factor (KGF) gene in fibroblasts. Fibroblasts synthesize KGF to stimulate surrounding keratinocytes to migrate to the wound area where they proliferate and differentiate into epithelium.

Fractures can be classified into two, namely open and closed fractures. Closed fractures are fractures in which bone fragments do not penetrate the skin so that the fracture site is not polluted by the environment, while open fractures are fractures in which bone fragments penetrate the skin causing significant damage to the surrounding soft tissue and contamination of the wound.[5]

Given these differences, the authors wanted to compare the levels of IL1β levels in open fractures and closed fractures in patients with long bone fractures in Padang City.

2. Methods

The study was an observational analytic study with a cross sectional design to compare the levels of interleukin-1β in open and closed long bone fractures. Data obtained by sampling technique using non-probability sampling with consecutive sampling method, namely all closed and open long bone fracture patients who meet the research criteria are included in the study until the number of subjects is met. The study used primary data. Data were taken from examination of interleukin-1β levels in patients with long bone fractures at RSUP DR M Djamil, RSKB Ropanasuri and RST Reksodiwiryo Padang from March 2021 to July 2021. The sample size in this study that met the inclusion criteria were 14 patients. The data were tested statistically by using the Independent sample Test.

3. Results

This study was conducted from March 2021 to July 2021, data collection was carried out through examination of Interleukin-1 levels in long bone fracture patients at DR M Djamil Hospital, Ropanasuri Hospital and Reksodiwiryo Hospital Padang. The results obtained by collecting data on sex, age, type of fracture, interleukin levels and fracture location. A total of 14 patients were included in the inclusion criteria of this study.

Table 1 Characteristics of gender and type of patient fracture

Variabel	N	%
Gender		
Man	13	92,9
Women	1	7,1
Fracture Type		
Open	7	50,0
Close	7	50,0
Location Fracture		
Radius and Ulna Bone	4	28,6
Tibia and Fibula Bone	5	35,7
Femur Bone	5	35,7
Total	**14**	**100**

The results showed that most (92.9%) of the patients were male and 7.1% were female. The results showed that the majority of fracture sites in the patient were the tibia and fibula (35.7%) and the femur (35.7%) and 28.6% were the radius and ulna.

Table 2 Characteristics of age and interleukin levels in 1 patient

Variabel	Mean	Median	SD	Min - Max
Age	34,14	34,00	9,502	18– 45
Interleukin 1β Level	555,951	513,711	192,961	386.381–1101.524

The results showed that the mean age of the patients was 34.14 or 34 years with a mean of 34. The mean level of interleukin 1 was 555.951 pq/L with a mean of 513.711 pq/L.

Table 3 Differences in the mean levels of interleukin 1 in patients with open and closed fractures of long bones.

Variabel	Fractures Type	n	Mean	Std. Deviasi	Std. Error	p-*Value*
Interleukin 1β	Open	7	416,257	29,541	11,165	0,007
	Close	7	695,645	185,114	69,966	

The results showed that there was a significant difference in the mean levels of Interleukin 1 in patients with open and closed fractures of long bones (p value = 0.007).

4. Discussion

In this study, 14 patients were declared to meet the inclusion criteria and were included in the study. Data analysis was performed using IBM SPSS version 24. Based on the collected data, it was found that the majority of patients were male, namely 92.9%, while only 7.1% were female (Figure 6.1). The results of this

study are similar to those found by Ridwan et al in their research in 2019 which found that men were 2.3 to 2.9 times higher risk than women.6 Hurmanto and Firmansyah O also found the same thing with the percentage Fracture incidence in men reaches 72.8%.[7]

Another study by Winda et al also found that more men experienced long bone fractures than women with a percentage of 63.3%. 8 The high incidence of fractures in men is due to the high mobility and activity in men, especially when driving, thereby increasing the risk of injury to men.[6]

However, the results of the sex distribution in this study were different from several other studies which found that the female sex was the most experienced fracture. As the study conducted by Chitnis et al found that the percentage of fractures in the long bones was found to be higher in women, namely 50.8% and 55.3% for the incidence of fractures in the femur and humerus, respectively.[9]

