

# Incidence of and risk factors for the development of asymptomatic heterotopic ossification after elbow fracture fixation

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## Abstract

**Objective:** This study was performed to investigate the incidence of and risk factors for asymptomatic heterotopic ossification (HO) after open reduction and internal fixation of elbow fractures.

**Methods:** This retrospective analysis involved 197 patients with elbow fractures treated operatively from 2014 to 2017 at our institution. Patient-related and clinical variables were recorded. Univariate analysis and multivariate logistic regression were performed to reveal independent risk factors for postoperative HO. In addition, a receiver operating characteristic (ROC) curve was performed to assess the ability of risk factors to predict the development of postoperative HO.

**Results:** The overall rate of asymptomatic HO after surgery was 18.78%. The incidence was highest in terrible triad injuries and lowest in capitellum fractures. Independent predictors of asymptomatic HO identified by the multivariate analysis were underlying diseases, fracture dislocation, and a prolonged operative time. The area under the ROC curve for underlying diseases, fracture dislocation, and a prolonged operative time were 0.593, 0.596, and 0.694, respectively.

**Conclusions:** The incidence of postoperative asymptomatic HO in patients with elbow fractures is high. Clinicians should employ prophylaxis to avoid HO when treating patients with elbow fractures who have underlying diseases, fracture dislocation, or a prolonged operative time.

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**Keywords**

Heterotopic ossification, elbow fracture, incidence, risk factors, fracture dislocation, operative time

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**Introduction**

Heterotopic ossification (HO) is defined as abnormal formation of mature lamellar bone in soft tissues. It is a common complication following surgical treatment of elbow fractures, occurring at an incidence of 7% to 62%.<sup>1,2</sup> If symptomatic, HO may cause postoperative pain, joint swelling, poor functional outcomes, and the need for secondary surgical procedures.<sup>3</sup> Although the etiology of HO is not fully understood, HO prophylaxis has been advocated for patients after open reduction and internal fixation (ORIF) for elbow fractures. Nonsteroidal anti-inflammatory drugs (NSAIDs) and radiotherapy are two effective treatments. However, both NSAIDs and radiotherapy may cause adverse events. Prolonged use of NSAIDs has been linked to gastrointestinal complications. Radiotherapy may induce malignancy, impaired fracture healing, and cause infertility.<sup>4</sup> Therefore, a more comprehensive understanding of the risk factors for HO could be helpful when screening patients who would benefit from HO prophylaxis.

Postoperative HO is typically asymptomatic and incidentally detected on postoperative radiographs.<sup>4</sup> Some previous studies have assessed risk factors for symptomatic HO after elbow fracture operations and identified dislocation/no dislocation,<sup>5</sup> compound/closed fracture,<sup>5</sup> fracture type,<sup>2,6</sup> and time from injury to surgery.<sup>1,5,6</sup> To the best of our knowledge, however, no study has focused on the risk factors for asymptomatic HO. In the present study,

we investigated the incidence of and risk factors for asymptomatic HO after elbow fracture surgery and compared our results with those of previous similar studies.

**Methods**

From March 2014 to March 2017, 291 patients with elbow fractures were treated surgically at our institution. The inclusion criteria were as follows: at least 18 years of age at the time of injury, treatment of elbow fractures with ORIF, absence of accompanying fractures, and at least 3 months of follow-up. We excluded patients younger than 18 years because of the likelihood that HO development differs between skeletally immature and skeletally mature patients.<sup>5</sup>

The patients' electronic medical records and radiographic examinations were reviewed. Demographic data included age, sex, body mass index, American Society of Anesthesiologists class, fracture side (left or right), fracture site, open fracture, underlying diseases (e.g., diabetes, cardiovascular disease, immune disorders), presence of associated dislocation, duration from injury to operation, number of surgeons, type of internal fixation (tension band or plate-screw fixation), operative time, and intraoperative blood loss. The time interval to the procedure was calculated from the date of injury to the date of surgery. Postoperative anteroposterior and lateral elbow radiographs were evaluated at 6 and 12 weeks after discharge. All elbow radiographs and reports were independently

analyzed by two authors (Zhang Zitao and Zhang Yan). In cases of disagreement, a third author (Chen Yixin) was involved.

