Risk factors for fracture-related infection after open reduction and internal fixation of proximal humerus fractures: A multicenter retrospective study of 496 fractures

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Introduction: One of the complications of the surgical therapy for proximal humerus fractures is fracture-related infection (FRI). This multicenter study aimed to investigate the incidence of FRI and clarify the risk factors associated with FRI in patients receiving open reduction and internal fixation for proximal humerus fracture.

Material and Methods: Among 684 patients diagnosed as having proximal humerus fracture and who were treated by surgical therapy in 13 institutions (named TRON group) from 2015 through 2020, 496 patients (men, n = 134, women, n = 362; mean [SD] age, 68.5 [14.5] years; mean [SD] body mass index [BMI], 23.0 [4.4] kg/m^2) were included as subjects. Excluded were 188 patients due to less than 12 month's follow-up, patients who underwent osteosynthesis using neither plate nor nail and those with open fracture. We extracted the following as risk factors of FRI: sex, BMI, smoking status, diabetes, glenohumeral fracture dislocation, fracture classification, approach, implant, waiting period, type of anesthesia, operative time and blood loss during surgery. We conducted logistic regression analysis to investigate the risk factors of FRI using these

extracted items as explanatory variables and the presence or absence of FRI as the response variable.

Result: FRI occurred after surgery for proximal humerus fracture in 9 of the 496 patients (1.8%). The causative organism was methicillin-susceptible *Staphylococcus aureus* in 4 patients, *Pseudomonas aeruginosa* in one patient and *Enterococcus faecalis* in one patient. In the other 3 patients, causative organisms were not detected. The univariate analysis showed significant differences for present of glenohumeral fracture dislocation ($p = 0.004$). Logistic regression analysis showed glenohumeral fracture dislocation to be the significant explanatory factor for FRI (odds ratio 12.3, $p = 0.0375$).

Conclusion: This study revealed an infection rate following open reduction and internal fixation of proximal humerus fracture of 1.8% (9 patients) and that *Staphylococcus* was the most frequent causative organism. Glenohumeral fracture dislocation is a significant risk for postoperative FRI.

Introduction

In the elderly, proximal humerus fracture (PHF) is the third most frequent fracture after hip fracture and distal forearm fracture and the second most common fracture of the upper extremity. PHFs have been increasing, which could present significant harm to the aging population [1]. Several previous studies have reported an incidence rate of 82 per 100,000 person-years, with an increase of 13.7% annually [2-4].

Despite development of new implants and awareness of new biomechanical fracture characteristics for PHF, the complication rate remains stagnant at a high level [5]. Complications of open reduction–internal fixation (ORIF) of PHFs are reported in up to 45% of patients and include avascular necrosis, nonunion, malunion, nerve injury and infection. Fracture-related infection (FRI) is a serious complication because it may require the additional multiple operations, which lead to poor functional outcomes and lower patient satisfaction. [6] The rate of infection reportedly ranges from 0% to 18% [7-10] after surgery for PHF. These studies have suggested that several variables such as delay to treatment and skin preparation are causative factors. However, these cohorts had relatively small sample sizes and did not include radiographic evaluation of such items as fracture type and presence of a glenohumeral fracture dislocation.

The present multicenter study aimed to clarify 1) the incidence of postoperative FRI 2) the causative organism of FRI and 3) the risk factors associated with FRI in patients who received ORIF for PHF.

Subjects and Methods

This multicenter retrospective study used data obtained from the TRON (Trauma Research Group of Nagoya) database in which member hospitals have registered orthopedic trauma surgery cases or inpatient treatment annually since 2014. This database consists of patients' data obtained from 13 hospitals, which are associated with the department of orthopedic surgery of our university. Of the 13 hospitals, seven hospitals provide tertiary care. The other six hospitals are primary care hospitals located in rural areas of Japan. We collected cases of PHFs from this database that were treated surgically from 2015 through 2020. The study was conducted under the ethical standards of the responsible committee and the ethical principles of the 1975 Declaration of Helsinki. This study was approved by the ethics commission at each participating hospital (reference number: 2020-0564). We have also obtained informed consent from the patients for the publication of this study.

