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PYOGENIC SPONDYLODISCITIS: RISK FACTORS FOR THERAPEUTIC FAILURE AND RECURRENCE

ESPONDILODISCITE PIOGÊNICA: FATORES DE RISCO PARA FALHA TERAPÊUTICA E RECORRÊNCIA

ESPONDILODISCITIS PIÓGENA: FACTORES DE RIESGO PARA FRACASO TERAPÉUTICO Y RECURRENCIA

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ABSTRACT

Objective: Evaluate the prognostic factors associated with therapeutic failure and recurrence in pyogenic spondylodiscitis (PS). Methods: A historical cohort study was conducted in a reference Brazilian hospital for locomotor system and neurodevelopmental diseases. All patients with PS treated between January 1999 and December 2018 and followed for at least one year were included. PS was defined based on clinical, laboratory, and radiological criteria. Microbiological data and clinical outcomes at the end of follow-up were also collected and analyzed. Results: Fifty patients (mean age 50.94 ± 15.84 years, men 76.00%) were included. After twelve months of follow-up, therapeutic failure was observed in 24.00% (n = 12) and recurrence in 18.00% (n = 09) patients. Among those who were cured, residual symptoms were found in 50.00% (19/38). No deaths were observed. After multivariate analysis, therapeutic failure was associated with the prescription of antibiotic therapy before culture results (p = 0.0153), spinal cord compression (p = 0.0053), and sensory deficits (p = 0.0341). Furthermore, recurrence was associated with previous nonspinal surgeries (p = 0.0350) and spinal cord compression (p = 0.0447). Conclusion: PS causes significant morbidity. The prognosis depends mainly on the clinical presentation at admission, especially when associated with spinal cord compression, which reinforces the importance of early diagnosis. ***Level of Evidence II; Prognostic Studies.***

Keywords: Discitis; Prognosis; Treatment Outcome.

RESUMO

Objetivo: Avaliar os fatores prognósticos associados à falha terapêutica e à recorrência na espondilodiscite piogênica (EP). Métodos: Um estudo de coorte histórica foi conduzido em um hospital brasileiro de referência nas doenças do sistema locomotor e do neurodesenvolvimento. Todos os pacientes com EP tratados entre janeiro de 1999 e dezembro de 2018 e acompanhados por pelo menos um ano foram incluídos. A EP foi definida com base em critérios clínicos, laboratoriais e radiológicos. Dados microbiológicos e desfechos clínicos ao final do tempo de seguimento também foram coletados e analisados. Resultados: Cinquenta pacientes (idade média 50,94 ± 15,84 anos, homem 76,00%) foram incluídos. Depois de doze meses de seguimento, a falha terapêutica foi observada em 24,00% (n = 12) e a recorrência em 18,00% (n = 09) dos pacientes. Entre os que curaram, sintomas residuais foram constatados em 50,00% (19/38). Nenhuma morte foi observada. Após análise multivariada, a falha terapêutica foi associada à prescrição de antibioticoterapia antes dos resultados de cultura (p = 0,0153), compressão medular (p = 0,0053) e déficits sensoriais (p = 0,0341). Além disso, a recorrência esteve associada a cirurgias não espinhais prévias (p = 0,0350) e à compressão medular (p = 0,0447). Conclusão: A EP causa morbidade significativa. O prognóstico depende principalmente da apresentação clínica na admissão, especialmente da existência de compressão medular, o que reforça a importância do diagnóstico precoce. ***Nível de Evidência II; Estudos de Prognóstico.***

