

Multilevel cervical disc replacement versus multilevel anterior discectomy and fusion

A meta-analysis

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Abstract

Background: Cervical disc replacement (CDR) has been developed as an alternative surgical procedure to anterior cervical discectomy and fusion (ACDF) for the treatment of single-level cervical degenerative disc disease. However, patients with multilevel cervical degenerative disc disease (MCDDD) are common in our clinic. Multilevel CDR is less established compared with multilevel ACDF. This study aims to compare the outcomes and evaluate safety and efficacy of CDR versus ACDF for the treatment of MCDDD.

Methods: A meta-analysis was performed for articles published up until August 2016. Randomized controlled trials (RCTs) and prospective comparative studies associated with the use of CDR versus ACDF for the treatment of MCDDD were included in the current study. Two reviewers independently screened the articles and data following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.

Results: Seven studies with 702 enrolled patients suffering from MCDDD were retrieved. Patients who underwent CDR had similar operative times, blood loss, Neck Disability Index (NDI) scores, and Visual Analog Scale (VAS) scores compared to patients who underwent ACDF. Patients who underwent CDR had greater overall motion of the cervical spine and the operated levels than patients who underwent ACDF. Patients who underwent CDR also had lower rates of adjacent segment degeneration (ASD). The rate of adverse events was significantly lower in the CDR group.

Conclusion: CDR may be a safe and effective surgical strategy for the treatment of MCDDD. However, there is insufficient evidence to draw a strong conclusion due to relatively low-quality evidence. Future long-term, multicenter, randomized, and controlled studies are needed to validate the safety and efficacy of multilevel CDR.

Abbreviations: ACDF = anterior cervical discectomy and fusion, ASD = adjacent segment degeneration, CDR = cervical disc replacement, CI = confidence interval, MCDDD = multilevel cervical degenerative disc disease, MD = mean difference, NDI = Neck Disability Index, OR = odds ratio, RCT = randomized controlled trial, ROM = range of motion, VAS = Visual Analog Scale.

Keywords: anterior cervical discectomy and fusion, cervical disc replacement, multilevel, multilevel cervical degenerative disc disease

1. Introduction

Multilevel cervical degenerative disc disease (MCDDD) is defined as a common pathological condition in which 2 or more segments of the cervical spine develop degeneration, resulting in radiculopathy and/or myelopathy and causing significant cervical disability and loss of productivity. During the past decades, anterior cervical discectomy and fusion (ACDF) has been the

most accepted surgical procedure for symptomatic cervical disc disease with satisfactory clinical outcomes. With respect to the treatment of MCDDD, ACDF has also been regarded as a routine operative strategy. Although the procedure is very safe and effective in terms of resolving symptoms, maintaining cervical stability and restoring cervical lordosis are challenging. Fusion sacrifices the motion of the operated level, which may result in increased intradiscal pressure, hypermobility at adjacent segments, and gradual development of adjacent segment degeneration (ASD) according to biomechanical studies, especially in MCDDD.^[1,2] In recent decades, cervical disc replacement (CDR) has been developed as an alternative surgical procedure to ACDF to preserve the motion of the operated level and to potentially decrease the occurrence of ASD. Single-level CDR has been used in clinical practice and has obtained similar or superior outcomes compared with ACDF for the treatment of symptomatic cervical degenerative disc disease as evidence by an accumulation of some mid- and a few long-term studies.^[3-7]

Currently, patients with MCDDD are common in our clinic. Although multilevel CDR is less established compared with multilevel ACDF, more and more studies have reported that CDR could be used to treat MCDDD based on success of single-level CDR, which has achieved similarly satisfactory outcomes as single-level CDR.^[8-10] Furthermore, 1 biomechanical study

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revealed that multilevel CDR can preserve near-normal mobility at the operated and adjacent levels with stabilizing implanted prostheses.^[11] However, multilevel CDR may add difficulty to the procedure and increase the possibility for device-related complications. Additionally, some surgeons are concerned about lower motion quality resulting from imperfect prosthesis position and endplate-device matching might amplify the adverse effect of CDR.^[12,13] Additionally, some surgeons considered the multilevel CDR as a contraindication for disc replacement.^[14] Therefore, it is still widely debated whether there is a clinical role for multilevel CDR.

Previous meta-analysis reviews have mainly concentrated on comparisons between single-level CDR and single-level fusion.^[15–17] Nevertheless, the outcomes of multilevel CDR compared with multilevel ACDF are rarely reported. The purpose of this study was to compare the clinical and radiological outcomes of multilevel CDR with multilevel ACDF and to preliminarily evaluate the safety and efficacy of multilevel CDR.

2. Methods

2.1. Study selection

We conducted a meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement.^[18] As all the analyses were performed based on preview published trials, the ethical approval and informed consent for this studies were not necessary. Electronic literature databases, including PubMed, Cochrane Central Register of Controlled Trials, Medline, and Embase, were searched to identify relevant studies published up until August 2016 without restricting language. All of the studies comparing multilevel CDR with ACDF for the treatment of MCDDD were identified using the following keywords: cervical disc arthroplasty, CDR, total disc replacement, and fusion. In addition, the reference lists of all the selected full-text articles were reviewed to identify more eligible articles.

