Total disc replacement compared with fusion for cervical degenerative disc disease
A systematic review of overlapping meta-analyses

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Abstract
Study design: The present study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.
Objective: The present study aimed to conduct a systematic review of overlapping meta-analyses comparing total disc replacement (TDR) with fusion for treating cervical degenerative disc disease (CDDD), their findings are inconsistent.
Summary of background data: Although several meta-analyses have been performed to compare total disc replacement and fusion for treating cervical degenerative disc disease, their findings are inconsistent.
Methods: Multiple databases were comprehensively searched for meta-analyses comparing TDR with fusion for treating CDDD. The meta-analyses that comprised only randomized controlled trials (RCTs) were included. Two authors independently assessed the meta-analysis study quality and extracted the data. The Jadad decision algorithm was used to ascertain which meta-analysis studies represented the best evidence.
Results: A total of 14 meta-analysis studies were included. All these studies only included RCTs and were determined as Level-II evidence.
Conclusions: Cervical disc arthroplasty was superior compared to anterior discectomy and fusion for the treatment of symptomatic cervical disc disease.
Abbreviations: ACDR = artificial cervical disc replacement, ASD = adjacent segment degeneration, CDDD = cervical degenerative disc disease, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis.
Keywords: anterior cervical disectomy and fusion, cervical degenerative disc disease, cervical fusion, meta-analysis, total disc replacement

1. Introduction
Anterior cervical discectomy and fusion (ACDF) has been reported as a well-accepted surgical alternative for radiculopathy and/or myelopathy refractory to conservative management. The procedure was initially described in the 1950s. It permits direct decompression of affected neural components and is generally accompanied by bone grafting and anterior plate fixation to provide mechanical stability and lordosis. However, adjacent segment degeneration (ASD) following ACDF has been reported at a rate of 2.9% per year. Furthermore, other postoperative problems, such as recurrent pain at the operated level must be taken into consideration. Due to ASD, the revision rates and revision surgery procedures have been extensively reported during the past decades.

Artificial cervical disc replacement (ACDR) has been clinically accepted as the most extensive non-fusion procedure. It was designed to perform neural decompression in a manner similar to that performed in ACDF. Moreover, ACDR aimed to preserve motion of the index disc, restore, and/or maintain mobility, reconstitute disc height and spinal alignment and theoretically avoid accelerating degeneration of the adjacent segment. Over the past decades, several investigators have demonstrated that ACDR can provide equivalent or better clinical outcomes than ACDF. Although ACDR was associated with less ASD, certain complications were noted in subsequent surgical interventions, including subsidence, migration and malposition. During the past years, the requirement for subsequent surgery following ACDR has attracted the attention of several investigators.

In recent years, systematic reviews of overlapping meta-analyses have been widely published in various medical fields.
These studies aided the selection of the highest quality level of evidence for decision-making. This was performed by evaluating meta-analyses with the discordant results on certain topics. The aims of the present study were the following:

1. to conduct a systematic review of meta-analysis studies comparing ACDR and ACDF,
2. to propose a guide through the currently discordant best available evidence in order to provide treatment recommendations and
3. to highlight gaps in the literature that requires future research.

The hypothesis was that ACDR and ACDF would exhibit similar clinical outcomes.

2. Materials and methods

The present study was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement. The design of the study was based on previous publications.\[15–33\]

2.1. Literature search

On February 10, 2018, the databases PubMed, EMBASE, and Cochrane Library were systematically searched. The following keywords were used: cervical, arthroplasty, prosthesis, replacement, arthrodesis, fusion, intervertebral disc degeneration, degenerative disc disease, systematic review, and meta-analysis. The search was independently performed by two in investigators. The references of the included studies were also assessed to identify potential meta-analysis studies. The titles and abstracts were initially reviewed and the full texts were acquired if the information was not sufficient. The disagreements were settled by discussion and a third author was consulted when necessary.

2.2. Eligibility criteria

The inclusion criteria of this systematic review were the following:

1. the comparison of ACDR with ACDF for treating cervical degenerative disease;
2. meta-analysis studies that exclusively included RCTs;
3. at least 24 months follow-up.

The narrative review, meetings abstracts, correspondence details, meta-analysis comprising non-RCTs and systematic review without meta-analysis were excluded.

