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

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Abstract

Background: Heterotopic ossication 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. 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 randomized cohort study or 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.

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.

2.4. Quality assessment

Here we used the methodological scoring system reported by Loney et al[8] 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 evaluate the heterogeneity. If $I^2$ value was bigger than 50%, we considered that significant heterogeneity was existing. In this meta-analysis, random-effects model was used. We use the following transformation to merge and analyze the two-category data:

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

$P = \frac{x}{n}$

$SE(P) = \sqrt{ \frac{P(1-P)}{n} }$
While one of the x or (n-x) is equal to or smaller than 5:

\[ P = \ln \left( \frac{x}{n-x} \right) \]

\[ \text{SE}(P) = \sqrt{\frac{1}{x} + \frac{1}{n-x}} \]

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.

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%), 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%), 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, 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, and the Linear-regression analysis (Figure-5C) showed us that there is a slight increasing trend \( (R^2=0.218) \).

3.4. Analysis of publication bias

As shown in Figure-6, the characteristics of the four parts are similar. The distribution of included data is relatively discrete and symmetrical, reminding us that the publication bias were found insignificant, while the data varied widely from one study to another.

**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.

In large joints replacement, for example the total hip arthroplasty (THA), HO is a frequent complication and the exact mechanism of it remains unknown[59, 60]. 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 [61]. 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.

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.

Declarations

Consent for Publication: Not applicable.

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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.

Abbreviation

ACDF: anterior cervical decompression and fusion

ASD: adjacent segment disease
References

1. Health Quality O: Cervical Artificial Disc Replacement Versus Fusion for Cervical Degenerative Disc Disease: A Health Technology Assessment. *Ontario health technology assessment series* 2019, 19(3):1-223.

2. MacDowall A, Canto Moreira N, Marques C, Skepholm M, Lindhagen L, Robinson Y, Lofgren H, Michaelsson K, Olerud C: Artificial disc replacement versus fusion in patients with cervical degenerative disc disease and radiculopathy: a randomized controlled trial with 5-year outcomes. *Journal of neurosurgery Spine* 2019, 30(3):323-331.

3. Joaquim AF, Makhni MC, Riew KD: Evidence-based use of arthroplasty in cervical degenerative disc disease. *International orthopaedics* 2019, 43(4):767-775.

4. Eijkelkamp MF, van Donkelaar CC, Veldhuizen AG, van Horn JR, Huyghe JM, Verkerke GJ: Requirements for an artificial intervertebral disc. *The international journal of artificial organs* 2001, 24(5):311-321.

5. Li J, Xu W, Zhang X, Xi Z, Xie L: Biomechanical role of osteoporosis affects the incidence of adjacent segment disease after percutaneous transforminal endoscopic discectomy. *Journal of orthopaedic surgery and research* 2019, 14(1):131.

6. Chen F, Yang J, Ni B, Guo Q, Lu X, Xie N: Clinical and radiological follow-up of single-level Prestige LP cervical disc replacement. *Archives of orthopaedic and trauma surgery* 2013, 133(4):473-480.

7. Tu TH, Wu JC, Huang WC, Guo WY, Wu CL, Shih YH, Cheng H: Heterotopic ossification after cervical total disc replacement: determination by CT and effects on clinical outcomes. *Journal of neurosurgery Spine* 2011, 14(4):457-465.

8. Loney PL, Chambers LW, Bennett KJ, Roberts JG, Stratford PW: Critical appraisal of the health research literature: prevalence or incidence of a health problem. *Chronic diseases in Canada* 1998, 19(4):170-176.

9. Mehren C, Suchomel P, Grochulla F, Barsa P, Sourkova P, Hradil J, Korge A, Mayer HM: Heterotopic ossification in total cervical artificial disc replacement. *Spine* 2006, 31(24):2802-2806.

