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Vertebral Osteomyelitis: A Mortality Analysis Comparing Surgical and Conservative Management

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Abstract

Study Design: Retrospective cohort study.

Objectives: To compare the mortality between patients treated for vertebral osteomyelitis (VO) with either surgical or conservative management and to construct a predictive model for mortality after VO.

Methods: All patients with a diagnosis of VO in Region North Denmark from 2004 to 2014 were followed for at least 2 years or until death. They were all treated according to a standardized guideline for the choice of treatment modality. Nineteen dichotomized variables with possible influence on the mortality were registered for all patients in the study. LASSO (least absolute shrinkage and selection operator) penalized Cox regression analysis was used to build a predictive model for 2-year survival after VO.

Results: A total of 125 patients were eligible for inclusion, mean age 67 years, 36 women. 75 were treated surgically. Twenty-one patients were dead 2 years after the diagnosis. Kaplan-Meier estimate of 2-year survival was 0.82 [0.75, 0.88]. Any difference in mortality between surgically and conservatively treated patients was nonsignificant at 1 and 2 years (univariate Cox regression analysis). Significant factors included in the predictive model after LASSO penalized Cox regression analysis was Charlson Comorbidity Index (CCI), cardiovascular disease, C-reactive protein (CRP) normalization, thoracic infection, and Karnofsky score. The area under the curve (AUC) for the predictive model ranged from 0.74 to 0.77.

Conclusion: Patients undergoing surgical management for vertebral osteomyelitis according to standardized and agreed-upon guidelines had no higher mortality than those allocated to conservative treatment. The predictive model included 5 variables associated with an increased mortality: CCI, CRP normalization, cardiovascular disease, thoracic infection, and Karnofsky score.

Keywords

osteomyelitis, spondylodiscitis, survival analysis, statistical models

Introduction

Vertebral osteomyelitis (VO) is a severe condition associated with high mortality and risk of permanent neurological deficits and chronic pain.[1,2] There is an increased short- and long-term mortality in VO patients compared with the background population.[3] The overall incidence of VO in Denmark increased from 2.2/100 000 to 5.8/100 000 in the years 1995-2008.[4] The increased incidence in Denmark could be real or the results of better diagnostics (magnetic resonance imaging [MRI] availability in Denmark has increased considerably the past 10-15 years) and workup.

In general, the possible reasons for the increased incidence of VO depend on a number of causes, such as: better diagnostic techniques (MRI and polymerase chain reaction), increased population longevity, more immunocompromised people and increased use of intravenous (IV) drugs and indwelling devices.[5-7] The most common bacterial organisms are *Staphylococcus aureus*, followed by gram-negative bacilli and Streptococcus/enterococci. The routes of infection may be hematogenous, contiguous, postoperative, or posttraumatic.[8]

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Predisposing factors such as diabetes mellitus, malnutrition, substance abuse (alcohol/drug users), sickle cell anemia, immunosuppressive conditions (HIV, steroid users), tumors, renal failure, and septicemia may aggravate the final outcome of spondylodiscitis.

Diagnosing VO may be challenging due to vague symptoms such as pain, fever, night sweats, anemia, loss of weight, and malaise.[9] Late diagnosis can result in general multiple organ failure and epidural abscesses.[10] On average, the diagnostic delay from onset of symptoms to diagnosis is approximately 2 to 6 months.[11] Management of VO is either medical treatment alone (conservative treatment) or a combination of medical treatment and surgery. To date, conservative treatment remains as first-line treatment of VO.[2] The indication for surgery is not entirely evidence based.[11]

The empirical indications for surgery are mechanical instability, abscess formation, compression of spinal cord or cauda equina, progressive neurologic compromise, intolerable pain, or failed nonsurgical therapy. Surgical intervention is followed by antibiotic treatment equivalent to conservative therapy.[12,13]

Surgery for VO is often major surgery. It is questionable if these rather frail elderly patients will fare better with surgical intervention especially as the candidates for surgery are those with the most advanced disease—bearing in mind that the mortality is high for VO.

The present study is a retrospective case cohort study from a single center, Aalborg University Hospital, Denmark. The aim of the study was to evaluate the mortality outcome of surgical treatment of VO at our institution compared with patients treated conservatively. Second, to evaluate factors influencing the mortality of patient with VO by predictive modeling.

