

ECONOMIC COST, DIAGNOSTIC AND PROGNOSTIC MARKERS IN IATROGENIC LUMBAR SPONDYLODISCITIS

İyatrojenik Lumbar Spondilodiskitlerde Ekonomik Maliyet, Tanısal ve Prognostik Belirteçler

Ulaş YÜKSEL¹, Mustafa ÖĞDEN², Süleyman AKKAYA³, Üçler KISA⁴, Bülent BAKAR⁵,
Mehmet Faik ÖZVEREN⁶

^{1,2,3,5}Kırıkkale Üniversitesi Tıp Fakültesi, Beyin ve Sinir Cerrahisi Anabilim Dalı, KIRIKKALE, TÜRKİYE

⁴Kırıkkale Üniversitesi Tıp Fakültesi, Biyokimya Anabilim Dalı, KIRIKKALE, TÜRKİYE

⁶Ankara Güven Hastanesi, Beyin ve Sinir Cerrahisi Kliniği, ANKARA, TÜRKİYE

ABSTRACT

ÖZ

Objective: In this study, the economic cost, diagnostic and prognostic laboratory markers of lumbar spondylodiscitis, which emerged as a complication after surgical intervention in the lumbar region, were investigated.

Material and Methods: Age and gender of the patients were recorded. Furthermore, surgical intervention type (spinal instrumentation, lumbar discectomy), biopsy results of infected tissue, concomitant morbidities, duration of hospital stay and microorganism growth in culture materials were evaluated in patients. In addition, values of serum C-reactive protein (CRP) level, erythrocyte sedimentation rate (ESR), leukocyte, neutrophil and lymphocyte count which were obtained from these patients at admission to hospital and at discharge from hospital were recorded. Moreover, treatment costs of these patients were examined.

Results: Nine patients (women=7, men=2) with a mean age of 58±14.92 years were included in this study. All parameters of patients were not different in terms of surgical intervention type. However, when the patients were discharged from the hospital, their ESR and neutrophil counts decreased and lymphocyte count increased in all of them. Although CRP level values decreased as numerical value at discharge, this decrease was not statistically significant. Correlation analysis showed that length of hospital stay and tissue biopsy performed to the patients increased the economic cost.

Conclusion: It was concluded that any routine laboratory parameter investigated in this study could not be a valid biomarker for diagnosis and follow-up of spondylodiscitis that emerged after surgical intervention. On the other hand, it was concluded that diagnosis and treatment of this disease, whose prevalence is increasing, may have a high economic cost for patients and countries.

Keywords: C-reactive protein, economic cost, iatrogenic, prognosis, erythrocyte sedimentation rate, spondylodiscitis

Amaç: Bu çalışmada lomber bölgeye cerrahi müdahale sonrası komplikasyon olarak ortaya çıkan lomber spondilodiskitte ekonomik maliyet ile tanısal ve prognostik laboratuvar belirteçleri araştırıldı.

Gereç ve Yöntemler: Hastaların yaşı ve cinsiyeti kaydedildi. Ayrıca, cerrahi girişim tipi (spinal enstrümantasyon, lomber diskektomi), enfekte olmuş dokunun biyopsi sonuçları, eşlik eden morbiditeler, hastanede kalış süresi ve alınan kültür materyallerinde mikroorganizma üremesi değerlendirildi. Ek olarak, hastaneye yatışta ve hastaneden taburcu edildiğinde bu hastalardan elde edilen serum C-reaktif protein (CRP) seviyesi, eritrosit sedimentasyon hızı (ESH), lökosit, nötrofil ve lenfosit sayıları kaydedildi. Ayrıca, bu hastaların tedavi maliyetleri incelenmiştir.

Bulgular: Çalışmaya yaş ortalaması 58 ± 14,92 yıl olan dokuz hasta (kadın=7, erkek=2) dahil edildi. Hastaların tüm parametreleri cerrahi girişim tipi açısından farklı değildi. Ancak, tüm hastalar için, hastaneden taburcu olurken ESH ve nötrofil sayıları azalmış ve lenfosit sayıları artmıştır. CRP düzeyleri taburculuk sırasında sayısal değer olarak düşse de bu düşüş istatistiksel olarak anlamlı değildi. Korelasyon analizi, hastanede kalış süresinin ve hastalara biyopsi yapılmasıyla ekonomik maliyeti artırabileceğini göstermiştir.