The fractures were classified as previously described with slight modifications.<sup>5</sup> The *Arbeitsgemeinschaft für Osteosynthesefragen* (AO) classification system<sup>7</sup> was used to characterize fractures of the distal humerus: extra-articular, partial articular, and complete articular fractures. Because of insufficient categorization of proximal forearm fractures in the AO classification system, we used the following descriptive terms for combined fractures of the proximal radius and ulna: olecranon fractures, radial head fractures, Monteggia injuries, and terrible triad injuries. Terrible triad injuries were defined as ulnohumeral dislocation with associated fractures of the radial head and coronoid process.

### **Ethics statement**

The study was approved by the Ethics Committee of the Affiliated Drum Tower Hospital of Nanjing University Medical School. Written informed consent was obtained from all patients before treatment commenced.

### **Statistical analyses**

Statistical analysis was performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Univariate logistic regression was performed to examine the association between potential risk factors and HO outcomes. Categorical variables were compared using the chi-squared test, and continuous variables were compared using the independent-samples Student's t-test. Risk factors in the univariate analysis that exhibited associations with HO (defined as  $p < 0.05$ ) were subsequently entered into a multivariable logistic regression model to identify independent risk factors for the development of HO. The effects of risk factors on

postoperative HO were analyzed by a receiver operating characteristic (ROC) curve. Statistical significance was set at  $p < 0.05$ .

## **Results**

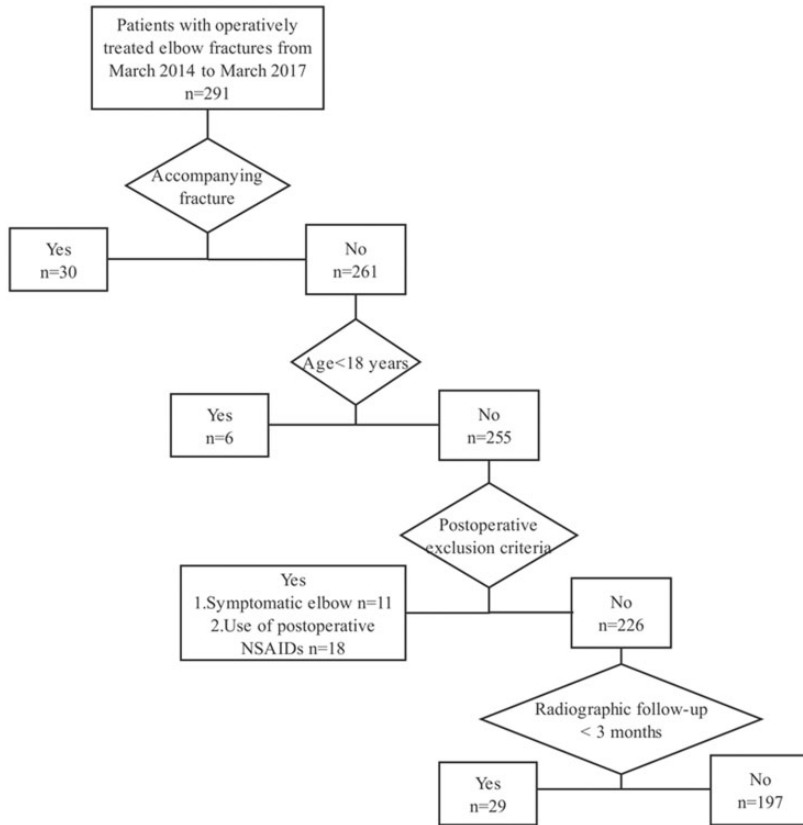
### **Patients and incidence of HO**

In total, 291 patients underwent surgical treatment of elbow fractures during the study period. Thirty patients were excluded because of accompanying fractures, and 6 were excluded because they were younger than 18 years. Eleven patients who complained of symptomatic complications were not involved in the study. Postoperative NSAIDs were used in 18 patients. Finally, 29 patients with less than 3 months of radiographic follow-up were excluded. Therefore, 197 patients remained (Figure 1).