Materials and Methods

All patients with a diagnosis of VO in Region North Denmark (population 580 000), from the first of January 2004 until the first of January 2014 and treated at Aalborg University Hospital, were included in the study. The unique 10-digit personal identification number assigned to all Danish citizens at birth was used to avoid multiple registration and to track individuals over time. The Danish National Registry of Patients was searched using the aforementioned criteria and the following ICD-10 (International Classification of Diseases, 10th Revision) diagnosis codes: DM462, DM463A, DM464, DM465A, DM490, DM491, DM492, DM493. A retrospective review of the electronic patient record (Clinical Suite version 18.0.4.0) for each patient was performed. The diagnosis was confirmed by a combination of the clinical history, C-reactive protein (CRP) elevation, MRI findings, histological findings, or positive tissue cultures. Tissue diagnostics was performed in all the surgically treated cases and in the conservatively treated cases except in cases where blood cultures were positive. The time of death was retrieved form the Danish Register of Causes of Death for those who died during the follow-up period.

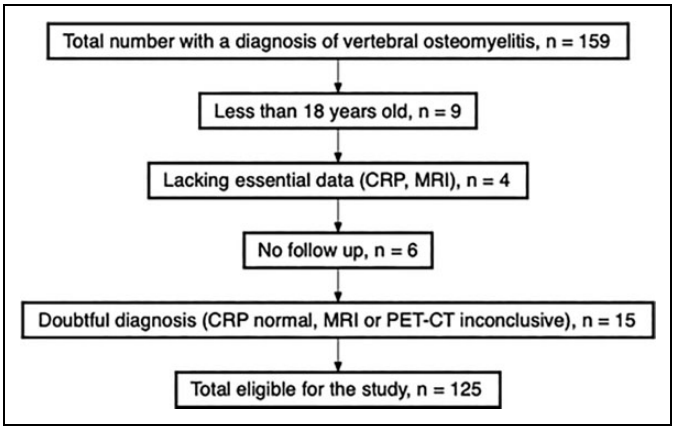

Figure 1. Flowchart for the 125 patients eligible for the study.

Exclusion criteria were unconfirmed VO diagnosis, incomplete data, or treatment not following standardized guidelines, age less than 18 years, patients with relapse, VO after lumbar spine surgery and a missing or normal CRP level at time of diagnosis (<10 mg/L). The chosen censoring date was March 9, 2017.

The study was approved by the local institutional review board and by the Danish Data Protection Agency. According to Danish law, no approval by the Medical Ethics Committee is required for observational studies.

The aforementioned search resulted in a cohort of 159 patients, and 125 patients fulfilled the inclusion criteria (Figure 1). The indications for surgery was mechanical instability, epidural abscess formation, paravertebral abscess not suitable for ultrasound guided drainage, neurologic deficit, compression of spinal cord or cauda equina, intolerable pain, or failed nonsurgical therapy. Standard surgical treatment consisted of debridement followed by pulsatile lavage with 1 to 3 L of isotonic saline, circumferential fusion with posterior instrumentation, bone grafting (posterolateral and interbody), and locally instilled antibiotics. IV antibiotics followed surgery for 10 to 14 days and oral antibiotics followed IV antibiotics for a duration of 10 weeks—all in all 3 months of antibiotic therapy.

Standard conservative therapy consisted of IV antibiotics for 10 to 14 days and oral antibiotics for a duration of 10 weeks (also for a total 3 months of antibiotic therapy). A lumbar or thoracolumbar orthosis was used as part of the pain treatment in most cases.

All patients were followed for at least 2 years from the date of diagnosis or until death. No patients were lost to follow-up.

Nineteen variables were registered from the electronic patient record for the 125 patients (Table 1). The data set was complete in all cases. All 19 variables were dichotomized. Age was dichotomized with cut point of 60 years. Charlson Comorbidity Index (CCI)[14] with cut point 1 (at the most 1 comorbidity). Frankel grade[15] with cut point grade E (normal neurology). Karnofsky score[16] with cut point 80 (able to work). CRP level was dichotomized with cut point 30 mg/L 14 days after treatment start.

Table 1. Variables, Coding, and Distribution According to Treatment.

