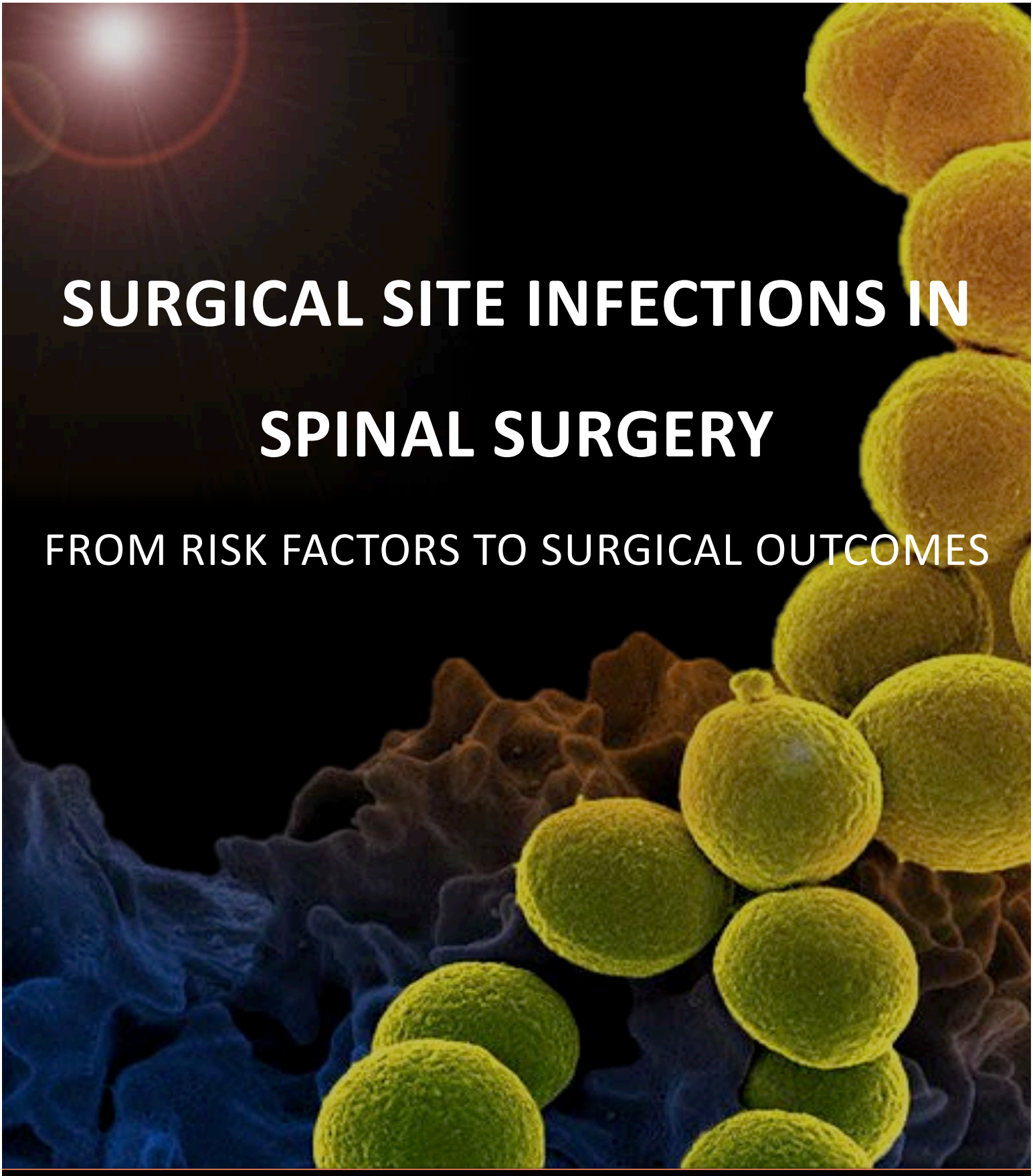
Universitat Autònoma de Barcelona

SURGICAL SITE INFECTIONS IN SPINAL SURGERY
FROM RISK FACTORS TO SURGICAL OUTCOMES

Sleiman Haddad



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DOCTORAL DISSERTATION

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Front cover: Scanning electron microscopy of a white blood cell phagocytizing a Methicillin-Resistant *Staphylococcus Aureus* (MRSA) colony.

Back cover: Scanning electron microscopy of a healthy cancellous bone matrix.

TABLE OF CONTENTS

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SCIENTIFIC CONTRIBUTIONS

The findings of this doctoral thesis have been partially presented in multiple national and international meetings where they were praised and awarded. Up to the finalization of this compendium, two peer-reviewed articles were published in indexed spinal journals.

PUBLISHED ARTICLES

1. **Diagnosis and Neurological Status as Predictors of Surgical Site Infection in Primary Cervical Spinal Surgery**
   Haddad S, Millhouse PW, Maltenfort M, Restrepo C, Kepler CK, Vaccaro AR
   Spine J. 2016 May; 16(5):632-42
   doi: 10.1016/j.spinee.2016.01.019.

2. **The impact of deep surgical site infection on surgical outcomes after posterior adult spinal deformity surgery: a matched control study**
   Haddad S, Núñez-Pereira S, Pigrau C, Rodríguez-Pardo D, Vila-Casademunt A, Alanay A, Acaroglu ER, Kleinstueck FS, Obeid I, Perez-Grueso FJS, Pellisé F; European Spine Study Group.
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CONTRIBUTIONS TO CONGRESSES AND MEETINGS:

1. **Impact of Surgical Site Infection on Surgical Outcomes in Adult Spinal Deformity: A Matched Control Study**
Sleiman Haddad, Susana Nuñez-Pereira, Alba Vila-Casademunt, Montse Domingo-Sabat, Emre Acaroglu, Francisco Javier Sánchez Pérez-Grueso, Ibrahim Obeid, Frank Kleinstück , Ahmet Alanay, Ferran Pellisé and ESSG, European Spine Study Group
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2. **Impacto de la Infeccion Postoperatoria En Cirugia de Deformidad Espinal del Adulto**
   Sleiman Haddad, Susana Nuñez-Pereira, Alba Vila-Casademunt, Montse Domingo-Sabat, Emre Acaroglu , Francisco Javier Sánchez Pérez-Grueso, Ibrahim Obeid, Frank Kleinstück , Ahmet Alanay, Ferran Pellisé and ESSG, European Spine Study Group
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   Sleiman Haddad, Susana Nuñez-Pereira, Alba Vila-Casademunt, Montse Domingo-Sabat, Emre Acaroglu, Francisco Javier Sánchez Pérez-Grueso, Ibrahim Obeid, Frank Kleinstück , Ahmet Alanay, Ferran Pellisé and ESSG, European Spine Study Group
   Oral Presentation at the British Association of Spine Surgeons BASS Annual Meeting – 15-17 March 2017 - Manchester, UK
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4. **Diagnosis and Neurological Status as predictors of Surgical Site Infection in Primary Cervical Spinal Surgery**
   Sleiman Haddad, Paul Millhouse, Mitchell Maltenfort, Camilo Restrepo, Alexander R. Vaccaro
   Poster at the ORS/PSRS 3rd International Philadelphia Spine Research Symposium; November 9 - 12, 2015 Philadelphia - USA

5. **Influence Of Neurological Status And Diagnosis On Surgical Site Infection In Cervical Spinal Surgery**
   Sleiman Haddad, Paul Millhouse, Mitchell Maltenfort, Camilo Restrepo, Alexander R. Vaccaro
   Poster at the North American Spine Society 30th Annual Meeting 14-18 October 2015; Chicago – USA

6. **Influence Of Neurological Status And Diagnosis On Surgical Site Infection In Cervical Spinal Surgery**
   Sleiman Haddad, Paul Millhouse, Mitchell Maltenfort, Camilo Restrepo, Alexander R. Vaccaro
   Oral Presentation at the 16th EFORT Congress, 27-29 May 2015; Prague – Czech Republic.

ABBREVIATIONS

ASA – American Society of Anaesthesiologists
ASD – Adult Spinal Deformity
CDC – Centers for Disease Control
CI – Confidence interval
COMI – Core Outcome Measure Index
Deg - Degenerative
ESSG – European Spine Study Group
HRQoL – Health Related Quality of Life
I&D – Irrigation and Debridement
ICU – Intensive Care Unit
LOS – Length of Stay
MCS – Mental Component Score
MP – Myelopathy
MRSA – Methicillin-resistant Staphylococcus aureus
NIS – Nationwide Inpatient Sample
ODI – Oswestry Disability Index
OR – Odds Ratio
PCS – Physical Component Score
PJK – Proximal Junctional Failure
PROM – Patient Reported Outcome Measure
SCI – Spinal Cord Injury
SF36 – Short Form 36
SRS – Scoliosis Research Society
SSI – Surgical Site Infection
TJUH – Thomas Jefferson University Hospital
USD – United States Dollars
VAC - Vacuum Assisted Closure
VAS – Visual Analog Scale

INTRODUCTION AND CURRENT STATE

THE GENERAL BURDEN OF SURGICAL SITE INFECTION

Surgical Site Infection (SSI) is the leading hospital-acquired infection in the United States of America (US) according to the Centers for Disease Control (CDC), accounting for nearly 22% of all nosocomial infections(1). Moreover, 77% of acute mortalities in patients with SSI were directly related to SSI(2). Not only does the occurrence of infection lead to an increased length of hospital stay - by a median of 2 weeks per patient - but it also increases the likelihood of readmission and reoperation by five folds and overall mortality by twofold (3, 4). This poses significant economic burden because of excess resource consumption (nearly $1.8 billion a year), increasing health-care costs by 300% (1, 3, 5-7). Also, the occurrence of infection would alter the final outcome of any surgical procedure (5). As such, SSI is currently considered one of the most tenuous adversaries to any surgical act. In an effort to fight SSIs, the Centres for Medicare and Medicaid Services have classified them as a non-reimbursable serious hospital-acquired condition that is "reasonably preventable" through the use of evidence-based guidelines(8). Even when it is considered to be an avoidable complication, its incidence rate and burden remain relatively unchanged over the years. Especially today, SSI is a morbid complication that increases medical, social and economical costs to patients and society.

SURGICAL SITE INFECTION IN SPINAL SURGERY

INTRODUCTION

In spine surgery, deep SSI is also recognized as one of the most common causes of morbidity. It has been reported to affect between 0.03–22.0 percent of patients (9). In fact, spinal surgeries report a higher rate of infection compared to other orthopaedic surgeries such as total joint replacement (10). Like in other surgical procedures, over the last few decades we have witnessed a steady increase in number of spinal surgeries performed for cervical pathologies as well as for adult spinal deformities (ASD) (11-13). Not only has the volume of spinal surgeries increased, but also the patient is generally older and with more medical co morbidities. As an example, the total ASD volume increased by 112.5% ($p = 0.029$), and both the average patient age ($p < 0.001$) and number of patients >65 years old significantly increased from 2003 to 2010 ($p =0.009$)(12). Over the same period, the number of patients undergoing cervical surgeries increased by 141% and the same increase in age was observed (11). The largest increase in surgical utilization was for patients aged 65-69 years with an increase of 0.68 patients per 100,000 people per year ($p<0.001$), followed by patients aged 70-74 years (14). Despite an older patient population with greater comorbidities, hospital length of stay (LOS) and mortality has not changed significantly (13). The overall morbidity however did increase by 22.7% in the ASD ($p <0.001$) and it increased with age (12). Based on these figures the reader would expect a steady increase in both the volume and incidence of SSI. No independent study has documented such an increase in the past and this was one of the objectives of this thesis project

DEFINITION

The most widely used definition of SSI is the one developed by the CDC. According to the CDC, SSI can be divided into three broad groups: Superficial, Deep and Organ/Space Related(15). Despite this definition that covers over 1 year after index surgery, the current literature lacks a uniform diagnosis of SSI and different studies establish the end point of vigilance differently. Most administrative databases limit the follow-up to 30 or 90 days and can give a falsely reduced incidence. In addition they use administrative diagnostic codes that might not be in accordance with clinical findings (16). The impact this has on quality of research is undoubtful however the real significance is still to be determined (16, 17).

SUPERFICIAL SURGICAL SITE INFECTION

Infection occurs within 30 days after the operation and infection involves only skin and subcutaneous tissue of the incision and at least one of the following:

- Purulent drainage with or without laboratory confirmation, from the superficial incision
- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
- At least one of the following signs or symptoms of infection: pain or tenderness, localised swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative
- Diagnosis of superficial incisional SSI made by a surgeon or attending physician

DEEP SURGICAL SITE INFECTION

Infection occurs within 30 days after the operation if no implant is left in place or within one year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissue (e.g. fascia, muscle) of the incision and at least one of the following

- Purulent drainage from the deep incision but not from the organ/space component of the surgical site
- A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain or tenderness, unless incision is culture-negative
- An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination
- Diagnosis of deep incisional SSI made by a surgeon or attending physician

ORGAN / SPACE SURGICAL SITE INFECTION

Infection occurs within 30 days after the operation if no implant is left in place or within one year if implant is in place and the infection appears to be related to the operation and infection involves any part of the anatomy (e.g., organs and spaces) other than the incision which was opened or manipulated during an operation and at least one of the following:

- Purulent drainage from a drain that is placed through a stab wound into the organ/space

- Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
- An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
- Diagnosis of organ/space SSI made by a surgeon or attending physician.

INCIDENCE

We know that incidence of SSI in spine surgery varies according to the diagnosis, surgical approach, operative region, number of involved levels, and use of instrumentation (18-20). Another source of variability is the diagnostic criteria for the infection itself (18, 19, 21). In a systematic review of the spinal literature, Patel et al. found the pooled average SSI rate to be 1.9% (median, 3.3%; range, 0.1%–22.6%) based on 196 different study cohorts (22). The highest rate was in patients undergoing instrumented spinal fusion where the pooled average SSI rate was 3.8% (median, 4.2%; range, 0.4%–20%) compared to 1% for patients undergoing non-instrumented laminectomies. (22). Infection usually occurs within the first 30 days after surgery (early SSI). The pooled average of early SSI rate is 2.1% compared with 0.8% for pooled average late SSI rate.

CAUSATIVE PATHOGENS

The leading causal agent of SSI after spine operations is *Staphylococcus aureus* (23). In the same systematic review by Patel et al, and after an analysis of 39 studies, the pooled average contribution of *S. aureus* infections to spinal SSIs was calculated to be 49.3% (median, 50%; range, 16.7%–100%; 2,272 SSIs in total) (22). The pooled average proportion of *S. aureus* SSIs attributable to MRSA was calculated to be 37.9% overall and climbed to 52.4% (median, 100%) among patients experiencing early *S. aureus* SSIs. The prevalence of MRSA is known to have geographical variations and is higher in the United States (US) (24). In Catalonia, the incidence of MRSA in orthopaedic procedures excluding spinal surgery are less than those reported in the North American literature and amount for 8-12% of all infections. Similarly, only 28% of all spinal SSIs between 2009 and 2016 were due to *S. aureus* in a recent intuitional review from Vall d'Hebron Hospital (25). Out of these, only 24% were due to MRSA.

Staphylococcus epidermidis (coagulase-negative staph) is another common organism that is often associated with the use of spinal instrumentation and accounts for up to 31.4% of SSIs (26). Gram-negative bacteria (*Enterococcus, E. coli*, and *Peptostreptococcus*) are found in up to 30% percent of SSIs, occurring more commonly at the lumbosacral junction due to proximity to the perianal area

(27). The prevalence of gram negative bacteria might be higher in the Mediterranean setting. At our centre, 38% of all spinal SSI were due to gram negative bacteria (28, 29).

Cutibacterium acnes (previously known as *Propionibacterium acnes*) is an anaerobic organism that is also part of the normal skin flora. It has been identified as a common cause of delayed surgical site infection and is commonly associated with the use of spinal instrumentation, mainly in idiopathic scoliosis (30). *Cutibacterium acnes* is a slow-growing organism that requires extended incubation time for growth; therefore, appropriate handling in the microbiology laboratory is essential to identify this organism as the cause of SSI (31).

BURDEN OF SURGICAL SITE INFECTION IN SPINAL SURGERY

SSI in spinal surgery is notorious to increase morbidity, mortality and costs (32, 33). It is also associated with increased LOS, more unplanned readmissions and revisions and even with more pseudoarthrosis (34). In a previous study by the spinal unit at Vall d'Hebron Hospital only 73% of patients maintained their original implants at 2 years after index surgery compromising final outcomes (35).

Overall, SSI account for nearly $1.6 billion per year in the US. Spine surgical patients incur approximately double the health care costs when they develop an SSI and nearly half of all 30 days readmissions are due to SSI (36). Yeramaneni et al. calculated the cost of infection in ASD to be between $15,817 and 38,701(32). Kuhns et al studied patients undergoing posterior cervical surgery and the average cost of infection was $12,619 (37). It should also be noted that the costs vary widely between studies in function of where the study was conducted and what types of costs were considered. It is hard therefore to precisely estimate costs and apply them to the local setting. Mainly the cost per day of hospitalization differed between studies, countries and hospital settings Prolonged LOS on general wards and in the Intensive Care Unit (ICU) as a result of contracting an SSI was reported to constitute the major cost burden in multiple studies of SSI not limited to spinal surgery. Alfonso et al. reported that in Spain and across multiple surgical specialties, the direct total healthcare cost of developing an SSI was $1,084,639, which was mainly attributable to prolonged hospitalization (37%) and other hospital costs (43%)(38). Primary healthcare costs and antibiotic costs accounted for 14% and 6%, respectively. Following discharge from hospital, SSI patients still rely on healthcare from other community care services, which will further contribute to the economic burden of infection. In the same study by Alfonso et al. when indirect costs such as SSI-related morbidity/mortality and societal costs were also considered, direct healthcare costs only accounted for only 10.5% of the total financial burden(38). When analyzing the wider impact of SSI we should not forget that absence from work while under prolonged treatment also constitutes an important

economic cost to both patient and society in terms of lost income and reduced work productivity. This personal cost has not been analyzed so far.

The mortality associated with SSI is not neglectful. A large prospective U.S. study of 24,774 veterans who had spine surgery for fusion, decompression, or instrumentation reported a 30-day mortality rate of 1.06% among patients who developed SSI compared with 0.5% among those who had no SSI (39). In a large Japanese retrospective study of 7,178 patients who had spine surgery, the mortality rate was reported to be 2.2% among those who developed SSIs at 1 year (40) . Similarly, in a study done at our centre of 473 patients who underwent posterior spinal fusion and instrumentation the mortality rate was 2.3% among patients who developed deep SSIs (35). A retrospective analysis of data from a Japanese nationwide administrative inpatient database reported that among 465 patients who underwent spinal fusion surgery for atlantoaxial subluxation and had rheumatoid arthritis, the in-hospital mortality rate was 6.7% among patients who developed SSIs (41). More recently, in an single centre review by Casper et al. ninety-day, 1-year, 2-year, and 5-year mortality rates were 1.54% versus 1.03% ($p=0.700$), 4.62% versus 1.2% ($p=0.006$), 7.73% versus 2.25% ($p=0.001$), and 15.45% versus 3.43% ($p<0.001$) for SSI versus control patients, respectively(33). Predictors of 2-year mortality in the SSI cohort were increased age ($P=0.020$) and increased Charlson Comorbidity Index ($p<0.001$).

RISK FACTORS AND PREVENTION OF SURGICAL SITE INFECTION IN SPINAL SURGERY

INTRODUCTION

Primary prevention is of major importance in the fight against SSI. As such, proper recognition of a patient's risk factors for SSI may allow for patient´s optimization and the implementation of interventions that prevent severe infections. Thus, several studies were performed to identify the specific risk factors for SSI. Under the same premises, identifying risk factors not only aids in preventing infections but also associated patient suffering and health care costs, as well as improving overall outcomes.

SSI RISK FACTORS

Risk factors can be divided broadly into two categories: modifiable and non modifiable. Recognizable but non-modifiable risk factors for spinal SSI are many and include: age, peripheral vascular disease, coronary artery disease, diabetes, renal insufficiency, American Society of Anesthesiologists (ASA) grade, revision surgery, prior infection, trauma, spinal oncology, or adjuvant radiation therapy among others (18-20). Many modifiable factors have also been reported. These include body mass index (BMI), glycaemic control, meticulous haemostasis and wound closure, the use of appropriate antibiotics 30 to 60 minutes before incision, double gloving and surgical team-wide maintenance of sterility, effective closure of durotomies and pseudomeningocele avoidance, reduced operating room traffic, accelerated operative times, use of intraoperative irrigation, and use of minimally invasive approaches when appropriate (42-44). However, these risk factors, and others, have been identified in heterogeneous patients' population, in big data series, or in small and specialized series. Also, the significance of some risk factors has been difficult to establish, and the significance of any given risk factors varies between different articles. As such, many systematic reviews have been conducted to scientifically summarize these findings, but none have specifically evaluated the influence of traumatic injury or neurological status (18, 19, 21).

TRAUMA AND NEUROLOGICAL STATUS AS PREDICTORS OF INFECTION

While numerous risk factors for SSI after cervical spinal surgery have been identified, the relationship between preoperative neurologic status and SSI has not been fully explored. Increased

approach-related perioperative morbidity was demonstrated in patients with cervical spondylotic myelopathy (45-48). Increased morbidity and mortality have been documented in patients following surgery for traumatic injuries compared to patients undergoing surgery for non-traumatic indications, and a single study linked spinal cord injury to infectious outcomes (43, 49-52). However, no studies have been done to compare incidence of SSI based on neurologic status in patients undergoing cervical procedures for either degenerative or traumatic indications.

SSI after a traumatic spinal surgery was shown to be between 3.4 and 17% (43, 51, 52). Rechtine et al. reported a SSI rate of 10.2% for 117 fractures at the thoracic-lumbar junction and Blam et al. reported a SSI rate of 9.4% for 256 cases of surgically treated spinal trauma (52). The series by Lonjon excluded polytraumatic patients and had an SSI of 3.4%. None of these had a homogenous patient sample (51). Only Blam et al directly compared elective surgery to traumatic Spinal Cord Injury (SCI) patients finding statistical significance (43). In a study by Yalda et al. focusing exclusively on cervical spine population, the authors found higher incidence of major and minor complications in infectious and oncological cases when compared to degenerative or traumatic cases, but this difference did not reach statistical significance. The authors however did not specifically study SSI as a single complication and instead looked at the overall complication rate(49).

As for the neurological status, SCI was found to be a predictor of infection in a single study by Rechtine et al (52). In this study the authors found a higher incidence of SSI after thoracic or lumbar fracture stabilization in patients with in complete SCI (7/17patients, incidence 41%) when compared to those with an intact neurological status (3/61patients, incidence 4.9%). They failed to find any difference between patients with incomplete SCI (2/39 patients; 5.1%) when compared to intact neurological status.

In patients undergoing elective surgical decompression, myelopathy was found to be a predictor of surgical complication or increased morbidity or mortality in only 5 studies (46-48, 53, 54). Only two of these found an increased infection rate in patients with myelopathy when compared to patient who did not have myelopathy. Boakye et al found higher rates of infections in patients with myelopathy (0.43 vs. 0.15%) linking it to a more severe compression or older age (46). Shamji et al found that posterior cervical approaches and myelopathy were associated with higher overall mortality and morbidity as well as costs and hospital stay after degenerative cervical spinal surgery (47). Infection rates were as follow: 0.02% (Anterior approach w/o myelopathy); 0.1% (anterior w myelopathy); 0.36% (posterior w/o myelopathy) and 0.55 (posterior with myelopathy).

SSI PREVENTION

When considering efforts to minimizing SSI, understanding these surgical tenets and recognizing risk factors for improved patient selection are paramount (42-44).

Prevention of SSI starts with the first encounter with a surgical candidate. The surgeon should proceed to a meticulous screening of preventable risk factors such as smoking, obesity, malnutrition, suboptimal hygiene or physical status and involve the patient in the fight against surgical complications. It is important to include patients and families as they have also been shown to be important in prevention strategies and that noncompliance is associated with poverty and longer time elapsed between instructions and surgery (55). Treating all remote infections including acne and skin candidiasis before surgery or accounting for immunosuppressive medication is also important. Finally surgical approach and invasiveness should be adapted to the patient's characteristics (56).

In the absence of a personalized risk calculator, stratifying patients into different risk groups based on their comorbidity index is of value for orienting both patients and physicians on the risks entailed. The ASA physical status score is the most widely used but remains highly subjective (57). Both Charslon and Elixhauser Indexes use patients' comorbidities to compute a score. However, the weight of each comorbidity as well as the number of comorbidities taken into account, vary between both scores. The interaction between patient's characteristics and surgical invasiveness is even harder to establish through a single score despite some recent intents (58). Therefore, in spinal infection, the quest for the perfect predictive index continues.

The perioperative prevention measures are also vital in lowering infection rates to bearable minimum. These include but are not limited to: strict prophylactic antibiotic protocol, positive pressure ventilation of the operating room, wearing surgical masks, wearing new head covering for each case, change contaminated or soiled scrub suits, proper skin preparation with alcohol-based solution removing all gross contamination, avoiding shaving of the surgical field and clipping only when necessary, avoiding adhesive drapes, and maintaining primarily closed incisions with a sterile dressing for 24-48 hours postoperatively (59-61).

Some interventions are still controversial but are safe to apply and should be considered in patients with high SSI risk. These include MRSA screening and treatment, intrasite vancomycin powder, diluted betadine irrigation, strict perioperative glycemic control, a silver-impregnated dressing, the use of negative pressure dressings, iodine impregnated spinal instruments and outer glove removal before using instrumentation(62, 63).

