Spinal tuberculosis, a Dutch perspective
Jutte, Paulus Christiaan
CHAPTER 7
PREDICTION OF DEFORMITY IN SPINAL TUBERCULOSIS

Jutte PC, Wiute S, The B, Van Altena R, Veldhuizen AG
Conditional acceptance for Clin Orthop Relat Res

ABSTRACT
Tuberculosis (TB) of the spine may cause kyphosis. Persisting large kyphosis may cause late paraplegia, ventilatory compromise and cosmetic problems. Routine surgery is not indicated, however large or progressive angles are considered indications for surgical correction. We retrospectively analyzed radiographic and clinical parameters as predictors for the final kyphotic angle in spinal tuberculosis to identify patients at risk of non-favorable outcome (progression > 10 degrees and/or a final angle > 40 degrees) at an early stage of the disease; surgery may be indicated here. Included were 53 patients with active spinal TB located in the thoracic (T1 to T10) and thoracolumbar spine (T11 to L2), with initial angles < 40 degrees. Clinical and radiological data were obtained and analyzed. Univariate analysis revealed no statistically significant independent predictors. Multivariate analysis showed that bone loss > 0.3 (fraction, 1.0 is equivalent to a whole body) on the initial radiograph in combination with a thoracolumbar localization indicated a 38% chance of non-favorable outcome, versus only 3% when bone loss was < 0.3 in combination with a thoracic localization. A simple and clinically useful algorithm for prediction of kyphosis in spinal TB is presented.

INTRODUCTION
Tuberculosis (TB) of the spine demineralizes and destroys the vertebral body, causing pain and deformity (kyphosis); even spinal cord compression can occur (Pott's paraplegia). A persisting large kyphosis may cause several problems. Late paraplegia may develop as a result of myelopathy due to chronically irritated and malnourished spinal cord at the punctum maximum of the curve. An operation for late paraplegia is very difficult and prone to major complications without subsidence of the neurological deficit. Another problem with large kyphosis can be ventilatory compromise because of diminished intrathoracic volume. Furthermore, many patients have problems with the cosmetic aspects of a large hunchback.

The British Medical Research Council Working Party on Tuberculosis of the
Spine (MRC) performed a series of trials to investigate the various methods of treatment of spinal TB. They concluded that chemotherapy on an outpatient basis is sufficient to treat the majority of people and routine surgery is not beneficial\textsuperscript{22,23}. This conclusion is attractive since most patients live in countries with limited resources. However, patients who had an initial kyphosis angle > 30 degrees developed mean final angles between 50 and 73 degrees after 10 years\textsuperscript{22}. Many authors state that kyphosis > 30 degrees is likely to deteriorate. Large or progressive angles are considered indications for surgery\textsuperscript{1,13,16-21,25,27,28,33-36}. With modern instrumentation techniques, large kyphotic angles can be corrected and correction can be maintained over the years\textsuperscript{13,19-22,28,34,35}.

Prediction at an early stage of patients at risk of developing large and/or progressive kyphotic angles can guide clinical decision making. Rajasekaran and Shanmugasundaram developed a formula to predict the final kyphotic angle\textsuperscript{23}. Unfortunately they included also patients with severe kyphosis who had a clear indication for surgery. Moreover, the reported accuracy of this formula varies widely (34\% to 90\%)\textsuperscript{23,24}. Therefore, a clear guideline for clinical decision making still lacks.

The aims of this study were to assess which radiographic and clinical parameters are early predictors for the final kyphotic angle in spinal tuberculosis. Our ultimate goal was to develop a means of identification of patients at risk of severe or progressive kyphosis at an early stage of the disease.

**PATIENT AND METHODS**

A retrospective radiographic survey on patients with active spinal TB in the normal range of kyphosis (T1 to L2) was performed. The radiographs and clinical data were obtained from the Beatrixoord Tuberculosis Center of the University Medical Center Groningen in the Netherlands.