Of the 197 patients who met inclusion criteria, the mean age at injury was  $42.33 \pm 17.06$  years and 45.69% were female. Fracture dislocation was present in 28 patients (14.21%). The mean time from injury to definitive fixation was  $7.42 \pm 4.53$  days. The mean operative time was  $102.88 \pm 53.06$  minutes. The incidences of HO according to different fracture types are shown in Table 1. Of the 197 enrolled patients, 37 (18.78%) developed asymptomatic HO. The incidence was highest in patients with terrible triad injuries, followed by lateral/medial condyle fractures of the humerus and intercondylar fractures of the humerus. The incidence was lowest in patients with capitulum fractures.

### **Univariate analysis of risk factors for HO**

Among the categorical variables, underlying diseases and fracture dislocation were identified as risk factors for asymptomatic HO ( $p < 0.05$ ). No significant associations



**Figure 1.** Flowchart showing the process by which patients were included and excluded in our study. NSAIDs, nonsteroidal anti-inflammatory drugs.

**Table 1.** Incidence of heterotopic ossification by fracture type.

Fracture types	Cases, n	Total fractures, n	Incidence (%)
Humeral supracondylar	2	14	14.28
Lateral/medial humeral condyle	6	18	33.33
Capitellum of humerus	0	4	0.00
Intercondylar fractures of humerus	5	16	31.25
Isolated olecranon	8	72	11.11
Isolated radial head	5	40	12.50
Coronoid process	7	23	30.43
Monteggia	1	4	25.00
Terrible triad	3	6	50.00
Total	37	197	18.78

were observed between asymptomatic HO and sex, side of fracture, American Society of Anesthesiologists class, open fracture, or type of internal fixation (Table 2).

**Table 2.** Univariate analysis of risk factors for heterotopic ossification (categorical variables).

Factor	HO (n)	No HO (n)	Statistical value
Sex			
Male	23	84	$\chi^2 = 1.131$ $p = 0.288$
Female	14	76	
Side			
Left	20	81	$\chi^2 = 0.141$ $p = 0.707$
Right	17	79	
Combined dislocation			
Yes	11	17	$\chi^2 = 8.995$ $p = 0.003^*$
No	26	143	
Underlying diseases			
Yes	18	48	$\chi^2 = 4.691$ $p = 0.030^*$
No	19	112	
ASA class			
II	32	142	$\chi^2 = 0.010$ $p = 0.918$
III	5	18	
Open fracture			
Yes	8	24	$\chi^2 = 0.968$ $p = 0.325$
No	29	136	
Type of internal fixation			
Tension band	4	46	$\chi^2 = 5.687$ $p = 0.058$
Plate-screw	21	80	
Screw	12	34	

\* $p < 0.05$ , statistically significant.

HO, heterotopic ossification; ASA, American Society of Anesthesiologists.

The analysis of continuous variables is shown in Table 3. The mean operative time in patients with and without asymptomatic HO was  $127.32 \pm 56.35$  and  $97.23 \pm 50.79$  minutes, respectively ( $p < 0.05$ ). The trend toward a higher risk of asymptomatic HO was significant among patients with longer operative times. The presence of ectopic bone was not associated with age, height, weight, duration from injury to operation, number of surgeons, or intraoperative blood loss. All three factors displaying significance at  $p < 0.05$  in the univariate analysis were included in the multivariate analysis.

### Multivariate analysis of risk factors for HO

As shown in Table 4, underlying diseases (odds ratio [OR] = 2.473, 95% confidence interval [CI] = 1.127–5.424,  $p = 0.024$ ), fracture dislocation (OR = 3.600, 95% CI = 1.420–9.129,  $p = 0.007$ ), and a prolonged operative time (OR = 4.670, 95% CI = 1.956–11.149,  $p = 0.001$ ) remained statistically significant and were therefore identified as independent risk factors for asymptomatic HO.

