Comparison of Two Anterior Fusion Methods in Two level Cervical Spondylosis Myelopathy: A Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004581
Article Type:	Research
Date Submitted by the Author:	03-Dec-2013

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Surgery
Keywords:	Spine < ORTHOPAEDIC & TRAUMA SURGERY, Orthopaedic & trauma surgery < SURGERY, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY

Title: Comparison of Two Anterior Fusion Methods in Two level Cervical Spondylosis Myelopathy: A Meta-Analysis

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Keywords: Cervical spondylosis myelopathy; Anterior cervical discectomy and fusion; Anterior cervical corpectomy and fusion.

Word count: 2448

ABSTRACT

Background: Anterior cervical corpectomy and fusion (ACCF) and anterior cervical discectomy and fusion(ACDF) are both the popular methods for treating cervical spondylosis myelopathy(CSM). However, it remains unclear that whether ACDF is superior or inferior to ACCF. The aim of this meta-analysis is performed to evaluate the efficacy and safety of above two treatments.

Methods: We searched electronic databases of PubMed, Cochrane Central Register of Controlled Trials , ScienceDirect, CNKI, WANFANG DATA, CQVIP. Risk of bias of included studies is assessed using the Cochrane Risk of Bias Tool. We generated pooled risk ratios of dichotomous outcomes and standardised mean differences of continuous outcomes. Using the chi-square and I-square tests, we assessed the statistical heterogeneity. Perioperative parameters (hospital stay, bleeding amounts, operation time), clinical parameters (Japaneses Orthopedic Association scores (JOA), neck and arm pain Visual Analog scale Scores (VAS)), radiologic parameters (cervical lordosis for C2-C7 and fusion, rang of motion (ROM) for total and fusion, fused segment height, graft collapse, fusion rate,adjacent-level ossification), and complications were compared.

Results: Nine eligible trials with a total of 631 patients were included in this meta-analysis. No significant difference was identified between the two groups regarding hospital stay, JOA, neck and arm pain VAS, total cervical ROM, fusion ROM, fusion rate, adjacent-level ossification, and complications. While ACDF has significantly less blood loss (SMD = 1.70, 95% CI: [0.62, 2.78]), shorter operative time (SMD =1.21, 95% CI: [0.73, 1.70]), greater cervical lordosis both total cervical (SMD= -2.95, 95% CI: [-4.79,-1.12]) and fused segment (SMD= -2.24, 95% CI: [-3.31,-1.17]), higher segmental height (SMD= -1.75, 95% CI: [-3.33,-0.16]), and less graft subsidence (SMD=0.40, 95% CI: [0.06,0.75]).

Conclusions: The results suggested that ACDF has more advantages for treating CSM. Further high-quality RCT and longer follow-up duration are needed to assess the two treatments.

Article summary

Strengths and limitations of this study

1) ACCF and ACDF are both effective and safe for treating CSM in our study. 2) ACDF has more advantages than ACCF in some aspects. 3) The trials in our study are not the high-quality RCTs, and do not have long enough follow-up duration.

Introduction

Cervical spondylosis is a common disease and a progressive degenerative process of the cervical spine result in loss of disc height and formation of osteophyte. When it develops into cervical spondylosis myelopathy (CSM), motion abnormalities and sensory disturbances will follow, resulting in decreasing life quality of patients.[1] Surgical intervention is recommended for these patients with severe symptoms.[2]

The choice between an anterior, posterior, or combined approach for decompression is based primarily on (1) the sagittal alignment of the spinal column, (2) the extent of disease, (3) the location of compressive abnormality, (4) the presence of preoperative neck pain, and (5) previous operations.[2]

ACDF and ACCF is two widely used anterior methods for CSM especially with two levels.[3 4] However, controversies still exist between ACCF and ACDF for treating CSM. This meta-analysis is to compare the efficacy and safety of ACCF and ACDF for patients with two-adjacent-level CSM.

Materials and Methods

Search Strategy

We searched electronic databases including PubMed (1966-2013), Cochrane Central Register of Controlled Trials (Issue 9 , 2013), ScienceDirect (1985-2013), CNKI(1996-2013), WANFANG DATA(1997-2013), CQVIP(1996-2013). The keywords of search strategy is: “cervical spondylosis myelopathy”, “anterior cervical discectomy and fusion”, “anterior cervical corpectomy and fusion”, “two level(s)”, or “single-level”).

Eligibility Criteria

Criteria for inclusion: We identified all comparative studies of adopting ACCF and ACDF to treat adjacent two-level cervical spondylosis regardless of published and unpublished, searched reference lists of articles, and included studies to identify other potentially eligible studies. 1) ACCF with tatanium mesh, cage or autologous ilium bone grafting, ACDF with interbody cage devices or autologous ilium bone grafting, moreover the two surgeries both used anterior cervical plate and screw fixation. 2) All patients included with a confirmed CSM at two adjacent segments that recommended surgical intervention. 3) The search was limited to trials with 12 months of follow-up results or long-term results reported were included in this meta-analysis.

Criteria exclusion: 1) Objects of studies and intervention measures did not meet the inclusion criteria. 2) Do not have enough material for data consolidation. 3) The number of samples was less than 30 cases.

Data Extraction

Two reviewers independently extracted data using a standardized form. 1) Basic characteristics, including published year, study design, inclusion/exclusion criteria, age, sex, enrolled number, and follow-up rate. 2) Intraoperative parameters, consisting of hospital stays, bleeding amounts, operation times. 3) Clinical parameters, including Japanese Orthopedic Association scores(JOA), Visual Analog Scale scores(VAS) for neck and arm pain. 4) Radiologic parameters, such as cervical lordosis for total cervical and fused segment, total cervical range of motion, segmental range of motion, graft collapse, segmental height, fusion rate, degeneration of the adjacent-level. 4) complications, including short term and long term complications.

Risk of Bias Assessment

We assessed the risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions. Seven domains were assessed in each included studies. 1) Random sequence generation. 2) Allocation concealment. 3) Blinding of participants and personnel. 4) Blinding of outcome assessment. 5) Incomplete outcome data. 6) Selective reporting. 7) Other sources of bias.

Statistical Analysis

We performed all meta-analysis with the Review Manager 5.2 software (Cochrane Collaboration, Oxford, UK). For continuous outcomes, means and standard deviations were pooled to generate a standardised mean difference (SMD), and 95% confidence intervals (CI) were generated. In study of Kim 2012,[14] we used a formula to get a combined mean and standard deviation (SD).[5] For dichotomous outcomes, the risk ratio (RR) and 95% CI were assessed. A probability of $P< 0.05$ was considered to be statistically significant. Assessment for statistical heterogeneity was calculated using the chi-square and I-square tests. When the test for heterogeneity was $P<0.1$ or $I^2 >$ 50% indicated very high heterogeneity. The source of heterogeneity was investigated by subgroup analysis and sensitivity analysis. Fixed effects model was used for non-significant heterogeneity, while a random effects model was used for data with high heterogeneity.

Results

Literature Search

A total of 606 potential reports were retrieved with the search strategy(Fig. 1). 597 reports were excluded according to our inclusion criteria. No additional studies were obtained after reference review.Finally nine studies were selected and analyzed.[6-14]

Risk of bias assessment

One trial described adequate method of random sequence generation,[13] which did not described in another trial,[6] In the quasi-RCT, patients were allocated according to sequence of hospitalization,[11] the remaining were all not randomized controlled trials.[7-10 12 14] Information of allocation concealment was not available in any of the studies. Due to the nature of the trials, it was impossible to perform blinding of participants and personnel. All studies did not reported blinding of outcome assessment. No patients were lost to follow-up except for Liu et al.,[13] in which eight patients were excluded because the time of follow-up was less than two years. Since the missing data was small in number, which also balances in both arms, we considered it with a low risk of bias of incomplete outcome data addressed. In all trials, the outcomes were provided in detail, we regarded them as a low risk of bias of selective reporting. Owing to insufficient information to assess whether an important risk of bias existed in a number of trials, we argued all trials had unclear risk of bias towards other potential sources of bias. The methodological quality assessment was summarized in Table 1.

Table 1.doc

Demographic Characteristics

The demographic characteristics of the studies included are presented in Table

Table 2 and 3.doc

2. A total of 631 patients with male to female ratio of 1.38:1 were included: 270 underwent anterior cervical corpectomy and fusion(ACCF) procedures, and 361 were treated by the anterior cervical discectomy and fusion(ACDF) approach, the two surgeries used various grafts, including autografts, allografts, and cage and/or plate systems. The mean age was 55.1 years. The average duration of follow-up ranged from 18.9 to 43.2 months. Statistically similar baseline characteristics were

Table 2 and 3.doc

observed between the ACCF and ACDF groups(Table 3).

Hospital Stay

Details regarding hospital stay were available in three papers(Table S1),[6 12 13] statistical heterogeneity was absent in these studies (I^2= 0%; P = 0.69). The pooled estimate revealed statistically insignificant difference (SMD=0.18, 95% CI: [-0.15, 0.51], $P = 0.28$)(Fig. 2).

Bleeding Amounts

Relevant data was documented in four articles(Table S1),[6 11-13] all the trials showed ACDF significantly reduced intraoperative Bleeding amounts. Pooling of relevant data also showed statistically significant difference between the two groups (SMD = 1.70, 95% CI: [0.62, 2.78], P=0.002). Significant heterogeneity was detected (I^2 =89%; P<0.00001)(Fig. 2).

Operative Time

Four trials reported significant decreased surgical time in the ACDF(Table S1).[6 11-13] Overall, the standardised mean difference was 1.21 (95% CI: [0.73, 1.70], P<0.00001) in favor of the ACDF group. There was obvious evidence for statistically significant heterogeneity (I^2 = 54%; P= 0.009)(Fig. 2).

JOA

Four studies reported JOA score(Table S2),[6 12 13] the pooled estimate revealed statistically insignificant difference (SMD=0.14, 95% CI: [-0.19, 0.47], P= 0.41) with low heterogeneity(I^2 = 12%)(Fig. 3).

Neck VAS

Three studies reported a postoperative neck VAS score(Table S2),[6 9 12] the pooled data from the two relevant studies did not reveal any significant difference(SMD=0.13, 95% CI: [-0.15,0.41], P= 0.36) with low heterogeneity(I^2 = 45%)(Fig. 3).

Arm VAS

Relevant data was documented in three articles(Table S2).[6 9 12] There was no significant difference between the two treatment groups(SMD=-0.15, 95%CI =[-0.43,0.13]; P = 0.28) with low heterogeneity (I^2 = 4%)(Fig. 3).

C2-C7 Cobb

Five studies reported the C2-C7 Cobb at final follow-up (Table S3a),[6 7 10 12 14] the available data demonstrated low heterogeneity(I^2 =8%), and ACCF had a significant lower cobb than ACDF(SMD= -0.32, 95% CI: [-0.53,-0.10], P= 0.004)(Fig. 4).

Fusion Cobb

There studies reported the fusion Cobb at final follow-up (Table S3a),[7 10 13] the available data demonstrated no heterogeneity(I^2 =0%), and ACCF had a significant lower cobb than ACDF(SMD= -0.50, 95% CI: [-0.75,-0.24], P=0.0001)(Fig. 4).

Total cervical ROM

Two studies reported the data of total cervical ROM at the final follow-up(Table S3b),[6 12] the other two studies demonstrated that there was no significant difference in total cervical ROM between the two groups(SMD= -0.02, 95% CI: [-0.42,0.37], P=0.90) with no heterogeneity(I^2 = 0%)(Fig. 4).

Fusion ROM

Two studies reported fusion ROM at the last follow-up(Table S3b),[6 12] there was no significant difference in fusion ROM between the two groups(SMD= -0.05, 95% CI: [-0.45,0.35], P=0.80) with low heterogeneity(I^2 = 20%)(Fig. 4).

Fused segment height

Five studies reported the data of fused segment height at final follow-up(Table S3b),[6 9 12-14] the pooled results demonstrated that ACCF had a significant lower height of fused segment than ACDF(SMD=-0.56, 95%CI: [-1.06,-0.06], P=0.03) with high heterogeneity(I^2 = 76%)(Fig. 5).

Graft collapse

Two studies reported graft collapse at last follow-up(Table S3c),[7 10] showing that there was a significant reduction in graft collapse for ACDF(SMD=0.40, 95% CI: [0.06,0.75], P=0.02) with moderate heterogeneity (I^2 = 68%)(Fig. 5).

Fusion rate

Six studies reported fusion rate at last follow-up(Table S3c),[6 9 10 11 12 14] there was no significant in fusion rate between the two groups(RR=1.00, 95% CI: [0.97,1.04],

P=0.79) with no heterogeneity(I^2 = 0%)(Fig. 6).

Degeneration

Three studies reported degeneration of the adjacent-level to the fusion(Table S3c),[6 9 10] showing that there was no significant difference in degeneration of the adjacent-level to the fusion between the two groups(RR=1.31, 95% CI: [0.44,3.93], P=0.63) with no heterogeneity(I^2 =0%)(Fig. 6).

Complications

Data regarding complications were provided in eight studies(Table S4).[6 8-14] There was no significant difference between ACCF and ACDF groups according to individual and pooled data(RR=1.25, 95%CI = [0.74, 2.13]; P= 0.40). Statistical heterogeneity was absent in these studies (I^2= 0%; P= 0.52)(Fig. 6).

Discussion

Although most studies included in this analysis reported consistent results,[6-14] the pooled estimates should be explained with caution. With regard to operative parameters, hospital stay was similar in both groups; blood loss and operative time were significant lower in the ACDF than in the ACCF. ACDF required less exposure of the spinal cord than corpectomy did as we know,[2] which caused less damage to the spinal column, accordingly, ACDF might decrease the blood loss than ACCF. In terms of ACCF, what must be done is a 15 to 19-mm anterior midline trough in the vertebral body down to the posterior longitudinal ligament or dura, with removal of the cephalad and caudad discs,[2] which would not only cost longer time to be removed, but also spend more time to obtain a graft material fitting the trough, consequently ACDF had a significant reduction about operative time.

In our meta analysis, JOA scores, VAS for neck and arm pain both significantly improved in each group without significant differences between two groups. The results suggested that both surgical methods are safe and effective in treatment of CSM, and improve the patients' neurologic function, quality of life and disability. The similar outcome was achieved between ACDF and ACCF for multilevel cervical spondylosis by Jiang et al..[15]

Total cervical ROM, fusion ROM, fusion rete, and adjacent-level ossification yielded no significant differences between the two groups. Concerning the high fusion rate in the two groups, it may be related to the following factors: 1) the use of poly ether ether ketone (PEEK) cage or titanium meshes packed with autogenous tricortical bone and fixed—screw titanium plate or Atlantis plate fixation.[6-14] 2) The fixation system provides a stably biomechanical environment which greatly promote bone healing. 3) Bone healing is a process of creeping substitution,[16] and the distance of creeping substitution for single-level ACCF and two-level ACDF are both short. We believed that the high fusion rate effectively reduced the range of motion no matter of total cervical or fused segment. Eck et al. demonstrated that significantly greater adjacent level disc pressures was achieved after cervical fusion.[17] The normal degenerative process plays a major role through impaired nutrition, loss of viable cells, matrix protein modification, and matrix failure.[18] This normal aging process, in combination with the increased mechanical pressures, may synergistically hasten the process of degeneration. While it has not been conclusively demonstrated.[19]

For C2-C7 Cobb, ACDF had a significantly greater lordosis angle than ACCF not only at the immediate postoperative but also at the final follow-up, the same to the fusion Cobb at the last follow-up. The reasons may be associated with the following two factors: 1) Single-level ACCF removes both the vertebral body and two discs while two-level ACDF just take out the two discs,[2] as a result ACDF allows the construction after surgery more like a normal spinal column. We can draw a conclusion carefully that the loss of Cobb is less in ACDF. In other words, ACDF preserve the sagittal alignment somewhat than ACCF does. 2) Eck et al. reported that each of the involved joints contributes to the total ROM.[17] With fusion, the contribution of one joint to ROM is reduced.

In terms of fused segment height, ACCF has a significant reduction than ACDF both at immediate postoperative and at the last follow-up. With ACDF, screws placed in the intervening segment and two caudal end plates synergistically share the load of the construct. In contrast, with a single-level corpectomy, screws are only at the cranial and caudal vertebral segments and the caudal end plate bears the full load of the construct,[7] additionally the graft contact area is less for ACCF than ACDF, which results in the higher shear stress for ACCF. These reasons might hasten the process that the grafts are absorbed into the cover plate of adjacent vertebral body leading to a significant subsidence of treated segment in ACCF especially at the anterior and caudal portion.

Concerning complications, data shows that there is no significant difference between the two groups and the incidence are low in each group. This result suggests that both the two treatments are safe.

The methodological quality assessment should be considered, which identified several limitations to the clinical evidence base. Only nine studies met the pre-defined eligibility criteria, which meaned all results were based on only 631 patients, what's worse, there were just three studies reported on randomization. All of the included studies had poor concealment of randomization, including selection and allocation bias. It is inevitable for patients or operators to have no knowledge to the surgical procedures because of informed consent, as a result of allowing further measurement and expectation bias. Not all the included studies had consistent baselines characteristics between the ACCF and ACDF groups. Additionally, various outcome measurements were reported in the studies. Therefore, larger randomized controlled trials with high quality are still needed in the future.

Conclusion

Based on this meta-analysis, we could not draw any firm conclusions regarding the superiority of one treatment over the other, but it should be kept in mind that ACDF was associated with significantly less blood loss,shorter operative time, greater cervical lordosis both total cervical and fused segment, higher segmental height, and less graft subsidence. This information give surgeons a deeper understanding of the difference between the two surgeries. Further high-quality RCT and longer follow-up duration are needed to assess the two treatments.

Acknowledgement:

This work is supported by Department of Health of Zhejiang Province, Backbone of Talent Project (2012RCB037); and Department of Science and Technology of Wenzhou, Wenzhou Science and Technology Project (Y20120073). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Conceived and designed the experiments: ZYH AMW WFN. Performed the experiments: ZYH AMW WFN. Analyzed the data: ZYH AMW. Contributed reagents/materials/analysis tools: QLL TL KYW HZX. Wrote the paper: ZYH AMW.

Data Sharing Statement

None

Competing interests

None

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Figure Legends

Fig.1: The search strategy for our meta-analysis.

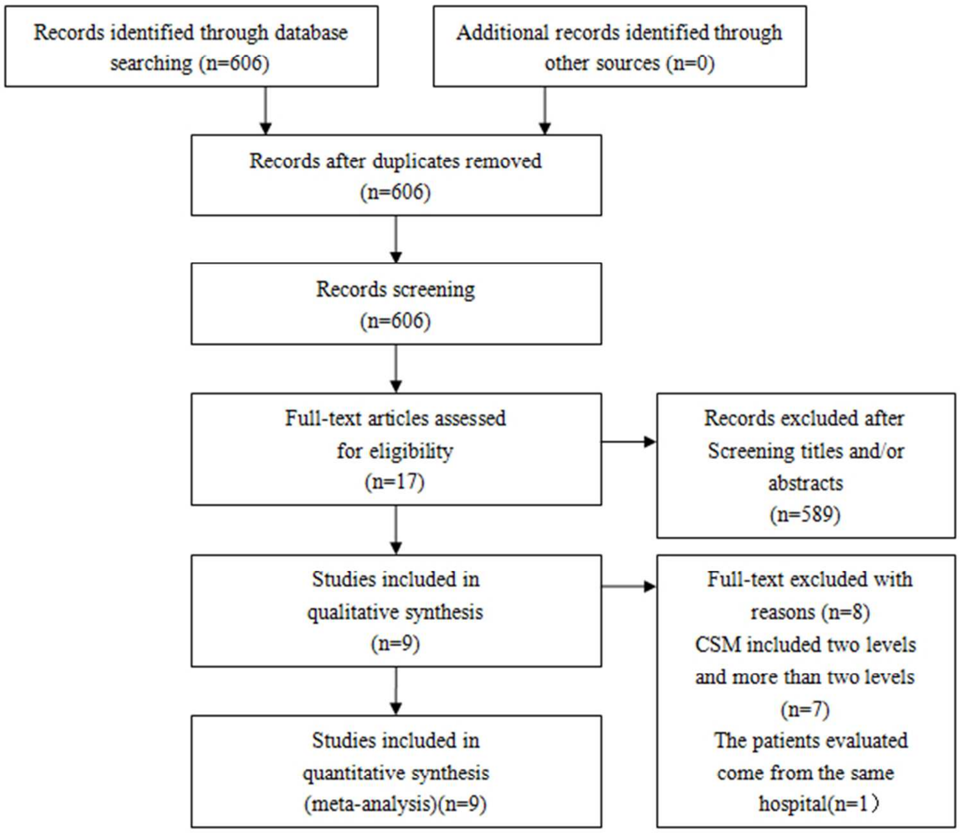
Fig.2: Perioperative parameters, **a:** Forest plot and tabulated data for hospital stay, **b:** Forest plot and tabulated data for bleeding amounts, **c:** Forest plot and tabulated data for operative time.

Fig.3: Clinical parameters, **a:** Forest plot and tabulated data for JOA, **b:** Forest plot and tabulated data for neck VAS, **c:** Forest plot and tabulated data for arm VAS.

Fig.4: Radiologic parameters, **a:** Forest plot and tabulated data for C2-C7 Cobb **b:** Forest plot and tabulated data for fusion Cobb, **c:** Forest plot and tabulated data for total cervical ROM. **d:** Forest plot and tabulated data for fusion ROM.

Fig.5: Perioperative parameters, **a:** Forest plot and tabulated data for fused segment height, **b:** Forest plot and tabulated data for graft collapse.

Fig.6: Perioperative parameters, **a:** Forest plot and tabulated data for fusion rate, **b:** Forest plot and tabulated data for degeneration of the adjacent-level, **c:** Forest plot and tabulated data for complications.



170x157mm (96 x 96 DPI)

Fig.2a hospital stay

Study or Subgroup	ACCF Mean	ACCF SD	ACCF Total	ACDF Mean	ACDF SD	ACDF Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Jia 2012	11.11	8.52	36	10.79	7.74	31	46.8%	0.04 [-0.44, 0.52]
Liu 2011	12.2	2.7	23	11.2	2.6	23	31.7%	0.37 [-0.21, 0.95]
Oh 2009	16.82	7.7	17	15.14	8.5	14	21.5%	0.20 [-0.51, 0.91]
Total (95% CI)			**76**			**68**	**100.0%**	**0.18 [-0.15, 0.51]**

Heterogeneity: $Chi^2 = 0.75$, df = 2 (P = 0.69); $I^2 = 0\%$
Test for overall effect: Z = 1.07 (P = 0.28)

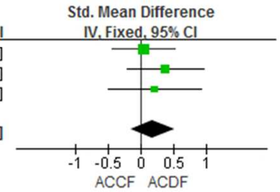


Fig.2b bleeding amounts

Study or Subgroup	ACCF Mean	ACCF SD	ACCF Total	ACDF Mean	ACDF SD	ACDF Total	Weight	Std. Mean Difference IV, Random, 95% CI
Jia 2012	279.93	63.21	36	102.21	31.71	31	24.6%	3.43 [2.67, 4.20]
Liu 2011	263	130.4	23	148.3	71.3	23	25.7%	1.07 [0.45, 1.69]
Oh 2009	778.8	644.3	17	306.43	151.1	14	24.7%	0.94 [0.19, 1.69]
Yu 2007	306.75	74.63	20	207.5	65.86	20	25.1%	1.38 [0.69, 2.08]
Total (95% CI)			**96**			**88**	**100.0%**	**1.70 [0.62, 2.78]**

Heterogeneity: $Tau^2 = 1.08$; $Chi^2 = 28.02$, df = 3 (P < 0.00001); $I^2 = 89\%$
Test for overall effect: Z = 3.08 (P = 0.002)

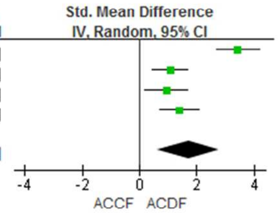
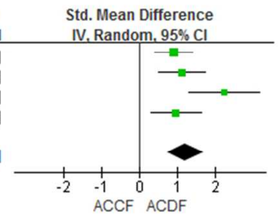


Fig.2c operative time

Study or Subgroup	ACCF Mean	ACCF SD	ACCF Total	ACDF Mean	ACDF SD	ACDF Total	Weight	Std. Mean Difference IV, Random, 95% CI
Jia 2012	141.23	63.21	36	97.37	17.72	31	31.1%	0.90 [0.40, 1.41]
Liu 2011	190.9	61.4	23	139.9	12.7	23	26.4%	1.13 [0.50, 1.76]
Oh 2009	210	6	17	140.71	44.5	14	17.3%	2.24 [1.31, 3.17]
Yu 2007	110.4	18.16	20	91.8	19.43	20	25.2%	0.97 [0.31, 1.63]
Total (95% CI)			**96**			**88**	**100.0%**	**1.21 [0.73, 1.70]**

Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 6.52$, df = 3 (P = 0.09); $I^2 = 54\%$
Test for overall effect: Z = 4.90 (P < 0.00001)



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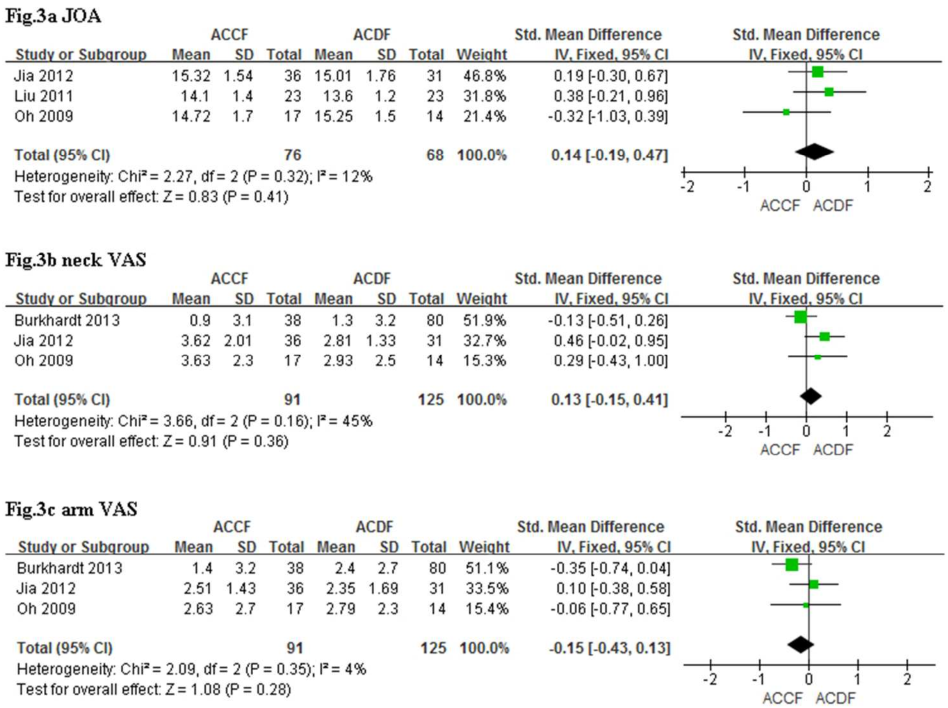

