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Does the Nonunion Rate of Atypical Femoral Fractures Differ According to Fracture Site?: A Meta-Analysis

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Background: The nonunion rate for atypical femoral fractures (AFF) is known to be higher than that for typical fractures of the femur. We performed a meta-analysis to determine the incidence of nonunion necessitating reoperation following fixation for AFF and compare the rates according to the fracture site (subtrochanter or midshaft).

Methods: A total of 742 AFFs from 29 studies were included. A proportion meta-analysis utilizing a random-effects model was conducted to estimate the prevalence of nonunion. The outcomes were the incidence of reoperations that included osteosynthesis. To determine the association of nonunion with patient mean age or average duration of bisphosphonate use, meta-regression analysis was done.

Results: In proportion meta-analysis, the estimated pooled prevalence of nonunion was 7% (95% confidence interval [CI], 5%–10%) from all studies. There was a significant difference in nonunion rate between the 2 groups (I^2 = 34.4%, p = 0.02); the estimated prevalence of nonunion was 15% (95% CI, 10%–20%) in subtrochanteric AFFs and 4% (95% CI, 2%–6%) in midshaft AFFs. From meta-regression analysis, significant correlations were identified between nonunion rate and patient mean age (coefficient: –0.0071, p = 0.010), but not in the average duration of bisphosphonate use (coefficient: –0.0024, p = 0.744).

Conclusions: A notable disparity existed in the nonunion rate among subtrochanteric AFFs and midshaft AFFs group. Therefore, it is critical for orthopedic surgeons to consider the complexity and challenges associated with AFF and to estimate the proper possibility of nonunion according to the fracture site.

Keywords: *Femoral fractures, Intramedullary fracture fixation, Internal fracture fixation, Union, Meta-analysis*

Atypical femoral fractures (AFF) are a rare but specific type of fracture that typically exhibits a short or transverse oblique orientation, occurs with minimal or no associated trauma, features a medial spike in complete fractures, and lacks comminution with high mortality when occurring in frail, elderly patients.[1)] While intramedullary (IM) full-length nailing is a common treatment of choice for AFF, substantial concern persists regarding the potential for delayed or unsuccessful healing even after the stabilization of AFF.[2,3)]

Studies have suggested that the nonunion rate for AFF is generally higher than that for typical fractures of the femur. The union rates have been reported to be ranging from 72% to 100% and the accurate incidence of nonunion following surgery is still uncertain. It is important to note that these rates can vary widely and may be influenced by factors such as choosing the implant and considering the possibility of bone grafting, teriparatide use, and the presence of other risk factors.[4-6)]

Previous reports have indicated that AFF are more difficult to treat surgically and more prone to delayed healing or nonunion due to several factors.[7,8)] Prolonged use

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of bisphosphonate treatment, causing an excessive suppression of bone turnover, results in an atypical metabolic activity that predominates at the edges of fractures in the affected extremity.[9,10] The quality of reduction is also the main factor and a previous study reported that achieving anatomical reduction with both maximal cortical displacement less than 4 mm and angulation less than 10° can improve the union rate of AFF.[6,11,12] However, reduction of AFF is more challenging due to their femoral bowing, which presents difficulties when attempting to achieve proper alignment and reduction of fractures.[12-15] Typical femoral fractures are classified according to their location as subtrochanter or midshaft, and the subtrochanteric area is more challenging due to the strong muscular forces and proximal femur anatomy.

Considering the complexity and challenges associated with AFF, it is crucial for patients and clinicians to estimate the possibility of nonunion and reoperation before surgery. Therefore, we conducted a meta-analysis that encompassed all eligible cohort studies assessing the outcomes of surgical treatment of AFF. Our aims were to determine the pooled rate of nonunion after surgery for AFF and to compare these outcomes according to the fracture site.

METHODS

Since this study used published data, ethical approval was not required.