2.3. Data extraction

Two authors independently extracted the following data from the included studies: name of first author, year of publications, primary study design, the number of RCTs included, heterogeneity or subgroup analyses of primary study, and meta-analysis results. When disagreements occurred between the two authors, a third author was consulted.

2.4. Quality assessment

The methodological quality was evaluated by the Oxford Levels of Evidence and the Assessment of Multiple Systematic Reviews (AMSTAR)\[9\] instrument. AMSTAR has been established as a methodological assessment tool with optimal reliability and validity. It is widely used to assess the quality of systematic reviews. Two authors independently evaluated the quality of the included meta-analyses. Disagreements between authors were settled by discussion and a third author was consulted if necessary.

2.5. Application of Jadad decision algorithm

The Jadad decision algorithm\[10\] was used to investigate the source of inconsistence among systematic reviews, comprising differences in clinical question, inclusion and exclusion criteria, data extraction, quality assessment, data pooling, and statistical analysis. It had been widely conducted to provide treatment recommendations among meta-analyses with discordant results. This algorithm was independently applied by three authors who reached a consensus regarding which meta-analysis provided the best available evidence.

2.6. Ethics statement

All data sources and statistical analyses were based on previous published studies; thus, no ethical approval and patient consent were required.

3. Results

3.1. Literature search

A flow diagram that depicts the search process can be found in Figure 1. A total of 309 titles were initially found. A total of 20 studies\[11–24\] met the inclusion criteria and were selected as appropriate for inclusion in this systematic review. A total of 6 studies were excluded since they did not meet the inclusion criteria with regard to RCT exclusion. A general description of the characteristics of each meta-analysis is provided in Table 1. The number of primary studies varied widely from 4 to 18 (Table 2). All studies contained meta-analysis and pooled data.

3.2. Search methodology

The majority of the studies were included in the databases. All of the included studies were searched in the Cochrane Library and Medline (PubMed). A heterogeneity was present as to whether these studies were also included in searches of Embase, OVID, and Google scholar. Table 3 provides the information regarding search methodology used by each included study.

3.3. Methodological quality

All studies that included RCTs were classified as Level II of evidence with the exception of Gao et al\[18\] which was classified as Level I (Table 3). Only two studies reported that the GRADE was used in their research. The AMSTAR results for each question from each meta-analysis are shown in Table 4. AMSTAR scores varied from 9 to 11. One study published from PLOS-ONE exhibited the highest quality score, with all of the AMSTAR criteria.

3.4. Results of Jadad decision algorithm

The results of all included meta-analyses are summarized in Figure 2. Given that all of the meta-analyses addressed the same study question, the included meta-analysis studies did not contain the same primary trials and the selection criteria were similar
among them. The Jadad algorithm suggested that the meta-analysis studies could be selected based on the search strategies and application of selection. As a result, Yan Hu[21] was selected (Fig. 3).

4. Discussion

Several meta-analyses have been performed with regard to the investigation of ACDR and ACDF. However, the quality of the studies is different and therefore the AMSTAR system was used in the present study to assess the level of the included studies and aid surgeons to select the best procedure in the clinical application.

The present study demonstrated that the majority of the meta-analysis studies identified by the literature search was published within a similar time period. However, they did not comprise the same primary trials and did not provide the same conclusions for the treatment of cervical degenerative disease.

The study by Hu et al[21] was the current best available evidence on the comparison of ACDR and fusion for this topic. It demonstrated that ACDR was superior over anterior discectomy and fusion for the treatment of symptomatic cervical disc disease in terms of the parameters overall success, NDI success, neurological success, implant/surgery-related serious adverse events, secondary procedure, functional outcomes, patient satisfaction, and recommendation and superior ASD.

This meta-analysis demonstrated that patients in the ACDR group exhibited a significantly higher overall success rate compared with those in the ACDF group. Pooled analysis of NDI success and neurological success data further suggested that ACDR patients were favored compared with those of the ACDF group. Moreover, we extracted NDI, VAS, and SF-36 scores at the last follow-up period in order to evaluate functional outcomes. Pooled estimates of these data indicated superiority in ACDR with the exception of an improvement in the arm pain score data, which indicated no significant difference. These findings suggested that ACDR seemed to be more effective than ACDF for the treatment of cervical spondylosis.