A study by Feldstein et al found that the incidence of fracture in women was 78.3%.10 and a study by Amin et al concluded that women had 1.5 times more fractures than men.[11] This difference may be due to the number of samples. and the age distribution of the samples in these studies. In these three comparative studies, it was found that the number of samples was much higher than this study which only amounted to 14 samples. The large number of samples also allows for a diverse age distribution which causes a large number of women who are no longer in their productive age or have gone through menopause to be included in the study. In contrast to this study, all of the samples were in the productive age with an average age of 34 years. Based on the literature, women who are over 60 years of age or have menopause, will be more at risk for fractures than men due to hormonal changes and increased incidence of osteoporosis.[12,13] Research by Bergh et al proves this, in his study found that the incidence Fractures were found to be higher in males than females up to the age of 48 years, but this proportion changed significantly after the age of 50-75 years where women were found to have more fractures at this age.[13]

The results showed that the majority of fracture sites in the patient were the tibia and fibula (35.7%) and the femur (35.7%) and 28.6% were the radius and ulna. This is in line with research conducted by Prabowo in 2018 in Palu, Indonesia regarding the epidemiology of orthopedic cases which showed 32% in the tibia and fibula and 32% femur, followed by 20% in the radius and ulna bones.[14]

The overall incidence of tibial fractures in Sweden in 2018 was 51.7/100,000 per year.15 In an epidemiological study by Norma In 2021 in Spain the average majority of fracture types were the tibia followed by the femur and humerus.16 The study multicenter conducted in India in 2020 in a tertiary hospital from data on all fractures specifically in the lower extremities, the most common fractures were fractures of the tibia and fibula (4.8%) and fractures of the femur (3.5%). In addition, the most common fractures in the upper extremity were the clavicle (4.1%), humerus (1.8%) and radius ulna (0.8%). This is related to the high incidence of motorcycle use, but the majority of drivers in India do not pay attention to safety.[17]

In a study conducted by Hongzhi in China in 2020 with an epidemiological study of fracture cases in the COVID-19 pandemic situation, there were differences with the results of this study. In Hongzhi's study it was found that in the epidemic group the majority were fractures of the femur (32.7%), followed by fractures of the tibia and fibula (15.1%) and radius/ulna (7.8%). In the control group, the majority were fractures of the femur (25.8%), fractures of the tibia and fibula 17.2% and the radius of the ulna (8.8%). This happens because in the context of COVID-19, less physical work, more activities at home, a more sedentary lifestyle, and psychological states of panic and depression generally place the elderly population at increased risk of falls and bone fractures, especially fractures of the femur.[18]

From the analysis by age, the patients in this study were 34 years old on average. In several studies, such as the study by Santos et al, Omagbemi, and Ghouri et al, it was found that the average age was 36, 36, and 31 years, respectively.[19,20,21] In this study, all of them found the average age of fracture was in the productive

age. In a study by Ridwan et al, it was found that the most patients with long bone fractures were aged > 18 years, as well as a study by Weber which found that the most age occurred at the age of 16 years. [6,33] Research by Chitnis et al found that the incidence of Most fractures occur at an average age of 45.3 years which are also included in the productive age group.[9] Based on the literature, the incidence of fractures is most common in people of productive age. This is associated with high-intensity activities in this age group, which can increase the risk of accidents. As it is known that accidents are the most common etiology of fractures.[23]

The results of the statistical data of this study showed the mean level of interleukin 1 was 555.951 pq/L with a median value of 513.711 pq/L. Research conducted by Khallaf in 2016 showed the average level of IL-1 was 1000 pq/L with a median value of 500 pq/L, this indicates a data distribution similar to this study. This equation is strongly suspected due to trauma to long bones which have a larger wound area than trauma to other bones.[24]

There are different results from the research conducted by Wang in 2018 in China by conducting research on the number of cytokines before surgery showing an average of 13.14 pq/L and seven days after surgery, namely 14.25 pq/L.[25] Research conducted by Iversen in 2021 in Denmark showed an average IL-1 result of 5.16 pq/L and a median value of 2.86 pq/L in patients with proximal tibial fractures, but when compared with the control group there was a five-fold increase from the mean IL-1 value of 0.127. and a median of 0.00 pq/L .[26] In addition, a study conducted by Hao in 2021 in the United States showed a mean IL-1 of 100 pq/L and a median value of 80 pq/L.[27] This difference may be due to differences in the area of the wound that became the subject of each study.[25,26,27]