Two reviewers (Dr Wu and Dr Meng) independently performed the screening of the abstracts of the primary identified studies and related references for eligibility in the study. Full-text articles were read and further evaluated when the eligibility was met within abstracts. All the authors discussed the articles to come to a decision regarding inclusion and exclusion. The inclusion criteria were original research on MCDDD relative to performing CDR with ACDF as controls, and at least 12-month follow-up evaluation by clinical and radiographic analyses. The exclusion criteria were case reports; inappropriate topics; letters to editors; reviews; single-level operation; single-site data as part of a multicenter trial, and articles from the same site. If there was any disagreement among the authors with respect to the inclusion and/or exclusion of an article, the senior author (Dr Liu) organized a discussion to reach a consensus.

2.2. Data extraction

Two independent reviewers (Dr Wu and Dr Meng) extracted the relevant data from the selected studies including the general characteristics of each study and the clinical and radiographic outcomes measured. General characteristics included study design, first author, demographic data (age, gender), type of disc prosthesis, type of control intervention, and follow-up period. The clinical outcomes in this analysis included the perioperative data, Neck Disability Index (NDI), and neck Pain Visual Analog Scale (VAS). The radiographic outcomes included

range of motion (ROM) of the operated levels and ROM of the overall cervical spine. Additionally, radiologic findings at adjacent levels and adverse events related to surgical procedures or implants were also selected.

2.3. Assessment of methodological quality

For randomized studies, quality assessment was conducted according to the guidelines in the Cochrane Handbook for Systematic Review of Interventions^[19] and the following domains were assessed: randomization, blinding (of the patients, surgeons, and assessors), allocation concealment, and follow-up coverage. Each domain was classified as adequate, unclear, or inadequate. For nonrandomized trials, methodological index for nonrandomized studies was used to assess quality.^[20] The methodological quality assessment contained 12 items, and each trial was scored from 0 to 24. Studies with scores ≥ 16 were regarded as high-quality studies. The quality of the studies was independently evaluated by 2 reviewers (Dr Wu and Dr Wang) and checked by the senior author (Dr Liu).

2.4. Heterogeneity

The I^2 test was used to evaluate the heterogeneity of the data. The I^2 test ranges from 0% to 100% according to the Cochrane Handbook for Systematic Review of Interventions.^[19] A fixed-effect model was adopted if the $I^2 < 50\%$, and a random-effect model was adopted if the $I^2 > 50\%$. The possibility of a publishing bias was not evaluated because of the small number of studies assessed.

2.5. Data analysis

The systematic review was conducted using the software Review Manager 5.3 provided by the Cochrane Collaboration. For dichotomized outcomes, an odds ratio (OR) and its 95% confidence interval (CI) were calculated. For continuous data, the mean difference (MD) and its 95% CI were calculated. A probability of $P < .05$ was considered to be statistically significant.

3. Results

3.1. Search results

The procedure of identifying relevant studies is shown in Fig. 1. By searching PubMed, Embase, Medline, and Cochrane Central Register of Controlled Trials and identifying from reference lists, 1790 studies were initially identified. A total of 1408 studies were excluded because they were duplicated or irrelevant. Next, 35 studies were excluded after assessing full-text. Finally, 7 studies^[21–27] met the inclusion criteria and were included into our meta-analysis, and the characteristics are presented in Table 1. A total of 702 patients with MCDDD were involved. Out of these patients, 371 patients received CDR and 331 patients received ACDF. All studies involved 2 levels: 6 of the studies^[21,23–27] included 2 contiguous levels, and 1 study^[22] included 2 noncontiguous levels.

3.2. Methodological quality

The methodological quality assessments are shown in Fig. 2 (randomized controlled trial [RCT]) and Table 2 (non-RCT). For

