The SPINE JOURNAL

The Spine Journal 000 (2024) 1−10

Clinical Study

Management of severe pyogenic spinal infections: the 2SICK study by the EANS spine section

Andreas Kramer, MD[a,*], Santhosh G. Thavarajasingam, MD[a,c], Jonathan Neuhoff, MD[b], Felipa Lange[a], Hariharan Subbiah Ponniah[c], Sara Lener, MD, PhD, PD[d], Claudius Thomé, MD[d], Felix C. Stengel, MD[e], Gregor Fischer, MD[e], Isabel C. Hostettler, MD, PhD, PD[e], Martin N. Stienen, MD, PD[e], Maxim Jemna[f], Konstantinos Gousias, MD[g], Aleksandra Nedeljkovic, MD[h], Danica Grujicic, MD[h], Zarko Nedeljkovic, MD[h], Jasmina Poluga, MD, PhD[i], Ralph T. Schär[j], Wiktor Urbanski, MD, PD[k], Carla Sousa, MD[l], Carlos Daniel Oliveira Casimiro, MD[l], Helena Harmer, MD[m], Barbara Ladisich, MD, PhD[m], Matthias Matt, MD[n], Matthias Simon, MD[n], Delin Pai, MD[o], Christian Doenitz, MD[o], Lorenzo Mongardi, MD[p], Giorgio Lofrese, MD, PhD[p], Melanie Buchta, MD[q], Lukas Grassner, MD, PhD, PD[q], Pavel Trávníček, MD[r], Tomáš Hosszú, MD, PhD[r], Maarten Wissels, MD[s], Sven Bamps, MD[s], Waeel Hamouda, MD, PhD[t,u], Flavio Panico, MD[v], Diego Garbossa, MD[v], Marcello Barbato, MD[w], Manlio Barbarisi, MD, PhD[w], Tobias Pantel, MD[x], Jens Gempt, MD[x], Tharaka Sai Kasula[y], Sohum Desai, MD[y], Julius Mautin Vitowanu, MD[z], Bekir Rovčanin, MD[aa], Ibrahim Omerhodzic, MD[aa], Andreas K. Demetriades, MD, MBBChir[bb], Benjamin Davies, MD, MRCS[cc], Ehab Shiban, MD[dd], Florian Ringel, MD[a]

[a] *Department of Neurosurgery, University Medical Center Mainz, Mainz, Germany*
[b] *Center for Spinal Surgery and Neurotraumatology, Berufsgenossenschaftliche Unfallklinik Frankfurt am Main, Germany*
[c] *Imperial Brain & Spine Initiative, Imperial College London, London, United Kingdom*
[d] *Department of Neurosurgery, Medical University Innsbruck, Innsbruck, Austria*
[e] *Department of Neurosurgery and Spine Center of Eastern Switzerland, Cantonal Hospital St. Gallen, St. Gallen, Switzerland*

FDA device/drug status: Not applicable.

Author disclosures: ***AK:*** Nothing to disclose. ***SGT:*** Nothing to disclose. ***JN:*** Nothing to disclose. ***FL:*** Nothing to disclose. ***HSP:*** Nothing to disclose. ***SL:*** Nothing to disclose. ***CT:*** Royalties: DePuySynthes (D); Consulting: Signus Medizintechnik (B), Kuros (B), Zeiss (B), NEOS Surgery (B); Speaking and/or Teaching Arrangements: Intrinsic Therapeutics (B), Signus Medizintechnik (B), Stryker (B), Zeiss (B). ***FC:*** Nothing to disclose. ***GF:*** Nothing to disclose. ***ICH:*** Nothing to disclose. ***MNS:*** Nothing to disclose. ***MJ:*** Nothing to disclose. ***KG:*** Nothing to disclose. ***AN:*** Nothing to disclose. ***DG:*** Nothing to disclose. ***ZN:*** Nothing to disclose. ***JP:*** Nothing to disclose. ***RTS:*** Nothing to disclose. ***WU:*** Nothing to disclose. ***CS:*** Nothing to disclose. ***CDOC:*** Nothing to disclose. ***HH:*** Nothing to disclose. ***BL:*** Nothing to disclose. ***MM:*** Nothing to disclose. ***MS:*** Nothing to disclose. ***DP:*** Nothing to disclose. ***CD:*** Nothing to disclose. ***LM:*** Nothing to disclose. ***GL:*** Nothing to disclose. ***MB:*** Nothing to disclose. ***LG:*** Nothing to disclose. ***PT:*** Nothing to disclose. ***TH:*** Nothing to disclose. ***MW:*** Nothing to disclose. ***SB:*** Nothing to disclose. ***WH:*** Nothing to disclose. ***FP:*** Nothing to disclose. ***DG:*** Nothing to disclose. ***MB:*** Nothing to disclose. ***MB:*** Nothing to disclose. ***TP:*** Nothing to disclose. ***JG:*** Nothing to disclose. ***TSK:*** Nothing to disclose. ***SD:*** Nothing to disclose. ***JMV:*** Nothing to disclose. ***BR:*** Nothing to disclose. ***IO:*** Nothing to disclose. ***AKD:*** Leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: fiduciary role: Board Member, EANSEuropean Association of Neurosurgical Societies (None), Non fiduciary role: Board Member, Global Neuro Foundation (None), Non fiduciary role: Steering Committee Member, AO Spine Knowledge Forum in Degenerative Spine (None). ***BD:*** Nothing to disclose. ***ES:*** Nothing to disclose. ***FR:*** Royalties: Spineart (B); Consulting: Stryker, Icotec, Brainlab (B); Speaking and/or Teaching Arrangements: Stryker, Spineart (B).

*Corresponding author. Department of Neurosurgery, University Medical Center Mainz, Johannes Gutenberg University, Langenbeckstraße. 1, 55131, Mainz, Germany.

