International Journal of Research and Review
[Indexed, Peer-Reviewed Journal]
Volume 13; Issue: 5; May 2026
Website: www.ijrrjournal.com
Research Paper *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Effect of Autologous Medullary Grafting on Transforming Growth Factor Beta-1 (TGF-β1) Levels and Radiographic Union Score Femur in Patients Undergoing ORIF Plate-Screw for Femoral Fractures Compared to Those Without Medullary Grafting

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DOI: https://doi.org/10.52403/ijrr.20260523

ABSTRACT

This study aimed to evaluate the effect of autologous medullary grafting on Transforming Growth Factor Beta-1 (TGF-β1) levels and the Radiographic Union Score for the Femur (RUSF) in patients undergoing open reduction and internal fixation (ORIF) with a plate-screw construct for femoral fractures, compared to those treated without medullary grafting. A comparative analytic observational study with a case-control design was conducted at RSUP Prof. Dr. I.G.N.G. Ngoerah, Denpasar, Bali, from September to November 2025. A total of 36 patients with femoral fractures undergoing ORIF were divided into two equal groups (n=18 each): a case group receiving autologous medullary grafting and a control group receiving no graft. Serum TGF-β1 levels and RUSF scores were assessed at three months postoperatively. Statistical analysis was performed using the Mann-Whitney U test, with a p-value <0.05 considered significant. The medullary graft group demonstrated significantly higher median serum TGF-β1 levels (324.71 ng/mL; range 22.77–678.77) compared to the non-graft group (24.91 ng/mL; range 6.70–76.36), with a p-value <0.001. Similarly, the median RUSF score was significantly higher in the graft group (10.00; range 9.00–12.00) than in the non-graft group (8.11; range 6.00–10.00), p = 0.001. All patients (100%) in the medullary graft group achieved good radiographic union, compared to only 44.4% in the non-graft group. The use of autologous medullary grafting in femoral fracture ORIF with plate-screw fixation is associated with significantly higher TGF-β1 levels and improved radiographic union scores at three months post-surgery. These findings suggest that medullary grafting enhances biological and radiological fracture healing, representing an effective and cost-efficient adjunct, particularly in resource-limited healthcare settings.

Keywords: Autologous medullary grafting, femoral fracture, ORIF, TGF-β1, Radiographic Union Score Femur (RUSF)

INTRODUCTION

Fracture healing is a complex biological process and represents a crucial aspect in the management of patients with bone injuries. This process is influenced by various intrinsic and extrinsic factors. In addition to the competence and surgical skills of the orthopedic surgeon, the patient's physical condition also plays an important role in determining healing outcomes. In efforts to achieve optimal healing quality with minimally invasive interventions, growth factors are expected to contribute to accelerating and optimizing bone tissue regeneration. Fractures constitute a major global public health problem. Besides causing morbidity and mortality, fractures also impose a substantial economic burden due to hospitalization, surgical procedures, long-term care, and outpatient treatment. The increasing incidence of fractures may be attributed to lifestyle changes leading to more trauma-related injuries, as well as reduced physical activity affecting bone mechanostat. Moreover, with increasing life expectancy, elderly populations are more susceptible to fractures due to decreased bone quality and altered skeletal biomechanics. [1,2]

Long bone fractures of the lower extremities exhibit a bimodal distribution, with high-energy trauma predominantly affecting young adults, while low-energy falls commonly occur in elderly individuals with osteoporotic bone.[3] The epidemiology of these fractures is evolving, with an increasing incidence of fragility fractures among the aging population.[2] Femoral fractures are among the most common orthopedic injuries in adults, with epidemiological characteristics varying based on age and trauma mechanism. In developing countries, femoral shaft fractures are commonly caused by high-energy trauma such as traffic accidents, particularly in males of productive age.[4] In contrast, proximal femoral fractures are more frequently observed in geriatric patients due to low-energy falls and are associated with high one-year mortality rates, reaching 20–30%.[5] The high incidence and functional impact of femoral fractures highlight the need for optimal and integrated management strategies.

