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The incidence of postoperative heterotopic ossification in cervical disc arthroplasty–A systematic review and meta-analysis

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Research article

Keywords: cervical disc arthroplasty (CDA), heterotopic ossification (HO), incidence, meta-analysis

Posted Date: October 16th, 2019

DOI: https://doi.org/10.21203/rs.2.11474/v2

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Abstract

Background: Heterotopic ossification has become a common disease after CDA, which has attracted much attention. Understanding the law of its occurrence and development can provide theoretical basis for the formulation of HO prevention strategies. To acquire the objective data and the change rule of HO incidence, a meta-analysis of all available evidence was performed. Methods: A search of the literature was conducted on Pubmed/MEDLINE, EMBASE, and Web of Science. Relevant studies including incidence-relative data of HO were selected according to eligibility criteria. Results: 52 studies were eligible and finally included and the quality assessment showed a relative high score of them. The results of the analysis reminded us that the incidence of HO increased with the extension of follow-up time, both based on the number of cases and the number of segments, and the increase mainly occurred after 6 years. Grade III-IV HO showed us a positive correlation with follow-up time (R2=0.218), while Grade I-II HO did not change a lot in different follow-up time points. Conclusions: The follow-up time after CDA should be long enough, so as to ensure the true clinical results. HO occurs all the postoperative time and Grade I-II HO will gradually develop into Grade III-IV, while continuous new HO keeps the number of Grade I-II in a dynamic balance. Through this study, we can preliminarily define the relatively objective incidence and change rule of HO, which provides data basis and theoretical basis for the future research of HO prevention strategy.

Background

At present, cervical disc degenerative disease (CDDD) has become the important cause of endangering health and affecting quality of life among middle-aged and elderly people[1-3]. Along with the development of the society and the acceleration of work pace, more and more young people are suffering from it. Late stage or severe CDDD will progress to herniated disc and cervical spinal stenosis, requiring operation with heavy financial burden.

Decades ago, anterior cervical decompression and fusion (ACDF) became the gold standard for treating CDDD. With the continuous development of clinical surgery technology, new generations of fusion devices keep appearing, the fusion rate keeps increasing, and postoperative complications are becoming less and less. And as the technology reaches its zenith, its own shortcomings are gradually being highlighted. The loss of cervical mobility after fusion, especially in multi-segment surgery, leads to a decrease in patients' quality of life. On the other hand, the adjacent segment disease (ASD) caused by the increase of compensatory activity also attracts the attention of spine surgeons.

In this medical background, the concept of non-fusion is particularly valuable. At first, clinical scholars tried to apply artificial disc and artificial nucleus pulposus in the treatment of lumbar disc degeneration, but the clinical effect was not significantly different from that of fusion surgery[4]. Considering the significant impact of cervical mobility on quality of life, more research was devoted to the study of artificial cervical disc or cervical dynamic stabilization device. Starting with Bryan disc of Medtronic, a series of bionic artificial prosthesis are coming into the market one by one, and all of them have achieved good clinical effects. Because the artificial disc can maintain the range of motion of the surgical segment, it can prevent the occurrence of ASD to some extent[5].

However, with the deepening of research and clinical follow-up, the heterotopic ossification (HO) after cervical disc arthroplasty (CDA) compromised the clinical value of this emerging operation greatly. HO is defined as the process by which trabecular bone forms outside of the normal skeletal structure, occupying space in soft tissue where it shouldn’t exist, which was firstly reported in the total hip arthroplasty-related postoperative complication[6, 7]. Presently, the mechanism of HO is not clear, and there is no well-accepted effective prevention strategy. In most of these researches, they would regard ACDF as a reference but have overlooked the uniqueness of CDA. Keeping physiological ROM of neck for patients is the primary destination when CDA was firstly designed for clinical use. Therefore, only with great recover from NDI, JOA, VAS or some other clinical assessment, we cannot get the conclusion that HO is not clinically relevant. We must first understand the occurrence of HO, which is also a theoretical premise to prevent the complication. In this paper, the incidence of HO was meta-analyzed and relevant conclusions were drawn.

Methods

The study is a systematic review and meta-analysis, and the ethics statement is not necessary.

2.1. Searching Strategy

We have searched Medline, Web of Science, and Embase for the articles published from the inception to March, 2019. The searching strategy was built with the following terms: (((cervical disc replacement[Title/Abstract]) OR cervical disc arthroplasty[Title/Abstract])) AND ((heterotopic ossification) OR HO). The references of all publications were also retrieved to obtain possible studies.

2.2. Inclusion and exclusion criteria

Studies were included if they met the following inclusion criteria:

(1). Study design was cohort study or randomized controlled trials.

(2). Patients in study had received CDA.

(3). The HO incidence of one or several time points were reported.

(4). The HO in the studies was graded by McAfee's classification system.

(5). Articles were written with English or Chinese.

Publications were excluded if they were with following characteristics:

(1). Review articles, meta-analysis, cases reports, animal/cadaver studies, editorials, or letters.

