Identification of a Novel Genetic Variant Associated with Adjacent Segment Disease: Analysis of Spinal Fusions in the UK BioBank

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INTRODUCTION: The prevalence of symptomatic spinal disease requiring fusion is increasing with an aging population. Patients are counseled there is a 3% annual risk of additional surgery due to AdSD, though this may not account for advances in surgical technique. The UKB is a large population-based cohort of 500,000 deidentified people, with in-depth genetic and non-genetic information, as well as linked hospital records. The database is regularly updated and includes >20 years of hospital records[5]. We investigated the rate of AdSD after primary cervical and lumbar fusion in the UKB cohort, as well as risk factors that may contribute

METHODS:

UKB patients that underwent primary lumbar or cervical fusion, as well as anterior (ACF) or posterior cervical spine fusion (PCF) were identified using OPCS-4 codes. AdSD was the endpoint, defined as subsequent fusion, revision, or decompression within the same spine. Risk factors were assessed using multivariable Cox regression analysis. Cumulative incidence was calculated to estimate the annualized risk of AdSD. GWAS analysis was performed to identify small nucleotide polymorphisms (SNPs) associated with AdSD.

RESULTS:

3487 patients underwent primary fusion in the cervical (N=1732, ACF = 1571, PCF = 121, combined = 42) or lumbar (N=1755) spine. 211 (12.1%) cervical and 230 (13.1%) lumbar patients were revised for AdSD. 5-year AdSD rate was 8.19% (cervical) and 10.16% (lumbar), and at 20-years was 20% (cervical) and 19.84% (lumbar), amounting to an annual risk of ~1% (Table 1, Figure 1). The 5-year AdSD rate for ACF and PCF was 8.02% and 1.98% ($p<0.05$). Subgroup sample size limited detection of significant demographic and genetic differences between ACF and PCF AdSD cases. Unemployed/Retired status achieved significance as a risk factor for all AdSD patients (p=0.0063). GWAS analysis (Figure 2) for all AdSD patients identified a novel SNP (rs116459848, Chromosome 5). Previously reported SNPs[6] associated with degenerative pathologies (spondylolisthesis, disc disease, spinal stenosis) failed to achieve significance.

DISCUSSION AND CONCLUSION:

The combined risk of AdSD for lumbar and cervical spine fusion is lower than previously reported, 1% annually with about 40% of cases occurring within the first 5 years. The rate of AdSD between the ACF and PCF was different at 5 years. The low patient population for PCF precluded AdSD projection beyond 5.3 years (3.43%). There may be risk factors accounting for the increased early rate of AdSD, including surgical factors and patient factors. We identified a novel SNP that associated with AdSD cases in the absence of SNPs associated with degenerative pathologies. This suggests there may be a novel genetic component to AdSD, and AdSD may represent a separate disease.

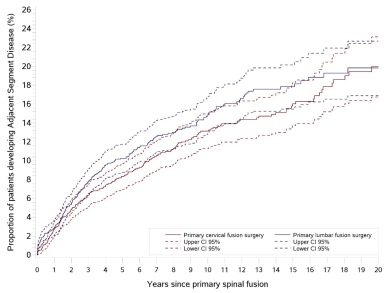

Figure 1: Rate of Adjacent Segment Disease for Cervical and Lumbar Spinal Fusion

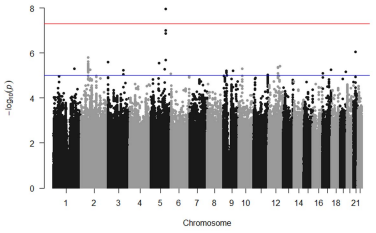

Figure 2: GWAS analysis for adjacent segment disease cases. The red line indicates genome-wide significance threshold set to $5x10^{-8}$

Table 1. Point Estimate for 5, 10, 15, 20 years since primary spinal fusion

Year since primary spinal fusion	For all types of primary spinal fusion surgery			For primary cervical fusion surgery			For primary lumbar fusion surgery		
	Survival Probability (%)	95% CI for Survival Probability	Cumulative Incidence (%)	Survival Probability (%)	95% CI for Survival Probability	Cumulative Incidence (%)	Survival Probability (%)	95% CI for Survival Probability	Cumulative Incidence (%)	95% CI for Cumulative Incidence
5	90.81	89.82-91.81	9.19	91.47	90.31-95.69	8.53	89.78	88.28-91.28	10.24	8.74-11.72
10	86.25	84.94-87.57	13.75	83.85	81.68-86.73	15.15	83.27	81.57-87.22	14.75	12.78-16.83
15	83.27	81.87-84.89	16.73	83.85	81.74-86.26	16.65	81.17	79.64-84.53	17.85	15.47-20.18
20	80.19	78.85-82.39	19.81	80	76.87-83.25	20	80.16	77.32-83.11	19.84	16.89-22.68

Year since primary spinal fusion	For anterior cervical fusion surgery			For posterior cervical fusion surgery		
	Survival Probability (%)	95% CI for Survival Probability	Cumulative Incidence (%)	Survival Probability (%)	95% CI for Survival Probability	Cumulative Incidence (%)	95% CI for Cumulative Incidence
5	91.98	90.58-93.41	8.02	98.02	95.33-100	1.98	0-4.67
10	87.92	85.76-89.5	12.08	95.53-94.22	96.57	92.75-100	3.43	0-7.25
15	84.89	82.64-87.2	15.11	124-17.35	96.57	92.75-100	3.43	0-7.25
20	80.96	77.72-84.3	19.04	15.7-22.25	96.57	92.75-100	3.43	0-7.25