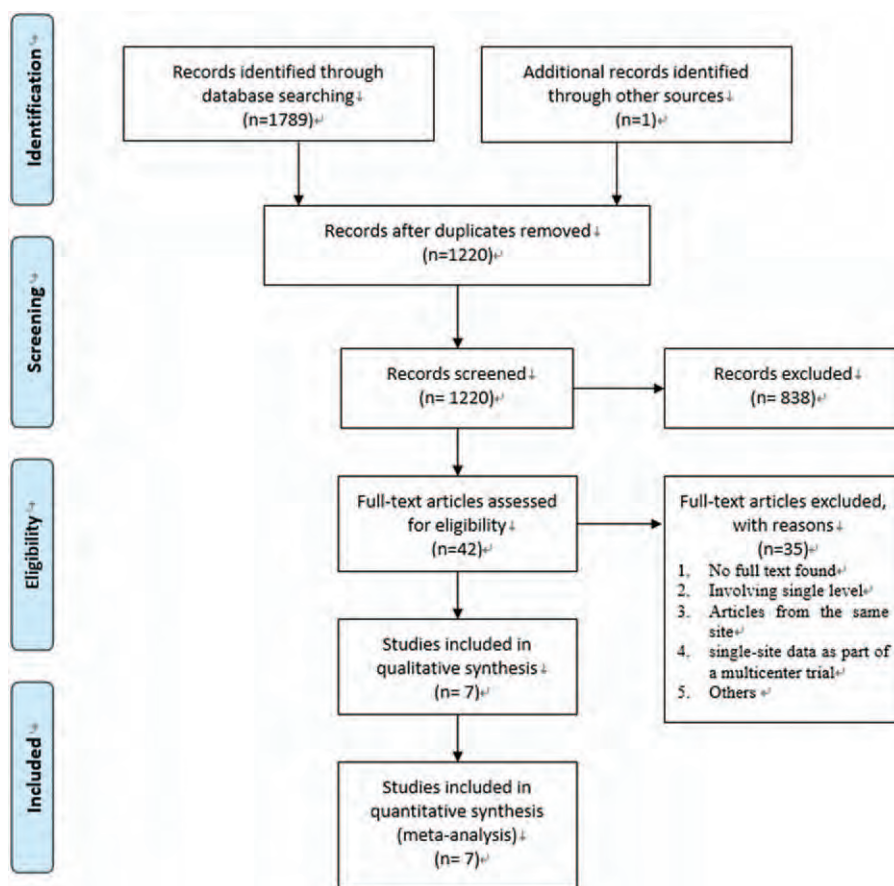


Figure 1. Flow chart of article selection process.

RCTs, only 3 studies^[21,22,27] met the inclusion criteria and were rated as “low risk of bias” according to the Cochrane Back Review Group criteria. Adequate concealment of allocation was unclear and the intention-to-treat analysis was high risk in RCTs. The drop-outs or withdrawals were described in all of the studies. For non-RCTs, the scores of the other 4 studies^[23–26] ranged 18 to 22 showing relatively good quality.

3.3. Outcome analysis

3.3.1. Perioperative data. The operative time was not detailed provided in any of the 7 studies. Four studies^[21–23,25] with a total of 477 patients (296 in the CDR group and 181 in the ACDF group) were analyzed. The pooled results show that the operative times were similarly between the 2 groups (MD, 38.48, 95%

CI $-0.26-77.23$; $P=.05$) with high heterogeneity ($I^2=97\%$). Therefore, the random-effect model was used (Fig. 3). In addition, 3 studies^[21,22,25] described in detail that blood loss was no significantly statistical different between the 2 groups (MD, -3.10 , 95% CI $-20.18-13.97$; $P=.62$) with low heterogeneity ($I^2=33\%$). Therefore, the fixed-effects model was used (Fig. 4).

3.4. NDI

NDI scores were provided in detail in 5 studies.^[21–24,26] Of these studies, a total of 560 patients (303 in the CDR group and 257 in the ACDF group) were analyzed. Due to the high heterogeneity ($I^2=79\%$), the random model was used for analysis, and the pooled results indicated that there was no statistically significant

Table 1 Characteristics of the included studies.

	Design	Year of publication	Area or country	Sample size		Mean age, y		Male, %		Prosthesis	Number of level	Follow-up, mo
				CDR	ACDF	CDR	ACDF	ACDR	ACDF			
Fay et al	Non-RCT	2014	Taiwan	37	40	52.1	63.0	75.7	65	Bryan	Two-level	39.6
Grasso	Non-RCT	2015	Italy	20	20	40.5	47.3	50.0	50.0	Prodisc-C	Two-level	24
Cheng et al	RCT	2009	China	31	34	45.0	47.0	61.3	58.8	Bryan	Two-level	24
Hou et al	Non-RCT	2014	China	32	88	46.3	51.2	62.5	43.2	Discover	Two-level	22–23
Kim et al	Non-RCT	2009	Korea	12	28	46.9	52.7	66.7	60.7	Bryan	Two-level	18–19
Radcliff et al	RCT	2016	America	225	105	45.3	46.2	50.2	42.9	Mobi-C	Two-level	60
Sun et al	RCT	2016	China	14	16	46.8	48.1	64.3	68.8	Discover	Two-level	32.4

ACDF=anterior cervical discectomy and fusion, CDR=cervical disc replacement, non-RCT=non-randomized controlled trails, RCT=randomized controlled trails.

