Establishment of a Nomogram-Based Model for Predicting the Prognostic Value of Inflammatory Biomarkers and Preoperative D-Dimer Level in Spinal Ewing's Sarcoma Family Tumors: A Retrospective Study of 83 Patients

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BACKGROUND: **Ewing's sarcoma family tumors (ESFTs) are the second most common malignancy in children and adolescents. The purpose of the present retrospective study was to evaluate the prognostic role of inflammatory biomarkers and preoperative D-dimer levels in patients with spinal ESFTs.**

METHODS: **The neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, lymphocyte/monocyte ratio, albumin/globulin ratio, C-reactive protein/albumin ratio (CAR), preoperative D-dimer level, and clinical parameters were evaluated and analyzed. Univariate and multivariate analyses for disease-free survival (DFS) and overall survival (OS) were performed using the log-rank test and Cox regression analysis, respectively. The DFS and OS rates were calculated using the Kaplan-Meier method. Nomograms were established to predict DFS and OS quantitatively.**

RESULTS: **The optimal cutoff values for D-dimer, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, lymphocyte/monocyte ratio, CAR, and albumin/globulin ratio were 0.3, 3.2, 168, 2.2, 1.5, and 1.4, respectively. The patients were stratified into 2 groups according to the cutoff values. Multivariate analysis revealed that age, resection mode, and D-dimer level were favorable prognostic factors for DFS and OS ($P < 0.05$). Metastasis and CAR <1.5 were significantly associated with OS ($P < 0.05$). Nomograms with all significant factors were established to predict DFS and OS.**

CONCLUSIONS: **Our results have indicated that the preoperative D-dimer level is an effective prognostic factor with discriminatory ability for DFS and OS, superior to other indicators. Also, CAR was favorable prognostic factor for OS. Nomograms of DFS and OS can be recommended as practical models to evaluate the prognosis for patients with spinal ESFTs.**

INTRODUCTION

Ewing's sarcoma family tumors (ESFTs) are collectively the second most common malignant bone tumors, with a peak occurrence in childhood and adolescence.[1,2] ESFTs comprise small round blue cell malignant neoplasms of neuroectodermal origin, including Ewing's sarcoma, Askin's tumor, and peripheral primitive neuroectodermal tumor.[3] These diseases occur in the bone or nearby soft tissue and mostly have the same classic cytogenetic translocation, t(11;22)(q24;q12).[4,5] ESFTs exhibit a different geographic distribution. The incidence is extremely high in white and relatively low in East Asian and African populations.[6] Multidisciplinary treatment, including

Key words
- D-dimer
- Ewing's sarcoma family tumors
- Inflammatory biomarker
- Nomogram
- Prognosis
- Spinal

Abbreviations and Acronyms
AGR: Albumin/globulin ratio
CAR: C-reactive protein/albumin ratio
C-index: Concordance index
CI: Confidence interval
CRP: C-reactive protein
D-D: D-dimer
DFS: Disease-free survival
ESFT: Ewing's sarcoma family tumor
HR: Hazard ratio
LMR: Lymphocyte/monocyte ratio
NLR: Neutrophil/lymphocyte ratio
OS: Overall survival
PLR: Platelet/lymphocyte ratio

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radical surgery, chemotherapy, and radiotherapy, has been used to achieve local control of ESFTs and improve the prognosis during the past decades.[7] Using the clinicopathological parameters obtained in our previous study,[8] the present study was intended to establish a novel nomogram-based model for predicting the prognosis of patients with spinal ESFTs.

