European Spine Journal (2023) 32:1455–1462
https://doi.org/10.1007/s00586-023-07578-8

ORIGINAL ARTICLE

Correlation between kidney function and mortality in pyogenic spondylodiscitis: the glomerular filtration rate (GFR) as new predictive parameter?

Maximilian Lenz[1] · Arne Harland[1] · Philipp Egenolf[1] · Maximilian Horbach[1] · Clara von Hodenberg[1] · Paul T. Brinkkoetter[2] · Thomas Benzing[2,3] · Peer Eysel[1] · Max J. Scheyerer[1]

Received: 6 April 2022 / Revised: 4 January 2023 / Accepted: 3 February 2023 / Published online: 24 February 2023

Abstract

Objective Pyogenic spondylodiscitis is a severe medical condition, often requiring surgical intervention. Numerous risk factors are known, such as obesity, neurological impairment and old age. In-hospital mortality remains high, therefore other factors may be contributing to the increased mortality. To evaluate kidney function as a risk factor for increased morbidity of pyogenic spondylodiscitis, the glomerular filtration rate (GFR) was correlated with the patients' clinical course.

Materials and methods We retrospectively reviewed the cases of 366 patients and 255 were included for analysis. Clinical, laboratory and surgical data were recorded with a minimum follow-up of three months. For clinical outcome measurement, mortality, length of stay and perioperative complications were analysed.

Results The study included 255 patients (173 men, 82 women; mean age 66.3 years). Patients with a GFR < 59 mL/min spent an average of 5 days longer in the hospital than those with a GFR ≥ 60 mL/min ($p = 0.071$). The mortality rate increased significantly with a decrease in GFR: A GFR of 30–59 mL/min had a mortality rate of 17.6%, whereas a GFR of < 29 mL/min had one of 30.4% ($p = 0.003$). Patients with impaired GFR showed an increased rate of postoperative complications (OR 4.7 $p = 0.002$) and higher rate of intensive care unit (ICU) stay (OR 8.7 $p = < 0.001$).

Discussion Preoperative GFR values showed a significant correlation with in-hospital mortality in patients with spondylodiscitis, when graded according to the KDIGO stages. Furthermore, a GFR of < 29 ml/mL contributes to a longer ICU stay, postoperative complications and a longer total hospital stay. Therefore, the preoperative GFR could be a marker of kidney function and as a valuable predictive risk factor regarding the clinical in-hospital course of patients suffering from pyogenic spondylodiscitis.

Keywords Pyogenic spondylodiscitis · Surgical treatment · Mortality · Kidney function · GFR levels

Introduction

Pyogenic spondylodiscitis is a challenging disease in spinal surgery, as the all-cause mortality rate is reported to be 5–20%, which is remarkably higher than the general mortality rate after spine surgery, which is reported to be 0.3–1.4% [1]. With an incidence rate of 0.2–2.4/100.000 per year, spondylodiscitis is the most common spinal infection, and the incidence rate is double for male patients [2, 3]. Incidence levels are rising mainly due to the ageing population, higher numbers of immunosuppressed patients and, in particular, improved diagnostic capabilities [4, 5].

Typically, bacteraemia, caused by a distant infectious process results in variable clinical presentations, and can cause spinal infections. Therefore, delays in diagnosis are

✉ Maximilian Lenz
maximilian.lenz@uk-koeln.de

1 Faculty of Medicine, Department for Orthopaedic and Trauma Surgery, University of Cologne, Joseph-Stelzmann Strasse 24, 50931 Cologne, Germany

2 Department II of Internal Medicine and Center for Molecular Medicine Cologne (CMMC), Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne, Germany

3 Cologne Cluster of Excellence On Cellular Stress Responses in Ageing-Associated Diseases (CECAD), Cologne, Germany

common. The treatment of pyogenic spondylodiscitis is challenging, as conservative treatment with long-term antibiotics usually require verification of the pathogen in blood culture or intervention sample taking. However, as the disc lacks significant vascularisation, the optimal duration of intravenous and oral antibiotic treatment is an ongoing debate. Moreover, numerous cases require surgical intervention, mainly indicated by neurological deficits, mechanical instability and spinal deformity [6]. Even with accurate therapy, all-cause mortality and morbidity remain high due to perioperative complications caused by either the infection or the intensive treatment [7–9].