E-mail address: andreas.kramer@unimedizin-mainz.de (A. Kramer).

https://doi.org/10.1016/j.spinee.2024.12.018

[f] Department of Neurosurgery, St Marien Hospital Lünen, Germany
[g] Department of Neurosurgery, Athens Medical Center, University of Münster Medical School, European University of Cyprus Medical School, Greece
[h] Clinic for Neurosurgery, University Clinical Center of Serbia, Belgrade, Serbia
[i] Clinic for Infectious and Tropical Diseases, University Clinical Center of Serbia, Belgrade, Serbia
[j] Department of Neurosurgery, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland
[k] Department of Neurosurgery, Wroclaw University Hospital, Wroclaw, Poland
[l] Neurosurgery, Hospital Garcia de Orta, Almada, Portugal
[m] Department of Neurosurgery, University Hospital St. Poelten, St Polten, Austria
[n] Department of Neurosurgery, Bethel Clinic University of Bielefeld Medical Center, Bielefeld, Germany
[o] Department of Neurosurgery, University Hospital Regensburg, Regensburg, Germany
[p] Neurosurgery Division - Department of Neuroscience, Cesena, Italy
[q] Department of Neurosurgery, Christian Doppler Clinic, Paracelsus Medical University, Salzburg, Austria
[r] Department of Neurosurgery, Faculty of Medicine in Hradec Kralove, University Hospital Hradec Kralove, Charles University, Hradec Kralove, Czech Republic
[s] Department of Neurosurgery Jessa Hospital, Hasselt, Belgium
[t] Department of Neurosurgery, Cairo University Medical School and Teaching Hospitals, Cairo, Egypt
[u] Security Forces Hospital Dammam, Saudi Arabia
[v] Neurosurgery Unit, Department of Neuroscience, University of Turin, Turin, Italy
[w] Neurosurgery Unit, Azienda Ospedaliera dei Colli, Naples, Italy
[x] Department of Neurosurgery, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[y] Valley Baptist Medical Center, Harlingen, Texas, USA
[z] Division of Neurological Surgery, Lagos State University Teaching Hospital, Ikeja, Lagos State, Nigeria
[aa] Department of Neurosurgery, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[bb] Department of Neurosurgery, Royal Infirmary Edinburgh, NHS Lothian, Edinburgh, United Kingdom
[cc] Department of Academic Neurosurgery, Addenbroke’s Hospital, Cambridge University Hospital NHS Healthcare Trust, Cambridge, United Kingdom
[dd] Department of Neurosurgery, University Hospital of Lausitz, Cottbus, Germany

Received 13 August 2024; revised 17 November 2024; accepted 3 December 2024

Abstract

BACKGROUND CONTEXT: Spondylodiscitis management presents significant clinical challenges, particularly in critically ill patients, where the risks and benefits of surgical intervention must be carefully balanced. The optimal timing of surgery in this context remains a subject of debate.

PURPOSE: This study aims to evaluate the effectiveness of early surgery versus delayed surgery or conservative management in critically ill patients with de novo pyogenic spondylodiscitis.

STUDY DESIGN/SETTING: This is an international, multicenter retrospective cohort study involving 24 centers, primarily in Europe.

PATIENT SAMPLE: The study included 192 critically ill patients (65.63% male) with a median age of 69 years, all severely affected by pyogenic spondylodiscitis characterized by an initial CRP level >200 mg/l or the presence of two out of four Systemic Inflammatory Response Syndrome criteria upon admission.

OUTCOME MEASURES: The primary outcome was 30-day mortality. Secondary outcomes included length of ICU stay, length of hospital stay, and relapse rates of spondylodiscitis.

METHODS: Patients were divided into three groups: early surgery (within three days of admission), delayed surgery (after three days of admission), and conservative therapy. Propensity score matching and multivariate regression analyses were performed to adjust for baseline differences and assess the impact of treatment modalities on mortality and other clinical outcomes.

RESULTS: Delayed surgery was associated with significantly lower 30-day mortality (4.05%) compared to early surgery (27.85%) and conservative therapy (27.78%) (p<.001). Delayed surgery also resulted in shorter hospital stays (42.76 days) compared to conservative therapy (55.53 days) and early surgery (26.33 days) (p<.001), and shorter ICU stays (4.52 days) compared to conservative therapy (16.48 days) and early surgery (7.92 days) (p<.001). The optimal window for surgery, minimizing mortality, was identified as ten to fourteen days post-admission (p=.02). Risk factors for increased mortality included age (p<.05), multiple organ failure (p<.05), and vertebral body destruction (p<.05), whereas delayed surgery (p<.05) and the presence of an epidural abscess were associated with reduced mortality (p<.05).

CONCLUSIONS: Delayed surgery, optimally between 10 to 14 days post-admission, was associated with lower mortality in critically ill spondylodiscitis patients. These findings highlight the potential benefits of considering surgical timing to improve patient outcomes.

Keywords: Conservative Stabilization; Mortality Rates; Pyogenic Spondylodiscitis; Sepsis; Severe Spinal Infection; Surgical Timing

Introduction

Pyogenic spondylodiscitis, a complex spinal infection, poses challenges in spine surgery and infectious disease due to its rising incidence and heterogeneous clinical presentation [1−3]. Influenced by factors such as neurological deficits, significant spinal deformity, or progressive disease, indications for surgery, surgical strategies, and timing remain subjects of ongoing debate and clinical uncertainty [4−9]. Recent evidence suggests early surgical therapy might improve short- and long-term survival in the general population of patients with pyogenic spondylodiscitis [10−13].

However, when it comes to critically ill patients with spondylodiscitis, the management becomes more complex. This subgroup necessitates the simultaneous addressing of sepsis-induced organ dysfunction and the eradication of the infectious focus. This situation is particularly critical given the heightened perioperative risks of bacterial dissemination, which can worsen circulatory instability in vulnerable patients[14,15].

Therefore, treatment strategies for critically ill patients with spondylodiscitis vary significantly, reflecting the complexity of managing this condition. Some advocate for early and aggressive surgical intervention to rapidly clear the infectious focus, accepting increased perioperative risks. Others propose delayed surgery after conservative stabilization in intensive care. A third approach supports conservative treatment, avoiding perioperative risks altogether. This diversity of strategies highlights the need for scientific evaluation [13,16−19].