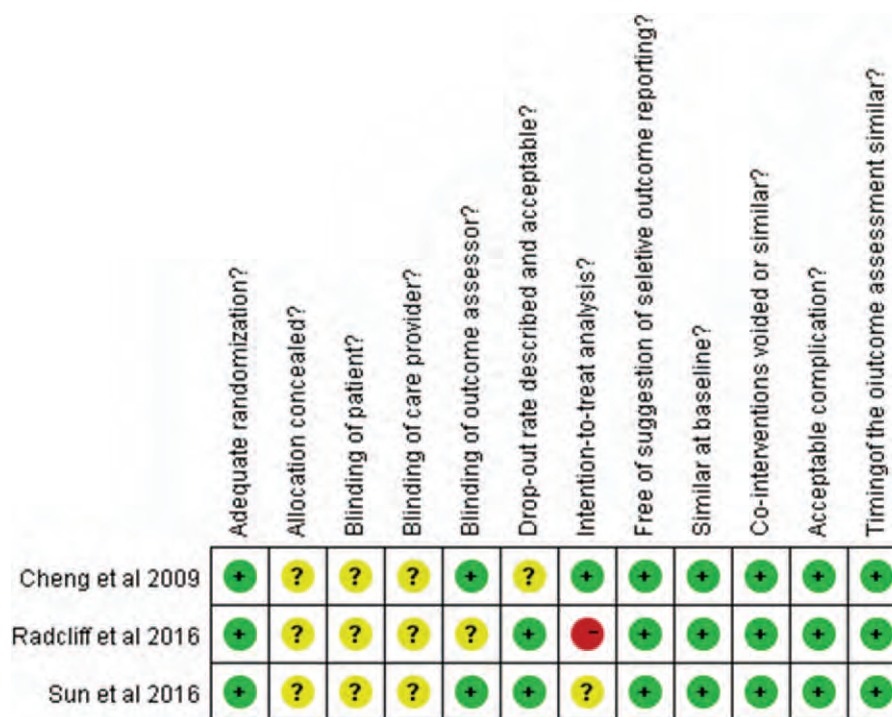


Figure 2. Risk of bias of the randomized controlled trials, +: low risk bias; ?: unclear risk bias; and -: high risk bias.

difference in NDI scores between the CDR group and the ACDF group (MD, -0.70, 95% CI -2.14-0.73; $P=.34$) (Fig. 5).

3.5. VAS

Neck VAS scores were reported in detail in 4 studies.^[21,23,24,26] Of these studies, a total of 530 patients (289 in the CDR group and 241 in the ACDF group) were analyzed. Due to the high heterogeneity ($I^2=65%$), the random model was used for analysis, and the pooled results indicate that there is no statistically significant difference in NDI scores between the CDR group and the ACDF group (MD, -0.33, 95% CI -1.10-0.44; $P=.40$) (Fig. 6).

3.6. ROM

3.6.1. ROM of overall cervical spine. Data on the ROM of the overall cervical spine were provided in 3 studies,^[23,24,26] with a total of 200 patients (64 in the CDR group and 136 in the ACDF group). Of these studies, the ROM was significantly higher in patients who underwent CDR than those who received ACDF (MD, 15.83, 95% CI 10.73-20.92; $P<.00001$) (Fig. 7) with significant heterogeneity ($I^2=84%$).

3.6.2. ROM of the operated levels. Data on the ROM at the operated levels were provided in 4 studies,^[21,24-26] with a total of 567 patients (306 in the CDR group and 261 in the ACDF group). Of these studies, the pooled results indicated that there were no statistically significant differences between the CDR

Table 2

Methodological quality of the non-randomized controlled trials.

	Fay et al	Grasso	Hou et al	Kim et al
A clearly stated aim	2	2	2	2
Inclusion of consecutive patients	2	2	2	2
Prospective data collection	2	2	2	2
Endpoints appropriate to the aim of the study	1	2	1	1
Unbiased assessment of the study endpoint	0	1	1	0
A follow-up period appropriate to the aims of study	2	2	2	2
Less than 5% loss to follow-up	2	2	2	1
Prospective calculation of the sample size	0	1	0	0
An adequate control group	2	2	2	2
Contemporary groups	2	2	2	2
Baseline equivalence of groups	2	2	2	2
Adequate statistical analyses	2	2	2	2
Total score	19	22	20	18

The items are scored 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The global ideal scores ≥ 16 .

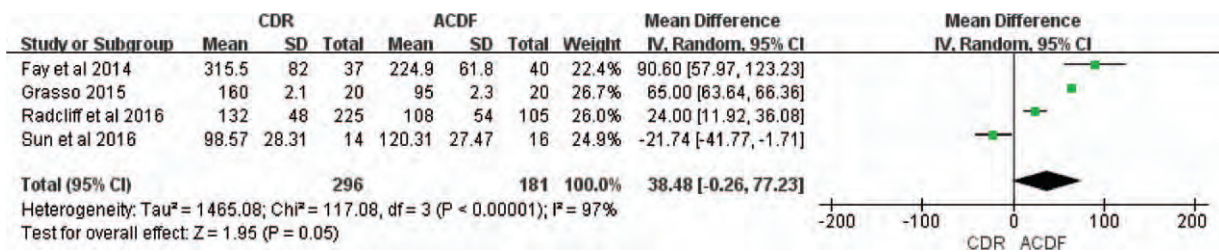


Figure 3. Surgery time. Forest plot of surgery time for CDR and ACDF. ACDF=anterior cervical discectomy and fusion, CDR=cervical disc replacement, CI=confidence interval, IV=inverse variance, SD=standard deviation.

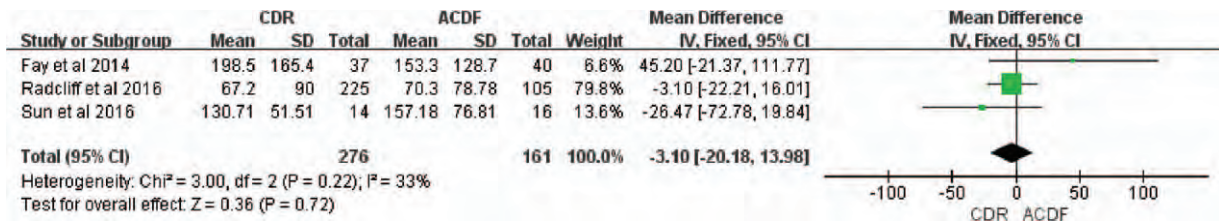


Figure 4. Blood loss. Forest plot of blood loss for CDR and ACDF. ACDF=anterior cervical discectomy and fusion, CDR=cervical disc replacement, CI=confidence interval, IV=inverse variance, SD=standard deviation.

