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Review Article

A meta-analysis of risk factors for heterotopic ossification after elbow trauma

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Abstracts: The objective of this meta-analysis was to determine the incidence and identify risk factors associated with heterotopic ossification after elbow trauma. CNKI, Embase, Medline, and Cochrane central database were searched using a broad range of terms to identify original research, published all through August 2015 and identified potentially studies. Qualified studies had to meet the quality assessment criteria by Newcastle-Ottawa Scale and evaluate the multiple risk factors for heterotopic ossification after elbow trauma. Six studies involving 1636 elbow injury patients and 214 HOs (13.1%) were eligible and included in this meta-analysis. Our meta-analysis identified the significant risk factors for HO about elbow were male gender (OR, 2.03; 95% CI, 1.09-3.81), combined radius/ulna fractures (OR, 3.46; 95% CI, 1.52-7.88), overall fracture dislocation (OR, 3.13; 95% CI, 1.37-7.16), ulnohumeral fracture dislocations (OR, 4.17; 95% CI, 2.44-7.13), terrible triad (OR, 3.37; 95% CI, 1.93-5.87), floating elbow (OR, 10.23; 95% CI, 3.20-32.68) and delay from injury to surgery (odds per day) (OR, 1.09; 95% CI, 1.04-1.13). The proximal ulna fracture of elbow was likely to be negatively correlated with development of HO about the elbow (OR, 0.31; 95% CI, 0.12-0.78). The other variables including other fracture types, other fracture dislocations, open fracture, infection, head injury and ipsilateral injury were identified not as the risk factors for development of HO. Related prophylaxis strategies should be implemented in patients involved with above-mentioned medical conditions to prevent HO after elbow trauma.

Keywords: Heterotopic ossification, elbow trauma, risk factors, meta-analysis

Introduction

Heterotopic ossification (HO) is the abnormal formation of mature lamellar bone at extra skeletal sites [1]. Severe elbow trauma can become complicated with the development of pathologic bone, often referred to as HO, which can lead to marked stiffness and functional limitations in elbow joint. The incidence of HO about elbow after major trauma has been reported to be ranging from 6% to 89% due to the numerous classification systems and multiple relevant risk factors [2-5]. Many risk factors have been identified for the HO after elbow injuries, including elbow fracture dislocation [3, 6-8], the fracture types [2, 3, 9], time from injury to surgery [2, 8], delay to postoperative mobilization [2] and severe combined injury [7, 10]. However, these studies had some limitations, such as a small sample and containing a single or very few potential risk factors in the individual study. In addition, some results obtained from individual studies were inconsistent and even contradictory. Thus, it is still uncertain whether these identified factors from individual studies could predict clinical HO after elbow trauma.

Until now, no formal systematic review or meta-analysis was performed to summarize the risk factors of HO after elbow injury to obtain a definitive conclusion. Therefore in this study, we summarized these risk factors from the previous original researches and conducted a meta-analysis to help clinicians to prevent postoperative HO of the elbow trauma and improve the prognosis of patients.

Materials and methods

Literature search

CNKI, Embase, Medline, and Cochrane central database were searched using a broad range of terms to identify original research, published all

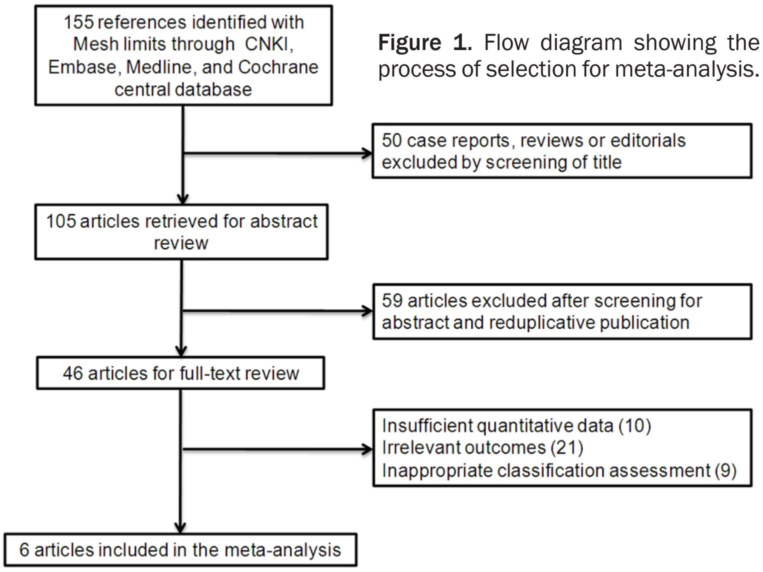


Figure 1. Flow diagram showing the process of selection for meta-analysis.

through August 2015 and identified potentially studies. The main key words were as follows: "factor" or "predictor" or "risk" AND "ectopic" or "heterotopic" AND "elbow" and "ossification". Also, a manual search of references in the identified articles and systematic reviews was performed for possible inclusion.