Variable Name and Coding	Conservative (0), n (%)	Surgery (1), n (%)	Total, n (%)	*P*
Male (0)	36 (72)	53 (71)	89 (71)	1
Female (1)	14 (28)	22 (29)	36 (29)	
Age >60 years (1)	37 (74)	55 (73)	92 (74)	1
Age ≤60 years (0)	13 (26)	20 (27)	33 (26)	
Diabetes (1)	6 (12)	17 (23)	23 (18)	.2
No diabetes (0)	44 (88)	58 (77)	102 (87)	
Cardiovascular disease (1)	16 (32)	25 (33)	41 (33)	1
No cardiovascular disease (0)	34 (68)	50 (67)	84 (67)	
Lung disease (1)	5 (10)	6 (8)	11 (9)	.95
No lung disease (0)	45 (90)	69 (92)	114 (91)	
Cancer (1)	6 (12)	12 (16)	18 (14)	.72
No cancer (1)	44 (88)	63 (84)	107 (86)	
Renal disease (1)	3 (6)	7 (9)	10 (8)	.74
No renal disease (0)	47 (94)	68 (91)	115 (92)	
Intravenous drug abuser (1)	0 (0)	8 (11)	8 (6)	.04
Not an intravenous drug abuser (0)	50 (100)	67 (89)	117 (94)	
Alcoholic (1)	9 (18)	11 (15)	20 (16)	.8
Not an alcoholic (0)	41 (82)	64 (85)	105 (84)	
Charlson Comorbidity Index > 1 (1)	23 (46)	45 (60)	57 (46)	.18
Charlson Comorbidity Index ≤ 1 (0)	27 (54)	30 (40)	68 (54)	
Frankel grade not E (1)	19 (38)	33 (44)	52 (42)	.63
Frankel grade E (0)	31 (62)	42 (56)	73 (59)	
Karnofsky score <80 (1)	24 (48)	32 (43)	56 (45)	.68
Karnofsky score ≥80 (0)	26 (52)	43 (57)	69 (55)	
Endocarditis (1)	8 (16)	10 (13)	18 (14)	.88
No endocarditis (0)	42 (84)	65 (87)	107 (86)	
Paravertebral or epidural abscess (1)	13 (26)	48 (64)	61 (49)	.00007
No abscess (0)	37 (74)	27 (36)	64 (51)	
Vertebral body destruction (1)	2 (4)	11 (15)	13 (10)	.11
No vertebral body destruction (0)	48 (96)	64 (85)	112 (90)	
Thoracic spine infection (1)	13 (26)	22 (29)	35 (28)	.84
Not thoracic spine infection (0)	37 (74)	53 (71)	90 (72)	
Staphylococcus aureus (1)	17 (34)	24 (32)	41 (33)	.97
No *Staphylococcus aureus* (0)	33 (66)	51 (68)	84 (67)	
C-reactive protein ≤30 mg/L 14 days after treatment start (0)	32 (64)	28 (37)	60 (48)	.006
C-reactive protein >30 mg/L 14 days after treatment start (1)	18 (36)	47 (63)	65 (52)	

The continuous variables are presented as mean and standard deviations (SD) and dichotomous parameters as frequencies and percentages. Continuous variables were compared using the unpaired Student's *t* test. The chi-square test was used to assess differences in the dichotomous variables ($P < .05$).

The statistical methods included univariate cox regression (likelihood ratio test) for all variables. Multicollinearity was investigated using the variance inflation factor (VIF; a value >4 was considered index of multicollinearity).

Because of the sparse data (large number of candidate predictors and few events) a multivariate L1 (least absolute shrinkage and selection operator–LASSO) penalized Cox regression model was used to build a predictive model for 2-year survival after diagnosis of vertebral osteomyelitis. We chose 2 years as censoring date because this is an agreed-upon follow-up time in clinical research.[17] The LASSO model automatically performs variable selection by shrinking the variables not related to outcome to zero. The LASSO method is also able to handle collinearity issues. The shrinkage penalty is weighted based on a tuning parameter λ. The optimal λ value was determined using 10-fold internal cross validation. Predicted survival profiles for specific patients were constructed from the LASSO model to illustrate the model's functionality. The model performance was evaluated with the area under the curve (AUC) at different time points.

The statistical analyses were all conducted with R statistical software version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) and the packages "survival," "penalized,"[17] and "hdnom."

Results

The characteristics of the 125 patients according to the type of treatment are presented in Table 1. For the variables IV drug abuse, abscess formation, and CRP normalization there was a significantly higher proportion of patients treated surgically (chi-square test). The coding of the variables is given in parentheses in Table 1. This coding was used in all subsequent

