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Original Article

Prediction of postoperative ambulatory status in patients with spinal cord compression resulted from metastatic cancers

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Abstract: This study aims to create a scoring model with which to predict postoperative ambulatory status and guild surgeons to select the appropriate therapy for patients with metastatic epidural spinal cord compression (MESCC). We retrospectively reviewed the records of 104 surgically treated patients with MESCC. Twelve preoperative characteristics were analyzed for postoperative ambulatory outcome. Significant factors were included in the scoring model. The c-statistic of ROC curve was calculated to assess the performance of the scoring model. Survival prognosis was also estimated according to the scoring model. The scoring model included four prognostic factors, namely, primary cancer type (P=0.04), preoperative ambulatory status (P=0.02), visceral metastases (P<0.01), and circumferential angle of spinal cord compression (CASCC, P=0.04). The prognostic scores ranged between 3 and 13 points, and three prognostic groups were designed. There were 3-5 points (group A, n=22), 6-8 points (Group B, n=43), and 9-13 points (group C, n=39). The corresponding postoperative ambulatory rates were 40.9%, 69.8%, and 97.4%, respectively (P<0.01), and the corresponding median survival was 4.1 months, 7.3 months, and 9.0 months, respectively (P<0.01). The ROC curve c-statistic for the prognostic groups as a predictor of postoperative ambulatory rate was 0.79. We created a useful scoring model for predicting postoperative ambulatory status in MESCC patients after surgery. Patients with 3 to 5 points who had relatively poor ambulatory outcome and short life expectancy appeared to be best treated with supportive care, patients with 6 to 8 points should be decompressive surgical candidates because the ambulatory outcome and survival prognosis were acceptable, and in patients with 9 to 13 points who had excellent function and survival outcome, more radical surgery should be considered.

Keywords: Metastatic cancer, spinal cord compression, ambulatory status, prognostic factors, scoring model

Introduction

Metastatic epidural spinal cord compression (MESCC) is an oncological emergency, which often leads to spinal cord edema, vascular damage, and even necrosis, thus consequently causing severe symptoms, impairing patient's ambulatory ability, and worsening patient's quality of remaining life [1, 2]. Prediction of function outcome is of importance when select the appropriate treatment for MESCC patients [3], since function outcome plays an essential role in patient's quality of life. In general, in patients with poor ambulatory and survival outcome, moderate interventions would do more comfort and less harm, while in patients with preferable ambulatory and survival prognosis, radical therapies should be taken into account in order to realize better control of local disease [4-6].

Above mentioned prediction can be achieved with the help of prognostic factors and scoring systems. Favorable ambulatory outcome was known to be associated with the duration of paralysis less than 48 hours [7, 8], pre-treatment ambulation [9], and surgery [10, 11]. In 2008, Rades et al. [3] proposed a scoring system for the prediction of post-radiotherapy ambulatory outcome in a large population to help doctors to identify best candidates for supportive care, surgery, or radiotherapy alone. The scoring system included five prognostic factors, namely, primary tumor type, interval between tumor diagnosis and MESCC, visceral metastases, motor function, and time developing motor

deficits. However, to our knowledge, participants included in the study of Rades were treated with radiotherapy alone. Moreover, the data that hormone sensitive cancer patients with MESCC had better neurological outcome than the patients with hormone refractory tumor after surgery have been shown in some studies [12-14]. Thus, preoperative systematic treatments should be considered.

Therefore, this study aims to create a new scoring model for predicting ambulatory status in patients with MESCC after surgical decompression and spine stabilization. The accuracy of the scoring model was calculated, and several new parameters, such as circumferential angle of spinal cord compression (CASCC), were identified for postoperative ambulatory outcome. Besides, preoperative systematic treatments were considered in the present study.

Patients and methods

Patients

We retrospectively analyzed the records of 104 surgically treated patients with metastatic epidural spinal cord compression at the Affiliated Hospital of Academy of Military Medical Sciences, Beijing, between January 2012 and December 2015. MESCC was confirmed by MRI, and bone metastasis was histologically proved. Patients were performed with surgical decompression and spine stabilization (laminectomy plus stabilization of vertebrae). Neurological deficit due to spinal cord compression was the surgical indication. The exclusion criteria were as follows: (1) age less than 18-year-old, (2) paralysis more than 42 hours, (3) health too poor to undergo surgery, (4) patients with history of other neuropathic diseases which may interfere with motor function, (5) motor deficit due to pathological fracture in the lower limbs, (6) intradural metastasis, (7) incomplete MRI and CT imaging which is necessary for data collection. This study was approved by the Medical Research Ethics Board of the Affiliated Hospital of Academy of Military Medical Sciences.