### ROC curve of risk factors for HO

The areas under the ROC curve for underlying diseases, fracture dislocation, and

**Table 3.** Univariate analysis of risk factors for heterotopic ossification (continuous variables).

Factor	HO (n)	No HO (n)	t value	p value
Age, years	$40.70 \pm 17.48$	$42.71 \pm 16.99$	0.643	0.521
BMI, $\text{kg}/\text{m}^2$	$21.95 \pm 3.20$	$22.70 \pm 2.57$	1.525	0.129
Duration from injury to operation, days	$8.11 \pm 5.45$	$7.26 \pm 4.28$	1.024	0.307
Number of surgeons	$3.97 \pm 0.79$	$4.97 \pm 0.80$	0.655	0.513
Operative time, minutes	$127.32 \pm 56.35$	$97.23 \pm 50.79$	3.181	0.002*
Intraoperative blood loss, mL	$114.86 \pm 133.26$	$110.28 \pm 130.99$	0.191	0.849

Data are presented as mean  $\pm$  standard deviation.

\* $p < 0.05$ , statistically significant.

HO, heterotopic ossification; BMI, body mass index.

**Table 4.** Multivariate logistic regression analysis of risk factors for heterotopic ossification.

Factor	$\beta$	Standard error	Wald $\chi^2$	p	OR	95% CI
Underlying diseases	0.905	0.401	5.105	0.024*	2.473	1.127–5.424
Combined dislocation	1.281	0.475	7.279	0.007*	3.600	1.420–9.129
Operative time	1.541	0.444	12.051	0.001*	4.670	1.956–11.149

\*p < 0.05, statistically significant.

**Table 5.** Results of ROC analysis of risk factors for heterotopic ossification.

Factor	Cutoff point	Sensitivity (%)	Specificity (%)	AUC	PPV (%)	Asymptomatic 95% CI (lower–upper bound)
Underlying diseases	0.186	70.0	48.6	0.593	23.9	0.489–0.697
Combined dislocation	0.191	89.4	29.7	0.596	22.7	0.487–0.704
Operative time, minutes	72.414	44.4	91.9	0.694	55.9	0.609–0.778
Underlying diseases + combined dislocation + operative time		55.0	86.5	0.744	48.5	0.664–0.823

AUC, area under the receiver operating characteristic curve; PPV, positive predictive value; ROC, receiver operating characteristic; CI, confidence interval.

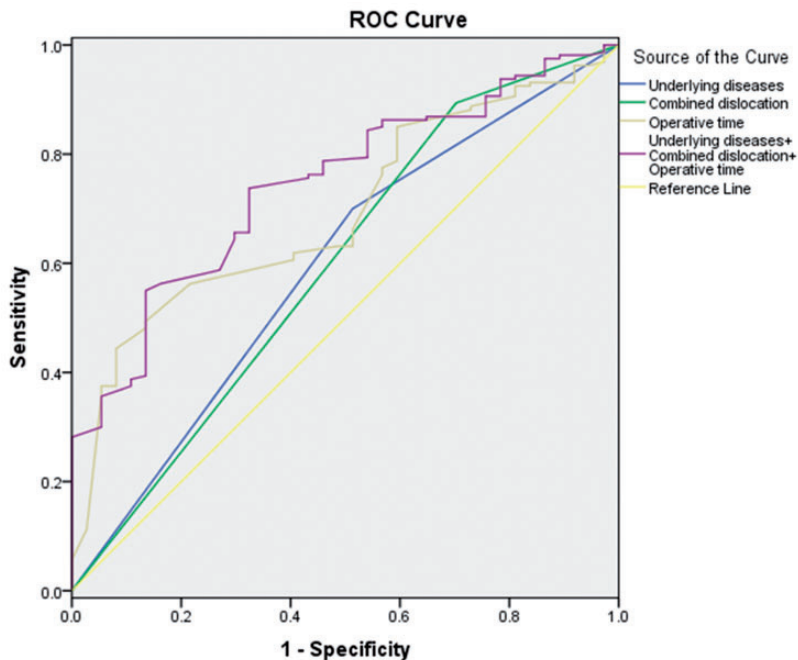
operative time were 0.593 (95% CI = 0.489–0.697), 0.596 (95% CI = 0.487–0.704), and 0.694 (95% CI = 0.609–0.778), respectively. Using a cutoff operative time of 72.41 minutes, the sensitivity, specificity, and positive predictive value were 44.4%, 91.9%, and 55.9%, respectively. Finally, underlying diseases, fracture dislocation, and operative time were combined with logistic regression in the ROC analysis. The sensitivity, specificity, positive predictive value, and area under the curve were 55.0%, 86.5%, 48.5%, and 0.744 (95% CI = 0.664–0.823), respectively (Table 5, Figure 2).