Inclusion criteria were patients with active spinal TB. A lesion is active when there is loss of the thin cortical outline and when there is rarefaction of the affected vertebral bodies. Inactive disease is considered bony fusion of the affected vertebral bodies or sclerosis of the contiguous surface of the affected vertebrae with reduction or disappearance of the intervening disc space\textsuperscript{1}. Localization of the lesions had to be in the thoracic (T1 to T10) or thoracolumbar spine (T11 to L2). Furthermore, a minimum follow-up of six months was required, this being the standard treatment period for chemotherapy\textsuperscript{17}. Radiographs at entry and final follow-up had to be of sufficient quality. Only patients older than 15 years of age were included to eliminate possible bias by growth. Patients with initial angles < 40 degrees were considered for this study.

Medical files, microfilms and a computerized archive were used to extract clinical data on age, sex, duration of symptoms, neurology and medication. Radiographs at entry and final follow-up were measured. The bone loss was measured on the initial lateral radiograph using the differences in anterior and posterior height in comparison with adjacent unaffected vertebrae (Figure 1). A negative bone loss means that the total measured surface of the affected vertebra is higher than the mean indexed surface. The initial and final angles were measured on the lateral and AP radiographs (Figure 2). Interobserver reliability of the measurement method for bone loss and deformity angle was assessed by having a randomly selected series of 10 radiographs measured by three independent observers (PJ, SW, BT). They were blinded for the measurement values of the other observers.

**STATISTICAL ANALYSIS**

Comparisons were made between people with a favorable outcome and a non-favorable outcome. A favorable outcome was defined as neither having a final kyphosis of 40 degrees or more, nor having progressed 10 degrees or more from the initially measured angle. An unfavorable outcome was a final kyphosis ≥ 40 degrees or ≥10 degrees of progression. For continuous variables, univariate analysis was performed using the Student t-test for independent samples. The Pearson Chi-square test was used for categorical variables when all cells of the contingency table contained at least five patients. Otherwise the Fisher exact test was used. An intraclass correlation coefficient was used to measure interobserver reliability of the measurement method for bone loss and deformity angle. A multivariate logistic regression with stepwise backward selection was used to identify predictors. Elimination was continued until no variables with a p-value > 0.25 were left. A predefined maximum of two variables in the final multivariate model was considered appropriate to prevent over fitting. A receiver operating characteristic (ROC) curve was used to assess diagnostic performance of the final model. The ROC curve is constructed by plotting the sensitivity on the y-axis and the false-positive rate (1 – specificity) on the x-axis. The larger the area under the curve, the larger the predictive performance of the model. A prediction rule with perfect diagnostic performance would have an area under the ROC curve of 1.0. Flipping coins would have an area under the curve of 0.5. The final regression model was used to construct an easy-to-use algorithm for use in clinical practice. All statistical procedures were performed using the software package SPSS version 12.0 (SPSS, Chicago).

**RESULTS**

Fifty-three patients fulfilled the inclusion criteria, 30 men and 23 women (57\% and 43\%). The patients had a mean age of 46 years with a mean follow-up of 54 months (Table 1). All patients used Isoniazid and 57\% of the patients used Pyrazinamide (Table 2).
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Figure 1
Expected normal vertebral height is calculated by measuring the anterior and posterior vertebral height of the first normal vertebra cranially and caudally from the affected lesion divided by four. The mean height of each affected vertebra is calculated by adding up the anterior and posterior height of the affected vertebra and dividing by two. Bone loss per affected vertebra is then calculated as follows: 1 – (mean height affected vertebra / mean height normal vertebrae). Adding up the bone loss per vertebra will give the total bone loss.

\[
\text{Bone loss A} = 1 - \frac{0.5}{\frac{10+10+10+10}{4}}
\]

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\text{Bone loss B} = 1 - \frac{0.5}{\frac{10+10+10+10}{4}}
\]

\[
\text{Total} = 0.75(A) + 0.50(B) = 1.25
\]

Figure 2
Measurement of the kyphotic angle is done with the method according to Cobb: a straight line is drawn through the superior surface of the first normal vertebra cranially from the lesion, and a second line through the inferior surface of the first normal vertebra caudally from the lesion. These two lines will cross and form angle A'. In mild angles perpendiculars can be drawn, and angle A is measured at their intersection.

