MID-MIS: MIDLIF versus MIS-TLIF in the treatment of discogenic low back pain, comparison of clinical outcomes, complications rate, and treatment costs: a randomized controlled, prospective trial protocol

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Study protocol

Keywords: MIS-TLIF, mini-TLIF, MIDLIF, dyscogenic pain, interbody fusion

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Abstract

Background

Degenerative disc disease (DDD) is the leading cause of lower back pain and disability, whose prevalence increases with age. When conservative treatment fails, surgical methods of spinal fusion are employed. Minimally invasive techniques, including minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF) and midline lumbar interbody fusion (MIDLIF), have well-documented advantages over traditional open transforaminal interbody fusion. However, data comparing these two minimally invasive methods in treating DDD are limited and sometimes contradictory.

Methods

This is a prospective, randomized, partially masked, two-arm trial comparing the outcomes, complications, and treatment costs of MIS-TLIF and MIDLIF in patients with discogenic low back pain. A total of 100 adult patients with lumbosacral spine pain and radicular symptoms, unresponsive to conservative treatment for over one year, will be enrolled. Patients will be randomized (1:1) into two arms: MIS-TLIF (control, n = 50) and MIDLIF (intervention, n = 50), with a 12-month follow-up period. Inclusion criteria include age ≥18 years and discopathy at one or two levels requiring interbody stabilization. Exclusion criteria include multilevel pathology, spinal deformities, and pain causes other than degenerative disease. Primary endpoints assess pain (VAS, NRS scales), disability (COMI, ODI questionnaires), and quality of life (EQ-5D-5L questionnaire) at 1, 3, 6, and 12 months post-surgery. Secondary endpoints include complication rates, costs (hospitalization, implants), length of hospital stay, procedure duration, blood loss, morphometric parameters (intervertebral space height), and adjacent segment disease, as determined by imaging studies (MRI, CT, X-ray). Data analysis uses parametric/non-parametric tests in the R software. The trial adheres to the Helsinki Declaration, with ethics approval (no. 112/2024).

Discussion

Data on the comparison of MIDLIF and MIS-TLIF in treating DDD are minimal and inconsistent. Some reports favor MIDLIF for shorter operative time, decreased intraoperative blood loss, and reduced hospital stays, while others prefer MIS-TLIF. This trial addresses these gaps by providing high-quality evidence on clinical superiority, cost-effectiveness, and long-term outcomes comparing MIDLIF and MIS-TLIF. There is a high need for high-quality, prospective studies to examine this problem.

Trail registration

The study had been retrospectively registered on ClinicalTrials.gov with the number NCT07127380. Registered 11 August 2025.

Keywords: MIS-TLIF, mini-TLIF, MIDLIF, dyscogenic pain, interbody fusion

Registration:

Primary registry and trial identifying number: ClinicalTrials.gov: NCT07127380

Date of registration in primary registry: 8 August 2025

Unique Protocol ID: 112/2024

Declarations:

Ethics approval and consent to participate:

The study will be carried out in strict accordance with the protocol, the current version of the Declaration of Helsinki, the ICH GCP guidelines, and Polish law. Both the Ethics Committee and the regulatory authority will receive safety reports on an annual and periodic basis during the study.

It has been approved by the Bioethics Committee at the Polish Mother Health Center Institute in Łódź (approval no. 112/2024) on 17 December 2024. The patient recruitment for this study is ongoing, seven patients were enrolled since January 2025. No sponsor was involved in the study design or conduct of the study.

Consent for publication

Written informed consent was obtained from all participants whose radiological images (X-rays) were used in this publication for the use of their anonymized imaging data for scientific and publication purposes.

Availability of data and materials

Not applicable

Competing interests

The authors declare that they have no competing interests

Funding

This research did not receive funding.

Acknowledgements

Not applicable

Background:

Degenerative Disc Disease (DDD) is a leading cause of radicular pain and Low Back Pain (LBP), significantly contributing to disability, with its prevalence increasing with age [1]. As populations grow older, managing degenerative spine conditions is expected to become a

significant challenge for healthcare systems [2]. Discogenic pain, mainly caused by degeneration of the intervertebral disc due to changes in its structure and function, is a common symptom of DDD [3]. Initial treatment for discogenic pain usually involves conservative methods such as analgesics, anti-inflammatory medications, and physical therapy [3]. However, when conservative treatments fail, surgical options are considered, including decompression of neural structures with fusion of adjacent vertebral bodies [4]. One established surgical approach for discogenic pain is open transforaminal lumbar interbody fusion (open-TLIF), which involves discectomy and placement of an interbody implant via a transforaminal approach, followed by stabilization with open pedicle screw fixation [4]. In recent years, minimally invasive techniques have gained prominence in spine surgery. Minimally invasive transforaminal lumbar interbody fusion (MIS-TLIF, also referred to as mini-TLIF) is one such technique, characterized by a smaller incision for transforaminal implant placement and percutaneous pedicle screw fixation. Numerous studies report that MIS-TLIF is associated with reduced tissue trauma, lower intraoperative blood loss, shorter hospital stays, and less postoperative pain compared to open-TLIF [5-7]. Another minimally invasive procedure for lumbosacral discopathy is midline lumbar interbody fusion (MIDLIF). Unlike MIS-TLIF, MIDLIF involves a midline skin incision and screw placement along the cortical trajectory [8]. Several studies suggest that MIDLIF offers improved clinical outcomes, fewer complications, and greater cost-effectiveness compared to open-TLIF [8,9]. Limited evidence also indicates that MIDLIF may serve as a safe alternative to MIS-TLIF for treating degenerative discopathy of the spine [10]. This study aims to compare the clinical outcomes, complication rate, and costs of the MIS-TLIF and MIDLIF in the treatment of DDD in the lumbosacral spine. The study is designed as a study comparing parallel group, with an allocation ratio of 1:1 and noninferoriority framework.

