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Original Article

Incidence and risk factors for heterotopic ossification after ORIF of acetabular fractures, a systematic review and meta-analysis

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Abstract: The study aims to comprehensively and quantitatively summarize risk factors for heterotopic ossification after acetabular fractures treated by open reduction and internal fixation. The computerized and additional manual searches were performed in Medline, Embase, CNKI, Wanfang and Cochrane central database (all through September 2015) for potential studies. Studies eligible after multiple screening and fulfiling quality assessment criteria by Newcastle-Ottawa Scale were included in this meta-analysis. Two reviewers independently extracted and evaluated the relevant data, any disagreement was solved by consensus. Stata11.0 was used to perform all the statistical analyses. Fifteen studies involving 2180 cases with acetabular fractures and subsequent development of 602 HOs were eligible and included in this meta-analysis. Meta-analysis revealed the significant increased risk factors for HO associated brain injuries [odd ratio (OR), 2.390; 95% confidence interval (CI), 1.180-4.841], Iliofemoral approach (OR, 5.521; 95% CI, 2.613-11.67) and no prophylaxis of indomethacin (OR, 3.450; 95% CI, 1.230-9.680). The other variables including race, gender, fracture type, associated chest/abdomen injuries, trochanteric osteotomy, spine injury, Kocher-Langenbeck (KL) approach and irradiation were identified not as the risk factors for HO after the acetabular fracture. Patients involved with associated traumatic brain are at high-risk for development of HO after acetabular fractures. When other approaches indicated, avoiding iliofemoral approach at surgery and perioperative prophylaxis of indomethacin could obviously reduce the occurrence of HO and should be advocated.

Keywords: Heterotopic ossification, acetabular fractures, open reduction and internal fixation, risk factors, meta-analysis

Introduction

Heterotopic ossification (HO) is potential complication of trauma, elective surgery and neurological injuries. The typical pathologic process is trabecular (mature lamellar) bone forms in nonosseous tissues such as muscles, ligaments and tendons [1]. Regarding the precise molecular pathogenesis of HO, there is little documented information. And the mainstream idea is that, pluripotent mesenchymal stem-cell is activated by several trauma or surgery-related biochemical factors and differentiates into osteoblastic precursors, whereby resulting in generation of HO [2-4]. However, there was no study to verify this mechanism in human beings and hence, to revise in molecular or in gene level in aim to prevent against HO appears to be impossible.

Acetabular fracture is a clinically severe trauma and predominantly caused by traffic accidents, representing a tremendous challenge for surgeons. Initially, this fracture was managed with conservative method, which was compromised by non-anatomical reduction, prolonged stay in bed and poorer functional results. With the improvement of technology and materials, open reduction and internal fixation (ORIF) has become the uppermost treatment for this complex injury. However, postoperative incidental HO is an important concern and the reported incidence ranged from 18.1% to 74.3% [5-7]. Consequently, inferior functional recovery and

20% or greater loss of hip motion might compromise this seemly successful surgery, especially in those with clinically significant HO (Brooker 2-4). In the past decades, prophylactic agents of indometacin and irradiation in the regional involved sites (trauma or surgery) have been the primary methods for the inhibition of generation of HO. However, regarding their effectiveness on prevention against HO there has been controversy existing, and some studies even demonstrated them useless in clinics and thereby considered it unnecessary in perioperative period for prevention of HO. In addition, as mentioned above, it appears infeasible to prevent against HO in molecular or gene level. So, many researchers shifted to the identification of risk factors associated with the generation of HO and in an attempt decreased the incidence of HO after ORIF after acetabular fractures, from the level of control of associated risk factors.

In the literature, many relevant risk factors were investigated and identified as significant ones, which predisposed to the generation of HO after ORIF for acetabular fractures. These risk factors mainly included race and gender [8, 9], associated chest/abdominal injuries [10], related brain or spinal cord trauma [11], fracture type [10], surgical approach [10-12], the delay from trauma to operation 1 [5, 7], not use of prophylactic indometacin or irradiation [6, 7, 11, 13, 14], multiple operative findings [10], injury Severity Score [11] and prolonged mechanical ventilation [15]. However, some limitations existed in the original studies such as a small sample size, the inclusion of a single or very few potential risk factors and poor study design which could result in significant biases. Besides, intense controversies even contradictory conclusions still undergo for one certain risk factors for HO development after ORIF for acetabular fractures in literature.

