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REVIEW ARTICLE

Clinical outcomes of locking stand-alone cage versus anterior plate construct in two-level anterior cervical discectomy and fusion: a systematic review and meta-analysis

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Abstract

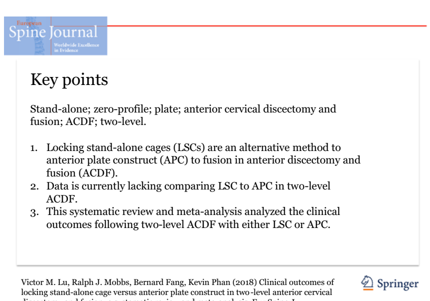
Background Two-level cervical degenerative disc disease (cDDD) can be effectively treated by anterior cervical discectomy and fusion (ACDF) similarly to single-level cDDD. Traditionally an anterior plate construct (APC) approach has been utilized, but ACDF without plate with a locking stand-alone cage (LSC) approach has emerged as an alternative option. The aim of this study was to compare the clinical outcome of LSC and APC in contiguous two-level ACDF used to treat cDDD the current literature.

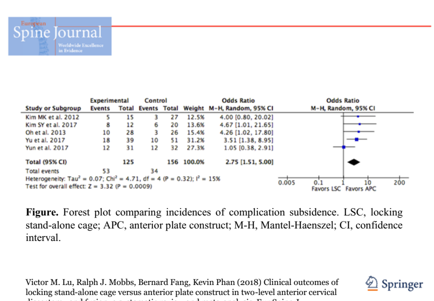
Methods Searches of seven electronic databases from inception to March 2018 were conducted following preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Extracted data were analysed using meta-analysis of proportions.

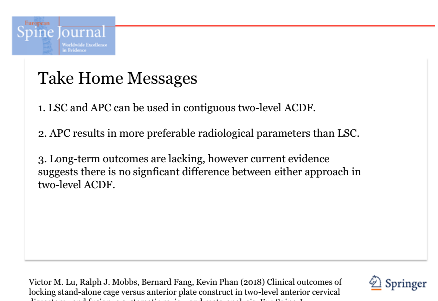
Results The nine observational studies that satisfied all criteria described a pooled cohort of 687 contiguous two-level cDDD cases managed by ACDF, with 302 (44%) and 385 (56%) managed by LSC and APC approaches, respectively. When compared with APC, LSC was associated with significantly increased subsidence likelihood (OR 2.75; $p < 0.001$), greater disc height (MD 0.60 mm; $p = 0.04$) and reduced cervical lordosis (MD $-2.52°$; $p = 0.04$) at last follow-up. Operative outcomes, fusion rates, functional scores and postoperative dysphagia rates were comparable.

Conclusion Although significant radiological differences were most evident, the comparability between LSC and APC in contiguous two-level ACDF with respect to all other clinical outcomes does not implicate one approach as clearly superior to the other in two-level ACDF. Larger, randomized studies with longer follow-up are required to delineate outcomes further to validate the findings of this study.

Graphical abstract These slides can be retrieved under Electronic Supplementary Material.







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Extended author information available on the last page of the article

Keywords Stand-alone · Zero-profile · Plate · Anterior cervical discectomy and fusion · Two-level

Introduction

Cervical degenerative disc disease (cDDD) presents commonly as radiculopathy and myelopathy [1]. This debilitating condition can be first managed conservatively. However, should this fail, anterior cervical discectomy and fusion (ACDF) is an established, effective surgical method for treatment [2]. After the discectomy component to remove the offending disc is performed, current options to facilitate intervertebral fusion include an interbody cage, e.g. polyetheretherketone (PEEK) cage, with or without anterior plate construct (APC) [3, 4]. When no plate construct is utilized, stabilization of the interbody cage is achieved by integrating screw systems that allow for locking stand-alone cage (LSC) [5].

The benefit of the APC approach is that there is significant immediate stabilization of the surgical site to prevent graft dislocation and subsidence prior to fusion [6]. However, hardware complications arise given the use of the additional structure during ACDF when compared with the LSC approach. These concerns include dysphagia, injury to surrounding tracheoesophageal structures and plate malposition/migration [7]. The LSC approach was developed to reduce the risk of these complications, while maintaining the benefits of interbody cage insertion in ACDF. Smaller surgical field and lower dissection volume when compared with APC are the premise by which LSC in ACDF may provide competitive clinical outcomes.