Methods and analysis:

The study is designed as a prospective, randomized, partially-blinded, two-arm trial conducted in accordance with the Helsinki Declaration. It has been approved by the Bioethics Committee at the Polish Mother Health Center Institute in Łódź (approval no. 112/2024) on 17 December 2024. The study is registered at Clinicaltrials.gov under the identifier NCT07127380. No sponsor was involved in the study design or conduct of the study.

A total of 100 patients with DDD will be recruited and evenly allocated to one of two study arms: the Intervention Group (Arm I) and the Control Group (Arm II) (1:1 ratio) according to the permuted block randomization procedure to compare their outcomes of the following interventions:

- Arm I (Intervention Group, n = 50): Patients will undergo the MIDLIF procedure.
- Arm II (Control Group, n=50) Patients will undergo the MIS-TLIF procedure.

To ensure balanced distribution of potential confounding factors, patients in both arms will be stratified based on a history of prior microdiscectomy. Stratification will be performed during randomization to minimize bias in treatment outcomes, as prior microdiscectomy may influence postoperative recovery and complication rates. Allocation concealment will be maintained. Data analysts will be blinded in the study.

Study Site

The trial has been launched in the community clinic - Copernicus Memorial Hospital in Łódź (Department of Neurosurgery and Neurooncology, Copernicus Memorial Hospital in Łódź, Łódź, Poland) since January 2025, the recruitment is ongoing. The data is collected only in Poland.

Steering committee

The Steering Committee (SC) will be led by KK (neurosurgeon, PhD). The SC will consist of MT (neurosurgeon, PhD), AK (medical doctors) and MJO (biostatistician, PhD). The SC will

oversee the study's progress, addressing decisions related to participant recruitment, retention, and study dropouts.

Protocol development

The study protocol was developed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [11]. The protocol adheres to established guidelines for the design, conduct, and reporting of clinical trials, ensuring a rigorous and transparent methodology throughout the study.

Recruitment:

The patient recruitment for this study is ongoing; seven patients were enrolled since January 2025. Patients with chronic degenerative disease of the lumbo-sacral spine are recruited from neurosurgical outpatient and hospital units. Reporting lower back pain, optionally with radicular symptoms, lasting for at least 12 months, is required for patient enrollment. Patients must be eligible for fusion and provide informed consent for the proposed treatment.
All patients treated at the Department of Neurosurgery and Neurooncology and the Neurosurgical Outpatient Clinic of the Copernicus Memorial Hospital in Łódź will be actively recruited for the study. Additionally, an information campaign will be conducted on the hospital's official website and through the social media profiles of both the hospital and the department to increase awareness and facilitate patient enrollment.

Screening and Study Qualification

Patient screening and qualification will be performed, involving the following procedures:

1. Radiological Imaging:
    a. Up to six months before treatment qualification, the MRI of the lumbo-sacral spine

    b. Radiographic stitching of the whole spine will be performed 1 day before the treatment.

2. Laboratory Tests:
    a. Complete blood count, electrolyte panel, coagulation profile, glucose levels, and renal function tests one day before treatment.
    b. Screening for hepatotropic viruses (Hepatitis B and C) and determination of blood type are conducted within three days before treatment.
3. Clinical and Neurological Evaluation:
    a. Assessment of general condition and neurological functions was evaluated during patient enrollment in the study.
    b. Intensity of pain measured in VAS (Visual Analog Scale) and NRS (Numerical Rating Scale) scales
4. Demographics and Medical History, such as age, sex, primary oncological diagnosis, and comorbidities, will be collected at the patient's admission for the procedure.

Randomization

Permuted block randomization will be performed to ensure that an equal number of participants is allocated to each of the planned treatment groups unpredictably, thereby providing an accurate representative sample. The randomization will be executed electronically between obtaining informed consent and the surgical procedure (blockrand R package). Patients will be stratified based on previous lumbar spine operation and assigned equally into two groups (the study group and the control group).