According to previously published studies, several risk factors for a severe case of spondylodiscitis are known, such as obesity (using body mass index—BMI), diabetes, age and epidural empyema [10–12]. Little is known about the role of renal function in spondylodiscitis. In a study suggesting an important role of kidney function, Chikuda et al. reported that dialysis in patients with spondylarthropathy significantly increased perioperative complications and mortality [13]. Moreover, chronic kidney diseases (CKD), which are increasing in incidence, were observed as significant risk factors for higher mortality and morbidity, especially in end-stage renal disease (ESRD) [14, 15]. Next to CKD, which is rising in prevalence in an elderly society, acute kidney injury defined by KIDGO as a rise of > 0.5 mg/dL of creatinine levels or limited urine output may contribute to a worse outcome in critically ill patients [16]. The severity of AKI even was significantly associated with higher mortality [17]. While AKI can have numerous reasons such as ischemia, direct nephrotoxic injury or inflammatory insults, sepsis due to severe infection is commonly seen [18]. Sepsis is the leading course of AKI in ICU patients and AKI is associated with 45–70% of all cases with sepsis [19, 20]. A possible reason for the elevated mortality could be distant organ injury induced by AKI, as cardiac-insufficiency, encephalic disorders and respiratory failure is seen regularly [21, 22]. The systemic inflammation in sepsis determines the clinical picture [23]. In the literature, the clinical presentation of spondylodiscitis varies from rare asymptomatic cases to patients in septic-shock requiring life-saving surgical intervention [8, 11].

Therefore, a key question in pyogenic spondylodiscitis research is the influence of AKI due to the infection and septic constellation. The glomerular filtration rate (GFR) is a parameter for kidney function. The clinical GFR value is determined by different calculations based on creatinine levels, ethnicity or age, and is measured in mL/min/1.73m^2 body surface area. Furthermore, the GFR levels are age dependent, with levels decreasing with ageing. According to the "Kidney Disease—Improving Global Outcomes" (KDIGO) guidelines, GFR values allow kidney function to be classified into several grades, ranging from G1 to G5. Grades G1 and G2 show GFR levels > 60 mL/min/1.73m^2 and concomitant proteinuria (group 1 in our present study). Grade G3 (30–59 mL/min), representing moderate impairment, is subdivided into grades G3a and G3b. For severe disease, grade G4 represents GFR values of 15–29 mL/min/1.73m^2 and grade G5 represents GFR values of < 15 mL/min/1.73m^2.

Therefore, the underlying aim of this study was to validate the preoperative GFR as a marker of kidney function and as a valuable predictive risk factor regarding the clinical in-hospital course of patients suffering from spondylodiscitis. Factors including mortality, revision surgery and postoperative complications, as well as length of stay in the ICU and hospital, were studied.

Methods

Study design

We performed a monocentre retrospective study, including patients undertaking surgical treatment of spondylodiscitis in a level I spine centre, which were investigated with respect to potential prognostic criteria. Any surgery including fusion surgery with either dorsal, ventral or combined dorsal–ventral fusion surgery, was included. The criteria for exclusion were any form of malignant disease that would modify the laboratory results, especially leukocytes and high CRP levels, as well as tuberculous spondylodiscitis. In addition, 19 patients were excluded as insufficient data were available, resulting in 255 eligible patients being included in analysis.