Back pain was present in 77% of the patients, and 15% had neurological deficit. The average number of affected vertebrae was 2.1. In 81% of the cases, one or two vertebrae were affected; in 19% three or four (Figure 3). The lesions were located in the thoracic region in 21 patients (40%) and in the thoracolumbar in 32 patients (60%). T11 was most commonly affected (34% of cases) (Figure 4).

An unfavorable outcome was found in eleven patients (21%). In 10 patients (19%) a progression of more than 10 degrees was found. In four patients (8%) a final angle of more than 40 degrees was found. Three of them had a progression of more than 10 degrees as well.

The most powerful predictors for a favorable or non-favorable outcome were bone loss and localization. Univariate analysis indicated that indexed initial bone loss more than 0.3 (OR 8.7, p = 0.07) and thoracolumbar involvement (OR 2.6, p = 0.2) were the most important predictive variables (Table 3). Multivariate analysis showed that the combination of bone loss and localization should be used in the predictive model. The intraclass correlation coefficient of the measurement method to determine bone loss was 0.97.

A 97% chance of a favorable outcome was found when the patient had neither bone loss > 0.3 nor a thoracolumbar localization of the lesion, while a 62% chance of a favorable outcome was found if both of these variables were present. The area under the ROC curve of this predictive model was 0.74 (Figure 5). A clinically useful algorithm was developed using the four possible combinations of the two variables (Table 4).
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Bone loss \( A = 1 - \frac{0 + 5}{2} \times \frac{10 + 10 + 10 + 10}{4} \)

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DISCUSSION

To identify patients at risk of developing severe or progressive kyphosis at an early stage of spinal tuberculosis, an analysis of radiographic and clinical parameters as predictors for the final kyphotic angle was performed. In the absence of bone loss > 0.3 and without thoracolumbar localization the chance of a favorable outcome was 97%, while this was 62% when both of these parameters were present. The area under the ROC curve of this final model was 0.74, indicating an adequate predictive performance.

Patients with initial kyphosis angles > 40 degrees were excluded because deterioration is very likely in this group given the results from the MRC studies. Prediction of the final angle is of minor importance for these more severe cases because they are generally indicated for surgical correction at the time of diagnosis. Many authors even consider a kyphotic angle > 30 degrees or a progressive angle an absolute indication for surgery. We included the patients with a kyphotic angle between 30 and 40 degrees to find out whether this 30-degree limit could be justified with our data. In the group of patients that had initial angles between 30 and 40 degrees there were only 2 of 15 patients that had a non-favorable outcome, compared to 9 of 38 patients that had initial angles < 30 degrees. This suggests that in the absence of pain or neurological deficit there is no need to routinely operate patients with initial kyphosis angles < 40 degrees.

We excluded lumbar lesions from our analysis because physiological lordosis in the lumbar region (L3-L5) interferes with accurate measurement of the gibbous deformity. The large bodies and the vertical articular facets of the lumbar spine allow the collapse to occur more by telescoping than by angulation. The lumbar kyphosis is usually minimal, and expressed as foreshortening of the trunk rather than kyphosis.

A limitation of our study is the large time span in the course of which patients were treated and the different chemotherapy regimens. More specifically, after the introduction of Pyrazinamide relapse rates for pulmonary tuberculosis dropped from 7.8% and 20.3% after two and five years follow-up to 1.4% and 3.4%, respectively. There was no influence of Pyrazinamide on the outcome in our patients. There are no previous reports in the literature about the influence of Pyrazinamide on spinal TB. Other clinical parameters like age, sex and duration of symptoms did not show any predictive value either.

The thoracolumbar area might be more at risk of kyphosis because the rib cage provides no structural support here, which is in concordance with the finding that deformities in cases of thoracolumbar localization of the lesions are larger. It has been stated that the number of affected vertebrae is a determinant of the kyphotic angle: more vertebrae lead to larger kyphotic angles. This was not the case in our analysis. Nineteen percent of our patients had three or four affected vertebrae, and there was no relation with unfavorable outcome.
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Rajasakaran and Shanmugasundaram constructed a formula to predict the final kyphotic angle according to the initial amount of bone loss, independently of lesion localization or initial kyphotic angle\(^\text{25}\). A 90\% accuracy of prediction was reported. However, a cross-validation of the formula revealed that only in 34\% of the cases the correct angle was predicted with a margin of error of 10 degrees. It was concluded that the angle of kyphosis at 10 years cannot be accurately predicted based on the initial vertebral loss in most patients\(^\text{25}\). Applying the original formula on our data it was possible to predict the final angle within 10 degrees in 64\% of our cases. However, the prediction of unfavorable outcome is in our opinion of more value than the prediction of the final angle, considering the margin of error here. We feel that 10 degrees is too wide a margin to guide clinical decision making.