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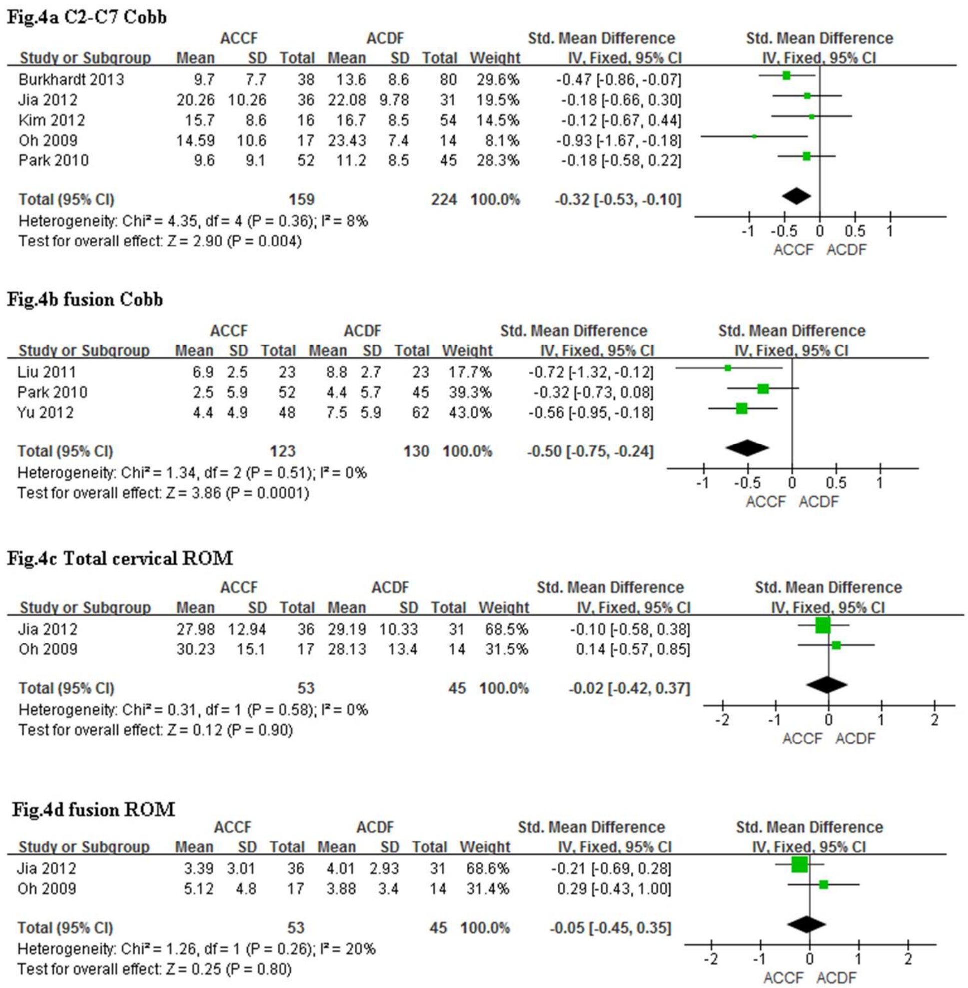


212x231mm (95 x 95 DPI)

Fig.5a fused segment height

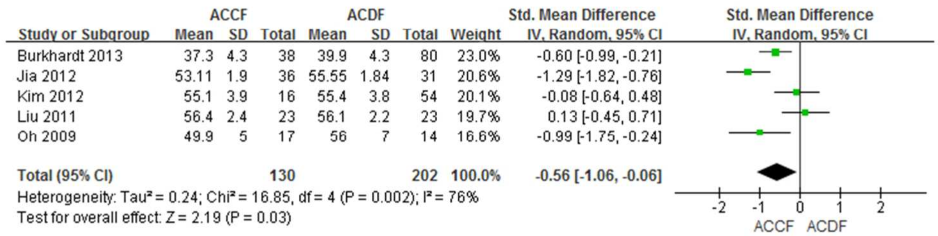
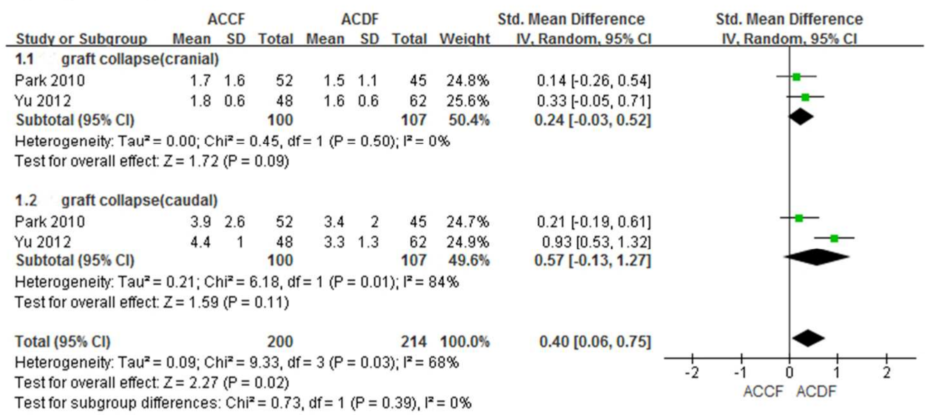


Fig.5b graft collapse



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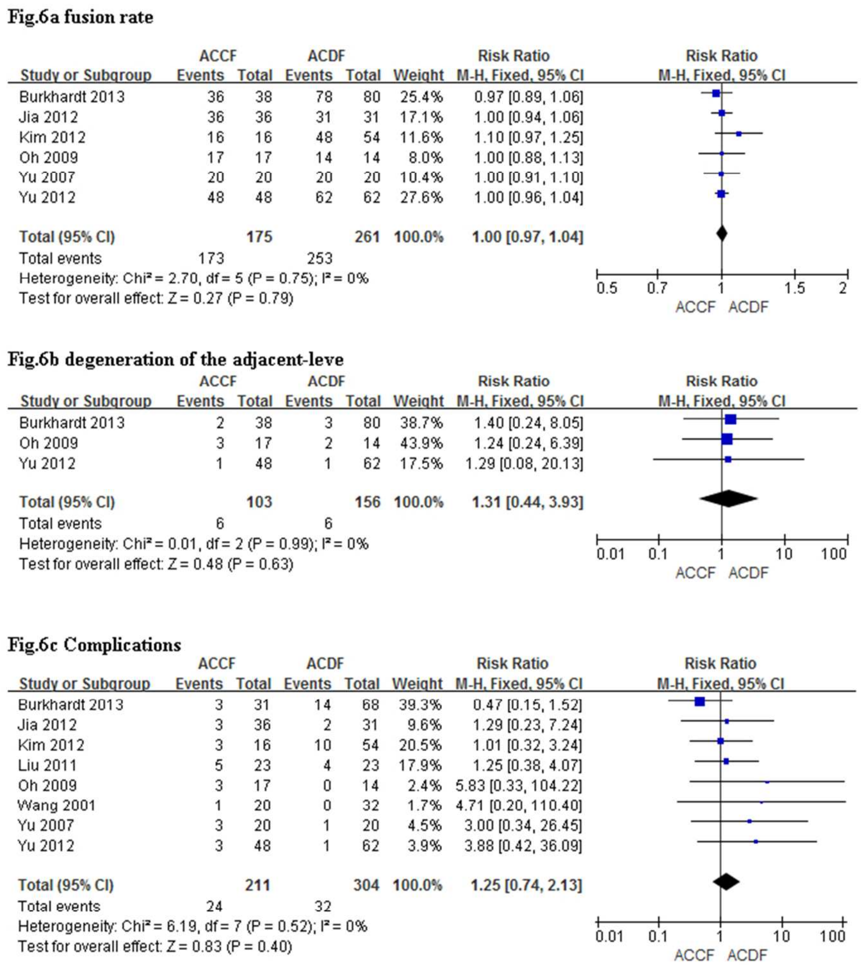

212x222mm (95 x 95 DPI)

Table 1. Risk of bias assessment of all included studies

Risk of bias assessment	Oh 2009	Park 2010	Wang 2001	Burkhardt 2013	Yu 2012	Yu 2007	Jia 2012	Liu 2011	Kim 2012
Random sequence generation	High risk	High risk	High risk	High risk	High risk	High risk	High risk	Low risk	High risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Blinding of participants and personnel	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk
Blinding of outcome assessment	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Incomplete outcome data	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Other sources of bias	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk

Table S1 Perioperative parameters of included studies.

Study	Hospital stay(days)		Bleeding amounts(ml)		Operative time(min)	
	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
Oh 2009	16.82±7.7	15.14±8.5	777.8±644.3	306.43±151.1	210±6	140.71±44.5
Park 2010	NA		NA		NA	
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		NA		NA	
Yu 2012	NA		NA		NA	
Yu 2007	NA		306.75±74.63	207.5±65.86	110.4±18.16	91.8±19.43
Jia 2012	11.11±8.52	10.79±7.74	279.93±63.21	102.21±31.71	141.23±63.21	97.37±17.72
Liu 2011	12.2±2.7	11.2±2.6	263.0±130.4	148.3±71.3	190.9±61.4	139.9±12.7
Kim 2012	NA		NA		NA	

NA=not available, ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion.

Table S2 Clinical parameters of included studies.

Study	Postoperative JOA at last visit		Postoperative neck VAS		Postoperative arm VAS	
	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
Oh 2009	14.72±1.7	15.25±1.5	3.63±2.3	2.93±2.5	2.63±2.7	2.79±2.3
Park 2010	NA		NA		NA	
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		0.9±3.1	1.3±3.2	1.4±3.2	2.4±2.7
Yu 2012	NA		NA		NA	
Yu 2007	NA		NA		NA	
Jia 2012	15.32±1.54	15.01±1.76	3.62±2.01	2.81±1.33	2.51±1.43	2.35±1.69
Liu 2011	14.1±1.4	13.6±1.2	NA		NA	
Kim 2012	NA		NA		NA	

NA= not available, JOA=Japanese Orthopedic Association scores, VAS= Visual Analog Scale scores. ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, * the study just reported the data at the sixth month of postoperative.

Table S3a Postoperative radiologic parameters of included studies.

Study	sagittal alignment		C2-C7 Cobb		fusion Cobb	
	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
Oh 2009	NA		14.59±10.6	23.43±7.4	NA	
Park 2010	32L	30L	9.6±9.1	11.2±8.5	2.5±5.9	4.4±5.7
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		9.7±7.7	13.6±8.6	NA	
Yu 2012	36L	47L	NA		4.4±4.9	7.5±5.9
Yu 2007	NA		NA		NA	
Jia 2012	NA		20.26±10.26	22.08±9.78	NA	

Liu 2011	NA	NA		6.9±2.5	8.8±2.7
Kim 2012	NA	15.7±8.6	16.7±8.5	5.8/4.6	6.8/6.8

ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, NA= not available.

Table S3b Postoperative radiologic parameters of included studies.

Study	total cervical ROM		fusion ROM		fused segment height	
	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
Oh 2009	30.23±15.1	28.13±13.4	5.12±4.8	3.88±3.4	49.9±5	56.0±7
Park 2010	NA		NA		NA	
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		NA		37.3±4.3	39.9±4.3
Yu 2012	NA		NA		NA	
Yu 2007	NA		NA		NA	
Jia 2012	27.98±12.94	29.19±10.33	3.39±3.01	4.01±2.93	53.11±1.90	55.55±1.84
Liu 2011	NA		NA		56.4±2.4	56.1±2.2
Kim 2012	33.5	26.8	NA		55.1±3.9	55.4±3.8

ACCF=anterior cervical corpectomy and fusion, ACDF=anterior cervical discectomy and fusion, NA=not available,ROM=range of motion.

Table S3c Postoperative radiologic parameters of included studies.

Study	graft collapse		fusion rate		degeneration[a]	
	ACCF(An/Po/Cr/Ca)	ACDF(An/Po/Cr/Ca)	ACCF	ACDF	ACCF	ACDF
Oh 2009	NA		100%	100%	3	2
Park 2010	5.0±2.9/3.5±2.5/1.7±1.6/3.9±2.6	4.2±2.6/3.0±2.4/1.5±1.1/3.4±2.0	NA		NA	
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		94.7%	97.5%	2	3
Yu 2012	3.7±1.3/5.2±2.2/1.8±0.6/4.4±1.0	2.9±1.2/3.6±2.3/1.6±0.6/3.3±1.3	100%	100%	1	1
Yu 2007	NA		100%	100%	NA	
Jia 2012	NA		100%	100%	NA	
Liu 2011	NA		NA		NA	
Kim 2012	NA		100%	88.9%	NA	

a degeneration means degeneration of the adjacent-level to the fusion. An= anterior, Po= posterior, Cr= cranial, Ca= caudal, ACCF= anterior cervical corpectomy and fusion, ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, NA= not available.

Table S4 Complications including short term and long term.

Study	Complications	
	ACCF	ACDF
Oh 2009	3	0
Park 2010	NA	
Wang 2001	1	0
Burkhardt 2013	3	14
Yu 2012	3	1
Yu 2007	3	1
Jia 2012	3	2
Liu 2011	5	4
Kim 2012	3	10

ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, NA= not available.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	The section that contains each item e#
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page, Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Fig. 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 6

Section/topic	#	Checklist item	The section that contains each item e#
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NO
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 7, Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 7, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 8, Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 8-12
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 7
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NO
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 12-14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 15

PRISMA 2009 Checklist

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 15-16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Comparison of Two Anterior Fusion Methods in Two level Cervical Spondylosis Myelopathy: A Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004581.R1
Article Type:	Research
Date Submitted by the Author:	01-May-2014

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Surgery
Keywords:	Spine < ORTHOPAEDIC & TRAUMA SURGERY, Orthopaedic & trauma surgery < SURGERY, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY

Title: Comparison of Two Anterior Fusion Methods in Two level Cervical Spondylosis Myelopathy: A Meta-Analysis

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Keywords: Cervical spondylosis myelopathy; Anterior cervical discectomy and fusion; Anterior cervical corpectomy and fusion.

Word count: 3423

ABSTRACT

OBJECTIVE: To evaluate the efficacy and safety of Anterior cervical corpectomy and fusion (ACCF) and Anterior cervical discectomy and fusion (ACDF) for treating two-adjacent-level CSM.

DESIGN: A meta-analysis of two anterior fusion methods was conducted. We searched electronic databases of PubMed, Cochrane Central Register of Controlled Trials , ScienceDirect, CNKI, WANFANG DATA, CQVIP. Quality assessment of included studies is evaluated using the Cochrane Risk of Bias Tool and the Methodological Index for Non-Randomized Studies(MINORS) criteria. We generated pooled risk ratios of dichotomous outcomes and standardised mean differences of continuous outcomes. Using the chi-square and I-square tests, we assessed the statistical heterogeneity. Subgroup and sensitivity analyses were also performed.

PARTICIPANTS: Nine eligible trials with a total of 631 patients with male to female ratio of 1.38:1 were included in this meta-analysis.

INCLUSION CRITERIA: Randomized controlled trials (RCTs) and Non-randomized controlled trials (NRCTs) of adopting ACCF and ACDF to treat two-adjacent-level cervical spondylosis.

RESULTS: No significant difference was identified between the two groups regarding hospital stay, JOA, neck and arm pain VAS, total cervical ROM, fusion ROM, fusion

rate, adjacent-level ossification, and complications. While ACDF has significantly less blood loss (SMD = 1.14, 95% CI: [0.74, 1.53]), shorter operative time (SMD =1.13, 95% CI: [0.82, 1.45]), greater cervical lordosis both total cervical (SMD= -2.95, 95% CI: [-4.79,-1.12]) and fused segment (SMD= -2.24, 95% CI: [-3.31,-1.17]), higher segmental height (SMD= -0.68, 95% CI: [-1.03,-0.34]), and less graft subsidence (SMD=0.40, 95% CI: [0.06,0.75]).

CONCLUSIONS: The results suggested that ACDF has more advantages in some aspects. Further high-quality RCT and longer follow-up duration are needed.

Article summary

Strengths and limitations of this study

1) ACCF and ACDF are both effective and safe for treating CSM in our study. 2) ACDF has more advantages than ACCF in some aspects. 3) The trials in our study are not the high-quality RCTs, and do not have long enough follow-up duration. 4) The number of studies used in the meta-analysis is small (9 studies). In fact for most of the outcomes the studies used in the meta-analyses are less than 5. 5) The pathological processes of patients are not always the same.

Introduction

Cervical spondylosis is a common disease and a progressive degenerative process of the cervical spine result in loss of disc height and formation of osteophyte. When it develops into cervical spondylosis myelopathy (CSM), motion abnormalities and sensory disturbances will follow, resulting in decreasing life quality of patients.[1] Surgical intervention is recommended for these patients with severe symptoms.[2]

The choice between an anterior, posterior, or combined approach for decompression is based primarily on (1) the sagittal alignment of the spinal column, (2) the extent of disease, (3) the location of compressive abnormality, (4) the presence of preoperative neck pain, and (5) previous operations.[2]

Shamji et al.[3] and Jiang et al.[4] had reviewed the efficacy and safety of anterior procedures for patients with multilevel CSM, covering the patients with two-adjacent-level CSM, which both of them did not pay attention to. Chang et al.[5] support the treatment of choice for cervical disc herniation and spondylotic radiculopathy or myelopathy is ACDF. Lu et al.[6] think ACCF is an effective surgical procedure for the treatment of multilevel cervical myelopathy because it can remove almost all pathology causing spinal cord compression like osteophytes, discs, and ossified PLL. KAZUO et al.[7] and Mamoru et al.[8] think that ACDF and ACCF are both widely used anterior methods for CSM especially with two levels. And patients with two-adjacent-level CSM often can be seen in clinical practice, while controversies still exist between ACCF and ACDF for patients with two-adjacent-level CSM when comparing perioperative, clinical, radiographic and complications outcomes. This meta-analysis is to compare the efficacy and safety of ACCF and ACDF for patients with two-adjacent-level CSM.

Materials and Methods

Search Strategy

We searched electronic databases including PubMed (1966-2013), Cochrane Central Register of Controlled Trials (Issue 9 , 2013), ScienceDirect (1985-2013), CNKI(1996-2013), WANFANG DATA(1997-2013), CQVIP(1996-2013). The keywords used for the search were: “cervical spondylosis myelopathy”, “anterior cervical discectomy and fusion”, “anterior cervical corpectomy and fusion”, “two level(s)”, or “single-level”).

Eligibility Criteria

Criteria for inclusion: We identified all comparative studies of adopting ACCF and ACDF to treat two-adjacent-level cervical spondylosis, searched reference lists of articles, and included studies to identify other potentially eligible studies. 1) ACCF with tatanium mesh, cage or autologous ilium bone grafting, ACDF with interbody cage devices or autologous ilium bone grafting, moreover the two surgeries both used anterior cervical plate and screw fixation. 2) All patients included with a confirmed

CSM at two adjacent segments that recommended surgical intervention. 3) The trials have been followed up for more than 12 months.

Criteria exclusion: 1) The studies did not meet the inclusion criteria. 2) Do not extract the data what we compare. 3) The number of samples was less than 30 cases. 4) The patients evaluated come from the same hospital.

Data Extraction

Two reviewers independently extracted data using a standardized form. 1) Basic characteristics, including published year, study design, inclusion/exclusion criteria, age, sex, enrolled number, and follow-up rate. 2) Intraoperative outcomes, consisting of hospital stays, bleeding amounts, operation times. 3) Clinical outcomes, including Japanese Orthopedic Association scores(JOA), Visual Analog Scale scores(VAS) for neck and arm pain. 4) Radiologic outcomes, such as cervical lordosis for total cervical and fused segment, total cervical range of motion, segmental range of motion, graft collapse, segmental height, fusion rate, degeneration of the adjacent-level. 4) complications, including short term and long term complications.

Risk of Bias Assessment

Two reviewers independently evaluated the quality assessment of included studies. Three randomized studies[9-11] was assessed with the Cochrane Handbook for Systematic Reviews of Interventions, six non-randomized studies[12-17] was evaluated according to the methodological index for non-randomized studies(MINORS) criteria, an established method for evaluating non-RCTs.[18]

Statistical Analysis

We performed all meta-analysis with the Review Manager 5.2 software (Cochrane Collaboration, Oxford, UK). For continuous outcomes, means and standard deviations were pooled to generate a standardised mean difference (SMD), and 95% confidence intervals (CI) were generated. In study of Kim 2012,[17] we used a formula to get a combined mean and standard deviation (SD).[19] For dichotomous outcomes, the risk ratio (RR) and 95% CI were assessed. A probability of $P< 0.05$ was considered to be statistically significant. Assessment for statistical heterogeneity was calculated using the chi-square and I-square tests. When the test for heterogeneity was $P<0.1$ or $I^2 >$ 50% indicated very high heterogeneity. The source of heterogeneity was investigated by subgroup analysis and sensitivity analysis. Fixed effects model was used for data with homogeneity, while a random effects model was used for data with high heterogeneity.

Results

Literature Search

A total of 606 potential reports were retrieved with the search strategy(Fig. 1). 597 reports were excluded according to our inclusion criteria. No additional studies were obtained after reference review. Finally nine studies were selected and analyzed.[9-17]

Risk of bias assessment

For three randomized studies,[9-11] two studies are randomized controlled trials,[9 11] one of which did not provide the information of allocation concealment. One study is a quasi-RCT, in which patients were allocated according to sequence of hospitalization.[10] Due to the informed consent right of procedures between patients and doctors, it was impossible to perform blinding of participants and personnel. All of the three studies did not reported blinding of outcome assessment. No patients were lost to follow-up except for Liu et al.,[11] in which eight patients were excluded, since the missing data was small in number, which also balances in both arms, we considered it as low risk of bias of incomplete outcome data addressed. In the three trials, the outcomes were provided in detail, we regarded them as low risk of bias of selective reporting. Owing to insufficient information to assess whether an important risk of bias existed in a number of trials, we argued all trials had unclear risk of bias towards other potential sources of bias. The methodological quality assessment was summarized in Table 1a. For six non-randomized studies,[12-17] according to the modified MINORS criteria,[18] all of them did not report the unbiased assessment of the study endpoint, the same to the item of prospective calculation of the study size. With regard to prospective collection of data, three studies did not report the relevant information.[13 15 17] Only one study reported the follow up rate.[14] The other eight items were all reported definitely. In summary, scores ranged from 16 to 18, with a median value of 16.5. The methodological quality assessment was summarized in Table 1b.

Demographic Characteristics

The demographic characteristics of the studies included are presented in Table 2. A total of 631 patients with male to female ratio of 1.38:1 were included: 270 underwent anterior cervical corpectomy and fusion(ACCF) procedures, and 361 were treated by the anterior cervical discectomy and fusion(ACDF) approach, the two surgeries used various grafts, including autografts, allografts, and cage and/or plate systems. The mean age was 55.1 years. The average duration of follow-up ranged from 18.9 to 43.2 months. Statistically similar baseline characteristics were observed between the ACCF and ACDF groups(Table 3).

Hospital Stay

Details regarding hospital stay were available in three papers(Table S1),[9 11 16] statistical heterogeneity was absent in these studies (I^2= 0%; P = 0.69). The pooled estimate revealed statistically insignificant difference (SMD=0.18, 95% CI: [-0.15, 0.51], P = 0.28)(Fig. 2).

Bleeding Amounts

Relevant data was documented in four articles(Table S1),[9-11 16] all the trials showed ACDF significantly reduced intraoperative bleeding amounts. Pooling of relevant data also showed statistically significant difference between the two groups (SMD = 1.14, 95% CI: [0.74, 1.53], P=0.002). Significant heterogeneity was detected (I^2 =89%; P<0.00001) from a subgroup analysis(Fig.2b). And the sensitivity analysis confirmed the stability of bleeding amounts outcomes(Fig.S1).

Operative Time

Four trials reported significant decreased surgical time in the ACDF(Table S1).[9-11 16] Overall, the standardised mean difference was 1.13 (95% CI: [0.82, 1.45], *P*<0.00001) in favor of the ACDF group. There was obvious evidence for statistically significant heterogeneity (I^2 = 54%; *P*= 0.009) from a subgroup analysis(.3). Furthermore, the sensitivity analysis confirmed the stability of operative time outcomes(Fig.S2).

JOA

Three studies reported JOA score(Table S2),[9 11 16] the pooled estimate revealed statistically insignificant difference (SMD=0.14, 95% CI: [-0.19, 0.47], *P*= 0.41) with low heterogeneity(I^2 = 12%)(Fig. 4a).

Neck VAS

Three studies reported a postoperative neck VAS score(Table S2),[9 14 16] the pooled data from the two relevant studies did not reveal any significant difference(SMD=0.13, 95% CI: [-0.15,0.41], *P*= 0.36) with low heterogeneity(I^2 = 45%)(Fig. 4b).

Arm VAS

Relevant data was documented in three articles(Table S2).[9 14 16] There was no significant difference between the two treatment groups(SMD=-0.15, 95%CI =[-0.43,0.13]; P = 0.28) with low heterogeneity (I^2 = 4%)(Fig. 4c).

C2-C7 Cobb

Five studies reported the C2-C7 Cobb at final follow-up (Table S3a),[9 12 14 16 17] the available data demonstrated low heterogeneity(I^2 =8%), and ACCF had a significant lower cobb than ACDF(SMD= -0.32, 95% CI: [-0.53,-0.10], P= 0.004)(Fig. 5a).

Fusion Cobb

There studies reported the fusion Cobb at final follow-up (Table S3a),[11 12 15] the available data demonstrated no heterogeneity(I^2 =0%), and ACCF had a significant lower cobb than ACDF(SMD= -0.50, 95% CI: [-0.75,-0.24], P=0.0001)(Fig. 5b).

