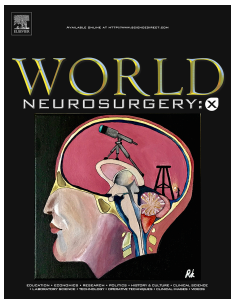

Relationship between lumbar lordosis, pelvic parameters, PI-LL mismatch and outcome after short fusion surgery for lumbar degenerative disease. Literature review, rational and presentation of public study protocol: RELApSE study (registry for evaluation of lumbar artrodesis sagittal alignEment)

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Short title: RELApSE study (Registry for Evaluation of Lumbar Artrodesis Sagittal alignEment)

Keywords: spine; neurosurgery; fusion surgery; lumbar degenerative disease; lumbar lordosis;

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Abstract

Background: Vertebral arthrodesis for degenerative pathology of the lumbar spine still remains burdened by clinical problems with significant negative results. The introduction of the sagittal balance assessment with the evaluation of the meaning of pelvic parameters and spinopelvic (PI-LL) mismatch offered new evaluation criteria for this widespread pathology, but there is a lack of consistent evidence on long-term outcome.

Methods: The authors performed an extensive systematic review of literature, with the aim to identify all potentially relevant studies about the role and usefulness of the restoration or the assessment of Sagittal balance in lumbar degenerative disease. They present the study protocol RELApSE (NCT05448092 ID) and discuss the rationale through a comprehensive literature review.

Results: From the 237 papers on this topic, a total of 176 articles were selected in this review. The analysis of these literature data shows sparse and variable evidence. There are no observations or guidelines about the value of lordosis restoration or PI-LL mismatch. Most of the works in the literature are retrospective, monocentric, based on small populations, and often address the topic evaluation partially.

Conclusions: The RELApSE study is based on the possibility of comparing a heterogeneous population by pathology and different surgical technical options on some homogeneous clinical and anatomic-radiological measures aiming to understanding the value that global lumbar and segmental lordosis, distribution of lordosis, pelvic tilt, and PI-LL mismatch may have on clinical outcome in lumbar degenerative pathology and on the occurrence of adjacent segment disease.

Abbreviations: Pelvic Index (PI), Lumbar Lordosis (LL), transforaminal interbody fusion (TLIF), posterior interbody fusion (PLIF), antero-lateral interbody fusion (ALIF), latero-lateral interbody fusion (LLIF), segmental lumbar lordosis (LS), Oswestry disability index, Short Form-12 (ODI-12), body mass index (BMI)

MANUSCRIPT

Introduction

Degenerative pathology of the lumbar spine is widespread, affecting approximately 5.7% of the European population[1]. Lumbar arthrodesis, with its different technical options, is a commonly adopted surgical therapy accounting for 30,000 procedures performed annually in Italy and over 450,000 in the United States [2]. However, lumbar vertebral arthrodesis for degenerative disease still remains burdened by clinical problems with significant negative results, including lack of clinical improvement, late symptoms relapse, or clinical worsening [3]. The evidence-based medicine on this topic is still insufficient and generally does not exceed evidence class B [4,5]. The available guidelines are mainly based on level II studies [6,7,8,9,10,11,12] and only offer recommendations that may support practitioners in clinical activity [5]. Thus, surgical treatment of lumbar degenerative disease remains extremely heterogeneous, considering the number of technical options available for the single pathology. Lack of standard of care leads to treatment strategies based on institutional, departmental, or personal experience planned on inconsistent scientific evidence [13].

The introduction in the clinical practice of the sagittal balance assessment with the evaluation of the meaning of pelvic parameters and spinopelvic mismatch offered new evaluation criteria for lumbar degenerative pathology [14,15] and the outcome of short lumbar arthrodesis surgery [16, 17, 18]. Restoration of Sagittal alignment and Pelvic Index (PI)-Lumbar Lordosis (LL) mismatch is closely associated with a better outcome in spinal deformities [19]. However, few studies in the literature report the impact of sagittal balance assisment on patients' post-surgical outcome.

At the same time, there is still a lack of consistent evidence regarding short-segment arthrodesis for lumbar degenerative pathology.

The definitive value for lumbar degenerative pathology of these aspects of the surgical outcome remains to be clarified without consolidated evidence. We conducted a comprehensive review of literature about this topic and here we propose our upcoming prospective study. The RELApSE study is, to our knowledge, the first prospective and multicenter study on these topics. We present the study protocol registered on trial.gov (NCT05448092 ID, protocol ID 012022) and discuss the rationale through a comprehensive literature review.

Methods

Background

Interbody fusion, including: transforaminal (TLIF), posterior (PLIF), anterior (ALIF), and lateral (LLIF); effectively treat lumbar degenerative pathology and provide spinopelvic balance and the impact of the interbody approach on segmental and adjacent level lordosis could be an important factor to consider during pre-operative planning to achieve pre-specified alignment goals.
From the literature search conducted (**Fig. 1**), 176 papers dealing with this topic were selected, and after careful analysis, we found that the results are often conflicting with each other and often incomplete. Over the past ten years, many studies reported associations between PI-LL mismatch, reduced lumbar lordosis, increased pelvic tilt, and outcome of lumbar arthrodesis for degenerative lumbar disease [16,20,21,22,23,24]. Other authors, on the other hand, reported an absence of correlation between the same parameters and clinical outcomes [25,26]. In addition, several authors have been reported evidence regarding association of adjacent level disc degeneration and elevated pelvic tilt, persistent PI-LL mismatch and altered LL4-S1/LL ratio [18,27,28,29,30,31,32,33,34,35,36]. Also, on this aspect, other studies identify different elements as predisposing factors for junctional pathology [37,38].

Review of Literature

The English literature is systematically investigate using MEDLINE, the NIH Library, Pubmed, web of science and Google Scholar according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, with the aim to identify all potentially relevant studies about the role and usefulness of the restoration or the assessment of Sagittal balance in lumbar degenerative disease. Searching for relevant studies, the reference section of included articles was analyzed.

The search was performed typing the following items: (Pelvic incidence) AND (mismatch); (Pelvic incidence-lumbar lordosis) AND (mismatch); (PI-LL) AND (mismatch); (PI-LL) AND (surgical assessment); (Pelvic incidence-lumbar lordosis) AND (surgical assessment), obtaining 237 potentially titles.

The first step of selection was focusing the usefulness of the study of Sagittal balance parameters in lumbar degenerative disease. In this regard, we chose to exclude by title and abstract papers that dealt with other segments of the spine, non-degenerative conditions such as congenital and pediatric forms, and discarding publications that had other languages outside of English, obtaining through these initial inclusion criteria 201 potentially relevant articles. As further criterion of inclusion, we

chose to consider adult populations with just degenerative conditions (excluding post-traumatic disease). It is worthwhile note that neurosurgical intervention was not considered as a criterion of inclusion itself since both patients eligible for neurosurgical treatment and non-surgical patients has been included.

Given these premises, we selected papers according to the following inclusion criteria:

- Availability of full-text articles
- English text only
- Patients older than 18-year-old without history of trauma
- Use of Sagittal balance parameters to select, plan or evaluate the treatment;
- Presence of neurological outcome evaluation. No specific limitation was applied regarding the timing of neurological evaluation after treatment.
- Papers published from 1985 onwards (for availability of recent imaging studies such MRI)

Conversely, exclusion criteria were:

- Full-text articles in languages other than English
- Studies reporting patients with post-traumatic disease, other spinal segment considered
- Patients younger than18-year-old
- No data available about neurological outcome or not focused on clinical outcome

Data extracted from each study were (1) authors, (2) year of publication, (3) study design, (4) purpose of the study, (5) disease condition, (6) number of patients included, (7) PI-LL parameters used, (8) lumbar spine segment evaluated, (9), neurological functions evaluated, (10) clinical outcome (11).

Results

A total of 237 studies were found through PubMed database search and reference section screening. Duplicates check was carried out by an automatic tool working on Microsoft Excel spreadsheets. Out of the initial papers, 1 duplicate, 20 were out of topic identifiable by the title, 9 with other languages, were removed; thus 201 titles with abstract were identified and, following the eligibility criteria, 185 papers were screened. A further qualitative skimming led to articles being selected for full text screening, out of which a total of 176 articles were included in the systematic review. (**Fig. 1**).

Study design

The study aims to evaluate the relationships between radiological data and patients' reported outcome. Starting from a heterogeneous population in terms of clinical conditions, pathology, and surgical treatment options, the study method is to make the population homogeneous on some data available in all patient's end that can be analyzed independently. These data are pelvic parameters (pelvic incidence, pelvic tilt, sacral slope), segmental lumbar lordosis (LS), global lumbar lordosis (LL), PI-LL mismatch, and L4-S1/LL lordosis ratio; clinical results based on administered questionnaires (Oswestry disability index, Short Form-12, ODI-12) and overall outcome assessment at FU (6 point scale: excellent (entirely resolved symptoms), good (good clinical improvement, minor signs), fair (improvement compared to preoperative but still with relevant symptoms), unchanged (symptoms similar to preoperative), negative (worsening of symptoms compared to preoperative); severely worsened (reduction of personal autonomy compared to preoperative due to neurological deficits); occurrence of symptomatic junctional pathology (yes / no), need for surgical revision of the operated level (yes / no) or of the adjacent level (yes / no).