Ambulatory outcome analysis

Twelve preoperative characteristics, namely, age (≤56 years vs. >56 years, conformed to previous studies), gender (female vs. male), primary cancer types (slow growth vs. moderate growth vs. rapid growth), preoperative ambulatory status (ambulatory vs. not ambulatory), Eastern Cooperative Oncology Group (ECOG) performance status (1-2 vs. 3-4), number of involved vertebrae (1-2 vs. ≥3, conformed to previous studies), visceral metastases (no vs. yes), preoperative chemotherapy (no vs. yes), bone metastasis at cancer diagnosis (no vs. yes), the time developing motor deficits (≤14 days vs. >14 days, conformed to previous studies), CASCC (0°~179° vs. 180°~360°), and radical surgery at primary site (no vs. yes), were retrospectively analyzed for postoperative ambulatory outcome in a single institution.

Primary cancer type was stratified into three subgroups based on survival prognosis [15]. There were as follows: (1) Rapid growth cancers, including lung cancer without molecularly targeted drugs, colorectal cancer, esophageal cancer, hepatocellular carcinoma, head and neck cancer, melanoma, malignant thymoma, gastric cancer, pancreatic cancer, and cancers of unknown origin; (2) Moderate growth cancers, including lung cancer treated with molecularly targeted drugs, hormone-independent breast/prostate cancer, renal cell carcinoma, endometrial cancer, ovarian cancer, and sarcoma; and (3) Slow growth cancers, including hormone-dependent breast/prostate cancer, thyroid cancer, multiple myeloma, and malignant lymphoma.

CASCC was defined as the centre angle of spinal cord circle, $\angle$ AOB. O was the centre of spinal cord circle, A and B were the compression points on the circle [16]. Postoperative ambulatory outcome was measured 4 weeks after surgery. Neurological status was determined by Frankel scores. Patients with Frankel A to C (non-ambulatory) were paralysis, while patients with Frankel D to E (ambulatory) were non-paralysis. Being ambulatory with or without aid was regarded as ambulatory status. Adjuvant radiotherapy, systematic chemotherapy, or targeted drug was routinely given approximately 4 weeks after surgery in our department, so we believe that the ambulatory status at 4 weeks primarily reflects the effect of decompressive surgery.

Survival analysis

The median postoperative survival time and survival rates were calculated in the entire cohort of patients and in each prognostic groups. The postoperative survival was defined as the period between the date of operation and death or the latest follow-up. Patients who were alive at the last follow-up were censored in the postoperative survival analysis.

Table 1. Univariate and multivariate analysis of preoperative characteristics for postoperative ambulatory status in patients with MESCC after surgical decompression and spine stabilization

Characteristics	Patients (n)	Simple logistic regression		Multiple logistic regression	
		OR (95% CI)	*P*	OR (95% CI)	*P*
Age					
≤56 years	55	1.06 (0.44-2.54)	0.90	NI	
>56 years	49				
Gender					
Female	54	1.23 (0.51-2.95)	0.65	NI	
Male	50				
Primary cancer type					
Slow growth	23	2.06 (1.09-3.92)	0.02	2.15 (1.02-4.53)	0.04
Moderate growth	28				
Rapid growth	53				
Preoperative ambulatory status					
Ambulatory	62	4.42 (1.74-11.24)	<0.01	3.41 (1.13-10.30)	0.02
Not Ambulatory	42				
ECOG performance status					
1-2	50	2.85 (1.11-7.30)	0.03	NI	
3-4	54				
Number of involved vertebrae					
1-2	54	1.50 (0.62-3.62)	0.37	NI	
≥3	50				
Visceral metastases					
No	56	3.13 (1.25-7.88)	0.01	4.08 (1.41-11.81)	□0.01
Yes	48				
Preoperative chemotherapy					
No	67	1.82 (0.69-4.84)	0.23	NI	
Yes	37				
Bone metastasis at cancer diagnosis					
No	48	2.05 (0.82-5.13)	0.12	NI	
Yes	56				
Time developing motor deficits					
≤14 days	54	1.23 (0.51-2.95)	0.65	NI	
>14 days	50				
CASCC					
0°~179°	48	5.57 (1.91-16.23)	<0.01	3.73 (1.08-12.86)	0.04
180°~360°	56				
Radical surgery at primary site					
No	66	1.93 (0.73-5.10)	0.19	NI	
Yes	38				