In the present study, we performed this meta-analysis in an attempt to achieve a quantitative and comprehensive evaluation of these risk factors for the HO development in patients with acetabular fractures treated by ORIF. As such, it is expected to provide an evidence base regarding this key issue, from which surgeons could be aware of who were at high-risk for HO and develop targeted prevention and intervention strategies to reduce and even avoid this complication.

Methods

Search strategy

Initially, a computerized search was performed in medical database of Medline, Embase, and Cochrane central (all through September 2015) for potentially relevant studies according to the following main key words: "risk" or "predictor" or "factor" AND "acetabular fracture" or "fracture of acetabulum" AND "heterotopic ossification" or "epitopic ossification" AND "open reduction internal fixation". All articles identified as potentially relevant were obtained and reviewed by an independent research assistant. Besides, a manual search of references by this assistant was performed in the identified original articles and systematic reviews for any additional eligible articles.

Two reviewers (Zhu and Ju) independently evaluated the titles and abstracts of the identified papers. Only full-text articles without language restriction were eligible and included in this meta-analysis. The inclusion criteria were as follows: (1) a study was performed to explore risk factors for the HO after acetabular fractures treated by ORIF; (2) cases and controls were defined based on the presence or absence of HO based on Brooker classification system or other classification defined by authors; (3) sufficient data was published in original study for estimating an odds ratio (OR) or hazard ratio (HR) with corresponding 95% confidence intervals (CIs).

Data extraction

The same two reviewers (Zhu and Ju) independently extracted the detailed information on relevant publications for meta-analysis. The following variables were extracted from each study: first author's name, publication year, country, significant risk factors, the number of case and control groups and the number of citations for each potential risk factor for HOs. Any disagreement was settled by discussion and a consensus was reached for all data.

Quality of included studies

The same two reviewers (Zhu and Ju) independently evaluated the quality of the included studies using the Newcastle-Ottawa Scale (NOS) [16] based on the three main items: the selection of the study groups (0-4 points), the