IL-1 is known to regulate bone resorption and formation. However, the results of different studies on the effect of IL-1 on osteoblast function are somewhat different. On the one hand, both IL-1α and IL-1β have been shown to inhibit osteoblast proliferation and promote bone formation, as demonstrated by increased alkaline phosphatase activity and bone nodule formation. On the other hand, depending on the stage of cell differentiation, prolongation of the culture period, and cytokine concentration, IL-1α and IL-1β can stimulate osteoblast proliferation, and inhibit bone formation, osteocalcin, and type I collagen production. Interleukin-1 can also stimulate osteoblasts to produce other proinflammatory cytokines, such as IL-6, IL-7, tumor necrosis factor-a (TNF-a), prostaglandin E2, and nitric oxide.[24,28]

The results showed that there was a significant difference in the mean levels of Interleukin 1 in patients with open and closed fractures of long bones (p value = 0.007). In a study conducted by Khallaf in 2016 there was a 3-week persistent increase of the cytokine human interleukin-1 (IL-1) with statistical significance in patients with spinal cord injury and concomitant long bone fractures. This situation can be explained because IL-1 is needed in the fracture healing process in producing an abundance of proinflammatory cytokines and inflammatory mediators to induce the early inflammatory stage of bone repair because the intense inflammatory process after fracture can promote bone healing. [24,28]

In a study conducted by Qing in 2019 in Wuhan, the results showed that serum IL-1 beta levels in the experimental group were higher than those in the control group ($P<0.05$) and serum IL-1 beta levels were significantly increased in patients with open fractures. . This happens because the open fracture process is more exposed to the outside world so that there is a faster body response to avoid contamination by increasing the inflammatory process.[29]

A study conducted by Iversen in 2021 in Denmark showed an increase in almost all investigated pro-inflammatory cytokines including IL-1β after the occurrence of proximal tibial fractures. This study compared with healthy contralateral bone. The results of this study indicate that there is an initiation of the inflammatory process after fracture which is characterized by an increase in pro and anti-inflammatory cytokines. [26] As in a study conducted by Xiaoen in 2017 in China, data showed that the level of expression and IL-1 was significantly increased in the cartilage of knee osteoarthritis patients and showed a significant positive correlation with the healing process

in trauma.[30]

A study conducted by Wang in 2018 in China that compared the results of IL-1 levels before surgery on the femur and seven days after surgery showed data that there was no significant difference in serum IL-1 levels before surgery. On the seventh day after surgery, serum IL-1 levels showed a statistically significant difference in the mean when compared between the two groups.[25] Bone healing is a complex process involving a series of events and changes in the expression of several thousand genes. The physiological processes involved in fracture healing occur in three stages: inflammatory, proliferative and reparative, and remodeling. The inflammatory phase is immediate, involving hematoma and granulation tissue formation. It is during this phase that proinflammatory molecules such as tumor necrosis factor-α (TNF-), IL-1, and IL-6, are secreted that promote angiogenesis and proliferation of osteoblasts and osteoclasts.[31]

In addition to the study conducted by Hao in 2021 in the United States, researchers carried out further analysis of markers in hematomas in fracture patients 6 hours after femoral osteotomy, in the smokers group showing higher concentrations of pro-inflammatory cytokines including IL-1β. Furthermore, marker analysis in hematoma 24 hours after femoral osteotomy showed that it was still high. IL-1, IL-6, IL-12p40, IFN-γ, IP-10, TNF-, KC, MCP-1 and macrophage inflammatory proteins are known proinflammatory mediators that regulate migration, infiltration, and function of different immune cells in acute inflammatory phase of fracture healing.[27]

Fracture healing occurs in four distinct phases: (1) inflammation, (2) soft callus, (3) hard callus, and (4) remodeling. After bone injury, the developmental process when bone regenerates is endochondral and intramembrane ossification. In contrast to development, bone healing requires inflammation. At the beginning of the bone healing process, various kinds of inflammatory cells enter the wound, clean the wound and stimulate the repair process. There is an effect of the pro-inflammatory cytokine, Interleukin 1beta (IL-1β) on osteoblasts because IL-1β exerts an effect on skeletal homeostasis and is regulated in response to fracture. IL-1β stimulates osteoblast proliferation and mineralized bone matrix production, but suppresses proliferation and inhibits bone marrow-derived MSC differentiation.[28]

