ADJACENT SEGMENT DEGENERATION AFTER ANTERIOR CERVICAL DISCECTOMY AND FUSION , ASYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: *Anterior cervical discectomy and fusion (ACDF), is commonly used for treatment of degenerative cervical spondylotic radiculopathy and myelopathy, and satisfactory out-comes have been reported in many studies. However, subsequent disc degeneration at levels adjacent to the fusion remains an important problem.*

Aim of the Work: *To perform a systematic review and meta-analysis to evaluate incidence, risk factors, and impact of radiographic and clinical postoperative adjacent segment degeneration (ASD) following anterior decompression and instrumented fusion.*

Method: *Medline databases (PubMed, Medscape, Science Direct. EMF-Portal) and all materials available in the Internet till 2020.*

Data Extraction: *If the studies did not fulfill the inclusion criteria, they were excluded. Study quality assessment included whether ethical approval was gained, eligibility criteria specified, appropriate controls, and adequate information and defined assessment measures.*

Conclusion: *If the former is true, index ACDF procedures may be adjusted to include additional levels now identified as higher risk. If the latter is true, motion preserving treatments such as CDR may gain more traction. This review illuminates the heterogeneous methodology of the literature on ASDeg and ASDz after ACDF and the paucity of high-quality data published on these phenomena. Standardized methodology for radiographic evaluation of ASDeg and clinical outcome measures for ASDz are critical before the fundamental question on their etiology can be resolved.*

Keywords: *Adjacent* segment degeneration, anterior cervical discectomy and fusion

INTRODUCTION:

Anterior cervical discectomy and fusion (ACDF), is commonly used for treatment of degenerative cervical spondylotic radiculopathy and myelopathy, and satisfactory out-comes have been reported in many studies. However, subsequent disc degeneration at levels adjacent to the fusion remains an important problem.

The reported risk factors related to the development of adjacent segment degenerate-ion are the number of fusion segments, the fusion level, age of the patient, combined underlying conditions, and previous degeneration.

Cervical radiculopathy and myelopathy can be severely debilitating to patients, causing numbness, pain, and weakness. First described by Robinson and Smith [1] and Cloward [2], anterior cervical discectomy and interbody fusion (ACDF) is currently the gold standard surgical treatment for affected patients who fail nonoperative measures [3,4].

Follow-up studies of ACDF have demonstrated that breakdown may occur at the level cranial or caudal to the fused motion segment(s) [5]. The adjacent segment degeneration (ASDeg) is defined as radiographic degenerative findings viewed on X-ray, computed tomography, or magnetic resonance imaging (MRI) at the adjacent motion segment, and adjacent segment disease (ASDz) is defined as clinical symptoms presumed to be related to the degenerative changes, have remained the subject of some debate[5–8]. The radiographic and clinical methods for detecting or classifying ASDeg and ASDz have been broad and inconsistent.

To date, no standard radiographic modality has been established to assess ASDeg and clinical end points for ASDz vary from validated outcome measures to reoperation rate.

Publications on ACDF out comes have reflected this heterogeneity of technique and analysis, likely contributing to the discrepancy in values reported for both ASDeg and ASDz. A broad range of published values for the incidence of ASDeg has been reported from 18.33% to 96% [6] with an equal variation in reported incidence of ASDz where values range from 0.8% [7] to 42.9% [9]

AIM OF THE STUDY:

The objective of this study is to perform a systematic review and meta-analysis to evaluate incidence, risk factors, and impact of radiographic and clinical postoperative adjacent segment degeneration (ASD) following anterior decompression and instrumented fusion.

MATERIAL AND METHODS:

The current study is a systematic review in which the following will be conducted:

Types of studies: All available studies meeting the eligible criteria including: well conducted descriptive studies and cases series, cohort, articles, accepted manuscripts, clinical trials, analytic studies and literature of reviews. Excluding other systematic reviews, technical notes, letters, comments and studies not written in English language.