Eligibility criteria

Two reviewers (Xin Zhao and Tianhua Dong) independently evaluated the titles and abstracts of the identified studies. Only full-text articles without language restriction were included in this meta-analysis. To be eligible for inclusion, studies needed to have: (1) a study was performed to explore risk factors for the HO about elbow; (2) cases and controls were defined based on the presence or absence of clinically significant HO (Brooker2 and greater, or Hastings class II and III accompanied by limited motion) after elbow trauma, respectively; (3) sufficient data was published for estimating an odds ratio (OR) or hazard ratio (HR) with 95% confidence intervals (CIs).

Quality of included studies

The quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) [11]: based on the three main items: the selection of the study groups (0-4 points), the comparability of the groups (0-2 points) and the determination of either the exposure or the outcome of interest (0-3 points), with a perfect score of 9.

Data extraction

All the data were carefully extracted from all eligible studies independently by the two reviewers (Xin Zhao and Tianhua Dong). The following variables were extracted from each study: first author's name, publication year, country, significant risk factors, definitions and numbers of cases and controls and numbers of citations for each potential risk factor for HO of elbow. Any disagreement was settled by discussion and a consensus was reached for all data.

Statistical analyses

We estimated OR and 95% CI and pooled across studies to assess the association between different variables and the risk of HOs with a $P<0.05$ indicating significant. Heterogeneity between the studies was tested by Q-test statistics with significance set at $P<0.10$ [12]. The I^2 statistics were used as a second measure of heterogeneity, with I^2 more than 50% indicating significant inconsistency. A random effects model was used to calculate pooled ORs in the case of significant heterogeneity ($P<0.10$ or $I^2>50\%$); otherwise, a fixed-effects model was used [13]. The meta-analysis of significant risks was summarized graphically using a forest plot. No publication bias test was performed due to the fewer studies included in this meta-analysis. Furthermore, to explore causes of heterogeneity, sensitivity analyses were performed according to the following factors: methodological quality and the size of the confidence interval of individual study. All analyses were performed using the software Stata 12.0 (Stata Corporation, College Station, TX).

Results

Characteristics of identified studies

Figure 1 indicates the flowchart of the article screening and the detailed selection process. We retrieved 155 full-text review articles, of which 6 were identified as eligible and included in this meta-analysis. Of them, 6 were published in English and all were published from

Table 1. The basic characteristics of these 6 included studies and participants

First author	Publication year	Country	Study years	Control	Case	Total	Age	Significant factors
Hong [14]	2015	Singapore	5	98	26	124	45.6	Fracture-dislocation and time to surgery
Douglas [3]	2012	USA	6	127	29	156	NA	Severe elbow injury and delay of fixation
Abrams [9]	2012	USA	10	127	29	156	54.4	Distal humeral fractures
Bauer [2]	2012	USA	8	731	55	786	49.6	Delay to surgery and mobilization
Wiggers [8]	2013	USA	7	257	27	284	54.3	Ulnohumeral fracture dislocation; delay to surgery and number of surgical procedures
Foruria [10]	2013	USA	5	82	48	130	56	Subluxation or dislocation, open fracture, severe chest injury, delay to surgery

Table 2. Detailed data on potential risk factors for the HO after major elbow trauma and the outcomes of meta-analysis

