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# Redundant nerve roots in lumbar spinal canal stenosis: Clinical significance, predictors and classification.

**Dissertation**

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***„Der Weg ist das Ziel”***

(Konfuzius, chinesischer Philosoph, *551 v. Chr.)

## Table of contents

## List of figures

## List of tables

## 1. Introduction

According to the evidence-based clinical guideline for diagnosis and treatment of degenerative lumbar spinal stenosis (LSS) by the North American Spine Society (NASS), degenerative LSS describes a condition in which there is diminished space for the neural and vascular structures in the lumbar spine, secondary to degenerative changes in the spinal canal [1].

Patients with LSS admitted for LSS decompression surgery sometimes show thickened, coiled and elongated nerve roots of the cauda equina, the so called redundant nerve roots (RNR), on their preoperative magnetic resonance (MR) images. RNR can be present as a serpentine or looped shape [2, 3]. The reported prevalence rate of RNR among patients with LSS varies from 15% [3] to 45% [4], with most studies reporting prevalence rates around 40% [5-8]. RNR were located in 82% of the patients above the stenotic level [3, 9]. However, RNR may also be observed below, or both above and below the stenotic level [3, 9].

Despite the different shapes (serpentine or looped) and the different directions in relation to the key stenotic level (above or below, sometimes both), a standardised nomenclature for describing and classifying RNR on MR images does not exist. A validated classification system would facilitate communication between the different professionals involved in the diagnosis and treatment of LSS patients. Furthermore, to study the clinical significance of RNR, a validated classification system is required. The following research questions could then be investigated:

- Does the severity of symptoms differ between patients with serpentine vs. loop-shaped RNR?
- Do patients with RNR both above and below stenosis have a worse clinical outcome than patients with RNR, which is only above the stenotic level?

In the present PhD thesis, the results of investigations into the following three research questions are presented:

- What is the clinical significance of RNR in patients diagnosed with LSS?
- Do patient demographics and MRI-based factors (potential predictors) predict the presence of RNR among patients with LSS scheduled for minimally-invasive decompression surgery?

- Does a new systematic classification of RNR (ASED classification) achieve passable intra and inter-rater reliability values?

In the introduction, a review of the literature is performed. The definition of LSS, its pathogenesis, symptoms, diagnostic options and a brief overview of treatment modalities are presented. In the second part of the manuscript, the methods used to investigate the three research questions referred above are described and their results are presented.

## 1.1. Anatomy

### 1.1.1. Lumbar spinal canal

The five lumbar vertebrae are aligned to form a continuous channel, known as the lumbar spinal canal. The anterior wall of the lumbar spinal canal is formed by the posterior surfaces of the lumbar vertebrae, the discs and the posterior longitudinal ligament (Fig. 1A). The posterior wall is formed by the laminae of the vertebrae and the ligamenta flava (Fig. 1B). The lateral walls of the lumbar spinal canal are shaped by the pedicles of the lumbar vertebrae. Between the pedicles of two lumbar vertebrae, the superior and inferior vertebral notches (incisura vertebralis superior and inferior) oppose one another to form the intervertebral foramina [10].

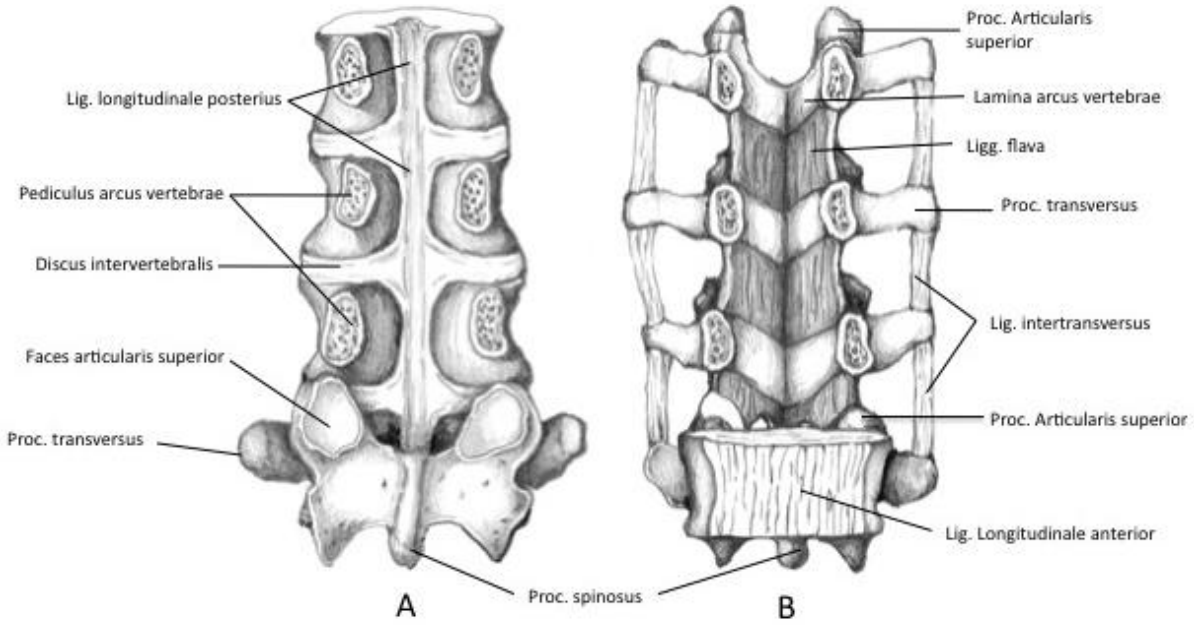



Figure 1 – (A) View of the anterior wall of the opened spinal canal at levels L2 – L5 with removed arcus vertebrae at pedicular level between L2 – L4; (B) view of the posterior wall of the spinal canal at levels L2 – L5, with removed corpus vertebrae between levels L2 - L4. Illustration by M.J. Verissimo based on illustrations in “Atlas of Anatomy” [11].

The intervertebral foramen is delimited above and below by a pedicle. Posteriorly, it is limited by the lamina and the zygapophysial joint. Anteriorly, the intervertebral foramen is surrounded by the intervertebral disc and the adjacent vertebral bodies above and below the disc [10].

Acquired spinal stenosis occurs whenever any of the structures surrounding the lumbar spinal canal and/or the intervertebral foramina are affected by disease or degeneration.

### 1.1.2. Cauda equina nerve roots

The lower end of the spinal cord is called the conus medullaris, and is located between D12 and L1. This reference, however, is subject to individual variation and is influenced by the degree of flexion or extension of the spine.

The lumbar enlargement of the spinal cord and the conus medullaris are the origins of a bundle of nerve roots that occupy the lumbar spinal canal from L2 to S5, the cauda equina (Fig.2a) [12]. The cauda equina is located in the subarachnoid space, within the dural sac, and is surrounded by cerebrospinal fluid (CSF). It comprises the lumbosacral, the coccygeal nerve roots and the filum terminale [13].

The nerve roots of the cauda equina have a certain degree of mobility within the dural sac [14], though nerve displacements are restricted by the arachnoidal trabecular ligaments [15].

A change from the neutral supine position (with flexed hip and knees) to the left lateral position significantly shifts the conus medullaris and the nerve roots anteriorly and laterally [16]. On an axial T2-weighted MR image, the cauda equina nerve roots normally lay on the posterior wall of the spinal canal, if the MRI is run with the patient in supine position (Fig. 2b).

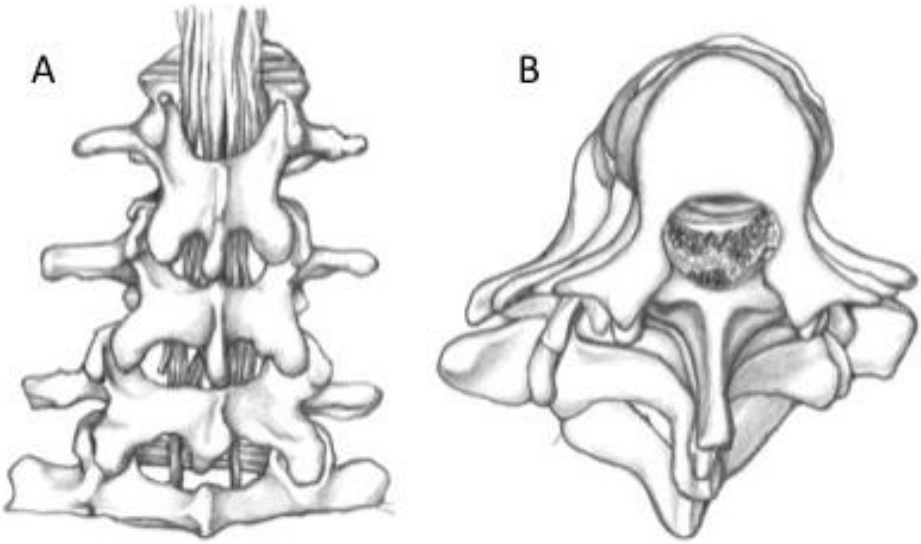



Figure 2 – (a) Posterior view of the cauda equina nerve roots within the spinal canal, without the dural sac; (b) cross-sectional image of the nerve roots. Illustration by M.J. Verissimo based on illustrations in Prats-Galino et al. [15].

The cauda equina nerve roots differ both in vascular supply and metabolically from other nerve roots [17]. According to Kobayashi et al. (2015), radicular arteries that run along the single cauda equine roots receive blood flow from both the proximal direction and the periphery [18]. Unlike peripheral nerves, cauda equina nerve roots have no regional, segmental blood supply [19]. Multiple anastomoses were seen among the radicular and the spinal cord arteries at the conus level [13].

Age-related degeneration of the lumbar spine, with hypertrophy of the yellow ligament and facet joints, along with shrinking of the discs may lead to a mismatch between the spinal canal and the cauda equina nerve roots.

### 1.2. Degenerative lumbar spinal stenosis: definition and epidemiological data

Degenerative LSS is a condition in which the narrowing of the central spinal canal, lateral recesses or intervertebral foramen (or a combination of these) impinges the vascular and neural structures [20]. The different location of the narrowing causes specific clinical symptoms.

LSS can be classified, according to the location of the narrowing, as follows:

- Central lumbar spinal stenosis (neurogenic claudication) (Fig. 3);
- Foraminal lumbar stenosis (radiculopathy)
- A combination of both.

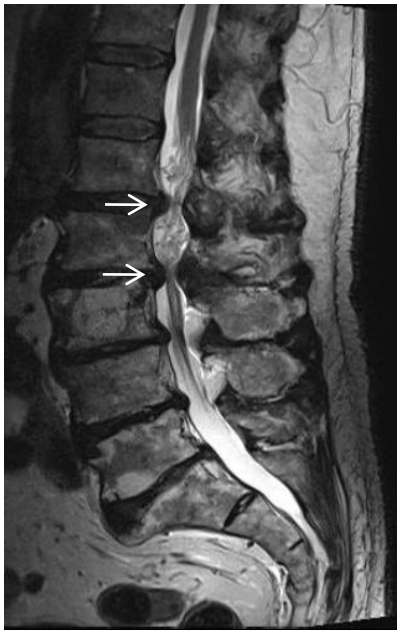


Figure 3 – Sagittal T2-weighted MR image showing a multilevel central lumbar spinal stenosis at levels L1-L2 and L2-L3 (white arrows), with coiled, apparently lengthened redundant nerve roots (RNR) above the stenotic levels.

Another LSS classification refers to the presence or absence of alignment deviations:

- Degenerative LSS with normal spinal alignment
- Degenerative LSS with spondylolisthesis [21]
- Degenerative LSS with de novo scoliosis [22]

LSS was first described by Verbiest in 1954 [23]. In his report of seven cases, the author described a clinical condition in which there were symptoms of compression of the caudal nerve roots while standing or walking, but not when at rest. The author suggested that the narrowing was due to constriction of the spinal canal by the articular processes. Epstein et al. (1962) referred to the work of Verbiest [23], who first identified the incongruity between the “capacity and the content” of the lumbar spinal canal as the cause of cauda equina nerve root compression [24]. Verbiest (1955) performed measurements of the spinal canal with a special instrument and concluded that an abnormally short antero-posterior diameter of the spinal canal was the cause of these symptoms [25].

LSS is now the most common cause of lumbar spinal surgery in patients over 65 [26]. According to the German Federal Statistical Office, the number of people aged 65 and over was 16.851 million in 2013, accounting for 20.9% of the entire population. By 2030, the number of people in this age group will have increased by 7% to

an estimated 21.794 million [27]. This predicted demographic evolution (Fig. 4) means the health care system in Germany (health insurance and health care providers) will be faced with new challenges, due to the increasing number of patients that will potentially need LSS decompression surgery.

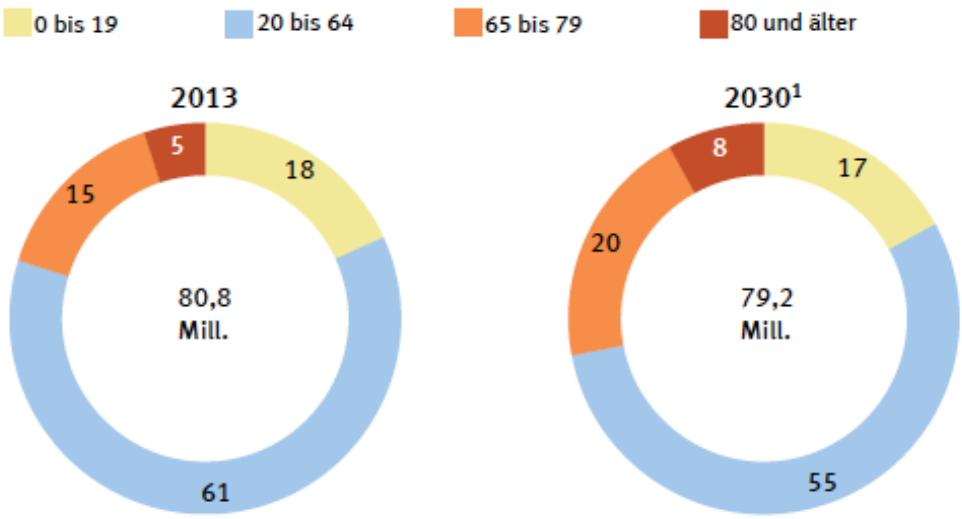



Figure 4 - Counted (2013) and predicted (2030) population in Germany by age group (%). Adapted from Pötzsch & Rößger [27]. Reproduced under terms of the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/)

According to a health report from the Federal Republic of Germany, lumbar spine surgery was placed third in the fifty most-performed surgeries nationwide, accounting for 289.249 (1.8%) procedures in 2015 [28]. The number of spine surgeries increased by 113.7%, from 52.036 in 2005 up to 111.243 in 2015 [28]. The massive increase of LSS decompressions within that time period contributed to the overall increase. This demographic trend will probably persist over the coming decades. Therefore, the importance of research on the diagnosis and treatment of LSS, as well as their socio-economic impact, cannot be overemphasised.

### 1.2.1. Pathogenesis of lumbar spinal stenosis

Degenerative LSS is the result of age-related changes in the lumbar spine. According to Griffith et al. (2016) factors that may influence the development of LSS are the pre-existing size of the central spinal canal and the degree of acquired degenerative spinal canal narrowing [29].

Watts (2013) performed measurements of the midsagittal and interpedicular diameters of the lumbar vertebral canal (L1-L5) in skeletal bones of 65 children aged between 3 and 17 and 120 adults (meaning those over 17) [30]. His investigation showed that children's midsagittal diameters were not significantly different to those of adults in any age category (3-5; 6-10; 11.14; and 15-17), indicating that midsagittal diameter reached adult size by 3 to 5 years of age. In contrast, the interpedicular diameter increased with age, until 15-17 [30]. According to these results, the anteroposterior spinal canal diameter is fully developed by the age of 5, and the transverse spinal canal diameter by 17.

In order to estimate the range for normal developmental size of the lumbar spinal canal size, Griffith et al. (2016) measured the mid-vertebral spinal canal cross-sectional area (CSA) and the depth and width of the spinal canal at each level, from L1 to L5, in 1,080 volunteers. The spinal canal CSA was smallest at L3 for both genders, increasing in size both cranially and caudally. The average spinal canal CSA at L3 was about 9% smaller than at L1, and 23% smaller than at L5 [29]. Furthermore, the spinal canal CSA was larger in males at all levels other than L2. After adjustment for body height and weight, the spinal canal was larger in females at L1, L2 and L3 and in males at L5. There was a weak but highly significant positive correlation between increasing body height and increasing overall lumbar spine CSA.

Spinal canal depth was also smallest at L3, increasing cranially and caudally. Once again, there was a weak but highly significant positive correlation between increasing body height and increasing overall lumbar spine depth for both genders. Spinal canal width increased gradually from L1 to L5 and was larger in males at all levels [29].

Despite the smallest spinal canal depth and CSA being at L3, as mentioned above, L4/L5 is the most common stenotic level [31]. Interestingly, L4/L5 is also the level with the largest flexion-extension range of motion in the lumbar spine [31]. This data shows that stability issues may also influence the narrowing of the spinal canal.

According to Lurie & Tomkins-Lane (2016) [20], age-related degenerative changes that may lead to LSS include (Fig. 5):

- Facet joint hypertrophy
- Disc bulging and / or loss of disc height
- Osteophyte formation
- Hypertrophy of the yellow ligament

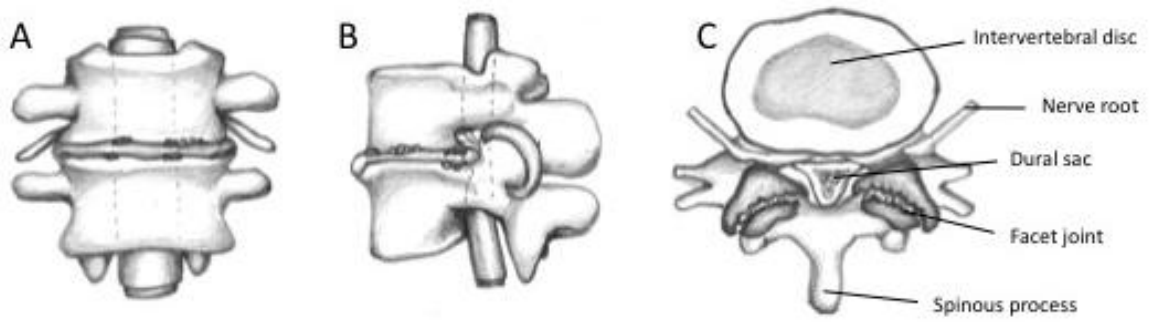



Figure 5 - Degenerative LSS: osteophyte formation and disc bulging (A+B) and facet joint hypertrophy (C). Thickening of the tissue surrounding the dural sac. The axial picture (C) shows only a minor degree of stenosis. Illustration by M.J. Verissimo according to an illustration in Lurie and Tomkins-Lane [20].

Kubosch et al. (2015) explained the pathogenesis of LSS as a dynamic process. According to the authors, “the progressive loss of height in a motion segment coupled with subluxation of the facet joints leads to changes in biomechanical forces, hypertrophy of the ligamentum flavum and spondylophyte formation around the facet joints. Together, the combination of a loss of height in the intervertebral space and the thickening of osseous and ligamentous structures result in progressive compression of the nerves” in the central spinal canal and/or in the intervertebral foramina. The compression can be exacerbated by bulging of the disc and spondylophytes of the vertebral endplates [32].

Depending on the anatomical structures involved in progressive degeneration, central or foraminal LSS can develop, or a combination of both. The narrowing of the lateral area of the central canal (subarticular recess) and/or of the foramen through which the nerve roots exit the spinal canal lead to the foraminal LSS [33]. In contrast, disc bulging, hypertrophy of the ligamentum flavum and hypertrophy of the subarticular recess are the causes of central spinal canal stenosis.

The available space within the lumbar spinal canal depends on the loading condition of the spine. Hansson et al. (2009) examined the lumbar spine of 24 patients by MRI, first without an external load and then with an axial load, corresponding to half of the body weight. External load decreased the CSA of the spinal canal significantly. Ligamentum flavum CSA increased significantly during external load and was responsible for 50% to 85% of the spinal canal narrowing [34].

Other causes of LSS can be excess proliferation of bone after spine surgery or as a result of infection or trauma [20]. Degenerative spondylolisthesis [21] and degenerative or idiopathic scoliosis [22] may also lead to LSS.

### 1.2.2. Pathophysiology of neurogenic claudication

The physiological mechanisms of neurogenic claudication are not completely clear [20]. There are two theories:

- The ischemic theory
- The venous stasis theory

These two theories are based on morphological observations made in specimens of patients who suffered from LSS.