Intrasite vancomycin might be one of the controversial measures in current spinal literature (62, 64). The most recent systematic review does support its use (64). Patients in the vancomycin group had significantly lower risk for any SSI (odds ratio [OR]: 0.41; 95% confidence interval [CI]: 0.30-0.57; P < .001; I2 = 47%). Subgroup analysis supported these findings for deep SSI and for both 1gr and 2gr groups. The studies included did suffer from methodological limitation and were mainly retrospective and observational. Opponents to the use of vancomycin sustain their claim with pathogen shift towards gram negatives and selection of more aggressive strains. However, in a series by Grabel et al, vancomycin powder was indeed associated with a higher prevalence of gram negative and polymicrobial organisms but this did not adversely affect the need for multiple reoperations, antibiotic regimen, or LOS for these patients (65). In summary, they proved that the course of infection is similar in patients who previously received vancomycin powder when compared to those who have not (65). Other hypothetical and anecdotic risks include allergic reaction as well as renal and hearing toxicity. Godil et al showed that the use of vancomycin powder led to a cost savings of $438,165 per 100 posterior spinal fusions performed for traumatic injuries by reducing infection from 13% to 0% in their cohort (66). Theologis et al. spoke of a cost saving of $244,402 per 100 complex spinal procedures by decreasing infection rate from 10.9% to 2.6% (67). Neither author reported adverse effects with vancomycin. These cost savings combined with a proved safety profile make vancomycin an attractive measure to adopt in complex spinal cases or in patients with high risk for SSI.

SSI should be considered a system's failure and therefore changes at many points and steps may need to occur. An institutionalized approach to infection prevention is of prime importance and strict adherence to institution protocols would allow quantifying the impact of perioperative interventions on overall incidence. This approach should be evidence-based and take into consideration the recommendations of experts such as the CDC guidelines for prevention SSI (60, 68). Several structured processes or bundles have proven efficacy in spinal surgery, which, when performed collectively and continuously do reduce the risk of SSI. Vitale et al proposed 14 consensus recommendations to prevent SSI in high-risk paediatric spine patients (69). Ryan et al utilized such a system in paediatric spine and found a reduction of SSI from 5.8% to 2.3% and that the majority of recently infected cases occurred when noncompliance to the protocol occurred (70). The approach itself should be adapted to the local conditioning factors such as pathogens´ prevalence and type of surgeries done and take into consideration local experts' opinion. Yamada et al implemented care bundles for high risk patients including additional vancomycin prophylaxis, diluted povidone-iodine irrigation and nasal and body decontamination (71). The SSI rate decreased significantly from 3.8% to 0.7% ($p<0.01$) and no MRSA-related SSIs were found among those that received care bundles, even though MRSA was the predominant pathogen in their population. In another study by the Mayo clinic authors advocate it is possible to reduce SSI rates in spine surgery with easy, safe, and

cost-effective protocols, when implemented in a standardized manner (72). They could reduce infection rates from 6% to 2% over 10 year period by the progressive introduction of standardized measures such as the application of intrawound vancomycin powder, wound irrigation with dilute betadine solution, preoperative chlorhexidine gluconate scrubs, preoperative screening with nasal swabbing and decolonization of *S. aureus*, and perioperative antibiotic administration.

The fight against infection is a team effort. The surgeon plays a central coordinating role but should be supported by institutional protocols, compliant patients and aware staff. Identifying risk factors, optimizing modifiable factors and introducing effective and evidence-based prophylactic measures go hand in hand.

PRIOR CONTRIBUTIONS OF THE UNIVERSITAT AUTONOMA DE BARCELONA

Efforts at identifying SSI risk factors and implementing preventive strategies have also been conducted at the Universitat Autonoma of Barcelona. At Vall d'Hebron hospital, three studies have evaluated the interaction between urinary tract infection (UTI) and spine surgery SSI as well as implant survival after SSI (28, 29, 35). Nuñez-Pereira et al. have proven that preoperative bacteriological screening, treatment for bacteriuria, and individualized antibiotic prophylaxis were effective at reducing Gram Negative Bacteria SSI (28). In another study, the same authors proved that postoperative UTI might be the cause of a subsequent SSI in up to 38% of cases (29). According to this study, patients receiving ciprofloxacin for UTI had higher microbial resistance rates to fluoroquinolones at SSIs (46.13%) than those without previous ciprofloxacin use (21.9%). They went on to recommend further efforts to reduce the incidence of postoperative UTI and provide adequate empirical antibiotic therapy that avoids quinolones whenever possible, which would help reduce SSI rates and potential microbial resistance.

Recently, Bosch et al. have presented the experience of our institution in the treatment of spinal SSI (73). The authors have reviewed the epidemiology of infection at our hospital and response to treatment in two historic cohorts. Patients receiving 6 weeks of targeted antibiotic regimen fared similarly to patients receiving longer regimens. Their work supports our current practice.

TREATMENT OF SURGICAL SITE INFECTION

Surgical site infections in spine surgery can be complex to manage. Patients often require prolonged hospitalization for extended antibiotic regimes and sometimes multiple wound debridement and irrigation (74). It is not unusual that instrumentation be removed - in patients failing multiple debridements or in chronic cases - with the risk that this entails on spinal stability or deformity progression (75). Also, soft tissue coverage can be a real concern in some circumstances (76).

The conventional approach to spinal SSI treatment resolves around early recognition, adequate irrigation and debridement (I&D) and prolonged culture-specific antibiotic administration.

Usually soon after the diagnosis of deep wound infection is made, the patient is brought to the operating theatre where the wound is thoroughly debrided and irrigated under general anaesthetic. Special care is taken to debride all devitalized tissue and bone. If the gross aspect is satisfactory and soft tissue coverage is possible with no tension, the wound is primarily closed over suction drain. If after the debridement the tissue still looks contaminated or the soft tissue coverage is questionable, the wound can be packed open or with vacuum-assisted dressing and re-debrided at a later stage (76-78). In cases of infection with a delayed onset and with solid fusion, the instrumentation can be removed. The surgeon should try to maintain the implants when fusion has not occurred or when removing them might cause instability or deformity recurrence. Unfortunately this is not always possible and more than 50% of patients with delayed onset infection might end up needing instrumentation removal (79). Cahil et al analysed their 30 years' experience treating adolescent scoliosis. On average, 2 surgeries were required to eradicate the infection and late infections (> 90days after index surgery) were harder to treat. In this subgroup only 13% could retain their original implants (vs. 75% in early infections; $p < 0.05$). Forty-four percent of patients who developed an infection had significant progression of their deformity, with an average increase in deformity magnitude of 27 degrees. Implant removal predisposed patients to progression of deformity. They concluded that in late infection implant removal is often required which puts patients at risk for deformity progression. Hedequist et al. reviewed 26 cases of delayed surgical site infections after spinal deformity surgery (75). In their series, no patient was able to clear their infection without spinal implant removal. They showed that the LOS and the cost were proportional to the number of I&Ds done before finally removing the implants. They therefore advocated for an early implant removal in delayed infections. Six patients in their series needed re-instrumentation at a later stage due to deformity progression despite evidence of fusion. Similarly, Munshick et al recommended re-instrumentation after implant removal to prevent deformity recurrence(80).

Dipaola et al. studied risk factors for failed I&Ds and concluded that the lumbar region, diabetes, the presence of instrumentation, the use of allograft, and a polymicrobial flora are significant predictors for the need for multiple I&D (74). They accordingly developed a predictive score for the need of multiple I&Ds.

Surgical management of deep wound infections needs to be combined to a long term antibiotic therapy. Antibiotics should be withheld until I&D. Directly after surgical samples are taken; patients should be placed on broad spectrum antibiotics that take into consideration the local pathogens and the patient's own personal history and risk factors (81). The definitive treatment depends on the culture results and sensibilities and is usually for 6-8 weeks. Surgeons and infectious disease specialists can agree to put patients on longer suppressive regimen for patients with resilient infections or when more I&Ds or implant removal has been ruled out (82).

IMPACT OF SURGICAL SITE INFECTION ON FINAL RESULTS

The benefit of surgical intervention is increasingly being evaluated based on patient-reported outcomes and standardized health-related quality of life (HRQoL) measures that allow comparison with alternative techniques, unrelated disease states, and population norms (83). This is especially true in elective corrective surgeries such as ASD. In spinal surgery, both patients and surgeons accept the high surgical risks entailed (including SSI) in the hope of achieving the ultimate goal, which is improving patients' quality of life. Little is known however of the effect SSI has on HRQoL, and whether the occurrence of an infection can ultimately jeopardize this anticipated surgical benefits. While most studies have focused on risk factors and prevention of SSI as well as on the economical and medical burden of SSI, patient's health and functional outcomes after SSI have received far less interest.

Only four studies set out to determine surgical outcome after SSI in spine surgery (84-87). In his matched control analysis in 16 patients with posterior spinal fusion, Mok et al detected no significant difference in the Physical Function, Role Physical, Bodily Pain, and General Health domains between the infection group and control group at an average of 62 months (84). In a similar study on the other hand, Petilon could only find a difference in back pain and Oswestry Disability Index (ODI) between patients suffering from a deep infection after a lumbar fusion and those who don't. (88). Rhin et al found no difference in the pain, function, self-image, satisfaction, or total Scoliosis Research Society 24 scores after SSI in adolescent patients with idiopathic scoliosis after a minimum of 2 years (86). Falavigna et al (85) studied patients having lumbar fusion for degenerative disc disease, and found no significant difference in pain, functional disability, quality of life, or depression and anxiety. However, 53.8% of the patients with infection were not satisfied with the procedure at the final evaluation, compared with 15.4% of the patients without a deep wound infection ($p = 0.003$).

Even though infection does not seem to significantly alter the ultimate functional outcome, these studies did not follow the recorded variables through time and they did not study the difference between infected and non-infected patients at defined time intervals. They included heterogeneous groups of patients with respect to preoperative diagnosis and surgical procedure, had a small sample size, lacked detailed preoperative records or did not specifically consider SSI.

CONTEXT AND JUSTIFICATION OF THE CURRENT WORK

In the current era of quality improvement and cost reduction, the need for spine-specific research on SSI reduction and management has never been higher. There remain many unexplored fields such as the real impact of SSI beyond costs and resource utilization, the trends in SSI, and the interplay between risk factors and clinical outcome.

Over the last decade there has been a significant increase in volume of spinal surgeries performed as well as in medical and surgical complexity of patients. This was accompanied with an increased overall morbidity and volume of complications. At the same time, health care professionals have become more aware of the impact of specific preventable complications such as SSI and huge efforts have been directed to reduce SSI incidence. Still, little is known about the trend in incidence of SSI over this time period - whether it increased with the overall morbidities or decreased as part of prevention campaigns.

In the absence of reliable individual risk calculators for SSI, it is important to identify key risk factors and predictive scores that can recognize patients at risk. In turn these patients need to be properly informed about SSI in terms of infection course and outcome. In addition, they need to be object to strict care, and preventive measures should be applied accordingly to decrease their risk. Also they should be under increased vigilance for SSI, for early diagnosis and treatment in the hope of reducing the overall impact of SSI.

Finally, while most studies have focused on risk factors and prevention of SSI as well as on the economical and medical burden of SSI, patient's health and functional outcomes after SSI have received far less interest.

For the exposed, the aim of this doctoral thesis is to review the risk factors for developing a SSI after spine surgery, as well as how SSI affects clinical outcome. It mainly focuses on the interaction between the diagnosis (Traumatic vs. Degenerative) and the neurological status (Spinal Cord Injury or Myelopathy) as a predictor for SSI. It also reports the associated morbidities and costs of SSI and evaluates the surgical outcomes after SSI. The National Inpatient Survey (NIS) as well as the Thomas Jefferson University Hospital (TJUH) databases were probed to analyse infection in patients with primary cervical spine surgery, based on the diagnosis and neurological status. Using a multivariate analysis, all interplaying comorbidities and risk factors have been identified in this population. A subsequent resource utilization analysis has been done. The European Spine Study Group (ESSG) prospective database has been used to study the functional and clinical outcomes of

SSI in patients with posterior fusion for Adult Spinal Deformity (ASD). Readmissions, reoperations, deformity correction and fusion rates were also studied.

The author chose a high volume procedure (cervical spine) and used big data (NIS) to probe for risk factors. These were later validated in a single centre US database. He then used a solid prospective database of ASD with well documented clinical and functional outcomes to check for the clinical impact of SSI. The relatively high prevalence of SSI in the ASD population has allowed obtaining an adequate cohort for analysis.

HYPOTHESIS

I. Study 1 (Cervical Spine):
   A. Primary Hypotheses:
      i. Patients with a traumatic diagnosis are more prone than patients with a degenerative diagnosis at developing SSI.
      ii. Patients with neurological deficit (Myelopathy and/or SCI) are more prone at developing SSI than patients with intact neurological status.
   B. Secondary Hypotheses:
      i. SSI rate has increased with increasing patient volume and complexity
      ii. SSI is associated to increasing age and comorbidities
      iii. SSI increases hospital stay and charges

II. Study 2 (ASD):
   A. Primary Hypotheses
      i. Patients who develop deep SSI have significantly worst short-term (6 months) HRQoL parameters, more pain and exhibit lower satisfaction compared to patients with no SSI.
      ii. Patients with resolved deep SSI have significantly equal mid-term (2 years) HRQoL parameters, pain and exhibit similar satisfaction as patients who had no SSI.
   B. Secondary Hypotheses:
      i. Deep SSI increases short and midterm term morbidity and mortality.
      ii. Deep SSI increases readmission and reoperation rates non-infectious causes.
      iii. Patients with deep SSI have worst radiological outcomes (deformity correction and pseudoarthrosis)

OBJECTIVES

This thesis project has two arms. In the first, we aim at studying patient's risk factors in a clean primary cervical surgery where SSI incidence was found to be lowest (0.03-0.5%). We also aim at directly comparing Traumatic and Degenerative cervical surgery as well as surgeries in the context of a neurological deficit (Spinal Cord Injury or Myelopathy). We would check if infection would affect hospital stay and hospital charges in this patient population as well as post discharge destination.

Under the second arm, we would compare surgical outcomes based on the occurrence of infection, in the context of patients with an extensive posterior fusion, as Adult Spinal Deformity (ASD). We would check if infection in this subgroup alters readmission rates, infectious and non-infectious reoperation rates, fusion rates, deformity correction as well as HRQoL parameters, pain and satisfaction. Specific objectives for the different studies that compose this thesis will be as such:

I. Study 1 (Cervical Spine):
   A. Primary Objectives:
      i. To compare rates of SSI in Traumatic and Degenerative cervical surgery (Study 1)
      ii. To compare rates of SSI in the context of a neurological deficit (Spinal Cord Injury or Myelopathy).
   B. Secondary Objectives:
      i. To study the trend in incidence of SSI
      ii. To compare and contrast the different risk factors including comorbidity indexes.
      iii. To compare hospital stay and hospital charges in function of SSI

II. Study 2 (ASD)
   A. Primary Objectives:
      i. To compare short and median term HRQoL parameters outcomes, pain and patients satisfaction based on the occurrence of deep infection
   B. Secondary Objectives:
      i. To establish incidence and course of deep SSI in adult spinal deformity population
      ii. To compare readmission rates and reoperation rates (for both infectious and non infectious causes).
      iii. To compare radiological outcomes, as are deformity correction and fusion rates in the context of SSI.

STUDY DESCRIPTION

This doctoral thesis is composed of two separate studies and has been done using a US nationwide and specialized European databases as well as single institutional charts review. The final objective is to empower statistical analysis while providing detailed descriptive patient's history.

STUDY DESIGN

CERVICAL SPINE: (STUDY 1)

STUDY POPULATION

The Nationwide Inpatient Sample (NIS) database was utilized to access patient information from the years 2000 to 2011. The NIS is the largest publicly available all-payer inpatient care database containing de-identified discharge data, approximating a 20% stratified sample of U.S. community hospitals(89). The Agency for Healthcare Research and Quality reports high NIS accuracy and agreement between data estimated by the NIS and the National Hospital Discharge Survey. NIS data quality is reported publicly on the Health Care Utilization Project website. Coding for the NIS is consistent with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Using an analogous billing code search, our institutional database was also used to collect data from 2000 to 2013 for comparison purposes.

Patients were selected for inclusion based on appropriate ICD-9-CM procedure codes linked to specific diagnosis codes (**Table 1**). Diagnostic codes were selected in order to stratify patients by one of four preoperative diagnoses:

1- Cervical radiculopathy without myelopathy
2- Cervical radiculopathy with myelopathy
3- Traumatic cervical injury without neurologic injury
4- Traumatic cervical injury with neurologic injury.

Patients were excluded based on diagnostic codes for congenital deformity, infection, inflammatory disease or neoplasia. Procedural codes were selected such that only primary procedures were considered and revisions were excluded. Patients undergoing multilevel fusion were arbitrarily grouped into those undergoing fusion at two or three levels and those undergoing surgery at between four and eight levels when the number of levels was available. This method of duplicate

patient selection on the basis of ICD9 codes inherently removed cases of inconsistency between coding search based on diagnosis and procedure.

Table 1. ICD-9-CM Diagnostic & Procedural Codes

Diagnostic Codes	
Group 1: Cervical Radiculopathy without Myelopathy	
Code	Description
721.0	Cervical spondylosis without myelopathy
722.0	Displacement of cervical intervertebral disc without myelopathy
722.4	Degeneration of cervical intervertebral disc
723.0	Spinal stenosis of cervical region
723.1	Cervicalgia
723.4	Brachial neuritis or radiculitis
723.7	Ossification of the posterior longitudinal ligament in the cervical region
Group 2: Cervical Myeloradiculopathy	
Code	Description
721.1	Cervical spondylosis with myelopathy
722.7	Intervertebral disc disorder with myelopathy
Group 3: Traumatic cervical injury without neurologic injury	
Code	Description
805.00 – 805.18	Fracture of vertebral column without mention of spinal cord injury
Group 4: Traumatic cervical injury with neurologic injury	
Code	Description
806.00 - 806.19	Fracture of vertebral column with spinal cord injury
952.00 - 952.09	C_1-C_4 level with central cord syndrome
Procedural Codes	
Code	Description
03.09	Exploration and decompression of spinal canal
03.53	Repair of Vertebral Fratcure
03.99	Other operations on spinal cord and spinal canal sturctures
80.50, 80.51	Excision of intervertebral disc
81.0	Spinal fusion
81.02	Other cervical fusion, anterior technique
81.03	Other cervical fusion, posterior technique
81.61	360 degree spinal fusion
81.62	Fusion of 2-3 vertebrae
81.63	Fusion of 4-8 vertebrae
81.64	Fusion of 9 or more vertebrae
84.51	Insertion of Interbody spinal fusion device
81.63	Fusion of 4-8 vertebrae

The same analysis using the same diagnostic and procedural codes was conducted using the institutional database (TJUH), including patients from the years 2000 to 2013.

ANALYZED VARIABLES AND MEASURED OUTCOMES

In the NIS sample, outcome variable was limited to SSI (postoperative infection deep or superficial, including wound complications such as hematoma and seroma). The following demographic variables were collected: age, BMI, sex, race, hospital location and region. Age was entered as a continuous variable, and the remaining as categorical variables. In the TJUH database and contrary to the NIS, we could account for multiple admissions for cervical surgeries, and only the first one was retained. Using this database, some comorbidity indexes were used to account for confounding factors. These included ASA Physical Status Score and both the Charlson and Elixhauser comorbidity index.

STATISTICAL ANALYSIS

Statistical analyses in this study were performed using R 3.2 (R Foundation, Auckland, NZ). Descriptive and bivariate comparisons of demographic variables were performed using the Wilcoxon test for age, BMI, LOS and costs and chi-squared analysis for the categorical variables (sex, race, hospital region…). Multi-variable logistic regression modelling was performed to determine odds ratios with corresponding confidence intervals for the outcome variables.

ADULT SPINAL DEFORMITY (STUDY 2)

STUDY POPULATION

This is a matched control study using a prospective multicentre database of patients with ASD.

We retrospectively analyzed prospectively collected data from ASD patients recruited in 6 European centres from 4 different countries sharing a common ASD comprehensive database (83).

All adult patients who had undergone posterior instrumented spinal fusion for ASD with a minimum two-year follow-up were included. Institutional Review Board (IRB) approval was obtained from all participating centres, and informed consent was obtained from all enrolled patients.

From this cohort, we then identified all patients who had been treated for deep SSI within the first six months of index surgery. The treating surgeon in each case made the diagnosis of infection clinically following the standard guidelines for deep SSI (2, 15). Diagnosis was later confirmed by positive results on samples sent for microbiology. Treatment consisted of repetitive debridement as clinically needed, combined with targeted antibiotic therapy based on the growth sensibility. The choices of antibiotics as well as the duration of treatment were dependent on local protocols in each participating centre. As these were acute infections, original implants were maintained except in cases were infection was settled and poorly controlled.

Patients who had undergone treatment for a deep SSI formed the case group. They were accordingly matched to controls based on demographic and surgical variables known to affect both exposure (infection) and outcomes (quality of life) (18, 19). These were: gender, Age, ASA Score (by categories: 0-1; 2; 3-4), Revision vs. Primary surgery, Extent of Fusion and the use of three-column osteotomies (Schwabb 3+). We excluded from the control group patients who had been diagnosed with other non-surgical infections. We aimed at the highest matching proportion to form the control group.

ANALYZED VARIABLES AND MEASURED OUTCOMES

Demographic and surgical variables were collected prospectively for all patients. All surgical and medical complications were recorded and were available for analysis. Patients were assessed at established time intervals (preoperatively, 6, 12 and 24 months post-operatively) with validated

HRQoL outcome tools, and sagittal and coronal deformity measurements on standard whole spine radiographs.

Parameters included Numerical Rating Scale for back pain and leg pain, ODI, 36-Item Short Form Health Survey (SF-36), Core Outcome Measures Index (COMI) and Scoliosis Research Society 22 Score (SRS-22 Score).

We were able to compare absolute HRQoL figures at the different time intervals between groups. We compared the changes relative to the preoperative value at these intervals.

Secondary outcome analysis included mortality, complications, unplanned readmission or reoperation, and size and maintenance of deformity correction. Radiological measures included overall deformity measurements, as well as sagittal and spino-pelvic alignment parameters: SVA, LL, PI, PT, PI-LL, GT and Major Cobb.

We also used the full sample to probe for factors associated with infection.

STATISTICAL ANALYSIS

We used SPSS (MAC Os version 24.1) for statistical analysis. Descriptive and bivariate comparisons of demographic variables were performed between cases and controls using independent t-test for continuous variable, and Fischer exact test for the categorical variables. The level of statistical significance was set at $p< 0.05$. A univariate and ordinary least square analysis with stepwise regression has been done to determine the risk factors for infection in our ASD population. Multivariate analysis was not possible due to low incidence and small sample size.

RESULTS

CERVICAL SPINE (STUDY 1)

PATIENT SAMPLE

A- NIS DATA:

A total of 1,872,327 patients were identified from the NIS database that met inclusion criteria from 2000 until 2011. Analysis detected high rates of inconsistent or missing data between the years 2000 and 2003. These four years were therefore dropped from the final analyses and only years 2004-2011 were considered for analysis. A total of 1.247.281 patients were finally retained. Only 68,482 patients had a traumatic diagnosis (5.49%). A total of 345,458 patients had myelopathy at the time of surgery, representing almost one quarter of all patients with a degenerative diagnosis. Nearly one in every 3 patients who underwent surgery for a traumatic cervical lesion had a spinal cord injury (SCI) (22,305 patients). While the yearly prevalence of traumatic diagnosis remained stable, the proportion of patients with myelopathy steadily and slowly increased over this 7-year period. **Table 2** presents the number of cases as well as the diagnostic class per year

Table 2: Number of cases per year, and prevalence of SCI and Myelopathy per year.

Year	Patients	Trauma Cases	% Trauma within All	Myelopathy Cases	% Myelo within Degenerative	SCI Cases	%SCI within trauma
2004	127339	7579	5,95%	30835	25,75%	2786	36,76%
2005	139334	6644	4,77%	36528	27,53%	2246	33,80%
2006	145415	7984	5,49%	36389	26,48%	2403	30,10%
2007	148779	7931	5,33%	40149	28,51%	2537	31,99%
2008	163092	8418	5,16%	44078	28,50%	2716	32,26%
2009	168564	9216	5,47%	47662	29,91%	2857	31,00%
2010	174938	12035	6,88%	52294	32,10%	3919	32,56%
2011	179820	8675	4,82%	57523	33,61%	2841	32,75%
Total	**1.247.281**	**68.482**	**5,49%**	**345.458**	**29,31%**	**22.305**	**32,57%**

Table 3 demonstrates the distribution of these patients by preoperative diagnosis and illustrates demographic and surgical differences between diagnostic groups. Patients with myelopathy in the degenerative group were significantly older and more frequently of male gender. Traumatic patients

and patients with SCI were more often male and younger compared to those patients without SCI. With respect to race, African-American, Asian and Hispanic patients presented more often with myelopathy or neurologic injury than without. Furthermore, the majority of patients in this cohort were treated in the Southern US hospitals, although no differences were observed between regions with regard to the incidence of patients presenting with myelopathy or neurological injury. Self-pay patients and patients with Medicaid presented more often with a traumatic injury than other patients. Medicare patients tended to present more often with myelopathy whereas patients covered under Medicaid were more likely to have a spinal cord injury. Patients with degenerative pathology were more often operated utilizing an anterior procedure while the posterior approach was more common in treating patients with for traumatic injury.