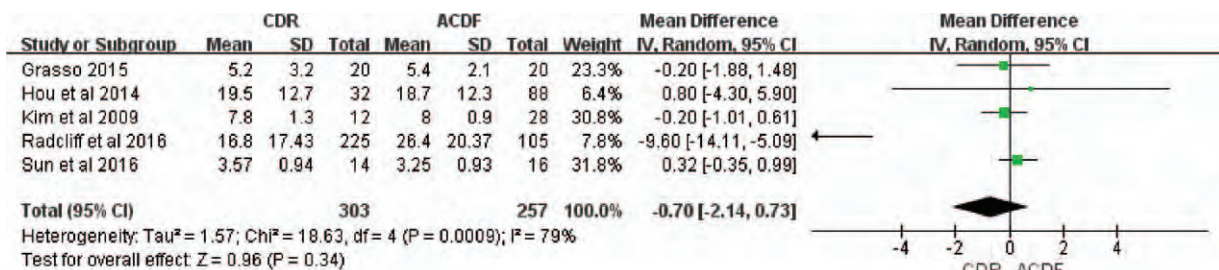


Figure 5. NDI. Forest plot of NDI for CDR and ACDF. ACDF=anterior cervical discectomy and fusion, CDR=cervical disc replacement, CI=confidence interval, IV=inverse variance, NDI Neck Disability Index, SD=standard deviation.

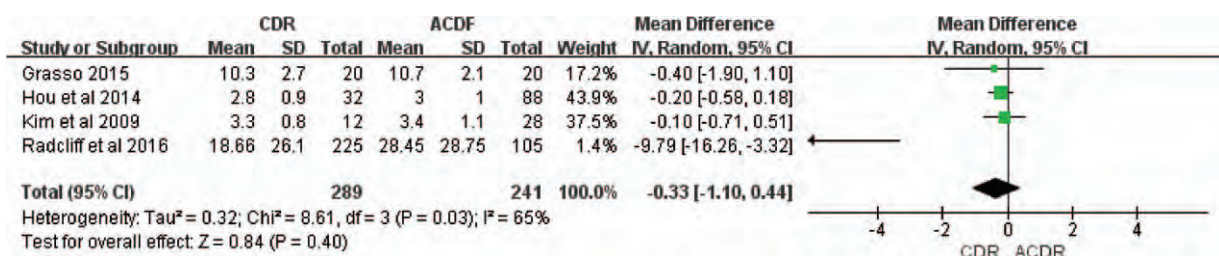


Figure 6. VAS. Forest plot of VAS for CDR and ACDF. ACDF=anterior cervical discectomy and fusion, CDR=cervical disc replacement, CI=confidence interval, IV=inverse variance, SD=standard deviation, VAS=Visual Analog Scale.

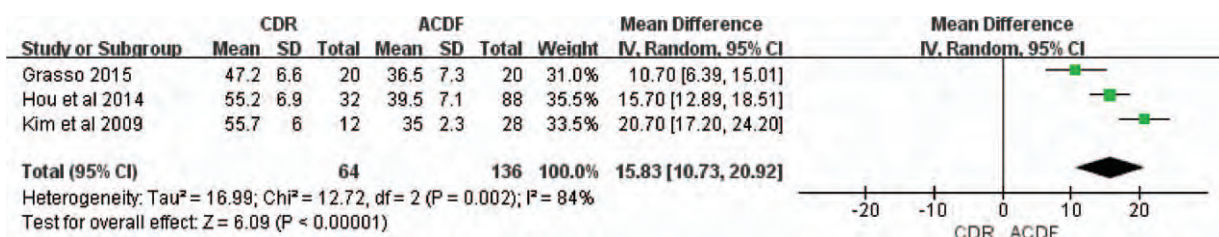


Figure 7. ROM of overall cervical spine. Forest plot of ROM of overall cervical spine for CDR and ACDF. ACDF=anterior cervical discectomy and fusion, CDR=cervical disc replacement, CI=confidence interval, IV=inverse variance, ROM=range of motion, SD=standard deviation.

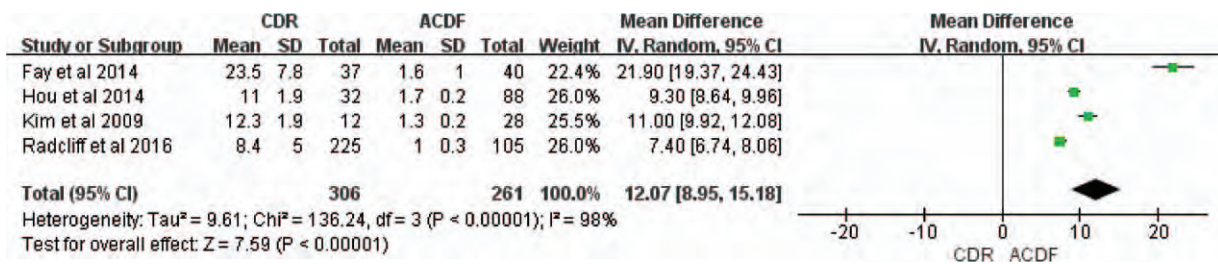


Figure 8. ROM at the operated level. Forest plot of ROM at operated level for CDR and ACDF. ACDF = anterior cervical discectomy and fusion, CDR = cervical disc replacement, CI = confidence interval, IV = inverse variance, ROM = range of motion, SD = standard deviation.

group and ACDF group (MD, 12.07 95% CI 8.95–15.18; $P < .00001$) (Fig. 8) with significant heterogeneity ($I^2 = 98\%$).