Endpoints

Primary end-point: analysis of the relationship between clinical results (ODI, SF-12, global outcome) and pelvic parameters, overall lumbar/segmental postoperative lordosis/ratio L4-S1-overall lumbar lordosis (delta pre-postoperative-follow-up values) in the hypothesis that the persistence of elevated PI-LL mismatch, reduced LL or altered pelvic parameters (pelvic tilt) may represent independent adverse prognostic factors for patients reported outcome, the occurrence of symptomatic junctional pathology and need for surgical revision.
Secondary end-points: 1) Comparison between different interbody fusion techniques (Anterior Lumbar Interbody Fusion (ALIF) vs. Posterior Lumbar Interbody Fusion (PLIF) vs. Transforaminal Lumbar Interbody Fusion (TLIF) vs. Extreme lateral Lumbar Interbody Fusion (XLIF)) in terms of increasing segmental lordosis; 2) Comparison between different interbody fusion techniques (ALIF vs. PLIF vs TLIF vs. XLIF) in terms of changing the global lumbar lordosis, spinopelvic parameters and PI-LL mismatch; 3) Long-term evaluation of lumbar lordosis stability in relation with occurrence of subsidence or pedicular screws failure.

Sample size and statistical analysis

The sample size is assessed in relation to the primary objective. We want to compare the variation in clinical parameters before and after the intervention (ODI, SF-12: MCS, PCS, global outcome) between the groups finally identified by the presence/absence of LL-PI mismatch.
In the hypothesis of no difference, the data necessary for the calculation will be referred to as reported by Divi et al. [26]. As regards MCS-12, the study says a delta equal to 4.1 in subjects without mismatch and equal to 4.1 in issues with mismatch, consequently, no difference is expected, and this parameter is not included in the calculation of sample size. Concerning ODI, the study going to reports a delta equal to -22.8 in subjects without mismatch and equivalent to -20.9 in subjects with a mismatch (hypothesized sd equal to 5). For PCS-12, the study will reports a delta equal to 9 in subjects without mismatch and similar to 10 in subjects with a mismatch (hypothesized sd equal to 2).
The significance is appointed at 0.05, a test power of 0.95, assuming to compare the two samples using a two-tailed t-test with a minimum sample size of 362 subjects is required. Since the study is multicentric and considering the risk of loss of information during follow-up or the presence of incorrect preoperative radiographic examinations, the enrollment of a total of 500 patients is considered exhaustive. The evaluation of the secondary end-points, which is not essential, will be carried out on the same population sample.
Quantitative variables will be expressed using means and standard deviations (medians and quartiles when appropriate). A comparison of proportions will be performed with the Chi-squared test for categorical variables. Qualitative data will be expressed as a raw number and a population percentage. Continuous variables will be compared using the Student t-test and ANOVA (or non-parametric analog). The correlation between numerical variables will be evaluated through Pearson's correlation coefficient and relative test (or similar Spearman coefficient and test, if appropriate). Any linear or non-linear regressions will be assessed for the relationship between lumbar lordosis delta, pelvic parameters, and clinical improvement. Depending on the results provided by the analyzes described, it may be appropriate to set up mixed-effects models to assess the longitudinal trend of the study parameters. The possible implementation of non-parametric models of supervised machine learning (e.g., random forest, SVM) will be evaluated to verify the actual predictive power of the variables under consideration concerning the clinical evaluation.
Due to the nature of the multicentre study and the high sample size, it is planned to create an interactive report (dashboard) for viewing the statistical results obtained.

Surgeons' identification criteria and patients recruitment

The participant's investigators will be identify in the Italian context among orthopedics or neurosurgeons with proven experience in the field of vertebral surgery (based the selection

concerning the number of year, number of procedures done by the surgeon) by direct invitation from one of the steering committee members. Surgeons interested in the study must sign a letter of intent to underline the commitment required and the roles of the investigator. Each participating investigator is required to obtain approval from their relevant ethics committee. Investigators will recruit patients in the context of their regular clinical and surgical activity. Recruitment must be prospective, and the patient must be enroll before surgery to avoid selection bias related to clinical results. Each participating surgeon will be required to recruit a minimum of 20 complete and evaluable patients to be included in the investigators, while the number of patients enrolled should not exceed 60 cases for the single surgeon with the objective to homogenize the contribution of individual investigators and avoiding, within the enrolled population, excessive imbalances and discrepancies. Once the programmed sample size has been reached, recruitment will be close. Eventually for some centers and some surgeons, consideration will be given to stratifying patients as private, insured or government-funded and whether they have claims or demands.

Patients inclusion, exclusion, and withdrawal criteria

All patients with the following requirements will be included in the observational study.

1. Patients undergoing to an instrumented lumbar arthrodesis operation at 1, 2, or 3 levels
2. Age between 18 and 75 years
3. Agree to inclusion in the study with a subscription of informed consent, available for five years follow-up, including phone interviews.
4. Availability of adequate preoperative radiological documentation: CT or MRI of the lumbar spine; standing lumbar spine x-ray performed in a neutral position in which the pelvic parameters (pelvic incidence, pelvic tilt) and all lumbar segments can be correctly assessed
5. Availability of adequate and comprehensive clinical information, including the presence of preoperative ODI and SF-12
6. availability of adequate information regarding surgery
7. availability of postoperative radiological documentation: lumbar spine X-ray with the exact requirements as point 4 performed in the postoperative period and at one year follow-up.
8. availability of adequate and comprehensive clinical information, including ODI score and SF-12 questionnaire at follow-up. The minimum follow-up for each patient included must be 12 months, to be continued for a total of 5 years.

Patients who, although already enrolled, do not meet the inclusion criteria at final evaluation will be excluded. Patients with a life expectancy of fewer than 5 years due to associated diseases must be excluded from the study.

Patients who, for various reasons, have to withdraw their consent to be included in the study will also be excluded. There are no other exclusion criteria.

Data collection

For the recruited patients, all the following data are collected:
- general: age, sex, smoking habit, previous diagnosis of osteoporosis
- surgical data: type of surgery performed, kind of arthrodesis performed, date of surgery, used cages material, used cage lordosis degrees, intraoperative adverse events, ODI, technical errors, complications, hardware failure, need for reoperation, the occurrence of junctional pathology, intervention-junctional pathology time
-clinical data: diagnosis (type of degenerative disease), duration of symptoms, presence of claudication or radicular pain, presence of neurological deficits, presence of L5 sacralization, ODI score, SF-12 PCS, SF-12 MCS, days of postoperative hospitalization, overall outcome assessment. ODI score and the SF-12 questionnaire (general health status) are used for outcome evaluation.
- radiological data: overall lumbar lordosis, segmental lordosis of all lumbar levels, pelvic incidence, pelvic tilt, sacral slope. The values will be calculated according to the criteria reported by Duval-Beaupère. From these data, theoretical pelvic tilt will be subsequently calculated regarding Vialle's formula (PT = PI x 0.37 - 7), pelvic delta tilt (PT - theoretical PT), PI-LL mismatch (expressed on the calculated ideal lordosis such as PI + 10 °), L4-S1 lordosis/LL lordosis (percentage). The vertical sagittal axis (SVA C7-S1) is not considered in this study about the need to obtain teleradiography of the entire spine, a non-routine and mainly not required examination for degenerative diseases.
All images must be centralized for measurements anonymously and coded. All radiological data, measured as angles or derived numbers, will be calculated by independent data managers recruited as volunteers among medical specialists or fellows (see Study Board). The angle values will be calculated by performing three successive measurements on the same radiological image by three independent examiners not involved in the surgical management. Subsequent calculation of the average of the nine values is obtained. Calculating pelvic angles and parameters can be done with freeware SurgimapÒ software developed by a group of vertebral surgeons and engineers to support anatomical evaluation and surgical planning (Nemaris Inc.TM innovation, New York, NY, USA). The software can be downloaded free from the website www.surgimap.com where all the policies and conditions of use are visible.

Follow-up

All patient follow up continues, unless the patient withdraws consent explicitly, for the entire study duration initially planned for five years.
The follow-up includes postoperative clinical evaluation three months after surgery, one year and up to 5 years annually. Any additional assessment will be dictated only by clinical needs and must be added to the follow-up with a related time of occurrence. The follow-up evaluations must include acquiring all clinical data, including ODI and SF-12 evaluation questionnaires. Follow-up is IN the responsibility of a single investigator. A telephone assessment may be performed on patients who are not available for outpatient assessments or who cannot be reached by completing ODI and SF-12 by interview.
The follow-up must also include the acquisition of a lumbar spine standing X-ray at three months and 12 months, as normally suggested by good clinical practice. According to the literature, implant settlement and cages subsidence occur mainly in the first 12 months [39,40, 90]. Further or subsequent radiological examinations will eventually be performed exclusively for clinical needs (persistent symptoms, clinical worsening) and must be added to the study data.