Data collection

Data were extracted from the hospital information system (HIS), such as gender and age, as well as admission, length of stay and peri- or postoperative complications. Mortality, revision surgery as well as pathogen levels were documented. Regarding laboratory results, pre- and postoperative GFR, creatinine and CRP levels were recorded over a two-week period. Patients were assessed until six weeks postoperative, although some patients presented symptoms later on and therefore had a longer follow-up. The BMI values, the perioperative antibiotics used and the American Society of Anesthesiologists (ASA) scoring were obtained from the anaesthesiological documentation. Surgical data, such as operation time, type of fusion surgery, extent of levels included in surgery and spinal location, were recorded. Microbiological testing from blood culture and intraoperative samples were recorded.

Statistics

Statistical analysis was performed using SPSS V.27 software (SPSS, Chicago, Illinois). We used descriptive statistics to summarise the means and standard deviations. A Pearson test was performed for detecting significant correlations. Two-sided t-tests were performed to detect any statistically significant differences. Binary logistic regression analysis was performed to analyse risk and likelihood (odds ratio). The level of significance was defined as a p-value of $p = < 0.05$.

Ethics

The analysis was revised by our institutional ethics committee and was approved by the Institutional Review Board of the Faculty of Medicine (approval no. 20-1631).

Results

A total of 255 patients were included in the study (173 men, 82 women). The mean age was 66.3 years (± 13.3). The mean BMI level was 23.5 ± 5. An overall in-hospital mortality of 10.2% was observed with a mean of 32.2 days of hospital stay. 85.1% of all spondylodiscitis was found in lumbosacral segments. Surgery included dorsal fusion surgery in 82% of all cases, with another 35% undergoing an additional ventral procedure for spinal stabilisation. Cervical spondylodiscitis was predominantly treated by an anterior approach (88% vs 12% posterior).

Regarding preexisting comorbidities, only 15.9% had no previous medical condition. The most common were cardiovascular diseases (hypertension, cardiac arrhythmia and heart valve defects) in 39.2%, of patients followed by diabetes in 23.5% and endocrinological diseases in 17.3% of patients. A preexisting chronic kidney disease was recorded in 14.1% of patients, and a chronic liver disease in 6.3% of all patients. Regarding further risk factors, obesity (BMI > 30) was observed in 18.8% of patients and another 18% were actively smoking. The main pathogen found was *Staphylococcus aureus* (25%), followed by other *Staphylococcus* species (15.3%) and Enterobacteriacae (10.2%). In 25% of all cases, no pathogen was detected despite blood culture and intraoperative probe analysis.

Based on the KDIGO guidelines, the cohort was subdivided into three groups: Group 1 with GFR values > 60 mL/min, group 2 with GFR values of 30–59 mL/min and group 3 with GFR < 29 mL/min.

The cohorts' group characteristics are described in detail in Table 1. As expected, GFR decreases as age increases and the mean age of group 1 was 64 (± 13.1), the mean age of group 2 was 72.1 (± 10.4) and mean age of group 3 was 74 (± 10.9).

The BMI levels are nearly equally distributed among the three categories, as well as the male/female ratio. However, the American Society of Anesthesiologists (ASA) classification score, which have been an established score for measuring perioperative risk since 1941 and regularly updated, do not seem to reflect the deteriorating kidney function, as measured by GFR. Moreover, a documented kidney impairment, chronic or acute, was only present in 14.1% of the cases, while the others presented acutely elevated retention parameters and decreased GFR levels.

Regarding mortality, 10.2% of in-hospital mortality was observed during the follow-up analysis (Fig. 1). Therefore, 26 patients died from spondylodiscitis while in hospital. For group 1, a mortality rate of 7.3% was recorded; for group 2, 11.8%; and for group 3, 30.4% ($p = 0.003$) (Table 1). The OR regarding mortality when GFR < 29 mL/min is 5.6 (95% CI 1.9–15.9, $p = 0.001$) (Table 2). Patients with preoperative antibiotic treatment showed significantly higher mortality

Table 1 Mean characteristics of cohorts categorised into three groups, according to GFR levels