Total cervical ROM

Two studies reported the data of total cervical ROM at the final follow-up(Table S3b),[9 16] the other two studies demonstrated that there was no significant difference in total cervical ROM between the two groups(SMD= -0.02, 95% CI: [-0.42,0.37], P=0.90) with no heterogeneity(I^2 = 0%)(Fig. 5c).

Fusion ROM

Two studies reported fusion ROM at the last follow-up(Table S3b),[9 16] there was no significant difference in fusion ROM between the two groups(SMD= -0.05, 95% CI:

[-0.45,0.35], P=0.80) with low heterogeneity($I^2 = 20\%$)(Fig. 5d).

Fused segment height

Five studies reported the data of fused segment height at final follow-up(Table S3b),[9 11 14 16 17] we exclude three studies because of the different method to measure the fused segment height,[11 16 17] the pooled results demonstrated that ACCF had a significant lower height of fused segment than ACDF(SMD= -0.68, 95% CI: [-1.03,-0.34]) with high heterogeneity($I^2 = 76\%$)(Fig. 6a).

Graft collapse

Two studies reported graft collapse at last follow-up(Table S3c),[12 15] showing that there was a significant reduction in graft collapse for ACDF(SMD=0.40, 95% CI: [0.06,0.75], P=0.02) with moderate heterogeneity ($I^2 = 68\%$)(Fig. 6b), no significant clinical heterogeneity and methodological heterogeneity are found, we consider that there exit a statistical heterogeneity, so we also pooled the two studies.

Fusion rate

Six studies reported fusion rate at last follow-up(Table S3c),[9 10 14-17] there was no significant in fusion rate between the two groups(RR=1.00, 95% CI: [0.97,1.04], P=0.79) with no heterogeneity($I^2 = 0\%$)(Fig. 7a).

Degeneration

Three studies reported degeneration of the adjacent-level to the fusion(Table S3c),[9 14 15] showing that there was no significant difference in degeneration of the adjacent-level to the fusion between the two groups(RR=1.31, 95% CI: [0.44,3.93], P=0.63) with no heterogeneity(I^2 =0%)(Fig. 7b).

Complications

Data regarding complications were provided in eight studies(Table S4).[9-11 13-17] There was no significant difference between ACCF and ACDF groups according to individual and pooled data(RR=1.25, 95%CI = [0.74, 2.13]; P= 0.40). Statistical heterogeneity was absent in these studies (I^2= 0%; P= 0.52)(Fig. 7c).

Discussion

Although most studies included in this analysis reported consistent results,[9-17] the pooled estimates should be explained with caution. With regard to operative outcomes, hospital stay was similar in both groups, less blood loss and shorter operative time was observed in ACDF than in ACCF. ACDF required less exposure of the spinal cord than corpectomy did as we know,[2] which caused less damage to the spinal column, accordingly, ACDF might decrease the blood loss than ACCF. In terms of ACCF, what must be done is a 15 to 19-mm anterior midline trough in the vertebral body down to the posterior longitudinal ligament or dura, with removal of the cephalad and caudad discs,[2] which would not only cost longer time to be removed, but also spend more time to obtain a graft material fitting the trough, consequently ACDF had a significant reduction about operative time.

In our meta analysis, JOA scores, VAS for neck and arm pain both significantly improved in each group without significant differences between two groups. The results suggested that both have a talent to be effective on treating two-adjacent-level CSM, and improve the patients' neurologic function, quality of life and disability. The similar outcome was achieved between ACDF and ACCF for multilevel cervical spondylosis by Shamji et al.[3] and Jiang et al.[4].

Total cervical ROM, fusion ROM, fusion rate, and adjacent-level ossification yielded no significant differences between the two groups. Concerning the high fusion rate in the two groups, it may be related to the following factors: 1) the use of poly ether ether ketone (PEEK) cage or titanium meshes packed with autogenous tricortical bone and fixed—screw titanium plate or Atlantis plate fixation.[9-17] 2) The fixation system provides a stably biomechanical environment which greatly promote bone healing. 3) Bone healing is a process of creeping substitution,[20] and the distance of creeping substitution for single-level ACCF and two-level ACDF are both short. We believed that the high fusion rate effectively reduced the range of motion no matter of total cervical or fused segment. Eck et al. demonstrated that significantly greater adjacent level disc pressures was achieved after cervical fusion.[21] The normal degenerative process plays a major role through impaired nutrition, loss of viable cells, matrix protein modification, and matrix failure.[22] This normal aging process, in combination with the increased mechanical pressures, may synergistically hasten the process of degeneration. While it has not been conclusively demonstrated.[23]

For C2-C7 Cobb, ACDF had a significantly greater lordosis angle than ACCF not only at the immediate postoperative but also at the final follow-up, the same to the fusion Cobb at the last follow-up. The reasons may be associated with the following two factors: 1) Single-level ACCF removes both the vertebral body and two discs while two-level ACDF just take out the two discs,[2] as a result ACDF allows the construction after surgery more like a normal spinal column. We can draw a conclusion carefully that the loss of Cobb is less in ACDF. In other words, ACDF preserve the sagittal alignment somewhat than ACCF does. 2) Eck et al. reported that each of the involved joints contributes to the total ROM.[21] With fusion, the contribution of one joint to ROM is reduced.

In terms of fused segment height, ACCF has a significant reduction than ACDF both at immediate postoperative and at the last follow-up. With ACDF, screws placed in the intervening segment and two caudal end plates synergistically share the load of the construct. In contrast, with a single-level corpectomy, screws are only at the cranial and caudal vertebral segments and the caudal end plate bears the full load of the construct,[12] additionally the graft contact area is less for ACCF than for ACDF, which results in the higher shear stress for ACCF. These reasons might hasten the process that the grafts are absorbed into the cover plate of adjacent vertebral body leading to a significant subsidence of treated segment in ACCF especially at the anterior and caudal portion.

Concerning complications, data shows that there is no significant difference between the two groups and the incidence are low in each group. This result suggests that both of the two treatments are safe.

The methodological quality assessment should be considered, which identified several limitations to the clinical evidence base. Only nine studies met the pre-defined eligibility criteria, which meaned all results were based on only 631 patients, what's worse, there were just three studies reported on randomization. All randomized studies had poor concealment of randomization, including selection and allocation bias. It is inevitable for patients or operators to have no knowledge to the surgical procedures because of informed consent, as a result of allowing further measurement and expectation bias. Four outcomes (bleeding amounts, operative time, fused segment height and graft collapse) have a high heterogeneity. Wu et al. summarized a method to deal with the heterogeneity in meta-analysis.[24] For bleeding amounts, we think that there exit a methodological heterogeneity because of different research types. From the sensitivity analysis(Fig.S1), we can easily learn that the result of Jia 2012[16] has a significantly heterogeneity which should be removed. And we owe the heterogeneity to the operative ability of surgeons, and the subgroup SMD and 95%CI were adopted to represent the outcomes of bleeding amounts because of the clinical homogeneity, the results of subgroup analysis about bleeding amounts was showed in Fig.2b. About operative time, we think that there also exit a methodological heterogeneity because of different research types. From the sensitivity analysis(Fig.S2), we can easily learn that the result that ACDF has shorter operative time will not be reversed regardless of which study was removed. So we owe the heterogeneity to the operative ability of surgeons, and the total SMD and 95%CI were adopted to represent the outcomes of operative time because of the clinical homogeneity, the results of subgroup analysis about operative time was showed in Fig.3. As to fused segment height, there exit a clinical heterogeneity, Oh et al.[9] and Burkhardt et al.[14] define the fused segment height as the distance between the midlines of involved cranial vertebral bodies and caudal vertebral bodies. Jia et al.[16] did not describe the method to measure the fused segment height. While Liu et al.[11] and Kim et al.[17] reported the anterior and posterior height of involved vertebral bodies. In summary, for fused segment height, we pooled the data of Oh et al.[9] and Burkhardt et al.[14], the outcome is displayed in Fig.6a. With regard to graft collapse, no significant clinical heterogeneity and methodological heterogeneity are found, we consider that there exit a statistical heterogeneity, so we also pooled the two studies.[12 15] The result is showed in Fig.6b. Not all the included studies had consistent baselines characteristics between the ACCF and ACDF groups. Therefore, larger randomized controlled trials with high quality are still needed in the future.

Conclusion

Based on this meta-analysis, we could not draw any firm conclusions regarding the superiority of one treatment over the other, but ACDF has some advantages such as less blood loss, shorter operative time, greater cervical lordosis both total cervical and fused segment, higher segmental height, and less graft subsidence. These information give surgeons a preliminary understanding of the difference between the two surgeries to treat two-adjacent-level CSM and will be helpful to clinical surgeons for choosing the surgeries to treat the patients with two-adjacent-level CSM. Further high-quality RCT and longer follow-up duration are needed to assess the two treatments.

Acknowledgement

This work is supported by Department of Health of Zhejiang Province, Backbone of Talent Project (2012RCB037); and Department of Science and Technology of Wenzhou, Wenzhou Science and Technology Project (Y20120073). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Conceived and designed the experiments: ZYH AMW WFN. Performed the experiments: ZYH AMW WFN. Analyzed the data: ZYH AMW. Contributed reagents/materials/analysis tools: QLL TL KYW HZX. Wrote the paper: ZYH AMW.

Competing Interests

None

Data sharing statement

No additional data are available.

Figure Legends

Fig.1: The search strategy for our meta-analysis.

Fig.2: Perioperative parameters, a: Forest plot and tabulated data for hospital stay, b: Forest plot and tabulated data for bleeding amounts.

Fig.3: Perioperative parameters, Forest plot and tabulated data for operative time.

Fig.4: Clinical parameters, a: Forest plot and tabulated data for JOA, b: Forest plot and tabulated data for neck VAS, c: Forest plot and tabulated data for arm VAS.

Fig.5: Radiologic parameters, a: Forest plot and tabulated data for C2-C7 Cobb b: Forest plot and tabulated data for fusion Cobb, c: Forest plot and tabulated data for total cervical ROM. d: Forest plot and tabulated data for fusion ROM.

Fig.6: Radiologic parameters, a: Forest plot and tabulated data for fused segment height, b: Forest plot and tabulated data for graft collapse.

Fig.7: a: Forest plot and tabulated data for fusion rate, b: Forest plot and tabulated data for degeneration of the adjacent-level, c: Forest plot and tabulated data for complications.

Fig.S1: The sensitive analysis for bleeding amounts.

Fig.S2: The sensitive analysis for operative time.

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Table 1a. Risk of bias assessment of randomized studies.

Risk of bias assessment	Oh 2009	Yu 2007	Liu 2011
Random sequence generation	Unclear risk	High risk	Low risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk
Blinding of participants and personnel	High risk	High risk	High risk
Blinding of outcome assessment	Unclear risk	Unclear risk	Unclear risk
Incomplete outcome data	Low risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk
Other sources of bias	Unclear risk	Unclear risk	Unclear risk

Table 1b. Quality assessment of non-randomized studies.

Methodological item for non-randomized studies	Park 2010	Wang 2001	Burkh-ardt 2013	Yu 2012	Jia 2012	Kim 2012
1.A clearly stated aim	2	2	2	2	2	2
2.Inclusion of consecutive patients	2	2	2	2	2	2
3.Prospective collection of data	2	0	2	0	2	0
4.Endpoints appropriate to the aim of the study	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	2	2	2	2	2	2

7. Loss to follow up less than 5%	0	0	1	0	0	0
8. Prospective calculation of the study size	0	0	0	0	0	0
9. An adequate control group	2	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	2	2	2	2	2	2
12. Adequate statistical analyses	2	2	2	2	2	2

Table 2 Characteristics of the studies included in the meta-analysis.

Year[ref]	Design	Sample size		Mean age (years)		Gender(M/F)		Mean follow-up time(months)	
		ACCF	ACDF	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
2009[6]	Retro	17	14	55.12	52.64	16/15		27.33	24.9
2010[7]	Retro	52	45	49.4±8.7	49.3±9.7	30/22	17/28	23.3±6.6	25.7±6.2
2001[8]	Retro	20	32	51.5(17-80)		27/25		43.2(24-84)	
2013[9]	Retro	38	80	60.3±11.1	60.9±9.9	25/13	41/39	20.4±13.7	
2012[10]	Retro	48	62	59.3±6.8(49-75)		65/45		32±4.2(24-60)	
2007[11]	Quasi-RCT	20	20	53.1±8.98	52.75±7.81	14/6	15/5	NA	
2012[12]	Retro	36	31	48.83±8.12	49.12±7.65	21/15	17/14	28.96±13.21	26.81±11.02
2012[13]	RCT	23	23	54.4±10.9	56.5±9.2	18/5	16/7	31(25-53)	29(26-48)
2012[14]	Retro	16	54	58±8.6	56.7±10.2	13/3	31/23	20±11.9	18.6±11.5

Retro meant Retrospective, Mean age was described as mean±SD or mean or mean (range) of all patients in the study or mean±SD of all patients in the study, Gender was described as M/F or M/F of all patients in the study, Mean follow-up time was presented as mean±SD or mean (range) or mean±SD of all patients in the study, RCT= randomized control trial, SD= standard deviation, ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, NA= not available.

Table 3 Comparison of baseline characteristics between the ACCF and ACDF groups.

Characteristic	Oh 2009	Park 2010	Wang 2001	Burkhardt 2013	Yu 2012	Yu 2007	Jia 2012	Liu 2011	Kim 2012
Mean age	*	*	*	*	*	*	*	*	*
Gender	*	*	*	*	*	*	*	*	*
Follow-up	*	*	*	*	*	*	*	*	*
Preoperative JOA	*	NA	NA	NA	NA	*	*	*	NA
Preoperative neck VAS	*	NA	NA	*	NA	NA	*	NA	NA
Preoperative arm VAS	*	NA	NA	*	NA	NA	*	NA	NA
Preoperative sagittal alignment	NA	*	NA	NA	*	NA	NA	NA	NA
Preoperative C2-C7 Cobb	*	*	NA	*	NA	NA	*	NA	*
Preoperative fused segment	*	NA	NA	*	NA	NA	NA	*	*

height									
Preoperative total cervical ROM	*	NA	NA	NA	NA	NA	0.02	NA	NA
Preoperative fused segment ROM	*	NA	NA	NA	NA	NA	0.01	NA	NA

1 JOA= Japanese Orthopedic Association scores, VAS= Visual Analog Scale scores. ROM= range of motion, NA=
2 not available, * Statistically insignificant (P>0.05).

Title: Comparison of Two Anterior Fusion Methods in Two level Cervical Spondylosis Myelopathy: A Meta-Analysis

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Keywords: Cervical spondylosis myelopathy; Anterior cervical discectomy and fusion; Anterior cervical corpectomy and fusion.

Word count: 3423

ABSTRACT

OBJECTIVE: To evaluate the efficacy and safety of Anterior cervical corpectomy and fusion (ACCF) and Anterior cervical discectomy and fusion (ACDF) for treating two-adjacent-level CSM.

DESIGN: A meta-analysis of two anterior fusion methods was conducted. We searched electronic databases of PubMed, Cochrane Central Register of Controlled Trials , ScienceDirect, CNKI, WANFANG DATA, CQVIP. Quality assessment of included studies is evaluated using the Cochrane Risk of Bias Tool and the Methodological Index for Non-Randomized Studies(MINORS) criteria. We generated pooled risk ratios of dichotomous outcomes and standardised mean differences of continuous outcomes. Using the chi-square and I-square tests, we assessed the statistical heterogeneity. Subgroup and sensitivity analyses were also performed.

PARTICIPANTS: Nine eligible trials with a total of 631 patients with male to female ratio of 1.38:1 were included in this meta-analysis.

INCLUSION CRITERIA: Randomized controlled trials (RCTs) and Non-randomized controlled trials (NRCTs) of adopting ACCF and ACDF to treat two-adjacent-level cervical spondylosis.

RESULTS: No significant difference was identified between the two groups regarding hospital stay, JOA, neck and arm pain VAS, total cervical ROM, fusion ROM, fusion rate, adjacent-level ossification, and complications. While ACDF has significantly less blood loss (SMD = 1.14, 95% CI: [0.74, 1.53]), shorter operative time (SMD =1.13, 95% CI: [0.82, 1.45]), greater cervical lordosis both total cervical (SMD= -2.95, 95% CI: [-4.79,-1.12]) and fused segment (SMD= -2.24, 95% CI: [-3.31,-1.17]), higher segmental height (SMD= -0.68, 95% CI: [-1.03,-0.34]), and less graft subsidence (SMD=0.40, 95% CI: [0.06,0.75]).

CONCLUSIONS: The results suggested that ACDF has more advantages in some aspects. Further high-quality RCT and longer follow-up duration are needed.

Article summary

Strengths and limitations of this study

1) ACCF and ACDF are both effective and safe for treating CSM in our study. 2) ACDF has more advantages than ACCF in some aspects. 3) The trials in our study are not the high-quality RCTs, and do not have long enough follow-up duration. **4) The number of studies used in the meta-analysis is small (9 studies). In fact for most of the outcomes the studies used in the meta-analyses are less than 5. 5) The pathological processes of patients are not always the same.**

Introduction

Cervical spondylosis is a common disease and a progressive degenerative process of the cervical spine result in loss of disc height and formation of osteophyte. When it develops into cervical spondylosis myelopathy (CSM), motion abnormalities and sensory disturbances will follow, resulting in decreasing life quality of patients.[1] Surgical intervention is recommended for these patients with severe symptoms.[2]

The choice between an anterior, posterior, or combined approach for decompression is based primarily on (1) the sagittal alignment of the spinal column, (2) the extent of disease, (3) the location of compressive abnormality, (4) the presence of preoperative neck pain, and (5) previous operations.[2]

Shamji et al.[3] and Jiang et al.[4] had reviewed the efficacy and safety of anterior procedures for patients with multilevel CSM, covering the patients with two-adjacent-level CSM, which both of them did not pay attention to. Chang et al.[5] support the treatment of choice for cervical disc herniation and spondylotic radiculopathy or myelopathy is ACDF. Lu et al.[6] think ACCF is an effective surgical procedure for the treatment of multilevel cervical myelopathy because it can remove almost all pathology causing spinal cord compression like osteophytes, discs, and ossified PLL. KAZUO et al.[7] and Mamoru et al.[8] think that ACDF and ACCF are both widely used anterior methods for CSM especially with two levels. And patients with two-adjacent-level CSM often can be seen in

clinical practice, while controversies still exist between ACCF and ACDF for patients with two-adjacent-level CSM when comparing perioperative, clinical, radiographic and complications outcomes. This meta-analysis is to compare the efficacy and safety of ACCF and ACDF for patients with two-adjacent-level CSM.

Materials and Methods

Search Strategy

We searched electronic databases including PubMed (1966-2013), Cochrane Central Register of Controlled Trials (Issue 9 , 2013), ScienceDirect (1985-2013), CNKI(1996-2013), WANFANG DATA(1997-2013), CQVIP(1996-2013). The keywords **used for the search were:** “cervical spondylosis myelopathy”, “anterior cervical discectomy and fusion”, “anterior cervical corpectomy and fusion”, “two level(s)”, or “single-level”).

Eligibility Criteria

Criteria for inclusion: We identified all comparative studies of adopting ACCF and ACDF to treat two-adjacent-level cervical spondylosis, searched reference lists of articles, and included studies to identify other potentially eligible studies. 1) ACCF with tatanium mesh, cage or autologous ilium bone grafting, ACDF with interbody cage devices or autologous ilium bone grafting, moreover the two

surgeries both used anterior cervical plate and screw fixation. 2) All patients included with a confirmed CSM at two adjacent segments that recommended surgical intervention. 3) The trials have been followed up for more than 12 months.

Criteria exclusion: 1) The studies did not meet the inclusion criteria. 2) Do not extract the data what we compare. 3) The number of samples was less than 30 cases. 4) The patients evaluated come from the same hospital.

Data Extraction

Two reviewers independently extracted data using a standardized form. 1) Basic characteristics, including published year, study design, inclusion/exclusion criteria, age, sex, enrolled number, and follow-up rate. 2) Intraoperative **outcomes**, consisting of hospital stays, bleeding amounts, operation times. 3) Clinical **outcomes**, including Japanese Orthopedic Association scores(JOA), Visual Analog Scale scores(VAS) for neck and arm pain. 4) Radiologic **outcomes**, such as cervical lordosis for total cervical and fused segment, total cervical range of motion, segmental range of motion, graft collapse, segmental height, fusion rate, degeneration of the adjacent-level. 4) complications, including short term and long term complications.

Risk of Bias Assessment

Two reviewers independently evaluated the quality assessment of included studies. Three randomized studies[9-11] was assessed with the Cochrane Handbook

for Systematic Reviews of Interventions, six non-randomized studies[12-17] was evaluated according to the methodological index for non-randomized studies(MINORS) criteria, an established method for evaluating non-RCTs.[18]

Statistical Analysis

We performed all meta-analysis with the Review Manager 5.2 software (Cochrane Collaboration, Oxford, UK). For continuous outcomes, means and standard deviations were pooled to generate a standardised mean difference (SMD), and 95% confidence intervals (CI) were generated. In study of Kim 2012,[17] we used a formula to get a combined mean and standard deviation (SD).[19] For dichotomous outcomes, the risk ratio (RR) and 95% CI were assessed. A probability of $P< 0.05$ was considered to be statistically significant. Assessment for statistical heterogeneity was calculated using the chi-square and I-square tests. When the test for heterogeneity was $P<0.1$ or $I^2 >$ 50% indicated very high heterogeneity. The source of heterogeneity was investigated by subgroup analysis and sensitivity analysis. Fixed effects model was used for data with homogeneity, while a random effects model was used for data with high heterogeneity.

Results

Literature Search

A total of 606 potential reports were retrieved with the search strategy(Fig. 1). 597 reports were excluded according to our inclusion criteria. No additional studies were obtained after reference review. Finally nine studies were selected and analyzed.[9-17]

Risk of bias assessment

For three randomized studies,[9-11] two studies are randomized controlled trials,[9, 11] one of which did not provide the information of allocation concealment. One study is a quasi-RCT, in which patients were allocated according to sequence of hospitalization.[10] Due to the informed consent right of procedures between patients and doctors, it was impossible to perform blinding of participants and personnel. All of the three studies did not reported blinding of outcome assessment. No patients were lost to follow-up except for Liu et al.,[11] in which eight patients were excluded, since the missing data was small in number, which also balances in both arms, we considered it as low risk of bias of incomplete outcome data addressed. In the three trials, the outcomes were provided in detail, we regarded them as low risk of bias of selective reporting. Owing to insufficient information to assess whether an important risk of bias existed in a number of trials, we argued all trials had unclear risk of bias towards other potential sources of bias. The methodological quality assessment was summarized in Table 1a. For six non-randomized studies,[12-17] according to the modified MINORS criteria,[18] all of them did not report the unbiased assessment of the study endpoint, the same to the item of prospective calculation of the study size. With

regard to prospective collection of data, three studies did not report the relevant information.[13 15 17] Only one study reported the follow up rate.[14] The other eight items were all reported definitely. In summary, scores ranged from 16 to 18, with a median value of 16.5. The methodological quality assessment was summarized in Table 1b.

Demographic Characteristics

The demographic characteristics of the studies included are presented in Table 2. A total of 631 patients with male to female ratio of 1.38:1 were included: 270 underwent anterior cervical corpectomy and fusion(ACCF) procedures, and 361 were treated by the anterior cervical discectomy and fusion(ACDF) approach, the two surgeries used various grafts, including autografts, allografts, and cage and/or plate systems. The mean age was 55.1 years. The average duration of follow-up ranged from 18.9 to 43.2 months. Statistically similar baseline characteristics were observed between the ACCF and ACDF groups(Table 3).

Hospital Stay

Details regarding hospital stay were available in three papers(Table S1),[9 11 16] statistical heterogeneity was absent in these studies (I^2= 0%; P = 0.69). The pooled estimate revealed statistically insignificant difference (SMD=0.18, 95% CI: [-0.15, 0.51], P = 0.28)(Fig. 2).

Bleeding Amounts

Relevant data was documented in four articles(Table S1),[9-11 16] all the trials showed ACDF significantly reduced intraoperative bleeding amounts. Pooling of relevant data also showed statistically significant difference between the two groups **(SMD = 1.14, 95% CI: [0.74, 1.53], *P*=0.002)**. **Significant heterogeneity was detected (I^2 =89%; *P*<0.00001) from a subgroup analysis(Fig.2b). And the sensitivity analysis confirmed the stability of bleeding amounts outcomes(Fig.S1).**

Operative Time

Four trials reported significant decreased surgical time in the ACDF(Table S1).[9-11 16] Overall, **the standardised mean difference was 1.13 (95% CI: [0.82, 1.45]**, *P*<0.00001) in favor of the ACDF group. **There was obvious evidence for statistically significant heterogeneity (I^2 = 54%; *P*= 0.009) from a subgroup analysis(Fig.3). Furthermore, the sensitivity analysis confirmed the stability of operative time outcomes(Fig.S2).**

JOA

Three studies reported JOA score(Table S2),[9 11 16] the pooled estimate revealed statistically insignificant difference (SMD=0.14, 95% CI: [-0.19, 0.47], *P*= 0.41) with low heterogeneity(I^2 = 12%)**(Fig. 4a).**

Neck VAS

Three studies reported a postoperative neck VAS score(Table S2),[9 14 16] the pooled data from the two relevant studies did not reveal any significant difference(SMD=0.13, 95% CI: [-0.15,0.41], P= 0.36) with low heterogeneity(I^2 = 45%)**(Fig. 4b)**.

Arm VAS

Relevant data was documented in three articles(Table S2).[9 14 16] There was no significant difference between the two treatment groups(SMD=-0.15, 95%CI =[-0.43,0.13]; P = 0.28) with low heterogeneity (I^2 = 4%)**(Fig. 4c)**.

C2-C7 Cobb

Five studies reported the C2-C7 Cobb at final follow-up (Table S3a),[9 12 14 16 17] the available data demonstrated low heterogeneity(I^2 =8%), and ACCF had a significant lower cobb than ACDF(SMD= -0.32, 95% CI: [-0.53,-0.10], P= 0.004)**(Fig. 5a)**.

Fusion Cobb

There studies reported the fusion Cobb at final follow-up (Table S3a),[11 12 15] the available data demonstrated no heterogeneity(I^2 =0%), and ACCF had a significant lower cobb than ACDF(SMD= -0.50, 95% CI: [-0.75,-0.24], P=0.0001)**(Fig. 5b)**.

