THE "CAROL DAVILA" UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST
DOCTORAL SCHOOL
THE FIELD OF MEDICINE

COMPARATIVE STUDY ON POSTOPERATIVE OUTCOMES IN PATIENTS WITH SPONDYLOLISTHESIS III AND V AND DETERMINATION OF FACTORS INFLUENCING THESE OUTCOMES

DOCTORAL THESIS SUMMARY

Doctoral supervisor:

PROF. UNIV. DR. STOICA IOAN CRISTIAN

PROF.UNIV. DR. POPESCU ION GHEORGHE

Doctoral student:

NEDELEA DANA-GEORGIANA

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The fundamental problem

Spondylolisthesis is a common pathology characterized by anterior or posterior displacement of a vertebral body relative to the one below, and most commonly affects the lumbosacral spine. The displacement can be caused by a wide variety of etiological factors including congenital anomalies, degenerative changes, trauma, or iatrogenic causes. Iatrogenic spondylolisthesis has shown an increasing incidence in recent years and is much more common than when it was initially described by Wiltse and White in 1976. It results from spinal surgical interventions such as decompression procedures and is of great importance in terms of clinical management.

The removal of components from the vertebral structure and the disruption of the posterior spinal stabilizing column can induce mechanical imbalances that can lead to vertebral instability and secondary, iatrogenic spondylolisthesis. It is considered that certain categories of patients are more prone to the evolution towards iatrogenic spondylolisthesis and in this sense a variety of factors have been invoked such as the morphotype of the patient, his age, biomechanical status and many others, but to date the relative impact of these factors is not known nor the role they have in predicting the evolution towards this complication.

Despite the numerous studies in the literature that evaluate the effectiveness of surgical intervention in spondylolisthesis, very few focus on the iatrogenic form or take into account the integration of clinical, radio-imaging and systemic predictive factors within a broad and complex analysis.

Working hypothesis and general objectives

The doctoral study addresses the differences between surgical outcomes from a clinical, paraclinical, pain, and functional status point of view of the patients, but also taking into account demographic, clinical parameters and possible comorbidities.

The working hypothesis is that there are significant differences between patients with primary spondylolisthesis and those with iatrogenic spondylolisthesis in terms of postoperative clinical, functional, and radiological outcomes, additionally influenced by systemic and perioperative factors that may affect the evolution and success of the surgical intervention.

The general objectives of the study were the following*:*

1. Performing a comparative clinical analysis of the evolution of pain and disability using validated scores in patients operated for primary vs. iatrogenic spondylolisthesis.
2. Studying the impact of surgical technique and pathology origin on radiological results, spinal alignment and arthrodesis success in order to improve the planning process and optimization of surgical techniques
3. Identifying clinical, demographic and systemic predictive factors that may influence short- and long-term recovery in patients with spondylolisthesis
4. Developing and substantiating a management algorithm that integrates clinical and paraclinical data in order to obtain a structured perspective on this pathology
5. Deepening the understanding of spinal biomechanics phenomena and specific changes characteristic of the positioning of osteosynthesis elements.

General research methodology

The general study was a retrospective cohort study, conducted at the Foișor Clinical Hospital of Orthopedics, Traumatology and Osteoarticular TB using clinical, paraclinical and surgical data. Patients gave their consent to participate in the study and all stages of the research respected academic rigor and the principles of ethics in scientific research.

The patients were divided into two groups, respectively:

- Group A: primary spondylolisthesis, represented by patients who have not undergone previous surgical interventions in the lumbar spine;
- Group B: iatrogenic spondylolisthesis, which includes patients with instability secondary to previous surgical interventions performed on the respective involved segment.

Patient data were centralized and structured in tabular format to allow easy access and statistical analysis. The types of data analyzed in the study patients were demographic, clinical, pre- and post-surgical radio-imaging, and surgical.

Chapter summary

The doctoral thesis consists of two parts, entitled "General Part" and "Personal Contributions". *The General Part* presents aspects related to the definition, diagnosis and classification of spondylolisthesis, as well as information on the surgical and non-surgical management of this pathology, highlighting and further detailing the relevant elements in the second part of the doctoral thesis. In the part entitled *Personal Contributions*, the working hypothesis is developed and the general objectives are achieved through three studies.

