Terminal Complement Complex (TCC): A Possible Target for Intervertebral Disc Degeneration Therapeutics

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Introduction: Inflammation is known to contribute to disc degeneration (DD). However, there is limited knowledge regarding a possible involvement of innate immunity. Terminal complement complex (TCC) immunopositivity was previously observed in human pathologic intervertebral discs (IVD), but the information is scarce. The present work aims to understand if TCC plays a specific role in the development and progression of DD.

Methods: Disc tissues were collected post-mortem from: 1) healthy donors, considering 2 different age groups (Young, 5F/6M, age 7 ± 7; Elder, 4F/4M, age 67 ± 14); 2) patients with scoliosis (Sc, 8F/3M, age 15 ± 4) displaying no signs of degeneration; and 3) patients with DD (23F/16M, age 64 ± 12, Pfirrmann grade 3-5), with ethical approval and patients’ informed consent. TCC deposition was investigated in nucleus pulposus (NP), annulus fibrosus (AF) and endplate (EP). Randomly selected Sc and DD patients’ AF, NP and EP expanded cells (passage 2-5) were analyzed for gene expression of TCC-inhibitors CD46, CD55 and CD59. Surface expression of TCC, CD46, CD55 and CD59 was analyzed by FACS in fresh and expanded cells. In vitro, cellular TCC deposition was stimulated by 5% human serum medium supplementation (containing components C5 to C9, necessary for TCC formation) and analyzed by ELISA. Serum-free medium was used as control. TCC’s lytic activity was measured in the supernatants by erythrocytes lysis test. Statistical analysis was performed with Kruskal-Wallis test.

Results: A significantly higher frequency of TCC+ cells was detected in the NP of DD compared to Elder and Sc groups (p<0.05), and in the EP of both Young (p<0.001) and DD (p<0.05) compared to Elder (Figure 1). Moreover, Young donors presented a significantly higher frequency of TCC+ cells in the EP versus NP (p<0.05). No correlations with age or degeneration degree in DD were observed. Overall, the frequency of TCC+, CD46+, CD55+ and CD59+ AF, NP and EP cells significantly increased with time in culture, becoming similar for Sc and DD cells in passages 2-5. CD46, CD55 and CD59 expression was also similar between Sc and DD cells. Moreover, in presence of human serum, no significant differences were observed between DD and Sc groups for AF, NP or EP expanded cells regarding TCC deposition and cell lysis.

Discussion: These data suggest that TCC is formed in NP cells of strongly degenerated samples, whereas it is detected in the EP of both Young and DD groups, which might correlate with vascularization. Moreover, although TCC deposition can be induced in vitro, AF, NP and EP cells isolated from tissues derived from patients with different pathologies seem to lose their native phenotype with time in culture. Further studies are ongoing to understand which microenvironmental factors can activate TCC deposition and if there is a possible functional

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Figure 1. Histopathological analysis of IVD tissue. (A) Representative images of IVD tissue collected during surgery, from patients suffering from disc degeneration (DD), stained for safranin-O (proteoglycans are stained red, while Fast Green counterstains the non-collagen sites) and for TCC, displaying cells positive (+) and negative (Δ) for TCC deposition, in the different IVD regions: annulus fibrosus (AF), nucleus pulposus (NP) and endplate (EP). (B) Frequency (%) of TCC+ cells in healthy IVD tissues collected post-mortem from Young (n=11) and Elder (n=8) donors, and during surgery from patients suffering from Sc (n=11) and DD (n=39). *P<0.05, ***P<0.001. Kruskal-Wallis test.
ARTIFICIAL INTELLIGENCE-BASED ADULT SPINAL DEFORMITY RISK-BENEFIT CLASSIFICATION: HIERARCHICAL CLUSTERING OF 1245 PATIENTS AND SURGERIES WITH MACHINE-BASED LEARNING AND SIMPLIFIED DECISION TREES


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Introduction
The Schwab-SRS ASD Classification is based on disability scores and the sagittal plane and is limited by the lack of preoperative information on associated risk or outcome. Unsupervised learning has classified ASD patients and surgeries based on risk and benefit. The combination of AI-based unsupervised learning and expert cluster interpretation will yield a risk-benefit ASD classification which does not require computer access. We aimed to improve the analysis with more than twice the 2-yr follow-up sample size and filter the results by reducing the number of groups to enable point of care clinical application.