10. Heidecke V, Burcket W, Brucke M, Rainov NG: Intervertebral disc replacement for cervical degenerative disease—clinical results and functional outcome at two years in patients implanted with the Bryan cervical disc prosthesis. *Acta neurochirurgica* 2008, 150(5):453-459; discussion 459.

11. Bhadra AK, Raman AS, Casey AT, Crawford RJ: Single-level cervical radiculopathy: clinical outcome and cost-effectiveness of four techniques of anterior cervical discisectomy and fusion and disc arthroplasty. *European spine journal*: official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 2009, 18(2):232-237.

12. Barbagallo GM, Corbino LA, Olindo G, Albanese V: Heterotopic ossification in cervical disc arthroplasty: Is it clinically relevant? *Evidence-based spine-care journal* 2010, 1(1):15-20.

13. Walraevens J, Demaerel P, Suetsens P, Van Calenbergh F, Van Loon J, Vander Sloten J, Goffin J: Longitudinal prospective long-term radiographic follow-up after treatment of single-level cervical disc disease with the Bryan Cervical Disc. *Neurosurgery* 2010, 67(3):679-687; discussion 687.

14. Kang KC, Lee CS, Han JH, Chung SS: The factors that influence the postoperative segmental range of motion after cervical artificial disc replacement. *The spine journal*: official journal of the North American Spine Society 2010, 10(8):689-696.

15. Lee JH, Jung TG, Kim HS, Jang JS, Lee SH: Analysis of the incidence and clinical effect of the heterotopic ossification in a single-level cervical artificial disc replacement. *The spine journal*: official journal of the North American Spine Society 2010, 10(8):676-682.

16. Ryu KS, Park CK, Jun SC, Huh HY: Radiological changes of the operated and adjacent segments following cervical arthroplasty after a minimum 24-month follow-up: comparison between the Bryan and Prodisc-C devices. *Journal of neurosurgery Spine* 2010, 13(3):299-307.

17. Suchomel P, Jurak L, Benes V, 3rd, Brabc R, Bradac O, Elgawhary S: Clinical results and development of heterotopic ossification in total cervical disc replacement during a 4-year follow-up. *European spine journal*: official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society 2010, 19(2):307-315.

18. Zhao YB, Sun Y, Chen ZQ, Liu ZJ: Application of cervical arthroplasty with Bryan cervical disc: long-term X-ray and magnetic resonance imaging follow-up results. *Chinese medical journal* 2010, 123(21):2999-3002.

19. Zhou L, Lu JY, Xu RM, Liang B, Sun SH, Zhao L: [Clinical observation of mid-stage complications after cervical disc replacement]. *Zhongguo gu shang = China journal of orthopaedics and traumatology* 2010, 23(7):514-517.
20. Quan GM, Vital JM, Hansen S, Pointillart V: Eight-year clinical and radiological follow-up of the Bryan cervical disc arthroplasty. *Spine* 2011, 36(8):639-646.

21. Ren X, Wang W, Chu T, Wang J, Li C, Jiang T: The intermediate clinical outcome and its limitations of Bryan cervical arthroplasty for treatment of cervical disc herniation. *Journal of spinal disorders & techniques* 2011, 24(4):221-229.

22. Chung SB, Muradov JM, Lee SH, Eoh W, Kim ES: Uncovertebral hypertrophy is a significant risk factor for the occurrence of heterotopic ossification after cervical disc replacement: survivorship analysis of Bryan disc for single-level cervical arthroplasty. *Acta neurochirurgica* 2012, 154(6):1017-1022.

23. Guerin P, Obeid I, Bourghli A, Meyrat R, Luc S, Gille O, Vital JM: Heterotopic ossification after cervical disc replacement: clinical significance and radiographic analysis. A prospective study. *Acta orthopaedica Belgica* 2012, 78(1):80-86.