Descritores: *Discite; Prognóstico; Resultado do Tratamento.*

RESUMEN

Objetivo: *Evaluar los factores pronósticos asociados con el fracaso terapéutico y la recurrencia en la espondilodiscitis piógena (EP).* ***Métodos:*** *Se realizó un estudio de cohorte histórica en un hospital de referencia brasileño para enfermedades del aparato locomotor y del neurodesarrollo. Se incluyeron todos los pacientes con EP tratados entre enero de 1999 y diciembre de 2018 y seguidos durante al menos un año. La EP se definió en base a criterios clínicos, de laboratorio y radiológicos. También se recopilaron y analizaron los datos microbiológicos y los resultados clínicos al final del tiempo de seguimiento.* ***Resultados:*** *Se incluyeron 50 pacientes (edad media 50,94 ± 15,84 años, sexo masculino 76,00%). A los doce meses de seguimiento, se observó fracaso terapéutico en el 24,00% (n=12) y recurrencia en el 18,00% (n=09) de los pacientes. Entre los que se curaron, se encontraron síntomas residuales en el 50,00% (19/38). No se observaron muertes. Tras el análisis multivariante, el fracaso terapéutico se asoció a la prescripción de antibioticoterapia antes de los resultados del cultivo (p = 0,0153), compresión medular (p = 0,0053) y déficits sensitivos (p = 0,0341). Además, la recurrencia se asoció con cirugías previas no espinales (p = 0,0350) y compresión medular (p = 0,0447).* ***Conclusión:*** *La EP causa una morbilidad significativa. El pronóstico depende principalmente de la presentación clínica al ingreso, especialmente de la existencia de compresión medular, lo que refuerza la importancia del diagnóstico precoz.* ***Nivel de Evidencia II; Estudios de Pronóstico.***

Descriptores: *Discitis; Pronóstico; Resultado del Tratamiento.*

Study conducted by the Rede Sarah de Hospitais de Reabilitação, Brasília, Distrito Federal, Brazil.
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INTRODUCTION

Pyogenic spondylodiscitis (PS) is a potentially fatal infectious disease with a high risk of chronic pain and permanent neurological deficits.[1-4] Although rare, its incidence has increased in recent decades, probably due to population aging, higher comorbidity burden, advances in diagnostic tools, and the growth of spine invasive procedures.[1-4]

Nevertheless, the optimum management of this infection remains controversial, and serious clinical outcomes continue to be observed, mainly in patients with multiple comorbidities, advanced age, or disseminated infectious processes.[2,5-8] Besides, there is a critical lack of information in the literature about the long-term clinical outcomes and the prognostic factors of this disease. There is also a significant gap in national data.

Therefore, the present study proposes to analyze the prognostic factors associated with therapeutic failure and recurrence in a cohort of patients with PS treated, between 1999 and 2018, at a quaternary reference center in Brasília, Federal District, Brazil.

METHODS

Study design and population

A historical cohort study was carried out involving patients with PS treated between January 1999 and December 2018 at the Sarah Brasília Hospital, a quaternary public hospital with 240 beds specialized in neurorehabilitation and treatment of locomotor system diseases.

Initially, all patients with infectious spondylodiscitis attending in the period of the study were selected from the hospital files (ICD-10: M46.2 / M 46.3 / M 46.4 / M 46.5 / M 49.0 / M 49.1 / M 49.2 / M 49.3). Then, the medical records were analyzed, and those with eligibility criteria (below) were enrolled in the study and reviewed for social and demographic information and clinical aspects.

Inclusion and Exclusion Criteria

All patients who presented with an initial episode of PS were included by the following criteria:

Clinical and Laboratory Criteria – two or more of the following: back pain, vertebral tenderness, axillary temperature $\geq$ 37.5°C, serum C-reactive protein (CRP) $>$ 0.5 mg/dl or erythrocyte sedimentation rate (ESR) $>$ 15 mm in the first hour, recent neurological symptoms (weakness or sensory deficits in the limbs or bladder or bowel dysfunction).

Radiological Criteria – the presence of destructive lesions in two or more adjacent vertebrae and in the intervertebral disc on nuclear magnetic resonance (NMR) or computed tomography (CT), suggesting spondylodiscitis as reported by a specialist radiologist.

Therapeutic Criteria – antibiotic prescriptions by the attending physician. [9]

Exclusion criteria were any of the: patients referred exclusively for a rehabilitation program, missing data in basic characteristics, follow-up period less than 12 months, confirmation of alternative diagnosis, spondylodiscitis caused by other infectious agents, treatment or follow-up notes not available, and incomplete antibiotic course of treatment.

Definitions

Recurrence was defined as when the patient experienced recurrent signs and symptoms (back pain, fever, new neurologic manifestations, leukocytosis or an increase in CRP or ESR values) between the end of initial treatment and 12 months of clinical follow-up, requiring a new course of antibiotic therapy or unplanned surgery.[10]

Therapeutic failure at one-year was defined as the persistence of signs and symptoms with high serum CRP ($>$ 0.5 mg/dl) in the first medical evaluation after 12 months of initial treatment ending.[11] In this evaluation, the persistence of signs and symptoms with serum CRP $\leq$ 0.5 mg/dl was considered cured but with sequelae.