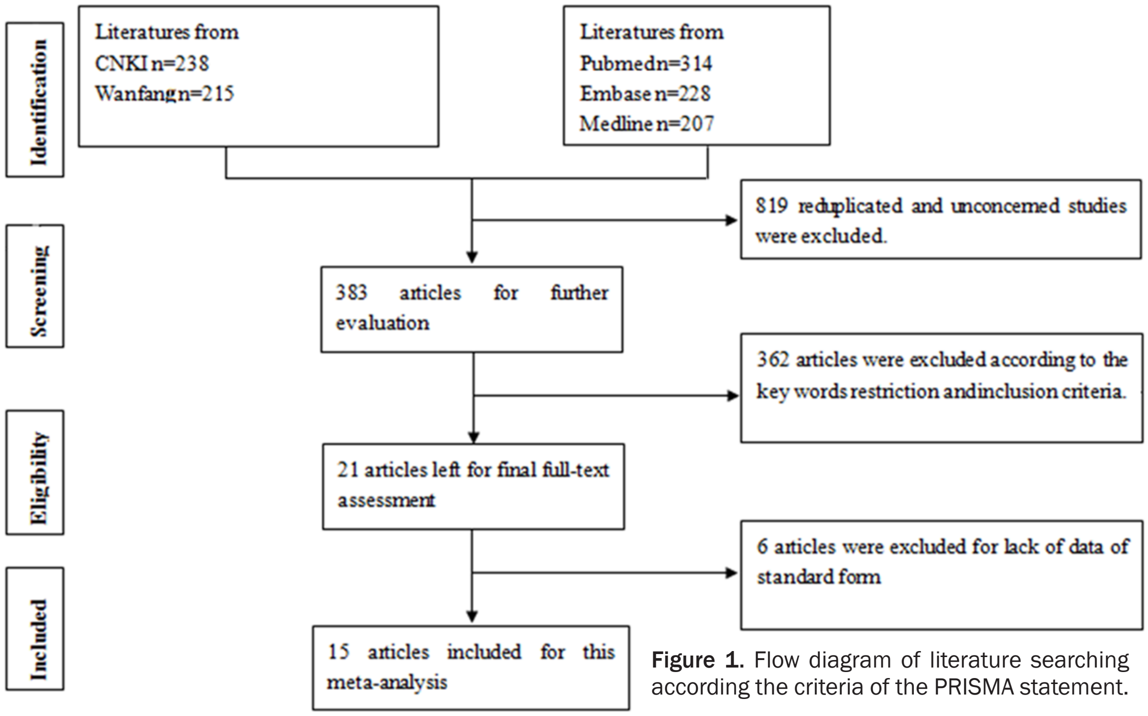

Figure 1. Flow diagram of literature searching according the criteria of the PRISMA statement.

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.

Meta-analyses

Odds ratios (ORs) and 95% confidence intervals (95% CI) for certain risk factor were estimated in each original study and pooled across studies to assess the association between potential risk factor and HOs after acetabular fractures with a $P<0.05$ as significance. Hetero geneity between studies was tested qualitatively by Q-test statistics with significance set at $P<0.10$ [17] and quantitatively tested by I^2 statistics, with I^2 more than 50% indicating significant inconsistency. A random-effect model was used to calculate pooled ORs in the case of statistically significant heterogeneity ($P<0.10$ or $I^2>50\%$); otherwise, a fixed-effect model was used [18]. The outcome of meta-analysis for risk factors was summarized using a forest plot. No publication bias was performed due to the inclusion of fewer studies for any risk factor. All analyses were performed using the software Stata 11.0 (Stata Corporation, College Station, TX).

Sensitivity analysis

Furthermore, to explore causes of heterogeneity and make the result more reliable, sensitivity analysis was performed based on the following factors: width of 95% CI, assessment quality of included studies, and publication year of studies.

Results

Literature search

Figure 1 depicts the screening process and after multiple screening, a total of 21 full-text studies were assessed, of which 6 studies were excluded due to the lack of data of standard form, leaving 15 studies finally included in this meta-analysis. Fourteen studies were published in English and 1 in Chinese, with publication time from 1988 to 2015. These 15 studies altogether included 2180 acetabular fractures patients treated by ORIF and 602 cases of HO, although with the different class in Brooker classification system. Detailed information about these included studies was shown in **Table 1**.

Quality assessment

The outcome of quality assessment for these studies was as follows: four studies scored 8 [2, 5, 8, 11, 14, 15, 20]; six studies scored 7 [6, 9, 10]; four studies scored 6 [7, 13, 19] and two studies scored 5 [12, 21].

Table 1. The basic characteristics of these 13 included studies and participants

First author	Publication	Country	Control	Case	Total	Age (years)	Significant factors
Mourad [5]	2012	US	479	106	585	36 (13-85)	Prolonged Time Interval Between Trauma and Prophylactic Radiation Therapy
Bosse [7]	1988	US	26	12	38	29.4 (mean)	Prophylaxis with low-dose irradiation
Ghalambor [10]	1994	US	197	40	237	37 (15-90)	Lliofemoral approach, T type fractures, Abdomen or chest injuries, Multiple operative findings
Johnson [13]	1994	US	30	34	64	35 (12-68)	Combined extended iliofemoral approach and no Prophylaxis of indomethacin
Baschera [11]	2015	Australia	74	16	90	34.6 (14-75)	Traumatic brain injury
Burd [2]	2001	US	149	17	166	42.7 (16-89)	The Injury Severity Score, Prophylaxis with indomethacin or irradiation
Kaempffe [19]	1991	US	21	29	50	38 (17-72)	Trochanteric osteotomy
Moed [6]	1994	US	9	26	35	32 (16-56)	Prophylaxis of indomethacin
Mclaren [14]	1990	Canada	18	26	44	39 (14-63)	Prophylaxis of indomethacin
Firoozabadi [15]	2014	US	274	38	312	41 (7-84)	Prolonged mechanical ventilation
Griffin [9]	2005	US	74	32	106	34 (11-79)	A worse Merle d'Aubigné and Postel score, gender
Slone [8]	2015	US	198	55	253	39.7	Race
Korovessis [12]	2000	Greece	57	18	75	38.7±17.9	Extensile iliofemoral approach
Matta [20]	1997	US	49	52	101	42.9 (17-79)	Male gender
Yu [21]	2003	China	15	9	24	32.4 (21-56)	Fracture types

