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Original Article

Validation of a scoring system predicting survival and function outcome in patients with metastatic epidural spinal cord compression (MESCC): a prospective and multicenter study

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Abstract: This prospective and multicenter study aims to validate a scoring system which were developed based on a retrospective date set consisting of 206 patients. It can guild surgeons to select the appropriate treatments for patients with MESCC. In this study, we prospectively analyzed 86 patients with MESCC from three hospitals. Those patients were divided into the same three prognostic groups according to our previous scoring system. Kaplan-Meier method and log-rank test were used to compare the survival prognosis in the three groups. ROC curves were performed to estimate the accuracy and c-statistic of the scoring model and the Tomita scoring model. This study was registered at Chinese Clinical Trial Registry (ChiCTR-POC-16008393). The median survival time was 3.9 months for patients with 0-2 points, 6.7 months for those with 3-5 points, and 12 months for those with 6-9 points, respectively (P<0.01). The corresponding postoperative ambulatory rates were 55.6%, 73.5%, and 94.1%, respectively (P<0.01). The ROC curve c-statistics for the scores as a predictor of 3, 6, and 12 months survival rates were 0.75, 0.74, and 0.70, respectively. The corresponding ROC curve c-statistics for the Tomita scores were 0.70, 0.68, and 0.66, respectively. This scoring system should be considered valid and reproducible to estimate the survival prognosis and functional outcome. This scoring model can help select the optimal therapy for patients with MESCC, and its capability to predict survival prognosis was relatively better than the Tomita scoring system.

Keywords: Metastatic epidural spinal cord compression, prospective and multicenter study, validation, scoring system, survival prognosis

Introduction

Metastatic epidural spinal cord compression (MESCC), a common complication of malignant tumors, occurs when malignant tumors metastasize to the vertebra or epidural space and consequently causes spinal cord compression in approximately 10% of patients with some type of tumor [1]. MESCC can lead to significant pain and neurological symptoms which negatively impacts the patient's quality of remaining life [2]. The therapeutic aims are to relieve pain, improve or maintain neurological status, and even prolong survival prognosis, which need the interplay with radiology, radio-oncology and medical oncology [1-3]. Survival prognosis and function outcome should be considered to choose optimal treatments for those patients. Survival prognosis and function outcome can be estimated with scoring systems [4-7].

Previously, we retrospectively developed a new scoring system to estimate the survival prognosis and functional outcome by analyzing 206 patients [7]. This scoring system included five prognostic factors: primary site, preoperative ambulatory status, visceral metastases, preoperative chemotherapy, and bone metastasis at cancer diagnosis. However, this scoring system was not validated. Therefore, this study was designed to validate the scoring system in a prospective and multicenter data set. Besides,

Table 1. The new scoring system for patients with MESCC

Prognostic factors	Scores
Primary site	
Slow growth	2
Moderate growth	1
Rapid growth	0
Preoperative ambulatory status	
Ambulatory	2
Not Ambulatory	0
Visceral metastases	
No	3
Yes	0
Preoperative chemotherapy	
No	0
Yes	2
Bone metastasis at cancer diagnosis	
No	1
Yes	0
Prognostic groups	
Group A	0-2
Group B	3-5
Group C	6-10

Abbreviations: MESCC, Metastatic epidural spinal cord compression. Slow growth: hormone-dependent breast cancer, hormone-dependent prostate cancer, thyroid cancer, multiple myeloma, and malignant lymphoma. Moderate growth: lung cancer treated with molecularly targeted drugs, hormone-independent breast cancer, hormone-independent prostate cancer, renal cell carcinoma, endometrial cancer, ovarian cancer, and sarcoma. Rapid growth: lung cancer without molecularly targeted drugs, colorectal cancer, gastric cancer, pancreatic cancer, esophageal cancer, other urological cancers, hepatocellular carcinoma, head and neck cancer, melanoma, malignant thymoma and cancers of unknown origin.

the capability of the score was calculated in the study.