Our ultimate goal was to predict which patients were at risk of an unfavorable outcome, but it turned out that we were better in predicting favorable outcome. Our algorithm is simple and can be used in clinical practice to identify at an early stage of spinal TB those patients at risk of unfavorable outcome as well as patients that will very likely have a favorable outcome. We recommend its use to guide clinical decision-making. Treatment can be started conservatively for all patients with kyphosis angles < 40 degrees, but one should monitor extra carefully those patients with initial bone loss >0.3 in combination with a thoracolumbar localization.

### TABLES

#### Table 1

Descriptive patient characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46</td>
<td>18 to 83</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>54</td>
<td>6 to 238</td>
</tr>
<tr>
<td>Duration of symptoms (months)</td>
<td>13</td>
<td>0 to 192</td>
</tr>
<tr>
<td>Indexed total bone loss T1-L2</td>
<td>0.5</td>
<td>-0.18 to 1.62</td>
</tr>
<tr>
<td>Indexed total bone loss T1-10</td>
<td>0.65</td>
<td>0.11 to 1.62</td>
</tr>
<tr>
<td>Indexed total bone loss T11-L2</td>
<td>0.47</td>
<td>-0.18 to 1.46</td>
</tr>
<tr>
<td>Initial kyphotic angle</td>
<td>20</td>
<td>-22 to 38</td>
</tr>
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<td>Initial anteroposterior deformity angle</td>
<td>4</td>
<td>0 to 16</td>
</tr>
<tr>
<td>Final kyphotic angle</td>
<td>23</td>
<td>-28 to 55</td>
</tr>
</tbody>
</table>

### Table 2

Use of modern drugs in percentages for all patients.

<table>
<thead>
<tr>
<th>Drug regimen</th>
<th>ISO</th>
<th>RIF</th>
<th>PYR</th>
<th>ETH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients</td>
<td>100</td>
<td>47</td>
<td>57</td>
<td>34</td>
</tr>
</tbody>
</table>

ISO=Isoniazid, RIF=Rifampicin, PYR=Pyrazinamide, ETH=Ethambutol

### Table 3

Univariate analysis of favorable versus non-favorable group.

<table>
<thead>
<tr>
<th>Group</th>
<th>Favorable (42)</th>
<th>Non-favorable (11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>49</td>
<td>45</td>
<td>0.6</td>
</tr>
<tr>
<td>Mean initial kyphotic angle</td>
<td>23</td>
<td>20</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean initial AP angle</td>
<td>5</td>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>Female gender</td>
<td>19 (45%)</td>
<td>4 (36%)</td>
<td>0.7</td>
</tr>
<tr>
<td>&gt; 3 affected vertebrae</td>
<td>8 (19%)</td>
<td>2 (18%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pyrazinamide use</td>
<td>22 (52%)</td>
<td>8 (73%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Thoracolumbar involvement</td>
<td>24 (57%)</td>
<td>8 (73%)</td>
<td>0.5</td>
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<td>24 (57%)</td>
<td>10 (91%)</td>
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<tr>
<td>Initial angle 30-40 degrees</td>
<td>13 (31%)</td>
<td>2 (18%)</td>
<td>0.5</td>
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### Table 4

Probability of favorable outcome for all combinations of the two strongest predictors.

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<tr>
<td>Yes</td>
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<td>62%</td>
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<tr>
<td>Yes</td>
<td>No</td>
<td>81%</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>93%</td>
</tr>
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<th>Drug regiment</th>
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<th>RIF</th>
<th>PYR</th>
<th>ETH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients</td>
<td>100</td>
<td>47</td>
<td>57</td>
<td>34</td>
</tr>
</tbody>
</table>

ISO=Isoniazid, RIF=Rifampicin, PYR=Pyrazinamide, ETH=Ethambutol

Table 3
Univariate analysis of favorable versus non-favorable group.