It has been noted that ACDF inherently involves complication risks; however, these may be augmented when involving more than one level [8]. Thus, although the LSC approach has been shown to provide non-inferior, if not competitive clinical outcomes, when compared with APC in the management of single-level cDDD by ACDF, this may not necessarily be the case in multiple levels [7, 9]. The aim of this study was to investigate whether differences in clinical outcomes existed between the LSC and APC approaches in the ADCF management of contiguous two-level cDDD by means of pooling all available evidence in the current literature.

Methods

Search strategy

The strategy was designed around the PICO question format—Do patients with two-level cDDD treated by ACDF (Population) with a LSC (Intervention) compared with those treated with an APC (Comparator) differ in clinical outcomes (Outcome)? The present review was conducted according to PRISMA guidelines and recommendations [10]. Electronic searches were performed using Ovid Embase, PubMed, SCOPUS, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), American College of Physicians (ACP) Journal Club and Database of Abstracts of Review of Effectiveness (DARE) from their dates of inception to March 2018. The literature involving all comparative studies was searched by using the following MeSH terms in all logical permutations: 'stand-alone', 'zero-profile', 'integrated', 'self-locking', 'anterior cervical discectomy and fusion', 'ACDF', 'degeneration' and 'degenerative disease'. The reference lists of all retrieved articles were reviewed independently by two investigators (V.M.L. and K.P.) for further identification of potentially relevant studies. All identified articles were then systematically assessed against inclusion and exclusion criteria.

Selection criteria

The inclusion criteria used to screen all identified articles were (1) reported clinical outcomes of contiguous two-level ACDF surgery (2) in separate cohorts involving both LSC and APC approaches in the (3) management of cDDD in (4) patients > 18 years. The exclusion criteria applied to all identified articles were cohorts that involved (1) mixed-/single-level cohorts and (2) non-contiguous ACDF. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up and when studies reported multiple time courses of the same treated cohort, only the most complete reports were included for quantitative assessment. All publications were limited to those involving human subjects and in the English language. Reviews, abstracts, case reports, conference presentations, editorials and expert opinions were excluded to minimize potential publication bias and duplication of results.

Data extraction and critical appraisal

All data were extracted from article texts, tables and figures with any estimates made based on the presented data and figures. This includes variance estimations based on established statistical methodologies when appropriate [11–13]. Clinical outcomes of interest were as follows: operative outcomes—operation time, estimated blood loss (EBL), length of stay (LOS); complication outcomes—postoperative dysphagia, subsidence; radiological outcomes—non-fusion, mean disc height, cervical lordosis, fused segment angle

(FSA) and fused segment height (FSH); and functional outcomes—visual analogue score (VAS) for arm pain, Japanese Orthopedic Association (JOA) score for impairment. Two investigators (V.M.L. and K.P.) independently reviewed each included article with any discrepancy resolved by discussion to reach consensus. All attempts were made to contact study authors for any clarification of data if needed. Because quality scoring is controversial in meta-analyses of observational studies, each article included in our analysis was appraised according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) criteria [14].

Meta-analysis

The mean difference (MD) and odds ratio (OR) were the summary statistics used. Each outcome was presented as a forest plot; the weighted MD or OR, the 95% confidence interval (CI) and the relative weightings were represented by the middle of the square, the horizontal line and the relative size of the square, respectively. The dotted line represents the pooled mean of the statistic. The I^2 statistic was used to estimate the percentage of total variation across studies, owing to heterogeneity rather than chance, with values greater than 50% considered as substantial heterogeneity [15]. The outcomes of the included studies were pooled together by meta-analysis of non-integer proportions using a random-effects (RE) model to take into account the possible clinical diversity and methodological variation between studies.

