UNIVERSITY OF COPENHAGEN
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PhD Thesis

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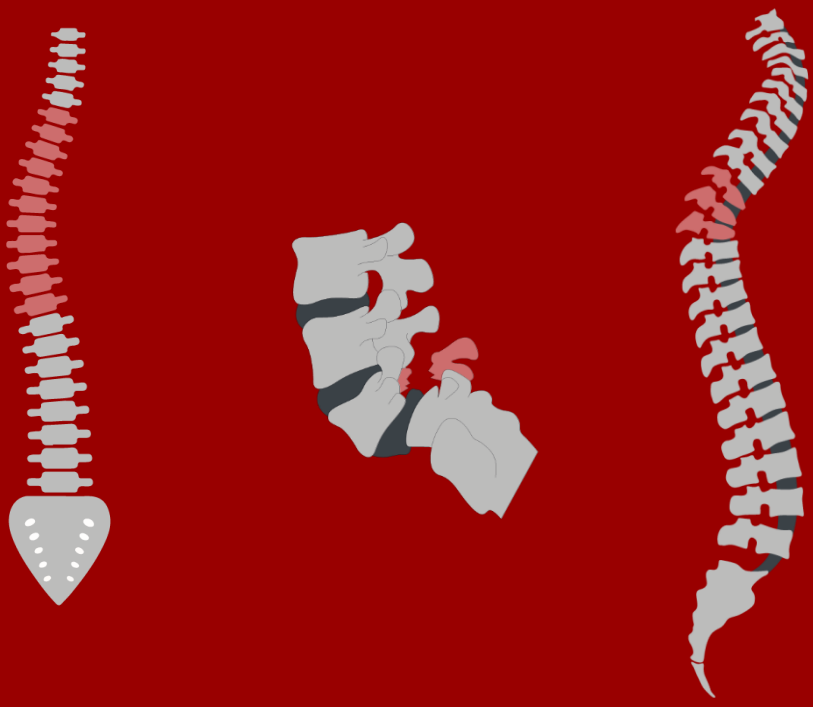
Pediatric Spinal Deformity Surgery – diagnostic challenges and postoperative morbidity



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Abbreviations

AIS	Adolescent idiopathic scoliosis
APR	Annual progression rate
CCI	Charlson comorbidity index
CD	Congenital deformity
CT	Computed tomography
DJF	Distal junctional failure
EOS	Early onset scoliosis
ERAS	Enhanced recovery after surgery
ID	Idiopathic deformity
IS	Idiopathic scoliosis
MIS	Minimally invasive surgery
MRI	Magnetic resonance imaging
NAA	Neural axis abnormality
ND	Neuromuscular deformity
PJF	Proximal junctional failure
PSD	Pediatric spine deformity
SP	Spondylolisthesis
SK	Scheuermann's kyphosis
SSI	Surgical site infection

Summary

Pediatric spinal deformities (PSDs) are complex but can be classified according to age of onset, etiology and radiological landmarks. The deformities may be classified as either idiopathic deformity, congenital deformity, neuromuscular deformity, syndromic deformity, spondylolisthesis or as Scheuermann's kyphosis. Curve progression, pain, neurological deficit, and cardiopulmonary compromise are indications for corrective surgery. The surgical strategy in pediatric scoliosis has evolved with the development of all-pedicle screw constructs, growing rod technologies and increasing use of osteotomies. Compared to adult spinal surgery, the morbidity and mortality rates are relatively low after PSD surgery but is highly dependent on the underlying etiology. With the increasing number of PSD procedures, the recognition of a uniform diagnostic evaluation as well as peri- and postoperative complications is critical for optimal patient counseling and quality assurance measures.
This thesis explores the diagnostic challenges and the surgical safety in patients with pediatric spinal deformity.

Study I is a retrospective study of 381 patients referred for evaluation of adolescent idiopathic scoliosis (AIS) and enrolled in an MRI-protocol for assessment of neural axis abnormalities (NAAs). The prevalence of NAAs was 8.9%, which did not vary with curve severity or treatment modality. In addition to this, it was not possible to validate previously proposed clinical and radiographical risk factors for NAAs. The reported NAAs did not have any clinical implication, neither did the NAAs result in surgical alterations or postoperative neurological deficits.

Study II is a nationwide register study of patients aged 0–21 years undergoing primary PSD surgery within a ten-year period. Data were retrieved from the Danish National Patient Registry (DNPR) and included length of stay, 90-day readmission and mortality. The most common reason for extended length of stay was pain and mobilization issues. Mortality and 90-day readmission risk were low and the most common reason for readmission was infection unrelated to the surgical site. Finally, risk factors for readmission were an etiology of neuromuscular disease, spondylolisthesis, Scheuermann's kyphosis and extended length of stay during index admission.

Study III focused on surgical revision risk within two years following primary PSD surgery. Data were retrieved from the DNPR and all medical records were reviewed for reason for revision. The cumulative two-year revision risk was 9.5% and differed markedly across etiologies. Risk factors

for revision were an etiology of congenital deformity, spondylolisthesis and Scheuermann's kyphosis. The most common reason for revision was implant failure followed by implant misplacement/prominence, however, this varied markedly across etiologies.

In conclusion, this thesis provides new and valuable information to improve the diagnostic evaluation and the safety in the postoperative period. This will hopefully lead to multidisciplinary initiatives to further improve the overall safety of PSD surgery.

Danish summary

Denne ph.d.-afhandling fokuserer på billeddiagnostiske udredningsmuligheder for børn med rygdeformiteter og den kirurgiske sikkerhed målt på indlæggelsestid, genindlæggelser og revisionsrisiko.

Den kirurgiske behandling af rygdeformiteter hos børn har gennemgået betydelige forbedringer gennem de seneste årtier. Sammenlignet med voksendeformiteter er morbiditeten og mortaliteten beskeden, men stærkt afhængig af deformitetstypen. Med et tiltagende antal patienter, der tilbydes kirurgisk behandling for deres rygdeformitet, synes det særligt vigtigt, at der foregår en ensartet og korrekt diagnostisk udredning, foruden en sikker kirurgisk procedure med færrest mulige komplikationer i form af forlænget liggetid, genindlæggelser og revisionskirurgi.

Børne-rygdeformiteter består af en kompleks gruppe af patienter, som typisk klassificeres ud fra alder, ætiologi og radiologiske fund. Baseret på ætiologien klassificeres deformiteterne enten som idiopatisk deformitet, kongenit deformitet, neuromuskulær deformitet, syndromrelateret deformitet, spondylolisthese eller Scheuermann's kyfose. Heterogeniteten blandt børnedeformiteterne medfører forskelligartede udredningsforløb og kirurgiske indgreb. Indikationerne for de kirurgiske indgreb strækker sig bredt fra progression af deformiteten, smerter, neurologisk udfald til forringet hjertelungefunktion.

Afhandlingen består af tre væsentlige studier.

Studie I er et retrospektivt studie af 381 patienter udredt med MR-scanning for adolescent idiopatisk skoliose. I studiet blev der fundet en prævalens på 8.9% af intraspinale anormaliteter. Det var ikke muligt at validere tidligere foreslåede kliniske risikofaktorer forbundet med intraspinale anormaliteter på MR. Yderligere var der ingen kliniske eller kirurgiske konsekvenser af de positive MR-fund.

Studie II er et registerstudie af patienter i alderen 0-21 år, der er blevet opereret over en tiårig periode i hele Danmark. Data er indhentet fra Landspatientregistreret, og studiet belyser årsager til forlænget liggetid, genindlæggelse og dødelighed indenfor 90 dage samt risikofaktorer for genindlæggelse. Studiet viser, at den hyppigste årsag til forlænget liggetid er smerte og mobiliseringsbesvær. Den hyppigste årsag til genindlæggelse er infektioner, der ikke er relateret til operationsområdet fx lungebetændelse og urinvejsinfektion. Endelig viser studiet, at patienter med

neuromuskulære deformiteter, spondylolisthese eller Scheuermann's kyfose samt de patienter der har haft forlænget liggetid ved den primære indlæggelse efter deformitetskirurgien, er i størst risiko for genindlæggelse.

Studie III er også et registerstudie af patienter med rygdeformitet i alderen 0-21 år, men med fokus på revisionskirurgi indenfor 2 år efter deres primære rygkirurgi. Studiet viser en kumuleret revisionsrisiko på 9.5%, og at revisionsrisikoen er øget hos patienter med kongenite deformiteter, spondylolisthese og Scheuermann's kyfose. Den hyppigst årsag til revisionskirurgi er implantatsvigt.

Denne ph.d.-afhandling angiver konkrete indsatsområder, der kan forbedre den diagnostiske udredning og det postoperative forløb. Årsagerne til forlænget liggetid viser et behov for forbedret smertebehandling og hurtigere mobilisering. Dette skal belyses i nye prospektive studier med implementering af protokoller for accelererede patientforløb. Afhandlingen identificerer samtidig diagnosegrupper i højrisiko for revisionskirurgi, hvor en forbedret og tværfaglig indsat kan føre til nye overvejelser forud for den omfattende rygkirurgi.

List of papers

Study I: **Neural Axis Abnormalities in Patients with Adolescent Idiopathic Scoliosis: Is Routine Magnetic Resonance Imaging Indicated Irrespective of Curve Severity?**

Sidsel Fruergaard, Søren Ohrt-Nissen, Benny Dahl, Nicolai Kaltoft, Martin Gehrchen, Neurospine 2019;16:339–46. https://doi.org/10.14245/ns.1836154.077.

Study II: **Length of Stay, Risk of Readmission and Mortality after Primary Surgery for Pediatric Spinal Deformities: A 10-year Nationwide Cohort Study**

Sidsel Fruergaard, MD, Søren Ohrt-Nissen, MD, PhD, Frederik Taylor Pitter, MD, PhD, Kristian Høy, MD, PhD, Martin Lindberg-Larsen, MD, PhD, Søren Eiskjær, MD, DMSc, Benny Dahl, MD, PhD, DMSc, Martin Gehrchen, MD, PhD

Manuscript in revision, The Spine Journal, August 2020.

Study III: **Revision risk, risk factors and reasons for revision following primary surgery for pediatric spinal deformities: A nationwide study with 2-year follow-up**

Sidsel Fruergaard, MD, Søren Ohrt-Nissen, MD, PhD, Frederik Taylor Pitter, MD, PhD, Kristian Høy, MD, PhD, Martin Lindberg-Larsen, MD, PhD, Søren Eiskjær, MD, DMSc, Benny Dahl, MD, PhD, DMSc, Martin Gehrchen, MD, PhD

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Introduction

Pediatric spine deformities (PSDs) consist of a heterogenic population of children with various disabilities[1]. The deformity is typically classified according to etiology, time of onset and radiological landmarks[2]. In patients with severe deformities, surgical intervention is often indicated[3,4]. The surgical procedures are often complex and may pose high risk of short-term morbidity and revision. With the increasing utilization of PSD surgery, an increased attention to reduce these risks is warranted[5]. The aim of this thesis is to examine the diagnostic imaging challenges prior to surgery and to provide an in-depth description of the short-term morbidity, mortality and revision risk after PSD surgery.

Background

Etiologies and definitions

Pediatric spinal deformity results from a variety of disorders. The underlying disorder form the basis for the deformity classification. However, the most common deformity, **idiopathic scoliosis (IS),** is a diagnosis of exclusion and the cause remains unknown[6]. Idiopathic scoliosis is broadly defined as a "*three-dimensional deformity of the spine with a coronal deviation of more than 10°"*[7] and is further divided according to age of onset. Originally, patients were divided according to age in infantile (< 3 years), juvenile (3–9 years) and adolescent scoliosis (≥10 years)[8].

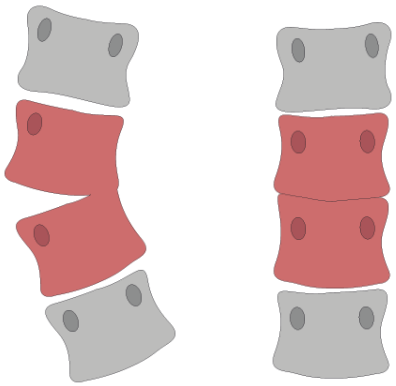

Figure 1. Failure of segmentation. Partial, unsegmented bar and fully segmented bar (block vertebrae).

Recently, there has been a gradual shift towards only two age definitions. Early onset scoliosis (EOS) and late onset scoliosis. Early onset scoliosis is defined as "*scoliosis diagnosed before the age of ten, regardless of etiology*"[9]. The underlying etiology for EOS can be either idiopathic, congenital/structural, neuromuscular or syndromic[9]. **Congenital/structural deformities (CDs)** are deformities developed due to structural abnormality (e.g. post-thoracotomy) or because of congenital defects[9]. The congenital defects are classified according to embryological development of the spine in three categories; segmental failure, formation failure or mixed failures[10]. Defects of segmentation generates unsegmented bars and can be partial or complete (block vertebra) (Fig 1). Defects of formation give rise to maldevelopment (e.g. hemivertebra and wedge vertebra) (Fig.2)[11]. These anomalies can disrupt the normal balanced spinal growth causing scoliosis, kyphosis, lordosis or a combination[8].

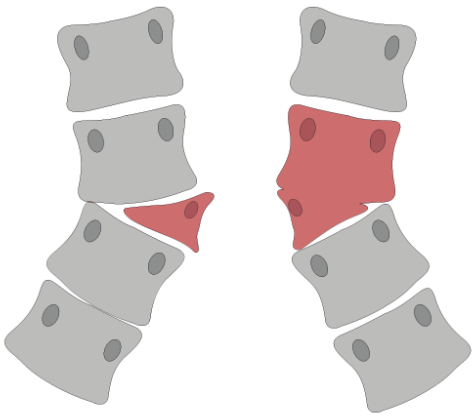

Figure 2. Failure of formation. Hemivertebrae and unilateral complete failure of formation.

Neuromuscular deformities (NDs) occur in patients with a pre-existing neuromuscular condition[12]. The deformity is attributable to either trunk muscle weakness, hypertonia or disharmonious control of the trunk musculature surrounding the spinal axis [13].The conditions usually leading to neuromuscular deformity are cerebral palsy, hereditary ataxia

or Duchenne myopathy. Not all children with neuromuscular disease develop spinal deformity. However, the incidence is significantly higher compared to the general population[8]. A prospective Scandinavian study reported that the risk of scoliosis in patients with cerebral palsy increased with patient age and decreased motor function[14]. By age 20, 75% of the patients with severely decreased motor function had developed moderate scoliosis[15]. Finally, PSD can be associated with **syndromes** such as Down syndrome, Marfan syndrome, achondroplasia, Ehlers-Danlos and Osteogenesis imperfecta[9,16].

In the coronal plane, any deviation of the spine of more than 10° is considered pathological but in the sagittal plane the definition of deformity is more complex. Typically, the thoracic kyphosis increases throughout life[17] but in some cases the thoracic kyphosis along with specific radiographic findings is considered pathological. **Scheuermann's kyphosis (SK)** was first described in 1920[18] and later classified as "*anterior wedging of at least 5° in three or more adjacent vertebrae in the thoracic spine*"[19]. Normally SK is diagnosed in the late juvenile age and appears more prominent during the growth spurt[20]. Surgery is considered in adolescent patients with SK if the kyphosis extend beyond 80° and conservative treatment has been unsuccessful[21].

Pediatric **spondylolisthesis (SP)** is an "*anterior displacement of the cranial vertebra body relative to the adjacent caudal vertebral body"*[22]. Spondylolisthesis is reported to be the most common cause of back pain in the pediatric and adolescent population[23]. The etiology for pediatric spondylolisthesis is classified as either isthmic or dysplastic referring to a defect of the pars interarticularis or congenital defect of the facet joint, respectively (Fig. 3)[24]. Most low-grade spondylolisthesis are benign and rarely causes symptoms or radiographic progression. For high grade symptomatic patients surgery is often warranted but can result in significant morbidity[25].

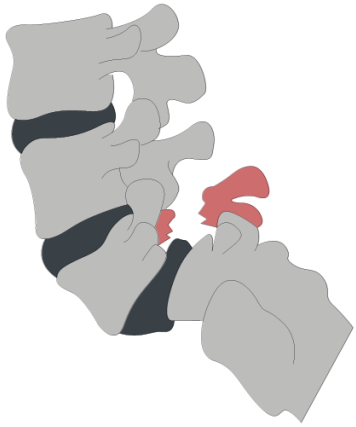

Figure 3. Isthmic spondylolisthesis.

Diagnostic challenges

The heterogeneity of PSD calls for careful diagnostic approach. Besides clinical evaluation including a complete medical history and physical examination, radiographic imaging is essential. Conventional x-rays in posteroanterior, lateral and bending films provide information regarding curve magnitude (scoliosis and kyphosis), degree of slippage and slip angle (spondylolisthesis), regional alignment and flexibility of the spine[8,26]. Computed tomography (CT) imaging can help define bony anatomy and complex congenital deformities, especially if 3D reconstruction is applied [11]. Magnetic resonance imaging (MRI) is used to assess the neural axis in patients with neurological conditions. In idiopathic scoliosis, MRI is often applied to visualize the neural axis and potential neural axis abnormalities (NAAs) before surgery. Neural axis abnormalities can range from a small size syrinx to potentially more severe conditions such as tethered cord, syringomyelia, Chiari malformation and intramedullary tumors[8,27].

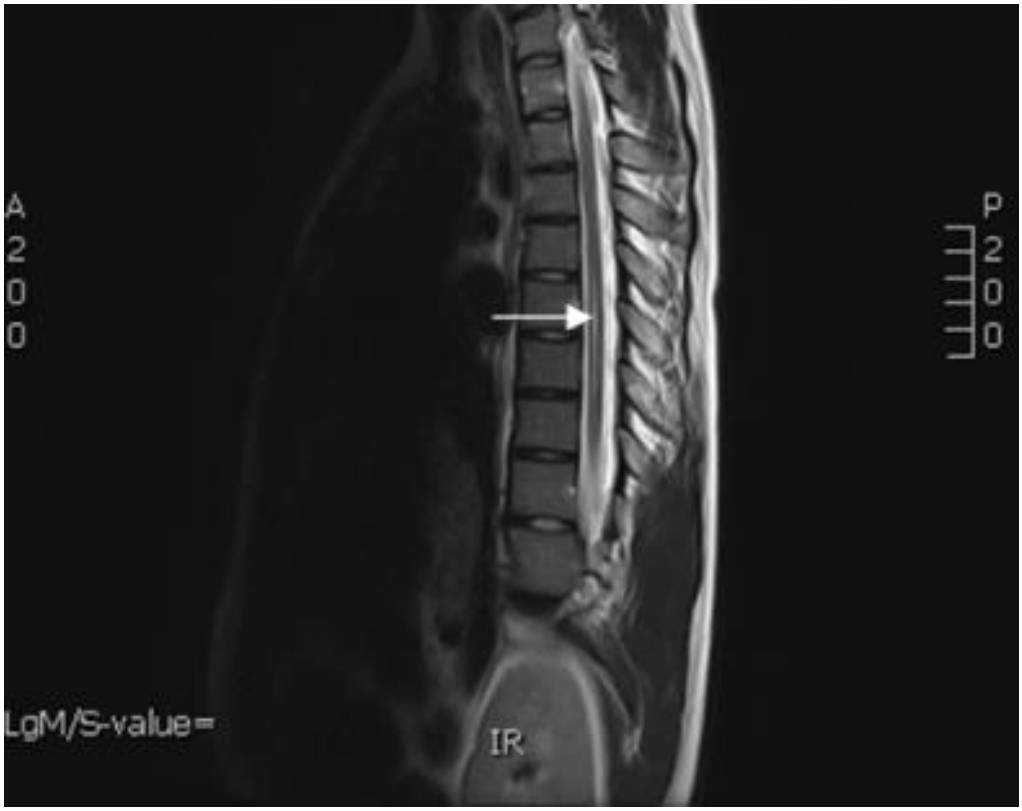

Figure 4. Magnetic resonance imaging with 1.5 Tesla scanner, sagittal T2-weighted from a patient with thoracic syrinx (arrow).

Approximately 2%–12% of patients with AIS are reported to have asymptomatic NAAs[27–30]. Concomitant NAAs can in some cases be the cause of the deformity and in other cases may influence the surgical strategy[6,31,32]. Several studies have suggested different risk factors for NAAs. These risk factors are early onset of the deformity[31,33–35], male sex[36], asymmetric

abdominal reflexes[27,35], atypical curve patterns[29,37], thoracic hyperkyphosis[28–30,32,36,38,39], rapid curve progression and pain[31,33]. However, results are inconsistent, and the applicability of the proposed risk factors has not been established since studies varies in methodology[40–42]. The indication for preoperative MRI screening in idiopathic deformities is therefore still unsettled. Additionally, only few studies have previously reported the possible consequences of NAAs before and after surgical interventions[32,43] and only few studies have reported the prevalence of NAAs in AIS patients who are not surgical candidates.

Surgical interventions

Surgical indications in PSD depend on the severity of the deformity, etiology and skeletal maturity[8,11,12,24,44–47]. In patients with remaining growth potential the aim is to stop progression and simultaneously allow spinal and pulmonary growth. Hence, in patients with EOS the surgical strategy is often growth-preserving. The growth-preserving approach is based on either growth guided-, compression- or distraction based systems[11,48]. Growth guided systems allow rods to slide along fixed implants, permitting gradual migration of the rod[11]. Compression based systems tries to correct the deformity through compression applied to the convex side of the curve. The most preferred method to correct the deformity is based on distraction principles. The distraction based systems correct the deformity by applying distraction forces across the deformity with anchors at both ends of the implant. The systems include vertical expandable titanium rib prosthesis (VEPTR), traditional growing rods (TGR) and magnetically controlled growing rods (MCGR)[48]. Traditional growing rods requires repetitive open surgery for lengthening every six months with a concomitant high revision and infection rate[49–51]. Magnetically controlled growing rods were developed later and allow for non-invasive lengthening in the outpatient clinic[52–54].

In patients closer to skeletal maturity, final fusion is obtained through either anterior, posterior, combined anteroposterior or lateral access. Many changes in spinal instrumentation have led to improvements of the treatment of PSD[55]. From the introduction of Harrington instrumentation more than 50 years ago[56], to segmental fixation using sublaminar wires[57] followed by the hook system by Cotrel and Dubousset[58] which finally was replaced by the pedicle screw construct[55,59]. Current surgical principles rely on all-pedicle constructs, with the option of using osteotomies to correct severe, rigid deformities[55,59,60].

The surgical treatment of pediatric SP stands out from scoliosis and kyphosis surgery. For patients with low grade isthmic SP, direct repair of the pars defect is an option. In patients with high grade SP, satisfactory surgical outcome can be achieved with several techniques. These includes in situ fusion with or without reduction, instrumented reduction and fusion, and combined anterior-posterior fusion techniques[26].

With the surgical progresses in recent years, there has been a concurrent increase in the incidence of PSD surgery[5,61]. This has naturally led to an increased focus on short-term morbidity such as extended length of stay and readmission as well as revision risk and mortality.

Short-term morbidity – length of stay and readmission

Complications after PSD surgery can vary substantially according to surgical technique and comorbidity[1,5,61–66]. This naturally leads to different risks of short-term morbidity such as extended length of stay (extLOS). Length of stay after PSD surgery has been reported between 4.9–9.2 days[5,67–70]. Recent improvements in surgical techniques, anesthesia, antibiotic prophylaxis and pain management form the basis for reducing length of stay (LOS)[71]. Variation in LOS can be attributed to both peri- and postoperative complications, but also represents differences in practice styles and evolution over time[72]. Still, extLOS is undesired since it slows recovery and increases the overall hospital costs. In several elective orthopedic procedures, enhanced recovery principles have helped decrease LOS and are at the same time considered feasible and safe[73,74]. Currently, there are no studies describing the association of reasons for extLOS and the outcome in PSD surgery. To address this, a nationwide multicenter study with high quality data would provide invaluable information.

Another important outcome potentially leading to increased short-term morbidity is unplanned readmissions. In the United States, unplanned readmissions are increasingly being used as an indicator of quality of care[72,75,76]. Unplanned readmissions can result from insufficient care, an unstable condition at discharge or inadequate post-discharge care[77]. It is of specific interest to identify risk factors and reasons for readmission to help improve early postoperative outcome. Previously, etiologies of ND, CD and SD have been associated with increased readmission risk[62,65,66,78]. Most studies on early postoperative morbidity use 30-day readmission risk as the outcome[62,66,79,80]. Nevertheless, early morbidity following extensive spine surgery can extend beyond the 30-days, but only few studies have reported the 90-day readmission risk in PSD

patients[65,81]. To generate a comprehensive understanding of reason for readmission and potential risk factors, a nationwide study with complete 90-day readmissions risk would provide crucial information.