The inflammatory response occurs immediately after fracture. Trauma causes the rupture of blood vessels in and around the fracture site, resulting in a hematoma. The microenvironment of the hematoma is initially characterized by localized hypoxia, acidity, and lower temperature, and is rich in calcium and lactic acid. The hematoma acts as a scaffold for recruited inflammatory cells and various cytokines, including IL1, IL6, TNFL, CCL2, and others, to initiate the inflammatory cascade. First, PMNs are recruited and then monocytes/macrophages infiltrate the fracture site. Macrophages are polarized to the M1 phenotype. After macrophage infiltration, the immune response shifts towards adaptive immunity, which is reflected by the invasion of lymphocytes into the fracture zone. PMNs and macrophages clear areas of dead cells and debris, and the process turns to resolution of inflammation, which is a complex and well-regulated activity. In this process, the agents that initiate the inflammatory response and the synthesis of pro-inflammatory mediators are reduced, and immune cells are gradually cleared from the tissues. Osteomacs, a specialized subtype of macrophages residing in bone tissue, are distributed among bone lining cells within the endosteum and periosteum and contribute to bone homeostasis. Osteomas not only sense the original noxious stimulus and initiate the inflammatory cascade, but also provide a source of molecules that initiate cellular events important for bone healing.[32,33,34,35]

During resolution of acute inflammation, macrophages are polarized from an M1 phenotype to an M2 phenotype by anti-inflammatory cytokines such as IL4, IL10, and IL13. BM-MSCs are attracted locally by cytokines such as TNFα and stromal cell-derived factor 1 (SDF1) (known as chemokine C-X-C motif chemokine ligand 12 [CXCL12]). Recruited inflammatory cells and BM-MSCs participate in critical inter-cell communication or crosstalk through pro-inflammatory cytokines, anti-inflammatory cytokines, as well as

growth factors (TGFβ), bone morphogenetic proteins (BMPs), and growth factors (eg. , vascular endothelial growth factor [VEGF], platelet-derived growth factor [PDGF] and fibroblast growth factor-2 [FGF-2]) to initiate osteogenesis and angiogenesis. This process can also create reparative granulomas that form the template for subsequent callus formation. The acute inflammatory response peaks within 24-48 hours and disappears about 1 week post-fracture.[36,37,38,39,40]

The limitations of this study are that it is hoped that there will be further studies with a larger sample so that a heterogeneous sample can be obtained that can be compared to assess the relationship between IL-1β levels with open and closed fracture types, especially in long bones.

5. Conclusion

The results showed that there was a significant difference in the mean levels of Interleukin 1 in patients with open and closed fractures of long bones (p value = 0.007). It is hoped that this study will become the basis for further research that directly links the examination of interleukin 1β levels to one of the markers of the wound and fracture healing process.

