Risk Factors for Neck Shortening in Patients with Valgus Impacted Femoral Neck Fractures Treated with Three Parallel Screws: Is Bone Density an Affecting Factor?

Yerl-Bo Sung, PhD, Eui-Yub Jung, MS, Kyung-Il Kim, MD, Soo-Yeon Kim, MD
Department of Orthopaedic Surgery, Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea

Purpose: The purpose of this study is to analyze the relationship between significant femoral neck shortening (SFNS) and bone density after three parallel screw fixation in valgus impacted femoral neck fracture, and to analyze the risk factors for SFNS.

Materials and Methods: This is retrospective study of 83 patients. We performed univariate analysis for patient information, bone density, fracture configuration and screw position divided into SFNS group (n=13) and non-SFNS group (n=70) and performed multivariate analysis using logistic regression model. We also analyzed the relationship between SFNS and complications such as osteonecrosis of femoral head and nonunion.

Results: There was a significant difference in age, screw non-parallelism and bone mineral density of intertrochanteric and total hip area in the univariate analysis between the two groups (P<0.05). In multivariate analysis, old age (odds ratio [OR], 1.10; 95% confidence interval [CI], 1.03-1.21) and screw non-parallelism (OR, 2.95; 95% CI, 1.44-6.59) were significant risk factors for SFNS. The incidence of SFNS was significantly higher in the complication group (P=0.027).

Conclusion: Bone density did not significantly affect SFNS in valgus impacted femoral neck fractures treated with three parallel screws. The risk factors of SFNS were old age and screw non-parallelism. Therefore, we recommend using other fixation method to prevent SFNS in older ages and making the screw position as parallel as possible when performing screw fixation in valgus impacted femoral neck fracture.

Key Words: Femoral neck fractures, Valgus impacted, Neck shortening, Bone density, Risk factors

INTRODUCTION

Femoral neck fracture is an increasing trend, accounting for about half of all hip fractures. Impacted femoral neck fracture is a fracture with a close apposition of the fracture fragment. Its frequency is known to be 15% to 20% of the femoral neck fracture. Impacted femoral neck fractures rarely form varus impaction, but usually have the form of valgus impaction. In the case of valgus impacted femoral neck fracture, non-surgical treatment was performed in the past, but now it is treated with multiple parallel screw...
fixation without reducing the fracture site. Parallel screw fixation in a femoral neck fracture is to promote fracture healing by compression of the fracture site, but this leads to a reduction in the abductor moment arm and shortening of the muscle, resulting in functional problems and is associated with postoperative complications. Most orthopedic surgeons think that femoral neck shortening is common and cause functional problems and the frequency of significant femoral neck shortening (SFNS) in screw fixation in femoral neck fractures is known to be about 30%. Despite the fact that SFNS is associated with clinically unfavorable outcomes, there are only two studies suggesting a risk factor for neck shortening in femoral neck fractures. In these studies, low bone density, old age, displaced fracture and poor reduction quality are commonly used as risk factors. Among these factors, low bone density and old age are associated with neck shortening in valgus impacted femoral neck. Chen et al. presents the T-score of –2.5 or less is the most relevant factor, and Liu et al. suggests low Singh index as one of the risk factors. However, these two studies can be pointed out as a limitation because they did not specify the method of measuring femoral neck shortening, used various fixation methods, or used Singh index, which is known to be less correlated with bone density.

In this study, unlike previous studies, the method of measurement of femoral neck shortening was clarified, only cases using only one fixation method were analyzed, and only cases measuring bone density using the dual energy X-ray absorptiometry (DXA) were analyzed. This study hypothesized that the lower bone density, the more SFNS will occur in valgus impacted femoral neck fractures and the purpose of this study is to identify risk factors that cause SFNS.

**MATERIALS AND METHODS**

We retrospectively reviewed 83 patients who met exclusion criteria among 530 patients operated femoral neck fractures by one senior surgeon (YBS) in Inje University Sanggye Paik Hospital from January 2009 to February 2016. The study was approved by Sanggye Paik Hospital’s institutional review board (No. 2017-08-009).