Patients and methods

Patients

We prospectively analyzed patients with MESCC between July 2015 and September 2016 from three hospitals. The inclusion criteria were as follows. Firstly, MRI evidence of spinal cord compression. Secondly, neurological deficits due to MESCC. Thirdly, tissue-proven diagnosis of bone metastasis or MRI (CT) indicting bone metastasis. Lastly, paralysis less than 42 hours. Exclusion criteria were as follows. Firstly, age less than 18 years old. Secondly, intradural metastases. Thirdly, fracture in the lower limbs, which may has impacts on the estimation of postoperative function outcome. Lastly, uncooperation with follow-up.

This study was registered at Clinical Trial Registry (ChiCTR-POC-16008393). This study was approved by the Medical Research Ethics Board of the three hospitals, and informed consents for review of patients' images and medical records were obtained.

Previous scoring system

Previously, we retrospectively developed a scoring system by analyzing a series of 206 cases in a single institution to estimate the survival and function outcome of patients with MESCC. This scoring system included the following five prognostic factors. Primary site, preoperative ambulatory status, visceral metastases, preoperative chemotherapy, and bone metastasis at cancer diagnosis. For each of the above mentioned five prognostic characteristics, the scoring points were obtained from the hazard ratios based on the multiple Cox proportional hazards regression model (round values). The total prognostic score for each patient was the sum of the scoring points of the five significant prognostic characteristics. The total prognostic scores were ranged from 0 to 10 points, and three risk groups were designed according to 6-month survival rate and median survival time of each prognostic score. Patients with 0 to 2 points were regarded as group A, patients with 3 to 5 points were considered as group B, and 6 to 10 points were group C (**Table 1**). Patients with scores more than 3 points were recommended to surgery (Case report was shown in **Figure 1**). Kaplan-Meier method and log-rank test were used to compare the survival prognosis in the above mentioned three groups, and Chi-square test was used to estimate difference in ambulatory rate according to the scoring system.

The scoring system would be applied in the same way in the present study to validate whether the scoring system was reproducible. Three prognostic groups were designed to be consistent with the previous scoring system. Besides, in order to evaluate and compare the capabilities of the scoring system and other scoring systems (Perhaps, the Tomita scoring system was the most widely used scoring mod-

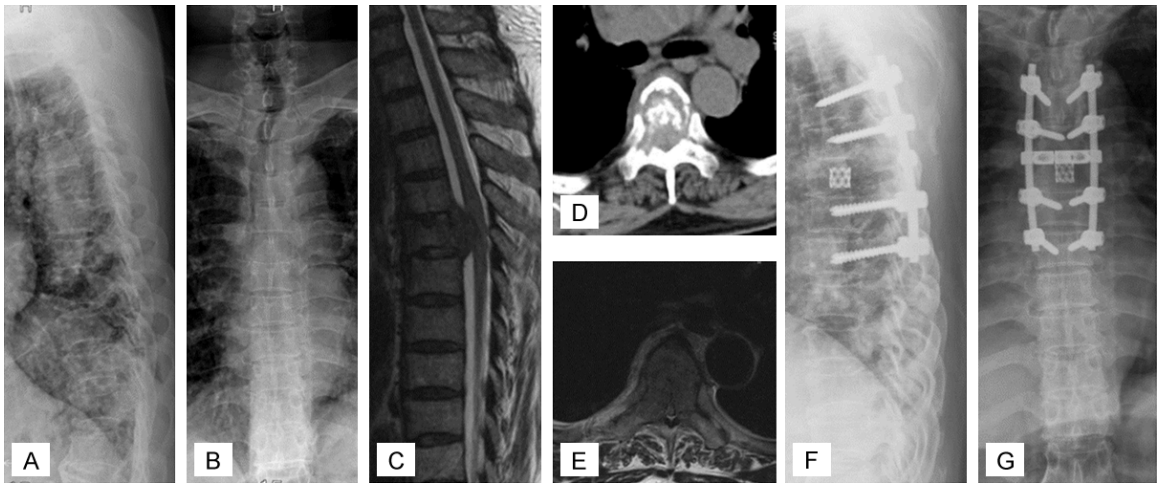

Figure 1. A 67-year-old man who unable to walk due to metastatic epidural spinal cord compression (MESCC) resulted from prostate cancer. A and B. Preoperative X-ray presented vertebral collapse at T5. C. Preoperative MRI showed spinal cord compression at T5. D. Preoperative CT showed bone destruction at T5. E. Preoperative MRI showed spinal cord compression at T5. F and G. Following laminectomy at T4 and T5, and pedicle screw fixation was conducted at T3, T4, T6, and T7 to spine stabilization. He died at postoperative 9.2 months and spine stability was maintained throughout the survival period.