Secondary procedure is an important clinical event with substantial clinical and financial burden for the patient as well as additional cost for the medical facilities. In this meta-analysis, we found that ACDR was superior to ACDF with regard to the rate of total secondary procedures. The pooled results of the secondary procedure data involved the index level or the adjacent level that further revealed superiority in the ACDR group. These

| First author       | Date of publication | Journal                  | Numbers of included RCTs | Date of last literature search |
|--------------------|---------------------|--------------------------|--------------------------|-------------------------------|
| Hui Lu             | 2017.10.3           | Medline                  | 4                        | 2016                          |
| Lei Shangguan      | 2017.3.30           | PLOS ONE                 | 6                        | 2016                          |
| Shi hua Zou        | 2016.7.5            | Eur Spine J              | 6                        | 2015                          |
| Yan Hu             | 2016.2.12           | PLOS ONE                 | 8                        | 2015                          |
| Lei JIANG          | 2016.5.5            | Clin Spine Surg          | 6                        | 2015                          |
| Qiang Yao          | 2015.9.28           | Arch Ortho Trauma        | 9                        | 2013                          |
| Fuging Gao         | 2015.7.15           | Spine                    | 18                       | 2014                          |
| Jiamei Luo         | 2014.8.9            | Eur J Orthop             | 13                       | 2013                          |
| Min-Jie Ruo        | 2014.12.5           | Arch Ortho Trauma        | 18                       | 2013                          |
| Chunpeng Ren       | 2014.1.27           | Eur Spine J              | 5                        | 2013                          |
| Dan Xing           | 2012.3.17           | J Clin Neuroscl          | 8                        | 2011                          |
| Yu Gao             | 2013.2.20           | J Bone Joint Surg        | 14                       | 2010                          |
| Si Yin             | 2013.2.7            | Clin Orthop Relat Res    | 13                       | 2011                          |
| Hua Jiang          | 2011.10.9           | Arch Ortho Trauma        | 6                        | 2009                          |
results were consistent with the findings reported by Wu et al. However, the latter study only included four randomized controlled trials with only 921 patients in total.

The pooled results indicated a lower rate in ACDR patients, suggesting that ACDR could be surgically safer than ACDF for the treatment of symptomatic cervical disc disease. In addition, three studies reported the data of patient satisfaction and patient recommendation. With regard to these self-assessed data, the current meta-analysis revealed higher scores reported in ACDR patients, supporting the superior efficacy of ACDR over ACDF.

Adjacent segment degeneration has been considered as a major concern for patients undergoing ACDF for degenerative disc disease. Compared to cervical fusion, disc arthroplasty provides theoretical biomechanical advantage of motion preservation and stress reduction at adjacent levels. However, it remains unclear whether ACDR can decrease the incidence of ASD compared to ACDF. In the present meta-analysis, no studies reported the rate of symptomatic adjacent segment disease, while three studies that reported the rate of radiological ASD where removed. A significantly lower rate of superior ASD and an insignificantly lower rate of inferior ASD were shown by a previous study in ACDR patients. These findings suggested that ACDR exerted positive effects on the process of ASD. We noticed that the statistical heterogeneity was high for these outcomes. This level of heterogeneity may be due to the difference of radiological criteria determined for ASD and the number of surgical levels. It is important to note that radiological ASD is not directly correlated with symptomatology. Therefore, prospective RCTs with long-term follow-up reporting symptomatic adjacent segment disease as an outcome are warranted to clarify this question (Table 5).

Several potential limitations should be acknowledged in our meta-analysis. First, only 8 RCTs were included with a follow-up period between 4 and 7 years. Further studies with larger sample sizes and longer follow-up periods are warranted. Secondly, certain methodological weaknesses were noted in the included studies, such as unclear methods of allocation concealment and inadequate blinding procedures. Moreover, missing information such as the absence of ITT analysis and follow-up loss was presented in almost every study. All these methodological drawbacks can weaken the credibility of pooled outcomes. Thirdly, patients undergoing an ACDF exhibited a tendency for poor follow-up rate compared to that noted in the ACDR group ($P = .04$). This may lead to biased results. The reasons for this bias are not clear and are probably multi-factorial such as the lack of binding of patients in all studies. Fourthly, almost all the studies utilized a non-inferiority study design, which was typically less stringent in demonstrating efficacy than standard clinical trials. Despite these limitations, we consider that this meta-analysis supports the superiority of ACDR over ACDF with regard to efficacy and safety for the treatment of symptomatic cervical disc disease in the mid- to long-term follow-up periods.