(2). The type of prosthesis was inappropriate, for example, the Dynamic Cervical Implant (DCI).

(3). Article was not formally published, only with an "accepted" status.

(4). Study was with repeated or un-extractable data.

(5). Multi-center trial.

The screen process of studies was carried out independently by 2 authors.

2.3. Data extraction

For each study included, the following data and information were collected: first author, year of publication, type of prosthesis, study design, follow-up period, sample size, HO incidence. The data were independently extracted by 2 professors, and any disagreements were resolved by discussion and consensus. Data on the incidence of HO were divided into several subgroups based on the length of follow-up of every single year from 6 months to 114 months.

2.4. Quality assessment

Here we used the methodological scoring system reported by Loney et al[8] to to evaluate the included studies. The evaluation system has a maximum score of 8 points as listed in **Table-1**. The quality of included studies was evaluated independently by 2 authors.

2.5. Statistical analysis

We calculated the overall incidence of HO with 95% confidence intervals (CIs), and obtained corresponding forest plots. The I^2 statistic and Q tests were used to quantify the heterogeneity (I^2 ≤25% as low heterogeneity, 25-75% as moderate heterogeneity, and ≥75% as severe heterogeneity). In this meta-analysis, random-effects model was used. We use the following transformation to merge and analyze the two-category data[9]:

While the x and (n-x) are both bigger than 5:

P = x/n

SE(P) = SQRT [P(1 - P)/n]

While one of the x or (n-x) is equal to or smaller than 5:

P = ln [x/(n - x)]

SE(P) = SQRT [1/x + 1/(n - x)]

All of the analyses were performed with RevMan 5.3.

Results

3.1. Searching results

The initial database search identified a total of 327 records and duplicate-check removed 123 of them. After the titles and abstracts were reviewed, 14 of them were eliminated. A full-text review was evaluated in the 190 records maintained, and 138 of them were excluded because of they didn't meet the inclusion criteria. Finally, 52 articles, meeting the inclusion criteria, were included in the present meta-analysis. **Figure-1** shows the selection process and the characteristics of included studies were listed in **Table-2**. After the quality assessment of the included studies, 15 of them scores 7, 16 of them scores 6, 12 of them scores 5, and 9 of them scores 4. Hence, the quality of included studies is relatively satisfactory.

3.2. Annual incidence of HO

According to the follow-up period, we classified the included data with the interval of 12 months. When we based our assessment on the number of cases, as shown in Figure-2A and Figure-2B, the total incidence of HO, without limitation of follow-up period, was 39% (95% CI: 32%-47%, I^2=94% among the whole part, I^2=71.6% among the subgroups), and with the extension of follow-up period, the incidence increased year by year. Similarly, based on the number of levels, as shown in Figure-3A and Figure-3B, the total incidence of HO was 39% (95% CI: 33%-45%, I^2=94% among the whole part, I^2=64.8% among the subgroups), and with the extension of follow-up period, the incidence also increased year by year. The two statistical methods ended up with similar results. Actually, within 6 years, the HO incidence did not obviously change, while after 6 years, the incidence, no matter case-based or level-based, significantly increased.

3.3. Annual incidence of low-grade (Grade I-II) and high-grade (Grade III-IV) HO

According to the McAfee's grading system, as listed in Table-3 we divided the HO-level into 4 grades. Grade I-II HO would not affect the range of motion (ROM) of the index segments, while Grade III-IV HO was clinically-significant. In low-grade group, as shown in Figure-4A and Figure-4B, the annual incidence fluctuated between 0.14-0.32 (I^2=86% among the whole part, I^2=63.7% among the subgroups), and the Linear-regression analysis (Figure-4C) reminded us that there was no increasing trend along with the follow-up (R^2=0.013). Differently, in the high-grade group, the incidence gradually increased in the order of follow-up period, as shown in Figure-5A and Figure-5B (I^2=93% among the whole part, I^2=89.9% among the subgroups), and the Linear-regression analysis (Figure-5C) showed us that there is a slight increasing trend (R^2=0.218).

Discussion

CDA have already been the classical surgical procedure in anterior cervical approach, whose effect of treatment is the same as that of traditional ACDF. What's more, the ROM of index level could also be remained and the living quality of patients was improved. But unfortunately, the superiority of CDA has been seriously compromised by the occurrence of HO, especially in Grade III-IV group.

In large joints replacement, for example the total hip arthroplasty (THA), HO is a frequent complication and the exact mechanism of it remains unknown[60, 61]. Several inflammatory processes including a series of mediators and growth factors are possibly involved in the formation of HO, which leads to the recruitment of mesenchymal stem cells and the formation of bone. In recent years, with the gradual development of CDA, more and more clinicians have realized the significance of HO after cervical spine surgery. The mechanism of HO is still unclear, and many studies have suggested that it may be related to soft tissue injury, improper prosthesis size, and other factors. Accordingly, many

clinicians have put forward corresponding prevention strategies, such as thorough irrigation of the surgical field, postoperative use of NSAIDs drugs, etc., but with little effect, and there is no well-accepted prophylaxis.