Table 3. Study population demographic and surgical information by preoperative diagnosis (NIS Sample)

Variables	Deg, no MP	Deg with MP	Trauma, no SCI	Trauma + SCI
Age (yrs) (mean +/- SD)	52.1+/- 11.7	57.3 +/- 12.6	50.7 +/- 22.3	46.6 +/- 21
Sex (%)				
Male	46,73%	53,78%	63,67%	74,54%
Female	53,27%	46,22%	36,26%	25,46%
Race (%)				
Caucasian	83,96%	76,07%	77,93%	70,93%
African-American	7,47%	13,55%	9,82%	13,34%
Hispanic	4,78%	5,83%	7,30%	9,54%
Asian	1,07%	1,71%	1,40%	2,25%
Native American	0,40%	0,46%	0,77%	1,03%
Other	2,33%	2,38%	2,78%	2,91%
Hospital Location (%)				
Rural	4,58%	4,12%	3,59%	2,43%
Urban Academic	45,83%	40,04%	25,53%	20,82%
Urban Private	49,59%	55,84%	70,88%	76,76%
Hospital Region (%)				
Northeast	14,34%	15,02%	15,92%	14,80%
Midwest	22,83%	20,30%	21,10%	20,96%
South	44,42%	43,62%	42,97%	42,18%
West	18,41%	21,06%	20,00%	22,06%
Primary Payer				
Medicare	22,10%	35,28%	27,67%	21,14%
Medicaid	5,11%	6,68%	8,91%	16,69%
Private Insurance	59,77%	48,31%	45,11%	44,25%
Self Pay	1,33%	2,05%	9,60%	8,94%
No Charge	0,17%	0,26%	0,63%	0,58%
Other	11,53%	7,41%	8,08%	8,40%
Surgical Approach				
Anterior	85,67%	78,96%	37,23%	43,51%
Unspecified	8,86%	1,81%	24,93%	7,40%
Posterior	4,53%	15,18%	30,40%	30,32%
Anterior + Posterior	0,94%	4,05%	7,44%	18,77%
Fusion Levels				
None or not Specified	8,86%	1,81%	24,93%	7,40%
2-3 Segments	79,26%	70,58%	62,92%	67,40%
4-8 Segments	11,79%	27,27%	11,54%	24,18%
9+	0,09%	0,35%	0,61%	1,02%

INSTITUTIONAL DATABASE (TJUH):

A total of 5490 patients had a primary cervical surgery between January 2000 and December 2013 and 96 (1.75%) developed a surgical site infection. In the institutional database we found a higher proportion of traumatic patients and patients presenting with a neurological deficit prior to surgery (**Figure 1**)

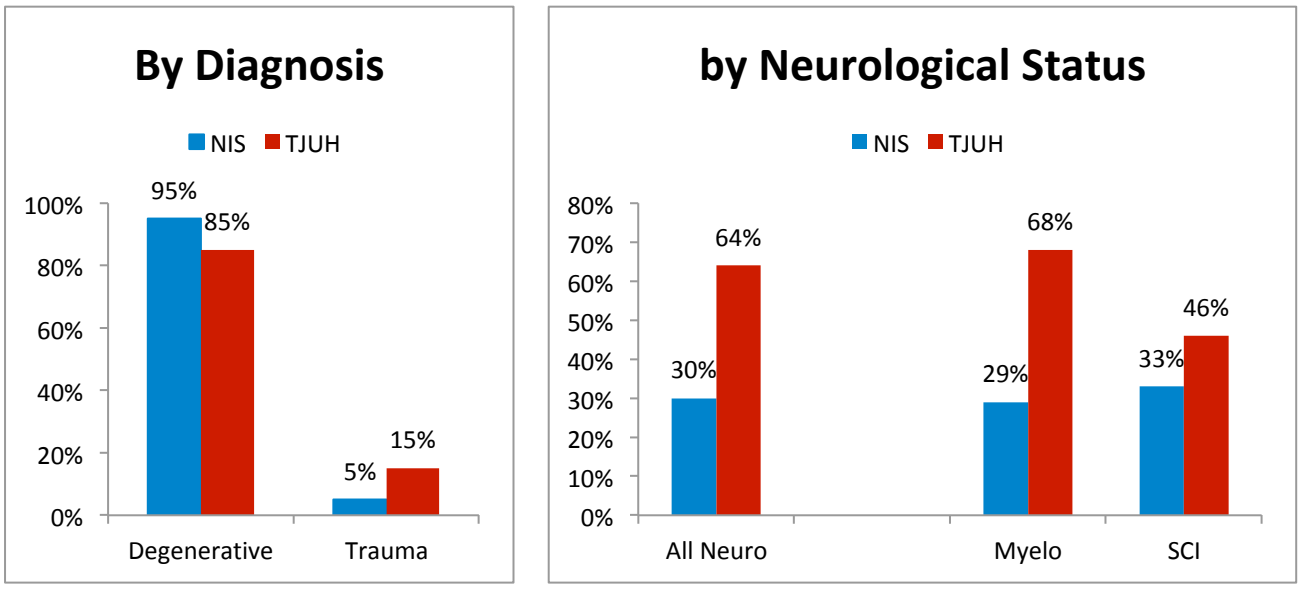


Fig. 1 Patient Distribution by diagnosis and by neurological status

In contrast to the NIS data, patients presenting with a traumatic diagnosis were more often older and with lower BMI than patients presenting with a degenerative diagnosis and were more often male. African-Americans presented more often after traumatic injury and with an associated neurological injury (myelopathy or SCI). Also, the ASA, Charlson and Elixhauser comorbidity indices increased moving across the 4 diagnostic groups, paralleling to some extent the increase in incidence of SSI. Those with workers' compensation claims most often presented with cervical degenerative pathology without associated myelopathy. More demographic and surgical details can be found in **Table 4**.

Table 4: Study population demographic and surgical information by preoperative diagnosis of the TJUH sample

	Degenerative		Traumatic	
Variables	**Simple**	**MP**	**Simple**	**SCI**
Age (years)	48.5 (SD 11.0)	55.5 (SD 12.4)	60.4 (SD 23.6)	53.3 (SD 23.0)
BMI	28.6 (SD 5.9)	29.3 (SD 6.3)	26.2 (SD 5.8)	26.4 (SD 5.9)
Sex (%)				
Male	51,42%	53,15%	61,81%	69,39%
Female	48,58%	46,85%	38,19%	30,61%
Race (%)				
Caucasian	80,84%	78,18%	87,42%	79,16%
African-American	7,56%	11,84%	7,51%	11,08%
Hispanic	1,21%	1,29%	1,55%	3,69%
Asian	0,54%	1,10%	0,22%	0,79%
Native American/Eskimo	0,07%	0,09%	0,00%	0,00%
Other	9,78%	7,49%	3,31%	5,28%
Primary Payer				
Medicare	8,84%	21,25%	38,41%	26,65%
Private	73,35%	68,20%	43,05%	46,17%
WC	12,48%	6,49%	2,43%	5,80%
NF	4,86%	3,53%	15,23%	18,47%
Labor	0,27%	0,28%	0,22%	0,00%
Self-Pay	0,20%	0,25%	0,66%	2,90%
Comorbidities Indices				
ASA	2.15(SD 0.55)	2.40 (SD 0.58)	2.69 (SD 0.74)	2.82 (SD 0.76)
Charlson	0.62 (1.01)	0.90 (1.43)	1.51 (2.40)	2.79 (3.16)
Elixhauser	1.25 (1.34)	1.63 (1.41)	1.78 (1.68)	2.23 (1.69)
Surgical Approach				
Anterior	79,76%	63,38%	14,79%	17,15%
Posterior	6,14%	20,97%	29,14%	33,25%
Combined	2,09%	11,59%	14,57%	37,73%
Not Specified	12,01%	4,06%	41,50%	11,87%
Fusion Level				
Unspecified/No fusion	23,89%	17,92%	26,05%	28,50%
2-3 Segments	65,18%	46,85%	58,72%	35,88%
4-8 Segments	10,39%	34,57%	13,69%	32,98%
9+	0,54%	0,66%	1,55%	2,64%

YEARLY VOLUMES AND SSI TRENDS

Figures 2 and 3 depict the trends in numbers and percentages in graphical format in both populations. The annual number of cases increased steadily over the study period (**Figure 2**) but the incidence of SSI remained relatively constant at 1.75% (Standard error 0.18%) (**Figure 4**). Both the number and proportion of patients with a degenerative diagnosis increased over this 10-year span. The proportion of patients with myelopathy within the degenerative population increased which is consistent with the NIS data **(Figure 3).**

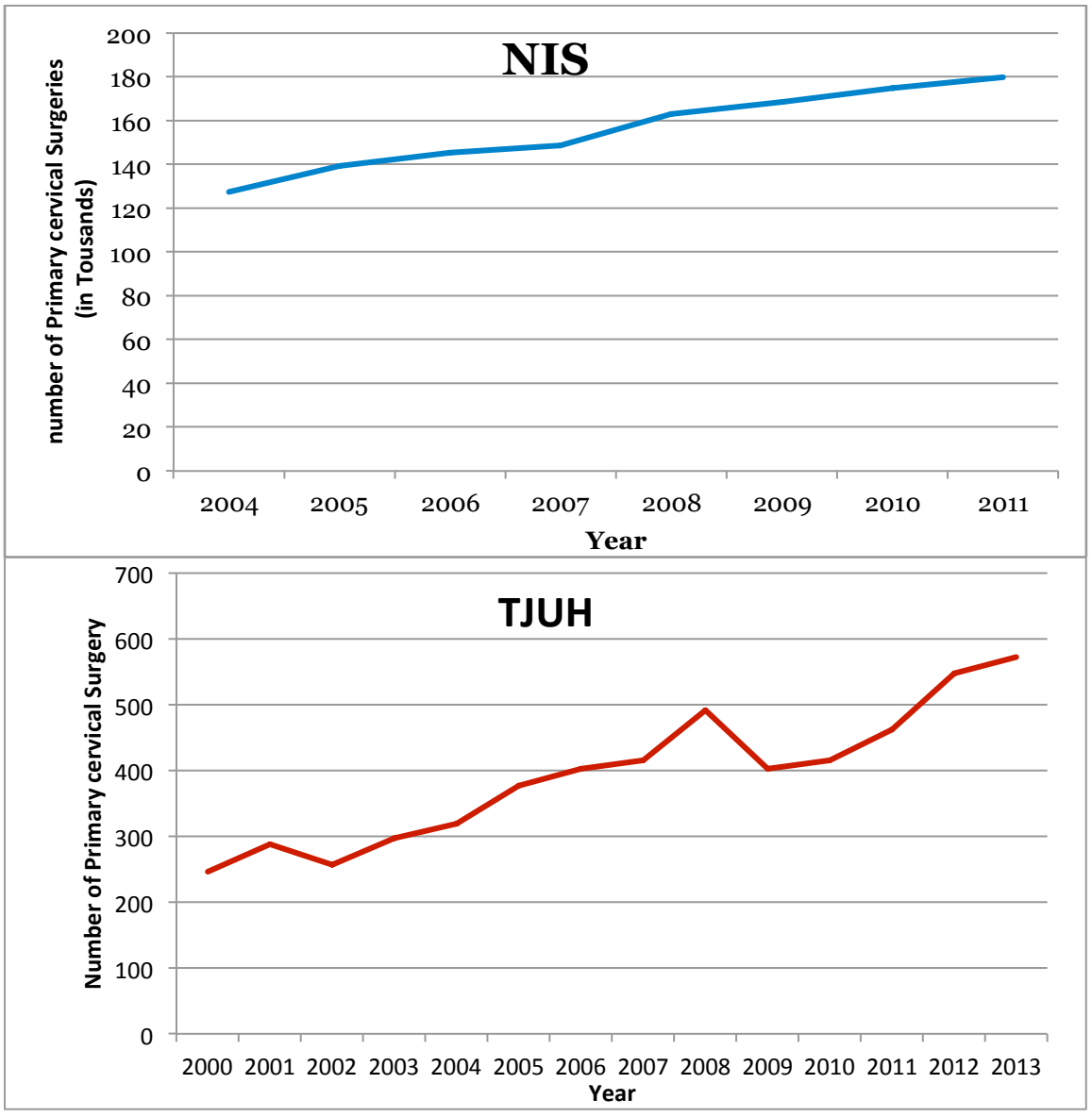
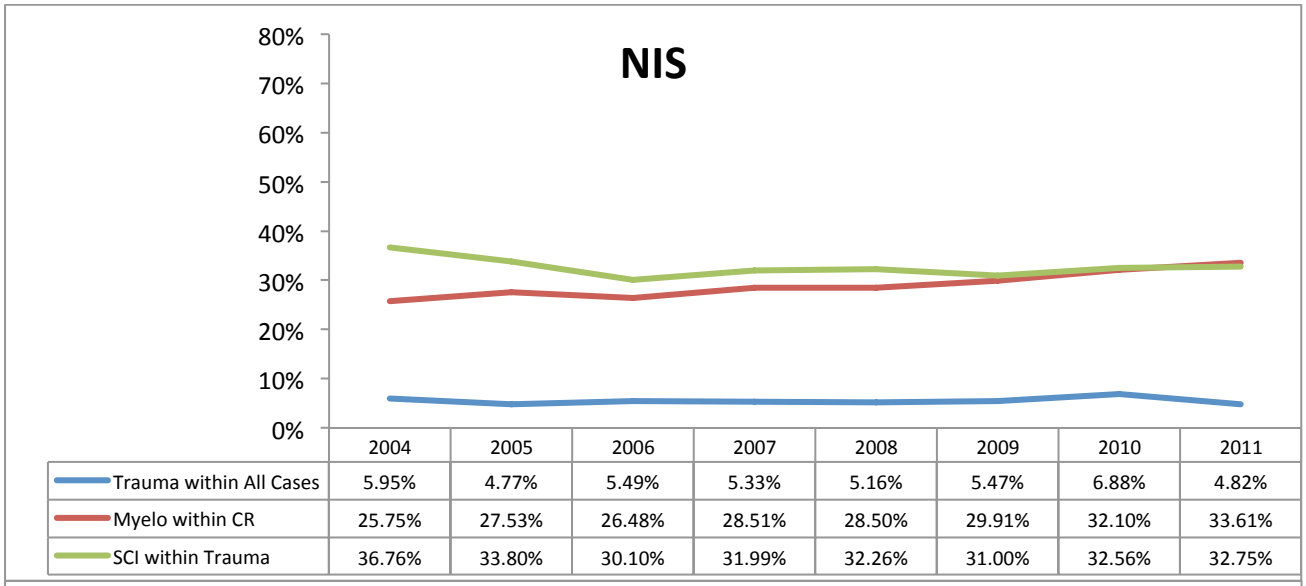
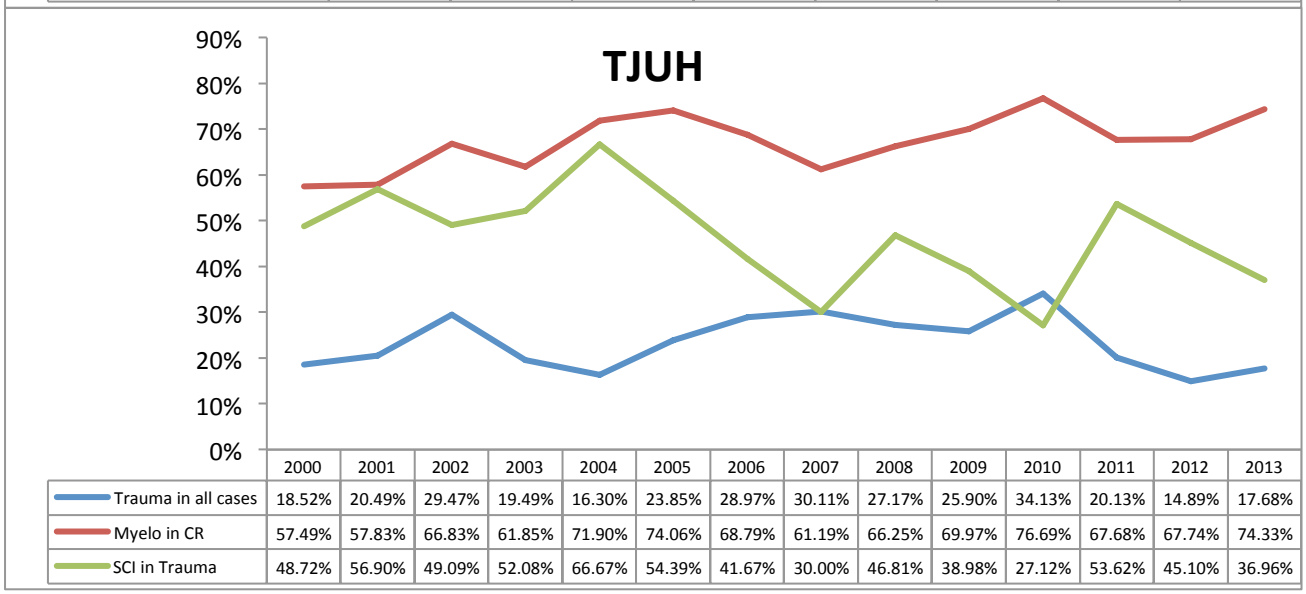


Fig . 2 Number of primary cervical spine surgeries performed yearly in both the NIS and TJUH

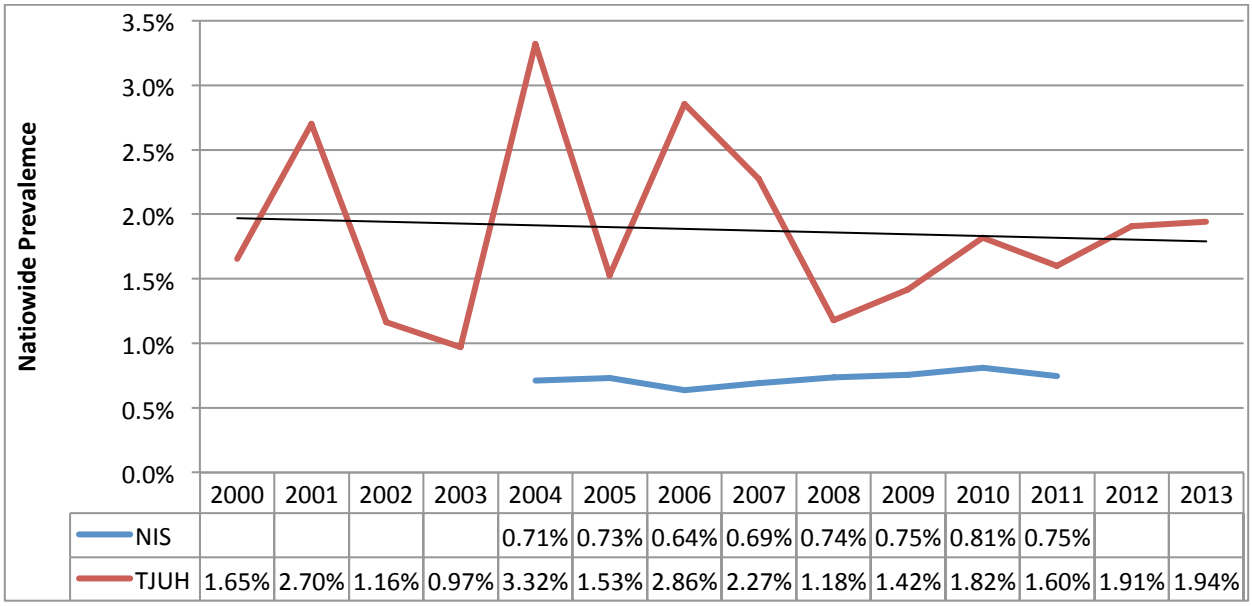


	2004	2005	2006	2007	2008	2009	2010	2011
Trauma within All Cases	5.95%	4.77%	5.49%	5.33%	5.16%	5.47%	6.88%	4.82%
Myelo within CR	25.75%	27.53%	26.48%	28.51%	28.50%	29.91%	32.10%	33.61%
SCI within Trauma	36.76%	33.80%	30.10%	31.99%	32.26%	31.00%	32.56%	32.75%



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Trauma in all cases	18.52%	20.49%	29.47%	19.49%	16.30%	23.85%	28.97%	30.11%	27.17%	25.90%	34.13%	20.13%	14.89%	17.68%
Myelo in CR	57.49%	57.83%	66.83%	61.85%	71.90%	74.06%	68.79%	61.19%	66.25%	69.97%	76.69%	67.68%	67.74%	74.33%
SCI in Trauma	48.72%	56.90%	49.09%	52.08%	66.67%	54.39%	41.67%	30.00%	46.81%	38.98%	27.12%	53.62%	45.10%	36.96%

Fig. 3. Proportion of patients with traumatic or neurologic injury in both the NIH and TJUH



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
NIS					0.71%	0.73%	0.64%	0.69%	0.74%	0.75%	0.81%	0.75%		
TJUH	1.65%	2.70%	1.16%	0.97%	3.32%	1.53%	2.86%	2.27%	1.18%	1.42%	1.82%	1.60%	1.91%	1.94%

Fig. 4. SSI Incidence by year in both the NIS and the TJUH

TRAUMA AND NEUROLOGICAL STATUS AS RISK FACTORS FOR SURGICAL SITE INFECTION

NIS SAMPLE

The results of bivariate analysis for SSI by diagnosis and neurological status are presented in **Table 5**. The incidence of SSI was higher in the traumatic cohort than in the degenerative cohort, and both myelopathy and spinal cord injury increased the incidence of SSI within these cohorts.

Table 5. Bivariate analysis of outcome variables (NIS and TJUH Samples)

	Overall	Degenerative		Traumatic		
Outcome Variable		**No MP**	**With MP**	**No SCI**	**With SCI**	**p value**
Infection (NIS)	0,73%	0,52%	1,11%	1,17%	1,97%	< 0.001
Infection (TJUH)	1,75%	0,88%	1,57%	2,65%	5,54%	< 0.001

SSI incidence was further analyzed in the NIS sample for differences in age, gender, surgical approach, number of spinal levels fused, hospital location and region, and annual trends for the four preoperative diagnoses **(Table 6).** Both Neurological Injury (OR 1,69, [95% CI 1,51-1,89] p < 0.001) and Trauma (OR 1.30, [95% CI 1,09-1,56 p = 0.003) were found to be predictors of SSI.

Table 6: Mutivariate Analysis of the NIS Sample

Variable		Odds Ratio	95% CI	p-value
Age		**1.01**	**1.01-1.02**	**<0.001***
Gender (Female)		0.69	0.62-0.76	**<0.001***
Race (Vs.) Caucasian	African-American	1.44	1.24-1.68	**<0.001***
	Hispanic	1.09	0.88-1.37	0.426
	Asian	0.73	0.45-1.19	0.207
	Native American	1.07	0.51-2.26	0.860
	Other	0.98	0.69-1.40	0.924
Payer (Vs. Medicare)	Medicaid	1.02	0.80-1.29	0.878
	Private	0.82	0.71-0.94	**0.005***
	Self-Pay	1.03	0.72-1.46	0.875
	No Charge	0.91	0.34-2.46	0.854
	Other	0.88	0.71-1.09	0.226
Hospital Size (Vs. Small)	Medium	1.41	1.15-1.73	**0.001***
	Large	1.33	1.11-1.60	**0.002**
Hospital Type (Vs. Urban Academic)	Rural	1.35	1.04-1.74	**0.025***
	Urban private	1.10	0.98-1.23	0.108
Hospital Region (Vs. Northwest)	Midwest	1.05	0.87-1.26	0.633
	South	1.04	0.90-1.20	0.608
	West	1.24	1.05-1.46	**0.013***
Calendar Year		0.98	0.96-1.01	0.157
Surgical Approach (Vs. Anterior)	Non Specified	2.11	1.77-2.51	**<0.001***
	Posterior	2.09	1.82-2.41	**<0.001***
	Combined	3.38	2.77-4.12	**<0.001***
Elixhauser Index		1.32	1.28-1.36	**<0.001***
Traumatic Diagnosis		1.30	1.09-1.56	**0.004***
Neurological Injury (SCI or MP)		1.69	1.51-1.89	**<0.001***

(* marks variables with statistical significance)

To account for any interaction between neurological injury and trauma in SSI, the Mantel-Haenszel statistics model was used. Controlling for neurological injury, the odds ratio (OR) for SSI in patients with traumatic injury was 2.09 (95% CI 1.79-2.43; $p < 0.001$). Similarly, controlling for Trauma, the OR for SSI in the setting of neurological injury was 2.12 (95% CI 1.93-2.32; $p < 0,001$). These statistics further corroborate the notion that Trauma and Neurological Status are independent predictors of SSI.

TJUH SAMPLE

SSI incidence was significantly different between the 4 diagnostic groups and between the two populations (**Figure 5**).