Total cervical ROM

Two studies reported the data of total cervical ROM at the final follow-up(Table S3b),[9 16] the other two studies demonstrated that there was no significant difference in total cervical ROM between the two groups(SMD= -0.02, 95% CI: [-0.42,0.37],

P=0.90) with no heterogeneity(I^2 = 0%)**(Fig. 5c)**.

Fusion ROM

Two studies reported fusion ROM at the last follow-up(Table S3b),[9 16] there was no significant difference in fusion ROM between the two groups(SMD= -0.05, 95% CI: [-0.45,0.35], P=0.80) with low heterogeneity(I^2 = 20%)**(Fig. 5d)**.

Fused segment height

Five studies reported the data of fused segment height at final follow-up(Table S3b),[9 11 14 16 17] **we exclude three studies because of the different method to measure the fused segment height,**[11 16 17] the pooled results demonstrated that ACCF had a significant lower height of fused segment than ACDF**(SMD= -0.68, 95% CI: [-1.03,-0.34])** with high heterogeneity(I^2 = 76%)**(Fig. 6a)**.

Graft collapse

Two studies reported graft collapse at last follow-up(Table S3c),[12 15] showing that there was a significant reduction in graft collapse for ACDF(SMD=0.40, 95% CI: [0.06,0.75], P=0.02) with moderate heterogeneity (I^2 = 68%)**(Fig. 6b), no significant clinical heterogeneity and methodological heterogeneity are found, we consider that there exit a statistical heterogeneity, so we also pooled the two studies.**

Fusion rate

Six studies reported fusion rate at last follow-up(Table S3c),[9 10 14-17] there was no significant in fusion rate between the two groups(RR=1.00, 95% CI: [0.97,1.04], *P*=0.79) with no heterogeneity(I^2 = 0%)**(Fig. 7a)**.

Degeneration

Three studies reported degeneration of the adjacent-level to the fusion(Table S3c),[9 14 15] showing that there was no significant difference in degeneration of the adjacent-level to the fusion between the two groups(RR=1.31, 95% CI: [0.44,3.93], *P*=0.63) with no heterogeneity(I^2 =0%)**(Fig. 7b)**.

Complications

Data regarding complications were provided in eight studies(Table S4).[9-11 13-17] There was no significant difference between ACCF and ACDF groups according to individual and pooled data(RR=1.25, 95%CI = [0.74, 2.13]; *P*= 0.40). Statistical heterogeneity was absent in these studies (I^2= 0%; *P*= 0.52)**(Fig. 7c)**.

Discussion

Although most studies included in this analysis reported consistent results,[9-17] the pooled estimates should be explained with caution. With regard to operative **outcomes**, hospital stay was similar in both groups, **less blood loss and shorter operative time was observed in ACDF than in ACCF**. ACDF required less exposure of the spinal cord than corpectomy did as we know,[2] which caused less damage to the spinal column, accordingly, ACDF might decrease the blood loss than ACCF. In terms of ACCF, what must be done is a 15 to 19-mm anterior midline trough in the vertebral body down to the posterior longitudinal ligament or dura, with removal of the cephalad and caudad discs,[2] which would not only cost longer time to be removed, but also spend more time to obtain a graft material fitting the trough, consequently ACDF had a significant reduction about operative time.

In our meta analysis, JOA scores, VAS for neck and arm pain both significantly improved in each group without significant differences between two groups. **The results suggested that both have a talent to be effective on treating two-adjacent-level CSM,** and improve the patients' neurologic function, quality of life and disability. The similar outcome was achieved between ACDF and ACCF for multilevel cervical spondylosis by **Shamji et al.[3] and Jiang et al.[4].**

Total cervical ROM, fusion ROM, fusion rate, and adjacent-level ossification yielded no significant differences between the two groups. Concerning the high fusion rate in the two groups, it may be related to the following factors: 1) the use of poly ether ether ketone (PEEK) cage or titanium meshes packed with autogenous tricortical bone and fixed—screw titanium plate or Atlantis plate fixation.[9-17] 2) The fixation system provides a stably biomechanical environment which greatly promote bone healing. 3) Bone healing is a process of creeping substitution,[20] and the distance of creeping substitution for single-level ACCF and two-level ACDF are both short. We believed that the high fusion rate effectively reduced the range of motion no matter of total cervical or fused segment. Eck et al. demonstrated that significantly greater adjacent level disc pressures was achieved after cervical fusion.[21] The normal degenerative process plays a major role through impaired nutrition, loss of viable cells, matrix protein modification, and matrix failure.[22] This normal aging process, in combination with the increased mechanical pressures, may synergistically hasten the process of degeneration. While it has not been conclusively demonstrated.[23]

For C2-C7 Cobb, ACDF had a significantly greater lordosis angle than ACCF not only at the immediate postoperative but also at the final follow-up, the same to the fusion Cobb at the last follow-up. The reasons may be associated with the following two factors: 1) Single-level ACCF removes both the vertebral body and two discs while two-level ACDF just take out the two discs,[2] as a result ACDF allows the construction after surgery more like a normal spinal column. We can draw a conclusion carefully that the loss of Cobb is less in ACDF. In other words, ACDF preserve the sagittal alignment somewhat than ACCF does. 2) Eck et al. reported that each of the involved joints contributes to the total ROM.[21] With fusion, the contribution of one joint to ROM is reduced.

In terms of fused segment height, ACCF has a significant reduction than ACDF both at immediate postoperative and at the last follow-up. With ACDF, screws placed in the intervening segment and two caudal end plates synergistically share the load of the construct. In contrast, with a single-level corpectomy, screws are only at the cranial and caudal vertebral segments and the caudal end plate bears the full load of the construct,[12] additionally the graft contact area is less for ACCF than **for ACDF**, which results in the higher shear stress for ACCF. These reasons might hasten the process that the grafts are absorbed into the cover plate of adjacent vertebral body leading to a significant subsidence of treated segment in ACCF especially at the anterior and caudal portion.

Concerning complications, data shows that there is no significant difference between the two groups and the incidence are low in each group. This result suggests that **both of the two treatments are safe.**

The methodological quality assessment should be considered, which identified several limitations to the clinical evidence base. Only nine studies met the pre-defined eligibility criteria, which meaned all results were based on only 631 patients, what's worse, there were just three studies reported on randomization. All randomized studies had poor concealment of randomization, including selection and allocation bias. It is inevitable for patients or operators to have no knowledge to the surgical procedures because of informed consent, as a result of allowing further measurement and expectation bias. **Four outcomes (bleeding amounts, operative time, fused segment height and graft collapse) have a high heterogeneity. Wu et al. summarized a method to deal with the heterogeneity in meta-analysis.[24] For bleeding amounts, we think that there exit a methodological heterogeneity because of different research types. From the sensitivity analysis(Fig.S1), we can easily learn that the result of Jia 2012[16] has a significantly heterogeneity which should be removed. And we owe the heterogeneity to the operative ability of surgeons, and the subgroup SMD and 95%CI were adopted to represent the outcomes of bleeding amounts because of the clinical homogeneity, the results of**

subgroup analysis about bleeding amounts was showed in Fig.2b. About operative time, we think that there also exit a methodological heterogeneity because of different research types. From the sensitivity analysis(Fig.S2), we can easily learn that the result that ACDF has shorter operative time will not be reversed regardless of which study was removed. So we owe the heterogeneity to the operative ability of surgeons, and the total SMD and 95%CI were adopted to represent the outcomes of operative time because of the clinical homogeneity, the results of subgroup analysis about operative time was showed in Fig.3. As to fused segment height, there exit a clinical heterogeneity, Oh et al.[9] and Burkhardt et al.[14] define the fused segment height as the distance between the midlines of involved cranial vertebral bodies and caudal vertebral bodies. Jia et al.[16] did not describe the method to measure the fused segment height. While Liu et al.[11] and Kim et al.[17] reported the anterior and posterior height of involved vertebral bodies. In summary, for fused segment height, we pooled the data of Oh et al.[9] and Burkhardt et al.[14], the outcome is displayed in Fig.6a. With regard to graft collapse, no significant clinical heterogeneity and methodological heterogeneity are found, we consider that there exit a statistical heterogeneity, so we also pooled the two studies.[12 15] The result is showed in Fig.6b. Not all the included studies had consistent baselines characteristics between the ACCF and ACDF groups. Therefore, larger randomized controlled trials with high quality are still needed in the future.

Conclusion

Based on this meta-analysis, we could not draw any firm conclusions regarding the superiority of one treatment over the other, **but ACDF has some advantages such as less blood loss, shorter operative time, greater cervical lordosis both total cervical and fused segment, higher segmental height, and less graft subsidence. These information give surgeons a preliminary understanding of the difference between the two surgeries to treat two-adjacent-level CSM and will be helpful to clinical surgeons for choosing the surgeries to treat the patients with two-adjacent-level CSM.** Further high-quality RCT and longer follow-up duration are needed to assess the two treatments.

Acknowledgement

This work is supported by Department of Health of Zhejiang Province, Backbone of Talent Project (2012RCB037); and Department of Science and Technology of Wenzhou, Wenzhou Science and Technology Project (Y20120073). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Conceived and designed the experiments: ZYH AMW WFN. Performed the experiments: ZYH AMW WFN. Analyzed the data: ZYH AMW. Contributed reagents/materials/analysis tools: QLL TL KYW HZX. Wrote the paper: ZYH AMW.

Data sharing statement

No additional data are available.

Figure Legends

Fig.1: The search strategy for our meta-analysis.

Fig.2: Perioperative parameters, a: Forest plot and tabulated data for hospital stay, b: Forest plot and tabulated data for bleeding amounts.

Fig.3: Perioperative parameters, Forest plot and tabulated data for operative time.

Fig.4: Clinical parameters, a: Forest plot and tabulated data for JOA, b: Forest plot and tabulated data for neck VAS, c: Forest plot and tabulated data for arm VAS.

Fig.5: Radiologic parameters, a: Forest plot and tabulated data for C2-C7 Cobb b: Forest plot and tabulated data for fusion Cobb, c: Forest plot and tabulated data for total cervical ROM. d: Forest plot and tabulated data for fusion ROM.

Fig.6: Radiologic parameters, a: Forest plot and tabulated data for fused segment height, b: Forest plot and tabulated data for graft collapse.

Fig.7: a: Forest plot and tabulated data for fusion rate, b: Forest plot and tabulated data for degeneration of the adjacent-level, c: Forest plot and tabulated data for complications.

Fig.S1: The sensitive analysis for bleeding amounts.

Fig.S2: The sensitive analysis for operative time.

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Table 1a. Risk of bias assessment of randomized studies.

Risk of bias assessment	Oh 2009	Yu 2007	Liu 2011
Random sequence generation	Unclear risk	High risk	Low risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk
Blinding of participants and personnel	High risk	High risk	High risk
Blinding of outcome assessment	Unclear risk	Unclear risk	Unclear risk
Incomplete outcome data	Low risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk
Other sources of bias	Unclear risk	Unclear risk	Unclear risk

Table 1b. Quality assessment of non-randomized studies.

Methodological item for non-randomized studies	**Park 2010**	**Wang 2001**	**Burkh-ardt 2013**	**Yu 2012**	**Jia 2012**	**Kim 2012**
1.A clearly stated aim	2	2	2	2	2	2
2.Inclusion of consecutive patients	2	2	2	2	2	2
3.Prospective collection of data	2	0	2	0	2	0
4.Endpoints appropriate to the aim of the study	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	2	2	2	2	2	2
7. Loss to follow up less than 5%	0	0	1	0	0	0
8. Prospective calculation of the study size	0	0	0	0	0	0
9. An adequate control group	2	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	2	2	2	2	2	2
12. Adequate statistical analyses	2	2	2	2	2	2

Table 2 Characteristics of the studies included in the meta-analysis.

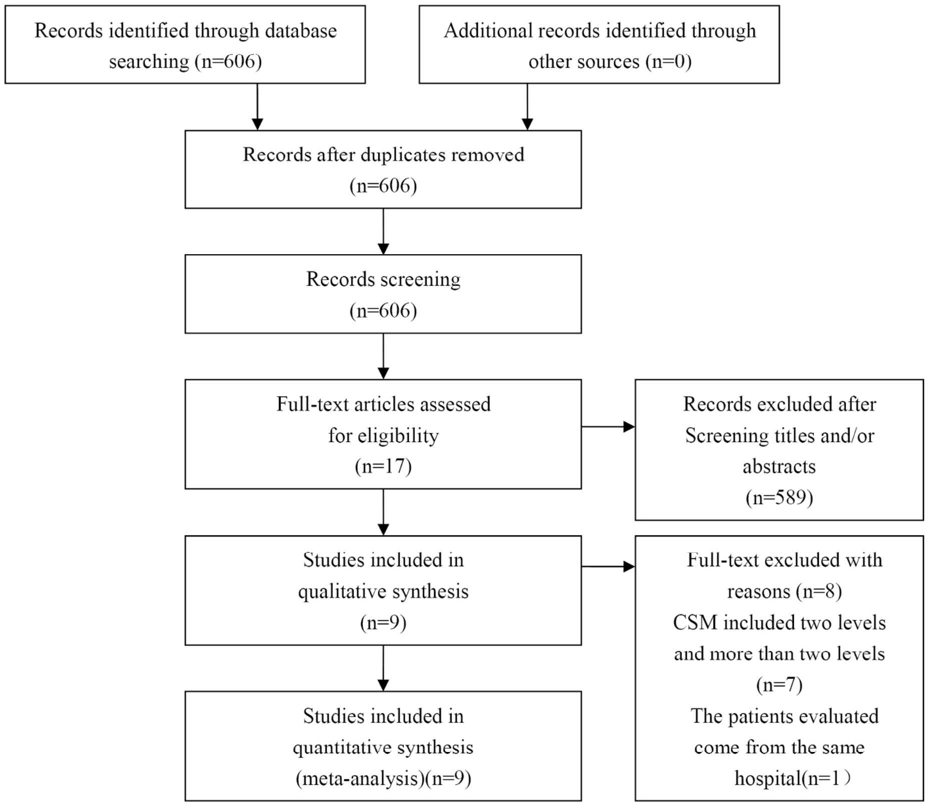
Year[ref]	Design	Sample size		Mean age (years)		Gender(M/F)		Mean follow-up time(months)	
		ACCF	ACDF	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
2009[6]	Retro	17	14	55.12	52.64	16/15		27.33	24.9
2010[7]	Retro	52	45	49.4±8.7	49.3±9.7	30/22	17/28	23.3±6.6	25.7±6.2
2001[8]	Retro	20	32	51.5(17-80)		27/25		43.2(24-84)	
2013[9]	Retro	38	80	60.3±11.1	60.9±9.9	25/13	41/39	20.4±13.7	
2012[10]	Retro	48	62	59.3±6.8(49-75)		65/45		32±4.2(24-60)	
2007[11]	Quasi-RCT	20	20	53.1±8.98	52.75±7.81	14/6	15/5	NA	
2012[12]	Retro	36	31	48.83±8.12	49.12±7.65	21/15	17/14	28.96±13.21	26.81±11.02
2012[13]	RCT	23	23	54.4±10.9	56.5±9.2	18/5	16/7	31(25-53)	29(26-48)
2012[14]	Retro	16	54	58±8.6	56.7±10.2	13/3	31/23	20±11.9	18.6±11.5

Retro meant Retrospective, Mean age was described as mean±SD or mean or mean (range) of all patients in the study or mean±SD of all patients in the study, Gender was described as M/F or M/F of all patients in the study, Mean follow-up time was presented as mean±SD or mean (range) or mean±SD of all patients in the study, RCT= randomized control trial, SD= standard deviation, ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, NA= not available.

Table 3 Comparison of baseline characteristics between the ACCF and ACDF groups.

Characteristic	Oh 2009	Park 2010	Wang 2001	Burkhardt 2013	Yu 2012	Yu 2007	Jia 2012	Liu 2011	Kim 2012
Mean age	*	*	*	*	*	*	*	*	*
Gender	*	*	*	*	*	*	*	*	*
Follow-up	*	*	*	*	*	*	*	*	*
Preoperative JOA	*	NA	NA	NA	NA	*	*	*	NA
Preoperative neck VAS	*	NA	NA	*	NA	NA	*	NA	NA
Preoperative arm VAS	*	NA	NA	*	NA	NA	*	NA	NA
Preoperative sagittal alignment	NA	*	NA	NA	*	NA	NA	NA	NA
Preoperative C2-C7 Cobb	*	*	NA	*	NA	NA	*	NA	*
Preoperative fused segment height	*	NA	NA	*	NA	NA	NA	*	*
Preoperative total cervical ROM	*	NA	NA	NA	NA	NA	0.02	NA	NA
Preoperative fused segment ROM	*	NA	NA	NA	NA	NA	0.01	NA	NA

JOA= Japanese Orthopedic Association scores, VAS= Visual Analog Scale scores. ROM= range of motion, NA= not available, * Statistically insignificant (*P*>0.05).



176x157mm (300 x 300 DPI)

Fig.2a hospital stay

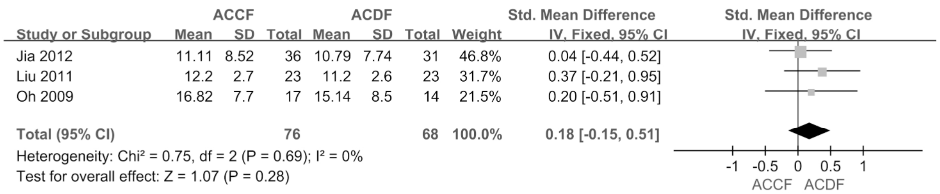
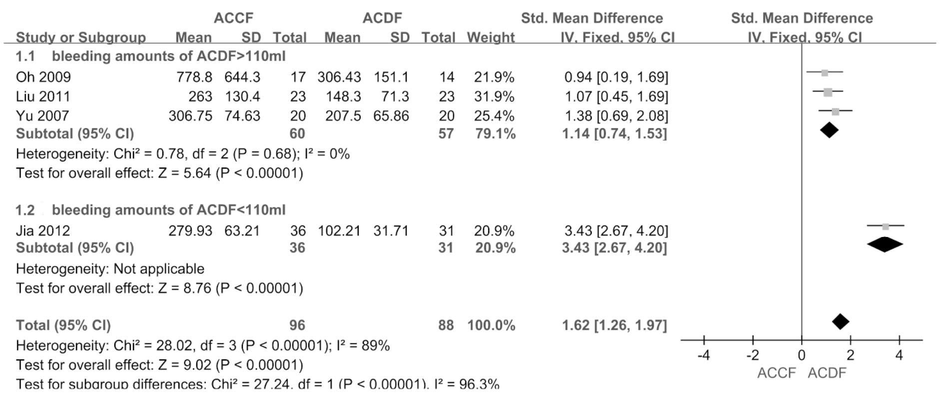


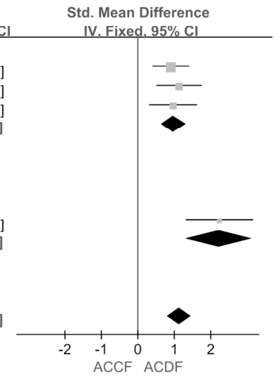
Fig.2b bleeding amounts



209x162mm (300 x 300 DPI)

Fig.3 Operative Time

	ACCF			ACDF				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
1.1 operative time of ACCF<200min								
Jia 2012	141.23	63.21	36	97.37	17.72	31	39.4%	0.90 [0.40, 1.41]
Liu 2011	190.9	61.4	23	139.9	12.7	23	25.7%	1.13 [0.50, 1.76]
Yu 2007	110.4	18.16	20	91.8	19.43	20	23.2%	0.97 [0.31, 1.63]
Subtotal (95% CI)			**79**			**74**	**88.2%**	**0.99 [0.65, 1.33]**
Heterogeneity: Chi² = 0.31, df = 2 (P = 0.86); I² = 0%								
Test for overall effect: Z = 5.73 (P < 0.00001)								
1.2 operative time of ACCF >200min								
Oh 2009	210	6	17	140.71	44.5	14	11.8%	2.24 [1.31, 3.17]
Subtotal (95% CI)			**17**			**14**	**11.8%**	**2.24 [1.31, 3.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.74 (P < 0.00001)								
Total (95% CI)			**96**			**88**	**100.0%**	**1.13 [0.82, 1.45]**
Heterogeneity: Chi² = 6.52, df = 3 (P = 0.09); I² = 54%								
Test for overall effect: Z = 7.01 (P < 0.00001)								
Test for subgroup differences: Chi² = 6.21, df = 1 (P = 0.01), I² = 83.9%								



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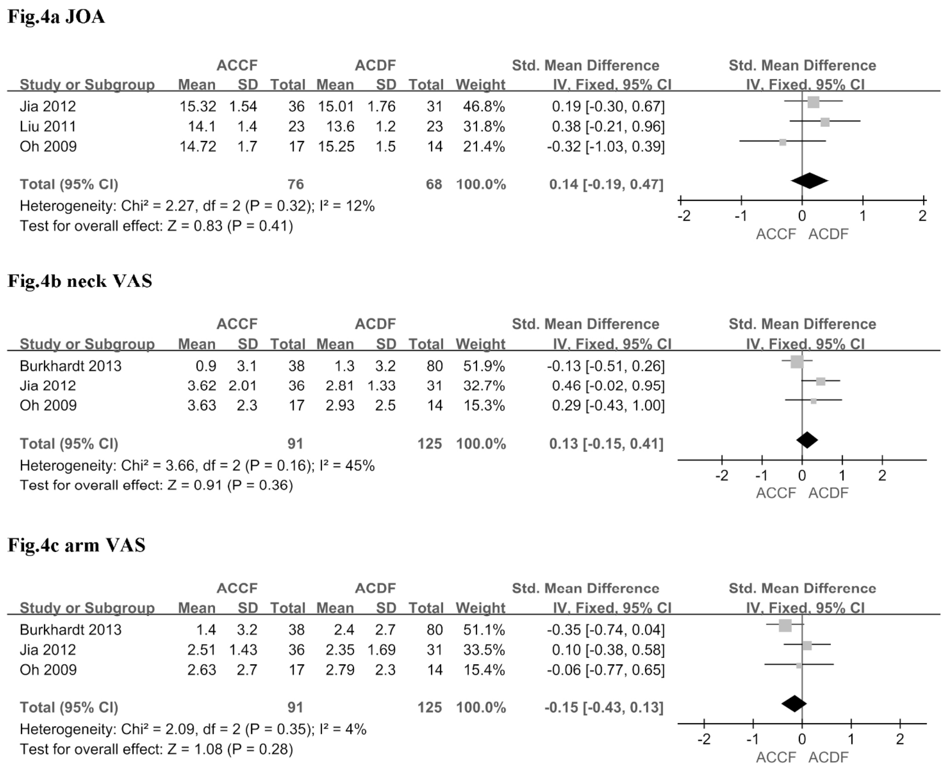

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Fig.5a C2-C7 Cobb

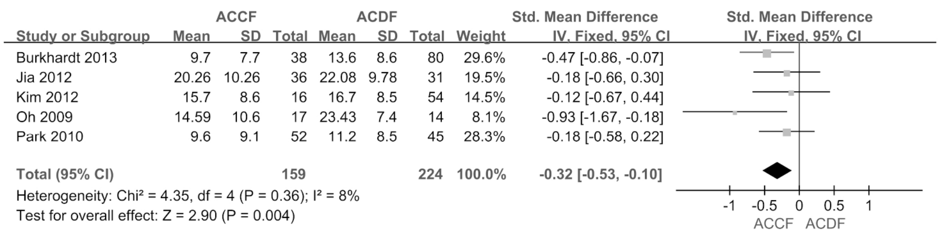

Fig.5b fusion Cobb

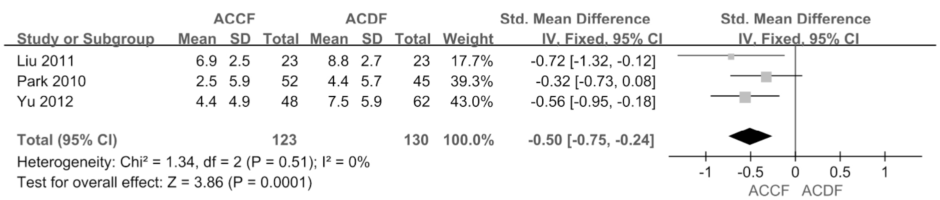

Fig.5c Total cervical ROM

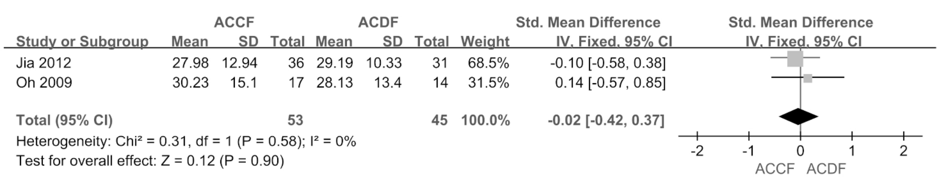

Fig.5d fusion ROM

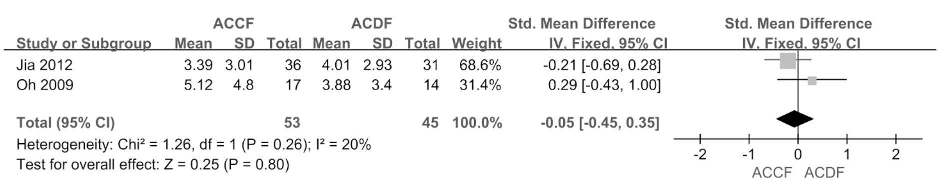

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Fig.6a fused segment height

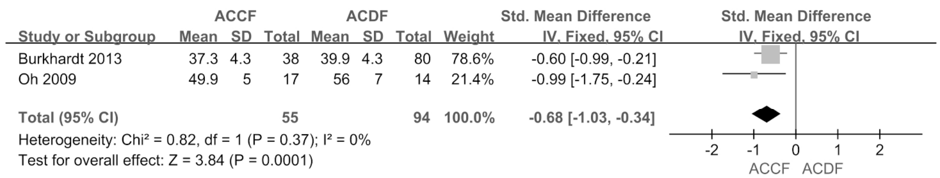
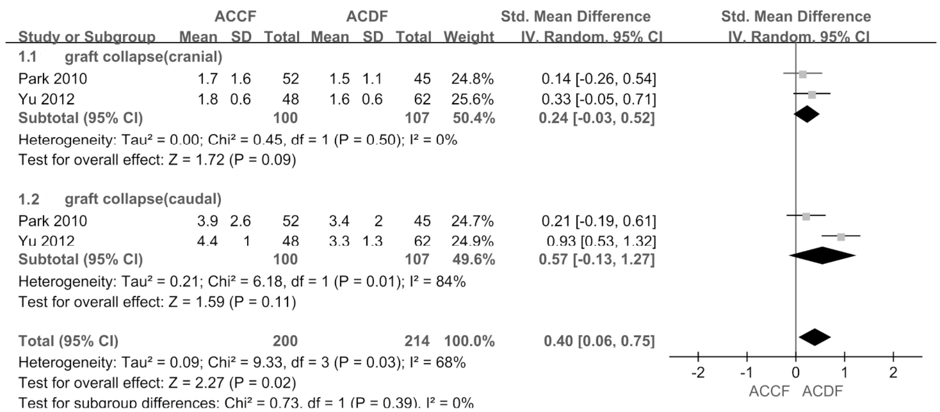