Search Methods for the Identification of Studies

We conducted a comprehensive search of electronic databases to identify studies comparing the outcomes according to the fracture site between the femur subtrochanter (within 5 cm distal to the lower margin of the lesser trochanter) and shaft (from 5 cm distal to the lower margin of the lesser trochanter to the upper margin of the femur supracondyle) from inception to June 2023 according to the updated guidelines of the systematic review and meta-analysis protocols 2020 statement (Supplementary Material 1). The current study's protocol was registered in the PROSPERO international registry (ID: CRD42023458895). We conducted searches across various comprehensive databases, including Medline (PubMed), Embase, Cochrane Library databases, and KoreaMed, to identify studies in June 2023. Developing a search strategy was conducted in collaboration with a librarian and an overview of the search strategy is provided in Supplementary Material 2. We included all single cohort studies that investigated clinical results after surgery for atypical femur fracture (not limited to prospective studies, including retrospective case-control studies).

Criteria for Selecting Studies

All publications were classified using Endnote X20 for Windows. Two reviewers (BHY and MSK) autonomously reviewed all relevant titles and abstracts of studies and subsequently selected studies based on a full-text review. A third reviewer (YHR) settled discrepancies between these 2 reviewers. Inclusion criteria were as follows: a study (1) published as an original article in English, (2) involving either a comparative analysis or a single-cohort investigation that evaluated the outcomes of patients treated with IM nails or plates for fixation of AFF defined according to the ASBMR criteria, (3) reporting the primary clinical outcome (the incidence of nonunion), and (4) with a minimum follow-up of 1 year.

Exclusion criteria were as follows: (1) inclusion of distal femur fractures or periprosthetic atypical fractures, (2) inclusions of pathologic fracture, (3) too small sample size (< 5 patients), (4) inclusion of re-osteosynthesis of failed fixation (nonunion), (5) use of national registry data, and (6) a review, expert opinion, case report, animal study, or basic science study.

Outcome Measures and Data Extraction

The main focus of this meta-analysis was on the incidence of nonunion. Nonunion was considered present when there were additional surgical interventions, such as additional plate fixation, bone grafting, or revision surgery due to hardware failures, and exchange nailing to promote fracture healing was undertaken. The following cases were not regarded as nonunion when the patient underwent a surgical procedure because of surgical site infection, arthritis following trauma, or femur neck fracture after IM fixation.

For each eligible study, the 2 reviewers extracted and recorded the following data in a spreadsheet: the last name of the first author, publication year, inclusion period, the number of patients, age of patients, fracture site, fixation device, the use of recombinant parathyroid hormone (e.g., teriparatide or abaloparatide), average duration of bisphosphonate use, and mean years after the index operation.

Quality Assessment and Publication Bias

Two authors (BHY and MSK) conducted separate evaluations of study quality using the Newcastle-Ottawa Scales designed for observational studies. This tool includes 3 key parameters: selection, comparability, and outcome, each with subcategories. Selection can receive up to 4 stars, comparability up to 2 stars, and exposure or outcome up to 3 stars. We examined publication bias using Begg's funnel plot and Egger's test.

Statistical Analysis (Subgroup Analysis and Sensitivity Analysis)

The main analysis consisted of a proportion meta-analysis utilizing data from all pertinent studies that reported the occurrence of nonunion. Meta-analysis of proportions serves as a method to compute a comprehensive proportion from studies that report a single proportion. In our investigation, the proportion (p) was determined by dividing the number of femurs developing nonunion by the total number of AFF (n). Standard errors and confidence intervals for a single proportion were computed, and adjusted proportions were subsequently calculated through a logit transformation, as outlined below:

$$\text{logit outcome} = \ln\frac{p}{1-p} \quad \text{logit standard error} = \sqrt{\frac{1}{n \, x \, p \, x \, (1-p)}}$$

Next, all AFFs were categorized into 2 groups based on the fracture site (subtrochanteric and midshaft). The heterogeneity between these groups was then computed. All AFFs were also divided according to fixation device: IM nailing or plate. Studies with zero cells were supplemented by adding 0.5 successes to each arm.

Sensitivity Analysis

The use of teriparatide/abaloparatide, which can promote fracture healing, could be an important covariant to clinical outcomes. So, we tried to perform a sensitivity analysis by including only studies that used teriparatide/abaloparatide. However, it was not possible to perform subgroup analysis because parathyroid hormone was used case by case in most studies. Fracture pattern also can be another covariant to union rate, but only 2 studies classified their results according to fracture pattern. The analyses were conducted using Stata software version 14.0 (Stata Corp.).