The first study had as its working hypothesis the fact that statistically significant differences can be identified in terms of clinical outcomes between patients with iatrogenic spondylolisthesis and those with primary spondylolisthesis, measurable by specific scores.

All patients underwent surgery and the following data were evaluated: surgical time, intraoperative bleeding, length of hospitalization, number of fused levels and achieved reduction of spondylolisthesis. Low back and lower limb pain were assessed using VAS, postoperative neurological impairment was assessed using the Frankel classification, and postoperative ODI was also applied. Implant failure, whether involving a rod or screw, was also assessed, along with low back pain, lower limb pain, and ODI.

The most relevant *results* of the first study are presented briefly below. The mean age in group A was 59.80 ± 12.36 years and in group B it was 64.95 ± 10.02 years ($p = 0.0334$). The surgical time was on average 152.28 ± 34.01 minutes in the primary spondylolisthesis group and 177.96 ± 30.99 minutes in the iatrogenic spondylolisthesis group ($p = 0.0003$). Regarding intraoperative bleeding, in group A (primary spondylolisthesis) it was, on average, 573.04 ± 197.22 mL while in group B (iatrogenic spondylolisthesis) it was 689.09 ± 151.21 mL, the difference between the two groups also being statistically significant ($p = 0.0024$).

Patients with grade IV spondylolisthesis had a significantly higher preoperative ODI score than patients with grade III and II spondylolisthesis ($p = 0.012$, F-ratio = 4.651). There were statistically significant differences between the levels of impairment in patients with primary spondylolisthesis in terms of preoperative lumbar pain ($p = 0.012$) and at 6 months ($p = 0.029$), respectively at the level of the lower limb, postoperatively ($p = 0.005$). Similarly, Oswestry Disability Index had significantly different values in relation to the level of impairment in patients with primary spondylolisthesis at the 12-month assessment ($p=0.006$).

From the relevant *discussions* of the study results, we note that increased surgical time and blood loss have been associated with increased risks of complications, such as infection and increased rates of non-fusion, in almost all works on spinal surgery. In a recent study of 336 patients, increased operative time was significantly associated with a higher rate of complications. Furthermore, for surgical times less than 120 minutes, the complication rate was calculated to be 2.4%, while for 120 to 240 minutes, the complication rate was 44.5%. Surgeries lasting between 240 and 360 minutes had a complication rate of 69.5%, while prolonged surgical times of more than 360 minutes had a complication rate of 85.7%. (Monetta et al., 2024). In a study of 112 patients undergoing posterior lumbar spine segmental decompression, fusion, and instrumentation, intraoperative blood loss and operative time were evaluated. After analyzing the results of multiple regression analysis, apparently the most important predictive factors were the number of levels fused and age. (Zheng et al., 2002).

By analyzing the Oswestry Disability Index (ODI) postoperatively, it was noted that patients with involvement at the L3-L4 level had significantly higher ODI scores at 12 months, and marginally statistically significant at 6 months postoperatively, compared with patients with involvement at the L4-L5 or L5-S1 levels. This may reflect the biomechanical complexity of the L3-L4 segment, which is less frequently involved in spondylolisthesis but may represent a greater surgical and functional challenge, due to its intermediate position between areas of greater mobility and more rigid upper lumbar structures and because the L3-L4 segment is the main segment involved in achieving sagittal balance (Kodsy et al., 2022). At the same time, the L3-L4 level is less tolerant of postoperative changes in alignment and stability, thus leading to a more difficult recovery and more markedly impacting the functionality and quality of life of patients. (O'Connor et al., 2024). In comparison, in patients with iatrogenic spondylolisthesis, no statistically significant correlation was found between lesion location and ODI score. This may be explained by the different pathophysiological substrate, with previous interventions being able to impact the functional status of the patient more uniformly, regardless of the affected level. Furthermore, in iatrogenic spondylolisthesis, muscle status or the degree of postoperative fibrosis may also contribute to functional disability, diminishing the relevance of lesion location and how it influences the ODI score.

The *conclusions* related to study 1 are as follows:

1. Laminectomy is an effective procedure but may lead to iatrogenic spondylolisthesis, for reasons dependent on technique and patient.
2. Iatrogenic spondylolisthesis requires longer surgical interventions with greater blood loss, suggesting increased technical difficulty.
3. Increased operative time and blood loss correlate with postoperative complications.
4. There were no statistically significant differences in postoperative VAS and ODI scores between the primary and iatrogenic spondylolisthesis groups.
5. Increased pain tolerance in the iatrogenic spondylolisthesis group may reflect a chronic evolution of the pathology.
6. In the medium and long term, the differences between the two forms are minimal in terms of pain, provided a correctly performed surgical intervention was performed.