Revision surgery

There is no well-established revision risk in PSD surgery. The reported revision risk varies between 0.9-34%[51,82–86]. This wide range is attributed to multiple reasons. First of all, the revision risk is related to the deformity etiology[82]. Secondly, the surgical procedure can affect revision rates with the highest incidence seen in patients treated with growing rods[51,87]. Thirdly, previous studies have been limited to data sources that do not allow for longer follow-up (>90 days) of patients[81]; are single center studies[83,88,89]; or state databases[82] that are not representative of nationwide practices. Finally, long-term studies are often prone to incomplete follow-up[85]. Revision surgery is both strenuous for the patients, and the surgical procedures are often more challenging and with higher complication rates[84,88,90]. Indications for revision surgery include infection, implant failure/pseudarthrosis, neurologic deficit, prominent and painful instrumentation or progression[90]. Previous studies suggest etiologies of CD , ND and SD are associated with increased revision risk[81,82]. Identification of revision risk and risk factors for revision in a nationwide cohort with complete follow-up have not previously been reported. This will provide important information regarding future revision prevention efforts especially in at-risk patient groups.

Objectives and hypotheses

Collectively, the purpose of this thesis was to assess several aspects of PSD –diagnostical aspect in terms of prevalence of NAAs in patients with AIS, the short term morbidity and the two-year revision risk in a nationwide cohort of patients with PSD. The aims for the three studies are presented below.

Study I: To determine the prevalence of NAAs and the role of routine MRI in the clinical evaluation of AIS patients. Furthermore, to assess clinical or radiographic features as risk factors for the presence of NAAs.

Study II: To describe the short-term morbidity leading to extLOS, readmissions and mortality within 90 days in a nationwide cohort. In addition, identify risk factors for readmissions.

Study III: To report on the two-year revision risk following surgery for primary pediatric spine deformity in a nationwide cohort. Secondarily, to evaluate potential risk factors for revision surgery and describe reasons for revision.

Methodological considerations

Overall study designs

Patients with PSD are typically diagnosed by their general practitioner or a secondary facility. From here, they are referred to our tertiary unit for surgical evaluation. The Spine Unit at Rigshospitalet, serves approximately 2.5 million citizens. This comprises approximately 120 patients with AIS seen in the outpatient clinic every year. Study I was a retrospective study with a cross-sectional design. The optimal design would have been a prospective study, because of the evaluation of an outcome. Since the outcome was rare, a prospective design would have resulted in markedly lower number of included patients and likely an underpowered study. The retrospective nature of the study, results in risk of bias from unidentified confounders. Nonetheless, with the centralization within spine surgery and an efficient public health care system, the data are considered representative and of high value.

Even though there has been an increase in surgical treatment of patients with PSD, it is still considered a rare event. This limits prospective studies unless performed in a multicenter or nationwide setting. Study II and III were conducted as nationwide register studies. The high quality Danish registries enables detailed, nationwide information regarding surgery, LOS and readmissions. Reporting on a large cohort, lower the risk of selection bias and strengthen the statistical interference. However, the observational setting only allows for establishing association and not causality.

Methods

Study I

Patient inclusion: All patients referred to a tertiary spine institution from January 1, 2010 to December 31, 2015 with AIS were included. As this study aimed to assess a certain group of patients with PSD, some specific study criteria were met. We included all patients with a verified idiopathic scoliosis diagnosed between 10–18 years of age and with long, standing spinal radiographs as well as whole-spine MRI. We excluded all patients with preexisting NAAs or neurological deficit.

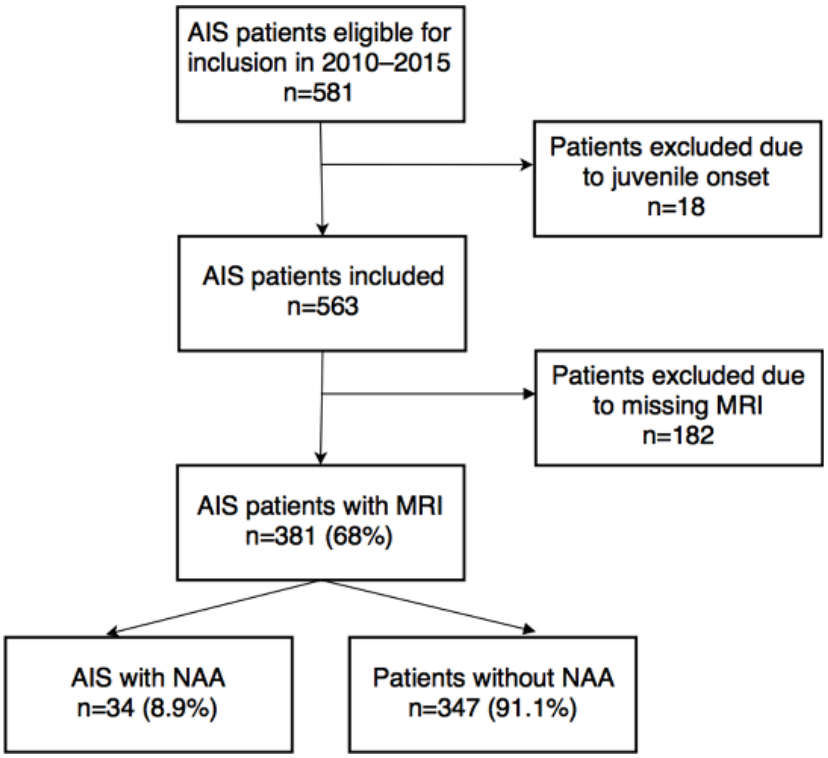

Figure 5. Inclusion process

Data collection

Clinical data: Electronic medical records were reviewed to assess clinical data. These data included age at referral, sex, presence of pain, brace treatment and surgical intervention.

Radiographic assessments: High quality radiographic images were obtained in Digital Imaging and Communications in Medicine (DICOM) format in the Radiology Information System and Picture Archiving and Communications System (IMPAX) 6® (Agfa Healthcare NV, Mortsel, Belgium).

All images were then uploaded to a validated online image management system KEOPS®(SMAIO, Lyon, France)[91]. After identifying key radiographic landmarks, the software generates a model of the spine and calculate specific radiographic parameters. In this study, these parameters included major curve angle, type of curve (left-sided, right-sided and thoracic, thoraco-lumbar, lumbar or double major), length of the curve (no. of vertebra), thoracic kyphosis and annual progression rate (APR). Annual progression rate was calculated based on the difference between the major curve size at the latest radiographs and the major curve size at the first radiograph multiplied with the time difference between the two radiographs (APR=(major curve t_2 – major curve t_1) x 12 months/(t_2-t_1))[9]. All included patients underwent MRI with a 1.5 or 3.0 Tesla Scanner and the results were analyzed by a neuroradiologist. Syrinx diameter was measured in the axial plane on T2 images and further subdivided in insignificant syrinx ≤3mm and significant syrinx >3mm[92]. Chiari 1 malformation was defined by herniation of the tonsils below the foramen magnum by 5 mm or more[93]. Finally, all positive MRI scans were confirmed by a second independent radiologist.

Outcomes: The main outcome was verified NAA on MRI. Furthermore, several radiographic and clinical measures were associated to the NAAs.

Study II and III

Patient inclusion: All patients with PSD undergoing surgery from January 1, 2006 to December 31, 2015 in Denmark, were included in the study. Inclusion criteria were age between 0–21 years and a surgery and diagnostic code for PSD (Appendix 1 and 2). Exclusion criteria were previous spinal surgery, concurrent spinal fractures or spinal cancer.

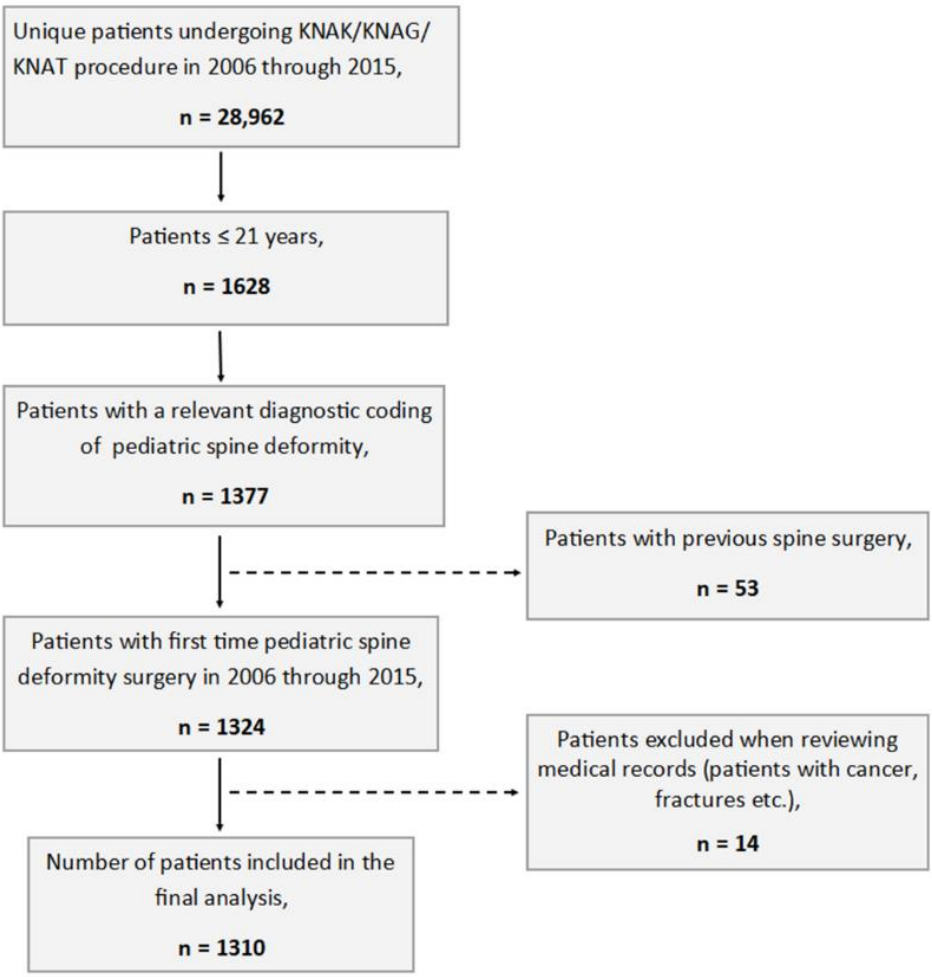

Figure 6. Inclusion process

Data collection: Since 1968 the Danish Civil Registration System (CRS) has monitored all persons alive and living in Denmark[94]. Furthermore, CRS encompasses information on immigration, emigrations and vital status of all Danish citizens. All persons registered in CRS, have a unique personal identification number which enables linking between all Danish registries[95]. Registration in CRS is required by law and the high quality of data is ensured by continuous validation[94]. Thus, CRS is considered an invaluable tool in epidemiological research in Denmark.

The Danish National Patient Registry is one of the oldest nationwide registries recording in- and outpatients contacts[96]. For each contact to a public/private hospital or private specialist, the DNPR record one primary diagnosis according to the International Classification of Diseases (ICD), examinations, certain medical treatments and surgical procedures[96]. Data from DNPR are used for reimbursement purposes and therefore the data has added incentive for diligent reporting of accurate information. Access to National Health Services is tax-financed and universal for all Danish citizens. Overall, this results in high quality nationwide data on all visits to hospitals, specialists and outpatient clinics. Data for study II and III were retrieved from the DNPR, and patients were defined by age (0–21 years of age), a relevant procedure code KNAG/KNAT/KNAK (Appendix 1) combined with a specific diagnostic code (Appendix 2). To ensure that only patients with first time PSD surgery were included in the cohort, we retrieved data from patients with spinal surgeries (same procedure codes as Appendix 1) in the period of 1996–2005 and combined them with the study cohort. If dual entries occurred, the patient was excluded (Fig. 6).

Medical record review: For study II, medical records of patients with extLOS were reviewed for reason for extLOS. All possible reasons were registered, but the most evident reason was chosen as the primary. For patients readmitted within 90 days, the discharge summary was reviewed for reason for readmission. If the readmission was planned or considered completely unrelated to the surgical procedure (e.g. acute allergic reaction to dietary products) it was excluded for further analysis. Reasons for extLOS and readmission were computed as either medical or surgical[97,98] and listed in table 1.

Table 1

Group	Reason for extLOS and readmission
Surgical	Surgical site infections (superficial vs. deep, early (<12 weeks following surgery) vs. late (≥12 weeks following surgery))
	Neurological deficit
	Surgical complications including revision
Medical	Anemia
	Gastrointestinal complication
	Infection not related to surgical site

	Side effect from medication
	Pulmonary complication
	Cardiac complication
	Neurological complication
	Urological/nephrotic complication
	Pain/mobilizations issues
	Other and Unknown

For study III, medical records of patients with revision surgery were reviewed for reason for revision. To distinguish planned sequential growth-preserving procedures from unplanned revision, all medical records of EOS patients were reviewed for a two-year period. Reason for revision was classified according to previous studies [85,99] as follows; implant failure (implant breakage or loosening and/or dislodgement and/or pseudarthrosis), infections (superficial vs. deep, early (<12 weeks following surgery) vs. late (≥12 weeks following surgery)), implant misplacement and/or prominence, residual deformity and/or curve progression, proximal junctional kyphosis (PJK)/distal junctional kyphosis (DJK), neurological deficit, translocation and other.

Covariates: Patients were grouped according to etiology in idiopathic, congenital/structural, neuromuscular, syndromic, spondylolisthesis or Scheuermann's kyphosis. If patients had more than one conflicting diagnostic code or an unspecific code (e.g. scoliosis unknown), the medical record was reviewed for exact etiology and classified according to the classification system for EOS[9]. Comorbidity burden was quantified using Charlson comorbidity index (CCI)[100]. This index conveys 19 comorbidity scores to a single numeric score. Reducing the set of variables is favorable when using administrative databases[101]. CCI was calculated based on the diagnostic codes in DNPR from all prior in- and outpatient contacts to index surgery. The coding of CCI in DNPR is found to be consistently high[101]. We subdivided the CCI score in three main categories; low (CCI=0), medium (CCI 1≤2) or high (CCI≥3). Moreover, we categorized age in three groups; "0-10 years of age", "10-15 years of age" and "> 15 years of age".

Outcomes: For study II, extLOS was defined as length of stay above the 75th percentile according to etiology. Readmission was defined as any unplanned admission leading to at least one overnight stay. For study III, revision was defined as any unplanned surgery, thereby excluding planned second stage procedures.

Statistical consideration

All statistical analyses were performed in R, version 3.6.1 (R Development Core Team, 2011, Vienna, Austria). A two-sided p-value of 0.05 or less was considered statistically significant.

Demographic data

The distribution of descriptive statistics was assessed using histograms or Q-Q plots. For continuous variables the results are reported as means with standard deviations (SD) or medians with interquartile ranges (IQR). For categorical variables the results are reported as frequencies (%). Student t test was used when comparing approximated Gaussian distributed data and Wilcoxon's sum rank test for non-Gaussian distributed. Categorical variables were analyzed using Chi-square test or Fisher exact test depending on results of expected counts.

Prevalence

For study I, the outcome (NAAs) is reported as period prevalence. Period prevalence is defined as the number of cases as a fraction of the total population at risk, in a specific time-period.

Association to outcome

The associations between the outcome NAAs (study I), readmission (study II) and revision (study III), and certain predefined clinical parameters were estimated using uni- and multivariate logistic regression models. Risk factors are reported as odds ratios (OR) with 95% confidence interval (CI). Variables for study I included age, sex, major curve angle, thoracic kyphosis and atypical curve type. Variables for study II and III included age, etiology, sex, extLOS, CCI and growth-preserving systems. C-statistics or area under the curve (AUC) were used to determine the discrimination of the logistic regression.

Risk and cumulative incidence

Risk was defined as the fraction of patients who underwent revision surgery in the originally revision-free cohort[102].

A modified survival analysis using the Aalen-Johansen estimator was used to calculate the cumulative incidence for revision in study III. The model account for death as a competing risk to the outcome of interest[103]. Cumulative incidence function assesses the expected proportion of

individuals experiencing a defined competing event over a time period. In study III, the time after primary PSD surgery was ended by either revision surgery or by death, whatever came first. Patients that did not undergo revision surgery or died in the two-year follow-up period were censored.

Ethics

Permission to store and review data was obtained from the Danish Data Protection Agency (no. RH-2017-86) and the Danish Patient Safety Authority (no. 3-3013-2059/1).

Summary of the results

Study I: Neural Axis Abnormalities in Patients with Adolescent Idiopathic Scoliosis: Is Routine Magnetic Resonance Imaging Indicated Irrespective of Curve Severity?

Objective: To report on the prevalence and risk factors of NAAs in AIS and evaluate on the role of routine MRI.

Results: A total of 381 patients were included. In 34 out of 381 (8.9%) NAAs were observed; 32 patients had a syrinx, one patient had an arachnoid cyst and one patient had Chiari 1 malformation. Previous proposed clinical and radiographic risk factors for NAAs showed no statistically significant association with NAAs (Figure 7).

Additionally, a multivariate logistic regression model reported no increase in odds of NAAs with lower age OR=0.83 (95% CI, 0.69–1.01), male sex OR=1.05 (95% CI, 0.40–2.79), increased major curve OR=1.01 (95% CI, 0.98–1.03), thoracic kyphosis > 30° OR=1.01 (95% CI, 0.48– 2.13) or atypical curve pattern OR=1.69 (95% CI, 0.35–8.19). A total of 17 patients with NAAs had deformity surgery and none of the patients experienced deterioration of their preoperative neurological status. When applying a more conservative definition of NAAs (syrinx ≥3mm), the overall prevalence for NAAs was 2.9%.

Main findings: I. NAAs were observed in 8.9% of AIS patients. II. There were no clinical implication of the findings of NAA. III. We could not reproduce previously proposed risk factors for NAA.

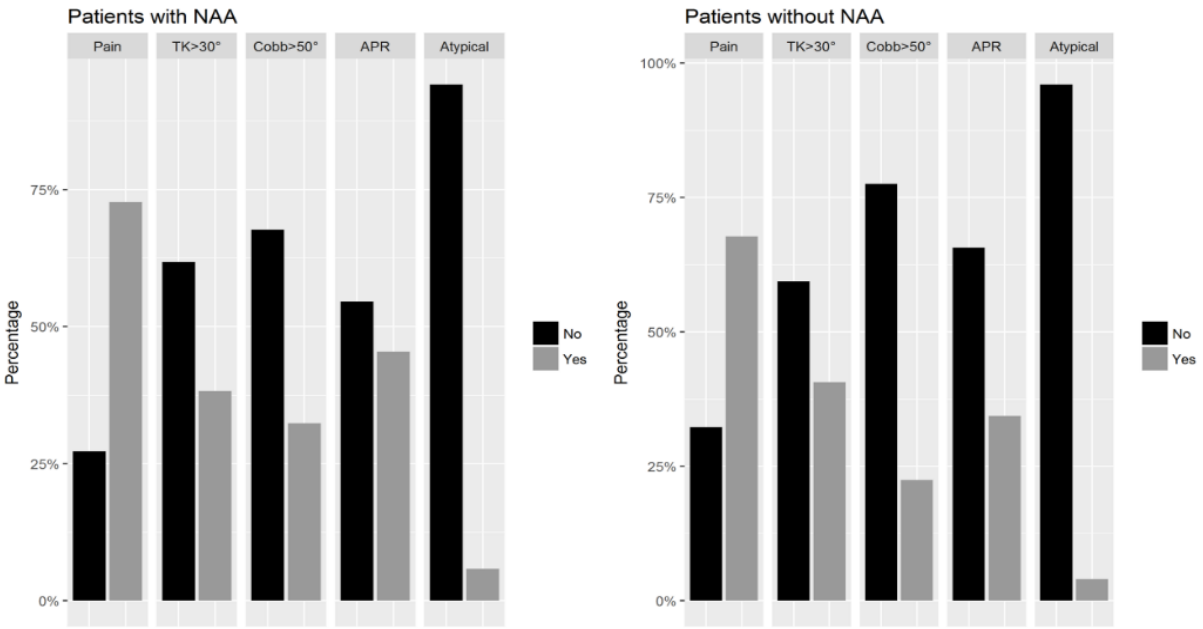

Figure 7. Proposed risk factors for neural axis abnormalities in adolescent idiopathic scoliosis. TK, thoracic kyphosis; APR, annual progression rate; Atypical, left side thoracic curve.

Study II: Length of Stay, Readmission and Mortality after Primary Surgery for Pediatric Spinal Deformities: A 10-year Nationwide Cohort Study

Objectives: Identify postoperative complications leading to extLOS and report 90-day readmission and mortality risks. Furthermore, to assess reasons for unplanned readmission.

Results: In total, 1310 patients had PSD surgery within the ten-year period. The deformity etiology was distributed as follow; ID (53%), ND (23%), CD (9%), SP (7%), SK (5%) and SD (3%). The incidence of PSD surgery increased during the study period with concurrent decrease in median LOS (Fig. 8). Median LOS was 8 days (IQR: 7-9) and mean LOS 9.1 days (SD: 11.0) and 21% of the patients had extLOS. The reasons for extLOS were assorted according to etiology (Fig. 9 and Appendix 5 in this thesis). Altogether, the most common reason was pain/mobilization issues.

In total, 6% were readmitted within 90-day; 33% were surgical related and 67% were medical related. The most usual reason for readmission was infection unrelated to the surgical site (23%) followed by gastrointestinal issues (19%), SSIs (13%), pulmonary complications (9%) and pain/mobilization issues (8%). In addition, a multivariate logistic regression showed increased odds of readmission in patients with neuromuscular deformity OR=4.4 (95%CI: 2.2-9.0), spondylolisthesis OR=3.0 (95%CI: 1.1-8.0), Scheuermann's kyphosis OR=4.9 (95%CI: 1.7-13.6) and LOS≥9 days OR=1.8 (95%CI: 1.0-3.1). The 90-day mortality risk was 0.4%.

Main findings: I. Pain/mobilization issues is a major postoperative challenge in PSD surgery. II. Patients undergoing PSD surgery were most frequently readmitted with infections unrelated to surgical site. III. Deformity etiologies of neuromuscular disease, spondylolisthesis and Scheuermann's kyphosis were associated with 90-day readmission.

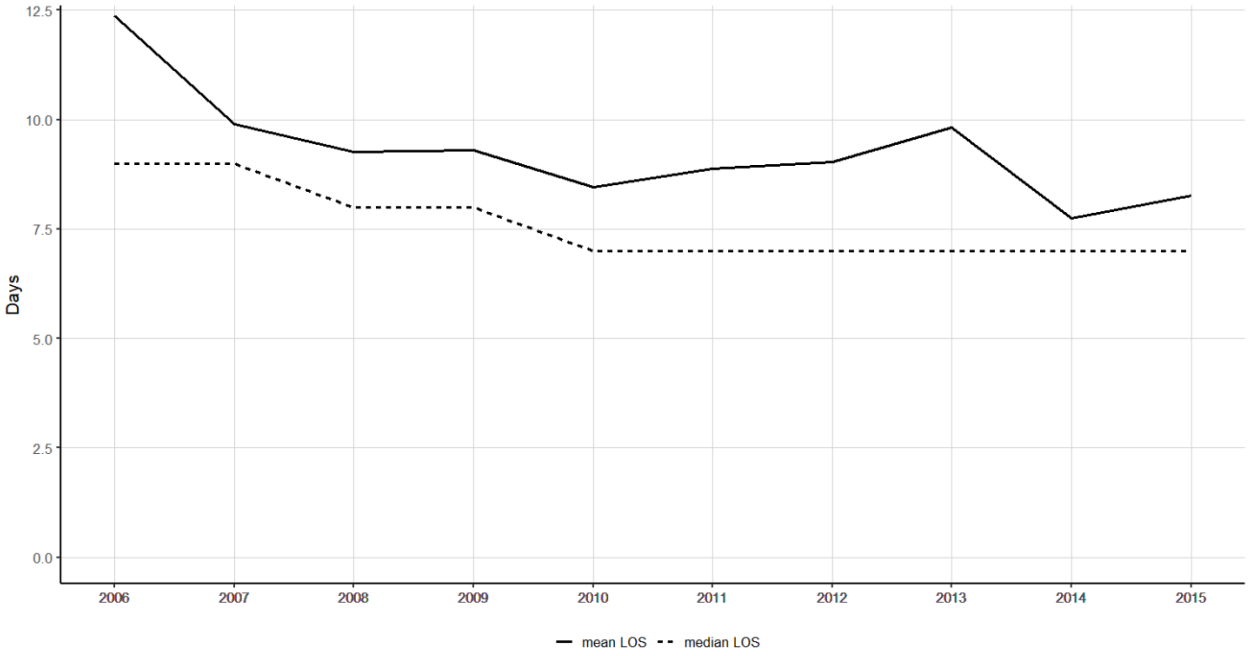

Figure 8. Mean and median LOS for each year of surgery.