Within healthcare systems such as Indonesia's National Health Insurance (JKN/BPJS), cost-efficiency is a major consideration in selecting treatment modalities, including the management of femoral fractures. The Dynamic Compression Plate (DCP), made of stainless steel, remains a widely used conventional implant due to its availability and affordability. Although not the most advanced technology, DCP remains effective when combined with appropriate biological approaches such as bone grafting. Autologous bone grafting, particularly medullary grafts, is believed to enhance bone healing by promoting osteogenesis through the presence of progenitor cells and growth factors.[6] Therefore, in the context of cost-efficiency and clinical outcome optimization in the BPJS era, combining DCP fixation with medullary grafting represents a rational strategy to achieve optimal fracture healing.

Based on this rationale, this study aims to evaluate differences in union outcomes by assessing Transforming Growth Factor Beta-1 (TGF-β1) levels and Radiographic Union Score Femur (RUSF) in patients undergoing open reduction and internal fixation (ORIF) plate-screw for femoral fractures.

MATERIALS & METHODS

Study Design and Setting

This study was a comparative analytic observational study using a case-control design to evaluate the relationship between autologous medullary grafting and fracture healing outcomes without direct intervention. The study was conducted at

RSUP Prof. dr. I.G.N.G. Ngoerah, Denpasar, Bali, Indonesia. Patient recruitment and data collection were carried out from September to November 2025, or until the minimum required sample size was achieved.

Participants

The target population consisted of all patients with femoral fractures undergoing open reduction and internal fixation (ORIF) using plate-screw constructs. The accessible population included patients treated at RSUP Prof. Dr. I.G.N.G. Ngoerah during the study period. Subjects were recruited using a consecutive sampling method until the required sample size was fulfilled. Patients were divided into two groups, namely the case group consisting of patients who received autologous medullary graft during ORIF and the control group consisting of patients who underwent ORIF without medullary graft. Matching was performed based on age, sex, fracture location, and fixation method in order to minimize confounding bias.

Eligible participants were Indonesian patients diagnosed with femoral fractures who underwent ORIF plate-screw and were willing to participate and attend follow-up evaluation. Patients were excluded if they had a history of previous ipsilateral femoral surgery, including osteotomy or osteosynthesis, idiopathic femoral head osteonecrosis, neurological or musculoskeletal disorders that could affect limb alignment, or postoperative complications such as tumor during follow-up. Patients who died during the follow-up period were considered dropouts and excluded from the final analysis.

Sample Size

The sample size was calculated using the formula for comparison of two independent numerical means as described by Dahlan. The calculation was based on a type I error (α) of 5% corresponding to a Z value of 1.96 and a type II error (β) of 20% corresponding to a Z value of 0.842. The standard deviation used in the calculation was 30.15, and the minimum clinically significant difference between groups was 22.1. Based on these parameters, the minimum required sample size was 15 subjects per group. To account for potential dropout, an additional 20% was added, resulting in 18 subjects per group. Therefore, the total sample size for this study was 36 patients.

Variables and Outcome Measure

The independent variables in this study included age and sex. The primary dependent variables were serum Transforming Growth Factor Beta-1 (TGF-β1) levels and Radiographic Union Score Femur (RUSF). Serum TGF-β1 levels were measured using blood samples collected at 3 months postoperatively and analyzed using standard laboratory methods, with results expressed in ng/mL. Radiographic healing was assessed using plain radiographs of the femur in anteroposterior and lateral views at 3 months postoperatively. The RUSF scoring system was used to evaluate fracture healing based on cortical continuity and callus formation. Controlled variables included a history of ipsilateral lower extremity surgery, idiopathic femoral head osteonecrosis, neurological or musculoskeletal disorders affecting limb alignment, and postoperative complications. These variables were controlled through exclusion criteria to reduce potential confounding effects.

Study Procedures

Prior to data collection, ethical clearance and research permission were obtained. Subjects were identified from inpatient registries and screened based on inclusion and exclusion criteria. Eligible patients were contacted via telephone or messaging applications to explain the study procedures and to confirm their willingness to participate. Patients who agreed to participate were scheduled for follow-up

evaluation and asked to complete a structured questionnaire regarding their medical history.

At the follow-up visit, patients attended the orthopedic outpatient clinic where written informed consent was obtained. Blood samples were collected for the measurement of serum TGF-β1 levels. Radiographic evaluation using plain X-ray in anteroposterior and lateral views was performed to assess fracture healing using the RUSF scoring system. All data obtained from clinical, laboratory, and radiological assessments were recorded for further analysis.