In different reports, the incidence rate of HO varies greatly, which may be due to the different degree of understanding and diagnostic method of HO by different authors[62]. Through meta-analysis of existing data, this study attempted to obtain a relatively objective incidence of HO and explore its variation rule during follow-up period.

The results of the analysis showed that the incidence of HO increased with the extension of follow-up time, both based on the number of cases and the number of segments, and the increase mainly occurred after 6 years. This result suggests that the follow-up time after CDA should be long enough, especially for young patients, so as to ensure the true clinical results. On the other hand, based on the McAfee's grading system, we analyzed Grade I-II and Grade III-IV respectively, and found that the incidence of HO in Grade I-II did not increase significantly with the extension of follow-up time. On the contrary, the incidence of Grade III-IV HO increased with the extension of follow-up time. The results were verified in the Linear-regression analysis. This indicates that HO occurs all the postoperative time and Grade I-II HO will gradually develop into Grade III-IV, while continuous new HO keeps the number of Grade I-II in a dynamic balance.

The deficiency of this study mainly lies in that, in order to observe the principle of "prefer less to more", we added the entry of "exclude polycentric study" in the exclusion criteria, which is to prevent possible data duplication. However, this standard also makes the amount of data available reduce greatly. In some follow-up points, only 1-2 articles are included, so the data obtained are not objective enough. Moreover, we haven't registered a protocol for the SR/MA, which should be perfected in the future.

Through this study, we can preliminarily define the relatively objective incidence and change rule of HO, which provides data basis and theoretical basis for the future research of HO prevention strategy.

Conclusion

With the extension of follow-up time, the incidence of HO increased year by year, both in case- and level-based analyses, to which the Grade III-IV HO contributed a lot. HO would happen in anytime of follow-up period and the existing HO, on the other hand, would develop into the more severe grades.

Abbreviations

ACDF: anterior cervical decompression and fusion

ASD: adjacent segment disease

CDA: cervical disc arthroplasty

CDDD: cervical disc degenerative disease

HO: heterotopic ossification

Declarations

Consent for Publication: Not applicable.

Acknowledgements: The authors wish to extend their gratitude to Hong Ying (Operation Center, West China Hospital of Sichuan University) for designing and executing the database searches.

Funding: This study was supported by the National Natural Science Foundation of China (grant no. 81702156 to Y Meng).

Availability of data and materials: All relevant data has been provided in figures, tables and supplements.

Authors' contributions: Guo YJ and Liu H conceived of the study and developed its design and protocol. Chen JL organized the search and selection process; i.e. the electronic database search, removal of duplicates, coordinated the contributions of the other authors and drafted the manuscript. Eligibility and quality assessments were done by the following pairs of authors: Meng Y/Ding C and Wang BY/Rong X. Reference hand search was done by Guo YJ. Data-extraction in preparation for meta-analysis was done by Guo YJ and Chen JL. Figures and tables were prepared by Guo YJ. Guo YJ conducted the statistical pooling of data in Revman and helped to draft the first manuscript. All authors have read and approved the final manuscript.

Conflicts of interests: There's no conflicts of interests among all of the authors.

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Tables

Table-1 Guidelines of quality evaluation for prevalence studies

		Evaluation Items	Score
he study metods valid?	1	Are the study design and sampling method appropriate for the research question?	1
	2	Is the sampling frame appropriate?	1
	3	Is the sample size adequate?	1
	4	Are objective, suitable and standard criteria used for measurement of the outcome?	1
	5	Is the outcome measured in an unbiased fashion?	1
	6	Is the response rate adequate?	1
t is the interpretation of the results?	7	Are the estimates of prevalence or incidence given with confidence intervals and in detail by subgroup, if appropriate?	1
t is the applicability of the results?	8	Are the study subjects and the setting described in detail and similar to those of interest to you?	1
		Total	8

