**SUPPLEMENTAL MATERIAL**

**Table 1. Risk factors for radiographic adjacent segment pathology**

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| **Risk Factor** | **Studies** |  |  | **P-value** |
| **Surgical Factors** |  |  |  |  |
| **Number of levels fused** | Komura 2012 | ≥ 4 levels: 26.0% (13/50)  ≤ 3 levels: 42.3% (22/52) | RR = 0.61 (95% CI, 0.35–1.08) | .083 |
|  |  |  |  |  |
|  | Nassr 2009 | ≥ 1 grade increase in degeneration:  2-level: 43.1% (22/51)  1-level: 27.8% (10/36) | RR = 1.55 (95% CI, 0.84–2.87) | .143 |
|  |  |  |  |  |
| **Level of fusion** | Faldini 2011 | C4-5: 43.5% (20/46)  C5-6 or C5-7: 37.7% (23/61) | RR = 1.15 (95% CI, 0.73–1.8) | .547 |
|  |  |  |  |  |
|  | Komura 2012 | Excluding C5-6 and/or C6-7 fusion: 48.4% (15/31)  Including C5-6 and C6-7 fusion: 28.2% (20/71) | RR = 1.7 (95% CI, 1.0–2.9) | .048 |
|  |  |  |  |  |
| **Needle localization** | Nassr 2009 | Increase of ≥ 1 grade ASP:  Incorrectly marked: 60.0% (9/15)  Correctly marked: 31.9 (23/72) | RR = 1.9 (95% CI. 1.1–3.2) | .04 |

**Table 2. Risk factors for RASP in studies that reported means only.**

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| **Risk Factor** | **Studies** | **CASP** | **No CASP** | ***P*-value** |
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| **Patient Factors** |  |  |  |  |
| **Age** | Nassr 2009 | NR | NR | .97  (R = 0.005) |
| **Radiographic factors** |  |  |  |  |
| **Pre-op sagittal alignment of fused vertebrae (mean ± SD, °)** | Katsuura 2001 | 2.0° ± 5.2° | 2.5° ± 3.9° | ns |
|  |  |  |  |  |
| **Pre-op alignment cervical spine (mean ± SD, °)** | Katsuura 2001 | 8.8° ± 12.1° | 19.0° ± 12.1° | .008 |