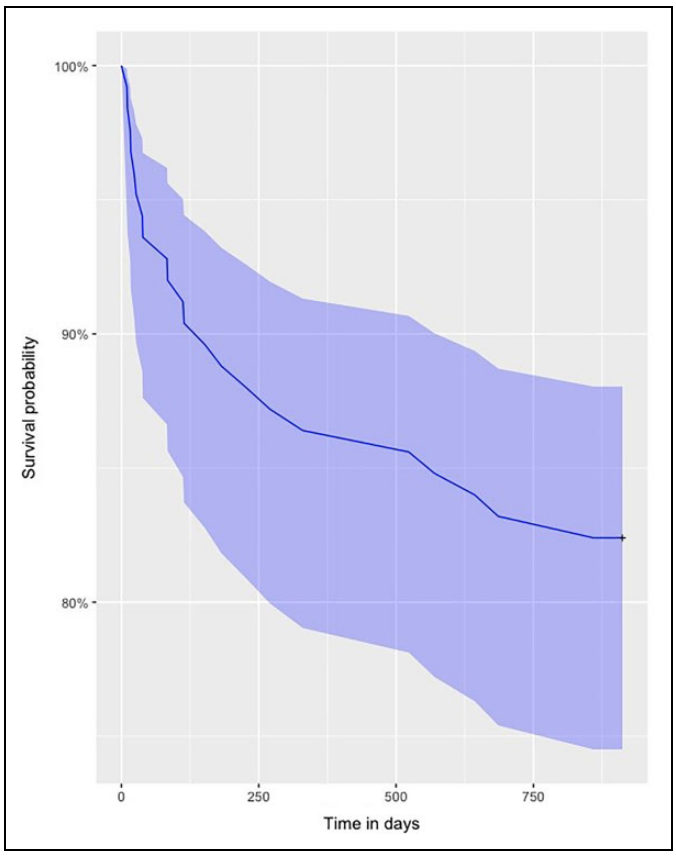

Figure 2. Overall survival for the 125 patients. Blue area indicates 95% confidence limits.

survival analysis. A coding of zero and a positive regression coefficient e.g. a coding of zero for CRP normalization ≤14 days signifies that patients with CRP normalized in less than or equal to 14 days will have a lesser risk of dying in a 1- or 2-year span. The mean age between the conservatively and surgically treated patients did not differ significantly (67.24 and 67.25 years, $P = .99$). Age range was 38-92 years. First quartile 59 years. The bacterial etiology was unknown in 17 cases, caused by *Staphylococcus aureus* in 41 cases, *Staphylococcus epidermis* in 3 cases, Streptococcus species in 14 (hemolytic streptococci in 6 cases), *Escherichia coli* in 12 cases, enterococci in 9 cases, and by diverse and rare bacteria in 29 cases. Seventeen and 21 patients were dead after 1 and 2 years, respectively. Kaplan-Meier estimate of 1- and 2-year survival was 0.86 (95% confidence interval [CI] 0.79-0.91) and 0.824 (95% CI 0.745-0.880), respectively. The survival curve for all 125 patients is presented in Figure 2. The results of the conventional univariate Cox regression are shown in Table 2—likelihood ratio test. Only the *P* values for cardiovascular disease, CCI, and CRP normalization were less than or equal to .05. The 95% CIs of the Kaplan-Meier curves for the surgically treated compared with the conservatively treated overlapped at any time point (Figure 3). The VIF was less than 1.8 in all cases indicating no evidence of multicollinearity in the model. The

Table 2. Conventional Univariate Cox Regression Analysis.

Variable	Hazard Ratio	95% CI	*P*
Sex	1.31	0.53-3.26	.56
Age	2.28	0.67-7.73	.14
Treatment	1.73	0.67-4.46	.24
Diabetes	1.93	0.75-4.96	.20
Cardiovascular disease	2.93	1.23-6.95	.015
Lung disease	0.5	0.07-3.75	.45
Cancer	1.45	0.49-4.32	.52
Renal disease	3.19	1.07-9.48	.07
Intravenous drug abuse	0.71	0.10-5.29	.72
Alcoholic	1.34	0.45-3.99	.61
Charlson Comorbidity Index	3.98	1.34-11.85	.005
Frankel grade	1.64	0.70-3.86	.26
Karnofski score	1.79	0.75-4.24	.19
Endocarditis	1	0.29-3.40	.99
Paravertebral or epidural abscess	0.93	0.39-2.18	.86
Vertebral body destruction	1.47	0.43-4.99	.55
Thoracic spine infection	2.12	0.89-5.04	.09
Staphylococcus aureus	1.03	0.42-2.56	.94
C-reactive protein ≤30 mg/L 14 days after treatment start	3.28	1.20-8.96	.01