Table-2 Characteristics of included studies

Reference	Year	Author	Article Type	Prothesis	Follow-up Period (mo)	Levels	Cases					Points
							Total	1 level	2 levels	3 levels	4 levels	
[9]	2006	Mehren	PCS	Prodisc-C	12	77	54					5
[10]	2008	Heidecke	PCS	Bryan	24	59	54	49	5			6
[11]	2009	Bhadra	RCT	Bryan	24	15	15	15				7
[12]	2010	Barbagallo	RCS	Prestige-LP/Prodisc-C	36	45	30	19	7	4		5
[13]	2010	Joris	PCS	Bryan	96	81	81	81				6
[14]	2010	Kang	RCS	Bryan/Prodisc-C	31	41	41	41				4
[15]	2010	Lee	RCS	Bryan	14	48	48	48				7
[16]	2010	Ryu	RCS	Bryan/Prodisc-C	27.1	36	36	36				5
[17]	2010	Suchomel	PCS	Prodisc-C	48	65	54	44	9	1		7
[18]	2010	Zhao	RCS	Bryan	60	24	22	20	2			6
[19]	2010	Zhou	RCS	Bryan	30	54	54	54				6
[20]	2011	Gerald	PCS	Bryan	96	27	21	15	6			4
[21]	2011	Ren	PCS	Bryan	35	51	45	39	6			5
[7]	2011	Tu	PCS	Bryan	26.8	52	36	20	16			7
[6]	2012	Chen	PCS	Prestige-LP	24	31	31	31				4
[22]	2012	Chung	RCS	Bryan	18	19	19	19				5
[23]	2012	Guerin	PCS	Mobi-C	21	83	71					7
[24]	2012	Sun	RCT	Bryan	60.8	26	26	26				6
[25]	2012	Wu	RCS	Bryan	46.2	98	70	42	28			6
[26]	2012	Yan	RCS	Bryan	34	26	20	14	6			6
[27]	2013	Jin	RCS	Bryan/PCM/Prestige-LP	38	95	81					5
[28]	2013	Lan	RCS	Bryan	24	43	39	35	4			7
[29]	2013	Li	RCS	Discover	24	55	55	55				7
[30]	2013	Miao	PCS	Discover	24	102	79	56	23			6
[31]	2013	Pimenta	RCS	PCM	72	272	158	71	66	15	6	5
[32]	2013	Zhang	PCS	Bryan	48	23	20	17	3			7
[33]	2013	Zhao	RCS	Prodisc-C	63	26	26	26				4
[34]	2014	Fay	RCS	Bryan/Prestige-LP	36.4	172	151					7
[35]	2014	Malham	PCS	Prodisc-C	92.4	22	19	16	3			6

Table-2 Characteristics of included studies (Continued)

Reference	Year	Author	Article Type	Prothesis	Follow-up Period (mo)	Levels	Cases					Points
							Total	1 level	2 levels	3 levels	4 levels	
[36]	2014	Qi	RCS	Discover	26	154	125	96	29			5
[37]	2014	Suchomel	PCS	Activ C(TM)	24	159	159	159				5
[38]	2014	Yi	RCS	Bryan/Mobi-C/Prodisc-C	36.9	67	67	67				6
[39]	2014	Zhang	RCT	Bryan/Prodisc-C	24		53					6
[40]	2015	Lee	RCT	Mobi-C	43.4	14	14	14				4
[41]	2015	Lei	RCT	Bryan	105	31	31	31				7
[42]	2015	Tu	PCS	Bryan	24	107	75	43	32			6
[43]	2016	Chang	RCS	Bryan/Prestige-LP /Prodisc-C	24	88	88	88				7
[44]	2016	Chen	RCS	Bryan	68.4	52	52	52				7
[45]	2016	Meisel	PCS	Activ C(TM)	48	151	151	151				4
[46]	2016	Shi	RCT	Discover	24	60	60	60				5
[47]	2016	Tian	RCS	Bryan	79.2	82	71	61	9	1		6
[48]	2016	Turner	RCS	NuNec(TM)	24	44	33	23	9	1		7
[49]	2016	Zhao	RCS	Bryan	120.5	42	33	27	7	1		4
[50]	2017	Dong	RCS	Baguera C	32	48	48	48				5
[51]	2017	Kim	RCT	Prestige-LP	82.5	17	17	17				4
[52]	2017	Mehren	PCS	Prodisc-C	120	70	50	27	17	3		7
[53]	2017	Vincent	PCS	Bryan	186	22	18	14	4			7
[54]	2017	Wu	RCS	Prestige-LP	24	50	25		25			5
[55]	2018	Feng	RCT	Bryan/Discover/Prestige-LP/Prodisc-C	46.8	218	218	218				6
[56]	2018	Gao	RCS	Prestige-LP	64	24	24	24				6
[57]	2018	Zeng	RCS	Prestige-LP	82.3	45	61	16				4
[58]	2018	Zhou	RCS	Bryan	94.2	76	61	47	13	1		6

NOTE. RCS, retrospective cohort study; PCS, prospective cohort study; RCT, randomized controlled study;

Table-3 McAfee Classification of Heterotopic Ossification

Grades	Description
Grade 0	No HO present
Grade 1	HO is detectable anterior to the vertebral body but not in the anatomic discal space
Grade 2	HO is growing into the disc space. Possible interference with function of the prosthesis
Grade 3	Bridging ossifications noted but motion of the prosthesis persists
Grade 4	Complete fusion of the treated segment without movement of prosthesis in flexion/extension