Sonuç: Bu çalışmada, incelenen herhangi bir rutin laboratuvar parametresinin cerrahi girişim sonrası ortaya çıkan spondilodiskit tanısı ve takibinde geçerli bir biyobelirteç olamayacağı sonucuna varıldı. Öte yandan, prevalansı artmakta olan bu hastalığın tanı ve tedavisinin hastalar ve ülkeler için yüksek bir ekonomik maliyete sahip olabileceği sonucuna varılmıştır.

Anahtar Kelimeler: C-reaktif protein, ekonomik maliyet, iyatrojenik, prognoz, eritrosit sedimentasyon hızı, spondilodiskit

This study was presented orally at the congress "Spine Surgery in 21 Century - Current Concept, Controversies, Perspectives" on 4-7 October 2018 in Niš, Serbia.



Correspondence / Yazışma Adresi:

Kırıkkale Üniversitesi Tıp Fakültesi Hastanesi, Beyin ve Sinir Cerrahisi A.D., Yahşihan, KIRIKKALE, TÜRKİYE

Phone / Tel: +90 532 2304940

Received / Geliş Tarihi: 09.09.2020

ORCID NO: ¹0000-0002-6398-4110, ²0000-0002-7129-0936

³0000-0002-6236-7647, ⁴0000-0001-7768-1519

Dr. Ulaş YÜKSEL

E-mail / E-posta: ulasyksl@hotmail.com

Accepted / Kabul Tarihi: 21.12.2020

³0000-0003-0597-1861, ⁴0000-0002-8131-6810

INTRODUCTION

Spondylodiscitis or vertebral osteomyelitis with discitis is one of the rare and sometimes life-threatening infections of the spine (1). Clinical studies have shown that the annual incidence of pyogenic spondylodiscitis in Europe is 0.4-5.8/100,000 people. Nowadays, the number of patients with spondylodiscitis which developed as a complication after the surgical intervention to the lumbar region is reported to show an increasing trend. The aging population, longer life expectancy of chronic and / or elderly patients, an increase in prevalence of chronic diseases as well as the increased use of immunosuppressive therapies, increasing number of invasive procedures (eg, puncture, fine needle aspiration, biopsy) and surgical interventions to the spine are considered the reasons for this trend (2).

The economic cost as well as diagnostic and prognostic laboratory markers in lumbar spondylodiscitis which emerged as a complication after surgical intervention to the lumbar region were investigated in this study.

MATERIALS AND METHODS

Material: The patients who were treated for spondylodiscitis which emerged as a complication after the surgical interventions to the lumbar region were included in this study. The age, gender and type of surgical intervention (spinal instrumentation, lumbar discectomy) of all patients were recorded (Figure 1). In addition, microorganism growth in culture materials taken from infected tissue, comorbidities (such as diabetes mellitus [DM]), length of hospital stay were recorded. Furthermore, serum C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), leukocyte, neutrophil and lymphocyte count which were obtained from the patients at their admission to hospital and at discharge from the hospital were also recorded. Treatment costs of patients were examined. Patients in the pediatric age group, patients with primary spondylodiscitis (without any surgical

treatment), patients with spinal tumor were excluded from the study. The study was approved by the local ethics committee (Kırıkkale University Ethics Committee of Non-interventional Research, date: 16.01.2019; number: 2019.12.13).

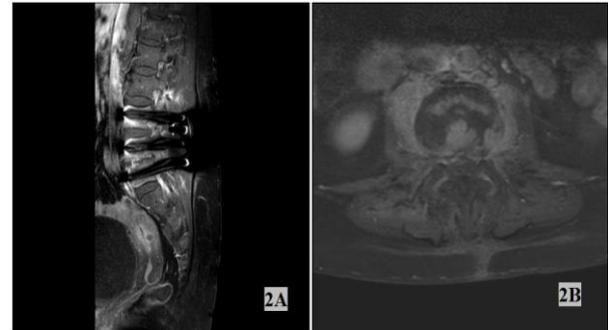


Figure 1: Sagittal (1A) and axial (1B) contrast-enhanced MR images showing the spondylodiscitis in a patient undergoing lumbar instrumentation

Biochemical analysis: The venous blood samples of the patients were analyzed biochemically. Serum CRP levels were obtained using the original commercial kits (Roche) (Roche Diagnostic COBAS c501). Serum CRP levels (reference range 0.15-5 mg/dl) were measured with the "immunoturbidimetric" method. The values of the hemoglobin level (reference interval: 10-18 g/dL), leukocyte count (reference interval: 4,400-11,300/uL), neutrophil count (reference interval: 1,100-9,600/uL), lymphocyte count (reference interval: 500-6,000/uL) were determined using an analyzer device (Mindray BC-6800, Shenzhen, China). ESR value (reference interval <20 mm/hour) was measured by automated system (ESR 40, Sistas Diagnostics).