cross-validated log partial likelihood for a range of values of lambda (Figure 4). The value of lambda producing the optimum goodness of fit was 2.49. The path of the coefficients for a range of values of lambda is presented in Figure 5. The 5 nonzero coefficients for CCI, CRP normalization, cardiovascular disease, thoracic spine infection, and Karnofsky score (Table 3). A subset analysis on the surgically and conservatively treated patients was undertaken but no nonzero variables were detected for these relatively small subgroups. The magnitude of these parameter estimates is not intended to be interpreted in terms of hazard ratios as the LASSO procedure has shrunken them and neither is it possible to calculate the confidence intervals for the penalized coefficients with certainty.[17,18] However, the coefficients can be used to calculate the predicted survival profile for specific patients (Figure 6) using the "predict" function in the R package penalized.[19] The predictive model had an acceptable discriminatory ability. The AUC was 0.77 at 6 months, 0.74 at 1 year, and 0.74 at 2 years (Figure 7).

Discussion

The principal finding of this retrospective cohort study stands in contrast to the general belief that surgical intervention in patients is directly associated with an increased mortality compared with those treated conservatively.[20] The fact that the mortality rate for those treated surgically does not differ significantly from the other group, is surprising. Especially when considering that the surgically managed patients had higher CCI scores, namely, they were frailer. The surgically treated also had more severe VO as most of them had epidural and/or paravertebral abscess.

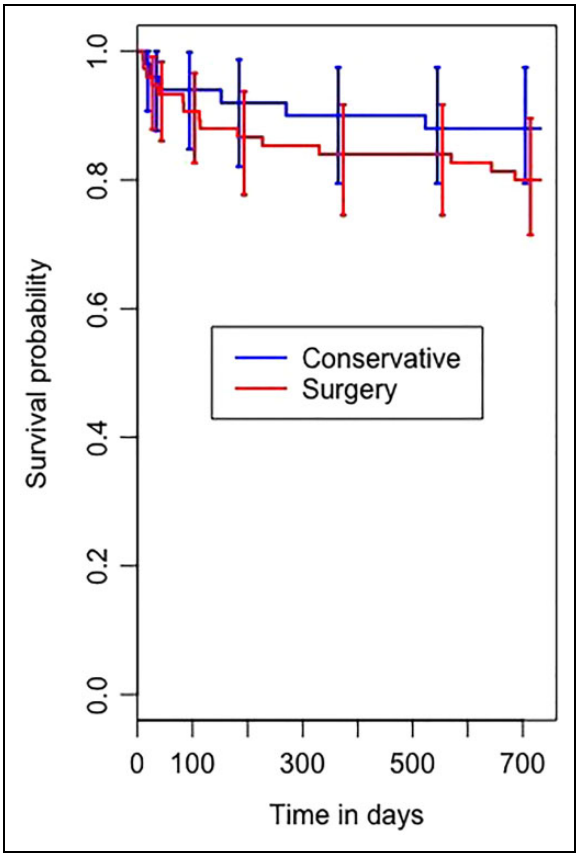

Figure 3. Kaplan Meier curves comparing conservative treatment and surgery. Vertical lines indicate 95% confidence intervals.

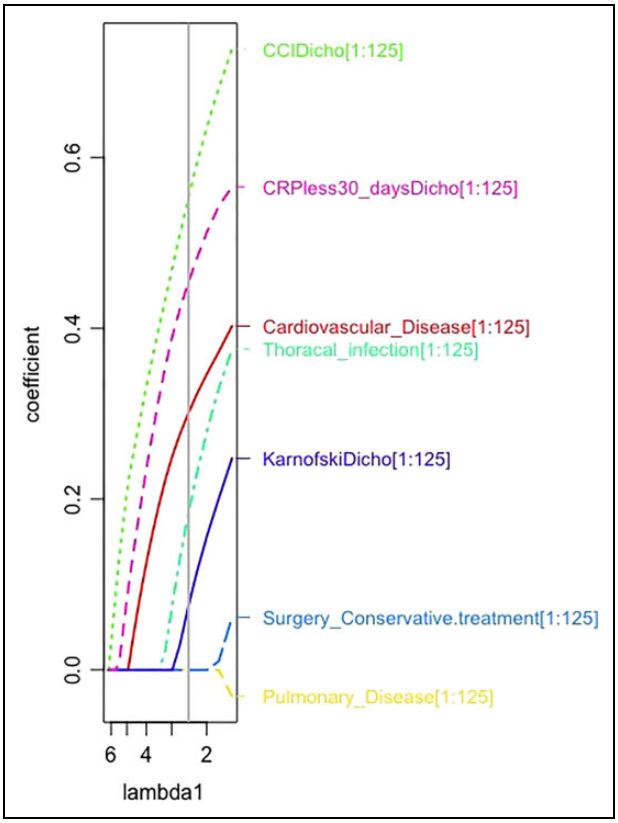

Figure 5. Path of the standardized coefficient estimates over a range of values of the LASSO constraint lambda1. The vertical gray line is the optimal value of lambda, the same value as in Figure 4.