PS was classified by: direct inoculation when associated with an invasive procedure or trauma of the spine before clinical manifestations; contiguous route when the infection spread from an adjacent infected tissue; hematogenous route in the absence of an invasive procedure or trauma of the spine or contiguous focus of infection.

The causative organism was determined by isolating the bacteria in blood or vertebral biopsy (bone or intervertebral disc) cultures. Regarding skin bacteria, such as coagulase-negative *Staphylococcus spp*. or *Cutibacterium acnes*, a minimum of two bacterial cultures yielding the same pathogen was required.

Statistical analysis

All data were stored in Microsoft Excel (Microsoft Corporation, Washington, USA), and statistical analyses were conducted using the statistical software SAS 9.4 (SAS Institute, North Carolina, USA). Initially, an exploratory analysis was carried out to obtain the patient's baseline characteristics. Then, categorical variables were compared using Pearson's chi-square or Fisher's exact tests. Finally, continuous variables were compared using Student's *t*-test or Mann- Whitney *U* tests.

The Poisson regression model with robust variance estimation and the Cox regression model was applied to assess the risk factors associated with therapeutic failure and recurrence, respectively. The analysis took place in two stages: bivariate and multivariate. Poisson or Cox simple regression models were adjusted for each independent variable. Those whose *p*-value was less than 0.20 were included in a stepwise multivariate model (backward elimination). At each step, the variable with the least influence was excluded, and the analysis was repeated until all remaining variables significantly influenced the outcome. The risk rates and their 95% confidence intervals were calculated. Differences were significant when the *p*-value was below 0.05.

Ethics

The study was submitted to and approved by the Human Research Ethics Committee of the SARAH Network of Rehabilitation Hospitals under protocol CAAE: 19249219.0.0000.0022 and follows the Declaration of Helsinki. The participants signed the Informed Consent Form, except those who died or were not located, in agreement with the Committee as mentioned above.

RESULTS

From January 1999 until December 2018, 288 hospitalizations with compatible codes (ICD-10) of spondylodiscitis were identified. Of those, 50 patients were included (Figure 1). The baseline characteristics of the study population are shown in Table 1.

At admission, 17 (34.00%) patients had anemia (Hemoglobin $<$ 12 g/dl), and only four (8.00%) had leukocytosis (Leukocytes $>$ 12,000 cells/mm^3). High CRP ($>$ 0.5 mg/dl) and ESR ($>$ 15 mm in the first hour) values were each observed in 88.00% (n = 44).

The lumbar spine was the most affected level in the radiological evaluation (n=21; 42,00%). Local infectious complications were detected in 26 (52.00%) patients, with the predominance of paravertebral phlegmon (n = 09; 18.00%), followed by a paravertebral abscess (n=08; 16.00%) and spinal cord compression (n = 08; 16.00%). (Table 2)

Regarding microbiological aspects, the causative agent was identified in 39 (78.00%) patients. The rate of positive blood cultures was 23.53% (04/17), and positive spine cultures were 78.72% (37/47). The most common microorganism was *Staphylococcus aureus* (19/39; 48.72%), followed by *Staphylococcus* spp. coagulase-negative (05/39; 12.82%), *Escherichia coli* (04/39; 10.25%), *Enterococcus faecalis* (03/39; 7.69%), *Pseudomonas aeruginosa* (03/39; 7.69%), and *Streptococcus* spp. (02/39; 5.13%). Only one (2.56%) case was registered for each of the following bacteria: *Salmonella* spp., *Serratia marcescens,* and *Sphingomonas paucimobilis*.

In this study, 33 (66.00%) patients were treated exclusively with antibiotics. Surgery was performed in 17 (34.00%) patients, mostly by posterior approach (12/17; 70.59%). After hospital discharge, a mean of 4.94 $\pm$ 1.55 consultations per patient was carried out until the end of the follow-up (13.56 $\pm$ 1.52 months). The aspects related to the treatment and the outcomes are specified in Table 3.