24. Sun Y, Zhao YB, Pan SF, Zhou FF, Chen ZQ, Liu ZJ: Comparison of adjacent segment degeneration five years after single level cervical fusion and cervical arthroplasty: a retrospective controlled study. *Chinese medical journal* 2012, 125(22):3939-3941.

25. Wu JC, Huang WC, Tsai HW, Ko CC, Fay LY, Tu TH, Wu CL, Cheng H: Differences between 1- and 2-level cervical arthroplasty: more heterotopic ossification in 2-level disc replacement: Clinical article. *Journal of neurosurgery Spine* 2012, 16(6):594-600.

26. Yan D, Xiao Z, Shen C, Huang Y: [Effectiveness of cervical disc replacement for cervical myelopathy]. *Zhongguo xiu fu chong jian wai ke zhi = Zhongguo xiu fu chong jian wai ke zazhi = Chinese journal of reparative and reconstructive surgery* 2012, 26(9):1058-1061.

27. Jin YJ, Park SB, Kim MJ, Kim KJ, Kim HJ: An analysis of heterotopic ossification in cervical disc arthroplasty: a novel morphologic classification of an ossified mass. *The spine journal : official journal of the North American Spine Society* 2013, 13(4):408-420.

28. Lan X, Xu JZ, Liu XM, Ge BF: [Curative effect evaluation and complication analysis of Bryan artificial cervical disc replacement] *Zhongguo gu shang = China journal of orthopaedics and traumatology* 2013, 26(3):182-185.

29. Li J, Liang L, Ye XF, Qi M, Chen HJ, Yuan W: Cervical arthroplasty with Discover prosthesis: clinical outcomes and analysis of factors that may influence postoperative range of motion. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2013, 22(10):2303-2309.

30. Miao J, Yu F, Shen Y, He N, Kuang Y, Wang X, Chen D: Clinical and radiographic outcomes of cervical disc replacement with a new prosthesis. *The spine journal : official journal of the North American Spine Society* 2014, 14(6):878-883.

31. Pimenta L, Oliveira L, Coutinho E, Marchi L: Bone formation in cervical total disk replacement (CTDR) up to 6-year follow-up: Experience from 272 levels. *NEUROSURGERY QUART* 2013, 23(1):1-6.

32. Zhang Z, Gu B, Zhu W, Wang Q, Zhang W: Clinical and radiographic results of Bryan cervical total disc replacement: 4-year outcomes in a prospective study. *Archives of orthopaedic and trauma surgery* 2013, 133(8):1061-1066.

33. Zhao YB, Sun Y, Zhou FF, Liu ZJ: Cervical disc arthroplasty with ProDisc-C artificial disc: 5-year radiographic follow-up results. *Chinese medical journal* 2013, 126(20):3809-3811.

34. Fay LY, Huang WC, Wu JC, Chang HK, Tsai TY, Ko CC, Tu TH, Wu CL, Cheng H: Arthroplasty for cervical spondylotic myelopathy: similar results to patients with only radiculopathy at 3 years’ follow-up. *Journal of neurosurgery Spine* 2014, 21(3):400-410.

35. Malham GM, Parker RM, Ellis NJ, Chan PG, Varma D: Cervical artificial disc replacement with ProDisc-C: clinical and radiographic outcomes with long-term follow-up. *Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia* 2014, 21(6):949-953.

36. Qi M, Chen H, Cao P, Tian Y, Yuan W: Incidence and risk factors analysis of heterotopic ossification after cervical disc replacement. *Chinese medical journal* 2014, 127(22):3871-3875.

37. Suchomel P, Jurak L, Antinheiro J, Pohjola J, Stullik J, Meisel HJ, Cabrera M, Woiciechowsky C, Bruchmann B, Shackleford I et al: Does sagittal position of the CTDR-related centre of rotation influence functional outcome? Prospective 2-year follow-up analysis. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2014, 23(5):1124-1134.