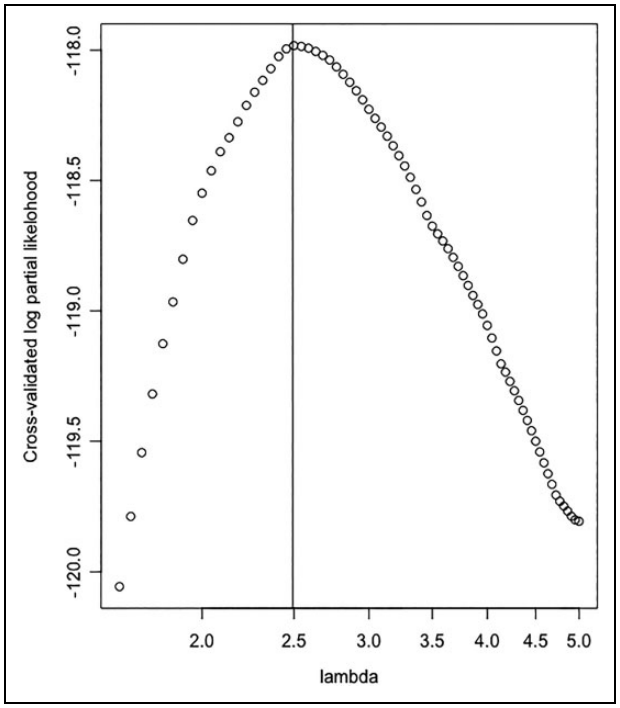

Figure 4. Maximum lambda1.

A major strength of this study lies in the fact that VO treatment for an entire geographically defined population group over a 10-year period has been described and evaluated. No patients were lost to follow-up and our data set was complete. All VO patients were treated at the same medical center according to the same algorithm agreed upon by both the Department of Infectious Diseases and the Department of Orthopedic Surgery. Patient data was acquired directly from the medical records and not from the national registers except for the mortality data and initial data on diagnosis which both rely on the unique 10-digit number every person of Danish nationality receives at birth.

The number of events per variable almost equaled 1. However, the LASSO penalized Cox proportional hazards regression is the statistical method of choice under these circumstances. Penalized regression helps avoiding overfitting and allows for variable selection better than classical stepwise regression.[17,18] If the predictors are severely correlated penalized regression has a tendency to select at random—selecting one at random from a group of highly correlated predictors.[18] The predictors in the current study were not highly correlated—all with VIFs <1.8. We also believe that the predictors were chosen based on well-founded clinical insight so that the number of "noise predictors" were few or none. LASSO penalized regression functions best when the number of noise

Table 3. Nonzero Coefficients From the LASSO Penalized Cox Proportional Hazard Regression.

Variable	Coefficient
Charlson Comorbidity Index	0.55
C-reactive protein normalization	0.45
Cardiovascular disease	0.30
Thoracic spine infection	0.18
Karnofsky score	0.07

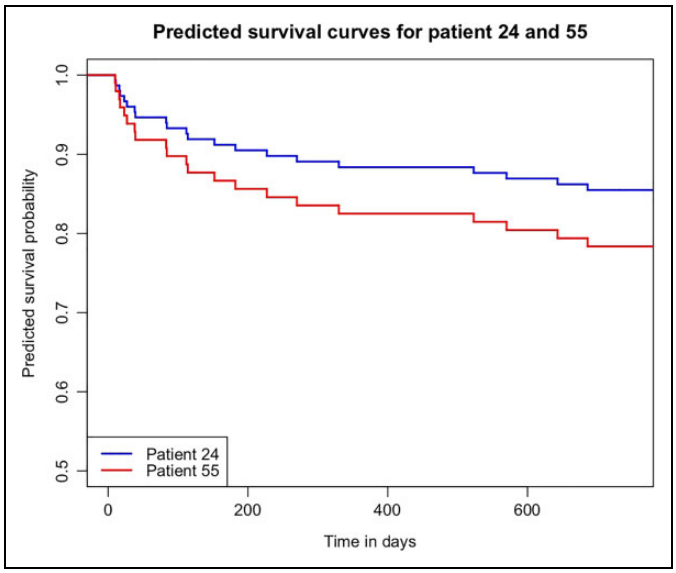

Figure 6. Predicted survival profiles for patients 24 and 55.