Fig.6b graft collapse



209x170mm (300 x 300 DPI)

Fig.7a fusion rate

Study or Subgroup	ACCF Events	ACCF Total	ACDF Events	ACDF Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burkhardt 2013	36	38	78	80	25.4%	0.97 [0.89, 1.06]
Jia 2012	36	36	31	31	17.1%	1.00 [0.94, 1.06]
Kim 2012	16	16	48	54	11.6%	1.10 [0.97, 1.25]
Oh 2009	17	17	14	14	8.0%	1.00 [0.88, 1.13]
Yu 2007	20	20	20	20	10.4%	1.00 [0.91, 1.10]
Yu 2012	48	48	62	62	27.6%	1.00 [0.96, 1.04]
Total (95% CI)		**175**		**261**	**100.0%**	**1.00 [0.97, 1.04]**
Total events	173		253			

Heterogeneity: Chi² = 2.70, df = 5 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)

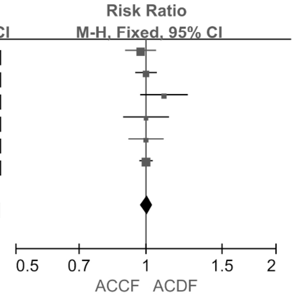


Fig.7b degeneration of the adjacent-level

Study or Subgroup	ACCF Events	ACCF Total	ACDF Events	ACDF Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burkhardt 2013	2	38	3	80	38.7%	1.40 [0.24, 8.05]
Oh 2009	3	17	2	14	43.9%	1.24 [0.24, 6.39]
Yu 2012	1	48	1	62	17.5%	1.29 [0.08, 20.13]
Total (95% CI)		**103**		**156**	**100.0%**	**1.31 [0.44, 3.93]**
Total events	6		6			

Heterogeneity: Chi² = 0.01, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)

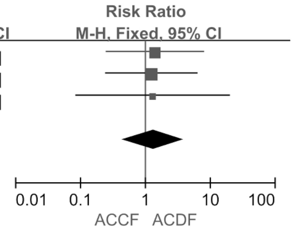
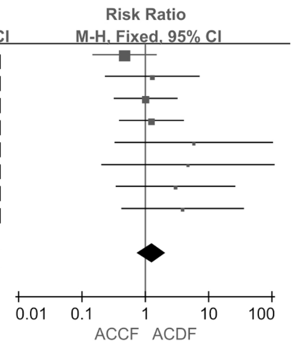


Fig.7c Complications

Study or Subgroup	ACCF Events	ACCF Total	ACDF Events	ACDF Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burkhardt 2013	3	31	14	68	39.3%	0.47 [0.15, 1.52]
Jia 2012	3	36	2	31	9.6%	1.29 [0.23, 7.24]
Kim 2012	3	16	10	54	20.5%	1.01 [0.32, 3.24]
Liu 2011	5	23	4	23	17.9%	1.25 [0.38, 4.07]
Oh 2009	3	17	0	14	2.4%	5.83 [0.33, 104.22]
Wang 2001	1	20	0	32	1.7%	4.71 [0.20, 110.40]
Yu 2007	3	20	1	20	4.5%	3.00 [0.34, 26.45]
Yu 2012	3	48	1	62	3.9%	3.88 [0.42, 36.09]
Total (95% CI)		**211**		**304**	**100.0%**	**1.25 [0.74, 2.13]**
Total events	24		32			

Heterogeneity: Chi² = 6.19, df = 7 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.40)



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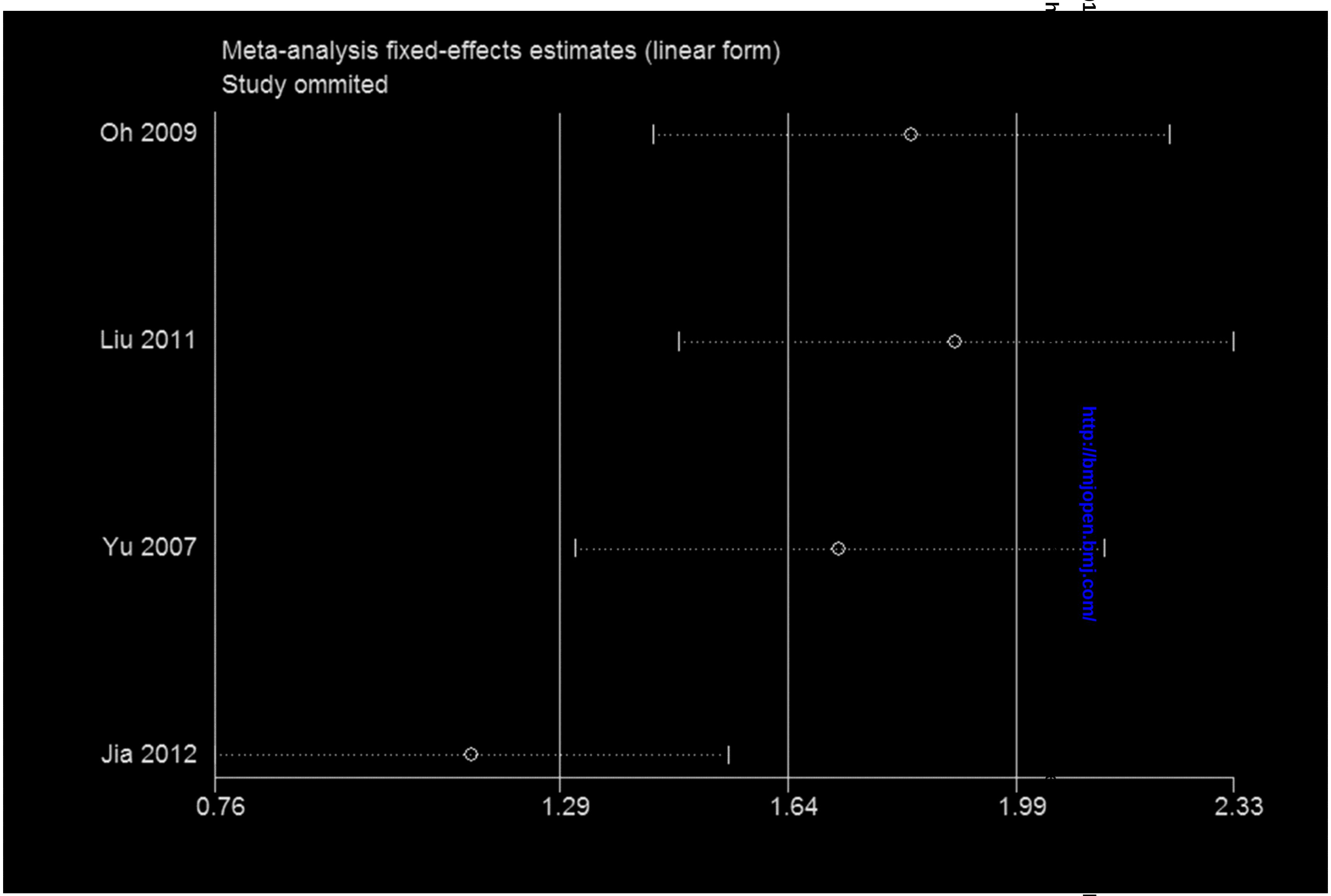
Meta-analysis fixed-effects estimates (linear form)
Study ommited
Oh 2009
Liu 2011
Yu 2007
Jia 2012
0.76
1.29
1.64
1.99
2.33

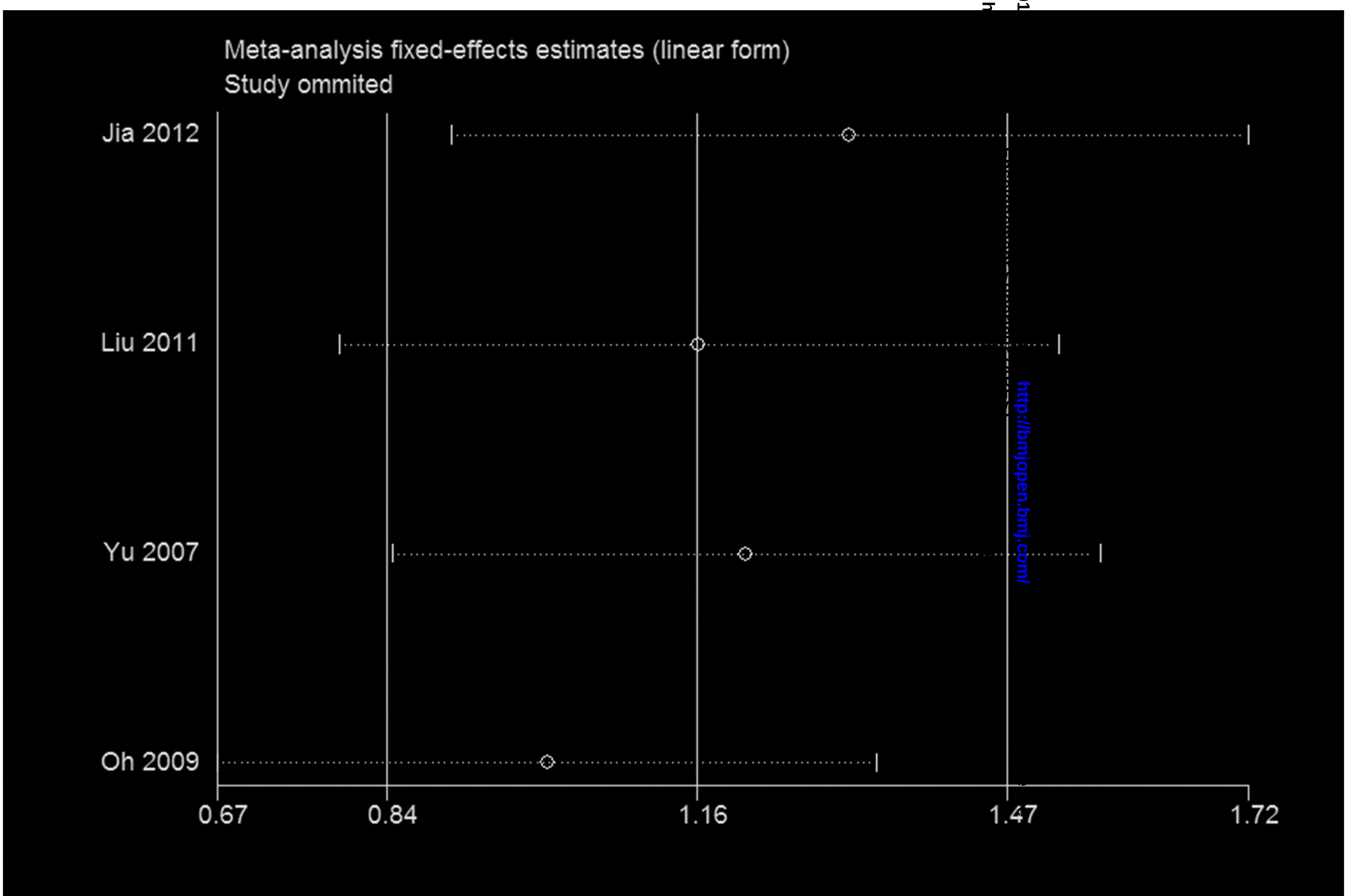
Meta-analysis fixed-effects estimates (linear form)
Study ommited
Jia 2012
Liu 2011
Yu 2007
Oh 2009
0.67
0.84
1.16
1.47
1.72

Table S1 Perioperative outcomes of included studies.

Study	Hospital stay(days)		Bleeding amounts(ml)		Operative time(min)	
	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
Oh 2009	16.82±7.7	15.14±8.5	777.8±644.3	306.43±151.1	210±6	140.71±44.5
Park 2010	NA		NA		NA	
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		NA		NA	
Yu 2012	NA		NA		NA	
Yu 2007	NA		306.75±74.63	207.5±65.86	110.4±18.16	91.8±19.43
Jia 2012	11.11±8.52	10.79±7.74	279.93±63.21	102.21±31.71	141.23±63.21	97.37±17.72
Liu 2011	12.2±2.7	11.2±2.6	263.0±130.4	148.3±71.3	190.9±61.4	139.9±12.7
Kim 2012	NA		NA		NA	

NA=not available, ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion.

Table S2 Clinical outcomes of included studies.

Study	Postoperative JOA at last visit		Postoperative neck VAS		Postoperative arm VAS	
	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
Oh 2009	14.72±1.7	15.25±1.5	3.63±2.3	2.93±2.5	2.63±2.7	2.79±2.3
Park 2010	NA		NA		NA	
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		0.9±3.1	1.3±3.2	1.4±3.2	2.4±2.7
Yu 2012	NA		NA		NA	
Yu 2007	NA		NA		NA	
Jia 2012	15.32±1.54	15.01±1.76	3.62±2.01	2.81±1.33	2.51±1.43	2.35±1.69
Liu 2011	14.1±1.4	13.6±1.2	NA		NA	
Kim 2012	NA		NA		NA	

NA= not available, JOA=Japanese Orthopedic Association scores, VAS= Visual Analog Scale scores. ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, * the study just reported the data at the sixth month of postoperative.

Table S3a Postoperative radiologic outcomes of included studies.

Study	sagittal alignment		C2-C7 Cobb		fusion Cobb	
	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
Oh 2009	NA		14.59±10.6	23.43±7.4	NA	
Park 2010	32L	30L	9.6±9.1	11.2±8.5	2.5±5.9	4.4±5.7
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		9.7±7.7	13.6±8.6	NA	
Yu 2012	36L	47L	NA		4.4±4.9	7.5±5.9
Yu 2007	NA		NA		NA	
Jia 2012	NA		20.26±10.26	22.08±9.78	NA	

Liu 2011	NA	NA		6.9±2.5	8.8±2.7
Kim 2012	NA	15.7±8.6	16.7±8.5	5.8/4.6	6.8/6.8

ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, NA= not available.

Table S3b Postoperative radiologic outcomes of included studies.

Study	total cervical ROM		fusion ROM		fused segment height	
	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
Oh 2009	30.23±15.1	28.13±13.4	5.12±4.8	3.88±3.4	49.9±5	56.0±7
Park 2010	NA		NA		NA	
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		NA		37.3±4.3	39.9±4.3
Yu 2012	NA		NA		NA	
Yu 2007	NA		NA		NA	
Jia 2012	27.98±12.94	29.19±10.33	3.39±3.01	4.01±2.93	53.11±1.90	55.55±1.84
Liu 2011	NA		NA		56.4±2.4	56.1±2.2
Kim 2012	33.5	26.8	NA		55.1±3.9	55.4±3.8

ACCF=anterior cervical corpectomy and fusion, ACDF=anterior cervical discectomy and fusion, NA=not available,ROM=range of motion.

Table S3c Postoperative radiologic outcomes of included studies.

Study	graft collapse		fusion rate		degeneration[a]	
	ACCF(An/Po/Cr/Ca)	ACDF(An/Po/Cr/Ca)	ACCF	ACDF	ACCF	ACDF
Oh 2009	NA		100%	100%	3	2
Park 2010	5.0±2.9/3.5±2.5/1.7±1.6/3.9±2.6	4.2±2.6/3.0±2.4/1.5±1.1/3.4±2.0	NA		NA	
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		94.7%	97.5%	2	3
Yu 2012	3.7±1.3/5.2±2.2/1.8±0.6/4.4±1.0	2.9±1.2/3.6±2.3/1.6±0.6/3.3±1.3	100%	100%	1	1
Yu 2007	NA		100%	100%	NA	
Jia 2012	NA		100%	100%	NA	
Liu 2011	NA		NA		NA	
Kim 2012	NA		100%	88.9%	NA	

a degeneration means degeneration of the adjacent-level to the fusion. An= anterior, Po= posterior, Cr= cranial, Ca= caudal, ACCF= anterior cervical corpectomy and fusion, ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, NA= not available.

Table S4 Complications including short term and long term.

Study	Complications	
	ACCF	ACDF
Oh 2009	3	0
Park 2010	NA	
Wang 2001	1	0
Burkhardt 2013	3	14
Yu 2012	3	1
Yu 2007	3	1
Jia 2012	3	2
Liu 2011	5	4
Kim 2012	3	10

ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, NA= not available.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	The section that contains each item e#
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page, Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Fig. 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 6-7

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 7

Section/topic	#	Checklist item	The section that contains each item e#
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 7, Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 8, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 9, Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 9-13
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 15-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 17-18

PRISMA 2009 Checklist

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Page 2 of 2

BMJ Open

Comparison of Two Anterior Fusion Methods in Two level Cervical Spondylosis Myelopathy: A Meta-Analysis

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004581.R2
Article Type:	Research
Date Submitted by the Author:	21-Jun-2014
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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Surgery
Keywords:	Spine < ORTHOPAEDIC & TRAUMA SURGERY, Orthopaedic & trauma surgery < SURGERY, Adult orthopaedics < ORTHOPAEDIC & TRAUMA SURGERY

SCHOLARONE™ Manuscripts

Title: Comparison of Two Anterior Fusion Methods in Two-level Cervical Spondylosis Myelopathy: A Meta-Analysis

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Keywords: Cervical spondylosis myelopathy; Anterior cervical discectomy and fusion; Anterior cervical corpectomy and fusion.

Word count: 3766

ABSTRACT

OBJECTIVE: The aim of this study was to evaluate the efficacy and safety of anterior cervical corpectomy and fusion (ACCF) and anterior cervical discectomy and fusion (ACDF) for treating two-adjacent-level cervical spondylosis myelopathy (CSM).

DESIGN: A meta-analysis of the two anterior fusion methods was conducted. The electronic databases of PubMed, Cochrane Central Register of Controlled Trials, ScienceDirect, CNKI, WANFANG DATA, and CQVIP were searched. Quality assessment of the included studies was evaluated using the Cochrane Risk of Bias Tool and the Methodological Index for Non-Randomized Studies criteria. Pooled risk ratios of dichotomous outcomes and standardized mean differences (SMDs) of continuous outcomes were generated. Using the chi-squared and I-squared tests, the statistical heterogeneity was assessed. Subgroup and sensitivity analyses were also performed.

PARTICIPANTS: Nine eligible trials with a total of 631 patients and a male-to-female ratio of 1.38:1 were included in this meta-analysis.

INCLUSION CRITERIA: Randomized controlled trials (RCTs) and nonrandomized controlled trials that adopted ACCF and ACDF to treat two-adjacent-level CSM were included.

RESULTS: No significant differences were identified between the two groups regarding hospital stay, Japanese Orthopedic Association (JOA) score, visual analog scale (VAS) scores for neck and arm pain, total cervical range of motion (ROM), fusion ROM, fusion rate, adjacent-level ossification, and complications. While ACDF had significantly less bleeding (SMD = 1.14, 95% CI: [0.74, 1.53]); a shorter operation time (SMD = 1.13, 95% CI: [0.82, 1.45]); greater cervical lordosis, both total cervical (SMD = -2.95, 95% CI: [-4.79, -1.12]) and fused segment (SMD = -2.24, 95% CI: [-3.31, -1.17]); higher segmental height (SMD = -0.68, 95% CI: [-1.03, -0.34]); and less graft subsidence (SMD = 0.40, 95% CI: [0.06,0.75]) compared to ACCF.

CONCLUSIONS: The results suggested that ACDF has more advantages compared to ACCF. However, additional high-quality RCTs and a longer follow-up duration are needed.

Article summary

Strengths and limitations of this study

1) According to our study, ACCF and ACDF are both effective and safe for treating CSM. 2) ACDF has more advantages than ACCF in some aspects. 3) The trials included in our study are not high-quality RCTs and do not have a long enough follow-up duration. 4) The number of studies used in the meta-analysis is small (nine studies). In fact, for most of the outcomes, fewer than five studies were used in the meta-analyses. 5) The pathological processes of patients are not always the same.

Introduction

Cervical spondylosis is a common disease and a progressive degenerative process of the cervical spine that results in loss of disc height and formation of osteophytes. When it develops into cervical spondylosis myelopathy (CSM), motion abnormalities and sensory disturbances will follow, resulting in a reduced quality of life for the patients.[1] Surgical intervention is recommended for these patients with severe symptoms.[2]

The choice between an anterior, posterior, or combined approach for decompression is based primarily on (1) the sagittal alignment of the spinal column, (2) the extent of disease, (3) the location of the abnormal compression, (4) the presence of preoperative neck pain, and (5) previous operations.[2]

Shamji *et al*.[3] and Jiang *et al*.[4] have reviewed the efficacy and safety of anterior procedures for patients with multilevel CSM, covering patients with two-adjacent-level CSM. Furthermore, the work by Chang *et al*.[5] supports that anterior cervical discectomy and fusion (ACDF) is the treatment of choice for cervical disc herniation and spondylotic radiculopathy or myelopathy. In addition, Lu *et al*.[6] have shown that anterior cervical corpectomy and fusion (ACCF) is an effective surgical procedure for the treatment of multilevel cervical myelopathy because it can remove almost all osteophytes, discs, and ossification of posterior longitudinal ligament pathology that cause spinal cord compression. Kazuo *et al*.[7] and Mamoru *et al*.[8] have shown that ACDF and ACCF are both widely used anterior methods for

CSM, especially with two levels. Although patients with two-adjacent-level CSM are often seen in clinical practice, controversies still exist between ACCF and ACDF for treating these patients. Therefore, the aim of this meta-analysis was to compare the efficacy and safety of ACCF and ACDF for patients with two-adjacent-level CSM by assessing the perioperative, clinical, and radiological outcomes as well as complications.

Materials and Methods

Search Strategy

The electronic databases including PubMed (1966–2013), Cochrane Central Register of Controlled Trials (Issue 9, 2013), ScienceDirect (1985–2013), CNKI (1996–2013), WANFANG DATA (1997–2013), and CQVIP (1996–2013) were searched. The keywords used for the search were as follows: "cervical spondylosis myelopathy," "anterior cervical discectomy and fusion," "anterior cervical corpectomy and fusion," "two level(s)," and "single-level."

Eligibility Criteria

All comparative studies that adopted ACCF and ACDF to treat two-adjacent-level cervical spondylosis were identified, and the reference lists of identified articles were searched to identify other potentially eligible studies. Criteria for inclusion were as follows: 1) ACCF with titanium mesh, cage, or autologous ilium bone grafting; ACDF with interbody cage devices or autologous ilium bone grafting;

and the two surgeries both used anterior cervical plate and screw fixation. 2) All patients included had a confirmed CSM at two adjacent segments, and surgical intervention was recommended. 3) The trials were followed up for more than 12 months.

Criteria for exclusion: 1) The studies did not meet the inclusion criteria. 2) The intraoperative outcome data (length of hospital stay, amount of bleeding, and operation time), clinical outcomes (Japanese Orthopedic Association (JOA) score and visual analog scale (VAS) score for neck and arm pain), radiological outcomes (cervical lordosis for total cervical and fused segments, total cervical range of motion (ROM), segmental ROM, graft collapse, segmental height, fusion rate, and degeneration of the adjacent-level), or complications (short-term and long-term complications) were not reported. 3) The number of samples was less than 30 cases. 4) The patients evaluated were treated at the same hospital.

Data Extraction

Two reviewers independently extracted the data using a standardized form, which covered the following items: 1) basic characteristics, including the year of publication, study design, inclusion/exclusion criteria, age, sex, enrolled number, and follow-up rate; 2) intraoperative outcomes, consisting of length of hospital stay, amount of bleeding, and operation time; 3) clinical outcomes, including JOA score and VAS score for neck and arm pain; 4) radiological outcomes, such as cervical lordosis for total cervical and fused segments, total cervical ROM, segmental ROM, graft collapse, segmental height, fusion rate, degeneration of the adjacent level; and 5) complications, including short-term and long-term complications.

Risk of Bias Assessment

Two reviewers independently evaluated the quality of the included studies. Three randomized studies[9-11] were assessed with the Cochrane Handbook for Systematic Review of Interventions, and six nonrandomized studies[12-17] were evaluated according to the methodological index for nonrandomized studies (MINORS) criteria, an established method for evaluating non-RCTs.[18]

Statistical Analysis

All meta-analyses were performed with Review Manager 5.2 software (Cochrane Collaboration, Oxford, UK). For continuous outcomes, means and standard deviations were pooled to generate a standardized mean difference (SMD), and 95% confidence intervals (CIs) were generated. According to the study by Kim,[17] a formula was used to obtain a combined mean and standard deviation (SD).[19] For dichotomous outcomes, the risk ratio (RR) and 95% CI were assessed. A probability of $P < 0.05$ was considered to be statistically significant. Assessment for statistical heterogeneity was calculated using the chi-squared and I-squared tests. When the test for heterogeneity was $P < 0.1$ or $I^2 > 50\%$, the data were considered very heterogeneous. The source of heterogeneity was investigated by subgroup analysis and sensitivity analysis. A fixed effects model was used for homogeneous data, and a random effects model was used for data with high heterogeneity. As for the data with significant methodological heterogeneity, sensitivity analysis was adopted to find the source of the heterogeneity. With regard to the data with significant clinical heterogeneity, subgroup analyses were applied to identify the source of the heterogeneity.