Table 2. Incidence rate of HO of each type, based on the Brooker classification system

Literature	Patients included	Overall HO cases	Brooker 1	Brooker 2	Brooker 3	Brooker 4	Moderate to severe HO (Brooker 2-4)	Severe HO (Brooker 3-4)
Mourad [5]	585	106	NA	NA	NA	NA	NA	50
Bosse [7]	38	NA	NA	NA	NA	NA	NA	12
Ghalambor [10]	237	NA	NA	NA	NA	NA	NA	NA
Johnson [13]	64	33	14	5	10	4	19	14
Baschera [11]	90	16	5	4	3	4	11	7
Burd [2]	166	17	NA	NA	NA	NA	NA	NA
Kaempffe [19]	50	29	6	11	5	7	23	12
Moed [6]	35	26	9	6	7	4	17	11
Mclaren [14]	44	26	12	4	7	3	14	10
Firoozabadi [15]	312	100	16	46	19	19	84	38
Griffin [9]	106	63	31	NA	NA	NA	32	NA
Slone [8]	253	NA	NA	NA	NA	NA	NA	55
Korovessis [12]	75	18	10	4	2	2	8	4
Matta [20]	101	52	47	NA	NA	NA	5	NA
Yu [21]	24	9	2	4	2	1	6	3
Sum	2180	495	152	84	55	44	219	216
Incidence rate (=Cases/patients totally included)		30.0% (495/1652)	16.9% (152/901)	12.1% (84/694)	7.9% (55/694)	6.3% (44/694)	24.3% (219/901)	22.8% (216/947)

Table 3. Detailed data on 13 potential risk factors for the HO after acetabular fractures

Potential risk	No of studies	Pooled OR	LL 95% CI	UL 95% CI	*P* value	Q-test (P)	$^{c}I^2$ (%)
Race							
African Americans	2	0.785	0.271	2.28	0.657[b]	0.004	87.9
Caucasians	2	1.088	0.408	2.904	0.866[b]	0.093	64.5
Male	4	0.900	0.647	1.250	0.528[a]	0.353	8.0
T-type fracture	3	1.193	0.534	2.663	0.667[b]	0.077	61.1
Associated head injury	7	2.390	1.180	4.841	0.016[a]	0.242	24.4
Chest/abdomen injuries	2	1.297	0.058	29.01	0.870[b]	0.001	90.1
Associated spine injury	2	1.516	0.630	3.65	0.353[a]	0.693	0
Trochanteric osteotomy	2	8.012	0.09	714.6	0.364[b]	<0.001	93.3
Multiple operative findings	2	0.901	0.08	10.15	0.933[b]	0.008	85.8
Iliofemoral approach	2	5.521	2.613	11.67	<0.001[b]	0.024	80.2
KL approach	3	0.643	0.205	2.015	0.116[a]	0.448	53.6
No indomethacin	4	3.45	1.23	9.68	0.019[b]	0.040	63.9
Irradiation	2	0.81	0.54	1.217	0.311[a]	0.135	55.2

OR, odds ratio; LL, lower limit; UL, upper limit; KL, Kocher-Langenbeck. [a]Fixed-effects model was performed. [b]Random-effects model was performed. $^{c}I^2$ statistic was defined as the proportion of heterogeneity not due to chance or random error.

Incidence rate of HO

As presented as **Table 2**, the overall incidence of HO was 30.0%; Class-1 HO based on Brooker classification system was the most common one with the incidence of 16.9, followed in sequence by Class-2 (12.1%), Class-3 (7.9%) and Class-4 (6.3%). In clinics, Classes 2-4 HO are recognized as contributors to functional damage and therefore considered as clinically significant ossification, associated with a loss of hip movement of more than 20%. In this study, 24.3% of acetabular fracture patients by ORIF developed Brooker class 2-4 HO and 22.8% developed into class 3-4.