Study 2 referred to the radio-imaging and functional evaluation of patients with surgically corrected iatrogenic spondylolisthesis. The retrospective study included 64 patients diagnosed with iatrogenic spondylolisthesis. All patients included in this study underwent surgical treatment.

The most important *results* of Study 2 are summarized below. Statistically significant differences were found between patients with Goutailler 1, who had a BMI of 28.29 ± 2.77 kg/m^2, and those with Goutailler 2 (30.59 ± 1.89 kg/m^2) and 3 (32.00 ± 2.98 kg/m^2), with a p value < 0.001. The age of the patients was also a factor that influenced the Goutallier classification, thus patients with class 1 had a mean age of 59.12 ± 12.13 years, significantly younger compared to those with Goutallier 2 (68.96 ± 6.04 years) and Goutallier 3 (68.75 ± 5.85 years), with a p value = 0.001. A statistically significant impact of the gender of the patients was identified regarding the intraoperative bleeding of patients with iatrogenic spondylolisthesis, namely men had greater bleeding (735.26 ± 141.87 mL) compared to women (647.78 ± 160.95 mL), with a p value = 0.0442.

At the same time, the surgeries lasted longer for men than for women, with a difference of 186.32 ± 27.53 minutes vs 170.89 ± 33.83 minutes, which is marginally statistically significant (p = 0.0842, standard error = 8.7907, t statistic = -1.755, degrees of freedom = 62, 95% confidence interval of the difference = -32.9993 to 2.1455).

Below are presented in an abbreviated manner, the *discussions* related to the results presented above. Biomechanical studies have shown that segmental mobility increases if the posterior osteoligamentous structures are affected after bilateral laminectomy. (Gillespie and Dickey, 2004). Fatty infiltration and atrophy of paraspinal muscles may contribute to changes in the normal lumbar lordosis and sacro-vertebral angle (promontory) (He et al., 2020). In the global population, the prevalence of sarcopenia can range from 9.9% to 40.4% (Mayhew et al., 2019). Furthermore, the prevalence of sarcopenia increases with age; starting at age 30, muscle mass declines by approximately 3% to 8% per decade, with accelerated decline over age 60. (Holloszy, 2000, Khosla et al., 2000). In addition, 69% of our patients are women with a mean age of 63.44 ± 10.79 years, in menopause or in the premenopausal period, affected by hormonal changes that can occur at this specific age, especially related to the decrease in estrogen levels. The statistically significant difference between men and women in our study regarding the amount of fatty infiltration and degeneration of paraspinal muscles more extensive in the female subgroup may be generated by the higher body mass index, but also as an effect of the menopausal musculoskeletal syndrome (Wright et al., 2024).

The main *conclusions* of Study 2 were the following:

1. There is a need to differentiate between patients with and without pre-existing biomechanical impairment, for a correct assessment of the postoperative risk of iatrogenic spondylolisthesis.
2. Significant MRI correlations between paravertebral fat infiltration, BMI and age reveal these potential predictors for the risk of iatrogenic spondylolisthesis.
3. Radiological reduction of vertebral slippage is associated with prolonged hospitalization, possibly as a result of greater complexity of the intervention.
4. Paravertebral fat infiltration is more common in postmenopausal women with increased BMI indicating the role of hormonal and metabolic changes in muscle degeneration.
5. No direct correlations have been identified between the degree of slippage and muscle infiltration, although there is a trend related to vertebral location.
6. The most commonly affected vertebral levels are L4-L5 and L5-S1; but the presence of lesions also at L2-L3 indicates a possible anatomical vulnerability.
7. The development of personalized treatment and postoperative follow-up protocols adapted to the patient's profile and biomechanical status is recommended.

The third study addressed the evaluation of systemic prognostic and risk factors in the postoperative recovery of patients with spondylolisthesis, assuming that patients with iatrogenic spondylolisthesis present postoperative outcomes significantly influenced by anthropomorphic, demographic, and systemic factors that have a direct impact on functional scores.