Ethical concern

RELApSE is a purely observational study registered and published on trials.gov with NCT05448092 ID (protocol ID 012022). No interference is foreseen on the patient's diagnostic-therapeutic path or technical treatment options chosen by participating surgeons. Furthermore, no form of experimentation with techniques or materials is envisaged. Data collection is prospective in the context of regular clinical activity. The study is not sponsored. The management of privacy and personal data is in full compliance with the current Italian law. The study guarantees the transmission and collection of data in a completely anonymous form. The study is observational and not sponsored and only represents an analysis and comparison of data obteined from regular clinical and surgical activity. No experimentation is envisage. There are no conflicts of interest for any of the board members.

Study Monitoring and Supervision

The supervision of the study provides for the verification of the patient's record completeness, the adequacy of the radiographs for the purpose of the study, and the correct presence of follow-ups. Random evaluation of the accuracy of the measurements. Evaluation of proper data analysis

procedures. Participation and supervision of the results analysis. Supervision is carried out by independent figures who are not part of the study board and are not investigators of the study.
A telephone evaluation will be performed anonymously on a sample of enrolled patients representative of all investigators to verify the data's accuracy and truthfulness.

Discussion

The latest AANS guidelines on arthrodesis for degenerative pathology (part 7-12, 2014) [6,7,8,9,10-11] report grade B and C recommendations based on evidence level II, III, and IV studies. Furthermore, all these chapters reported," There is no evidence that conflicts with the previous recommendations published in the original version of the Guidelines" (Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine, 2005). There are no observations in the guidelines about the value of lordosis restoration or PI-LL mismatch. Therefore, between 2005 and 2014, there has not been a significant evolution of scientific evidence in this field of vertebral surgery. Therefore, the evaluation of the sagittal balance and related parameters could likely represent a new area of discussion and a possible way to generate some further criteria for evaluating the outcome of surgical treatment for lumbar degenerative disease. This could also help to create some evidence for lumbar arthrodesis. Afterward, an increasing number of publications have reported on the role of lumbar lordosis, pelvic parameters, and PI-LL mismatch.
A recent systematic meta-analysis highlighted a strong relationship between LBP and reduced lumbar lordotic curve mainly when patients were analyzed with age-matched healthy controls [15]. In 2000 Lazennec et al. firstly analyzed the relationship between radiological parameters and postfusion pain, focusing attention on the vertical position of the sacrum [17]. Patients with pain persisting after arthrodesis showed both reduced SS and increased PT, with PT reaching almost twice the normal value. Authors postulated that "achieving a strong fusion should not be the only goal. Appropriate position of the fused vertebrae is also paramount to minimize muscle work during posture maintenance"[20-22]. An increased LL and SL was associated with better outcome (VAS, ODI) after unilateral instrumented TLIF for single-level lumbar degenerative disease [41,42,43] and after 1 level [43] or 2-level PLIF for 2-level (L3-L4 and L4-L5) degenerative spondylolisthesis [20]. Hioki et al. described a positive linear correlation between the increase in lordotic angle and improvement of JOA score at outcome evaluation after two-level PLIF [22].
Furthermore, postoperative reduction of pelvic tilt was associated with better outcomes after PLIF surgery for spondylolisthesis [24,44,45] and sacral slope increased to more than 30° after single-level TLIF [43]. The review by Le Huec et al. suggested that the increase in PT after surgery is associated with significant low back pain. At the same time, the restoration of a regular PT results

in an excellent clinical outcome [18]. The study of Aoki et al. was the first investigating influence of PI-LL mismatch on postoperative residual symptoms after 1 or 2 levels TLIF [16]. More considerable PI-LL mismatch was significantly associated at one year follow-up with VAS for LBP, leg pain, and leg numbness but not with postoperative disability (ODI). Detailed VAS analysis highlights the association of mismatch with standing low back pain but not with LBP while sitting or in motion. Worse ODI scores were associated at 2 years follow-ups with PI-LL mismatch after four-level lumbar (L2-S1) fusion surgery [46]; moreover, significant correlations between PI-LL mismatch and improvement in both JOA score-VAS for LBP at two year follow up has been described for patients with degenerative lumbar scoliosis treated with short-segment fusion (1, 2 or 3 level TLIF) at the affected levels [47]. Radovanovic et al. reported a better patient-reported outcome, after surgery for degenerative spondilosthesys, in patients with SVA less than 50 mm. Patients with an SVA ≥ 50 mm presented reduced lumbar lordosis with increased mismatch and had a worse SF-36 PCS and Oswestry Disability Index (ODI; $p = 0.043$) as well as more back pain [21]. Better improvement of PI-LL mismatch with reduced PT and higher LL was found in patients without residual back pain after the OLIF procedure [48], and similarly a significant linear association with ODI was reported for independent variables LL, delta LL, and PI-LL status after Interbody fusion for degenerative disc disease [49]. A cutoff value of 27,5 ° for preoperative PI-LL mismatch is reported as a negative factor for outcome of patients who underwent second PLIF surgery for ASD and as a predisposing factor for subsequent long corrective surgery [23]. Finally, sagittal malalignment with PI-LL mismatch greater than 10° was also associated with the occurrence of pseudarthrosis [50].

On the contrary, Hsu et al. reported no correlation between LL or LL restoration ratio and the outcome of patients undergoing PLIF for degenerative spondylolisthesis [51], while Jia et al. concluded that PI-LL mismatch is not associated with clinical outcome (VAS, ODI) after MIS-TLIF for lumbar stenosis [25]. A comparative study between ALIF and PLIF also showed no relationship between LL and patients outcome [52]. A 2017 systematic review by Rhee et al. selected only 4 articles for final statistical analysis and pointed out the lack of well-powered studies on this topic. No statistically significant improvement in both ODI and VAS was related to the restoration of segmental lordosis. So the correction of malalignment does not seem to yield clinical improvements for short lumbar arthrodesis [53].

A recent large retrospective study shows that patient outcomes in short-segment lumbar fusion for the degenerative lumbar disease are equivalent in patients with and without a postoperative PI-LL mismatch at one year follow-up. The two groups' preoperative, postoperative, or delta outcome scores (PCS-12, ODI, VAS back, VAS leg) were noted. PI-LL mismatch was not found to be an independent predictor for patient-reported outcome on multivariate analysis ($P > 0.05$). This study

suggests that limited surgery addressed to focal neurological disease has equivalent effects of corrective surgery [26].

Adjacent segment degeneration (ASD) after lumbar arthrodesis, both symptomatic and radiological, is a well-known problem. Many studies discuss this topic, and several aspects were analyzed as causes or risk factors. A prospective study by Ekman shows that surgical fusion accelerates the occurrence of degenerative discopathy at the adjacent level compared with natural history [54]. Incidence has a wide range between 2,62 and 84% with a prevalence of proximal level and main associated factors were old age, body mass index (BMI), previous degenerative disc o facet disease, type of pathology, multiple-level fusion, male, intraoperative superior facet joint violation, laminectomy, sagittally oriented facet joint angle, PLIF and progressive fatty degeneration of the multifidus muscle [54,55,56,57,58,59,60,61,62,63,64,65].

In 2001 Kumar et al. firstly reported a significant association between ASD and the C7 sagittal plumb line. A vertical sacrum was highly associated with ASD even with regular C7 plumb line. Sacral inclination was considered an essential aspect of sagittal alignment as an expression of the compensation mechanism [66]. Several authors reported a correlation between ASD and reduced lumbar lordosis as a significant independent factor [27,67,68,69] or associated with other factors [57,70,71,72]. Also, reduced postoperative segmental lordosis was associated with the occurrence of ASD [29,70,73,74]. Soh et al. and Bae et al. suggested that the most important factor for the prevention of ASD is the restoration of segmental lordosis [29,73]. Kim KH et al. described association between reduced segmental lordotic angle and symptomatic ASD in isolated L4–L5 spondylolisthesis treated with interbody fusion and pedicle screw fixations [75]. Again the pre-postoperative segmental lordosis delta was reported as a significant risk factor for ASD, especially with early onset [50,76].

The relationship between pelvic parameters and ASD was also studied. Nakashima et al. identified a high degree of pelvic incidence as a risk factor for early-onset radiological ASD, probably in relation to the reduced probability of obtaining appropriate lordosis after surgery [28]. This association was also confirmed by a recent meta-analysis [69].