Figures

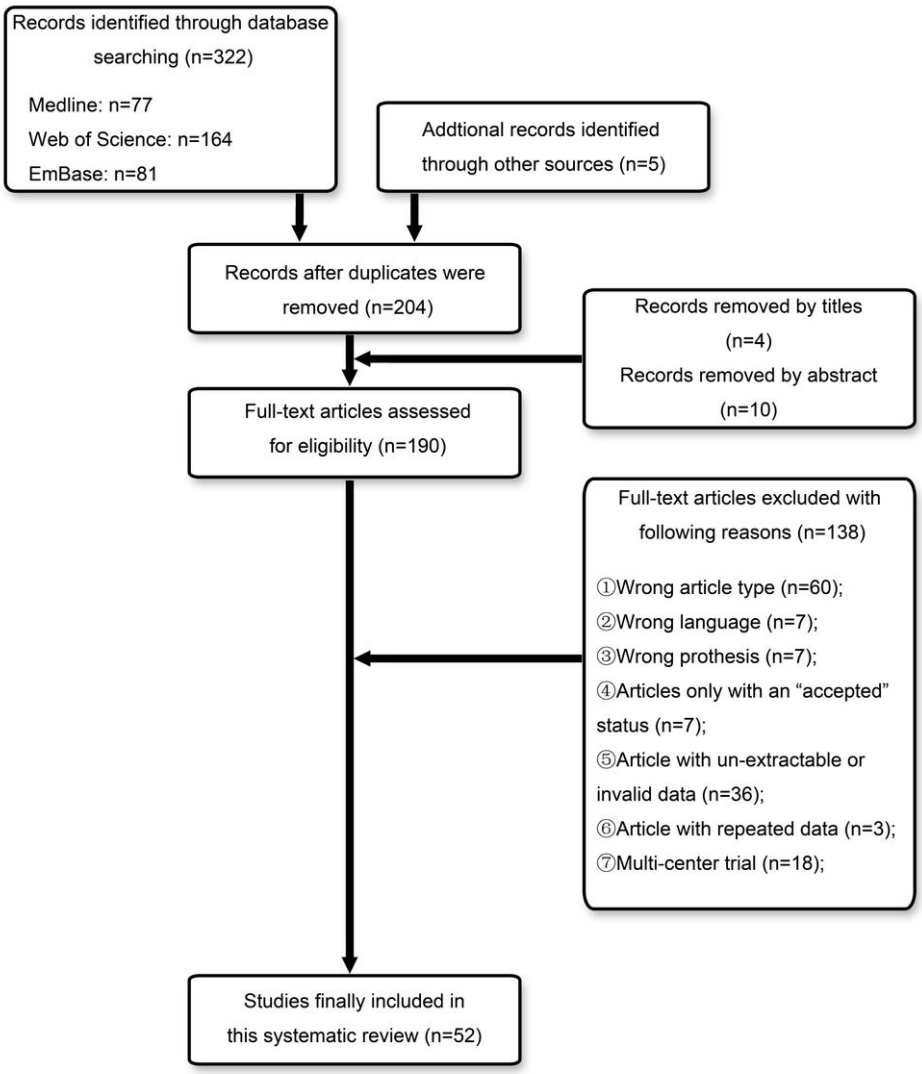

Figure 1

Flowchart for identification and inclusion of relevant studies

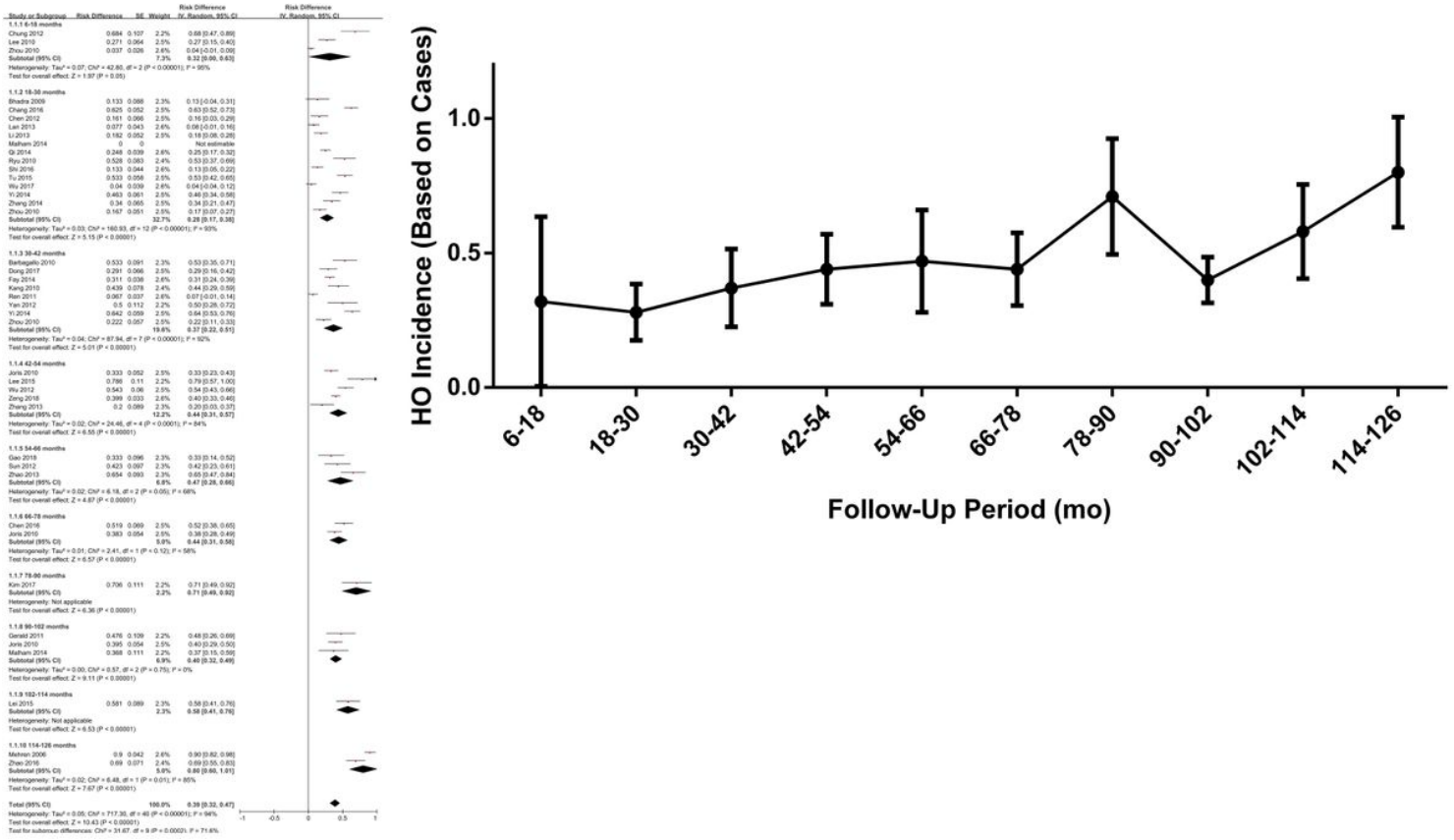

Figure 2

a Forest plots of annual incidence of HO based on cases number b Annual incidence of HO based on cases number Annual incidence of HO based on cases number showed us an increasing trend along with the follow-up period.