GRF Levels	Group 1 178 (> 60 mL/min)	Group 2 51 (30–59 mL/min)	Group 3 23 (< 29 mL/min)
Age (years ± SD)	64.0 ± 13.1	72.1 ± 10.4	74.0 ± 10.9
Male—(numbers) (%)	121 (68.0)	33 (64.7)	17 (73.9)
BMI—kg/m^2	23.1 ± 4,9	24.0 ± 5.0	25.0 ± 6.0
Length of hospital stay (days)	31.4 ± 19.0	32.7 ± 14.7	43.8 ± 23.9
Mortality—(numbers) (%)	13 (7.3)	6 (11.8)	7 (30.4)
ASA-Classification	$n = 173$	$n = 46$	$n = 23$
1—n (%)	3 (1.7)	0 (0.0)	0 (0.0)
2—n (%)	49 (28.3)	2 (4.3)	2 (8.7)
3—n (%)	107 (61.8)	35 (76.1)	13 (56.5)
4—n (%)	14 (8.1)	9 (19.6)	8 (34.8)

Mean, standard deviation (SD), total numbers and percentages are shown. (ASA, American Society of Anesthesiologists)

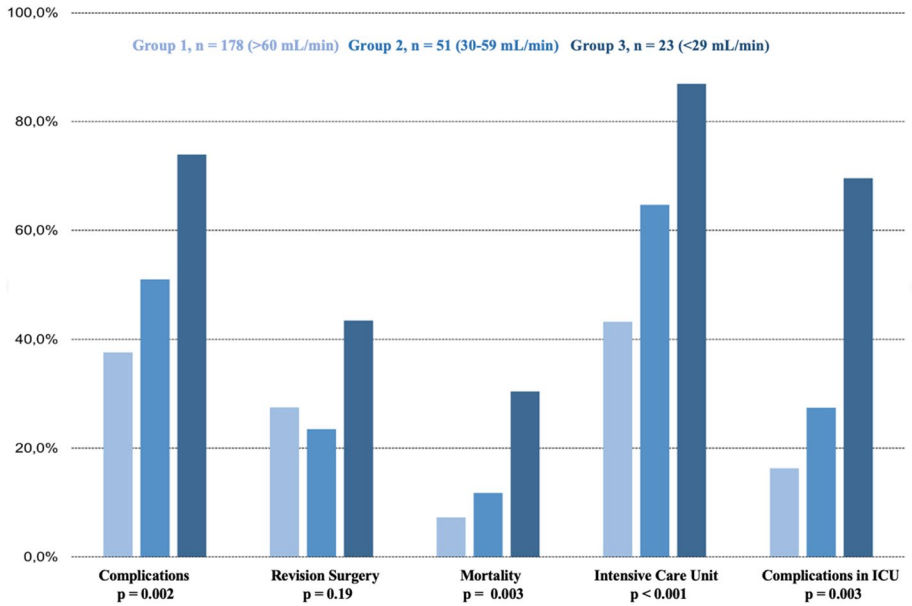

Fig. 1 Distribution of mortality, intensive care unit (ICU) stay, complications, and revision surgery, grouped by GFR levels

Table 2 Binominal regression analysis showing statistically significant odds ratio (OR) with increased risk when GFR levels are lowered, compared to reference group 1 (> 60 mL/min) (CI confidence interval in %; $p = < 0.05$); Intensive Care Unit (ICU)

GFR	Mortality			Complications			ICU		
	OR	CI 95%	*p*	OR	CI 95%	*p*	OR	CI 95%	*p*
30–59 mL/min	1.7	(0.6–4.7)	0.313	1.7	(0.9–3.2)	0.089	2.4	(1.3–4.6)	0.008
< 29 mL/min	5.6	(1.9–15.9)	0.001	4.7	(1.8–12.5)	0.002	8.7	(2.5–30.5)	< 0.001

than patients without previous antibiotic treatment (16.2% vs. 6%; $p = 0.008$).