Some authors found a significant reduction of sacral slope angle in patients with ASD [18,30]. Similarly, Di Martino et al. reported in ASD patients significantly lower SS and consequent higher PT values related to pelvic retroversion and hyperlordosis compensation mechanism [31]. In this study, the Authors defined SS value below 39° or PT above 21° as a vital risk factor for symptomatic ASD (relative risk 1.73 for SS and 3.663 for PT). Another study confirmed that a PT greater than 24.1 ° could be considered predictive of ASD after lumbar TLIF [77]. Also, preoperative PT with a 22.5° cutoff was strongly associated with ASD (risk 5.1 greater) [32]. A meta-analysis by Phan et al. concludes that the development of ASD may be predicted from the

evaluation of Spinopelvic alignment parameters (PT, SS, PI-LL mismatch, and LL) in patients with lumbar fusion for degenerative disease [78]. An elevated PI-LL mismatch has been reported to be closely associated with the development of symptomatic ASD [33,68] or radiological ASD [46]. A PI-LL mismatch greater than 15° was identified as a significant independent risk factor for radiographical ASD in patients with L5-S1 spondylolytic spondylolisthesis treated with single-level PLIF [34]. Moreover Wang et al reported a strong association between symptomatic ASD after lumbar fusion and more significant PI-LL mismatch but identified different PI-LL mismatch cutoffs in patiens below 60 years (PI-LL >10°) and older patients (PI-LL > 20°) to reach statistical significance. The authors hypothesize that the ideal correction of LL may vary with increasing age [79]. Rothenfluh et al. reported 10-times higher risk of ASD occurrence for patients with elevated PI-LL mismatch (>10°) [35]. Patients with ASD have higher PI, higher PT, and lower lumbar lordosis.The authors conclude that when fusion surgery is performed without treatment of intrinsic deformity and PI-LL mismatch the occurrence of ASD can be expected. Finally lumbar distribution index (LDI=L4-S1 lordosis/lumbar lordosis x 100) was strongly associated with the occurrence of ASD: patients with reduced distal L4-S1 lordosis and consequent low LDI present more significant risk of developing ASD [36]. Kim et al. reported frequent occurrence of ASD in patients with LDI less than 50% also when PI–LL was satisfactorily corrected to less than 10°[80]. Obtaining an appropriate postoperative LDI in L4-S1 may have a crucial role in preventing ASD. In both clinical analysis and mechanistic simulation environments the increased loading and biomechanical shear forces at fusion adjacent level have been postulated and discussed for patients with PI-LL mismatch. These experimental data offer a different element in evaluating the association between ASD occurrence and sagittal malalignment [81,82].

On the contrary, some authors have highlighted the absence of a relationship between ASD and sagittal alignment. Anandjiwala et al. reported that LL is not a risk factor for ASD occurrence [83], while Chen et al. reported no differences in lumbar lordosis between patients presenting ASD and those who did not [84]. Masevin et al. analyzing the risk factors for ASD, reported the absence of a role of the sagittal balance in short fixations for which the only risk factor is preoperative degenerative changes [85]. A meta-analysis by Wang et al., based on 19 papers, showed that postoperative PT and SS are not associated with ASD occurrence [69]. Multivariate analyses showed that segment distraction was the most significant risk factor after L4-L5 PLIF [86] or only multilevel surgery associated with high rate reoperation [87]. Finally, a recent study on the prognostic factors of ASD after L4-L5 fusion does not consider sagittal alignment at all, suggesting that many surgeons still underestimate these aspects [88].

The analysis of these literature data shows sparse and variable evidence. It highlights how clarification and greater understanding of this argument are still needed, evoking the need for

methodologically correct and high-level studies [89]. Most of the works in the literature are retrospective, generally monocentric, based on small populations, and often address the topic evaluation partially. Indeed, the generation of standards based on scientific evidence remains very difficult for degenerative lumbar spine pathology. However, evaluating data collected on a sufficiently large population in a prospective, uniform, and methodologically correct manner could allow highlighting and underlining some associations. This future multicentric study is based on the possibility of comparing a heterogeneous population by pathology and different surgical technical options on some homogeneous clinical and anatomic-radiological measures (**Fig. 2**). The data analysis will contribute to understanding the value that global lumbar and segmental lordosis, distribution of lordosis, pelvic tilt, and PI-LL mismatch may have, as independent factors, on clinical outcome in lumbar degenerative pathology and on the occurrence of adjacent segment disease. Consequently, it will focus on and enhance at least some rational aspects of lumbar arthrodesis, such as, in particular, the need to adopt surgical strategies aimed at restoring segmental lordosis and correcting the sagittal profile (**Fig. 3**). Carrying on the follow-up for several years, the study will finally provide information on long-term evolution, particularly on the occurrence of symptomatic adjacent level degeneration.

DISCLOSURE

This study is not sponsored, and there are no conflicts of interest within the steering committee or for single investigators in front of the final results. The study is dedicated to the memory of Vincenzo Di Stefano, an excellent friend, person, and vertebral neurosurgeon.

Figure Captions

Fig.1 : The flow-chart showing the selection according to PRISMA criteria of the articles used for the review

Fig. 2: The figure shows the main Sagittal balance parameters used for the study (part A) namely Lumbar lordosis (red A), Sacral slope (red B), Pelvic Tilt (red C), Pelvic incidence (red D) and as can be seen in the X-ray images in maximum extension (part B) and maximum flexion (part C) of the patients, they can vary even significantly.

Fig. 3: We report the clinical case of a 57-year-old woman with chronic low back pain and degenerative discopathy with L4-L5 listhesis (standing Rx A, and preoperative MRI, B) who

benefited from a significant improvement in sagittal balance parameters after stabilization surgery with double MS-TLIF L3-L4-l5 with lordotic cages (CT scan after 1 month, C and MRI control after 6 months).

References

1. Ravindra VM, Senglaub SS, Rattan A, Dewan MC, et al. Degenerative Lumbar Spine Disease: Estimating Global Incidence and Worldwide Volume. Global Spine J. 2018;8(8):784-794. https:/doi.org/10.1177/2192568218770769.

2. Martin B, Mirza SK, Spina N, Spiker WR, Lawrence B, Brodke DS. Trends in Lumbar Fusion Procedure Rates and Associated Hospital Costs for Degenerative Spinal Diseases in the United States 2004-2015. Spine. 2018;1:2004-2015. https://doi.org/10.1097/BRS.0000000000002822.

3. Makino T, Kaito T, Fujiwara H, Honda H, et al. Risk Factors for Poor Patient-Reported Quality of Life Outcomes After Posterior Lumbar Interbody Fusion: An Analysis of 2-Year Follow-up. Spine 2017;42(19):1502-1510. https://doi.org/10.1097/BRS.0000000000002137.

4. Kaiser MG, Eck JC, Groff MW, Watters WC, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 1: introduction and methodology. J Neurosurg Spine. 2014;21(1):2-6. https://doi.org/10.3171/2014.4.SPINE14257.

5. Costa F, Anania CD, Zileli M, Servadei F, Fornari F. Lumbar Spinal Stenosis: Introduction to the World Federation of Neurosurgical Societies (WFNS) Spine Committee Recommendations. World Neurosurgery X 2020;10;7:100076. https://doi.org/10.1016/j.wnsx.2020.100076.

6. Eck JC, Sharan A, Ghogawala Z, Resnick DK, et al. Guideline update for performing fusion procedures for degenerative disease of the lumbar spine. Part 7: lumbar fusion for intractable low-back pain without stenosis or spondylolisthesis
J. Neurosurg Spine. 2014; 21(1):42-7. https://doi.org/10.3171/2014.4.SPINE14270.

7. Wang JC, Dailey AT, Mummaneni PV, Ghogawakla Z, resnick DK, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 8: lumbar fusion for disc herniation and radiculopathy.J Neurosurg Spine. 21(1):48-53. https://doi.org/10.3171/2014.4.SPINE14271.

8. Resnick DK, Watters WC, Sharan A, Mummaneni PV, Dailey AT, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 9: lumbar fusion for

stenosis with spondylolisthesis. J Neurosurg Spine. 2014;21(1):54-61. https://doi.org/10.3171/2014.4.SPINE14274.

9. Resnick DK. J Neurosurg Spine 21:62–66, 2014. Resnick DK, Watters WC 3rd, Mummaneni PV, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 10: lumbar fusion for stenosis without spondylolisthesis. J Neurosurg Spine. 2014; 21:62-66.

10. Mummanemi PV, Dhall SS, Eck JC, Groff MW, Ghogawala Z , et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 11: interbody techniques for lumbar fusion. J Neurosurg Spine. 2014;21(1):62-6. https://doi.org/10.3171/2014.4.SPINE14275.

11. Groff MW, Dailey AT, Ghogawala Z, Resnick DK, Watters WC 3rd, et al. Guideline update for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 12: pedicle screw fixation as an adjunct to posterolateral fusion. J Neurosurg Spine. 2014;21(1):75-8. https://doi.org/10.3171/2014.4.SPINE14277.