Parke & Watanabe (1985) reported that cauda equina nerve roots show a unique structural, vascular and metabolic pattern. They hypothesised that the intrinsic vasculature and the connective tissue may be responsible for a “neuroischemic” response to pathologic mechanical stress (narrowing), associated with the degeneration of the lumbar spine [17]. Watanabe & Parke (1986) reported the case of an 83-year old patient with intermittent claudication, whose walking distance was restricted to 100m. Cessation of walking for a few minutes was accompanied by a significant pain reduction, which allowed the patient to continue walking. The autopsy revealed an extensive hypertrophy of L4/L5 facet joints combined with a spondylolisthesis of approximately 25% at the same level. The radicular arteries, although straightened, still demonstrated continuity across the narrowing. However, the veins were reduced in number and collapsed. Histological sections of this specimen showed neural changes, such as the loss in the number of neurons, especially large calibre fibres, numerous empty axons and various degrees of demyelisation. Visible non-neural changes included pia-arachnoid adhesions, interstitial fibrosis, and thick-walled congested veins. Distal from the narrowing, chronic demyelisation was observed [35]. The authors hypothesised that the thickening of the roots reduced the permeability of their membranes. At rest, the metabolism was sufficient for steering minimal activity in the muscles. However, following increased muscular activity, the discrepancy between increased metabolic requirements and nutritionally compromised fibres intensified the ischemia of the nerve roots in the stenotic area, leading to paresthesias, pain and weakness [20]. These are the basics of the ischemic theory.

The venous stasis theory postulates that inadequate oxygenation and the accumulation of catabolites of the squeezed nerve roots in thickened and congested veins increase the degree of root compression [20].

The narrowed central canal compressing vascular and neural structures are the key elements of the pathogenesis of LSS as demonstrated by Olmarker et al. (1990) [36]. In their study, progressive compression of the cauda equina in a porcine model was induced by an inflatable balloon. Impairment of the microcirculation with congested venular blood flow was achieved at pressures as low as 10mmHg. A 50mmHg compression caused an overall reduction of the nerve roots nutrition by 55%. The nutritional impairment was evaluated in terms of reduced solute transport and was seen as a consequence of the intraneural edema. Sensory fibres seemed to be slightly more susceptible to compression than motor fibres [19]. Furthermore, the changes induced by progressive compression were dependent on systemic blood pressure, since the threshold for nerve root impulse transmission was lowered by experimental hypotension and elevated by hypertension [36].

The effects of two-level cauda equina compression were also investigated: the impairment of nerve root nutrition and function was much more pronounced than in the case of single-level stenosis [19].

Long-lasting compression of the nerve roots leads to nutritional impairment, demyelination and axonal degeneration. The resulting ectopic impulse generation is thought to cause the typical claudication pain, paresthesias and cramps reported by LSS patients [19].

### 1.2.3. Diagnosis of LSS

The clinical diagnosis of LSS is mostly grounded in the patient's history. Physical examination may provide additional clues. Imaging, especially MRI, is instrumental [20, 37, 38].

The diagnosis of LSS may be considered in elderly patients presenting with a history of gluteal or lower extremity symptoms exacerbated by walking or standing, which improve or resolve with sitting or bending the trunk forward. Patients whose pain is not worsened by walking have a low likelihood of stenosis [39].

### 1.2.4. LSS Symptoms

The clinical symptoms of patients with LSS depend on the location of the narrowing. Therefore, patients with LSS present different clinical pictures. LSS may cause glute-

al and/or lower extremity pain or fatigue, progressive painful shortening of walking distance (neurogenic claudication), sensory disturbances of the lower limbs and occasional bladder dysfunction [1, 8]. These symptoms can occur with or without back pain. Walking or standing exacerbates the symptoms, while neutral sitting or sitting with a flexed trunk usually relieves symptoms [1].
According to Yamada et al. (2014) the only significant difference between symptoms of foraminal and central LSS was leg pain at rest. The prevalence of leg pain at rest, also characteristic for lumbar disc herniation, was significantly higher in the foraminal stenosis group (76% vs. 35%) [40].

As demonstrated by Kubosch et al. (2015), the diameter of the lumbar neuroforamen and central canal varies according to the position of the subject [32]. In an upright MRI study, the patients were examined in the supine position, in an 80° upright position and an 80° upright position with extension of the lumbar spine. The mean diameter of the neuroforamen at L5/S1 was smaller in the 80° upright position than in the supine position and even smaller in the 80° upright position with extension of the lumbar spine. The mean volume of the central spinal canal at L5/S1 was also smaller in an 80° upright position with extended lumbar spine than in a supine position. These dynamic changes of volume and diameter of the spinal canal and neuroforamen explain the body position dependent reduction or exacerbation of symptoms reported by LSS patients. These results may also explain the reported discrepancy between patient complaints and MR imaging.
In a study by Kuittinen et al. (2014) on the correlation between foraminal stenosis and patients' symptoms, there was no statistically significant correlation between MR images and clinical symptoms [33]. The MR images were run in the supine position, and this may have influenced the results.
Based on the data generated in the SPORT research trial by Weinstein et al. [41], Radcliff and colleagues reported that patients with LSS showing symptoms for under 12 months experienced significantly better outcomes with surgical and non-surgical treatment than those who had showed symptoms for over 12 months [42].

### 1.2.5. Differential diagnosis

LSS patients may complain about gluteal and/or lower-extremity pain or fatigue, progressive painful shortening of walking distances (neurogenic claudication) and sen-

sory disturbances in the lower limbs [1, 8]. An elderly patient who reports an exacerbation of symptoms by walking and standing and shows improvement with sitting or flexing the torso has a high likelihood of LSS. In contrast, patients whose pain does not increase with walking have a low likelihood of LSS [1].

Differential diagnosis is helpful, as some LSS symptoms are associated with other diseases. The most common diagnostic challenge consists of differentiating neurogenic claudication caused by LSS from vascular claudication related to peripheral arterial disease [43]. In both diseases, the patient complains of leg pain while walking, with a shortening in walking distance. Patients with vascular claudication often improve with rest while standing, whereas patients with neurogenic claudication need to sit down and flex the torso, or lean over something [20].

The following table highlights the main differences in symptom patterns between neurogenic and vascular claudication.

Table 1 - Symptom patterns of neurogenic vs. vascular claudication. Adapted from Thomas (2003) [44].

| Findings | Neurogenic Claudication | Vascular Claudication |
|---|---|---|
| Symptoms with sitting | No | No |
| Symptoms with flexion | No | No |
| Symptoms with extension | Yes | No |
| Symptoms with prolonged standing | Yes | No |
| Symptoms with prolonged walking | Yes | Yes |
| Symptoms when walking up an incline or in a flexed posture | No | Yes |
| Symptoms with stationary bicycling | No | Yes |

Differential diagnosis of LSS should exclude the following diseases [43, 45-47]:

- Vascular claudication (peripheral arterial disease)
- Radiating pain from the knee or hip joints
- Polyneuropathy
- Lumbar disc herniation (LDH)

### 1.2.6. Diagnostic imaging

Because of its outstanding soft-tissue contrast, MRI is considered the first choice for LSS imaging [48]. Other options are Computed Tomography (CT), CT- myelography, and plain X-ray films, which also are used in the evaluation of LSS patients.
The North American Spine Society (NASS) recommended the use of MRI in patients with a history and physical examination findings, which are consistent with LSS. In their guideline for the diagnosis and treatment of degenerative LSS, MRI is recommended as the most appropriate non-invasive tool to confirm the narrowing of the spinal canal or the presence of nerve root impingement [39]. In patients in whom MRI and CT-myelography are contraindicated, the NASS suggests the use of stand-alone CT. Furthermore, MRI or CT with axial loading is suggested for use as an additional test in selected cases [1, 39].

Several studies addressed the reliability of CT vs. MRI in the diagnosis of LSS. The results were sometimes contradictory. In a study by Alsaleh et al. (2017), three raters reviewed the CT and MR images of 54 patients with both a quantitative and a qualitative method. The intra- and inter-rater reliability showed that MRI was the more reliable tool [49]. In contrast, Morita et al. (2011), showed that the number of levels for LSS decompression as planned by MRI were less than by CT-myelography. The authors concluded that CT-myelography is more reliable and reproducible than MRI for the preoperative evaluation of LSS patients [48]. However, it should be noted that CT-myelography is an invasive procedure.
According to Lurie & Tomkins-Lane (2016) imaging should be used for diagnostic confirmation and procedure planning in patients considered for invasive therapy interventions, rather than as a routine initial evaluation [20].

There is no consensus regarding the specific diagnostic criteria for LSS based on MRI [50]. Different methods with a wide variability of criteria have been reported in the literature. They can be divided in three groups: quantitative criteria, semi-quantitative criteria, and qualitative criteria.
In a systematic review by Andreisek et al. (2013) to evaluate semi-quantitative and qualitative radiologic criteria used for the diagnosis of LSS, 14 different semi-quantitative or qualitative radiologic criteria were identified. They showed a wide variability in terms of their definitions and their intra- and inter-rater reliability [37].

The measurement of the dural sac CSA [51] and the assessment of the thickness of the ligamentum flavum [52] are examples of quantitative criteria. The evaluation of the distribution of cerebrospinal fluid (CSF) around the nerve roots in the central spinal canal (on axial T2-weighted MR images) [53] and the assessment of the nerve root sedimentation sign [54] are examples of qualitative methods.
In a survey to assess the strength of agreement among experts on the most relevant radiologic criteria, Mamisch et al. (2012) reported that there were no broadly-accepted quantitative criteria and only partially accepted qualitative criteria for the diagnosis of LSS. The partly accepted qualitative criteria included the lack of perineural intraforaminal fat, hypertrophic facet joint degeneration and absent fluid around the cauda equina nerve roots [55]. In the present study, a qualitative grading system based on the root-cerebrospinal fluid relationship on axial T2-weighted MRI images was used to assess LSS-grade [53].

### 1.2.7. Treatment options for lumbar spinal stenosis

The treatment options for LSS comprise non-surgical (conservative) therapies and surgical therapy procedures. Several studies investigated the effectiveness of non-surgical vs. surgical management of LSS, and came to differing conclusions [56-58].

#### 1.2.7.1. Conservative treatment modalities

According to Lurie & Tomkins-Lane (2016) [20], conservative treatment options for LSS are:

- Epidural injections (an invasive, non-surgical treatment)
- Physiotherapy
- Physical therapy
- Drug therapy
- Multimodal rehabilitation

In a Cochrane meta-analysis by Ammendolia et al. (2013) on the conservative treatment of LSS patients with neurogenic claudication [59], the authors concluded that the lack of moderate and high-quality evidence for non-operative treatment did not allow recommendations for the clinical practice. Twenty-one trials were included. There was some evidence that some drugs (prostaglandin, gabapentin or methylcobalamin) could potentially increase walking distance. There was also some evidence (from a single trial) that epidural steroid injections may improve pain relief,

function and quality of life for up to two weeks compared to home exercise or inpatient physiotherapy. Furthermore, there was some evidence that multimodal non-operative treatment is less effective than surgical decompression with or without fusion [59].

In a study by Matsudaira et al. (2016) on the predictive factors for subjective improvement with non-surgical treatment of LSS patients, 274 patients (mean age 71) were followed for a period of three years [60]. In 30% of the patients, nonsurgical treatment resulted in subjective improvements. The LSS condition worsened or did not change in 25.4% of the patients. In 44.3% (82) of the patients, surgery was performed within the 3-year follow-up. Significant predictors for subjective improvement in LSS symptoms through non-surgical treatment were the absence of cauda equina symptoms (OR= 3.31; p= 0.003); the absence of degenerative spondylolisthesis/degenerative scoliosis (OR= 2.53; p= 0.02); and duration of symptoms for under 1 year (OR= 3.81; p= 0.007) [60]. In other words, the likelihood of subjective symptom improvement with non-surgical therapy increased if the patient had a foraminal stenosis (no central stenosis), no lumbar spine alignment deviations and the onset of symptoms had lasted for under 1 year.

*1.2.7.1.1. Epidural injections*

Epidural steroid and/or lidocaine injections are widely used in the treatment of LSS symptoms. However, there is no consensus as to whether these injections are effective and safe. Flores et al. (2015) reported that epidural steroid injections probably give little or no symptom reduction in LSS patients [61]. In contrast, Davis et al. (2017) concluded that epidural steroid injections are a reasonable treatment for LSS and can result in long-term relief in a high percentage of patients [62].

Bresnahan et al. (2013) performed a systematic review to assess the effectiveness of epidural steroid injections for the treatment of LSS patients. The authors found a limited amount of data that suggested epidural steroid injections are effective in some patients for improving short-term outcomes. However, results differed depending on study design, outcome measurements used and comparison groups [63].

*1.2.7.1.2. Physiotherapy and physical therapy in the treatment of LSS*

According to the NASS guidelines for the diagnosis and treatment of degenerative LSS [39], there is insufficient evidence to make recommendations for or against the use of physical therapy or exercise as stand-alone treatment for degenerative LSS.

There is also not enough evidence to make recommendations for or against traction, electrical stimulation and TENS in the treatment of patients with LSS.

Studies published in recent years have compared different physical therapy modalities [64, 65], physical or physiotherapy modalities with decompression surgery [66-68], and physical therapy vs. epidural injections [69]. LSS severity levels in the patients' inclusion criteria being not very well described, together with interventions which were not well described and small sample sizes compromising the internal and external validity of these studies may explain the lack of results.

As mentioned above, symptoms of LSS patients differ depending on the structures affected by the narrowing and on the degree of LSS severity. Patients with different complaints may respond differently to the same therapy. Further studies should consider subgroups of patients, defined by the severity of symptoms or other criteria.

The assumption that "one physical therapy treatment fits all patients with LSS" may be challenged when investigating the effectiveness of different physiotherapy and physical therapy treatment options for LSS. While evaluating the effectiveness of such treatment options, the assessment of long-term results should be considered. A massage might decrease local muscle pain immediately, but the effect of this intervention will probably not last long.

Despite the lack of evidence, Lurie & Tomkins-Lane (2016) [20] reported that physiotherapy is an acceptable treatment for LSS. Physiotherapy-related treatments include: exercise (aerobics, strength, flexibility); specific exercises in lumbar flexion (e.g. cycling); bodyweight-supported treadmill walking; muscle coordination training; balance training, etc.

Tomkins et al. (2010) performed a telephone survey to provide preliminary insight in current physiotherapy practice in the treatment of LSS patients. The authors interviewed 50 LSS patients and 75 physiotherapists. The patients reported massage (27%), strengthening exercises (23%), flexibility exercises (18%) and thermotherapy (heat/ice) (14%) as the most frequent treatment modalities they had received. In comparison, the most advocated treatment modalities by the physiotherapists were flexibility exercises (87%), stabilisation (86%), strengthening exercises (83%), thermotherapy (76%), acupuncture (63%) and joint mobilisation (62%) [70].

Goren et al. (2010) investigated whether physiotherapy exercises vs. exercises plus ultrasound were effective in the treatment of patients with LSS. According to their

results, therapeutic exercises were effective for pain and disability, and the addition of ultrasound to exercise therapy lowered analgesic intake substantially [64].
In a systematic review by Macedo et al. (2013) on the effectiveness of physical therapy, 10 studies were included. The authors could not draw conclusions from their review regarding the best treatment option for LSS. There was some evidence which suggested that surgery leads to better long-term (2 year) outcomes for pain and disability (but not for walking distance) when compared to physical therapy [68].
In a secondary analysis based on the SPORT research trial data [41], Fritz and colleagues investigated the association between physical therapy and long-term outcomes in patients receiving conservative treatment. Physical therapy was associated with the reduced likelihood of patients receiving surgery within one year [71].
The NASS suggest developing randomised controlled trials with long-term follow-ups and validated outcome measures to generate level II evidence concerning the efficacy of physical therapy and physiotherapy in the treatment of LSS [39]. While planning such trials, measures to avoid bias during the patient selection should be taken. Patients with different LSS severity grades may respond differently to conservative therapy.

#### 1.2.7.2. Surgical therapy

Surgical therapy for LSS is considered for patients who do not respond to conservative treatments. Therefore, surgical therapy for LSS is almost always an elective procedure.
However, there is no widely-accepted consensus among surgeons regarding indications for surgery [20]. Among surgery treatment modalities, decompression of the neural structures is usually the first option.
There are a variety of different decompression techniques and approaches, the description of which falls beyond the scope of this work.
In a study by Fukushima et al. (2017) on the prognostic factors associated with the need for surgical treatment in patients with LSS, 274 patients were followed for a period of 3 years. In 82 (29.9%) of patients, surgery was performed during the follow-up period. The presence of cauda equina symptoms (central stenosis) and degenerative spondylolisthesis/scoliosis were prognostic factors associated with the need for surgery in patients with LSS [72].

In a meta-analysis performed by Machado et al. (2016) on the surgical options for lumbar spinal stenosis, 24 trials were included, with a total of 2,352 patients. None of the trials compared surgery with no treatment, placebo or sham surgery. Each trial compared two or more surgical techniques. The primary outcomes were pain intensity, physical function, quality of life and recovery. In their conclusions, the authors pointed out the lack of evidence on the efficacy of surgery for LSS, since to date, no trials have compared surgery with no treatment, placebo or sham surgery. Furthermore, the results show that decompression plus fusion and interspinous process spacers were not superior to conventional decompression alone [73].

The two-year results of the Spine Patient Outcome Research Trial (SPORT) have shown that surgery for spinal stenosis was more effective when compared to non-operative treatment. The patients treated surgically had a greater improvement in pain relief and function [41]. The same results were obtained after four years [74]. However, the long-term results of this randomised trial with a concurrent observational cohort trial after 8 years have shown that the early benefits of surgery registered out of 4 years converged over time, with no significant treatment effect for surgery seen 6-8 years afterwards for any of the primary outcomes of the study. The authors concluded that patients with symptomatic spinal stenosis showed diminished benefits of surgery between 4 and 8 years, while outcomes in the observational cohort remained stable [75].

### 1.3. Redundant nerve roots of the cauda equina in LSS patients

Around 40% [5-8] of patients with LSS scheduled for decompression surgery have evidence of thickened, buckling, serpentine- or loop-shaped redundant nerve roots (RNRs) of the cauda equina on their T2-weighted sagittal or axial MR images.

RNRs have been associated with the pathogenesis of cauda equina claudication in degenerative LSS [5].

#### 1.3.1. Definition of redundant nerve roots (RNRs)

RNRs were first described by Verbiest in 1954 [23] and named by Cressman and Pawl in 1968 [76]. In the decade following the first publication by Cressman and Pawl [76], several further case reports on RNRs were published [77-82]. Neurogenic claudication was present in the history of most of the reported cases. Since advanced imaging techniques (CT, MRI) were not available at that time, RNRs were only visible

by means of myelography. In all cases, RNRs were confirmed by surgical exploration, including laminectomy and intradural inspection (Fig. 6 and 7).

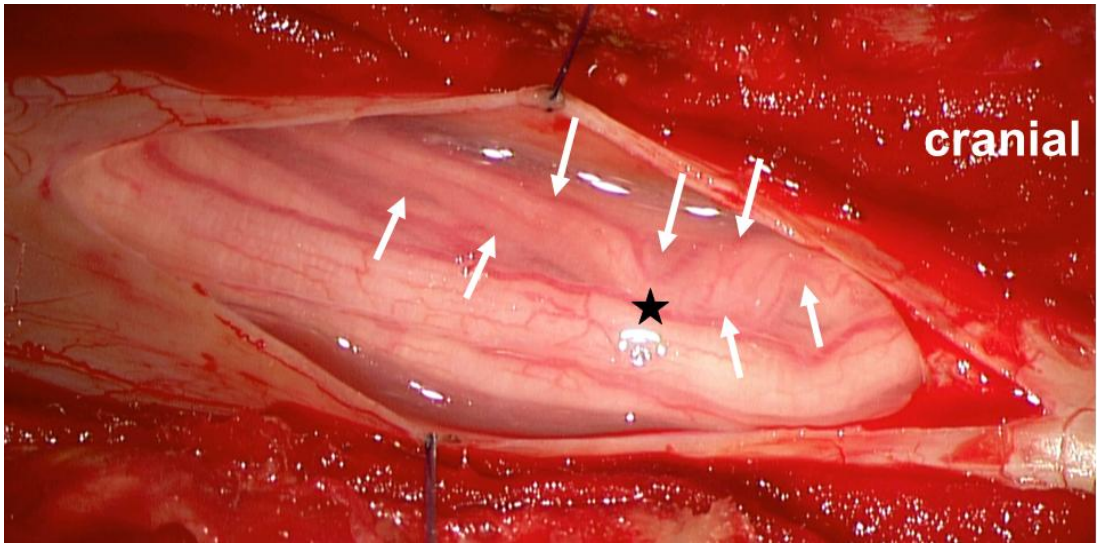



Figure 6 - Midline opening of the dural sac at L3 level. The arachnoid is still intact and a tortuous cauda nerve root (white arrows) with kinking of the vessel (black star) is visible.