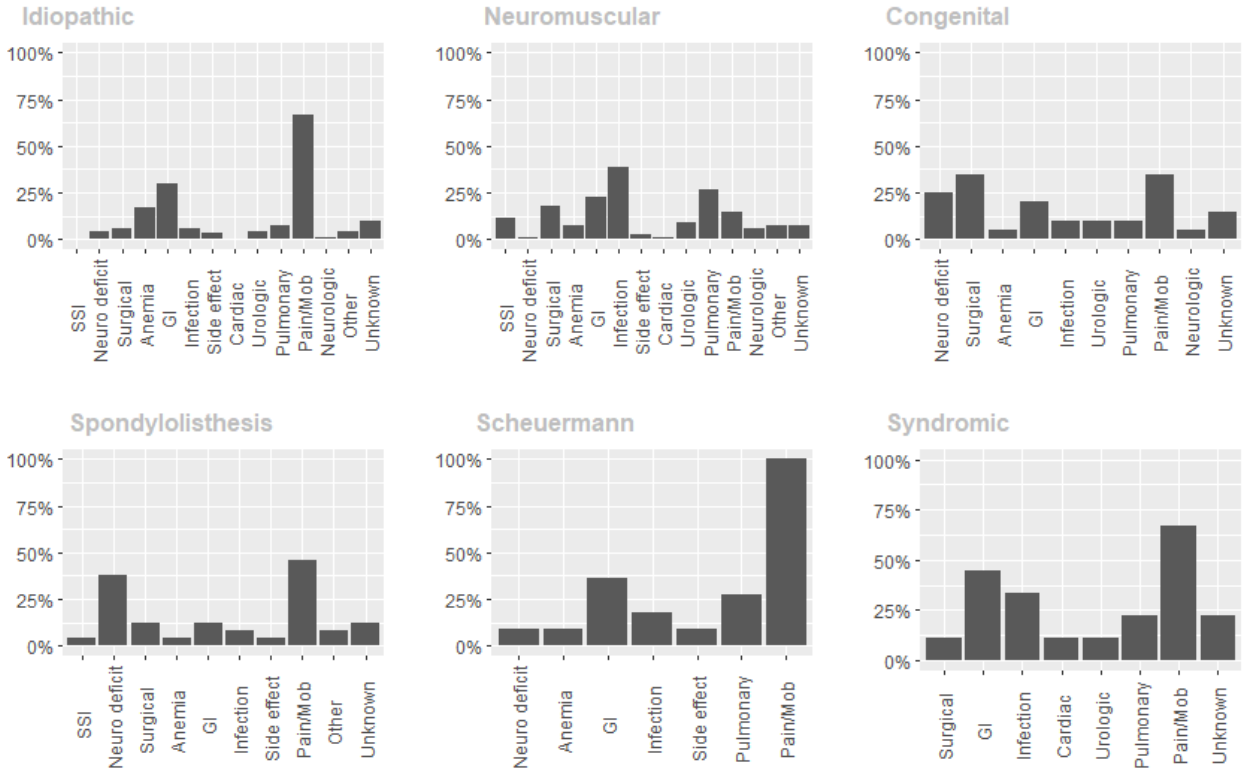

Figure 9. Reasons for extLOS across etiologies. SSI, surgical site infection; Neuro deficit, neurological deficit; Surgical, surgical complication; GI, gastrointestinal; Side effect, side effect from medication; Pain/Mob, pain and mobilization.

Study III: Revision risk, risk factors and reasons for revision following primary surgery for pediatric spinal deformity: A nationwide study with two-year follow-up

Objectives: To assess the two-year revision risk in patients operated for PSD and report risk factors and reasons for revision.

Results: During the ten-year study period, a total of 1310 patients undergoing first time PSD surgery were included. The cumulative incidence (95% confidence interval) of revision was 2.1% (1.4-2.9%) at 30 days, 3.0% (2.1-3.9%) at 90 days, 6.2% (4.8-7.5%) at one year and 9.5% (7.8-11.1%) at two years from index procedure (Fig. 10).

As expected, the cumulative two-year incidence varied across deformity etiology, with deformity etiologies of Scheuermann kyphosis (20.6%, 95% CI (10.6-30.6)), spondylolisthesis (17.3%, 95% CI (9.6-25.0)) and congenital deformity (15.6%, 95% CI (8.7-22.4)) reporting the highest incidence. In evaluating the association between predefined clinical parameters and revision, we found an increased odds in patients with growth-preserving system (OR=4.0, 95% CI 2.3-7.1), CD (OR=4.0, 95% CI 2.3-7.1), SP (OR=4.0, 95% CI 2.3-7.1), SK (OR=4.0, 95% CI 2.3-7.1) as well as high CCI (OR=4.0, 95% CI 2.3-7.1). The reasons for revision were implant failure (33%), implant misplacement/prominence issues (15%), SSIs (12%) and neurological deficit (11%) (for a detailed description see Fig. 11 or Appendix 5).

Main findings: I. The two-year cumulative revision risk was 9.5% and deformity etiologies associated with highest odds of revision were congenital, spondylolisthesis and Scheuermann's kyphosis. II. Main reason for revision was implant failure.

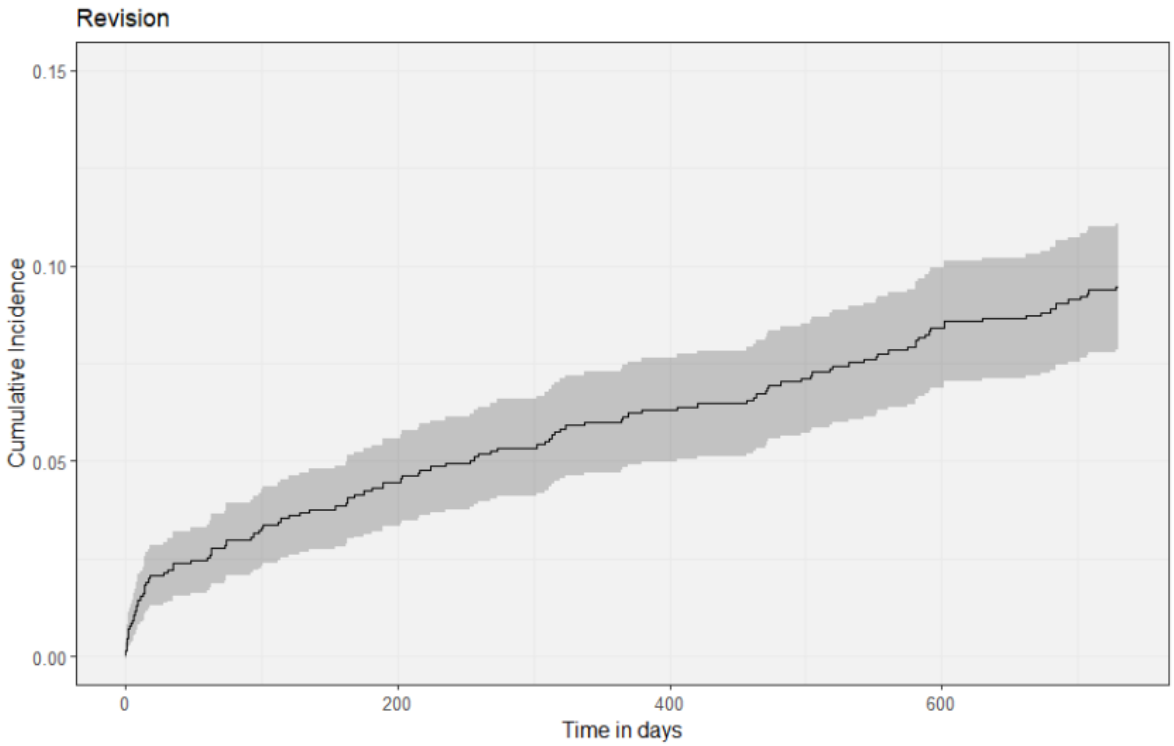

Figure 10. The overall cumulative incidence of any revision (with 95% confidence interval) during the two-year follow-up period.

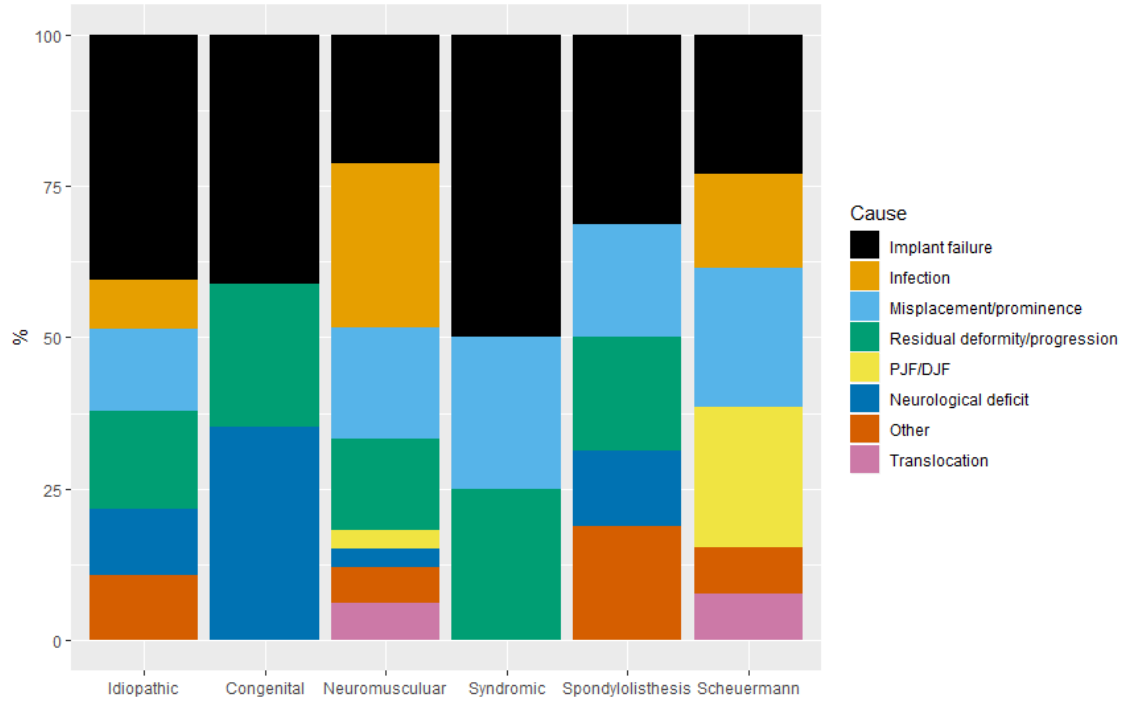

Figure 11. Reasons for revision according to etiology

Discussion

The clinical implications of routine MRI

Adolescent idiopathic scoliosis is a diagnosis of exclusion and careful evaluation is therefore a prerequisite for a correct diagnosis to be made. However, the role of routine MRI is still undecided. Identification of NAAs in study I was based on a five-year AIS MRI-protocol aiming to investigate all presentations of AIS, regardless of curve severity or treatment modality. Our study is one of the largest studies to assess the occurrence of NAA, especially in patients that are not surgical candidates. The reported prevalence of 8.9% is consistent with studies of similar design[27,35,104]. However, approximately one third of the eligible patients were excluded due to missing MRI, which could bias our results. Excluded patients were generally older, had smaller curves and less frequently received any treatment. As lower age is a known risk factor for NAAs this could overestimate the prevalence. Nonetheless, when adjusted for additional proposed risk factors, an association between age and NAAs could not be demonstrated. Moreover, the NAA prevalence is reported higher in AIS patients regardless of treatment modality compared to only surgical candidates[105]. This supports the theory, that the increasing use of MRI in general, leads to numerous coincidental findings of cavities in the neural axis. The large proportion of the NAAs considered insignificant in study I, adds weight to this hypothesis. In summary, these findings support the reported prevalence as being representative for entire AIS populations.

Normal MRI findings can reassure the surgeon and patients prior to surgery. However, small abnormalities without clinical implications can lead to unnecessary patients concerns, excessive medical testing and insecurity in the surgical decisions. Therefore, studies have searched for clinical and radiographical landmarks to guide the MRI assessment. Results from the risk factor analysis in study I, could not validate the previously proposed risk factors for NAAs. Previously proposed risk factors vary among studies and often directly contradict one another[28,29,31,36,38,39,106,107]. The variation in study methodologies and the possible publication bias (positive outcome bias) are likely explanations. The methodological variations include non-consecutive cohorts[28,29], differences in measurements of radiographical parameters[38,39,42] and pre-selected patient populations[31,36,106]. These differences make application of the study results difficult and their results susceptible to confounding. A systematic review with meta-analysis, affirmed the results from study I and did not support any of the previously proposed demographic variables indicating

increased risk of NAAs[108]. Unfortunately, pain and asymmetric superficial abdominal reflexes were not consistently reported in study I, and thus could not be assessed properly.

In study I, the NAAs did not alter the planned surgical procedure and none of the patients were offered neurosurgical intervention. In addition, there were no neurological complications in patients with NAAs undergoing posterior spinal fusion. Several studies have reported it safe for patients with NAAs to undergo spinal fusion[109–111], whereas some report an increased risk of neurological deficit due to perioperative spinal cord distraction[112]. Nevertheless, most studies concerning increased perioperative neurological risk in NAA patients are from studies with outdated surgical techniques or case reports[112,113].

One of the underlying research questions of study I was to assess, whether there were cases of AIS, irrespective of curve severity, that would benefit from neurosurgical treatment of NAAs and thereby limit progression or reverse the scoliosis. Brockmeyer et al. reported 62% of patients with Chiari 1 malformation and scoliosis experienced curve improvement or stabilization after neurosurgical decompression[114]. The included patients had either abnormal neurological examination, atypical age at presentation or unusual radiographic characteristics. These presentations do not concur with a diagnosis of AIS. Furthermore, the study did not follow all patients to skeletal maturity which makes conclusion on progression status uncertain. In conclusion, these data cannot be applied to an AIS population without neurological deficit.

Overall, results from study I show that AIS patients have a low risk of clinically relevant NAAs or neurologic deficit following surgery. Therefore, there is a good reason to challenge the existing guidelines for routine MRI.

Length of stay – can we reduce it?

Compared to most US database studies, the reported LOS in study II is high [24,67–70]. However, it is similar to another nationwide Scandinavian study[5]. Differences in health care systems (private financing vs public financing) might explain this variation. In the United States, LOS is often a proxy for resource use and therefore a more comprehensive effort to reduce LOS has been applied[72]. Shorter LOS is preferable, not only because of decreased costs, but mainly to improve postoperative recovery.

In total 21% of the patients had extLOS. Even though the reason for extLOS varied across etiologies, the overall most common reasons were medical; i.e. pain and mobilization issues, pulmonary complications and gastrointestinal issues. These complications could indicate a need for implementation of enhanced recovery after surgery (ERAS) principles. The rationale behind ERAS is a maintenance of homeostasis after the surgical stress. Surgical stress can be influenced by a number of factors – postoperative pain, catabolism, nausea and vomiting, ileus, impaired pulmonary functions, and immune dysfunction[74,115–117]. A corner stone in ERAS, is non-opioid multimodal analgesia, which reduces nausea, vomiting and sedation and at the same time allows for early mobilization [118–121]. Many patients experienced both pain/mobilization and gastrointestinal issues as a reason for extLOS, which emphasizes both undesirable use of opioids but also possible side-effects. Sedation from opioids can results in serious complications, especially in patients with ND, who are more prone to respiratory compromise[122]. This issue is also reflected in one of the mortality cases from study II (respiratory failure due to aspiration pneumonia). Patients with ND were in general more susceptible to infections and pulmonary complications as a reason for extLOS, which is in accordance with previous studies[122–124]. Reducing LOS could result in less potential exposure to nosocomial infections in these fragile patients.

Reassuringly, only 15% of the reasons for extLOS were surgical and in this group, patients with SP and CD were overrepresented. Patients with SP more often experienced neurological deficit as a reason for extLOS. Transient radiculopathy can be expected in SP surgery because of L5 root stretching related to the reduction technique [125]. Few larger studies add weight to this finding, reporting higher neurological deficit in patients with SP[126] and especially in patients requiring reduction[64]. However, these studies are from the Scoliosis Research Society (SRS) morbidity and mortality database which relies on self-reported data from members. This naturally has some concerns of selection bias. Additionally, these studies included both primary and revision procedures which could affect the interpretation of the results, since revision surgery is associated with higher complication rates[84]. The surgical reasons for extLOS in CD patients were primarily postoperative partial or complete paraplegia. There was no obvious biomechanical reason for the sudden major neurological deficit in any of the cases. Patients with CD are more susceptible to other congenital organ defects and comorbidities[127], which might make them less responsive and tolerant to conventional therapies, such as perioperative permissive hypotension. Hence, the postoperative paraplegia could be a result of ischemia.

The results from study II reveal areas of improvement in reducing length of stay following PSD surgery. Especially, focus on pain/mobilization and gastrointestinal issues could help reduce the number of patients with extLOS. Accelerated discharge protocols have shown promising results in AIS populations[128–130] and similar concepts could be applied to other etiologies.

Readmission risk – is it acceptable?

In study II, the 30-day and 90-day readmission risk were 3% and 6%, respectively. These results are similar to previous studies[65,66,81]. However, two of the previous studies are single center or database studies where only readmissions to own institutions are recorded. This can result in an underestimation of the readmission risk. Identification of readmission from study II was based on DNPR data with complete nationwide follow-up and confirmation through meticulous medical record review. The readmission risk and reason for readmission could therefore serve as a point of reference, in future studies.

The risk analysis in study II, revealed increased risk of readmissions in patients with extLOS at index admission and etiologies of ND, SK and SP. Other register studies concur with extLOS as a risk factor for readmission, even after adjusting for comorbidities and infections [65,70]. However, extLOS can still be an indication of frailty and complications extending beyond the admission period and thus comprise a risk factor for readmission. Previous studies have reported higher morbidity rates in patients with ND, especially in terms of readmissions[65,66,81]. Bearing in mind that not all readmissions are avoidable, this could also be a result from non-preventable progression of an existing disease, rather than suboptimal care. This is affirmed in the ND patients with readmission because of deterioration of existing neurological disorder. Patients with ND were likely to be readmitted for medical reasons, especially infections and pulmonary- and nutritional issues. Pulmonary dysfunction is a common complication of ND patients[131]. Although deformity surgery aims to reduce the decline in respiratory function, the vital capacity may be reduced at the time of surgery due to changes in alveolar perfusion and sedation from opioids. Study II further supports the importance of pre- and postoperative expert pulmonary and nutritional management in this patient group. Finally, patients with SP and SK had increased risk of readmission. The primary reason for readmission in patients with SP and SK were surgical. Patients with SP were more likely to experience neurological deficit as a reason for readmission and patients with SK were often revised. Neurological deficits in SP patients were also a major factor leading to extLOS. However,

all SP patients with neurological deficit were treated conservatively, thus a more careful patient selection and preoperative information may reduce the short-term morbidity in these patients.

Not all readmissions are avoidable, but there is still considerable room for improvement. Close attention to postoperative nutrition, bowel regiment, opioid treatment and respiratory compromise is warranted to minimize readmission risk. Again, this could indicate increased focus on ERAS principles, especially in patients with ND.

Revision risk and risk factors for revision surgery

In study III, we reported an overall two-year cumulative revision risk of 9.5%. Few studies have examined the revision risk in PSD patients and most of the studies are with limited follow-up [62,81]. Other studies are limited to small cohorts, thus little is known of the differences in revision risk across etiologies[88,132]. However, one study has reported prolonged revision risk across etiologies. Paul et al. reported an overall four-year revision risk of 3% in PSD surgery, using data from a US state database[82]. The overall lower revision risk can be due to more stringent inclusion criteria (excluding patients with EOS, SP, SK and short fusions) and unreported loss to follow-up.

The result from the risk analysis in study III, showed increased odds of revision in patients with an etiology of SP, SK and CD, growth-preserving surgery and high comorbidity score. Revision risk is reported high in pediatric SP. A recent multicenter study reported 40% revision risk in pediatric SP patients treated with posterior spinal fusion[125]. The reported reasons for revision were implant failure and persistent radiculopathy. This finding is congruent with the reasons for revision in SP addressed by study III. The high risk of neurological deficit, especially during reduction procedures, is supported by numerous studies[25,88,126]. But whether neurological deficit is inherent to the reduction technique or is a result of the degree of the deformity needs further examination. Unfortunately, the setting for this thesis did not allow for such analysis. A multicenter study with one-year follow-up reported revision risk in SK significantly higher compared with AIS patients (14.4% vs 1.4%, respectively)[86]. In study III, the two-year revision risk for patients with SK was 20.6% vs. 5.4% for ID. The higher revision risk may be attributable to the more extensive surgery in patients with SK (longer instrumentation and routine use of osteotomies). Combined with the cantilever forces to correct the kyphosis and pull-out forces at both ends of the construct, it may result in increased risk of implant failure as well as PJF and DJF[133–137]. The reasons for revisions in SK patients emphasize this theory. To avoid these complications a careful selection of

fusion levels, optimal upper instrumented level and avoidance of overcorrection is essential[136]. Patients with CD are generally reported to have higher risk of revision compared to patients with IS[62,81,82]. The revision risk in CD is closely related to the type of congenital deformity, surgical approach and age at surgery[138,139]. In study III, the primary reasons for revision in CD patients were implant failure, neurological deficit and curve progression. Previously, studies have described concern of neurological deficit, implant failure and progression (especially the crankshaft phenomenon) seen in CD surgery[132,139–142]. In summary, the etiologies at-risk have some common ground. Primarily, they are all relatively poorly represented in many cohort studies or subjected to small single-center studies due to their limited prevalence. Secondly, there is significant variability in the surgical threshold and approach for both CD, SP and SK patients[25,26,132,143–149]. The management of these patients is therefore often considered a test of judgement. An introduction of a more uniform national pathway may contribute to reduce the revision risk in these patient groups.

It was anticipated that patients with a growth-preserving approach had higher risk of revision, since the surgical procedure is prolonged with a concomitant increase in the risk of infections and implant failure[51,150]. Studies report unplanned revision risk of 33% in patients treated with MCGR and an overall complication rate of 58% in patients treated with TGR[51,87]. The revision risk for patients with growth-preserving systems were significantly lower in study III (16.5%), but most patients were not followed until final fusion. The high revision risk in these patients is still a major and unsolved challenge. Finally, high CCI was associated with increased revision risk in study III. It is well-known that patients with comorbidities have higher risk of complications and death, have longer hospital stays and higher resource use[151,152]. That increased comorbidity burden is associated with increased risk for postoperative events, has been reported in both adult and pediatric spinal deformity surgery[65,97,99]. Increased attention should be directed towards identifying these patients and careful surgical planning with less aggressive surgical approach might be an option.

Overall, the results from study III indicate an increased focus on specific deformity etiologies and surgical procedures, in terms of reducing the revision risk.

Strength and limitations

The *limitations* to the three studies are presented below.

Study I: The inclusion process is susceptible to selection bias due to the large number of excluded patients. As most of the excluded patients were low-risk surgical candidates, it is likely that the treating physicians neglected the MRI protocol. Moreover, we assessed numerous predictive variables in a small NAA population, which induces a risk of type 2 error. Despite these limitations, our findings suggest that specific radiographical and clinical variables should be used with caution. In addition, the original studies suggesting these predictors are with the same or considerably smaller sample sizes.

Study II and III: The major limitations are those related to registry studies, particularly the validity of the diagnosis/etiology and the lack of clinical perioperative data. We acknowledge the development of enhanced coding during the study period which can lead to misclassification bias. In total, 16% of patients had conflicting or unspecific diagnostic codes. However, we did confirm all these cases through medical record review following classification according to the recently suggested classification system[9]. The classification system was first implemented in 2014 and therefore a risk of misclassification bias remains. The use of CCI as an indicator of comorbidity in patients with PSD may be questionable. But postoperative morbidity is closely related to preoperative comorbidity and thus should be accounted for in multivariate analysis. To date, no comorbidity index has been validated in a pediatric setting with revision as outcome. However, CCI has been validated to predict revision in other orthopedic areas[153] and is validated on DNPR data[101]. Nevertheless, we acknowledge the lack of certain diagnostic codes in CCI in a pediatric patient cohort with neuromuscular and syndromic conditions.

The *strengths* of the studies are presented below.

Study I: We included patients referred to a tertiary spine institution in a five-year period regardless of treatment modality. Our center serves a population consisting of approximately 2.5 million citizens. We therefore believe that the NAA prevalence is representative in patients with AIS, also because of the broad inclusion criteria.

For study II and III the cohort consisted of all patients in Denmark with primary PSD surgery in a ten-year period. The cohort is consecutive and not susceptible to selection bias as opposed to many

other database studies. The combination of a procedure code for spine surgery and a relevant diagnosis of PSD was applied to only assess deformity patients. This method have been validated with DNPR data in adult spinal deformity[97]. Study II and III are based on data from the DNPR where data accuracy and completeness has been validated on multiple occasions[96,154,155]. The strengthening of the data was improved with the medical record review in patients with extLOS, readmission and revision. This ensured best available information in terms of true risk and the pathophysiological mechanism behind the outcomes. In addition, it included more detailed information regarding reason for extLOS and revision, not previously reported in register or database studies.

Perspectives and future research

Exact diagnostic assessment is important for the surgical outcome in PSD. The rapidly rising costs in the healthcare system must lead to critical evaluation of the value and efficacy of the diagnostic tests. The increasing use of MRI adds to the overall costs in PSD surgery. The benefits of MRI evaluation in AIS patients should be weighed against the cost of MRI. A cost-effectiveness study of routine MRI in AIS surgery must be addressed to answer this question.