Publication bias was assessed through the generation of funnel plots for all outcomes and assessed for asymmetry. The final inclusion of any outlying study was reconsidered in the context of overall trend direction and significance upon their exclusion. All p values were two-sided with significance set at $p < 0.05$. Statistical analyses were conducted with Review Manager version 5.3.3 (Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search

The search strategy identified a total of 8024 studies (Fig. 1). Screening of all titles and abstracts by selection criteria after duplicate removal yielded 40 studies that underwent full-text analysis. Nine comparative studies [4, 5, 16–22] were included in this systematic review for quantitative analysis. The characteristics of these studies and particular clinical features are summarized in Tables 1 and 2, respectively.

Demographics and clinical features

In the pooled cohort of 687 contiguous two-level cDDD cases managed by ACDF, there were 302 (44%) and 385 (56%) managed by LSC and APC approaches, respectively, with 183 (61%) and 219 (57%) of them being male (Table 1). Mean ages for the LSC and APC cohorts ranged from 48–59 to 48–61 years, respectively. There was no statistically significant difference between the two cohorts with respect to these demographic features.

With respect to clinical features, indications for surgery were cervical radiculopathy and spondylotic myelopathy (Table 2). The most common contiguous cervical levels

Fig. 1 Flow diagram of search strategy results conducted per preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines

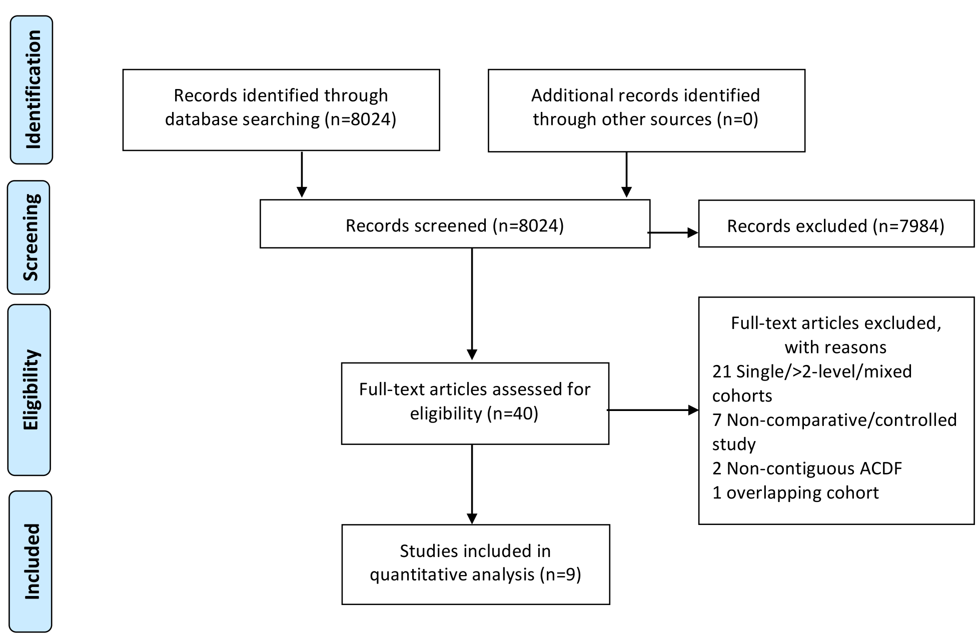

Table 1 Study characteristics and demographics

Study	Country	Study period	Design (no. surgeons)	Overall			LSC			ACP		
				Size (n)	Age (years)	Male (%)	Size (n)	Age (years)	Male (%)	Size (n)	Age (years)	Male (%)
Burkhardt et al. [4]	Switzerland	2004–2012	R, OS, 1 (NR)	144	60	68	31	58.8 ± 9.5	16	113	60.8 ± 10.6	52
Kim et al. [16]	Korea	2006–2010	R, OS, 1 (NR)	42	57	24	15	54 ± 12.2	9	27	58 ± 8.4	15
Kim et al. [17]	Korea	2012–2015	P, OS, 1 (NR)	32	56	24	12	60.7 ± 8.6	10	20	53.1 ± 12.5	14
Kwon et al. [18]	Korea	2013–2015	R, OS, 1 (3)	45	54	34	23	57.39 ± 11.84	17	22	50.73 ± 10.47	17
Oh et al. [19]	Korea	2007–2009	R, OS, 1 (NR)	54	56	33	28	58	13	26	54	20
Perrini et al. [20]	Italy	2013–2015	R, OS, 1 (NR)	78	52	42	56	51.07 ± 10.4	31	22	55.56 ± 7.76	11
Yang et al. [21]	China	2011–2014	R, OS, 1 (NR)	139	48	71	67	47.9 ± 8.84	36	72	48.03 ± 8.46	35
Yu et al. [22]	Korea	2008–2013	R, OS, 1 (4)	90	56	55	39	55.6 ± 10.9	29	51	55.7 ± 8.6	26
Yun et al. [5]	Korea	2006–2015	R, OS, 1 (NR)	63	54	51	31	53.29 ± 7.55	22	32	54.18 ± 9.87	29