Abbreviations: MESCC, Metastatic epidural spinal cord compression; OR, odds ratio; CI, confidence interval; NI, not included; ECOG, Eastern Cooperative Oncology Group; CASCC, circumferential angle of spinal cord compression.

Statistical analysis

CASCC was assessed by Adobe Photoshop CS6. Univariate and multivariate analysis of preoperative characteristics for postoperative ambulatory status were performed by the simple and multiple logistic regression models, respectively. Significant characteristics for postoperative ambulatory status according to the multivariate analysis were included in the scoring model. The scoring point for each significant factor was obtained from the odds

Table 2. A scoring system for predicting ambulatory status in patients with MESCC after surgical decompression and spine stabilization

Prognostic factors	OR	Scores
Primary site		
Slow growth	2.15	2
Moderate growth		1
Rapid growth		0
Preoperative ambulatory status		
Ambulatory	3.41	3
Not Ambulatory		1
Visceral metastases		
No	4.08	4
Yes		1
CASCC		
0°~179°	3.73	4
180°~360°		1
Prognostic groups	Patients (n)	
Group A	22	3-5
Group B	43	6-8
Group C	39	9-13

Abbreviations: MESCC, metastatic epidural spinal cord compression; OR, odds ratio; CASCC, circumferential angle of 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.

ratios, which were rounded off to the nearest integer, on multiple logistic regression model. The total prognostic score of each patients represents the sum of all the scores from the significant prognostic characteristics. Receiver operating characteristic (ROC) curve was used to calculate the accuracy and c-statistic of the scoring model for predicting ambulatory rates was also given. The c statistic which is equivalent to the area under ROC curve is the probability of concordance between predicted and observed survival, with a value of 0.7 to 0.8 representing a useful scoring model and a value of more than 0.8 indicating a good scoring model. Ambulatory status in prognostic groups was compared with Chi-square test. Survival prognosis of prognostic groups was analyzed by Kaplan-Meier method and log-rank test. A *P* value of 0.05 or less was considered statistical significance. Statistical analysis was performed using SAS 9.2.

Results

Patient's characteristics

In the series of 104 patients, 50 patients were male and 54 patients were female. The median age was 56 years old (95% CI: 52-59 years old). Of the 104 patients, 53 patients (51%) with rapid growth cancer, 28 patients (26.9%) with moderate growth cancer, and 23 patients (22.1%) with slow growth cancer. Lung cancer was the most common primary cancer type (n=45, 33 patients with lung cancer without molecularly targeted drugs and 12 patients with lung cancer treated with molecularly targeted drugs), followed by breast cancer (n=25, 16 patients with hormone-dependent breast cancer and 9 patients with hormone-independent breast cancer). Other primary cancer types were prostate cancer (5 cases), hepatocellular carcinoma (4 cases), and renal cell carcinoma (3 cases). At the last follow-up, twenty patients were still alive with a mean follow-up of 5.1 months (range, 1.0 to 26.9 months).

Scoring model for postoperative ambulatory status

According to the simple logistic regression model, of the twelve investigated preoperative characteristics, five were significantly associated with postoperative ambulatory outcome (**Table 1**), namely, primary cancer type (OR, 2.06, 95% CI: 1.09-3.92; P=0.02), preoperative ambulatory status (OR, 4.42, 95% CI: 1.74-11.24; P<0.01), ECOG performance status (OR, 2.85, 95% CI: 1.11-7.30; P=0.03), visceral metastases (OR, 3.13, 95% CI: 1.25-7.88; P=0.01), and CASCC (OR, 5.57, 95% CI: 1.91-16.23; P<0.01). Based on the multiple logistic regression model, four of above mentioned five prognostic factors, primary cancer type (OR, 2.15, 95% CI: 1.02-4.53; P=0.04), preoperative ambulatory status (OR, 3.41, 95% CI: 1.13-10.30; P=0.02), visceral metastases (OR, 4.08, 95% CI: 1.41-11.81; P<0.01), and CASCC (OR, 3.73, 95% CI: 1.08-12.86; P=0.04) maintained significant impact on postoperative ambulatory outcome, and these factors were included in the scoring model. The scoring points for each of the four significant characteristics were