RESULTS

Description of the Included Studies

The primary search of the databases yielded 711 records. After duplicates were removed, 521 articles were screened by title and abstract. As a result, 102 full-text articles were selected and reviewed for eligibility. A total of 29 studies were finally included in the systematic review (Fig. 1). Among 29 studies, 11 cohort articles included both sites of AFF (subtrochanteric and midshaft),[7,13,16-24] 9 cohort studies reported outcomes after surgery of subtrochanteric AFFs,[6,9-11,14,25-28] and 9 single cohort studies reported midshaft AFF.[8,12,15,29-33] The overall incidence of nonunion was 10.3% (77 / 742) in total, 17.5% (52 / 297) in the subtrochanteric AFFs group, and 5.6% (25 / 445) in the midshaft AFFs group (Table 1).

Incidence of Nonunion According to Fracture Site

In proportion meta-analysis, the pooled prevalence of nonunion was 7% (95% confidence interval [CI], 5%–10%) from all studies; 15% (95% CI, 10%–20%) in subtrochanteric AFFs and 4% (95% CI, 2%–6%) in midshaft AFFs (Fig. 2). There was a significant difference in the nonunion rate between the 2 groups (I^2 = 34.4%, p = 0.02).

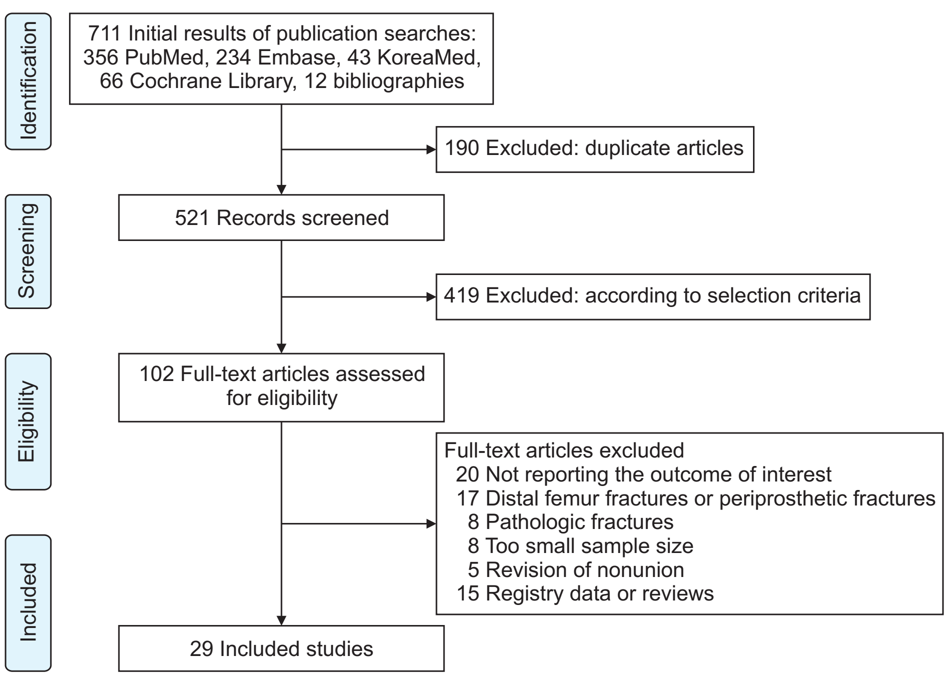

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram detailing the selection process of relevant clinical studies.