Potential risks	No of studies	Pooled OR	LL 95% CI	UL 95% CI	*P* value	Q-test (P)	CI^2 (%)
Male (VS female)	2	2.03	1.09	3.81	0.027^a	0.930	0
Fracture types							
Distal humerus	4	1.74	0.74	4.10	0.206^b	0.009	74.0
Radial head	5	1.21	0.73	2.01	0.460^a	0.286	20.1
Proximal ulna	5	0.31	0.12	0.78	0.012^b	0.004	73.9
Combined radius/ulna	4	3.46	1.52	7.88	0.003^a	0.478	0
Fracture dislocation	5	3.13	1.37	7.16	0.007^b	0.003	74.6
Transolecranon fracture-dislocation	3	1.49	0.65	3.43	0.345^a	0.258	26.2
Monteggia fracture-dislocation	2	0.56	0.25	1.22	0.143^a	0.476	0
Ulnohumeral fracture dislocations	3	4.17	2.44	7.13	<0.001^a	0.314	13.6
Terrible triad	3	3.37	1.93	5.87	<0.001^a	0.674	0
Floating elbow	2	10.23	3.20	32.68	<0.001^a	0.574	0
Open fracture (VS closed)	2	1.76	0.44	7.03	0.425^b	0.107	61.5
Infection	2	2.33	0.73	7.38	0.151^a	0.174	45.9
Head injury	2	1.87	0.69	5.09	0.221^a	0.607	0
Ipsilateral injury	2	0.56	0.06	5.56	0.618^b	0.034	77.7
Delay from injury to surgery (odd s per day)	5	1.09	1.04	1.13	<0.001^a	0.723	0

HO, Heterotopic ossification; OR, odds ratio; LL, Lower limit; UL, Upper limit; SI, Singh index. ^{a}Fixed-effect model was performed. ^{b}Fandom-effect model was performed. $^cI^2$ statistic was defined as the proportion of heterogeneity not due to chance or random error.

2012 to 2015. These 6 studies altogether included 1636 patients with elbow trauma, and during a study time window of 5 to 10 years 214 cases of HO occurred, suggesting the accumulated incidence of 13.1%. Detailed information about these included studies was shown in **Table 1**.

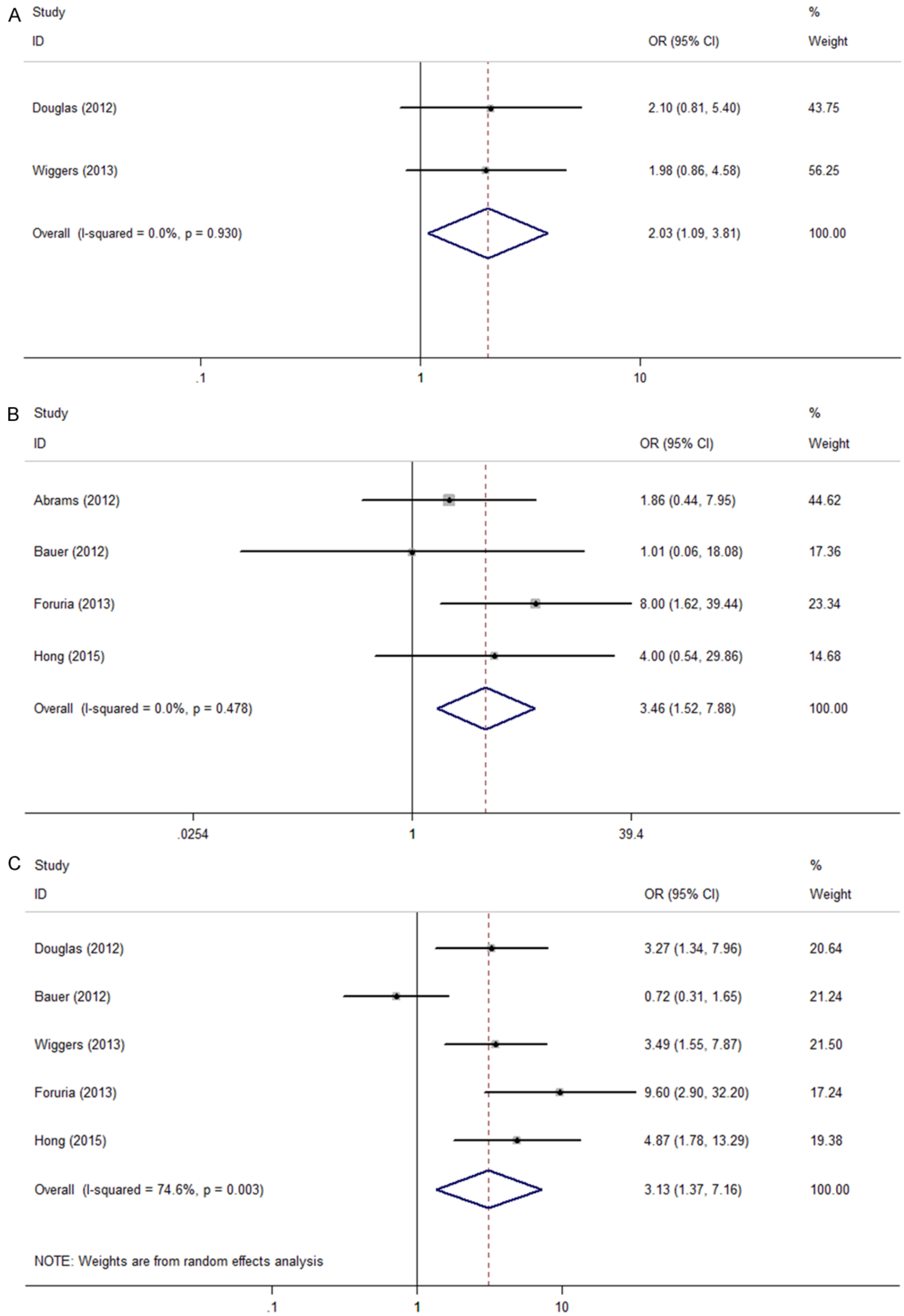
The outcome of quality assessment for these studies was as follows: four studies scored 8 [2, 3, 9, 14]; two studies scored 7 [8, 10].