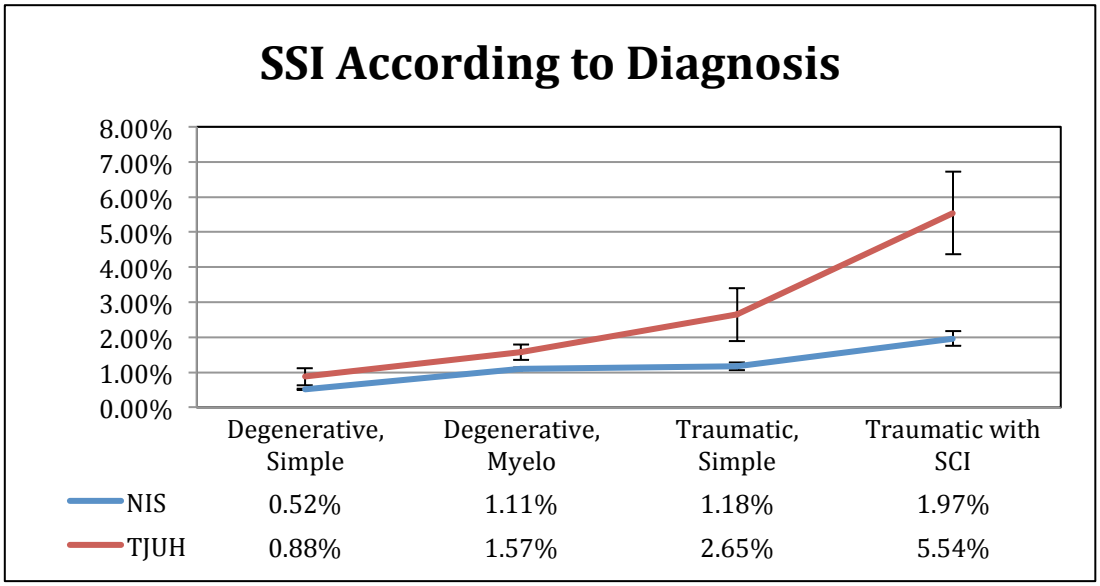


Fig 5. SSI incidence by diagnostic group

ASA was excluded from the multivariate analysis because it was not reported in the institution database before 2006 and was inconsistently present between 2006 and 2008. When including all other variables, the multivariate analysis showed significance for fusion levels (OR 2.80 [95% CI 1.38-5.67] for 4-8 segments vs. no instrumented fusion, p = 0.004), Charlson index (OR 1.32, [95% CI 1,19-1,47] p < 0.0001), Elixhauser index (OR 1.21, [95% CI 1,05-1,39] p = 0.008) , age (OR 0.98, [95% CI 0,97-0,99] p = 0.001) and calendar year (R 0.93 [95% CI 0.86-1.00] p = 0,04.) Trauma (OR 2.22 [95% CI 1.12-4,37] p = 0.02) reached statistical significance whereas neurological status did not (OR 1.47 [95% CI 0.87-2,49] p = 0.151). When excluding the Elixhauser comorbidity index and the Charslon score both Neuro (OR 1,72) and Trauma (OR 2,42) reached statistical significance

Using a Mantel-Haenszel test to account for covariates, neurological injury and trauma were both shown to be independent variables for predicting infection in our model (trauma vs. infection: Odds Ratio 3.45 (95% CI 2.22-5.45) p < 0.0001 and neurological injury vs. infection: Odds ratio 1.945 (95% CI 1.21-3.10) P 0 0,007)

LENGTH OF STAY AFTER SURGICAL SITE INFECTION

NIS SAMPLE

The length of stay was dependent on diagnosis, neurological status and infection in Pairwise comparisons ($p < 0.01$). It increased in a stepwise matter across the 4 categories considered (Figure 6)

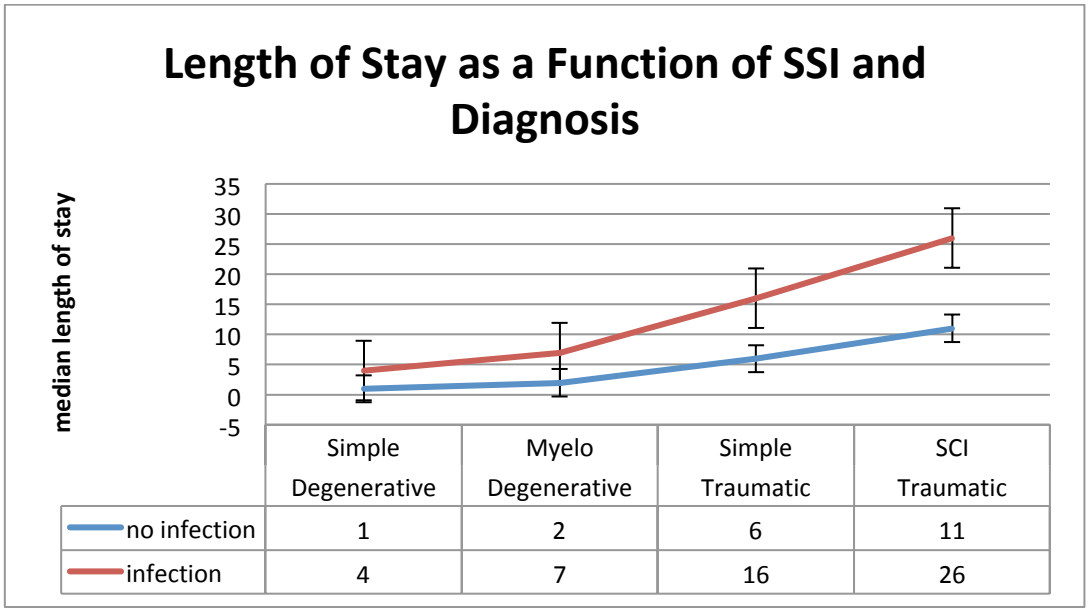


Fig 6. Length of Stay as a function of SSI and diagnosis

TJUH SAMPLE

Similarly, LOS was dependent on diagnosis, neurological status and infection in Pairwise comparisons ($p < 0.001$). It significantly increased in a stepwise matter across the 4 categories considered **(Table7) (Figure 7).**

Table 7: Length of stay as a function of infection across diagnosis

Length of Stay (in days) (Median; 95%CI)				
		No complication	Infection	P value
Degenerative	w/o Myelopathy	1 (1-1)	7 (6-17)	< 0.001
	With Myelopathy	2 (2-2)	11 (9-13)	< 0.001
Traumatic	W/o SCI	8 (7-8)	25 (16-NA)	<0,001
	With SCI	14 (12-15)	30 (22-38)	<0,001

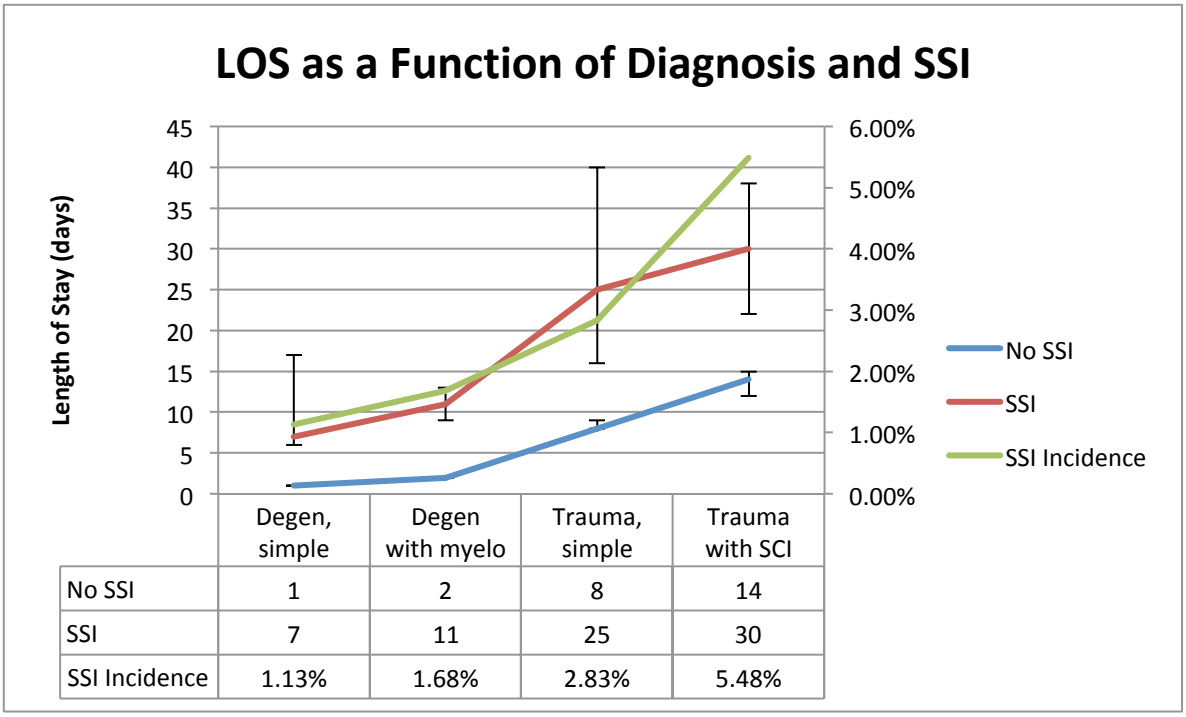
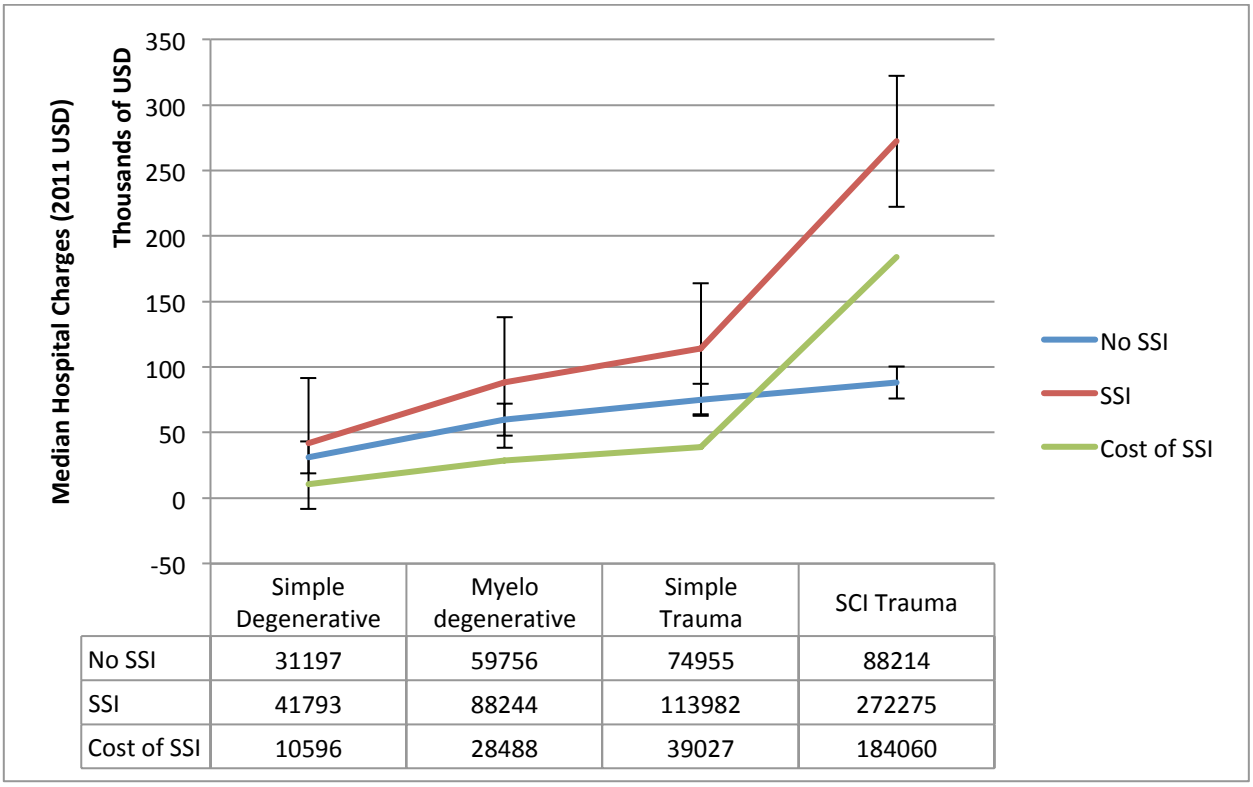


Fig 7 Length of Stay as a function of SSI and diagnosis

DIRECT AND INDIRECT COSTS OF INFECTION

The total direct hospital costs were analyzed as reported in the NIS data.

Basal costs were increased in a stepwise fashion across the diagnostic groups even in patients without infection. Traumatic patients and patients with myelopathy/SCI consumed more resources. Costs also increased significantly in all diagnostic groups as a function of infection (Figure 8). The highest increase due to infection was observed in the spinal cord injury group (184060 USD on average). This represented a net increase of 208% of the total bill **(Figure 8)**



	Simple Degenerative	Myelo degenerative	Simple Trauma	SCI Trauma
No SSI	31197	59756	74955	88214
SSI	41793	88244	113982	272275
Cost of SSI	10596	28488	39027	184060

Fig 8. Hospital Charges as a function of SSI and Diagnosis

We analyzed the discharge destination of patients in the TJUH as a proxy for total costs as no other direct or indirect costs were available for analysis in our database. Patients with infection were more likely to be discharged to nursing home or rehabilitation centre than patients with no infection. At the same time, discharges to destinations other than home also increased in a stepwise fashion across the four diagnostic groups regardless of infection **(Table 8; Figure 9).**

Table 8: Discharge destination as a function of diagnosis and neurological status

	Degenerative		Trauma		P value
Discharge Destination	**No MP**	**With MP**	**No SCI**	**With SCI**	
Home	93,66%	83,47%	46,58%	14,25%	<0.001
Nursing Home	2,63%	6,05%	23,84%	8,44%	<0.001
Rehabilitation facility	3,64%	9,89%	22,74%	69,39%	<0.001

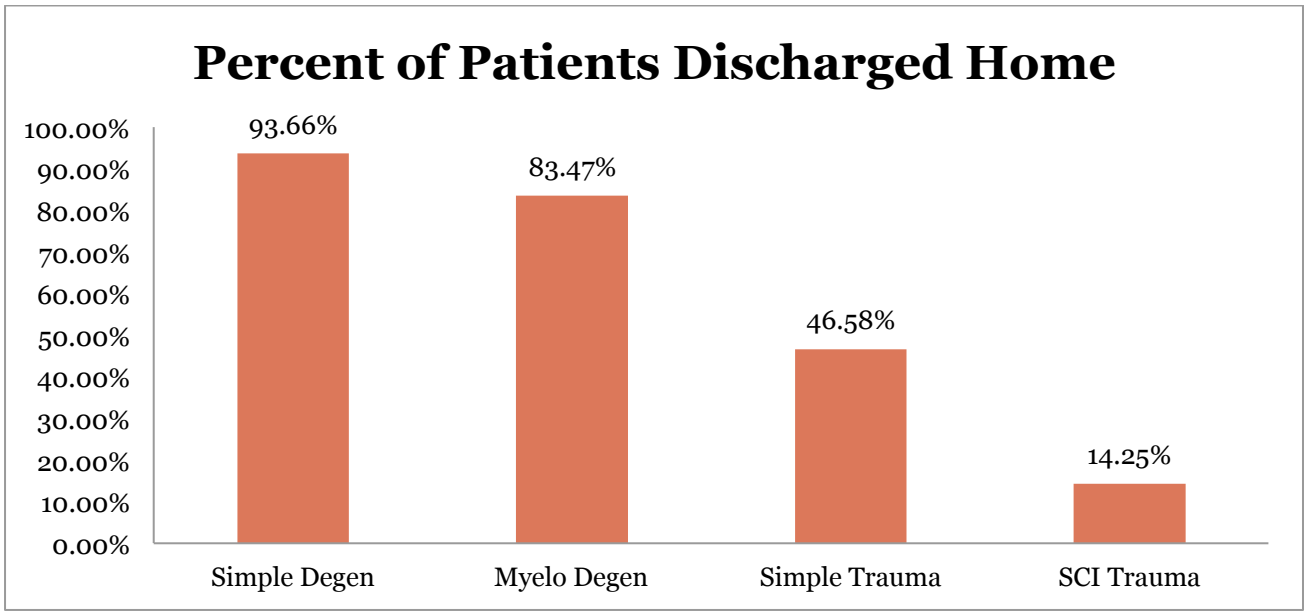


Fig 9. Percent of patients discharged home as a function of diagnosis and neurological status

ADULT SPINAL DEFORMITY (STUDY 2)

PATIENT SAMPLE

Between January 2010 and January 2016 we identified 689 patients with ASD undergoing Posterior Spinal Instrumentation for deformity correction. 444 had more than 2 years of follow-up available. 23 Patients had been treated for a deep SSI (5,2%) and out of these 20 within the first 6 months of their index surgery. From the remaining 421 patients, 391 had not suffered from any postoperative infection and were available for matching. We could yield a 1:3 matching proportion after applying the 6 matching criteria. As such we had a 20:60 case:control cohort available for analysis **(Figure 10, Flowchart).**

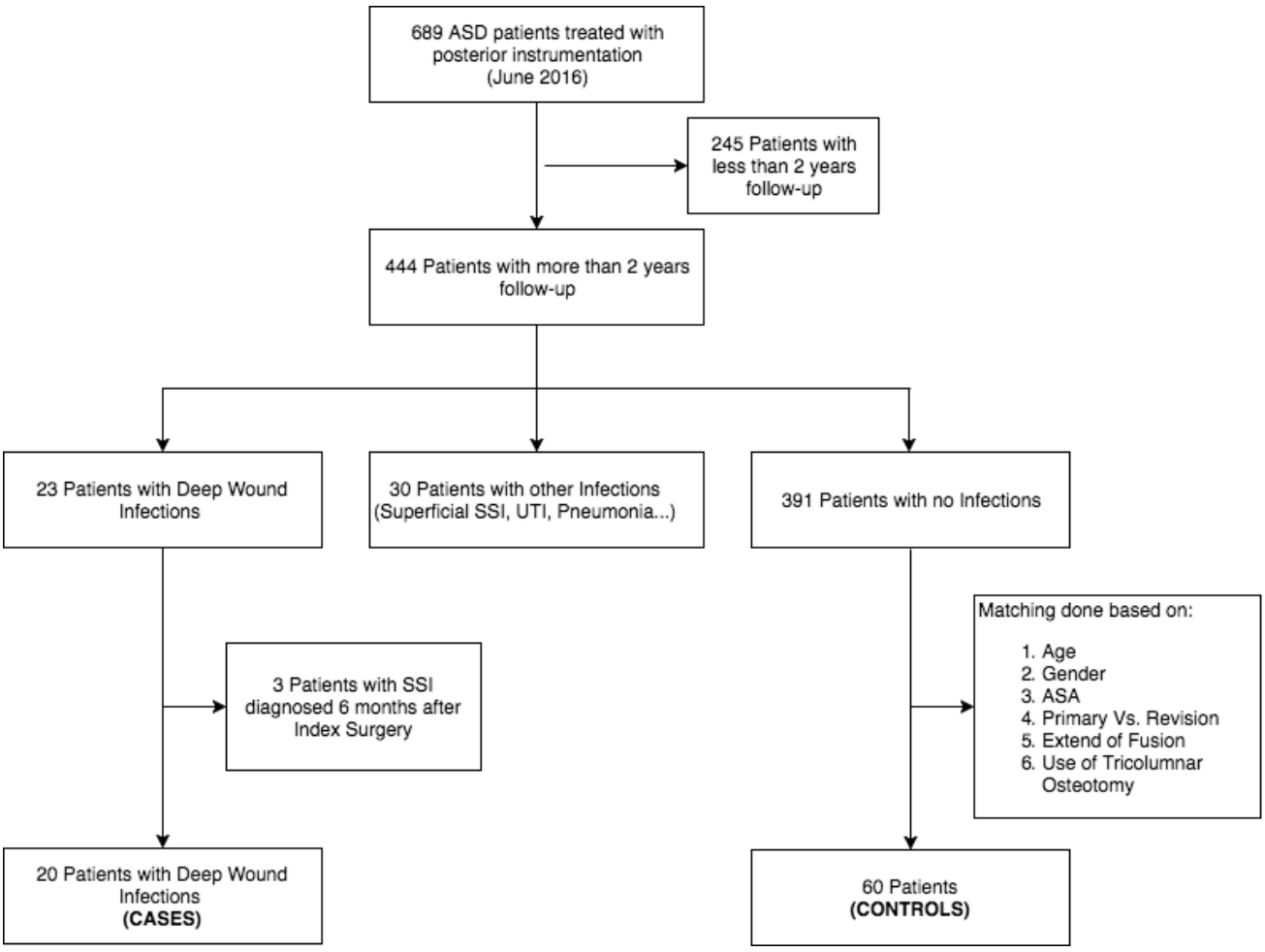


Fig 10. Flowchart of patients participating in this study

No significant differences were detected between cases and controls in matched or non-matched preoperative variables including radiological and HRQoL, confirming comparable samples (**Table 9**).

The mean age was 54.825 (range 18-80) and 30% had a prior surgery. Mean surgical length was 347.66 minutes (range 120-715 mns) and blood loss was 1868.60ml (300 – 5800). Patient stayed on average 17.9 days (12.8 days if not infected vs. 33.3 if infected, p 0.004). 44% had a major complication and 26% needed a revision.

Non-matched risk factors for infection were equally balanced between both groups; e.g. BMI (p=0.587) Diabetes (p=0.672), Smoking (p=0.696), Blood loss (p=0.577). Furthermore, both groups had similar proportion of patients coming same centres (p 0.562), limiting any site biases.

Table 9: Baseline Comparison between Cases and Controls

Preoperative Variables	Cases (N=20)	Controls (N=60)	p Value
*Female	14 (70.0%)	42 (70.0%)	*1*
*Male	6 (30.0%)	18 (30.0%)	
No comorbidities	5 (28.3%)	17 (28.3%)	*1*
Cancer	3 (15.0%)	5 (8.3%)	*0.405*
Diabetes	1 (5.0%)	7 (11.7%)	*0.672*
Liver Disease	2 (10.0%)	1 (1.7%)	*0153*
Osteoporosis	0 (0.0%)	1 (1.7%)	*1*
Smoker	3 (15.0%)	7 (11.7%)	*0.696*
*Tricolumnar Osteomomies	6 (30.0%)	18 (30.0%)	*1*
*Revision Surgery	6 (30.0%)	18 (30.0%)	*1*
* ASA 0-I	7 (35.0%)	21 (35.0%)	*1*
*ASA II	7 (35.0%)	21 (35.0%)	
*ASA III-IV	6 (30.0%)	18 (30.0%)	
Demographic and Surgical Variables	**Mean**	**Mean**	**p Value**
BMI	27.4	26.6	0.587
*Age (years)	57.9	53.8	0.377
Surgical Duration (Minutes)	375.5	338.4	*0.343*
*Number of Fused Segments	10.10	10.00	*0.920*
Number of Osteotomies	1.60	1.63	*0.947*
Blood Loss (ml)	1736.3	1911.6	*0.577*
ICU Stay (hours)	95.9	63.1	*0.599*
Hospital Stay (Days)	*33.3*	*12.8*	*0.004*
Preoperative Radiological Parameters	**Mean**	**Mean**	**p Value**
SVA (mm)	75.53	53.05	0.239
PI	52.2	57.2	0.166
LL	-39.5	-43.4	0.620
PI-LL	12.7	13.8	0.864
SS	32.5	34.2	0.640
PT	19.6	23.0	0.273
Global Tilt	31.2	28.9	0.640
Major Cobb Coronal	34.2	38.2	0.556
Preoperative HRQoL Parameters	**Mean**	**Mean**	**p Value**
Back Pain	7.2	6.8	0.567
Radicular Pain	4.8	4.0	0.376
COMI	7.1	7.2	0.896
ODI	50.1	47.0	0.581
SF 36 MCS	38.8	39.5	0.828
SF 36 PCS	30.8	34.6	0.108
SRS22 Function	2.6	2.9	0.254
SRS22 Mental	3.0	3.1	0.779
SRS22 Pain	2.2	2.4	0.310
SRS22 Satisfaction	2.8	2.7	0.981
SRS22 Self Image	2.1	2.4	0.254
SRS22 Subtotal	2.5	2.7	0.255
*Matched Variable			

RISK FACTORS OF SURGICAL SITE INFECTION

RISK FACTORS ANALYSIS

A bivariate analysis using fisher´s exact test for categorical variables and independent t test for continuous variables yielded the following significant correlations in the total population of this study before matching was done **(Table 10)**

Table109: Significant Correlations with SSI in the general Sample

Variable	Pearson Correlation	p value
BMI	0.101	0.024
Prior Blood Clot	0.092	0.036
Liver Disease	0.100	0.022
Smoking History	0.173	0.000
Participating Center	-0.110	0.011
ADSCI Score	0.091	0.046
Fusion Extension	0.113	0.010
ICU Length	0.114	0.009
Intraoperative Complication	0.108	0.013
Neurological Complication	0.138	0.002
Intrahospital Complication	0.096	0.028
Wound complication including seroma and hematoma	0.103	0.019

Patients with SSI were more likely to be obese, have a prior history of blood clots or liver disease be a smoker or come from the Barcelona site. They also were more likely to have longer extensions, more complex surgeries, stay longer in the ICU or suffer an Intraoperative complication, mainly neurological, prior to infection. They were also more likely to suffer a medical complication on the ward (pneumonia or acute myocardial infarct…) prior to developing SSI.

A subsequent ordinary least square (OLS) model was employed with a stepwise forward variable inclusion approach to obtain a linear probability model that had the highest predictive power. Coefficients represent the associated probabilistic marginal effect. The model retained Smoking history, fusion extension, BMI, Liver disease, prior blood clot, sex, height and site as variables significantly associated with SSI. The highest probabilistic weight was attributed to male gender, followed by smoking, and history of blood clots. A male patient had 35.1% higher chances of suffering an infection than a female (p 0.003) and smoking increased SSI risk by 18.5% (p<0.001). With every 4 additional levels, the probability of having an infection increased by 11% (p 0.015)

whereas a 9cm increment in height reduced it by 11% (p 0.031). Full results are reproduced in **Table 11**.

Table 11: Ordinary Least Square Analysis of SSI Dependent Variables

Variable	Estimate	Std. Error	t value	Pr(>|t|)
Smoking History	0.184692	0.042209	4.376	<0.001
Fusion Extension	0.113413	0.046359	2.446	0.015
Liver Disease	0.087655	0.042407	2.067	0.039
History of blood clots	0.10796	0.042822	2.521	0.012
Male Gender	0.350978	0.118905	2.952	0.003
Height	-0.1121	0.05208	-2.153	0.032

NARRATIVE DESCRIPTION OF THE COURSE OF INFECTION

The mean time to diagnosis of SSI was 20.1 days (Range 1-76; Standard Deviation 20.4) in our retained cohort and 13 were diagnosed during the same initial hospital admission. 6 Patient had a nosocomial infection during their hospital stay prior to developing infection. The most common nosocomial infection was Urinary Tract Infection (UTI) (4 patients). The most commonly isolated single microorganism was methicillin sensitive *Staphylococcus aureus* (5 cases) and the infection was due to multiple organisms in 6 patients. Patients needed on average 1.7 wound debridements (range 1-3) and 3.5 months of antibiotics (range 2.5-6.5 months) to treat their SSI. Priority was to retain implants in all patients especially that infection was acute (Mean 20 days. range 1-76 days). 65% patients needed a single debridement. Two patients needed partial implant exchange. Prior to implant exchange both patients had at least one failed debridement. One patient had a *S. epidermidis* and the other patient a multi-organism infection. All patients have been deemed to be clear of infection at their last review.