LSC locking stand-alone cage, *ACP* anterior plate construct, *P* prospective, *R* retrospective, *OS* observational study, *NR* not recorded

Table 2 Description of clinical features of studies

Study	Indication(s)	LSC device	Levels fused (n)				Bone graft type		Follow-up (mo)	
			C3–5	C4–6	C5–7	C6–T1	LSC	APC	LSC	APC
Burkhardt et al. [4]	CR, CSM	PEEK	13	53	77	1	Autograft	Autograft	18.2 ± 13.3	18.2 ± 13.3
Kim et al. [16]	CR	Unspecified	5	18	40	–	Autograft	Autograft	23 ± 15.5	15 ± 6.8
Kim et al. [17]	CSM	PEEK	6	12	14	–	DBM	DBM	24	24
Kwon et al. [18]	CR, CSM	PEEK	5	16	24	–	Autograft	Autograft	6	6
Oh et al. [19]	CR, CSM	PEEK	5	24	25	–	Autograft, DBM	Autograft, DBM	23	21
Perrini et al. [20]	CR	PEEK	7	27	44	–	–	–	30.55 ± 13.07	33.55 ± 12.77
Yang et al. [21]	CSM	Zero-P	–	–	–	–	SBG	SBG	36	36
Yu et al. [22]	CR, CSM	PEEK	11	51	70	–	DBM	DBM	24	24
Yun et al. [5]	CR, CSM	Zero-P	1	15	47	–	DBM	Allograft, DBM	12.77 ± 7.85	13.62 ± 9.21
		Overall % of reported	9%	35%	56%	< 1%				

LSC locking stand-alone cage, *ACP* anterior plate construct, *CR* cervical radiculopathy, *CSM* cervical spondylotic myelopathy, *PEEK* polyetheretherketone, *DBM* demineralized bone matrix, *SBG* synthetic bone graft fused where reported was C5–7 (56%), followed by C4–6 (35%), C3–5 (9%) and one reported case [4] of C6–T1. The vast majority of LSC device utilized was the PEEK cage; however, two studies [5, 21] reported outcomes utilizing the Zero-P cage. Multiple bone graft types were used including autograft, demineralized bone matrix and synthetic bone graft.

Operative outcomes

LSC was not associated with significantly different operation duration (MD −6.88 min; $p=0.21$), EBL (MD 1.52 mL; $p=0.90$) or LOS (MD = −0.12 days; $p=0.39$), when compared with APC based on three, two and two studies, respectively (Supplementary).

Complication outcomes

LSC was associated with significantly greater likelihood of subsidence at follow-up (OR 2.75, 95% CI 1.51–5.00; $p<0.001$; $I^2=15\%$) when compared with APC based on five studies (Fig. 2a). Pooled incidences of subsidence in LSC and APC were 53/125 (42%) and 34/156 (22%), respectively.

LSC was not associated with significantly different likelihood of postoperative dysphagia (OR 0.58; $p=0.09$) when compared with APC based on three studies (Fig. 2b). Pooled incidences of postoperative dysphagia in LSC and APC were 27/154 (18%) and 38/126 (30%), respectively.

Radiological outcomes

The radiological criteria used by each study to determine fusion status, cervical lordosis and subsidence are provided in Supplementary. LSC was associated with significantly greater disc height (MD 0.60 mm; 95% CI 0.03–1.16 mm; $p=0.04$; $I^2=45\%$) and significantly reduced cervical lordosis (MD −2.52°; 95% CI −4.93° to −0.10°; $p=0.04$; $I^2=56\%$), when compared with APC based on two and eight studies, respectively (Fig. 3a, b, respectively).