Male gender

Because of the limited number of research studies, only two studies [3, 8] were provided information on male gender. Using a fixed-effects model, the mete-analysis showed that male was more significantly associated with HO than female (OR, 2.03; 95% CI, 1.09-3.81), with no evidence of heterogeneity among studies (P=0.930, I^2=0; **Table 2**; **Figure 2A**).

Combined radius/ulna fractures

Four studies [2, 9, 10, 14] reported combined radius/ulna fractures caused HO after major elbow trauma. Overall, 13 out of 142 patients developed to clinically significant HO after elbow trauma surgery with radius/ulna fractures. Using a fixed-effects model, we observed


A
Study
ID
OR (95% CI)
%
Weight
Douglas (2012)
2.10 (0.81, 5.40)
43.75
Wiggers (2013)
1.98 (0.86, 4.58)
56.25
Overall (I-squared = 0.0%, p = 0.930)
2.03 (1.09, 3.81)
100.00
.1
1
10
B
Study
ID
OR (95% CI)
%
Weight
Abrams (2012)
1.86 (0.44, 7.95)
44.62
Bauer (2012)
1.01 (0.06, 18.08)
17.36
Foruria (2013)
8.00 (1.62, 39.44)
23.34
Hong (2015)
4.00 (0.54, 29.86)
14.68
Overall (I-squared = 0.0%, p = 0.478)
3.46 (1.52, 7.88)
100.00
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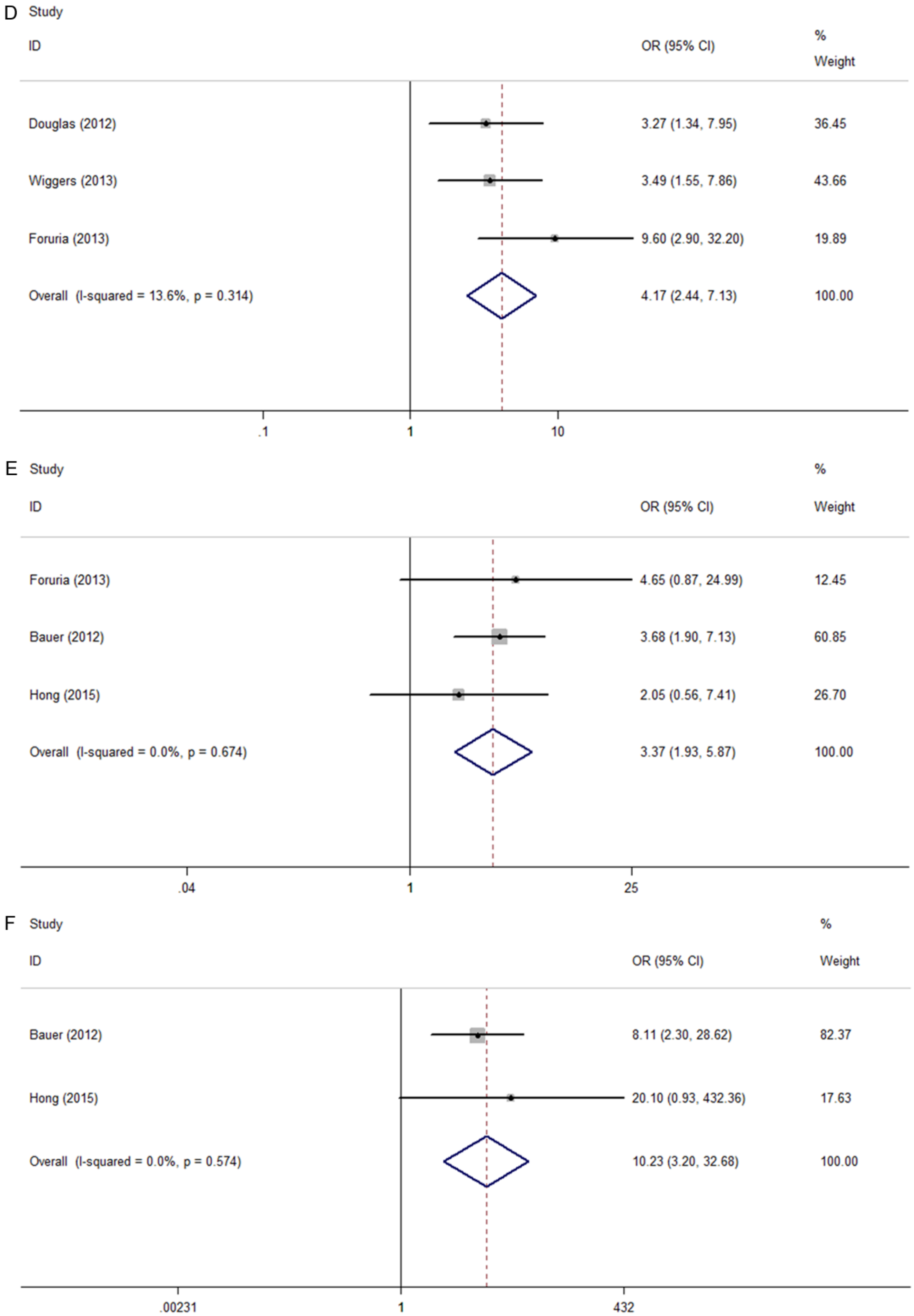
1
39.4
C
Study
ID
OR (95% CI)
%
Weight
Douglas (2012)
3.27 (1.34, 7.96)
20.64
Bauer (2012)
0.72 (0.31, 1.65)
21.24
Wiggers (2013)
3.49 (1.55, 7.87)
21.50
Foruria (2013)
9.60 (2.90, 32.20)
17.24
Hong (2015)
4.87 (1.78, 13.29)
19.38
Overall (I-squared = 74.6%, p = 0.003)
3.13 (1.37, 7.16)
100.00
NOTE: Weights are from random effects analysis
.1
1
10