Complications were recorded as would any complication occurring during the in-hospital clinical course (Fig. 1). The most common postoperative complication was wound healing disorder ($n = 30$; 27%) followed by pneumonia ($n = 18$; 16.36%) and material failure ($n = 6$; 5.45%). During the ICU stay, the most common complication encountered was circulatory disorder ($n = 31$; 40.92%) and pulmonary complications such as pleural effusion, pneumonia or pulmonary embolism ($n = 14$; 18.48%). Dialysis was required in nine patients (11.88%). Of all the patients included, 145 had no perioperative complications (56.86%) and 123 required no ICU stay (48.23%). The group distribution showed significantly higher complication rate with 73.9% of group3 compared to group 1 with 37.6% and group 2 with 51%, respectively. The tendency for revision surgery was higher in the group 3, however, no significant correlation was found (p 0.198) (see Table 2). The OR for complications of group 2 was 1.7 (95% CI 0.9–3.2, $p = 0.089$) and for group 3 was 4.7 (95% CI 1.8–12.5, $p = 0.002$) (Table 2).

The mean length of total hospital stay was 31.4 days for group 1, 32.7 for group 2 and 43.8 for group 3, and showed significant correlation with the GFR values ($p = 0.012$) (Fig. 2). Group 1 had a mean stay of 10 days, group 2 had 7.6 days and group 3 had 12.5 days, respectively (Fig. 2). The total length of stay in hospital showed no significant correlation to the GFR levels ($p = 0.22$).

However, the need for intensive care treatment was significantly less in group 1 compared to groups 2 and 3 ($p = < 0.01$), and the complications during intensive care unit were significantly higher (38.5% vs 80% ($p = 0.003$)) for group 3 (Table 2). The risk of requiring an ICU stay was higher when GFR levels were lower (group 2, OR 2.4 (CI 95%, 1.3–4–6, p = 0.008) and group 3 8.7 (CI 95%, 2.5–30.5, $p = < 0.001$) (Table 2).

Discussion

We have provided a detailed analysis of relationship between complications arising in pyogenic spondylodiscitis vs, kidney function, as measured by GFR levels. The results demonstrate an increased complication rate in patients with lower GFR levels. The complications include higher in-hospital all-cause mortality rates, longer hospital stays and higher postoperative complication rates.

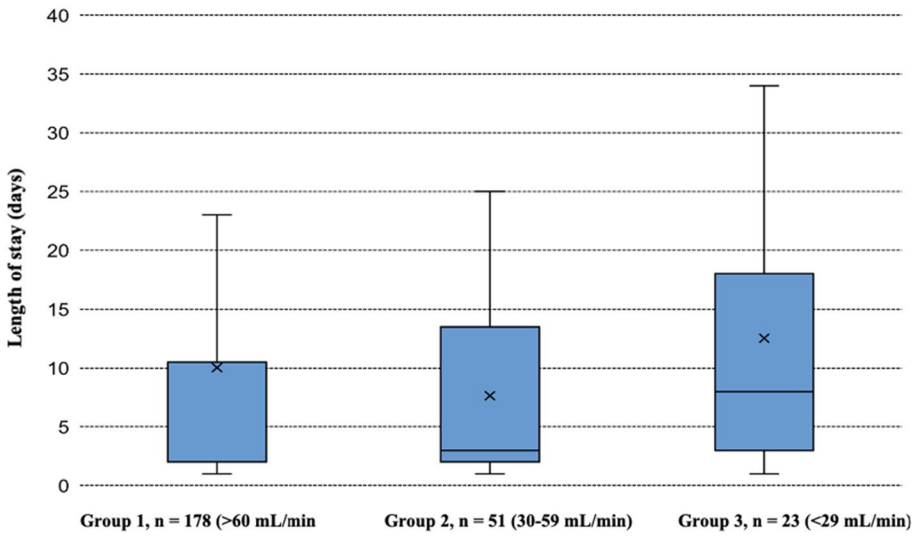

Fig. 2 Boxplot of Length of stay ICU (in days) of the three groups

Compared to previously published studies, which are in accordance with our findings, we provide a larger cohort of surgically treated patients. A high mortality rate of spondylodiscitis of up to 20% is previously reported, while a mean mortality rate of 10% was observed for our cohort, which is comparable to previous data [24, 25]. The high rate of in-hospital mortality is often described as multi-organ failure, owing to septic shock and progressive circulatory instability, with the need for increased support. Supporting these data, *S. aureus* is seen as the most deadly pathogen detected in spondylodiscitis.