Eligibility criteria

1. Inclusion criteria for the study are:

- Discogenic lower lumbar-sacral pain lasting longer than one year.
- Failure of conservative treatment, including rehabilitation and pain management

- Lumbar discopathy qualified for interbody fusion and pedicle screw stabilization.
- Age ≥ 18 years
- Informed consent of the patient for the study and proposed treatment

2. Exclusion criteria for the study are:
    - Lumbar-sac discopathy requiring surgical treatment at more than two levels
    - Spinal deformities: adult idiopathic scoliosis, degenerative scoliosis, deformity due to spinal malignancy, inflammatory spinal disease, post-traumatic, or associated with congenital anomalies
    - Lower lumbar-sacral pain syndrome, which, in the investigator's opinion, has an etiology other than degenerative spine disease (e.g., cancer-related pain, ankylosing spondylitis)
    - Spinal oncology disease
    - True and degenerative spondylolisthesis
    - Contraindications to performing MRI of the lumbar-sacral spine
    - Contraindications to surgery under general anesthesia
    - Pregnancy, breastfeeding
    - Lack of informed consent to participate in the study

All eligible patients will be offered the opportunity to participate in the trial. After the neurosurgeon delineates the study design and intervention, patients should confirm their intention to participate and sign the written informed consent form (ICF).

Patients who do not meet all inclusion criteria, meet any exclusion criteria, or withdraw consent will be managed according to standard care for spinal degenerative disease. Reasons for screening failures will be documented.

Criteria for discontinuation

Proceeding with the allocated intervention may be cancelled or deferred if adherence to the study protocol would expose the participant to an unreasonable risk or unduly influence clinical decision-making in the treatment of degenerative disc disease (DDD).A participant will be withdrawn from the study if any of the following occur:

• An intraoperative change in the surgical plan at the surgeon's discretion, resulting in the use of a different method of interbody stabilization or abandonment of stabilization.

• Qualification for an additional surgical procedure for DDD during the follow-up period.

• Occurance of contraindications to MRI or other required diagnostic tests during follow-up period

Participants may also be withdrawn if new factors arise that could confound the study patient-reported outcomes or influence pain and disability scores, particularly those that substantially increase or decrease spinal pain, including:

• Diagnosis of new conditions that increase spinal pain (e.g., spinal tumor metastases, new disc herniation, vertebral fracture).

Interventions leading to a relevant reduction of spinal pain are prohibited during the follow-up period and will result in exclusion from the study. These include:

- Invasive pain management procedures such as epidural or facet joint steroid injections, selective nerve root blocks, radiofrequency thermocoagulation, cryoablation, or other neuroablative interventions.
- Implementation of spinal cord stimulation or intrathecal drug delivery systems.

Standard physiotherapy and rehabilitation after the procedure is permitted.

Any prohibited or restricted intervention undertaken for urgent medical reasons must be fully documented in the Case Report Form (CRF) with the indication and date, and the principal investigator must be notified within 24 hours. Such cases will be analyzed according to the intention-to-treat principle but classified as protocol deviations.

Definition of Study Completion and Early Termination

Study completion is the point at which all data has been entered and all queries resolved. Interim analyses are planned once 50% and 75% of the patients are enrolled. If the study's statistical assumptions are met at these interim points, the trial will be terminated before the planned date.

Informed Consent

The participant must personally sign and date the approved version of the informed consent form before any procedures begin. Both written and oral versions of the participant information and the informed consent form will be provided, ensuring that at least the following details are included: a comprehensive description of the study, implications for the participant, the protocol's limitations, known adverse effects, and associated risks. It will be explicitly stated that the participant may withdraw from the study at any time, for any reason, without any impact on future care or the participant's rights, and without the need to justify the decision. The participant will be given as much time as demanded to review the information and will have the opportunity to ask questions to the researcher, their primary care physician, or other independent individuals before deciding to participate. Subsequently, written informed consent will be obtained based on the participant's dated signature and the signature of the individual providing the information and obtaining consent. The person responsible for obtaining consent must have the appropriate qualifications, experience, and

authorization from the principal investigator. The participant will receive a copy of the signed informed consent form, while the original signed document will be kept at the research center.

Follow-Up Assessments

Follow-up will be continued for 1 year post-surgery. Follow-up will involve neurological assessment on the day of surgery and subsequent days during hospitalization to monitor for acute complications, as well as scheduled appointments in 1 month, 3 months, 6 months, and 12 months after the operation. Imaging with X-ray and CT of the lumbosacral spine within 24 hours post-intervention will be performed to assess stabilization efficacy and potential complications. Moreover, X-rays will be performed at 3 and 12 months post-intervention to evaluate changes in sagittal and coronal balance. CT of the lumbosacral spine will be performed to assess stabilization further.

Additionally, radiological assessments, including MRI in 12 months post-intervention, will be performed to assess the existence of adjacent segment disease, recurrence of disc herniation, and other level discopathy. Finally, documentation of any surgical or nonsurgical treatment of degenerative spine disease will be done, as well as postoperative wound evaluation. Periodic quality-of-life assessments and pain scoring using the Visual Analog Scale (VAS) and NRS (numeric rating scale) will be performed. The questionaries including Core Outcome Measures Index Back (COMI-back), Oswestry Disability Index (OSI), European Quality of Life - 5 Dimensions, 5 Levels (EQ-5D-5L) will be performed on vist 1 month, 3 months, 6 months and 12 months post-intervention to examine the outcome of treating back disease, disability caused by back disease and quality of life, retrospectively. In Table 1, the scheme of visits and tests is presented.