Increasing evidence has confirmed that the inflammatory response and hypercoagulation are associated with tumor invasion, metastasis, and prognosis.[9-13] Tumor-infiltrating inflammatory cells are known to promote tumor progression by producing various inflammatory mediators and cytokines.[14,15] Simultaneously, the preoperative D-dimer (D-D) level, a biomarker of hypercoagulation, has been reported to be related to the survival of sarcoma, breast, and lung cancer cells.[16-18] Accordingly, evaluation of the preoperative D-D, neutrophil, monocyte, lymphocyte, platelet, C-reactive protein (CRP), globulin, and albumin (ALB) levels can predict for tumor progression and prognosis of these tumors. In addition, combinations of these factors, such as the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), ALB/globulin ratio (AGR), CRP/ALB ratio (CAR), and preoperative D-D level, have been widely used to identify the prognostic factors in various cancers. However, to the best of our knowledge, no study has reported on the use of these inflammatory biomarkers and the preoperative D-D level to predict the prognosis of spinal ESFTs.

Knowing that nomograms have been used in oncology for prognostic prediction,[19-22] the present study was intended to establish a nomogram-based model for determining the prognostic value of the inflammatory biomarkers NLR, PLR, LMR, AGR, CAR, and preoperative D-D level in patients with spinal ESFTs.

METHODS

Patients

The present retrospective study included 83 patients with spinal ESFTs who had undergone surgical treatment in our bone tumor center from July 2007 to March 2016. The ethics committee of Changzheng Hospital (Shanghai, China) approved the study protocol, and the surviving patients or their legal guardians provided informed consent.

The flow diagram of the 83 patients with spinal ESFTs is shown in Figure 1. The patients' medical records, including clinical reports, radiographic images, inflammatory biomarker levels, and preoperative D-D level were reviewed retrospectively. The preoperative neurological status was assessed according to the Frankel score.[23] All laboratory test results were obtained before surgery. The radiological imaging studies and intraoperative photographs from 1 typical case from the 83 patients are shown in Figure 2.

Recurrence was diagnosed according to the clinical manifestations and imaging findings obtained at the outpatient follow-up visits or pathological evaluation of the specimen from the second surgery. The primary outcome measures were disease-free survival (DFS) and overall survival (OS). Event frequency was defined as the interval from the date of surgery to local recurrence, death, or March 2018 for living patients. All patients were followed up on an outpatient basis at 3, 6, and 12 months postoperatively, every 6 months for the second year, and then annually for life.

Statistical Analysis

Statistical analyses were performed using SPSS, version 22.0 (IBM Corp., Armonk, New York, USA) and R, version 3.3.2