LSC was not associated with significantly different likelihood of non-fusion (OR 1.32; $p=0.45$), FSA (MD −2.00°; $p=0.12$) and FSH (MD −0.61 mm; $p=0.49$) when compared with APC based on six, seven and six studies, respectively (Supplementary). Pooled incidences of non-fusion in LSC and APC were 20/192 (10%) and 18/228 (8%), respectively.

Functional outcomes

LSC was not associated with significantly different assessment scores by VAS of the arm (MD −0.59; $p=0.14$) or JOA (MD −0.05; $p=0.77$) when compared with APC based on three and two studies, respectively (Supplementary).

Study quality and bias assessment

Assessment with the MOOSE criteria of each included study did not indicate obvious bias risk (Table 3). No significant

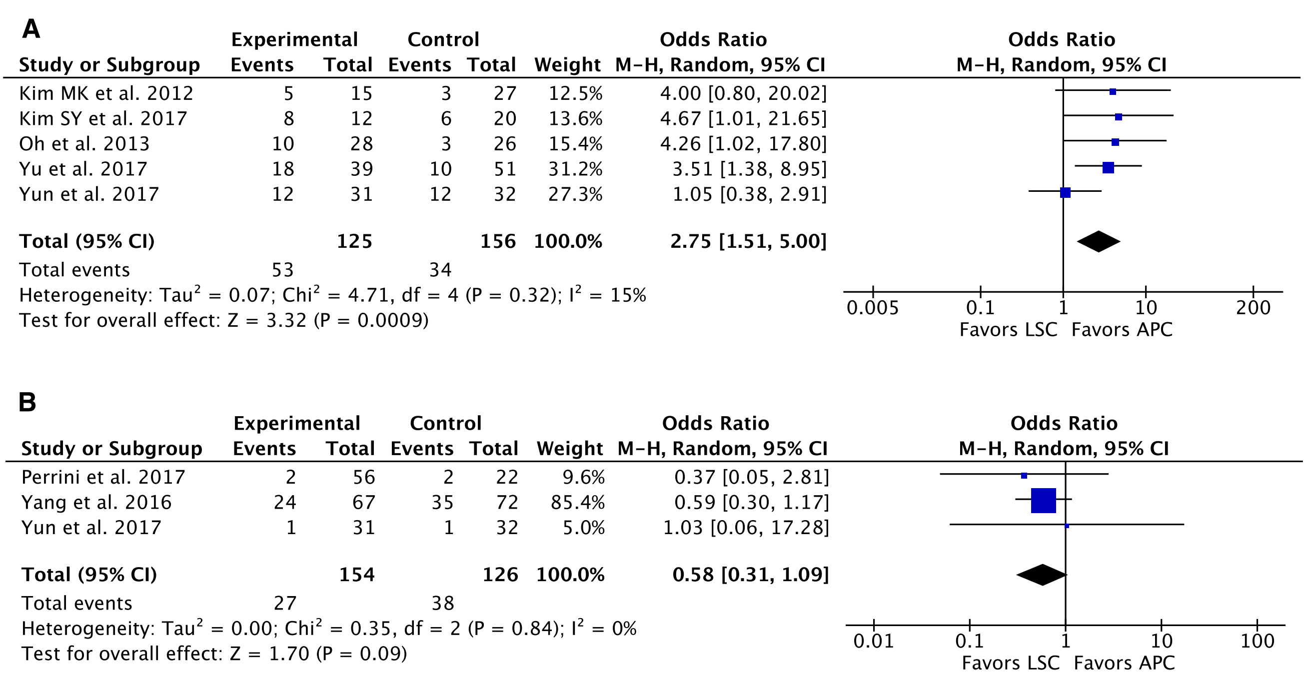

Fig. 2 Forest plot comparing incidences of complications; **a** subsidence and **b** postoperative dysphagia. *LSC* locking stand-alone cage, *APC* anterior plate construct, *M–H* Mantel–Haenszel, *CI* confidence interval