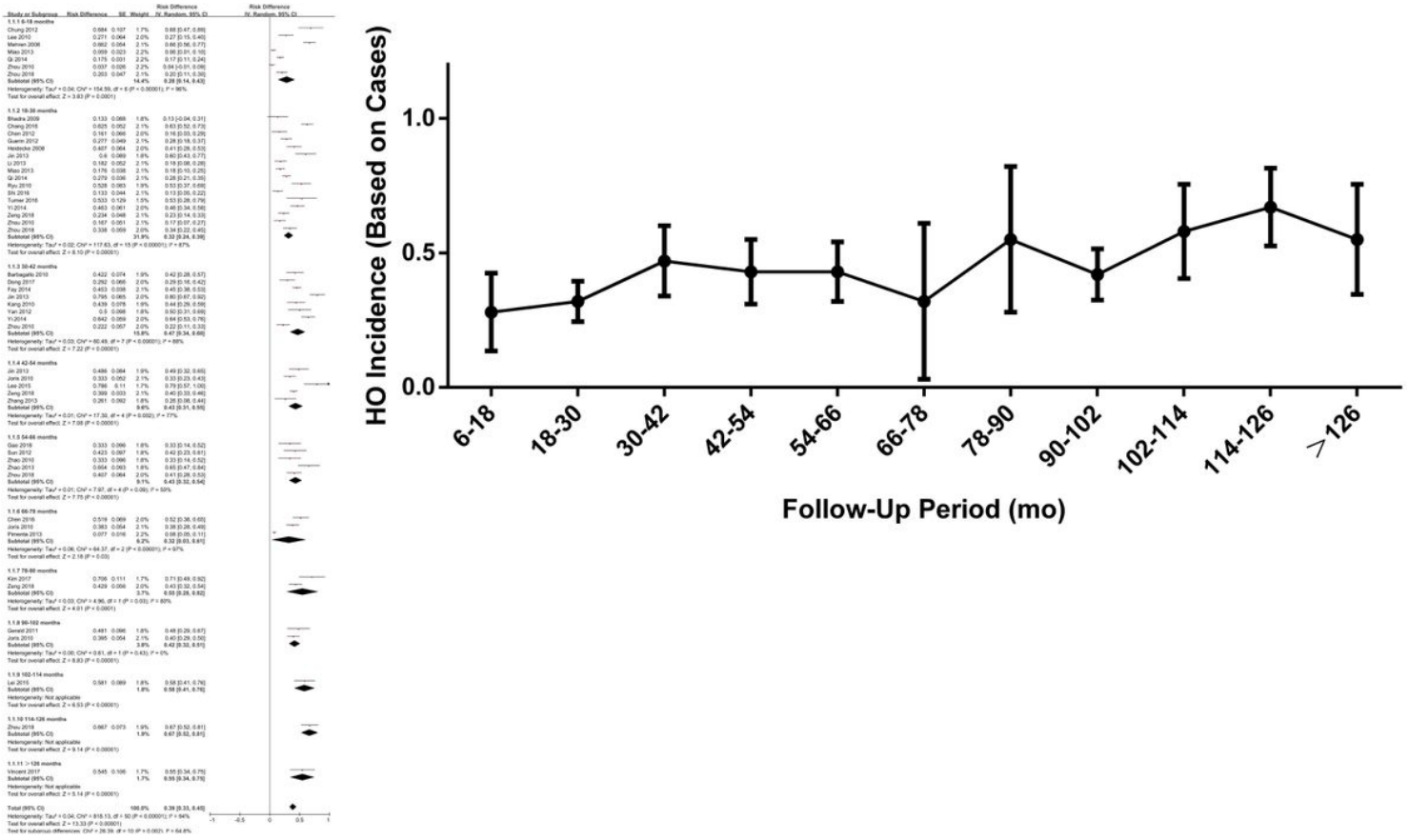

Figure 3

a Forest plots of annual incidence of HO based on levels number b Annual incidence of HO based on levels number Annual incidence of HO based on levels number showed us an increasing trend along with the follow-up period.

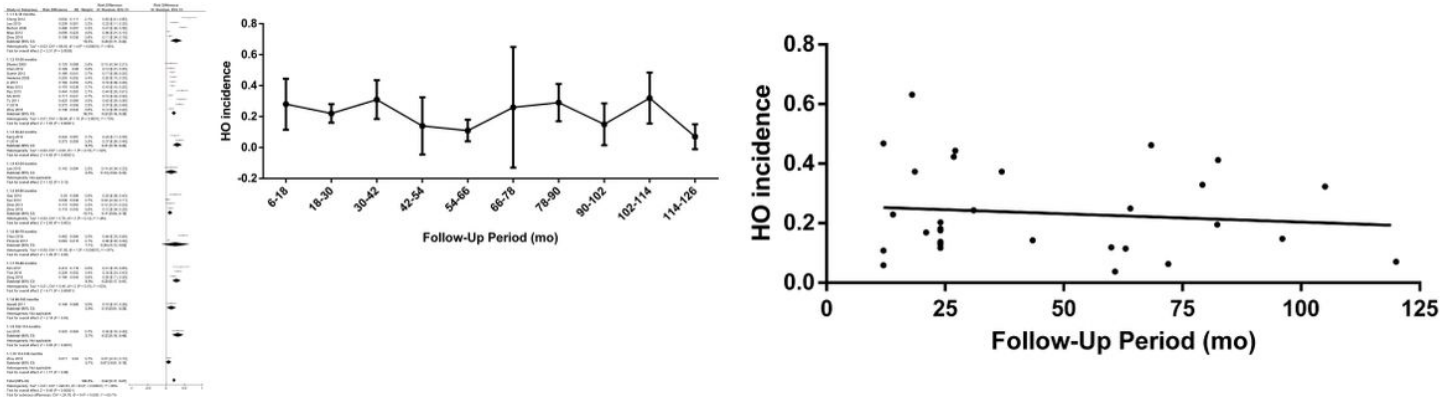

Figure 4

a Forest plots of annual incidence of Grade I-II HO b Annual incidence of Grade I-II HO There's no obvious increasing trend in the annual incidence of Grade I-II HO. c Linear-regression analysis of Grade I-II HO incidence and Follow-up Period The linear-regression analysis of Grade I-II HO incidence and follow-up period showed no significant correlation (R2=0.013).