Table 1. The Outcomes from Included Studies Investigating the Clinical Results of Atypical Femoral Subtrochanteric and Shaft Fractures

Study	Enrollment period	Mean age (yr)	Mean follow-up (yr)	Average duration of bisphosphonate (yr)	Use of PTH	Fixation device	Fx site	No. of fractures	No. of nonunions
Murphy et al. (2022)[16]	2012–2019	75.2	8	7.35	None	IM nail	STN	7	2
						IM nail	Midshaft	8	0
Mishra et al. (2022)[25]	2018–2021	65.12	> 1	3	NA	IM nail	STN	20	2
Cho et al. (2022)[30]	2007–2015	75.9	2.7	4	Case by case	Plate	Midshaft	16	0
Oh et al. (2022)[29]	2004–2019	72.4	2.5	7.5	Case by case	IM nail	Midshaft	48	2
Shon et al. (2021)[7]	2013–2018	76.8	1.6	6.1	Case by case	IM nail	STN	1	0
						IM nail	Midshaft	24	0
Byun et al. (2021)[31]	2012–2020	78.1	4.3	5	Case by case	IM nail	Midshaft	29	4
Nishino et al. (2020)[17]	NA	63.9	4.8	6.2	Case by case	IM nail	STN	6	2
							Midshaft	6	2
Mizutani et al. (2020)[18]	2013–2016	77.7	3.5	7.8	Case by case	IM nail	STN	1	0
							Midshaft	13	0
Kim et al. (2020)[6]	2011–2018	71.3	1.9	3.9	Case by case	IM nail	STN	45	3
Canbek et al. (2020)[8]	2012–2016	74.0	3.1	6.9	None	IM nail	Midshaft	32	2
Sahin et al. (2019)[19]	2009–2017	69.6	5.1	8.6	Case by case	IM nail & plate	STN	8	2
							Midshaft	15	2
Rajput et al. (2019)[20]	2013–2018	68.6	1	5.9	None	IM nail	STN	9	0
							Midshaft	2	0
Rocos et al. (2018)[26]	2009–2013	71.0	> 1	NA	None	IM nail	STN	12	4
Donnelly et al. (2018)[9]	2010–2014	71.3	NA	NA	None	IM nail	STN	25	1
Miura et al. (2018)[32]	2010–2015	80.7	1.5	NA	Case by case	IM nail & plate	Midshaft	17	0
Yeh et al. (2017)[27]	2008–2014	70.2	> 1	4	Case by case	IM nail	STN	10	1
Phillips et al. (2017)[10]	2009–2014	71.6	3	8.3	None	IM nail	STN	12	2
Lee et al. (2017)[22]	2009–2014	70.1	1.8	5.1	Case by case	IM nail	STN	15	1
							Midshaft	31	1
Kim et al. (2017)[33]	2008–2015	NA	2.2	4.5	Case by case	IM nail	Midshaft	82	9
Cho et al. (2017)[11]	2005–2013	70.2	2.1	5.8	None	IM nail	STN	48	15
Park et al. (2017)[21]	2005–2016	73.6	1.2	7.6	NA	IM nail	STN	3	0
							Midshaft	27	0
Zenke et al. (2016)[23]	2010–2015	73	NA	6.1	Case by case	IM nail	STN	16	0
							Midshaft	18	0
Shin et al. (2016)[13]	2004–2014	77.9	1.4	6.1	NA	IM nail	STN	7	1
							Midshaft	8	0
Kulachote et al. (2016)[14]	2013–2014	67.0	1.9	8.2	NA	IM nail	STN	18	3
Schilcher (2015)[12]	2007–2013	78.0	NA	6.5	Case by case	IM nail	Midshaft	24	1
Miyakoshi et al. (2015)[15]	2006–2013	78.3	> 1	4.2	NA	IM nail & plate	Midshaft	37	1
Teo et al. (2014)[28]	2004–2009	67.5	1.9	4.9	NA	IM nail & plate	STN	30	5
Weil et al. (2011)[24]	2005–2009	73.0	NA	7.8	NA	IM nail & plate	STN	4	0
							Midshaft	8	0

PTH: parathyroid hormone, Fx: fracture, IM: intramedullary, STN: subtrochanteric nail, > 1: for a minimum of 12 month, NA: non-available.