12. Peul WC, Moojen WA. Fusion for lumbar spinal stenosis—safeguard or superfluous surgical implant? N Engl J Med. 2016;374(15):1478-1479. https://doi.org/10.1056/NEJMe1600955.

13. Heary RF. Introduction to the Guidelines for the Performance of Fusion Procedures for Degenerative Disease of the Lumbar Spine. J Neurosurg: Spine. 2(6):637-8. https://doi.org/10.3171/spi.2005.2.6.0637.

14. Zarate-kalfopulos B, Reyes-Tarrago F, Navarro-Aceves LA, Garcia-Ramos CL, et al. Characteristics of Spinopelvic Sagittal Alignment in Lumbar Degenerative Disease. World Neurosurgery. 2019;126:e417-e421. https://doi.org/10.1016/j.wneu.2019.02.067.

15. Chun SW, Lim CY, Kim K, Hwang J, Chung SG. The relationships between low back pain and lumbar lordosis: a systematic review and metaanalysis. Spine J 2017;17(8):1180-1191. https://doi.org/10.1016/j.spinee.2017.04.034.

16. Aoki Y, Nakajima A, Takahashi H, Sonobe M, et al. Influence of pelvic incidence-lumbar lordosis mismatch on surgical outcomes of short-segment transforaminal lumbar interbody fusion. BMC Musculoskelet Disord. 2015;16:213. https://doi.org/10.1186/s12891-015-0676-1.

17. Lazennec J-Y, Ramaré S, Arafati N, et al. Sagittal alignment in lumbosacral fusion: relations between radiological parameters and pain. Eur Spine J. 2000;9(1):47–55. https://doi.org/10.1007/s005860050008

18. Le Huec J-C, Faundez A, Dominguez D, et al. Evidence showing the relationship between sagittal balance and clinical outcomes in surgical treatment of degenerative spinal diseases: a literature review. Int Orthop. 2015;39(1):87–95. https://doi.org/10.1007/s00264-014-2516-6.

19. Schwab FJ, Blondel B, Bess S, Hostin R, Shaffrey CI, et al. Radiographical spinopelvic parameters and disability in the setting of adult spinal deformity: a prospective multicenter analysis. Spine. 2013; 38(13):E803-12. https://doi.org/10.1097/BRS.0b013e318292b7b9.

20 Takahashi Y, Okuda S, Nagamoto Y, Matsumoto T, Sugiura T, Iwasaki M. Effect of segmental lordosis on the clinical outcomes of 2-level posterior lumbar interbody fusion for 2-level degenerative lumbar spondylolisthesis. J Neurosurg Spine. 2019;12:1-6. https://doi.org/10.3171/2019.4.SPINE181463

21 . Radovanovic I, Urquhart JC, Ganapathy V, Siddiqi F, Gurr KR, Bailey SI, Bailey CS. Influence of postoperative sagittal balance and spinopelvic parameters on the outcome of patients surgically treated for degenerative lumbar spondylolisthesis. J Neurosurg Spine. 2017;26(4):448-453. https://doi.org/10.3171/2016.9.SPINE1680.

22. Hioki A, Miyamoto K, Kodama H, Hosoe H, Nishimoto H, Sakaeda H, Shimizu K. Two-level posterior lumbar interbody fusion for degenerative disc disease: improved clinical outcome with restoration of lumbar lordosis. Spine J. 2005;5(6):600-7. https://doi: 10.1016/j.spinee.2005.04.001.

23. Nagamoto Y, Okuda S, Matsumoto T, Takenaka S, Takahashi Y, et al. Preoperative Pelvic Incidence Minus Lumbar Lordosis Mismatch in Repeat PLIF Induces Subsequent Corrective Long Fusion. World Neurosurg. 2021;154:e762-e769. https://doi.org/10.1016/j.wneu.2021.07.141.

24.Kim MK, Lee SH, Kim ES, Eoh W, Chung SS, Lee CS. The impact of sagittal balance on clinical results after posterior interbody fusion for patients with degenerative spondylolisthesis: a pilot study. BMC Musculoskelet Disord. 2011;12:69. https://doi.org/10.1186/1471-2474-12-69.

25 Jia J, Zhao Y, Liu X. Impact of sagittal imbalance correction on clinical outcomes in patients undergoing MIS-TLIF for LSS. Clin Neurol Neurosurg. 2019;181:119-126. https://doi.org/10.1016/j.clineuro.2019.04.017.

26. Divi SN, Kepler CK, Hilibrand AS, et al. Patient Outcomes Following Short-segment Lumbar Fusion Are Not Affected by PI-LL Mismatch. Clin Spine Surg. 2021;1;34(2):73-77. https://doi.org/10.1097/BSD.0000000000001051.

27 Djurasovic MO, Carreon LY, Glassman SD, Dimar JR 2nd, Puno RM, Johnson JR. Sagittal alignment as a risk factor for adjacent level degeneration: a case-control study. Orthopedics. 2008;31(6):546.

28. Nakashima H, Kawakami N, Tsuji T, et al. Adjacent segment disease after posterior lumbar interbody fusion: based on cases with a minimum of 10 years of follow-up. Spine. 2015;40:E831-E841. https://doi.org/10.1097/BRS.0000000000000917.

29. Soh J, Lee JC, Shin BJ. Analysis of risk factors for adjacent segment degeneration occurring more than 5 years after fusion with pedicle screw fixation for degenerative lumbar spine. Asian Spine J. 2013;7(4):273-81. https://doi.org/10.4184/asj.2013.7.4.273.

30. Alentado VJ, Lubelski D, Healy AT, Orr RD, Steinmetz MP, Benzel EC, Mroz TE. Predisposing characteristics of adjacent segment disease after lumbar fusion. Spine. 2016;41(14):1167-1172. https://doi.org/10.1097/BRS.0000000000001493.

31. Di Martino A, Quattrocchi CC, Scarciolla L, Papapietro N, Beomonte Zobel B, Denaro V. Estimating the risk for symptomatic adjacent segment degeneration after lumbar fusion: analysis from a cohort of patients undergoing revision surgery. Eur Spine J. 2014;Suppl 6:693-8. https://doi.org/10.1007/s00586-014-3551-0.

32. Yamasaki K, Hoshino M, Omori K, Igarashi H, et al. Risk factors of adjacent segment disease after Transforaminal inter-body fusion for degenerative lumbar disease. 2017;42(2):E86-E92. https://doi.org/10.1097/BRS.0000000000001728.

33. Tempel ZJ, Gandhoke GS, Bolinger BD, Khattar NK, et al. The influence of pelvic incidence and lumbar lordosis mismatch on development of symptomatic adjacent level disease following single-level transforaminal lumbar interbody fusion. Neurosurgery. 2017;80(6):880-886. https://doi.org/10.1093/neuros/nyw073.

34. Takeda K, Okada E, Shinozaki Y, Ozaki M, et al. Risk Factors for Early-onset Radiographical ASD in Patients With Spondylolytic Spondylolisthesis After Single-level PLIF. Spine J. 2022;S1529-9430(22)00046-8. https://doi.org/10.1016/j.spinee.2022.02.001.

35.Rothenfluh DA, Mueller DA, Rothenfluh E, Min K. Pelvic incidence- lumbar lordosis mismatch predisposes to adjacent segment disease after lumbar spinal fusion. Eur Spine J. 2015;24(6):1251-8. https://doi. Org/10.1007/s00586-014-3454-0.

36. Zheng G, Wang C, Wang T, Hu W, et al. Relationship between postoperative lordosis distribution index and adjacent segment disease following L4-S1 posterior lumbar interbody fusion. J Orthop Surg Res. 2020 Apr 3;15(1):129. https://doi.org/10.1186/s13018-020-01630-9.

37. Okuda S, Yamashita T, Matsumoto T, Nagamoto Y, et al. Adjacent Segment Disease After Posterior Lumbar Interbody Fusion: A Case Series of 1000 Patients. Global Spine J. 2018;8(7):722-727. https://doi.org/10.1177/2192568218766488.

38. Epstein NE. A review: Reduced reoperation rate for multilevel lumbar laminectomies with noninstrumented versus instrumented fusions. Surg Neurol Int. 2016;7(Suppl 13):S337-46. https://doi.org/10.4103/2152-7806.182546.

39. Tartara F. Fulvio Tartara F, Bongetta D, Pilloni G, Colombo EV, Giombelli E. Custom-made trabecular titanium implants for the treatment
of lumbar degenerative discopathy via ALIF/XLIF techniques: rationale
for use and preliminary results. Europ Spine J. 2020;29(2):314-320. https://doi.org/10.1007/s00586-019-06191-y.

40. Marchi L, Abdala N, Oliveira L, Amaral R, Coutinho E, Pimenta L. Radiographic and clinical evaluation of cage subsidence after stand-alone lateral interbody fusion. J Neurosurg Spine. 2013;19(1):110-8. htpps://doi.org/10.3171/2013.4.SPINE12319.