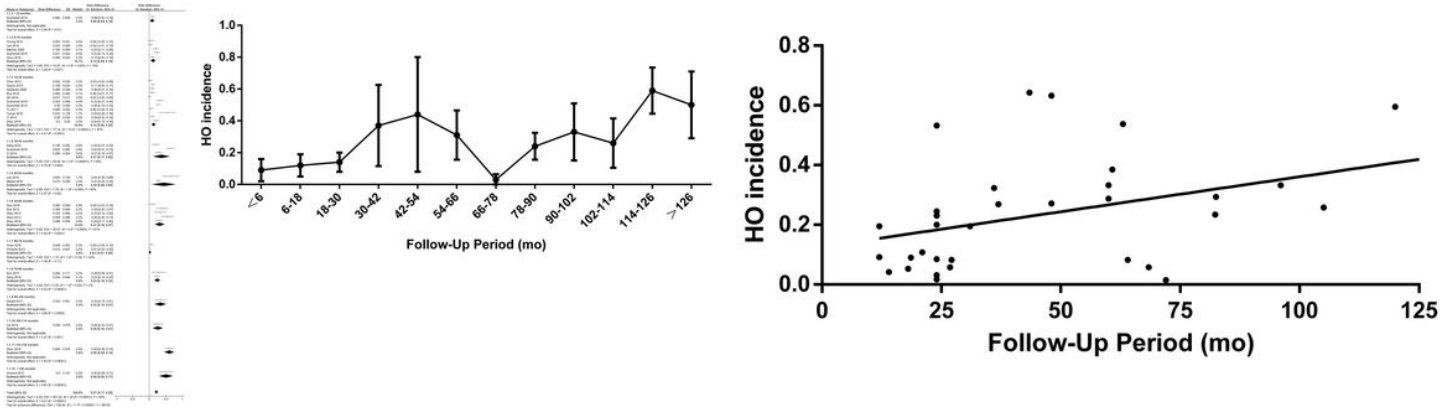

Figure 5

5A Forest plots of annual incidence of Grade III-IV HO 5B Annual incidence of Grade III-IV HO There's a slightly increasing trend in the annual incidence of Grade III-IV HO. 5C Linear-regression analysis of Grade III-IV HO incidence and Follow-up Period The linear-regression analysis of Grade III-IV HO incidence and follow-up period showed a slight correlation (R2=0.218).

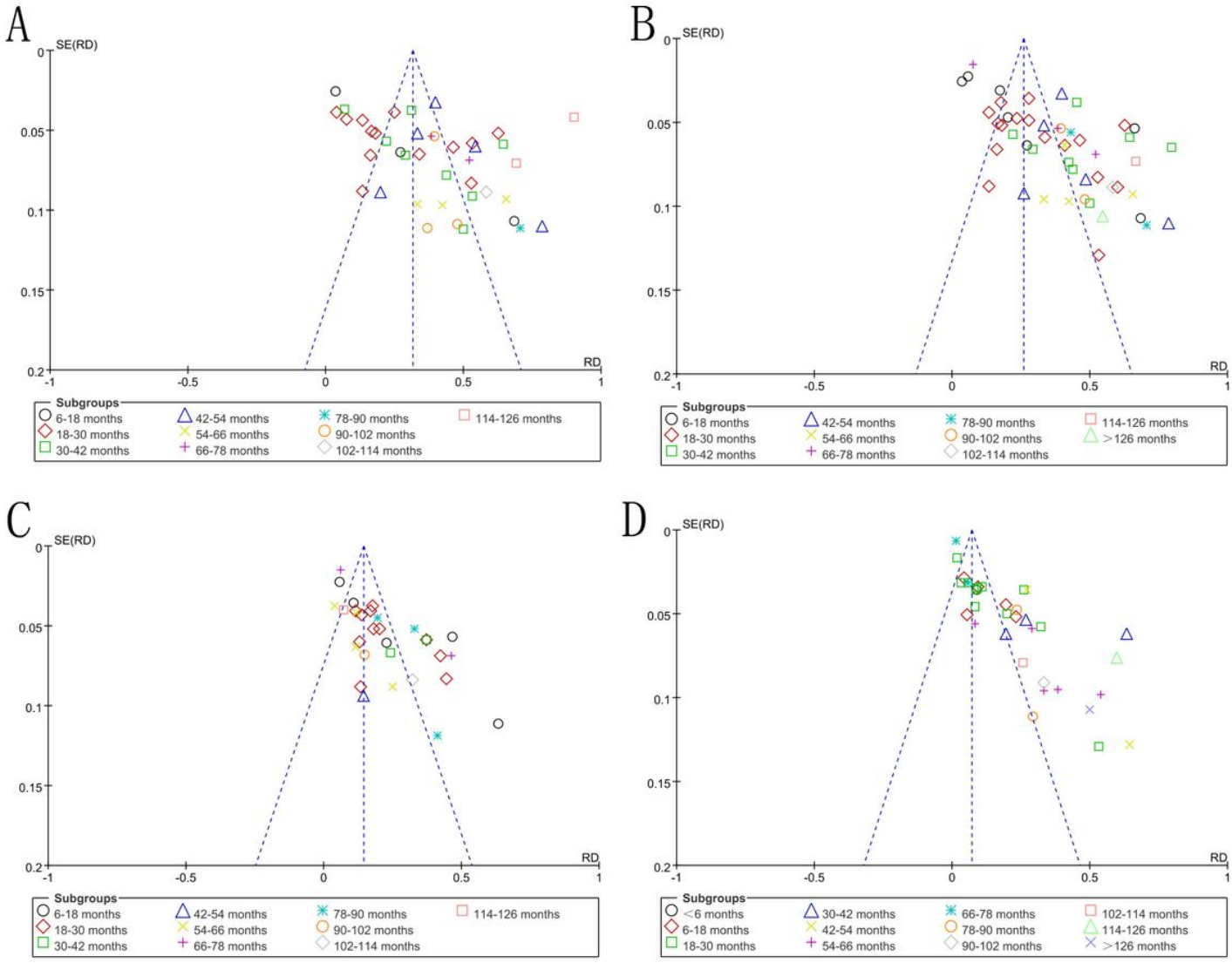

Figure 6

Funnel plots of included data. Figure-6A: Funnel plot of case-based data; Figure-6B: Funnel plot of level-based data; Figure-6C: Funnel plot of Grade I-II data; Figure-6D: Funnel plot of Grade III-IV data.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAchecklist.pdf
- Listofallexcludedstudies.xlsx