Meta-analysis for associated risk factors

A meta-analysis of combinable data was conducted to analyze the risk factors for HO after acetabular fractures, and the main results were summarized in **Table 3**. The combined odds ratios ranged from 0.785 to 8.012. Significant heterogeneity was observed among studies when evaluating the potential risk factors including race, fracture type, associated chest/abdomen injuries, trochanteric osteotomy and approach. On the basis of the combined ORs and corresponding 95% CI, the significantly increased risk factors were associated head injury (OR, 2.390; 95% CI, 1.180-4.841), Iliofemoral approach (OR, 5.521; 95% CI, 2.613-11.67) and no prophylaxis of indomethacin (OR, 3.450; 95% CI, 1.230-9.680). Male gender appears not a significant risk factor for development of HO. The outcomes of these variables were presented by forest plots (**Figure 2**). The other variables including race, fracture type, associated chest/abdomen injuries, trochanteric osteotomy, spine injury, Kocher-Langenbeck (KL) approach and irradiation were identified not as the risk factors for HO after the acetabular fracture (P>0.05).

We performed the sensitive analysis for the risk factor of no prophylaxis of indomethacin 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 that the I^2-value from 63.9% lowered stepwise to 54.2% and to 0, and the significance did not alter, indicating the result robust. The detailed information of sensitive analysis was presented in Supplementary Figure 1.

Discussion

HO after acetabular fractures treated by ORIF is an important postoperative complication that compromises this successful procedure for treatment of severe injuries. Typical clinical signs and symptom as swelling, pain and reduced ROM commonly occurred within months of the causal injury [35]. In this study, we revealed the overall incidence of HO after acetabular fractures was 30.0% ranging from 10.2% to 74.3%, and clinically significant HO of Brooker 2-4 and 3-4 developed in 24.3% and 22.8% of acetabular fracture patients, respectively. Given the