D
Study
ID
OR (95% CI)
%
Weight
Douglas (2012)
3.27 (1.34, 7.95)
36.45
Wiggers (2013)
3.49 (1.55, 7.86)
43.66
Foruria (2013)
9.60 (2.90, 32.20)
19.89
Overall (I-squared = 13.6%, p = 0.314)
4.17 (2.44, 7.13)
100.00
.1
1
10
E
Study
ID
OR (95% CI)
%
Weight
Foruria (2013)
4.65 (0.87, 24.99)
12.45
Bauer (2012)
3.68 (1.90, 7.13)
60.85
Hong (2015)
2.05 (0.56, 7.41)
26.70
Overall (I-squared = 0.0%, p = 0.674)
3.37 (1.93, 5.87)
100.00
.04
1
25
F
Study
ID
OR (95% CI)
%
Weight
Bauer (2012)
8.11 (2.30, 28.62)
82.37
Hong (2015)
20.10 (0.93, 432.36)
17.63
Overall (I-squared = 0.0%, p = 0.574)
10.23 (3.20, 32.68)
100.00
.00231
1
432

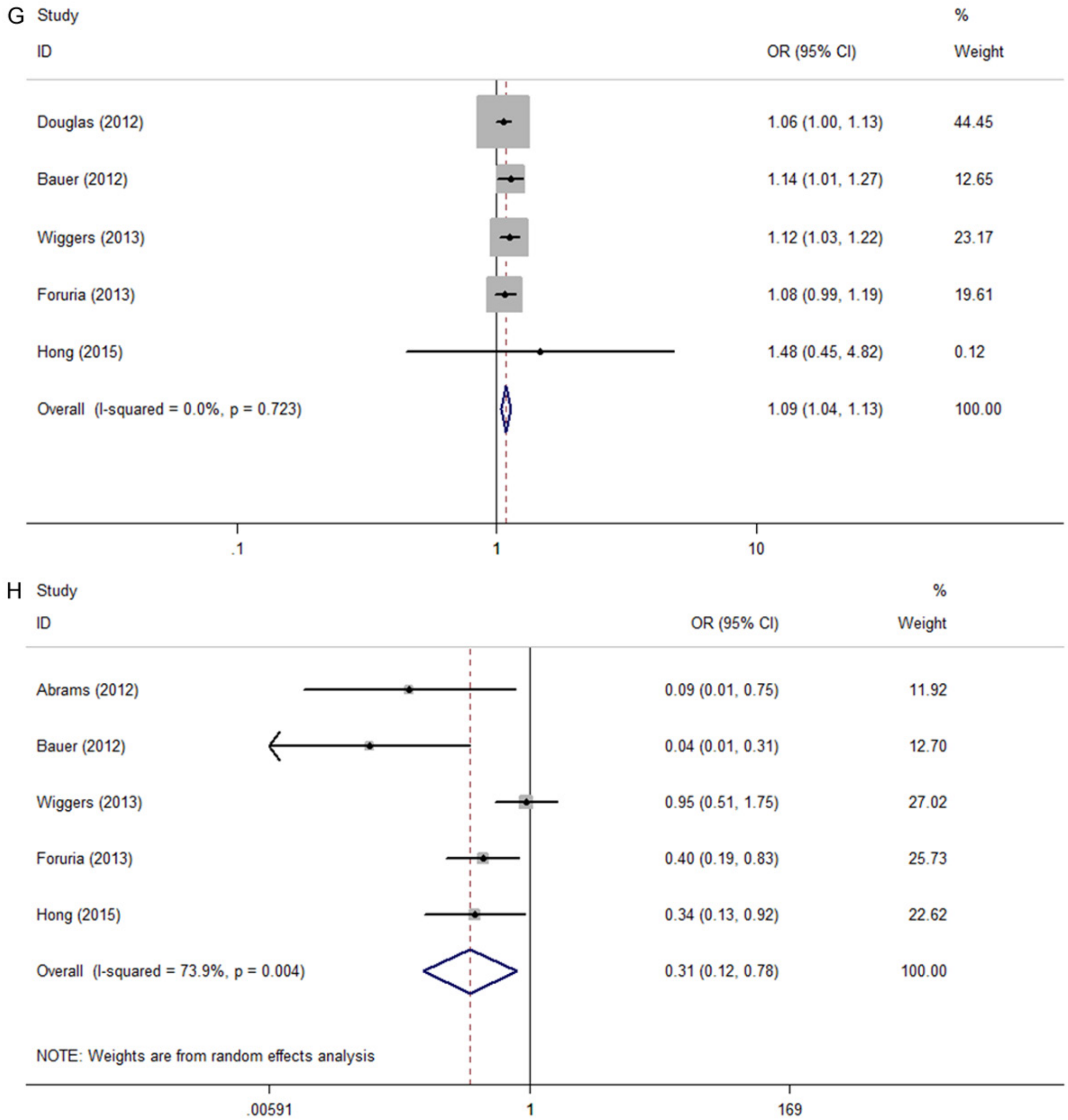


Figure 2. A. Forest plots for male gender. B. Forest plots for combined radius/ulna fractures. C. Forest plots for overall fracture dislocation. D. Forest plots for ulnohumeral fracture dislocations. E. Forest plots for terrible triad. F. Forest plots for floating elbow. G. Forest plots for delay from injury to surgery. H. Forest plots for proximal ulna fractures.

a significant difference (OR, 3.46; 95% CI, 1.52-7.88), with no evidence of heterogeneity among studies (P=0.478, I^2=0; **Table 2**; **Figure 2B**).

Fracture dislocation and ulnohumeral fracture dislocations

There were five included studies [2, 3, 8, 10, 14] reported the fracture dislocation. The meta-analysis showed there was a significant difference between fracture dislocation of elbow and none (OR, 3.13; 95% CI, 1.37-7.16), with evidence of heterogeneity (P=0.003, I^2=74.6%; **Table 2**; **Figure 2C**). In terms of ulnohumeral fracture dislocations, three articles [3, 8, 10] reported. We observed a significant difference in these patients by a fixed-effects model (OR, 4.17; 95% CI, 2.44-7.13), with low heterogeneity (P=0.314, I^2=13.6%; **Table 2**; **Figure 2D**).