In response to this critical dilemma and the paucity of data, the 2SICK study (*S*evere *S*pinal *I*nfection Retrospective Multicenter *C*ohort Benchmar*K*ing of Surgery Versus Conservative Therapy) was initiated. This international multicenter retrospective cohort investigation evaluates outcomes of early surgery, delayed surgery, and conservative management, focusing on 30-day mortality as the primary outcome. Secondary outcomes include length of hospital stay, intensive care unit stay, and relapse of spondylodiscitis.

Material and methods

Study design and participants

The 2SICK study, endorsed by the European Association of Neurosurgical Societies (EANS) Spine Section, retrospectively assessed clinical data from patients with pyogenic spondylodiscitis treated between January 2015 and June 2022. It aimed to evaluate the optimal treatment approach for critically ill patients with pyogenic spondylodiscitis across all spinal regions. Patients were divided into three treatment groups: conservative management, early surgery (within 3 days of admission), and delayed surgery (after 3 days).

The study included individuals aged 18 years and above with a definitive diagnosis of unspecific primary spondylodiscitis, evidenced by acute or chronic back pain, CT or MRI imaging consistent with spondylodiscitis, and either microbiological growth in blood culture or vertebral/disc tissue or histological signs of chronic inflammation. ‘Critically ill’ patients were defined by the presence of two out of four Systemic Inflammatory Response Syndrome (SIRS) criteria (fever above 38˚C or below 36˚C, heart rate over 90 beats per minute, respiratory rate over 20 breaths per minute, or abnormal white blood cell count) or an initial CRP level of ≥200 mg/l. These criteria served as the study’s inclusion criteria.

Patients were excluded if they had secondary (postoperative) spondylodiscitis or specific forms of the disease such as tuberculosis, brucellosis, fungal, or parasitic infections.

Data collection and outcome measures

Comprehensive datasets were collected from 24 centers, predominantly in Europe, with additional sites in North America and Africa. Participation was invited through the EANS Spine Section mailing list, ensuring that contributing centers were actively affiliated with the European Association of Neurological Surgeons and dedicated to advancing spine surgical care. These centers provided detailed patient characteristics such as demographic data, vital signs, comorbidities, clinical indicators, laboratory values, and treatment-related parameters. They also documented specific characteristics of discitis including diagnosis details, treatment strategies, surgical specifics, and postoperative outcomes.

The primary focus of the study was to evaluate the impact of different treatment modalities on 30-day mortality rates. Secondary outcomes included the length of ICU stay, overall hospital stay, and relapse rates of spondylodiscitis. These measures were essential to assess the effectiveness and efficiency of the various treatment approaches.

Data management and statistical analyses

Anonymized patient data collection was completed by March 2023, ensuring confidentiality. Statistical analyses were conducted using R software (version 4.0.4), with a significance threshold set at $p < .05$. A power analysis confirmed the study's capacity to detect significant differences in 30-day mortality.

To evaluate the outcomes across the defined treatment groups, statistical tests such as chi-square, t-test, and ANOVA were applied to identify variations in baseline characteristics and treatment effects. Univariate analyses were conducted to compare variables between patients who survived and those who did not, with p-values indicating the statistical significance of these comparisons. Factor Analysis for Mixed Data (FAMD) was used to address missing data, enabling a comprehensive multivariate logistic regression analysis. Regularization techniques—Ridge, LASSO, and Elastic Net—were applied to enahnce the predictive model and select the most relevant variables, guided by a Directed Acyclic Graph (DAG), that combined domain knowledge and empirical evidence. To minimize the impact of data heterogeneity and enhance the reliability of comparisons, propensity-score matching, was emploxed, balancing patients across treatment groups based on key baseline characteristics to facilitate precise outcome comparisons.

Results

Overall demographic and clinical characteristics

The study included 192 patients with pyogenic spondylodiscitis, with a wide range of clinical characteristics and treatment approaches. Detailed demographic data, clinical symptoms, comorbidities, pathogen profiles, and treatment details, including surgical techniques and outcomes, are summarized in Supplementary Table 1 and 2. These include the cohort's general health status, the prevalence of key symptoms and conditions, and the specific medical and surgical management strategies employed.

The violin plots (Fig. 1A) indicated no significant differences in the baseline variables age, ASA score and CRP at admission across the three treatment groups. On the other hand, initial analyses identified relevant differences in baseline characteristics across the treatment groups, such as diabetes, kidney disease and hepatopathy as well as motor deficits, which were more prevalent in the early surgery group but did not reach statistical significance (Fig. 1B and Supplementary Table 3).

Mortality analysis

Mortality rates varied significantly among treatment groups for spondylodiscitis, as detailed in Supplementary Table 4. The conservative treatment group (36 patients) had a mortality rate of 27.78% (10 deaths), similar to the early surgery group (79 patients) with 27.85% (22 deaths), whereas the delayed surgery group (74 patients) had a markedly lower rate of 4.05% (3 deaths). Statistical analysis revealed a highly significant difference between the groups ($p<.001$, Supplementary Table 7).

Optimal timing for surgical intervention

Fig. 2 illustrates the association between surgical timing and mortality risk in critically ill patients with spondylodiscitis. Dichotomized patient outcomes—dead or alive—represented by red dots, are plotted against days from admission to surgery, illustrating a clear trend where the mortality risk decreases within the initial ten days. The blue line indicates the model's predicted risk, stabilizing after the tenth day. This pattern suggests that surgery between 10

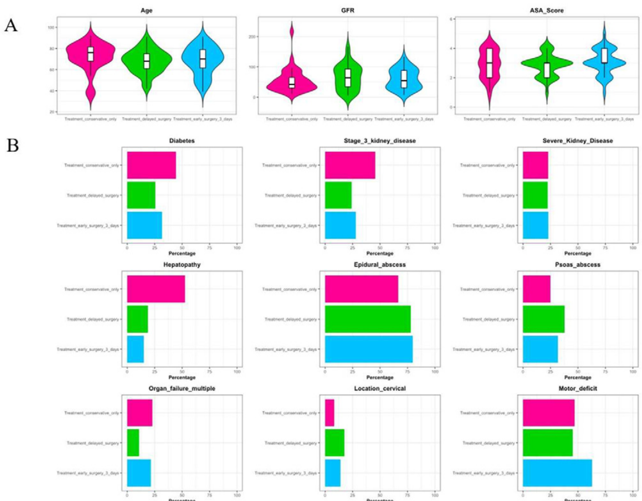

Fig. 1. Distribution of Age, CRP Levels, and ASA Scores: Violin plots display the distribution of age, CRP levels at admission, and ASA score for patients undergoing conservative treatment, delayed surgery (>3 days), and early surgery (within 3 days). Box plots overlaid on the violins indicate medians and quartiles, with group distinctions color-coded. B: Bar plots compare the prevalence of the most relevant categorical variables as identified by our statistical analyses and Directed Acyclic Graph.