Types of participants: This is a systematic review including a discussion of all available studies done on adjacent segment degeneration.

Types of interventions: Anterior cervical discectomy and fusion (ACDF)

Types of outcome measures: Visual analogue scale (VAS). Clinical radiculopathy or myelopathy. Radiological measures. Neck Disability Index (NDI).

Search strategy for identification of studies: The following electronic databases were searched up to 2019: PubMed, Google Scholar search engine, Cochrane database of systematic reviews, EMBASE and Science Direct, using the key words "Adjacent segment degeneration, Anterior cervical discectomy and fusion".

Methods of the review:

Locating and selecting studies: Abstracts of articles identified using the above search strategy were viewed, and articles that appear to fulfill the inclusion criteria were retrieved in full, when there was a doubt, a second viewer assessed the article and consensus was reached.

Data extraction: Data was independently extracted by two reviewers and cross-checked.

Statistical considerations: Outcomes from included trials were combined using the systematic review manager software and manually screened for eligibility to be included. To facilitate the assessment of possible risk of bias for each study, information was collected using the (Cochrane collaboration tool for assessing risk of bias).

Evidence of publication bias: This was done using the funnel plot method: A funnel plot method is a simple scatter plot of the intervention effect estimates from individual studies against some measure of each study's size or precision.

	Literature search database PUB MED, Cochrane Library and MEDLINE (n=500)			
1st screening: Titles& abstracts				Excluded - Language other than English. - Before2000. - Duplicates. - Non clinical outcome studies (n=290)
	Included (n=210)			
2nd screening: Full text review				Excluded - Case reports & Reviews. - Studies not describing Functional outcome. - Inaccessible articles. (n=200)
	Included (n=10)			

Graph (1): PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) flow diagram for study selection.

Table (1): Demographic data.

Study	Levels	Study type	Number of patients(M/F)	Age, Avarege	Radiographic modality	Follow up, months:
Komura et al [9] 2012	One level 7 Two levels 21 Three levels 24 Four levels 45 Five levels 5	Retrospective	102	52.8	X-ray, MRI, CT scan	58.9
Song et al [8] 2011	One level	Retrospective	87 (54/33)	54.4 (38-67)	X-ray, CT	84.8 (62-121)
Marotta et al.[10] 2011	One level	Retrospective	167 (85/82)	56	X-ray, CT	77 (54-90)
Matsumoto et al [11] 2010	One or two levels	Retrospective	64 (48/16)	47.3 (19-67)	MRI	145.2
Burkus et al. 2010[12]		Prospective	265 (144 investigational, 121 control pts)	43	X-ray, MRI, CT scan	60
Maldonado et al. 2011[13]		Prospective	190	47	X-ray, MRI	36
Garrido et al.[14] 2011		Prospectivel	ACDF 25 TDR 21	N/A	X-ray, MRI	48 24
. Burkhardt [15] 2016		Retrospective	59 (36, 23	70 (51-79 yr)	X-ray, MRI	324
Jawahar et al. 2010 [16]		Prospectivel	TDR 113 ACDF 57	44.5	X-ray, MRI	38
Shin 2019 [17]	One level:78 pts Two level:49 pts Three level: 38 pts	Retrospective	165	54	X-ray, MRI	32

RESULTS:

Table (2): Demographic data.