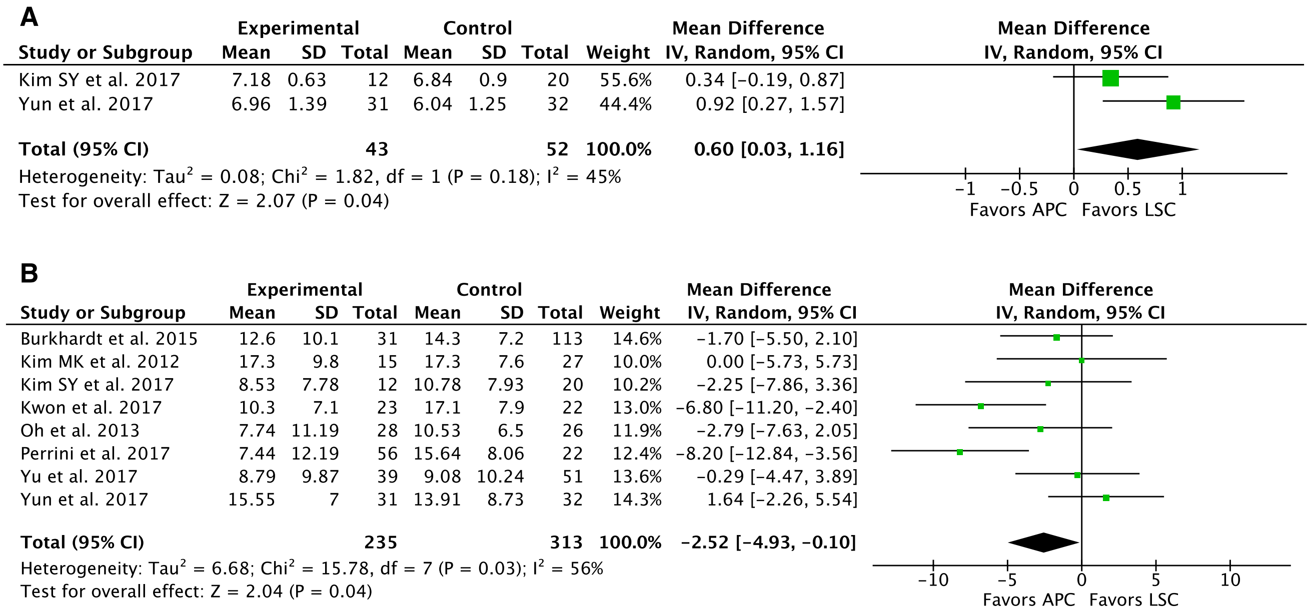

Fig. 3 Forest plots comparing radiological outcomes; **a** disc height and **b** cervical lordosis. *LSC* locking stand-alone cage, *APC* anterior plate construct, *CI* confidence interval, *IV* inverse variance, *SD* standard deviation

Table 3 Results of MOOSE assessment for quality of evidence for all included studies

Study	Burkhardt et al. [4]	Kim et al. [16]	Kim et al. [17]	Kwon et al. [18]	Oh et al. [19]	Perrini et al. [20]	Yang et al. [21]	Yu et al. [22]	Yun et al. [5]
Clear definition of study population?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Clear definition of outcomes and outcome assessment?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Independent assessment of outcome parameters?	U	U	U	U	Y	Y	U	Y	U
Sufficient duration of follow-up?	Y	Y	Y	U	Y	Y	Y	Y	Y
No selective loss during follow-up?	Y	Y	Y	Y	Y	Y	Y	Y	Y
Important confounders and prognostic factors identified?	Y	Y	Y	Y	Y	Y	Y	Y	Y

Y yes, *U* unclear

asymmetry observed in generated funnel plots indicated absence of publication bias with respect to the overall trends and significances of each outcome upon leave-one-out analysis.

Discussion

This systematic review and meta-analysis compared the use of LSC versus APC in the surgical management of cDDD with contiguous two-level ACDF. It demonstrated that when compared with APC, LSC was associated with significantly greater disc height, higher likelihood of subsidence and reduced cervical lordosis at follow-up. With respect to operative outcomes, postoperative dysphagia, fusion, FSA and FSH and performance outcomes, LSC was comparable and non-inferior to that of APC. Overall, the differences between the LSC and APC approach in ACDF management of cDDD with contiguous two-level ACDF based on the current literature do not clearly indicate either approach as superior to the other. These differences require longer-term surveillance to establish if such a superiority does indeed exist.