There was one death in the SSI group related to the infection itself whereas no deaths were recorded at an average of 4.2 years after index surgery in the control group (p=0.250) (Table 2). Patient in question was a 33 year-old lady with a background history of childhood poliomyelitis and lower extremity motor paralysis. She had a lumbar osteotomy and T2 to Pelvis fixation. She started complaining of fatigue and discomfort 2 days after index surgery and had a purulent discharge by the 3rd day. She underwent surgical debridement and lavage that evidenced an extensive muscular necrosis. Intraoperative cultures grew *Acinetobacter bowmanii* and MRSA. Despite extensive debridement and broad-spectrum antibiotics her condition deteriorated and she went into sepsis in

her immediate postoperative stay at the ICU. She soon developed a multi-organ failure and passed away on the 8th day after index surgery. We have accordingly removed this patient and its paired controls from the radiological and clinical outcomes analysis.

IMPACT OF INFECTION ON SURGICAL OUTCOMES

CLINICAL RESULTS

In terms of surgical complications and morbidity, the SSI group had a longer hospital stay (33.3 days Vs. 12.8 days; p 0.004). Patients with infection were also more likely to have other associated wound problems such as seromas or hematomas (p 0.021). 52.6% of patients with an SSI had at least one associated major complication (vs. 42.1% in the control group. p 0.439) and on average. they had more non-infectious major complications than the control group (2.32 vs. 1.46 complications/patient; p 0.049). Both groups had similar rates of mechanical/radiological complications (42.1% vs. 29.8% p 0.400). The SSI group had 3 times more Proximal Junctional Kyphosis (PJKs) (31.6% vs. 10.5% p=0.023) (**Table 12).**

Table 12: Postoperative Complications

	Cases (N=19)		Controls (N=57)		
Variables	**N**	**%**	**N**	**%**	**p value**
ICU Needed	18	94.7%	50	87.7%	*0.354*
Intraoperative Complications	6	31.6%	13	22.8%	0.543
Neurological Complications	5	26.3%	12	21.1%	0.752
Intra-hospital Complications	7	36.8%	11	19.3%	0.132
Wound Complications (Seroma, Hematoma, Dehiscence)	**5**	**26.3%**	**3**	**5.3%**	**0.021***
Implant Complications (Pullout, loosening)	6	31.6%	16	28.1%	0.777
Radiological/Mechanical Complications (PJK, Rod Breakage, Pseudoarthrosis)	8	42.1%	17	29.8%	0.400
Pseudoarthrosis	2	10.5%	12	19.3%	0.498
Proximal Junctional Kyphosis	**6**	**31.6%**	**5**	**10.5%**	**0.023***
Any Major Complications other than infection	10	52.6%	24	42.1%	0.439
Any Complication other than infection	15	78.9%	39	68.4%	0.560
Any Revisions for reasons other than infection	8	42.1%	13	22.8%	0.139
Any Readmission for reason other than infection	6	31.6%	13	22.8%	0.543

RADIOLOGICAL RESULTS

There were no differences in deformity correction between the groups at the different time intervals of the study. The primary sagittal deformity parameters improved significantly after surgery in both groups ($p < 0.05$) and this correction was maintained over time (**Table 13**).

Table 13: Overall Radiological Results at 24 months as compared to baseline (N=76)

Variable		Mean	Std. Deviation	P Value
SVA	Preop	61.50	70.50	0.048*
	24 Months	38.15	53.58	
PI	Preop	56.16	14.13	0.655
	24 Months	55.10	10.99	
LL	Preop	-41.71	25.42	0.020*
	24 Months	-50.24	15.42	
PI-LL	Preop	14.45	26.98	0.011*
	24 Months	4.84	14.85	
SS	Preop	33.39	13.74	0.720
	24 Months	34.22	10.62	
PT	Preop	22.72	12.08	0.230
	24 Months	20.74	9.53	
Global Tilt	Preop	30.16	18.22	0.046*
	24 Months	24.54	14.03	
Major Cobb	Preop	35.56	25.87	<0.001*
	24 Months	19.16	17.29	

HEALTH RELATED QUALITY OF LIFE (HRQOL) RESULTS

When analyzing HRQoL scores we could see that both the groups benefited from the surgery and this improvement was maintained throughout the follow-up period. All PROMs were significantly better at the 24 months mark ($p<0.05$) except for the Leg pain (p 0.123). SF36 MCS (p 0.271) and SRS22 Mental Score (p=0.348) (**Table 14**).

Table 14: Overall HRQoL Results at 24 months as compared to Baseline (N=76)

Variable		Mean	Std. Deviation	P Value
Back Pain	Preop	6.93	2.32	<0.001*
	24 Months	4.32	3.18	
Leg Pain	Preop	4.33	3.64	0.123
	24 Months	3.34	3.37	
COMI	Preop	7.43	2.24	<0.001*
	24 Months	4.69	2.56	
ODI	Preop	49.15	19.11	0.002*
	24 Months	37.76	19.97	
SF 36 MCS	Preop	39.31	12.29	0.271
	24 Months	41.71	11.30	
SF 36 PCS	Preop	33.21	8.26	0.004*
	24 Months	38.64	11.05	
SRS 22 Function	Preop	2.73	0.89	0.021*
	24 Months	3.13	0.98	
SRS22 Mental	Preop	3.04	0.90	0.348
	24 Months	3.20	0.92	
SRS22 Pain	Preop	2.33	0.89	<0.001*
	24 Months	3.20	1.07	
SRS22 Satisfaction	Preop	2.74	1.21	<0.001*
	24 Months	3.72	1.06	
SRS22 Self Image	Preop	2.25	0.82	<0.001*
	24 Months	3.08	0.91	
SRS22 Subtotal	Preop	2.59	0.69	<0.001*
	24 Months	3.14	0.83	

We did find that the results up to one year after surgery did vary between both groups in favor of the controls mostly in the ODI (6 months), COMI (6 and 12 months), SF 36 PCS (6 months) and SRS 22 Mental (6 months). Full results are reproduced in **Table 15**.

Table 15: HRQoL Analysis – Difference between groups at interval points (N=76)

Variable		6 months		12 months		24 months	
			p-Value		*p-Value*		*p-Value*
Back Pain	Cases	3.81	0.944	4.07	0.854	3.36	0.923
	Controls	3.87		4.24		4.57	
Leg Pain	Cases	2.94	0.798	2.21	0.404	3.00	0.467
	Controls	2.72		2.96		3.43	
COMI	Cases	6.17	**0.049***	5.86	**0.047***	5.74	0.092
	Controls	4.86		4.15		4.46	
ODI	Cases	45.87	**0.049***	42.43	0.075	40.64	0.701
	Controls	34.22		34.33		37.02	
SF 36 Mental Component	Cases	38.97	0.398	41.41	0.806	39.93	0.493
	Controls	42.03		42.34		42.17	
SF 36 Physical Complonent	Cases	31.48	**0.027***	34.99	0.051	36.64	0.707
	Controls	37.24		40.22		39.15	
SRS22 Function	Cases	2.69	0.101	3.18	0.722	2.73	0.573
	Controls	3.12		3.28		3.23	
SRS22 Mental	Cases	2.77	**0.036***	3.17	0.745	3.29	0.177
	Controls	3.24		3.25		3.17	
SRS22 Pain	Cases	3.09	0.830	2.90	0.226	3.18	0.846
	Controls	3.15		3.30		3.20	
SRS22 Satisfaction	Cases	3.62	0.318	3.50	0.326	3.68	0.813
	Controls	3.94		3.83		3.73	
SRS22 Body Image	Cases	3.11	0.629	3.06	0.285	2.95	0.311
	Controls	3.29		3.33		3.12	
SRS22 Subtotal	Cases	2.92	0.212	3.09	0.402	3.03	0.201
	Controls	3.19		3.29		3.17	

The non-infected group also experienced more pronounced improvement compared to baseline values during the first year. This was apparent when analysing the differences from baseline in each group and comparing both groups. The COMI and ODI scores were the best parameter that could reflect the differences from baseline values between both groups at 6 and 12 months. Differences from baseline value were initially noted in the ODI (-14.69 Vs -1.5 p=0.029) and in SRS22-Mental component score (0.20 Vs -0.34 p=0.049) at 6 months but were later diluted at 1 year. **(Table 16)**

Table 16: HRQoL Analysis – Difference with Baseline Value

Variable		6 months	*p-Value*	12 months	*p-Value*	24 months	*p-Value*
Back Pain	Cases	-3.19	0.749	-2.93	0.667	-4.27	**0.045***
	Controls	-2.86		-2.53		-2.21	
Leg Pain	Cases	-1.31	0.870	-1.64	0.651	-2.18	0.264
	Controls	-1.48		-1.21		-0.95	
COMI	Cases	0.14	**0.001***	-1.27	**0.049***	-1.68	0.303
	Controls	-2.66		-3.13		-2.91	
ODI	Cases	-1.50	**0.029***	-4.69	0.052	-6.40	0.424
	Controls	-14.69		-14.53		-11.03	
SF 36 Mental Component	Cases	-1.42	0.425	2.33	0.916	1.83	0.893
	Controls	1.69		1.87		1.33	
SF 36 Physical Component	Cases	0.09	0.220	2.66	0.211	4.61	0.795
	Controls	3.32		6.36		5.42	
SRS22 Function	Cases	-0.04	0.137	0.38	0.735	-0.11	**0.034***
	Controls	0.31		0.46		0.41	
SRS22 Mental	Cases	-0.34	**0.049***	0.09	0.452	0.32	0.349
	Controls	0.20		0.29		0.05	
SRS22 Pain	Cases	0.84	0.869	0.63	0.410	0.91	0.633
	Controls	0.79		0.89		0.77	
SRS22 Satisfaction	Cases	0.61	0.457	0.44	0.304	0.38	0.214
	Controls	1.04		1.00		1.02	
SRS22 Body Image	Cases	0.94	0.831	0.99	0.832	0.76	0.794
	Controls	1.03		1.05		0.85	
SRS22 Subtotal	Cases	0.35	0.281	0.54	0.521	0.47	0.873
	Controls	0.56		0.66		0.50	

We failed to demonstrate any other difference beyond 12 months between the groups in the different analysis conducted (**Tables 14 to 16**).

DISCUSSION

CERVICAL SPINE STUDY:

INCIDENCE OF INFECTION

A steady increase in number of cervical surgeries performed nationwide was apparent. Whereas the ratio of degenerative/traumatic remained constant, the proportion of patients with myelopathy in the degenerative population is also increasing. This, together with an aging population with increased index of comorbidities would predict a rise in overall SSI incidence. The incidence reported in both our dataset as well as the NIS sample however showed a steady incidence.

SSI occurred in 0.73-1.75% of patients in our study when taking all patients. Was lower than those reported by Medvedev et al. (2.6%)(90) and the 2.9% of patients in Sebastian et al., a study of 5441 patients who underwent posterior cervical surgery (91). Our infection rate is similar to the rate in either the ACDF group (0.4%) or the PLF group (1.8%) in the study by Bohl et al.(92). These differences might be due to longer observation time, different definition and search criteria, and prospectively collected data.

The incidence of SSI in TJUH was higher than that reported in the NIS for each category. The discrepancy in the results between the two populations could be explained by the different patient profiles. TJUH performed a higher proportion of traumatic procedures (15% vs. 5%) with a higher proportion patients with neurologic injury compared to the national sample (SCI 45% vs. 32%; myelopathy 68% vs. 29%). The local population was also older and with more comorbid conditions. Both age and comorbidities increased across the diagnostic classes. This, in association with a smaller sample size and an overall low incidence of SSI (1.75% at TJUH vs. 0.76% in NIS) could justify the loss of significance in the institutional series. These factors also might explain, although partially, a higher incidence of SSI in the institutional records.

TRAUMA AND NEUROLOGICAL STATUS AS A RISK FACTORS

Through stratification based on primary diagnosis and neurological status, our data identified neurologic deficit and traumatic injury to be independent risk factors for SSI in the NIS population. In fact, a progression in SSI between degenerative and traumatic diagnoses was found, as well as between patients who were neurologically intact (without SCI or Myelopathy) and those with neurological injury (with Myelopathy or SCI) within the same diagnostic group and between the two

diagnostic groups. As such, both traumatic injury and neurological status are predictive of SSI. These findings, however, could only be partially confirmed when analyzing records from our institution and considering comorbidities. In contrast to the NIS data, we found that traumatic patients at our institution were older and had more comorbidities. SSI increased significantly as we progressed along the four diagnostic groups However, after accounting for, Charlson and Elixhauser indexes, neurological status lost statistical significance whereas trauma was still a significant independent risk factor. When these factors were not accounted for, Neurological status achieved statistical significance. Finally, Using a Mantel-Haenszel test to account for third variable, Neuro and Trauma were both proven to be independent variables at predicting infection.

Several factors may contribute to the increased incidence of SSI after traumatic injury. Patients with a traumatic injury, especially those with SCI, typically have suffered a higher energy impact with an increased energy transfer and damage to soft tissues (52). These patients might also suffer from posttraumatic immunosuppression which may be physiologic or iatrogenic and localized tissue hypoxia secondary to soft tissue injury(93). Patients with neurological deficits are more likely to spend more time in bed, are more often in the recumbent position with a collar(50), and ambulate less, all of which increase local temperature and humidity at the surgical site; these factors are especially concerning in patients with a posterior cervical approach. Patients with traumatic injury are more frequently admitted to an ICU, have longer ICU and overall hospital LOS, and may experience delays before surgical stabilization all of which also increase their likelihood of being colonized with resistant microorganisms. Surgical site infections may in some cases be a result of seeding from nosocomial infections such as urinary and upper respiratory tract infections, which are twice as common in trauma patients versus patients with degenerative conditions, especially after spine, chest, or extremity injuries (94). Malnutrition (95) might be an important yet overlooked concomitant risk factor in the traumatic population. In his study, Klein (95) showed that nearly 75% of patients with SCI became malnourished during their hospital stay, and that all infections identified in the study occurred in malnourished patients. Finally, many institutions still use steroids in their SCI protocols, whereas the impact of steroids on neurological recovery is very doubtful, the use of steroids has been associated with significant morbidity (96). Especially, steroids in SCI have been associated with a higher rate of nosocomial infections, mainly pneumonia. Ito et al have compared two historical cohorts to study the effect of steroids, and could not however find a significant difference in their cohorts in terms of SSI (5/38; 13.2% vs. 4/41; 9.8%)(96).

On the other hand, degenerative patients with myelopathy are more often older and with more comorbidities (46). Age, comorbidities, myelopathy and severity of compression are often closely linked. More invasive surgeries, with additional decompression, longer surgical time and more soft tissue dissection, are often required (48). Also these patients generally require longer ICU stay,

more need for intermittent ventilation, longer hospital stays and higher overall complication rates (48).

With the steady increase in volume of surgeries performed we would expect the absolute number of SSIs to steadily increase even in the setting of a stable incidence. Hence there is a need for more research in this field, and the implementation of preventive strategies. Such strategies could include: controlled use of steroids, improved nutrition, judicious use of cervical collars, decreased ICU stay (43), and reductions in preventable delays to surgical intervention (43). Lastly, special caution should be taken with elderly patients or with patients with multiple comorbidities undergoing cervical surgery to treat myelopathy (47).

IMPACT OF INFECTION

This study could show that despite the increased cost between the 4 diagnostic groups, SSI increased costs differently in each group. In patients with cervical degenerative pathologies without myelopathy the additional cost represented 34% of the baseline cost whereas this figure arose 208% in the context of SCI. This combined with the higher baseline charges for SCI led to exponential increase in total charges. These findings highlight that while the four diagnostic groups consume resources differently, SSI would make what is costly even pricier. By identifying these costly diagnostic groups, researchers could focus on finding preventive measures that would reduce the total costs. They could also gauge cost effectiveness of prevention. Preventing a single infection in this group could finance a research project and multiple prophylactic measures.

The costs of infection in our study for degenerative patients without myelopathy were comparable to those published by Kuhns et al for patients undergoing posterior cervical surgery and the ($10,596 in our study Vs. $12,619) (37). However the cost increased with myelopathy to $28,488 with myelopathy and even more in the context of trauma. In cervical trauma it was even higher than those reported by Yeramaneni et al. in ASD to (between $15,817 and $38,701) (32).

Finally our study confirmed that the costs of infection do not stop after discharge and indeed patients with SSI are more likely to consume community resources by being discharged to centres other than home. This is in concordance with the findings of Alfonso et al. (38).

STUDY LIMITATION

This study establishes a correlation between the different variables and infection. A causative relationship cannot be established with the statistical method employed or by the study design. It constitutes the best available evidence in the absence of prospective randomization which is unethical to perform in the human setting (i.e. provoking a trauma or neurological injury). Confounders to Trauma and Neurological injury could not be accounted for properly and include ICU stay, associated nosocomial infections, use of hard brace or collar, prolonged immobilization, unfavourable nutritional status among others.

In addition, this study potentially suffers from bias inherent in any large database analysis(97). Large-scale population-based studies focusing on complications are conducted in a retrospective fashion by searching hospital-originated databases and registries. This methodology relies strongly on the accuracy of initial data entry by non-medical professionals, and the completeness of database queries. The accuracy of these databases has not been established and has recently been challenged (49, 98). Individual records could not be verified nor double-checked and only preexisting variables could be analyzed. As such ASA was excluded from final analysis, as it was available for less than 50% of our population. The retained Charlson and Elixhauser indexes were taken from the institutional database and could not be verified. Also, the incidence of infection was dependent on the coding and data entry and we could not verify how the diagnosis of SSI was made. The impact of these limitations must be balanced against the large sample size and the associated benefits in study power. Some of these factors may be more carefully controlled and accurately defined in our institutional records, which might help explain the higher incidence of infection. When comparing NIS data with hospital data we found a higher incidence of infection in all four groups, although the relationship with diagnosis and neurological status was maintained. Factors which may explain the increased rate of complications in our institutional data include greater accuracy of record keeping, prospective coding, reporting of complication greater than 90 days after surgery, more thorough databasing, and a more liberal definition of infection (49, 99, 100).

Despite the fact that the study of SSI is influenced by the definition of infection and coding, major risk factors are not altered as much as the frequency of infection (16). Nota et al. have proven that major risk factors for spinal surgery remained unaltered when reviewing the institutional database using ICD-9 codes, CDC criteria or operative records of D&I(16). The incidence was highest with ICD-9 Codes (6%) and lowest using the revision records (3%). Authors and editors justified using big data for risk factors, however, when studying SSI they recommend researchers to determine infections by different definitions for quality assurance purposes (16, 17).

As a final note, neurological status could not be stratified based on its severity, and this variable was categorized only as present or not. We could not therefore confirm Rechtine et al. findings of a higher SSI in complete SCI when compared to incomplete SSI or prove a relationship between severity of myelopathy and SSI. Also the findings of this report are a starting point and should be extrapolated with caution in the thoracolumbar spine where the implication of neurological injury are less severe and therefore the confounding factors associated to neurological injury lose their weight (ICU stay, immobilization, bed rest, use of hard collar/brace...)

ADULT SPINAL DEFORMITY STUDY

INCIDENCE OF INFECTION

Few studies have specifically analyzed the incidence of SSI after ASD Surgery.

In a multicenter study by Lee et al, the 30 days wound complication was 2.4% overall in ASD, and deep infection was 1% (101). This study was retrospective and pooled wound complication from administrative data by ICD codes. Observation was limited to 30 days. This can explain the lower incidence in this series.

Pul ter Gunne et al. analyzed their institution records and collected data on 3174 patients operated for ASD (102). In total, 132 (4.2%) patients were found to have an SSI with 84 having deep based infection. They then analyzed all patients having spinal osteotomies (including posterior column osteotomies) for ASD(103). Twenty patients of 363 (5.5%) were found to have an SSI, with nine (2.5%) having deep SSI. Their figures are similar to the ones we report (5.2%). Our higher figures might be due to a more meticulous reporting and the prospective nature of our database.

RISK FACTORS FOR INFECTION IN ASD

Lee et al., through a multivariate analysis of patients having surgery for ASD found that posterior fusion (OR=1.8; P =0.010), obese class II (OR=1.7; p=0.046), obese class III (OR = 2.8; p<0.001), preoperative blood transfusion (OR=6.1; p=0.021), ASA class ≥3 (OR = 1.7; p=0.009), and operative time >4 hours (OR=1.8; p=0.006) were statistically significant risk factors for wound complications (including infection) (101).

In the study by Pull ter Gunner, estimated blood loss over 1 litre (p= 0.017), previous SSI (p=0.012) and diabetes (p= 0.050) were found to be independent statistically significant risk factors for SSI (104). Obesity (p= 0.009) was found to significantly increase the risk of superficial infection, whereas anterior spinal approach decreased the risk (p=0.010). Diabetes (p=0.033), obesity (P = 0.047), previous SSI (p=0.009), and longer surgeries (2-5 hours [p= 0.023] and 5 or more hours [P = 0.009]) were found to be independent significant risk factors for deep SSI. In a subsequent study, the same authors found that patients undergoing VCR (p=0.042) had a significant increased risk for deep SSI (11.1%) (103).

Our sample identified several factors not previously linked to SSI in the ASD population. These included smoking, fusion extension, male gender, liver disease and history of blood clot.

In the general spinal surgical population, smoking has been established as an important risk factor. Similarly to our findings, a systematic review of available literature established that smoking increased SSI risk by 26%(105). Male gender(106) and extend of fusion(19) were also found to be risk factors in other general spinal reviews. Neither liver disease nor history of blood clot was found in the spinal litteratue to be associated with infection.

IMPACT OF INFECTION

The impact of a resolved infection on the final outcome has not been fully exposed in the current literature. This is the first study specifically aimed at defining the impact of deep SSI on patient outcomes after ASD surgery. In the short-term, SSI was associated with a longer hospital stay (p 0,001), and more wound complications (p=0.021) in our study. The infected group had a higher number of major complications (p=0.049). We also demonstrated that initial improvements in PROMs in the infected group were less sizable than in the non-infected group. This negative impact of SSI seems to be diluted by the second year however as PROMS seem to catch-up.

The present study proves again that ASD surgery is a risky procedure with nearly 56% of our patients suffering any complication and 43% suffering a major complication. Unfortunately, we had one death directly related to infection. In the recent spinal literature, infection has been associated with increased mortality up to 5 years after infection. Risk factors for increased mortality included age and comorbidities (33).

Despite this added morbidity and mortality, we have shown that both the infected and non-infected groups benefited equally from surgery in terms of deformity correction and quality of life at final review. At 24 months, and with the resolution of the infection, patients maintained good sagittal deformity correction combined with improvement in all their PROMs except SF36-MCS, SRS22-Mental Score and leg pain. In the absence of a non-surgical control group, we cannot compare the benefit gained with surgery to non-operative management. When analysing the HRQoL parameters, the COMI score was the single most sensitive outcome measure to detect any difference between these two groups. This is in line with recent literature and especially the recent work by Mannion et al. (107) who showed that despite its brevity, the COMI score was highly sensitive to any change in the patient´s condition or disease itself.

Scheer et al. showed that psychological scores (SRS22 Mental and SF 36 MCS) improved less if patients had a complication needing a secondary intervention after ASD surgery (108). In the present study we could show that psychological scores (SF 36 MCS and SF22 Mental score) did not differ significantly from baseline at last follow-up (Table 5), but that was across the whole sample. When we analyzed differences in absolute figures between both groups, there was an initial difference in SRS-22 Mental at 6 months that was lost thereafter (p0.036). We could also see that the SRS 22 Mental was less likely to improve at 6 months in the infected group (p 0.049). There was no difference beyond 6 months in these parameters.

Four other studies tried to assess the impact of infection on clinical results after posterior spinal surgery (84-86) with differing conclusions. In the matched control analysis in 16 patients with posterior spinal fusion, Mok et al. detected no significant difference in the Physical Function, Role Physical, Bodily Pain, and General Health domains between the infection group and control group at an average of 62 months (84). However, in a similar study, Petilon did demonstrate a difference in back pain and ODI in patients suffering from a deep infection after a lumbar fusion (88). This was a matched cohort study of 30 patients with SSI and 30 controls after a lumbar fusion. Patient population was heterogeneous in terms of diagnosis and they included anterior only surgeries such as ALIFs, but did not include ASD patients.

Rhin et al. found no difference in the pain, function, self-image, satisfaction, or total Scoliosis Research Society 22 scores after deep SSI in adolescent patients with idiopathic scoliosis after a minimum of 2 years (86). Falavigna et al. (85) studied patients having lumbar fusion for degenerative disc disease, and found no significant difference in pain, functional disability, quality of life, or depression and anxiety. However, 53.8% of the patients with infection were not satisfied with the procedure at the final evaluation, compared with 15.4% of the patients without a deep wound infection ($p = 0.003$).

Even if infection does not seem to significantly alter the final functional outcome, these studies did not follow the recorded variables through time and they did not study the difference between infected and non-infected patients at defined time intervals. They also included heterogeneous groups of patients with respect to preoperative diagnosis and surgical procedure. They also didn't stratify infections by timing. In addition, they had small samples and lacked detailed preoperative records.

Nuñez-Pereira et al. analyzed implant survival after SSI in Spinal surgery (35). In their sample of 43 patients with posterior instrumented fusion only 90% of the implants or patients survived the first debridement. At 2 years, 73% of patients were alive with implants. This survivorship rate was

maintained thereafter. These results were reproduced in the literature (109, 110). In ASD surgery, especially when associated to tricolumnar osteotomies, implants are essential during the first two postoperative years to ensure a stable environment for fusion. Fusion itself is a fundamental prerequisite to any surgical success. Risk factors for implant removal includes late infections, delayed surgery, delayed antibiotic treatment, greater number of past surgeries, high postoperative infection treatment score for the spine, and the presence of MRSA (74, 109, 110). Infection occurring in the first 90 days have higher chances to preserve original implants(79). In our series only two patients needed a partial exchange of instrumentation and we had one death. The survival rate with original implants was therefore 85% at 2 years. Two patients were re-instrumented with no further loss of sagittal correction and all had their infection controlled by 6 months from diagnosis. The fact that all infections in our sample were successfully treated and that there were no infection relapses explains in part our good overall results

Even when implants are maintained, SSI patients seem to suffer from more pseudoarthrosis with rates varying between 38 and 44% (34, 111). Risk factors for non-fusion with SSI seem to be female gender, extension to sacrum, use of allograft and not using cages (34, 111). In our series, we did not find any significant difference between both groups (10.5% vs. 19.3%). When we analysed mechanical complications as a whole (PJK, rod Breakage and non unions) we saw that there was a higher prevalence in the infected group (42.1% vs. 29.8%, P 0.400). This did not reach statistical significance. When analysed alone, PJK was much more prevalent in the context of infection (31.6% vs. 10.5% p 0.023) than in patients without SSI. No other study has investigated the rate of PJK in the context of SSI. We hypothesise that this higher rate of PJK in infected patients is due to a weakened posterior tension band or muscles due to the infection itself, the decreased activity of patients with infection or repeated surgical injury during revision.