Study	Method of fixation	Graft material		ASDeg % of patients	ASDz (% of patients)
Study	Method of fixation	Graft material	Clinical outcome measure	ASDeg % of patients	ASDz % of patients
Komura et al. [9] One level	ACDF	Cancellous bone graft (PEEK cage)	clinical radiculopathy or myelopathy	One level 71.34 Two levels 38.10 Three levels 37.50 Four levels 26.67 Five levels 20.00	One level 42.86 Two levels 23.81 Three levels 12.50 Five levels 20.00
Song et al. [8]	ACDF	Cancellous bone graft (PEEK)	clinical radiculopathy or myelopathy	16.09	2.30
Marotta et al. [10]	ACDF	carbon fiber cage	clinical radiculopathy or myelopathy VAS,NDI	20.00	10.83
Matsumoto et al.[11]	ACDF	NA	clinical radiculopathy or myelopathy	30.84	4.41
Burkus et al. [12]	ACDF (control pts) vs TDR (investigational pts)		radiculopathy or myelopathy VAS, NDI	N/A	13
Maldonado et al. [13]	ACDF versus TDR		Radiculopathy, Myelopathy VAS, NDI	10.5 ACDF 8.8 TDR	N/A
Garrido et al.[14]	ACDF vs TDR		clinical radiculopathy or myelopathy	64 ACDF 25 TDR	N/A
Jawahar et al.[16]	ACDF versus TDR		radiculopathy or myelopathy VAS, NDI	14 ACDF 16.8 TDR	14 ACDF 16.8 TDR
Burkhardt et al. [15]	ACDF	Autogeneous iliac crest graft	clinical radiculopathy or myelopathy	20	17
Shin et al. [17]	ACDF	Cervical cage (PEEK cage) or autologous iliac bone graft	radiculopathy or myelopathy VAS, NDI	One level 15.38 Two levels 28.75 Three levels 39.47	

Functional Results:

PEEK cage cancellous graft was mentioned in three papers, while the carbon fiber cage was only mentioned by one paper.

Regarding the outcome measures, five papers used clinical radiculopathy or myelopathy and radiographic modality while other five papers used VAS (Visual Analog Scale), NDI (Neck Disability Index) and clinical radiculopathy or myelopathy.

Table (3): Visual analogue scale (VAS).

Study	ACDF	TDR
Jawahar [16]	Preoperative 7.6 Postoperative 6.1	Preoperative 8 Postoperative 6.1
Maldonado [13]	Pre. 7.9 Post. 2.9	pre. 7.9 post. 3.2
Burkus [12]	Pre. 6.9 Post. 5.2	Pre. 6.8 Post. 5.6
Marotta [10]	Pre. 8.3 Post. 3.5	
Shin [17]	One level Pre. 5.4 Post. 1.7 Two level Pre. 5.3 Post. 1.7 Three level Pre. 4.9 Post. 2.3	

Table (4): Neck Disability Index (NDI).

Study	ACDF	TDR
Jawahar [16]	Pre. 60 Post. 43	Pre. 61 Post. 44.9
Maldonado [13]	Pre. 41.4 Post. 18.1	Pre. 42.8 Post. 18.4
Burkus [12]	Pre. 56.4 Post. 34.1	Pre. 55.7 Post. 38.4
Marotta [10]	Pre. 23.5 Post. 11	
Shin [17]	One level Pre. 19.3 Post. 7.1 Two level Pre. 20.4 Post. 8.3 Three level Pre. 20.5 Post. 9.1	

Radiological evaluation:

Regarding radiological analysis, **Jun jae Shin et al, Burkus et al.** and **Maldonado et al**. used cobb's angle (the angle between superior end plate of superior vertebra to inferior end plate of inferior vertebra) determining sagittal plane angulation while Maldonado stated that the radiological evidence of adjacent disc disease was determined by anterior osteophyte formation or narrowing of a disc space (>30%) or calcification of the anterior longitudinal ligament and the formation of radial osteophytes.

As for **Benedikt W. Burkhardt et al.,** mentioned that radiographs are limited in their ability to assess the degeneration of the disc itself. MRI is frequently used in diagnosis, and it is the most sensitive technique in order to evaluate degeneration of the disc.

Regarding Song et al. radiological degenerative changes evaluated by Hilibrand's classification grade 1 narrowing of disc space of <50%, grade 2 narrowing of disc space from 50 to 75 % or grade 3 n0arrowing of disc space by > 75%.