The conservative and surgical treatment of patients with PSD continues to evolve. With the rapidly and continuous development, there is little understanding of the short- and long-term outcomes. Additionally, there is lacking high-level evidence to guide the development of the new techniques. This highlights the need for continuous, critical evaluation of the surgical safety.

Optimizing postoperative care

This thesis has uncovered some potential problems regarding postoperative safety. Optimizing the postoperative care could help in reducing the length of stay and the unplanned readmissions. The pain/mobilization issues in terms of reducing LOS, might start with preoperative counselling. Expectation about early mobilization to allow for shorter LOS must be explained to patients and their caregivers, prior to surgery. Besides this, non-opioid analgesia, fast initiations of solid food, early mobilization and incentive spirometry could reduce some of the postoperative complications uncovered in this thesis. Studies assessing accelerated discharge protocols in AIS patients have shown feasible results in terms of reducing LOS without increasing complications or readmission risk[115,128,130]. Use of an accelerated discharge pathway in patients with ND has also shown promising results in reducing LOS[156]. However, the full effect of implementation of a comprehensive ERAS program in PSD surgery is still to be published. Minimally invasive surgery (MIS) is another option to improve surgical safety. Minimally invasive surgery has shown promising results in terms of short-term morbidity with reported reduced blood loss, pain and LOS[157,158]. However, future multicenter prospective studies are needed to clarify the true benefits of MIS.

Reducing the risk of revision

The high revision risk in some deformity etiologies is an unsolved problem. The right patient selection seems to be essential for an optimal outcome. To solve this, a uniform language and

treatment strategy is essential. The proposed classification system for EOS patients (C-EOS) have enabled uniform classification of PSD patients since 2014[9]. A recent validation study reported substantial agreement for classifying etiologies according to C-EOS[159]. However, discrepancies between certain etiologies and inconsistencies in the original classification system still warrant further specifications. A more precise classification system would allow for more valid comparison of study results between institutions. This seems especially important in evaluation the revision risk of PSD surgery, in large register studies. Moreover, prospective multicenter studies reporting revision risk in PSD surgery, using uniform classification, may improve the understanding of the risk factors for revision. As both patients with ID, SP and SK are in generally good health and rarely suffer from severe comorbidities, continued advancement in surgical technique should ensure a minimal risk of revision.

Concluding remarks

Overall this thesis provides new aspects of the diagnostic challenges, the short-term morbidity and revision risk in PSD surgery. The reported prevalence of neural axis abnormalities in AIS patients is similar to previous studies and considered valuable as an estimate of the true prevalence. We could not reproduce previously findings of risk factors for NAAs. However, the consequences of NAAs in patients with AIS undergoing spinal surgery are questionable in a patient cohort without neurological symptoms, comorbidities or pain. Overall, study II and III revealed challenges regarding the postoperative safety. A total of 21% of patients experienced extended length of stay, and pain and mobilization difficulties were of major concern. This highlights the need for improvement of the postoperative care in both reducing length of stay but also concerning safety and costs. Finally, this thesis presents nationwide two-year revision risk with complete follow-up in patients with PSD. Establishing the overall revision risk and risk factors in PSD surgery is important for allocating resources to at-risk patient groups. There was an association between etiologies of congenital deformity, spondylolisthesis and Scheuermann's kyphosis and the risk of revision. The high revision risk in these etiologies warrants further investigation to improve and initiate preventive measures.

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Appendices

Appendix 1 Surgery coding	
KNAG	
Code	**Text**
KNAG3	Anterior spinal fusion without fixation
KNAG30	Anterior spinal fusion without internal fixation in the cervical spine
KNAG31	Anterior spinal fusion without internal fixation in the cervicothoracic spine
KNAG32	Anterior spinal fusion without internal fixation in the thoracic spine
KNAG33	Anterior spinal fusion without internal fixation in the thoracolumbar spine
KNAG34	Anterior spinal fusion without internal fixation in the lumbar spine
KNAG35	Anterior spinal fusion without internal fixation in the cervicothoracolumbar spine
KNAG36	Anterior spinal fusion without internal fixation in the lumbosacral spine
KNAG4	Anterior spinal fusion with internal fixation
KNAG40	Anterior spinal fusion with internal fixation in the cervical spine
KNAG41	Anterior spinal fusion with internal fixation in the cervicothoracic spine
KNAG42	Anterior spinal fusion with internal fixation in the thoracic spine
KNAG43	Anterior spinal fusion with internal fixation in the thoracolumbar spine
KNAG44	Anterior spinal fusion with internal fixation in the lumbar spine
KNAG45	Anterior spinal fusion with internal fixation in the cervicothoracolumbar spine
KNAG46	Anterior spinal fusion with internal fixation in the lumbosacral spine
KNAG5	Anterior spinal fusion with external fixation
KNAG50	Anterior spinal fusion with external fixation in the cervical spine
KNAG51	Anterior spinal fusion with external fixation in the cervicothoracic spine
KNAG52	Anterior spinal fusion with external fixation in the thoracic spine
KNAG53	Anterior spinal fusion with external fixation in the thoracolumbar spine

KNAG54	Anterior spinal fusion with external fixation in the lumbar spine
KNAG55	Anterior spinal fusion with external fixation in the cervicothoracolumbar spine
KNAG56	Anterior spinal fusion with external fixation in the lumbosacral spine
KNAG6	Posterior spinal fusion without fixation
KNAG60	Posterior spinal fusion without fixation in the cervical spine
KNAG61	Posterior spinal fusion without fixation in the cervicothoracic spine
KNAG62	Posterior spinal fusion without fixation in the thoracic spine
KNAG63	Posterior spinal fusion without fixation in the thoracolumbar spine
KNAG64	Posterior spinal fusion without fixation in the lumbar spine
KNAG65	Posterior spinal fusion without fixation in the cervicothoracolumbar spine
KNAG66	Posterior spinal fusion without fixation in the lumbosacral spine
KNAG7	Posterior spinal fusion with internal fixation
KNAG70	Posterior spinal fusion with internal fixation in the cervical spine
KNAG71	Posterior spinal fusion with internal fixation in the cervicothoracic spine
KNAG72	Posterior spinal fusion with internal fixation in the thoracic spine
KNAG73	Posterior spinal fusion with internal fixation in the thoracolumbar spine
KNAG74	Posterior spinal fusion with internal fixation in the lumbar spine
KNAG75	Posterior spinal fusion with internal fixation in the cervicothoracolumbar spine
KNAG76	Posterior spinal fusion with internal fixation in the lumbosacral spine
KNAG8	Hemispondylodesis
KNAG80	Hemispondylodesis in the cervical spine
KNAG81	Hemispondylodesis in the cervicothoracic spine
KNAG82	Hemispondylodesis in the thoracic spine
KNAG83	Hemispondylodesis in the thoracolumbar spine
KNAG84	Hemispondylodesis in the lumbar spine
KNAG85	Hemispondylodesis in the cervicothoracolumbar spine

KNAG86	Hemispondylodesis in the lumbosacral spine
KNAK	
Code	**Text**
KNAK	Surgery on spine vertebrae
KNAK1	Resection or excision of vertebrae
KNAK10	Resection or excision of vertebrae in the cervical spine
KNAK11	Resection or excision of vertebrae in the cervicothoracic spine
KNAK12	Resection or excision of vertebrae in the thoracic spine
KNAK13	Resection or excision of vertebrae in the thoracolumbar spine
KNAK14	Resection or excision of vertebrae in the lumbar spine
KNAK15	Resection or excision of vertebrae in the cervicothoracolumbar spine
KNAK16	Resection or excision of vertebrae in the lumbosacral spine
KNAK9	Other surgery on a vertebra
KNAK90	Other surgery on a vertebra in the cervical spine
KNAK91	Other surgery on a vertebra in the cervicothoracic spine
KNAK92	Other surgery on a vertebra in the thoracic spine
KNAK93	Other surgery on a vertebra in the thoracolumbar spine
KNAK94	Other surgery on a vertebra in the lumbar spine
KNAK95	Other surgery on a vertebra in the cervicothoracolumbar spine
KNAK96	Other surgery on a vertebra in the lumbosacral spine
KNAT	
Code	**Text**
KNAT	Different surgeries in the spine and neck
KNAT1	Anterior traction and correction with internal fixation in the spine
KNAT10	Anterior traction and correction with internal fixation in the cervical spine
KNAT11	Anterior traction and correction with internal fixation in the cervicothoracic spine

KNAT12	Anterior traction and correction with internal fixation in the thoracic spine
KNAT13	Anterior traction and correction with internal fixation in the thoracolumbar spine
KNAT14	Anterior traction and correction with internal fixation in the lumbar spine
KNAT15	Anterior traction and correction with internal fixation in the cervicothoracolumbar spine
KNAT16	Anterior traction and correction with internal fixation in the lumbosacral spine
KNAT2	Posterior traction and correction with internal fixation in the spine
KNAT20	Posterior traction and correction with internal fixation in the cervical spine
KNAT21	Posterior traction and correction with internal fixation in the cervicothoracic spine
KNAT22	Posterior traction and correction with internal fixation in the thoracic spine
KNAT23	Posterior traction and correction with internal fixation in the thoracolumbar spine
KNAT24	Posterior traction and correction with internal fixation in the lumbar spine
KNAT25	Posterior traction and correction with internal fixation in the cervicothoracolumbar spine
KNAT26	Posterior traction and correction with internal fixation in the lumbosacral spine
KNAT9	Other surgery in the spine
KNAT90	Other surgery in the cervical spine
KNAT91	Other surgery in the cervicothoracic spine
KNAT92	Other surgery in the thoracic spine
KNAT93	Other surgery in the thoracolumbar spine
KNAT94	Other surgery in the lumbar spine
KNAT95	Other surgery in the cervicothoracolumbar spine
KNAT96	Other surgery in the lumbosacral spine

Appendix 2

Diagnostic coding according to data extraction

Code	Text
DM400	Postural kyphosis
DM401	Other secondary scoliosis
DM401A	Secondary scoliosis, unspecified
DM402	Other or non-specified kyphosis
DM402A	Kyphosis, unspecified
DM403	Erect spine
DM404	Other form of lordosis
DM404A	Acquired lordosis
DM404B	Postural lordosis
DM404C	Hyperlordosis
DM405	Lordosis, unspecified
DM420	Juvenile osteochondrosis in the spine
DM421	Adult osteochondrosis in the spine
DM418	Other form of scoliosis
DM432A	Ankylosis in the spine
DM438	Other form of deformity of the spine
DM439	Deformity of the spine, unspecified
DM410	Juvenile idiopathic scoliosis
DM400	Postural kyphosis
DM401	Other secondary scoliosis
DM401A	Secondary scoliosis, unspecified
DM402	Other or non-specified kyphosis
DM402A	Kyphosis, unspecified

DM403	Erect spine
DM404	Other form of lordosis
DM404A	Acquired lordosis
DM404B	Postural lordosis
DM404C	Hyperlordosis
DM405	Lordosis, unspecified
DM420	Juvenile osteochondrosis in the spine
DM421	Adult osteochondrosis in the spine
DM418	Other form of scoliosis
DM432A	Ankylosis in the spine
DM438	Other form of deformity of the spine
DM439	Deformity of the spine, unspecified
DM410	Juvenile idiopathic scoliosis
DM410A	Juvenile idiopathic kyphoscoliosis
DM411	Adolescent idiopathic scoliosis
DM411A	Adolescent idiopathic kyphoscoliosis
DM412	Other form of idiopathic scoliosis
DM413	Thoracic scoliosis
DM413A	Thoracic kyphoscoliosis
DM419	Scoliosis, unspecified
DQ675	Congenital spine deformity
DQ675A	Congenital kyphoscoliosis, unspecified
DQ675B	Congenital postural scoliosis
DQ675C	Congenital scoliosis, unspecified
DQ762A	Congenital spondylolysis
DQ763	Congenital scoliosis due to bone malformation

DQ763A	Congenital kyphoscoliosis due to bone malformation
DQ764	Other form of congenital spine deformity without scoliosis
DQ764C	Agenesis of a vertebra
DQ764E	Aplasia of the sacrum
DQ764F	Aplasia of a vertebra
DQ764G	Hemilumbarization of the sacrum
DQ764H	Hemisacralization of a lumbar vertebra
DQ764I	Hemispondylia congenital
DQ764J	Hemivertebra
DQ764K	Congenital kyphosis
DQ764L	Congenital lordosis
DQ762	Congenital spondylolisthesis
DQ764M	Lumbarization
DQ764N	Sacralization
DQ764O	Abnormal lumbosacral symphysis
DQ764P	Synostosis in the vertebra
DQ764Q	Spare vertebra
DQ766	Other congenital deformity of a costa
DQ766A	Costa agenesis
DQ766B	Costa aplasia
DQ766C	Extra costa
DQ766D	Synostosis costae
DQ767	Congenital malformation of sternum
DQ768	Other congenital malformation of the thorax
DQ769	Congenital deformity of the thorax, unspecified
DM432	Block vertebra

DM429	Osteochondrosis in the spine, unspecified
DM414	Neuromuscular scoliosis
DM414A	Secondary scoliosis in Friederichs ataxia
DM414B	Secondary scoliosis in cerebral palsy
DM414C	Neuromuscular kyphoscoliosis
DM414D	Secondary kyphoscoliosis in cerebral palsy
DM414E	Secondary kyphoscoliosis in Friederichs ataxia
DM414F	Secondary kyphoscoliosis in poliomyelitis
DM415	Other form of secondary scoliosis
DM415A	Secondary scoliosis, unspecified
DM415B	Secondary kyphoscoliosis, unspecified
DQ760	Spina bifida occulta
DG800	Spastic tetraplegic cerebral palsy
DQ777	Spondyloepiphyseal dysplasia
DG824	Spastic tetraplegic
DQ850	Neurofibromatosis
DG121D	Muscle dystrophia, type II
DG710H	Duchenne’s muscle dystrophia
DG600	Inherited motoric sensory neuropathy
DG801	Spastic diplegic cerebral palsy
DQ761	Klippel-Feil’s syndrome
DQ871	Congenital deformity syndrome with dwarfism
DQ871A	Cockaynes syndrome
DQ871B	Cornelia de Langes syndrome
DQ871C	Dubowitz' syndrome
DQ871D	Noonan’s syndrome

DQ871E	Prader-Willis syndrome
DQ871F	Robinow-Silverman-Smiths syndrome
DQ871G	Russell-Silvers syndrome
DQ871H	Seckels syndrome
DQ871I	Smith-Lemli-Opitz' syndrome
DQ871J	Facialgenital dysplasia
DQ872G	VATER syndrome
DQ873	Syndromes with congenital malformation and early height growth
DQ873A	Beckwith-Wiedemann’s syndrome
DQ873B	Sotos syndrome
DQ873C	Weavers syndrome
DQ874	Marfans syndrome
DQ875	Other congenital malformation syndrome with other skeletal deformities
DQ878	Other congenital malformation syndrome, IKA
DQ878A	Alports syndrome
DQ878B	Laurence-Moon-Biedl-Bardets syndrome
DQ878C	Zellwegers syndrome
DQ878D	Cowdens disease
DQ878E	Goltz syndrome
DQ878J	LEOPARD syndrome

Appendix 3

Charlson comorbidity index

Disease category	ICD-8	ICD-10
Myocardial infarction	410	I21.x, I22.x, I23.x
Congestive heart failure	427.09, 427.10, 427.11, 427.19, 428.99, 782.49	I11.0, I13.0, I13.2, I50.x,
Peripheral vascular disease	440–445	I70.x, I71.x, I73.x, I74x, I77.x
Cerebrovascular disease	430–438	G45.x, G46.x, I60.x–I69.x
Dementia	290.09–290.19, 293.09	F00.x - F03.x, F05.1, G30.x
Chronic pulmonary disease	490–493, 515–518	J40.x–J47.x, J60.x–J67.x, J68.4, J70.1, J70.3, J84.1, J92.0, J96.1, J98.2–J98.3
Connective tissue disease	135.99, 446, 712, 716, 734	M05.x, M06.x, M08.x, M09.x, M30.x–M36.x, D86
Ulcer disease	530.91, 530.98, 531–534	K22.1, K25.x–K28.x
Mild liver disease	571, 573.01, 573.04	B18.x, K70.0–K70.3, K70.9, K71.x, K73.x, K74.x, K76.0
Diabetes	249.00, 249.06, 249.07, 249.09, 250.00, 250.06, 250.07, 250.09	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9,
Hemiplegia	344	G81.x, G82.x
Moderate to severe renal disease	403, 404, 580–584, 590.09, 593.19, 753.10–753.19, 792	I12.x, I13.x, N00–N05, N07, N11, N14, N17–N19, Q61
Diabetes with end organ damage	249.01–249.05, 249.08, 250.01–250.05, 250.08	E10.2–E10.8, E11.2–E11.8
Any tumor	140–169, 172–192.48, 193–194	C00.x–C75.x
Leukemia and lymphoma	204–207, 200–203, 275.59	C91.x–C95.x, C81–C85, C88, C90, C96
Moderate to severe liver disease	070.00, 070.02, 070.04, 070.06, 070.08, 456.00– 456.09, 573.00	B15.0, B.16.0, B16.2, B19.0, K70.4, K72.x, K76.6, I85
Metastatic solid tumor	195–199	C76.x–C80.x
AIDS	079.83	B21.x–B24.x

Appendix 4

All reasons for the 274 patients with extLOS according to etiology

Etiology	Median LOS, days	Reason	Comment
ID **n=143** **Reasons: 234**	9 (IQR: 9-11)	Surgical	SSI (1%): 1 patient (antibiotic treatment).
			Neurological (4%): 6 patients; 3 with complete paralysis and revision, 3 with dysesthesia (1 revised).
			Surgical (6%): 9 patients; 2 patients had revision (1 due to ploughing of screw and 1 due to drainage tube broke at removal), 1 patient with misplaced epidural, 1 with misplaced screw, 1 patient due to dura lesion, 4 with neurological deficit.
		Medical	GI (30%): 43 patients; 33 with vomitus and nausea, 9 with obstipation, 3 with nutrition issues, 2 with ileus.
			Infection (6%): 9 patients; 6 with UTI, 3 with unknown focus.
			Cardiac (1%): 1 patient with tachycardia.
			Anemia (17%): 25 patients.
			SE (3%): 5 patients; 2 with urticaria, 1 with double vision, 2 with epidural complications.
			Urological (4%): 6 patients with urinary retention.
			Pulmonary (8%): 11 patients; 8 patients with pneumothorax (all of them with anterior procedure and pleura drainage), 2 patients with hemothorax, 1 patient with respiratory failure.
			Pain/mobilization (67%): 96 patients; 38 patients with primarily mobilization issues, 42 patients with pain difficulties and 17 patients with a combination.
			Neurological (1%): 2 patients; 1 patient with suspected cerebral infarction, 1 patient with acute psychosis
			Other (3%): 6 patients; 3 patients with transportation issues, 2 patients with planned second stage procedure, 1 patient with initial halo traction.
			Unknown (4%): 14 patients; no apparent cause in the medical record.
CD	11.5 (IQR:10-14.5)	Surgical	Neurological (25%): 5 patients with paresis/paralysis post-operatively and revision surgery.

n=20 **Reasons: 34**			Surgical (35%): 7 patients; 1 patient with missing IOM signal and final fusion postponed, 1 with dura lesion and 5 patients with neurological deficit and revision.
		Medical	Anemia (5%): 1 patient with increasing INR and anemia.
			GI (20%): 4 patients; 2 patients with vomitus and nausea, 1with GI pain and 1 with ileus.
			Infection (10%): 2 patients; 1 with skin infection, 1 with unknown origin.
			Urogenital (10%): 2 with urinary retention.
			Pulmonary (10%): 2 patients with respiratory insufficiency.
			Pain/mobilization (35%): 7 patients.
			Neurological (5%): 1 patient with deterioration in epileptic seizures.
			Unknown (15%): 3 patients.
ND **n=67** **Reasons: 118**	15 (IQR:13-26)	Surgical	SSI (12%): 8 patients, 4 were revised.
			Neurological (1%): 1 patient with paresis and revision.
			Surgical (18%): 12 patients; 2 patients with screw misplacement and revision surgery, 1 owing to administration of cell saver giving intradermal resulting in compartment syndrome, 3 with prolonged ICU due to large blood loss and hypothermia, 1 due to cardiac arrest because of excessive blood loss, 1 due to intubation complication and edema of the airways, 1 revised due to breakage of drainage tube, 4 revised due to SSI, 1 with postoperative paralysis.
		Medical	Anemia (7%): 5 patients.
			Cardiac (1%): 1 with cardiac arrest due to respiratory insufficiency
			GI (22%): 15 patients; 1 with dilated colon (surgery/deflation), 1 with string ileus (surgery), 1 paralytic ileus, 5 with nutrition issues, 1 with obstipation and vomitus.
			Infection (39%): 26 patients; 13 pneumonia, 9 UTI, 3 with unknown origin, 1 with sepsis.
			SE (3%): 2 patients; 1 with complete liver failure owing to acetaminophen intoxication and liver necrosis, 1 with opioid intoxication and respiratory depression.
			Urological (9%): 6 patients; 5 with urinary retention, 1 with bladder tamponade.

			Pulmonary (27%): 18 patients; 16 with respiratory insufficiency, 1 with atelectasis, 2 with pleural effusion.
			Pain/mobilization (15%): 10 patients.
			Neurological (6%): 4 patients; 1 with altered neurological status, 2 with increase grand mal epileptic seizure, 1 with status epilepticus.
			Other (7%): 5 patients; 1 patient treated with traction prior to final fusion, 1 patient with planned second staged procedure, 3 awaited assistive technology.
			Unknown (7%): 5 patients; 2 with no apparent cause and 3 with missing medical record.
SD **n=9** **Reasons: 20**	13 (IQR: 12-14)	Surgical	Surgical (11%): 1 patient due to screw misplacement.
		Medical	GI (44%): 4 patients; 3 patients with obstipation, 1 with nutrition issue.
			Infection (33%): 3 patients; 1 patient with unknown origin, 2 with pneumonia.
			Pulmonary (22%): 2 patients with respiratory insufficiency due to aspiration pneumonia and pneumonia.
			Cardiac (11%): 1 with supraventricular arrythmia.
			Urological (11%): 1 patient with urinary retention.
			Pain/mobilization (66%): 6 patients.
			Unknown (22%): 2 patients with missing medical records.
SP **n=24** **Reasons: 36**	10 (IQR: 9.8-12.2)	Surgical	SSI (4%): 1 patient, antibiotic.
			Neurological deficit (38%): 9 patients; 1 patient was revised due to screw misplacement, 2 with food drop, 1 with spastic paresis and 5 with radiculitis.
			Surgical (13%): 3 patients; 1 with dura lesion and revision, 1 patient with progression and revision, 1 patient with radiculitis (screw misplacement) and revision.
		Medical	Anemia (4%): 1 patient
			GI (13%): 3 patients; 1 patient with obstipation and 2 patients with abdominal pain, vomitus and nausea.
			Infection (8%): 2 patients; 1 with unknown origin, 1 with UTI.
			SE (4%): 1 patient with CNS depression due to opioids.
			Pain/mobilization (46%): 11 patients (primarily pain).

			Other (8%): 2 patients with planned second stage procedure.
			Unknown (13%): 3 patients with missing medical record.
SK **n =11** **Reasons:** **23**	11 (IQR: 10-11.5)	Surgical	Neurological deficit (9%): 1 patient with dysesthesia in lower extremities and MRI.
		Medical	Anemia (9%): 1 patient.
			GI (36%): 4 patients; 2 with obstipation, 2 with nutritional issues and nausea.
			Infection (18%): 2 patients; 1 UTI and 1 OMI.
			Urological (9%): 1 patient with urinary retention.
			Pulmonary (27%): 3 patients; 1 patient with DVT and peripheral pulmonary embolism, 2 patients with pneumothorax.
			Pain mobilization (100%): 11 patients.
% in the comment column is number of reasons divided by the total number of patients with extLOS within the etiology (>100%); IQR, interquartile range; SSI, surgical site infection; GI, gastrointestinal; SE, side effects; UTI, urinary tract infection; OMI, otitis media infection; MRI, magnetic resonance imaging; DVT, deep vein thrombosis;			

Appendix 5

Reason for revision in the 120 pediatric patients

Reason	n (%)	Type of revision
Implant failure	39 (33)	15 patients with ID; 14 patients with implant loosening; (2 removal, 6 reinstrumentation and 6 reinstrumentation and elongation). 1 patient with implant breakage (removal).
		7 patients with ND; 6 with implant loosening (4 reinstrumentation, 2 removal and rod shortening), 1 rod breakage (removal and reinstrumentation).
		7 patients with CD; 1 with pseudarthrosis (instrumentation), 4 with loosening (2 reinstrumentation, 2 reinstrumentation and elongation), 2 with rod breakage (reinstrumentation).
		5 patients with SP; 2 screw loosening (reinstrumentation), 1 screw breakage (removal), 1 pseudarthrosis (reinstrumentation and elongation), 1 fracture of arcus (reinstrumentation).
		3 patients with SK; 2 rod loosening (reinstrumentation and elongation), 1 screw loosening (reinstrumentation and elongation).
		2 patients with SD; 2 rod breakage (removal and reinstrumentation).
Residual deformity/curve progression	19 (16)	6 patients with ID; 2 patients with adding on (elongation), 2 patients with residual deformity (elongation), 2 patients with curve progression cranial to primary fusion (elongation).
		4 patients with CD; 2 with curve progression after prior hemi epiphysiodesis (elongation). 2 with residual deformity (1 reinstrumentation, 1 elongation).
		3 patients with SP; 2 patients with postoperative slip (instrumented fusion), 1 patient with new spondylolisthesis cranial to previous (instrumented fusion).
		1 patient with SD; curve progression (final fusion).
Implant misplacement/prominence	18 (15)	5 patients with ID; 3 with implant prominence (2 removal and 1 reinstrumentation). 2 patients with implant misplacement (reinstrumentation).
		6 patients with ND; 4 patients with implant misplacement (1 removal and 3 removal and reinstrumentation). 2 patients with implant prominence (removal/shortening of rods).