Burkhardt et al. [4] report the largest single-study cohort to study LSC, with PEEK cage, versus APC in 144 two-level ACDF surgeries, in which they found that APC conferred a significantly greater result with respect to preservation of cervical lordosis, with other clinical outcomes comparable between the two approaches. Their findings align with the overall pooled findings of this meta-analysis. They concluded that there was no clear superiority of either approach. Recently, Yun et al. [5] reported the outcome of 63 two-level ACDF cases, of which 31 (59%) were performed using the novel LSC zero profile device. They did not observe statistical differences between approaches in terms of final cervical lordosis or FSA, but did note that the change in FSA and after surgery was greater following the LSC approach. Nonetheless, their conclusions echoed similar sentiments to the previous study with regard to no clear superiority between approaches.

One of the primary premises in ACDF in the management of cDDD is preservation of cervical lordosis. This study found APC to offer significantly superior control which is in agreement with the trends of large individual studies [4, 22]. The greater preservation of lordosis with plate construction is possibly associable with earlier stabilization of the operated segments [23]. Yet, given the practical difference in LSC and APC, it is not surprising that such differences in particular clinical outcomes have, and have not, been demonstrated. We suspect in the future, the lordosis and other alignment metrics will grow in clinical relevance, as emerging evidence suggests that pre- and postoperative metrics can influence surgical outcomes of cervical fusion operations such as ASD incidence, which could confound future comparisons between LSC and APC if differences were established to exist [24, 25]. However, it must be acknowledged that currently, there is no one standardized measure technique for lordosis interpretation used in the included studies (Supplementary), and as such weakens the statistical strength of our current finding [26]. Efforts to report transparent and consistent techniques in the future are strongly encouraged, with relatively novel techniques such as interspinous motion analysis providing more options to be considered to improve validity [27].

With respect to functional outcomes such VAS (arm) and JOA scores, no significant difference was found in this study. Kim et al. [17] remain the only reporters of neck disability index (NDI) in this comparison and found non-inferior outcomes with LSC versus APC. Given patient-centric outcomes remain a large influencer of the decision paradigm, this is a welcome finding when the differences in cervical lordosis and subsidence likelihood are considered. Conceptually, one would expect the absence of intraoperative fixation planning involved with APC to result in shorter operative time as well. This was found to be significantly different by Yun et al. [5], and pooled data in the literature currently imply that this trend will likely attain significance with greater cohort sizes in the future.

A theoretical advantage in the design of LSC is the reduction in interference with anterior soft tissues and organs of the implant, a key concern being irritation of the oesophagus leading to dysphagia [28]. It is thus interesting to note that this study did not detect a significant difference in likelihood of postoperative dysphagia between approaches, despite it being the case in single-level ACDF [7]. This suggests that the volume of plate construct in APC may not be the sole determinant of postoperative dysphagia in two-level ACDF patients, with its increased surgical field compared with one-level ACDF [5]. Indeed, many other intraoperative factors that augment the risk of dysphagia after surgery are increased with greater surgical field, including use of oesophageal retraction, incidental nerve damage and adjacent tissue swelling [9]. The study by Yang et al. [21] remains the only comparative study to report long-term dysphagia results in two-level ACDF, in which they found LSC resulted in significantly lower rates of dysphagia when compared with APC 3 years after index surgery, with incidences of 3/60 (5%) and 9/63 (14%), respectively. The consequence of this is that significant merit may still exist in reduction in dysphagia using the LSC approach in two-level ACDF; however, it may not be immediate and requires longer-term follow-up to be validated.