38. Yi S, Oh J, Choi G, Kim TY, Shin HC, Kim KN, Kim KS, Yoon DH: The fate of heterotopic ossification associated with cervical artificial disc replacement. *Spine* 2014, 39(25):2078-2083.

39. Zhang Z, Jiao L, Zhu W, Du Y, Zhang W: Comparison of Bryan versus ProDisc-C total disk replacement as treatment for single-level cervical symptomatic degenerative disk disease. *Archives of orthopaedic and trauma surgery* 2015, 135(3):305-311.

40. Lee SE, Jahng TA, Kim HJ: Correlation between cervical lordosis and adjacent segment pathology after anterior cervical spinal surgery. *European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2015, 24(12):2899-2909.

41. Lei T, Liu Y, Wang H, Xu J, Ma Q, Wang L, Shen Y: Clinical and radiological analysis of Bryan cervical disc arthroplasty: eight-year follow-up results compared with anterior cervical discectomy and fusion. *International orthopaedics* 2016, 40(6):1197-1203.
42. Tu TH, Wu JC, Huang WC, Chang HK, Ko CC, Fay LY, Wu CL, Cheng H: Postoperative nonsteroidal antiinflammatory drugs and the prevention of heterotopic ossification after cervical arthroplasty: analysis using CT and a minimum 2-year follow-up. *Journal of neurosurgery Spine* 2015, 22(5):447-453.

43. Chang PY, Chang HK, Wu JC, Huang WC, Fay LY, Tu TH, Wu CL, Cheng H: Differences between C3-4 and other subaxial levels of cervical disc arthroplasty: more heterotopic ossification at the 5-year follow-up. *Journal of neurosurgery Spine* 2016, 24(5):752-759.

44. Chen J, Li J, Qiu G, Wei J, Qiu Y, An Y, Shen Y: Incidence and risk factors of axial symptoms after cervical disc arthroplasty: a minimum 5-year follow-up study. *Journal of orthopaedic surgery and research* 2016, 11(1):103.

45. Meisel HJ, Jurak L, Antinheiro J, Arregui R, Bruchmann B, Cabrava M, Caroli F, Kroppenstedt S, Kryl J, Pohjola J et al: Four-year results of a prospective single-arm study on 200 semi-constrained total cervical disc prostheses: clinical and radiographic outcome. *Journal of neurosurgery Spine* 2016, 25(5):556-565.

46. Shi S, Zheng S, Li XF, Yang LL, Liu ZD, Yuan W: Comparison of 2 Zero-Profile Implants in the Treatment of Single-Level Cervical Spondylotic Myelopathy: A Preliminary Clinical Study of Cervical Disc Arthroplasty versus Fusion. *PloS one* 2016, 11(7):e0159761.

47. Tian W, Fan MX, Liu YJ, Han X, Yan K, Wang H, Lyu YW: An Analysis of Paravertebral Ossification in Cervical Artificial Disc Replacement: A Novel Classification Based on Computed Tomography. *Orthopaedic surgery* 2016, 8(4):440-446.

48. Turner I, Choi D: NuNec Cervical Disc Arthroplasty Improves Quality of Life in Cervical Radiculopathy and Myelopathy: A 2-yr Follow-up. *Neurosurgery* 2018, 83(3):422-428.

49. Zhao Y, Zhang Y, Sun Y, Pan S, Zhou F, Liu Z: Application of Cervical Arthroplasty With Bryan Cervical Disc: 10-Year Follow-up Results in China. *Spine* 2016, 41(2):111-115.

50. Heo DH, Lee DC, Oh JY, Park CK: Bone loss of vertebral bodies at the operative segment after cervical arthroplasty: a potential complication? *Neurosurgical focus* 2017, 42(2):E7.

51. Kim KT, Cho DC, Sung JK, Kim YB, Kim DH: Comparative Analysis between Total Disc Replacement and Posterior Foraminotomy for Posterolateral Soft Disc Hemiation with Unilateral Radiculopathy: Clinical and Biomechanical Results of a Minimum 5 Years Follow-up. *Journal of Korean Neurosurgical Society* 2017, 60(1):30-39.