STRENGTH OF THE PRESENT STUDY

The present study is the largest cohort study specifically studying the effect of SSI on surgical outcomes in spinal surgery. It also aims at studying this negative impact in long-term follow-up. The study contained a homogenous diagnostic and surgical population that was further matched using demographic and surgical variables known to affect both infection and outcome scores. In addition, the matched cohorts included in this analysis showed no differences in other non-matched known risk factors such as diabetes, liver disease, smoking, length of surgery and blood loss. The size of the deformity and the baseline HRQoL parameters were also comparable between both groups. This further increases the validity of our conclusions.

STUDY LIMITATION

This study suffers from inherent limitations applicable to all multicentre studies. One of these might be the non-standardized approach and management of infection in the different participating centres. Another major limitation is the small sample size and the lack of statistical power to detect differences between groups. Failure to find differences does not imply that there are none. The differences in some variable were wide enough to be clinically significant but did not reach clinical significance. We also did not stratify infections according to their virulence nor to their course. We are conscious that infection cannot be considered as a homogeneous entity and patients might fare differently and their results vary accordingly. We only included acute infections that were diagnosed and treated very early on and all of our patients cleared the infection with the exception of the patient that died. With a bigger sample, possible differences might be better delimited and/or patients could be stratified according to infection characteristics. The impact death has on the final outcome, even though real, could not be measured in our study. There was no reliable precedence in the literature on how to treat death in a PROM analysis when death is directly related to the main variable. We omitted the dead patient along with her matched pairs from our result analysis. This decision was based on the fact that death secondary to SSI is extremely rare in the ASD population. Leaving the patient and keeping her PROMs at worst values would have severely distorted our analysis with the small sample. Detected differences would be harder to interpret. We nevertheless believe that death´s impact cannot be obviated and a better way to account for it would be through a QALY (Quality Adjusted Life Year) analysis.

Finally, in the absence of a non-surgical control group, we cannot compare the benefit gained with surgery to non-operative management.

FUTURE TRENDS

The findings of this report help shed the light on SSI as a highly morbid condition and to develop new prevention and treatment strategies that would limit the medical, social and economic impact of the infection on both patient and society. It highlights that infection does not seem to affect final results provided it has been diagnosed early and treated successfully. It also provides surgeons with more insight when counselling potential surgical patients on the risks and benefits of surgery, and likely outcomes.

The recent development of strong predictive models has optimized resource utilization in different economical sectors. It has recently been applied to medicine in an effort to compensate inherent limitation with regression models. It also provided the first real step towards a “personalized” medicine. The ESSG has already used this promising technology to predict the risk for major complication in ASD as well as readmission and reoperation (CITA GEER) (CITA EUROSPINE). The sample principles could be applied to our database to create a personalized risk calculator for SSI in ASD Surgery. The applications of such model are endless. From uncovering new risk factors as well as interactions between factors, to establishing the efficiency of some prevention measures, to shifting healthcare resources accordingly. A preoperatively high risk for SSI despite patient´s optimization should also pose serious doubts on whether some complications are really “avoidable” in certain surgical settings. The relatively low incidence of SSI (5% in our series) and the small number of patients (444) are still a major hindrance in the development of such calculators.

A more detailed descriptive narrative of the course of infection could provide some clues on which infections or patients fare well after infection or which have a long lasting – or even fatal – sequel. This could fuel efforts to gauge therapeutic aggressiveness without compromising neither infection eradication nor surgical outcomes.

Finally, all of the above could be included in a personalized consent form for patients to ponder upon before decision-making. This consent form would naturally include other vital information such as personalized surgical benefits, natural course without surgery and detailed complication profile. The present report helps to give patients a more detailed picture of what to expect after SSI.

CONCLUSIONS

MAIN CONCLUSIONS:

- Both primary diagnosis (traumatic injury vs. degenerative) and neurological status (myelopathy or SCI) are strong and independent predictors of SSI after cervical spine surgery.
- SSI significantly affects recovery in the first postoperative year with ASD patients having worst quality of life when compared to their non-infected counterparts.
- The negative impact of SSI in ASD seems to wear off by the second year, as differences in outcome scores become less pronounced.

SECONDARY CONCLUSIONS:

- The incidence of SSI has remained stable in cervical spine despite the rise in number of surgeries performed and increasing age of patients.
- Independent risk factors for SSI in cervical spine include: fusion extension, approach, male gender, African American, rural hospital, Elixhauser comorbidity index, Medicare coverage and age
- Infection increases hospital charges and indirect costs after discharge irrespective of aetiology and neurological status.
- Patients with neurological deficits or trauma consume more resources at baseline however, costs related to infection increase in a stepwise fashion across the four studied diagnostic groups
- ASD patients have a high rate of SSI
- SSI in ASD increases the length of hospital stay and is associated with more complications and unrelated revisions.
- SSI can even be deadly in extreme of cases.
- Patients with SSI seem to benefit from posterior ASD surgery just as much as their non-infected counterparts.
- SSI does not seem to have a significant bearing on the size of deformity correction provided that the implants are maintained

ETHICAL CONSIDERATIONS

This study is mainly a retrospective and prospective database and chart review. It abided by protecting patients confidentiality according to the HIPAA Privacy Rule and European legislation. It has sought necessary Institutional Board Review approval and individual patient´s consent for the enrolment in the ESSG database.

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ADDITIONAL MATERIAL

ARTICLE 1: DIAGNOSIS AND NEUROLOGICAL STATUS AS PREDICTORS OF SURGICAL SITE INFECTION IN PRIMARY CERVICAL SPINAL SURGERY (THE SPINE JOURNAL 2016)

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Clinical Study

Diagnosis and neurologic status as predictors of surgical site infection in primary cervical spinal surgery

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Abstract

BACKGROUND CONTEXT: Surgical site infection (SSI) incidence after cervical spinal surgery ranges from 0.1% to 17%. Although the general risk factors for SSI have been discussed, the relationship of neurologic status and trauma to SSI has not been explicitly explored.

PURPOSE: This study aimed to study associated risk factors and to report the incidence of SSI in patients who have undergone cervical spinal surgery with the following four preoperative diagnoses: (1) degenerative disease with no myelopathy (MP), (2) degenerative disease with MP, (3) traumatic cervical injury without spinal cord injury (SCI), (4) traumatic cervical injury with SCI. We hypothesize that SSI incidence would increase from Group (1) to Group (4).

STUDY DESIGN: Retrospective database analysis was carried out.

PATIENTS SAMPLE: We used International Classification of Diseases codes to identify the four groups of patients in the U.S. Nationwide Inpatient Sample (NIS) from the years 2000 to 2011. We complemented this study with a similar search in our institutional database (ID) from the years 2000 to 2013. Patients with concomitant congenital deformity, infection, inflammatory disease, and neoplasia were excluded, as were revision surgeries.

OUTCOME MEASURES: The primary outcome studied was the occurrence of SSI. Statistical analyses included bivariate comparisons and chi-square distribution of demographic data and multivariable regression for demographic, surgical, and outcome variables.

FDA device/drug status: Not applicable.

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The disclosure key can be found on the Table of Contents and at www.TheSpineJournalOnline.com.

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RESULTS: A total of 1,247,281 and 5,540 patients met inclusion criteria in the NIS database and the ID, respectively. Overall SSI incidence was 0.73% (NIS) versus 1.75% (ID). Surgical site infection incidence increased steadily from 0.52% in Group (1) to 1.97% in Group (4) in the NIS data and from 0.88% to 5.54% in the ID. Differences between diagnostic groups and cohorts reached statistical significance. Surgical site infection was predicted significantly by status (odds ratio [OR] 1.69, p<.0001) and trauma (OR 1.30, p=.0003) in the NIS data. Other significant predictors included the following: approach, number of levels fused, female gender, black race, medium size hospital, rural hospital, large hospital, western US hospital and Medicare coverage. In the ID, only trauma (OR 2.11, p=.03) reached significance when accounting for comorbidities.
CONCLUSIONS: Both primary diagnosis (trauma vs. degenerative) and neurologic status (MP or SCI) were found to be strong and independent predictors of SSI in cervical spine surgery.

Keywords: Cervical; Degenerative; Infection; Myelopathy; NIS; Spinal cord injury; Spine; Surgery; Surgical site infection; Trauma

Introduction

The annual volume of cervical spine operations performed in the United States has increased steadily over the past decades [1,2]. These surgeries are typically performed to treat cervical stenosis causing radiculopathy or myelopathy, and less commonly for trauma, neoplasm, or infection [3]. Not only has the absolute number of patients undergoing spine surgeries increased, but also has the average age and comorbidity index [1,2]. However, this rise was associated with neither higher morbidity nor mortality, and in fact, average total length of hospital stay has decreased over the same time period [2]. Wound-related complications, including infections, are a relatively common postoperative problem, increasing overall morbidity, mortality, and health-care costs [4,5]. The overall incidence of infections in spine surgeries varies from 0% to 17% depending on the diagnosis, surgical approach, operative region, number of levels, and use of instrumentation [6–10]. This incidence varies between studies based on the definition and methods used to monitor for infection. Other common risk factors for surgical site infections (SSIs) include comorbidities such as age over 60 years, diabetes, malnutrition, and obesity, among others [11–15]. Multiple studies have demonstrated a relatively high risk of infection after posterior cervical surgery ranging from 3% to 94% [15,16] compared with a much lower rate with anterior-only approaches [7,17,18]. Higher complication rates have also been reported after posterior stabilization for traumatic cervical injuries, rheumatoid cervical disease, and in patients with myelopathy, upward of 17% in some cases [6,7,16,19]. Infection after posttraumatic posterior cervical fusion has also been associated with delays to operative intervention, increased postoperative intensive care unit stay, and use of a postoperative semi-rigid cervical orthosis [20].

Although numerous risk factors for infection after cervical spinal surgery have been identified, the relationship between preoperative neurologic status and infection has not been fully explored. Increased approach-related perioperative morbidity was demonstrated in patients with cervical spondylotic myelopathy [3,7,10,21]. Increased morbidity and mortality have also been documented in patients following surgery for traumatic injuries compared with patients undergoing surgery for non-traumatic indications, and a single study linked spinal cord injury (SCI) to infectious outcomes [6,8,20,22,23]. However, no studies have been done to compare incidence of SSI based on neurologic status in patients undergoing cervical procedures for either degenerative or traumatic indications. Thus, the premise of this study was to report the incidence of SSI in patients who have undergone cervical spinal surgery with the following four preoperative diagnoses: (1) cervical radiculopathy, (2) cervical myeloradiculopathy, (3) traumatic cervical injury without neurologic injury, and (4) traumatic cervical injury with neurologic injury.

The hypothesis is that the infection rate—and thus perioperative morbidity—will increase in a stepwise fashion moving from Group (1) to Group (4).

Methods

Data sources

The U.S. Nationwide Inpatient Sample (NIS) database was used to access patient information from the years 2000 to 2011. The NIS is the largest publicly available all-payer inpatient care database containing de-identified discharge data, approximating a 20% stratified sample of U.S. community hospitals [24]. The Agency for Healthcare Research and Quality reports high NIS accuracy and agreement between data estimated by the NIS and the National Hospital Discharge Survey. The NIS data quality is reported publicly on the Health Care Utilization Project website. Coding for the NIS is consistent with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). Using an analogous billing code search, our institutional database (ID) was also used to collect data from 2000 to 2013 for comparison purposes.

Patients were selected for inclusion based on appropriate ICD-9-CM procedure codes linked to specific diagnosis codes (Table 1). Diagnostic codes were selected to stratify patients by one of four preoperative diagnoses: (1) cervical

EVIDENCE & METHODS

Context

The authors maintain that the influence of cervical spine trauma and neurologic compromise on the risk of surgical site infection (SSI) is not well understood. To evaluate this, they examined 11 years of data from the Nationwide Inpatient Sample and 13 years of surgical experience at a single center to develop a better understanding of this issue.

Contribution

This study included more than one million patient records from the NIS and 5,540 patients from a single academic center. Logistic regression analysis revealed a number of factors responsible for increased SSI risk including neurologic status and cervical spine trauma. The institutional analysis was limited by a small number of SSI events but did find a significant increased risk of infection for patients treated surgically for cervical trauma.

Implications

This study presents information that can be used during the consent process and when counseling patients and families regarding post surgical expectations. It is unclear whether a rare event such as cervical spine fractures, as identified in the NIS, may be poorly calibrated to the logistic model used by the authors. Some of the statistical findings may not be generalizable to all patients, particularly if the model is overfit. Cervical trauma as an independent risk may be seen as more robust, as it was confirmed in the institutional analysis.

—The Editors

radiculopathy without myelopathy, (2) cervical radiculopathy with myelopathy, (3) traumatic cervical injury without neurologic injury, or (4) traumatic cervical injury with neurologic injury. Patients were excluded based on diagnostic codes for congenital deformity, infection, inflammatory disease, or neoplasia. Procedural codes were selected such that only primary procedures were considered and revisions were excluded. Patients undergoing multilevel fusion were arbitrarily grouped into those undergoing fusion at two or three levels and those undergoing surgery at between four and eight levels when the number of levels was available. This method of duplicate patient selection on the basis of ICD-9 codes inherently removed cases of inconsistency between coding search based on diagnosis and procedure. Outcome variables were limited to surgical site infection (postoperative infection, including hematoma and seroma). The following demographic variables were collected: age, body mass index (BMI), sex, race, hospital location, and region. Age was entered as a continuous variable, and the remaining as categorical variables.

The same analysis was conducted using our ID, including patients from the years 2000 to 2013. Our hospital is a major academic medical center and a Level 1 trauma facility with a spine fellowship and an active research program. In our database and contrary to the NIS, multiple admissions for cervical surgeries could be accounted for, and only the first incident was retained. We also had some ability to trace infections occurring after discharge and were not limited to the admission episode as is the NIS. Using this database, comorbidity indexes were used to account for confounding factors. These included American Society of Anesthesia (ASA) Physical Status Score and both the Charlson and Elixhauser comorbidity indexes.

Table 1
ICD-9-CM Diagnostic and Procedural Codes

Diagnostic codes	
Group 1: Cervical radiculopathy without myelopathy	
Code	Description
721.0	Cervical spondylosis without myelopathy
722.0	Displacement of cervical intervertebral disc without myelopathy
722.4	Degeneration of cervical intervertebral disc
723.0	Spinal stenosis of cervical region
723.1	Cervicalgia
723.4	Brachial neuritis or radiculitis
723.7	Ossification of the posterior longitudinal ligament in the cervical region
Group 2: Cervical myeloradiculopathy	
Code	Description
721.1	Cervical spondylosis with myelopathy
722.7	Intervertebral disc disorder with myelopathy
Group 3: Traumatic cervical injury without neurologic injury	
Code	Description
805.00–805.18	Fracture of vertebral column without mention of spinal cord injury
Group 4: Traumatic cervical injury with neurologic injury	
Code	Description
806.00–806.19	Fracture of vertebral column with spinal cord injury
952.00–952.09	C_1–C_4 level with central cord syndrome
Procedural codes	
Code	Description
03.09	Exploration and decompression of spinal canal
03.53	Repair of vertebral fratcure
03.99	Other operations on spinal cord and spinal canal structures
80.50, 80.51	Excision of intervertebral disc
81.0	Spinal fusion
81.02	Other cervical fusion, anterior technique
81.03	Other cervical fusion, posterior technique
81.61	360 Degree spinal fusion
81.62	Fusion of two to three vertebrae
81.63	Fusion of four to eight vertebrae
81.64	Fusion of nine or more vertebrae
84.51	Insertion of interbody spinal fusion device
81.63	Fusion of four to eight vertebrae

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

Statistical analysis

Statistical analyses were performed using R 3.2 (R Foundation, Auckland, NZ). Descriptive and bivariate comparisons of demographic variables were performed using the Wilcoxon

Table 2
Number of cases per year, and prevalence of SCI and myelopathy per year

Year	Patients	Trauma cases	% Trauma within all	Myelopathy cases	% Myelopathy within degenerative	SCI cases	% SCI within trauma
2004	127,339	7,579	5.95%	30,835	25.75%	2,786	36.76%
2005	139,334	6,644	4.77%	36,528	27.53%	2,246	33.80%
2006	145,415	7,984	5.49%	36,389	26.48%	2,403	30.10%
2007	148,779	7,931	5.33%	40,149	28.51%	2,537	31.99%
2008	163,092	8,418	5.16%	44,078	28.50%	2,716	32.26%
2009	168,564	9,216	5.47%	47,662	29.91%	2,857	31.00%
2010	174,938	12,035	6.88%	52,294	32.10%	3,919	32.56%
2011	179,820	8,675	4.82%	57,523	33.61%	2,841	32.75%
Total	**1,247,281**	**68,482**	**5.49%**	**345,458**	**29.31%**	**22,305**	**32.57%**

SCI, spinal cord injury.

test for age and BMI, and chi-squared analysis for the categorical variables (sex, race, hospital region). Multivariable logistic regression modeling was performed to determine odds ratios (ORs) with corresponding confidence intervals (CIs) for the outcome variables.

Results

(a) NIS data

A total of 1,872,327 patients were identified from the NIS database that met inclusion criteria from 2000 until 2011. Analysis detected high rates of inconsistent or missing data between the years 2000 and 2003. These four years were therefore dropped from the final analyses and only years 2004–2011 were considered. A total of 1,247,281 patients remained in the final cohort. Only 68,482 patients had a traumatic diagnosis (5.49%). A total of 345,458 patients had myelopathy at the time of surgery, representing almost one quarter of all patients with a degenerative diagnosis. Nearly one in every three patients who underwent surgery for a traumatic cervical lesion had an SCI (22,305 patients). Although the annual prevalence of traumatic diagnosis remained stable, the proportion of patients with myelopathy steadily and slowly increased over this 7-year period. Table 2 presents the number of cases as well as the diagnostic class per year. Figs. 1 and 2 depict the trends in numbers and percentages in graphical format in both populations.

Table 3 demonstrates the distribution of these patients by preoperative diagnosis and illustrates demographic and surgical differences between diagnostic groups. Patients with myelopathy in the degenerative group were significantly older and more frequently of male gender. Traumatic patients and patients with SCI were younger and more often male compared with those patients without SCI. With respect to race, African-American, Asian and Hispanic patients presented more often with myelopathy or neurologic injury than without. Furthermore, the majority of patients in this cohort were treated in the southern U.S. hospitals, although no differences were observed between regions with regard to the incidence of patients presenting with myelopathy or neurologic injury. Self-pay patients and patients with Medicaid presented more with a traumatic injury than other patients. Medicare patients tended to present with myelopathy whereas patients covered under Medicaid were more likely to have an SCI. Patients with degenerative pathology were typically treated using an anterior procedure whereas the posterior approach was more common for traumatic injuries.

The results of bivariate analysis for SSI by diagnosis and neurologic status are presented in Table 4. The incidence of infection was higher in the traumatic cohort than in the

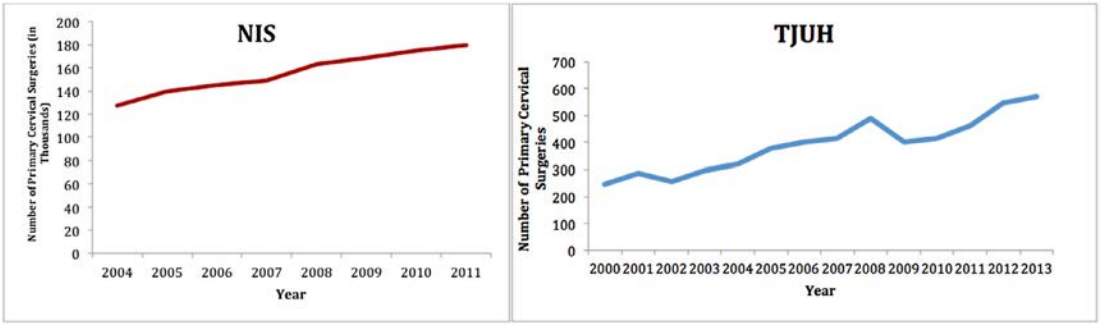


Fig. 1. Number of primary cervical spine surgeries performed yearly in both the Nationwide Inpatient Sample (NIS) and institutional populations.

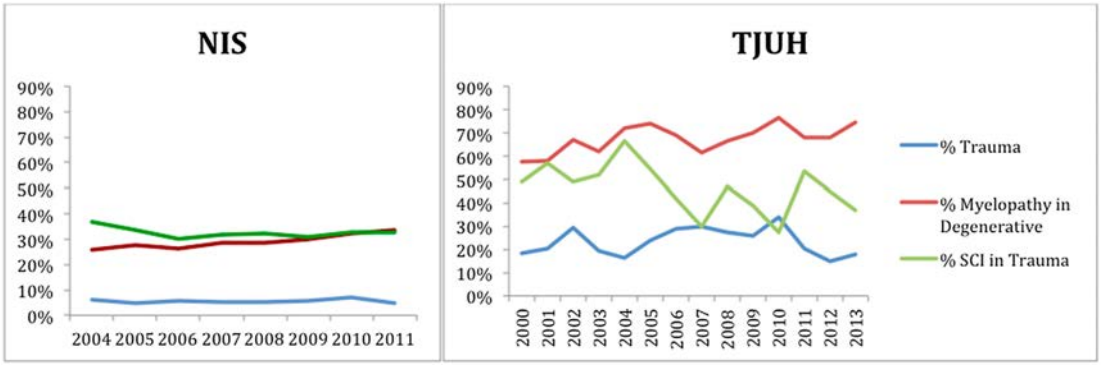


Fig. 2. Proportion of patients with traumatic or neurologic injury in both the the Nationwide Inpatient Sample (NIS) and institutional populations.

degenerative cohort, and both myelopathy and SCI increased the incidence of infection within these cohorts.

Surgical site infection incidence was further analyzed for differences in age, gender, surgical approach, number of spinal levels fused, hospital location and region, and annual trends for the four preoperative diagnoses (Table 5). Both neurologic injury (OR 1.69, 95% CI 1.51–1.89, p<.0001) and trauma (OR 1.30, 95% CI 1.09–1.56. p=.003) were found to be predictors of infection. Other significant predictors included the following: approach, number of levels fused, female gender, black race, medium size hospital, rural hospital, large hospital, western US hospital, and Medicare coverage.

To account for any interaction between neurologic injury and trauma among SSIs, the Mantel-Haenszel statistics model was used. Controlling for neurologic injury, the OR for infections in patients with traumatic injury was 2.09 (95% CI 1.79–2.43, p<.0001). Similarly controlling for trauma, the OR for infection in the setting of neurologic injury was 2.12 (95% CI 1.93–2.32, p<.001). These statistics further corroborate the notion that trauma and neurologic status are independent predictors of SSI.

(b) Institutional database

A total of 5,490 patients had a primary cervical surgery between January 2000 and December 2013 and 96 (1.75%) developed an SSI. The annual number of cases increased steadily over the study period (Fig. 1), but the incidence of SSI remained relatively constant at 1.75% (standard error 0.18%) (Fig. 3). Both the number and proportion of patients with a degenerative diagnosis increased over this 10-year span. The fraction of patients with myelopathy within the degenerative population increased, which is consistent with the national data (Fig. 2).

In the ID we found a higher proportion of traumatic patients and patients presenting with a neurologic deficit before surgery (Fig. 4).

In contrast to the national data, patients presenting with a traumatic diagnosis were more often older and with lower

Table 3
Study population demographic and surgical information by preoperative diagnosis (NIS)

Variables	Degen, no MP	Degen with MP	Trauma, no SCI	Trauma with SCI
Age (years) (mean±SD)	52.1±11.7	57.3±12.6	50.7±22.3	46.6±21
Sex (%)				
Male	46.73%	53.78%	63.67%	74.54%
Female	53.27%	46.22%	36.26%	25.46%
Race (%)				
Caucasian	83.96%	76.07%	77.93%	70.93%
African-American	7.47%	13.55%	9.82%	13.34%
Hispanic	4.78%	5.83%	7.30%	9.54%
Asian	1.07%	1.71%	1.40%	2.25%
Native American	0.40%	0.46%	0.77%	1.03%
Other	2.33%	2.38%	2.78%	2.91%
Hospital location (%)				
Rural	4.58%	4.12%	3.59%	2.43%
Urban academic	45.83%	40.04%	25.53%	20.82%
Urban private	49.59%	55.84%	70.88%	76.76%
Hospital region (%)				
Northeast	14.34%	15.02%	15.92%	14.80%
Midwest	22.83%	20.30%	21.10%	20.96%
South	44.42%	43.62%	42.97%	42.18%
West	18.41%	21.06%	20.00%	22.06%
Primary payer				
Medicare	22.10%	35.28%	27.67%	21.14%
Medicaid	5.11%	6.68%	8.91%	16.69%
Private insurance	59.77%	48.31%	45.11%	44.25%
Self-pay	1.33%	2.05%	9.60%	8.94%
No charge	0.17%	0.26%	0.63%	0.58%
Other	11.53%	7.41%	8.08%	8.40%
Surgical approach				
Anterior	85.67%	78.96%	37.23%	43.51%
Unspecified	8.86%	1.81%	24.93%	7.40%
Posterior	4.53%	15.18%	30.40%	30.32%
Anterior+posterior	0.94%	4.05%	7.44%	18.77%
Fusion levels				
None or not specified	8.86%	1.81%	24.93%	7.40%
2–3 Segments	79.26%	70.58%	62.92%	67.40%
4–8 Segments	11.79%	27.27%	11.54%	24.18%
9+	0.09%	0.35%	0.61%	1.02%

Degen, degenerative; MP, myelopathy; SCI, spinal cord injury; NIS, Nationwide Inpatient Sample.