Subjects

The patients' background was collected from TRON database. We followed all patients every month until fracture union or until additional treatments were completed. We initially collected 684 cases. The exclusion criteria were (1) patients who underwent osteosynthesis using neither plate nor nail, (2) had an open fracture and (3) had less than 12 months' follow-up (Fig. 1).

Clinical evaluation

We recorded age, sex, body mass index, smoking status, diabetes, glenohumeral fracture dislocation [10-12], fracture classification (AO/OTA classification) [13], approach [12], implant type (nail or plate), waiting period, operative time and blood loss during surgery. We defined the waiting period as the period from the date of injury day to the date of surgery. The estimate blood loss values were obtained from the operative report in the patient record. The amount of blood loss was calculated from the change in the weight of the gauze and the total amount of blood aspirated during the surgery. To assess the functional results, we used University of California-Los Angeles (UCLA) shoulder rating scale at the last follow-up. The UCLA Shoulder Score is a jointly completed score, with both physician and patient completed portions. The UCLA score

system mainly grades five aspects: pain, function, active forward flexion, manual muscle testing (MMT), and patient satisfaction. Scores range from 0 to 35 with a score of 0 indicating worse shoulder function and 35 indicating better shoulder function. Its categories include "active forward flexion" (maximum of 5 points and physician completed), "strength of forward flexion" (maximum of 5 points and physician completed), "pain" (maximum of 10 points and patient completed), "satisfaction" (maximum of 5 points and patient completed), and "function" (maximum of 10 points and patient completed).[14]

Radiographic evaluation

For diagnosis and preoperative classification, X-rays in the true shoulder anteroposterior and oblique views were used, as well as CT scan when there was doubt regarding articular fracture involvement. The AO/OTA classification was also recorded for fracture type. We defined glenohumeral fracture dislocation as the complete displacement of head fragment from the glenoid fossa on CT [15] and the case of humeral fracture associated with dislocation of the glenohumeral joint. Displacement was defined as an angulation of >45° or a separation of >1 cm [16].

Surgical procedure

We have performed ORIF for PHFs patients with general anesthesia or scalene block anesthesia during surgery. According to the AO/ASIF principles of fracture repair, the patient was placed in the supine or half-sitting position and treated with ORIF. Intramedullary nail or locking plates were used for internal fixation.

Intramedullary nail: We used antegrade locking nails in our study. We used six kinds of implants: MultiLoc (Synthes GmbH, Oberdorf, Switzerland), T2 nail (Stryker, Mahwah, NJ, USA), ARISTO Proximal humeral nail (MDM, Shinjuku, Tokyo, Japan), POLARUS humeral nail (Acumed LLC, Portland, OR, USA), TRIGEN humeral nail (Smith & Nephew, Memphis, TN, USA), and the HAI humeral nail system (HOMS, Chino, Nagano, Japan). After skin incision, the supraspinatus tendon was split in a longitudinal direction, and the entry point for the nail was located along the axis of the humeral diaphysis, in the articular zone at the tip of the head. The medullary canal was opened using a cannulated awl or drill and a temporary K-wire was inserted. The nail was inserted until its proximal end was located approximately 5 mm under the subchondral zone of the humeral head, after which the K-wire was removed. Proximal and distal locking was performed using the aiming device, and the appropriate screws were inserted after drilling and length measurement.

Locking plates

While we used five kinds of implants were used: PHILOS (Synthes GmbH), AxSOS 3 Ti proximal humerus (Stryker), MODE proximal humeral plate (MDM), HAI proximal humeral plate system (HOMS), and NCB proximal humerus (Zimmer, Warsaw, IN, USA). After skin incision, fracture fragments were reduced using tension cords placed at the insertion site of the rotator cuff tendons. Additional temporary K-wires or an elevatorium was used if reduction of the humeral head was unstable. The plate was positioned about 1 cm under the tip of the greater tuberosity in the middle of the shaft. Afterwards, it was attached to the humeral diaphysis by a screw placed in the gliding hole after drilling and length measurement. The humeral head and the diaphysis were then stabilized with various locking screws as proposed by the plate manufacturer.

Antibiotic prophylaxis and skin preparation

All patients received prophylactic antibiotics immediately prior to surgery, and all hospitals used first-generation cephalosporins (1 g of cefazolin) as standard therapy, although some patients used other antibiotics due to allergic reactions or other reasons. Standard skin preparation with 1% povidone-iodine was performed in all patients.