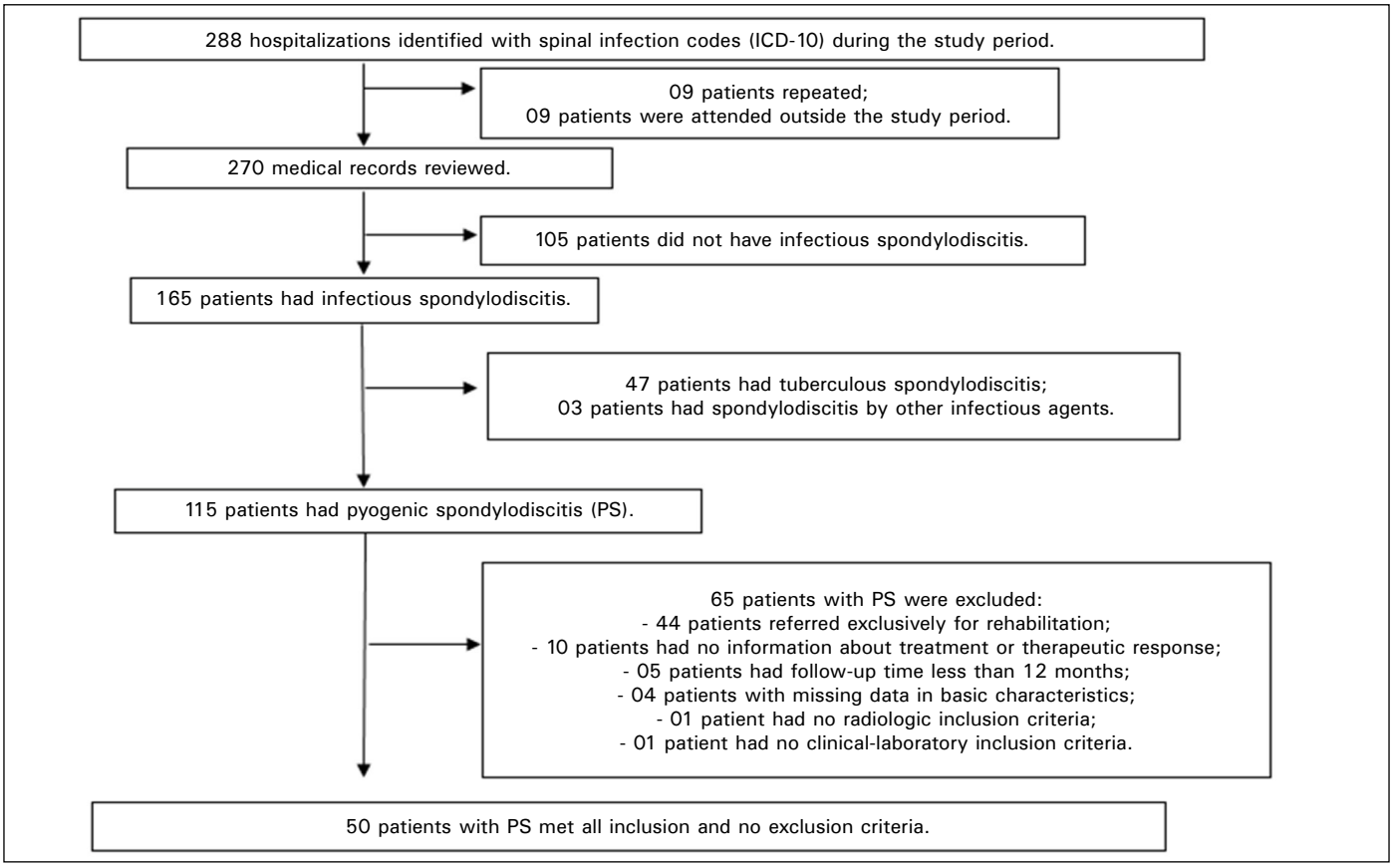

Figure 1. Flowchart of the study selection process.

Table 1. Baseline characteristics of 50 patients with pyogenic spondylodiscitis.