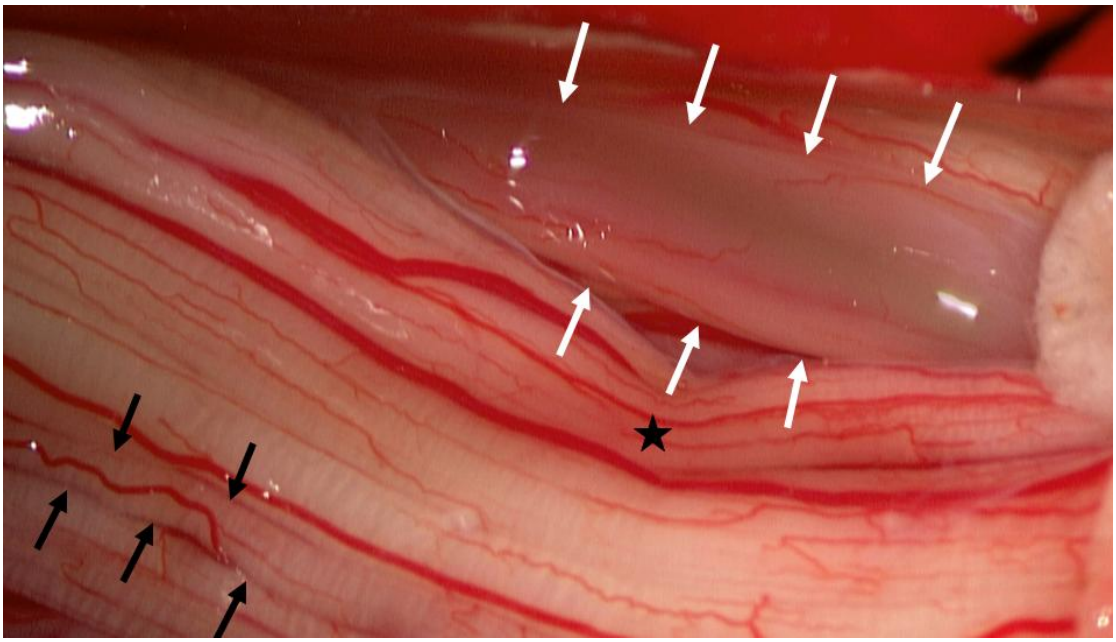


Figure 7 - A normal sized cauda nerve root (black arrows). An edematous root appears glossy and with increased diameter (white arrows); it runs underneath the tortuous root (black star) visible in figure 6.

Banse et al. [2] defined RNRs as “loops” whenever the root had a fully horizontal course, which can be visualised in the sagittal plane as either a linear horizontal course of the root (Fig. 8b, yellow arrow) a “dot” sign corresponding to the right-left course of the orthogonal cut of the root (Fig. 8b, blue arrows), or as a straight line

instead of a dot in the axial plane (Fig. 8c, yellow arrow). Roots were defined as “serpentine” when a sinusoidal deflection was observed on saggital T2-weighted slices without horizontalization (Fig. 8a).

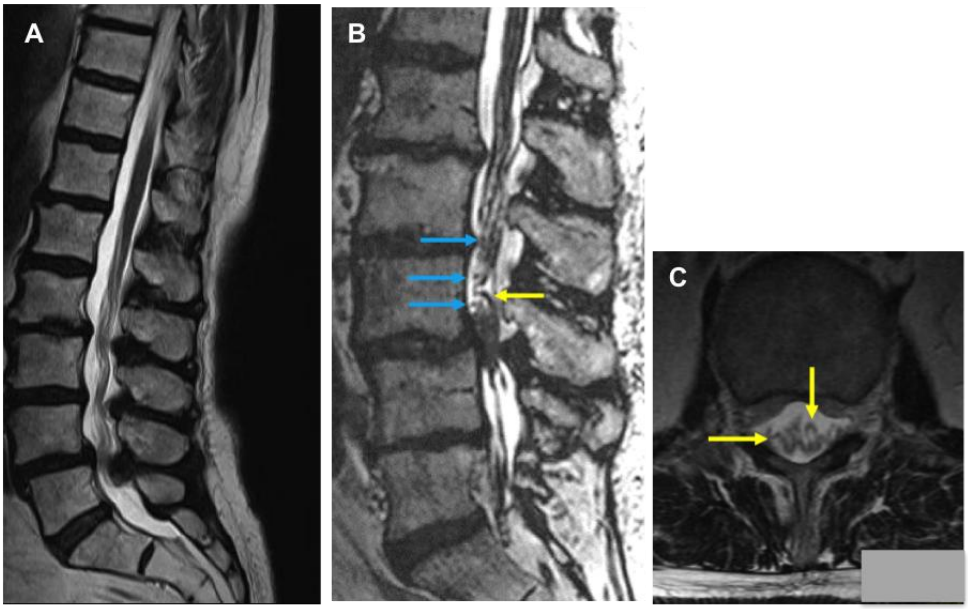



Figure 8 - (a) Sagittal T2-weighted MR image with serpentine shaped redundant nerve roots (RNRs); (b) Sagittal T2-weighted MR image with loops as dots (blue arrows) or as a linear horizontal course of the root (yellow arrows); (c) axial T2-weighted image showing horizontal loops (yellow arrows)

### 1.3.2. Etiology of RNR

The origin of RNRs is not clear. In a case report, Cressman and Pawl (1968) wrote that “there must be a compressive factor, such as the osteoarthritic bar, to constrict the caudal sac and produce the serpentine myelographic defect by displacing most of the redundant root in one direction” [76].

A decade later, Thulin et al. (1978) [82] reported on five cases, stating that “the pathogenesis of root redundancy is obscure”. The authors concluded that neurogenic claudication was likely due to at least two factors: the compression of the spinal content and the existence of one or more redundant roots. They foresaw that a wider use of modern imaging and surgical exploration would probably show a higher prevalence of RNRs than was supposed [82]. The authors were correct. Recent MRI-based studies have shown that around 40% of LSS patients admitted for surgery show RNRs on their MR images [5-8].

Tsuji et al. (1985) investigated the pathogenesis of RNRs and neurogenic claudification in patients with LSS. The authors reported that RNRs might be a sort of

“neuronal compensation resulting from a longer duration stenosis that causes a sort of friction neuritis” [4]. They hypothesised that multiple factors might contribute to neurogenic claudication, such as the magnitude of RNRs, the severity of stenosis, a narrowed thecal sac, the age-dependent shortening of the spinal canal, and dynamic or postural factors. They observed that redundant root configurations were more severe in older patients. The authors concluded that cauda equina redundancy is related to the spinal ageing process and the magnitude of mechanical gripping by the narrowed spinal canal [4]. They were the first investigators to bring an ageing-dependent shortening of the lumbar spine in connection to the pathogenesis of RNR. This hypothesis was not further investigated in any publications that followed.

Suzuki et al. (1989) published a paper entitled “Redundant nerve roots of the cauda equina: clinical aspects and consideration of pathogenesis” [8]. In their study, the authors confirmed that RNRs were not rare, since they were found in 42% of LSS patients. Almost all RNRs cases were associated with evident dural constriction caused by severe LSS. The authors concluded that redundancy of the nerve roots was probably the long-term pathological consequence of thecal sac constriction: the nerve roots were gradually squeezed out by the stenotic level. Under this squeezing force, the nerve roots tended to become elongated and thickened [8]. This is the so-called “squeeze theory”, which is the most-cited explanatory model for RNRs, and indeed, recent studies continue to refer to it [3, 5, 83].

### 1.4. Aims of the present study

The aims of the present work are threefold:

- To investigate the clinical significance of the redundant nerve roots of the cauda equina in patients with lumbar spinal stenosis.
- To investigate whether patient demographics and MRI-based measurements can predict redundant nerve roots in LSS.
- To test the inter- and intra-rater reliability of a new classification system for RNRs, the ASED classification.

The three aims described above were transformed into three research questions. Each research question was investigated as a single project, with its own methodology.

The first research question was investigated by means of a systematic literature review with meta-analysis. The second research question was investigated with a ret-

rospective database-based cohort study. The third research question was investigated with an inter- and intra-rater reliability study.
Hereafter, the three projects, with their methodologies and results, will be described in detail.

## 2. The clinical significance of redundant nerve roots of the cauda equina in lumbar spinal stenosis patients: A systematic literature review and meta-analysis.



### 2.1. Introduction

Degenerative lumbar spinal stenosis (LSS) is a narrowing of the spinal canal, with constriction of the neural structures by the surrounding bone and yellow ligament. Depending on the exact location of the narrowing, patients present neurogenic claudication symptoms (e.g. buttock or leg pain while walking or standing which is relieved by sitting or lumbar flexion) or radicular leg pain [41]. LSS is the most common reason for lumbar spine surgery in adults over 65 [26].
LSS patients with neurogenic claudication symptoms often present thickened, buckling, serpentine or loop-shaped redundant nerve roots (RNR) on their T2-weighted sagittal or axial MR images. Studies have revealed that the prevalence rates of RNR among LSS patients can range from 33.8% to 43.3% [5, 6, 84, 85].

#### 2.1.1. Definition of redundant nerve roots

RNRs were first described by Verbiest in 1954 [23] and were named by Cressman and Pawl in 1968 [76]. In their case report, the authors referred to the myelogram of a 67 year old patient who showed serpentine defects at L3/ L4 level, with an almost complete block at L4/L5 level. The authors reported that after the dura was opened, “a markedly redundant nerve root, coiled upon itself in a serpentine manner” was visible [76]. In the decade after this first publication, several case reports were published [77-82]. Neurogenic claudication was present in the history of most of the reported cases. Since advanced imaging techniques (CT, MRI) were not available by that

time, RNRs were only visible by means of myelography and were confirmed intraoperatively. In an anatomical study by Suzuki et al. [84], six specimens with evidence of RNRs were investigated. The authors clearly stated that RNRs are nerve roots that become elongated and thick through constriction.

The development of computer tomography (CT), CT-myelography and magnetic resonance (MR) imaging enabled the reliable diagnosis of RNRs outside the operating room. Nowadays, lumbar sagittal and axial T2-weighted MR images are the most widespread examination used in detecting RNRs.

RNRs can be described as “serpentines” when a sinusoidal deflection of the cauda equina nerve roots is observed on sagittal T2-weighted MR images without horizontalization (Fig. 8A). RNRs can be defined as “loops” whenever the root has a fully horizontal course, which can be visualised in the sagittal plane as either a linear horizontal course of the root (Fig. 8B), as a dot sign corresponding to the right-left course of the orthogonal cut of the root (Fig. 8B), or as a straight line instead of a dot in the axial plane (Fig. 8C).

#### 2.1.2. Why it is important to perform this review

Little is known about the etiology and clinical significance of RNRs of the cauda equina in patients with LSS. Do patients with LSS that show evidence of RNRs on their MR images differ from those without RNRs in time since the onset of symptoms, pre- and postoperative clinical scores, and postoperative recovery? The objective of this meta-analysis is to investigate the effects of RNRs on the clinical outcomes in patients with LSS.

### 2.2. Materials and methods

#### 2.2.1. Study design

This systematic review and meta-analysis was performed according to the preferred reporting items for systematic reviews and meta-analysis (PRISMA) statement [86].

#### 2.2.2. Criteria for considering studies for this review

Prospective or retrospective cohort studies in which LSS patients with evidence of RNRs were compared to LSS patients without evidence of RNRs on their MR images were considered. Older adults with a clinical diagnosis of LSS were the target population for the study samples.

The outcomes to be investigated were patient-specific variables (e.g. age, gender) and clinical variables (e.g. clinical scores before and after decompression surgery, time since the onset of symptoms, cross-sectional area of the affected level and recovery rates).

### 2.2.3. Search methods for the identification of studies

A systematic electronic database search was conducted on PubMed, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Web of Science and MEDLINE by one author (CJM), who received training from the Cochrane Collaboration at the Cochrane Center, Freiburg University, Germany. The first three databases were last searched on 9th April 2018; MEDLINE was last searched on 16th April 2018.

### 2.2.4. Search strategy

The search strategy used in PubMed is presented in Table 2. Different medical subject heading (Mesh) terms were used and combined. Since the term "redundant nerve roots" is not defined as a Mesh-term by PubMed, the full-term was used. Identical strategies were used to search the Web of Science, MEDLINE and CINAHL. The results of the three searches were imported with the use of the software program EndNote™ X8.1 (Clarivate Analytics, Philadelphia, PA, USA).

Table 2 - Search Strategy PubMed (last search on April 9th 2018)

| Search | Term |
|---|---|
| #1 | Spinal stenosis (Mesh) |
| #2 | Lumbar vertebrae (Mesh) |
| #3 | Intermittent claudication (Mesh) |
| #4 | Cauda equina (Mesh) |
| #5 | Polyradiculopathy (Mesh) |
| #6 | Spinal nerve roots (Mesh) |
| #7 | Nerve compression syndromes (Mesh) |
| #8 | Spinal canal (Mesh) |
| #9 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 |
| #10 | Redundant nerve root (full term) |
| #11 | Redundant nerve roots (full term) |
| #12 | RNR |
| #13 | #10 OR #11 OR #12 |
| #15 | #10 AND #13 |

### 2.2.5. Eligibility criteria and study selection

After duplicates and studies not related to RNRs were removed, two authors (CJM and LP) screened the remaining studies for eligibility. To be eligible, the studies had to be directly related to RNRs and had to be available in full.

To be selected for meta-analysis purposes the studies had to fulfil the following criterion: cohort study design (prospective or retrospective) with group comparison of LSS patients with evidence vs. without evidence of RNRs. Prospective or retrospective cohort studies without group comparison, case reports and reports of case series were excluded.

### 2.2.6. Data extraction and management

Two authors (CJM and HH) extracted data from the studies included independently, using a data extraction sheet. Disagreements were resolved by consensus. The following data was extracted from each study into a data extraction sheet: First authors name, publication year, total number of patients involved, number of patients in each group (with and without evidence of RNRs), mean age of the patients, gender, mean cross-sectional area (CSA) of the affected level, symptom duration, clinical score before surgery, clinical score after surgery and recovery rate. One author (CJM) entered the data into the Review Manager software. A second author (HH) conducted random checks on accuracy.

In the study by Ono et al. [87], groups A and B were merged together as RNR+ for meta-analysis purpose, because the patients in both groups showed evidence of RNRs. Group C was labelled RNR-.

### 2.2.7. Data analysis

Mean ± standard deviation (SD) for each group was recorded from the available data for continuous variables. Frequency was used for nominal variables. To determine the clinical significance of RNRs, RNR+ and RNR- groups were compared. The weighted mean difference (WMD) and its 95% confidence interval (95% CI) were calculated for continuous variables. Odd ratios with 95% CI were calculated for nominal variables. Forest plots were created to display effect estimates with 95% CI for individual studies and pooled results. In each case, we tested for statistical heterogeneity. This was examined graphically on the forest plot and statistically through the calculation of the $I^2$ statistic. The $I^2$ statistic estimates the percentage of variability in ef-

fect estimates due to heterogeneity rather than sampling error (chance). An $I^2$ value greater than 50% was considered substantially heterogeneous, and a random-effects meta-analysis was used in these instances, rather than a fixed-effect model. The Review Manager (RevMan) software program version 5.3 (The Nordic Cochrane Center, Copenhagen, Denmark) [88] was used to perform the statistical analyses. For each test, a level of 0.05 was accepted as the criterion for statistical significance.

#### 2.2.8. Assessment of risk of bias in the studies included

Two authors (CJM and HH) independently assessed the potential risk of bias of the studies included with the use of the Methodological Index for Non-randomised Studies (MINORS) [89]. The MINORS tool consists of eight items specially designed for non-comparative studies and four additional items for comparative studies. The items are scored 0 if not reported; 1 when reported but inadequate; and 2 when reported and adequate. The global ideal score for comparative studies is 24. For ambiguities, final scores were decided upon in a consensus meeting.

## 2.3. Results

### 2.3.1. Results of the search

The records identified through the electronic database search were screened. After removal of duplicates and studies not related to the subject, 51 records directly related to RNRs remained for detailed viewing. Of these, 43 studies did not pass the inclusion criteria and were excluded: there were thirty single or multiple case reports [76-82, 90-112], two cohort studies without group comparison [4, 113], one meta-analysis [114], one narrative review [115], one cadaver study [84], two commentaries [83, 116], two letters [117, 118], three references for which the abstract was unavailable [119-121] and one abstract for a conference poster without any detailed data [2]. A total of eight studies remained, and were assessed in detail. Of these, one further study was excluded due to a cohort comparison not having been performed [122]. The remaining seven studies [3, 5-9, 87], comprising a total of 1046 LSS patients (308 patients with evidence of RNRs and 738 patients without evidence of RNRs), were included for analysis (Fig. 9). The oldest study was published in 1989 [8] and the latest in 2016 [5]. The characteristics of the studies are displayed in Table 3.

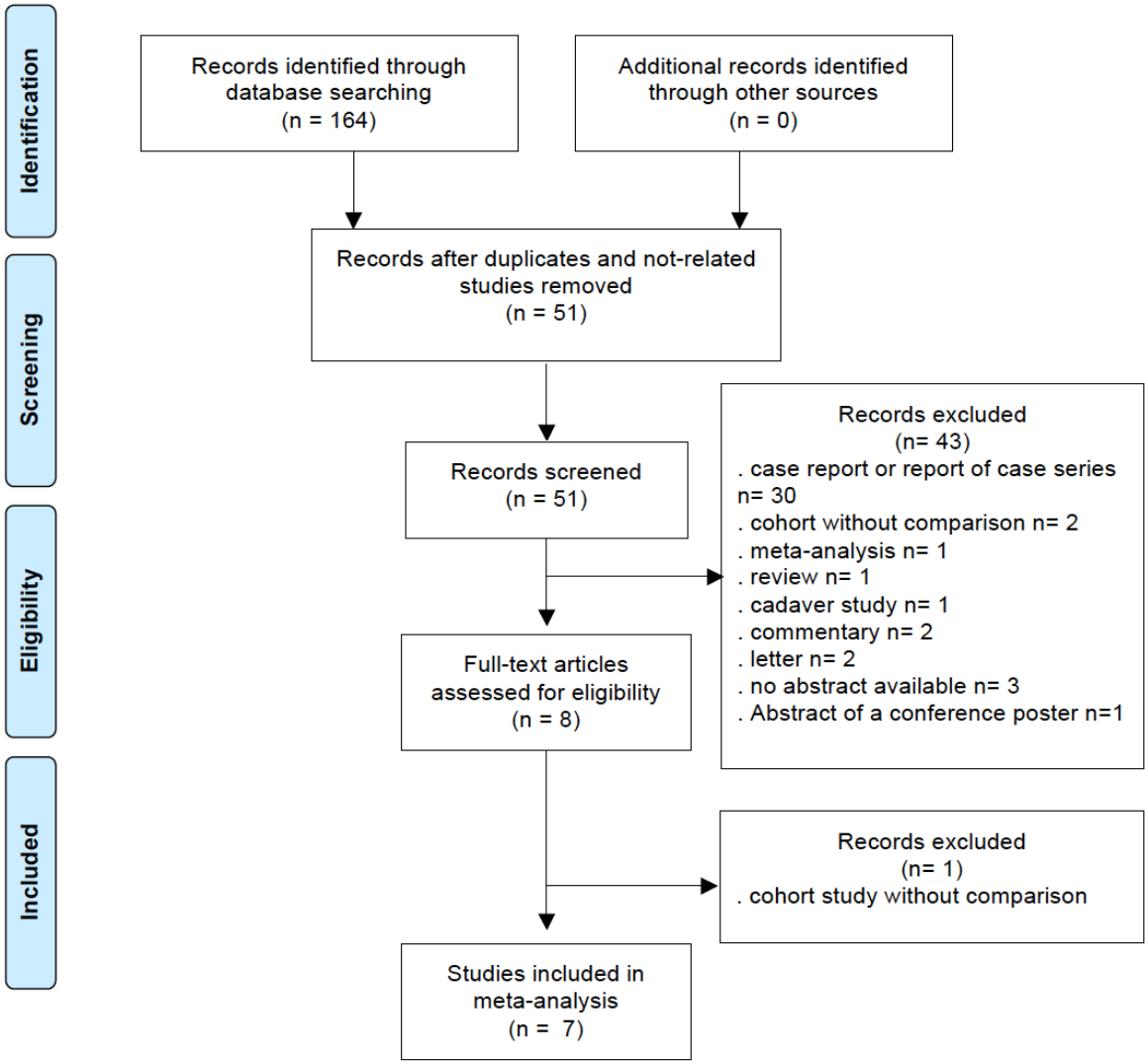



Figure 9 - PRISMA flow diagram for retrieved and selected studies

Table 3 - Characteristics of the studies included

| Reference | Year | Origin | Design | Sample size N (RNR+/RNR-) | Outcomes assessed |
|---|---|---|---|---|---|
| Suzuki et al. [8] | 1989 | Japan | NR | N= 130 (55/75) | Age, gender, symptom duration, pre- and post-operative SCS scores, SCS score improvement, constriction of the dural sac |
| Ono et al. [87] | 2007 | Japan | PC | N= 44 (30*/14) | Age, gender, symptom duration, CSA, pre-operative JOA scores, post-operative JOA scores, RNR shape (loop vs. serpentine) |
| Min et al. [9] | 2008 | Korea | PC | N= 68 (23/45) | Age, gender, symptom duration, pre-operative JOA score, post-operative JOA score, recovery rate, success rate, mean diameter of the spinal canal |
| Hur et al. [6] | 2012 | Korea | RC | N= 106 (45/61) | Age, Pre-operative pain, symptom duration, CSA, dural sac CSA, Oswestry disability index (ODI) |
| Savarese et al. [7] | 2014 | Brazil | RC | N= 105 (43/66) | Age, CSA, presence or absence of spondylolisthesis |
| Pouresia et al. [3] | 2015 | Iran | RC | N= 500 (75/425) | Age, gender, level of stenosis, intracanal protuberance in the site of stenosis, length of RNR, location of RNR in relation to stenosis, shape of RNR |
| Chen et al. [5] | 2016 | China | RC | N= 93 (37/56) | Age, gender, pre-operative JOA score, symptom duration, post-operative JOA score, recovery rate, lumbar lordosis angles, ROM, lumbar extension |

NR= Not reported; PC= Prospective cohort; RC= Retrospective cohort; RNR+= Group with evidence of RNRs; RNR- = Group with no evidence of RNR; SCS = Objective evaluation system for patients with Lumbar Spinal Stenosis (LSS); CSA= cross sectional area; JOA= Japanese Orthopedic Association Score

* = Groups A and B were merged together as RNR+ group, because in both groups patients had evidence of RNRs. Group C= RNR-

### 2.3.2. Risk of bias in studies

The average MINORS score for the studies was 14.1 (11 to 16) out of 24 (Table 4). Two of the studies were cohort comparisons performed prospectively [9, 87] and four were retrospective comparisons [3, 5-7]. In one study, it was not clear whether it was conducted prospectively or retrospectively [8]. In none of the studies was a sample size calculation performed. Only one study [7] included a control group of subjects without LSS symptoms. Due to the research question, baseline equivalence of the groups (RNR+ vs. RNR-) was not possible. These are some of the reasons for the low mean MINORS scores.