Terrible triad and floating elbow

Terrible triad and floating elbow were both very serious damages of elbow traumas. Using a fixed-effects model, we observed a significant difference of the two factors, with terrible triad

Table 3. Results of sensitive analysis for variables

Variables	OR and corresponding 95% CI (original)	P for heterogeneity	I^2	The outlier study excluded	OR and corresponding 95% CI (afterwards)	P for heterogeneity	I^2
Proximal ulna	0.31 (0.12-0.78)	0.012	73.9%	Wiggers 2013	0.23 (0.10-0.54)	0.138	45.5%
Fracture dislocation	3.13 (1.37-7.16)	0.007	74.6%	Bauer 2012	4.32 (2.69-6.93)	0.496	0

(OR, 3.37; 95% CI, 1.93-5.87) and floating elbow (OR, 10.23; 95% CI, 3.20-32.68), respectively. There were no evidence of heterogeneity among studies (P=0.674, I^2=0; P=0.574, I^2=0, respectively; **Table 2**; **Figure 2E** and **2F**).

Delay from injury to surgery

When we assessed delay from injury to surgery, five studies [2, 3, 8, 10, 14] have previously been shown to associate with HO after elbow trauma, with a significant difference in these patients by a fixed-effects model (OR, 1.09; 95% CI, 1.04-1.13), again consistent with no observed heterogeneity (P=0.723, I^2=0; **Table 2**; **Figure 2G**).

Proximal ulna fractures

The proximal ulna fracture of elbow was less likely to develop HO about the elbow (OR, 0.31; 95% CI, 0.12-0.78), with evidence of heterogeneity (P=0.004, I^2=73.9%; **Table 2**; **Figure 2H**).

The outcome of analysis for some variables mentioned above as significant risk factors were presented by forest plots (**Figure 2**). The other variables including other fracture types, types of fracture dislocations, open fracture, infection, head injury and ipsilateral injury were not identified as the risk factors for clinically significant HO of elbow (P>0.05).

Sensitivity analysis

We performed a sensitive analysis for the risk factors (proximal ulna fracture and fracture dislocation) presenting with significant heterogeneity by excluding outlier studies due to poorer assessment quality or larger size of the confidence interval for some ORs. Results revealed, the I^2-value lowered to below than 50% but meta-analysis results of these factors did not change the significance, indicating the results robust. The detailed information of sensitive analysis was presented in **Table 3**.

Discussion

Heterotopic ossification (HO) was characterized histologically by abnormal formation of mature bone tissues and clinically by restricted joint movement, swelling, pain and even complete anchylosis [15]. Patients who encounter direct injuries, central nervous system trauma, and thermal burns are at an increased risk for development of HO [9]. The incompletely understood pathophysiology of this condition is likely polyfactorial [16]. The incidence of HO about elbow after major trauma has been reported to be ranging from 6% to 89% due to the numerous classification systems and multiple relevant risk factors [2-5]. In this study, the overall incidence of HO after major trauma was 13.1%. Given the controversies about the potential risk factors still existing, this meta-analysis was performed and the associated significant risk factors were male gender, combined radius/ulna fractures, overall fracture dislocation, ulnohumeral fracture dislocations, terrible triad, floating elbow and delay from injury to surgery. The proximal ulna fracture of elbow was less likely to develop HO about the elbow (OR, 0.31; 95% CI, 0.12-0.78).

Among patient-related demographic factors, we found that male gender was associated with HO. This suggests that men may be less tolerant of anchylosis and more willing to undergo the risks of operative intervention for resection of elbow heterotopic ossification, but repeat elbow surgery with muscle manipulation and retraction with repeated early surgeries may increase the risk of HO [8]. Since only two studies have mentioned the risk of sex, future prospective research will be needed to further address the influence.

Of injury-related factors, this meta-analysis identified combined radius/ulna fractures, overall fracture dislocation, ulnohumeral fracture dislocations, terrible triad and floating elbow as predictors of HO. The most common reason of the ectopic bone formation in elbow is direct damage [17]. There appears to be a direct correlation between the severity of trauma and the dimensions of heterotopic bone that develops. In fact, the development of ectopic bone increases fivefold when someone has sustained an elbow dislocation along with a radial head fracture [18]. The rate of HO after elbow fracture dislocations has been reported to range from 5% to 50% [19-21]. Complete ulnohumeral dislocation likely presents greater soft tissue injury and a more severe trauma, which in itself was identified as a predictor by Douglas et al. [3].