To improve adherence to the protocol, the participants will be notified and reminded about control vists and test via phone call by both the researchers and medical registrars.

Examination Time	Medical examination	MRI of lumbo-sacral spine	X-ray of lumbo-sacral spine	Scalometry	CT of lumbo-sacral spine	Laboratory Tests	VAS	NRS	COMI-back	OSI	EQ-5D-5L
Up to 6 months before randomization	×	×									
1-2 days before randomization (hospital admission)	×			×		×	×	×	×	×	×
Up to 24 hours after randomization	×		×		×		×	×			
2 days after randomization	×						×	×	×	×	×
1 month after randomization	×						×	×	×	×	×
3 months after randomization	×		×				×	×	×	×	×
6 months after randomization	×				×		×	×	×	×	×
12 months after randomization	×	×		×			×	×	×	×	×

Table 1 Scheme of visits and examination

Intervention

Fusion and instrumented spinal stabilization will be the primary interventions for all subjects. To accomplish this, two different procedures will be used.

MIDLIF procedure utilizes a median approach to the spine, involving retraction of the segmental back muscles to expose the lamina and articular processes. Screw placement is medialized, with the entry point along the pars intercularis or the joint surface. This approach

allows for a smaller muscle dissection, resulting in less muscle retraction and reduced postoperative back pain. Screw are placed through cortical and stronger bone, allowing for stronger fixation, improved biomechanical stability, and decreased risk of screw loosening or pullout over time. Decompression is achieved by resecting the inferior articular process and the superior articular process, followed by a bilateral discectomy. Subsequently, a lumbar interbody fusion is performed. Figure 1 presents postoperative anteroposterior and lateral radiographs illustrating an example of the MIDLIF procedure in this study.

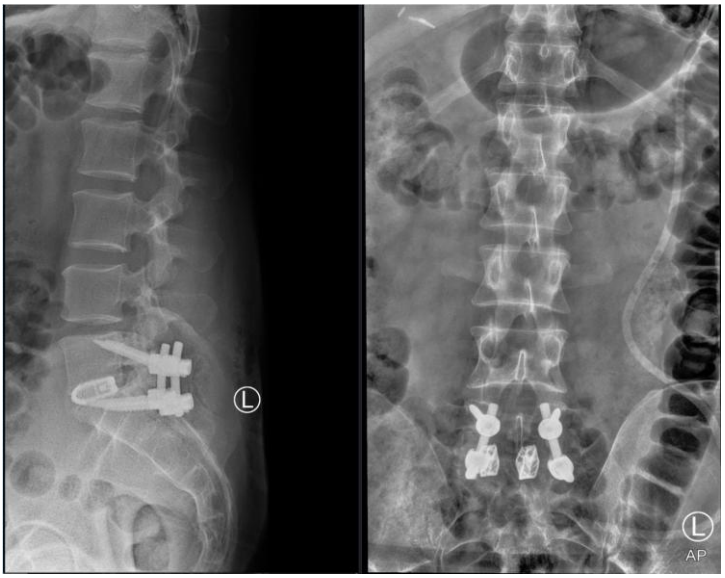

Figure 1 MIDLIF postoperativ Figure 1 MIDLIF postoperative anteroposterior and lateral radiographs

MIS-TLIF employs a percutaneous approach for pedicle screw placement through the pedicles. Decompression is performed using a lateral approach, with 2-3 cm lateral to the median line. This is followed by resection of the unilateral inferior and superior articular processes and removal of the ligamentum flavum, facilitating discectomy. An interbody cage is then inserted to achieve fusion. Figure 2 presents postoperative anteroposterior and lateral radiographs illustrating an example of the MIS-TLIF procedure in this study.