Statistical analysis: Non-parametric data were analyzed using the *Mann Whitney U* test and *Wilcoxon Signed Ranks* test ($p < 0.05$). Parametric data were analyzed using the *Independent Samples t* test and *Paired Samples t* test ($p < 0.05$). *Spearman's rho Correlation* test was used to determine the correlation among the variables ($p < 0.05$).

RESULTS

The study included 9 patients (female: 7, male: 2) with a mean age of 58 ± 14.92 years. Three patients had hypertension, 3 had DM, one had hypothyroidism and one had chronic hepatitis B infection. *Kocuria kristinae* was isolated in one patient's tissue culture. *Staphylococcus aureus* was isolated in another patient's tissue culture, while *Staphylococcus epidermidis* and *Aerococcus viridans* were isolated in two other patients. No microorganism was detected in other patients.

All parameters of the patients (especially duration of the hospital stay and economic cost parameters) were not statistically different in terms of surgical intervention type (Table 1, Table 2, Figure 2, Figure 3). However, for all patients, the first and last measured values of ESR ($t=2.941$, $p=0.037$), neutrophil ($t=2.359$,

$p=0.046$) and lymphocyte count ($t=-3.289$, $p=0.011$) were different while the leukocyte counts and serum CRP levels were not statistically different. These findings revealed that ESR and neutrophil counts were decreased and lymphocyte counts increased at discharge. Although CRP level values were observed to decrease as numerical value when the patients discharge from the hospital, this decrease was not statistically significant (Table 3).

For correlation analysis of all parameters, a positive correlation was found between the treatment cost and length of hospital stay ($r = 0.731$, $p = 0.040$) and between the treatment cost and tissue biopsy performed ($r = 0.756$, $p = 0.030$). It was considered with these findings that the increase of the duration of the hospital stay and performing the biopsy could cause an increase the economic cost.