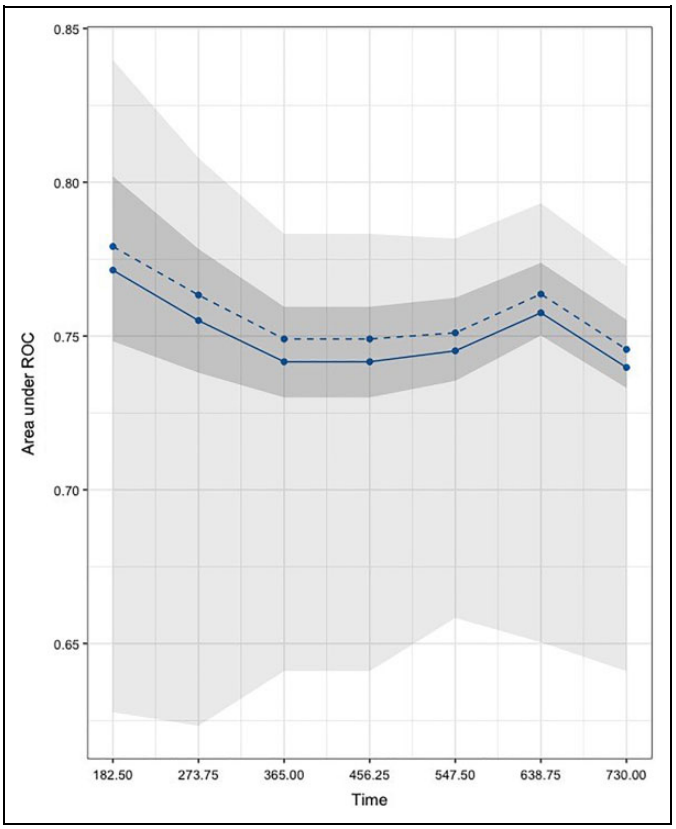

Figure 7. Time-dependent AUC (area under the receiver operating characteristic [ROC] curve) for the LASSO model. Solid line indicates mean of the AUC and dashed line indicates the median of the AUC. Darker interval indicates 25% and 75% quantiles of AUC. Lighter interval indicate minimum and maximum of AUC.

predictors are few. We chose not to calculate standard errors for the coefficients as these are not very meaningful for strongly biased estimators such as the LASSO penalized regression coefficients.[18]

Even though the discriminatory ability of the predictive model was acceptable with an AUC between 0.70 and 0.80 one must expect the discriminatory ability to decrease when applied to new patients or patients with VO from another medical center. However, we believe that the selected variables make sense. CCI has been shown to be a strong predictor of mortality in other studies[1,21] and a CCI $\geq$ 2 was associated with higher mortality in a study by Loibl et al.[21] The Karnofsky score is well correlated to frailty but was only a weak predictor in this study. A modified frailty score was associated with a 30-day postoperative mortality in patients with tuberculous spondylodiscitis.[22] Thoracic VO is an infection at the level of the spinal cord which must be considered more severe than VO at the level of the cauda equina (lumbar level). The findings by Appalanaidu et al[23] corroborate our findings—thoracic and thoracolumbar infection indicated more severe disease. CRP normalization will be delayed after surgery due to the surgical trauma. But the decrease to a CRP level less than 30 mg/L also depends on the CRP level at treatment start. Loibl et al[21] has shown that a CRP $\geq$ 100 mg/L at admission is associated with an increased mortality in VO and our data somehow corroborates their findings as we did find that a normalization of CRP in less than or equal to 14 days was associated with decreased mortality (remember the coding in Table 1—zero coding indicating normalization in $\leq$14 days). The initial CRP was not recorded precisely at the start of treatment in all cases, thus it was not possible to use this in the statistical analysis as a complete data set is required. The requirement for a full data set implicates that some other predictors might have been omitted in the statistical analysis but nevertheless, we consider the 19 variables important and relevant in this context.