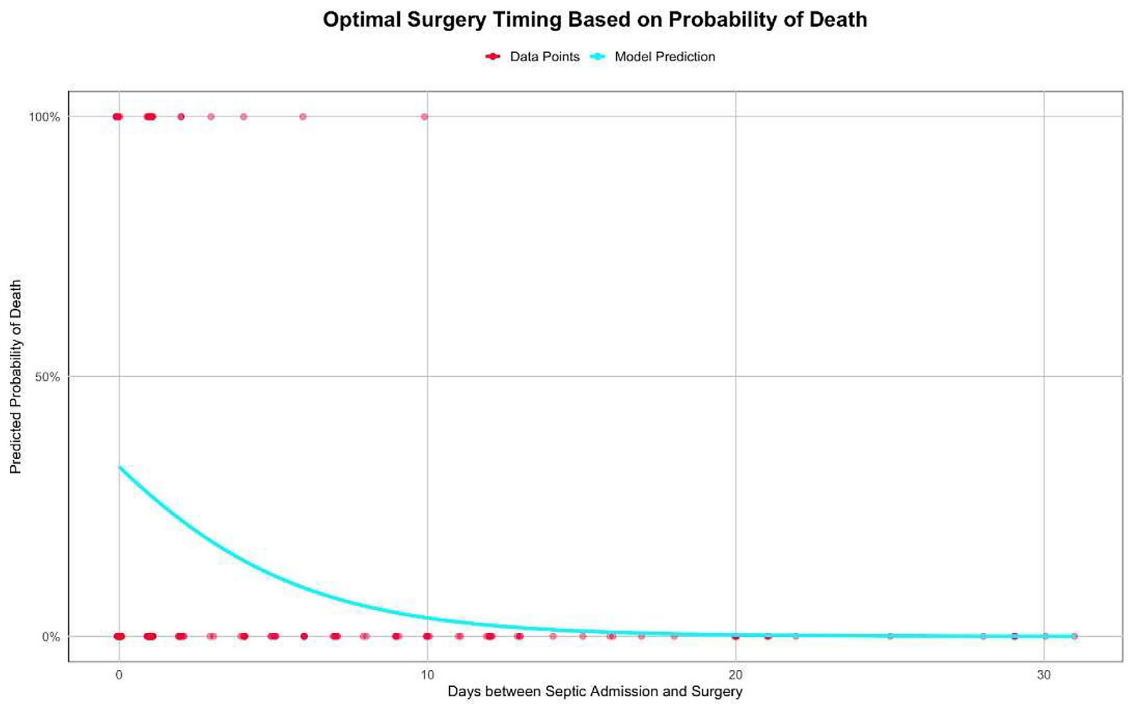

Fig. 2. Analysis of Surgical Timing and Patient Mortality: The red dots represent individual outcomes of patients, with higher points indicating deaths and lower points indicating survivors. The blue trend line models the predicted mortality risk based on the timing of surgical intervention after admission. The steepest decline in mortality risk is observed within the first ten days following admission, after which the risk plateaus at a low percentage. The timing of surgery between 10 and 14 days is associated with sustained low mortality risk, implying an optimal window for surgical intervention.

to 14 days post-admission aligns with the lowest mortality risk, proposing an optimal surgical window for these patients.

Relapse of spondylodiscitis analysis

The rate of disease relapse showed considerable variation, with the early surgery group (18 out of 77 patients, 23.38%) experiencing the highest rate, compared to a significantly lower rate in the delayed surgery group (8 out of 73 patients, 10.96%). The conservative treatment group had the lowest relapse rate (1 out of 32 patients, 3.12%). These differences highlighted the impact of treatment choices on disease recurrence ($p<.05$), as presented in Supplementary Tables 4 and 7.

Length of hospital stay analysis

Average hospital stays differed across treatment strategies, as reported in Supplementary Table 5. The conservative group averaged 55.53 days, the delayed surgery group 42.76 days, and the early surgery group had the shortest average hospital stay at 26.33 days. These differences were statistically significant ($p<.001$, Supplementary Table 7).

Length of ICU stay analysis

Mean ICU stays (Supplementary Table 5) were longest for the conservative treatment group (16.48 days), followed by the early surgery group (7.92 days), and were shortest for the delayed surgery group (4.52 days), indicating significant differences in ICU resource utilization ($p<.001$).

Predictors of mortality

Stepwise multivariate regression analysis in the pre-matched cohort revealed several predictors of mortality (Supplementary Table 7). Increased mortality was significantly associated with early surgery within 3 days ($p<.05$), multiple organ failure ($p<.05$), and the specific antibiotic regimen of Piperacillin-Tazobactam combined with Fosfomycin ($p<.05$). Conversely, the presence of an epidural abscess was associated with a significant reduction in mortality risk ($p<.05$). Higher Karnofsky Performance Status at discharge was also linked to decreased mortality ($p<.05$). These findings informed subsequent analyses.