Demographic parameters were recorded for the study, namely age, sex, body mass index, smoking status, as well as parameters related to the type, degree, and level of spondylolisthesis. These parameters were correlated with surgical and outcome parameters obtained by reviewing medical data during the first year after the surgical procedure. The study groups included a number of 46 patients for the group of patients with primary spondylolisthesis and 44 patients for the group of patients with iatrogenic spondylolisthesis.

The most relevant *results* from Study 3 are presented below. The proportion of male smokers (75.67%) is higher than that of female smokers (49.06%), with a p value = 0.0205. A lower mean age of smoking patients (59.96 ± 12.24 years) was recorded compared to non-smoking patients (65.86 ± 9.40 years), with a p value = 0.0167. A direct correlation was identified between the age of patients with primary spondylolisthesis and the time interval required to obtain arthrodesis (p = 0.0238). BMI is a statistically significant and reasonably accurate predictor for predicting implant failure in the studied cohort. ROC analysis suggests that a higher BMI is associated with a higher risk of implant failure. A BMI threshold of >30 is a satisfactory compromise between sensitivity (85.7%) and specificity (63.9%).

The *discussions* related to the third study are summarized below. Patients with iatrogenic spondylolisthesis were significantly older than patients with primary spondylolisthesis. This observation aligns with the literature data that emphasize that iatrogenic forms of spondylolisthesis are more common complications that occur in the older population (Nedelea et al., 2025, Mobbs et al., 2015).

Implant failure occurred in a small number of cases, with no significant differences between study groups. However, a higher BMI was an important predictor of implant failure, highlighting the biomechanical challenges associated with a high patient weight. Thus, the need for adequate preoperative planning and the possible development of appropriate consolidation strategies in overweight patients is required. For example, establishing a threshold value for body mass index whose value does not jeopardize implant stability and fusion achievement. The data presented in the Results section suggested that a body mass

index cut-off of 30 provides a sensitivity of 85.7% and a specificity of 63.9%, so we present below the following proposed algorithm for the management of these patients, also considering the impact on the risk of persistent neurological deficit and delayed arthrodesis. In the absence of new neurological deficit, patients proposed for surgical correction of spondylolisthesis will undergo preoperative evaluation and if they have a BMI ≤ 30 and are at standard risk, they will be planned for surgery. If the BMI is >30, they will be considered at high risk and will be referred for physiotherapy and lifestyle adjustment, to be re-evaluated after BMI reduction.

These results align with data from the literature that present obesity as a risk factor for poor outcomes of spinal surgery, delayed healing, and increased mechanical stress on the fixation elements (Goyal et al., 2019). However, given the small number of implant failures in our study group, the results should be interpreted with caution, but still support the inclusion of BMI as a relevant variable in preoperative stratification and surgical planning.

In the management of iatrogenic spondylolisthesis, surgery is a risk factor for neurological deficit; it is highly likely that fibrous scar tissue is a contributing factor to epidural hematoma (Lewik et al., 2024). In revision surgeries, a "dead" epidural space is found which, together with the lack of contractility of the paravertebral muscles, the presence of fibrous scar tissue and the absence of peridural fat tissue, allows epidural hematomas to easily form (Guner et al., 2021). Frequently, in patients with revision surgeries, lumbar hypolordosis is also found, which requires a greater and more complex correction (Uribe et al., 2003).

The *conclusions* of the third study were as follows:

1. Patients with iatrogenic spondylolisthesis are significantly older than those with primary forms, suggesting an increased vulnerability to post-laminectomy biomechanical changes.

2. Multi-level interventions are more common in elderly patients, suggesting more advanced degeneration and the need for a more complex procedure.

3. Age and BMI are predictors of the complexity of the intervention, the duration of the operation, blood loss and the time to obtain arthrodesis, with older age being negatively correlated with early functional recovery.

4. Iatrogenic spondylolisthesis involves longer operative times and bleeding, being a more difficult procedure due to previous interventions that induce adhesions, changes in zonal anatomy and other local factors.
5. Arthrodesis is obtained more quickly in patients with primary spondylolisthesis, probably due to a more favorable biological terrain and the lack of previous interventions.
6. Increased BMI is positively correlated with the time to arthrodesis due to the additional mechanical stress to which the implants and the operated area are subjected.
7. Implant failure was associated with a higher BMI, without significant correlations with other factors studied (age, sex, location, etc.).
8. Although pain and disability improvement were similar between the two groups, younger patients with a lower BMI had a faster and more efficient functional recovery in the immediate postoperative period.