Statistical Analysis

Statistical analysis was performed using SPSS version 22 (IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize patient characteristics, with numerical data presented as mean and standard deviation for normally distributed variables or median and interquartile range for non-normally distributed variables, while categorical variables were presented as frequency and percentage. The normality of numerical data was assessed using the Shapiro–Wilk test.

Comparative analysis between groups was performed using the independent t-test for normally distributed data and the Mann–Whitney U test for non-normally distributed data. A p-value of less than 0.05 was considered statistically significant.

RESULT

Baseline Characteristics

This study included 36 patients who underwent open reduction and internal fixation (ORIF) with plate and screw for femoral fractures at RSUP Prof. Dr. I.G.N.G. Ngoerah, Denpasar, Bali. The study population consisted of 23 males (63.9%) and 13 females (36.1%). A total of 18 patients received autologous medullary grafting, while the remaining 18 patients did not receive medullary grafting. In the medullary graft group, there were 11 males (61.1%) and 7 females (38.9%), whereas in the non-medullary graft group, there were 12 males (66.7%) and 6 females (33.3%). Regarding radiographic outcomes, 26 patients (72.2%) demonstrated good RUSF scores, while 10 patients (27.8%) were categorized as fair. All patients in the medullary graft group achieved good RUSF scores (100%), whereas in the non-medullary graft group, only 8 patients (44.4%) achieved good outcomes and 10 patients (55.6%) were categorized as fair **(Table 1)**.

Table 1. Baseline characteristics of the study participants

Characteristics	Total (n=36, %)	Medullary Graft (n=18, %)	Non-Medullary Graft (n=18, %)
Sex			
Male, n (%)	23 (63.9)	11 (61.1)	12 (66.7)
Female, n (%)	13 (36.1)	7(38.9)	6 (33.3)
RUSF Score			
Good	26 (72.2)	18 (100)	8 (44.4)
Fair	10 (27.8)	0(0)	10 (55.6)

TGF-β1 Analysis

This study analyzed serum TGF-β1 levels as a biological marker of fracture healing in patients receiving medullary graft compared with those who did not receive grafting. Normality testing was performed using the Shapiro–Wilk test due to the sample size being less than 50. The data were not normally distributed; therefore, a non-parametric Mann–Whitney U test was used for analysis. The results showed that the medullary graft group had significantly higher median TGF-β1 levels compared with the non-medullary graft group ($p < 0.001$). The median TGF-β1 level in the medullary graft group was 324.71 ng/mL (range 22.77–678.77), whereas in the non-

medullary graft group it was 24.91 ng/mL (range 6.70–76.36) **(Table 2)**.

Table 2. TGF-β1 Analysis		
Group	**TGF-β1 Level (ng/mL) Median (min–max)**	**p-value**
Medullary graft	324.71 (22.77–678.77)	<0.001
Non-medullary graft	24.916.70–76.36)	

Radiographic Union Score Femur (RUSF) Analysis

Radiographic Union Score Femur (RUSF) was used to evaluate the degree of fracture union on radiographic assessment, reflecting postoperative bone healing. Normality testing was conducted using the Shapiro–Wilk test, and as the data were not normally distributed, analysis was performed using the Mann–Whitney U test. The results demonstrated that the medullary graft group had a higher median RUSF score of 10.00 (range 9.00–12.00), compared with 8.11 (range 6.00–10.00) in the non-medullary graft group. This difference was statistically significant, with a p-value of 0.001 **(Table 3)**.

Table 3. RUSF Analysis		
Patient Group	**Median (minimum–maximum)**	**p-value**
Medullary graft (n=18)	10.00 (9.00–12.00)	0.001
Non-medullary graft (n=18)	8.11 (6.00–10.00)	

DISCUSSION

This study included 36 patients who underwent ORIF with plate-screw fixation for femoral fractures, with a predominance of male patients. This finding is consistent with previous studies reporting that femoral fractures are more common in males, particularly due to a higher incidence of high-energy trauma such as traffic accidents in this population.[7,8] The distribution of sex and group allocation in this study was relatively balanced between the medullary graft and non-medullary graft groups, supporting comparability between groups and reducing the likelihood of demographic bias influencing the outcomes.

The overall results demonstrated that patients who received autologous medullary grafting had better biological and radiological outcomes compared to those without grafting. Specifically, significantly higher TGF-β1 levels and improved RUSF scores were observed in the medullary graft group, suggesting a more active and effective bone healing process.