Covariate selection

Using regularization techniques, including LASSO, Ridge, and Elastic Net models, we refined the identification of variables significantly impacting mortality, as detailed in Supplementary Figs. 1 and 2, along with the stepwise selection and covariate-regulated models in Supplementary Tables 8 and 9. This analytical approach emphasized the timing of surgical intervention as pivotal. Delayed surgery emerged as a protective factor, reducing mortality risk ($p=.02$), whereas early surgery was associated with an increased risk of mortality (p<.05). Other significant predictors included multiple organ failure (p<.001), erosion of endplates (p<.05) and the presence of an epidural abscess, which continued to demonstrate a protective effect (p<.001). In contrast, a psoas abscess was associated with an increased mortality (p<.05).

Propensity-score matched sensitivity analysis

To address potential confounding, we conducted a propensity-score matched analasys, adjusting for imbalances in baseline risk factors. This analysis, guided by a DAG illustrated in Fig. 3, validated the findings of the multivariate regression. The covariates identified as significant predictors of mortality were further balanced through this matching process, as shown in Fig. 4 and detailed in Table 1.

The propensity-score matched analysis confirmed the advantage of delayed surgery, which was associated with a significantly reduced risk of death (p<.05). Other variables that remained significant in the propensity-matched model included age (p<.05), multiple organ failure (p<.05), vertebral body destruction (p<.05), and the presence of an epidural abscess, which continued to be protective (p<.05). Importantly, no statistically significant difference in mortality risk was observed when comparing early surgery (conducted within 3 days of admission) to conservative treatment (p=.352). These findings reinforce the benefit of a delayed surgical strategy over both conservative management and early surgery.

Discussion

Management of critically Ill patients with spondylodiscitis

The 2SICK study offers unprecedented insights into managing spondylodiscitis patients, challenging traditional treatment paradigms and illuminating the path toward more effective clinical strategies. By analyzing a cohort across multiple centers, this study underlines the critical importance of timing in surgical interventions, revealing that delayed surgery not only significantly reduces mortality rates compared to early surgical and conservative treatments but also contributes to shorter hospital and ICU stays. This suggests that allowing time for clinical stabilization before undertaking surgical measures can markedly improve outcomes of critically ill patients with pyogenic spondylodiscitis.

Bridging the gap in current guidelines

The international multicentric approach of the 2SICK study, pivotal in gathering a comprehensive dataset of the relatively rare cases of spondylodiscitis with severe systemic inflammation, marks a significant stride in an area where high-quality data are notably lacking. This scarcity of robust data has led to an absence of solid, specific recommendations in international guidelines for the management of this subset of spondylodiscitis patients. The 2015 published IDSA guidelines articulate the need for empirical antimicrobial therapy in septic patients or those with neurological compromise, concomitantly emphasizing the importance of establishing a microbiological diagnosis [17]. They recommend surgical intervention in cases of progressive neurological deficits, deformity or instability, and persistent infection or pain despite adequate medical therapy. The lack of explicit consideration of primary surgical intervention in patients with spondylodiscitis in a septic state in these guidelines is likely due to the absence of reliable data on this patient cohort. More recently, a consensus statement by Urrutia et al. (2023) recommended surgery in cases where sepsis remains uncontrolled despite broad-spectrum intravenous antibiotics [20]. However, our findings suggest that this recommendation could be further extended. Based on the results of the 2SICK study, delayed surgery should

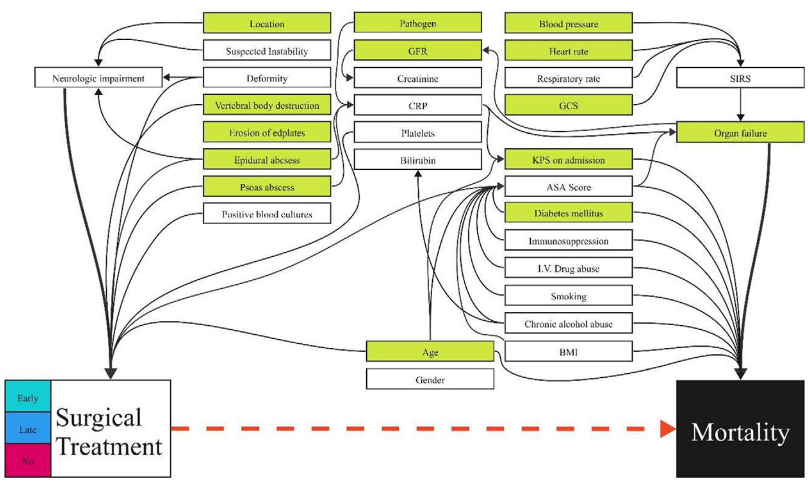

Fig. 3. Directed acyclic graph (DAG) for treatment decisions and mortality risks: The DAG delineates potential influences on treatment choices and mortality in criticall ill spondylodiscitis patients. Key variables affecting treatment strategy and patient outcomes are indicated, with a focus on green-highlighted factors like diabetes, GCS score, and abscess presence, which were used for Propensity Score Matching to balance treatment comparisons.