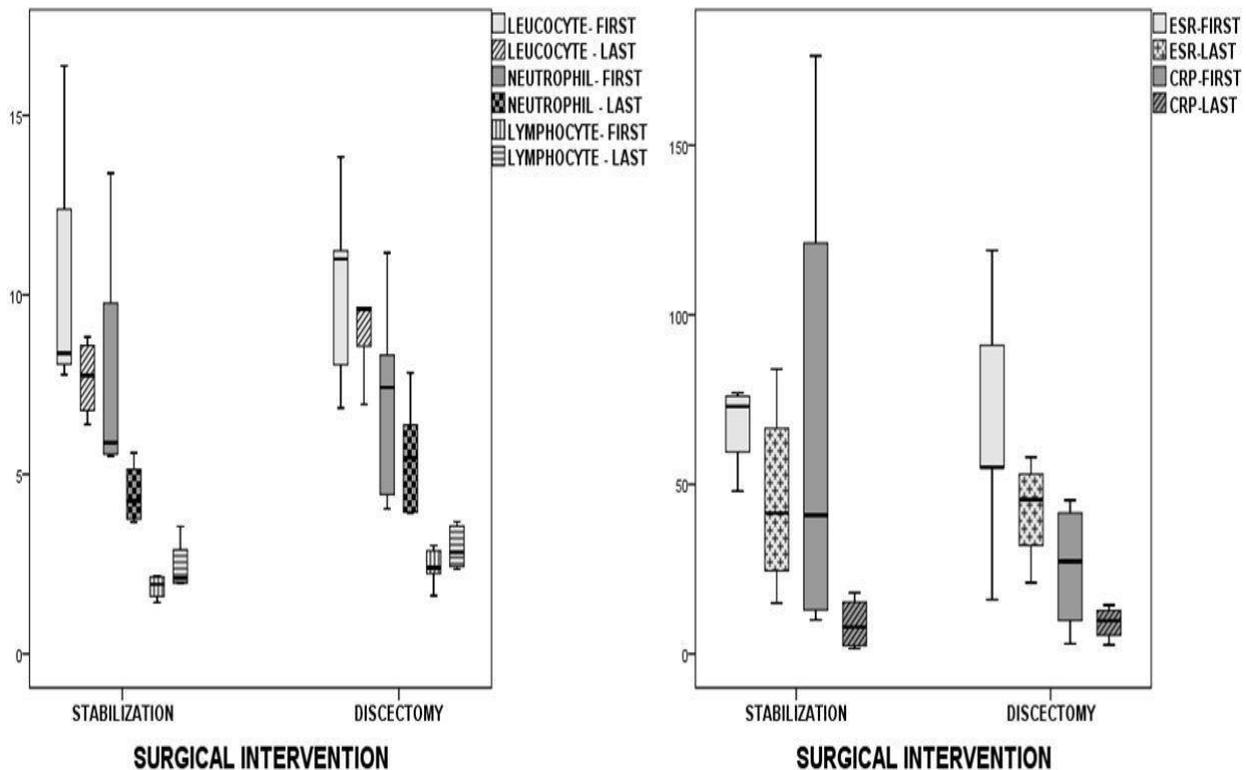


Figure 2: Graphics showing the distribution of laboratory findings of patients obtained during admission and discharge (ESR: erythrocyte sedimentation rate, CRP: C-reactive protein)

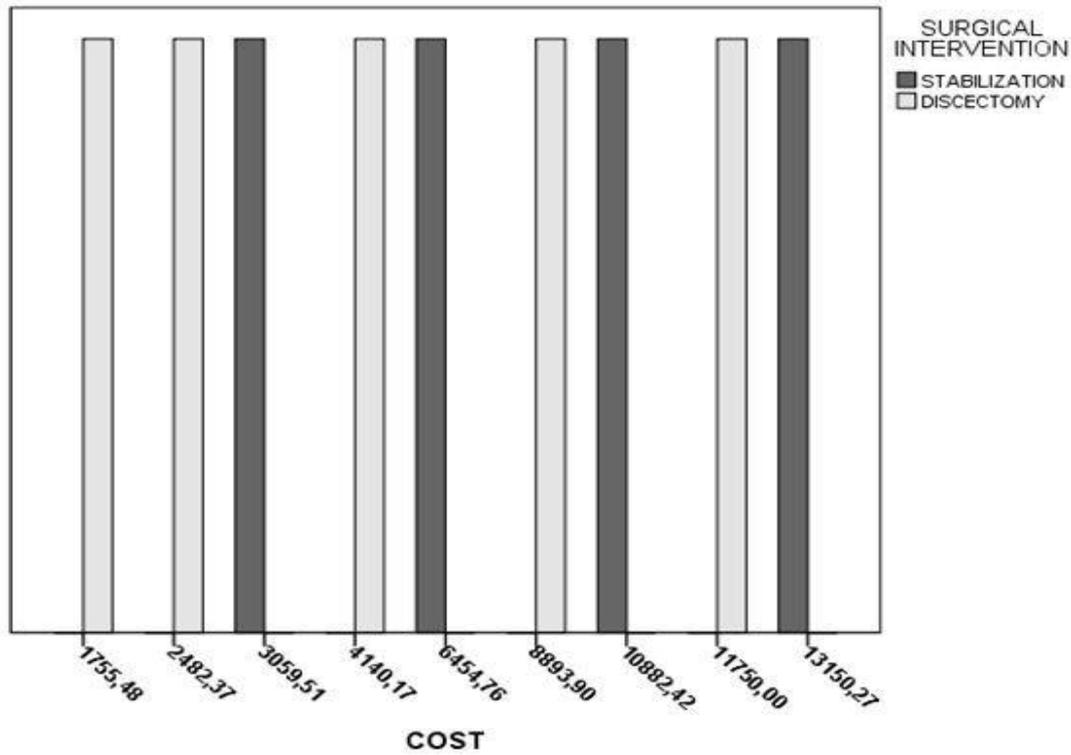


Figure 3: Bar graph showing distribution of cost results according to the surgical intervention types.

Table 1: Descriptive analysis of demographic characteristics and laboratory findings of all patients

Variable	Minimum	Maximum	Mean / Median	SD
Age	30	78	60	14.92
Gender	1	2	1	0.44
Tissue biopsy	0	1	1	0.44
Tissue culture	0	1	0	0.53
Duration of hospital stay (day)	10	75	22	24.71
Morbidity	0	1	0	0.50
Esr-first	16.00	119.00	67*	28.96
Crp- first	3.00	246.70	68.64*	85.18
Leucocyte- first	6.85	16.38	10.209*	3.19
Neutrophil- first	4.04	13.39	7.339*	3.15
Lymphocyte- first	1.43	3.02	2.181*	.54
Esr-last	15.00	122.00	53*	33.01
Crp- last	1.57	34.80	11.87*	10.30
Leucocyte - last	6.39	11.87	8.597*	1.68
Neutrophil - last	3.67	7.83	5.038*	1.41
Lymphocyte - last	1.97	3.68	2.734*	.69
Cost	1755.48	13150.27	6352.36*	4226.58