52. Mehren C, Heider F, Siepe CJ, Zillner B, Kothe R, Korge A, Mayer HM: Clinical and radiological outcome at 10 years of follow-up after total cervical disc replacement. *European spine journal: official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society* 2017, 26(9):2441-2449.

53. Pointillart V, Castelain JE, Coudert P, Cawley DT, Gille O, Vital JM: Outcomes of the Bryan cervical disc replacement: fifteen year follow-up. *International orthopaedics* 2018, 42(4):851-857.

54. Wu T, Wang B, Ding C, Meng Y, Lou J, Yang Y, Liu H: Artificial cervical disc replacement with the Prestige-LP prosthesis for the treatment of non-contiguous 2-level cervical degenerative disc disease: A minimum 24-month follow-up. *Clinical neurology and neurosurgery* 2017, 152:57-62.

55. Zeng J, Liu H, Rong X, Wang B, Yang Y, Gao X, Wu T, Hong Y: Clinical and radiographic outcomes of cervical disc arthroplasty with Prestige-LP Disc: a minimum 6-year follow-up study. *BMC musculoskeletal disorders* 2018, 19(1):285.

56. Gao X, Yang Y, Liu H, Meng Y, Zeng J, Wu T, Hong Y: Cervical disc arthroplasty with Prestige-LP for the treatment of contiguous 2-level cervical degenerative disc disease: 5-year follow-up results. *Medicine* 2018, 97(4):e9671.

57. Zeng J, Liu H, Chen H, Ding C, Rong X, Meng Y, Yang Y: Comparison of Heterotopic Ossification After Fixed- and Mobile-Core Cervical Disc Arthroplasty. *World neurosurgery* 2018, 120:e1319-e1324.

58. Zhou F, Ju KL, Zhao Y, Zhang F, Pan S, Heller JG, Sun Y: Progressive Bone Formation After Cervical Disc Replacement: Minimum of 5-Year Follow-up. *Spine* 2018, 43(3):E163-E170.

59. Di Benedetto P, Zangari A, Magnanelli S, Cainero V, Beltrame A, Gisonni R, Causero A: Heterotopic Ossification in Primary Total Hip Arthroplasty: is which the role of drainage? *Acta bio-medica : Atenei Parmensis* 2019, 90(1-S):92-97.

60. Cai L, Wang Z, Luo X, She W, Zhang H: Optimal strategies for the prevention of heterotopic ossification after total hip arthroplasty: A network meta-analysis. *International journal of surgery* 2019, 62:74-85.

61. Gornet MF, Burkus JK, Shaffrey ME, Schranck FW, Copay AG: Cervical disc arthroplasty: 10-year outcomes of the Prestige LP cervical disc at a single level. *Journal of neurosurgery Spine* 2019:1-9.

**Tables**

Table 1 Guidelines of quality evaluation for prevalence studies
The study methods 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

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

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 | Total | 1 level | 2 levels | 3 levels | 4 levels | Points |
|-----------|------|--------|--------------|-----------|-----------------------|--------|-------|---------|---------|---------|---------|-------|
| [9]       | 2006 | Mehren | PCS          | Prodisc-C  | 12                    | 77     | 54    |          |         |         |         | 5      |
| [10]      | 2008 | Heidecke| PCS         | Bryan     | 24                    | 59     | 54    | 49      | 1       |         |         | 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      |         |         |         | 6      |
| [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    |         |       |         |         | 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/Prodisc-C | 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/Prodisc-C | 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 | Total | 1 level | 2 levels | 3 levels | 4 levels | Points |
|-----------|------|--------|--------------|-----------|----------------------|--------|-------|---------|---------|---------|---------|--------|
| [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/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          | Bryan     | 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          | Prestige-LP | 120     | 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**

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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 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.