Table 2. Patient's characteristics of the three hospitals

Characteristics	Hospitals			Total (N=86)	P
	A (n=34)	B (n=25)	C (n=27)		
Gender					
Male	18	14	16	48	0.89
Female	16	11	11	38	
Age (mean)	59.2	55.2	56.2	56.9	0.26
Primary site					
Slow growth	5	9	8	22	0.29
Moderate growth	14	5	9	28	
Rapid growth	15	11	10	36	
Preoperative ambulatory status					
Ambulatory	25	17	17	59	0.68
Not Ambulatory	9	8	10	27	
Visceral metastases					
No	19	11	13	43	0.65
Yes	15	14	14	43	
Preoperative chemotherapy					
No	26	21	20	67	0.67
Yes	8	4	7	19	
Bone metastasis at cancer diagnosis					
No	15	15	20	50	0.06
Yes	19	10	7	36	
Median survival (m)	6.4	9.2	7.5	7.5	0.25

Hospital A: the First People's Hospital of Shanghai Jiao Tong University, B: Xiangya Hospital Central South University, and C: the Affiliated Hospital of Academy of Military Medical Sciences.

els in clinical routine), the receiver operating characteristic (ROC) curve c-statistics were calculated in the study. When we initially designed this study, visceral metastasis was recorded as being present or not present. In the analysis of the c-statistics for the Tomita score, if the patients presented with visceral metastasis, they were regarded as "non-removable".

Statistical analysis

Chi-square test, Wilcoxon analysis and Kruskal-Wallia test were used to compare the distribution of patient's characteristics in three hospitals. Kaplan-Meier method and log-rank test were used to compare the survival prognosis. Chi-square test was used to compare ambulatory rate according to the scoring system. ROC curves were performed to estimate the accuracy and c-statistic of the scoring model and the Tomita scoring model for the prediction of three, six, and twelve months survival rates. The c statistic is equivalent to the area under ROC curve, and it is the probability of concordance between predicted and observed survival. The c statistic value of 0.7 to 0.8 indicting a useful scoring system and of more than 0.8 indicating a good scoring system. Statistical significance

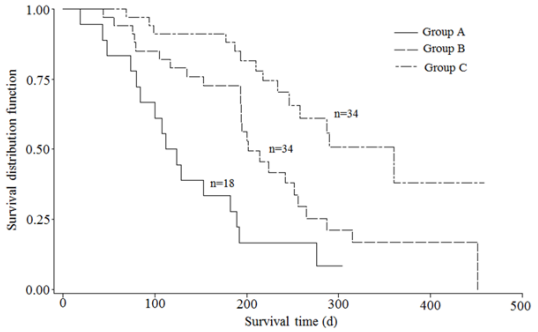

Figure 2. Survival curves for the three prognostic groups (P<0.01, log-rank test).

was determined as P<0.05, and statistical analysis was carried out using SAS 9.2 software.

Results

Patient's characteristics

As a result, 89 patients were enrolled in the study, but three of them were lost follow-up within a month. Thus, 86 patients were analyzed in this present study (The First People's Hospital of Shanghai Jiao Tong University: 34 cases, the Xiangya Hospital Central South University: 25 cases, and the Affiliated Hospital of Academy of Military Medical Sciences: 27 cases). In the entire cohort of patients, 22 patients with slow growth cancer, 28 patients with moderate growth cancer, and 36 patients with rapid growth cancer. Lung were the most common primary site, and lung cancer occurred in 33 patients. Sixty-three patients were treated with surgery, and twenty-three patients were treated with non-operative treatments. In the surgically treated patients, 54 patients were operated with posterior decompressive surgery and spine stabilization, 6 patients were operated with anterior procedures, and 3 patients were operated with anterior and posterior procedures. The median overall survival was 7.5 months (95% CI, 6.5-8.6 months), and 6-month and 12-month survival rates were 69.2% and 24%, respectively. At the latest follow up, 25 patients were alive with a mean follow-up of 9.7 months (range, 4.1-15.3 months), and 6 patients who were lost follow-up had a mean follow-up of 5.9 months (range, 2.3-7.8 months). **Table 2** showed the patient's characteristics, which demonstrated that the distribution of characteristics was similar in three hospitals (P>0.05).