(*) Mean value (ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, SD: standard deviation)

Table 2: Demographic characteristics and laboratory findings of patients with spinal instrumentation or lumbar discectomy

Surgical Intervention Variable	Stabilization		Discectomy		t / Z	p
	Mean/Median	SD	Mean/Median	SD		
Age	63.50	20.68	60	11.08	-0.490	0.624
Gender	1	0.50	1	0.45	-0.169	0.866
Tissue biopsy	1	0.00	1	0.55	-1.352	0.176
Tissue culture	0.50	0.58	0	0.58	-0.283	0.777
Duration of hospital stay (day)	23	27.38	16	25.50	-0.861	0.389
Morbidity	0	0.50	0	0.55	-0.447	0.655
Esr-first	72	31.70	52	4.95	0.026*	0.980
Crp- first	83.60	92.18	16.25	0.54	-0.047*	0.964
Leucocyte- first	10.953	3.24	7.605	1.07	0.015*	0.989
Neutrophil- first	7.980	3.27	5.095	1.49	0.261*	0.801
Lymphocyte- first	2.210	0.59	2.080	0.45	-1.749*	0.124
Esr-last	59.429	33.87	29	19.80	-0.557*	0.595
Crp- last	13.19	11.27	7.240	5.71	-0.767*	0.468
Leucocyte - last	9.037	1.66	7.055	0.15	-1.594*	0.155
Neutrophil - last	5.244	1.55	4.315	0.52	-1.144*	0.290
Lymphocyte - last	2.887	0.71	2.200	0.33	-1.162*	0.283
Cost	7101.44	4484.18	4105.1200	3322.89	1.470*	0.192

(*) t value (Mann Whitney U test and Independent Samples t test, p <0.05).

(ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, SD: standard deviation, t: t value, Z: Z score)

Table 3: Erythrocyte sedimentation rates, neutrophil and lymphocyte counts of the patients before surgery and during discharge.

Variable	t*	p
Esr-first /esr-last	2.491	0.037
Neutrophil-first / neutrophil-last	2.359	0.046
Lymphocyte-first / lymphocte-last	3.289	0.011

(ESR: erythrocyte sedimentation rate, t: t value)

*Paired Samples t test, p <0.05

DISCUSSION

Spondylodiscitis may develop in 58% of patients in the lumbar region, 30% in the thoracic region and 11% in the cervical region. Additionally, 5% -18 patients have been shown to have multiple spine involvement. It has been reported that males have an incidence of 1.5-3 times higher than women after the age of 20 years. The age distribution usually shows two different distributions in childhood and over sixty years of age (1). The mean age of the patients included in the current study was 58 ± 14.92 years and it was consistent with the literature, but the majority of the patients were female.

In patients with spondylodiscitis, the symptoms are usually not specific and the disease often shows an insidious onset. Common symptoms are persistent back pain (90%), fever (60-70%) and neurological deficits (10-50%). A pathognomonic laboratory marker has not been defined for this disease. However, detecting abnormalities in serum CRP level, ESR value and number of blood defense cells should increase the suspicion for this disease in general practitioners. Magnetic resonance imaging (MRI) with gadolinium demonstrates the highest diagnostic sensitivity in the diagnosis of this disease and provides a basic view of biomechanical stability and neurological structures. Computerized tomography can be useful when there are doubts about osteonecrosis prolongation or biomechanical stability (3).

In this study, it was determined that there was no difference in laboratory findings between the patients in terms of the surgical intervention type. Furthermore, all measured laboratory parameters except the CRP levels and ESR values were found to be within the normal limits. On the other hand, it was found that the values of the variables examined after the treatment showed a statistically significant decrease except for the leukocyte count and CRP levels. With these findings, it was thought that monitoring CRP and ESR values would not be useful in evaluating the patient's post-treatment status. To conclude, it is considered that any laboratory parameter investigated in this study cannot be used as a diagnostic or prognostic biomarker in the lumbar spondylodiscitis that occurs after the surgical intervention.