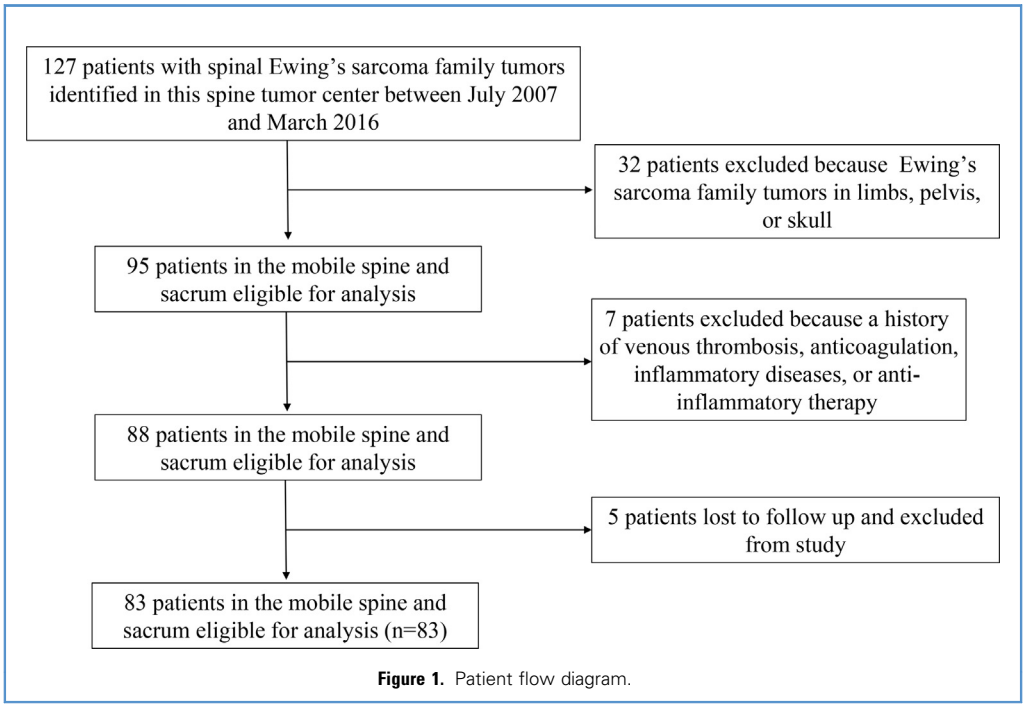

Figure 1. Patient flow diagram.

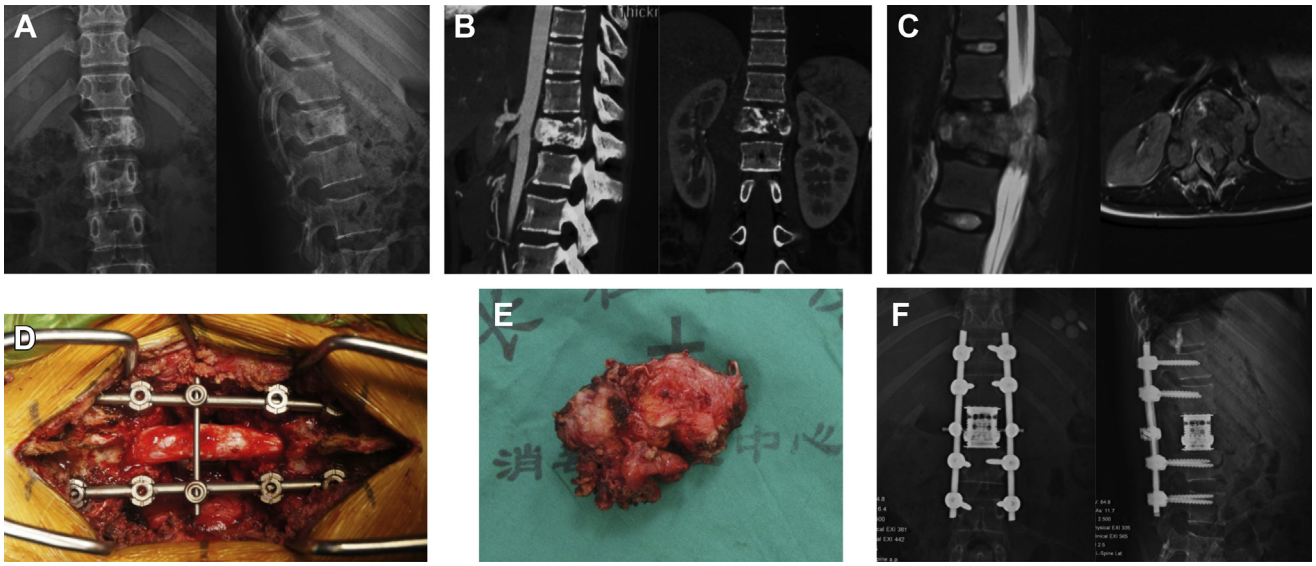

Figure 2. Imaging studies and intraoperative photographs from a typical case of a patient who had undergone tumor removal by total en bloc spondylectomy at our center that was diagnosed as Ewing sarcoma family tumor. (**A**) Preoperative radiographs of anteroposterior and lateral spine demonstrating straightening of lumbar physiological curvature and osseous destruction in the first lumber spine. (**B**) Preoperative computed tomography scan showing osteolytic destruction in the first lumber vertebra and its posterior elements, a paravertebral soft tissue mass, and compression of the spinal cord. (**C**) Preoperative magnetic resonance imaging studies showing low-intensity signal of tumor on T1-weighted image and high-intensity signal on T2-weighted image. (**D, E**) Gross total resection by en bloc spondylectomy was performed, and the first lumber vertebral body and appendix were removed. (**F**) Postoperative radiographs showing the first lumber spine was removed and replaced by an artificial vertebral body, with solid internal fixation.