Table 4 - Risk of bias assessment of the studies, with the use of the methodological index for non-randomised studies (MINORS)

| **Criteria / Included studies** | **Suzuki, K. et al. (1989) [8]** | **Ono, A. et al. (2007) [87]** | **Min, J.H. et al. (2008) [9]** | **Hur, J.W. et al. (2012) [6]** | **Savarese, L.G. et al. (2014) [7]** | **Pouresia, M. et al. (2015) [3]** | **Chen, J. et al. (2016) [5]** |
|---|---|---|---|---|---|---|---|
| 1. A clear stated aim | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 2. Inclusion of consecutive patients | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| 3. Prospective/Retrospective collection of data | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 4. Endpoints appropriate to the aim | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 5. Unbiased assessment of endpoints | 1 | 2 | 1 | 1 | 2 | 2 | 2 |
| 6. Follow-up period appropriate to the aim | 0 | 0 | 2 | 0 | 0 | 0 | 2 |
| 7. Loss to follow up less than 5% | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 8. Prospective calculation of the study size | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Additional criteria in the case of comparative study | | | | | | | |
| 9. An adequate control group | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| 10.Contemporary groups | 1 | 2 | 2 | 2 | 2 | 2 | 2 |
| 11. Baseline equivalence of groups | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 12. Adequate statistical analyses | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| **Final score** | **11** | **14** | **15** | **13** | **16** | **14** | **16** |

The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate). The global ideal score for non-comparative studies is 16, and for comparative studies, 24.

### 2.3.3. Clinical significance of RNRs

#### 2.3.3.1. Patients' age

All the studies included [3, 5-9, 87] provided data on the patients' ages. RNR+ patients were significantly older than RNR- patients, WMD 5.7, 95% CI [2.2 to 9.2], p= 0.001 (Fig. 10A).

#### 2.3.3.2. Duration since symptom onset

Five studies [5, 6, 8, 9, 87] provided data on symptom duration, which was defined as the time frame in months since the onset of symptoms until the patients were scheduled for decompression surgery. RNR+ patients showed a longer time since the onset of symptoms, WMD 13.2, 95% CI [-0.2 to 26.7], p= 0.05 (Fig. 10B).

#### 2.3.3.3. Cross-sectional area (CSA)

In three studies [6, 7, 87], the CSA of the most affected level was measured. The CSA ($mm^2$) was smaller in RNR+ patients, WMD -12.2, 95% CI [-17.7 to -6.7], p< 0.0001 (Fig. 10C).

#### 2.3.3.4. Preoperative clinical scores

Five studies assessed preoperative clinical scores [5, 6, 8, 9, 87] with four different instruments. Two versions of the Japanese Orthopedic Association scoring system (JOA) were used in three studies [5, 9, 87]. Two studies [5, 9] used a JOA scores version with a scale ranging from 0 to 17, with 17 being the best possible score. Another study [87] used a JOA score version with a scale reaching from -6 to 29, with 29 being the best possible score. The Objective Evaluation System for Patients with Lumbar Spinal Stenosis (SCS score) was used in one study [8] and the Oswestry Disability Index (ODI score) was used in another study [6]. For means of comparison, the data from the JOA and ODI was converted into a 0 to 100 scale, with 100 being the best possible score. The formula used for JOA score data conversion was (measured JOA score x 100)/17 or (measured JOA score x 100)/29, depending on the JOA score version used.

RNR+ patients had lower preoperative clinical scores than RNR- patients. The WMD of -3.8, 95% CI [-7.9 to 0.2] was not statistically significant, p= 0.07 (Fig. 10D).

#### 2.3.3.5. Postoperative clinical scores

Four studies [5, 8, 9, 87] assessed postoperative clinical scores. In one study [8], the mean follow-up time was not reported. The reported mean follow-up times in the other three studies were 51.3 [87], 14 [9] and 17 [5] months. In the study by Suzuki et al. [8], the postoperative clinical score was assessed in a lower number of patients. The pooled postoperative clinical score of RNR+ patients was significantly lower than RNR- patients, WMD -4.7, 95% CI [-7.32 to -2.1], p= 0.0004 (Fig. 10E).

#### 2.3.3.6. Recovery rate

Four studies [5, 8, 9, 87] calculated the recovery rates (%) of patients after decompression surgery. In the study by Suzuki et al. [8], the recovery rate was calculated only for a lower number of patients, whose postoperative SCS scores were available. The recovery rate of RNR+ patients was lower, WMD -9.8, 95% CI [-14.8 to -4.7], p= 0.0001 (Fig. 10F).

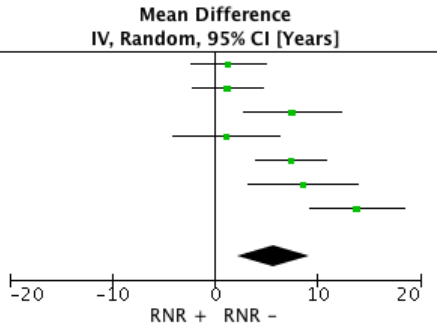
#### 2.3.3.7. Gender

Four studies [3, 5, 8, 9] provided data on the distribution of male and female patients across the RNR+ and RNR- groups. The calculated odd ratios for male and female group affiliation (RNR+ or RNR-) were statistically insignificant in both cases (Fig. 10 G).

A

| Study or Subgroup | Mean Age RNR + Mean [Years] | SD [Years] | Total | Mean Age RNR − Mean [Years] | SD [Years] | Total | Weight | Mean Difference IV, Random, 95% CI [Years] |
|---|---|---|---|---|---|---|---|---|
| Chen 2016 | 64.1 | 8.2 | 37 | 62.8 | 9.4 | 56 | 15.3% | 1.30 [-2.31, 4.91] |
| Hur 2012 | 66.3 | 9 | 45 | 65.1 | 9 | 61 | 15.5% | 1.20 [-2.27, 4.67] |
| Min 2008 | 66.6 | 8 | 23 | 59.1 | 11.8 | 45 | 13.7% | 7.50 [2.75, 12.25] |
| Ono 2007 | 67.6 | 4.4 | 30 | 66.5 | 9.6 | 14 | 13.0% | 1.10 [-4.17, 6.37] |
| Pouresia 2015 | 59 | 13.7 | 75 | 51.6 | 14.9 | 425 | 15.6% | 7.40 [3.99, 10.81] |
| Savarese 2014 | 61.6 | 12.6 | 43 | 53 | 15.4 | 62 | 12.8% | 8.60 [3.23, 13.97] |
| Suzuki 1989 | 59.1 | 10.6 | 55 | 45.3 | 16.1 | 75 | 14.0% | 13.80 [9.20, 18.40] |
| **Total (95% CI)** | | | **308** | | | **738** | **100.0%** | **5.74 [2.21, 9.28]** |

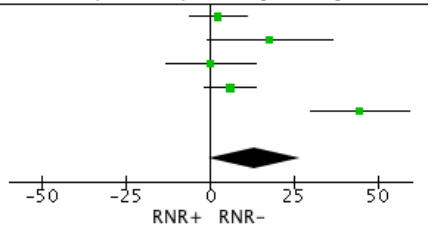
Heterogeneity: Tau² = 17.79; Chi² = 29.40, df = 6 (P < 0.0001); I² = 80%
Test for overall effect: Z = 3.19 (P = 0.001)




B

| Study or Subgroup | Symptom Duration RNR+ Mean [Months] | SD [Months] | Total | Symptom Duration RNR− Mean [Months] | SD [Months] | Total | Weight | Mean Difference IV, Random, 95% CI [Months] |
|---|---|---|---|---|---|---|---|---|
| Chen 2016 | 30.9 | 22.4 | 37 | 28.6 | 17.4 | 56 | 22.2% | 2.30 [-6.24, 10.84] |
| Hur 2012 | 37 | 58.2 | 45 | 19.2 | 30.9 | 61 | 16.6% | 17.80 [-0.89, 36.49] |
| Min 2008 | 23.3 | 24.8 | 23 | 23.1 | 29.3 | 45 | 19.7% | 0.20 [-13.07, 13.47] |
| Ono 2007 | 16.8 | 13.4 | 30 | 10.8 | 11.4 | 14 | 22.6% | 6.00 [-1.66, 13.66] |
| Suzuki 1989 | 56.5 | 53.4 | 55 | 12 | 19.8 | 75 | 18.8% | 44.50 [29.69, 59.31] |
| **Total (95% CI)** | | | **190** | | | **251** | **100.0%** | **13.25 [-0.24, 26.74]** |

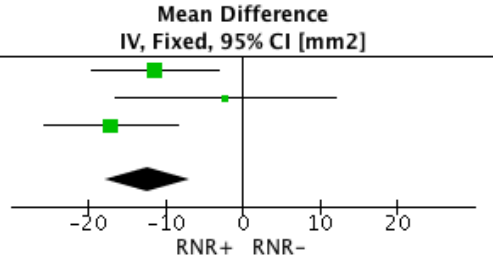
Heterogeneity: Tau² = 194.43; Chi² = 27.58, df = 4 (P < 0.0001); I² = 85%
Test for overall effect: Z = 1.92 (P = 0.05)




C

| Study or Subgroup | CSA RNR+ Mean [mm2] | SD [mm2] | Total | CSA RNR− Mean [mm2] | SD [mm2] | Total | Weight | Mean Difference IV, Fixed, 95% CI [mm2] |
|---|---|---|---|---|---|---|---|---|
| Hur 2012 | 49.4 | 18.6 | 45 | 60.7 | 24.3 | 61 | 45.1% | -11.30 [-19.47, -3.13] |
| Ono 2007 | 61.9 | 18.6 | 30 | 64.1 | 24.1 | 14 | 14.8% | -2.20 [-16.47, 12.07] |
| Savarese 2014 | 51.2 | 22.8 | 43 | 68.3 | 21.5 | 62 | 40.1% | -17.10 [-25.76, -8.44] |
| **Total (95% CI)** | | | **118** | | | **137** | **100.0%** | **-12.28 [-17.77, -6.79]** |

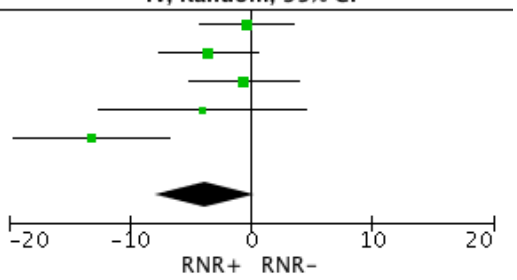
Heterogeneity: Chi² = 3.16, df = 2 (P = 0.21); I² = 37%
Test for overall effect: Z = 4.39 (P < 0.0001)



D

| Study or Subgroup | Pre-OP CS RNR+ Mean | SD | Total | Pre-OP CS RNR- Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Chen 2016 | 48.1 | 9.4 | 37 | 48.4 | 9.3 | 56 | 24.0% | -0.30 [-4.19, 3.59] |
| Hur 2012 | 76.3 | 11.2 | 45 | 79.8 | 10.1 | 61 | 23.3% | -3.50 [-7.64, 0.64] |
| Min 2008 | 48.8 | 8.2 | 23 | 49.4 | 10.5 | 45 | 22.2% | -0.60 [-5.14, 3.94] |
| Ono 2007 | 48 | 12 | 30 | 52 | 14.1 | 14 | 13.1% | -4.00 [-12.54, 4.54] |
| Suzuki 1989 | 58.9 | 19.8 | 55 | 72.1 | 16.8 | 75 | 17.3% | -13.20 [-19.67, -6.73] |
| **Total (95% CI)** | | | **190** | | | **251** | **100.0%** | **-3.83 [-7.91, 0.24]** |

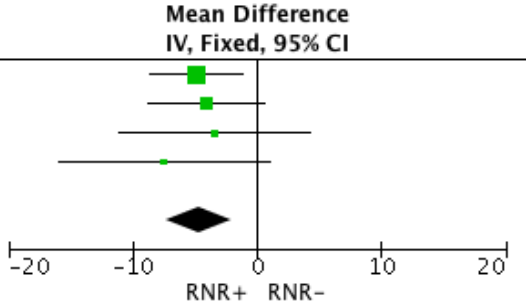
Heterogeneity: $Tau^2 = 14.07$; $Chi^2 = 12.59$, df = 4 (P = 0.01); $I^2 = 68\%$
Test for overall effect: Z = 1.84 (P = 0.07)




E

| Study or Subgroup | Post-OP CS RNR+ Mean | SD | Total | Post-OP CS RNR- Mean | SD | Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Chen 2016 | 66.2 | 8.9 | 37 | 71.1 | 9.3 | 56 | 47.7% | -4.90 [-8.66, -1.14] |
| Min 2008 | 69.4 | 9.4 | 23 | 73.5 | 8.8 | 45 | 31.6% | -4.10 [-8.72, 0.52] |
| Ono 2007 | 87.2 | 8.9 | 30 | 90.6 | 13.4 | 14 | 11.4% | -3.40 [-11.11, 4.31] |
| Suzuki 1989 | 83.6 | 14.3 | 22 | 91.1 | 9.3 | 9 | 9.3% | -7.50 [-16.02, 1.02] |
| **Total (95% CI)** | | | **112** | | | **124** | **100.0%** | **-4.72 [-7.32, -2.12]** |

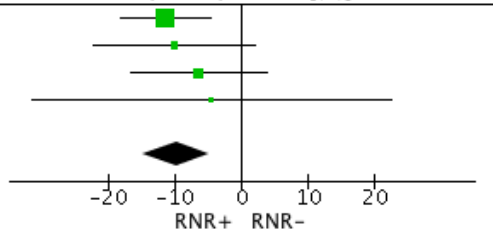
Heterogeneity: $Chi^2 = 0.60$, df = 3 (P = 0.90); $I^2 = 0\%$
Test for overall effect: Z = 3.56 (P = 0.0004)




F

| Study or Subgroup | Recorery Rate RNR+ Mean [(%)] | SD [(%)] | Total | Recovery Rate RNR- Mean [(%)] | SD [(%)] | Total | Weight | Mean Difference IV, Fixed, 95% CI [(%)] |
|---|---|---|---|---|---|---|---|---|
| Chen 2016 | 46.6 | 14.4 | 37 | 58.1 | 18.8 | 56 | 55.6% | -11.50 [-18.27, -4.73] |
| Min 2008 | 52.1 | 25.4 | 23 | 62.2 | 22.3 | 45 | 16.9% | -10.10 [-22.36, 2.16] |
| Ono 2007 | 74.1 | 14.2 | 30 | 80.5 | 17.1 | 14 | 24.0% | -6.40 [-16.70, 3.90] |
| Suzuki 1989 | 63.8 | 31.5 | 22 | 68.3 | 36.3 | 9 | 3.5% | -4.50 [-31.62, 22.62] |
| **Total (95% CI)** | | | **112** | | | **124** | **100.0%** | **-9.80 [-14.84, -4.75]** |

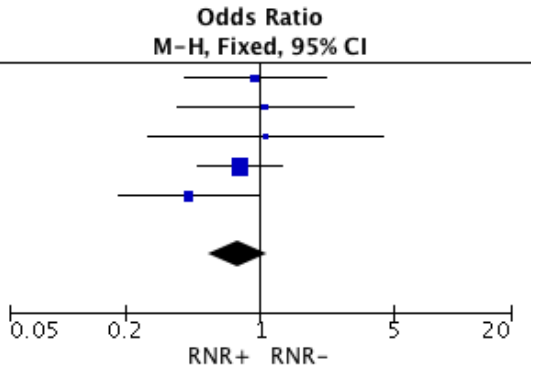
Heterogeneity: $Chi^2 = 0.81$, df = 3 (P = 0.85); $I^2 = 0\%$
Test for overall effect: Z = 3.81 (P = 0.0001)



G

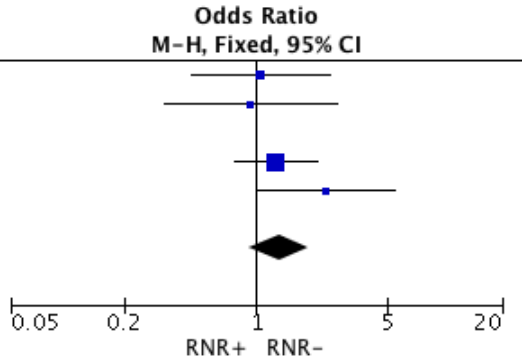
| Study or Subgroup | Male Patients RNR+ Events | Total | Male Patients RNR− Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Chen 2016 | 16 | 37 | 25 | 56 | 15.5% | 0.94 [0.41, 2.18] |
| Min 2008 | 8 | 23 | 15 | 45 | 9.1% | 1.07 [0.37, 3.07] |
| Ono 2007 | 9 | 30 | 4 | 14 | 5.3% | 1.07 [0.26, 4.34] |
| Pouresia 2015 | 28 | 75 | 183 | 425 | 47.4% | 0.79 [0.48, 1.31] |
| Suzuki 1989 | 38 | 55 | 63 | 75 | 22.7% | 0.43 [0.18, 0.99] |
| **Total (95% CI)** | | **220** | | **615** | **100.0%** | **0.77 [0.54, 1.09]** |
| Total events | 99 | | 290 | | | |

Heterogeneity: Chi² = 2.72, df = 4 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.47 (P = 0.14)




| Study or Subgroup | Female Patients RNR+ Events | Total | Female Patients RNR− Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Chen 2016 | 21 | 37 | 31 | 56 | 20.6% | 1.06 [0.46, 2.44] |
| Min 2008 | 15 | 23 | 30 | 45 | 13.6% | 0.94 [0.33, 2.70] |
| Ono 2007 | 31 | 30 | 10 | 14 | | Not estimable |
| Pouresia 2015 | 47 | 75 | 242 | 425 | 52.3% | 1.27 [0.77, 2.10] |
| Suzuki 1989 | 17 | 55 | 12 | 75 | 13.5% | 2.35 [1.01, 5.45] |
| **Total (95% CI)** | | **220** | | **615** | **100.0%** | **1.33 [0.92, 1.90]** |
| Total events | 131 | | 325 | | | |