**Table 3. Detailed results for included studies**

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| Author  (Year) | Outcomes | | Risk factors evaluated | Risk or mean by significant risk factor | Author’s Conclusions |
| RASP | CASP |
| Faldini  (2011) | Grade 2-4:  43/107 (40%) | NR | * Post-op sagittal segmental alignment (SSA) ≤ 0˚ * Post-op SSA > 0˚ * Sagittal alignment of the cervical spine (SACS) * Level of fusion | * Post-op SSA ≤ 0˚ = 61% * Post-op SSA > 0˚ = 27% (odds ratio (OR), 2.2; p < 0.001) * Logistic regression for post-op SSA and ASP: OR = 0.79 (95% CI, 0.71-0.88; p < 0.001), and +2.0˚ cutoff value of post-op SSA predicting ASP * No correlation between post-op or last f/u SACS and ASP * No correlation between level of fusion and ASP | To prevent ASP, proper lordotic sagittal segmental alignment (SSA) should be used when anterior interbody fusion of the cervical spine is indicated |
| Hilibrand (1999) | NR | 55/374 (15%) | * Number of levels * Surgery performed adjacent to the C5-C6 and/or C6-C7 levels * Age | * Anterior cervical fusions performed at more than one level had a significantly lower rate of ASP than those performed at a single level (12% vs. 18%, p ≤ .001) * A significant inverse correlation was noted between the degree of radiographic changes at the adjacent level at the time of the procedure and the time until symptomatic disease developed at that level (r2 = -0.985) * The relative risk at the interspaces between C3-C4 and between C4-C5 (levels at immediate risk) was 3.2 times that at the interspace between the C2-C3 or that at the cervicothoracic interspace (levels at low risk) * The relative risk at the interspaces between C5-C6 and C6-C7 (levels at high risk) was 4.9 times that at the levels at low risk * The differences in relative risk between the low and intermediate-risk groups and between the low and high-risk groups were significant (p < 0.01 and p < 0.001) * Significant direct correlation between the patient’s age at the time of the operation and the degree of degeneration at the adjacent segment (r2 = 0.994) | CASP may affect more than one-fourth of all patients within ten years after an anterior cervical arthrodesis. A single-level arthrodesis involving the fifth or sixth cervical vertebra and preexisting radiographic evidence of degeneration at adjacent levels appear to be the greatest risk factors for new disease. |
| Ishihara  (2004) | NR | 19/112 (17%)   * 0% (0/9) at C2-C3 * 7.7% (2/26) at C3-C4 * 13.3% (10/75) at C4-C5 * 13.0% (3/23) at C5-C6 * 10.3% (6/58) at C6-C7 * 0% (0/33) at C7-T1 | Clinical parameters:   * Age * Sex * Number of levels fused   Radiological parameters:   * Pre-op cervical spine alignment * Pre-op range of motion of C2-C7 cervical spine * Anteroposterior spinal canal diameter * Pre-op existence of an adjacent segment pathology on plain radiograph, myelography and MRI | * Incidence of indentation of dura matter on pre-op myelography on MRI at the adjacent level were significantly higher in disease cases (p=0.0087) * Incidence of disc protrusion on MRI at the adjacent level was significantly higher in disease cases (p = 0.0299)   All other parameters showed no statistically significant differences:   * Age (p = 0.146) * Sex (p = NR) * Number of levels fused (p = 0.374) * Pre-op cervical spine alignment (p = 0.262) * Pre-op range of motion of C2-C7 cervical spine (p = 0.575) * Anteroposterior spinal canal diameter (p = NR) | The incidence of clinical adjacent segment pathology after ACIF was higher when pre-op myelography or MRI revealed asymptomatic disc degeneration at that level regardless of the number of the levels fused, pre-op alignment, spinal canal diameter or fusion alignment |
| Katsuura  (2001) | 21/42 (50%)  4/21 (19%) above the fusion  11/21 (52%) below fusion  6/21 (29%) both above and below fusion | NR | * Malalignment of the cervical spine: * Alignment of the whole cervical spine (angle A) * Alignment of the fused segment (angle B) | * Physiological cervical lordosis was preserved in 18 cases (85.7%) in the group with normal adjacent levels; preserved in only 9 cases (42.8%) in the group with adjacent level degeneration * This difference was significant (*P*=0.015) * Alignment of the whole cervical spine (angle A) before operation and at f/u were both significantly smaller in the degeneration group than in the normal group (*P*=0.0081 and 0.0015, respectively) * In contrast, the fused segment (angle B) was significantly smaller (*P*=0.0096) in the degeneration group only at f/u * Pre-op angle A was highly significant of a determinant (*P*<0.0001) * Post-op angle B was a possible determinant (*P*=0.0671) | One of the factors promoting degenerative change in adjacent intervertebral levels after anterior cervical fusion for degenerative disorders is postoperative kyphotic change in the cervical spine and the fused segment |