Conclusions and personal contributions

Following the conduct of the three studies, a series of general conclusions can be drawn that provide validity to the study as a whole and allow for a global vision of the research conducted.

The extent to which scientific research objectives have been achieved

The studies conducted comparatively evaluated iatrogenic and primary spondylolisthesis, monitoring a series of clinical, imaging, functional and outcome variables.

Study 1 aimed to compare the evolution of pain and disability in these categories of patients, the objectives regarding the longitudinal evaluation of parametric scores being clearly achieved. The conclusions revealed that, although the surgical intervention is more complex in iatrogenic cases, the improvement of pain and functional status are comparable in the medium term in the two groups. Thus, the validity of the correct surgical treatment performed for iatrogenic spondylolisthesis is confirmed.

Study 2 included an imaging component that evaluated the degree of fatty infiltration of the paraspinal muscles assessed by Magnetic Resonance Imaging and also assessed radiographic parameters of the reduction of spondylolisthesis and the clinical effect of this process. Correlations were found between body mass index, age and degree of muscle degeneration, which supports the hypothesis of a common pathophysiological basis in iatrogenic spondylolisthesis. The objective of demonstrating the usefulness of preoperative methods for personalizing the therapeutic plan was achieved.

Study 3 integrated systemic and anthropometric factors as predictors of postoperative outcomes, supporting the understanding of the biological and functional substate of recovery. It was demonstrated that age and body mass index influence the complexity of the intervention, the time to obtain arthrodesis, but also the risk of implant failure. It also emerged that patients with iatrogenic spondylolisthesis have an increased risk of intraoperative complications and a slower recovery compared to those with primary spondylolisthesis. The objectives of the study were thus achieved and the conclusions support the importance of considering demographic parameters and preoperative systemic assessment in the assessment of surgical risk and in the perioperative management of patients.

Technical and economic advantages and disadvantages

From a technical and economic point of view, the conclusions of the studies provide evidence regarding the role of predictive variables that can guide therapeutic decisions and reduce the rate of reinterventions as well as the costs associated with these procedures.

Regarding the economic advantages of surgical correction of spondylolisthesis, these include restoring the biomechanical stability of the spine, improving the patient's pain and functionality, improving the quality of life and reducing the need for symptomatic treatment over long periods of time. These benefits are possible by judiciously deciding on the opportunity of primary intervention or correction of iatrogenic spondylolisthesis, and this decision must be based on a correct and complex analysis of the factors that can influence the surgical procedure and the short, medium and long-term results.

Appropriate execution of surgical treatments and the correct establishment of indications can reduce the average length of hospitalization compared to conservative treatment of these patients, and can reduce the possible costs associated with frequent readmissions, insufficient treatments and unnecessary additional diagnostic tests.

At the same time, the surgical procedure to correct iatrogenic spondylolisthesis is more complex and expensive than the primary intervention, often requiring bone reconstructions, dedicated implants, and a spinal surgery team with specific experience in revision surgery. These factors can limit patients' access to high-performance services and can lead to high treatment costs. In addition, revision surgery is accompanied by a longer surgical procedure, involves greater blood loss, and may entail a greater consumption of medical resources, the need for more advanced imaging, more careful perioperative monitoring, and potentially more severe complications.

Unresolved issues and directions for further research

Although the literature data supports the conclusions of this paper, namely that revision surgery in iatrogenic spondylolisthesis is effective, there are a number of questions that currently remain unanswered. It is unclear to what extent certain factors such as the degree of fatty infiltration of the paraspinal muscles, metabolic status, or the degree of preoperative disability have an impact on the outcome of the intervention. Currently, there are no standardized guidelines available regarding the appropriate time for surgery, optimal patient selection criteria, or the choice of surgical technique depending on the type and severity of spondylolisthesis.

Future research directions should include the development of predictive algorithms that include patient-specific demographic parameters (age, sex, body mass index), clinical parameters (type and degree of spondylolisthesis, associated deficit, comorbidities, complications), as well as imaging and functional parameters. Future studies could also include the use of artificial intelligence to perform complex calculations and run computational models that depict how these variables interact and the extent to which they determine a predictable outcome.