Validation of the scores

In the present study, the median survival time was 3.9 months (95% CI, 2.7-6.1 months) for patients with 0-2 points, 6.7 months (95% CI, 6.4-8.5 months) for those with 3-5 points, and 12 months (The lower limit of 95% CI: 8.2 months) for those with 6-9 points, respectively. The corresponding 6-months survival rates was 27.8%, 66.0%, and 88.0%, respectively (P< 0.01, **Figure 2**). In the previous study, the corresponding median survival time was 3.3 months, 6.6 months, and 16.4 months, respectively, and the corresponding 6-months survival rates were 8.2%, 56.5%, and 91.5%, respectively.

In the current study, the ROC curve c-statistic for the scores as a predictor of 3 months survival rate was 0.75 (OR, 0.66, 95% CI: 0.49-0.88, P<0.01), c-statistic as a predictor of 6 months survival rate was 0.74 (OR, 0.65, 95% CI: 0.52-0.82), and c-statistic as a predictor of 12 months survival rate was 0.70 (OR, 0.73, 95% CI: 0.53-1.01) (Supplementary Figures 1, 2, 3). The accuracy rates for predicting 3, 6, and 12 months survival were 69.1%, 69.2%, and 64.9%, respectively. The ROC curve c-statistics for the Tomita scores as a predictor of 3 months, 6 months, and 12 months survival rate were 0.70 (OR, 1.35, 95% CI: 1.05-1.75), 0.68 (OR, 1.31, 95% CI: 1.09-1.59), and 0.66 (OR, 1.26, 95% CI: 0.95-1.67), respectively (Supplementary Figures 4, 5, 6). The accuracy rates for predicting 3, 6, and 12 months survival were 58.4%, 58.4%, and 56.4 %, respectively.

The postoperative ambulatory rates were 55.6% in patients with 0-2 points, 73.5% in patients with 3-5 points, and 94.1% in patients with 6-10 points, respectively (P<0.01, **Table 3**). In the previous study, the corresponding ambulatory rates were 35.7%, 73.3%, and 95.9%, respectively. In the entire cohort of patients, 77.9% patients (67/86) had the ability to walk after surgery, and 51.9% (14/27) of nonambulatory patients before operation became ambulatory after surgery.

Discussion

Personalized treatment has been widely studied in the palliative context of MESCC. Rades *et al*. [8] clearly showed that the outcome of radiotherapy alone appeared similar to those of sur-

Table 3. Ambulatory status of the patients in the three prognostic groups 4 weeks after surgery or conservative treatments. *P*-value was obtained from Chi-square test

Groups	Scores	Patients (n)	Neurological status		*P*-value
			Not ambulatory	ambulatory	
A	0-2	18	8	10	<0.01
B	3-5	34	9	25	
C	6-10	34	2	32	

gery plus radiotherapy. However, many other investigations revealed that direct decompressive and stabilized surgery followed by radiotherapy was superior to radiotherapy alone in terms of postoperative ambulatory status, pain outcome, and even survival prognosis for selected patients [9-11]. The personalized treatment for patients with MESCC should consider the patient's survival and function outcome [4-7]. In general, patients with shortest survival time and poorest function outcome appear to be best treated with radiotherapy or best supportive care alone. Patients with preferable survival prognosis and function outcome can be treated with surgery to realize better local control of disease and improvement of patient's quality of remaining life.

Previously, we retrospectively developed a new scoring system to estimate the survival prognosis and functional outcome by analyzing 206 patients [7]. This scoring system included five prognostic factors: primary site, preoperative ambulatory status, visceral metastases, preoperative chemotherapy, and bone metastasis at cancer diagnosis. The prognostic scores ranged from 0 to 10 points, and three risk groups were designed. There were those with 0 to 2 points (Group A), those with 3 to 5 points (Group B), and those with 6 to 10 points (Group C). The corresponding median overall survival time was 3.3 months, 6.6 months, and 16.4 months, respectively, the 6-month survival rates were 8.2%, 56.5%, and 91.5%, respectively, and the corresponding ambulatory rates were 35.7%, 73.3%, and 95.9%, respectively.