Characteristics	Values *
Age (years)[1]	50.94 ± 15.84
Sex	
Male	38 (76.00)
Female	12 (24.00)
Diagnostic delay (months)	6.32 ± 5.27
Clinical manifestations	
Back pain	48 (96.00)
Fever	16 (32.00)
Weight loss	20 (40.00)
Radicular pain	18 (36.00)
Neurological deficit (motor or sensory)	11 (22.00)
Spinal deformities	7 (14.00)
Risk factors[2]	
Diabetes mellitus	6 (12.00)
Hypertension	21 (42.00)
Smoking	7 (14.00)
Alcoholism	8 (16.00)
Disc herniation	13 (26.00)
Spinal osteoarthritis	21 (42.00)
Rheumatological disease	2 (4.00)
Use of immunosuppressive agents	6 (12.00)
Distant bacterial infections (last year)	24 (48.00)
Hospitalization in the last three years	34 (68.00)
Invasive spinal procedures (last three years)	24 (48.00)
Surgery in the last three years (nonspinal)	8 (16.00)
Pathophysiological classification[3]	
Hematogenous spondylodiscitis	29 (58.00)
Spondylodiscitis by direct inoculation	21 (42.00)

* Values expressed as mean ± standard deviation or frequency (%). 1. Only two patients were under 18. 2. Malignancy, intravenous drug abuse, end-stage renal disease, congestive heart failure, hepatitis C virus, and previous tuberculosis were reported only once each. 3. There was no record of spondylodiscitis by a contiguous focus of infection.

Table 2. Radiological findings in the study population.

Characteristics	Values *
Affected level	
Cervical	2 (4.00)
Thoracic	9 (18.00)
Thoracolumbar	4 (8.00)
Lumbar	21 (42.00)
Lumbosacral	14 (28.00)
Number of vertebrae affected	
Two vertebrae	40 (80.00)
More than two vertebrae	10 (20.00)
Complications	
Psoas abscess	1 (2.00)
Paravertebral abscess	8 (16.00)
Epidural abscess	5 (10.00)
Paravertebral phlegmon	9 (18.00)
Epidural phlegmon	4 (8.00)
Spinal cord compression	8 (16.00)
Cauda equina compression	2 (4.00)

* Values expressed as frequency (%).

Most patients who experienced recurrence (n=09; 18.00%) did not meet the cure criteria (08/09; 88.89%). Recurrence occurred particularly in the first six months (06/09; 66.67%; mean = 178.66 ± 95.41 days), and microbiological confirmation was obtained in seven (77.78%) patients, all caused by the same original bacteria.

Regarding therapeutic failure, on multivariate analysis, antibiotic therapy before culture results, spinal cord compression, and sensory deficits were independently associated with therapeutic failure (Table 4). Additionally, the predictors of recurrence on multivariate analysis were previous nonspinal surgeries and spinal cord compression. (Table 5)

It was interesting to note that, of eight patients with previous nonspinal surgeries, four (50.00%) experienced a recurrence of spondylodiscitis. The reasons for surgery in these four cases were

related to the treatment of other chronic infections (osteomyelitis: 03; lung abscess: 01). Except in one case (without primary culture), a concordance of the etiological agent between the two infection foci was observed.

Notably, no significant difference in PS recurrence or therapeutic failure was found according to the etiological agent, affected spine segment, or treatment modalities – surgical *versus* nonsurgical. (Table 6)

Table 3. Treatment and outcomes in the study population.

Characteristics	Values *
Treatment modalities	
Nonsurgical	33 (66.00)
Surgical	17 (34.00)
Use of orthoses	38 (76.00)
Type of antibiotic therapy	
Exclusively empiric therapy	11 (22.00)
Exclusively definitive therapy based on microbiology results	28 (56.00)
Empiric followed by definitive therapy based on microbiology results	11 (22.00)
Antimicrobial treatment time (weeks)	
Intravenous	5.07 ± 2.49
Oral	4.44 ± 2.89
Total	9.33 ± 3.08
Hospital length of stay (days)	55.88 ± 31.22
Outcomes - during one-year follow-up	
Deaths	0 (0.00)
Recurrence	9 (18.00)
Outcomes – in the first medical evaluation after a one-year follow-up	
Cured without sequelae	19 (38.00)
Cured with sequelae (neurological impairment or chronic pain)	19 (38.00)
Therapeutic failure	12 (24.00)

* Values expressed as mean ± standard deviation or frequency (%).