Results

Literature Search

A total of 606 potential reports were retrieved with the search strategy (Fig. 1). Of these, 597 reports were excluded because they did not fit our inclusion criteria. No additional studies were obtained after reference review. Finally, nine studies were selected and analyzed.[9-17]

Risk of bias assessment

For three randomized studies,[9-11] two studies were RCTs,[9,11] one of which did not provide information regarding allocation concealment. One study was a quasi-RCT, in which patients were allocated according to their sequence of hospitalization.[10] Due to the informed consent rights between patients and doctors, it was impossible to blind all participants and personnel. None of these three studies reported blinding of outcome assessment. No patients were lost to follow-up, except for eight patients who were excluded from the study by Liu *et al.*[11] due to missing data. Thus, there was a low risk of bias due to incomplete outcome data. In these three trials, the outcomes were provided in detail and there was a low risk of bias due to selective reporting. Owing to insufficient information to assess whether an important risk of bias existed in a number of trials, it was hypothesized that all trials had an unclear risk of bias towards other potential sources of bias. The methodological quality assessment is summarized in Table 1a. For six nonrandomized studies,[12-17] according to the modified MINORS criteria,[18] none of them reported an unbiased assessment of the study endpoint or a prospective calculation of the study size. With regard to the prospective collection of data, three studies did not report the relevant information.[13,15,17] Only one study reported the follow-up rate.[14] The other eight items were all specifically reported. In summary, scores ranged from 16 to 18, with a median value of 16.5. The methodological quality assessment is summarized in Table 1b.

Demographic characteristics

The demographic characteristics of the patients included in the selected studies are presented in Table 2. A total of 631 patients, with a male-to-female ratio of 1.38:1, were included. Of these, 270 underwent ACCF procedures and 361 were treated by the ACDF approach; the two surgeries used various grafts, including autografts, allografts, and cage and/or plate systems. The mean age of the patients was 55.1 years old. The average duration of follow-up ranged from 18.9 to 43.2 months. Statistically similar baseline characteristics were observed between the ACCF and ACDF groups (Table 3).

Hospital Stay

Details regarding hospital stay were available in three papers (Table S1),[9,11,16] and statistical heterogeneity was absent in these studies (I^2 = 0%; P = 0.69). The pooled estimate revealed a statistically insignificant difference (SMD = 0.18, 95% CI: [-0.15, 0.51], P = 0.28) (Fig. 2).

Bleeding Amount

Relevant data regarding the bleeding amount were documented in four articles (Table S1),[9-11,16] and all the trials showed that the ACDF approach had significantly reduced intraoperative bleeding amounts compared to the ACCF procedure. Pooling of relevant data also showed a statistically significant difference between the two groups (SMD = 1.14, 95% CI: [0.74, 1.53], P = 0.002). Significant heterogeneity was detected (I^2 = 89%; P < 0.00001) (Fig. 2b). In addition, sensitivity analysis confirmed the stability of bleeding amount outcomes (Fig. S1).

Operation Time

Four trials reported a significantly shorter surgical time in the ACDF group compared to the ACCF group (Table S1).[9-11,16] Overall, the SMD was 1.13 (95% CI: [0.82, 1.45], P < 0.00001) in favor of the ACDF group. There was obvious evidence of statistically significant heterogeneity (I^2 = 54%; P = 0.009), according to subgroup analysis (Fig. 3). Furthermore, sensitivity analysis confirmed the stability of operation time outcomes (Fig. S2).

JOA

Three studies reported the JOA score (Table S2),[9,11,16] and the pooled estimate revealed a statistically insignificant difference (SMD = 0.14, 95% CI: [-0.19, 0.47], P= 0.41), with low heterogeneity (I^2 = 12%) (Fig. 4a).

Neck VAS

Three studies reported a postoperative neck VAS score (Table S2),[9,14,16] and the pooled data from the two relevant studies did not reveal any significant difference (SMD=0.13, 95% CI: [-0.15, 0.41], P = 0.36), with low heterogeneity (I^2 = 45%) (Fig. 4b).

Arm VAS

Relevant VAS data were documented in three articles (Table S2).[9,14,16] There was no significant difference between the two treatment groups (SMD = -0.15, 95%CI = [-0.43, 0.13]; P = 0.28), with low heterogeneity (I^2 = 4%) (Fig. 4c).

C2-C7 Cobb

Five studies reported the C2-C7 Cobb at the final follow-up (Table S3a),[9,12,14,16,17] the available data demonstrated low heterogeneity (I^2 = 8%), and the ACCF group had a significantly lower Cobb than the ACDF group (SMD = -0.32, 95% CI: [-0.53, -0.10], P = 0.004) (Fig. 5a).

Fusion Cobb

Three studies reported the fusion Cobb at the final follow-up (Table S3a),[11,12,15] the available data demonstrated no heterogeneity ($I^2 = 0\%$), and the ACCF group had a significantly lower Cobb than the ACDF group (SMD = -0.50, 95% CI: [-0.75, -0.24], $P = 0.0001$) (Fig. 5b).

Total cervical ROM

Two studies reported the total cervical ROM data at the final follow-up (Table S3b),[9,16] and the other two studies demonstrated that there was no significant difference in total cervical ROM between the two groups (SMD = -0.02, 95% CI: [-0.42, 0.37], $P = 0.90$), with no heterogeneity ($I^2 = 0\%$) (Fig. 5c).

Fusion ROM

Two studies reported fusion ROM at the last follow-up (Table S3b),[9,16] and there was no significant difference in fusion ROM between the two groups (SMD = -0.05, 95% CI: [-0.45, 0.35], $P = 0.80$), with low heterogeneity ($I^2 = 20\%$) (Fig. 5d).

Fused segment height

Five studies reported the fused segment height data at the final follow-up (Table S3b);[9,11,14,16,17] however, data from three studies were excluded from this analysis because of the different methods used to measure the fused segment height.[11,16,17] The pooled results demonstrated that the ACCF group had a significantly lower fused segment height than the ACDF group (SMD = -0.68, 95% CI: [-1.03, -0.34]), with high heterogeneity (I^2 = 76%) (Fig. 6a).

Graft collapse

Two studies reported graft collapse at the last follow-up (Table S3c),[12,15] showing that there was a significant reduction in graft collapse for the ACDF group (SMD = 0.40, 95% CI: [0.06, 0.75], P = 0.02), with moderate heterogeneity (I^2 = 68%) (Fig. 6b). No significant clinical heterogeneity or methodological heterogeneity was found; however, statistical heterogeneity likely exists, so the data from the two studies were pooled.

Fusion rate

Six studies reported the fusion rate at the last follow-up (Table S3c),[9,10,14-17] and there was no significant difference in the fusion rate between the two groups (RR = 1.00, 95% CI: [0.97, 1.04], P = 0.79), with no heterogeneity (I^2 = 0%) (Fig. 7a).

Degeneration

Three studies reported degeneration of the level adjacent to the fusion (Table S3c),[9,14,15] showing that there was no significant difference in degeneration of the level adjacent to the fusion between the two groups (RR = 1.31, 95% CI: [0.44, 3.93], P = 0.63), with no heterogeneity (I^2 = 0%) (Fig. 7b).

Complications

Data regarding complications were provided in eight studies (Table S4).[9-11,13-17] There was no significant difference between the ACCF and ACDF groups according to individual and pooled data (RR = 1.25, 95%CI = [0.74, 2.13]; $P = 0.40$). Statistical heterogeneity was absent in these studies ($I^2 = 0\%$; $P = 0.52$) (Fig. 7c).

Discussion

Although most studies included in this analysis reported consistent results,[9-17] the pooled estimates should be explained with caution. With regard to the operative outcomes, the length of hospital stay was similar in both groups, and less blood loss and a shorter operation time were observed in the ACDF group than in the ACCF group. ACDF requires less exposure of the spinal cord than does corpectomy;[2] therefore, less damage to the spinal column occurs. Accordingly, ACDF might result in less blood loss than ACCF. In terms of ACCF, a 15 to 19-mm anterior midline trough should be performed in the vertebral body down to the posterior longitudinal ligament or dura, with removal of the cephalad and caudad discs,[2] which would require more time to be removed, similarly it will cost more time to obtain a graft material to fit the trough. Consequently, ACDF had a significantly shorter operation time.

In our meta-analysis, JOA scores as well as VAS scores for neck and arm pain both significantly improved in each group, without significant differences between the two groups. These results suggest that both procedures effectively treat two-adjacent-level CSM and improve the patients' neurological function, quality of life, and disability. Similar outcomes were achieved for both ACDF and ACCF in the treatment of multilevel cervical spondylosis by Shamji *et al*.[3] and Jiang *et al*.[4]

Total cervical ROM, fusion ROM, fusion rate, and adjacent-level ossification yielded no significant differences between the two groups. Concerning the high fusion rate in the two groups, it may be related to the following factors: 1) the use of a polyether ether ketone (PEEK) cage or titanium mesh packed with autogenous tricortical bone and fixed by titanium plates and screws or by Atlantis plate fixation;[9-17] 2) the fixation system provides a stable biomechanical environment, which greatly promotes bone healing; and 3) bone healing is a process of creeping substitution,[20] and the distance of creeping substitution for single-level ACCF and two-level ACDF are both short. The high fusion rate effectively reduced the total cervical and fused segment ROM. For example, Eck *et al*. demonstrated that a significantly greater adjacent level disc pressure was achieved after cervical fusion.[21] In addition, the normal degenerative process plays a major role through impaired nutrition, loss of viable cells, matrix protein modification, and matrix failure.[22] This normal aging process, in combination with increased mechanical pressures, may synergistically hasten the degeneration process, although it has not been conclusively demonstrated.[23]

For C2-C7 Cobb, ACDF had a significantly greater lordosis angle than ACCF, not only immediately postoperation but also at the final follow-up. Similar results were found for the fusion Cobb at the last follow-up. The reasons may be associated with the following two factors: 1) Single-level ACCF removes both the vertebral body and two discs, while two-level ACDF just takes out the two discs;[2] as a result, ACDF allows the construction of an almost normal spinal column after surgery. Thus, the loss of Cobb is less common in ACDF. In other words, ACDF preserves the sagittal alignment somewhat better than does ACCF. 2) Eck *et al*. have reported that each of the involved joints contributes to the total ROM.[21] With fusion, the contribution of one joint to ROM is reduced.

In terms of the fused segment height, ACCF causes a significant reduction compared to ACDF, both immediately postoperative and at the last follow-up. With ACDF, screws placed in the intervening segment and two caudal end plates synergistically share the load of the construct. In contrast, with a single-level corpectomy, screws are only at the cranial and caudal vertebral segments and the caudal end plate bears the full load of the construct.[12] Additionally, the graft contact area is less for ACCF than for ACDF, which results in a higher shear stress for ACCF. These reasons might hasten the graft absorption process into the cover plate of the adjacent vertebral body, leading to a significant subsidence of the treated segment in ACCF, especially at the anterior and caudal positions.

Concerning complications, the data show that there is no significant difference between the two groups and that the incidence of complications is low in each group. This result suggests that both of the two treatments are safe.

The methodological quality assessment should be considered, which identified several limitations of the clinical evidence. Only nine studies met the predefined eligibility criteria, meaning that all the results were based on only 631 patients. More importantly, there were only three studies that were randomized. All randomized studies had poor concealment of randomization, including selection and allocation bias. Due to informed consent requirements, patients and operators had knowledge regarding the surgical procedures, thus allowing further measurement and expectation bias. Four outcomes (bleeding amount, operation time, fused segment height, and graft collapse) had a high heterogeneity. Wu *et al*. have summarized a method to deal with heterogeneity in meta-analysis.[24] For the bleeding amount, it was reasonable to perform sensitivity analysis (Fig. S1) because of the different research types. As shown in Fig. S1, the results of Jia 2012[16] have significant heterogeneity, which should be removed. The bleeding amount results are shown in Fig. 2b. Regarding the operation time, sensitivity analysis was performed analyze the data because of the different research types. As shown by the sensitivity analysis results (Fig. S2), ACDF had a shorter operation time that could not be reversed regardless of which study was removed. Therefore, the heterogeneity did not come from the methodological heterogeneity. Accordingly, there probably exists clinical heterogeneity. Due to the strict eligibility criteria, the patient data had a good homogeneity; thus, the heterogeneity was due to the ability of the surgeons. The subgroup analysis results regarding operation time are shown in Fig. 3. As for the fused segment height, clinical heterogeneity existed. Oh *et al*.[9] and Burkhardt *et al*.[14] have defined the fused segment height as the distance between the midlines of the involved cranial vertebral bodies and the caudal vertebral bodies. In contrast, Jia *et al*.[16] did not describe the method to measure the fused segment height. Meanwhile, Liu *et al.*[11] and Kim *et al.*[17] reported the anterior and posterior heights of the involved vertebral bodies. In summary, for the fused segment height, we pooled the data of Oh *et al.*[9] and Burkhardt *et al.*,[14] and the outcome is displayed in Fig. 6a. With regard to graft collapse, as the two literature examples are both retrospective studies, it is believed that no methodological heterogeneity existed. Regarding the clinical heterogeneity, the patient data had a good homogeneity due to the strict eligibility criteria and the fact that the methods of measuring the graft collapse were the same. As a result, no significant clinical heterogeneity or methodological heterogeneity was found. However, statistical heterogeneity likely existed, so the studies were pooled. Not all of the included studies had consistent baseline characteristics between the ACCF and ACDF groups. Therefore, larger randomized controlled trials with high quality are still needed in the future to compare the two surgeries.

Conclusion

Based on this meta-analysis that compared ACDF and ACCF to treat two-adjacent-level CSM, ACDF has some advantages such as less blood loss, a shorter operation time, greater cervical lordosis both in the total cervical and fused segments, a higher segmental height, and less graft subsidence. However, no significant differences in JOA, VAS, ROM, or complications were found. This information will provide surgeons a preliminary understanding of the differences between the two surgeries to treat two-adjacent-level CSM and will be helpful to clinical surgeons for choosing which surgical method to treat patients with two-adjacent-level CSM. Further high-quality RCTs and longer follow-up durations are needed to assess these two treatments.

Acknowledgement

This work was supported by the Department of Health of Zhejiang Province, Backbone of Talent Project (2012RCB037); and the Department of Science and Technology of Wenzhou, Wenzhou Science and Technology Project (Y20120073). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. We thank Medjaden Bioscience for assisting in the preparation of this manuscript.

Author Contributions

Conceived and designed the review: ZYH, AMW, and WFN. Performed the review: ZYH, AMW, and WFN. Analyzed the data: ZYH and AMW. Contributed reagents/materials/analysis tools: QLL, TL, KYW, and HZX. Wrote the paper: ZYH and AMW.

Competing Interests

None

Data sharing statement

No additional data are available.

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Table 1a. Risk of bias assessment of randomized studies.

Risk of bias assessment	Oh 2009	Yu 2007	Liu 2011
Random sequence generation	Unclear risk	High risk	Low risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk
Blinding of participants and personnel	High risk	High risk	High risk
Blinding of outcome assessment	Unclear risk	Unclear risk	Unclear risk
Incomplete outcome data	Low risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk
Other sources of bias	Unclear risk	Unclear risk	Unclear risk

Table 1b. Quality assessment of non-randomized studies.

Methodological item for non-randomized studies	Park 2010	Wang 2001	Burkh-ardt 2013	Yu 2012	Jia 2012	Kim 2012
1.A clearly stated aim	2	2	2	2	2	2
2.Inclusion of consecutive patients	2	2	2	2	2	2
3.Prospective collection of data	2	0	2	0	2	0
4.Endpoints appropriate to the aim of the study	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	2	2	2	2	2	2
7. Loss to follow up less than 5%	0	0	1	0	0	0
8. Prospective calculation of the study size	0	0	0	0	0	0
9. An adequate control group	2	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	2	2	2	2	2	2
12. Adequate statistical analyses	2	2	2	2	2	2

Table 2 Characteristics of the studies included in the meta-analysis.

Year[ref]	Design	Sample size		Mean age (years)		Gender(M/F)		Mean follow-up time(months)	
		ACCF	ACDF	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
2009[9]	RCT	17	14	55.12	52.64	16/15		27.33	24.9
2007[10]	Quasi-RCT	20	20	53.1±8.98	52.75±7.81	14/6	15/5	NA	
2011[11]	RCT	23	23	54.4±10.9	56.5±9.2	18/5	16/7	31(25-53)	29(26-48)
2010[12]	Retro	52	45	49.4±8.7	49.3±9.7	30/22	17/28	23.3±6.6	25.7±6.2
2001[13]	Retro	20	32	51.5(17-80)		27/25		43.2(24-84)	
2013[14]	Retro	38	80	60.3±11.1	60.9±9.9	25/13	41/39	20.4±13.7	
2012[15]	Retro	48	62	59.3±6.8(49-75)		65/45		32±4.2(24-60)	
2012[16]	Retro	36	31	48.83±8.12	49.12±7.65	21/15	17/14	28.96±13.21	26.81±11.02
2012[17]	Retro	16	54	58±8.6	56.7±10.2	13/3	31/23	20±11.9	18.6±11.5

Retro meant Retrospective, Mean age was described as mean±SD or mean or mean (range) of all patients in the study or mean±SD of all patients in the study, Gender was described as M/F or M/F of all patients in the study, Mean follow-up time was presented as mean±SD or mean (range) or mean±SD of all patients in the study, RCT= randomized control trial, SD= standard deviation, ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, NA= not available.

Table 3 Comparison of baseline characteristics between the ACCF and ACDF groups.

Characteristic	**Oh 2009**	**Park 2010**	**Wang 2001**	**Burkhardt 2013**	**Yu 2012**	**Yu 2007**	**Jia 2012**	**Liu 2011**	**Kim 2012**
Mean age	*	*	*	*	*	*	*	*	*
Gender	*	*	*	*	*	*	*	*	*
Follow-up	*	*	*	*	*	*	*	*	*
Preoperative JOA	*	NA	NA	NA	NA	*	*	*	NA
Preoperative neck VAS	*	NA	NA	*	NA	NA	*	NA	NA
Preoperative arm VAS	*	NA	NA	*	NA	NA	*	NA	NA
Preoperative sagittal alignment	NA	*	NA	NA	*	NA	NA	NA	NA
Preoperative C2-C7 Cobb	*	*	NA	*	NA	NA	*	NA	*
Preoperative fused segment height	*	NA	NA	*	NA	NA	NA	*	*
Preoperative total cervical ROM	*	NA	NA	NA	NA	NA	0.02	NA	NA
Preoperative fused segment ROM	*	NA	NA	NA	NA	NA	0.01	NA	NA

JOA= Japanese Orthopedic Association scores, VAS= Visual Analog Scale scores. ROM= range of motion, NA= not available, * Statistically insignificant (P>0.05).

Figure Legends

Fig. 1: The search strategy for our meta-analysis and reasons for exclusion.

Fig. 2: Perioperative parameters. a: Forest plot and tabulated data for length of hospital stay; no significant difference between the two types of surgery was observed. b: Forest plot and tabulated data for bleeding amount; the ACDF group had significantly less intraoperative bleeding than the ACCF group.

Fig. 3: Perioperative parameters. Forest plot and tabulated data for operation time; the ACDF group had a significantly shorter surgical time compared to the ACCF group.

Fig. 4: Clinical parameters. a: Forest plot and tabulated data for JOA; b: Forest plot and tabulated data for neck VAS; c: Forest plot and tabulated data for arm VAS. There were no significant differences in these parameters between the two types of surgery.

Fig. 5: Radiological parameters. a: Forest plot and tabulated data for C2-C7 Cobb; b: Forest plot and tabulated data for fusion Cobb; c: Forest plot and tabulated data for total cervical ROM; d: Forest plot and tabulated data for fusion ROM. The ACCF group had a significantly lower Cobb than the ACDF group. There was no significant difference in the cervical or fusion ROM between the two types of surgery.

Fig. 6: Radiological parameters. a: Forest plot and tabulated data for the fused segment height; the ACCF group had a significantly lower fused segment height than the ACDF group. b: Forest plot and tabulated data for graft collapse; the ACDF group had a significantly lower graft collapse than the ACCF group.

Fig. 7: a: Forest plot and tabulated data for fusion rate; b: Forest plot and tabulated data for degeneration of the adjacent level; c: Forest plot and tabulated data for complications. There was no significant difference in any of these parameters between the two types of surgery.

Fig. S1: The sensitivity analysis for bleeding amounts. Significant heterogeneity was found between the four studies.

Fig. S2: The sensitivity analysis for operation time. No significant heterogeneity was found between the four studies.

Title: Comparison of Two Anterior Fusion Methods in Two-level Cervical Spondylosis Myelopathy: A Meta-Analysis

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Keywords: Cervical spondylosis myelopathy; Anterior cervical discectomy and fusion; Anterior cervical corpectomy and fusion.

Word count: 3766

ABSTRACT

OBJECTIVE: The aim of this study was to evaluate the efficacy and safety of anterior cervical corpectomy and fusion (ACCF) and anterior cervical discectomy and fusion (ACDF) for treating two-adjacent-level cervical spondylosis myelopathy (CSM).

DESIGN: A meta-analysis of the two anterior fusion methods was conducted. The electronic databases of PubMed, Cochrane Central Register of Controlled Trials, ScienceDirect, CNKI, WANFANG DATA, and CQVIP were searched. Quality assessment of the included studies was evaluated using the Cochrane Risk of Bias Tool and the Methodological Index for Non-Randomized Studies criteria. Pooled risk ratios of dichotomous outcomes and standardized mean differences (SMDs) of continuous outcomes were generated. Using the chi-squared and I-squared tests, the statistical heterogeneity was assessed. Subgroup and sensitivity analyses were also performed.

PARTICIPANTS: Nine eligible trials with a total of 631 patients and a male-to-female ratio of 1.38:1 were included in this meta-analysis.

INCLUSION CRITERIA: Randomized controlled trials (RCTs) and nonrandomized controlled trials that adopted ACCF and ACDF to treat two-adjacent-level CSM were included.

RESULTS: No significant differences were identified between the two groups regarding hospital stay, Japanese Orthopedic Association (JOA) score, visual analog scale (VAS) scores for neck and arm pain, total cervical range of motion (ROM), fusion ROM, fusion rate, adjacent-level ossification, and complications. While ACDF had significantly less bleeding (SMD = 1.14, 95% CI: [0.74, 1.53]); a shorter operation time (SMD = 1.13, 95% CI: [0.82, 1.45]); greater cervical lordosis, both total cervical (SMD = -2.95, 95% CI: [-4.79, -1.12]) and fused segment (SMD = -2.24, 95% CI: [-3.31, -1.17]); higher segmental height (SMD = -0.68, 95% CI: [-1.03, -0.34]); and less graft subsidence (SMD = 0.40, 95% CI: [0.06,0.75]) compared to ACCF.

CONCLUSIONS: The results suggested that ACDF has more advantages compared to ACCF. However, additional high-quality RCTs and a longer follow-up duration are needed.

Article summary

Strengths and limitations of this study

1) According to our study, ACCF and ACDF are both effective and safe for treating CSM. 2) ACDF has more advantages than ACCF in some aspects. 3) The trials included in our study are not high-quality RCTs and do not have a long enough follow-up duration. 4) The number of studies used in the meta-analysis is small (nine studies). In fact, for most of the outcomes, fewer than five studies were used in the meta-analyses. 5) The pathological processes of patients are not always the same.

Introduction

Cervical spondylosis is a common disease and a progressive degenerative process of the cervical spine that results in loss of disc height and formation of osteophytes. When it develops into cervical spondylosis myelopathy (CSM), motion abnormalities and sensory disturbances will follow, resulting in a reduced quality of life for the patients.[1] Surgical intervention is recommended for these patients with severe symptoms.[2]

The choice between an anterior, posterior, or combined approach for decompression is based primarily on (1) the sagittal alignment of the spinal column, (2) the extent of disease, (3) the location of the abnormal compression, (4) the presence of preoperative neck pain, and (5) previous operations.[2]

Shamji *et al.*[3] and Jiang *et al.*[4] have reviewed the efficacy and safety of anterior procedures for patients with multilevel CSM, covering patients with two-adjacent-level CSM. Furthermore, the work by Chang *et al.*[5] supports that anterior cervical discectomy and fusion (ACDF) is the treatment of choice for cervical disc herniation and spondylotic radiculopathy or myelopathy. In addition, Lu *et al.*[6] have shown that anterior cervical corpectomy and fusion (ACCF) is an effective surgical procedure for the treatment of multilevel cervical myelopathy because it can remove almost all osteophytes, discs, and ossification of posterior longitudinal ligament pathology that cause spinal cord compression. Kazuo *et al.*[7] and Mamoru *et al.*[8] have shown that ACDF and ACCF are both widely used anterior methods for

CSM, especially with two levels. Although patients with two-adjacent-level CSM are often seen in clinical practice, controversies still exist between ACCF and ACDF for treating these patients. Therefore, the aim of this meta-analysis was to compare the efficacy and safety of ACCF and ACDF for patients with two-adjacent-level CSM by assessing the perioperative, clinical, and radiological outcomes as well as complications.

Materials and Methods

Search Strategy

The electronic databases including PubMed (1966–2013), Cochrane Central Register of Controlled Trials (Issue 9, 2013), ScienceDirect (1985–2013), CNKI (1996–2013), WANFANG DATA (1997–2013), and CQVIP (1996–2013) were searched. The keywords used for the search were as follows: "cervical spondylosis myelopathy," "anterior cervical discectomy and fusion," "anterior cervical corpectomy and fusion," "two level(s)," and "single-level."

Eligibility Criteria

All comparative studies that adopted ACCF and ACDF to treat two-adjacent-level cervical spondylosis were identified, and the reference lists of identified articles were searched to identify other potentially eligible studies. Criteria for inclusion were as follows: 1) ACCF with titanium mesh, cage, or autologous ilium bone grafting; ACDF with interbody cage devices or autologous ilium bone grafting;

and the two surgeries both used anterior cervical plate and screw fixation. 2) All patients included had a confirmed CSM at two adjacent segments, and surgical intervention was recommended. 3) The trials were followed up for more than 12 months.

Criteria for exclusion: 1) The studies did not meet the inclusion criteria. 2) The intraoperative outcome data (length of hospital stay, amount of bleeding, and operation time), clinical outcomes (Japanese Orthopedic Association (JOA) score and visual analog scale (VAS) score for neck and arm pain), radiological outcomes (cervical lordosis for total cervical and fused segments, total cervical range of motion (ROM), segmental ROM, graft collapse, segmental height, fusion rate, and degeneration of the adjacent-level), or complications (short-term and long-term complications) were not reported. 3) The number of samples was less than 30 cases. 4) The patients evaluated were treated at the same hospital.

Data Extraction

Two reviewers independently extracted the data using a standardized form, which covered the following items: 1) basic characteristics, including the year of publication, study design, inclusion/exclusion criteria, age, sex, enrolled number, and follow-up rate; 2) intraoperative outcomes, consisting of length of hospital stay, amount of bleeding, and operation time; 3) clinical outcomes, including JOA score and VAS score for neck and arm pain; 4) radiological outcomes, such as cervical lordosis for total cervical and fused segments, total cervical ROM, segmental ROM, graft collapse, segmental height, fusion rate, degeneration of the adjacent level; and 5) complications, including short-term and long-term complications.