However, the high mortality rate may instead be linked to the handful of risk factors known so far. Detailed knowledge of these could potentially decrease mortality. Detecting more significant risk factors and predictive factors in the outcome in pyogenic spondylodiscitis would help to assign patients to the most appropriate treatment option. Moreover, a preoperative improvement of kidney function by electrolyte control, the adaption of accurate volume status and the discontinuation of all nephrotoxic medication might be helpful. Consultation of nephrologists in clinical settings might improve the outcome, as seen in antibiotic stewardship by infectiologists. However, this hypothesis must be analysed in randomised controlled clinical trials and cannot be answered by these data.

Analysing the role of kidney function in pyogenic spondylodiscitis, our results showed significant predictive factors in outcome and mortality. In our case series, only 14.2% of all patients had recorded a known kidney disease. We see this as the main reason to believe that the acute kidney injury resulting in lower GFR levels is related to the infectious spondylodiscitis. Most of the patients are presented to our hospital only after a medical consultation either by their general-practitioner or another hospital. Therefore, we assume fundamentally elaborated medical findings and a comprehensible medical history. Hence, only 14.2% had a previously diagnosed CKD, while 29.4% had compromised GFR levels of < 60 mL/min. This fact corroborates the association to an acute infectious process resulting in sepsis and kidney dysfunction.

However, GFR levels of < 60 ml/min result in a higher rate of complications and mortality. The findings of this study concur with previously published data regarding mortality and complications in patients with spondylodiscitis, the need for haemodialysis, or diabetes [13]. In a wide multicentre analysis by Kushioka, dialysis-related spondyloarthropathy and infectious spondylodiscitis showed highest mortality rates [26]. Here, diabetic nephropathy could be the main impact of the disease, which is associated with higher mortality and morbidity. A compromised kidney function in ESRD has already been shown to increase mortality in any lumbar spinal surgery [14, 15].

While a trias of inflammation, direct toxic injury of the kidney and ischemia are causes of AKI, the infection and sepsis caused by severe pyogenic spondylodiscitis which is often caused by bacteriaemia, is thought to result in AKI [18]. In a recent systematic review, Lee et al. stated distant organ dysfunction caused by AKI including lung, heart, brain and even liver [22]. These organs seem to be harmed by several mechanisms, including the accumulation of uremic toxins accumulation and change in circulation including ischemia leading to oxidative stress, inflammation, electrolyte imbalance as well as acid/base imbalances [22]. Molecular mechanisms found so far, include inflammatory mediators such as Interleukin-6 (IL-6), plasminogen activator inhibitor-1 and soluble tumour necrosis factor receptors (TNF-alpha) [27].

The current epidemiologic outline the increased mortality and morbidity in patients with acute renal failure [28]. This poses a heavy burden with high costs for the healthcare

system due to intensive-care treatment [29]. Understanding the complexity of interactions between the kidney and distant organs could lead to new diagnostics and therapies to improve the outcomes in patients with AKI. This could lead to improved therapy and management of sepsis in case of severe spondylodiscitis, thus resulting in lower mortality rates.

Of course, the GFR level itself does not represent the complete risk-stratification in patients, and additional parameters, such as retention parameters, or albuminuria and hypoalbuminemia, can play an important role. A new scoring system that implements the KDIGO guidelines, as well as including other risk factors for spondylodiscitis, may help to make targeted treatment decisions. Not every patient receives full urine diagnostics on admission, making GFR, as well as other retention parameters, an easy marker to determine for risk stratification. This is particularly important as the GFR can be seen as parameter for the multimorbidity of patients. Kidney function is lowered by numerous influences resulting from several diseases, with cardiac, pulmonary, endocrinological and malignant diseases all impairing the function of the kidneys [30]. This is also elucidated by our results, as the GFR was more accurate in predicting complications and mortality than the ASA score.