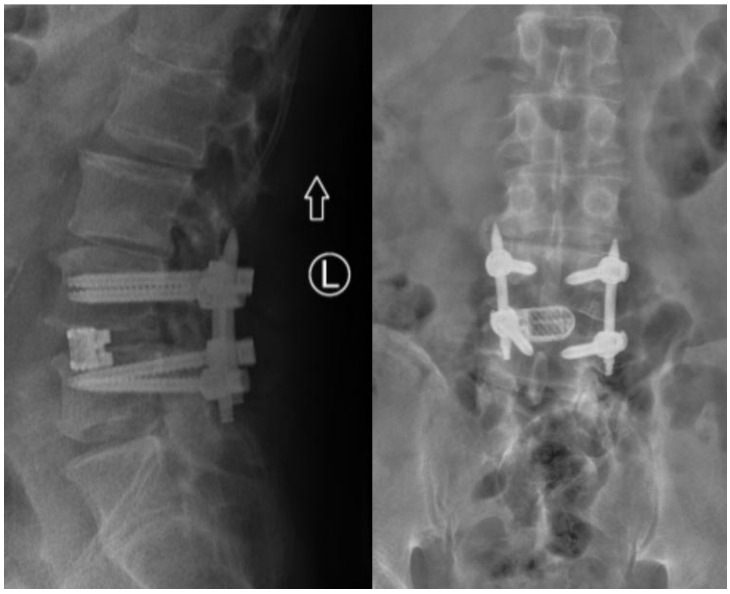

Figure 2 MIS-TLIF postoperative anteroposterior and lateral radiographs

Outcomes

Primary outcomes

The primary objective of the study is to evaluate the results of surgical treatment on pain intensity over time. This will be based on reported syndromes and physical examinations. A comparative analysis between groups will be conducted on the results of questionnaires measuring pain intensity using the VAS scale, NRS, the effectiveness of surgical treatment using the COMI scale (Core Outcome Measures Index), the degree of disability in patients with spinal pain assessed by the Oswestry Disability Index (ODI), and quality of life evaluated by the EQ-5D-5L (European Quality of Life - 5 Dimensions, 5 Levels).

Figure 2 MIS-TLIF postoperative anteroposterior and lateral radiographs

Secondary outcomes

Secondary outcomes of the study involve:

1. **Complication Rates and Types**: Evaluation of the frequency and nature of complications between groups, including nerve root damage, cerebrospinal fluid leak, instrumentation failure, postoperative wound infection, and other adverse events.

2. **Direct Treatment Costs**: Analysis of direct treatment costs with a breakdown by category, including total hospitalization costs, costs of implants used, costs of medications administered, and costs of the surgical procedure.
3. **Hospitalization Duration**: Measurement of the length of stay (LOS) in the hospital.
4. **Procedure Duration**: Evaluation of the operating room time (OR time) required for the surgery.
5. **Blood Loss**: Quantification of estimated blood loss (EBL) during the surgical procedure.
6. **Spinal Morphometric Parameters**: Evaluation of intervertebral space height (ISH), foraminal height (FH), radiological evidence of bone fusion, and global and segmental lordosis of the lumbar-sacral spine. These parameters are assessed using X-ray imaging performed 1–2 days before surgery, within 24 hours post-surgery, and at 3 and 12 months post-surgery.
7. **Time to Return to Professional Activity**: Measurement of the duration required for working patients to resume professional activities.
8. **Radiological Assessment of Adjacent Segment Disease (ASD)**: Evaluation of the occurrence of adjacent segment disease based on MRI of the lumbar-sacral spine conducted 12 months post-surgery.

Allocation and masking

Participants will be randomly assigned to one of two study arms using a block randomization method (blockrand R package) to ensure an equal distribution of participants across the groups throughout the trial. Randomization will be based upon a computer-drawn sequence provided in a sealed envelope between the signing of the informed consent form and the scheduled surgical procedure. Participants in both study arms will be stratified based on their surgical history of the lumbar spine (primary surgery versus revision surgery). The study is

partially blinded; investigators who will examine the patient on the postoperative visits will be blinded.

All statistical analyses will be performed by an independent biostatistician who will remain blinded to group allocation throughout the study. The randomisation code will be unmasked for this analyst only after the final database lock and completion of the primary analysis.

The personnel responsible for enrolling participants will not have access to the randomization sequence. Enrollment staff will input each eligible participant's details into a secure, web-based randomization system. The randomization algorithm (permuted blocks) is stored centrally on a password-protected server, and the sequence is only released after the data are submitted.

The designated study coordinator (or operating surgeon) who performs the assigned intervention will learn the allocation only after the system provides it; they also have no prior knowledge of the sequence itself or upcoming assignments. Therefore, both enrollment staff and intervention-assigning staff remain blinded to the random allocation list, ensuring complete allocation concealment until the moment of assignment.
To maintain standardization across the study arms, all surgical procedures will be performed according to standardized protocols, unifying the surgical technique.

Data collection, management and analysis

Clinical data collected will be anonymized by encoding personal identifiers when the physician completes the questionnaire. Study data will be stored on password-protected external drives accessible only to the study investigators. Trained study coordinators will subsequently transcribe these data into an electronic eCRF housed on a password-protected server. Access to the eCRF is role-restricted and granted solely to the principal investigator,

the study biostatistician, and designated coordinators. Data collection, management, and analysis All imaging and laboratory analyses will be conducted in accredited, standardized facilities that operate under validated protocols and adhere to external quality assurance schemes. Publication of the study results will ensure complete patient anonymity, with no possibility of identifying personal data. All collected data will be processed in accordance with Article 13(1) and (2) of the European Parliament and Council Regulation (EU) 2016/679 of April 27, 2016, regarding the protection of natural persons in relation to the processing of personal data and the free movement of such information.

Participant flow coordination and follow-up procedures

Clinical report form Study coordinators will actively manage patient during follow up period in the Neurosurgical Ambulatory. Coordinators will schedule outpatient appointments, relay detailed information about treatment plans and visit schedules, and document. If a participant fails to respond or does not attend a scheduled visit, a second telephone contact attempt will be made within 48 h. Continued non-compliance will result in the issuance of a formal written summons, and, if necessary, outreach to designated family members to facilitate re-engagement and ensure continuity of follow-up.