Song et al. and **Garrido et al.** evaluated the radiological degenerative changes by using Park's classification which is grade 1 anterior ossification < 50% of the disc space, grade 2 ossification > 50% of disc space and grade 3 complete bridging of the adjacent disc space.

Regarding **Komura et al.** the evaluation of ADD was carried out using the criteria of Hilibrand et al. in addition to Panjabi classification, grade 1 segmental instability more than 3.5 mm horizontal displacement of 1 vertebra in relation to an adjacent vertebra, grade 2 rotational instability greater than 11 degree rotational difference to that of either adjacent vertebra.

Table (5): Complications.

Study	Post operative complication
Burkus et al. 2010 (12)	• Dysphonia, Dysphagia • Adjacent segment osteophyte formation. • Revision surgery (1.9% in controlled group) • Implant removal (7.5%)
Komura et al. 2012 (9)	• Pseudoarthrosis • ASDeg: 13 cases in long level group, 22 cases in short levels • C5 palsy and dysphasia • Postoperative kyphosis
Marotta et al.(10)	• Non fusion rate 13% • Less satisfactory results in patients over 61 years old. • Hematoma at wound site
Burkhardt 2016 (15)	• 12 pts revision surgery
Shin et al. 2019 (17)	• 25% ASDeg • Increased cervical lordosis • 6 pts revision surgery • 5.6 % New radiculopathy or myelopathy
Song et al. 2011 (8)	• 4 patients developed myelopathic symptoms

Regarding complications, as for **Barkus (12)**, 5 revision surgeries occurred. One revision surgery was at the index level alone; 4 revision surgeries included the index level and an adjacent level. Barkus mentioned that patients who underwent removal of the implant (prestige disc) and interbody fusion because of persistant radicular pain was 2.5% in investigational group (TDR group) and 5% in control group (ACDF group). Dysphonia and dysphagia is estimated to be 50% at 1 month after surgery and 21% at 12 months.

As for **Komura (19)**, he stated that the incidence of pseudoarthrosis was lower for 3 or fewer disc levels when compared to those with 4 or more-disc levels. Moreover, it was obvious that ADDeg occurs less frequently among patients in whom

C5-6 and C6-7 are fused than among those in whom C5-6 or C6-7 is left at an adjacent level, irrespective of the length of the fusion. In the long level group (4 or more segments), there were 13 cases of ADDeg (26.0%), including 1 case of symptomatic ADD (2.0%), whereas in the short level group (3 or less segments), there were 22 cases of ADDeg (42.3%), including 11 cases of symptomatic ADD (21.2%).

Marotta (10) mentioned that in his study, the non-fusion rate was 13%. 20% of patients with ASDeg did not show clinical evidence and while 10% required a second operation. Patients over 61 had a less satisfactory outcome, probably attributable to ongoing pathophysiological degeneration of the cervical spine.

Jawahar et al. [(16)], mentioned that 14% of patients who had ACDF developed ASD, with taking into consideration smoking habits, initial number of diseased levels and concurrent adjacent segment degeneration, with the last being a significant risk factor for developing adjacent segment disease.

Benedict W. Burkhardt [(15)] mentioned twelve patients underwent repeat surgery for degenerative changes. One patient had a third procedure 3 yr. after repeat procedure and 11 yr after initial ACDF. Ten among those 12 repeat procedures were caused by sASD, and the main cause of other two pts was`nt mentioned.

Regarding **Jun Jae Shin** [(17)]**,** the increase of lordotic angle was greater for the 2-level ACDF group than for the 1-level or 3-level ACDF groups. Overall, 41 patients had radiological ASDeg after anterior cervical fusion at final follow-up. 12 of 78 patients (15.38%) underwent 1-level fusion, 14 of 49 patients (28.57%) underwent 2-level fusion, and 15 of 38 patients (39.47%) underwent 3-level fusion (p=0.015). Patients who underwent multilevel fusions demonstrated greater reduction of global ROM and increased compensatory motion at the upper adjacent segment. Patients with greater numbers of fused levels more frequently developed radiological ASD.