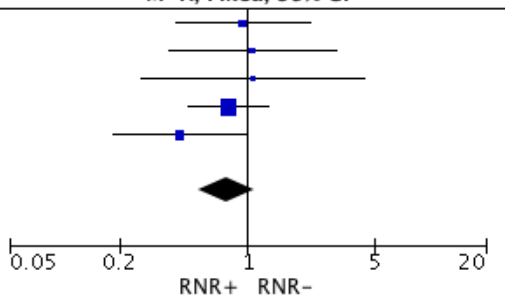
Heterogeneity: Chi² = 2.49, df = 3 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.54 (P = 0.12)



G

| Study or Subgroup | Male Patients RNR+ Events | Total | Male Patients RNR− Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Chen 2016 | 16 | 37 | 25 | 56 | 15.5% | 0.94 [0.41, 2.18] |
| Min 2008 | 8 | 23 | 15 | 45 | 9.1% | 1.07 [0.37, 3.07] |
| Ono 2007 | 9 | 30 | 4 | 14 | 5.3% | 1.07 [0.26, 4.34] |
| Pouresia 2015 | 28 | 75 | 183 | 425 | 47.4% | 0.79 [0.48, 1.31] |
| Suzuki 1989 | 38 | 55 | 63 | 75 | 22.7% | 0.43 [0.18, 0.99] |
| **Total (95% CI)** | | **220** | | **615** | **100.0%** | **0.77 [0.54, 1.09]** |
| Total events | 99 | | 290 | | | |

Heterogeneity: Chi² = 2.72, df = 4 (P = 0.61); I² = 0%
Test for overall effect: Z = 1.47 (P = 0.14)




| Study or Subgroup | Female Patients RNR+ Events | Total | Female Patients RNR− Events | Total | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Chen 2016 | 21 | 37 | 31 | 56 | 20.6% | 1.06 [0.46, 2.44] |
| Min 2008 | 15 | 23 | 30 | 45 | 13.6% | 0.94 [0.33, 2.70] |
| Ono 2007 | 31 | 30 | 10 | 14 | | Not estimable |
| Pouresia 2015 | 47 | 75 | 242 | 425 | 52.3% | 1.27 [0.77, 2.10] |
| Suzuki 1989 | 17 | 55 | 12 | 75 | 13.5% | 2.35 [1.01, 5.45] |
| **Total (95% CI)** | | **220** | | **615** | **100.0%** | **1.33 [0.92, 1.90]** |
| Total events | 131 | | 325 | | | |

Heterogeneity: Chi² = 2.49, df = 3 (P = 0.48); I² = 0%
Test for overall effect: Z = 1.54 (P = 0.12)

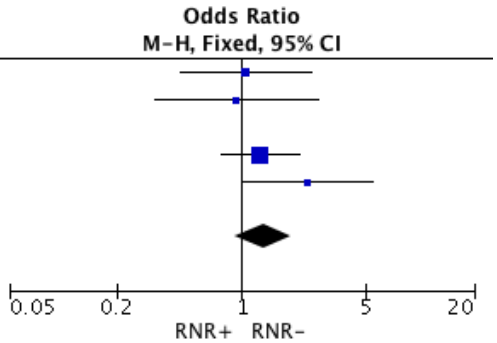



Figure 10 - Forest plots for (A) mean patient age before decompression surgery; (B) mean duration since symptom onset for RNR+ vs. RNR- patients; (C) mean cross-sectional area (CSA); (D) mean preoperative clinical scores; (E) mean postoperative clinical scores; (F) mean recovery rate; and (G) forest plots for the odd ratios for group affiliation (RNR+ or RNR-) for male and female patients.

## 2.4. Discussion

### 2.4.1. Summary of main results

LSS patients with evidence of RNRs on their MR images were older, had a longer duration of symptoms and higher degrees of spinal canal stenosis, as given by a narrow CSA, than LSS patients without evidence of RNRs. After surgery, RNR+ patients had worse clinical scores and lower recovery rates. These are the main results of the meta-analysis.

### 2.4.2. Quality of the evidence

The quality of the results of a meta-analysis always depends on the quality of the studies included. It is not possible to implement a randomised controlled trial to study the effect of RNRs on clinical outcomes in LSS patients, because the patients cannot be randomised into groups. A cohort design with group comparison must therefore be used. Such a study can be carried out with a prospective or retrospective data collection design. The studies included were all cohort studies with group comparisons. There were two prospective studies and four retrospective studies. The design of one study was not clear. All the studies had weak points, as revealed by the risk of bias assessment. The quality of studies investigating this question should be improved in the future. Sample size calculation should be performed in advance, regardless of the use of a prospective or retrospective design. The follow-up period should be well defined, and should comprise at least two repeated measures after surgery, e.g. six and 12 months after surgery. The outcomes assessed in future studies should be extended to other patients-related factors (e.g. body height, body weight, body mass index, degree of LSS and number of levels involved). Additionally, functional parameters should be assessed, such as the maximal walking distance pre- and postoperatively, or the timed-up and go test. These are functional tests, which could provide additional quantitative information on the physical condition of the patients.

RNR+ patients had worse clinical scores and lower recovery rates after decompression surgery. The factors responsible for these poorer outcomes are unclear. Do incomplete decompressions and/or permanent nerve injuries play a role? In a study by Yokoyama et al. [122], the dural sac CSA was measured pre and post decompression surgery in LSS patients with evidence of RNRs. After surgery, the patients

were divided in two groups: patients with RNRs resolution and patients with persistent RNRs. The patients with persistent RNRs had worse functional outcomes, although their mean dural sac CSA expanded significantly after surgery and was not significantly different to that of the patients with resolution of RNRs. Longer symptom duration and permanent nerve injury caused by the compression may be behind the worse clinical outcomes of RNRs after decompression surgery.

### 2.4.3. Agreements and disagreements with other studies or reviews, and study limitations

One systematic narrative review [115] has been published on this issue. The authors reported that the clinical significance of RNRs in the progression of LSS is controversial, but some literature suggested that RNRs indicate a tendency towards worse postoperative results. The results of our meta-analysis confirm the negative prognostic value of RNRs in patients with LSS. The same authors suggested that radiologists should look for RNRs and describe them in their reports. We share this opinion, however, to the best of our knowledge, a validated and reliable classification system that allows the systematic description of RNRs on MR images still does not exist.

More recently, a meta-analysis was published which comprised four studies involving a total of 297 patients [114]. The authors concluded that RNRs in association with LSS could be viewed as a potentially powerful prognostic indicator of worse postoperative recovery. Our results confirm their findings but are more robust, as our review included 7 studies involving a total of 1046 patients.

The present meta-analysis also has limitations. In three of the outcomes analysed, the $I^2$ test showed moderate to substantial heterogeneity. We have searched for the reasons for heterogeneity, but haven't been able to find a plausible explanation. There is only limited advice for authors on how to deal with heterogeneity in meta-analyses. In these three cases, we have decided to perform a random effects meta-analysis. Other options would have been omitting meta-analysis or excluding studies. In view of the limited number of studies on this topic, omitting meta-analysis or excluding studies were not considered to be alternative options. This may be considered a limitation of the study.

Only four studies assessed clinical outcomes after decompression surgery [5, 8, 9, 87]. In one of the studies, the follow-up time was not reported [8]. The follow-up time of the other three studies differed, ranging from 14 to 51 months. Despite the wide

array of follow-up times, the authors decided to perform a meta-analysis for this outcome. The different follow-up times may have influenced the results and are also a potential limitation of the study

In a study by Yokoyama et al., 33 RNR+ patients were followed after surgical decompression surgery [122]. Of these, 24 (73%) showed no evidence of RNRs seven days after surgery, whereas nine (27%) patients still showed persistent RNRs. Four months after surgery, five further patients showed resolution of RNRs and at nine months, one more patient joined this group. The remaining three patients had persistent RNRs, even with sufficient expansion of the dural sac after surgery, as measured by the dural sac CSA. All these three patients had loop-shaped RNRs preoperatively. In view of this, the question arises as to whether loop-shaped RNRs are a sign of advanced LSS progression with worse prognostic value in comparison to serpentine-shaped RNRs. The influence of RNR shape, extension and direction on clinical symptoms, symptom onset, functional status and recovery of the patients has still not been clarified. To investigate these questions, a validated classification system for RNRs is needed.

### 2.4.4. Implications for practice

There is limited quality evidence that RNR+ patients are older, have longer symptom duration, worse preoperative clinical scores and show higher degrees of lumbar stenosis as given by their narrow CSA of the affected level in comparison to RNR- patients. There is also limited quality evidence that RNR+ patients recover slowly and achieve worse clinical scores after decompression surgery in comparison to RNR- patients. In view of these results, RNR can be seen as a negative prognostic factor in LSS patients.

### 2.4.5. Implications for research

More high-quality prospective cohort studies are required to confirm the negative effects of RNRs on clinical outcomes in patients with LSS. Studies with larger study samples that consider the assessment of more patient-related variables and functional tests beside clinical scores are needed.

## 3. Do patient demographics and MRI-based measurements predict redundant nerve roots in lumbar spinal stenosis? A retrospective database cohort comparison.



### 3.1. Introduction

Lumbar spinal stenosis (LSS) is the most common reason for lumbar spine surgery in patients over 65 [26]. Around 40% of all LSS patients scheduled for decompression surgery show evidence of RNRs of the cauda equina on their preoperative magnetic resonance (MR) images [5, 6, 84, 85].

RNRs are described as thickened, buckling or coiled nerve roots that typically assume serpentine or loop-shapes in T2-weighted MR images [2]. When the standard T2-weighted sequence is equivocal, adding a single slice MRI-myelography sequence may help to identify RNRs [92]. Serpentine-shaped RNRs are present when a sinusoidal deflection is observed on sagittal T2-weighted MR images without horizontalization (Fig. 8A). The roots can be defined as loops whenever they show a fully horizontal course, which can be visualised in the sagittal plane as either a linear horizontal course of the root (Fig. 8B), as a “dot” sign corresponding to the right-left course of the orthogonal cut of the root (Fig. 8B), or as a straight line instead of a dot in the axial plane (Fig. 8C) [122]. RNRs were mostly observed above the stenotic level, but can also be found below, or both above and below the stenotic level [9, 92].

Reports indicate that LSS patients with preoperative evidence of RNRs (RNR+) have a significantly longer mean duration of neurological symptoms and experience less improvement in their ability to walk after surgery than patients without RNRs (RNR-) [5, 8, 9, 87].

The aetiology and pathogenesis of RNRs are still unclear. RNRs seem to be a negative prognostic factor in LSS patients. Therefore, the investigation of factors that may predict the presence of RNRs is of clinical importance. The present study aims to investigate whether patients’ demographics and MRI-based measurements can predict RNRs in patients scheduled for LLS decompression surgery.

## 3.2. Materials and methods

### 3.2.1. Study design and sample

This is a retrospective database-based cohort comparison study. Reporting of the present study follows the STROBE Statement guidelines for reporting observational studies [123].

Sample size was calculated using G*Power version 3.1.9.2 (Psychology Department, Duesseldorf University, Germany) [124]. For sample size calculation, the variable LSS level was chosen and the following assumptions were used: 68% of RNR+ patients show one stenotic level and 32% show two or more stenotic levels; in contrast, 84% of RNR- patients show one stenotic level and 16% show two or more stenotic levels. Based on these assumptions, an odds ratio of 2.47 was calculated. Thereby, if $\alpha = 0.05$ and 1-ß error probability = 0.90, there is a 90% chance of correctly rejecting the null hypothesis that a particular value of the main predictor variable (LSS Level) is not associated with the outcome variable, with a total sample size of 300 patients (150 per group) (Appendix I).

#### 3.2.1.1. Inclusion criteria

Inclusion criteria included a symptomatic lumbar spinal canal stenosis requiring surgical decompression without fixation, and the availability of good quality preoperative MRI, including sagittal T1- and T2-weighted images and axial T2-weighted images in the picture archive and communication system (PACS) of the institution (Schön Clinic Hamburg Eilbek).

#### 3.2.1.2. Exclusion criteria

Exclusion criteria included a previous history of lumbar spine surgery, lumbar deformity as scoliosis or vertebral slip requiring fixation and congenital, traumatic, infectious or neoplastic diseases of the lumbar spine.

#### 3.2.1.3. Sample

The preoperative data of 300 consecutive LSS patients who underwent single or multi-level microsurgical bilateral decompression via a unilateral approach (also known as a “cross-over” or “over the top” technique) without any fixation were evaluated. The ipsilateral facet was resected one third and the contralateral was left alone, whereas the thickened yellow ligament was completely removed. The surgery was

performed between December 2012 and August 2016 at the Clinic for Spine Surgery, Schön Clinic Hamburg. During this time window, 2273 patients underwent decompression surgery for LSS. 2113 thereof underwent decompression surgery without fixation. Of this second group, patients with and without RNRs on their preoperative MR images were selected from August 2016 backwards, until both groups contained 150 patients.

The Ethics Committee of the Federal State of Hamburg deliberated upon the research proposal of the present study (File PV5817). According to the ethics committee, retrospective database-based studies do not require approval when the data is acquired, saved and treated anonymously. This applies to the present study.

### 3.2.2. Procedures

Firstly, the 300 patients were independently assigned to either the RNR+ or the RNR- group by a senior neuroradiologist, a senior orthopedic surgeon and a senior neurosurgeon. The definition of RNRs used to assign the patients into groups is that which is described in the “Introduction” section to this chapter. The agreement between the three raters concerning patient group affiliation was almost perfect (Fleiss $k$ = .92; $p < 0.001$). The transition between a normal course of the cauda equina nerve roots and a very beginning type of serpentine RNRs is sometimes subtle, and may lead to disagreement between the raters. In such cases, the amount of straight roots on one side of the key stenotic level and the amount of serpentine RNRs on the opposite side of the stenotic level was evaluated. If the pathologic pattern (serpentine RNRs) was agreed to be prevalent (most of the roots showed a serpentine shape), the case was considered RNR+. Eighteen disagreements were reclassified in a consensus conference. Next, LLS and SLLS were measured. Finally, an LSS level and LSS grade were assessed for each patient.

### 3.2.3. Potential predictors

The following patient-related and MRI-based factors were used as potential predictors: age, gender, body height (BH), length of the lumbar spine (LLS), segmental length of the lumbar spine (SLLS), relative LLS (rLLS), relative SLLS (rSLLS), the amount of lumbar spine alignment deviation (LSAD) as given by the difference between SLLS and LLS, the number of stenotic levels involved (LSS level) and the grade of severity of the stenosis (LSS grade) on a progressive scale from A to D [53].

3.2.3.1. Length of lumbar spine (LLS) and segmental length of lumbar spine (SLLS) measurements

Three authors (LP, JL, TF) measured LLS and SLLS independently on the sagittal T2-weighted image showing the mid-plane of the conus using the AGFA Impax 6 software (AGFA Health Care, GmbH, Bonn, Germany). For LLS measurements, a straight line was drawn from the posterior-superior corner of the L1 vertebral body to the posterior-superior corner of the S1 vertebral body (Fig. 11, red line). For SLLS measurements, a line was drawn from the posterior-superior corner of the L1 vertebral body to the posterior-superior corner of the L2 vertebral body. This procedure was repeated until the line reached the posterior-superior corner of the S1 vertebral body (Fig. 11, blue line). LLS and SLLS were both determined by the length of the line (mm) [125]. Inter-rater reliability for both measurements had been tested previously. The estimated intraclass correlation coefficient (ICC) calculated with a two-way mixed effects model with an absolute agreement definition was .99 (95% C.I. ranging from .98 to .99) and .99 (95% C.I ranging from .97 to .99) for LLS and SLLS measurements, respectively.

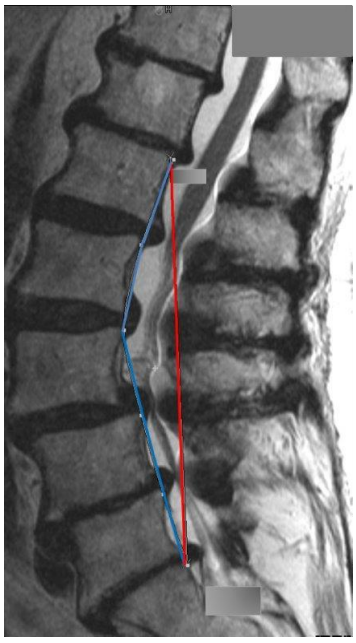


Figure 11 - Sagittal T2-weighted MR image used for length of lumbar spine (LLS, red vector) and segmental length of lumbar spine (sLLS, blue vector) measurements.

3.2.3.2. Calculation of rLLS and rSLLS

Absolute LLS and SLLS values were used to compute relative (%) rLLS and rSLLS values in relation to the patient's body height.

3.2.4. Calculation of the amount of lumbar spine alignment deviation (LSAD)

The arithmetic difference between the SLLS and LLS values of each patient was calculated as an indicator of the degree of lumbar spine alignment deviations (LSAD). Greater differences are caused by higher degrees of alignment deviations, such as hyper-lordosis or scoliosis.

3.2.3.3. Qualitative assessment of LSS grade

There is no consensus regarding the specific diagnostic criteria for lumbar spinal stenosis (LSS) based on MR imaging [50]. A qualitative grading system based on the root-cerebrospinal fluid (CSF) relationship was described by Schizas et al. and found to have prognostic value [53]. The classification includes four progressive LSS grades, with grades A and B usually responding to conservative treatment, while grades C and D often requiring surgical decompression [126] (Fig. 12).
Three raters independently classified the LSS grade of the patients, and the few cases with classification discrepancies were discussed in a consensus conference.

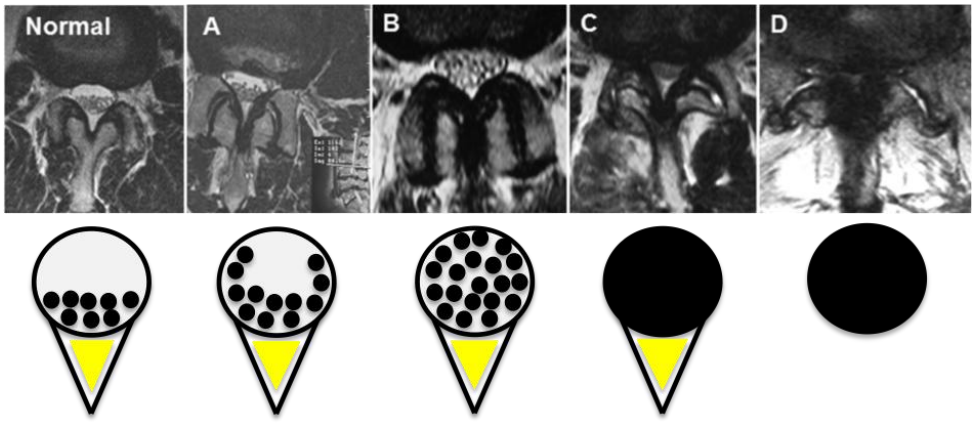



Figure 12 - Qualitative lumbar spinal stenosis (LSS) severity grade classification, according to Schizas et al. (2010): Normal: The roots lie dorsally and occupy less than half of the dural sac area. Grade A: (A) Cerebro-spinal fluid (CSF) is clearly visible within the dural sac and the distribution of the roots is irregular. Grade B: (B) The roots are distributed through the entire cross section of the thecal sac but they can still be individualised. Some CSF is still present, giving the sac a grainy appearance. Grade C: (C) single roots can not longer be recognised. They appear as one grey mass that completely fills the narrowed thecal sac. There is an epidural triangle of fat between the arch and thecal sac. Grade D: (D) Unlike grade C, the triangle of fat has been completely squeezed out.

#### 3.2.3.4. Quantitative assessment of LSS level

The number of LSS levels involved was assessed from the MR images. A level was defined as stenotic if affected by a grade B or higher narrowing of the spinal canal. Patients were classified in three groups according to the number of stenotic levels: group 1: one stenotic segment, group 2: two stenotic segments, and group 3: three or more stenotic segments involved.

### 3.2.4. Statistical analysis

The study sample was characterised by the use of mean ± standard deviation (SD) values for continuous variables (age, BH, LLS, SLLS, rLLS, rSLLS, LSAD) and frequencies for categorical variables (gender, RNR, LSS grade, LSS level). Demographic data comparisons between the groups were performed, with t-tests for independent samples for continuous variables. In cases in which the variable data were expressed in frequencies, chi-square tests were used to test for group dependency. Binomial logistic regressions were carried out to investigate whether the presence of RNRs could be predicted by patient demographics and MRI-based measurements. Age, gender, BH, LLS, SLLS, rLLS, rSLLS, LSAD, LSS grade and LSS level were considered as independent variables (potential predictors). The dependent variable was group affiliation (RNR+ or RNR-). For logistic regression, LSS grade categories A and B and LSS levels 2 and 3 were merged, due to a low number of cases in one of the categories. Single predictors were tested in the 10 models. IBM SPSS software version 21 for Macintosh (IBM Corp. Armonk, New York) was used for all statistical analyses. The 0.05 level of probability was set as the criterion for statistical significance.