| Komura  (2012) | Overall: 35/102 (34%)  L group: 13/50 (26%)  S group: 22/52 (42%)  C group: 20/71 (28%)  NC group: 15/31 (48%) | Overall: 12/102 (12%)  L group: 1/50 (2%)  S group: 11/52 (21%)  C group: 4/71 (5.6%)  NC group: 8/31 (26%) | * Number of fusion levels (long ≥ 4 levels vs. short < 3) * Location of fusion levels (including C5-6 and C6-7 vs. including only one level) | * Tendency of higher incidence of ADD in the S group (*P* = 0.083) than in the L group * The incidence of symptomatic ADD (sADD) was significantly higher in the S group than in the L group (*P* = 0.024) * The incidence of ADD and sADD were significantly (*P* = 0.048, 0.0066) higher in the NC group than in the C group | Symptomatic ADD is less frequently associated with long-level ADF (≥ 4 disc levels) than short-level ADF (< 3 levels)  ADD 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 as an adjacent level, irrespective of the length of fusion |
| Nassr  (2009) | Overall increase\*: 32/87 (37%)  Correctly marked discs: 23/72 (32%)  Incorrectly marked discs: 9/15 (60%) | NR  \*When comparing cervical disc degeneration grade on pre- and post-op radiographs, the correctly marked discs stayed the same in 68%, increased by 1 grade in 29%, and increased by 2 grades in 3%. In the incorrect group, 40% stayed the same and 60% advanced 1 disc grade. | * Age * Length of follow-up * Levels of fusion (1 vs. 2) * Correct vs. incorrect needle localization | * No correlation between age and ASP (*R* = 0.005, *P* = 0.97) * No correlation between length of follow-up and ASP (*R* = 0.11, *P* = 0.17) * When comparing 1 vs. 2-level fusion, they were equally likely to develop disc degeneration above the level of fusion (28% of the 1-level fusion patients advanced at least 1 grade; 43% of the 2-level fusion patients advanced at least 1 grade, *P* = 0.143) * Patients in the incorrectly marked group were statistically more likely to demonstrate progressive disc degeneration (odds ratio 3.2; 95% CI 1.02-10.05) | There is a 3-fold increase in risk of developing adjacent level disc degeneration in incorrectly marked discs after ACDF at short-term follow-up.  This may indicate that either needle related trauma or unnecessary surgical dissection contributes to accelerated adjacent segment pathology. |
| Wu  (2012) | 568/19,385 (2.9%) received 2 ACDFs  29/19,385 (0.1%) received ≥ 3 ACDFs | NR | * Age * Gender * Diabetes mellitus * Hypertension * Cerebrovascular disease * Heart disease * Socioeconomic factors (insurance amount, urbanization level) | * Among those with secondary surgery (ASP):   + 367 (64.6%) were male and 201 (35.4%) were female   + 335 (59.0%) were 40 to 59 years of age, 141 (24.8%) > 60 years of age, and 92 (16.2%) 15 to 39 years of age * Secondary ACDF operations more likely for male patients (adjusted hazard ratio = 1.27) than for female patients with statistical significance (*P* = .008) * Patients 15 to 39 and 40 to 59 years of age were more likely to receive a secondary operation than those > 60 years of age (hazard ratio = 1.45 and 1.41; *P* = .009 and .002, respectively) * Comorbid systemic diseases, including diabetes mellitus, hypertension, cerebrovascular disease, and heart disease had no significant influence on the incidence of a secondary ACDF operation (hazard ratio = 1.10, 1.17, 1.39, and 1.40; *P* = 0.523, 0.213, 0.064, and 0.134, respectively) * No significant influences on the incidence of a secondary ACDF operation were found among the socioeconomic groups (insurance amount and urbanization levels) | Repeat ACDF surgery for ASP cumulated steadily for an annual incidence of approximately 0.8%. This is remarkably lower than the reported incidence of CASP by Hilibrand et al.  At the end of the 10-year cohort, a considerable portion of patients (5.6%) underwent reoperation for ASP.  Male and younger patients (< 60 years of age) were more likely to undergo reoperations. |