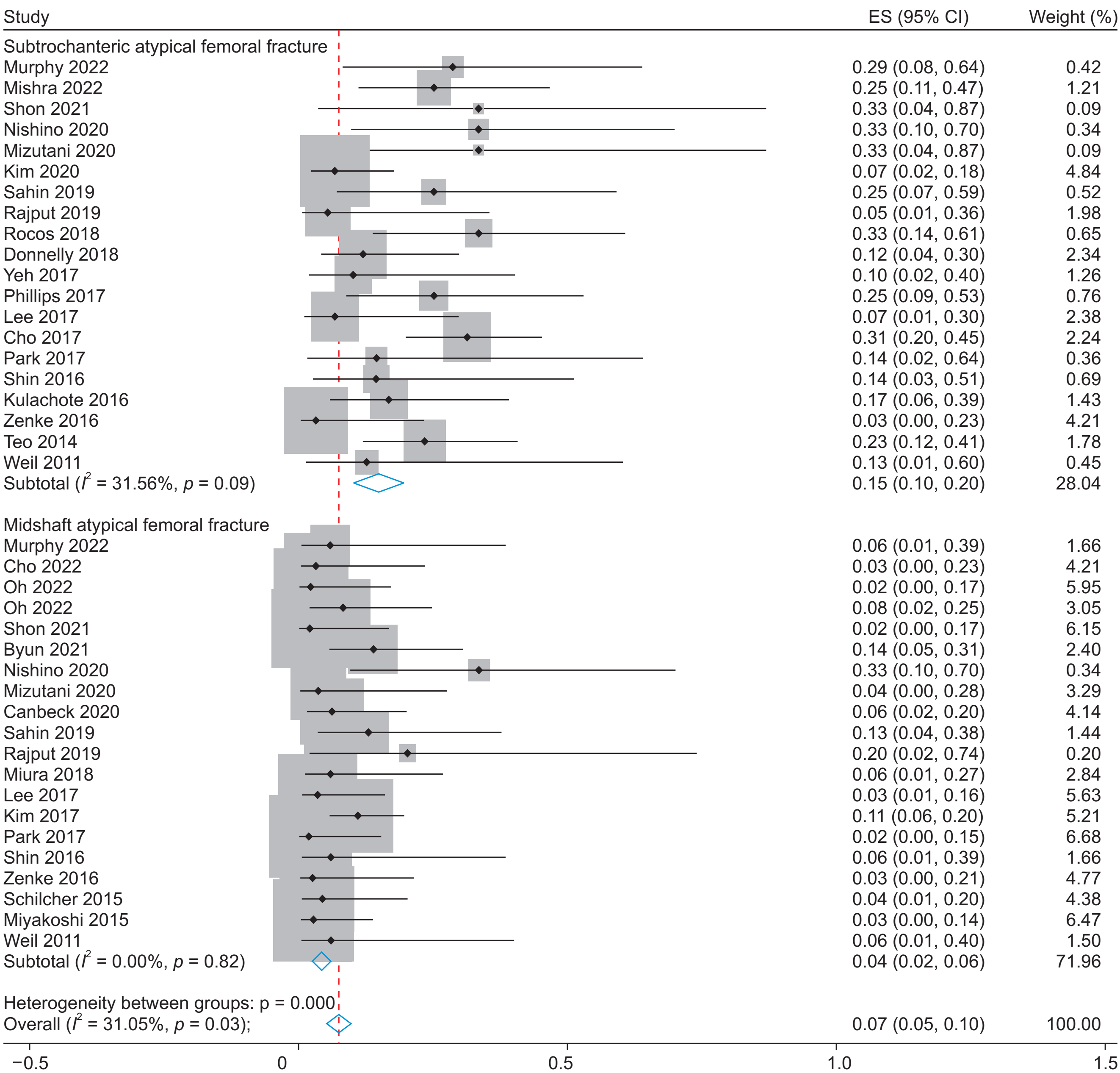

Fig. 2. The overall pooled incidence of nonunion was calculated using proportion meta-analysis. ES: effect size, CI: confidence interval.

Incidence of Nonunion According to Fixation Device

In proportion meta-analysis, the pooled prevalence of nonunion was 7% (95% CI, 5%–10%) from all studies; 7% (95% CI, 5%–10%) in IM nailing and 7% (95% CI, 2%–12%) in plate fixation. There was no difference in the nonunion rate between the 2 groups (I^2 = 86.5%, p = 0.873).