![Flowchart](https://via.placeholder.com/150)

**Fig. 1.** The flowchart shows patient selection and exclusion criteria. BMD: bone mineral density.
1. Operative Technique and Postoperative Management

All patients maintained bed rest until the operation and underwent 1 pound skin traction. Surgery was performed under general anesthesia or regional anesthesia and the patient was placed in the supine position on the fracture table and anteroposterior (AP) and lateral radiographs were obtained using image intensifier. After applying 2-5 cm skin incision, three screws were inserted in parallel with the inverted triangular configuration using guide pins as close as possible to the cortex of femoral neck. Screws were used for 6.5 mm, titanium alloy, partial cancellous threaded, cannulated screw (Stryker, Kalamazoo, MI, USA) and the threads of the screws were positioned past the fracture site. We did not use washer for screw insertion.

Immediately after surgery, knee and hip passive range of motion were performed. Patients began partial weight bearing of the affected side using a walker immediately after surgery until 6 weeks and full weight bearing was allowed in the tolerable range after 6 weeks. We performed standard AP and lateral radiographs of hip at 2 weeks, 6 weeks, 3 months, and 6 months postoperatively, and from 6 months after surgery, we performed the radiographs every 6 months.

2. Evaluation of Patient Information

We investigated the age, sex, fractured side and body mass index (kg/m²). The time taken from injury to operation was examined and divided into two groups based on 24 hours. The degree of preoperative walking ability was divided into 1) independent ambulation, 2) cane ambulation, 3) walker assistant ambulation, 4) wheelchair ambulation, and 5) bed ridden state. The preoperative physical status was divided into 4 groups according to the American Society of Anesthesiologists (ASA) grade. This was confirmed by an anesthesiologist’s preoperative evaluation chart. We examined the use of drugs that affect bone turnover for more than 3 months before surgery such as bisphosphonate, selective estrogen receptor modulator and teriparatide.

3. Radiographic Analysis

1) Fracture configuration

The valgus impacted femoral neck fracture was defined as the following. 1) In the AP radiograph, the fragment should be closed apposition and impaction at the medial or lateral side of the fracture site. 2) The angle of the medial group of trabeculae at the fracture site should be valgus configuration. 3) In the lateral radiograph, the angle between the mid line of the neck and the radius line of the head should be less than 15°. Modified Pauwels angle were measured and divided into three groups: less than 30°, 30 to 50°, and 50°.

2) Amount of neck shortening

To measure the degree of neck shortening, we measured articular-trochanteric distance (ATD), the distance from the proximal point to the superior margin of the femoral head at the proximal point of the greater trochanter of the fractured side and the unfractured side, on AP radiographs immediately after surgery7). To standardize the ATD on the fractured side, the ATD index was obtained by dividing it by the ATD on the unfractured side10) (Fig. 2). In the same way, ATD index was measured at 6 weeks, 3 months, and 6 months, respectively, and the reduction rate was calculated based on the ATD index immediately after surgery. We defined the SFNS group as a reduction rate of 30% or more and the non-SFNS group as a reduction rate of less than 30% based on the 6-month ATD index. When reoperation was performed with complication before 6 months, neck shortening was judged using ATD index just before reoperation. A radiographic measurement was performed without knowing the patient’s clinical information to reduce bias.

3) Position of screws

Screw non-parallelism, screw-tip distance, and spread of screws were measured on plain radiographs immediately after surgery. Screw non-parallelism was determined to be the largest angle between the longitudinal axes of the three screws in AP and lateral radiographs4). The screw-tip distance was measured as the sum of the distance between the three screw tips and the cortex of the femoral head in the AP radiographs4). The spread of screws was measured by calibrating the distance between the two most peripherally placed screws of the three screws on the AP and lateral radiographs to the head diameter4).?

4. Assessment of Bone Density

As a surrogate of bone density, bone mineral density (BMD, g/cm²) was determined by measuring the bone mineral contents (g) and area (cm²) of the contralateral proximal femur using DXA. The region of interest (ROI) is divided into neck, greater trochanter, intertrochanteric area and total hip to actually measure the area through
which the three parallel screws pass, and total hip is defined as the combined area of neck, greater trochanter, and intertrochanteric area (Fig. 3). BMD results were included only within 3 months after surgery (mean, 14.7 days; 1 to 89 days). DXA was used with GE Lunar Prodigy (GE Healthcare, Madison, WI, USA) and calibration was performed daily through density phantom for quality control.