**Table 4. Evidence Summary**

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| Baseline quality: HIGH = majority of article Level I/II. LOW = majority of articles Level III/IV.  UPGRADE: Large magnitude of effect (1 or 2 levels); dose response gradient (1 level)  DOWNGRADE: Inconsistency of results (1 or 2 levels); indirectness of evidence (1 or 2 levels); imprecision of effect estimates (1 or 2 levels) | | | | | |
|  | **Strength of evidence** | **Conclusions/Comments** | **Baseline** | **UPGRADE (levels)** | **DOWN-GRADE**  **(levels)** |
| **Key Question 1: What is the estimated risk of CASP after cervical fusion for degenerative disease?** | | | | | |
| Risk | Low | * The prevalence of CASP ranged from 11 to 12% at 5 years and from 16 to 38% at 10 years | Low | No | No |
| **Key Question 2: Among patients undergoing cervical fusion, are there factors associated with an increased risk of CASP in the following categories: patient factors, disease factors and surgical factors?** | | | | | |
| *Patient Factors* | | | | | |
| Sex | Insufficient | * Risk of CASP: slightly greater for females, though not statistically significant (1 retrospective cohort): 18.4% vs. 16.2% | Low | No | (1) single study |
|  | Moderate | * Risk of subsequent operation due to CASP: statistically greater for males (1 database study): aHR = 1.27 (95% CI, 1.07–1.52) | High | No | (1) single study |
| Age | Insufficient | * Risk of CASP: older age was highly correlated with CASP (r2 = 0.994) in one retrospective cohort; in another, younger age appeared to be a slight risk factor for CASP, though not statistically significant | Low | No | (1) inconsistent results |
|  | Moderate | * Risk of subsequent operation due to CASP: statistically greater in patients < 60 years vs. ≥ 60 years (1 database study) | High | No | (1) single study |
| Comorbidities | No evidence | * Risk of CASP: none reported | N/A |  |  |
|  | Moderate | * Risk of subsequent operation due to CASP: diabetes mellitus, hypertension, cerebrovascular disease, and heart disease not significant risk factors (1 database study) | High | No | (1) single study |
| Socioeconomics | No evidence | * Risk of CASP: none reported | N/A |  |  |
|  | Moderate | * Risk of subsequent operation due to CASP: income and urbanization level not significant risk factors (1 database study) | High | No | (1) single study |
| *Surgical Factors* |  |  |  |  |  |
| Number of levels fused | Low | * Risk of CASP: slightly greater, though not statistically significant, following single- vs. multilevel fusion in 2 retrospective cohorts; in a third cohort, 11-times greater risk when ≤ 3 levels fused vs. ≥ 4 levels (RR = 10.6; 95% CI, 1.42–78.9; *P* = .004) | Low | No | No |
|  | No evidence | * Risk of subsequent operation due to CASP: none reported | N/A |  |  |
| Level of fusion | Moderate | * Risk of CASP: Fusing adjacent to but not including the C5-6 and/or C6-7 disc space appears to consistently increase the risk of developing CASP | Low | (1) magnitude of effect | No |
|  | Moderate | * Risk of subsequent operation due to CASP: statistically greater when C5-6 and C6-7 were not fused (vs. fused): 9.7% vs. 0% | High | No | (1) single study |
| *Radiographic Factors* |  |  |  |  |  |
| Preoperative radiographic parameters | Insufficient | * Risk of CASP: 3-times greater with the presence (vs. absence) of disc protrusion (RR = 3.5, 95% CI, 1.6–7.6) and indentation of dura matter (RR = 3.0, 95% CI, 1.4–6.7), and twice the risk with a low density area (RR = 2.1, 95% CI, 0.92–4.9) as reported by 1 retrospective cohort; alignment of the cervical spine, range-of-motion of the cervical spine and at the upper and lower adjacent levels were not significant risk factors in the same study | Low | No | (1) single study |
|  | No evidence | * Risk of subsequent operation due to CASP: none reported | N/A |  |  |
| Anteroposterior diameter of spinal canal | Insufficient | * Risk of CASP: significantly smaller mean diameter was reported in those with versus without CASP in one retrospective cohort but not in the other | Low | No | (1) inconsistent results |
|  | No evidence | * Risk of subsequent operation due to CASP: none reported | N/A |  |  |

**Level of Evidence Summary Table for Included Studies**

*Critical appraisal for article on prognosis*

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| --- | --- | --- | --- | --- | --- |
| Methodological Principle | Hilibrand (1999) | Ishihara (2004) | Katsuura (2001) | Komura (2012) | Wu (2012) |
| Study design |  |  |  |  |  |
| Prospective cohort study |  |  |  |  |  |
| Retrospective cohort study | √ | √ | √ | √ | √ |
| Case-series |  |  |  |  |  |
| Patients at similar point in the course of their disease or treatment | √ | √ | √ | √ | √ |
| Patients followed long enough for outcomes to occur | √ | √ | √ | √ | √ |
| Complete follow-up of >80% | √ | √ |  |  | √ |
| Accounting for other prognostic factors\* |  |  | √ | √ | √ |
| Evidence Level | III | III | III | III | II |