## 3.3. Results

### 3.3.1. Demographic data comparisons between groups (RNR+ vs. RNR-)

RNR+ patients were 2.6 years older ($p = 0.01$) and their BH was significantly shorter - by 2.9cm ($p = 0.01$) - than RNR- patients. There was no significant difference in the distribution of male and female patients in both groups ($p = 0.3$).

The mean LLS and SLLS in the RNR+ group were significantly shorter - by 8.9 mm ($p < 0.001$) and 7.5mm ($p < 0.001$) respectively. The patients in the RNR+ group had a shorter lumbar spine in relation to their BH, as evidenced by their significantly

smaller rLLS and rSLLS ($p < 0.001$). There were no differences between the groups concerning the amount of LSAD ($p = 0.07$) (Tab. 5).

Table 5 - Demographic data

| | | All | RNR+ | RNR- | Mean diff. (*p*-value) [95% C.I.] |
|---|---|---|---|---|---|
| **Number of patients (n)** | | 300 | 150 | 150 | |
| **Age (years)** | | 73.5 ± 9.2 | 74.8 ± 8.2 | 72.1 ± 9.9 | 2.6 ($p = 0.01$) [-4.7 to -0.6] |
| **Body height (cm)** | | 173.2 ± 10.2 | 171.7 ± 9.9 | 174.6 ± 10.3 | 2.9 ($p = 0.01$) [0.6 to 5.2] |
| **LLS (mm)** | | 157.6 ± 12.6 | 153.2 ± 12.3 | 162.1 ± 11.3 | 8.9 ($p < 0.001$) [6.2 to 11.5] |
| **SLLS (mm)** | | 159.6 ± 11.8 | 156.1 ± 11.5 | 163.7 ± 11.0 | 7.5 ($p < 0.001$) [4.8 to 10.1] |
| **rLLS (%)** | | 13.4 ± 1.0 | 13.0 ± 0.9 | 13.7 ± 0.8 | 0.7 ($p < 0.001$) [0.5 to 0.9] |
| **rSLLS (%)** | | 13.6 ± 0.9 | 13.3 ± 0.9 | 13.9 ± 0.8 | 0.6 ($p < 0.001$) [0.4 to 0.8] |
| **LSAD (mm)** | | 2.6 ± 2.6 | 2.9 ± 2.7 | 2.3 ± 2.4 | 0.5 ($p =0.07$) [-1.1 to 0.05] |
| **Gender** | **Male (%)** | 196 (65.3) | 94 (62.7) | 102 (68.0) | $x^2$ (1)= 0.94 ($p = 0.3$) |
| | **Female (%)** | 104 (34.7) | 56 (37.3) | 48 (32.0) | |

Values are mean ± SD for age, body height, length of lumbar spine (LLS), segmental length of lumbar spine (SLLS), relative length of lumbar spine (rLLS), relative segmental length of lumbar spine (rSLLS), lumbar spine alignment deviation (LSAD), and frequency (%) for gender.

The distribution of patients across the LSS grade categories was significantly different between the RNR+ and RNR- groups ($p <0.001$). In the RNR+ and RNR- groups, there were 33.3% and 12.7% of patients with LSS grade D, respectively. Patients with LSS grade C were equally distributed over both groups, with 65.3% and 78.0% for RNR+ and RNR-, respectively. There were also significantly more patients with two and three stenotic levels in the RNR+ group ($p < 0.001$) (Tab. 6).

Table 6 - Distribution of LSS grade and LSS level

| | | RNR+ | RNR- | $x^2$ (*P*-value) |
|---|---|---|---|---|
| **LSS-grade** | A | 0 | 1 (0.7) | $x^2$ (3)= 24.6 ($p < 0.001$) |
| | B | 2 (1.3) | 13 (8.7) | |
| | C | 98 (65.3) | 117 (78.0) | |
| | D | 50 (33.3) | 19 (12.7) | |
| **LSS-level** | 1 level | 102 (68.0) | 127 (84.7) | $x^2$ (2)= 12.5 ($p = 0.002$) |
| | 2 levels | 42 (28.0) | 22 (14.7) | |
| | 3 levels | 6 (4.0) | 1 (0.7) | |

Values are frequencies (%)

### 3.3.2. Predictors of RNRs

Gender was not a significant predictor of RNR ($p$ = 0.3). The likelihood of RNR+ (Odds Ratio) increased 1.06 times as the patient's age increased by two years ($p$ = 0.02). A 3cm decrease in BH increased the chance of RNR+ group membership by 1.09 times ($p$ = 0.01).

As LLS and SLLS decreased by 5mm, the likelihood of RNR+ increased by 1.36 and 1.34 times, respectively ($p$ < 0.001). A 1% decrease in rLLS and rSLLS increased the odds of RNR+ by 2.26 and 2.17 times, respectively ($p$ < 0.001).

The amount of LSAD was not a significant RNRs predictor ($p$ = 0.07).

In patients with LSS levels 2 and 3, the odds of RNR+ increased 2.59 times when compared to patients with LSS level 1 ($p$ = 0.001) (Fig. 13).

Patients with LSS grade C were 5.86 times more likely to show RNRs signs ($p$ = 0.02), and LSS grade D had 18.4 times more chance of RNR+ ($p$ < 0.001) when compared to patients affected by LSS grades A and B (Tab. 7).

Table 7 - Results of the binomial logistic regression models

| Model | Independent variables | Negelkerke $R^2$ | Odds ratio (OR) | [95% C.I.] | $p$-value |
|---|---|---|---|---|---|
| 1 | Gender (Female) | .00 | 1.26 | [0.78 to 2.03] | $p$ = 0.3 |
| 2 | Age [(1)] | .02 | 1.06 | [1.01 to 1.12] | $p$ = 0.01 |
| 3 | Body height [(2)] | .02 | 1.09 | [1.01 to 1.16] | $p$ = 0.01 |
| 4 | LLS [(3)] | .16 | 1.36 | [1.23 to 1.52] | $p$ < 0.001 |
| 5 | SLLS [(4)] | .13 | 1.34 | [1.20 to 1.50] | $p$ < 0.001 |
| 6 | rLLS [(5)] | .17 | 2.26 | [1.76 to 2.95] | $p$ < 0.001 |
| 7 | rSLLS [(6)] | .14 | 2.17 | [1.63 to 2.90] | $p$ < 0.001 |
| 8 | LSAD | .01 | 1.08 | [0.99 to 1.19] | $p$ = 0.07 |
| 9 | LSS-level [(7)] | .05 | 2.59 | [1.48 to 4.55] | $p$ = 0.001 |
| 10 | LSS-grade | .11 | | | $p$ < 0.001 |
| | grade C [(8)] | | 5.86 | [1.30 to 26.42] | $p$ = 0.02 |
| | grade D [(9)] | | 18.42 | [3.82 to 88.8] | $p$ < 0.001 |

Odd ratios (OR) for group membership in RNR+, LSS= Lumbar Spinal Stenosis, LLS= Length of Lumbar Spine

[(1)] OR for a 2 year increase in patient's age; [(2)] OR for a 3 cm decrease in body height; [(3)] OR for a 5 mm decrease in LLS; [(4)] OR for a 5 mm decrease in SLLS; [(5)] OR for a 1% decrease in rLLS; [(6)] OR for a 1% decrease in rSLLS; [(7)] OR for patients classified at LSS levels 2+3; reference for patients classified at LSS level 1; [(8)] OR for patients classified at LSS grade C; reference for patients classified at LSS grades A+B; [(9)] OR for patients classified at LSS grade D, reference for patients classified at LSS grades A+B

## 3.4. Discussion

The reported prevalence rates of RNRs among LSS patients vary, ranging from 15% [3] to 45.5% [4], with the majority of studies reporting RNRs prevalence rates of around 40% [5-7]. Although some studies have shown the negative prognostic effect of RNRs on post-surgical recovery of LSS patients [5, 87, 122], no work had previously investigated the potential weight of patient demographics and MRI-based measurements in predicting RNRs in patients with LSS. The main findings of the present study are as follows:

Patient-related and MRI-based measurements can predict the presence of RNRs in LSS patients. The strongest predictors of RNRs were LSS severity grade D, OR= 18.4, 95% C.I. [3.8 to 88.8], LSS severity grade C, OR= 5.8, 95% C.I. [1.3 to 26.4], LSS-level, OR= 2.5, 95% C.I. [1.4 to 4.5] and rLLS, OR= 2.2, 95% C.I. [1.7 to 2.9].

In the present study, patients in the RNR+ group were 2.6 years older ($p$ = 0.01). This finding is in line with previous observations [3, 7-9]. In the literature, the mean age difference between patients with or without RNRs varies from 7.8 years [9] to 13.8 years [8]. Comparable mean ages between patients with or without RNRs signs had been reported in only two studies [6, 94].

The mean BH of RNR+ patients was shorter by 2.9 cm ($p$ = 0.01), and their LLS and SLLS were also significantly shorter, by 8.9 mm and 7.5 mm respectively ($p$ < 0.001). It is also interesting that the rLLS in RNR+ was shorter by 0.7% in relation to patients BH in comparison to RNR- patients ($p$ < 0.001). The same was observed for rSLLS (mean diff. 0.6%, $p$ < 0.0001). In view of these findings, the question is whether an age-related degeneration of the lumbar spine with an absolute and a relative shortening of LLS, and consequently a reduction in the length of the spinal canal, plays a role in the pathogenesis of RNR?

The pathogenesis of RNR is still unclear. Suzuki et al. suggested that the squeezing force from the constricted spinal canal acting on the nerve roots causes elongation and is the origin of RNRs [8]. This explanation has not been questioned since. In the present study, we have searched for significant predictors of RNRs among patient-related factors. To the authors' best knowledge, no previous study has measured and compared the LLS, SLLS, rLLS and rSLLS in patients with or without RNRs.

In the mid-eighties, Tsuji et al. [4] brought about the idea that age-dependent shortening of the lumbar spine may be connected to the pathogenesis of RNRs. This assumption has not been investigated since then, but the present results seem to con-

firm it. rLLS and rSLLS were both significant predictors of RNR+ ($p < 0.001$). A 1% reduction in rLLS increased the odds of RNR+ by 2.26 times. rLLS was the third strongest patient-related predictor of RNRs.

Our results are also consistent with the explanation given by Suzuki et al. [8], as compression of the cauda equina nerve roots (LSS-grade) was the strongest RNR+ predictor. LLS grade C increased the odds of RNR+ by 5.8 times, 95% C.I. [1.3 to 26.4], and LLS grade D increased the chance of RNR+ by 18.42 times, 95% C.I. [3.8 to 88.8]. Our results also identified additional important factors in the pathogenesis of RNRs, such as the number of stenotic levels involved and the rLLS or rSLLS (Fig. 13).

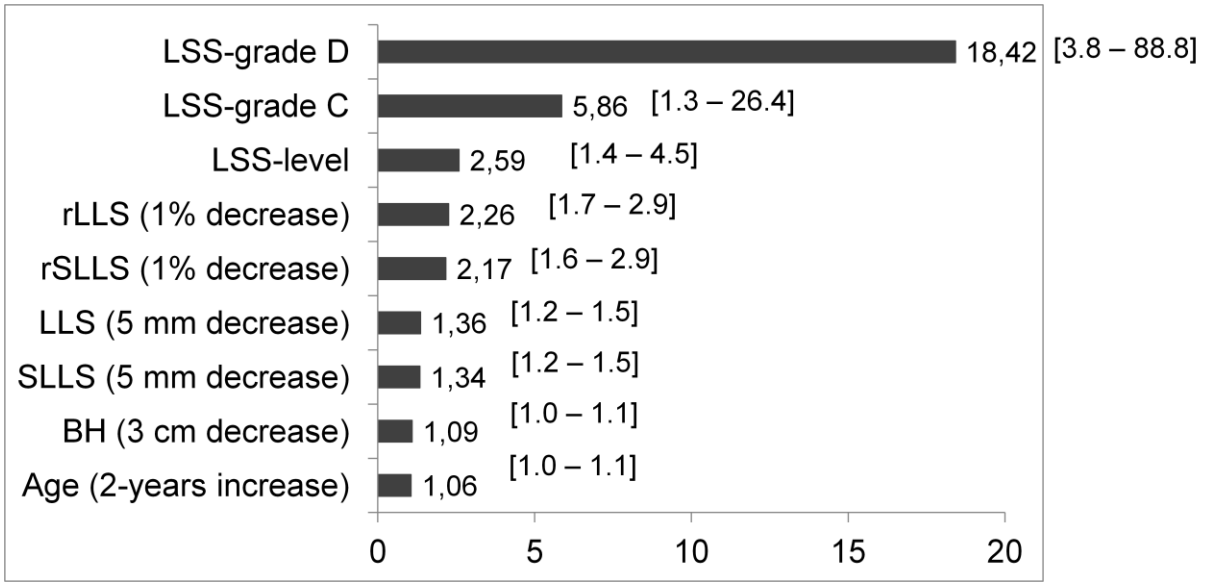



Figure 13 - Significant predictors of RNRs, with their estimated odd ratios and 95% confidence interval.

When considering LSS severity, it is interesting to note that patients with LLS grade C were similarly distributed in the RNR+ (65.3%) and RNR- (78.0%) groups. Furthermore, 12.7% of RNR- patients were classified at LSS grade D. How can the high percentage of RNR- patients (77%) that did not develop RNRs be explained, though affected by LSS grades C or D? Age-related LLS shrinking could have made the difference. To clarify this question, further investigation is required.

Based on the present results, the lumbar spine could be considered the discal-osseous-ligamentous “container” of the cauda equina nerve roots. The nerve roots could be considered the “content”. The container shrinks due to age-related degenerative changes in the lumbar spine, but at the same time the roots of the cauda

equina, fixed between conus medullaris and intraforaminal ganglia, keep their length. It seems plausible that a progressive mismatch between container and content could give a relative “over-length” of the cauda nerve roots. These can develop a serpentine-like shape at the beginning and a loop-like course at a further stage. The mismatch seems to be grounded on individual changes in the relationship between “container” and “content”, and is evidenced by a smaller rLLS in relation to the patient’s height.

There was a significant difference in the distribution of LSS levels between RNR+ and RNR- patients ($p$ = 0.002) (Tab. 6). Thirty-two percent of RNR+ but only 15.4% of RNR- patients had two or more stenotic levels. Multi-segmental stenosis seems to interfere more with the natural course of the cauda nerve roots than single-level stenosis. This result confirms that reported by Hur et al. [6]. It also confirms the importance of the “total amount” of compression in the pathogenesis of RNRs that could be quantified as the sum of LSS grade and LSS levels.

Poureisa et al. [3] reported that age (OR= 1.0, $p$ = 0.01), the location of the stenosis (OR= 2.5, $p$ < 0.001) and the presence of a sharp intracanal protuberance at the stenotic level (OR= 7.2, $p$ < 0.001) were significantly and independently associated with RNRs. Chen et al. [5] have recently demonstrated that greater lumbar lordosis angles in extended and neutral positions, as well as a greater overall range of motion, were significantly associated with RNRs. These results reinforce the assumption that RNRs in LSS patients are caused by multiple factors and not only by compression.

Degenerative spondylolisthesis higher than grade 1 according to the Meyerding [127] classification was an exclusion criterion in the present study. This likely explains why the amount of lumbar spine alignment deviation (LSAD) was not different between both groups ($p$ = 0.07) and was not a significant RNRs predictor. In contrast, Savarese et al. included patients with any degree of spondylolisthesis and reported that vertebral slip increased the prevalence of RNRs by 3.5 times [7]. They also concluded that spondylolisthesis is an independent risk factor for RNRs. For this reason we have decided, in the planning stage of the present work, to exclude patients diagnosed with LSS secondary to spondylolisthesis from the sample.

Due to the retrospective study design, the number of potential predictors was restricted to the available data. This is a study limitation. There was no available data on clinical scores. A future study with a prospective study design should consider the

assessment of clinical scores and functional data, such as the preoperative walking distance.

## 3.5. Conclusions

Patient-related factors were different between patients with and without RNRs signs on their MR images. Multiple factors are associated with the presence of RNRs in patients with LSS. Severe stenosis at grade D or C, two or more stenotic levels and a shorter relative length of the lumbar spine were strong determinants of RNRs.

## 4. Inter- and intra-rater reliability of an MRI-based classification system for redundant nerve roots of the cauda equina in patients with lumbar spinal stenosis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### 4.1. Introduction

Decompression treatment for lumbar spinal stenosis (LSS) is the most-performed surgical procedure in patients over 65 in the USA [26]. In roughly 60% of patients with LSS scheduled for surgery, the natural course of the cauda nerve roots (CNR) remains unaltered, even in the presence of severe stenosis (Fig. 14).

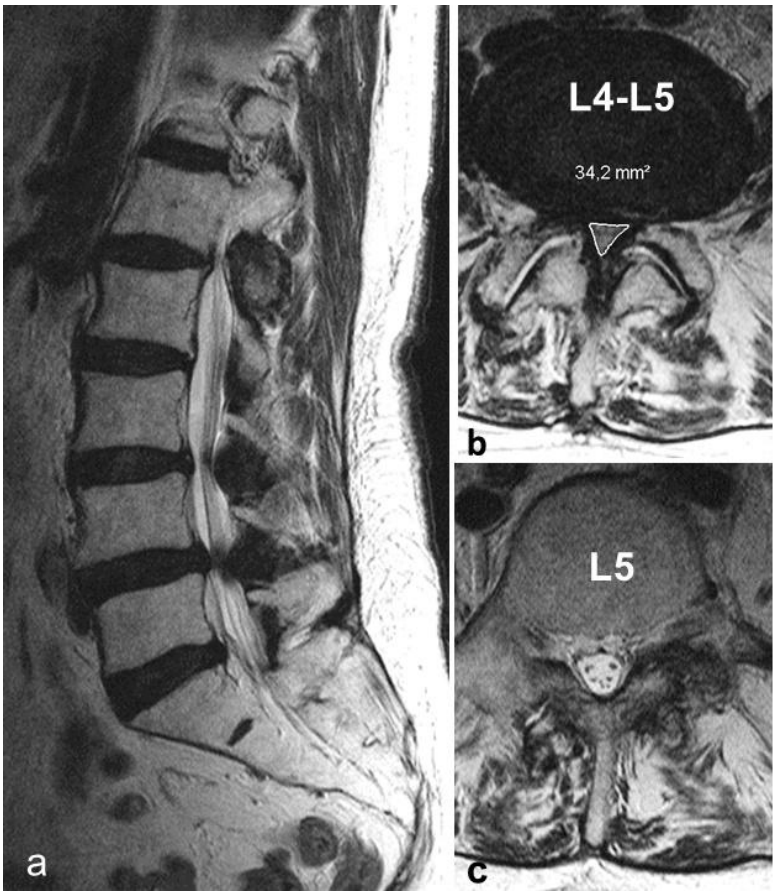


Figure 14 - (a) Sagittal T2 weighted images (WI) with almost-typical course of the cauda nerve roots (CNR) despite a (b) stenotic level grade D at L4/L5 according to Schizas et al (17) in the axial T2WI. (c) The CNR are distributed throughout the cross-sectional area of the dural sac (positive nerve roots sedimentation sign). No evidence of redundant nerve roots (RNR-).

In the remaining 40% of patients, redundant nerve roots (RNRs) of the cauda equina are evident on preoperative magnetic resonance (MR) images [5-7, 9] (Fig. 15).