Diagnosis of fracture related infection

We diagnosed the FRI according to the previous report described by Baertl et al. [17]. The diagnostic criteria 1) fistula or sinus tract, 2) purulent drainage or pus, 3) microbial growth in two or more deep tissue samples, 4) histological evidence of pathogens and inflammation in peri-implant tissue. [17]

The diagnosis of FRI was made by each surgeon. If the patients with PHF developed fever and deteriorated general condition, we suspected bacteremia and performed blood cultures. For diagnosis of FRI, all samples were collected at least three samples as tissue specimen. Initially, Gram staining was performed. Thus, these specimens were then cultured on 5% sheep blood and chocolate agar media under aerobic conditions with 5% carbon dioxide, bromothymol blue lactate (BTB) agar medium under anaerobic conditions. CNA blood agar medium was used for Staphylococcus aureus. When methicillin-resistant Staphylococcus aureus (MRSA) is suspected, the MRSA strains were examined with oxacillin and cefoxitin disks. MRSA was then validated by detection of the mecA gene. In most cases, the incubation period was 3 days, but in negative cases, long-term incubation was done for 7 days.

Statistical analysis

Categorical variables were analyzed by Fisher's exact test. Continuous variables with normal distribution were analyzed by *t*-test, and those with non-normal distribution were analyzed by the Mann-Whitney U Test. Subsequently, using logistic-regression analysis, the risk factors were identified with the presence or absence of infection as the response variable and with all factors examined in this study as the explanatory variables. The fracture types were grouped into A, B, and C fracture sites for analysis due to the small number of cases of infection. A p-value of <0.05 was considered to indicate statistical significance. Statistical analysis was conducted with the use of EZR software version 1.40 (Jichi Medical University, Tochigi Prefecture, Japan).[18]

Results

Patient backgrounds are shown in Table 1. In this cohort of 496 patients, the mean age at surgery was 68.5 years (SD, 18.5 years; range, 18–95 years), and 362 patients (74.0%) were women. The mean follow-up period was 28.5 months (range, 12–80 months). FRI occurred in 9 of the 496 patients (1.8%) after surgery for PHFs. Among the 9 cases of acute infection, only 5 needed a second surgery (5/496, 1.0%). All FRI occurred within 90 days.

The causative organism was methicillin-susceptible *Staphylococcus aureus* (MSSA) in 4 patients and *Pseudomonas aeruginosa* and *Enterococcus faecalis* in one patient each. In the other patients, causative organisms were not detected, or they were unknown.

When factors related to the FRI were examined, the results of univariate analysis showed significant differences for glenohumeral fracture dislocation ($p = 0.004$). Thus, we identified the glenohumeral fracture dislocation is an independent risk factor for FRI using logistic regression analysis (odds ratio 12.3, 95% confidence interval: 1.16–131), $p = 0.0375$) (Table 3). Surgical factors including implants and approach, as well as patient-specific background factors such as age, sex, body mass index, smoking status, and diabetes were not significant risk factors. (Table 3)

Discussion

We retrospectively analyzed the relationship between patient background and FRI in 496 patients. The study revealed an FRI rate of 1.8% (9 patients), that *Staphylococcus* was the most frequent causative organism, and that glenohumeral fracture dislocation was significantly related to an increased risk of FRI.

This result is similar to the rates of infection reported in the literature of 0% to 8% depending on the techniques and criteria used to define infection [8-10,19]. The incidence of FRI after surgical treatment for PHF may be relatively low.

In a report of 259 cases, the most common causative bacteria were polymicrobial and then *S. aureus* [6]. We thus think that staphylococcal infection should be considered first when infection is observed. While three cases (33%) causative organisms were not detected. Microbiology cultures are currently the gold standard for the identification of pathogens and the diagnosis of FRI. It is estimated that 10% of FRI are culture negative [20] To culture the slower growing organisms, cultures should obtain at least 5 samples and continue for 10–14 days. [21-23] Recently, it has been highlighted that *Cutibacterium acnes* (*C. acne*) is the common pathogen in shoulder surgery. Both et al. reported that 27 of 34 samples grew *C. acne* from their removed clavicle plate.[84] Kajita et al. also demonstrated that a high detection rate of C. acnes was observed in male skin for open shoulder surgery including ORIF. [25] Recent studies have shown that a longer incubation period (9 days longer) results in a higher detection rate of *C. acnes*. [26] In our cohort, we did not have cultures targeting *C. acne*. It is possible that the *C. acne* might be the cause of FRI in the "Negative" patients.