As for **Song et al.** [(8)], 4 patients had post-surgical myelopathic symptoms after follow up period (2-6 years). Two of these patients responded to conservative treatment, while the other 2 patients had secondary surgeries to relieve the neurological symptoms that happened. The author stated that fusion may increase mechanical stress at adjacent disc levels, accelerate degenerative changes and eventually lead to adjacent segment disease.

Statistical methods

Statistical analysis was done using the jamovi project (2020); *jamovi* (Version 1.2) [Computer Software]; Retrieved from https://www.jamovi.org.

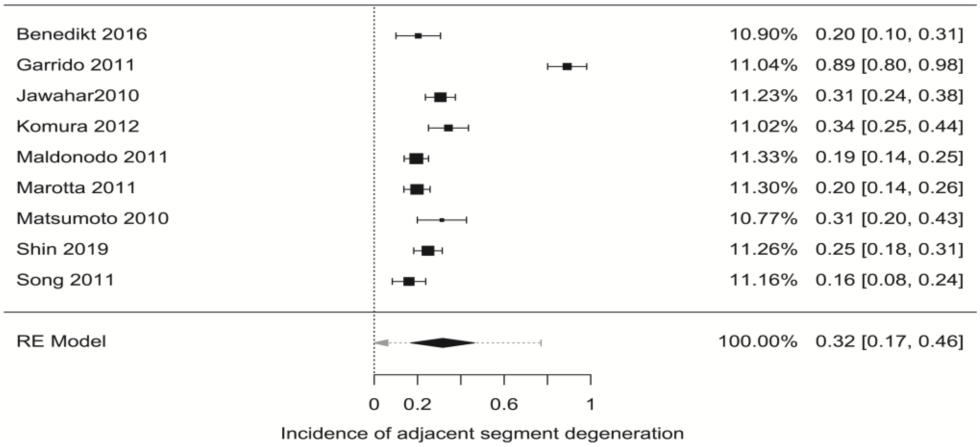
Assessment of publication bias

Publication bias was assessed by

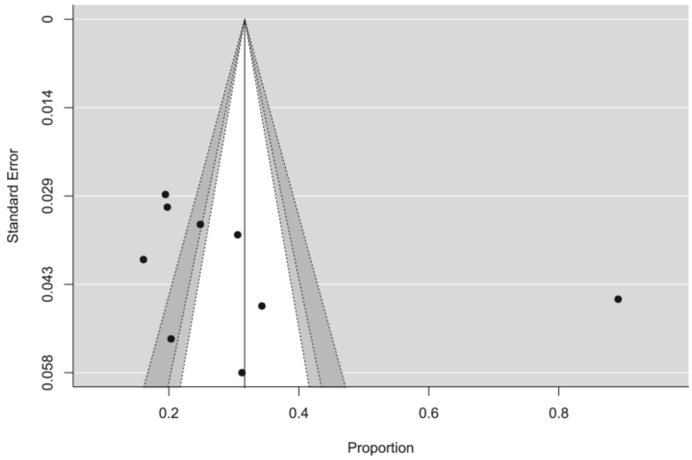
- Examination of funnel plots of the estimated effect size on the horizontal axis versus a measure of study size (standard error for the effect size) on the vertical axis.
- Examination of precision plots of the estimated effect size on the horizontal axis versus a measure of precision (1/standard error for the effect size) on the vertical axis.
- Rosenthal fail-safe number.
- Begg-Mazumdar rank correlation test for funnel plot asymmetry.
- Egger’s regression test for funnel plot asymmetry.