<table>
<thead>
<tr>
<th>Group</th>
<th>Favorable (42)</th>
<th>Non-favorable (11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>49</td>
<td>45</td>
<td>0.6</td>
</tr>
<tr>
<td>Mean initial kyphotic angle</td>
<td>23</td>
<td>20</td>
<td>0.4</td>
</tr>
<tr>
<td>Mean initial AP angle</td>
<td>5</td>
<td>3</td>
<td>0.5</td>
</tr>
<tr>
<td>Female gender</td>
<td>19 (45%)</td>
<td>4 (36%)</td>
<td>0.7</td>
</tr>
<tr>
<td>&gt; 3 affected vertebrae</td>
<td>8 (19%)</td>
<td>2 (18%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Pyrazinamide use</td>
<td>22 (52%)</td>
<td>8 (73%)</td>
<td>0.3</td>
</tr>
<tr>
<td>Thoracolumbar involvement</td>
<td>24 (57%)</td>
<td>8 (73%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Bone loss &gt; 0.3</td>
<td>24 (57%)</td>
<td>10 (91%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Initial angle 30-40 degrees</td>
<td>13 (31%)</td>
<td>2 (18%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Table 4
Probability of favorable outcome for all combinations of the two strongest predictors.

<table>
<thead>
<tr>
<th>&gt;0.3 bone loss</th>
<th>Thoracolumbar involvement</th>
<th>Probability of favorable outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>62%</td>
</tr>
<tr>
<td>Yes</td>
<td>No</td>
<td>81%</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>93%</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>97%</td>
</tr>
</tbody>
</table>


An increasing number of patients with bone and joint tuberculosis (BJTB), including spinal tuberculosis (TB), has been seen in the Netherlands in recent years, raising our orthopaedic interest in TB. In Chapter 2 an analysis was made of this increased incidence. All data were extracted from the Netherlands Tuberculosis Register (NTR) held by the Royal Netherlands Tuberculosis Association KNCV. This unique register contains data on over 95% of all TB patients in the Netherlands from 1993. Between 1993 and 2000, a total of 532 patients with BJTB were registered, 308 (58%) with spinal lesions. This is in accordance with the percentages in the literature.

There was no significant change in the incidence of BJTB in the native Dutch population during the study period. Univariate analysis showed that the increase in incidence was restricted to foreign nationals from endemic areas. They constituted a relatively larger proportion of people with BJTB and spinal TB. The fact that certain ethnic groups showed a significantly higher chance of developing BJTB surprised us. This means that, with the same infection prevalence, some ethnic groups progress more often to BJTB, suggesting a genetic component in TB expression. A detailed genetic analysis might shed new light on this issue.

Regarding the genetics of the micro-organism, DNA type clustering of the different strains of *M. tuberculosis* did not reveal any association between certain strains and BJTB.

The study demonstrated that only 15% of BJTB patients also suffered from pulmonary TB. The routinely taken chest radiograph hardly contributes in differential diagnostics and may never be used to exclude the possibility of spinal TB in differential diagnostics. We cannot compare the Dutch situation to neighbouring countries, as there are no recent reports on this topic in the literature.

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The epidemiological analysis revealed a 3-month doctors’ delay in diagnosis for spinal TB. This clearly demonstrates that many physicians in the Netherlands have a problem diagnosing spinal TB. The potentially devastating consequences of misdiagnosis are illustrated in Chapter 3. Two patients are reported who were misdiagnosed as having malignant lesions of the spine instead of TB. Both received radiotherapy, both experienced growth of the lesion, and in one patient the neurological deficit increased and did not reverse after initiation of the proper TB treatment.

The most common diagnosis in patients with spinal lesions of unknown origin is obviously metastasis. To prove the metastatic origin of a lesion screening is done for primary lesions like carcinoma of the prostate, lung or breast. If the primary lesion is revealed, radiation therapy is started. If not, biopsy is mandatory to confirm malignancy and exclude TB before radiation therapy is started. Radiation