41. Liang Y, Shi W, Jiang C, et al. Clinical outcomes and sagittal alignment of single-level unilateral instrumented transforaminal lumbar interbodycfusion with a 4 to 5-year follow-up. Eur Spine J. 2015;24(11):2560-6. https://doi.org/10.1007/s00586-015-3933-y.

42. Kepler CK, Rihn JA, Radcliff KE, et al. Restoration of lordosis and disk height after single-level transforaminal lumbar interbody fusion. Orthop Surg. 2012;4(1):15-20. https://doi.org/10.1111/j.1757-7861.2011.00165.x

43. Liow MH, Goh GS, Chua JL, Ling ZM, et al. Sagittally balanced degenerative spondylolisthesis patients with increased sacral slope and greater lumbar lordosis experience less back pain after short-segment lumbar fusion surgery. Clin Spine Surg. 2020;33(5):E231-E235. https://doi: 10.1097/BSD.0000000000000923.

44. Kong LD, Zhang YZ, Wang F, Kong FL, Ding WY, Shen Y. Radiographic restoration of sagittal spinopelvic alignment after posterior lumbar interbody fusion in degenerative spondylolisthesis. Clin Spine Surg. 2016;29(2):E87-92. https://doi.org/10.1097/BSD.0000000000000104.

45. Bourghli A, Aunoble S, Reebye O, Le Huec JC.
Correlation of clinical outcome and spinopelvic sagittal alignment after surgical treatment of low-grade isthmic spondylolisthesis. Eur Spine J. 2011; Suppl 5:663-8. https://doi.org/10.1007/s00586-011-1934-z.

46. Kim SI, Min HK, Ha KY, Park HY, Cho CH, Cho RK, Kim YH. Effects of Restoration of Sagittal Alignment on Adjacent Segment Degeneration in Instrumented Lumbar Fusions. Spine. 2020;45(23):E1588-E1595. https://doi.org/10.1097/BRS.0000000000003682.

47. Hori Y, Matsumura A, Namikawa T, Kato M, et al. Does sagittal imbalance impact the surgical outcomes of short-segment fusion for lumbar spinal stenosis associated with degenerative lumbar scoliosis? J Ortop Sci. 2019;24(2):224-229. https://doi/10.1016/j.jos.2018.10.005.

48. Li J, Zhang D, Shen Y, Qi X. Lumbar degenerative disease after oblique lateral interbody fusion: sagittal spinopelvic alignment and its impact on low back pain. J Orthop Surg Res. 2020;15(1):326. https://doi.org/10.1186/s13018-020-01837-w.

49. Xiao L, Zhao Q, Sun X, Liu C, Zhang Y, Xu H. Relationship between alterations of spinal/pelvic sagittal parameters and clinical outcomes after oblique lumbar interbody fusion. World Neurosurg. 2020;133:e156-e164. https://doi.org/10.1016/j.wneu.2019.08.158.

50. Vezifehdan F, Karantzoulis VG, Igoumenou G. Sagittal alignment assessment after short-segment lumbar fusion for degenerative disc disease. Int Orthop. 2019;43(4):891-898. https://doi.org/10.1007/s00264-018-4222-2.

51. Hsu HT, Yang SS, Chen TY.The correlation between restoration of lumbar lordosis and surgical outcome in the treatment of low-grade lumbar degenerative spondylolisthesis with spinal fusion. Clin Spine Surg. 2016;29(1):E16-20. https://doi: 10.1097/BSD.0000000000000061.

52. Hsieh PC, Koski TR, O'Shaughnessy BA, et al. Anterior lumbar interbody fusion in comparison with transforaminal lumbar interbody fusion: implications for the restoration of foraminal height, local disc angle, lumbar lordosis, and sagittal balance. J Neurosurg Spine. 2007;7(4):379-386. https://doi.org/10.3171/spi-07/10/379

53. Rhee C, Visintini S, Dunning CE, Oxner WM Glennie RA. Does restoration of focal lumbar lordosis for single level degenerative spondylolisthesis result in better patient-reported clinical outcomes? A systematic literature review. J Clin Neurosci. 2017;44:95-100. https://doi.org/10.1016/j.jocn.2017.06.039.

54. Ekman P, Mo¨ ller H, Shalabi A, Yu YX, Hedlund R. A prospective randomised study on the long-term effect of lumbar fusion on adjacent disc degeneration. Eur Spine J. 2009;18(8):1175-86. https://doi.org/10.1007/s00586-009-0947-3.

55. Park P, Garton HJ, Gala VC, Hoff JT, McGillicuddy JE. Adjacent segment disease after lumbar or lumbo¬sacral fusion: review of the literature. Spine. 2004;29(17):1938-44. https://doi.org/10.1097/01.brs.0000137069.88904.03.

56. Aota Y, Kumano K, Hirabayashi S. Postfusion instability at the adjacent segments after rigid pedicle screw fixation for degenerative lumbar spinal disor¬ders. J Spinal Disord 1995 Dec;8(6):464-73.

57. Bagheri SR, Alimohammadi E, Zamani Froushani A, Abdi A. Adjacent segment disease after posterior lumbar instrumentation surgery for degenerative disease: Incidence and risk factors. Bagheri SR, Alimohammadi E, Zamani Froushani A, Abdi A. J Orthop Surg. 2019;27(2):2309499019842378. https://doi.org/10.1177/2309499019842378.

58 Ahn DK, Park HS, Choi DJ, Kim KS, Yang SJ. Survival and prognostic analysis of adjacent segments after spinal fusion. Clin Orthop Surg. 2010; 2(3):140-7. https://doi.org/10.4055/cios.2010.2.3.140.

59. Sato S, Yagi M, Machida M, Yasuda A, et al. Reoperation rate and risk factors of elective spinal surgery for degenerative spondylolisthesis: minimum 5-year follow-up. Spine J. 2015;15(7):1536-44. https://doi.org/10.1016/j.spinee.2015.02.009.

60. Lee CS, Hwang CJ, Lee SW, et al. Risk factors for adjacent segment disease after lumbar fusion. Eur Spine J. 2009;18(11):1637-43. https://doi.org/10.1007/s00586-009-1060-3.

61. Lawrence BD, Wang J, Arnold PM, Hermsmeyer J, Norvell DC, Brodke DS. Predicting the risk of adjacent segment pathology after lumbar fusion: a systematic review. Spine. 2012;37(22 Suppl):S123-32. https://doi.org/10.1097/BRS.0b013e31826d60d8.

62.Ye J, Yang S, Wei Z, Cai C, Zhang Y, Qiu H, Chu T. Incidence and Risk Factors for Adjacent Segment Disease After Transforaminal Lumbar Interbody Fusion in Patients with Lumbar Degenerative Diseases.Int J Gen Med. 2021;15;14:8185-8192://doi.org/10.2147/IJGM.S337298.

63. Yun YI, Jeon I, Woo-Kim S, Yu D. Risk factors for adjacent segment disease requiring reoperation after posterior lumbar interbody fusion with screw fixation: focus on paraspinal muscle, facet joint, and disc degeneration. Acta Neurochirurgica. 2022;164(3):913-922. https://doi.org/10.1007/s00701-021-05073-x.

64. KIM JY, Kim JY, Ryu DS, Paik HK, Ahn SS, Kang MS, et al. Paraspinal muscle, facet joint, and disc problems: risk factors for adjacent segment degeneration after lumbar fusion. Spine J. 2016;16(7):867-75. https://doi.org/10.1016/j.spinee.2016.03.010.

65. Lee JC, Kim Y, Soh JW, Shin BJ. Risk factors of adjacent segment disease requiring surgery after lumbar spinal fusion: comparison of posterior lumber interbody fusion and posteriorlateral fusion. Spine. 2014;39(5):E339-E345. https://doi.org/10.1097/BRS.0000000000000164.

66. Kumar MN, Baklanov A, Chopin D. Correlation between sagittal plane changes and adjacent segment degeneration following lumbar spine fusion. Eur Spine J. 2001;10(4):314-9. https://doi.org/10.1007/s005860000239.

67. Ramirez-Villaescusa J, Lopez-Torres Hidalgo J, Martin-Benlloch A, Ruiz-Picazo D, Gomar-Sancho F. Risk factors related to adjacent segment degeneration: retrospective observational cohort study and survivorship analysis of adjacent unfused segments. Br J Neurosurg. 2019;33(1):17-24. https://doi.org: 10.1080/02688697.2018.1523365. Epub 2018 Oct 13.

68. Matsumoto T, Okuda S, Maeno T, Yamashita T, et al. Spinopelvic sagittal imbalance as a risk factor for adjacent-segment disease after single-segment posterior lumbar interbodyfusion. J Neurosurg Spine. 2017;26(4):435-440. https://doi.org/10.3171/2016.9.SPINE16232.