Methods
Two prospective cohorts were queried for surgical ASD patients with baseline, 1-yr, and 2-yr SRS-22/SF-36v2 data. Dendrograms were fitted, one with surgical features and one with patient characteristics. Both were built with Ward distances and optimized with the gap method. Normalized 2-yr improvement and major complications (MC) were computed for patient and surgery clusters. Patient clusters and surgery types were filtered to enhance interpretability and back walked to provide a decision tree.

Results
1245 patients were included (mean 55.7 yrs; 77.6% female) in this analysis. The 3 patient types were: Young Coronal (YC, n=200), Old Primary (OPrim, n=527), and Old Revision (ORev, n=516). 5 surgical types were drawn: 3-column osteotomy (PSO/3CO, n=254), interbody fusion (IBF with [n=296] or without decompression [n=216]), single PCO [n=258], and multiple PCO [n=219]. The figure shows normalized improvement in outcomes and cumulative incidence of MC based on patient type and surgical plan.

Conclusion
Unsupervised hierarchical clustering can identify data patterns that may guide preoperative decision making by predicting outcomes and MC. In addition to creating a novel AI-based preop risk-benefit ASD classification, pattern identification may facilitate treatment optimization by educating surgeons on which treatment patterns yield optimal improvement with lowest risk.
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SPINO-PELVIC ALIGNMENT AFTER SHORT SEGMENT TRANSFORAMINAL LUMBAR INTERBODY FUSION (TLIF) - IS CORRECTION POSSIBLE AND WORTHWHILE?
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Introduction
Sagittal alignment is governed by radiological parameters such as pelvic incidence (PI), pelvic tilt (PT), sacral slope (SS) and lumbar lordosis (LL). Matching LL and PI, and a low Global Alignment and Proportion (GAP) Score influence both clinical outcome and the risk of revision in long fusion. The influence of short transforaminal lumbar interbody fusion (TLIF) on the sagittal profile is equivocal. This retrospective study aimed to evaluate the magnitude of the change in segmental and regional lordosis in short segment TLIF (1-3 segments), and its effect on spino-pelvic alignment and prospectively evaluated clinical outcome.

Materials and Methods
From our local spine outcomes database (linked to the Spine Tango Registry), we identified 196 patients with no coronal deformity >20° and no previous spine surgery who had undergone TLIF (1-3 segments) for degenerative spinal disorders in 2012. The following were measured on standing lumbar spine radiographs taken before and six weeks after surgery: PI, PT, SS, LL, L4-S1 lordosis, fused segments lordosis (FSL), and remaining unfused segments lordosis (RSL). Based on these measurements, spino-pelvic alignment (PI-LL) and L-GAP Score were assessed, and patients were categorized as PI-LL balanced, unbalanced, or uncompensated and L-GAP proportioned, moderately disproportioned or severely disproportioned. The Core Outcome Measures Index (COMI) was used to assess patient-rated outcome pre-, and 2- and 5- years post-operatively.

Results
TLIF was performed in 1 segment in 140, 2 segments in 50 and 3 segments in 6 patients. 106 patients had degenerative spondylolisthesis, 32 isthmic spondylolisthesis, and 58 osteochondrosis. The radiological measurements (PT, SS, LL, L4-S1) showed no significant differences, pre-to postoperatively. FSL was increased from 21.9±10.4° pre- to 23.4±9.2° postoperatively (1.3±4.5° per fused segment) (both p<.01); however, the proportion of patients in the PI-LL and L-GAP Score categories showed no significant differences. There was a low but significant correlation between the increase in FSL and the decrease in RSL (R=0.285, p<.01). The COMI improved significantly from 7.2±1.7 at baseline to 2.5±2.5 and 2.8±2.5 at 2- and 5-years' postoperatively, respectively (each p<.01). Patients were more likely to achieve the minimal clinically important change (MCIC) in COMI score at 5 years' postoperatively with FSL>3° (87.9%) than with FSL<3° (72.6%) (p=.03).

Conclusion
Short segment TLIF can increase lordosis within fused segments, and reduce compensatory mechanisms in the unfused lumbar spine. A good clinical outcome is achieved for the majority of patients at five-years' follow-up independent of spino-pelvic alignment. An increase of lordosis in the fused segments of more than 3 degrees appears to be associated with better clinical outcome.

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RISK FACTORS FOR IMMEDIATE ENDPLATE INJURY AFTER MINIMALLY-INVASIVE LATERAL LUMBAR INTERBODY FUSION

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Introduction
Immediate endplate injury (EpI) after minimally-invasive lateral lumbar interbody fusion (MIS-LLIF) is quite common and can lead subsequent cage subsidence and deterioration of surgical outcomes. The purpose of this study was to identify risk factors for immediate EpI after MIS-LLIF.