**5. Conclusion**

In the present systematic review of overlapping meta-analyses we compared ACDR and ACDF with regard to their efficacy and safety for the treatment of symptomatic cervical disc disease. The best available evidence was provided by using the Jadad Decision Algorithm. Therefore, we concluded that cervical disc arthroplasty was superior compared to anterior discectomy and fusion for the treatment of symptomatic cervical disc disease.
### Table 3
Methodological information for each included study.

| Authors         | Date of publication | Design of included studies | Level of evidence | Software | GRADE use | Subgroup analysis |
|-----------------|---------------------|-----------------------------|-------------------|----------|-----------|-------------------|
| Hui Lu          | 2017.10.3           | RCT                         | Level II          | RevMan   | NO        | YES               |
| Lei Shangguan   | 2017.3.30           | RCT                         | Level II          | RevMan   | NO        | YES               |
| Shi hua Zou     | 2016.7.5            | RCT                         | Level II          | RevMan   | NO        | YES               |
| Yan Hu          | 2016.2.12           | RCT                         | Level II          | RevMan   | NO        | YES               |
| Lei KUANG       | 2016.5.5            | RCT                         | Level II          | RevMan   | NO        | NO                |
| Qiang Yao       | 2015.9.28           | RCT                         | Level II          | RevMan   | NO        | NO                |
| Fuqing Gao      | 2015.7.15           | RCT                         | Level I           | RevMan   | NO        | NO                |
| Jianguan Luo    | 2014.8.9            | RCT                         | Level II          | RevMan   | NO        | NO                |
| Min-Jie Rao     | 2014.12.5           | RCT                         | Level II          | RevMan   | NO        | NO                |
| Chunpeng Ren    | 2014.1.27           | RCT                         | Level II          | RevMan   | YES       | NO                |
| Dan Xing        | 2012.3.17           | RCT                         | Level II          | RevMan   | NO        | NO                |
| Yu Gao          | 2013.3.20           | RCT                         | Level II          | RevMan   | NO        | NO                |
| Si Yin          | 2013.2.7            | RCT                         | Level II          | RevMan   | YES       | NO                |
| Hua Jiang       | 2011.10.9           | RCT                         | Level II          | RevMan   | NO        | NO                |

### Table 4
AMSTAR scores for the include studies.

| Items                                                | Hua Jiang (2011) | Si Yin (2013) | Yu Gao (2013) | Dan Xing (2012) | Chunpeng Ren (2014) | Min-Jie Rao (2014) | Jianguan Luo (2014) | Fuqing Gao (2015) | Qiang Yao (2015) | Lei Kuang (2016) | Yan Hu (2016) | Shi hua Zou (2016) | Lei Shangguan (2017) | Hui Lu (2017) |
|------------------------------------------------------|------------------|----------------|---------------|------------------|----------------------|--------------------|---------------------|-------------------|-----------------|------------------|----------------|-------------------|----------------------|---------------|
| 1. Was an a priori design provided?                   | 1                | 1              | 1             | 1                | 1                    | 1                  | 1                   | 1                 | 1               | 1                | 1              | 1                  | 1                    | 1              |
| 2. Was there duplicate study selection and data extraction? | 1                | 1              | 1             | 1                | 1                    | 1                  | 1                   | 1                 | 1               | 1                | 1              | 1                  | 1                    | 1              |
| 3. Was a comprehensive literature search performed?  | 1                | 1              | 1             | 1                | 1                    | 1                  | 1                   | 1                 | 1               | 1                | 1              | 1                  | 1                    | 1              |
| 4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? | 1                | 1              | 1             | 1                | 1                    | 1                  | 1                   | 1                 | 1               | 1                | 1              | 1                  | 1                    | 1              |
| 5. Was a list of studies (included and excluded) provided? | 0                | 0              | 0             | 0                | 0                    | 0                  | 0                   | 0                 | 0               | 0                | 0              | 0                  | 0                    | 0              |
| 6. Were the characteristics of the included studies provided? | 0                | 1              | 0             | 1                | 1                    | 1                  | 1                   | 1                 | 1               | 1                | 1              | 1                  | 1                    | 1              |
| 7. Was the scientific quality of the included studies assessed and documented? | 1                | 1              | 1             | 1                | 1                    | 1                  | 1                   | 1                 | 1               | 1                | 1              | 1                  | 1                    | 1              |
| 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? | 1                | 1              | 1             | 1                | 1                    | 1                  | 1                   | 1                 | 1               | 1                | 1              | 1                  | 1                    | 1              |
| 9. Were the methods used to combine the findings of studies appropriate? | 1                | 1              | 1             | 1                | 1                    | 1                  | 1                   | 1                 | 1               | 1                | 1              | 1                  | 1                    | 1              |
| 10. Was the likelihood of publication bias assessed?   | 1                | 1              | 1             | 1                | 1                    | 1                  | 1                   | 1                 | 1               | 1                | 1              | 1                  | 1                    | 1              |
| 11. Was the conflict of interest stated?              | 1                | 1              | 1             | 1                | 1                    | 1                  | 1                   | 1                 | 1               | 1                | 1              | 1                  | 1                    | 1              |
| Total scores                                         | 9                | 10             | 9             | 10               | 10                   | 10                 | 10                   | 10                 | 10              | 10                | 10             | 10                 | 10                   | 10             |
Figure 2. Results of each included meta.