5. Assessment of Complications

Complication was defined as the occurrence of osteonecrosis of femoral head (ONFH) and nonunion. ONFH was defined as the presence of a cystic and sclerotic change, a visible crescent sign, or flattening or collapse of the femoral head in plain radiographs, and as a single density line delineating a necrotic-viable bone interface at the femoral head in a T1-weighted image or a double density line created by a hypervascular granulation tissue at a necrotic-viable bone interface in a T2-weighted image in magnetic resonance imaging16). Nonunion was defined as the patient’s pain persisted with a fracture line up to 6 months postoperatively17).

6. Statistical Analysis

We performed a univariate analysis between the SFNS group and the non-SFNS group. For continuous variables, Kolmogorov-Smirnov test and Shapiro-Wilk test for normality test. Independent sample t-test was performed if normal distribution was assumed, and Mann-Whitney test was used if not. For the categorical variables, the chi-square test was performed. But if more than 20% of the cells with an expected frequency of less than 5, Fisher’s exact test was performed. To adjust variables related to the occurrence of SFNS, multivariate analysis was performed by logistic regression model for variables with a P-value less than 0.05.
in univariate analysis. Three orthopedic surgeons (EYJ, KIK, SYK) independently measured the radiographic measurements such as modified Pauwels angle, screw non-parallelism, screw-tip distance, spread of screws on AP and lateral radiographs and reduction rate of ATD index at 6 months. The interclass coefficient (ICC) was measured as 0.93, 0.86, 0.91, 0.83, 0.89, and 0.88, respectively. This means that there is reliability between the radiographic measurements according to Landis and Koch\(^{18}\). All statistical assessments are two-tailed and are evaluated at the 0.05 level of significance. Statistical analyses were performed with use of PASW Statistics ver. 18.0 software (IBM Co., Armonk, NY, USA).

**RESULTS**

The mean age of the patients was 69.1 years (range, 28-94 years) and the mean follow-up period was 29.1 months (range, 12-98 months). Of the 83 patients who underwent three parallels screw fixation in a valgus impacted femoral neck fracture, 13 patients (15.7%) had SFNS.

Among the patient information between the SFNS group and the non-SFNS group, only the age was significantly different between the two groups (\(P=0.002\)) (Table 1). The average age of SFNS group was 76.85 \(\pm\) 6.77 years and that of non-SFNS group was 67.70 \(\pm\) 14.12 years. In radiologic parameters, BMD of intertrochanter, BMD of total hip, and screw non-parallelism were significantly different between the two groups (\(P<0.05\)) (Table 2).

In multivariate analysis using logistic regression model, age and screw non-parallelism were less than 0.05 \(P\)-value and adopted as a risk factor for SFNS (Table 3). The adjusted odds ratio (OR) for SFNS for age was 1.10 (95% confidence interval [CI], 1.03-1.21) and the estimated OR for SFNS for screw non-parallelism was 2.95 (95% CI, 1.44-6.59) (Fig. 4).

Of the 13 SFNS patients, 4 patients (30.8%) at the 6th week, 4 patients (30.8%) at the 3rd month, and 5 patients (38.5%) at the 6th month were diagnosed with SFNS.