69. Wang T, Ding W. Risk factors for adjacent segment degeneration after posterior lumbar fusion surgery in treatment for degenerative lumbar disorders: a meta-analysis. J Orthop Surg Res. 2020;15(1):582. https://doi.org/10.1186/s13018-020-02032-7.

70. Heo Y, Park JH, Seong HY, et al. Symptomatic adjacent segment degeneration at the L3-4 level after fusion surgery at the L4-5 level: evaluation of the risk factors and 10-year incidence. Eur Spine J. 2015;24(11):2474-80. https://doi.oirg/10.1007/s00586-015-4188-3.

71. Gillet P. The fate of the adjacent motion segments after lumbar fusion. J Spinal Disord Tech. 2003 Aug;16(4):338-45. https://doi.org/10.1097/00024720-200308000-00005.

72. Radcliff KE, Kepler CK, Jakoi A, Sidhu GS, Rhin J, Vaccaro AR, Hilibrand AS. Adjacent segment disease in the lumbar spine following different treatment interventions. Spine J. 2013;13(10):1339-49. https://doi.org/10.1016/j.spinee.2013.03.020.

73. Bae JS, Lee SH, Kim JS, Jung B, Choi G. Adjacent segment degeneration after lumbar interbody fusion with percutaneous pedicle screw fixation for adult low-grade isthmic spondylolisthesis: minimum 3 years of

follow-up. Neurosurgery. 2010;67(6):1600-7; discussion 1607-8. https://doi.org/10.1227/NEU.0b013e3181f91697.

74. Hikata T, Kamata M, Furukawa M. Risk factors for adjacent segment disease after posterior lumbar in¬terbody fusion and efficacy of simultaneous decom¬pression surgery for symptomatic adjacent segment disease. J Spinal Disord Tech. 2014;27(2):70-5. https://doi.org/10.1097/BSD.0b013e31824e5292.

75. Kim KH, Lee SH, Shim CS, Lee DY, Park HS, Pan WJ, Lee HY. Adjacent segment disease after interbody fusion and pedicle screw fixations for isolated L4–L5 spondylolisthesis: a minimum five-year follow-up. Spine. 2010;35(6):625-34. https://doi.org/10.1097/BRS.0b013e3181bb8168.

76. Okuda S, Nagamoto Y, Takenaka S, Ikuta M, Matsumoto T, et al. Effect of segmental lordosis on early-onset adjacent-segment disease after posterior lumbar interbody fusion. J Neurosurg Spine. 2021;35(4):454-459. Httpsa://doi.org/10.3171/2020.12.SPINE201888.

77. Sun J, Wang JJ, Zhang LW, Huang H, Fu NX. Sagittal alignment as predictor of adjacent segment disease after lumbar transforaminal interbody fusion. World Neurosurg. 2018;110:e567-e571. https://doi.org/10.1016/j.wneu.2017.11.049.

78. Phan K, Nazareth A, Hussain AK, et al. Relationship between sagittal balance and adjacent segment disease in surgical treatment of degenerative lumbar spine disease: meta-analysis and implications for choice of fusion technique. Eur Spine J. 2018;27(8):1981-1991. https://doi.org/10.1007/s00586-018-5629-6.

79. Wang SJ, Zhang SB, Yi YY, Xu HW, Wu DS. Estimation of the ideal correction of lumbar lordosis to prevent reoperation for symptomatic adjacent segment disease after lumbar fusion in older people. BMC Muscoloskelet Disord. 2020;21(1):429. https://doi.org/10.1186/s12891-020-03463-3.

80. Kim WJ, Ma CH, Kim SA, Min YS, Lee JW, et al. Prevention of ASD after Fusion in Degenerative Spinal Disorder Correlation between Segmental Lumbar Lordosis Ratio and PI–LL Mismatch for a Minimum 5 Year FU. Asian Spine J. 2019;13(4):654-662. https://doi/10.31616/asj.2018.0279.

81. Senteler M, Weisse B, Snedeker JG, Rothenful DA. Pelvic incidence-lumbar lordosis mismatch results in increased segmental joint loads in the unfused and fused lumbar spine. Eur Spine J. 2014;23(7):1384-93. https://doi.org/10.1007/s00586-013-3132-7. Epub 2014 Mar 20.

82. Umehara S, Zindrick MR, Patwardhan AG, et al. The biomechanical effect of postoperative hypolordosis in instrumented lumbar fusion on instrumented and adjacent spinal segments. Spine. 2000;25(13):1617-24. https://doi.org/10.1097/00007632-200007010-00004.

83. Anandjiwala J, Seo JY, Ha KY, Oh IS, Shin DC. Adjacent segment degeneration after instrumented posterolateral lumbar fusion: a prospective cohort study with a minimum five-year follow-up. Eur Spine J. 2011;20(11):1951-60. https://doi.org/10.1007/s00586-011-1917-0.

84. Chen BL, Wei FX, Ueyama K, Xie DH, Sannohe A, Liu SY. Adjacent segment degeneration after single-segment PLIF: the risk factor for degeneration and its impact on clinical outcomes. Eur Spine J. 2011;20(11):1946-50. https://doi.org/10.1007/s00586-011-1888-1.

85. Masevnin S, Ptashnikov D, Michaylov D, Meng H, Smekalenkov O, Zaborovskii N. Risk factors for ad¬jacent segment disease development after lumbar fu¬sion. Asian Spine J. 2015;9(2):239-44. https://doi.org/10.4184/asj.2015.9.2.239.

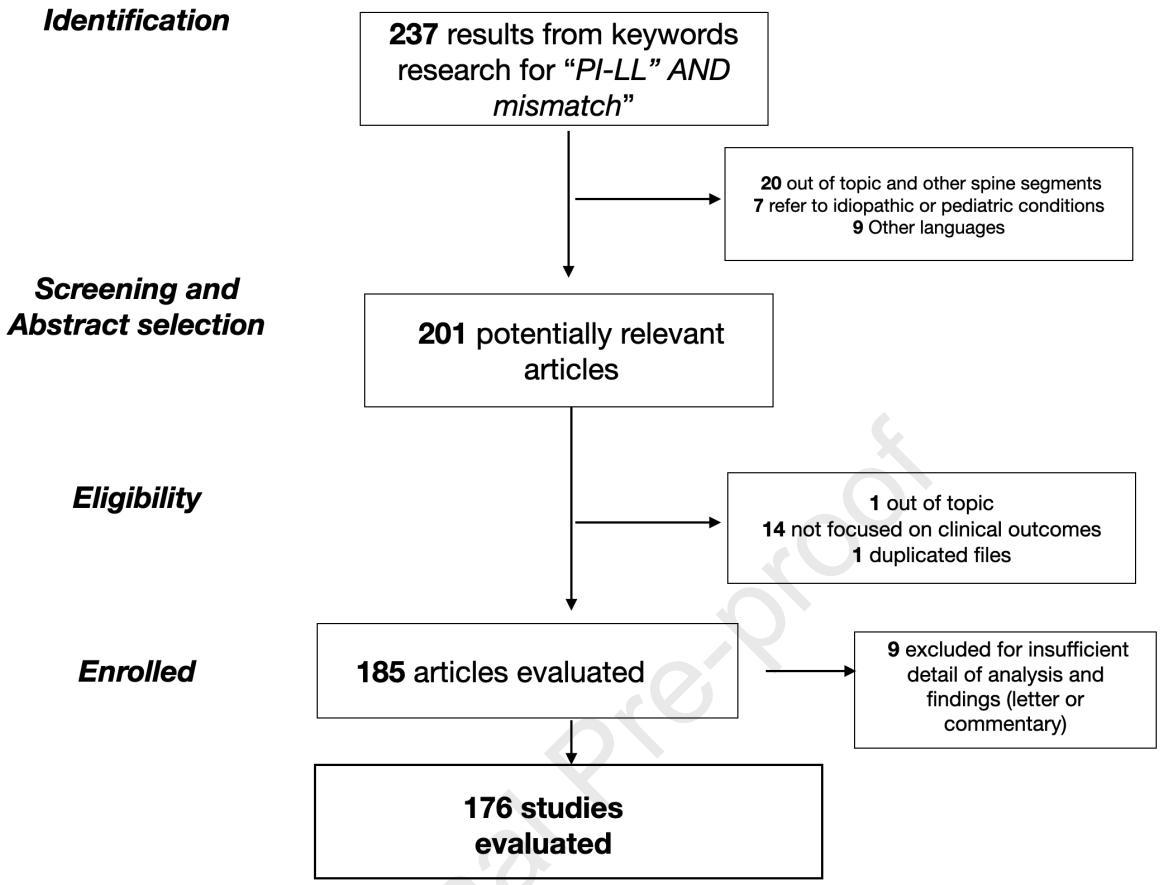
86. Kaito T, Hosono N, Mukai Y, Makino T, Fuji T, Yonenobu K. Induction of early degeneration of the adjacent segment after posterior lumbar interbody fusion by excessive distraction of lumbar disc space. J Neurosurg Spine. 2010;12(6):671-9. https://doi.org/10.3171/2009.12.SPINE08823.