Meta-Regression

In meta-regression analysis, we found significant associations between the nonunion rate and patient mean age (coefficient: –0.0071, p = 0.010) (Fig. 3A), but not in the average duration of bisphosphonate use (coefficient: –0.0024, p = 0.744) (Fig. 3B).

Quality Assessment and Publication Bias

After evaluation of methodologic quality, the mean value of awarded stars was 6.4 (5 stars in 1 1 study, 6 stars in 15 studies, and 7 stars in 13 studies) (Supplementary Material 3). The Begg's funnel plot was symmetrical, and the p-values for bias were not significant for all outcomes (Fig. 4).

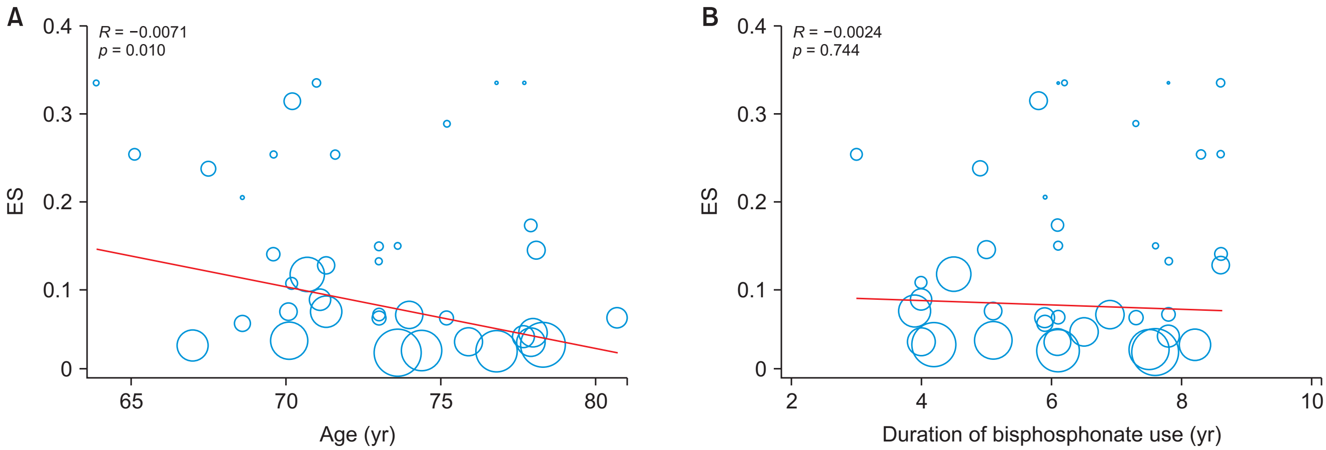

Fig. 3. Meta-regression plot for the occurrence of pelvic insufficiency fracture and continuous variables from each study. (A) The mean patient age. (B) The mean duration of bisphosphonate use. ES: effect size.

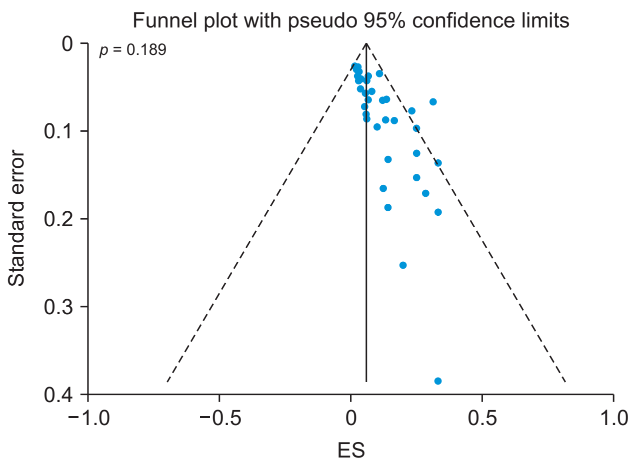

Fig. 4. The Begg's funnel plot and *p*-value by Egger's test showing publication bias. There was asymmetry, but no significant publication bias. ES: effect size.

DISCUSSION

This is the first study that estimated the incidence of nonunion in AFF through a meta-analysis and analyze it according to fracture location to provide basic information on nonunion rates to patients in future clinical practice. Our meta-analysis showed that the rate of nonunion differ significantly between subtrochanteric AFFs and midshaft AFFs: 15% (95% CI, 10%–20%) in subtrochanteric AFFs and 4% (95% CI, 2%–6%) in midshaft AFFs. The different union rates of these fractures can be explained by several factors.