## Discussion

HO after surgical management of elbow fractures is a postoperative complication that may result in elbow stiffness. The incidence of HO after elbow fractures varies from 7% to 62% according to recent publications.<sup>1,2</sup> In the present study, the incidence of asymptomatic HO was 18.78%

(37/197) following surgical treatment of elbow fractures or fracture dislocation at the final follow-up. Race, multitudinous classified methods, various relevant risk factors, and exclusion of symptomatic HO may account for the difference in the prevalence between our study and other reports. We found the highest incidence of HO in terrible triad injuries (50%) and the lowest in capitellum fractures (0%). This finding is similar to an earlier study in which the incidence of HO in terrible triad injuries was 58.3%.<sup>5</sup>

The risk factors related to HO following elbow injuries have been evaluated in several series, but the risk factors remain uncertain among these studies.<sup>1,2,5,6,8–10</sup> One of the most recent studies by Hong et al.<sup>5</sup> identified fracture dislocation and delayed surgery as potential risk factors for the development of ectopic bone. In a series of 786 patients, Bauer et al.<sup>1</sup> also demonstrated that waiting more than 8 days after injury significantly increased the risk of HO after surgical repair of elbow fractures. In



**Figure 2.** ROC curves for optimal cutoff values of risk factors. ROC, receiver operating characteristic.

addition to delayed surgery, distal humeral fractures may also be associated with an increased risk.<sup>2</sup> Sustaining a severe elbow injury has been demonstrated to be a risk factor for Brooker class 3 or 4 HO.<sup>6</sup> The method of fracture fixation is also a risk factor for the development of ectopic bone after surgery for distal humeral fractures.<sup>8</sup>

In the current study, we examined the incidence of and risk factors for asymptomatic HO after ORIF of elbow fractures. Three significant risk factors were identified: underlying diseases, fracture dislocation, and prolonged operative time.

Our results indicated that fracture dislocation was strongly associated with the presence of HO after ORIF for elbow fractures. This is consistent with the results of previous studies (Table 6). Foruria et al.<sup>9</sup> examined 130 patients with elbow fractures and noted a 10-times higher risk of HO in patients who presented with elbow

dislocation or subluxation. Similarly, Shukla et al.<sup>10</sup> found postoperative HO in 12 of 28 (43%) elbows of patients with fracture-dislocation. The authors pointed out that the incidence of HO was much greater in patients who underwent multiple reduction maneuvers preoperatively (78%) than in patients who underwent only one maneuver (31%). They concluded that multiple closed reduction maneuvers before definitive surgical management had an obvious effect on the formation of postoperative HO.<sup>10</sup>

In the current study, we found that patients who developed postoperative HO had significantly longer operative times. Additionally, the best cutoff point of 72.41 minutes for prediction of postoperative HO had a low sensitivity of 44.4% but a high specificity of 91.9%. After reviewing the literature concerning HO in orthopedic trauma, we found that the impact of the