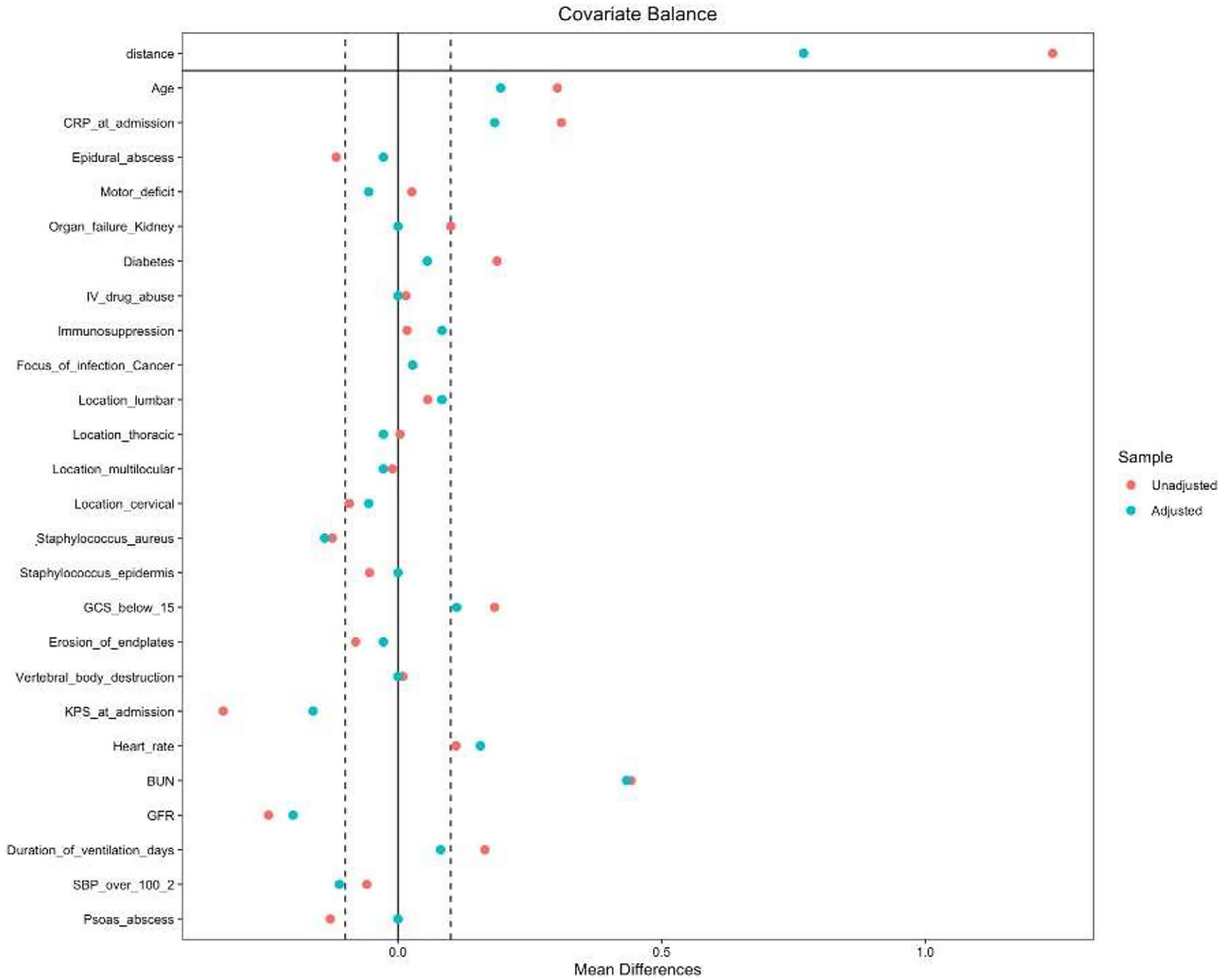

Fig. 4. Covariate balance via propensity score matching: the covariate balance achieved through propensity score matching is visualized via a love plot. The love plot contrasts the standardized biases of covariates before (red dots) and after (blue dots) matching, providing a clear visual indicator of matching efficacy in reducing covariate imbalance.

Table 1
Propensity score-matched multivariate logistic regression analysis for predictors of mortality in patients with severe pyogenic spinal infections.

Death Covariables	Estimate	Standard Error	z-statistic	p-value
Erosion of endplates	0.8586568	1.9158207	0.4481927	.6540141
Vertebral body destruction	7.8979966	3.5361983	2.2334710	.0255179
Epidural abscess	-9.3628096	4.0037114	-2.3385326	.0193596
Age	0.5140040	0.2518128	2.0412146	.0412295
KPS at admission	0.0893812	0.0544801	1.6406220	.1008759
Heart rate	0.1230863	0.0561762	2.1910754	.0284463
Duration of ventilation days	-0.0255856	0.2126818	-0.1202998	.9042456
Delayed surgery	-8.5147708	3.9530915	-2.1539524	.0312439
Early surgery within 3 days	1.9190367	2.0661276	0.9288084	.3529884
SBP over 100	-0.5897974	1.5682303	-0.3760910	.7068492
Psoas abscess	7.5229689	4.1496809	1.8129030	.0698468
Multiple organ failure	6.5242259	2.9868146	2.1843425	.0289371
Cervical location	5.4795434	2.8946603	1.8929832	.0583601
GFR	-0.0158419	0.0232951	-0.6800546	.4964699
Total Bilirubin	0.4253545	0.4034880	1.0541938	.2917942
Erosion of endplates	0.8586568	1.9158207	0.4481927	.6540141

This table presents the covariates adjusted through propensity score matching to account for baseline imbalances among treatment groups. The analysis evaluated associations between mortality and clinical, radiological, demographic, and treatment-related factors.

be considered not only when sepsis is refractory to antibiotic treatment but in patients presenting in a septic state more broadly.

Comparative analysis with other studies

The need for rigorous subgroup analyses and standardized treatment protocols has been highlighted by Rutges and colleagues, who point out the lack of direct comparisons between surgical and conservative treatments for pyogenic spondylodiscitis [19]. Similarly, the study by Hohenberger et al. explores the effects of early versus late surgical interventions in patients with lumbar spondylodiscitis, revealing that early surgery significantly reduces hospital stays [13]. However, their research did not specifically focus on critically ill patients, which limits comparability with our results, which concentrate on this more critical subgroup. This distinction emphasizes the necessity for tailored treatment approaches that consider systemic inflammation, underscoring the need for precise clinical assessments before deciding on the timing of surgical interventions. The 2SICK study addresses these gaps by offering an analysis of different treatment concepts, emphasizing the advantages of delayed surgery.

Investigations by Al Afif and colleagues into early, limited surgical interventions for critically ill patients suggest benefits for rapid infection control and long-term outcomes [16]. However, this study's small sample size and focused approach underline the need for broader research. Contrarily, our study, while supporting surgical intervention's superiority in terms of reducing mortality rates, recommends a less aggressive, delayed surgery after patient stabilization, highlighting the importance of surgical timing.