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

Groups	Scores	Patients (n)	Ambulatory status		*P*-value
			Not ambulatory (%)	Ambulatory (%)	
A	3-5	22	59.1	40.9	<0.01
B	6-8	43	30.2	69.8	
C	9-13	39	2.6	97.4	

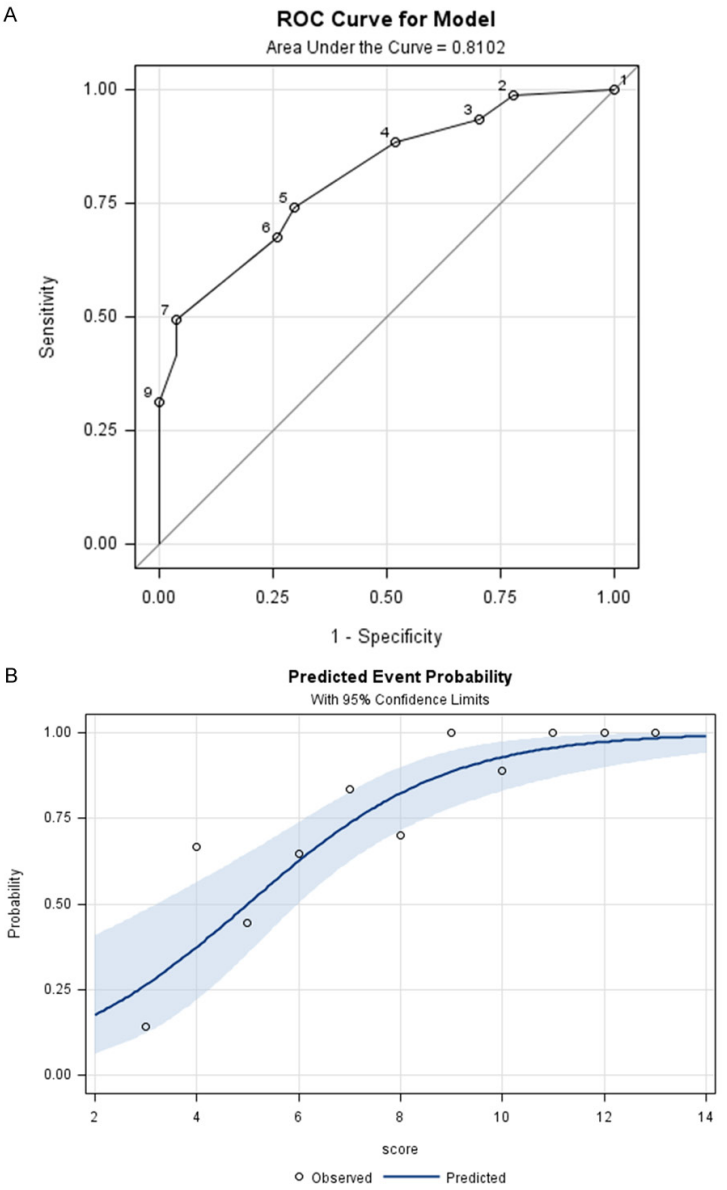

Figure 1. A: The ROC curve for the prognostic scores as a predictor of postoperative ambulatory rate. B: The predicted and observed postoperative ambulatory rates of prognostic scores as a predictor.

obtained from the odds ratios based on the multiple logistic regression model (**Table 2**). The odds ratios were rounded off to the nearest integer.

The prognostic score for each patient was calculated by adding the scoring points of the four significant preoperative characteristics. An example of how the prognostic score for each patient was assessed as follows. A lung cancer patient who was treated with Gefitinib (score =1 point) was ambulatory (score =3 points) and presented with visceral metastases (score =1 point). The CASCC of the patient was more than 180° (score =1 point). Therefore, the prognostic score of the patient was 1+3+1+1=6 points.