3.6.3. Adjacent segment degeneration (ASD). Data on ASD were provided in 4 studies.^[21,22,24,26] Of these studies, a total of 520 patients (283 in the CDR group and 237 in the ACDF group) were analyzed. The pooled results showed that the incidence of ASD in the ACDF group was significantly higher compared with the CDR group (OR 0.18, 95% CI 0.1–0.31; $P < .00001$) with low heterogeneity ($I^2 = 32.6\%$) (Fig. 9). In a subgroup, the pooled results also showed that the incidence of ASD in the ACDF group was significantly higher compared with the CDR group (Fig. 9).

3.6.4. Adverse events. Information on adverse events was provided in 4 studies,^[21,22,24,27] with a total of 545 patients (302 in the CDR group and 243 in the ACDF group). The pooled results showed that adverse postoperative events were significantly different between the 2 groups (OR 0.40, 95% CI 0.26–0.62; $P < .0001$) with low heterogeneity ($I^2 = 14\%$) (Fig. 10). With respect to dysphagia, 4 studies^[21,22,24,27] provided information in detail, and the pooled results showed that the rate of postoperative dysphagia was significantly different between the 2 groups (OR 0.55, 95% CI 0.32–0.95; $P = .03$), with no heterogeneity ($I^2 = 0\%$) (Fig. 11). For device-related adverse

event, 2 studies^[21,24] provided detailed information and the pooled results showed that device-related adverse events were not significantly different between the 2 groups (OR 0.48, 95% CI 0.20–1.17; $P = .11$), with no heterogeneity ($I^2 = 0\%$) (Fig. 12).

4. Discussion

In recent decades, artificial CDR has been increasingly regarded as an alternative surgical procedure for the treatment of cervical degenerative disc disease that causes radiculopathy and/or myelopathy. Many studies have reported the comparison between CDR and ACDF; however, most studies have focused exclusively on single-level treatment. Although the safety and efficacy of single-level CDR has been increasingly accepted, CDR for the treatment of MCDDD remains controversial. This meta-analysis intended to investigate whether or not the reliability of multilevel CDR is inferiority to multilevel ACDF.

A previous meta-analysis^[15] reported that CDR was associated with longer operative times and more blood loss in the treatment of patients with single-level cervical degenerative disc disease. According to the Murrey et al^[28] study, they attributed the increased the operative time to time required to learn the new technique and time for the additional use of fluoroscopy in

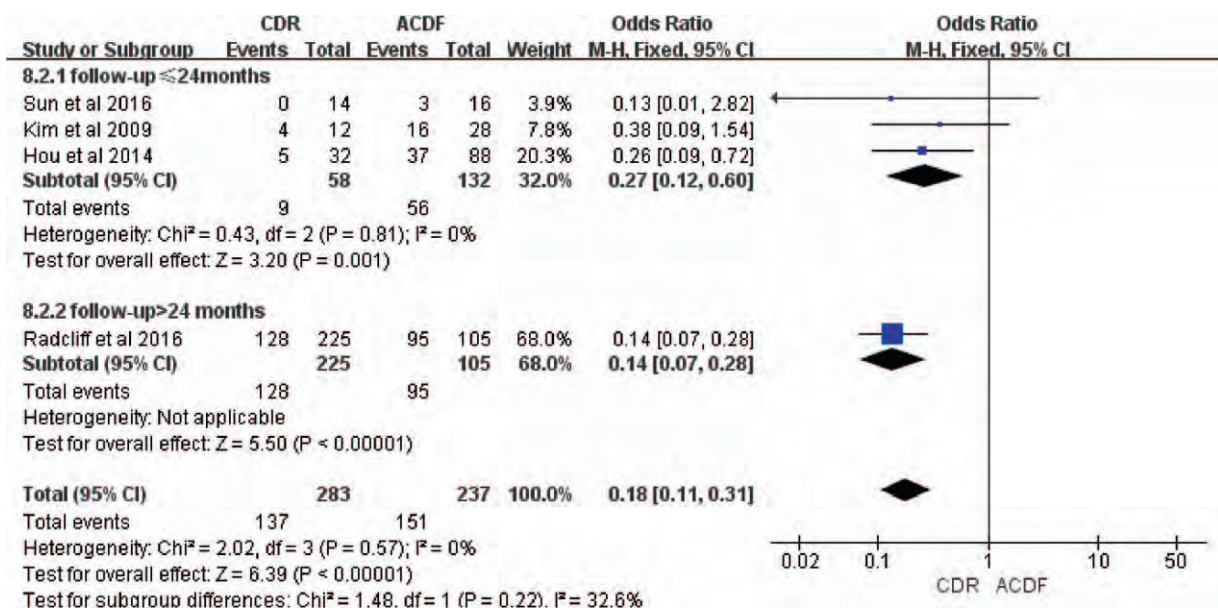


Figure 9. ASD. Forest plot of ASD for CDR and ACDF. ACDF = anterior cervical discectomy and fusion, ASD = adjacent segment degeneration, CDR = cervical disc replacement, CI = confidence interval, M-H = Mantel-Haenszel.