6. References

1. Gellman, RE. Fracture Care Challenges in the Austere and Humanitarian Environments. Curr Trauma Rep.2016;2:100–105. https://doi.org/10.1007/s40719-016-0046-y https://link.springer.com/article/10.1007/s40719-016-0046-y
2. Barrena EG, et al. Bone Fracture healing: Cell therapy in delayed unions and nonunions. 2015. Bone 70;93-101
3. Sathyendra V, Darowish M. Basic science of bone healing. Hand Clin. 2013 Nov;29(4):473-81. doi: 10.1016/j.hcl.2013.08.002. Epub 2013 Oct 15. PMID: 24209946. https://pubmed.ncbi.nlm.nih.gov/24209946/
4. Baht GS, Vi L, Alman BA. The Role of the Immune Cells in Fracture Healing. Current Osteoporosis Reports (2018) 16:138–145 https://doi.org/10.1007/s11914-018-0423-2
5. Solomon, Louis. Apley's System of Orthopaedics and Fractures Ninth Ed. 2010.London. Hodder Arnold.
6. Ridwan UN, Pattiha AM, Selomo PAM. Karakteristik Kasus Fraktur Ekstremitas Bawah Di Rumah Sakit Umum Daerah Dr. H. Chasan Boesoirie Ternate Tahun 2018. Kieraha Medical Journal. 2019; 1(1): 9-15
7. Hurmaryanto, Firmansyah O. Pengaruh Faktor Status Sosioekonomi Terhadap Pemilihan Penanganan Pasien Patah Tulang Tertutup Komplit Di Rsud Raden Mattaher Jambi. JMJ. 2019; 7(2): 215-24
8. Winda RI, Nauli FA, Hasneli Y. Faktor-Faktor Yang Mempengaruhi Tingkat Kecemasan Pasien Fraktur Tulang Panjang Pra Operasi Yang Dirawat Di Rsud Arifin Achmad Pekanbaru. JOM PSIK. 2014; 1(2): 1-10
9. Chitnis A, Ray B, Sparks C, Grebenyuk Y, Vanderkan M, Holy CE. Long bone fractures: treatment patterns and factors contributing to use of intramedullary nailing. 202; 17(7): 731-7
10. Fleidstein AC, Black D, Perrin N, Rosales AG, Friess D, Broadman D, et al. Incidence and Demography of Femur Fractures With and Without Atypical Features. JBMR. 2012; 27(5): 977-86
11. Lee YM, Fujikado N, Manaka H, Yasuda H, Yoichiro I. IL-1 plays an important role in the bone metabolism under physiological conditions. International immunology . 2009. 22;805-816
12. Amin S, Achenbach SJ, Atkinson EJ, Khosia S, Melton LJ. Trends in Fracture Incidence: A Population-Based Study Over 20 Years. 2014. J Bone Miner Res. 2014 March ; 29(3): 581–589
13. Bergh C, Wennergren D, Moller M, Brisby H. Fracture incidence in adults in relation to age and gender: A study of 27,169 fractures in the Swedish Fracture Register in a well-defined catchment area. Plos One. 2020: 1-18

14. Prabowo Y, Kamal AF, Latief W, Ramang DS, Daniel V, Liastuti LD. Epidemiology of orthopaedic injuries at the local hospital following earthquake in Palu, Indonesia, 2018. Journal of orthopaedics trauma surgery and related research. 2019 Dec 27;14(3).
15. Wennergren D, Bergdahl C, Ekelund J, Juto H, Sundfeldt M, Möller M. Epidemiology and incidence of tibia fractures in the Swedish Fracture Register. Injury. 2018 Nov 1;49(11):2068-74.
16. Padilla-Eguiluz NG, Gómez-Barrena E. Epidemiology of long bone non-unions in Spain. Injury. 2021 Feb 18.
17. Kashid M, Rai SK, Nath SK, Gupta TP, Shaki O, Mahender P, Varma R. Epidemiology and outcome of trauma victims admitted in trauma centers of tertiary care hospitals–A multicentric study in India. International journal of critical illness and injury science. 2020 Jan;10(1):9.
18. Lv H, Zhang Q, Yin Y, Zhu Y, Wang J, Hou Z, Zhang Y, Chen W. Epidemiologic characteristics of traumatic fractures during the outbreak of coronavirus disease 2019 (COVID-19) in China: A retrospective & comparative multi-center study. Injury. 2020 Aug 1;51(8):1698-704
19. Santos ADL, Nitta CT, Boni G, Sanchez GT, Tamaoki MJS. Evaluation And Comparison Of Open And Closed Tibia Shaft Fractures In a Quaternary Reference Center. Acta Ortop Bras. 2018; 26(3): 194-7
20. Omagbemi DOO. Open fractures: epidemiological pattern, initial management and challenges in a sub-urban teaching hospital in Nigeria/ Pa African Medical Journal. 2019: 1-8
21. Ghouri SI, Asim M, Mustafa F, Kanbar A, Ellabib M, Jogol HA. Patterns, Management, and Outcome of Traumatic Femur Fracture: Exploring the Experience of the Only Level 1 Trauma Center in Qatar. International Journal of Environtmental Research and Public Health. 2021; 18: 1-13
22. Weber CD, Hildebrand F, Kobbe P, Lefering R, Sellei RM, Pape HC, et al. Epidemiology of open tibia fractures in a population-based database: update on current risk factors and clinical implications. Springer-Verlag GmbH Germany. 2018; 45: 445-53
23. Ghouri SI, Asim M, Mustafa F, Kanbar A, Ellabib M, Jogol HA. Patterns, Management, and Outcome of Traumatic Femur Fracture: Exploring the Experience of the Only Level 1 Trauma Center in Qatar. International Journal of Environtmental Research and Public Health. 2021; 18: 1-13
24. Khallaf FG, Kehinde EO, Mostafa A. Growth factors and cytokines in patients with long bone fractures and associated spinal cord injury. journal of orthopaedics. 2016 Jun 1;13(2):69-75.
25. Wang B, Liu Q, Liu Y, Jiang R. Comparison of proximal femoral nail antirotation and dynamic hip screw internal fixation on serum markers in elderly patients with intertrochanteric fractures. J Coll Physicians Surg Pak. 2019 Jul 1;29(7):644-8
26. Iversen IJ, Pham TM, Schmal H. Do acute inflammatory cytokines affect 3-and 12-month postoperative functional outcomes–a prospective cohort study of 12 patients with proximal tibia fractures. BMC musculoskeletal disorders. 2021 Dec;22(1):1-1.
27. Hao Z, Li J, Li B, Alder KD, Cahill SV, Munger AM, Lee I, Kwon HK, Back J, Xu S, Kang MJ. Smoking alters inflammation and skeletal stem and progenitor cell activity during fracture healing in different murine strains. Journal of Bone and Mineral Research. 2021 Jan;36(1):186-98.
28. Doll J, Moghaddam A, Daniel V, Biglari B, Heller R, Schmidmaier G, et al. LIPUS vs reaming in non-union treatment: cytokine expression course as a tool for evaluation and differentiation of non-union therapy. Journal of Orthopaedics. 2020;17:208-214.