Source Data and Data Access

Source documents refer to the original media on which data are recorded and from which the participants' data are subsequently transferred into the Case Report Forms (CRFs). This includes, among others, hospital records (from which CRFs can be supplemented with data regarding the medical history and concurrently or previously administered medications), clinical and hospital files, laboratory and pharmacy documentation, diaries, imaging results, and correspondence. Entries in the CRF will be considered source data if the CRF serves as the primary record (e.g., in the absence of any other written or electronic record). All documents will be stored securely while ensuring confidentiality. In all study documents,

except for the signed informed consent form, participants will be identified by a number/code rather than by name. Direct access will be granted only to the receiving institution and the regulatory authorities for monitoring, audits, and inspections related to the study.

Data Collection and Documentation Storage

Both paper and electronic CRFs will collect all research data. In all databases, participants will be identified using a unique number and/or study code. No names or other personally identifiable information will be included in any electronic research records.

Clinical Observation Form

Study data will be collected by both paper and electronic Clinical Observation Forms (CRFs). A separate CRF will be maintained for each enrolled participant and will be continuously updated to ensure that the data reflect the participant's current status at each phase of the study. The CRF will not include any personally identifying information, such as the participant's name, initials, or date of birth. Instead, identification will be carried out using a code, for example, by combining the participant number with the randomization code. Only the principal investigator, study coordinator, and medical biostatistician are permitted to edit the CRFs. Data collected through the CRFs will then be entered into an electronic database for analysis by the study coordinator.

Quality Assurance Procedures

Risk Assessment

The study will be conducted in accordance with the currently approved protocol, the principles of Good Clinical Practice (GCP), all applicable regulatory requirements, and standard operating procedures. Given the nature of this study, there is no anticipated risk associated with participation in this trial.

Monitoring

Regular monitoring of the clinical trial will be performed. Data will be evaluated for compliance with the protocol and the source documents, as defined herein. Coordinators and authorized personnel will verify that the clinical trial, including data generation, documentation, and reporting, is conducted in accordance with the protocol, GCP, and all relevant regulatory requirements.

Audits and Inspections

Study documentation and source data/documents will be made available to auditors and inspectors. During inspections, any queries will be promptly clarified. All parties involved are obliged to maintain strict confidentiality regarding participant data.

Confidentiality of Personal Data

Direct access to source documents will be permitted for monitoring, audits, and inspections only. The entire research team involved in the study will be given access to the protocol. However, the randomization sequence will be restricted solely to the Medical Biostatistician, drawn in order only when needed and provided in sealed envelopes.

Harms definition and assessment

Harms will be defined as any adverse events or complications that occur during or after the intervention, potentially resulting from the surgical procedure or the use of the stabilization implants. These may include, but are not limited to, surgical site infections, hardware failure, neurological deterioration, or other treatment-related side effects. Harms will be systematically assessed throughout the study. All participants will be monitored closely during the postoperative period and follow-up visits. Adverse events will be evaluated in terms of severity, causality, and the need for intervention.

Additionally, a non-systematic assessment will be conducted, where participants will be encouraged to report any side effects or complications that arise outside of regular follow-up

visits. This will be done through patient-reported outcome measures and direct communication with the study team. Regular assessments will be conducted at predefined intervals to ensure early detection and proper management of any harm, with all findings reported promptly to the ethics committee and regulatory authorities.

All patients experiencing harm or any adverse event related to the study intervention will receive appropriate treatment and follow-up care at the Neurosurgical Outpatient Clinic and the Department of Neurosurgery and Neurooncology, Copernicus Memorial Hospital in Łódź, even after study participation has ended. The study is insured, and any patient who suffers complications directly related to the study intervention will be entitled to appropriate compensation in accordance with applicable regulations.

Deviations from the protocol and serious violations

A deviation is defined as any departure from the ethically approved content of the study protocol, any other study document, or any research process (e.g., the consent procedure or administration of the investigational product), from GCP, or from any applicable regulatory criteria. All protocol deviations will be documented on a protocol deviation form and appended to the primary study documentation.

Statistics

Below is a detailed description of the planned statistical analysis for the study. No separate statistical analysis plan will be utilized.

Statistical Analysis Plan

Statistical analyses will include both parametric and non-parametric tests. For quantitative variables that are typically distributed, a Student's t-test will be employed for two-group comparisons or an ANOVA for comparisons among three or more groups, followed by post hoc Student's t-tests. For non-normally distributed quantitative variables, the Mann–Whitney–Wilcoxon test will be applied for two groups or the Kruskal–Wallis test for three or

more groups, followed by post hoc Wilcoxon tests. Where justified, the Bonferroni correction will be applied to account for multiple hypothesis testing. For qualitative variables, either the chi-square test or Fisher's exact test will be used, depending on expected frequencies. Additionally, Cohen's kappa coefficient will be calculated to assess inter-rater agreement. All statistical analyses will be conducted using R (version ≥ 4.2.0).

Hypothesis and Significance Level

The study hypothesis assumes that patients undergoing the MIDLIF procedure will respond slightly better to the treatment and have somewhat fewer complications than those undergoing the miniTLIF operation. The entirety of the treatment is not anticipated to be associated with additional late adverse effects. The significance level for the study is set at $\alpha = 0.05$.