Illustrating the complexities and potential risks of surgical interventions, the study by Hempelmann et al. focuses on septic spondylodiscitis patients who deteriorated despite conservative treatment [18]. Despite its valuable insights into surgery's role in managing high-risk patients, the study's small scale and single-center nature limit broader applicability. In contrast, the 2SICK study expands on this perspective by demonstrating that delayed surgery, not necessarily predicated on the failure of conservative measures, confers a survival advantage. This distinction underlines the importance of timely, but not immediate, surgical intervention in a broader patient cohort, suggesting initial patient stabilization followed by delayed surgical treatment.

Lener et al.'s studies on spinal infections offer insights into the impact of sepsis and multi-organ failure on mortality rates in spondylodiscitis patients [11]. Their research underscores the importance of a carefully considered surgical strategy, which resonates with the 2SICK study's emphasis on the critical timing of surgical interventions after initial patient stabilization. Additionally, their development of the MSI-20 score proposes an innovative approach for assessing mortality risk, though it is derived from a single-center retrospective cohort and thus requires external validation [21]. Both contributions highlight the need for specialized care protocols in managing spondylodiscitis and acknowledge the importance of further research to refine patient management strategies.

Clinical implications and future directions

The 2SICK study significantly enhances our understanding of spondylodiscitis management, emphasizing the importance of precise timing of surgical interventions in critically ill patients. This aligns with emerging research, suggesting a pivotal shift in treatment approaches. Insights from the study advocate for revising current treatment protocols to not only emphasize timely surgical intervention in patients with primary spondylodiscitis but also underscore the necessity of medical stabilization prior to surgery. Our findings indicate that the benefits of surgery may extend beyond rapid source control, potentially involving long-term microbiological stability and improved mobilization. This nuanced understanding could guide more tailored and effective treatment strategies for spondylodiscitis, fostering better long-term patient outcomes. Future studies should explore these aspects in greater detail to fully elucidate the mechanisms through which surgical interventions confer these benefits. Additionally, further investigation into potential differences in outcomes among patients with neurological deficits could reveal insights into the unique needs of this subset, potentially leading to more nuanced management recommendations.

Limitations

The study has several limitations that warrant a cautious interpretation of the findings. Firstly, its retrospective design and emphasis on short-term outcomes may not capture the full spectrum of clinical impacts associated with different treatment strategies. Furthermore, the diversity across international healthcare settings included in the study could affect the generalizability of the findings. Treatment decisions and outcomes may vary significantly due to local expertise, cultural approaches to medical care, and the size of the treating center, which could introduce biases. Large centers may have different referral patterns and a broader array of available treatments compared to smaller centers, potentially influencing the chosen treatment modalities and their outcomes. Additionally, we did not analyze the association between medical center volume or geographic area and mortality due to limited patient numbers per center, making such an analysis statistically challenging and prone to insufficient power for reliable results. For surgical indications, we did not specifically differentiate patients by their indications for surgery, as our primary focus was on the timing of intervention. While this approach streamlined the analysis, we acknowledge that factors such as neurological deficits may influence treatment decisions and patients' outcomes.

An additional limitation is the potential underrepresentation of patients treated conservatively. This cohort is often managed in ICU or Infectiology departments rather than Neurosurgery alone, which might skew the data towards more surgically active centers and outcomes. Moreover, the disparate impact observed between the presence of an epidural abscess, which appeared protective - potentially due to earlier recognition and intervention - and a psoas abscess, which increased mortality, calls for further investigation into the roles these conditions play in the disease's pathology and treatment outcomes.

Prospectively designed studies that examine long-term outcomes and scrutinize the efficacy of different surgical interventions across uniformly stratified treatment settings are essential. Such studies could provide a more robust evidence base for the treatment of spondylodiscitis and help mitigate the biases observed due to the heterogeneous nature of the contributing centers.

Conclusion

The 2SICK study enhances our understanding of spondylodiscitis management by indicating that delayed surgery may offer advantages over early surgery or conservative management in terms of reducing mortality and hospital stay in critically ill patients. The study suggests that strategic timing of surgical interventions, particularly delaying surgery to 10 to 14 days post-admission, allows for initial patient stabilization, which may improve outcomes.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT, an AI-assisted technology, for language editing and improving readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Ethical considerations

Ethical approval for the study was obtained from the leading ethics committee associated with the study. All participating centers obtained local ethics committee approval or waivers in accordance with their institutional guidelines.

Consent to participate

Informed consent to participate in this study was obtained from all participants at the time of treatment, as per the protocols approved by the respective local ethics committees.

Consent for publication

Consent for publication of anonymized data was obtained from all participants or their legally authorized representatives, as applicable. The actual written informed consent documents are held by the authors/investigators in the respective patient hospital records.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. Due to ethical and legal considerations, the data are not publicly available.

Declaration of Competing Interest

One or more of the authors declare financial or professional relationships on ICMJE-TSJ disclosure forms.

CRediT authorship contribution statement

Andreas Kramer: Writing − review & editing, Writing − original draft, Visualization, Validation, Supervision, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Santhosh G. Thavarajasingam:** Visualization, Software, Methodology, Formal analysis, Data curation. **Jonathan Neuhoff:** Validation, Data curation. **Felipa Lange:** Data curation. **Hariharan Subbiah Ponniah:** Formal analysis, Data curation. **Sara Lener:** Validation, Data curation. **Claudius Thomé:** Validation, Data curation. **Felix C. Stengel:** Data curation. **Gregor Fischer:** Data curation. **Isabel C. Hostettler:** Data curation. **Martin N. Stienen:** Validation, Data curation. **Maxim Jemna:** Data curation. **Konstantinos Gousias:** Data curation. **Aleksandra Nedeljkovic:** Data curation. **Danica Grujicic:** Data curation. **Zarko Nedeljkovic:** Data curation. **Jasmina Poluga:** Data curation. **Ralph T. Schär:** Data curation. **Wiktor Urbanski:** Data curation. **Carla Sousa:** Data curation. **Carlos Daniel Oliveira Casimiro:** Data curation. **Helena Harmer:** Data curation. **Barbara Ladisich:** Data curation. **Matthias Matt:** Data curation. **Matthias Simon:** Data curation. **Delin Pai:** Data curation. **Christian Doenitz:** Data curation. **Lorenzo Mongardi:** Data curation. **Giorgio Lofrese:** Data curation. **Melanie Buchta:** Data curation. **Lukas Grassner:** Data curation. **Pavel Trávníček:** Data curation. **Tomáš Hosszú:** Data curation. **Maarten Wissels:** Data curation. **Sven Bamps:** Data curation. **Waeel Hamouda:** Data curation. **Flavio Panico:** Data curation. **Diego Garbossa:** Writing − review & editing. **Marcello Barbato:** Data curation. **Manlio Barbarisi:** Data curation. **Tobias Pantel:** Data curation. **Jens Gempt:** Data curation. **Tharaka Sai Kasula:** Data curation. **Sohum Desai:** Data curation. **Julius Mautin Vitowanu:** Data curation. **Bekir Rovčanin:** Data curation. **Ibrahim Omerhodzic:** Data curation. **Andreas K. Demetriades:** Writing − review & editing, Supervision, Data curation. **Benjamin Davies:** Writing − review & editing, Validation, Methodology, Formal analysis, Data curation. **Ehab Shiban:** Writing − review & editing. **Florian Ringel:** Writing − review &