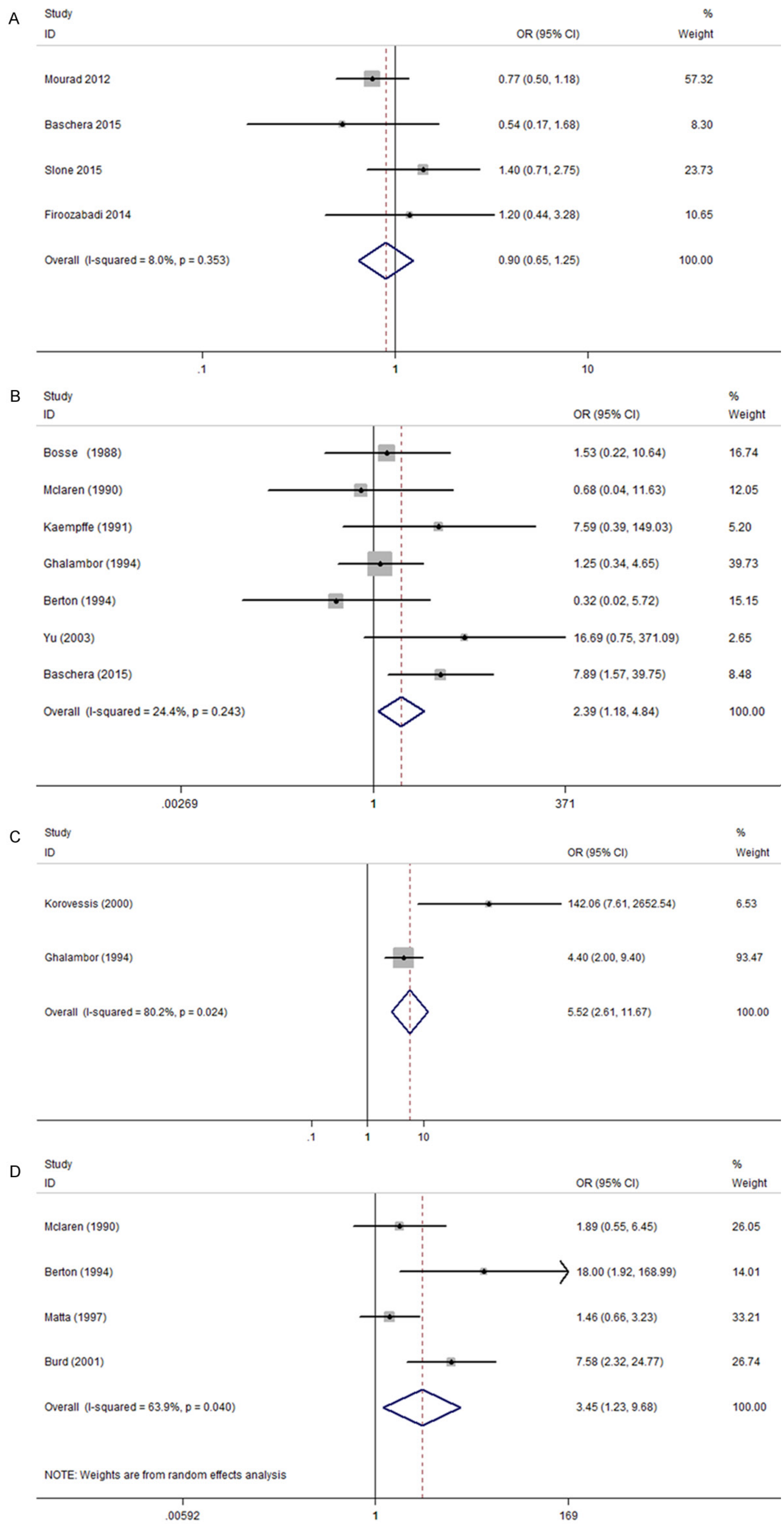
A
Study ID
OR (95% CI)
% Weight
Mourad 2012 0.77 (0.50, 1.18) 57.32
Baschera 2015 0.54 (0.17, 1.68) 8.30
Slone 2015 1.40 (0.71, 2.75) 23.73
Firoozabadi 2014 1.20 (0.44, 3.28) 10.65
Overall (I-squared = 8.0%, p = 0.353) 0.90 (0.65, 1.25) 100.00
.1
1
10
B
Study ID
OR (95% CI)
% Weight
Bosse (1988) 1.53 (0.22, 10.64) 16.74
Mclaren (1990) 0.68 (0.04, 11.63) 12.05
Kaempffe (1991) 7.59 (0.39, 149.03) 5.20
Ghalambor (1994) 1.25 (0.34, 4.65) 39.73
Berton (1994) 0.32 (0.02, 5.72) 15.15
Yu (2003) 16.69 (0.75, 371.09) 2.65
Baschera (2015) 7.89 (1.57, 39.75) 8.48
Overall (I-squared = 24.4%, p = 0.243) 2.39 (1.18, 4.84) 100.00
.00269
1
371
C
Study ID
OR (95% CI)
% Weight
Korovessis (2000) 142.06 (7.61, 2652.54) 6.53
Ghalambor (1994) 4.40 (2.00, 9.40) 93.47
Overall (I-squared = 80.2%, p = 0.024) 5.52 (2.61, 11.67) 100.00
.1
1
10
D
Study ID
OR (95% CI)
% Weight
Mclaren (1990) 1.89 (0.55, 6.45) 26.05
Berton (1994) 18.00 (1.92, 168.99) 14.01
Matta (1997) 1.46 (0.66, 3.23) 33.21
Burd (2001) 7.58 (2.32, 24.77) 26.74
Overall (I-squared = 63.9%, p = 0.040) 3.45 (1.23, 9.68) 100.00
NOTE: Weights are from random effects analysis
.00592
1
169

Figure 2. Forest plots of the meta-analysis of risk factors for HO after acetabular fractures: (A) Male gender, (B) Associated brain trauma, (C) Iliofemoral approach and (D) No prophylaxis of Indomethacin. The width of the horizontal line represents the 95% CI of the individual studies, and the square represents the proportional weight of each study. The diamond represents the pooled ORs and 95% CI.

controversies on the potential risk factors still existing, we also performed a meta-analysis and significantly increased risk factors associated were associated brain injury, iliofemoral approach and no perioperative prophylaxis of indomethacin. Other factors including race, fracture type, associated chest/abdomen injuries, trochanteric osteotomy, spine injury, Kocher-Langenbeck (KL) approach and irradiation were identified not as the risk factors for HO after the acetabular fracture were not contributors for the development of HO.