Risk of Bias Assessment

Two reviewers independently evaluated the quality of the included studies. Three randomized studies[9-11] were assessed with the Cochrane Handbook for Systematic Review of Interventions, and six nonrandomized studies[12-17] were evaluated according to the methodological index for nonrandomized studies (MINORS) criteria, an established method for evaluating non-RCTs.[18]

Statistical Analysis

All meta-analyses were performed with Review Manager 5.2 software (Cochrane Collaboration, Oxford, UK). For continuous outcomes, means and standard deviations were pooled to generate a standardized mean difference (SMD), and 95% confidence intervals (CIs) were generated. According to the study by Kim,[17] a formula was used to obtain a combined mean and standard deviation (SD).[19] For dichotomous outcomes, the risk ratio (RR) and 95% CI were assessed. A probability of $P < 0.05$ was considered to be statistically significant. Assessment for statistical heterogeneity was calculated using the chi-squared and I-squared tests. When the test for heterogeneity was $P < 0.1$ or $I^2 > 50\%$, the data were considered very heterogeneous. The source of heterogeneity was investigated by subgroup analysis and sensitivity analysis. A fixed effects model was used for homogeneous data, and a random effects model was used for data with high heterogeneity. As for the data with significant methodological heterogeneity, sensitivity analysis was adopted to find the source of the heterogeneity. With regard to the data with significant clinical heterogeneity, subgroup analyses were applied to identify the source of the heterogeneity.

Results

Literature Search

A total of 606 potential reports were retrieved with the search strategy (Fig. 1). Of these, 597 reports were excluded because they did not fit our inclusion criteria. No additional studies were obtained after reference review. Finally, nine studies were selected and analyzed.[9-17]

Risk of bias assessment

For three randomized studies,[9-11] two studies were RCTs,[9,11] one of which did not provide information regarding allocation concealment. One study was a quasi-RCT, in which patients were allocated according to their sequence of hospitalization.[10] Due to the informed consent rights between patients and doctors, it was impossible to blind all participants and personnel. None of these three studies reported blinding of outcome assessment. No patients were lost to follow-up, except for eight patients who were excluded from the study by Liu *et al.*[11] due to missing data. Thus, there was a low risk of bias due to incomplete outcome data. In these three trials, the outcomes were provided in detail and there was a low risk of bias due to selective reporting. Owing to insufficient information to assess whether an important risk of bias existed in a number of trials, it was hypothesized that all trials had an unclear risk of bias towards other potential sources of bias. The methodological quality assessment is summarized in Table 1a. For six nonrandomized studies,[12-17] according to the modified MINORS criteria,[18] none of them reported an unbiased assessment of the study endpoint or a prospective calculation of the study size. With regard to the prospective collection of data, three studies did not report the relevant information.[13,15,17] Only one study reported the follow-up rate.[14] The other eight items were all specifically reported. In summary, scores ranged from 16 to 18, with a median value of 16.5. The methodological quality assessment is summarized in Table 1b.

Demographic characteristics

The demographic characteristics of the patients included in the selected studies are presented in Table 2. A total of 631 patients, with a male-to-female ratio of 1.38:1, were included. Of these, 270 underwent ACCF procedures and 361 were treated by the ACDF approach; the two surgeries used various grafts, including autografts, allografts, and cage and/or plate systems. The mean age of the patients was 55.1 years old. The average duration of follow-up ranged from 18.9 to 43.2 months. Statistically similar baseline characteristics were observed between the ACCF and ACDF groups (Table 3).

Hospital Stay

Details regarding hospital stay were available in three papers (Table S1),[9,11,16] and statistical heterogeneity was absent in these studies (I^2 = 0%; P = 0.69). The pooled estimate revealed a statistically insignificant difference (SMD = 0.18, 95% CI: [-0.15, 0.51], P = 0.28) (Fig. 2).

Bleeding Amount

Relevant data regarding the bleeding amount were documented in four articles (Table S1),[9-11,16] and all the trials showed that the ACDF approach had significantly reduced intraoperative bleeding amounts compared to the ACCF procedure. Pooling of relevant data also showed a statistically significant difference between the two groups (SMD = 1.14, 95% CI: [0.74, 1.53], P = 0.002). Significant heterogeneity was detected (I^2 = 89%; P < 0.00001) (Fig. 2b). In addition, sensitivity analysis confirmed the stability of bleeding amount outcomes (Fig. S1).

Operation Time

Four trials reported a significantly shorter surgical time in the ACDF group compared to the ACCF group (Table S1).[9-11,16] Overall, the SMD was 1.13 (95% CI: [0.82, 1.45], P < 0.00001) in favor of the ACDF group. There was obvious evidence of statistically significant heterogeneity (I^2 = 54%; P = 0.009), according to subgroup analysis (Fig. 3). Furthermore, sensitivity analysis confirmed the stability of operation time outcomes (Fig. S2).

JOA

Three studies reported the JOA score (Table S2),[9,11,16] and the pooled estimate revealed a statistically insignificant difference (SMD = 0.14, 95% CI: [-0.19, 0.47], P= 0.41), with low heterogeneity (I^2 = 12%) (Fig. 4a).

Neck VAS

Three studies reported a postoperative neck VAS score (Table S2),[9,14,16] and the pooled data from the two relevant studies did not reveal any significant difference (SMD=0.13, 95% CI: [-0.15, 0.41], P = 0.36), with low heterogeneity (I^2 = 45%) (Fig. 4b).

Arm VAS

Relevant VAS data were documented in three articles (Table S2).[9,14,16] There was no significant difference between the two treatment groups (SMD = -0.15, 95%CI = [-0.43, 0.13]; P = 0.28), with low heterogeneity (I^2 = 4%) (Fig. 4c).

C2-C7 Cobb

Five studies reported the C2-C7 Cobb at the final follow-up (Table S3a),[9,12,14,16,17] the available data demonstrated low heterogeneity (I^2 = 8%), and the ACCF group had a significantly lower Cobb than the ACDF group (SMD = -0.32, 95% CI: [-0.53, -0.10], P = 0.004) (Fig. 5a).

Fusion Cobb

Three studies reported the fusion Cobb at the final follow-up (Table S3a),[11,12,15] the available data demonstrated no heterogeneity ($I^2 = 0\%$), and the ACCF group had a significantly lower Cobb than the ACDF group (SMD = -0.50, 95% CI: [-0.75, -0.24], $P = 0.0001$) (Fig. 5b).

Total cervical ROM

Two studies reported the total cervical ROM data at the final follow-up (Table S3b),[9,16] and the other two studies demonstrated that there was no significant difference in total cervical ROM between the two groups (SMD = -0.02, 95% CI: [-0.42, 0.37], $P = 0.90$), with no heterogeneity ($I^2 = 0\%$) (Fig. 5c).

Fusion ROM

Two studies reported fusion ROM at the last follow-up (Table S3b),[9,16] and there was no significant difference in fusion ROM between the two groups (SMD = -0.05, 95% CI: [-0.45, 0.35], $P = 0.80$), with low heterogeneity ($I^2 = 20\%$) (Fig. 5d).

Fused segment height

Five studies reported the fused segment height data at the final follow-up (Table S3b);[9,11,14,16,17] however, data from three studies were excluded from this analysis because of the different methods used to measure the fused segment height.[11,16,17] The pooled results demonstrated that the ACCF group had a significantly lower fused segment height than the ACDF group (SMD = -0.68, 95% CI: [-1.03, -0.34]), with high heterogeneity (I^2 = 76%) (Fig. 6a).

Graft collapse

Two studies reported graft collapse at the last follow-up (Table S3c),[12,15] showing that there was a significant reduction in graft collapse for the ACDF group (SMD = 0.40, 95% CI: [0.06, 0.75], *P* = 0.02), with moderate heterogeneity (I^2 = 68%) (Fig. 6b). No significant clinical heterogeneity or methodological heterogeneity was found; however, statistical heterogeneity likely exists, so the data from the two studies were pooled.

Fusion rate

Six studies reported the fusion rate at the last follow-up (Table S3c),[9,10,14-17] and there was no significant difference in the fusion rate between the two groups (RR = 1.00, 95% CI: [0.97, 1.04], *P* = 0.79), with no heterogeneity (I^2 = 0%) (Fig. 7a).

Degeneration

Three studies reported degeneration of the level adjacent to the fusion (Table S3c),[9,14,15] showing that there was no significant difference in degeneration of the level adjacent to the fusion between the two groups (RR = 1.31, 95% CI: [0.44, 3.93], *P* = 0.63), with no heterogeneity (I^2 = 0%) (Fig. 7b).

Complications

Data regarding complications were provided in eight studies (Table S4).[9-11,13-17] There was no significant difference between the ACCF and ACDF groups according to individual and pooled data (RR = 1.25, 95%CI = [0.74, 2.13]; P = 0.40). Statistical heterogeneity was absent in these studies (I^2 = 0%; P = 0.52) (Fig. 7c).

Discussion

Although most studies included in this analysis reported consistent results,[9-17] the pooled estimates should be explained with caution. With regard to the operative outcomes, the length of hospital stay was similar in both groups, and less blood loss and a shorter operation time were observed in the ACDF group than in the ACCF group. ACDF requires less exposure of the spinal cord than does corpectomy;[2] therefore, less damage to the spinal column occurs. Accordingly, ACDF might result in less blood loss than ACCF. In terms of ACCF, a 15 to 19-mm anterior midline trough should be performed in the vertebral body down to the posterior longitudinal ligament or dura, with removal of the cephalad and caudad discs,[2] which would require more time to be removed, similarly it will cost more time to obtain a graft material to fit the trough. Consequently, ACDF had a significantly shorter operation time.

In our meta-analysis, JOA scores as well as VAS scores for neck and arm pain both significantly improved in each group, without significant differences between the two groups. These results suggest that both procedures effectively treat two-adjacent-level CSM and improve the patients' neurological function, quality of life, and disability. Similar outcomes were achieved for both ACDF and ACCF in the treatment of multilevel cervical spondylosis by Shamji *et al*.[3] and Jiang *et al*.[4]

Total cervical ROM, fusion ROM, fusion rate, and adjacent-level ossification yielded no significant differences between the two groups. Concerning the high fusion rate in the two groups, it may be related to the following factors: 1) the use of a polyether ether ketone (PEEK) cage or titanium mesh packed with autogenous tricortical bone and fixed by titanium plates and screws or by Atlantis plate fixation;[9-17] 2) the fixation system provides a stable biomechanical environment, which greatly promotes bone healing; and 3) bone healing is a process of creeping substitution,[20] and the distance of creeping substitution for single-level ACCF and two-level ACDF are both short. The high fusion rate effectively reduced the total cervical and fused segment ROM. For example, Eck *et al*. demonstrated that a significantly greater adjacent level disc pressure was achieved after cervical fusion.[21] In addition, the normal degenerative process plays a major role through impaired nutrition, loss of viable cells, matrix protein modification, and matrix failure.[22] This normal aging process, in combination with increased mechanical pressures, may synergistically hasten the degeneration process, although it has not been conclusively demonstrated.[23]

For C2-C7 Cobb, ACDF had a significantly greater lordosis angle than ACCF, not only immediately postoperation but also at the final follow-up. Similar results were found for the fusion Cobb at the last follow-up. The reasons may be associated with the following two factors: 1) Single-level ACCF removes both the vertebral body and two discs, while two-level ACDF just takes out the two discs;[2] as a result, ACDF allows the construction of an almost normal spinal column after surgery. Thus, the loss of Cobb is less common in ACDF. In other words, ACDF preserves the sagittal alignment somewhat better than does ACCF. 2) Eck *et al*. have reported that each of the involved joints contributes to the total ROM.[21] With fusion, the contribution of one joint to ROM is reduced.

In terms of the fused segment height, ACCF causes a significant reduction compared to ACDF, both immediately postoperative and at the last follow-up. With ACDF, screws placed in the intervening segment and two caudal end plates synergistically share the load of the construct. In contrast, with a single-level corpectomy, screws are only at the cranial and caudal vertebral segments and the caudal end plate bears the full load of the construct.[12] Additionally, the graft contact area is less for ACCF than for ACDF, which results in a higher shear stress for ACCF. These reasons might hasten the graft absorption process into the cover plate of the adjacent vertebral body, leading to a significant subsidence of the treated segment in ACCF, especially at the anterior and caudal positions.

Concerning complications, the data show that there is no significant difference between the two groups and that the incidence of complications is low in each group. This result suggests that both of the two treatments are safe.

The methodological quality assessment should be considered, which identified several limitations of the clinical evidence. Only nine studies met the predefined eligibility criteria, meaning that all the results were based on only 631 patients. More importantly, there were only three studies that were randomized. All randomized studies had poor concealment of randomization, including selection and allocation bias. Due to informed consent requirements, patients and operators had knowledge regarding the surgical procedures, thus allowing further measurement and expectation bias. Four outcomes (bleeding amount, operation time, fused segment height, and graft collapse) had a high heterogeneity. Wu *et al*. have summarized a method to deal with heterogeneity in meta-analysis.[24] For the bleeding amount, it was reasonable to perform sensitivity analysis (Fig. S1) because of the different research types. As shown in Fig. S1, the results of Jia 2012[16] have significant heterogeneity, which should be removed. The bleeding amount results are shown in Fig. 2b. Regarding the operation time, sensitivity analysis was performed analyze the data because of the different research types. As shown by the sensitivity analysis results (Fig. S2), ACDF had a shorter operation time that could not be reversed regardless of which study was removed. Therefore, the heterogeneity did not come from the methodological heterogeneity. Accordingly, there probably exists clinical heterogeneity. Due to the strict eligibility criteria, the patient data had a good homogeneity; thus, the heterogeneity was due to the ability of the surgeons. The subgroup analysis results regarding operation time are shown in Fig. 3. As for the fused segment height, clinical heterogeneity existed. Oh *et al*.[9] and Burkhardt *et al*.[14] have defined the fused segment height as the distance between the midlines of the involved cranial vertebral bodies and the caudal vertebral bodies. In contrast, Jia *et al*.[16] did not describe the method to measure the fused segment height. Meanwhile, Liu *et al.*[11] and Kim *et al.*[17] reported the anterior and posterior heights of the involved vertebral bodies. In summary, for the fused segment height, we pooled the data of Oh *et al.*[9] and Burkhardt *et al.*,[14] and the outcome is displayed in Fig. 6a. With regard to graft collapse, as the two literature examples are both retrospective studies, it is believed that no methodological heterogeneity existed. Regarding the clinical heterogeneity, the patient data had a good homogeneity due to the strict eligibility criteria and the fact that the methods of measuring the graft collapse were the same. As a result, no significant clinical heterogeneity or methodological heterogeneity was found. However, statistical heterogeneity likely existed, so the studies were pooled. Not all of the included studies had consistent baseline characteristics between the ACCF and ACDF groups. Therefore, larger randomized controlled trials with high quality are still needed in the future to compare the two surgeries.

Conclusion

Based on this meta-analysis that compared ACDF and ACCF to treat two-adjacent-level CSM, ACDF has some advantages such as less blood loss, a shorter operation time, greater cervical lordosis both in the total cervical and fused segments, a higher segmental height, and less graft subsidence. However, no significant differences in JOA, VAS, ROM, or complications were found. This information will provide surgeons a preliminary understanding of the differences between the two surgeries to treat two-adjacent-level CSM and will be helpful to clinical surgeons for choosing which surgical method to treat patients with two-adjacent-level CSM. Further high-quality RCTs and longer follow-up durations are needed to assess these two treatments.

Acknowledgement

This work was supported by the Department of Health of Zhejiang Province, Backbone of Talent Project (2012RCB037); and the Department of Science and Technology of Wenzhou, Wenzhou Science and Technology Project (Y20120073). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. We thank Medjaden Bioscience for assisting in the preparation of this manuscript.

Author Contributions

Conceived and designed the review: ZYH, AMW, and WFN. Performed the review: ZYH, AMW, and WFN. Analyzed the data: ZYH and AMW. Contributed reagents/materials/analysis tools: QLL, TL, KYW, and HZX. Wrote the paper: ZYH and AMW.

Data sharing statement

No additional data are available.

Figure Legends

Fig. 1: The search strategy for our meta-analysis and reasons for exclusion.

Fig. 2: Perioperative parameters. a: Forest plot and tabulated data for length of hospital stay; no significant difference between the two types of surgery was observed. b: Forest plot and tabulated data for bleeding amount; the ACDF group had significantly less intraoperative bleeding than the ACCF group.

Fig. 3: Perioperative parameters. Forest plot and tabulated data for operation time; the ACDF group had a significantly shorter surgical time compared to the ACCF group.

Fig. 4: Clinical parameters. a: Forest plot and tabulated data for JOA; b: Forest plot and tabulated data for neck VAS; c: Forest plot and tabulated data for arm VAS. There were no significant differences in these parameters between the two types of surgery.

Fig. 5: Radiological parameters. a: Forest plot and tabulated data for C2-C7 Cobb; b: Forest plot and tabulated data for fusion Cobb; c: Forest plot and tabulated data for total cervical ROM; d: Forest plot and tabulated data for fusion ROM. The ACCF group had a significantly lower Cobb than the ACDF group. There was no significant difference in the cervical or fusion ROM between the two types of surgery.

Fig. 6: Radiological parameters. a: Forest plot and tabulated data for the fused segment height; the ACCF group had a significantly lower fused segment height than the ACDF group. b: Forest plot and tabulated data for graft collapse; the ACDF group had a significantly lower graft collapse than the ACCF group.

Fig. 7: a: Forest plot and tabulated data for fusion rate; b: Forest plot and tabulated data for degeneration of the adjacent level; c: Forest plot and tabulated data for complications. There was no significant difference in any of these parameters between the two types of surgery.

Fig. S1: The sensitivity analysis for bleeding amounts. Significant heterogeneity was found between the four studies.

Fig. S2: The sensitivity analysis for operation time. No significant heterogeneity was found between the four studies.

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Table 1a. Risk of bias assessment of randomized studies.

Risk of bias assessment	**Oh 2009**	**Yu 2007**	**Liu 2011**
Random sequence generation	Unclear risk	High risk	Low risk
Allocation concealment	Unclear risk	Unclear risk	Unclear risk
Blinding of participants and personnel	High risk	High risk	High risk
Blinding of outcome assessment	Unclear risk	Unclear risk	Unclear risk
Incomplete outcome data	Low risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk
Other sources of bias	Unclear risk	Unclear risk	Unclear risk

Table 1b. Quality assessment of non-randomized studies.

Methodological item for non-randomized studies	**Park 2010**	**Wang 2001**	**Burkhardt 2013**	**Yu 2012**	**Jia 2012**	**Kim 2012**
1.A clearly stated aim	2	2	2	2	2	2
2.Inclusion of consecutive patients	2	2	2	2	2	2
3.Prospective collection of data	2	0	2	0	2	0
4.Endpoints appropriate to the aim of the study	2	2	2	2	2	2
5. Unbiased assessment of the study endpoint	0	0	0	0	0	0
6. Follow-up period appropriate to the aim of the study	2	2	2	2	2	2
7. Loss to follow up less than 5%	0	0	1	0	0	0
8. Prospective calculation of the study size	0	0	0	0	0	0
9. An adequate control group	2	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	2	2	2	2	2	2
12. Adequate statistical analyses	2	2	2	2	2	2

Table 2 Characteristics of the studies included in the meta-analysis.

Year[ref]	Design	Sample size		Mean age (years)		Gender(M/F)		Mean follow-up time(months)	
		ACCF	ACDF	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
2009[9]	RCT	17	14	55.12	52.64	16/15		27.33	24.9
2007[10]	Quasi-RCT	20	20	53.1±8.98	52.75±7.81	14/6	15/5	NA	
2011[11]	RCT	23	23	54.4±10.9	56.5±9.2	18/5	16/7	31(25-53)	29(26-48)
2010[12]	Retro	52	45	49.4±8.7	49.3±9.7	30/22	17/28	23.3±6.6	25.7±6.2
2001[13]	Retro	20	32	51.5(17-80)		27/25		43.2(24-84)	
2013[14]	Retro	38	80	60.3±11.1	60.9±9.9	25/13	41/39	20.4±13.7	
2012[15]	Retro	48	62	59.3±6.8(49-75)		65/45		32±4.2(24-60)	
2012[16]	Retro	36	31	48.83±8.12	49.12±7.65	21/15	17/14	28.96±13.21	26.81±11.02
2012[17]	Retro	16	54	58±8.6	56.7±10.2	13/3	31/23	20±11.9	18.6±11.5

Retro meant Retrospective, Mean age was described as mean±SD or mean or mean (range) of all patients in the study or mean±SD of all patients in the study, Gender was described as M/F or M/F of all patients in the study, Mean follow-up time was presented as mean±SD or mean (range) or mean±SD of all patients in the study, RCT= randomized control trial, SD= standard deviation, ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, NA= not available.

Table 3 Comparison of baseline characteristics between the ACCF and ACDF groups.

Characteristic	Oh 2009	Park 2010	Wang 2001	Burkhardt 2013	Yu 2012	Yu 2007	Jia 2012	Liu 2011	Kim 2012
Mean age	*	*	*	*	*	*	*	*	*
Gender	*	*	*	*	*	*	*	*	*
Follow-up	*	*	*	*	*	*	*	*	*
Preoperative JOA	*	NA	NA	NA	NA	*	*	*	NA
Preoperative neck VAS	*	NA	NA	*	NA	NA	*	NA	NA
Preoperative arm VAS	*	NA	NA	*	NA	NA	*	NA	NA
Preoperative sagittal alignment	NA	*	NA	NA	*	NA	NA	NA	NA
Preoperative C2-C7 Cobb	*	*	NA	*	NA	NA	*	NA	*
Preoperative fused segment height	*	NA	NA	*	NA	NA	NA	*	*
Preoperative total cervical ROM	*	NA	NA	NA	NA	NA	0.02	NA	NA
Preoperative fused segment ROM	*	NA	NA	NA	NA	NA	0.01	NA	NA

JOA= Japanese Orthopedic Association scores, VAS= Visual Analog Scale scores. ROM= range of motion, NA= not available, * Statistically insignificant (P>0.05).

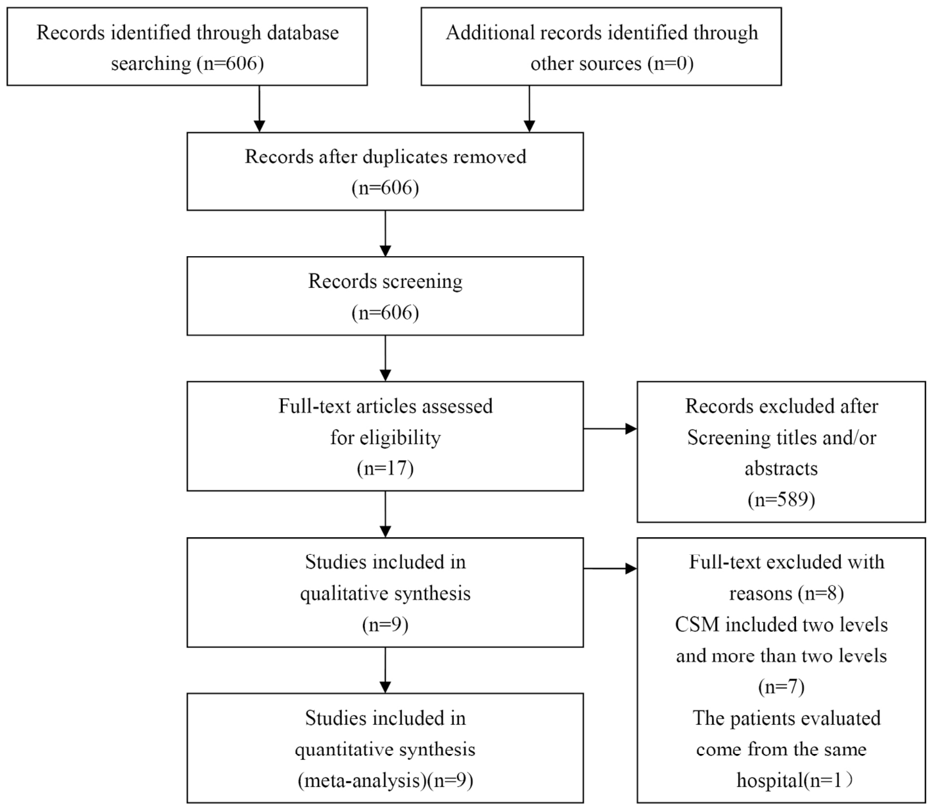

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Fig.2a hospital stay

Study or Subgroup	ACCF Mean	ACCF SD	ACCF Total	ACDF Mean	ACDF SD	ACDF Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Jia 2012	11.11	8.52	36	10.79	7.74	31	46.8%	0.04 [-0.44, 0.52]
Liu 2011	12.2	2.7	23	11.2	2.6	23	31.7%	0.37 [-0.21, 0.95]
Oh 2009	16.82	7.7	17	15.14	8.5	14	21.5%	0.20 [-0.51, 0.91]
Total (95% CI)			**76**			**68**	**100.0%**	**0.18 [-0.15, 0.51]**

Heterogeneity: Chi² = 0.75, df = 2 (P = 0.69); I² = 0%

Test for overall effect: Z = 1.07 (P = 0.28)

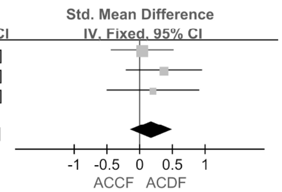

Fig.2b bleeding amounts

Study or Subgroup	ACCF Mean	ACCF SD	ACCF Total	ACDF Mean	ACDF SD	ACDF Total	Weight	Std. Mean Difference IV, Random, 95% CI
Liu 2011	263	130.4	23	148.3	71.3	23	40.3%	1.07 [0.45, 1.69]
Oh 2009	778.8	644.3	17	306.43	151.1	14	27.7%	0.94 [0.19, 1.69]
Yu 2007	306.75	74.63	20	207.5	65.86	20	32.1%	1.38 [0.69, 2.08]
Total (95% CI)			**60**			**57**	**100.0%**	**1.14 [0.74, 1.53]**

Heterogeneity: Tau² = 0.00; Chi² = 0.78, df = 2 (P = 0.68); I² = 0%

Test for overall effect: Z = 5.64 (P < 0.00001)