		3 patients with SP; 2 implant prominence (1 removal and reinstrumentation, 1 removal only), 1 patient with implant misplacement (removal and reinstrumentation).
		3 SK patient; 1 implant misplacement (removal and reinstrumentation), 2 implant prominence (removal and rod shortening).
		1 patient with SD; implant misplacement (removal and elongation).
Infection	14 (12)	3 patients with ID; 1 with early superficial (surgical debridement), 2 with late deep infection (1 removal of hardware, 1 surgical debridement).
		9 patients with ND; 7 patients with early and deep infection (3 with removal and 4 surgical debridement), 2 patients with late and deep infection (1 removal, 1 surgical debridement).
		2 patients with SK; 2 early and deep infection (surgical debridement).
Neurological deficit	13 (11)	4 patients with ID: 2 with complete paralysis (removal and reinstrumentation) and 2 with paresis and dysesthesia (removal and reinstrumentation).
		1 patient with ND; paresis (removal of pedicle screw and rods).
		6 patients with CD: 3 with paresis; (1 reinstrumentation cause of translocation, 1 evacuation of small hematoma, 1 decompression). 2 patients with complete paralysis (1 decompression and evacuation of small hematoma, 1 evacuation of hematoma). 1 patient with missing IOM signal and surgery postponed.
		2 patients with SP: 2 patients with radiculitis (lateral misplaced screw, removal).
Other	10 (8)	4 patients with ID; 1 patient with pain and removal of hardware, 1 patient with breakage of drainage tube at removal, 2 patients with wound dehiscence.
		2 patients with ND; 1 patient with acute bleeding and final fusion postponed avoiding vascular collapse. 1 patient with breakage of drainage tube at removal.
		3 patients with SP: 1 patient with dural tear, 2 patients with pain and removal of hardware and small decompression of nerve rood and 1 with intracorporal fusion for further stabilization.
		1 patient with SK: pain and anterior supporting fusion with cage.
	4 (3)	1 patient with ND; PJF (elongation and osteotomy).

Proximal junctional failure/distal junctional failure		3 patients with SK; 2 with PJF (elongation and correction osteotomies), 1 with DJF (elongation and osteotomy).
Translocation	3 (2)	2 patients with ND: 1 elongation, 1 removal, elongation and halo traction.
		1 patient with SK: removal, elongation and correction osteotomies.

Papers

Paper I

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Neural Axis Abnormalities in Patients With Adolescent Idiopathic Scoliosis: Is Routine Magnetic Resonance Imaging Indicated Irrespective of Curve Severity?

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Objective: Magnetic resonance imaging (MRI)-verified neural axis abnormalities (NAAs) have been described in adolescent idiopathic scoliosis (AIS), and several risk factors have been associated with the presence of NAAs in AIS patients. However, the clinical significance of these findings is unclear. The purpose of the present study was to determine the prevalence of NAAs in a large consecutive cohort of AIS patients and to evaluate the clinical significance of previously proposed risk factors.
Methods: We prospectively included AIS patients referred to a tertiary facility for evaluation. Full-spine MRI scans were performed on all included patients irrespective of curve magnitude or proposed treatment modality. MRI scans were prospectively analyzed by a neuroradiologist and the pathologic findings were confirmed by a second independent radiologist.
Results: NAA was observed in 34 of the 381 patients (8.9%): 32 patients had a syrinx, 1 patient had an arachnoid cyst, and 1 patient had a Chiari malformation. Four patients were referred for a neurosurgical evaluation but none received any neurosurgical treatment. No statistically significant difference was observed between the NAA and non-NAA groups in terms of sex, major curve size, thoracic kyphosis, left thoracic curve, curve convexity, curve progression, or level of pain ($p > 0.05$).
Conclusion: In this prospective study examining the risk factors for NAA in AIS patients, we found that previously proposed risk factors could not predict the MRI outcomes. The finding of an NAA had no clinical implications and we do not support MRI scans as a routine diagnostic modality in all AIS patients.

Keywords: Neural axis abnormality, Adolescent idiopathic scoliosis, Magnetic resonance imaging, Syrinx, Syringomyelia

INTRODUCTION

Adolescent idiopathic scoliosis (AIS) is a common condition in the adolescent population. The diagnosis is traditionally based on an uneventful medical history, a thorough clinical examination and radiographs showing a typical coronal deformity without congenital abnormalities. However, between 2%–12% of patients with a diagnosis of AIS have a neural axis abnormality (NAA).[1,2] These range from small size syrinx to potentially more severe conditions like Chiari malformations, tethered cord or

intramedullary tumors. The NAAs are inherently difficult to predict on clinical examination as the majority of patients present without neurological deficits. Several risk factors have been associated with the presence of NAA. These include juvenile onset of the deformity, male sex, neurologic deficit (i.e., asymmetric superficial abdominal reflexes), atypical curve patterns (left-sided thoracic curves), thoracic hyperkyphosis, rapid curve progression, severe curves, and the presence of pain.[2-10] The majority of studies have focused on NAAs in AIS patients requiring surgery. Since curve magnitude is not a reliable predictor for NAA there is a need for a large-scale study on all AIS patients irrespective of curve size to determine the actual prevalence and the clinical implications. Currently, there is no consensus regarding the role of routine MRI scans in AIS evaluation and the decision is based on local preferences. Additionally, there is a lack of consensus regarding the terminology of NAAs and whether NAAs without neurologic deficit have an increased risk of neurologic complications during deformity surgery.[11-13]

The purpose of the present study was to determine the prevalence of NAA and the role of routine MRI in the clinical evaluation of AIS patients. Furthermore, we aimed to clarify whether clinical or radiographic features could predict the presence of NAAs.

MATERIALS AND METHODS

The study population included all patients referred to a single tertiary spine unit from January 1, 2010 to December 31, 2015 with suspected or known AIS. We included all patients with verified idiopathic scoliosis diagnosed between 10–18 years of age. We excluded patients with congenital anomalies, neuromuscular disorders, pre-existing NAA or any syndrome known to be associated with skeletal deformities. Permission to review patients record without informed consent was obtained from the Danish Patient Safety Authority (No. 3-3013-2059/1) and The Danish Data Protection Agency (No. RH-2017-86).

All patients underwent a thorough medical history and physical examination by one of 5 experienced spine surgeons. Medical charts were reviewed for clinical and demographic variables. The presence of pain was noted as a binary variable.

1. Radiographic Examination

Radiographic assessment was performed with standing posterior-anterior and lateral radiographs as well as total spine MRI. Radiographs were retrieved from PACS in DICOM format and uploaded to an online imaging software KEOPS (S.M.A.I.O, Lyon, France). Measurements included major curve magnitude, right-sided or left-sided main curve, curve type (thoracic, thoraco-lumbar, lumbar or double major), length of curve and thoracic kyphosis. Annual progression rate (APR) was calculated as the difference between major curve size at the last obtained radiograph and the major curve at the first radiograph multiplied with the difference in time between the 2 radiographs; APR = (major curve t_2–major curve t_1) × 12 months/(t_2–t_1) with t_1 and t_2 spaced a minimum of 6 months apart.[14] A progression above 5° was considered significant. Thoracic kyphosis was measured as the Cobb angle between Th5–Th12 and a curvature of more than 30° was considered hyperkyphotic. We defined atypical curves as main thoracic curves with a left-sided convexity.

2. MRI Examination

All patients included in the study underwent MRI with 1.5 or 3.0 Tesla Scanner. In cases where the initial examination was considered pathologic, gadolinium was injected as contrast. All MRI's were analyzed by a neuroradiologist for any NAA. If MRI was conducted outside our hospital the external report and images were acquired. We found inconsistencies between the terminology used to describe syrinx as both "hydromyelia," "dilated central canal," "syringomyelia" and "hydrosyringomyelia" were used interchangeably. We chose to use the term "syrinx" to describe all fluid-filled cavities in the spinal cord. Syrinx diameter was measured in the axial plane on T2 images. Since it is unclear whether a central canal with a diameter of 1–3 mm is pathologic or an anatomic variant, syrinx was classified in 2 groups: insignificant syrinx ≤ 3 mm and significant syrinx > 3 mm.[11] The diagnostic criterion of Chiari I malformation was herniation of the tonsils below the foramen magnum by 5 mm or more.[15] All MRI scans with NAA were analyzed by a second independent radiologist to confirm the diagnosis.

3. Statistical Analysis

Patients were categorized based on MRI findings (NAA group and non-NAA group). Continuous data were tested for normal distribution using histograms and are reported as mean ± standard deviation. For normal distributed data, group comparison between NAA and non-NAA were performed using unpaired t-test. Nonnormally distributed data are reported with median (interquartile range [IQR]). Differences in distribution for categorical data were assessed with Pearson chi-square test of independence or Fischer exact test where appropriate. Multiple lo-

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gistic regression was used to examine the association between the 5 most commonly proposed risk factors and MRI results. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using R ver. 3.2.3 (R Core Team, 2015, Vienna, Austria).

RESULTS

During the study period a total of 563 AIS patients were identified as eligible for inclusion and 381 patients underwent MRI scan corresponding to a 68% inclusion rate (Fig. 1). The mean age at inclusion was 14 ± 2.05 years and 80% were women. Mean major Cobb angle was 39° ± 15.91° and 58% of the curves were thoracic. NAA was observed in 34 of 381 patients (8.9%). Thirty-two patients had a syrinx, 1 patient had an arachnoid cyst and 1 patient had a Chiari 1 Malformation without syrinx. Four patients with syrinx were referred to a neurosurgeon and 1 patient was consulted with the Neurosurgical Department. The patient with an arachnoid cyst was seen by our Orthopedic Tumor Department and is being followed with MRI every year. The patient with a Chiari malformation was referred to the Neurosurgical Department and a neuropediatrician due to headache. No hindbrain decompression was indicated. None of the NAA patients received any neurosurgical intervention and none of the patients presented with major clinical neurological abnormalities. Six patients with syrinx obtained serial imaging studies with MRI and none of the MRI scans showed signs of progression. The 6 patients referred or consulted with the Neurosurgical Department had a maximal syrinx diameter of 3.5 mm (IQR, 2–4) and the median span was 4.5 (IQR, 3–8) vertebral length. Furthermore, two patients had a follow-up MRI with contrast to rule out tumor pathology.

Including all the patients with syrinx, the median syrinx maximal diameter was 2 mm (IQR, 1–4). The median span of syrinx was 4.5 vertebral levels (IQR, 2–7.25) and 84% were in the thoracic spine (Fig. 2). Nine patients (2.4%) presented with a significant syrinx > 3 mm at the largest axial diameter. In this group the median syrinx size was 4 mm (IQR, 4–5) and median length was 6 vertebral levels (IQR, 3–6). Difference of other measurements between the 2 syrinx groups was without significance (p > 0.05) (Table 1).

There was no statistically significant difference between the NAA and non-NAA groups in terms of sex, major curve size, thoracic kyphosis, curve type, left thoracic curve, curve progression or level of pain (p ≥ 0.085) (Table 2). Median age was 14.2 ± 2.0 and 13.5 ± 2.0 years in the non-NAA and NAA groups, respectively (p = 0.043).

To explore the applicability of clinical and radiographic predictors, patients were categorized as previously described (Fig. 3). We found no difference between NAA and non-NAA groups in terms of the presence of pain, thoracic kyphosis > 30°, major curve > 50°, APR > 5° and left thoracic curve (p ≥ 0.277). The multiple logistic regression showed no significant change in the risk of NAA for either decreased age (odds ratio [OR], 0.83; 95% confidence interval [CI], 0.69–1.01), male sex (OR, 1.05; 95% CI, 0.40–2.79), increased major curve (OR, 1.01; 95% CI,

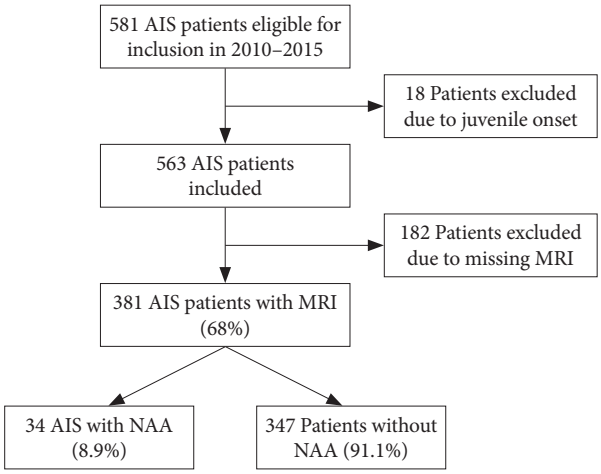

Fig. 1. Inclusion process. AIS, adolescent idiopathic scoliosis; MRI, magnetic resonance imaging; NAA, neural axis abnormality.

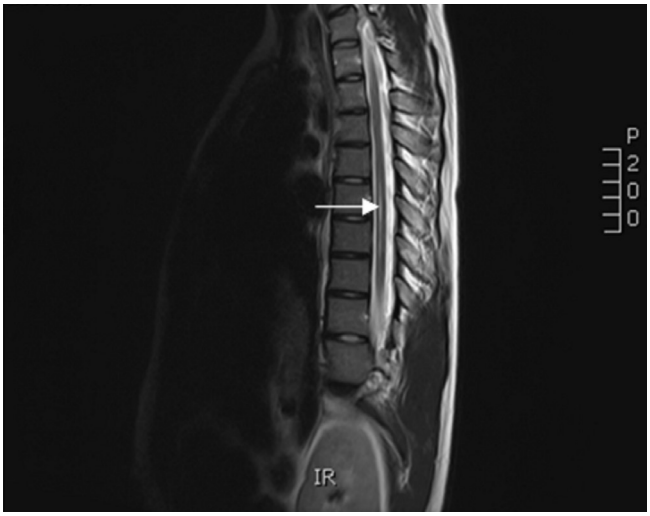

Fig. 2. Magnetic resonance imaging with 1.5 Tesla Scanner, sagittal T2-weighted from a patient with a thoracic syrinx (arrow).

Table 1. Comparison between the significant syrinx and the insignificant syrinx

Variable	Syrinx > 3 mm (n = 9)	Syrinx ≤ 3 mm (n = 23)	p-value
Age at referral (yr)	13 (12–15)	14.0 (11.5–15.0)	0.899
Sex			
Female	6 (66.7)	20 (87)	
Male	3 (33.3)	3 (13)	0.319
Syrinx diameter (mm)	4.0 (4–5)	2.0 (1–2)	
Syrinx length (mm)	6.0 (3–6)	4.0 (2–8)	0.553
Syrinx location			
Cervical and thoracic	0 (0)	3 (13)	
Cervical, thoracic, and lumbar	0 (0)	1 (4.3)	
Thoracic	9 (100)	18 (78.3)	
Thoracic and lumbar	0 (0)	1 (4.3)	
Major curve at referral (°)	41 (32–58)	35.0 (29.0–54.5)	0.737
Thoracic kyphosis (°)	25 (15–33)	23 (13–34)	0.644
Levels fused (n)	12.5 (11.8–13.0)	10.5 (10.0–12.0)	0.083

Values are presented as median (interquartile range) or number (%).

Table 2. Comparison between proposed risk factors and magnetic resonance imaging results

Variable	Non-NAA (n = 347)	NAA (n = 34)	p-value
Age (yr)	14.2 ± 2.0 (10–19)	13.5 ± 2.0 (10–17)	0.043
Sex			0.868
Female	276 (79.5)	28 (82.4)	
Male	71 (20.5)	6 (17.6)	
Major curve at referral (°)	39.0 ± 15.8 (10.0–97.0)	40.5 ± 16.9 (10.0–75.0)	0.614
Major curve at follow-up (°)	48.4 ± 18.8 (2.0–99.0)	49.2 ± 21.1 (10.0–93.0)	0.818
Annual curve progression (°)	4.4 ± 7.0 (-15.3 to 57.7)	4.8 ± 5.3 (-4.3 to 21.0)	0.686
Left thoracic curve			0.644
Yes	14 (4)	2 (5.9)	
No	333 (96)	32 (94.1)	
Curve length (No. vertebrae)	6.3 ± 1.4 (3–13)	6.9 ± 1.5 (4–11)	0.035
Thoracic kyphosis (°)	27.6 ± 13.0 (0–73)	24.9 ± 13.3 (1–50)	0.262
Follow-up time (mo)	28.2 ± 17.7 (1–90)	23.7 ± 13.6 (6–53)	0.085
Pain[a)]			0.697
No	101 (32.3)	9 (27.3)	
Yes	212 (67.7)	24 (72.7)	
Surgery during follow-up			1.000
No	176 (50.7)	17 (50)	
Yes	171 (49.3)	17 (50)	
Brace treatment during follow-up			1.000
No	179 (51.6)	18 (52.9)	
Yes	168 (48.4)	16 (47.1)	

Values are presented as mean ± standard deviation (range) or number (%).
NAA, neural axis abnormality.
[a)]Missing data: non-NAA group, 34; NAA group, 1.

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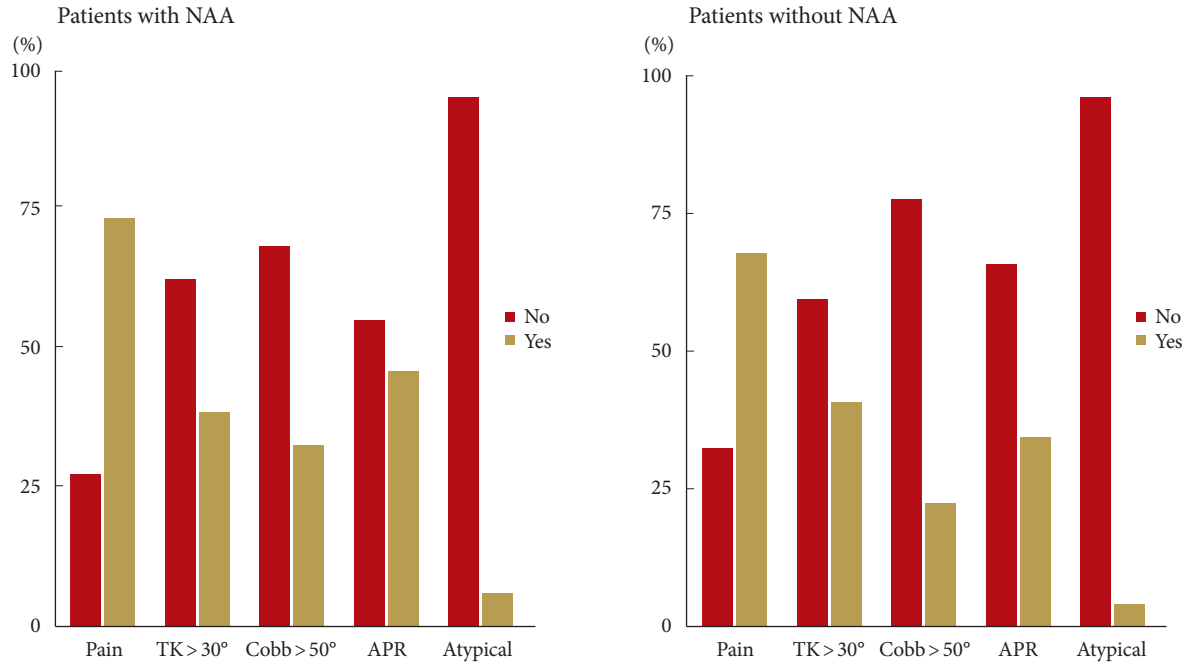

Fig. 3. Proposed risk factors for neural axis abnormalities (NAAs) in adolescent idiopathic scoliosis. TK, thoracic kyphosis; APR, annual progression rate; Atypical, left side thoracic curve.

0.98–1.03), thoracic kyphosis > 30° (OR, 1.01; 95% CI, 0.48–2.13), or atypical curve (OR, 1.69; 95% CI, 0.35–8.19).

A total of 188 underwent deformity surgery in the follow-up period and 183 had a preoperative MRI scan. In this group we found similar results with no difference between the NAA and non-NAA group in terms of major curve size, thoracic kyphosis, left thoracic curve, length of curve, annual curve progression or pain ($p > 0.086$). Seventeen of the patients with NAA underwent deformity surgery and 12 patients had confirmed intraoperative monitoring (IOM) including motor evoked potential and somatosensory evoked potential. Neuromonitoring changes occurred in 2 patients in the insignificant syrinx group and none in the group with significant syrinx. The amplitude drop in one of the patients improved with elevated blood pressure. The other patient lost signal to both legs, which in part came back when the blood pressure was elevated. Furthermore, a wake-up call at the end of surgery ensured that no neurologic complication had occurred. None of the patients experienced any peri- or postoperative neurological complications. One patient experienced severe pain both pre- and postoperatively. The patient had a persistent ventriculus terminalis in the conus medullaris with an axial diameter of 4 mm and a vertebral span of 2 and was referred to our Pain Management Unit without improvement during the follow-up period.

A total of 182 patients did not have an MRI according to protocol. Compared to the MRI-group these patients had a significantly smaller curve at first visit, older age and less likely to receive brace or surgical treatment. There was not statistically sig-

Table 3. Comparison between AIS patients without MRI and AIS patients with MRI

Variable	AIS patients without MRI (n = 182)	AIS patients with MRI (n = 381)	p-value
Age (yr)	14.8 ± 2.1	14.2 ± 2.0	< 0.001
Sex			0.336
Female	138 (75.8)	304 (79.8)	
Male	44 (24.2)	77 (20.2)	
Brace treatment			< 0.001
Yes	37 (20.3)	184 (48.3)	
No	145 (79.7)	197 (51.7)	
Surgery			< 0.001
Yes	5 (2.7)	188 (49.3)	
No	177 (97.3)	193 (50.7)	
Major curve (°)	26.3 ± 11.9	39.1 ± 15.9	< 0.001
Left thoracic curve			0.310
Yes	12 (6.6)	16 (4.2)	
No	170 (93.4)	365 (95.8)	

Values are presented as mean ± standard deviation or number (%).
AIS, adolescent idiopathic scoliosis; MRI, magnetic resonance imaging.

nificant difference in terms of sex and atypical curve type between the 2 groups (Table 3).

DISCUSSION

The need for routine preoperative MRI to detect subclinical NAA in patients with AIS has been widely investigated, but data are lacking on AIS patients irrespective of treatment modality. Frequently proposed indications of NAAs are early age of onset, male sex, thoracic hyperkyphosis, atypical curve patterns, rapid curve progression and the presence of pain. We aimed to assess whether these clinical and radiographic factors could predict NAA. Additionally, we aimed to determine the prevalence of NAA in a wide cohort of AIS patients irrespective of treatment modality. The overall prevalence of NAA in pediatric spine deformity ranges from 2%–54% depending on study design, inclusion criteria and the definition of NAA.[1,8] Studies on AIS patients report a lower prevalence between 2%–12%[1,2] which is in line with the prevalence in the current study of 8.9%. To our knowledge, this is the largest MRI study on AIS patients irrespective of major curve size, treatment strategy, curve progression, sex or convexity. We could not reproduce the findings of previous studies proposing clinical and radiographic predictors of NAA and question the clinical applicability of these. We assessed a series of predictive parameters, which leads to a risk of type 2 error due to lack of sample size. However, these predictors were originally suggested in studies with considerably smaller sample sizes and larger patient heterogeneity. Therefore, we conclude that the current level of evidence suggests that they have limited clinical applicability and should not be applied in daily clinical practice until further substantiated.

The prevalence of NAAs is often found to be appreciably higher in both congenital, infantile and juvenile scoliosis.[16,17] Benli et al.[3] included 104 surgically treated patients over a period of 12 years. None of the adolescent patients (n = 55) had NAAs but in the juvenile group they found a prevalence of 14.3%.[3] The authors found early onset of scoliosis and pain, to be predictive of NAA. In our study, we found a modest difference between the NAA and non-NAA groups in terms of age, but the difference was small and we do not consider it clinically relevant. Importantly, this association was not present when adjusted for additional proposed risk factors. Diab et al.[6] included 2,206 surgically treated patients from the Prospective Pediatric Scoliosis Study and found significant risk factors for NAA to be thoracic hyperkyphosis > 40° and juvenile onset. Nevertheless, there was a marked difference between patients with and without MRI in terms of these 2 risk factors, indicating a preselected group of patients. Former studies evaluating risk factors for NAAs in scoliosis conclude conspicuously different results.[2,6,18] This might be explained by different study methods, patient populations and lack of identical terminology.