Pooling of estimates

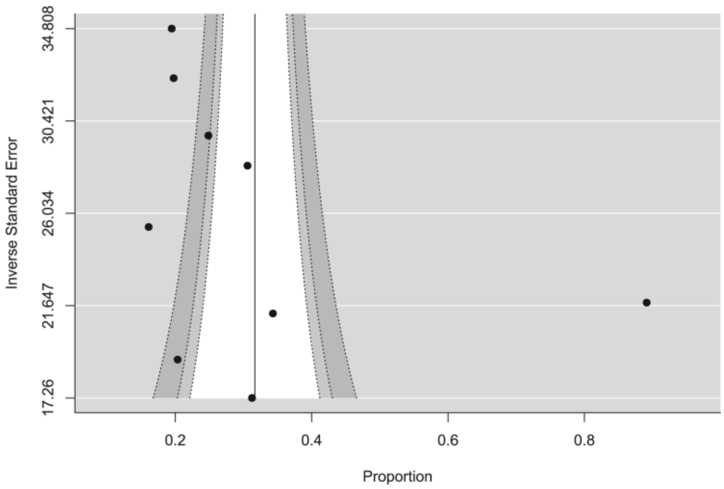
Binary outcomes were expressed as proportions (event rates) with 95% confidence limits (95% CI). Estimates from included studies were pooled using the restricted maximum likelihood method (RML).



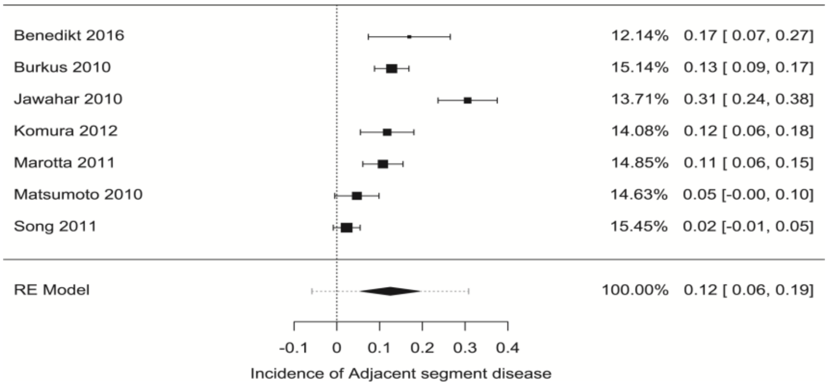
Graph (2): Forest plot for incidence of adjacent segment degeneration after anterior cervical discectomy and fusion. Pooled rate = 32% (95% CI = 17% to 46%). There is considerable heterogeneity across studies (Cochran Q test P-value < 0.001, I-squared = 97%).



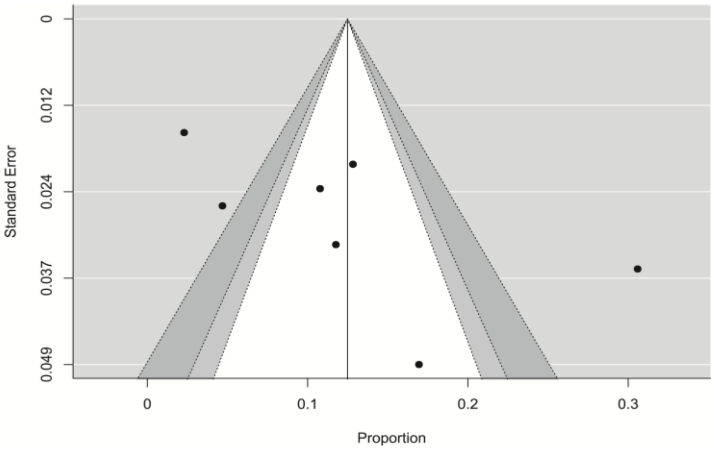
Graph (3): Funnel plot for incidence of adjacent segment degeneration after anterior cervical discectomy and fusion. There is no evidence of publication bias (Rosenthal fail-safe number = 1767, P-value < 0.001; rank correlation and regression tests for funnel plot asymmetry P-value = 0.180 and 0.425, respectively).