This study revealed that, the traumatic brain is the only preoperative trauma-related significant risk factor for development of HO (OR, 2.39), which is consistent with literature [2, 11, 19, 22-24]. As commonly accepted in literature that, HO is more frequent in patients with a combination of fractures and neurological damage than in those only have fractures, local trauma of joints and muscles or brain injuries [23, 25-27]. However, the pathophysiology of HO formation secondary to combined traumatic brain remains poorly understood. Several hypothetical views were performed which may contribute to its formation. Lerner et al. proposed that, activated certain neuro-osseous signals released from traumatic brain might have direct effect on bone metabolism and differentiation of progenitor cells, potential molecules include leptin, calcitonin gene related protein, glutamate, substance P, vasoactive intestinal peptide, and catecholamines [28]. In the study of Nauth et al., it is suggested systemic factors in conjunction with local tissue stimuli activated by CNS signals promote the osteogenic differentiation of progenitor cells and result in the development of HO [29]. Molecular mechanism of HO formation needs to be illuminated. In contrast, combined spine injury was identified not a significant risk factor for HO occurrence after acetabular fractures, which might be compromised by the insufficient patients in the original studies. The traumatic brain as a significant factor was decided upon the trauma occurring and could hardly be modified. Patients with combined traumatic brain should be kept in mind to prepare primary prophylaxis or as a reminder to reduce the risk of HO.

The extensile iliofemoral approach was a significant intra-operative risk factor for HO after acetabular fractures, similar with findings in other studies [9, 10, 12, 30]. A high incidence of 26.0% for clinically significant HO was observed in complex acetabular fracture even treated through a modified extended iliofemoral approach [30]. Regarding the efficacy and safety, how to objectively and impartially evaluate the role of extensile iliofemoral approach in treatment of complex acetabular fractures especially involving both columns with extension into the sacroiliac joint seems difficult. On one hand, for those complex acetabular fractures precise reduction was a primary and decisive factor that influences the postoperative functional recovery, which to a significant degree necessities best surgical exposure and iliofemoral approach and mostly extensile one exactly right meets this requirement. On the other hand, more soft tissue stripping and more bone debris in extensile iliofemoral approach are performed, which could be the very important risk factors for development of HO and other comorbidities such as avascular femoral head necrosis. Furthermore, the extended iliofemoral approach is the most challenging of the standard three approaches including ilioinguinal or Kocher-Langenbeck (KL) and need a very long learning curve. Therefore, Routt et al. suggested the use of combined or sequential exposure of KL ilioinguinal approaches for surgeons unfamiliar with this approach [31]. Similar as Routt et al., Griffin held that avoidance of extended iliofemoral approach ideally minimized the intra and post-operative comorbidities [9].

Irradiation as a prophylaxis has been used for several decades and was commonly recognized effective for reduction of HO after acetabular fractures. However in this study, no significance was found regarding its efficacy (P>0.05), which might be due to the inclusion of insufficient cases. Recently, some complications after primary prophylaxis of irradiation for development of HO after acetabular fractures were reported sporadically, such as malignant transformation and fracture mal-union or non-union, but existing clinical evidence did not support a developmen at recommended doses [32]. Besides, high-cost of therapy and the need for transportation for patients with multiple injuries and unstable medical conditions limit its utility.

The efficacy of indomethacin as a prophylactic measure for HO is controversial, even is compromised by complications such as gastrointestinal tract intolerance, disturbance of anticoagulation profile, and platelet inhibition in patients, especially when interacting with other anti-thromboembolic agents. In this study, prophylactic indomethacin was found to significantly reduce the incidence of HO (OR, 3.45; P=0.019). Despite some concerns about its clinical use existing, for example up to 45 percent of surgeons deciding to use this agent are driven by literature support and 2% prescribed HO prophylaxis due to medico-legal concerns [33], this significance did provide a robust evidence base on this key issue. Similar finding was observed in the study by Slone et al. [8], and his suggested standard post-operative protocol of prophylactic indomethacin in selected circumstances, such as severe head injury, the use of the extended iliofemoral approach, or observation of extensive muscle damage, is worth advocating. We are hopeful that this inexpensive, safe and simple treatment would yield its greatest value in acetabular fracture patients at high-risk for HO.