Recommended treatment for spondylodiscitis consists of 6-week intravenous antibiotics followed by at least 6 weeks of oral antibiotic therapy. (4). These patients are recommended to take a long-term rest and use spinal corsets to prevent spinal deformities which may occur in the chronic period. It has been reported that the treatment outcome is better when the surgical treatment is simple and less invasive (1,5-7). *S. aureus*, *M.*

tuberculosis, *Brucella spp.*, gram-negative and anaerobic bacteria are the most common pathogens in pyogenic spondylodiscitis and spinal infections (8). In present study, an etiological pathogen was detected in four of the patients, but no pathogen was detected in the rest. The average length of hospital stay was 22 days and the average economic cost during the hospitalization was approximately 6,350 Turkish Liras (TL) (maximum cost 13,150 TL). When all patients were examined, the total cost was around 60,000 TL during the hospitalization. Although this cost could be considered low, it was thought that this cost might be very high when evaluated nationwide. In addition, it was found at the end of the correlation analysis of all parameters that the duration of hospital stays and performing biopsy to infected tissues could increase the economic cost. Moreover, results of microbial cultures were predicted to increase the duration of hospital stay and increase the economic cost indirectly. However, when the literature was examined, it was seen that there was no study on this subject and this study could be a preliminary study.

Limitations: There were some limitations in this study. *Firstly*, the number of patients of this study was small. Furthermore, its participants consisted of only the patients with lumbar spondylodiscitis due to surgical intervention. Therefore, it could not reflect the general patient population. However, the unexpected findings of this preliminary study showed that this issue should be investigated with large samples and more detailed methods. *Secondly*, this study did not cover long-term follow-up of patients. Therefore, the long-term results of the treatment regimens could not be expressed at the end of this study.

It was concluded that any routine laboratory parameter investigated in this study could not be valid biomarker for diagnosing and follow-up of the spondylodiscitis that emerged after surgical intervention. On the other hand, it was concluded that the diagnosis and treatment of this disease, which has an increasing prevalence,

may have a high economic cost for patients and countries.

Conflict of interest and financial disclosure statements:

The authors declare that they have no conflict of interest. They also declare that they have not engaged in any financial relationship with any company whose product might be affected by the research described or with any company that makes or markets a competing product.

Ethics Committee Approval: Kırıkkale University Ethics Committee of Non-interventional Research, date: 16.01.2019; number: 2019.12.13.

REFERENCES

1. Czigléczi G, Benkő Z, Misik F, Banczerowski P. Incidence, morbidity, and surgical outcomes of complex spinal inflammatory syndromes in adults. *World Neurosurg.* 2017;107:63-8. Doi:10.1016/j.wneu.2017.07.096.
2. Pola E, Taccari F, Autore G, Giovannenze F, Pambianco V, Cauda R et al. Multidisciplinary management of pyogenic spondylodiscitis: epidemiological and clinical features, prognostic factors and long-term outcomes in 207 patients. *Eur Spine J.* 2018;27(Suppl 2):229-36.
3. Wang X, Tao H, Zhu Y, Lu X, Hu X. Management of postoperative spondylodiscitis with and without internal fixation. *Turk Neurosurg.* 2015;25(4):513-8.
4. Bernard L, Dinh A, Ghout I, Simo D, Zeller V, Issartel B et al and Duration of Treatment for Spondylodiscitis (DTS) study group. Antibiotic treatment for 6 weeks versus 12 weeks in patients with pyogenic vertebral osteomyelitis: an open-label, non-inferiority, randomised, controlled trial. *Lancet.* 2015;385(9971):875-82.
5. Noh SH, Zhang HY, Lim HS, Song HJ, Yang KH. Decompression alone versus fusion for pyogenic spondylodiscitis. *Spine J.* 2017;17(8):1120-6.
6. Tschugg A, Lener S, Hartmann S, Rietzler A, Neururer S, Thome C. Primary acquired spondylodiscitis shows a more severe course than spondylodiscitis following spine surgery: a single-center retrospective study of 159 cases. *Neurosurg Rev.* 2018;41(1):141-7.
7. Tschugg A, Hartmann S, Lener S, Rietzler A, Sabrina N, Thome C. Minimally invasive spine surgery in lumbar spondylodiscitis: a retrospective single-center analysis of 67 cases. *Eur Spine J.* 2017;26(12):3141-6.
8. Sheikh AF, Khosravi AD, Goodarzi H, Nashibi R, Teimouri A, Motamedfar A et al. Pathogen identification in suspected cases of pyogenic spondylodiscitis. *Front Cell Infect Microbiol.* 2017;7:60. Doi:10.3389/fcimb.2017.00060.