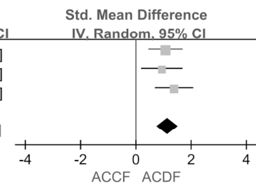

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Fig.3 Operative Time

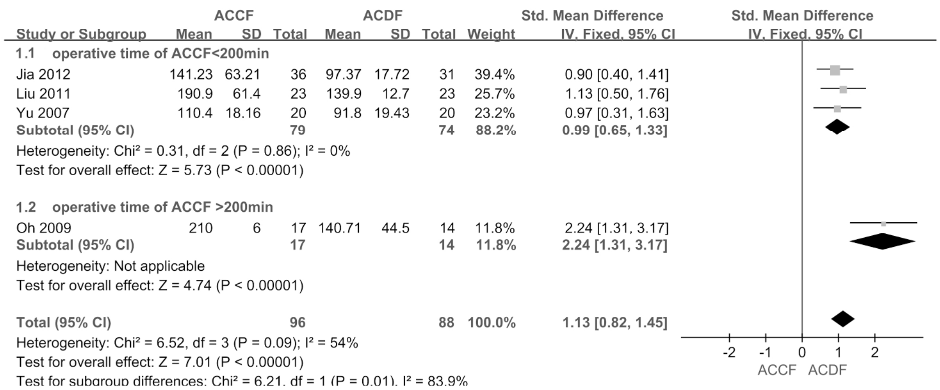

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Fig.4a JOA

Study or Subgroup	ACCF Mean	ACCF SD	ACCF Total	ACDF Mean	ACDF SD	ACDF Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Jia 2012	15.32	1.54	36	15.01	1.76	31	46.8%	0.19 [-0.30, 0.67]
Liu 2011	14.1	1.4	23	13.6	1.2	23	31.8%	0.38 [-0.21, 0.96]
Oh 2009	14.72	1.7	17	15.25	1.5	14	21.4%	-0.32 [-1.03, 0.39]
Total (95% CI)			**76**			**68**	**100.0%**	**0.14 [-0.19, 0.47]**

Heterogeneity: Chi² = 2.27, df = 2 (P = 0.32); I² = 12%
Test for overall effect: Z = 0.83 (P = 0.41)

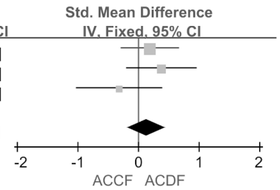

Fig.4b neck VAS

Study or Subgroup	ACCF Mean	ACCF SD	ACCF Total	ACDF Mean	ACDF SD	ACDF Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Burkhardt 2013	0.9	3.1	38	1.3	3.2	80	51.9%	-0.13 [-0.51, 0.26]
Jia 2012	3.62	2.01	36	2.81	1.33	31	32.7%	0.46 [-0.02, 0.95]
Oh 2009	3.63	2.3	17	2.93	2.5	14	15.3%	0.29 [-0.43, 1.00]
Total (95% CI)			**91**			**125**	**100.0%**	**0.13 [-0.15, 0.41]**

Heterogeneity: Chi² = 3.66, df = 2 (P = 0.16); I² = 45%
Test for overall effect: Z = 0.91 (P = 0.36)

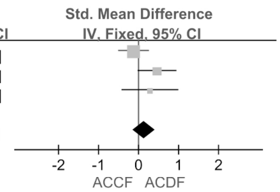

Fig.4c arm VAS

Study or Subgroup	ACCF Mean	ACCF SD	ACCF Total	ACDF Mean	ACDF SD	ACDF Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Burkhardt 2013	1.4	3.2	38	2.4	2.7	80	51.1%	-0.35 [-0.74, 0.04]
Jia 2012	2.51	1.43	36	2.35	1.69	31	33.5%	0.10 [-0.38, 0.58]
Oh 2009	2.63	2.7	17	2.79	2.3	14	15.4%	-0.06 [-0.77, 0.65]
Total (95% CI)			**91**			**125**	**100.0%**	**-0.15 [-0.43, 0.13]**

Heterogeneity: Chi² = 2.09, df = 2 (P = 0.35); I² = 4%
Test for overall effect: Z = 1.08 (P = 0.28)

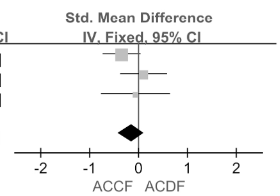

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Fig.5a C2-C7 Cobb

Study or Subgroup	ACCF Mean	ACCF SD	ACCF Total	ACDF Mean	ACDF SD	ACDF Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Burkhardt 2013	9.7	7.7	38	13.6	8.6	80	29.6%	-0.47 [-0.86, -0.07]
Jia 2012	20.26	10.26	36	22.08	9.78	31	19.5%	-0.18 [-0.66, 0.30]
Kim 2012	15.7	8.6	16	16.7	8.5	54	14.5%	-0.12 [-0.67, 0.44]
Oh 2009	14.59	10.6	17	23.43	7.4	14	8.1%	-0.93 [-1.67, -0.18]
Park 2010	9.6	9.1	52	11.2	8.5	45	28.3%	-0.18 [-0.58, 0.22]
Total (95% CI)			**159**			**224**	**100.0%**	**-0.32 [-0.53, -0.10]**

Heterogeneity: Chi² = 4.35, df = 4 (P = 0.36); I² = 8%
Test for overall effect: Z = 2.90 (P = 0.004)

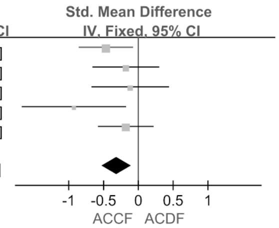

Fig.5b fusion Cobb

Study or Subgroup	ACCF Mean	ACCF SD	ACCF Total	ACDF Mean	ACDF SD	ACDF Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Liu 2011	6.9	2.5	23	8.8	2.7	23	17.7%	-0.72 [-1.32, -0.12]
Park 2010	2.5	5.9	52	4.4	5.7	45	39.3%	-0.32 [-0.73, 0.08]
Yu 2012	4.4	4.9	48	7.5	5.9	62	43.0%	-0.56 [-0.95, -0.18]
Total (95% CI)			**123**			**130**	**100.0%**	**-0.50 [-0.75, -0.24]**

Heterogeneity: Chi² = 1.34, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 3.86 (P = 0.0001)

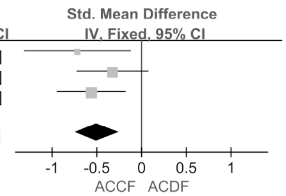

Fig.5c Total cervical ROM

Study or Subgroup	ACCF Mean	ACCF SD	ACCF Total	ACDF Mean	ACDF SD	ACDF Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Jia 2012	27.98	12.94	36	29.19	10.33	31	68.5%	-0.10 [-0.58, 0.38]
Oh 2009	30.23	15.1	17	28.13	13.4	14	31.5%	0.14 [-0.57, 0.85]
Total (95% CI)			**53**			**45**	**100.0%**	**-0.02 [-0.42, 0.37]**

Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.12 (P = 0.90)

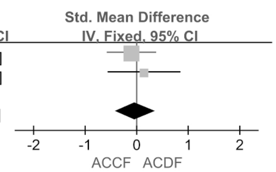

Fig.5d fusion ROM

Study or Subgroup	ACCF Mean	ACCF SD	ACCF Total	ACDF Mean	ACDF SD	ACDF Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Jia 2012	3.39	3.01	36	4.01	2.93	31	68.6%	-0.21 [-0.69, 0.28]
Oh 2009	5.12	4.8	17	3.88	3.4	14	31.4%	0.29 [-0.43, 1.00]
Total (95% CI)			**53**			**45**	**100.0%**	**-0.05 [-0.45, 0.35]**

Heterogeneity: Chi² = 1.26, df = 1 (P = 0.26); I² = 20%
Test for overall effect: Z = 0.25 (P = 0.80)

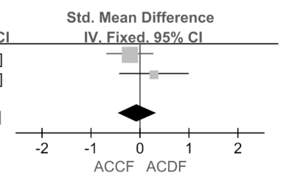

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Fig.6a fused segment height

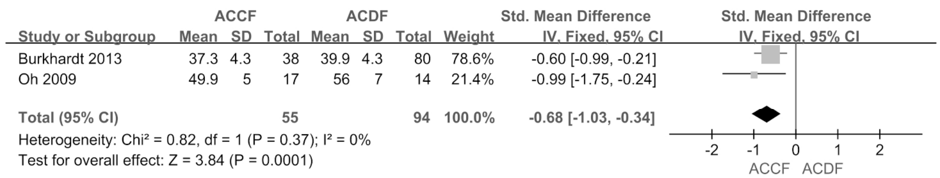
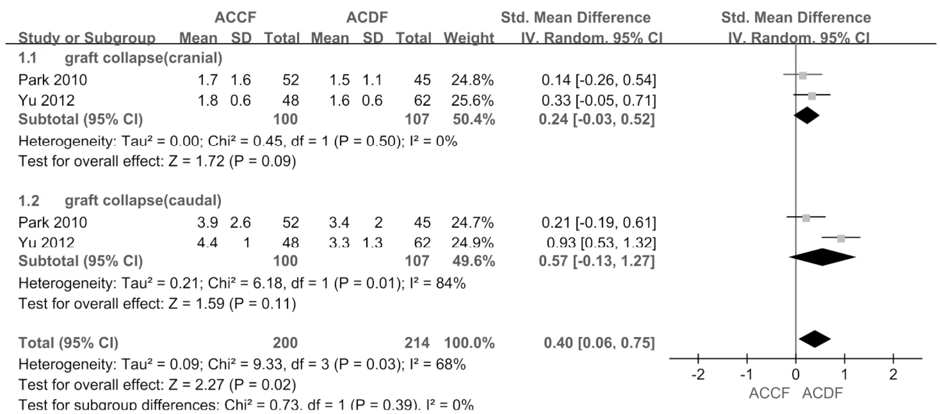


Fig.6b graft collapse



209x170mm (300 x 300 DPI)

Fig.7a fusion rate

Study or Subgroup	ACCF Events	ACCF Total	ACDF Events	ACDF Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burkhardt 2013	36	38	78	80	25.4%	0.97 [0.89, 1.06]
Jia 2012	36	36	31	31	17.1%	1.00 [0.94, 1.06]
Kim 2012	16	16	48	54	11.6%	1.10 [0.97, 1.25]
Oh 2009	17	17	14	14	8.0%	1.00 [0.88, 1.13]
Yu 2007	20	20	20	20	10.4%	1.00 [0.91, 1.10]
Yu 2012	48	48	62	62	27.6%	1.00 [0.96, 1.04]
Total (95% CI)		**175**		**261**	**100.0%**	**1.00 [0.97, 1.04]**
Total events	173		253			

Heterogeneity: Chi² = 2.70, df = 5 (P = 0.75); I² = 0%
Test for overall effect: Z = 0.27 (P = 0.79)

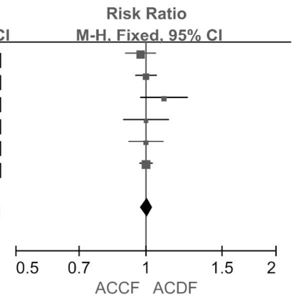


Fig.7b degeneration of the adjacent-level

Study or Subgroup	ACCF Events	ACCF Total	ACDF Events	ACDF Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burkhardt 2013	2	38	3	80	38.7%	1.40 [0.24, 8.05]
Oh 2009	3	17	2	14	43.9%	1.24 [0.24, 6.39]
Yu 2012	1	48	1	62	17.5%	1.29 [0.08, 20.13]
Total (95% CI)		**103**		**156**	**100.0%**	**1.31 [0.44, 3.93]**
Total events	6		6			

Heterogeneity: Chi² = 0.01, df = 2 (P = 0.99); I² = 0%
Test for overall effect: Z = 0.48 (P = 0.63)

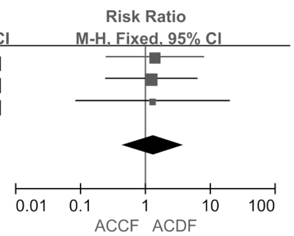
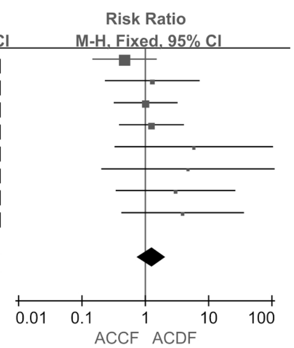


Fig.7c Complications

Study or Subgroup	ACCF Events	ACCF Total	ACDF Events	ACDF Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Burkhardt 2013	3	31	14	68	39.3%	0.47 [0.15, 1.52]
Jia 2012	3	36	2	31	9.6%	1.29 [0.23, 7.24]
Kim 2012	3	16	10	54	20.5%	1.01 [0.32, 3.24]
Liu 2011	5	23	4	23	17.9%	1.25 [0.38, 4.07]
Oh 2009	3	17	0	14	2.4%	5.83 [0.33, 104.22]
Wang 2001	1	20	0	32	1.7%	4.71 [0.20, 110.40]
Yu 2007	3	20	1	20	4.5%	3.00 [0.34, 26.45]
Yu 2012	3	48	1	62	3.9%	3.88 [0.42, 36.09]
Total (95% CI)		**211**		**304**	**100.0%**	**1.25 [0.74, 2.13]**
Total events	24		32			

Heterogeneity: Chi² = 6.19, df = 7 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.40)



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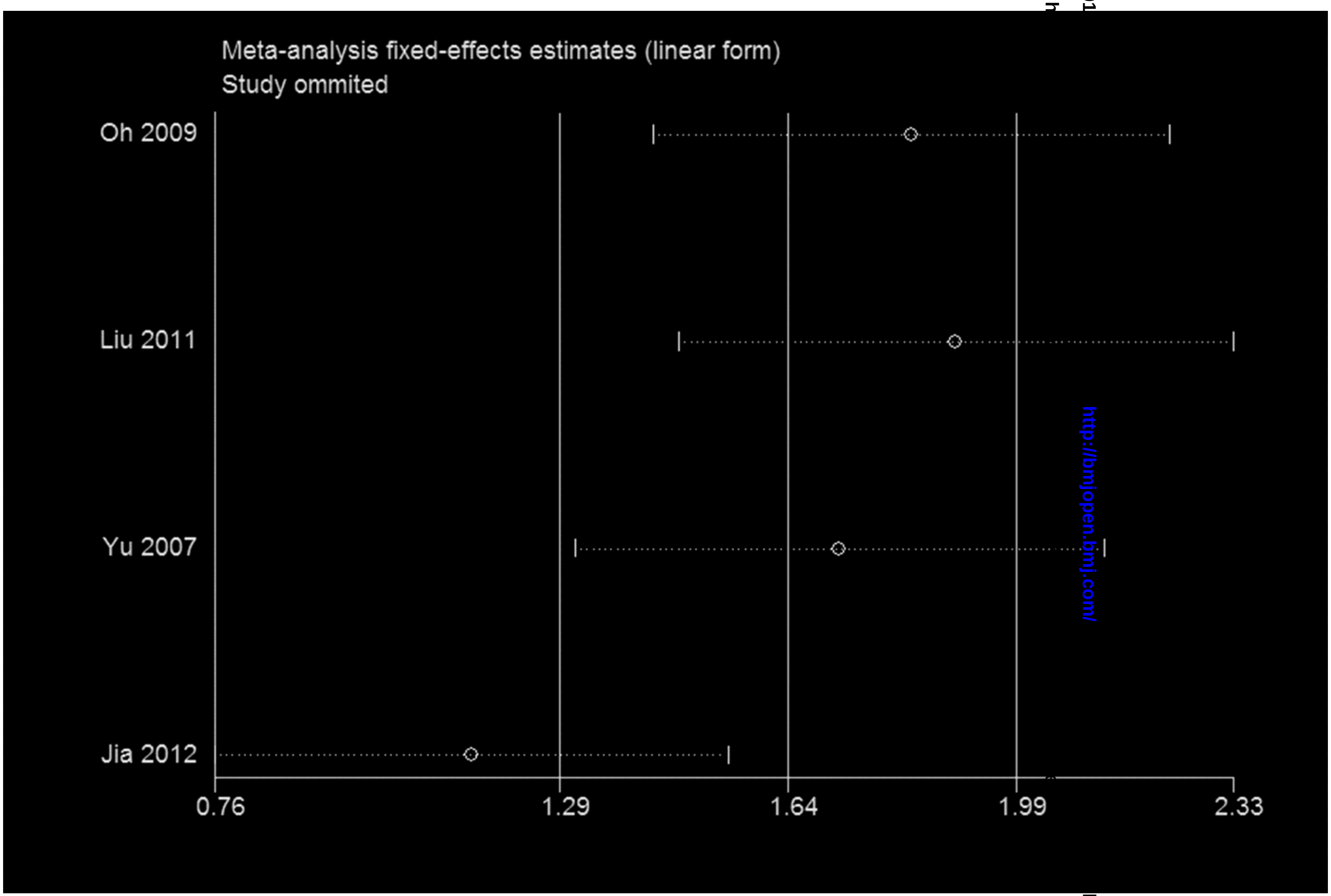
Meta-analysis fixed-effects estimates (linear form)
Study ommited
Oh 2009
Liu 2011
Yu 2007
Jia 2012
0.76
1.29
1.64
1.99
2.33

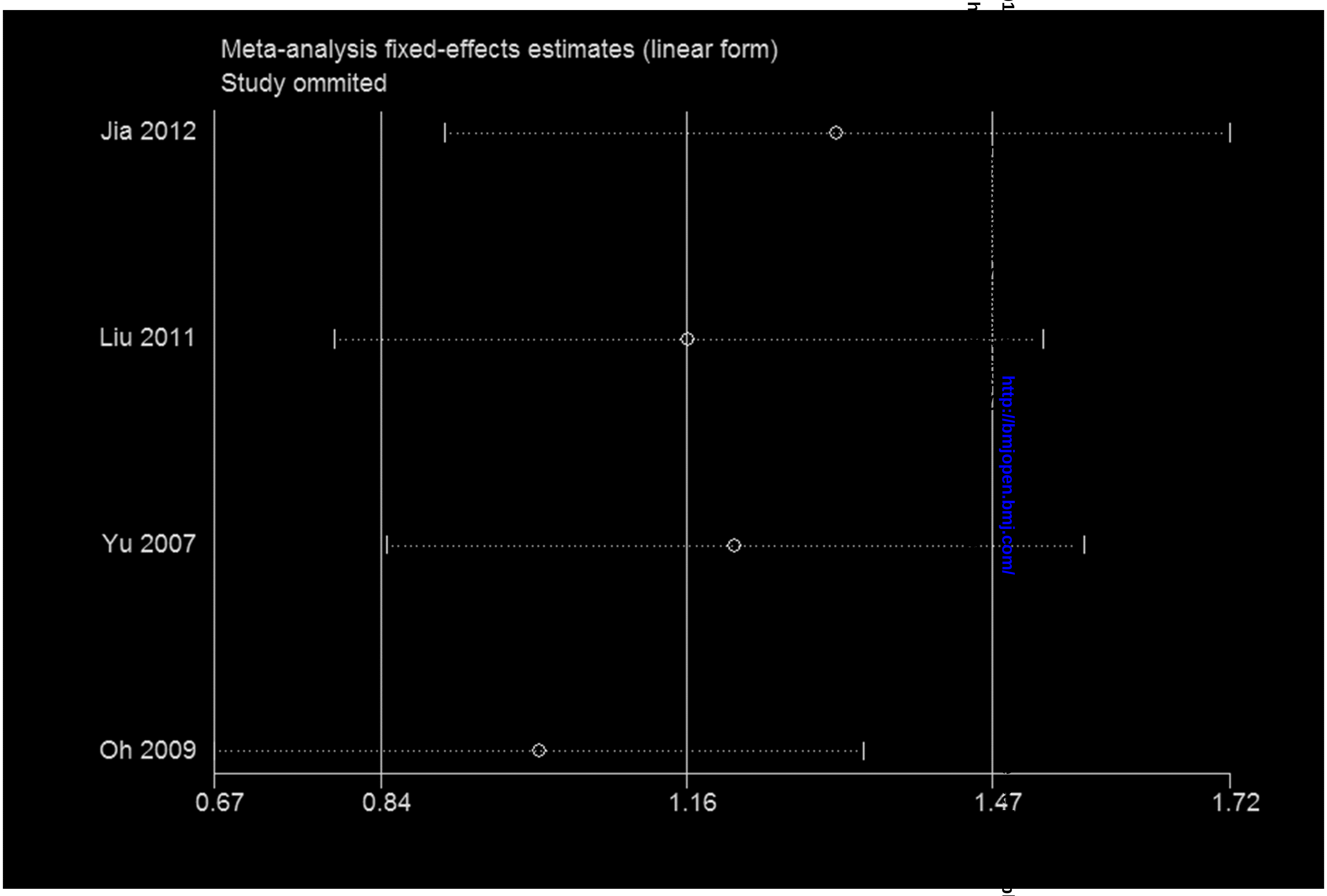
Meta-analysis fixed-effects estimates (linear form)
Study ommited
Jia 2012
Liu 2011
Yu 2007
Oh 2009
0.67
0.84
1.16
1.47
1.72

Table S1 Perioperative outcomes of included studies.

Study	Hospital stay(days)		Bleeding amounts(ml)		Operative time(min)	
	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
Oh 2009	16.82±7.7	15.14±8.5	777.8±644.3	306.43±151.1	210±6	140.71±44.5
Park 2010	NA		NA		NA	
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		NA		NA	
Yu 2012	NA		NA		NA	
Yu 2007	NA		306.75±74.63	207.5±65.86	110.4±18.16	91.8±19.43
Jia 2012	11.11±8.52	10.79±7.74	279.93±63.21	102.21±31.71	141.23±63.21	97.37±17.72
Liu 2011	12.2±2.7	11.2±2.6	263.0±130.4	148.3±71.3	190.9±61.4	139.9±12.7
Kim 2012	NA		NA		NA	

NA=not available, ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion.

Table S2 Clinical outcomes of included studies.

Study	Postoperative JOA at last visit		Postoperative neck VAS		Postoperative arm VAS	
	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
Oh 2009	14.72±1.7	15.25±1.5	3.63±2.3	2.93±2.5	2.63±2.7	2.79±2.3
Park 2010	NA		NA		NA	
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		0.9±3.1	1.3±3.2	1.4±3.2	2.4±2.7
Yu 2012	NA		NA		NA	
Yu 2007	NA		NA		NA	
Jia 2012	15.32±1.54	15.01±1.76	3.62±2.01	2.81±1.33	2.51±1.43	2.35±1.69
Liu 2011	14.1±1.4	13.6±1.2	NA		NA	
Kim 2012	NA		NA		NA	

NA= not available, JOA=Japanese Orthopedic Association scores, VAS= Visual Analog Scale scores. ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, * the study just reported the data at the sixth month of postoperative.

Table S3a Postoperative radiologic outcomes of included studies.

Study	sagittal alignment		C2-C7 Cobb		fusion Cobb	
	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
Oh 2009	NA		14.59±10.6	23.43±7.4	NA	
Park 2010	32L	30L	9.6±9.1	11.2±8.5	2.5±5.9	4.4±5.7
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		9.7±7.7	13.6±8.6	NA	
Yu 2012	36L	47L	NA		4.4±4.9	7.5±5.9
Yu 2007	NA		NA		NA	
Jia 2012	NA		20.26±10.26	22.08±9.78	NA	

Liu 2011	NA	NA		6.9±2.5	8.8±2.7
Kim 2012	NA	15.7±8.6	16.7±8.5	5.8/4.6	6.8/6.8

ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, NA= not available.

Table S3b Postoperative radiologic outcomes of included studies.

Study	total cervical ROM		fusion ROM		fused segment height	
	ACCF	ACDF	ACCF	ACDF	ACCF	ACDF
Oh 2009	30.23±15.1	28.13±13.4	5.12±4.8	3.88±3.4	49.9±5	56.0±7
Park 2010	NA		NA		NA	
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		NA		37.3±4.3	39.9±4.3
Yu 2012	NA		NA		NA	
Yu 2007	NA		NA		NA	
Jia 2012	27.98±12.94	29.19±10.33	3.39±3.01	4.01±2.93	53.11±1.90	55.55±1.84
Liu 2011	NA		NA		56.4±2.4	56.1±2.2
Kim 2012	33.5	26.8	NA		55.1±3.9	55.4±3.8

ACCF=anterior cervical corpectomy and fusion, ACDF=anterior cervical discectomy and fusion, NA=not available,ROM=range of motion.

Table S3c Postoperative radiologic outcomes of included studies.

Study	graft collapse		fusion rate		degeneration[a]	
	ACCF(An/Po/Cr/Ca)	ACDF(An/Po/Cr/Ca)	ACCF	ACDF	ACCF	ACDF
Oh 2009	NA		100%	100%	3	2
Park 2010	5.0±2.9/3.5±2.5/1.7±1.6/3.9±2.6	4.2±2.6/3.0±2.4/1.5±1.1/3.4±2.0	NA		NA	
Wang 2001	NA		NA		NA	
Burkhardt 2013	NA		94.7%	97.5%	2	3
Yu 2012	3.7±1.3/5.2±2.2/1.8±0.6/4.4±1.0	2.9±1.2/3.6±2.3/1.6±0.6/3.3±1.3	100%	100%	1	1
Yu 2007	NA		100%	100%	NA	
Jia 2012	NA		100%	100%	NA	
Liu 2011	NA		NA		NA	
Kim 2012	NA		100%	88.9%	NA	

a degeneration means degeneration of the adjacent-level to the fusion. An= anterior, Po= posterior, Cr= cranial, Ca= caudal, ACCF= anterior cervical corpectomy and fusion, ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, NA= not available.

Table S4 Complications including short term and long term.

Study	Complications	
	ACCF	ACDF
Oh 2009	3	0
Park 2010	NA	
Wang 2001	1	0
Burkhardt 2013	3	14
Yu 2012	3	1
Yu 2007	3	1
Jia 2012	3	2
Liu 2011	5	4
Kim 2012	3	10

ACCF= anterior cervical corpectomy and fusion, ACDF= anterior cervical discectomy and fusion, NA= not available.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	The section that contains each item e#
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page, Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Fig. 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 7

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page 7-8

Section/topic	#	Checklist item	The section that contains each item e#
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page 8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 8, Fig. 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page 8-9, Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page 9, Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Page 10-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Page 8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Page 8
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 14-16
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 16-18
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 18-19

PRISMA 2009 Checklist

FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 19

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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