### Table 1. Univariate Analysis (Patient’s Information)

| Variable                      | Total (n=83) | SFNS (n=13) | Non-SFNS (n=70) | P-value |
|-------------------------------|-------------|-------------|----------------|---------|
| Age* (yr)                     | 69.13 \(\pm\) 13.69 | 76.85 \(\pm\) 6.77 | 67.7 \(\pm\) 14.12 | 0.002   |
| Sex†                          |             |             |                 | 1.000   |
| Female                        | 70 (84.3)   | 11 (84.6)   | 59 (84.3)       |         |
| Male                          | 13 (15.7)   | 2 (15.4)    | 11 (15.7)       |         |
| Fracture side*                |             |             |                 | 1.000   |
| Right                         | 35 (42.2)   | 5 (38.5)    | 30 (42.9)       |         |
| Left                          | 48 (57.8)   | 8 (61.5)    | 40 (57.1)       |         |
| Body mass index\(^{'}\) (kg/m\(^{2}\)) | 22.12 \(\pm\) 3.50 | 23.46 \(\pm\) 4.64 | 21.88 \(\pm\) 3.23 | 0.136   |
| Ambulation status\(^{'}\)     |             |             |                 | 0.624   |
| Independent                   | 63 (75.9)   | 10 (76.9)   | 53 (75.7)       |         |
| Cane                          | 12 (14.5)   | 3 (23.1)    | 9 (12.9)        |         |
| Walker                        | 6 (7.2)     | 0 (0.0)     | 6 (8.6)         |         |
| Wheel chair                   | 2 (2.4)     | 0 (0.0)     | 2 (2.9)         |         |
| Bed ridden                    | 0 (0.0)     | 0 (0.0)     | 0 (0.0)         |         |
| ASA grade*                    |             |             |                 | 0.346   |
| Grade 1                       | 10 (12.0)   | 0 (0.0)     | 10 (14.3)       |         |
| Grade 2                       | 38 (45.8)   | 6 (46.2)    | 32 (45.7)       |         |
| Grade 3                       | 35 (42.2)   | 7 (53.8)    | 28 (40.0)       |         |
| Grade 4                       | 0 (0.0)     | 0 (0.0)     | 0 (0.0)         |         |
| Time to surgery*              |             |             |                 | 0.766   |
| <24 hr                        | 40 (48.2)   | 7 (53.8)    | 33 (47.1)       |         |
| ≥24 hr                        | 43 (51.8)   | 6 (46.2)    | 37 (52.9)       |         |
| Osteoporosis medication\(^{'}\) |             |             |                 | 0.583   |
| Taking for ≥3 months          | 5 (6.0)     | 1 (7.7)     | 4 (5.7)         |         |
| No taking                     | 78 (94.0)   | 12 (92.3)   | 66 (94.3)       |         |

Values are presented as mean \(\pm\) standard deviation or number (%). SFNS: significant femoral neck shortening. \(P\)-values are based on * the Mann-Whitney test, † the Fisher’s exact test, ‡ the chi-square test, and ′ the independent sample t-test.
Five patients (38.5%) had ONFH or nonunion (Table 4). Complications occurred in 13 of 83 patients. There were 11 ONFH patients and 4 nonunion patients. SFNS occurred in 5 patients (38.5%) in the complication group and in 8 patients

### Table 2. Univariate Analysis (Radiologic Parameters)

| Variable                        | Total (n=83) | SFNS (n=13) | Non-SFNS (n=70) | P-value |
|---------------------------------|--------------|-------------|-----------------|---------|
| Bone mineral density* (g/cm²)   |              |             |                 |         |
| Neck                            | 0.652±0.138  | 0.584±0.106 | 0.665±0.140     | 0.052   |
| Greater trochanter              | 0.534±0.131  | 0.474±0.113 | 0.545±0.132     | 0.072   |
| Intertrochanter                 | 0.820±0.179  | 0.708±0.113 | 0.841±0.182     | 0.013   |
| Total hip                       | 0.688±0.144  | 0.604±0.107 | 0.703±0.145     | 0.022   |
| Screw non-parallelism* (°)      |              |             |                 | 0.739   |
| Grade 1                         | 8 (9.6)      | 2 (15.4)    | 6 (7.3)         |         |
| Grade 2                         | 66 (79.5)    | 10 (76.9)   | 56 (80.0)       |         |
| Grade 3                         | 9 (10.8)     | 1 (7.7)     | 8 (11.4)        |         |
| Screw-tip distance* (mm)        | 28.21±6.00   | 28.98±5.39  | 28.09±6.13      | 0.659   |
| Spread of 3 anteroposterior screws* | 32.28±4.16 | 33.13±4.31  | 32.12±4.14      | 0.424   |
| Spread of 3 lateral screws*     | 22.78±5.76   | 21.35±4.72  | 23.04±5.93      | 0.335   |

Values are presented as mean±standard deviation or number (%). SFNS: significant femoral neck shortening. P-values are based on * the independent sample t-test and † the Fisher’s exact test.

### Table 3. Multivariate Analysis of the Risk Factors of Significant Femoral Neck Shortening

| Risk factors                      | B     | Adjusted OR (95% CI)        | P-value |
|-----------------------------------|-------|----------------------------|---------|
| Age                               | 0.099 | 1.10 (1.03-1.21)            | 0.011   |
| BMD of intertrochanter            | -1.932| 0.14 (0.00-24.93)           | 0.468   |
| BMD of total hip                  | -1.961| 0.14 (0.00-71.29)           | 0.544   |
| Screw non-parallelism             | 1.081 | 2.95 (1.44-6.59)            | 0.005   |

Risk factors were obtained by logistic regression model using a backward elimination to determine the variables needed for the model. OR: odds ratio, CI: confidence interval, BMD: bone mineral desity.