Recent advances in 3D printing technology could provide the opportunity for more precise preoperative planning, with a better estimate of the necessary technical resources and the appropriate approach by printing anatomical models that replicate the patient's anatomy. Furthermore, the development of new biocompatible materials could allow the printing of personalized implants that feature a better fit, superior biomechanical support, and a simpler and faster procedure tailored to the specifics of the patient.

Own contributions

- Conducting comparative study, innovative for our country, regarding the patient group and the evaluated parameters, providing an applied and useful perspective on the approach to primary and iatrogenic spondylolisthesis.
- Implementing Visual Analog Scale and Oswestry Disability Index scores in the patients in the study through a form for evaluating the functional, imaging and neurological outcomes of the patients at the time points established for the evaluation.
- Identifying factors that significantly influence the results in the surgical treatment of spondylolisthesis and characterizing the magnitude of their impact.
- Performing an analysis of comparative pain and functional scores between patients with primary and iatrogenic spondylolisthesis, providing an innovative perspective on the outcome parameters in this category of patients.
- Recording and analysis of data related to iatrogenic spondylolisthesis regarding lower levels of lumbar pain preoperatively, which may suggest an increased tolerance to pain due to a slow and chronic evolution of the respective pathology.
- Issuing the proposal for radiological evaluation of all patients undergoing simple decompression interventions in relation to the results demonstrated in Study 1 and 2.
- Creation of the algorithm for identifying the threshold value of BMI to avoid complications such as delayed fusion, implant failure and neurological deficit.
- Proposals for additional analysis and then the creation of specific algorithms for selecting patients candidates for fusion at the primary intervention and the correct identification of risk factors that can be monitored and rebalanced prior to surgery to ensure optimal results.

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List of published scientific papers on the topic of the doctoral thesis

1. **NEDELEA, D.-G.**, VULPE, D. E., DRAGOSLOVEANU, S. & STOICA, I. C. 2025. Primary Versus Iatrogenic Spondylolisthesis: A Multi-Dimensional Comparison of Outcomes. Journal of Clinical Medicine, 14 (7), 2193. Indexed in ISI (Web of Science, Science Citation Index Expanded), impact factor 3.0, https://doi.org/10.3390/jcm14072193 (Chapter 5).

2. **NEDELEA, D.-G.**, VULPE, D. E., GHERGHICEANU, F., CAPITANU, B.S., DRAGOSLOVEANU, S., STOICA, I.C. 2025. Surgical and non-surgical management of spondylolisthesis: a comprehensive review. Journal of Medicine and Life, 18(3), 196-207. Indexed in PubMed. https://pubmed.ncbi.nlm.nih.gov/40291940 (Chapters 1,2).

3. **NEDELEA, D.-G.**, VULPE, D. E., DRAGOSLOVEANU, S., STOICA, I.C. 2025. Evaluation of short- and mid-term benefits of re-operative surgery in iatrogenic spondylolisthesis cases. Journal of Medicine and Life, 18(3), 223-228. Indexed in PubMed. https://pubmed.ncbi.nlm.nih.gov/40291935 (Chapter 6).

4. **NEDELEA, D.-G.**, VULPE, D., ENYEDI, M., CERGAN, R., SCHEAU, C., BAZ, R. O. & DRAGOSLOVEANU, S. 2024. Comprehensive Approach of the Diagnosis, Treatment, and Medical Rehabilitation of Patients with Spondylolisthesis. Balneo and PRM Research Journal, 15 (2), 709. Indexed in ISI (Web of Science, Emerging Sources Citation Index), impact factor 0.7, https://doi.org/10.12680/balneo.2024.709 (Chapter 2).

5. **NEDELEA, D.-G.**, VULPE, D. E., VISCOPOLEANU, G., RADULESCU, A. C., MIHAILESCU, A. A., GRADINARU, S., ORGHIDAN, M., SCHEAU, C., CERGAN, R. & DRAGOSLOVEANU, S. 2024. Progressive Thoracolumbar Tuberculosis in a Young Male: Diagnostic, Therapeutic, and Surgical Insights. Infectious Disease Reports, 16(5), 1005-1016. Indexed in ISI (Web of Science, Emerging Sources Citation Index), impact factor 3.4, https://doi.org/10.3390/idr16050080 (Chapters 4,7).