ACDF surgery is applicable to single- and multi-level ACDF. However, it has been noted that increasing the number of levels fused at the time of index surgery correlates with increased rate of reoperations [29]. It appears reasonable that single-level and multi-level fusions should be considered separately in terms of success, and this appears to be the case with respect to LSC versus APC as well. Basques et al. [30] reported that in multi-level ACDF with APC alone, that lordosis metrics pre- and postoperative differed with single-level ACDF, and incidences of complications were comparable. In their meta-analysis of single-level ACDF, Nambiar et al. [7] demonstrated significant trends of shorter operating time and lower postoperative dysphagia rates with LSC compared with APC, as well as no difference with respect to cervical lordosis. Although it is difficult to interpret given the limited data currently available, these results indicate LSC may confer a different magnitude of effect with respect to various clinical outcomes in two- versus single-level ACDF. This would reason to be so from a biomechanics perspective, as two-level ACDF with LSC involves the creation of a vertebral segment isolated between adjacent interbodies, which does not occur in single-level ACDF. This also applies to the APC approach as well, for it has been shown that segmental stability decreases with the number of instrumented segments with plate construction as well [31]. Additionally, given APC provides greater stabilization capacity than LSC, this could allude to the increased incidence of subsidence in the LSC group as found in this meta-analysis [32].

Strengths and limitations

This meta-analysis adhered strictly to its selection criteria and the PRISMA guidelines. Although studies of cDDD managed by two-level ACDF comparing LSC versus APC are uncommon, we only incorporated this only type of study to reduce intra-study variability and enhance the validity of the findings. Furthermore, only two-level ACDF was involved in this study to reduce the expected biomechanical bias of single- or multi-level groups, as well as non-contiguous cases [31]. Admittedly the clinical heterogeneity inherent in ACDF surgery is difficult to neutralize completely; however, the use of RE model in meta-analyses when indicated by the I^2 statistic was used to reduce this statistical interference, augmenting the confidence in our results. Nonetheless, better accounting for cervical location, radiographic measure techniques and materials used for the operation will improve future studies.

There are many limitations to this study that need recognition. Firstly, there is a small cohort currently published in the literature. This may be a consequence of the naturally smaller incidence of two-level surgery when compared with single-level surgery. As a consequence, it is likely some outcomes in the present study are underpowered. Particular examples such as operative duration and postoperative dysphagia may attain significance in favour of LSC as more data become available. Also, greater numbers will allow for the stratification of results based on LSC type. Secondly, there is a desperate need of a randomized controlled trial investigating this topic as none such exist currently. All included studies were observational and primarily retrospective in nature, which reduces our ability to account for the diverse clinical heterogeneity inherent in ACDF surgery, as well as the selection bias between LSC and APC groups.

Thirdly, the distinct lack of long-term follow-up limits our ability to formulate robust conclusions about the comparability of these two approaches. If indeed the long-term dysphagia advantage with LSC found by Yang et al. [21] can be confirmed by other studies, then LSC could appear superior if all other clinical outcomes remain comparable with respect to functional outcomes. Measures of dysphagia remained inconsistently reported between studies, and an independent, established method to assess and report this outcome would benefit the validity of future analyses, such as the Bazaz grading system [33]. Finally, although subsidence rate following two-level ACDF is well reported, explicit data regarding other longer-term potential complications will also assist in evaluating LSC versus APC, which is severely lacking in the current literature. This is because there is some evidence to suggest the phenomenon of subsidence is radiographic in significance only, without serious clinical manifestation in multi-level ACDF [34]. Other complications, such as adjacent segment disease (ASD), adjacent level ossification disease (ALOD) and pseudoarthrosis incidences, may require future revision surgery, which would be a significant factor in the decision algorithm of both clinicians and patients when deciding between the two options. Anecdotally however, ASD itself may not be a significant concern, as the one study to report this outcome to date by Oh et al. [19] reported incidences of 1/28 (4%) and 0/26 with LSC and APC use, respectively.

Conclusion

In the management of two-level cDDD, ACDF can be performed with either LSC or APC. This systematic review and meta-analysis investigated the differences in clinical outcomes using these two approaches. We found that differences do exist that are not completely similar to that of one-level ACDF. The primary differences were LSC resulting in higher incidence of subsidence and lesser cervical lordosis when compared with APC in two-level ACDF. However, decreased postoperative dysphagia trended in favour of LSC, and with respect to operative and functional outcomes, these two approaches remained comparable. Thus, there is no clear overall superiority of one approach over the other, yet. Given that there is a relative paucity of literature currently available, larger, randomized, longer-term studies are needed to validate these findings to assist in determining whether such a superiority does exist in two-level ACDF.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interests.

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