The role of kidney function and GFR might become more evident in further clinical trials, which might alter the preoperative decisions for these patients. A higher tendency for conservative therapy with intravenous antibiotics, or minimally invasive sample taking by radiologists using CT-controlled puncture, might minimise morbidity and mortality. For accurate and successful antibiotic treatment, it is extremely important to identify the pathogens before starting antibiotics among patients with spondylodiscitis as the clinical presentation can differ. Empiric antibiotic treatment can even lead to a delay in diagnosis of spondylodiscitis causing further progress of the infection [31]. Lora-Tamayo et al. showed a significant delay in patients without positive microbiological cultures [32].

The aim is to generate a new severity scoring in pyogenic spondylodiscitis, to perform a more accurate risk stratification for patients who need surgical treatment, and to minimise complications and mortality. These factors known so far include age, obesity (BMI), diabetes, renal dysfunction (GFR), the pathogen detected and any preoperative antibiotic treatment, as well as neurologic impairment [33]. Based on an automatic intelligence (AI) algorithm, an individual risk profile can be established, eventually determining the adequate treatment option in the future.

Limitations

Limitations of this study are its retrospective, non-randomised nature; the inhomogeneous patient population; and the limited follow-up after the hospital course (minimum 6 weeks maximum 12 weeks postoperative). Furthermore, the GFR grade alone is usually not used as stand-alone parameter to evaluate kidney function; other parameters, such as creatinine, albuminuria and serum albumin levels are also considered. The modification in the KDIGO grading system was used to gain higher statistical power and to facilitate application in standard clinical evaluation. Nevertheless, in our opinion, the results from the in-patient course, in addition to the epidemiological data obtained, provide interesting findings that should be further investigated, especially the GFR value as predictive factor in pyogenic spondylodiscitis. Compared to other studies, we provide a large cohort of analysed cases. Consideration of the comorbidities with regard to the chronic and acute courses is desirable for further studies, as well as a longer follow-up of at least 12 months. Ideally, the studies are in the sense of a prospectively designed multicentre study. Furthermore, a multicentre prospective analysis could elucidate therapeutic consequences in pyogenic spondylodiscitis.

Conclusion

In conclusion, our study provides significant evidence that kidney function measured by GFR levels can be a significant predictive factor for estimating the length of hospital stays, mortality and the risk of complications throughout the course. Other risk factors, such as age, BMI, diabetes, pathogen, neurologic deficits and now GFR, should be used to create a new scoring system for the severity of spondylodiscitis, which considers the mortality and morbidity even after radical surgical procedures.

Authors Contribution Conceptualisation: Maximilian Lenz, Max J. Scheyerer; Methodology: Maximilian Horbach, Clara von Hodenberg; Formal analysis and investigation: Maximilian Lenz, Maximilian Horbach, Clara von Hodenberg, Max J. Scheyerer; Writing—original draft preparation: Maximilian Lenz; Arne Harland, Philipp Egenolf, Max J. Scheyerer; Writing—review and editing: Peer Eysel, Max J Scheyerer, Paul T. Brinkoetter, Thomas Benzing; Resources: Peer Eysel; Supervision: Peer Eysel, Max J. Scheyerer.

Funding Open Access funding enabled and organized by Projekt DEAL. No funds, grants, or other support was received.

Declarations

Conflict of interest The authors declare they have no financial interests. The authors have no competing interests to declare that are relevant to the content of this article.

Ethical approval All procedures performed in our study were in accordance with Declaration of Helsinki (1964) with the institutional ethics committee (Ethical Committee (No. 20–1586).

Informed consent Informed consent was obtained from all participants.

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