29. Qing Y, Lei W, Yang L, CaiMing W, JunFeng T. Distribution of pathogens and changes of serum proinflammatory cytokines levels in patients with open fracture infection. Chinese Journal of Nosocomiology. 2019;29(16):2482-99
30. Xiaoen SU, Sun Z, Zhu J, Deng H, Zhang Z, Feng W. The expressions and related discussion of YKL-40 and IL-1β in the cartilage of knee osteoarthritis. Chongqing Medicine. 2017 Jan 1;46(4):480-2.
31. Varughese R, Semprini R, Munro C, Fingleton J, Holweg C, Weatherall M, Beasley R, Braithwaite I. Serum periostin levels following small bone fractures, long bone fractures and joint replacements: an observational study. Allergy, Asthma & Clinical Immunology. 2018 Dec;14(1):1-0
32. Lange J, Sapozhnikova A, Lu C, et al. Action of IL-1beta during fracture healing. J Orthop Res. 2010;28(6):778-784. doi:10.1002/jor.21061
33. Walters G, Pountos I, Giannoudis PV. The cytokines and micro-environment of fracture haematoma: current evidence. J Tissue Eng Regen Med. 2018.12:e1662–77. 10.1002/term.2593
34. Bastian O, Pillay J, Alblas J, Leenen L, Koenderman L, Blokhuis T. Systemic inflammation and fracture healing. J Leukoc Biol. 2011.89:669–73. 10.1189/jlb.0810446
35. Fullerton JN, Gilroy DW. Resolution of inflammation: a new therapeutic frontier. Nat Rev Drug Discov. 2016.15:551–67. 10.1038/nrd.2016.39
36. Miron RJ, Bosshardt DD. OsteoMacs: key players around bone biomaterials. Biomaterials. 2016.82:1–19. 10.1016/j.biomaterials.2015.12.017
37. Batoon L, Millard SM, Raggatt LJ, Pettit AR. Osteomacs and bone regeneration. Curr Osteoporos Rep. 2017.15:385–95. 10.1007/s11914-017-0384-x
38. Karnes JM, Daffner SD, Watkins CM. Multiple roles of tumor necrosis factor-alpha in fracture healing. Bone. 2015.78:87–93. 10.1016/j.bone.2015.05.001
39. Toosi S, Behravan J. Osteogenesis and bone remodeling: a focus on growth factors and bioactive peptides. Biofactors. 2019. 10.1002/biof.1598. [Epub ahead of print].
40. Gerstenfeld LC, Cullinane DM, Barnes GL, Graves DT, Einhorn TA. Fracture healing as a post-natal developmental process: molecular, spatial, and temporal aspects of its regulation. J Cell Biochem.2003.88:873–84. 10.1002/jcb.10435