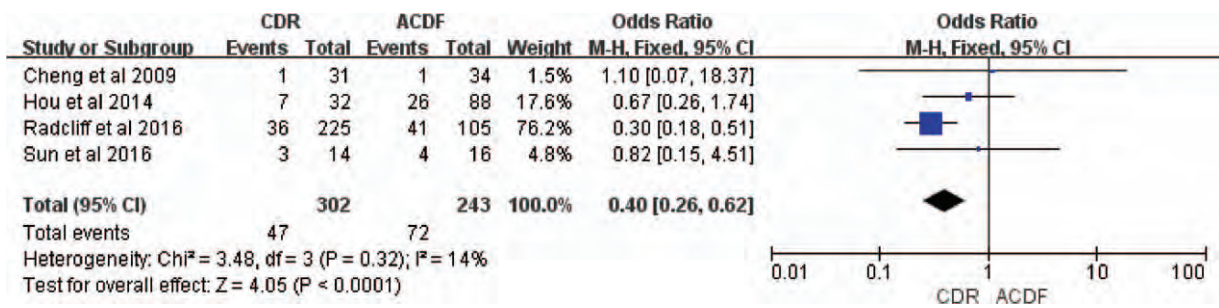


Figure 10. Adverse events. Forest plot of adverse events for CDR and ACDF. ACDF=anterior cervical discectomy and fusion, CDR=cervical disc replacement, CI=confidence interval, M-H=Mantel-Haenszel.

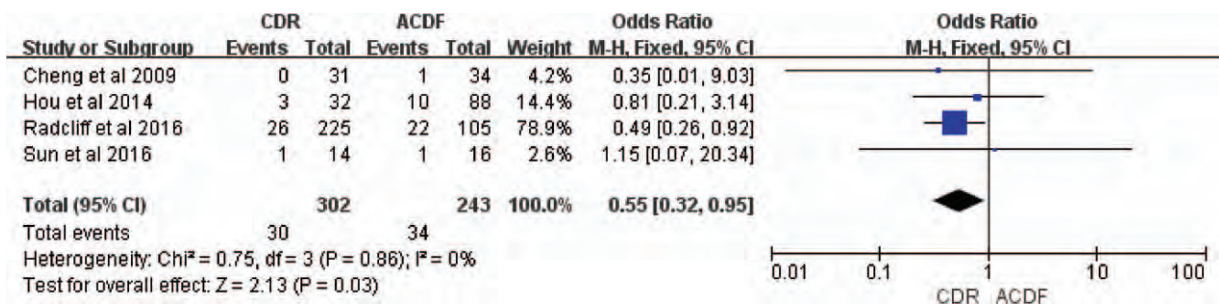


Figure 11. Dysphagia. Forest plot of dysphagia for CDR and ACDF. ACDF=anterior cervical discectomy and fusion, CDR=cervical disc replacement, CI=confidence interval, M-H=Mantel-Haenszel.

ProDisc-C cases. Furthermore, they suggested that the increased blood loss was attributable to bleeding from the keel cuts into spongy bone required by the CDR technique. Fay et al^[29] explained that arthroplasty consume more time because care must be taken to achieve wide decompression, fine preparation of endplates, and an appropriated size of the device. However, in the current meta-analysis, the results revealed that CDR had similar blood loss and operative time compared to ACDF. This inconsistency may be associated with the treated level, the type of prostheses, and the surgeons' skill levels. Some fusion devices, such as Zero-profile, require much more time to obtain the optimal angle when screwing in the lower screws of C3/C4 and the upper screws of the C6/C7.^[22]

The pooled results of the current meta-analysis showed that NDI and neck VAS were not statistically significant differences between patients who underwent multilevel CDR and those who underwent multilevel ACDF. Therefore, we hypothesized that the clinical improvement may be primarily associated with

intraoperative decompression and the time to surgical completion rather than the prosthesis. McAfee et al^[30] performed a meta-analysis of pooled results from 4 IDE clinical trials for approved cervical CDRs and concluded that CDR was at least equivalent to ACDF in NDI success after 24 months, but the results of their meta-analysis did not include VAS scores unfortunately. Zou et al^[31] performed a meta-analysis of CDR versus ACDF for 2 contiguous levels of cervical disc disease, and they found statistically significant improvement in NDI in the CDR group. However, some obvious faults caused inaccuracy of the results. On one hand, they regarded non-RCTs as RCTs in the quality evaluation and extracted data mixing single-level and 2-level cases. On the other hand, the fixed-effect model was used for analysis even with significant heterogeneity.