Table 4
Bivariate analysis of outcome variables (NIS and TJUH sample)

Outcome variable	Overall	Degenerative: No MP	Degenerative: With MP	Traumatic: No SCI	Traumatic: With SCI	p-Value
Infection (NIS)	0.73%	0.52%	1.11%	1.17%	1.97%	<.001
Infection (TJUH)	1.75%	0.88%	1.57%	2.65%	5.54%	<.001

MP, myelopathy; SCI, scpinal cord injury; NIS, Nationwide Inpatient Sample; TJUH, Thomas Jefferson University Hospital.

BMI than patients presenting with a degenerative diagnosis and were more often male. African-Americans presented more often after traumatic injury and with an associated neurologic injury (myelopathy or SCI). Also, the ASA, Charlson and Elixhauser comorbidity indexes increased moving across the four diagnostic groups, paralleling to some extent the increase in incidence of infection. Those with workers' compensation claims most often presented with cervical degenerative pathology without associated myelopathy. Additional demographic and surgical details can be found in Table 6.

Table 5
Mutivariate analysis of the NIS

Variable		Odds ratio	95% CI	p-Value
Age		**1.01**	**1.01–1.02**	**<.0001**
Gender (Female)		**0.69**	**0.62–0.76**	**<.0001**
Race (vs. Caucasian)	**African-American**	**1.44**	**1.24–1.68**	**<.0001**
	Hispanic	1.09	0.88–1.37	.425913744
	Asian	0.73	0.45–1.19	.207060525
	Native American	1.07	0.51–2.26	.860291476
	Other	0.98	0.69–1.40	.924333284
Payer (vs. Medicare)	Medicaid	1.02	0.80–1.29	.877955744
	Private	**0.82**	**0.71–0.94**	**.004957448**
	Self-pay	1.03	0.72–1.46	.875327006
	No charge	0.91	0.34–2.46	.853827241
	Other	0.88	0.71–1.09	.226205355
Hospital size (vs. small)	**Medium**	**1.41**	**1.15–1.73**	**.001086913**
	Large	**1.33**	**1.11–1.60**	**.002419993**
Hospital type (vs. urban academic)	**Rural**	**1.35**	**1.04–1.74**	**.025250785**
	Urban private	1.10	0.98–1.23	.107768348
Hospital region (vs. Northwest)	Midwest	1.05	0.87–1.26	.632882487
	South	1.04	0.90–1.20	.608131574
	West	**1.24**	**1.05–1.46**	**.013223017**
Calendar year		0.98	0.96–1.01	.157052881
Surgical approach (vs. anterior)	**Not specified**	**2.11**	**1.77–2.51**	**<.0001**
	Posterior	**2.09**	**1.82–2.41**	**<.0001**
	Combined	**3.38**	**2.77–4.12**	**<.0001**
Traumatic diagnosis		1.30	1.09–1.56	**.003456341**
Neurologic injury (SCI or MP)		1.69	1.51–1.89	**<.0001**

SCI, spinal cord injury; MP, myelopathy.
The variables highlighted in bold were the variables found to be statistically significant.

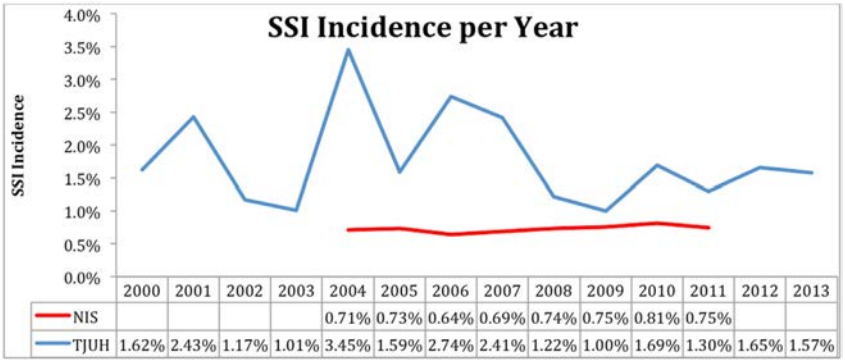
Surgical site infection incidence was significantly different between the four diagnostic groups and between the two populations (Fig. 5). The ASA was excluded from the multivariate analysis because it was not reported in the institution database before 2006 and was inconsistently present between 2006 and 2008. When including all other variables, the multivariate analysis showed significance for fusion levels (OR 2.80, 95% CI 1.38–5.67 for 4–8 segments vs. no instrumented fusion, p=.004), Charlson index (OR 1.32, 95% CI 1.19–1.47, p<.0001), Elixhauser index (OR 1.21, 95% CI 1.05–1.39, p=.008), age (OR 0.98, 95% CI 0.97–0.99, p=.001), and calendar year (OR 0.93, 95% CI 0.86–1.00, p=.04). Trauma (OR 2.22, 95% CI 1.12–4.37, p=.02) reached statistical significance whereas neurologic status did not (OR 1.47, 95% CI 0.87–2.49, p=.15). When excluding the Elixhauser comorbidity index and the Charslon score, both neuro (OR 1.72) and trauma (OR 2.42) reached statistical significance.

Using a Mantel-Haenszel test to account for covariates, neurologic injury and trauma were both shown to be independent variables for predicting infection in our model (trauma vs. infection: OR 3.45, 95% CI 2.22–5.45, p<.0001 and neurologic injury vs. infection: OR 1.945, 95% CI 1.21–3.10, p=.0068).

Discussion

Published SSI incidence for spine surgery ranges from 0.5% to 12% [25]. This wide range of infection rates is related to the variations in average age, indication, approach, type(s) of procedures, and use of instrumentation, among other factors. Another source of variability is the diagnostic criteria and the length of monitoring for the infection itself [26–28]. Other proposed risk factors include ethnicity [29], insurance status [12,30], and the hospital setting. As such, many systematic reviews have been conducted to scientifically summarize these findings, but none have specifically evaluated the influence of traumatic injury or neurologic status [26–28].

Surgical site infection after spinal surgery for traumatic indications was shown to be between 3.4% and 17% [20,22,23]. Rechtine et al. reported an infection rate of 10.2% for 117 fractures at the thoracolumbar junction [23], and Blam et al. reported an infection rate of 9.4% for 256 cases of surgically treated spinal trauma. The series by Lonjon excluded polytrauma patients and had an SSI rate of 3.4% [22]. None of these studies focused exclusively on the cervical region. Only Blam et al. directly compared elective surgery with surgery after traumatic SCI and reported significantly higher infection rates in the traumatic patient population [20]. In a study by Yadla et al. focusing exclusively on a cervical spine population, the authors found a higher incidence of major and minor complications in patients treated for infection or malignancy when compared with those treated for degenerative



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
NIS					0.71%	0.73%	0.64%	0.69%	0.74%	0.75%	0.81%	0.75%		
TJUH	1.62%	2.43%	1.17%	1.01%	3.45%	1.59%	2.74%	2.41%	1.22%	1.00%	1.69%	1.30%	1.65%	1.57%

Fig. 3. Surgical site infection (SSI) incidence by year in both the Nationwide Inpatient Sample (NIS) and institutional populations.

or traumatic indications, but this difference did not reach statistical significance. The authors, however, did not specifically study SSI and instead looked at the overall complication rate [8].

As for neurologic status, cord injury was found to be a predictor of infection in a single study by Rechtine et al. [23]. In this study the authors found a higher incidence of infections after thoracic or lumbar fracture stabilization in patients with complete SCI (7/17patients, incidence 41%) when compared with those with an intact neurologic status (3/61patients, incidence 4.9%). They failed to find any difference between patients with incomplete SCI (2/39 patients, 5.1%) when compared with patients without a neurologic deficit.

In patients undergoing elective surgical decompression, myelopathy was found to be a predictor of surgical complication or increased morbidity or mortality in five studies [7,10,21,31,32]. Only two of these reported an increased infection rate in patients with myelopathy when compared with patients without myelopathy. Boakye et al. found higher rates of infection in patients with myelopathy (0.43% vs. 0.15%) and suggested this may be due to more severe neural element compression or older age. Shamji et al. [7] found that posterior cervical approaches and myelopathy were associated with higher overall mortality and morbidity as well as costs and hospital stay after degenerative cervical spinal surgery. Infection rates were as follows: 0.02% (anterior approach without myelopathy); 0.1% (anterior with myelopathy); 0.36% (posterior without myelopathy), and 0.55 (posterior with myelopathy).

Several factors may contribute to the increased incidence of infections after traumatic injury. Patients with a traumatic injury, especially those with cord injury, typically have suffered a higher energy impact with an increased energy transfer and damage to soft tissues [23]. These patients might also suffer from posttraumatic immunosuppression which may be physiological or iatrogenic and localized tissue hypoxia secondary to soft tissue injury [33]. Patients with neurologic deficits are more likely to spend more time in bed, are more often in the recumbent position with a collar [6], and ambulate less, all of which increase local temperature and humidity at the surgical site; these factors are especially concerning in patients with a posterior cervical approach.

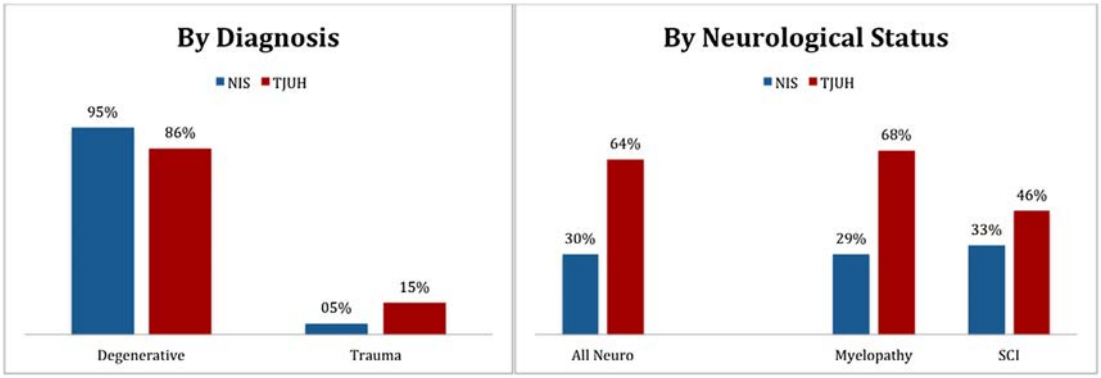


Fig. 4. Patient distribution by diagnosis and by neurologic status.

Table 6
Study population demographic and surgical information by preoperative diagnosis of the TJUH sample

	Degenerative		Traumatic	
Variables	Simple	MP	Simple	SCI
Age (years)	48.5 (SD 11.0)	55.5 (SD 12.4)	60.4 (SD 23.6)	53.3 (SD 23.0)
BMI	28.6 (SD 5.9)	29.3 (SD 6.3)	26.2 (SD 5.8)	26.4 (SD 5.9)
Sex (%)				
Male	51.42%	53.15%	61.81%	69.39%
Female	48.58%	46.85%	38.19%	30.61%
Race (%)				
Caucasian	80.84%	78.18%	87.42%	79.16%
African-American	7.56%	11.84%	7.51%	11.08%
Hispanic	1.21%	1.29%	1.55%	3.69%
Asian	0.54%	1.10%	0.22%	0.79%
Native American/Eskimo	0.07%	0.09%	0.00%	0.00%
Other	9.78%	7.49%	3.31%	5.28%
Primary payer				
Medicare	8.84%	21.25%	38.41%	26.65%
Private	73.35%	68.20%	43.05%	46.17%
WC	12.48%	6.49%	2.43%	5.80%
NF	4.86%	3.53%	15.23%	18.47%
Labor	0.27%	0.28%	0.22%	0.00%
Self-pay	0.20%	0.25%	0.66%	2.90%
Comorbidity indices				
ASA	2.15 (SD 0.55)	2.40 (SD 0.58)	2.69 (SD 0.74)	2.82 (SD 0.76)
Charlson	0.62 (1.01)	0.90 (1.43)	1.51 (2.40)	2.79 (3.16)
Elixhauser	1.25 (1.34)	1.63 (1.41)	1.78 (1.68)	2.23 (1.69)
Surgical approach				
Anterior	79.76%	63.38%	14.79%	17.15%
Posterior	6.14%	20.97%	29.14%	33.25%
Combined	2.09%	11.59%	14.57%	37.73%
Not specified	12.01%	4.06%	41.50%	11.87%
Fusion level				
Unspecified/no fusion	23.89%	17.92%	26.05%	28.50%
2–3 Segments	65.18%	46.85%	58.72%	35.88%
4–8 Segments	10.39%	34.57%	13.69%	32.98%
9+	0.54%	0.66%	1.55%	2.64%

SD, standard deviation; SCI, spinal cord injury; MP, myelopathy; ASA, American Society of Anesthesiologists; TJUH, Thomas Jefferson University Hospital.

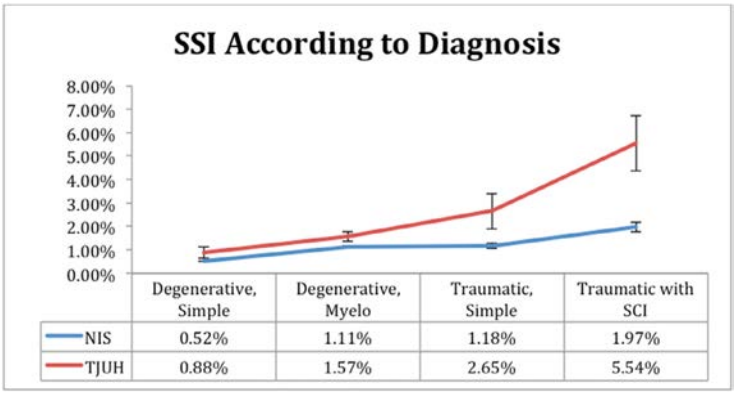


Fig. 5. Surgical site infection (SSI) incidence by diagnostic group.

Patients with traumatic injury are more frequently admitted to an ICU, have longer ICU and overall hospital length of stay, and may experience delays before surgical stabilization. Surgical site infections may in some cases be a result of seeding from nosocomial infections such as urinary and upper respiratory tract infections, which are twice as common in trauma patients versus patients with degenerative conditions, especially after spine, chest, or extremity injuries [34]. Finally, malnutrition [35] might be an important yet overlooked concomitant risk factor in the traumatic population. In his study, Klein [35] showed that nearly 75% of patients with SCI became malnourished during their hospital stay, and that all infections identified in the study occurred in malnourished patients.

On the other hand, degenerative patients with myelopathy are more often older and with more comorbidities [10]. Age, comorbidities, myelopathy, and severity of compression are often closely linked. More invasive surgeries, with additional decompression, longer surgical time, and more soft tissue dissection, are often required [21]. Also these patients generally require longer ICU stay, more need for intermittent ventilation, longer hospital stays, and higher overall complication rates [21].

Through stratification based on primary diagnosis and neurologic status, our data identified neurologic deficit and traumatic injury to be independent risk factors for SSI in the NIS population. In fact, a progression in infection rates between degenerative and traumatic diagnoses was found, as well as between patients who were neurologically intact (without SCI or myelopathy) and those with neurologic injury (with myelopathy or SCI) within the same diagnostic group and between the two diagnostic groups. As such, both traumatic injury and neurologic status are predictive of infection. These findings, however, could only be partially confirmed when analyzing records from our institution and considering comorbidities. In contrast to the national data, we found that traumatic patients at our institution were older and had more comorbidities. Infection increased significantly as we progressed along the four diagnostic groups; however, after accounting for Charlson and Elixhauser indexes, neurologic status lost statistical significance whereas trauma was still a significant independent risk factor. Finally, using a Mantel-Haenszel test to account for third variables, neuro and trauma were both shown to be independent variables for predicting infection.

The discrepancy in the results between the two populations might be explained by the different patient profiles and longer infection monitoring. Our institution performed a greater share of procedures for trauma (15% vs. 5%) with a higher proportion of patients with neurologic injury compared with the national sample (SCI 45% vs. 32%, myelopathy 68% vs. 29%). Our local population was also older and with more comorbid conditions. Both age and comorbidities increased across the diagnostic classes. This, in association with a smaller sample size and an overall low incidence of infection (1.75% at the institutional vs. 0.76% in the national database), could justify the loss of significance in the institutional series. These factors could help explain, although partially, a higher incidence of infections in the institutional records. Another contributing factor might be that in our population, and contrary to the NIS, we monitored and could report infection even after discharge.

A steady increase in number of cervical surgeries performed nationwide was apparent. Whereas the ratio of degenerative/traumatic remained constant, the proportion of patients with myelopathy in the degenerative population also increased. However, this trend reflects only surgical patients and might not represent an increased prevalence of myelopathy in the general population. This also might be partially explained by the selection methods for patients undergoing degenerative spinal surgeries, a more aggressive approach to treating patients with myelopathy or simply by evolving coding practices. This increase, together with an aging population with a higher index of comorbidities, would predict a rise in overall infection incidence. Hence, there is a need for more research in this field and the implementation of preventive strategies. Such strategies could include controlled use of steroids, improved nutrition, judicious use of cervical collars, decreased ICU stay [20], and reductions in preventable delays to surgical intervention [20]. Lastly, special caution should be taken with elderly patients or with patients with multiple comorbidities undergoing cervical surgery to treat myelopathy [7].

Finally, this study potentially suffers from bias inherent in any database analysis [36]. Large-scale population-based studies focusing on complications are conducted in a retrospective fashion by searching hospital-originated databases and registries. This methodology relies strongly on the skill of initial data entry by non-medical professionals, and the completeness of database queries. The accuracy of these databases has not been established and has recently been challenged [8,37]. Individual records could not be verified nor double-checked and only preexisting variables could be analyzed. As such the ASA was excluded from final analysis, as it was available for less than 50% of our population. The retained Charlson and Elixhauser indexes were taken from the ID and could not be verified. Also, the incidence of infection was dependent on the coding and data entry, and we could not verify how the diagnosis of infection was made. The impact of these limitations must be balanced against the large sample size and the associated benefits in study power. Some of these factors may be more carefully controlled and accurately defined in our institutional records, which might help explain the higher incidence of infection. When comparing NIS data with hospital data we found a higher incidence of infection in all four groups, although the relationship with diagnosis and neurologic status was maintained. Factors which may explain the increased rate of complications in our institutional data include greater accuracy of record keeping, prospective coding, reporting of complications up to 90 days after surgery, more thorough databasing, and a more liberal definition of infection [8,38,39].

It is worth noting that the NIS sample only accounts for events occurring during admission. This might explain two observations in this study. First, as discussed, our institutional records allow for longer infection monitoring, therefore partially explaining the higher infection incidence. Also, patients who require longer hospitalization in the national population (traumatic event or a neurologic compromise) would have a longer monitoring and therefore a higher incidence of infection. This bias, on the other hand, is not present in our institutional record.

As a final note, neurologic status could not be stratified based on severity, and this variable was categorized only as present or not. We could not therefore confirm the Rechtine et al. findings of higher infection rates in complete SCI when compared with incomplete SCI or show a relationship between severity of myelopathy and infection.

Conclusions

This is the first report directly linking diagnosis and neurologic status to the occurrence of SSI. We found a higher incidence of infection in patients presenting with spinal trauma as well as patients with neurologic injury irrespective of the etiology. Both primary diagnosis (traumatic injury vs. degenerative) and neurologic status (myelopathy or SCI) were found to be strong and independent predictors of SSIs after cervical spine surgery. These findings underscore the importance of preventative measures for site infections and highlight the vulnerability of patients who present for spinal surgery with associated neurologic dysfunction or trauma. Although this study's methodology is likely limited by underreporting of complications in the national data, predictors of SSI based on preoperative diagnosis were reinforced by our institutional data.

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ARTICLE 2: THE IMPACT OF DEEP SURGICAL SITE INFECTION ON SURGICAL OUTCOMES AFTER POSTERIOR ADULT SPINAL DEFORMITY SURGERY: A MATCHED CONTROL STUDY (EUROPEAN SPINE JOURNAL 2018)

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ORIGINAL ARTICLE

The impact of deep surgical site infection on surgical outcomes after posterior adult spinal deformity surgery: a matched control study

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Abstract

Purpose The impact of deep surgical site infection (SSI) on surgical outcomes after adult spinal deformity (ASD) surgery is still unclear. We aimed to study the morbidity of SSI in ASD and its impact on deformity correction and functional outcome.

Methods Prospective multicenter matched-cohort study including consecutively enrolled ASD patients. Patients developing SSI were matched to similar controls in terms of age, gender, ASA, primary or revision, extent of fusion, and use of tri-columnar osteotomies. Preoperative parameters, surgical variables, and complications were recorded. Deformity parameters and Health Related Quality of Life (HRQoL) scores were obtained preoperatively and at 6, 12, and 24 months. Independent *t* test and Fischer's exact test were used for comparisons.

Results 444 surgical ASD patients with more than 2 years of follow-up were identified. 20 sustained an acute SSI and 60 controls were accordingly matched. No differences were observed between groups in preoperative radiological and HRQoL variables confirming comparable groups. SSI patients had longer hospital stay and more mechanical complications including proximal junctional kyphosis. Infection was associated with more unrelated complications and revisions. Deformity correction was maintained equally at the different time intervals. One death was related to SSI. SSI patients had worse overall HRQoL status at 1 year and were less likely to experience improvement. However, no significant differences were recorded thereafter.

Conclusion SSI significantly affects the first postoperative year after posterior ASD surgery. It is associated with more complications, unrelated revisions, and worst quality of life. However it's negative impact seems to be diluted by the second postoperative year as differences in HRQoL scores between the two groups decrease.

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

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00586-018-5583-3) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

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Keywords Adult spinal deformity · Scoliosis · Surgery · Deep surgical site infection · Complication · Clinical outcome

Introduction

Adult spinal deformity (ASD) surgery is one of the most challenging surgical specialties. Significant deformities need tri-columnar osteotomies, or combined anterior and posterior approaches, increasing the technical complexity, and surgical morbidity [1–3] of these procedures. Despite this, its ability to improve the quality of life in these patients justifies its use [4, 5]. The short-term morbidity of ASD surgery has been extensively studied [1, 2, 6, 7], and so there is now an increasing interest in determining the impact of these complications on the final functional results of ASD [2, 7, 8].

Whilst most studies have focused on risk factors for, and the prevention of, surgical site infection (SSI), as well as on the economical and medical burden it has, no other study has investigated the impact of SSI on the final outcomes after ASD surgery [9–14]. The available knowledge in the literature is based on reported studies from the general spinal population, [9–11] and not on studies targeted specifically at SSI and its outcomes. Although no significant differences could be found in terms of functional outcomes, postoperative pain, or general health, these studies' conclusions were limited by their small and heterogeneous samples and did not specifically consider ASD or deep SSI in their results. They did not assess the impact of infection on non-union rates that can deleteriously affect the amount of deformity correction achieved, nor the functional outcomes after ASD surgery [9, 15, 16].

The primary objective of this study was to investigate the impact deep SSI has on ASD on Patient Reported Outcome Measures (PROMs) at different time intervals. The secondary objectives were to analyze the associated morbidity of SSI and its impact on deformity correction in this population.

Our hypothesis is that successfully treated deep SSI does not alter the functional outcome at 2 years even though it is likely to be associated with increased short-term morbidity.

Methods

This is a matched control study using a prospective multicentre database of patients with ASD.

We retrospectively analyzed prospectively collected data from ASD patients recruited in six European centres from four different countries sharing a common ASD comprehensive database.

All adult patients who had undergone posterior instrumented spinal fusion for ASD with a minimum 2-year follow-up were included. Institutional Review Board (IRB) approval was obtained from all participating centres, and informed consent was obtained from all the enrolled patients.

From this cohort, we then identified all patients who had been treated for deep SSI within the first 6 months of index surgery. The treating surgeon in each case made the diagnosis of infection clinically following the standard guidelines for deep SSI [17, 18]. Diagnosis was later confirmed by positive results on samples sent for microbiology. Treatment consisted of repetitive debridement as clinically needed, combined with targeted antibiotic therapy based on the growth sensibility. The choices of antibiotics as well as the duration of treatment were dependent on local protocols in each participating centre. As these were acute infections, original implants were maintained except in cases were infection was settled and poorly controlled.

Demographic and surgical variables were collected prospectively for all patients. All surgical and medical complications were recorded and were available for analysis.

Patients were assessed at established time intervals (preoperatively, 6, 12, and 24 months post-operatively) with validated Health Related Quality of Life (HRQoL) outcome tools, and sagittal and coronal deformity measurements on standard whole-spine radiographs.

HRQoL parameters included Numerical Rating Scale for back pain and leg pain, Oswestry Disability Index (ODI), 36-Item Short Form Health Survey (SF-36), Core Outcome Measures Index (COMI) and Scoliosis Research Society 22 Score (SRS-22 Score).

Patients who had undergone treatment for a deep SSI formed the case group. They were accordingly matched to controls based on demographic and surgical variables known to affect both exposure (infection) and outcomes (quality of life) [19, 20]. These were: gender, age, American Society of Anesthesiologists Score (by categories 0–1, 2, 3–4), revision vs. primary surgery, extent of fusion and the use of tricolumnar osteotomies (Schwab 3 +). We excluded from the control group patients who had been diagnosed with other non-surgical infections. We aimed at the highest matching proportion to form the control group.

We were able to compare absolute HRQoL figures at the different time intervals between groups. We compared the changes relative to the preoperative value at these intervals.