The prognostic scores ranged from 3 to 13 points. Three prognostic groups were designed based on the postoperative ambulatory rates of each prognostic score. There were as follows. 3-5 points (group A, n=22), 6-8 points (Group B, n=43), and 9-13 points (group C, n=39). The corresponding postoperative ambulatory rates were 40.9%, 69.8%, and 97.4%, respectively (P<0.01, **Table 3**).

In the entire cohort of patients, 59.6% (62/104) patients was ambulatory before surgery, and 74.0% (77/104) patients had ability to walk after surgery (P=0.02). 57.1% (24/42) non-ambulatory patients regained the ambulatory status, and 85.5% (53/62) ambulatory patients maintained the ability to walk after surgery.

Accuracy of the scoring model

The ROC curve c-statistic for the prognostic scores as a predictor of postoperative ambulatory rate was 0.81 (**Figure 1A**). The accuracy rate for predicting postoperative ambulatory rate was 76.3%, and the predicted and observed postoperative ambulatory rates were shown in **Figure 1B**. The

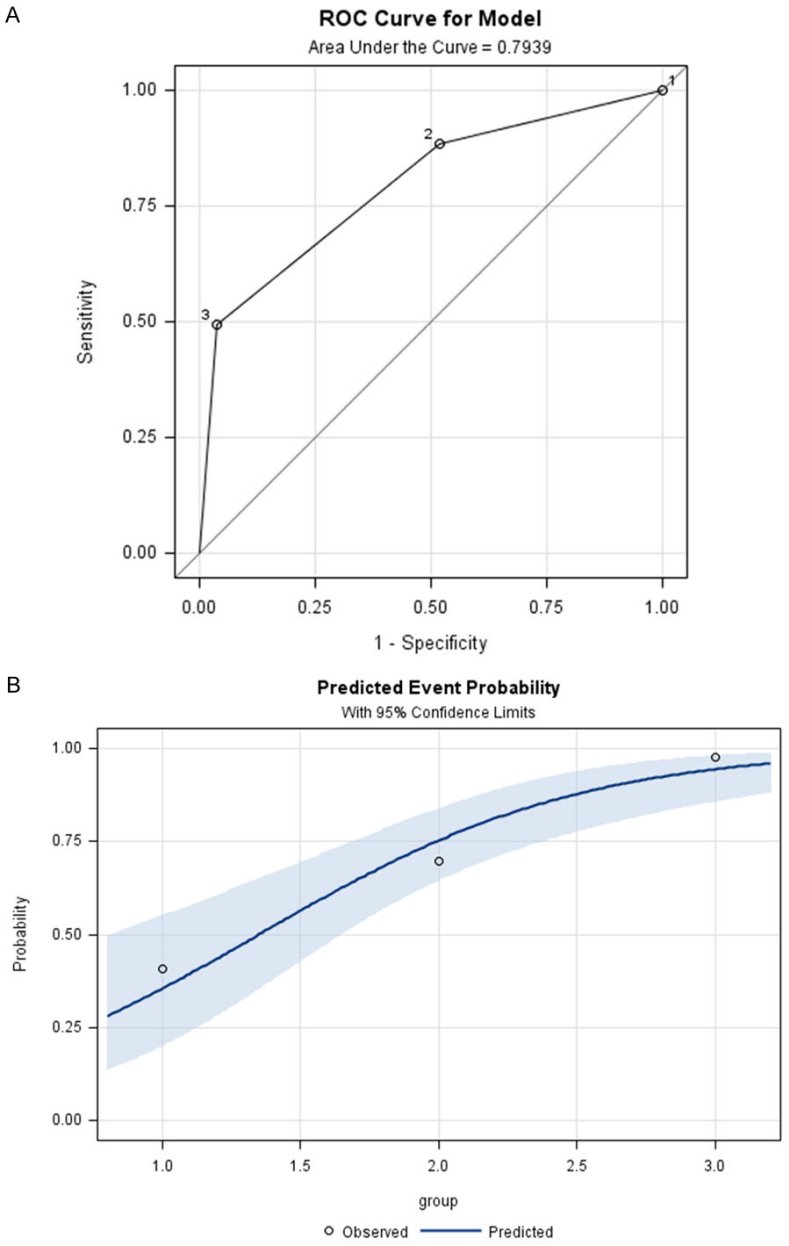

Figure 2. A: The ROC curve for the prognostic groups as a predictor of postoperative ambulatory rate. B: The predicted and observed postoperative ambulatory rates of prognostic groups as a predictor.