Table 5

Heterogeneity or subgroup analyses of primary studies.

| Items                      | Hua Jiang (2011) | Si Yin (2013) | Yu Gao (2012) | Dan Xing (2014) | Chunpeng Ren (2014) | Min-Jie Rao (2014) | Jiaquan Luo (2014) | Fuqing Gao (2015) | Qiang Yao (2015) | Lei Kuang (2016) | Yan Hu (2016) | Shi hua Zou (2016) | Lei Shangguan (2017) | Hui Lu (2017) |
|----------------------------|------------------|---------------|---------------|------------------|---------------------|-------------------|-------------------|------------------|----------------|----------------|--------------|---------------------|---------------------|--------------|
| NDI                        | +                | +             | +             | +                | +                   | +                 | +                 | +                | +              | +              | +            | +                   | +                   | +            |
| SF-36                      | _                | _             | _             | _                | _                   | _                 | _                 | _                | _              | _              | _            | _                   | _                   | _            |
| Neurologic status          | +                | +             | +             | +                | +                   | +                 | +                 | +                | +              | +              | +            | +                   | +                   | +            |
| ROM                        | +                | +             | +             | +                | +                   | +                 | +                 | +                | _              | _              | +            | +                   | +                   | +            |
| Reoperation                | +                | +             | +             | +                | +                   | +                 | +                 | +                | _              | _              | +            | +                   | +                   | +            |
| Complications              | +                | +             | +             | +                | +                   | +                 | +                 | +                | _              | _              | +            | +                   | +                   | +            |
| VAS Neck Pain              | +                | _             | +             | +                | +                   | +                 | +                 | _                | +              | +              | +            | +                   | +                   | +            |
| VAS Arm Pain               | +                | +             | +             | +                | +                   | +                 | +                 | +                | +              | +              | +            | +                   | +                   | +            |
| Operative Time             | +                | +             | +             | +                | +                   | +                 | +                 | +                | +              | +              | +            | +                   | +                   | +            |
| Blood Loss                 | +                | +             | +             | +                | +                   | +                 | +                 | +                | +              | +              | +            | +                   | +                   | +            |
| Length of Hospital Stay    | +                | +             | +             | +                | +                   | +                 | +                 | +                | _              | _              | +            | +                   | +                   | +            |
| ASD                        | +                | _             | _             | _                | _                   | _                 | _                 | _                | _              | _              | _            | _                   | _                   | _            |
| Patient satisfaction       | +                | _             | _             | _                | _                   | _                 | _                 | _                | _              | _              | _            | _                   | _                   | _            |
| JOA                        | +                | _             | _             | _                | _                   | _                 | _                 | _                | _              | _              | _            | _                   | _                   | _            |
Author contributions

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Investigation: Xiang Li.
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Figure 3. Flow diagram of Jadad decision algorithm.