(R Foundation, Vienna, Austria). Quantitative data were recorded as the median and range and qualitative data as counts and percentages. X-tile 3.6.1 software, version 20 (Yale University, New Haven, Connecticut, USA) was used to determine the optimal cutoff values for D-D, NLR, PLR, LMR, AGR, and CAR. Univariate and multivariate analyses were performed to identify independent prognostic factors for DFS and OS. DFS and OS were calculated using the Kaplan-Meier method. Univariate analysis was performed using the log-rank test. Possible prognostic factors with $P < 0.1$ on univariate analysis were included in the multivariate analysis by Cox regression analysis. Factors with $P < 0.05$ were considered to indicate statistical significance.

Nomograms for the possible prognostic factors associated with DFS and OS were established using R software, version 3.3.2 (R Foundation). Predictive accuracy was assessed by discrimination and calibration. The discrimination was measured using Harrell's concordance index (C-index). In addition to measuring the discriminative capacity using the C-index, each model was evaluated by the calibration curve in which the predicted outcomes versus the observed outcomes were graphically depicted to allow for further comparisons of the accuracy in estimating the prognosis.

RESULTS

Baseline Patient Characteristics and Inflammatory Biomarkers and Preoperative D-D Cutoff Values

The clinical characteristics of the 83 patients are listed in Tables 1 and 2. Of the 83 patients, 54 were male and 29 were female, with a mean age of 25.8 years (median, 21; range, 5–82). The mean follow-up duration was 20.3 months (median, 15; range, 1–84). Recurrence was confirmed by the radiological findings and pathological results of the next surgery in 40 patients, for a recurrence rate of 48.2%. The mean interval from surgery to recurrence was 17.4 months (median, 6; range, 1–76), and the mean duration from the initial surgery to death was 20.3 months (median, 8; range, 1–84). Of the 83 patients, 54 died during the follow-up period, for a mortality rate of 65%.

The optimal cutoff value for the D-D level, NLR, PLR, LMR, CAR, and AGR was 0.3, 3.2, 168, 2.2, 1.5, and 1.4, respectively, as determined using the X-tile program (Yale University; Figure 3). The log-rank value for the D-D level, NLR, PLR, LMR, CAR, and AGR for DFS was 3.4, 5.4, 5.7, 4.3, 6.6, and 3.1, respectively. The log-rank value for the D-D level, NLR, PLR, LMR, CAR, and AGR for OS was 4.0, 5.4, 6.4, 3.4, 12.2, and 3.5, respectively. Using these cutoff values, the patients were stratified into 2 groups.

Univariate and Multivariate Analysis Results for the Prognostic Factors for DFS

The overall DFS rate after gross total resection was 51.8%, with a median DFS of 15 months. The results of the univariate and multivariate analyses are listed in Table 1. All potential prognostic factors found on univariate analysis were submitted to Cox proportional hazards analysis. Patients aged <25 years had significantly shorter DFS than those >25 years (hazard ratio [HR], 0.357; $P = 0.007$). The risk of recurrence decreased significantly for patients who had undergone en bloc

Table 1. Univariate and Multivariate Analysis Results for Prognostic Factors Affecting Disease-Free Survival of Patients with Spinal Ewing's Sarcoma Family Tumors