Secondary outcome analysis included mortality, complications, unplanned re-admission or re-operation, and size and maintenance of deformity correction. Radiological measures included overall deformity measurements, as well

as sagittal and spino-pelvic alignment parameters: SVA, LL, PI, PT, PI-LL, GT, and Major Cobb.

We used SPSS (MAC Os version 24.1) for statistical analysis. Descriptive and bivariate comparisons of demographic variables were performed between cases and controls using independent *t* test for continuous variable, and Fischer's exact test for the categorical variables. The level of statistical significance was set at $p < 0.05$.

Results

Between January 2010 and January 2016, we identified 689 patients with ASD undergoing posterior spinal instrumentation for deformity correction. 444 had more than 2 years of follow-up available. 23 Patients had been treated for a deep SSI (5.2%) and out of these 20 within the first 6 months of their index surgery. From the remaining 421 patients, 391 had not suffered from any postoperative infection and were available for matching. We could yield a 1:3 matching proportion after applying the six matching criteria. As such we had a 20:60 case–controlcohort available for analysis (Fig. 1, Flowchart).

The mean time for the diagnosis of SSI was 20.1 days (range 1–76; standard deviation 20.4) in our retained cohort and 13 were diagnosed during the same initial hospital admission. Six patients had a nosocomial infection during their hospital stay prior to developing infection. The most common nosocomial infection was urinary tract infection (UTI) (four patients). The most commonly isolated single microorganism was methicillin-sensitive *Staphylococcus aureus* (five cases) and the infection was due to multiple organisms in six patients. Patients needed an average of 1.7 wound debridements (range 1–3) and 3.5 months of antibiotics (range 2.5–6.5 months) to treat their SSI. Priority was to retain implants in all patients, especially that infection was acute (mean 20 days, range 1–76 days). 65% patients needed a single debridement. Two patients needed partial implant exchange and they had all been deemed to be clear of infection at their last review. Prior to implant exchange, both

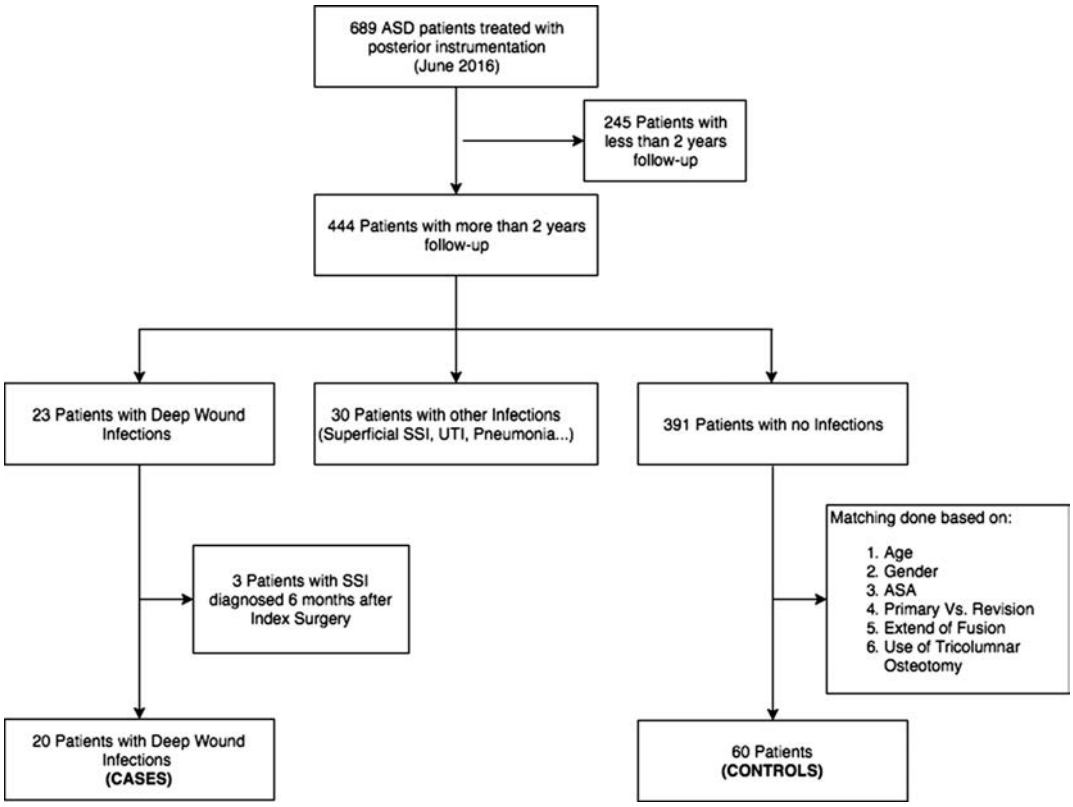

Fig. 1 Flowchart of patients participating in the study

patients had at least one failed debridement. One patient had *Staphylococcus epidermidis,* and the other patient, a multi-organism infection.

No significant differences were detected between cases and controls in matched or non-matched preoperative variables including radiological and HRQoL, confirming comparable samples (Table 1). Non-matched risk factors for infection were equally balanced between both groups; e.g. BMI ($p=0.587$) diabetes ($p=0.672$), smoking ($p=0.696$), and blood loss ($p=0.577$). Furthermore, both groups had similar proportion of patients from each participating centres (p 0.562), limiting any site biases.

There was one death in the SSI group related to the infection itself, whereas no deaths were recorded at an average of 4.2 years after index surgery in the control group ($p=0.250$) (Table 2). The patient in question was a 33-year-old lady with a background history of childhood poliomyelitis and lower-extremity motor paralysis. She had a lumbar osteotomy and T2 to pelvis fixation. She started complaining of fatigue and discomfort 2 days after index surgery and had a purulent discharge by the third day. She underwent surgical debridement and lavage that evidenced an extensive muscular necrosis. Intraoperative cultures grew *Acinetobacter bowmanii* and methicillin-resistant *S. aureus*. Despite extensive debridement and broad-spectrum antibiotics, her condition deteriorated and she went into sepsis in her immediate postoperative stay at the ICU. She soon developed a multi-organ failure and passed away on the eighth day after index surgery. We have accordingly removed this patient and its paired controls from the radiological and clinical outcomes analysis.

In terms of surgical complications and morbidity, the SSI group had a longer hospital stay (33.3 days vs. 12.8 days; p 0.004). Patients with infection were also more likely to have other associated wound problems such as seromas or hematomas (p 0.021). 52.6% of patients with an SSI had at least one associated major complication (vs. 42.1% in the control group, p 0.439) and on average, they had more non-infectious major complications than the control group (2.32 vs. 1.46 complications/patient; p 0.049). Both the groups had similar rates of mechanical/radiological complications (42.1 vs. 29.8%; p 0.400). The SSI group had three times more proximal junctional kyphosis (PJKs) (31.6 vs. 10.5%; $p=0.023$) (Table 2).

There were no differences in deformity correction between the groups at the different time intervals of the study. The primary sagittal deformity parameters improved significantly after surgery in both groups ($p<0.05$) and this correction was maintained over time (Table 3).

When analyzing HRQoL scores, we could see that both groups benefitted from the surgery and this improvement was maintained throughout the follow-up period. All PROMs were significantly better at the 24-month mark ($p<0.05$) except for the leg pain (p 0.123), SF36 Mental Component Score (SF36 MCS) (p 0.271), and SRS22 Mental Score ($p=0.348$) (Table 4).

We did find that the results up to 1 year after surgery did vary between both groups in favour of the controls, mostly in the ODI (6 months), COMI (6 and 12 months), SF 36 Physical Component Score (SF36 MCS) (6 months), and SRS 22 Mental Score (6 months). Full results are reproduced in Table 5.

The non-infected group also experienced more pronounced improvement compared to baseline values during the first year. This was apparent when analysing the differences from baseline in each group and comparing both groups. The COMI and ODI scores were the best parameters that could reflect the differences from baseline values between both groups at 6 and 12 months. Differences from baseline value were initially noted in the ODI (-14.69 vs. -1.5, $p=0.029$) and in SRS22-Mental component score (0.20 vs. -0.34, $p=0.049$) at 6 months, but were later diluted at 1 year (Table 6).

We failed to demonstrate any other difference beyond 12 months between the groups in the different analysis conducted (Tables 4, 5, 6).

Discussion

SSI in spinal surgery is notorious to increase morbidity, mortality and costs [21, 22]. It is also associated with increased length of stay, more unplanned re-admissions and revisions, and more pseudoarthrosis [16]. The impact of a resolved infection on the final outcome is less clear. This is the first study specifically aimed at defining the impact of deep SSI on patient outcomes after ASD surgery. In the short-term, SSI was associated with a longer hospital stay (p 0.001), and more wound complications ($p=0.021$) in our study. The infected group had a higher number of major complications ($p=0.049$). We also demonstrated that initial improvements in PROMs in the infected group were less sizeable than in the non-infected group. This negative impact of SSI seems to be diluted by the second year; however, as PROMs seem to catch-up.

The present study proves again that ASD surgery is a risky procedure with nearly 56% of our patients suffering any complication and 43% suffering a major complication. Unfortunately, we had one death directly related to infection. In the recent spinal literature, infection has been associated with increased mortality up to 5 years after infection. Risk factors for increased mortality included age and co-morbidities [22]. The impact that death has on the final outcome, even though real, could not be measured in our study. There was no reliable precedence in the literature on how to treat death in a PROM analysis when death is directly

Table 1 Comparison of preoperative and surgical variables between groups

Preoperative variables	Cases ($N=20$)	Controls ($N=60$)	p value
Female[a]	14 (70.0%)	42 (70.0%)	1
Male[a]	6 (30.0%)	18 (30.0%)	
No co-morbidities	5 (28.3%)	17 (28.3%)	1
Cancer	3 (15.0%)	5 (8.3%)	0.405
Diabetes	1 (5.0%)	7 (11.7%)	0.672
Liver disease	2 (10.0%)	1 (1.7%)	0153
Osteoporosis	0 (0%)	1 (1.7%)	1
Smoker	3 (15%)	7 (11.7%)	0.696
Tri-columnar osteotomies[a]	6 (30%)	18 (30%)	1
Revision surgery[a]	6 (30%)	18 (30%)	1
ASA 0–I[a]	7 (35%)	21 (35%)	1
ASA II[a]	7 (35%)	21 (35%)	
ASA III–IV[a]	6 (30%)	18 (30%)	
	Mean	Mean	p value
Demographic and surgical variables			
BMI	27.4	26.6	0.587
Age (years)[a]	57.9	53.8	0.377
Surgical duration (min)	375.5	338.4	*0.343*
Number of fused segments[a]	10.10	10.00	*0.920*
Number of osteotomies	1.60	1.63	*0.947*
Blood loss (ml)	1736.3	1911.6	*0.577*
ICU stay (h)	95.9	63.1	*0.599*
Hospital stay (days)	33.3	12.8	*0.004*
Preoperative radiological parameters			
SVA (mm)	75.53	53.05	0.239
PI	52.2	57.2	0.166
LL	−39.5	−43.4	0.620
PI-LL	12.7	13.8	0.864
SS	32.5	34.2	0.640
PT	19.6	23.0	0.273
Global tilt	31.2	28.9	0.640
Major Cobb coronal	34.2	38.2	0.556
Preoperative HRQoL parameters			
Back pain	7.2	6.8	0.567
Radicular pain	4.8	4.0	0.376
COMI	7.1	7.2	0.896
ODI	50.1	47.0	0.581
SF 36 MCS	38.8	39.5	0.828
SF 36 PCS	30.8	34.6	0.108
SRS22 function	2.6	2.9	0.254
SRS22 mental	3.0	3.1	0.779
SRS22 pain	2.2	2.4	0.310
SRS22 satisfaction	2.8	2.7	0.981
SRS22 self image	2.1	2.4	0.254
SRS22 subtotal	2.5	2.7	0.255

[a]Matched variable

Table 2 Postoperative complications

Variables	Cases ($N=19$)		Controls ($N=57$)		p value
	N	%	*N*	%	
ICU needed	18	94.7	50	87.7	*0.354*
Intraoperative complications	6	31.6	13	22.8	0.543
Neurological complications	5	26.3	12	21.1	0.752
Intra-hospital complications	7	36.8	11	19.3	0.132
Wound complications (seroma, hematoma, dehiscencies)	5	26.3	3	5.3	0.021*
Implant complications (Pullout, loosening)	6	31.6	16	28.1	0.777
Radiological/mechanical complications (PJK, rod breakage, pseudoarthrosis)	8	42.1	17	29.8	0.400
Pseudoarthrosis	2	10.5	12	19.3	0.498
Proximal junctional kyphosis	6	31.6	5	10.5	0.023*
Any major complications other than infection	10	52.6	24	42.1	0.439
Any complication other than infection	15	78.9	39	68.4	0.560
Any revisions for reasons other than infection	8	42.1	13	22.8	0.139
Any re-admission for reason other than infection	6	31.6	13	22.8	0.543

Asterisk values indicate significance of p value ($p < 0.05$)

Table 3 Overall radiological results at 24 months as compared to baseline ($N=76$)

	Mean	Std. deviation	*P* value
SVA			
Pre-op	61.50	70.50	0.048*
24 months	38.15	53.58	
PI			
Pre-op	56.16	14.13	0.655
24 months	55.10	10.99	
LL			
Pre-op	−41.71	25.42	0.020*
24 months	−50.24	15.42	
PI-LL			
Pre-op	14.45	26.98	0.011*
24 months	4.84	14.85	
SS			
Pre-op	33.39	13.74	0.720
24 months	34.22	10.62	
PT			
Pre-op	22.72	12.08	0.230
24 months	20.74	9.53	
Global Tilt			
Pre-op	30.16	18.22	0.046*
24 months	24.54	14.03	
Major Cobb			
Pre-op	35.56	25.87	0.000*
24 months	19.16	17.29	

Asterisk values indicate significance of p value ($p < 0.05$)

related to the main variable. We omitted the dead patient along with her matched pairs from our result analysis. This decision was based on the fact that death, secondary to SSI, is extremely rare in the ASD population. Leaving the patient and keeping her PROMs at worst values would have severely distorted our analysis with the small sample. Detected differences would be harder to interpret. We, nevertheless, believe that death's impact cannot be obviated and a better way to account for it would be through a QALY (quality adjusted life year) analysis.

Despite this added morbidity and mortality, we have shown that both the infected and non-infected groups benefited equally from surgery in terms of deformity correction and quality of life at final review. At 24 months, and with the resolution of the infection, patients maintained good sagittal deformity correction combined with improvement in all their PROMs except SF36-MCS, SRS22-Mental Score, and leg pain. In the absence of a non-surgical control group, we cannot compare the benefit gained with surgery to non-operative management. When analysing the HRQoL parameters, the COMI score was the single most sensitive outcome measure to detect any difference between these two groups. This is in line with the recent literature and especially the recent work by Mannion et al. [23] who showed that despite its brevity, the COMI score was highly sensitive to any change in the patient's condition or disease itself.

Scheer et al. showed that psychological scores (SRS22 Mental Score and SF 36 MCS) improved less if patients had a complication needing a secondary intervention after ASD surgery [8]. In the present study, we could show that psychological scores (SF 36 MCS and SF22-Mental score) did not differ significantly from baseline at last follow-up (Table 5),

Table 4 Overall HRQoL results at 24 months as compared to baseline ($N=76$)

	Mean	Std. deviation	*P* value
Back pain			
Pre-op	6.93	2.317	0.000*
24 months	4.32	3.179	
Leg pain			
Pre-op	4.33	3.640	0.123
24 months	3.34	3.374	
COMI			
Pre-op	7.4347	2.23807	0.000*
24 months	4.6918	2.56483	
ODI			
Pre-op	49.15	19.114	0.002*
24 months	37.76	19.974	
SF 36 MCS			
Pre-op	39.3110	12.28955	0.271
24 months	41.7120	11.30408	
SF 36 PCS			
Pre-op	33.2139	8.25521	0.004*
24 months	38.6356	11.05318	
SRS 22 function			
Pre-op	2.7294	0.89427	0.021*
24 months	3.1287	0.98324	
SRS22 mental			
Pre-op	3.040	0.9028	0.348
24 months	3.196	0.9223	
SRS22 pain			
Pre-op	2.3309	0.89230	0.000*
24 months	3.1954	1.06560	
SRS22 satisfaction			
Pre-op	2.744	1.2133	0.000*
24 months	3.721	1.0591	
SRS22 self image			
Pre-op	2.253	0.8222	0.000*
24 months	3.081	0.9122	
SRS22 subtotal			
Pre-op	2.5963	0.68574	0.000*
24 months	3.1444	0.83266	

Asterisk values indicate significance of p value ($p < 0.05$)

but that was across the whole sample. When we analyzed differences in absolute figures between both groups, there was an initial difference in SRS 22 Mental Score at 6 months that was lost thereafter (p 0.036). We could also see that the SRS 22 Mental Score was less likely to improve at 6 months in the infected group (p 0.049). There was no difference beyond 6 months in these parameters.

Four other studies tried to assess the impact of infection on clinical results after posterior spinal surgery [9–11] with differing conclusions. In the matched control analysis in 16 patients with posterior spinal fusion, Mok et al. detected no significant difference in the physical function, role physical, bodily pain, and general health domains between the infection group and control group at an average of 62 months [9]. However, in a similar study, Petilon did demonstrate a difference in back pain and Oswestry Disability Index in patients suffering from a deep infection after a lumbar fusion [13]. This was a matched-cohort study of 30 patients with SSI and 30 controls after a lumbar fusion. Patient population was heterogeneous in terms of diagnosis and they included anterior-only surgeries such as ALIFs, but did not include ASD patients.

Rhin et al. found no difference in the pain, function, self image, satisfaction, or total Scoliosis Research Society 22 scores after deep SSI in adolescent patients with idiopathic scoliosis after a minimum of 2 years [11]. Falavigna et al. [10] studied patients having lumbar fusion for degenerative disc disease, and found no significant difference in pain, functional disability, quality of life, or depression and anxiety. However, 53.8% of the patients with infection were not satisfied with the procedure at the final evaluation, compared with 15.4% of the patients without a deep wound infection ($p=0.003$).

Even if infection does not seem to significantly alter the final functional outcome, these studies did not follow the recorded variables through time and they did not study the difference between infected and non-infected patients at defined time intervals. They also included heterogeneous groups of patients with respect to preoperative diagnosis and surgical procedure. They also did not stratify infections by timing. In addition, they had small samples and lacked detailed preoperative records.

Nuñez-Pereira et al. analysed implant survival after SSI in Spinal surgery [24]. In their sample of 43 patients with posterior instrumented fusion, only 90% of the implants or patients survived the first debridement. At 2 years, 73% of patients were alive with implants. This survivorship rate was maintained thereafter. These results were reproduced in the literature [25, 26]. In ASD surgery, especially when associated to tri-columnar osteotomies, implants are essential during the first two postoperative years to ensure a stable environment for fusion. Fusion itself is a fundamental prerequisite to any surgical success. Risk factors for implant removal includes late infections, delayed surgery, delayed antibiotic treatment, greater number of past surgeries, high postoperative infection treatment score for the spine, and the presence of methicillin-resistant *S. aureus* [25–27]. Infection occurring in the first 90 days has higher chances to preserve original implants [28]. In our series, only two patients needed a partial exchange of instrumentation and we had one death. The survival rate with original implants was, therefore, 85% at 2 years. Two patients were re-instrumented with no further loss of sagittal correction, and all had their

Table 5 HRQoL analysis—difference between groups at interval points ($N=76$)

	6 months		12 months		24 months	
		p value		*p* value		*p* value
Back pain						
Cases	3.81	0.944	4.07	0.854	3.36	0.923
Controls	3.87		4.24		4.57	
Leg pain						
Cases	2.94	0.798	2.21	0.404	3.00	0.467
Controls	2.72		2.96		3.43	
COMI						
Cases	6.17	**0.049**	5.86	**0.047**	5.74	0.092
Controls	4.86		4.15		4.46	
ODI						
Cases	45.87	**0.049**	42.43	0.075	40.64	0.701
Controls	34.22		34.33		37.02	
SF 36 mental component						
Cases	38.97	0.398	41.41	0.806	39.93	0.493
Controls	42.03		42.34		42.17	
SF 36 physical component						
Cases	31.48	**0.027**	34.99	0.051	36.64	0.707
Controls	37.24		40.22		39.15	
SRS22 function						
Cases	2.69	0.101	3.18	0.722	2.73	0.573
Controls	3.12		3.28		3.23	
SRS22 mental						
Cases	2.77	**0.036**	3.17	0.745	3.29	0.177
Controls	3.24		3.25		3.17	
SRS22 pain						
Cases	3.09	0.830	2.90	0.226	3.18	0.846
Controls	3.15		3.30		3.20	
SRS22 satisfaction						
Cases	3.62	0.318	3.50	0.326	3.68	0.813
Controls	3.94		3.83		3.73	
SRS22 body image						
Cases	3.11	0.629	3.06	0.285	2.95	0.311
Controls	3.29		3.33		3.12	
SRS22 subtotal						
Cases	2.92	0.212	3.09	0.402	3.03	0.201
Controls	3.19		3.29		3.17	

Bold values indicate significance of *p* value ($p < 0.05$)

infection controlled by 6 months from diagnosis. The fact that all infections in our sample were successfully treated and that there were no infection relapses explains in part our good overall results.

Even when implants are maintained, SSI patients seem to suffer from more pseudoarthrosis with rates varying between 38 and 44% [15, 16]. Risk factors for non-fusion with SSI seem to be female gender, extension to sacrum, use of allografts, and not using cages [15, 16]. In our series, we did not find any significant difference between both groups (10.5 vs. 19.3%). When we analysed mechanical complications as a whole (PJK, rod breakage and non-unions), we saw that there was a higher prevalence in the infected group (42.1 vs. 29.8%, p 0.400). This did not reach statistical significance. When analysed alone, PJK was much more prevalent in the context of infection (31.6 vs. 10.5%; *p* 0.023) than in patients without SSI. No other study has investigated the rate of PJK in the context of SSI. We hypothesise that this higher rate of PJK in infected patients is due to a weakened posterior tension band or muscles due to the infection itself, the decreased activity of patients with infection or repeated surgical injury during revision.

Table 6 HRQoL analysis—difference with baseline value

	6 months		12 months		24 months	
		p value		*p* value		*p* value
Back pain						
Cases	−3.19	0.749	−2.93	0.667	−4.27	**0.045**
Controls	−2.86		−2.53		−2.21	
Leg pain						
Cases	−1.31	0.870	−1.64	0.651	−2.18	0.264
Controls	−1.48		−1.21		−0.95	
COMI						
Cases	0.14	**0.001**	−1.27	**0.049**	−1.68	0.303
Controls	−2.66		−3.13		−2.91	
ODI						
Cases	−1.50	**0.029**	−4.69	0.052	−6.40	0.424
Controls	−14.69		−14.53		−11.03	
SF 36 mental component						
Cases	−1.42	0.425	2.33	0.916	1.83	0.893
Controls	1.69		1.87		1.33	
SF 36 physical component						
Cases	0.09	0.220	2.66	0.211	4.61	0.795
Controls	3.32		6.36		5.42	
SRS22 function						
Cases	−0.04	0.137	0.38	0.735	−0.11	**0.034**
Controls	0.31		0.46		0.41	
SRS22 mental						
Cases	−0.34	**0.049**	0.09	0.452	0.32	0.349
Controls	0.20		0.29		0.05	
SRS22 pain						
Cases	0.84	0.869	0.63	0.410	0.91	0.633
Controls	0.79		0.89		0.77	
SRS22 satisfaction						
Cases	0.61	0.457	0.44	0.304	0.38	0.214
Controls	1.04		1.00		1.02	
SRS22 body image						
Cases	0.94	0.831	0.99	0.832	0.76	0.794
Controls	1.03		1.05		0.85	
SRS22 subtotal						
Cases	0.35	0.281	0.54	0.521	0.47	0.873
Controls	0.56		0.66		0.50	

Bold values indicate significance of *p* value ($p < 0.05$)

The present study is the largest cohort study specifically studying the effect of SSI on surgical outcomes in spinal surgery. It also aims at studying this negative impact in long-term follow-up. The study contained a homogenous diagnostic and surgical population that was further matched using demographic and surgical variables known to affect both infection and outcome scores. In addition, the matched cohorts included in this analysis showed no differences in other non-matched known risk factors such as diabetes, liver disease, smoking, length of surgery, and blood loss. The size of the deformity and the baseline HRQoL parameters were also comparable between both groups. This further increases the validity of our conclusions.

This study suffers from inherent limitations applicable to all multicentre studies. One of these might be the non-standardised approach and management of infection in the different participating centres. Another major limitation is the small sample size and the lack of statistical power to detect differences between groups. We also did not stratify infections according to their virulence nor to their course. We are conscious that infection cannot be considered as a homogeneous entity, and patients might fare differently and

their results vary accordingly. We only included acute infections that were diagnosed and treated very early on, and all of our patients cleared the infection with the exception of the patient that died. With a bigger sample, possible differences might be better delimited and/or patients could be stratified according to infection characteristics. Finally, the present study as mentioned, could not account for death when comparing both groups due to intrinsic limitations in methodology. A better way to measure the impact of infection and associated mortality would be to analyse QALY differences between both groups.

Conclusion

ASD patients have a high rate of SSI. When occurring, deep SSI significantly affects recovery in the first postoperative year. It increases the length of hospital stay and is associated with more complications, unrelated revisions, and a worse quality of life during the first year. SSI can even be deadly in extreme of cases. However, when successfully treated, its negative impact seems to wear-off by the second year, as differences in outcome scores become less pronounced. Despite early SSI, patients seem to benefit from posterior ASD surgery just as much as their non-infected counterparts. Also, at the 2-year follow-up, resolved SSI does not seem to have a significant bearing on the size of deformity correction, provided that the implants are maintained. These findings increase our understanding of the impact of early SSI on final outcome. It also provides surgeons with more insight when counselling potential surgical patients on the risks and benefits of surgery, and likely outcomes.

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Compliance with ethical standards

Conflict of interest None of the authors has any potential conflict of interest.

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