editing, Validation, Supervision, Project administration, Methodology, Conceptualization.

Acknowledgments

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2024.12.018.

References

[1] Conan Y, Laurent E, Belin Y, et al. Large increase of vertebral osteomyelitis in France: a 2010-2019 cross-sectional study. Epidemiol Infect 2021;149:e227.
[2] Kramer A, Thavarajasingam SG, Neuhoff J, et al. Epidemiological trends of pyogenic spondylodiscitis in Germany: an EANS Spine Section Study. Sci Rep 2023;13(1):20225.
[3] Thavarajasingam SG, Ponniah HS, Philipps R, et al. Increasing incidence of spondylodiscitis in England: an analysis of the national health service (NHS) hospital episode statistics from 2012 to 2021. Brain Spine 2023:101733.
[4] Appalanaidu N, Shafafy R, Gee C, et al. Predicting the need for surgical intervention in patients with spondylodiscitis: the Brighton Spondylodiscitis Score (BSDS). Eur Spine J 2019;28(4):751–61.
[5] Fantoni M, Trecarichi EM, Rossi B, et al. Epidemiological and clinical features of pyogenic spondylodiscitis. Eur Rev Med Pharmacol Sci 2012;16(2):2–7. Suppl.
[6] Herren C, Jung N, Pishnamaz M, Breuninger M, Siewe J, Sobottke R. Spondylodiscitis: diagnosis and treatment options. Dtsch Arztebl Int 2017;114(51-52):875–82.
[7] Kramer AG, Thavarajasingam S, Neuhoff J, et al. Variation of practice in the treatment of pyogenic spondylodiscitis: a European Association of Neurosurgical Societies Spine Section study. J Neurosurg: Spine 2024:1–10.
[8] Neuhoff J, Kramer A, Thavarajasingam SG, et al. Comparing conservative and early surgical treatments for pyogenic spondylodiskitis: an international propensity score-matched retrospective outcome analysis. Neurosurgery 2024.
[9] Neuhoff J, Berkulian O, Kramer A, et al. Single- and Multilevel Corpectomy and Vertebral body replacement for treatment of spinal infections. A retrospective single-center study of 100 cases. Brain and Spine 2023:102721.
[10] Alas H, Fernando H, Baker JF, et al. Comparative outcomes of operative relative to medical management of spondylodiscitis accounting for frailty status at presentation. J Clin Neurosci 2020;75:134–8.
[11] Lener S, Wipplinger C, Stocsits A, Hartmann S, Hofer A, Thome C. Early surgery may lower mortality in patients suffering from severe spinal infection. Acta Neurochir (Wien) 2020;162(11):2887–94.
[12] Thavarajasingam SG, Vemulapalli KV, Vishnu K S, et al. Conservative versus early surgical treatment in the management of pyogenic spondylodiscitis: a systematic review and meta-analysis. Scient Rep 2023;13(1):15647.
[13] Hohenberger C, Schmidt NO, Doenitz C, Ullrich OW, Schebesch KM. Infectious Spondylodiscitis of the Lumbar Spine: Conservative Antibiotic Therapy vs. Antibiotic Therapy with Surgery, and the Time of Surgery. Neurol India 2022;70(1):155–9.
[14] Gupta A, Kowalski TJ, Osmon DR, et al. Long-term outcome of pyogenic vertebral osteomyelitis: a cohort study of 260 patients. Open Forum Infect Dis 2014;1(3):ofu107.
[15] Kehrer M, Pedersen C, Jensen TG, Hallas J, Lassen AT. Increased short- and long-term mortality among patients with infectious spondylodiscitis compared with a reference population. Spine J 2015;15(6):1233–40.
[16] Al-Afif S, Atallah O, Scheinichen D, et al. Surgical treatment of spondylodiscitis in critically ill septic patients. Acta Neurochir (Wien) 2023;165(12):3601–12.
[17] Berbari EF, Kanj SS, Kowalski TJ, et al. 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults. Clin Infect Dis 2015;61(6):e26–46.
[18] Hempelmann RG, Mater E, Schon R. Septic hematogenous lumbar spondylodiscitis in elderly patients with multiple risk factors: efficacy of posterior stabilization and interbody fusion with iliac crest bone graft. Eur Spine J 2010;19(10):1720–7.
[19] Rutges JP, Kempen DH, van Dijk M, Oner FC. Outcome of conservative and surgical treatment of pyogenic spondylodiscitis: a systematic literature review. Eur Spine J 2016;25(4):983–99.
[20] Urrutia J, Camino-Willhuber G, Guerrero A, Diaz-Ledezma C, Bono CM. An international consensus based on the Delphi method to define failure of medical treatment in pyogenic spinal infections. Spine J 2024;24(2):250–5.
[21] Lener S, Wipplinger C, Lang A, Hartmann S, Abramovic A, Thome C. A scoring system for the preoperative evaluation of prognosis in spinal infection: the MSI-20 score. Spine J 2022;22(5):827–34.