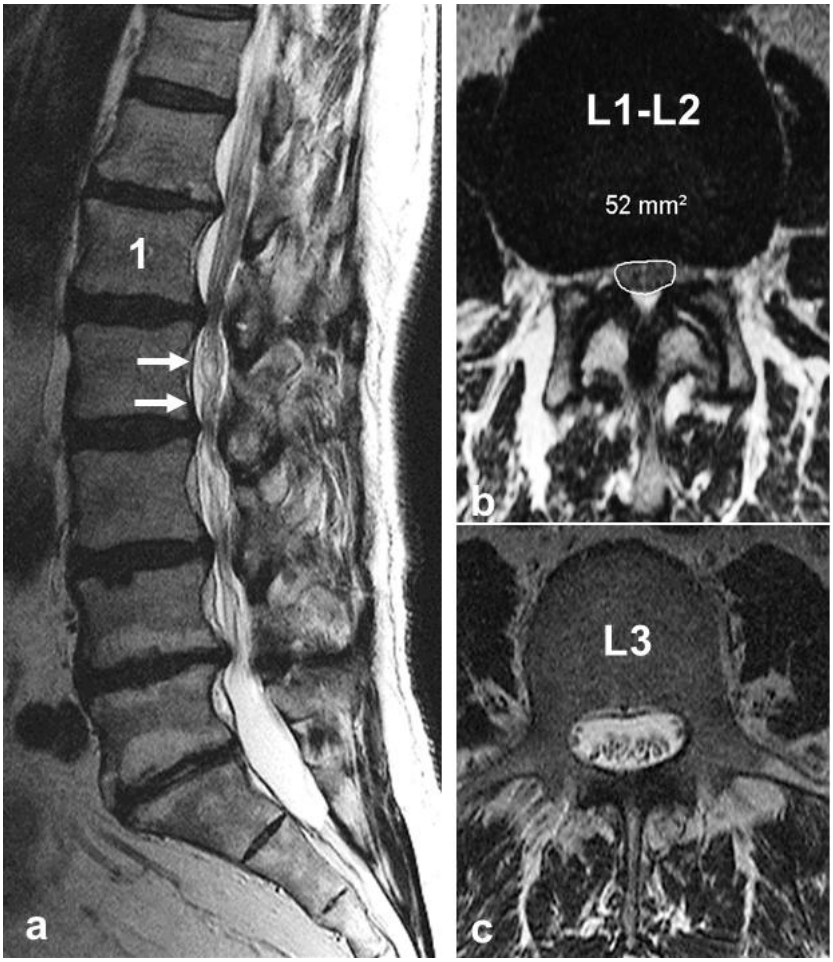


Figure 15 - (a) Sagittal T2WI with stretched cauda nerve roots cranially and serpentine redundant nerve roots caudally from the key stenotic level (KSL) at L1/L2. (b) The KSL corresponds to a grade C stenosis and was decompressed. (c) Positive nerve roots sedimentation sign.

RNRs were first described by Verbiest in 1954 [23], and named fourteen years later by Cressman & Pawl [76]. RNRs were described as thickened, buckling and coiled cauda nerve roots that present a serpentine (Fig. 15) or looped shape (Fig. 16) in sagittal T2-weighted images (WI).

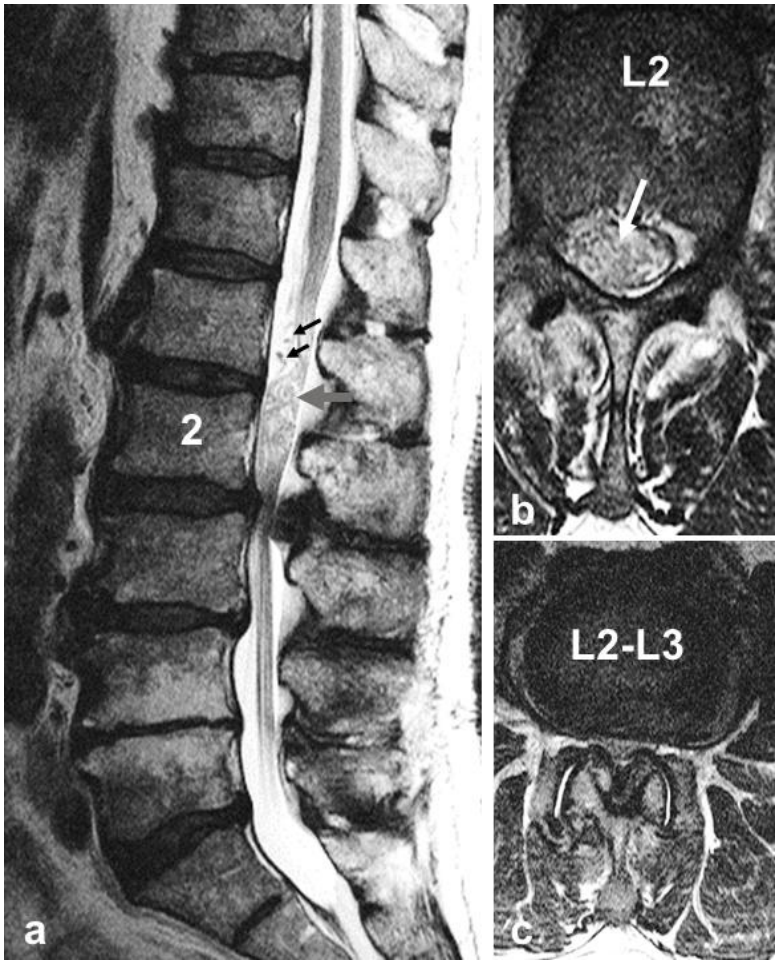


Figure 16 - (a) Sagittal T2WI with the key stenotic level (KSL) at L2/L3 showing stretched cauda nerve roots (CNR) caudally and loop-shaped redundant nerve roots cranially (black arrows). (b) The axial T2WI slice shows the tortuous and coiled (white arrow) CNR at L2 level. (c) The KSL corresponds to a grade C stenosis and was decompressed.

In more than 80% of cases, RNRs are visible above the stenotic level [3, 9], but can sometimes be below or both above and below the stenotic level.

Little is known about the clinical significance of RNRs in the cauda equina of patients with LSS. A recent meta-analysis revealed that among patients with LSS, those that showed evidence of RNRs were older, had a longer symptom history and presented higher degrees of lumbar stenosis preoperatively than those without RNRs. Moreover, after decompression surgery, patients with RNRs showed worse clinical scores and lower recovery rates than those without RNRs [128]. A study of potential RNRs predictors demonstrated that patients with LSS that showed evidence of RNRs on preoperative MR images were older, displayed stenosis at more levels, had a shorter lumbar spine canal and higher stenosis severity than patients without RNRs [129].

Yokoyama et al. studied patients with LSS and found that most RNRs resolved postoperatively, though some did not. Among patients with unresolved postoperative

RNRs, functional outcome remained poor, even when the dural sac was sufficiently expanded. Furthermore, among patients with LSS, those with loop-shaped RNRs performed more poorly than those with serpentine-shaped RNRs [122]. These results suggest that RNRs can be seen as negative prognostic factors in LSS patients scheduled for decompression surgery.

In daily radiological practice, MRI reports of patients with LSS mostly describe changes in bony structures, disc facet joints and yellow ligament. A validated classification system for RNRs could facilitate descriptions of changes in the CNR, and could provide clinicians with additional relevant information. To the best of our knowledge, a classification system for RNRs does not yet exist [37].

In this study, we present a classification system for RNRs. The aim of the present study was to test the inter-rater and intra-rater reliability of an MRI-based classification system for RNRs in LSS.

## 4.2. Material and methods

### 4.2.1. Study design

An inter- and intra-reliability study with retrospective database-based data acquisition was carried out.

The study was developed in accordance with the “Guidelines for Reporting Reliability and Agreement Studies” (GRRAS) [130]. The reporting follows the STROBE Statement guidelines for reporting observational studies [123].

The Ethics Commission of the Federal State of Hamburg approved the research proposal (File PV 5767). Informed consent was not necessary, because the data was collected and treated anonymously.

### 4.2.2. Study sample

Sample size calculation was performed previously, based on the work by Rotondi & Donner [131]. First, we assumed that the proportions of the three items in the category “allocation” were .10, .20 and .70. We determined that the required number of MR images to ensure that a two-sided 95% confidence interval (CI) for a target kappa-value (*k*) of 0.80, which did not exceed the lower bound of 0.70 was 126.

The data for 126 (47 female) patients with LSS who had submitted for decompression surgery was used. The mean age of the patients was 74.2 ± 9 years. Women (mean age 76.4 ± 8.9 years) were 3.4 years older (p= 0.03) than men (mean age

72.9 ± 8.9 years). All the patients had evidence of RNRs on their MR images and underwent decompression surgery at the Schön Clinic Hamburg Eilbek, Hamburg, Germany, between December 2012 and August 2016.

#### 4.2.2.1. Inclusion criteria

Inclusion criteria were symptomatic central LSS that required surgical decompression without fixation, available preoperative MR images of at least 1.5 Tesla (T) which included sagittal T1- and T2-WI and axial T2-WI in the picture archive and communication system (PACS) of the clinic), and evidence of RNRs.

#### 4.2.2.2. Exclusion criteria

Exclusion criteria were: previous history of lumbar spine surgery, no evidence of RNRs, scoliosis or vertebral slip requiring fixation, and congenital, traumatic, infectious, or neoplastic diseases of the lumbar spine.

### 4.2.3. The raters

Three senior raters (one neuroradiologist, one orthopedic surgeon and one neurosurgeon with 15, 10 and 35 years of experience, respectively) and three junior raters (orthopedic surgeons in-training) independently classified all RNRs on the 126 MRI.

### 4.2.4. The MRI-based definition of redundant nerve roots (RNR+)

An MRI was defined as RNR+ when the key stenotic level (KSL) altered the natural course of the CNR. In most cases, CNR were straight on one side of the KSL and were serpentine or loop shaped on the opposite side. Rarely did CNR look to be serpiginous or coiled on both sides of the KSL. RNRs appear mostly cranially to the key stenotic level, to a lesser extent caudally, and in few cases cranial-caudally [3].

### 4.2.5. The ASED-classification system of RNRs

The system classifies the morphological properties of RNRs into four categories: Allocation, Shape, Extension and Direction (ASED). The ASED classification system is shown in Table 8. Examples are illustrated in Fig. 17.

Table 8 - ASED classification for RNRs

| ASED | Categories / Definition | Items | Definition | Notation |
|---|---|---|---|---|
| **A**llocation | Refers to the stenotic reference level (SRL). The SRL shows the switch between straightened cauda nerve roots (CNR) and RNR or, shows adjacent cranio-caudal RNR. When a doubt between two potential SRL occurs, the most stenotic level (with the smallest CSA) is defined as SRL. | L1/L2 | | Notation of the RSL (i.e. L3/L4) |
| | | L2/L3 | | |
| | | L3/L4 | | |
| | | L4/L5 | | |
| | | L5/S1 | | |
| **S**hape | Shape refers to the form of RNR. This category comprises two items. | Serpentines | Serpentines are present when a sinusoidal deflection (complete crest-trough wave) of the majority of CNR occurs within the height of a vertebral body without any horizontalization of the involved roots. | S |
| | | Loops | Loops are present when at least in two different areas dots or horizontal roots in the sagittal T2WI-slice were combined with tortuous, serpiginous roots in the axial T2WI- slice. Mixed ser-pentine and loop findings are scored as loops. | L |
| **E**xtension | Refers to the length of RNR. This category comprises two items. | 1 | When RNR extend up to one vertebral height adjacent to the SRL they are notated with “1”. | 1 |
| | | 1+ | When RNR extend beyond one vertebral height they are notated with “1+”. Cranio-caudal RNRs are always notated as “1+”. | 1+ |
| **D**irection | Refers to the localization of RNR in relation to the SRL. This category comprises three items. | Cranial | RNR are only present cranially from the SRL | Cr |
| | | Caudal | RNR are only present caudally from the SRL | Ca |
| | | Cranial-caudal | RNR are present cranially and caudally from the SRL | Cc |

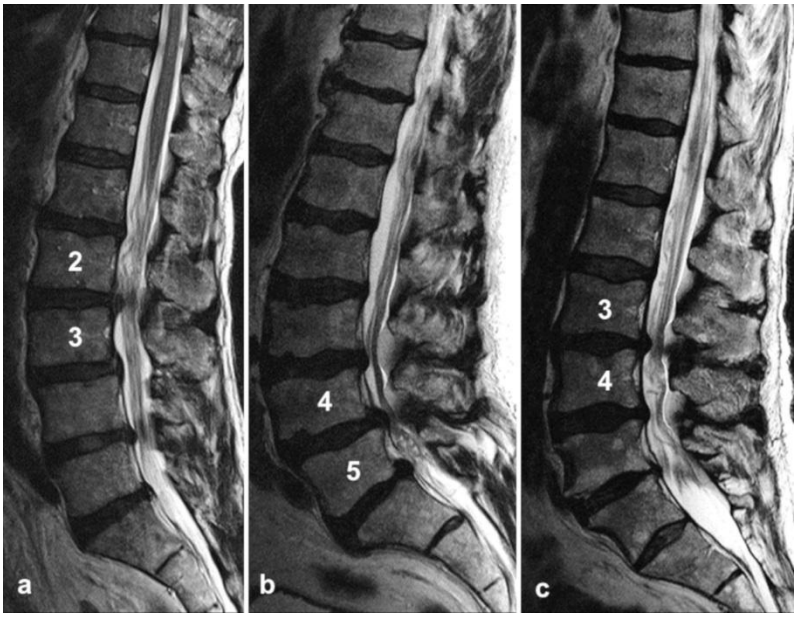


Figure 17 - Sagittal T2WI with (a) redundant nerve roots cranial, (b) caudal, and (c) cranial-caudal from the key stenotic level (KSL). The ASED notation would be as follows: a= RNR+: L2/L3.S.1+.cr; b= RNR+: L4/L5.L.1.ca and c= RNR+: L3/L4.L.1+.cc.

### 4.2.6. Procedures for data acquisition

The classifications of Shape, Extension and Direction depend on the Allocation. Therefore, all raters first classified the category Allocation independently. The inter-rater kappa value for Allocation was then calculated. In 22 cases, discordances occurred between at least two raters. These cases were discussed and resolved by consensus. Thereafter, all raters independently classified the RNRs on the 126 MRI according to the definitions for Shape, Extension, and Direction, considering the previously agreed-upon KSL allocations. In the second read, performed four weeks later after altering the order of cases, the Allocation values were used from the first read. These were fixed after calculating the inter-rater kappa values. Because the Allocation category was only rated once, intra-rater kappa values for this category were not calculated.

In addition to the ASED classification, all raters classified the LSS grade within the qualitative grading system, based on the root-to-cerebrospinal fluid (CSF) relationship described by Schizas et al. [53].

### 4.2.7. Statistical analysis

To determine the proportion of agreement beyond that expected by chance, the Fleiss kappa (*k*) was used to assess inter-rater reliability. The Fleiss kappa is an extension of Cohen's kappa, which can be used when nominal categories are assessed by more than two raters [132]. In this study, mean Fleiss kappa values were calculated for junior raters, senior raters, and for all 6 raters, for both reads. Cohen's Kappa (k) was used to calculate intra-rater reliability [133]. Mean kappa values for intra-rater reliability were calculated separately for junior and senior raters. Kappa values were categorised, to reflect different levels of agreement, as follows: k ≤ 0.00 was considered poor, 0.00 – 0.20 slight, 0.21 – 0.40 = fair, 0.41 – 0.60 = moderate, 0.61 – 0.80 substantial and ≥ 0.81 almost perfect agreement [134].

To determine whether inter-rater kappa values differed significantly between the two reads, paired sample t-tests were used. Comparisons of inter-rater kappa values between junior and senior raters within the 1st and 2nd read were carried out with independent sample t-tests. The assumptions associated with the different tests were verified previously.

IBM SPSS software version 21 for Macintosh (IBM Corp. Armonk, New York) was used for all statistical analyses. For all statistical tests, the 0.05 level of probability was set as the criterion for statistical significance.

## 4.3. Results

The results for inter-rater reliability are presented in Table 9. The ASED classification showed moderate-to-almost perfect inter-rater reliability. In the 1$^{st}$ read, all 6 raters achieved kappa values that ranged from k= 0.56 [0.51 - 0.60], for Extension, to k= 0.86 [0.83 - 0.90] for Allocation. The kappa values of junior raters did not change significantly between the 1st and the 2nd reads (p= 0.06). In contrast, senior raters achieved higher inter-rater kappa values in the 2nd read (p= 0.008) than in the first read. When all raters (n= 6) were considered, there was no significant difference between the inter-rater kappa values of both reads (p= 0.5).

The results for intra-rater reliability are presented in Table 10. The ASED classification showed almost perfect intra-rater reliability. For junior raters, the mean kappa values ranged from k= 0.83 [0.76 - 0.90], for Shape, to k= 0.86 [0.82 - 0.90] for Extension. Senior raters achieved similar mean kappa values, with the exception of that in the Shape category (k= 0.90 [0.88 - 0.92]).

Inter-rater reliability for LSS-Grade was substantial in the first read for all raters (k= 0.69 [0.65 - 0.74]). The Intra-rater reliabilities were substantial (k= 0.78 [0.67 - 0.89]), and almost perfect (k= 0.88 [0.83 - 0.93]) for senior and junior raters, respectively.

In 95.6% of cases, the SRL was in the central part of the lumbar spine, with n= 56 (44.4%) at L3/L4, n= 35 (27.8%) at L4/L5, and n= 31 (24.6%) at L2/L3. In four cases (3.2%), the KSL was located at L1/L2, but it was never located at L5/S1.

The severity of LSS was scored according to the classification purposed by Schizas et al. (17) “Surgical” Grade C in 94 (75%) cases and grade D in 30 (24%) cases. Stenosis grade B was observed in two cases (1%).

Table 9 - Inter-rater reliability for the ASED classification of RNRs

| **ASED** | **1st read** | | | | | | **2nd read** | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Categories / Items** | **Junior raters (n=3)** | | **Senior raters (n= 3)** | | **All raters (n= 6)** | | **Junior raters (n= 3)** | | **Senior raters (n= 3)** | | **All raters (n= 6)** | |
| | **Kappa** | **(95% CI)** | **Kappa** | **(95% CI)** | **Kappa** | **(95% CI)** | **Kappa** | **(95% CI)** | **Kappa** | **(95% CI)** | **Kappa** | **(95% CI)** |
| **Allocation** | .89 | [.82 – .96] | .82 | [.70 – .94] | **.86** | **[.83 – .90]** | .89 | [.82 – .96] | .82 | [.70 – .94] | **.86** | **[.83 – .90]** |
| **Shape** | .66 | [.56 – .76] | .62 | [.52 – .72] | **.62** | **[.57 – .66]** | .59 | [.49 – .69] | .63 | [.53 – .73] | **.59** | **[.55 – .64]** |
| **Extension** | .57 | [.47 – .67] | .60 | [.49 – .70] | **.56** | **[.51 – .60]** | .53 | [.43 – .63] | .68 | [.58 – .78] | **.59** | **[.55 – .64]** |
| **Direction** (overall) | .64 | [.57 – .72] | .74 | [.64 – .82] | **.66** | **[.63 – .70]** | .62 | [.55 – .70] | .82 | [.74 – .90] | **.65** | **[.62 – .69]** |
| Cranial (Cr) | .74 | [.64 – .84] | .80 | [.70 – .90] | .76 | [.72 – .81] | .68 | [.58 – .78] | .89 | [.79 – 1] | .75 | [.71 – .80] |
| Caudal (Ca) | .67 | [.56 – .77] | .80 | [.70 – .91] | .72 | [.67 – .76] | .63 | [.53 – .73] | .83 | [.73 – .93] | .68 | [.63 – .72] |
| Cranio-caudal (Cc) | .48 | [.37 – .58] | .38 | [.28 – .48] | .39 | [.35 – .44] | .53 | [.43 – .63] | .54 | [.44 – .64] | .42 | [.38 – .47] |
| **LSS-Grade** (*) | .77 | [.67 – .87] | .64 | [.54 – .74] | .69 | [.65 – .74] | .68 | [.58 – .78] | .76 | [.67 – .86] | .67 | [.62 – .71] |

Values are Fleiss kappa with 95% CI for junior raters, senior Raters and for all six raters, for the 1st and 2nd reads. (*) Grade of LSS according to Schizas et al. (2010) [53].

Table 10 - Intra-rater reliability for the ASED classification of RNRs

| | **Junior raters** | | | | | | | | **Senior raters** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Rater A (KS)** | | **Rater B (HH)** | | **Rater C (NA)** | | **Mean *Kappa*** | | **Rater D (LP)** | | **Rater E (JL)** | | **Rater F (TF)** | | **Mean *Kappa*** | |
| | ***k*** | **95% C.I.** | ***k*** | **95% C.I.** | ***k*** | **95% C.I.** | ***k*** | **95% C.I.** | ***k*** | **95% C.I.** | ***k*** | **95% C.I.** | ***k*** | **95% C.I.** | ***k*** | **95% C.I.** |
| Shape | .91 | [.84 – .98] | .90 | [.83 – .91] | .68 | [.55 – .81] | **.83** | **[.76 – .90]** | .96 | [.93 – .99] | .89 | [.82 – .97] | .85 | [.78 – .92] | **.90** | **[.88 – .92]** |
| Extension | .92 | [.85 – .99] | .90 | [.83 – .91] | .76 | [.61 – .91] | **.86** | **[.82 – .90]** | .87 | [.80 – .94] | .81 | [.72 – .90] | .90 | [.83 – .97] | **.86** | **[.84 – .88]** |
| Direction | .91 | [.85 – .97] | .90 | [.85 – .95] | .76 | [.67 – .85] | **.85** | **[.85 – .89]** | .91 | [.86 – .96] | .84 | [.77 – .91] | .78 | [.69 – .87] | **.84** | **[.81 – .87]** |
| LSS-grade | .97 | [.93 – 1] | .91 | [.84 – .98] | .78 | [.67 – .89] | **.88** | **[.83 – .93]** | .95 | [.90 – 1] | .54 | [.39 – .69] | .85 | [.76 – .94] | **.78** | **[.67 – .89]** |

Values are Cohen’s kappa with 95% CI for the single raters and mean Cohen’s Kappa with 95% CI for the three junior and three senior raters.