The present study showed that serum TGF-β1 levels were significantly higher in the medullary graft group compared to the non-medullary graft group, with an approximate 13-fold difference between groups. This finding supports the established role of TGF-β1 as a key regulator in fracture healing. TGF-β1 is known to stimulate mesenchymal stem cell proliferation, osteoblast differentiation, and extracellular matrix production, all of which are essential for bone regeneration.[9] Clinical evidence has demonstrated that TGF-β1 levels increase during the early phases of fracture healing both locally and systemically. In particular, concentrations of TGF-β1 within fracture hematoma may exceed those found in peripheral circulation, highlighting its critical role in initiating the reparative cascade.[10] Furthermore, reduced levels of TGF-β1 have been associated with delayed union, suggesting that adequate availability of this growth factor is necessary for optimal bone healing.[11]

The higher TGF-β1 levels observed in the medullary graft group may be explained by the biological properties of autologous bone marrow grafts, which contain mesenchymal stem cells and growth factors that enhance the osteogenic environment. Experimental studies have shown that local administration

of TGF-β can increase callus formation and fracture strength, while the combination of bone marrow and TGF-β1 has been shown to improve healing in critical-sized bone defects.[12,13] However, it is important to note that TGF-β1 levels may also be influenced by host-related factors such as age, sex, smoking status, and metabolic conditions. These potential confounders should be considered when interpreting the results, as they may affect the systemic inflammatory and reparative response.[14]

In addition to biological markers, radiographic outcomes in this study demonstrated that the medullary graft group had significantly higher RUSF scores compared to the non-medullary graft group. This indicates superior fracture union and structural healing in patients receiving medullary grafts. Radiographic Union Score Femur (RUSF) is a validated tool used to assess fracture healing based on cortical bridging and callus formation. Higher RUSF scores reflect better mechanical stability and progression toward complete bone union.[15] In this study, all patients in the medullary graft group achieved good radiographic outcomes, whereas more than half of the patients in the non-medullary graft group demonstrated only fair healing.

These findings are consistent with previous studies reporting that autologous bone grafting enhances fracture healing by improving both biological and mechanical aspects of bone regeneration. The presence of osteogenic cells, osteoinductive growth factors, and osteoconductive scaffolding within the graft contributes to accelerated callus formation and improved structural integrity.[16]

The results of this study have important clinical implications, particularly in resource-limited healthcare systems. The combination of conventional fixation methods such as dynamic compression plates with biological augmentation using medullary grafts represents a cost-effective strategy to improve fracture healing outcomes. In settings such as Indonesia's national health insurance system (BPJS), where cost efficiency is a major consideration, the use of readily available autologous graft material may provide a practical and effective solution to enhance healing without significantly increasing treatment costs.

This study has several limitations that should be acknowledged. First, the relatively small sample size may limit the generalizability of the findings. Second, the observational case-control design does not allow for full control of confounding variables. Third, follow-up duration was limited to three months, which may not fully capture long-term outcomes such as delayed union or non-union. Future studies with larger sample sizes, longer follow-up periods, and prospective designs are needed to validate these findings.

CONCLUSION

In conclusion, the use of autologous medullary grafting in patients with femoral fractures undergoing ORIF plate-screw is associated with significantly higher Transforming Growth Factor Beta-1 (TGF-β1) levels and improved Radiographic Union Score Femur (RUSF) compared to patients without medullary grafting, indicating enhanced biological and radiological fracture healing. These findings support the role of medullary grafting as an effective biological adjunct in fracture management. However, further studies with longer follow-up periods are needed to better evaluate long-term outcomes. Additionally, the use of biomarkers such as TGF-β1 has the potential to be further developed as a tool for monitoring fracture healing and stratifying patient response, thereby assisting clinicians in guiding more targeted and personalized evaluation and treatment strategies.

Declaration by Authors

Ethical Approval: Approved

Acknowledgement: None

Source of Funding: None
Conflict of Interest: No conflicts of interest declared.

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How to cite this article: Putu Bihan Surya Kinanta, I Gusti Ngurah Wien Aryana, Made Bramantya Karna. Effect of autologous medullary grafting on transforming growth factor Beta-1 (TGF-β1) levels and radiographic union score femur in patients undergoing ORIF plate-screw for femoral fractures compared to those without medullary grafting. *International Journal of Research and Review*. 2026; 13(5): 279-285. DOI: *10.52403/ijrr.20260523*

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