We showed that glenohumeral fracture dislocation was the independent risk factor for FRI. Conversely, age, sex, body mass index, smoking status, diabetes, fracture type, operative approach, implant type (locking plate or intramedullary nail), waiting period, operation time were not significant risk factors for FRI. Glenohumeral fracture dislocation causes massive damage to the surrounding tissues, including blood vessels. Previous studies identified an ascending branch of the anterior circumflex artery as providing the humeral head with blood supply [27,28]. Glenohumeral fracture dislocation can lead to injury of these peripheral vascular vessels. This may lead to make hematoma. A previous report suggest hematoma formation after shoulder surgery is often accompanied by infection.[29]

Blonna et al. reported that the washing the shoulder with chlorhexidine gluconate and the use of first-generation cephalosporin antibiotics are effective in preventing infection in shoulder surgery for PHF.[7] In addition, we have identified dislocated-humeral head on radiographic as an additional risk factor in the patient background. Care bundles in infection prevention and safety are simple sets of evidence-based practices. The bundling of our findings with those of the past will help us to prevent the FRI on the PHF.

This study has some limitations. First, this study is a retrospective case review, and thus, selection bias should be considered. Second, we excluded about 20% of the patients due to loss to follow-up, and thus, the number of infections may be underestimated. Third, the follow-up period is relatively short. Forth, we also performed surgical treatment for patients without glenohumeral fracture dislocation. This wider indication for surgery may have affected the results. Fifth, it is known that sonication of retrieved implants during surgical revision is important in modern diagnosis of FRI. [30] A separate study examined the diagnostic yield of sonication of explanted prosthetic or fracture fixation devices and found that sensitivity improved from 87% to 100% when sonification fluid was placed in blood culture bottles [31] .We did not used sonication for diagnosis of FRI. This would be a major limitation of our study and explain the high number of culture-negative infections.

Conclusions

The rate of postoperative wound infection in patients with a closed PHF was 1.8%. MSSA was the most frequent causative organism, and glenohumeral fracture dislocation is a significant risk for postoperative FRI.

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Introduction: One of the complications of the surgical therapy for proximal humerus fractures is fracture-related infection (FRI). This multicenter study aimed to investigate the incidence of FRI and clarify the risk factors associated with FRI in patients receiving open reduction and internal fixation for proximal humerus fracture.

Material and Methods: Among 684 patients diagnosed as having proximal humerus fracture and who were treated by surgical therapy in 13 institutions (named TRON group) from 2015 through 2020, 496 patients (men, n = 134, women, n = 362; mean [SD] age, 68.5 [14.5] years; mean [SD] body mass index [BMI], 23.0 [4.4] kg/m^2) were included as subjects. Excluded were 188 patients due to less than 12 month's follow-up, patients who underwent osteosynthesis using neither plate nor nail and those with open fracture. We extracted the following as risk factors of FRI: sex, BMI, smoking status, diabetes, glenohumeral fracture dislocation, fracture classification, approach, implant, waiting period, type of anesthesia, operative time and blood loss during surgery. We conducted logistic regression analysis to investigate the risk factors of FRI using these

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Conclusion: This study revealed an infection rate following open reduction and internal fixation of proximal humerus fracture of 1.8% (9 patients) and that *Staphylococcus* was the most frequent causative organism. Glenohumeral fracture dislocation is a significant risk for postoperative FRI.

Table1

Table 1

Patient demographics.