ROC curve c-statistic for the prognostic groups as a predictor of postoperative ambulatory rate was 0.79 (**Figure 2A**). The accuracy rate for predicting postoperative ambulatory rate was 66.3%, and the predicted and observed postoperative ambulatory rates were shown in **Figure 2B**.

Survival analysis

The median survival was 4.1 months (95% CI, 1.5-5.7 months) in group A, 7.3 months (95% CI, 5.1-9.1 months) in group B, and 9.0 months (95% CI, 6.4-15.0 months) in group C. The corresponding 6-month survival rates were 22.9%, 60.8%, and, 76.4%, and the 12-month survival rates were 0%, 24.3%, and 44.7%, respectively (P< 0.01, log-rank test, **Figure 3**).

In the entire cohort of patients, the median survival was 7.1 months (95% CI, 5.7-8.4 months), the 6-month survival rate was 59.7%, and the 12-month survival rate was 27.6%.

Discussion

Metastatic epidural spinal cord compression (MESCC) is an oncological emergency [1, 17, 18]. Importantly, the ambulatory ability of patients with the duration of paralysis more than 48 hours is often hard to restoration even after removing the compression of the involved neural elements. Thus, it is of great importance to start the treatment as soon as possible despite the fact that patients have ability to walk with or without aid [7, 12, 19]. Recently, rapid direct decompression and immediate spine stabilization has become the standard treatment for selected MESCC patients due to its increased efficacy over conventional radiotherapy in maintaining or preserving neurological function and prolonging life expectancy [10, 20, 21]. Generally speaking, patients with poor ambulatory and survival outcome appeared to be appropriately treated with moderate interventions which would do more comfort and less harm for those patients. In contrast, patients with preferable ambulatory and survival prognosis should receive more radical therapies in order to realize better control of local disease [4-6].

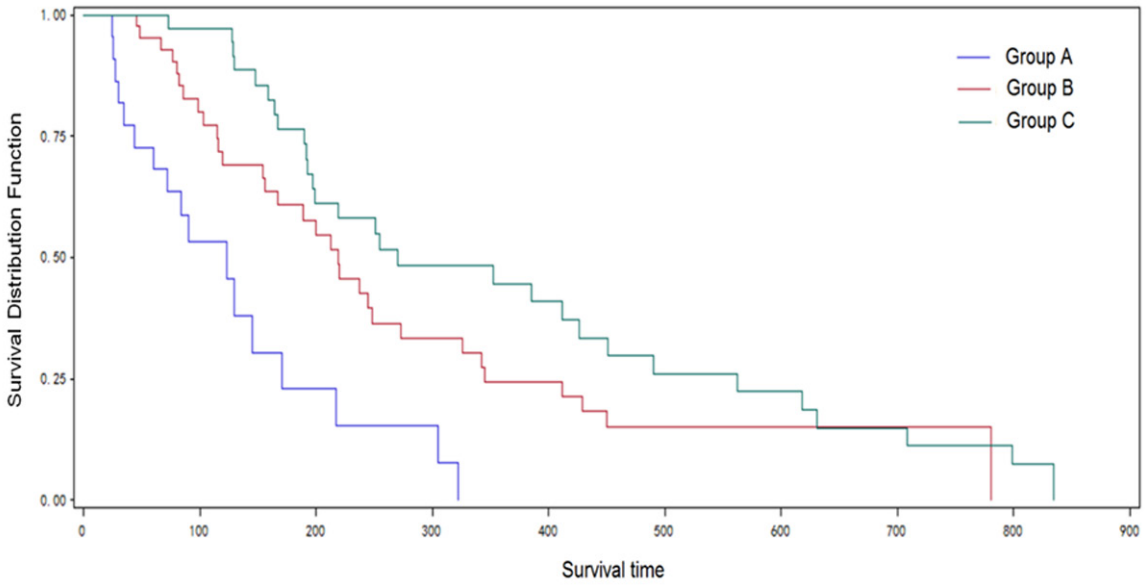

Figure 3. Kaplan-Meier survival curves for the three prognostic groups (P<0.01, log-rank test).