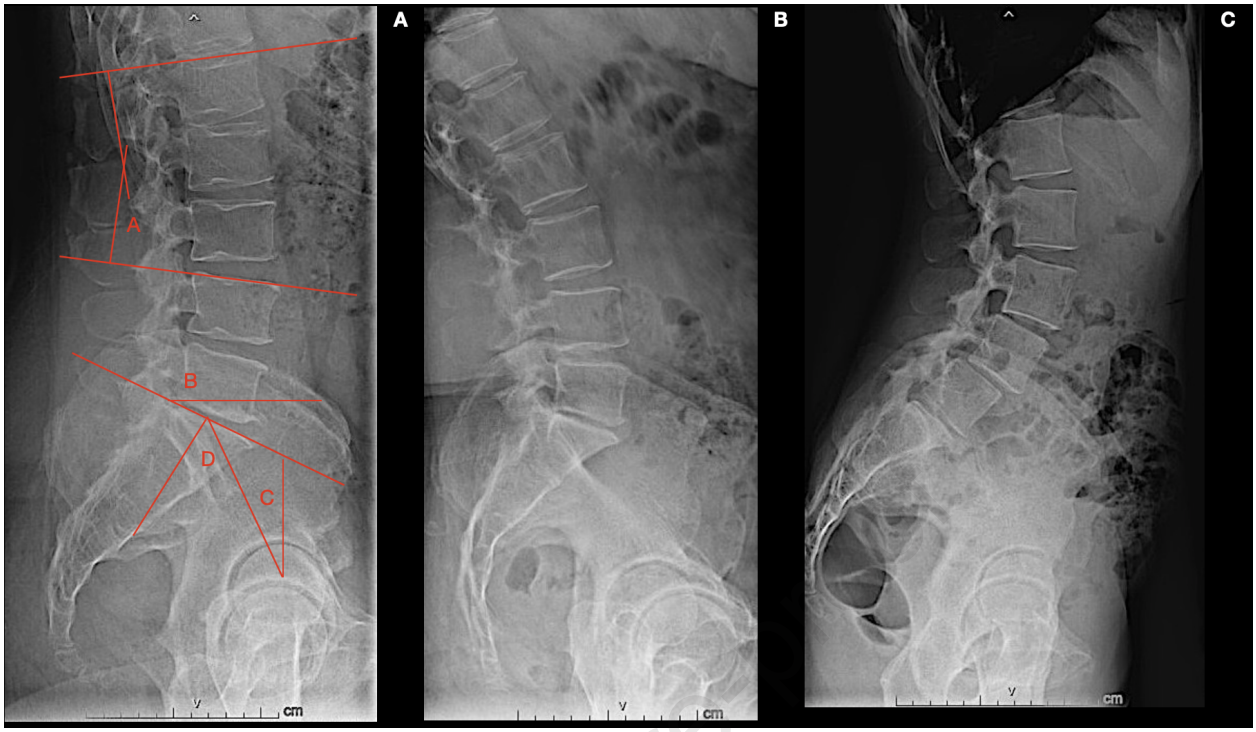
87. Aiki H, Ohwada O, Kobayashi H, Hayakawa M, Kawaguchi S, Takebayashi T, Yamashita T. Adjacent segment stenosis after lumbar fusion requiring second operation. J Orthop Sci. 2005;10(5):490-5. https://doi.org/10.1007/s00776-005-0919-3.

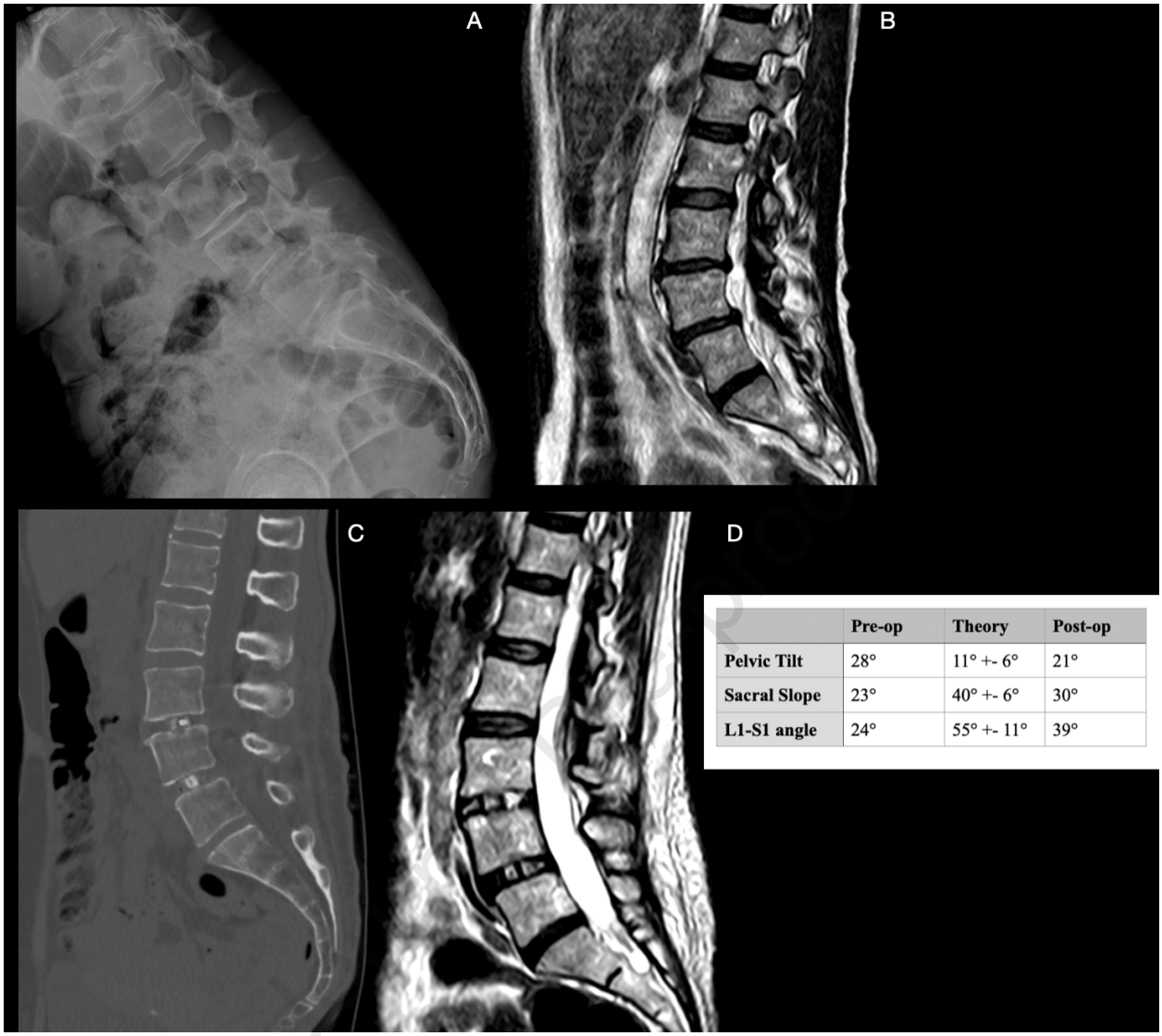
88. Maragkos GA, Atesok K, Papavassiliou E. Prognostic factors for adjacent segment disease after L4-L5 lumbar fusion. Neurosurgery. 2020;86(6):835-842. https://doi.org/10.1093/neuros/nyz241.

89. Carlson BB, Saville P, Dowdell J, Goto R, et al. Restoration of lumbar lordosis after minimally invasive transforaminal lumbar interbody fusion: a systematic review. Spine J. 2019; 19(5):951-958. https://doi.org/10.1016/j.spinee.2018.10.017.

90. Armocida D, Pesce A, Cimatti M, Proietti L, Santoro A, Frati A. Minimally Invasive Transforaminal Lumbar Interbody Fusion Using Expandable Cages: Increased Risk of Late Postoperative Subsidence Without a Real Improvement of Perioperative Outcomes: A Clinical Monocentric Study. World Neurosurg. 2021 Dec;156:e57-e63. doi: 10.1016/j.wneu.2021.08.127. Epub 2021 Sep 4. PMID: 34492389.







	Pre-op	Theory	Post-op
Pelvic Tilt	28°	11° +- 6°	21°
Sacral Slope	23°	40° +- 6°	30°
L1-S1 angle	24°	55° +- 11°	39°

AUTHOR DECLARATION TEMPLATE

Roma, Italy 31/10/2022

We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

Relationship between lumbar lordosis, pelvic parameters, PI-LL mismatch and outcome after short fusion surgery for lumbar degenerative disease. Literature review, rational and presentation of public study protocol: RELApSE study (Registry for Evaluation of Lumbar Artrodesis Sagittal alignEment)

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

We further confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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