## 4.4. Discussion

Previous reports have shown that patients with LSS that displayed RNRs in preoperative MR images had worse postoperative outcomes than patients without evidence of RNRs. Those findings suggested that RNRs comprise a negative prognostic factor [114, 122, 128].

To the best of our knowledge, a validated MRI-based RNRs classification for LSS patients has not yet been established. Such a systematic classification would enable radiologists to complete the MRI report with clinical relevant information. It would also facilitate communication between the different professionals involved in the treatment of LSS patients.

In the present work, we have presented the ASED classification system for RNRs. The aim of the study was to test its inter- and intra-rater reliability. Six raters with different grades of experience independently scored 126 MR images with the ASED classification. The ASED classification exhibited moderate to almost perfect inter-rater and almost perfect intra-rater reliabilities. These results indicate that the ASED classification could be used in daily radiological practice to complete the MRI reports on patients with LSS.

The qualitative grading system presented by Schizas et al. [53] that was used in our study to access LSS severity grade is a widely-used instrument in clinical practice. The authors assessed its intra- and inter-rater reliability with 57 axial T2 images patients with LSS. They reported average kappa values of $k = 0.44 \pm 0.17$ and $k = 0.65 \pm 0.14$ for inter- and intra-rater reliabilities, respectively. Raters from the originating study unit achieved higher kappa values ($k = 0.67 \pm 0.08$ and $k = 0.77 \pm 0.06$). In line with our results, inter-rater kappa values were lower than intra-rater kappa values. This tendency can be observed in most studies of this type. In contrast to our results, neither inter-rater nor intra-rater reliability achieved mean kappa values beyond substantial agreement. In our study, we have confirmed their results in a sample that was twofold larger: we found $k = 0.69$ and $k = 0.78$ for inter- and intra-rater reliabilities, respectively (Tables 9 and 10). The ASED classification system comprised 4 categories with 12 different items overall. This classification is more complex than the LSS grading system by Schizas et al. Our results indicated that the system could be used in clinical practice.

The inter-rater kappa values of all 6 raters in the 1st read for the three items in the Direction category were *k*= 0.76 [0.72 - 0.81], for cranial, *k*= 0.72 [0.67 - 0.76], caudal, and *k*= 0.39 [0.35 - 0.44], for cranio-caudal. Kappa values are affected by the distribution of data across the categories (prevalence bias). The frequency distribution that we observed in the Direction category was n= 84 (66.7%), for Cranial, n= 35 (27.8%), for Caudal, and n= 7 (5.6%), for Cranio-caudal. This unequal distribution influenced the kappa values, as outlined previously by Byrt et al. [135].

The surgical relevance of the KSL, the key element of the ASED classification, was confirmed in the present study. When the readers rated the KSL, they were blinded to the surgical levels. Interestingly, all KSL (97%) were decompressed. Moreover, in 42 patients (33%) a second level was decompressed, and in 8 other patients (6%) two additional levels were decompressed. Of the four cases that showed a discrepancy between the KSL and operated level, two patients displayed more stenosis at the operated level than at the KSL, and the two other patients displayed disc herniations associated with a stenotic level adjacent to the KSL.

Physicians that care for patients with LSS expect the MRI report to answer the following questions: Is there any LSS, and how severe is it? Which level(s) and anatomic structures are involved? In our opinion, to counsel patients with LSS regarding adequate treatment, clinicians also need information about the degree of compromise at the CNR. Thus, the MRI report should answer the question: Are RNRs present, and what is their shape, extension and direction?

A previous study by Min et al. [9] examined associations between the relative length of RNRs and the symptom duration and recovery rate; they found moderately positive (r= 0.38) and a strongly positive correlations (r= 0.53), respectively. Ono et al. [87] reported that a group with higher numbers of loop-shaped RNRs had a higher mean duration of neurological symptoms and poorer preoperative walking ability than the group with a higher number of serpentine-shaped RNRs. To further investigate these issues, a validated RNR-classification system is necessary.

In a previous review, Nogueira-Barbosa et al. [115] suggested that radiologists should examine MRI for RNRs in the cauda equina, and when applicable, describe those findings in the MRI report. We share this opinion, and to facilitate the descriptions, we have presented the ASED classification.

Although imaging should not influence the surgical indication [37, 55], our results pointed out the relevance of imaging in surgical planning.

We defined the MRI quality of sample by choosing a field strength of at least 1.5T. However, in daily practice, different observers have different perceptions of the image quality of 1.5T MR images. For a long time, researchers have debated the validity of the signal-to-noise ratio as an objective quality measure for biomedical images [136]. In the present study, different image resolutions may have led to differences in scoring. This was a study limitation.

## 4.5. Conclusion

We demonstrated that the ASED classification for RNRs was reliable and feasible. It should be included in complete MRI reports for patients with LSS that display evidence of RNRs.

## 5. Conclusions (overall)

Three single projects were planned and carried out within the PhD project presented. The results of the meta-analysis showed the that there is limited quality evidence supporting the following: LSS patients with evidence of RNRs are older, have longer symptom duration, worse preoperative clinical scores and show higher degrees of lumbar stenosis as given by their narrow CSA of the affected level in comparison to LSS patients without evidence of RNRs. There is also limited quality evidence that patients with LSS that show evidence of RNRs recover slowly and achieve poorer clinical scores after decompression surgery than patients without evidence of RNRs. In view of these results, RNRs may be a negative prognostic factor in patients with LSS.

The origins of RNRs are not yet fully understood. The results of the RNRs predictor study showed that multiple factors are associated with the presence of RNRs in patients with LSS. Severe stenosis grades D or C, two or more stenotic levels and a shorter relative length of the lumbar spine were the strongest determinants of RNRs in patients with LSS.

The ASED classification system for RNRs was presented, and its inter-rater and intra-rater reliabilities were tested. The ASED classification showed moderate to almost perfect inter-rater and almost perfect intra-rater reliabilities. These results indicate that the ASED classification can be used in daily practice to complete the MRI report of patients with LSS that show RNRs on their MR images. The ASED classification enables the systematic classification of RNRs, with a high proportion of agreement between and within raters.

## 6. Abstract (English and German)

**Introduction**: Around 40% of all patients with LSS that are scheduled for decompression surgery present evidence of redundant nerve roots (RNRs) on their magnetic resonance (MR) images. RNRs are described as elongated and thickened cauda equina nerve roots that are visible in MR images in connection with LSS. Neither the aetiology nor the clinical significance of RNRs is completely understood. An RNRs classification system does not yet exist.

**Objectives**: To investigate the clinical significance of RNRs in patients with LSS; to test for significant predictors of RNRs; and to test the inter-rater and intra-rater reliability of a classification system for RNRs (ASED classification).

**Materials and methods**: A systematic literature search with meta-analysis and two retrospective cohort studies were carried out.

**Results**: Seven studies comprising a total of 1046 LSS patients were included in the meta-analysis. LSS patients with RNRs were older, weighted mean difference (WMD) 5.7, 95% CI [2.2 to 9.2], p= 0.001, had a smaller cross-sectional area (CSA) of the stenotic level, WMD -12.2, 95% CI [-17.7 to -6.7], p< 0.0001, and longer symptom onset duration, WMD 13.2, 95% CI [-0.2 to 26.7], p= 0.05. After decompression surgery, RNRs patients had poorer clinical scores, -4.7, 95% CI [-7.32 to -2.1], p= 0.0004, and lower recovery rates, -9.8, 95% CI [-14.8 to -4.7], p= 0.0001.

The strongest predictors of RNRs were a 1% decrease in the relative length of the lumbar spine (rLLS) (OR 2.17; p < 0.001), LSS-level ≥ 2 (OR 2.59; p = 0.001), LLS-grade C (OR 5.86; p = 0.02) and LLS-grade D (OR 18.4; p < 0.001).

The ASED classification showed moderate to almost perfect inter-rater reliability, with kappa values of 0.86 [0.83, 0.90], for Allocation, 0.62 [0.57, 0.66], for Shape, 0.56 [0.51, 0.60], for Extension, and 0.66 [0.63, 0.70] for Direction. For Intra-rater reliability, almost perfect kappa values were achieved: 0.90 [0.88 – 0.92], for Shape, 0.86 [0.84, 0.88] for Extension, and 0.84 [0.81, 0.87] for Direction.

**Conclusions**: RNRs are a negative prognostic factor in LSS patients. There are multiple factors strongly associated with the presence of RNRs in patients with LSS. LSS severity grade and LSS levels are the strongest predictors of RNRs.

The ASED classification for RNRs is reliable and feasible. It should be used to complete the MRI reports of LSS patients with evidence of RNRs.

**Abstract (German)**

**Einleitung**: Bis zu 40% aller Patienten mit lumbaler Spinalkanalstenose (SKS), die eine Dekompressionsoperation benötigen, weisen Redundant Nerve Roots (RNR) in den präoperativen Magnetresonanz (MRT) Bildern auf. RNR werden als verlängerte, verdickte und geschlängelte cauda equina Nerven beschrieben, die im Zusammenhang mit SKS im MRT sichtbar sind. Weder die Ätiologie noch die klinische Bedeutung von RNR sind eindeutig untersucht. Eine Klassifikation für RNR existiert nicht.

**Ziele**: Die klinische Bedeutung von RNR zu untersuchen, signifikante Prädiktoren von RNR zu identifizieren und die Reliabilität von einem Klassifikationssystem für RNR zu testen.

**Materialien und Methoden**: Eine systematische Literaturrecherche mit Metaanalyse und zwei retrospektive Kohort Studien wurden durchgeführt.

**Ergebnisse**: Sieben Studien mit insgesamt 1046 SKS-Patienten wurden in der Metaanalyse eingeschlossen. SKS-Patienten mit RNR waren älter, gewichtete Mittlererdifferenz (WMD) 5.7 Jahre, 95% CI [2.2 bis 9.2], p= 0.001; hatten engere Stenosen (CSA) WMD -12.2 $mm^2$, 95% CI [-17.7 bis -6.7], p< 0.0001; und länger andauernde Symptome, WMD 13.2 Momate, 95% CI [-0.2 bis 26.7], p= 0.05. Nach Dekompressionsoperation hatten SKS-Patienten mit RNR schlechtere klinische Scores, WMD -47.9, 95% CI [-7.3 bis -2.1], p= 0.0004; und niedrigere Erholungsrate, WMD -9.8, 95% CI [-14.8 bis -4.7], p= 0.0001.

Stärkste Prädiktoren von RNR waren: 1% Verringerung der relativen Länge der LWS (OR 2.17, p< 0.001), SKS-Levels ≥ 2 (OR 2.59, p= 0.001), SKS-Grad C (OR 5.86, p= 0.02) und SKS-Grad D (OR 18.4, p< 0.001).

Die ASED-Klassifikation zeigte moderate bis fast-perfekte Inter-Rater Reliabilität mit Kappa-Werte von 0.86 [0.83, 0.90], 0.62 [0.57, 0.66], 0.56 [0.51, 0.60] und 0.66 [0.63, 0.70] entsprechend für Allocation, Shape, Extension und Direction. Die Intra-Rater Reliabilität war fast perfekt mit k= 0.90 [0.88, 0.90], 0.86 [0.84, 0.88] und 0.84 [0.81, 0.87] entsprechend für Shape, Extension und Direction.

**Schlussfolgerungen**: RNR sind ein negativ prognostischer Faktor für SKS-Patienten. Es gibt multiple Faktoren, welche mit der Entstehung von RNR verbunden sind. SKS-Grad und Anzahl der SKS-Levels waren die stärksten Prädiktoren. Die ASED-Klassifikation ist zuverlässig und einfach zu benutzen. Sie sollte den MRT-Befund von SKS-Patienten ergänzen.

## 7. List of abbreviations

| | |
|---|---|
| ASED | Allocation, Shape, Extension, Direction |
| BH | Body height |
| CI | Confidence interval |
| CSA | Cross sectional area |
| CSF | Cerbrospinal fluid |
| CT | Computer tomography |
| JOA | Japanese orthopedic association score |
| KSL | Key stenotic level |
| LDH | Lumbar disc herniation |
| LSAD | Lumbar spine alignment deviation |
| LSS | Lumbar spinal stenosis |
| MINORS | Methodological index for non-randomised studies |
| MRI | Magnetic resonance imaging |
| MR | Magnetic resonance |
| NASS | North American Spine Society |
| NR | Not reported |
| ODI | Oswestry Disability Index |
| OR | Odds ratio |
| PC | Prospective cohort |
| RC | Retrospective cohort |
| RevMan | Review Manager Sofware |
| rLLS | Relative length of lumbar spine |
| RNR | Redundant nerve roots |
| RNR- | No evidence of RNR |
| RNR+ | Evidence of RNR |
| rSLLS | Relative segmental length of lumbar spine |
| SCS | Objective evaluation System for LSS patients |
| SD | Standard deviation |
| SLLS | Segmental length of lumbar spine |
| SPORT | Spine patient outcome research trial |
| T | Tesla |
| TENS | Transcutaneous electrical nerve stimulation |
| WI | Weighted image |
| WMD | Weighted mean difference |

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## 9. Publications

### 9.1. Publications in peer-reviewed journals

**Marques CJ**, Hillebrand H, Papavero L (2018) The clinical significance of redundant nerve roots of the cauda equina in lumbar spinal stenosis patients: a systematic literature review and meta-analysis. Clinical Neurology and Neurosurgery 174: 40-47. https://doi.org/10.1016/j.clineuro.2018.09.001

Papavero L[*], **Marques CJ**[*], Lohmann J, Fitting T (2018) Patient demographics and MRI-based measurements predict redundant nerve roots in lumbar spinal stenosis: a retrospective database cohort comparison. BMC Musculoskeletal Disorders. Dec 22 2018; 19(1): 452. ([*]First and second authors share the first authorship) https://doi.org/10.1186/s12891-018-2364-4

Papavero L[*], **Marques CJ**[*], Lohmann J, Fitting T, Schawjinski K, Ali N, Hillebrand H, Maas R (2019) Redundant nerve roots in lumbar spinal stenosis: Inter- and intra-rater reliability of an MRI-based classification. Neuroradiology. Accepted for publication. ([*]First and second authors share the first authorship) https://doi.org/10.1007/s00234-019-02337-3

### 9.2. Publications in conference proceedings

Papavero L, **Marques CJ**, Lohmann J, Fitting T, Kothe R (2017) Redundant nerve roots in lumbar spinal stenosis – a retrospective database study on patient-related predictors. 12. Jahrestagung der Deutschen Wirbelsäulengesellschaft. 30. November – 2. Dezember 2017, Stuttgart, Germany (E-Poster). Eur Spine J (2017) 26: 2978. DOI: 10.1007/s00586-017-5336-8

**Marques C**, Hillebrand H, Papavero L (2018) Die klinische Bedeutung von Redundant Nerv Roots der cauda equina in Patienten mit Spinalkanalstenose: eine systematische Literaturreview und Metananalyse. 13. Jahrestagung der Deutschen Wirbelsäulengesellschaft (DWG), 6 – 8 Dezember, Wiesbaden, Germany (E-Poster).

**Marques CJ**, Lohmann J, Fitting T, Papavero L (2019) If function determines shape, why do redundant nerve roots of the cauda equina in lumbar spinal stenosis patients

develop? 11. Kongress der Deutschen Gesselschaft für Biomechanik (DGfB), 3-5 April, Berlin, Germany (Poster Präsentation)

**Marques C**, Hillebrand H, Papavero L (2019) Die klinische Bedeutung von Redundant Nerve Roots der cauda equina in Patienten mit Spinalkanalstenose: Eine systematische Literaturreview und Metaanalyse. NOUV-Jahrestagung 2019. 23-25. Mai, Dortmund, Germany (Vortrag)

Papavero L, **Marques CJ**, Lohmann J, Fitting T, Schawjinski K, Ali N, Hillebrand H, Maas R Redundant nerve roots in der lumbalen Spinalkanalstenose: Inter- und Intra-Rater Reliabilität einer MRT-basierten Klassifikation (2019). 14. Jahrestagung der Deutschen Wirbelsäulengesellschaft (DWG), 28. – 30. November 2019, München, Germany (Vortrag).

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## 11. Curriculum Vitae

(For protection of data privacy the CV was removed)

(Der Lebenslauf wurde aus datenschutzrechtlichen Gründen entfernt)

## 12. Eidesstattliche Versicherung

Ich versichere ausdrücklich, dass ich die Arbeit selbständig und ohne fremde Hilfe verfasst, andere als die von mir angegebenen Quellen und Hilfsmittel nicht benutzt und die aus den benutzten Werken wörtlich oder inhaltlich entnommenen Stellen einzeln nach Ausgabe (Auflage und Jahr des Erscheinens), Band und Seite des benutzten Werkes kenntlich gemacht habe.
Ferner versichere ich, dass ich die Dissertation bisher nicht einem Fachvertreter an einer anderen Hochschule zur Überprüfung vorgelegt oder mich anderweitig um Zulassung zur Promotion beworben habe.
Ich erkläre mich einverstanden, dass meine Dissertation vom Dekanat der Medizinischen Fakultät mit einer gängigen Software zur Erkennung von Plagiaten überprüft werden kann.

Unterschrift:  .....

## Appendix I - Sample size calculation “RNR Predictor Study”

**Sample size calculation – Predictors of RNR-Study**

*[2] -- Thursday, April 26, 2018 -- 12:21:40*

**Assumptions**:

. For sample size calculation the variable LSS-Level (number of stenotic levels involved) was used.

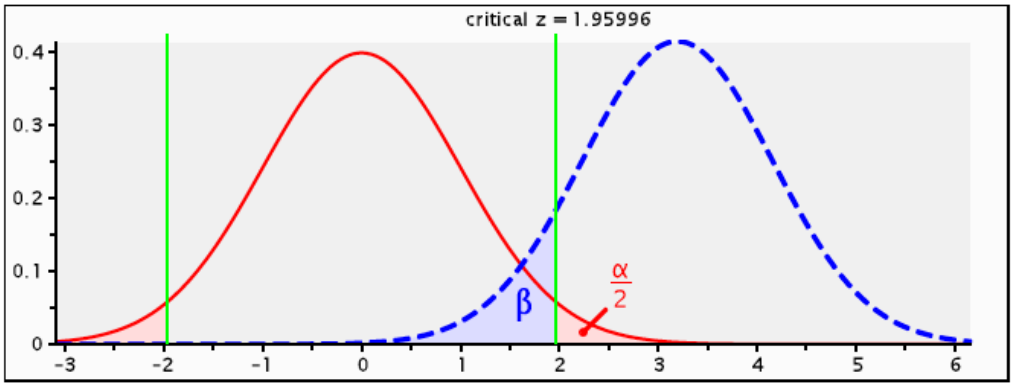
. 68% of RNR+ patients show one stenotic level and 32% show two or more stenotic levels

. 84% of RNR- patients show one stenotic level and 16% show one or two stenotic levels

. If Pr (Y=1 I X=1) H1= 0.32 and Pr (Y=1 I X=1) H0= 0.16 the odds ratio= 2.4705882

**z tests** – Logistic regression

| | | | |
|---|---|---|---|
| **Options**: | Large sample z-Test, Demidenko (2007) with var corr | | |
| **Analysis**: | A priori: Compute required sample size | | |
| **Input**: | Tail(s) | = | Two |
| | Odds ratio | = | 2.4705882 |
| | Pr(Y=1\|X=1) H0 | = | 0.16 |
| | α err prob | = | 0.05 |
| | Power (1-β err prob) | = | 0.90 |
| | $R^2$ other X | = | 0 |
| | X distribution | = | Binomial |
| | X parm π | = | 0.5 |
| **Output**: | Critical z | = | 1.9599640 |
| | Total sample size | = | 300 |
| | Actual power | = | 0.9001553 |




Result: Result: There is a 90% chance of correctly rejecting the null hypothesis that a particular value of the main predictor variable (LSS-Level) is not associated with the outcomes variable (Presence of RNR), with 300 patients (150 patients per group).