However, this scoring system was not validated. In the present study, we validated the scoring system in a prospective and multicenter data set. Eighty-six patients who were from three different hospitals were included in the study. The median survival time was 3.9 months for patients with 0-2 points, 6.7 months for those with 3-5 points, and 12 months for those with 6-9 points. The corresponding 6-months survival rates was 27.8%, 66.0%, and 88.0%, respectively. The results were similar to those in our previous study. The ROC curve c-statistic for the scores as a predictor of 3 months survival rate was 0.75, c-statistic as a predictor of 6 months survival rate was 0.74, and c-statistic as a predictor of 12 months survival rate was 0.70. The accuracy rates for predicting 3, 6, and 12 months survival were 69.1%, 69.2%, and 64.9%, respectively. The ROC curve c-statistics for the Tomita scores as a predictor of 3 months, 6 months, and 12 months survival rate were 0.70, 0.68, and 0.66, respectively. The corresponding accuracy rates for predicting 3, 6, and 12 months survival were 58.4%, 58.4%, and 56.4 %, respectively. Those founding showed that the capability of the scores to predict survival prognosis was relatively better than the Tomita scoring system.

In conclusion, this scoring system should be considered valid and reproducible to estimate the survival prognosis and functional outcome. This scoring model can help select the optimal therapy for patients with MESCC, and its capability to predict survival prognosis was relatively better than the Tomita scoring system.

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Disclosure of conflict of interest

None.

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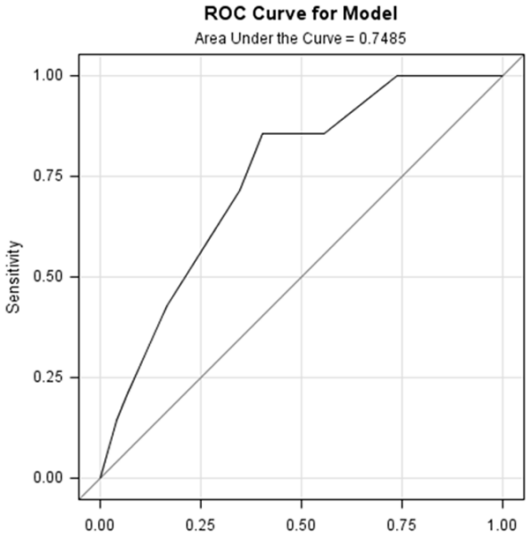
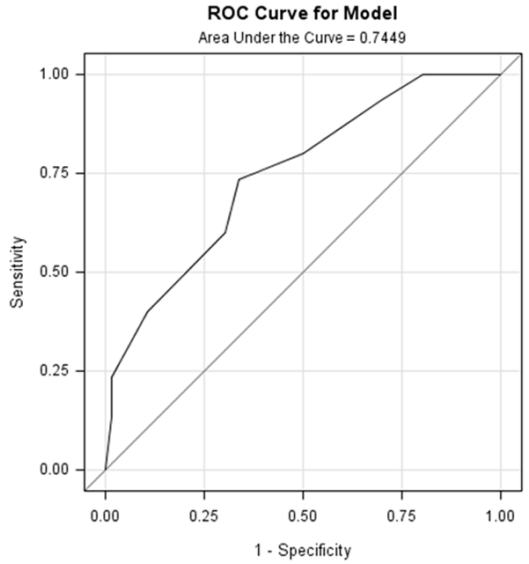
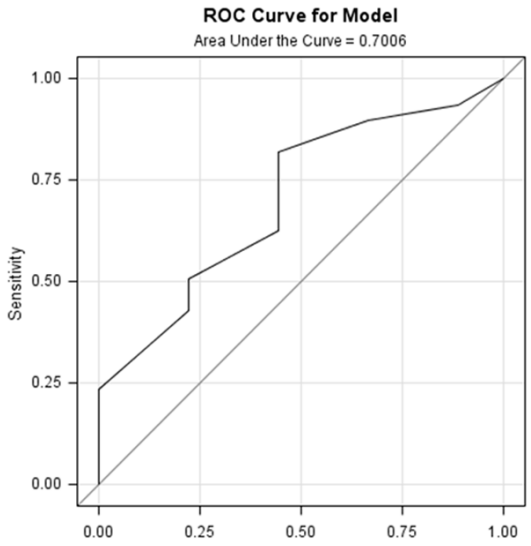