**Table 6.** Summary of studies examining risk factors for heterotopic ossification following elbow trauma.

Study	Year	n	Follow-up (months)	Incidence (%)	Risk factors
Bauer et al. <sup>1</sup>	2012	786	>1	7.00	1) Longer time to surgery 2) Longer time to postoperative mobilization
Abrams et al. <sup>2</sup>	2012	89	6	61.80	1) C3 fracture type 2) Distal humeral fractures
Hong et al. <sup>5</sup>	2015	124	6	30.65	1) Fracture dislocation 2) Longer time to surgery
Douglas et al. <sup>6</sup>	2012	156	3	39.74	1) Severe elbow injury 2) Delay from injury to ORIF
Shukla et al. <sup>10</sup>	2015	28	14	42.86	1) Multiple closed reduction maneuvers
Current study	2018	197	>3	18.78	1) Underlying diseases 2) Fracture dislocation 3) Prolonged operative time

ORIF, open reduction and internal fixation.

operative time has been poorly studied. Our results are consistent with those in other studies showing an increased risk of surgical site infection following orthopedic surgery.<sup>11</sup> Spinarelli et al.<sup>12</sup> stated that HO was more likely in the setting of edema or muscle necrosis. We speculate that a prolonged operative time might induce greater destruction of soft tissues and increased swelling around the elbow, both of which could increase the incidence of HO. Using radiographic and clinical features, surgeons can obtain a more thorough understanding of fracture characteristics, allowing them to establish well-prepared preoperative plans and thus achieve a lower operative time.

Relatively few reports have focused on the associations between underlying diseases and HO after surgical repair of elbow fractures. We identified underlying diseases as an independent risk factor for developing asymptomatic HO. In the present study, the incidence of HO was much higher in patients with than without underlying diseases. In contrast, Abrams et al.<sup>2</sup> found that medical comorbidities did not play a significant role in postoperative HO development. However, they did not clarify

what the pre-existing diseases were in their study. In our analysis, because of the wide variety of underlying diseases, the small sample in each subgroup sorted by underlying diseases prevented us from determining the significance of every disease. Further studies are therefore needed.

Several investigators have confirmed that the formation of heterotopic bone following elbow fracture is correlated with delayed surgery.<sup>1,13</sup> Bauer et al.<sup>1</sup> found an independent association between the number of days from injury to first surgery and the development of HO, whether analyzed continuously or categorically. In a retrospective study by Hong et al.,<sup>5</sup> patients with a >1-week delay to surgery had nearly 10 times the odds of having radiographic HO. In addition, Elhassan et al.<sup>14</sup> demonstrated that a >3-week delay until surgery was associated with a 50% higher risk of developing HO. In contrast, we did not find that the time to the operative intervention was significantly correlated with postoperative HO outcomes. Despite this, we do not deny that the time between injury and surgery plays an important role in the postoperative formation of ectopic bone. This



discrepancy can be ascribed to the differences among surgical techniques used by different surgeons.<sup>15</sup>

This study had several limitations. First, it was a retrospective study. Several patient-related or clinical factors such as the exact mechanism of injury, history of tobacco or alcohol abuse, and evaluation of systemic injury in patients with multiple trauma were not identified because of incomplete medical records. Second, the size and classification of HO was not determined because of insufficient final radiographs. Finally, many patients who had been followed up for <3 months were excluded. It is possible that HO may further develop in these patients, leading to an underestimation of the incidence of asymptomatic HO after ORIF of elbow fractures.

## Conclusions

The overall incidence of asymptomatic HO was 18.78% after ORIF of elbow fractures, with the highest incidence in terrible triad injuries. Underlying diseases, fracture dislocation, and prolonged operative time independently predicted HO following ORIF. Understanding these factors may help in the appropriate implementation of NSAID use or radiotherapy when treating high-risk patients with postoperative HO.

## Author contributions

CYX and ZYT contributed to the conception and design of the current study as well as the review and editing of the manuscript. QXS and WZ followed up the patients and collected the data. CYX, ZYT, and ZY were responsible for the review of the radiographs and exclusion of patients. ZY and ZYT were responsible for the data analysis and drafting of the manuscript. All authors read and approved the final manuscript.

## Declaration of conflicting interest

The authors declare no conflicts of interest in this work.

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