Methods
One hundred eighty-six patients underwent MIS-LLIF and posterior instrumentation for degenerative lumbar diseases with one-staged or two-staged manner between 2012 and 2017. All surgeries were performed with the same manner by a single surgeon. Age, sex, BMI, and BMD were recorded. On preoperative standing X-ray, coronal disc angle, and each sagittal disc angle in neutral, flexed, extended positions were measured. Also, anterior and posterior disc heights were measured on lateral neutral X-ray. Other radiographic parameters including osteophyte formation, Kellgren-Lawrence grading, facet degeneration grading, endplate sclerosis were assessed. EpI was defined as compromise of bony endplate with more than 1mm. recorded on immediate postoperative X-ray. All parameters were analyzed statistically regarding endplate injury at each disc level.

Results
372 discs underwent MIS-LLIF in 186 patients and 76 levels (20.4%) showed EpI. Among them, 67 had single-side injury and 9 had both-side injury. One case with two adjacent EpI showed vertebral body fracture leading to early revision. The incidences were similar for each level. When periodic analysis was performed for each 100 levels, the incidences were steady from the first period to the last one. BMD of vertebrae with EpI was not different from BMD of vertebrae without EpI. The differences between cage height and disc height were also not different according to EpI. Multivariate regression analysis demonstrated that sagittal disc angle in extension, gender, and endplate sclerosis were correlated with EpI. Bone mineral density was not correlated with EpI.

Conclusion
The incidence of EpI was 20.4% and showed steady tendency. The smaller sagittal disc angle in extension, female gender, and endplate sclerosis was correlated with EpI. The development of EpI is correlated with various factors: surgeon-related, patient-related, and implant-related. In this study, there was no learning curve and no significant correlation between EpI and implant dimensions. Immediate postoperative EpI seemed not to be procedure-related, but to be patient-related. At the beginning of this study, authors had expected that bone mineral density might be correlated with EpI, however, no significance was noted. When performing MIS-LLIF, spine surgeons should check X-ray thoroughly and pay more attention to female patients with smaller sagittal disc angle in extension.

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THE SCIATICA-GILL TRIAL: ISTHMIC SPONDYLOLISTHESIS: DECOMPRESSSION WITH VS. WITHOUT INSTRUMENTED FUSION: A RANDOMIZED CONTROLLED TRIAL

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Background: The most advocated surgical technique to treat symptoms of isthmic spondylolisthesis is decompression with instrumented fusion. A less invasive classical approach has also been reported, which consists of merely decompression.

Methods: We randomly assigned 84 patients with lumbar radiculopathy or neurogenic claudication due to a grade I or II isthmic spondylolisthesis to decompression (D) or decompression with instrumented fusion (DF). Scores on the Roland Disability Questionnaire, visual-analogue scale for back pain and for leg pain separately, and the patient’s report of perceived recovery were evaluated as primary outcome parameters at 12 weeks and 2 years postoperatively. Secondary outcome measures were the proportion of repeat surgery for persistence of complaints, and the SF-36 functionality scale. Repeated-measures analysis according to the intention-to-treat principle was used.

Results: Between the 43 patients assigned to decompression and the 41 patients assigned to decompression and fusion, there was no significant difference in disability scores at 12 weeks follow up (P = 0.32 95% CI [-4.02 - 1.34]), nor in the other outcome measures. At 2 years follow-up, disability scores improved more in the fusion group (10.3 vs 6.0 points improvement (P < 0.01 95% CI [-7.3 - -1.3]). Likewise, back pain (P = 0.01) and perceived recovery (P = 0.04) improved more in the fusion group. The cumulative probability for reoperation at 2-year follow-up was 47% in the decompression and 13% in the fusion group (P < 0.01).

Conclusion: In isthmic spondylolisthesis decompression with instrumented fusion resulted in significantly better outcomes and less re-operations compared to decompression without fusion. Nearly half of the patients who underwent only decompression needed secondary instrumented fusion during follow-up. Therefore, decompression alone is an inferior surgical technique for isthmic spondylolisthesis, and should generally not be offered as a first treatment option.

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Anterior cervical decompression and fusion (ACDF) is the leading surgical treatment of cervical radiculopathy caused by disc herniation or spondylotic nerve root compression. ACDF procedures have been suggested to lead to accelerated degeneration of the adjacent cervical discs (adjacent segment disease, ASD). Occurrence of ASD is of particular interest when treating young individuals as the cumulative disease burden form degenerative cervical disease may become increasingly significant during their expectedly long lifetime. However, the overall impact a surgical intervention on life time prognosis for degenerative cervical disease is incompletely understood.