DISCUSSION

PS is recognized as a challenging disease with potentially devastating clinical consequences.[2,4,9,11-13] In keeping with the literature, most of the patients were middle-aged or elderly men.[1-11] Other findings also described in previous studies included back pain in nearly all cases,[4,10,14] fever in about one-third of patients, [10] an increase in systemic inflammatory markers as a common feature,[5,10] and the predominance of *Staphylococcus aureus* among the causative agents.[4,11,12,14-17]

Despite no deaths, our data showed that PS is associated with a high risk of recurrence or therapeutic failure. Furthermore, antibiotic therapy required before culture results, spinal cord compression, and sensory deficits were independently associated with therapeutic failure. In contrast, previous nonspinal surgeries and spinal cord compression were independently associated with recurrence.

Following the broad literature, our study also reported a high prevalence of residual symptoms among those recovering from infection.[5,13,18] This finding highlights that PS continues to lead to neurological sequelae, chronic pain, and long-term disability. However, its mortality has dropped over the last decades due to the wide use of antibiotics.[5,13,18]

Although its growing importance, few studies report prognostic factors associated with therapeutic failure or recurrence. Besides, the outcomes definitions related to PS are not well standardized, which makes it difficult to compare results among different studies. According to Berbari et al.,[5] the most specific measure for these outcomes is microbiologically confirmed persistent or recurrence infection. However, like other studies,[8,10,11] we adopted the definitions based on the clinical status and the systemic inflammatory markers. Despite reflecting clinical practices, these criteria may lead to overestimating these outcomes.

Regarding therapeutic failure, a cohort study conducted by Graeff et al.[19] found a treatment failure rate of 29%, which was slightly higher than our data. The authors also noted that *diabetes mellitus*, current other osteomyelitis, fever, and epidural abscess

Table 4. Univariate and multivariate analyses (final model) of risk factors for therapeutic failure in the study population.

	Risk Relative (RR)		RR Adjusted	
Variables	**RR (95 % CI)**	**p-value**	**RR (95% IC)**	**p-value**
Diagnostic delay > 6 months	1.93 (0.71 – 5.26)	0.1967	2.23 (0.50 – 9.89)	0.2923
Alcoholism	2.62 (1.03 – 6.67)	0.0424	1.99 (0.54 – 7.34)	0.3037
Surgery in the last three years (nonspinal)	2.62 (1.03 – 6.67)	0.0424	1.30 (0.22 – 7.73)	0.7755
Spondylodiscitis (pathophysiological classification)		0.0605		0.2328
Direct inoculation	2.76 (0.96 – 7.98)	0.0605	2.29 (0.59 – 8.91)	0.2328
Hematogenous	1	-	1	-
Spinal cord compression (imaging evaluation)	3.75 (1.58 – 8.89)	0.0027	5.27 (1.64 – 16.95)	0.0053
More than two vertebrae affected	2.86 (1.14 – 7.13)	0.0245	2.14 (0.46 – 9.98)	0.3303
Type of antibiotic therapy		0.1343		0.0260
Exclusively empiric therapy	0.42 (0.06 – 3.13)	0.4005	1.05 (0.11 – 9.80)	0.9688
Exclusively definitive therapy based on microbiology results	1	-	1	-
Empiric followed by definitive therapy based on microbiology results	2.12 (0.81 – 5.54)	0.1248	3.82 (1.29 – 11.27)	0.0153
Sensory deficit at admission	2.27 (0.86 – 5.88)	0.0925	4.76 (1.12 – 20.17)	0.0341
Total antimicrobial treatment time > eight weeks	2.35 (0.81 – 6.80)	0.1158	1.90 (0.43 – 8.37)	0.3963
Pyogenic spondylodiscitis caused by multidrug-resistant bacteria[1]	4.00 (1.63 – 9.78)	0.0024	0.97 (0.23 – 4.04)	0.9666

1. Methicillin-resistant Staphylococcus aureus (n= 06), multidrug-resistant Pseudomonas aeruginosa (n= 02), and extended-spectrum β-lactamase producing Gram-negative bacteria (n= 02).

Table 5. Univariate and multivariate analyses (final model) of risk factors for recurrence in the study population.