![Fig. 4](image)

**Fig. 4.** This figure shows the plot for odds ratio for the final model of multiple logistic regression. CI: confidence interval.
(11.4%) in the non-complication group. There was a significant difference between the two groups ($P=0.027$) (Table 5).

**DISCUSSION**

In a retrospective study of 83 patients, old age and screw non-parallelism were risk factors for SFNS in three parallel screw fixation in valgus impacted femoral neck fracture. Bone density between the SFNS and non-SFNS groups significantly differed in the intertrochanteric area and the total hip area, but it was not a risk factor for SFNS.

This study can provide sufficient reliable support for the opinion that low bone density is not associated with femoral neck shortening in valgus impacted femoral neck fracture for the following reasons: 1) we analyzed BMD itself using DXA as a surrogate of bone density, unlike previous studies. 2) Unlike previous studies that included displaced fractures in the study of femoral neck shortening, this study, in which only valgus impacted femoral neck fractures were studied, could be more clear about bone density and screw fixation. As a basis for the first reason, in a systemic review of the relationship between fracture fixation and osteoporosis, Goldhahn et al.\(^1\) found that in most *in-vitro* studies, low bone density was associated with fixation failure, whereas clinical studies have shown inconsistent results. In this review, the reasons for this result were that most clinical studies have used Singh index, which is less related to bone density than BMD using DXA and BMD of other parts other than fracture site using DXA. Therefore, the authors recommended the use of site-specific BMD using DXA to measure local bone density, as suggested by Eckstein et al\(^2\). But in most previous studies of femoral neck shortening, bone density was measured using Singh index or T-score not using BMD itself and the result are different from each other\(^3,4,9,10,11\). As a basis for the second reason, Viberg et al.\(^21\) noted that the OR of low BMD for fixation failure was higher, although not significantly, in the nondisplaced femoral neck fracture than in the displaced femoral neck fracture. This study explained that in the case of nondisplaced fractures, the main reason for fixation failure was probably low BMD because of the relatively good blood supply and bone contact. Therefore, the results of our study, which excluded displaced femoral fractures, may be more reliable to explain the relationship between bone density and femoral neck shortening than in previous studies.

In this study, age was presented as a risk factor for SFNS in a valgus impacted femoral neck fracture treated with three

### Table 4. Analysis of Thirteen Patients with Significant Femoral Neck Shortening (SFNS)

| Sex/age (yr) | At the time of diagnosis of SFNS after surgery | ONFH | Nonunion |
|--------------|-----------------------------------------------|------|---------|
| F/94         | 6th week                                      | –    | –       |
| F/84         | 6th week                                      | –    | ○       |
| F/69         | 6th week                                      | –    | –       |
| F/78         | 6th week                                      | –    | –       |
| F/73         | 3rd month                                     | –    | –       |
| F/76         | 3rd month                                     | ○    | –       |
| M/79         | 3rd month                                     | –    | –       |
| F/75         | 3rd month                                     | ○    | ○       |
| F/80         | 6th month                                     | –    | –       |
| F/74         | 6th month                                     | –    | ○       |
| M/83         | 6th month                                     | –    | ○       |
| F/64         | 6th month                                     | ○    | ○       |
| F/70         | 6th month                                     | –    | –       |

ONFH: osteonecrosis of femoral head, F: female, M: male.

### Table 5. Comparisons of Femoral Neck Shortening between Complication Group and Non-complication Group

| Variable            | Total (n=83) | Complication (n=13) | Non-Complication (n=70) | P-value |
|---------------------|--------------|---------------------|------------------------|---------|
| Femoral neck shortening | 13 (15.7)    | 5 (38.5)            | 8 (11.4)               | 0.027   |