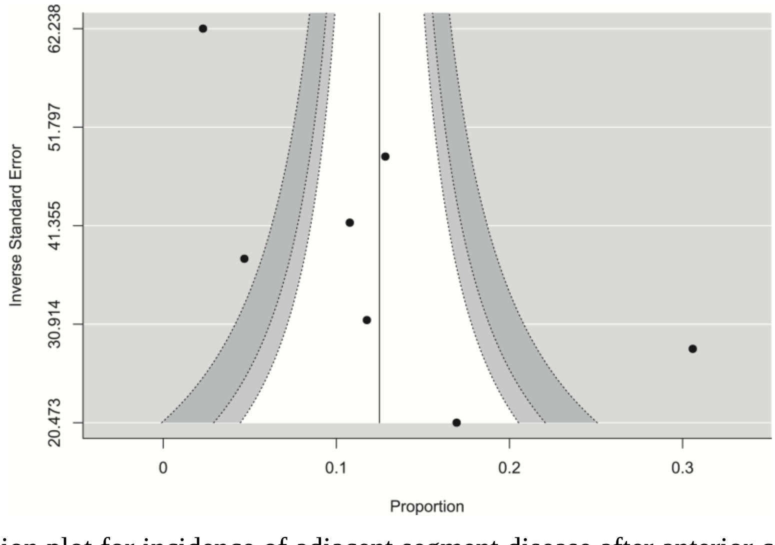
Graph (4): Precision plot for incidence of adjacent segment degeneration after anterior cervical discectomy and fusion. There is no evidence of publication bias (Rosenthal fail-safe number = 1767, P-value < 0.001; rank correlation and regression tests for funnel plot asymmetry P-value = 0.180 and 0.425, respectively).



Graph (5): Forest plot for incidence of adjacent segment disease after anterior cervical discectomy and fusion. Pooled rate = 12% (95% CI = 6% to 19%). There is considerable heterogeneity across studies (Cochran Q test P-value < 0.001, I-squared = 92.1%).



Graph (6): Funnel plot for incidence of adjacent segment disease after anterior cervical discectomy and fusion. There is no evidence of publication bias (Rosenthal fail-safe number = 321, P-value < 0.001; rank correlation and regression tests for funnel plot asymmetry P-value = 0.239 and 0.078, respectively).



Graph (7): Precision plot for incidence of adjacent segment disease after anterior cervical discectomy and fusion. There is no evidence of publication bias (Rosenthal fail-safe number = 321, P-value < 0.001; rank correlation and regression tests for funnel plot asymmetry P-value = 0.239 and 0.078, respectively).

DISCUSSION:

Our systematic review retrieved 10 studies from 2010 to 2019. Six studies were retrospective and four studies were prospective.

Early investigations into the long-term sequelae of cervical spinal fusion described radiographic breakdown and associated clinical findings at levels adjacent to fusions as a single group. More recent studies have differentiated between radiographic and clinical findings separately describing and reporting ASDeg and ASDz.

In our study, the total ASDeg incidence was (4.4%) while total ASDz incidence was (1.8%).The ASDeg rate was mentioned in 9 studies with a mean post operative value of 0.32 (0.17-0.46), P value was <0.001 which was statistically significant. While the ADSz rate was stated by 7 studies with a mean value 0.12 (0.06-0.15), P value was <0.001which was statistically significant. Regarding revision surgeries, 3 authors involved percentage of patients who needed surgery in their studies, while no revision surgeries were mentioned in the rest of studies. Patients who needed revision were 23 ptients out of 489 pts with 5% revision rate.

Regarding timing of occurrance of ASDeg, ASDz non of our authors revealed accurate timing of these complications.

Regaring to **Komura et al.**, **Song et al**. and **Matsumoto et al**. it's evident that high risk levels for ASD to occur are C5-6 and C6-7 but Jun Jae Shin et al.[54] mentioned that high risk levels are C3-4 and C4-5.