There is inconsistency regarding the terminology of fluid-filled cavities in the spinal cord as the terms syringomyelia, hydromyelia, dilated central canal, and the hybrid term syringohydromyelia are used interchangeably.[19] Also, the debate is ongoing about the true etiology and prevalence. Despite the general disagreement on the terminology and etiology, numerous cavities are found with the increasing use of MRI. When applying a broad definition of syrinx, one study found a prevalence of 1.5% of accidental findings.[12] The term idiopathic syrinx is used when there is no association between the syrinx and any known lesion such as neoplasm, traumatic injury, infection or congenital malformation.[20] Most studies[11,12] suggest that idiopathic syrinx are rarely symptomatic, remains stable or decrease in size and could be considered an normal variation, which is in accordance with the syrinx found in our cohort. Magge et al.[20] evaluated idiopathic syrinx in a pediatric population and concluded that syrinx size did not correlate with the major curve or the outcome in patients with idiopathic scoliosis. Our findings are akin with these results in terms of syrinx size, curve size and syrinx progression. Jones[11] suggest that in the absence of underlying pathology, there is no justification in labeling a central canal with a diameter of 1–3 mm, pathologic. Applying these guidelines, we found a prevalence of only 2.9% with "true" pathology. These findings are in line with several studies evaluating only surgically treated AIS patients[1,21] and give weight to the hypothesis of the relatively high prevalence we found is due accidental findings of idiopathic syrinx.

Syrinx and other NAAs present challenges in the surgical correction of spinal deformity. At present, it is difficult to deduct whether a surgical treatment of the syrinx can stop or reverse the scoliosis in some cases. Sengupta et al.[22] reported on 16 patients with syrinx and scoliosis with absence of major neurological deficit. All patients underwent hindbrain decompression and 6 patients experience improvement or arrest in their major curve. Similarly, studies on patients with scoliosis and Arnold Chiari Malformation type 1 undergoing posterior decompression found older children and adolescent with larger curves, kyphosis and double curves more likely to progress. In younger patients without these features the curve often stabilizes and occasionally resolves completely.[23]

Another surgical aspect is the risk of neurologic complica-

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tions in patients with NAAs and scoliosis undergoing deformity surgery. The finding of a preexisting NAA could alter the surgical approach. In the current study, however, there were no cases of preoperative MRI's changing the planning of surgery. Some studies suggest increase risk of neurologic damage due to spinal cord distraction and instrumentation of the spine.[13,24] Nevertheless, newer studies report no increase in complication rate when surgically addressing only the scoliosis and not the NAAs. Wang et al.[25] reported it safe to leave syrinx untreated when patients were without neurologic symptoms and the correction rate was kept according to the bending film. Samdani et al.[26] reported on the outcome of patients with syringomyelia undergoing spine deformity surgery and found that syrinx size had an impact on outcome. Large syrinx >4 mm were fused longer had a higher estimated blood loos and less correction. Moreover, they found less reliable IOM but no increase in neurologic sequela. We were not able to reproduce these findings and found no increased risk of labile IOM in patients with increased syrinx size. More importantly, we found no increased risk of neurologic sequela in patients with NAAs undergoing deformity surgery. Thus, we find it safe to operate AIS patients with moderate NAAs and lack of major neurologic findings prior to surgery.

Our study has several limitations. Approximately one third of the patient population was eligible for inclusion but did not have an MRI. The non-MRI group had smaller curves, where older and generally did not receive any treatment. As these patients were low-risk it is likely that the treating physician neglected to do MRI as protocolled. Hence, we may have overestimated the prevalence of NAAs in the current study given that age was the only positive predictor of NAAs in this study cohort. Moreover, the markedly lower age in the MRI group compared with the non-MRI group supports this theory and could indicate a potential age effect. We found a relatively large curve size at referral. We have previously showed that in a public health care system without school screening, patients referred from general practitioners have larger curves (median, 35°) compared to systems with school screening.[27]

Due to the retrospective collection of the clinical data, the precision of some of the clinical variables is limited. The medical reports showed inconsistency in evaluating the superficial abdominal reflexes as well as a systematic description of pain. This is a weakness since a number of studies have shown a correlation between asymmetrical superficial abdominal reflexes and NAA.[2,5,9] The presence of pain was not systematically registered and our relatively high prevalence of reported pain could be an overestimation of "real pain" (in contrast to conditions such as muscle fatigue).

Essentially, our findings provide a representative prevalence of NAA in AIS patients due to the broad inclusion criteria irrespective of proposed treatment modality, sex, curve size, or convexity. Our results have broad applicability to all physicians managing AIS patients and underline that routine MRI scans in AIS patients may not be indicated and have limited clinical consequence.

CONCLUSION

In this study, a large AIS cohort underwent MRI examination irrespective of treatment modality. We found NAA in 8.9% of patients but found no clinical implications for the patients. Applying more conservative definitions of NAA, we found a prevalence of only 2.9%. The results of our study do not support the hypothesis of previously proposed radiographic and clinical parameters as predictors for NAAs. Furthermore, we found no increased neurologic complications in AIS patients with modest NAA undergoing deformity surgery. As a result, MRI scans does not appear to be crucial as a routine diagnostic modality in all AIS patients. We suggest that MRI should be reserved for patients with neurological symptoms, relevant comorbidities or atypical symptoms (e.g., severe pain).

CONFLICT OF INTEREST

Benny Dahl received institutional grants from K2M and MEDTRONIC outside the submitted work. Martin Gehrchen received institutional grants from K2M and MEDTRONIC outside the submitted work. Sidsel Fruergaard received institutional grants from MEDTRONIC. Søren Ohrt-Nissen received institutional grants from K2M outside the submitted work. The other authors have nothing to disclose.

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Paper II

Length of Stay, Readmission and Mortality after Primary Surgery for Pediatric Spinal Deformities: A 10-year Nationwide Cohort Study

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Abstract

Background context: Extended length of stay (extLOS) and unplanned readmissions after first time pediatric spinal deformity surgery are a considerable challenge to both the patient and the healthcare system. To our knowledge, only a limited number of nationwide studies reporting short-term comorbidity with complete follow-up exist.

Purpose: The purpose of this study was to identify the postoperative complications leading to extLOS, readmissions and mortality within 90 days after surgery. Furthermore, to identify risk factors for readmission.

Design: Retrospective national cohort study.

Patient Sample: A nationwide registry study including all pediatric spinal deformity patients (≤ 21 years of age) undergoing primary surgery from 2006 through 2015 (n=1310).

Outcome measures: Reasons for extLOS and 90-day readmissions as well as mortality risk.

Methods: Patients were identified by procedure and diagnosis codes in the Danish National Patient Registry (DNPR). From the DNPR, data on length of stay (LOS), readmissions and mortality within 90 days were retrieved. Patients were categorized in six groups according to etiology. Reasons for extLOS and readmission were collected from medical records and discharge summaries.

Results: For the 1310 patients, the median LOS was 8 days (interquartile range 7–9). Etiologies were idiopathic deformity (53%), neuromuscular deformity (23%), congenital/structural deformity (9%), spondylolisthesis (7%), Scheuermann's kyphosis (5%) and syndromic deformity (3%). A total of 274 (21%) patients had extLOS and most common reason was pain/mobilization issues but with considerable variation between etiologies; Scheuermann's kyphosis (91%), idiopathic (59%), syndromic (44%), spondylolisthesis (38%) and congenital (30%). Pulmonary complications were the primary reason for extLOS in the neuromuscular group (22%). The 90-day readmission rate was 6%; 67% of readmissions were medical, mainly infections unrelated to the surgical site (23%); 33% of readmissions were surgical and 14% of patients required revision surgery. Neuromuscular deformity, spondylolisthesis, Scheuermann's kyphosis and LOS>9 days were independent risk factors for readmission; OR 4.4 (95% CI: 2.2–9.1, p<0.01), OR 3.0 (1.1-8.0, p=0.03), OR 4.9 (1.7–13.6, p<0.01) and OR 1.8(1.0-3.1, p=0.04), respectively. The 90-day mortality risk was 0.4%.

Conclusions: In this nationwide cohort, pain/mobilization issues were the most common reason for extLOS. The most common reason for readmission was infection unrelated to the surgical site. Readmission after pediatric spinal surgery is related to the etiology and increased focus on patients operated for neuromuscular deformity, spondylolisthesis and Scheuermann's kyphosis is warranted.

Keywords: pediatric spinal deformity; complication; readmission; mortality; scoliosis; kyphosis; congenital scoliosis; Scheuermann's kyphosis; neuromuscular scoliosis; idiopathic scoliosis

Introduction

Pediatric spinal deformity (PSD) consists of a complex group of patients, ranging from otherwise healthy children to children with severe disabilities[1]. The deformities are typically classified according to age of onset, etiology and radiological characteristics[2]. Patients with severe deformities may have marked disability, and in these cases surgical correction is often warranted[3]. In recent years there has been an increase in the number of surgical procedures for pediatric deformities[4]. Concurrently, we have seen improvement in development of surgical technologies, perioperative optimization and focus on postoperative rehabilitation[5–8]. The surgical procedures can vary substantially according to severity, etiology and type of curve. As a result, patients may have different risk of complication and mortality. In the United States, length of stay (LOS) and unplanned readmissions are considered a proxy for complications and quality of care[9–11]. Some studies show that readmission- and mortality risk are higher in spinal deformities secondary to neuromuscular, congenital or syndromic diseases [1,4,12–18]. However, previous studies have been limited to databases with input from only a sample of hospitals, and with incomplete follow-up [12,13,17,19–21]. With the increasing incidence of PSD surgery, the recognition of short-term morbidity and readmission patterns is critical for optimal patient counseling and quality of care. The administrative databases in Denmark enable research on a complete nationwide cohort of patients with PSD. The purpose of this study was to identify the postoperative complications leading to extended LOS (extLOS), readmissions and mortality within 90 days. Furthermore, to identify risk factors for readmissions.

Methods

This was a retrospective nationwide cohort study on a consecutive series of pediatric patients undergoing first time spinal deformity surgery from 2006 through 2015.

Settings

All Danish citizens have a personal, unique social security number, which enables individual tracking of patients and linkage between all national health registries. In this way, all contacts within the health care system, including private hospitals, are registered. The National Health Service is a tax-financed universal healthcare system serving all Danish citizens. This guarantees an unfettered access to hospitals, as well as free visit to specialist and outpatient clinics.

Data Source

A complete, nationwide follow-up on all admissions is possible since all hospitals must report to the Danish National Patient Registry (DNPR) to receive reimbursement. The DNPR provides nationwide, longitudinal description of all inpatient hospitalizations in Denmark since 1977 and all outpatient and emergency room visits to hospital clinics since 1995. For each patient visit, one primary and optional secondary diagnosis codes according to the International Classification of Diseases (ICD)[22] are recorded. The DNPR has been validated for epidemiological research in Denmark[23]. From DNPR, data on LOS, readmissions within 90 days and mortality were retrieved.

Study population

All patients ≤ 21 years of age at time of surgery, operated between January 1, 2006 and December 31, 2015, were identified via the DNPR. Patients were identified using procedure codes KNAG/KNAT/KNAK (Appendix A) and a concurrent relevant diagnosis code (Appendix B). Patients were then categorized according to etiology: idiopathic deformity (ID), congenital/structural deformity (CD), neuromuscular deformity (ND), syndromic deformity (SD), spondylolisthesis (SP), and Scheuermann's kyphosis (SK). All patients with unspecific diagnostic coding (e.g. DM419 scoliosis) had their medical record reviewed for exact etiology and were classified according to the recently suggested classification system for early onset scoliosis (EOS)[24]. The date of the first deformity surgery in the inclusion period was defined as the index procedure. We excluded all patients who underwent spinal surgery between 1995 and 2006, to ensure only first time PSD surgery was included. Patients with concurrent cancer and/or fractures were excluded from the study.

Covariates

Charlson comorbidity index (CCI) was calculated from all in- and outpatient contacts registered before the index procedure in the DNPR [25]. This is a validated method to calculate CCI score[26]. We classified the patients according to three levels of CCI score: low (CCI score of 0), medium (CCI score of 1 or 2), or high (CCI score ≥ 3).

Outcome variables

LOS was computed as postoperative nights spend in hospital, including transfer to other departments/hospitals until discharge. For each etiology, the cut-off for extLOS was set as above the 75th percentile[9,27]. Readmission was defined as a minimum of one overnight stay in any department/hospital nationwide. Only unplanned readmissions within 90 days, with a potential relation to the index procedure, were included in the final analyses (e.g. allergic reaction to dietary product was excluded).

Medical Records

Medical records of all patients with extLOS were reviewed for in-hospital complications. In 4% of patients with extLOS, the medical record was missing. We retrieved discharge summaries for patients readmitted within 90 days. Reasons for readmission and extLOS were categorized as either surgical or medical[28,29]. Surgical reasons were; surgical site infection (SSI), neurological deficit or surgical complication including revision. Medical reasons were; anemia, infection unrelated to surgical site, gastrointestinal (GI), side effect from medication, pulmonary, cardiac, neurological, urologic/nephrotic and pain/mobilization issues, other and unknown. In case of multiple reasons for extLOS and readmission, only the main reason was included in the statistical analysis. The main reason for extLOS was decided by the primary author and if in doubt discussed with the author group. The medical records of patients deceased within 90 days were reviewed to determine the cause of death.

Statistical analysis

Data distribution was assessed using histograms. Continuous data are presented as means with standard deviation (SD) or medians with interquartile range (IQR). Categorical data are presented as actual

number (%). Risks are calculated as patients with outcome/total number of patients. Readmission to any type of department within 90 days of discharge were analyzed for risk factors using logistic regression. In analysis of outcomes, risk factors were assessed using uni- and multivariable models and reported as odds ratios (ORs) with 95% confidence intervals (CI). Variables included age, etiology, length of stay and sex. C-statistics were used to determine the discrimination of the logistic regression and the Homer-Lemeshow test was used to assess the goodness of fit. Statistical significance was defined as $p < 0.05$. All analysis was performed using R version 3.6.2 (R Core Tam, 2015, Vienna, Austria) and the packages DescTools (Andri Signorell et al.), ggplot2 (Hadley Wickham et al.), wesanderson (Karthik Ram et al.).

Ethics

No ethical approval was necessary due to the non-interventional study design. Permission to store and review data without prior informed consent was obtained from the Danish Data Protection Agency (no. RH-2017-86) and the Danish Patient Safety Authority (no. 3-3013-2059/1).

Results

We identified 1377 eligible patients with relevant procedure and diagnostic codes in DNPR from 2006–2015. A total of 53 patients were excluded because of previous spinal surgery and 14 excluded due to miscoding (Fig. 1), leaving 1310 patients for primary analysis (Table 1). Distribution of etiology; ID (53%), ND (23%), CD (9%), SP (7%), SK (5%) and SD (3%). The majority (98%) of the patients had surgery at one of four tertiary spine units. The remaining patients, primarily patients with SP, were treated at smaller orthopedic departments (1%) or at private hospitals (1%). The overall number of PSD surgeries increased in the study period from 105 procedures in 2006 to 191 procedures in 2015 (82% increase). Median LOS decreased from 9 days in 2006 to 7 days in 2015 whereas readmission risk increased from 6% in 2006 to 7% in 2015 (Fig. 2 and 3).

Extended length of stay

Mean LOS during index admission was 9.1 days (SD: 11.0) and median LOS was 8 days (IQR: 7–9). Overall, 274 (21%) patients had extLOS. The primary reason for extLOS was surgical in 15% and medical in 85% of patients. The most common reason for extLOS was pain/mobilization issues (44%) followed by pulmonary (10%) and GI (9%) complications. In several patients, there was more than one reason for extLOS and in total we registered 465 reasons. For a detailed description see Appendix C. The reason for extLOS varied across etiologies as illustrated in Fig. 4.

Readmission risk

Readmission risk was 3% (36/1310) within 30 days and 6% (75/1310) within 90 days. Overall, surgical readmissions accounted for 33% and medical readmissions 67%. The most frequent reason for readmission was infections unrelated to the surgical site (23%), GI related (19%) followed by SSIs (13%). The surgical and medical readmissions are described in table 2. An etiology of ND, SP and SK were significantly associated with readmission in the multivariable analysis; OR=4.4 (95%CI: 2.2–9.0, $p<0.0001$), OR=3.0 (95%CI: 1.1-8.0, $p=0.03$) and OR=4.9 (95%CI: 1.7–13.6, $p<0.01$). Furthermore, “all etiology LOS”

above the 75 percentiles (LOS≥9 days) showed to be an independent risk factor 90-day readmission with OR=1.8 (95%CI: 1.0-3.1, p=0.04). In the univariate logistic regression, a significant increased OR was seen in patients with medium and high CCI score, OR=2.4 (95% CI 1.4-4.0) and OR=4.8 (95% CI 2.2-10.5), respectively. However medium and high CCI score did not remain statistically significant in the subsequent multivariable analysis (Table 3).

Mortality

The 90-day mortality risk was 0.4% (n=5) and all patients had ND. Patient 1 died of acute liver failure possibly because of liver ischemia and acetaminophen intoxication. Patient 2 had a long recovery due to pneumonia and SSI requiring revision. The patient died 65 days postoperatively of unknown reason. Patient 3 had a postoperative period without complication and died after 85 days outside hospital units. Patient 4 died two days postoperatively from respiratory failure possibly due to aspiration pneumonia. Patient 5 died 33 days postoperatively of respiratory failure.

Discussion

This study reports three major findings. First, we found a decrease in LOS over a ten-year period and that pain/mobilization issues were a major challenge leading to extended LOS in the early postoperative period (Fig. 4). Secondly, the 90-day readmission rate was 6% and almost half of the readmissions occurred within 30 days. An etiology of ND, SP and SK were independent risk factors for readmission. Finally, we found a 90-day mortality rate of 0.4% — all patients with ND.

Another Scandinavian study has recently reported on the development of PSD surgery in a nationwide study[4]. The present study supports some of their findings and adds some valuable information. First of all, the average length of stay decreased during the study period and an increase in the surgical activity was observed in both studies. However, our study adds important information regarding reasons for extended length of stay, as well as a complete 90-day readmission risk and reasons for readmission, missing in the previous study.

Extended length of stay

The overall median LOS was 8 days and decreased from 9 to 7 days within the ten-year study period. Compared to most other large population-based studies, the reported LOS is relatively high[14,30–34], although comparable with Heideken et al. (median LOS of 9 days (IQR: 8-11))[4]. Likely, the variations in LOS could be attributed to the differences in healthcare systems. In the present study a total of 274 patients had extLOS, with pain and mobilization difficulties being the main reasons for extLOS across etiologies. This underlines the importance of pain management and early mobilization as previously shown in adult spinal deformity patients[28]. The second most common reason was GI issues, mainly nausea and obstipation. Studies in both adults and children report that postoperative ileus after spinal deformity surgery is frequent and most likely results from the considerable surgical stress[35–37]. The heterogenic study population led us to determine the extLOS according to etiology. Pain/mobilization issues were especially seen in patients with ID and SK whereas patients with CD and SP had a high percentage of neurological deficits. These

findings are in accordance with a study from the Scoliosis Research Society's (SRS) morbidity and mortality database reporting that neurological deficits are primarily seen in patients undergoing surgery for dysplastic SP and congenital kyphosis[38]. Furthermore, our study shows that patients with ND are more susceptible to infections and pulmonary complications, as seen in previous studies[13,31]. These patients generally have increased LOS, more postoperative complications and increased revision risk[1,4,39]. Our cohort consist of few patients with SD and extLOS (n=9). Their reasons for extLOS were primarily pain and GI symptoms. A recent study has shown an increased risk of complications in these patients compared to patients with ID, especially regarding neurological deficit, infection and procedural complication[14]. We could not reproduce these findings, possibly due to a small population sample.

In total, 6% of the patients had an unknown reason for extLOS when reviewing their medical records. These findings support the theory by Krell et al. that variation in extLOS may not be attributable to patient illness or complications but moreover represent different practice style and evolution over time[9]. However, we believe that extLOS can serve as a surrogate of complications and increased attention should be payed because of the potential strain for both patients and the health care system. We therefore suggest an increased focus on efficiency of care such as adoption of enhanced recovery pathways with opioid sparring pain management and strict bowel regimen. Enhanced recovery principles have shown promising results in the adolescent idiopathic scoliosis (AIS) populations. Studies report up to 50% reduction in LOS without comprising patient safety in terms of complications and readmissions[6,7,40].

Readmission risk

We found 90-day readmission risk of 6% and readmissions occurring more frequently in patients with ND, SP, and SK compared to the other etiologies. Our findings are in line with previous register studies reporting 90-day readmission rate of 6-8% for all patients with PSD[18,41]. In our study, the readmission risk varied according to etiology (Table 2) and as expected was higher in patients with ND. This corroborate previous studies reporting generally lower readmission rates in ID compared to more complex pathological conditions[13,17,33,42]. Surprisingly, our study also revealed an increased risk of readmission in pediatric patients with SP and SK. These patients are generally not expected to have severe comorbidities or increased risk of short-term morbidity. However, a large register study by Roddy et al. found similar results in terms of 90-day readmission risk. Furthermore, they found male sex, ND, CD and SK to be individual risk factors for readmission[18]. Information on complications and readmission risk for pediatric SK and SP is sparse. Our study found increased odds of readmission and the reason for readmission was primarily surgical related. These results may have implications for guidance of practice improvement e.g. nationwide introduction of uniform pathway of care. We did not find increased odds of readmission in patients with high CCI score in the multivariable logistic regression analysis. Lastly, we found extLOS to be an independent predictor of readmission in line with a register study of 13,387 patients with PSD[18] and 1286 patients with AIS[33]. These results support the hypothesis that extLOS is

associated with hospital-acquired infection and/or complications causing frailty in the first discharge period with a concomitant increase in readmission risk. Moreover, we found the most common reason for readmission was infections unrelated to surgical site and GI issues (Table 2). These findings are in line with previous studies reporting primarily wound complication, infection, GI and pulmonary issues as primary reasons for readmission[17,18,41]. This could suggest that close attention to postoperative nutrition, opioid treatment, and bowel regiments is important to minimize readmission risk. In addition, patients with ND are prone to acute respiratory decompensation due to infections, aspiration and impaired secretion clearance. Therefore, these patients need additional attention and postoperative optimization in terms of early mobilization, pulmonary physiotherapy and careful opioid treatment to avoid aspiration complications[43]. Again, these results indicate increased focus on adaption of enhanced recovery pathways including opioid sparring regimens.

Mortality

The current study reports an overall mortality risk of 0.4% within 90-days of primary PSD surgery. However, all the patients who died had ND hence the neuromuscular mortality risk was 1.7%. Previous studies have reported risk ranging from 0.1-1.7%[4,15,44]. Our results are in line with the nationwide study by Heideken et al., reporting a 90-day mortality risk of 0.5% and neuromuscular mortality risk of 1.3%[4].

Strengths and Limitations

This study is based on a large, up-to-date, nationwide consecutive pediatric cohort. Compared to previous studies, this cohort had almost complete follow-up and detailed information regarding reasons for extLOS, readmissions and mortality through medical record review.

The major limitations of this study are those of registry reporting; as this is an observational study, we can only report associations and not causality. Our data were obtained from the DNPR, which has shown varying reliability in terms of specific diagnostic coding [45,46] but >99% overall reliability regarding somatic admissions[22]. We only reviewed medical records from patients with LOS ≥9 days, readmission, and/or death within 90 days. A case of surgical complication during primary admission with LOS <9 days and without a diagnostic code of revision would be missed. However, the possibility that a patient with major surgical complication would be discharged within 8 days without a diagnostic code is unlikely. To ensure high granularity, we obtained discharge summaries on all patients with 90-day readmission and full medical records in all patients with LOS ≥ 9 days and 90-day mortality. This was done to ensure best available information on incidence and pathophysiological mechanism[47]. We used CCI as a measure of comorbidity burden in our cohort. The CCI was originally designed to predict 1-year mortality and validated in the adult population[48] and is an easy tool to investigate end points such as survival in large register studies[49]. However, its generalizability implies low specificity[50,51] and to our knowledge CCI has never been validated in a pediatric setting with revision as outcome. In addition, coding trends have evolved to a greater detail during the study period, which can lead to misclassification bias. This is also reflected in 16% of the patient with an unspecific diagnostic code or more

than two conflicting codes (e.g. idiopathic and neuromuscular scoliosis). However, we did confirm all unspecified diagnostic coding (Appendix B) according to the recently suggested classification system[24]. This is potential conflicting since the implementation of this classification system extend beyond the inclusion period. Finally, we recognize the lack of pre- and perioperative data that are important risk factors for postoperative morbidity.