Values are presented as number (%). P-values are based on the Fisher’s exact test.
parallel screw fixation. This is consistent with previous studies on the risk factors of femoral neck shortening\(^{14,15}\). Conn and Parker\(^{20}\) reported a significant increase in age in the nonunion group in a study of internal fixation in a nondisplaced femoral neck fracture. This study explains that as the age increases, the bone becomes weaker and the blood supply to the femoral head becomes more unstable. Because of the higher failure rate at older ages than at younger ages in internal fixation of nondisplaced femoral neck fracture, some studies suggest that primary arthroplasty should be considered in older ages\(^{20}\). However, primary arthroplasty has not been accepted as a common treatment method for nondisplaced femoral neck fractures due to disadvantage such as deep infection, periprosthetic fracture, dislocation, loosening, and acetabular wear\(^{20}\). Recently, a length-stable implant has emerged as a method to solve femoral neck shortening without having disadvantages of primary arthroplasty. Multiple full threaded screws, sliding hip screw with two fully threaded screws and dynamic locking plate (Targon\(^6\) femoral neck; B. Braun, Sheffield, UK) are currently reporting clinical results in femoral neck fracture\(^{24,25}\).

In this study, the relationship between SFNS and screw position was different from previous studies. First, screw non-parallelism among screw positions was a risk factor for SFNS in valgus impacted femoral neck fractures treated with three parallel screw fixation. On the other hand, in previous studies, the degree of screw parallelism when screw fixation in femoral neck fractures was not related to nonunion\(^{14,15}\). However, previous studies cannot be compared with the results of this study because of the different measurement criteria of screw parallelism\(^{10}\) and no analysis of the screw version. Papanastassiou et al.\(^{21}\) reported that divergent screw fixation showed better clinical results compared to parallel screw fixation in a femoral neck fracture. Gümüş\(\text{"u}\)tas\(\text{"u}\)\(^{27}\) reported that the fixation of the oblique screws added to the parallel screw fixation showed better results in the biomechanical study. Therefore, we concluded that even with the same amount of non-parallelism, the clinical outcome may vary depending on the version of the screw, and it is necessary to analyze the effect of screw version on SFNS by subdividing screw non-parallelism. Second, in most studies, screw-tip distance and spread of screws are considered to be important factors in clinical outcomes\(^{14,15}\). However, in our study, screw-tip distance and spread of screws were not related to SFNS. One of the reasons for this result is that the screw-tip distance and spread of screws were much smaller in both two groups of this study than in successful group of the previous studies\(^{14,15}\).

This means that both groups of this study had better purchase of the screw to femoral head and neck than the successful group of previous studies.

In this study, 5 of 13 SFNS patients underwent neck shortening until 6 months postoperatively (Table 4). Stockton et al.\(^{20}\) emphasized that measuring shortening only shortly after surgery could underestimate the actual amount of shortening. Chen et al.\(^{13}\) reported that most shortening occurred between 4 weeks and 3 months. However, based on the results of this study, we suggest that shortening should be evaluated for at least 6 months, since shortening may progress to 6 months. In addition, as in this study, 44% (4/9) of patients with progressing neck shortening after 3 months are associated with nonunion or ONFH (Table 4). In some of the previous studies, the criteria for nonunion in femoral neck fractures included neck shortening or absorption of femoral neck at 3 months or later\(^{15,20}\). This suggests that there is a close relationship between neck shortening and nonunion in femoral neck fracture. In our study, SFNS occurred in all 4 nonunion patients. Therefore, we recommend that patients undergoing neck shortening for up to 3 months be sure to investigate complications, especially nonunion.

The limitations of this study are as follows. First, there is a selection bias because it is a retrospective design. In order to reduce the selection bias as much as possible, this study measured all radiographic measurements without any clinical outcome. Second, the number of patients analyzed is small. The third is that the bone density of the fractured side could not be measured before surgery. However, to reflect the preoperative status of the fractured side as much as possible, this study used only BMD data within 3 months postoperatively and only BMD data of the contralateral proximal femur.

**CONCLUSION**

We commonly observe SFNS when parallel screw fixation is performed on valgus impacted femoral neck fractures. To investigate the relationship between low bone density and SFNS, unlike previous studies, our study used BMD value itself using DXA. As a result, low bone density was not associated with SFNS. In addition, we tried to investigate the risk factors of SFNS, and old age and screw non-parallelism were analyzed as risk factors of SFNS. Therefore, we recommend the use of other fixation method such as length-stable implants to prevent SFNS in older ages and making the screw position as parallel as possible when performing three screw fixation in valgus impacted femoral...
neck fracture. In future studies, it is necessary to analyze the effect of screw version on SFNS by subdividing screw non-parallelism.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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