According to the causes of ASD, the most common cause was preoperative cervical spondylosis which was mentioned by **Garrido et al**., **Song et al.**, **Marotta et al**. and **Kumora et al**. also **Garrido et al.** and **Burkus et al**. mentioned that stripping of the anterior longitudinal ligament and the use of Caspar pins are associated with increase incidence of ASD while **Marotta** mentioned that old age and pseudoarthrosis which caused by malpositioning of a carbon fiber cage are causes of adjacent segment degeneration.

As for **Jun Jae Shin et al**. cervical arthrodesis, multi level fusion, decrease upper and lower segment range of motion, decrease adjacent disc height and thickening of ligamentum flavum are causes of adjacent disc degeneration.

Benedict W. Burkhardt has reported that the risk of developing degenerative changes at the adjacent segment is 3 times higher in case of a falsely punctured cervical disc.

Its clear from the above studies (**Benedikt W. Burkhardt, Garrido, Burkus, Jawahar, Maldonodo**) that TDR demonstrates equivalence of safety and efficacy when compared with ACDF in the management of cervical spine degeneration as TDR has the potential to maintain anatomical disc space height, normal segmental lordosis, and physiological motion patterns after surgery. These characteristics may reduce or delay the onset of degenerative disc disease by reducing the stress and strain on the adjacent segment.

Conclusion:

If the former is true, index ACDF procedures may be adjusted to include additional levels now identified as higher risk**.** If the latter is true, motion preserving treatments such as CDR may gain more traction. This review illuminates the heterogeneous methodology of the literature on ASDeg and ASDz after ACDF and the paucity of high-quality data published on these phenomena. Standardized method-logy for radiographic evaluation of ASDeg and clinical outcome measures for ASDz are critical before the fundamental question on their etiology can be resolved.

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تآكل القطاعات المجاورة بعد استئصال القرص الفقري الأمامي والاندماج مراجعة منهجية و تحليل بعدى

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المقدمة: يتم استخدام استئصال القرص العنقي الأمامي والاندماج (ACDF) بشكل شائع لعلاج اعتلال الجذور العصبية العنقية التنكسية واعتلال النخاع، وقد تم الإبلاغ عن نتائج مرضية في العديد من الدراسات. ومع ذلك، يظل تنكس القرص اللاحق عند المستويات المجاورة للاندماج مشكلة مهمة.

الهدف من العمل: إجراء مراجعة منهجية وتحليل تلوي لتقييم الإصابة وعوامل الخطر وتأثير تنكس الجزء المجاور بعد الجراحة الشعاعية والسريري (ASD) بعد إزالة الضغط الأمامي والاندماج الآلي.

مصادر البيانات: قواعد بيانات Medline PubMed و Medscape و Science Direct. EMF-Portal وجميع المواد المتاحة على الإنترنت حتى عام ٢٠٢٠.

استخراج البيانات: إذا لم تستوف الدراسات معايير الاشتمال، فقد تم استبعادها. تضمن تقييم جودة الدراسة ما إذا تم الحصول على الموافقة الأخلاقية، ومعايير الأهلية المحددة، والضوابط المناسبة، والمعلومات الكافية وإجراءات التقييم المحددة.

الخلاصة: إذا كان الأول صحيحًا، فيمكن تعديل إجراءات مؤشر ACDF لتشمل مستويات إضافية محددة الآن على أنها مخاطر أعلى. إذا كان الأخير صحيحًا، فقد تكتسب علاجات الحفاظ على الحركة مثل CDR مزيدًا من التطبيق. توضح هذه المراجعة المنهجية غير المتجانسة للأدبيات المتعلقة بـ ASDeg وASDz بعد ACDF وندرة البيانات عالية الجودة المنشورة حول هذه الظواهر. تعد المنهجية الموحدة للتقييم الشعاعي لـ ASDeg ومقاييس النتائج السريرية لـ ASDz أمرًا بالغ الأهمية قبل حل السؤال الأساسي حول مسبباتها.