There is in fact a risk that given a higher number of patients we might have found a significant difference in mortality between the 2 treatments, and the nonsignificant finding of mortality difference could be a result of a type 2 error. However, even if there was to be a significant difference in mortality between the treatment groups, it would still be small, and the results of our study would still be in favor of treating more severe cases of VO with surgery even with some increase in mortality. Besides helping reduce mortality for the severely ill, other benefits of surgery are higher post-VO functional level and less pain.[2] Delaying a necessary surgical intervention is associated with an increased mortality and morbidity.[24]

As has been stated in the introduction, different treatment algorithms and approaches for the management of VO exist.[2] Most studies have looked at the effect of medical or surgical treatment and only a few studies have dealt with the direct comparison of mortality between surgery and medical treatment, most likely owing to the fact that the 2 groups are not easily comparable without turning to relatively sophisticated statistical methods. Surgery is usually the secondary choice of treatment and reserved to patients with more severe symptoms or for those not responding to conservative medical treatment alone.

In the present study, vertebral body destruction was not seen significantly more often for the surgically treated patients although there was a strong tendency ($P = .11$). MRI is probably less effective in judging the extent of destruction and in the authors' opinion the clinical signs are more important—the presence of excruciating pain when shifting position especially when shifting from lying down to standing and vice versa is a more pathognomonic sign for significant bony destruction.

The incidence of VO in this study of 2.74/100 000 is comparable to data from the literature, which is 2.2/100 000 to 5.8/100 000.[4,25]

A comparison of mortality rates between the current study and earlier studies is fraught with difficulties. The age distribution will differ as some studies include children with zero mortality. Many studies do not even report the 1- and 2-year mortality rates of the population in question.

Mortality from VO at different time has been described with some discrepancy ranging from 11% to 20% at 1 year.[3,7,26] Kehrer et al[3] reported a 1-year mortality of 20%, which seems high when compared with our study and literature in general. The characteristics of their study group was similar to ours, though, lower CCI and comorbidities were reported compared with our group. Brummerstedt et al[27] reported a 1-year mortality of 18%. Our 1-year mortality rate corresponds very well to the 1-year mortality in a large randomized controlled French trial comparing 6 and 12 weeks of antibiotic treatment in patients with VO (13%).[28] The 2 studies mentioned above included only patients treated conservatively and one cannot help wondering if surgical intervention with the well-established indications and agreed upon by the involved departments might have resulted in a decreased mortality rate.

We had no patients with VO caused by methicillin-resistant *Staphylococcus aureus* (MRSA) so we were not able to conclude anything regarding the influence of drug resistance on mortality or that VO caused by *Staphylococcus aureus* were more severe than any other causative organism. This is possibly a result of a very efficient tracking and eradication program for MRSA in our region. Likewise, endocarditis was not a factor in the predictive model. All patients with VO undergo both transthoracic and transesophageal echocardiography at our institution—1 out of 7 had endocarditis. Prompt diagnosis and treatment is probably the key word. Neurological deficits measured with the Frankel score did not find a place in the predictive model. However, some correlations existed between the Frankel score and the Karnofsky score. The Frankel score is a crude measure of neurological deficits with no grading of muscle strength and does not register sphincter functions. Diabetes was not a significant factor influencing mortality in this study though this has been associated with increased mortality in other studies.[29] No doubt the CCI functions as a container for the different comorbidities, for example, diabetes, chronic obstructive lung disease, and so on.

Figure 5 can be explained by the individual characteristics of the specific patient.[17] Patient 55 was a 70-year-old woman who died 523 days after the time of diagnosis. She had cardiovascular disease as well as kidney disease (CCI coded as 1). She had thoracic infection. Karnofsky was coded as zero. CRP was normalized 8 days after the start of treatment (0). In contrast, patient 24, a woman of 51 years, had no risk factors and was alive 4634 days after the diagnosis. Patient 55 was treated without surgery and patient 24 with surgery.

Can the current study give precise indications for the choice between surgical or conservative treatment based on the 19 independent variables? This choice depends not only the mortality but also on the quality of life after the different interventions.[2,24] What this study indicates is that there is no reason for hesitation (late normalization of CRP was associated with increased mortality) in using the aforementioned indications for surgery even if the patient in question has some or even considerable comorbidities.

Conclusion

Patients undergoing surgical management for VO according to standardized and agreed-upon guidelines had no higher mortality than those allocated to conservative treatment even though the surgically treated patients had more comorbidities and more severe disease. A LASSO penalized Cox regression analysis found 5 nonzero coefficients; CCI, CRP normalization, cardiovascular disease, thoracic infection and Karnofsky score, which were associated with an increased mortality. The predictive model can be used to predict survival profiles for patients on an individual level with an acceptable certainty as the AUC for the predictive model in this study was between 0.74 and 0.77.

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Declaration of Conflicting Interests

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