	Hazard Ratio (HR)		HR Adjusted	
Variables	**HR (95 % IC)**	**p-value**	**HR (95 % IC)**	**p-value**
Age ≥ 60 years old	5.44 (0.67 – 43.86)	0.1119	3.55 (0.27 – 46.62)	0.3347
Hypertension	3.40 (0.75 – 15.38)	0.1120	2.28 (0.39 – 13.44)	0.3607
Nonspinal surgeries in the last three years	9.35 (1.71 – 51.11)	0.0099	5.74 (1.00 – 34.37)	0.0350
Erythrocyte sedimentation rate > 15 mm in the first hour at admission	4.45 (0.47 – 42.28)	0.1934	3.93 (0.21 – 72.27)	0.3573
Spinal cord compression (imaging evaluation)	5.94 (1.56 – 22.57)	0.0089	3.83 (1.00 – 15.97)	0.0447
Pyogenic spondylodiscitis caused by multidrug-resistant bacteria[1]	2.67 (0.66 – 10.82)	0.1693	0.38 (0.03 – 4.32)	0.4346

1. Methicillin-resistant *Staphylococcus aureus* (n= 06), multidrug-resistant *Pseudomonas aeruginosa* (n= 02), and extended-spectrum β-lactamase-producing Gram-negative bacteria (n= 02).

Table 6. Therapeutic failure and recurrence according to the study population's etiological agent, affected spine segment, and treatment modalities.

	Therapeutic failure			Recurrence		
Variables*	**Yes**	**No**	**p-value ****	**Yes**	**No**	**p-value****
Etiological Agent			0.2088			0.2141
Staphylococcus aureus	5 (26.32)	14 (73.68)		6 (31.58)	13 (68.42)	
Other Gram-positive	2 (20.00)	8 (80.00)		1 (10.00)	9 (90.00)	
Gram-negative	4 (40.00)	6 (60.00)		2 (20.00)	8 (80.00)	
Negative culture	0 (0.00)	9 (100.00)		0 (0.00)	9 (100.00)	
No culture collected	1 (50.00)	1 (50.00)		0 (0.00)	2 (100.00)	
Spine segments			0.305			0.406
Cervical	1 (50.00)	1 (50.00)		1 (50.00)	1 (50.00)	
Thoracic	3 (33.33)	6 (66.67)		2 (22.22)	7 (77.78)	
Thoracolumbar	2 (50.00)	2 (50.00)		1(25.00)	3 (75.00)	
Lumbar	5 (23.81)	16 (76.19)		5 (23.81)	16 (76.19)	
Lumbosacral	1 (7.14)	13 (92.86)		0 (0.00)	14 (100.00)	
Treatment modalities			0.294			0.465
Nonsurgical	6 (18.18)	27 (81.82)		5 (15.15)	28 (84.85)	
Surgical	6 (35.30)	11 (64.70)		4 (23.53)	13 (76.47)	

* Values expressed as frequency (%). ** p-value calculated using Pearson's chi-square / Fisher's exact tests.

were independently associated with treatment failure.[19] On the other hand, in 2015, a randomized controlled trial published by Bernard et al.[11] revealed a 9.1% treatment failure rate. It showed that patients aged 75 years or older and those with *Staphylococcus aureus* infection were at higher risk of therapeutic failure. Other variables associated with therapeutic failure reported by other authors include higher CRP levels, history of previous spinal surgery, severe sepsis, Methicillin-resistant *Staphylococcus aureus* (MRSA) or *Escherichia coli* infections, longer duration of symptoms before the diagnosis, intravenous drug use, and recurrent bloodstream infection.[5,12,18,20,21]

Our study identified three other factors associated with therapeutic failure: spinal cord compression, sensory deficit, and antibiotic therapy required before culture results. The literature highlights the role of neurologic deficits and spinal cord compression as emergency medical conditions associated with a higher rate of disease complications, such as pressure ulcers, urinary tract infections, circulatory dysregulation, and poor functional outcomes.[5,14,17,22] We hypothesized that these factors might also decrease the chances of eradicating the infection by the possible extensive area of necrosis associated. Alternatively, it may be a marker for an advanced infectious process or increased organism virulence.