Interim Analyses

Interim analyses will be conducted after 50% and 75% of patients have been enrolled. If the study's statistical assumptions are met at any of these interim points, the trial may be terminated earlier. The principal investigator will have access to the interim analysis results and will decide whether to continue the study based on these findings.

Handling of missing data

Missing data will be addressed using appropriate statistical methods to minimize bias and ensure the robustness of the analysis. The approach to handling missing data will depend on the nature and extent of the missing information:

Descriptive Statistics: Before applying any imputation techniques, the extent and pattern of missing data will be assessed. Descriptive statistics will be used to evaluate the missing data at each time point and identify any systematic patterns.

Imputation Methods: If missing data is deemed to be missing at a rate of up to 10% randomly, multiple imputation techniques will be employed to estimate the missing values

based on the observed data. This approach will help maintain statistical power and ensure valid inferences while preserving the variability in the dataset.

Complete Case Analysis: In cases where the proportion of missing data is minimal and does not significantly impact the dataset, a complete case analysis may be performed, where only participants with complete data for the variables of interest are included in the study.

Sensitivity Analysis: Sensitivity analyses will be conducted to assess the potential impact of missing data on the study results. This will involve comparing the results of the imputed data with those from the complete case analysis to ensure that missing data does not significantly impact the study's conclusions.

Handling of Dropout Data: Participants lost to follow-up will be accounted for in the analysis, with dropouts carefully considered as part of the sensitivity analysis. If necessary, last observation carried forward or other methods for handling missing follow-up data may be considered, depending on the nature of the study design and data.

Additional plan analysis

Additional analyses will be performed to test the robustness and generalisability of the primary findings. Prespecified subgroup analyses will first explore potential effect modification by key baseline characteristics: patient age (< 65 vs. ≥ 65 years), sex, history of lumbar spine operation (study intervention as a first surgical treatment vs further procedure), reported symptoms (only lower back pain vs only radicular pain vs both), occurance of neurological deficits before the treatment (present vs absent), the intensity of the pain (NRS $\leq$ 5 vs NRS >5).

A series of sensitivity analyses will then be conducted to address potential sources of bias. These will include: repeating the primary analysis after multiple imputation of missing covariates and outcomes under the missing-at-random assumption; a per-protocol analysis

restricted to participants without significant deviations from their assigned intervention; a competing-risks regression treating non-spine-cancer deaths as competing events for local progression; and re-estimation of treatment effects using robust standard errors to account for clustering by recruiting centre.

Data management

All clinical data will be anonymized by coding personal identifiers at the time the physician completes the questionnaire. The collected and coded clinical data will be stored on password-protected external drives accessible only to the research team. The publication of study findings will ensure complete anonymity of patients, with no possibility of identifying personal data. All data will be processed in accordance with Article 13(1) and (2) of the European Parliament and Council Regulation (EU) 2016/679 on the protection of natural persons regarding the processing of personal data and the free movement of such information.

Source Data and Data Access

Source documents are the original media on which data are recorded and from which data are transferred into the participants' Case Report Forms (CRFs). These documents include, but are not limited to, hospital records (used to complete CRFs regarding the patient's medical history and concurrently or previously administered medications), clinical and hospital files, laboratory and pharmacy documentation, diaries, imaging results, and correspondence. Entries in the CRF are considered source data if the CRF serves as the primary record (e.g., in the absence of any other written or electronic record). All documents will be stored securely and maintained in strict confidentiality.

Plans to Communicate Trial Results to Participants, Healthcare Professionals, the Public, and Other Relevant Groups

Reporting in the Trial Registry

The trial results will be reported in the clinical trial registry (ClinicalTrials.gov, NCT07127380) once the study is complete. This will include the final study outcomes, including primary and secondary endpoints, adverse events, and any other relevant findings. The registry will ensure that the study results are publicly accessible and transparent, in accordance with ethical guidelines and international standards for clinical trial reporting.

Communicating Results to Healthcare Professionals

The findings will be shared with the medical and scientific community through the publication of the full trial results in peer-reviewed journals. These journals will focus on spine surgery and neurosurgery ensuring that relevant healthcare professionals are informed about the trial's outcomes. In addition to peer-reviewed articles, results will be presented at national and international scientific conferences related to spine surgery and neurosurgery to foster discussion and dissemination within the professional community.

Public Communication of Results

A plain language summary of the study's results will also be made available to the public through the trial registry, as well as through press releases and the institution's website. This will ensure that the results are accessible to a broader audience, including patients, caregivers, and other members of the public interested in the trial's outcomes. The public summary will highlight the impact of the findings on the treatment of disc degeneration disease and provide context for how the results may influence future clinical practice.

Ethics

The study will be conducted in strict accordance with the protocol and the provisions of the current version of the Declaration of Helsinki, as well as the ICH GCP guidelines, and Polish law. Both the Ethics Committee and the regulatory authority will receive annual and periodic safety reports during the study's conduct. They will be promptly informed of any study discontinuation or termination in accordance with the regulations.