First, AFFs known to occur at the maximal tensile loading area of femur curvature and AFFs occurring in the diaphyseal region of the femur, which is under maximal tensile loading, may have a better prognosis in terms of healing compared to those occurring in the subtrochanteric region, which may be subject to different mechanical stresses.[34-36] Second, the increased occurrence of varus malreduction and insufficient proximal 3-point fixation (involving lateral cortex engagement, tip contact at the greater trochanteric cortex, and a tip-apex distance of less than 25 mm) along with the influence of abduction force exerted by abductor muscles have been demonstrated to be more prevalent in subtrochanteric nail (STN) cases, thus contributing to these distinctions.[27,34,35] Third, the working length and the distance from the fracture to the interlocking screw in STN fractures treated with IM nails are shorter compared to midshaft fractures. This increase in nail-cortical bone engagement is more pertinent to the diaphysis rather than the subtrochanteric region.[6,15,28]

AFFs are known to heal poorly compared to typical femoral fractures and poor healing is partially attributed to the long-term use of bisphosphonates, which can suppress bone turnover.[37-39] In our meta-regression analysis, we did not find a clear-cut causality relationship between the duration of bisphosphonate use and nonunion rate in AFFs. Although bisphosphonates are known to have a relation to AFF, this may suggest that other factors play a greater role in the healing process of these fractures such as malreduction, which may decrease the contact area between the main fragments.[7,14,19] However, cessation of bisphosphonate after surgery of AFF should be recommended according to the guidelines of American Society for Bone and Mineral Research.[40]

Surgical implants or constructs used to repair AFF should cover all the femur and be durable enough to support the bone as it heals for an extended period compared to that in typical fractures. Although IM nailing is the currently preferred method for treating AFFs, the nonunion rate was almost similar between studies according to fixation devices with a pooled prevalence of nonunion of 7%. IM nailing offers benefits like better biomechanical stability and less stress on the hardware but IM nail insertion poses significant challenges when dealing with severely bowed or narrow femurs. Byun et al.[31)] found that postoperative malalignment was found in all cases of AFFs with severe bowing, so malreduction including fracture gap and distraction is not rare after nailing in subtrochanteric AFFs. Leg-length discrepancy resulting from femoral straightening and lengthening is also unavoidable when employing an IM nail.[41,42)]

Cho et al.[30)] demonstrated plate fixation can be beneficial with the tension band principle, which involves placing a plate on the lateral cortex of the femur, without comminution on the medial side, to facilitate fracture healing by converting tensile force into compressive force. Rocos et al.[26)] also highlighted that the lateral side of the atypical proximal femoral fractures should be considered a primary nonunion. They recommended a surgical approach involving the placement of an IM nail and lateral tension plate positioned just posterior to the nail on the lateral view at the fracture level to enhance the union of STN AFFs. However, plate fixation is also very challenging owing to the technical impracticability caused by the bowing of the femur, cortex thickening, and the inability to protect the entire femur.[43,44)] Lateral bowing of the femur was associated with difficulties in choosing the fixation material in AFF, so mastering one of them is essential for clinicians.[7,9,19,29)]

This study has limitations. Firstly, there are other potential factors to consider, including associated injuries, the extent of reduction, the presence of osteoporosis or obesity, and the curvature of the femur, which could not be included in the analysis. However, this is the first meta-analysis to estimate the nonunion rate of AFF after surgery. Second, due to a lack of information, nonunion rates based on recombinant-parathyroid hormone usage could not be analyzed.

In conclusion, there was significant difference in the nonunion rate between subtrochanteric AFF and midshaft AFF groups. Therefore, estimating the possibility of nonunion according to fracture site is critical for orthopedic surgeons in addition to understanding the biomechanical complexity and surgical challenges associated with AFF to improve outcomes.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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SUPPLEMENTARY MATERIAL

Supplementary material is available in the electronic version of this paper at the CiOS website, www.ecios.org.

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