Moreover, our data showed that patients who required antibiotic therapy before culture results had a higher risk of therapeutic failure. In managing PS, it is widely recognized that, except in life-threatening conditions (hemodynamic instability, sepsis, severe neurologic symptoms), antimicrobial therapy should be initiated only after the microbiologic diagnosis.[5,23-25] Thus, this association may reflect a more severe clinical condition and supports the recommendation to not use empiric antimicrobial treatment for non-critical PS patients before culture results.[5]

In this research, the recurrence rate was 18.00%, which has been reported up to 32.00% in other studies.[10,17,26] As observed in therapeutic failure, spinal cord compression was also a risk factor for recurrence in our cohort. The aforementioned reasons for higher therapeutic failure rate in patients with spinal cord compression may also explain the higher incidence of recurrence in this condition and highlight the relevance of spinal cord compression as a prognostic factor.

Another relevant finding was the association of previous nonspinal surgeries with recurrence. PS secondary to nonspinal surgical procedures is rare, with few cases published.[27] In a retrospective study, Hasan et al.[27] reported 40 patients with PS following nonspinal surgery. This study's common surgical procedures associated with PS were obstetric and gastrointestinal surgeries. The authors also described excellent clinical outcomes with conservative treatment in all patients at 12 months after treatment.[27]

This contradicts our data and can be explained by the different study populations. In most cases, these surgeries involved patients with other chronic infection conditions, such as osteomyelitis. Graeff et al.[19] reported that patients with PS with an additional osteomyelitis site have at least one extra focus of infection. We hypothesized that the eventual persistence of this focus might contribute to intermittent bacteremia and increases the chance of recurrent spondylodiscitis. Besides, concurrent infections usually occur in elderly patients with more comorbidities, which may explain a higher recurrence rate in this scenario.

Also, in contrast to our results, previous studies reported different risk factors for recurrence. In a historical cohort of 314 patients with hematogenous vertebral osteomyelitis, Park et al.[8] found that MRSA infection, undrained paravertebral/psoas abscesses, and end-stage renal disease were independent risk factors for recurrence. Foreman et al.[28] also identified a higher recurrence rate in patients with high CRP at admission (>10.1 mg/dl). Other risk factors reported in the literature for recurrence included recurrent bloodstream infection, endocarditis, rheumatoid arthritis, epidural abscess, corticosteroid treatment, and cutaneous fistulas.[16,17,29]

Regarding the duration of antibiotic treatment, our data revealed no clinical advantage with a prolonged course of antimicrobial (> eight weeks). This finding is consistent with the study conducted by Bernard et al.[11], which found no inferiority of a short treatment regimen (6 weeks) compared to a long treatment regimen (12 weeks), concerning the proportion of cured at one year. However, the literature points out that patients at high risk of recurrence may benefit from prolonged duration of antibiotic therapy (≥ 8 weeks).[8]

Moreover, in line with Park et al.,[30] our findings showed no relevant differences in clinical outcomes between spondylodiscitis due to Gram-negative bacteria and *Staphylococcus aureus*. Additionally, following previous reports,[3,31] had no significant effect on treatment outcomes between PS with and without organism isolation. Although these results do not contradict the relevance of microbiologic diagnosis, they reveal that antibiotic therapy may eradicate infection without identifying the causative organism.[31]

Despite the efficacy of conservative regimens, some patients indicate surgical intervention. In our study, surgery was done in 34% of all cases, mostly by posterior approach, and the reasons were mainly related to the presence of spinal cord compression or infected implants. Notably, various surgical procedures are described in the literature, all lacking high-quality evidence.[5,16,22]

Our results should be interpreted carefully considering several limitations of this study. The small number of participants may have reduced the power of the results. Furthermore, as with all retrospective studies, incomplete data may have introduced information bias. Besides, unrecognized bias may have been developed by the heterogeneity of the cohort, and the lack of uniformity in the

treatment regimen. An underestimation of mortality may also have occurred because only "likely survivors" are referred to rehabilitation centers. Finally, as a single-center study, microbial patterns and clinical features may not be generalizable to other regions.

CONCLUSION

Our data indicate that, in a Brazilian setting, PS is associated with significant morbidity, including a high risk of therapeutic failure, recurrence, and sequelae. Long-term prognosis depends mainly on the stage of the infection on admission and its neurological repercussions. In particular, the presence of spinal cord compression showed to be a relevant prognostic factor for both therapeutic failure and recurrence. These findings need to be corroborated in large prospective studies.

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