The principal investigator affirms and upholds the participant's right to privacy and commits to complying with all applicable regulations in this regard. The medical information obtained from individual participants during the study will be treated as confidential and must not be disclosed to any third parties. For the purpose of data verification, the relevant regulatory authority, or the ethics committee may require direct access to portions of the medical records about the study, including the participants' medical history.

Substantial amendments to the protocol shall only be implemented after obtaining approval from the Bioethics Committee and the regulatory authorities. In situations where immediate deviations from the protocol are necessary to protect the rights, safety, and welfare of the participants, such deviations may be implemented without prior approval from the sponsor or the responsible authorities. These deviations must be documented and reported to the sponsor and the ethics committee/the appropriate regulatory authority as soon as possible. Any minor amendments must be reported to the proper authority promptly, if applicable, and to the Bioethics Committee as part of the annual safety report.

Conflict of Interest

The authors declare that they have no competing interests.

Approvals

The protocol, the informed consent form, the patient information sheet, and all other materials/documents used in the study were approved by the appropriate Bioethics Committee, regulatory authorities, and receiving organizations for written approval. The

investigator shall submit any substantive amendments to the original documents for review and, if necessary, obtain permission from the entities above before implementing those changes.

Funding

The study was not granted.

Discussion

Both MIDLIF and MIS-TLIF are well-established minimally invasive surgical methods for lumbar spine fusion [8, 12]. Numerous studies have reported that MIDLIF and MIS-TLIF achieved comparable fusion rate, long-term clinical and radiological outcome, [6, 13] to open-TLIF, while offering several advantages. Minimally invasive approaches reduce pain faster, the time of the operation, and the blood loss compared to open-TLIF [14-15]. Moreover, MIS-TLIF is associated with a lower incidence of surgical site infection compared to open-TLIF [16]. MIDLIF had lower blood loss and shorter operative time compared to the traditional open TLIF technique [17].

Data comparing MIDLIF and MIS-TLIF in the management of DDD are minimal. In a single-center study involving 133 patients, MIDLIF and MIS-TLIF were compared for the treatment of lumbar degenerative disease. MIDLIF had several advantages over MIS-TLIF, including a shorter operative time (135.2 ± 15.70 vs. 160.1 ± 17.2 min, $P < 0.001$), decreased intraoperative blood loss (147.9 ± 36.4 vs. 169.5 ± 24.7 mL, $P < 0.001$), and a shorter length of hospital stay (10.8 ± 3.1 vs. 12.4 ± 4.1d; $P = 0.014$) [10]. Contrary to the retrospective study comparing open TLIF, MIDLIF, and MIS-TLIF, patients who underwent MIS-TLIF had significantly shorter lengths of hospitalization and less blood loss compared with MIDLIF (both $p< 0.001$) [18]. The discrepancy in these findings and their limited amount emphasize the need for further prospective, randomized trials to examine these two surgical methods.

MIDLIF and MIS-TLIF were also compared in managing spondylolisthesis. In a retrospective study, in which 87 patients were enrolled, postoperative VAS, operation time, and the facet joint violation were significantly lower in the MIDLIF group [9]. Another retrospective study involving 80 patients revealed that MIDLIF and MIS-TLIF had similar results in terms of general complication rates [19], even though the cited studies referring to the treatment of spondylolisthesis presented data showing that comparing MIS-TLIF and MIDLIF is difficult and has not yet been well explored.

There is a high need for a good prospective study comparing MIS-TLIF and MIDLIF in DDD. Existing literature on this comparison remains scarce, with most available evidence derived from retrospective cohort studies or small-scale analyses that often yield conflicting results on key outcomes such as operative time, blood loss, and fusion rates. Furthermore, fusion rates between the two techniques have shown no significant differences in limited follow-ups. Still, long-term data are lacking, and potential disparities (e.g., slightly lower fusion rates in MIDLIF) [10] require clarification through larger samples. The predominance of retrospective designs introduces biases, such as selection bias and incomplete data, underscoring the necessity for high-quality prospective, randomized controlled trials to resolve these discrepancies, establish definitive clinical superiority, and guide evidence-based practice in treating DDD.

List of abbreviations:

ASD - Adjacent Segment Disease

comi-BACK - Core Outcome Measures Index Back

DDD - Degenerative Disc Disease

EBL - estimated blood loss

EQ-5D-5L - European Quality of Life - 5 Dimensions, 5 Levels

FH - foraminal height

ICF - informed consent form

ISH - intervertebral space height

LBP - Low Back Pain

LOS - length of stay

MIDLIF - midline lumbar interbody fusion

mini-TLIF - minimally invasive transforaminal lumbar interbody fusion

MIS-TLIF - minimally invasive transforaminal lumbar interbody fusion

NRS - Numerical Rating Scale

Open-TLIF - open transforaminal lumbar interbody fusion

OSI - Oswestry Disability Index

VAS - Visual Analog Scale: Data availability

Data availability

Data will be available on demand by contacting the corresponding author (AK).

Supporting information

None

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None

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Formal analysis

Writing - review and editing

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