Some associated risk factors in the development of HO include traumatic brain injuries and thermal burns. The incidence of ectopic bone appears to increase when an elbow trauma is coupled with either of these associated risk factors. Garland and O'Hollaren [7] reported a notable difference in the frequency of HO at elbow between those who sustained a neural axis trauma only (5%) versus those patients who sustained both a neural axis and an elbow trauma (89%). In addition, Wiggers et al. [8] found the HO incidence was more than twice that in controls (15% VS 7%) in central nervous system trauma patients. These data suggest that there is possibly a hormone-related or systemic cascade mechanism responsible for the development of HO. Nevertheless, in this study, no significance was found for the risk of head injury, which was uniform with the reports in original studies [2, 8]. On the one hand, Computed tomography scans were invented in the past but were not yet widely used clinically, so it is feasible that these clinically diagnosed head injuries were more severely than many of the radiographically diagnosed head injuries in the current. On the other hand, because of the minor injuries including abrasions or hematoma of scalp were pertained to the head injury realm, which was not accurate, this was lacking of power to detect associations between suspected risk factors such as head trauma and HO. Therefore, we believe, this condition could approach to significance if a lager sample size was provided.

Among treatment-related predictors of HO, longer time from injury to surgery has previously been shown to associate with HO after elbow trauma [2, 3, 8, 10, 14]. Reasons for delaying surgery vary significantly, from comorbidities in multisystem traumas to soft tissue injuries requiring delayed definitive fixation and operating room availability in the ambulatory setting. Theoretically, the delayed fixation could allow further differentiation of pluripotent stem cells, which then results in abnormal bone formation in undesired locations following delayed fixation. Delayed surgery also translates into longer immobilisation, as rehabilitation can start only after surgery, and a prolonged immobilisation is associated with HO [2, 22]. Waiting longer than 1 week until surgery resulted in tenfold the odds of having any radiographic HO and sevenfold the odds of having clinically relevant HO responsible for ROM limitation [14]. Bauer et al. [2] found that, patients treated within one day of injury had one twelfth the decreased risk of HO than those adopting surgery within 8-14 days of injury. Casavant et al. [23] reported that repeat elbow operations may be a risk factor for HO. Patients who require multiple initial operations typically have long open wounds, compromised large soft tissue, infection, or neurovascular injuries, which put them at increased risk of fracture non union, infection, and other wound-healing complications [24, 25]. Consequently, this patient population is inherently risky to treat with HO prophylaxis and requires surgery regardless of the risk of secondary ectopia bone formation. Thus, whether these patients are at an increased risk of HO probably would not change the clinical decision making regarding prophylaxis.

The Injury Severity Score (ISS) has been associated with knee ankylosis from heterotopic ossification in one study [26]. The higher ISS might provide predictive value for the development of HO after elbow trauma, but relevant individual results were not pooled and calculated in our study due to the inconsistent quantitative criteria or only reported in a single study. Similarly, race, mechanism of injury and Gustilo grade categories of fractures were not pooled for the non-uniform quantitative criteria.

Turning to the limitations of this meta-analysis, firstly, it is possible that the samples recruited for the primary studies were not broadly representative of the elbow trauma population. Secondly, not all the ORs on the potential risk factors for the meta-analysis are adjusted because some studies could only provide the univariate rather than multivariate statistics; similarly, some articles might choose not to report the insignificant results or no interest, thus resulting in a considerable amounts of missing information. Hence, our overall effect may be somewhat over-estimate. Thirdly, there was significant heterogeneity between the included studies. The majority of heterogeneity was clinical, related to study population differences. Therefore, a significant heterogeneity was unavoidable in this study, but the sensitive analysis by excluding outlier studies was performed and the corresponding pooled results were robust.

Despite these defects, some advantages should be mentioned. Firstly, a broad range search strategy based on computer-assisted and manual searching avoided any eligible study to negligence. Secondly, sensitive analysis was performed by excluding the outlier studies and similar results were observed, suggesting that the results were responsible. Finally, this is the first study to quantitatively summarize potential risk factors for development of HO after elbow trauma by now. Identification of these risk factors could contribute to complementing prevention strategies for at-risk patients.

In summary, the present meta-analysis suggests that male gender, combined radius/ulna fractures, overall fracture dislocation, ulnohumeral fracture dislocations, terrible triad, floating elbow and delay from injury to surgery were significant risk factors for HO after elbow trauma. Patients having the above medical conditions should be paid close attention by surgeons to reduce HO after elbow fracture surgery and might benefit more from primary prophylaxis.

Disclosure of conflict of interest

None.

Authors' contribution

Y.Y. and X.Z. were responsible for conception and design, coordinated the study, and wrote the article. Y.Y., D.C. and D.T. were involved in the review of literature, acquisition of data, analyzed the data. Y.Y. and Q.Z. provided critical revisions. All authors read and approved the final article.

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