Perspectives and conclusion

This study has uncovered some potential challenges to ensure further improvements in PSD surgery. Our findings suggest an increased focus on pain/mobilization management including GI regimens. Many areas of the orthopedic surgery field have introduced enhanced recovery protocols and reduced the length of stay without increasing the postoperative morbidity[52,53]. The most common reason for readmission in our study was preventable and multidisciplinary initiatives to reduce these readmissions should be applied.

In conclusion, this nationwide cohort reports pain/mobilization issues as the most common reason for extLOS. The most common reason for readmission was infection unrelated to the surgical site. Readmission after pediatric spinal surgery is related to the etiology and increased focus on patients operated for neuromuscular deformity, spondylolisthesis and Scheuermann's kyphosis is warranted.

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Table 1. Demographic data on the 1310 pediatric patients undergoing first time spinal deformity surgery						
	Idiopathic deformity (n=692)	**Neuromuscular deformity (n=298)**	**Congenital deformity (n=116)**	**Spondylolisthesis (n=97)**	**Scheuermann's kyphosis (n=63)**	**Syndromic deformity (n=44)**
Female	562 (81)	131 (44)	59 (51)	59 (61)	17 (27)	22 (50)
Age, median [IQR]	16 [14, 17]	15 [13, 17]	13 [7, 16]	17 [14, 18]	18 [17, 19]	14 [12, 16]
Age, mean (SD)	15.5 (2.3)	14.7 (2.9)	11.7 (5.3)	16.3 (2.9)	17.6 (1.8)	13.8 (3.6)
LOS, median [IQR]	7 [7, 8]	9 [7, 11]	7 [6, 9]	6 [5, 8]	7 [7, 9]	8 [6, 10]
CCI score, low	604 (87)	122 (41)	91 (78)	78 (80)	54 (86)	29 (65)
CCI score, medium	84 (12)	131 (44)	24 (21)	18 (19)	9 (14)	13 (230)
CCI score, high	4 (1)	45 (15)	1 (1)	1 (1)	0 (0)	2 (5)
IQR, interquartile range; SD, standard deviation; CCI, Charlson comorbidity index						

Table 2. Causes of readmission in 75 patients according to etiology and divided in surgical vs. medical			
Etiology	**Type of readmission**	**% (n)**	**Reason for readmission**
Idiopathic	Surgical	25% (4)	SSI: 1 patient; revision surgery.
			Surgical complication:2 patients; 1 patient was revised due to implant failure, 1 patient was admitted due to spinal headache after epidural analgesia.
	Medical	75% (12)	GI: 4 patients; 2 patients with toxic liver disease in both cases suspected anesthesia or acetaminophen induced, 1 patient cause of abdominal pain and discomfort and suspected withdrawal symptoms, 1 patient admitted cause of abdominal pain and bloody diarrhea (diagnosed with colitis ulcerous).
			Infection: 4 patients; 1 patient with meningitis, 1 patient with pyelonephritis, 1 patient with gastroenteritis and UTI, 1 patient with upper airway infection.
			Pulmonary: 1 patient; exacerbation of asthma.
			Pain and mobilization (19%): 3 patients; 1 patient experienced sudden pain, 2 patients with pain in the thoracic and spinal region; suspected acute myocardial infarction and pneumothorax, respectively.
Neuromuscular	Surgical	23% (9)	SSI: 5 patients; 2 patients had revision surgery.
			Neurological deficit: 2 patients; altered bladder function and incontinence.
			Surgical complication: 2 patients; implant misplacement and implant failure.
	Medical	77% (30)	GI: 7 patients; diarrhea, insufficient nutrition, vomitus and dehydration.
			Infection: 10 patients; 7 patients with pneumonia, 1 patient with unknown origin, 1 patient with UTI, 1 patient with infected baclofen pump.
			Pulmonary: 6 patients; respiratory decompensation.
			Pain and mobilization: 2 patients; pain.
			Neurological: 2 patients; deterioration of existing neurological disorder.
			Other: 1 patient suspected of DVT.
Congenital	Surgical	60% (3)	SSI: 2 patients; treated with antibiotic.
			Neurological deficit: 1 patient; dysesthesia in lower extremities and had acute MRI, conservative treatment.

	Medical	40% (2)	Infection: 2 patients; 1 patient admitted with Staphylococcus Scalded Skin Syndrome, 1 patient with viral infection.
Spondylolisthesis	Surgical	67% (4)	Neurological deficit: 4 patients; dysesthesia and pain, conservative treatment regime
	Medical	33% (2)	GI: 1 patient; malnutrition
			Neurological: 1 patient; suspicion of TIA
Scheuermann's kyphosis	Surgical	50% (5)	SSI: 2 patients; 1 patient was revised.
			Surgical complication: 3 patients (all revised); 1 patient with translation at upper level of osteotomy, 1 patient with curve progression/implant failure, 1 patient with severe pain leading to anterior supporting fusion.
	Medical	2% (1)	Pain and mobilization: 1 patient; severe pain since ending opioid treatment.
Syndromic	Surgical	0 % (0)	None
	Medical	100% (3)	GI: 2 patients; 1 patient with leukocytosis and abdominal pain, 1 patient with vomitus and diarrhea to ensure enough nutrition.
			Infection: 1 patient; UTI
GI, gastrointestinal; TIA, transient ischemic attack; SSI, surgical site infection; UTI, urinary tract infection.			

Table 3. Uni- and multivariable logistic regression on potential risk factors for 90-day readmission

		Absolute risk %	**Univariable**			**Multivariable**		
			OR	**95 % CI**	**P**	**OR**	**95% CI**	**P**
Sex	Female	5.1	Ref	-	-	Ref	-	-
	Male	7.0	1.4	0.9-2.3	0.2	0.7	0.4-1.2	0.2
Age group, year	>15	5.6	Ref	-	-	Ref	-	-
	0-9	7.9	1.4	0.6-3.5	0.4	1.5	0.5-4.2	0.5
	10-15	5.5	1.0	0.6-1.6	0.9	0.9	0.5-1.5	0.6
Etiology	Idiopathic	2.3	Ref	-	-	Ref	-	-
	Neuromuscular	13.1	6.4	3.5-11.6	<0.01****	4.4	2.2-9.0	**<0.01****
	Congenital	4.3	1.9	0.7-5.3	0.2	1.7	0.6-5.2	0.4
	Spondylolisthesis	6.2	2.8	1.1-7.3	0.04	3.0	1.1-8.0	**0.03***
	Scheuermann	9.5	4.5	1.7-11.8	<0.01**	4.9	1.7-13.6	<**0.01****
	Syndromic	6.8	3.1	0.9-11.0	0.1	2.6	0.7-9.8	0.2
Length of stay, days	7-9	4.5	Ref	-	-	Ref	-	-
	0-6	3.3	0.7	0.4-1.5	0.4	0.7	0.3-1.5	0.4
	>9	12.1	2.9	1.7-4.8	<0.01****	1.8	1.0-3.1	**0.04***
CCI group	Low	4.1	Ref	-	-	Ref	-	-
	Medium	9.3	2.4	2.4-4.0	<0.01***	1.4	0.8-2.6	0.2
	High	17.0	4.8	2.2-10.5	<0.01****	2.1	0.9-4.9	0.1

*indicates <0.5

**indicates <0.01

***indicates <0.001

****indicates <0.0001

CCI, Charlson comorbidity index; OR, odds ratio, CI, confidence interval.

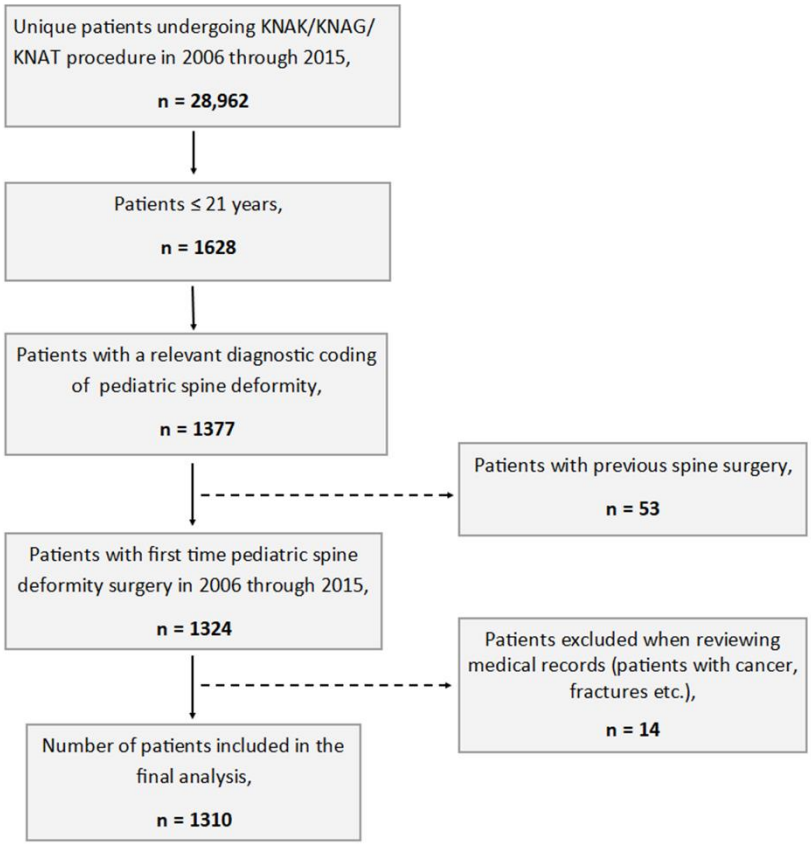

Figure 1. Flowchart of patient selection.

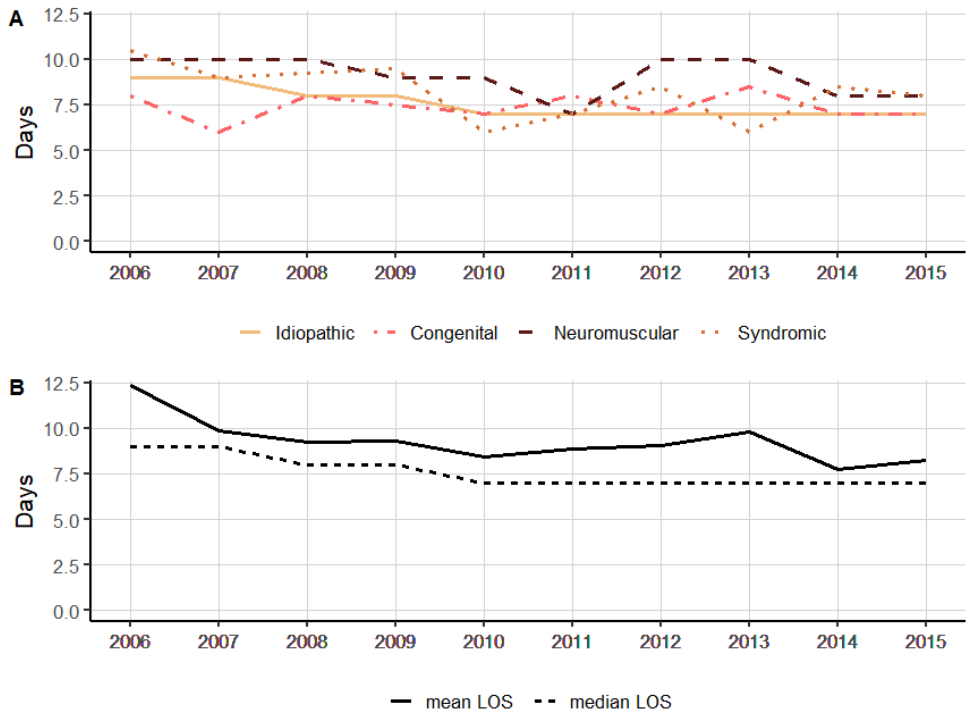

Figure 2. A: Median LOS for each year of surgery across deformity etiologies. The figure only represents idiopathic, neuromuscular, congenital and syndromic deformities. B: Mean and median LOS for each year of surgery.

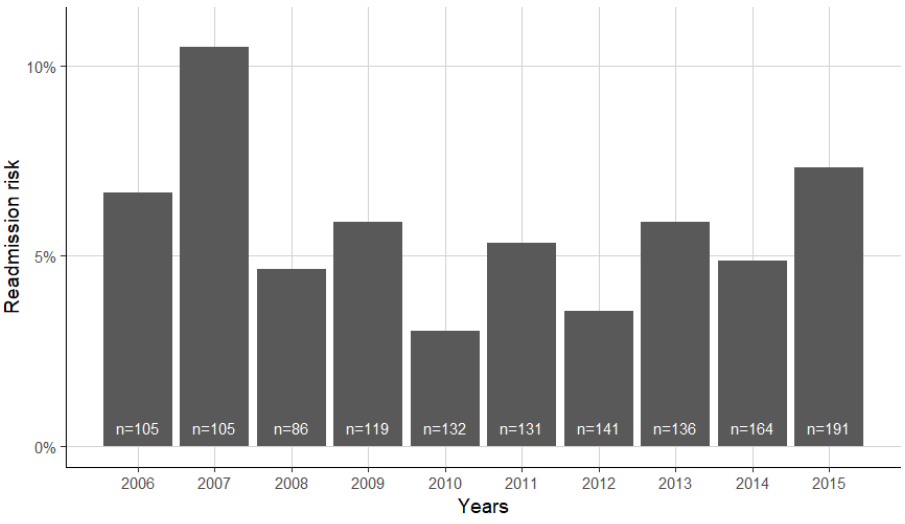

Figure 3. Readmission risk within 90 days for each year of surgery

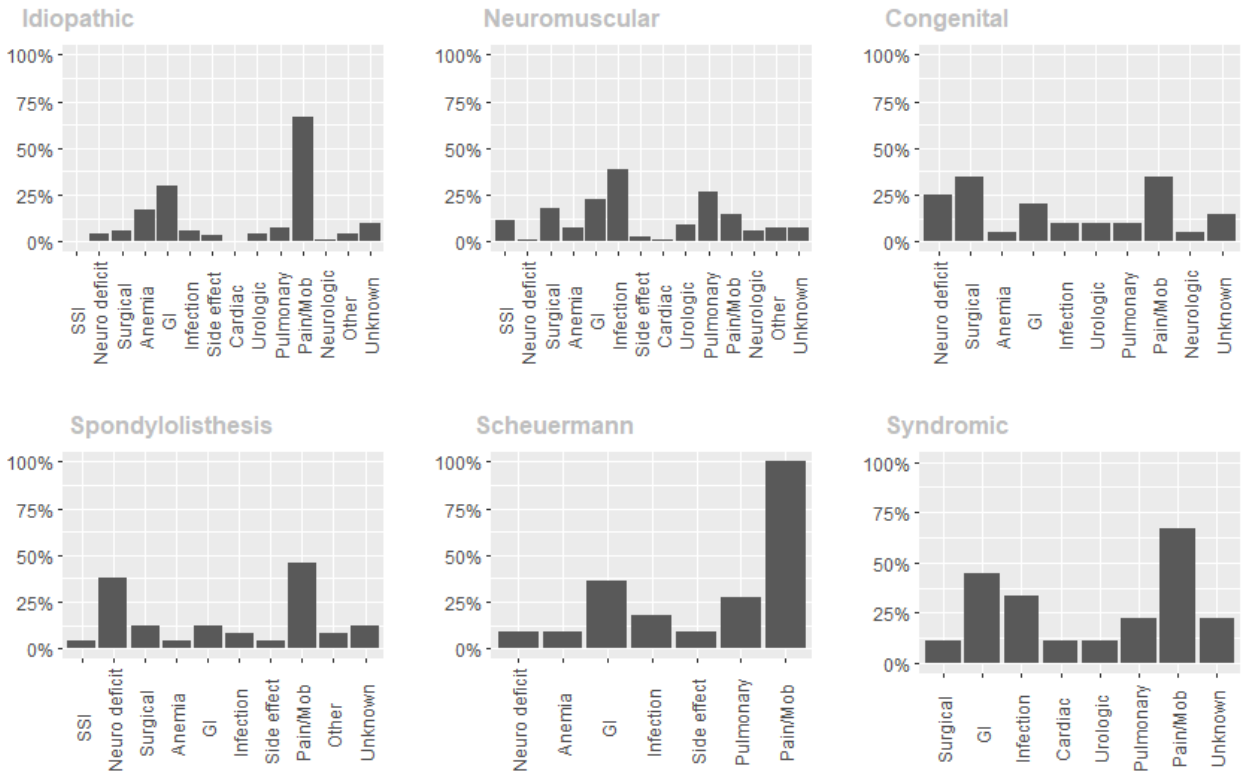

Figure 4. Reasons for extLOS according to etiology

Paper III

Revision risk, risk factors and reasons for revision following primary surgery for pediatric spinal deformity: A nationwide study with two-year follow-up

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Abstract

Background context: Revision risk after pediatric spine surgery is not well established and varies between deformity etiologies.

Purpose: To report the two-year revision risk following surgery for primary pediatric spinal deformity in a nationwide cohort. Secondarily, to evaluate potential risk factors and reasons for revision surgery.

Design: Retrospective nationwide cohort study.

Patient Sample: We conducted a national registry study of all pediatric spinal deformity patients undergoing surgery from 2006 through 2015 (n=1310).

Outcome measures: The outcome was two-year revision risk.

Methods: All patients ≤ 21 years of age undergoing spinal deformity surgery in Denmark from 2006 through 2015 were identified by procedure and diagnosis codes in the Danish National Patient Registry (DNPR). From the DNPR, data on revision surgery were retrieved. Patients were categorized in six groups according to etiology. Medical records were reviewed for reason for revision in all patients. Potential risk factors for revision were assessed with multiple logistic regression analyses and included age, etiology, sex, Charlson comorbidity index and growing-rod treatment.

Results: Patients were categorized according to etiology; idiopathic deformity (53%), neuromuscular deformity (23%), congenital/structural deformity (9%), spondylolisthesis (7%), Scheuermann's kyphosis (5%) and syndromic deformity (3%). Of 1310 included patients, 9.2% underwent revision surgery within 2 years and 1.5% were revised more than once. Median time to revision was 203 (interquartile range 35-485) days. The multivariable logistic regression found significantly higher odds ratio (OR) for revision in patients with growth-preserving approach (OR = 4.8, 95% confidence interval (CI) 2.5-9.6, congenital deformity (OR=2.6, 95% CI 1.3-5.3), spondylolisthesis (OR=3.4, 95% CI 1.8-6.5), Scheuermann kyphosis (OR=3.9, 95% CI 1.9-8.2) and CCI score ≥3 (OR=2.5 95% CI 1.1-5.6). The most common reason for revision was implant failure (32.5%) followed by residual deformity and/or curve progression (15.8%).

Conclusions: In this nationwide study, the two-year revision risk after primary pediatric spinal deformity surgery was 9.2%. Risk factors for revision were etiology of congenital deformity, spondylolisthesis, Scheuermann kyphosis as well as patients with growth-preserving approach and higher Charlson comorbidity score.

The most common reason for revision was implant failure.

Keywords: pediatric spinal deformity; complication; revision; scoliosis; kyphosis; congenital deformity; Scheuermann's kyphosis; neuromuscular deformity; idiopathic scoliosis; spondylolisthesis; structural deformity.

Introduction

Revision risk after primary surgical treatment of pediatric spinal deformity (PSD) is not well established. In recent years, there has been an increase in pediatric spinal deformity surgery[1] and a growing focus on the safety of these procedures. The surgical options are numerous and depend on deformity etiology, severity of the deformity and skeletal maturity[2–8]. The risk of revision varies between deformity etiologies[9,10]. Short-term morbidity ranges between 7.6-29.2% [11–17] and revision risk varies between 0.9-34%[9,10,18–21]. The large variation in revision risks may be due to different study designs, included etiologies and different follow-up periods. Furthermore, higher volume hospitals and high volume surgeons have shown a lower rate of complications and revisions [22,23]. Revision procedures are often more challenging than primary surgery[18,24] and typical indications include infection, implant failure/pseudarthrosis, neurologic deficit or deformity progression[25]. Studies with more than one-year follow-up are sparse and do not differentiate between deformity etiologies[26]. The primary aim of this study was to report the two-year revision risk following primary pediatric spinal deformity surgery in a complete, nationwide cohort. Secondarily, we aimed to evaluate potential risk factors for revision surgery and describe the reasons for revision.

Methods

This is a nationwide cohort study of all pediatric patients undergoing spine surgery from 2006 and through 2015.

Settings

All Danish residents have a unique personal social security number. This enables individual record linkage across all Danish health registries. Furthermore, the Danish Civil Registration System tracks and continuously updates information on migration and vital status allowing long-term follow-up with concise censoring at emigration or death. The National Health Service is government-funded and free of charge for all citizens. All access to hospitals is therefore universal, unfettered and unselective.

Data Source

The Danish National Patient Registry (DNPR) is a population-based administrative registry that has collected data with complete nationwide coverage since 1978[27,28]. The primary aim of the DNPR is a continuous monitoring of hospitals and health services as well as the occurrence of diseases and treatments. Reporting to the DNPR is compulsory for private practice specialists, public- and private hospitals. Data reported to the DNPR includes administrative data (demographic, admission data), diagnosis code (one primary and optional secondary diagnosis), treatments (surgery and anesthesia) and examinations (radiological procedures)[28]. The DNPR has been validated in different studies[29,30]. Using medical record as the reference standard, a study reported 73% correctly categorized primary diagnoses and with the highest positive predictive value (83%) for diagnosis associated with orthopedic surgery[28].

Study population

We included all PSD patients between the ages of 0 to 21 years surgically treated between

January 1, 2006 and December 31, 2015. Patients were identified using a relevant diagnosis (Appendix A) and procedure code KNAG/KNAT/KNAK (Appendix B). We classified the patients according to etiology into the following groups; idiopathic deformity (ID), neuromuscular deformity (ND), congenital deformity (CD), spondylolisthesis (SP), Scheuermann's kyphosis (SK) and syndromic deformity (SD). In cases of unspecific diagnostic coding (e.g. scoliosis unspecified, kyphosis unspecified) medical records were reviewed for exact diagnosis and then classified according to recently suggested classification of early onset scoliosis (EOS)[31]. The first PSD procedure was labeled as the index procedure. All patients with PSD surgery in 1996 through 2005 were registered and linked to the cohort. If doublet occurred, the patient was excluded, this to avoid misclassification of revision surgeries as index procedure. Moreover, patients with concurrent spinal cancer/metastasis and/or spinal trauma were excluded. Based on previous work[20,32], the indication for revision was classified into seven groups: (1) Implant failure (implant breakage and/or dislodgement and/or pseudarthrosis), (2) Infection (superficial vs. deep, early (< 12 weeks following surgery) vs. late (≥ 12 weeks following surgery)), (3) Implant misplacement and/or prominence, (4) Residual deformity and/or curve progression, (5) Proximal junctional failure (PJF) and distal junctional failure (DJF), (6) neurologic deficit, (7) translocation and (8) Other.

Covariates

Charlson comorbidity index (CCI) was calculated based on diagnosis codes, from all in- and outpatient contacts registered before the index procedure in the DNPR [33]. This is a validated method to calculate CCI score[34]. Patients were classified according to one of three levels of CCI score: low (CCI score of 0), medium (CCI score of 1 or 2), or high (CCI score ≥ 3). Age were categorized in three groups "0-9", "9-15"and ">15" years.

Outcomes and medical Records

All patients were followed for two years after primary surgery to identify revision procedures. All revisions in the two-year period were registered but only the first revision was included in the final analysis. Revision was defined as an unplanned return to the operating room, therefore, planned second stage procedure was not included in the final analysis. In all cases of revisions, the medical record was reviewed for reason for revision surgery. In patients with growth-preserving treatment, medical records were reviewed to distinguish normal sequential growing-rod treatment from an unplanned revision. If a patient had final fusion within the follow-up period, it was not classified as a revision.

Statistical analysis

The distribution of descriptive statistics was assessed using histograms. The results are reported as means with standard deviations (SD), medians with interquartile ranges (IQR) or proportions (%). Revision risk were calculated using a modified survival analysis (the Aalen-Johansen estimator). This model uses death as a competing risk of revision to estimate the cumulative incidence. Student t test was used when comparing approximated Gaussian distributed data and Wilcoxon's sum rank test for non-Gaussian distributed. Categorical variables were analyzed using Chi-square test or Fisher exact test depending on results of expected counts. Risk factors for

revision were assessed using uni- and multivariable logistic regression and reported as odds ratios (OR) with 95% confidence interval (CI). Variables included age, etiology, sex, CCI and growing-rod treatment. C-statistics were used to determine the discrimination of the logistic regression and the Homer-Lemeshow test to assess the goodness of fit. A two-sided p-value of 0.05 or less was considered statistically significant. Statistical analyses were performed with the use of R software, version 3.6.1 (R Foundation for Statistical Computing) and the packages riskRegression[35] and survival [36].

Ethics

No ethical approval was necessary due to the non-interventional study design. Permission to store and review data without prior informed consent was obtained from the Danish Data Protection Agency (no. RH-2017-86) and the Danish Patient Safety Authority (no. 3-3013-2059/1).