In this study, some potential risk factors were not pooled and calculated in current study due to the inconsistent quantitative criteria or reported in only a single study, such as combined femoral head injury, debris in joint and prolonged interval from injury to treatment and so on, which required more prospective studies to confirm.

Some limitations in this meta-analysis have to be mentioned. Firstly, a weakness exists in the analyses that not all the ORs regarding the potential risk factors applied for the meta-analysis are adjusted because a lot of reports could only provide the univariate rather than multivariate statistics; likewise, some studies might choose not to report the insignificant results or results of no interest, potentially resulting in a considerable amount of missing data. Hence, our overall effect may be somewhat over-estimate. Secondly, most of the included studies were observational and therefore with inevitable recall and interviewer biases, which might affect the associations between the risk and HO. Thirdly, the measurements of various risk factors differed from each other, and follow-up periods ranged widely from several months to several years. Therefore, a significant heterogeneity was unavoidable in this review, but the sensitive analysis by excluding outlier studies was performed indicating the corresponding pooled results robust.

Despite these limitations, this study has some advantages. Firstly, a comprehensive search strategy based on computer-assisted and manual searching avoided any eligible study to omission. Secondly, sensitive analysis by excluding outlier studies was performed and no abnormal results were observed, suggesting the results reliable. Finally but above all, this is by far the first study to quantitatively summarize risk factors for development of HO after acetabular fractures treated by ORIF. Identification of these risk factors could contribute to screening for at-risk patients and thereby targeting them for relevant primary prophylaxis especially use of indomethacin.

Conclusion

In summary, the present meta-analysis suggested that patients involved with associated traumatic brain are at high-risk for development of HO after acetabular fractures. When possible, avoiding iliofemoral approach at surgery and perioperative prophylaxis of indomethacin could obviously reduce the occurrence of HO and should be advocated.

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Disclosure of conflict of interest

None.

Authors' contribution

Yingze Zhang designed the study; Yanbin Zhu and Linlin Ju searched relevant studies and abstracted the data; Wei Chen and Xiuting Li analyzed and interpreted the data; Yanbin Zhu, Chenni Ji and Xiuting Li wrote the manuscript and Yingze Zhang approved the final version of the manuscript.

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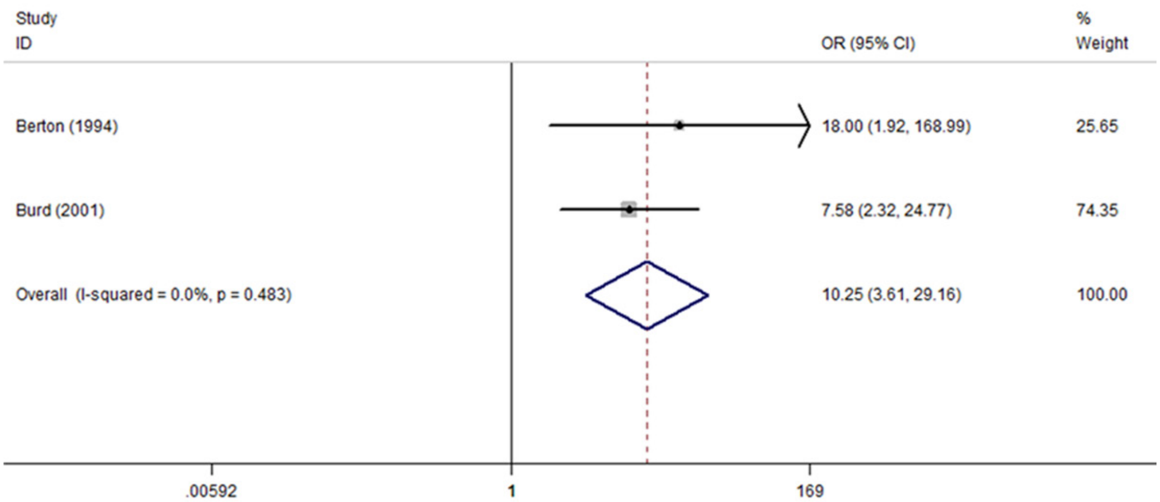

Supplementary Figure 1. Sensitive analysis for the risk factor of no prophylaxis of indomethaxin for HO after acetabular fractures treated by ORIF by excluding outlier studies written by Mclaren and metta et al.