Potential clinical prognostic factors for postoperative ambulatory outcome have been reported in many investigations. There were duration of paralysis [7, 8], pre-treatment ambulatory status, ECOG performance status [9], therapeutic methods (surgery vs. radiotherapy) [10, 11], and postoperative adjuvant treatment [8]. In the present study, we excluded the patients with the duration of paralysis more than 48 hours. All patients were treated with laminectomy plus stabilization of vertebrae. Besides, adjuvant radiotherapy, systematic chemotherapy, or targeted drug was routinely administrated approximately 4 weeks after surgery in our department. Therefore, we believed that the duration of paralysis and therapeutic methods couldn't lead to potential bias in the study, and we also thought that the ambulatory status at 4 weeks primarily reflected the effect of decompressive surgery. Notably, there was a strong correlation between preoperative ambulatory status and ECOG performance status. Preoperative ambulatory status and ECOG performance status both were significantly associated with postoperative ambulatory status in the simple logistic regression model. However, ECOG performance status was excluded by the multiple logistic regression model. Therefore, it was not included in the scoring model.

A scoring system has been designed for the prediction of post-radiotherapy ambulatory outcome. In 2008, Rades et al. [3] proposed the scoring system in a large population (n=2096) to help surgeons to identify best candidates for supportive care, surgery, or radiotherapy alone. In 2011, Rades et al. [22] validated this scoring system in a prospective cohort of 653 patients and reduced the number of prognostic groups from five to three in order to adjust to clinical routine. However, to our knowledge, participants included in the study of Rades were treated with radiotherapy alone. Moreover, the data that hormone sensitive cancer patients with MESCC had better neurological outcome than the patients with hormone refractory tumor after surgery have been shown in some studies [12]. Thus, preoperative systematic treatments should be considered.

In the present study, primary cancer type, preoperative ambulatory status, ECOG performance status, visceral metastases, and CASCC were significantly associated with postoperative ambulatory outcome according to the simple logistic regression model. In the multiple analysis of postoperative ambulatory status, four of above mentioned five prognostic factors, namely, primary cancer type, preoperative ambulatory status, visceral metastases, and CASCC, maintained significance and were included in the scoring model. Primary cancer type was stratifying into three subgroups: (1) rapid growth group, such as lung cancer without molecularly targeted drugs; (2) moderate growth, such as lung cancer treated with molecularly targeted drugs and hormone-indepen-

dent breast and prostate cancer; and (3) slow growth, such as hormone-dependent breast and prostate cancer. Therefore, preoperative systematic treatments were considered in the scoring model. In this scoring model, three prognostic groups were designed. The postoperative ambulatory rates were 40.9% in group A, 69.8% in group B, and 97.4% in group C, and the median survival was 4.1 months in group A, 7.3 months in group B, and 9.0 months in group C, which indicated that patients with higher scoring points would have better ambulatory outcome and longer survival time. The ROC curve c-statistic for the prognostic groups as a predictor of postoperative ambulatory rate was 0.79, which suggested that the scoring model was a useful tool to predict postoperative ambulatory outcome.

The study had some limitations. First of all, this scoring model was derived from retrospective date and didn't include a relatively larger population, so hidden biases might have existed. Then, the data were collected in a single institution, and the differences of surgical skill among experts could lead to bias. Lastly, the decision about the treatment of MESCC patients was so complicated and should never relay on prognostic scores alone. The patients' individual intention should also be respected. Therefore, although this scoring model was a useful reference tool and had excellent predictive value, this scoring model still needs a prospective study to validation.

In conclusion, we created a useful scoring model for predicting postoperative ambulatory status in patients with MESCC after surgery. This scoring model can guild surgeons to select the appropriate therapy for patients with metastatic epidural spinal cord compression: Patients with 3 to 5 points who had relatively poor ambulatory outcome and short life expectancy appeared to be best treated with supportive care, patients with 6 to 8 points should be decompressive surgical candidates because the ambulatory outcome and survival prognosis were acceptable, and in patients with 9 to 13 points who had excellent function and survival outcome, more radical surgery should be considered. Still, a validation study was really needed.

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Disclosure of conflict of interest

None.

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