Results

A total of 1310 pediatric patients underwent primary spinal deformity surgery in the study period (Fig. 1). Patients etiology were; ID (53%), ND (23%), CD (9%), SP (7%), SK (5%) and SD (3%). The majority (98%) of the patients had surgery at one of four tertiary spine units. Baseline characteristics can be found in table 1.

In total, 9.2% (n=120) of patients were revised within the two-year follow-up period and 1.5% (n=19) of patients were revised more than once. Median time to revision was 203 (IQR 35-485) days. Mean time to revision was 269 days (SD: 237).

Rates of cumulative incidence (95% CI) for any revision were 2.1% (1.4-2.9%) at 30-days, 3.0% (2.1-3.9%) at 90-days, 6.2% (4.8-7.5%) at one year and 9.5% (7.8-11.1%) at two years from index procedure (Fig. 2). Cumulative incidence risks are summarized in table 2. The distribution was different between etiologies, with SK, SP and CD carrying the highest incidence (table 2).

During the two-year follow-up, 11 patients died. The overall mortality risk was 0.2%, 0.4%, 0.5% and 0.8% at 30 days, 90 days, one year and two years, respectively. Patients who died all had neuromuscular deformity. Comorbidity burden in patients who died was as followed; low 45.5%, medium 45.5%, high 9% compared with patients who did not; low 75%, medium 21%, high 4%. The distribution of sex between the groups were 65% female in patients who died vs. 36% in patients who did not.

Risk factors for revision

Patients characteristics, year of surgery and one surgical variable were analyzed for prediction of two-year revision using univariable logistic regression model (Table 3). None of the age groups were correlated to increased odds of two-year revision. However, a significant increased revision risk was seen in patients with growth-preserving approach (OR=4.0, 95% CI 2.3-7.1), etiology of ND (OR=2.2, 95% CI 1.4-3.6), CD (OR=3.0, 95% CI 1.7-5.6), SP (OR=3.5, 95% CI 1.9-6.6), SK (OR=4.6, 95% CI 2.3-9.2), male sex (OR=1.8, 95% CI 1.3-2.7) and high CCI score (OR=3.1, 95% CI 1.6-6.2). Apart from male sex and patients with ND, they all remained statistically significant in a subsequent multivariable analysis adjusted for age, sex,

etiology, growth-preserving approach and CCI (Table 3).

Reason for revision

The main reason for revision was implant failure (n=39, 33%) (Table 4). In all patients, the implants were removed and all but six had new implants inserted and in 13 patients, the instrumentation was extended (Table 6). The second most common reason for revision was residual deformity or curve progression (n=19, 16%) followed by implant misplacement/prominence (n=18, 15%), infection (n=14, 12%) and neurological deficit (n=13, 11%). A detailed description of the reasons for revision can be found in Appendix C.

Discussion

This 10-year, nationwide study on 1310 pediatric patients undergoing primary PSD surgery reports a two-year revision risk of 9.2%. Previous studies have reported risks ranging from 0.9–20.4%[9,10,20,21]. This variation in revision risk can be explained by differences in deformity etiologies, development of new surgical strategies and differences in study design. Previous studies are from national databases or single institutions[9,10,26,37,38]. The limitations of these studies are primarily incomplete follow-up, short follow-up periods and inability to distinguish between first time PSD surgery and revision. This emphasizes the strength of this study; a complete nationwide study of patients with primary PSD surgery with no loss to follow-up [28,30]. Moreover, large database studies typically fail to report specific reasons for revisions. This study provides such reasons through meticulous medical record review.

Risk factors for revision

We found that an etiology of CD increased the odds of revision (Table 3). Revision studies in CD are generally on small cohorts with short follow-up periods[26,38,39], but a few larger studies report results similar to ours. Paul et al. performed a large database study reporting one-year revision risk in CD of 4.7% and four-year revision risk of 41.6%[9]. This was significantly higher compared to patients with idiopathic scoliosis (IS). Jain et al. reported that revision was 5.4 times more likely in patients with CD compared to patients with adolescent idiopathic scoliosis (AIS)[26]. However, this study was limited to 90-days follow-up and included only patients fused more than five levels. Moreover, we found increased odds of revision in patients with both SP and SK (Table 3). There is limited information regarding revision risk associated with pediatric SP. Nevertheless, a recent multicenter study reports 40% revision risk in pediatric SP treated with posterior spinal fusion [40]. The follow-up period was minimum two years (mean follow-up 5.5 years) and the reasons for revision were consistent with our results (implant failure, persistent radiculopathy) (Table 4). The higher revision risk reported by Nielsen et al. (40% vs. 16.5%) might be explained by their long-term follow-up and could indicate a need for closer and longer postoperatively observation of pediatric patients with SP. The absolute risk for revision in SK patients was 20.6%. The revision risk in patients with SK is generally reported higher than in patients with IS (1.4 vs. 14.4%)[21]. The difference in revision between SK and IS patients may be attributed to the more extensive surgery in patients with SK (i.e. more frequently use of osteotomies), the cantilever forces required to correct the

kyphosis and the persistent pull-out forces of the proximal and distal ends of the construct. Adequate terminal fixation and appropriate selection of fusion levels are important in minimizing these complications including PJF and DJF. Concurrent with our data, patients with SK are at higher risk of PJF and DJF leading to revision[41]. As expected, growth-preserving treatment was associated with increased odds of revision. The higher revision risk is anticipated in the management of patients with EOS. This is regardless of treatment modality since the treatment and surgical procedures are prolonged[19]. Patients with traditional as well as magnetically controlled growing rods have an estimated 30-33% revision risk[19,42]. We report a markedly lower revision risk of 16.5% in patients with growth-preserving, however we did not follow all the patients to final fusion. Finally, we found high CCI score associated with increased revision risk. The CCI score was originally validated in the adult population[43] but has been used in pediatric populations as well[44–46]. To our knowledge, CCI score has never been validated in a pediatric setting with revision as outcome. Additionally, several essential diagnostic codes relevant to patients with PSD are missing in the CCI[47], e.g. microcephaly, cerebral palsy and syndromic diagnoses. This is also reflected in our data, where 50% of the patients who died within two years had a low CCI score (CCI=0) because the CCI does not take all neuromuscular disorders into account.

Reason for revision

In this study, the main reason for revision was implant failure (Table 4). This tendency was observed across all etiologies. Implant failure is a major cause for revision in pediatric spine surgery[9,10,18,20,48] but with a wide range (8-56%) across studies, mainly explained by differences between deformity etiologies. Accordingly, a systematic review reported incidence of pseudarthrosis in 1.4% of patients with AIS and in 2.2% of patients with neuromuscular scoliosis[49]. The incidence of pseudarthrosis in patients with spondylolisthesis has been reported up to 45% in patients treated with posterior fusion without decompression[37]. We also report a high overall rate of deformity progression (16%). This is in line with Ahmed et al. reporting five-year revision risk in AIS patients of 5.2% and 15.0% because of progression but also PFJ and DJF[20]. The average time to revision was 3.7 years, hence our data could potentially underestimate this factor due to the shorter follow-up period. Similar to our results, a small single center study by Huang et al. reported 10% revision due to curve progression in CD after hemivertebrae resection[50] (Table 4). The two-year revision risk caused by implant misplacement/prominence was 15%. Other studies have reported misplacement/prominence as a reason for revision in 12.5%- 20.0% of procedures, and half of the revision occurring within the first three months[20,51]. Infection was the reason for revision in 12% of our cases. Infection rates after PSD surgery are reported to occur more often in patients with non-idiopathic scoliosis[9] and ranges from 4.5%-12.0%[16,52–55]. Various factors have been associated with an increased risk of postoperative infections such as poor preoperative nutrition, high degree of cognitive impairment, allograft bone and stainless steel vs titanium implants[55–59]. These findings correspond well with our results with the highest rate of SSIs seen in patients with ND (27%). Furthermore, our

findings are in line with another Scandinavian national study reporting 3% revision risk due to SSI and with the highest incidence in patients with neuromuscular disease[1]. In our study a total 3.2% of SK patients had SSI leading to revision. SSI in patients with SK is reported ranging from 3.8-10.3 %[21,60]. In contrast to our study, most of previous studies report on all SSIs and not only SSIs leading to revision.

One of the most serious complications in spine surgery is new neurological deficit. This study reports an overall 1.0% risk of new neurologic deficit leading to revision and new neurological deficit to be the cause of revision in 11% of cases. The overall risk is in line with a large register study from the SRS database reporting a risk of 1.4% with same deformity etiologies but also reporting trauma and tumor[24]. They found highest risk among patients with kyphosis and spondylolisthesis and the lowest rate between scoliosis but without distinguishing between different scoliosis etiologies. Furthermore, they failed to report neurological deficit leading to revision. In our study the highest rate of new neurological deficit leading to revision was seen in patients with CD and SP (table 4). These findings are supported by studies by Qui et al. and Fu et. Al. Qiu et al. reported CD as a significant risk factor for new neurological deficits compared to AIS[61]. In addition, Fu et al. reported pediatric patients with spondylolisthesis requiring reduction were associated with higher risk of new neurological deficits[24].

Strength and limitations

This study is based on a large up-to-date nationwide pediatric cohort. In contrast to previous studies, this cohort has complete follow-up and detailed information regarding two-year revision through medical record review. However, due to the observational setting of this study, we can only report associations and not causality. As in all register studies, data can be inaccurate, but the data completeness and diagnostic coding for orthopedic surgery has been validated[27]. Finally, we acknowledge the methodological limitation of using nationwide database in lack of clinical data such as pre- and peri-operative data as risk factors for revision surgery. Conversely, we find it acceptable considering the advantages of large register studies which includes large sample size, strengthening of the statistical interference and lowering the risk of selection bias.

Perspectives

Establishing overall risk of revision, reason for revision and risk factors for revision is essential to establish preventive measures and allocate appropriate resources to specific groups of patients. All revisions are unwanted because of the increased risk of complications[18,24], the strenuous burden to the patients and the higher cost for society. The present results can prove to be an important tool in the understanding of patient-specific risks and optimizing pre- and post-operative clinical care and observation after PSD surgery. Steps such as multidisciplinary assessment of high risk patients, minimally invasive surgeries[62] and nationwide introduction of uniform pathway of care, could reduce the revision risk.

Conclusion

In conclusion, we found a two-year revision risk of 9.2% after primary pediatric spine surgery. Risk factors for revision were etiology of congenital deformity, spondylolisthesis, Scheuermann's kyphosis, patients with growth-preserving approach and high CCI score. Implant failure was the most common reason for revision. The present results may form the basis of a more informed discussion with the patients and parents about prognosis and postsurgical risk as well as setting the basis for multidisciplinary assessments of high risk patients.

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Table 1. Demographic data according to deformity etiologies

Variable	Idiopathic (n=692)	Neuromuscular (n=298)	Congenital (n=116)	Spondylolisthesis (n=97)	Scheuermann's kyphosis (n=63)	Syndromic (n=44)	Total (n=1310)
Sex (female)	562 (81.2)	131 (44.0)	59 (50.9)	59 (60.8)	17 (27.0)	22 (50.0)	850 (64.9)
Age (years)	16 [14, 17]	15 [13, 17]	13 [7, 16]	17 [14, 18]	18 [17, 19]	14 [12, 16]	15 [14, 17]
Length of stay (days)	7 [7, 8]	9 [7, 11]	7 [6, 9]	6 [5, 8]	7 [7, 9]	8 [6, 10]	8 [7, 9]
CCI low (score 0)	604 (87.3)	122 (40.9)	91 (78.4)	78 (80.4)	54 (85.7)	29 (65.9)	978 (74.7)
CCI medium (score 1-2)	84 (12.1)	131 (44.0)	24 (20.7)	18 (18.6)	9 (14.3)	13 (29.5)	279 (21.3)
CCI high (score≥3)	4 (0.6)	45 (15.1)	1 (0.9)	1 (1.0)	0 (0.0)	2 (4.5)	53 (4.0)

Data are numbers (%) or medians [interquartile ranges]; CCI, Charlson comorbidity index

Table 2. Cumulative incidences of revision across etiologies							
Time after discharge	**Idiopathic**	**Neuromuscular**	**Congenital**	**Spondylolisthesis**	**Scheuermann's kyphosis**	**Syndromic**	**Total**
30 days	1.0% (0.3-1.8%)	3.0% (1.1-5.0%)	5.2% (1.1-9.2%)	4.1% (0.2-8.1%)	1.6% (0.0-4.7%)	2.3% (0.0-6.8%)	2.1% (1.4-2.9%)
90 days	1.3% (0.5-2.1%)	4.7% (2.3-7.2%)	5.2% (1.1-9.2%)	4.1% (0.2-8.1%)	7.9% (1.3-14.6%)	2.3% (0.0-6.8%)	3.0% (2.1-3.9%)
1 year	2.9% (1.6-4.2%)	8.7% (5.4-12.0%)	8.8% (3.6-14.1%)	11.8% (5.2-18.3%)	14.3% (5.6-22.9%)	9.9% (0.7-19.1%)	6.2% (4.8-7.5%)
2 years	5.4% (3.7-7.1%)	11.7% (7.9-15.4%)	15.6% (8.7-22.4%)	17.3% (9.6-25.0%)	20.6% (10.6-30.6%)	9.9% (0.7-19.1%)	9.5% (7.8-11.1%)
Data are Cumulative Incidences (95% confidence intervals) and calculated using the Aalen-Johansen estimator.							

Table 3. Univariable and multivariable logistic regression on potential risk factors for two-year revision risk								
		Absolute risk %	**Univariable**			**Multivariable**		
			OR	**95 % CI**	**P**	**OR**	**95% CI**	**P**
Sex	Female	7.3	Ref	-	-	Ref	-	-
	Male	12.6	1.8	1.3-2.7	**<0.01****	1.3	0.9-2.0	0.20
Age group, year	>15	9.8	Ref	-	-	Ref	-	-
	0-9	15.8	1.7	0.9-3.4	0.11	0.7	0.3-1.6	0.40
	10-15	7.7	0.8	0.5-1.1	0.18	0.7	0.5-1.2	0.18
Etiology	Idiopathic	5.3	Ref	-	-	Ref	-	-
	Neuromuscular	11.1	2.2	1.4-3.6	**<0.01****	1.6	0.9-2.9	0.14
	Congenital	14.7	3.0	1.7-5.6	**<0.01*****	2.6	1.3-5.3	**<0.01****
	Spondylolisthesis	16.5	3.5	1.9-6.6	**<0.01******	3.4	1.8-6.5	**<0.01*****
	Scheuermann	20.6	4.6	2.3-9.2	**<0.01******	3.9	1.9-8.2	**<0.01*****
	Syndromic	9.1	1.8	0.6-5.2	0.30	1.1	0.3-3.4	0.90
Growth-preserving treatment	No	8.2	Ref	-	-	Ref	-	-
	Yes	16.7	4.0	2.3-7.1	**<0.01******	4.8	2.5-9.6	**<0.01******
CCI group	Low	8.6	Ref	-	-	Ref	-	-
	Medium	8.6	1.0	0.6-1.6	0.99	0.9	0.5-1.4	0.56
	High	22.6	3.1	1.6-6.2	**<0.01****	2.5	1.1-5.6	**0.02**
*indicates <0.5; **indicates <0.01; ***indicates <0.001; ****indicates <0.0001; CCI, Charlson comorbidity index								

Table 4. Summary of revision across deformity etiologies							
	Idiopathic (n=37)	**Neuromuscular (n=33)**	**Congenital (n=17)**	**Spondylolisthesis (n=16)**	**Scheuermann (n=13)**	**Syndromic (n=4)**	**Total (n=120)**
Age (year)	15 [13, 16]	15 [11, 17]	14 [12, 17]	17 [16, 19]	17 [16, 19]	12 [10.8, 13.2]	16 [13, 17]
Sex (female)	30 (81.1%)	8 (24.2%)	7 (41.2%)	11 (68.8%)	4 (30.8%)	2 (50.0%)	62 (51.7%)
LOS at revision	5 [2, 8]	6 [3, 18]	8 [6, 14]	3.5 [2.0, 5.5]	6 [2, 7]	4.5 [3.5, 10.2]	6 [2.8, 10.0]
Time to revision (days)	329.2 (249)	226.9 (231.4)	245.3 (240)	289.1 (226.1)	253.4 (247.6)	138.8 (86.7)	269.3 (236.8)
Implant failure	15 (40.5%)	7 (21.2%)	7 (41.2%)	5 (31.2%)	3 (23.1%)	2 (50.0%)	39 (32.5%)
Residual deformity/curve progression	6 (16.2%)	5 (15.2%)	4 (23.5%)	3 (18.8%)	0 (0.0%)	1 (25.0%)	19 (15.8%)
Implant misplacement or prominence	5 (13.5%)	6 (18.2%)	0 (0.0%)	3 (18.8%)	3 (23.1%)	1 (25.0%)	18 (15.0%)
Infection	3 (8.1%)	9 (27.3%)	0 (0.0%)	0 (0.0%)	2 (15.4%)	0 (0%)	14 (11.7%)
Neurological deficit	4 (10.8%)	1 (3.0%)	6 (35.3%)	2 (12.5%)	0 (0%)	0 (0%)	13 (10.8%)
Other	4 (10.8%)	2 (6.1%)	0 (0%)	3 (18.8%)	1 (7.7%)	0 (0%)	10 (8.3%)
PJF/DJF	0 (0%)	1 (3.0%)	0 (0%)	0 (0%)	3 (23.1%)	0 (0%)	4 (3.3%)
Translocation	0 (0%)	2 (6.1%)	0 (0%)	0 (0%)	1 (7.7%)	0 (0%)	3 (2.5%)

Data are means (standard deviation), medians [interquartile ranges] or numbers (%)

LOS: Length of stay; PJF: proximal junctional failure; DJF: distal junctional failure

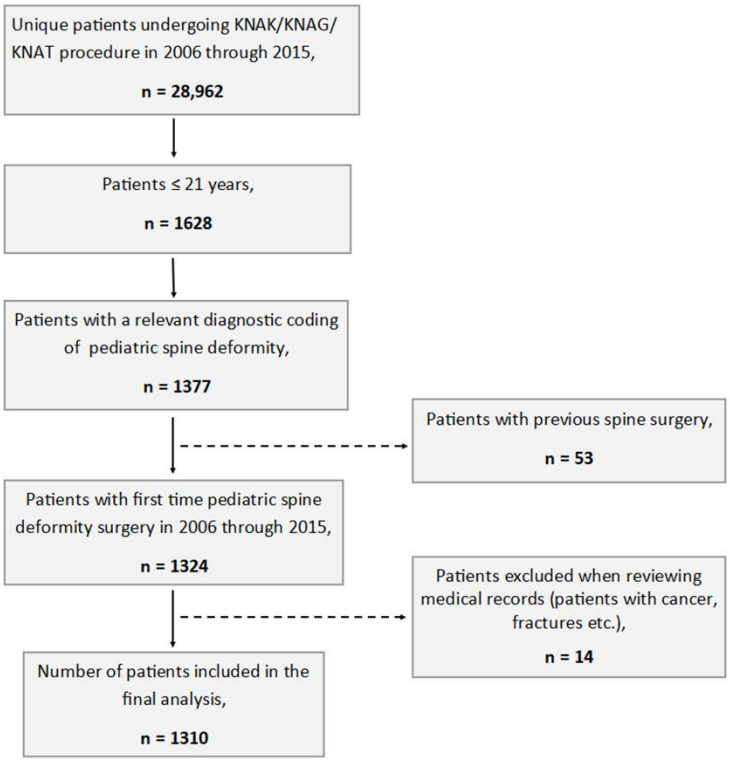

Figure 1. Inclusion process of pediatric patients with first time spine surgery.

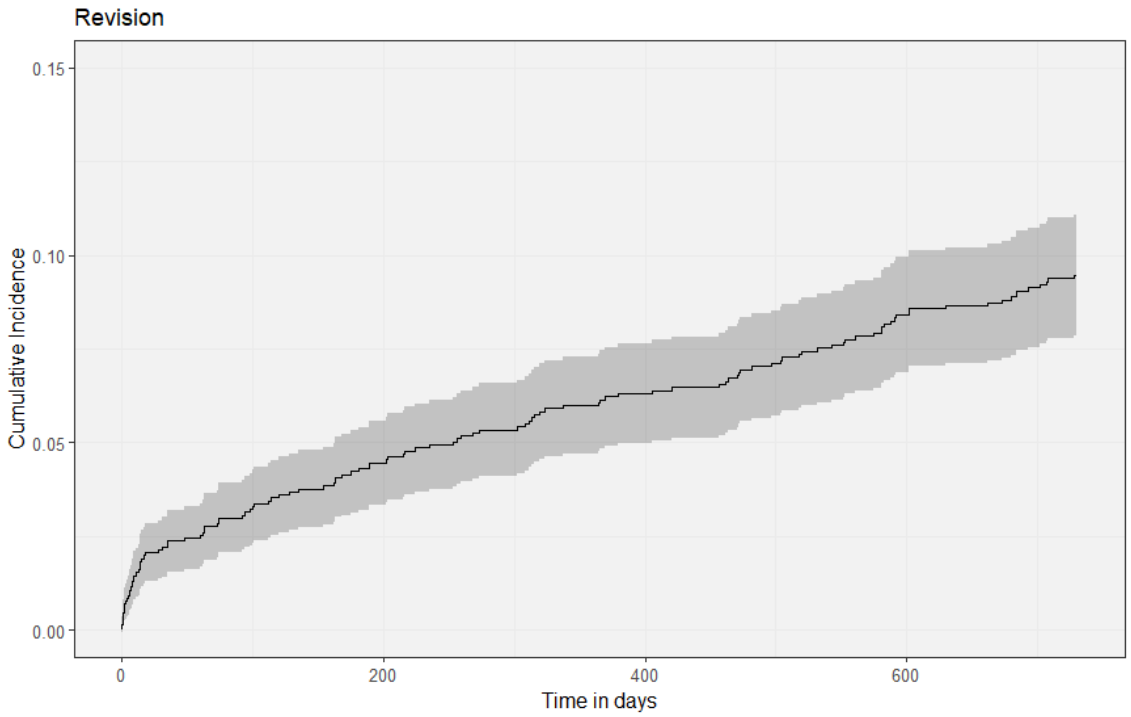

Figure 2. Cumulative incidence of revision. The overall cumulative incidence of any revision during the two-year follow-up period. The grey area adjacent to the curve represent the 95% confidence interval.

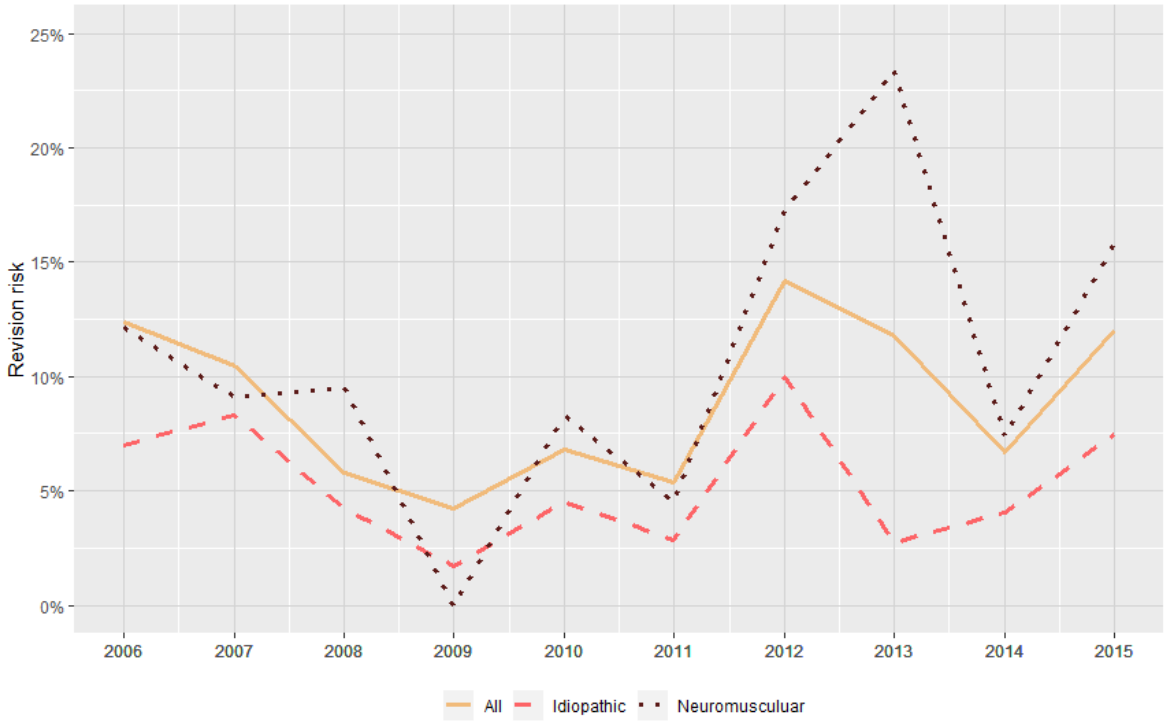

Figure 3. Revision rate at two-year follow for each year of index surgery.