	Infection (n=9)	Non-infection (n=487)	P value
Age, mean (SD)	72.6 (4.4)	68.5 (14.5)	0.150
Sex, n (%)			
Male	3 (33.3)	131 (26.9)	0.708
Female	6 (66.7)	356 (73.7)	
Body mass index, kg/m^2 (SD)	21.7 (4.4)	23.3 (4.3)	0.361
Smoking status, yes (%)	1 (11.1)	95 (19.5)	1.000
Diabetes, yes (%)	3 (33.3)	104 (21.4)	0.708
Glenohumeral fracture dislocation , yes (%)	3 (33.3)	17 (3.4)	0.004*
AO/OTA classification, n (%)			0.006
11A1	0(0)	1 (0.2)	
A2	5 (55.6) †	145(29.8)	
A3	0 (0)	71 (14.6)	
11B1	2(22.2)	66 (13.6)	
B2	0(0)	90(18.5)	
B3	0(0)	4(0.8)	
11C1	0(0)	42(8.6)	
C2	0(0)	53(10.9)	
C3	2(22.2)	15(3.1)	
Approach (%)			0.459
Deltoid split	5 (55.6)	345 (73.9)	
Deltopectoral	4 (44.4)	142 (26.1)	
Implant			0.896
Nail/Plate, n (%)	5 (55.6)/4 (44.4)	168(34.5)/319(65.4)	
Waiting period, d (SD)	11.2 (11.9)	8.3 (16.9)	0.601
Operative time, min (SD)	120.89 (59.2)	120.61 (59.3)	0.989
Blood loss during surgery, mL (SD)	244.6 (230.49)	113.9 (140.7)	0.007

*P＜0.05, † Humeral fracture associated with dislocation of the glenohumeral joint

Table2

Table 2

Details of the infected patients

Patient No.	Sex	Age (years)	Comorbidity	AO/ OTA	glenohumeral fracture dislocation	Operation Time (min)	Surgery	Waiting period	Culture result	Treatment	Last UCLA score	prognosis
1	F	63	None	11-A2	No	133	Locking plate	12	MSSA	Open debridement and plate removal	13	Complete recovery
2	F	85	None	11-A2	No	74	Intramedullary nail	7	MSSA	Antibiotics	15	Complete recovery
3	M	68	Hepatitis B Liver Cirrhosis	11-B1	No	57	Locking plate	4	Negative	Open debridement and plate removal	28	Complete recovery
4	M	74	Diabetes	11-C3	Yes	230	Locking plate	6	Negative	Open debridement and plate removal	13	Head Osteotomy
5	F	70	Diabetes	11-A2	No	79	Intramedullary nail	9	MSSA	Open debridement and plate removal	13	Complete recovery
6	F	74	None	11-A2	No	78	Intramedullary nail	5	Negative	Antibiotics	16	Osteonecrosis
7	F	83	None	11-B1	Yes	124	Intramedullary nail	5	*Pseudomonas aeruginosa*	Open debridement and plate removal	15	Complete recovery
8	F	59	None	11-C3	Yes	271	Locking plate	11	MSSA	Antibiotics	13	Complete recovery
9	M	77	Cerebral infarction	11-A2	No	199	Locking plate	12	*Enterococcus faecalis*	Antibiotics	20	Complete recovery

Table 3

Risk factors of infection by multiple regression analysis

	Odds ratio (95% confidence interval)	P value	VIF
Age	1.06 (0.98, 1.14)	0.14	1.07
Sex			1.11
Male	1 (Ref)		
Female	0.41 (0.06, 2.53)	0.34	
Body mass index	0.89 (0.73, 1.09)	0.28	1.21
Smoking status			1.14
No	1 (Ref)		
Yes	0.34 (0.05, 2.46)	0.29	
Diabetes		0.09	1.08
No	1 (Ref)		
Yes	3.57 (0.81, 15.6)		
Glenohumeral fracture dislocation			1.36
No	1(Ref)	0.0375*	
Yes	12.3(1.16, 131.0)		
AO/OTA classification			1.22
11A	1 (Ref)		
11B	0.30 (0.26, 3.10)	0.32	
11C	0.77 (0.04, 5.20)	0.70	
Approach		0.52	1.49
Deltoid split	1 (Ref)		
Deltopectoral	0.47 (0.05, 4.43)		
Implant			1.40
Locking plate	1 (Ref)		
Intramedullary nail	0.32(0.05, 2.01)	0.12	
Waiting period	1.01 (0.99, 1.03)	0.22	1.05
Anesthesia			
General	1	0.90	1.02
Scalene block	0.92 (0.88, 1.10)		
Operative time	0.99 (0.97, 1.01)	0.10	2.51
Blood loss during surgery	1.00 (0.99, 1.01)	0.08	2.51