Intradiscal pressure and hypermobility at the adjacent levels would increase if the operated levels are completely motion restricted, which would contribute to acceleration of degeneration at adjacent levels. Several biomechanical studies have

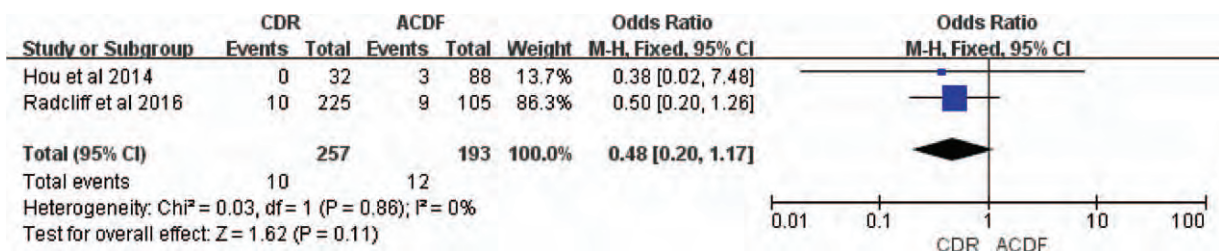


Figure 12. Device-related adverse event. Forest plot of device-related adverse event for CDR and ACDF. ACDF=anterior cervical discectomy and fusion, CDR=cervical disc replacement, CI=confidence interval, M-H=Mantel-Haenszel.

performed to explore the reasons for ASD after ACDF. Eck et al^[11] reported a cadaveric study in which the intradiscal pressure increased significantly in ACDF with a plate, which could result in cell death and disrupt metabolism. Finn et al^[32] also conducted a cadaveric study and found a significant increase in biomechanical forces at the infra- and supraadjacent levels of a 3-level fusion compared with both the intact spine and a 2-level noncontiguous fusion with cages. They also found that improper sagittal alignment was identified as a risk factor for the development of ASD. Furthermore, the segment location was another risk factor for ASD, which was suggested by Komura et al.^[33] In their studies, they found that either C5-6 or C6-7 as an adjacent level increased the likelihood of developing ASD. By preserving the operated levels near-natural motion and overall cervical spine biomechanics, multilevel CDR may decrease the risk for ASD. Our meta-analysis showed that the CDR group had better ROM postoperatively and significantly lower rates of ASD than the ACDF group. Fay et al^[25] reported that the quality of CDA for the maintenance of physiologic segmental motion is more evident in multilevel diseases than in single-level diseases.

The incidence of ASD is time-dependent. However, controversy remains on whether ASD is a result of the natural progression of age or a result of cervical fusion. This meta-analysis suggests that multilevel CDR has a significantly lower incidence of ASD compared with multilevel fusion regardless of short-term or mid-term follow-up. Due to the inconsistent rate of ASD, we have reason to believe that fusion accelerates the progression of ASD. Matsumoto et al^[34] conducted a valuable study in which they compared 64 patients who underwent ACDF with 201 healthy subjects to clarify the incidence of ASD after fusion. After a 10-year follow-up period, although both ACDF patients and healthy subjects demonstrated progression of disc degeneration, ACDF patients had significantly higher incidences of ASD than healthy subjects. Gore^[35] reported that approximately 12% of 159 asymptomatic patients developed symptomatic cervical spondylosis after a 10-year follow-up period. Although the studies imply that ASD results from several factors, fusion is one of the important factors to increase the incidence of ASD. In theory, it is more effective to treat MCDDD with CDR due to its potential protective effect against reducing ASD.

In addition to lower incidences of ASD, we found that the CDR group had fewer adverse events than the ACDF group. Dysphagia is a common approach-related adverse event. Its prevalence following anterior cervical spine surgery ranges from 2% to 60% depending on disease severity and the time frame of assessment.^[36] Surgical level, multilevel surgery, female patients, and instrumentation are related to an increased prevalence of postoperative dysphagia, but CDR could significantly reduce postoperative dysphagia compared with ACDF.^[37,38] In our meta-analysis, we also found that dysphagia had lower occurrences rate in the CDR group than the ACDF group. With respect to device-related adverse events such as migration and subsidence, there was no significant difference between the 2 groups, confirming the safety of multilevel CDR.

There are several limitations in our study. The primary limitation of this review is the lack of included studies. Due to the small number of included studies, some parameters could not be analyzed in subgroups to avoid high heterogeneity, which might result from different indications, measurements, and devices. Also, the sample sizes of the included studies were relatively small and the follow-up period was quite different between the included studies, so we could not obtain stronger conclusions. There were some methodological weaknesses in the included RCT and

non-RCTs. The types of prostheses used in the included studies, including plates, cages, zero-p, Bryan, Mobi-C, and Discover, may have effects on the accuracy of the conclusion. The blinding of the patients, surgeons, and assessors is a high risk for conclusions of several included studies.

5. Conclusion

This study provides an overview of the current knowledge on CDR for MCDDD. Compared with multilevel ACDF, multilevel CDR has similar or superior clinical and radiographic outcomes, potentially reduces the rate of ASD and eliminates adverse events. Overall, the results provided suggest that CDR may be a safe and effective alternative surgical procedure to fusion for the treatment of MCDDD. However, there is insufficient evidence to draw a strong conclusion due to the lack of included studies and the relatively low-quality evidence. We expect that this meta-analysis will help surgeons to have a better understanding of multilevel CDR. However, future long-term, multicenter, randomized, and controlled studies are needed to validate the safety and efficacy of multilevel CDR.

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