We retrospectively collected and analyzed the medical records of all patients between 18 and 40 years of age at the time of surgery who underwent ACDF due to degenerative cervical disease at Helsinki University Hospital between the years 1990 and 2005 (n=476). The follow-up time was 12-28 years (median 17 years). The end points of the study were long-term outcome, satisfaction to the surgery, quality of life and long-term risk of reoperations. Questionnaires were sent to patients now at the end of the follow-up to asses overall neck symptoms at current time point and health related quality of life.

The most common complications were persistent dysphagia (2%) and dysphonia (4%). The incidence of postoperative haematomas was 1.4%. 24% of patients were re-operated at least once during the follow-up period (median time to the re-operation 5.5 years). Excluding early re-operations (<28 days from the index surgery), the reoperation rate during the rest of the follow-up period was 19.5%. The 10-year total reoperation rate was 16.8% and 12.8% with early reoperations excluded. Altogether 23% of late reoperations (>28 days) involved further decompression of the index level, 82% decompression of an adjacent level and 3% decompression of a non-adjacent level.

Statistically significant risk factors of needing at least one re-operation were male sex, central spinal cord compression, discectomy without implant as surgical technique, the primary operation done in acute setting and smoking at the time of the operation. Time to re-operation was analyzed with Kaplan-Meier analysis (Figure 1).

In general, the satisfaction to the surgery was high. Now 12-28 years after the surgery, 92% of patients were still satisfied to the result of the surgery. 67% of patients were working, 7% were unemployed and 7% were on disability pension due to cervical problems. These proportions resemble that of the general population in Finland. Smoking was more common both now and at index time than in general population. Median NDI now was 12%, resembling closely that of general population. NDI was significantly higher among patients with spondylosis or clinical myelopathy and among patients operated more than once.
Figure 1: The proportion of patients, not undergone reoperation as function of time. Patients grouped by a) surgical technique according to discectomy alone or use of artificial cage or bone auto graft for fusion, b) gender, c) presence of no, radiological spinal cord compression only or radiological and clinical myelopathy and d) smoking status.

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RISK FACTORS FOR REOPERATION FOR SURGICAL SITE INFECTIONS IN INSTRUMENTED SPINE TRAUMA PATIENTS

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Introduction: In the USA, it is estimated that 300,000-500,000 surgical site infections occur each year. These are associated with increased healthcare related costs. Few studies have looked specifically at surgical site infections in spine trauma. Rates in the literature suggest a 4-10% incidence of post-operative wound infection.

Purpose: To investigate the incidence of surgical site infections requiring surgical irrigation and debridement within 90 days of instrumented spinal stabilization in traumatic spine injuries and identify risk factors for re-operation.

Methods: After obtaining institutional IRB, spine trauma patients (>18 years old), who underwent spine surgical fixation, at a level I trauma center covering a four-state area were identified by searching CPT codes (22851, 22325, 22326, 22327) and linked with ICD-9 codes (codes beginning with 8) from January 2005 to October 2015. From the larger group, we then identified patients with CPT codes 998.59 or 996.67 who required a secondary irrigation and debridement, within 90 days of the index procedure. In this study, we did not include patients who had superficial infection managed nonoperatively. Incidence of reoperation and statistical analysis of the possible risk factors: age, body mass index (BMI), tobacco use, intravenous (IV) drug use, diabetes (DM) status, location of fracture, surgical approach, injury severity score, intensive care unit stay and hospital length of stay, was performed.

Results: 2,276 adult patients underwent operative management of spine fractures between January 2005 and October 2015. The distribution of injuries by region were 637 (28%) cervical injuries, 887 (39%) thoracic, and 752 (33%) lumbar. 92% of the patients had a posterior approach, 6% anterior approach, and 2% a combined anterior/posterior. The overall incidence of irrigation and debridement for surgical site infections, within 90 days of instrumented spine trauma surgery, was 2.8% (64/2,276). Patients who demonstrated a higher risk of undergoing irrigation and debridement for surgical site infection include: tobacco use (p=0.0123), patients with intensive care unit admissions (p=0.041), and patients with longer hospital lengths of stay (p=0.004).

Conclusions: This study suggests that the incidence of irrigation and debridement for infection within 90 days of instrumented spine trauma surgery is 2.8%. This is lower than what has previously been suggested in prior studies. Tobacco use, longer hospital lengths of stay and intensive care unit admissions are risk factors correlated with increased risk for infections requiring a secondary irrigation and debridement.

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