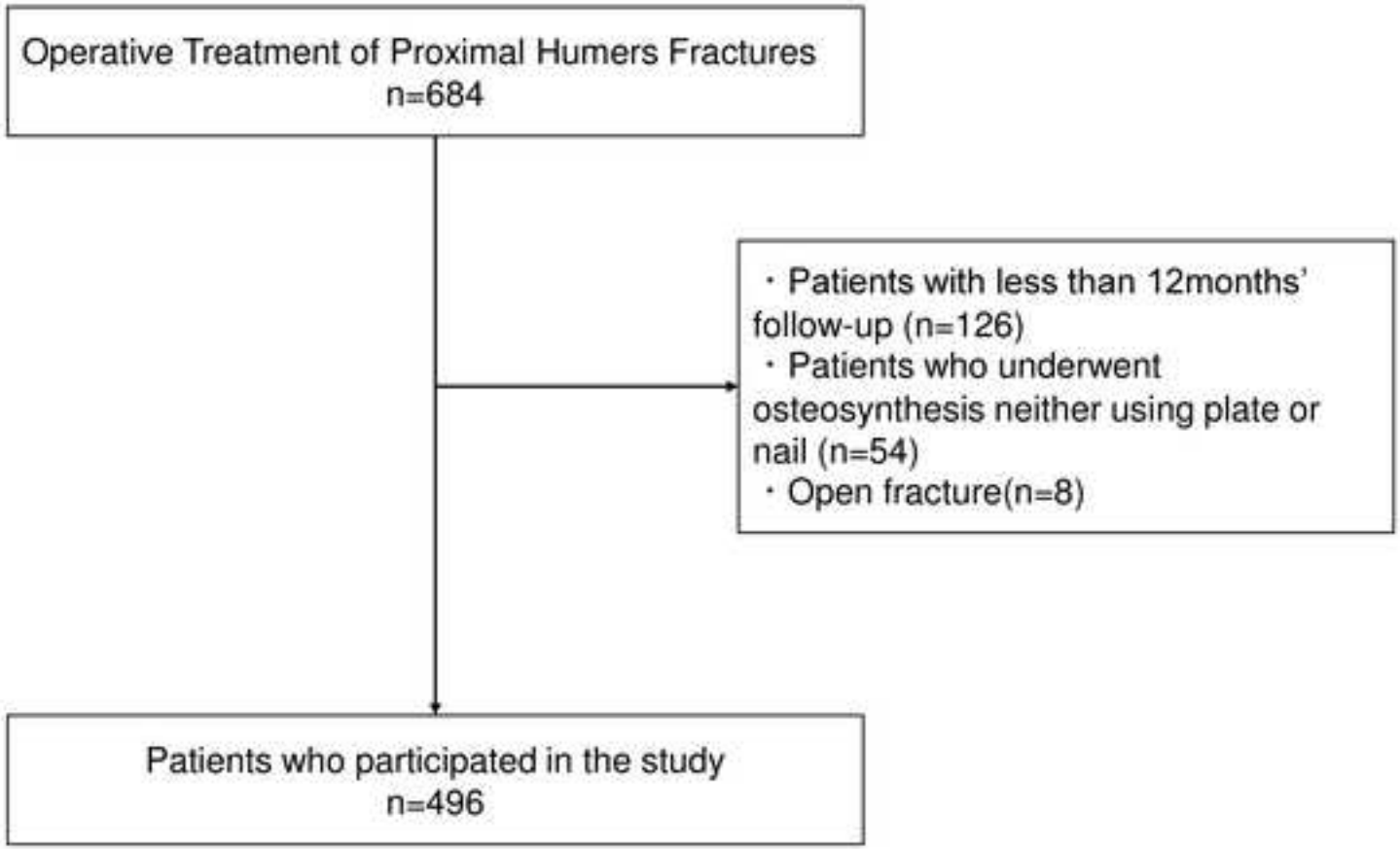
VIF, variance inflation factor.

*P<0.05

Figure legend

Fig1. Patient Flowchart

Figure1


Operative Treatment of Proximal Humers Fractures
n=684
・Patients with less than 12months' follow-up (n=126)
・Patients who underwent osteosynthesis neither using plate or nail (n=54)
・Open fracture(n=8)
Patients who participated in the study
n=496