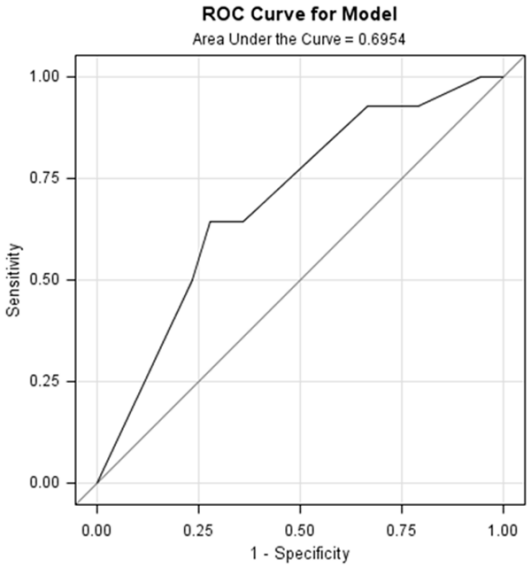
Supplementary Figure 1. ROC curve for the scores as a predictor of 3 months survival rate.



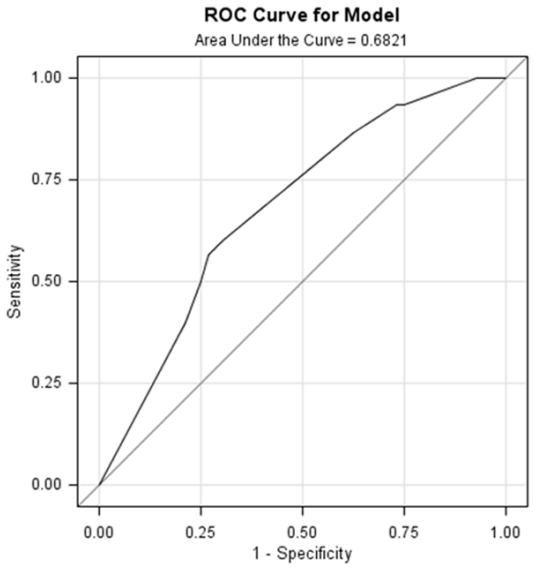
Supplementary Figure 2. ROC curve for the scores as a predictor of 6 months survival rate.



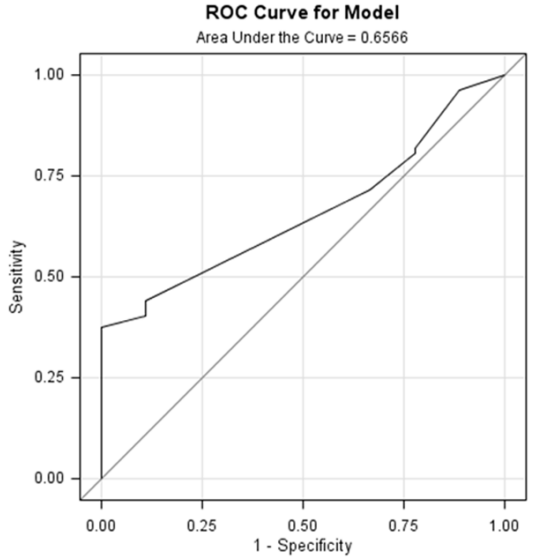
Supplementary Figure 3. ROC curve for the scores as a predictor of 12 months survival rate.



Supplementary Figure 4. ROC curve for the Tomita scores as a predictor of 3 months survival rate.



Supplementary Figure 5. ROC curve for the Tomita scores as a predictor of 6 months survival rate.



Supplementary Figure 6. ROC curve for the Tomita scores as a predictor of 12 months survival rate.