	Disease-Free Survival			
Variable	Univariate Analysis (n, %)	*P* Value	Multivariate Analysis (HR, 95% CI)	*P* Value
Age (years)		0.001*		0.007†
<25	55 (66.3)		1.000	
≥25	28 (33.7)		0.357 (0.169—0.752)	
Gender		0.899	NA	
Male	54 (65.1)			
Female	29 (34.9)			
Treatment history		0.708	NA	
Primary	64 (77.1)			
Recurrent	19 (22.9)			
Metastasis		0.257	NA	
Yes	9 (10.8)			
No	74 (89.2)			
Tumor size (cm)		0.574	NA	
<6	47 (56.6)			
≥6	36 (43.4)			
Location		0.269	NA	
Cervical spine	20 (24.1)			
Thoracic spine	15 (18.1)			
Lumber spine	27 (32.5)			
Sacral spine	21 (25.3)			
Involved segment		0.240	NA	
Monosegment	23 (27.7)			
Multisegment	60 (72.3)			
Enneking stage		0.051*	NA	
II	71 (85.5)			
III	12 (24.5)			
PFS		0.200	NA	
A—C	49 (59)			
D—E	34 (41)			
Resection mode		0.076*		0.011†
Subtotal	19 (22.9)		1.000	
Piecemeal	41 (49.4)		0.562 (0.361—0.875)	
En bloc	23 (27.7)			
D-dimer (μg/mL)		<0.001*		0.007†
<0.3	36 (43.4)		1.000	
≥0.3	47 (56.6)		2.704 (1.314—5.566)	
NLR		0.843	NA	
<3.2	47 (56.6)			
≥3.2	36 (43.4)			
PLR		0.025*	NA	
<168	40 (48.2)			
≥168	43 (51.8)			
CAR		<0.011*		0.093
<1.5	43 (51.8)		1.000	
≥1.5	40 (48.2)		1.687 (0.916—3.106)	
LMR		0.531	NA	
<2.2	51 (61.5)			
≥2.2	32 (38.5)			
AGR		0.216	NA	
<1.4	37 (44.6)			
≥1.4	46 (55.4)			

HR, hazard ratio; CI, confidence interval; NA, not applicable; PFS, preoperative Frankel score; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; CAR, C-reactive protein/albumin ratio; LMR, lymphocyte/monocyte ratio; AGR, albumin/globulin ratio.

*$P < 0.1$.

†$P < 0.05$.

spondylectomy compared with that of the patients who had undergone subtotal or total piecemeal spondylectomy (HR, 0.562; P = 0.011). Patients with a preoperative D-D level of <0.3 μg/mL had significantly longer DFS than those with a preoperative D-D level of ≥0.3 μg/mL (HR, 2.704; P = 0.007). Thus, age, resection mode, and preoperative D-D level were independent prognostic factors for DFS.

Univariate and Multivariate Analysis Results for the Prognostic Factors for OS

Of the 83 patients with spinal ESFTs in our series, 54 died during the follow-up period of tumor recurrence and surgical complications, for an OS rate of 35% and median OS duration of 8 months. The results of the univariate and multivariate analyses of the prognostic factors affecting OS are listed in Table 2. All potential factors were included in the multivariate analysis. The results showed that age ≥25 years, metastasis, en bloc spondylectomy, preoperative D-D level <0.3 μg/mL, and CAR <1.5 were independent prognostic factors (age ≥25 years: HR, 0.392; P = 0.014; metastasis: HR, 2.180; P = 0.049; en bloc spondylectomy: HR, 0.594; P = 0.018; D-dimer level <0.3 μg/mL: HR, 2.589; P = 0.009; and CAR <1.5: HR, 1.930; P = 0.037).

Table 2. Univariate and Multivariate Analysis Results for Prognostic Factors Affecting Overall Survival for Patients with Spinal Ewing's Sarcoma Family Tumors

	Overall Survival			
Variable	Univariate Analysis (n, %)	*P* Value	Multivariate Analysis (HR, 95% CI)	*P* Value
Age (years)		0.001*		0.014†
<25	55 (66.3)		1.000	
≥25	28 (33.7)		0.392 (0.185–0.833)	
Gender		0.747	NA	
Male	54 (65.1)			
Female	29 (34.9)			
Treatment history		0.461	NA	
Primary	64 (77.1)			
Recurrent	19 (22.9)			
Metastasis		0.028*		0.049†
Yes	9 (10.8)		1.000	
No	74 (89.2)		2.180 (0.224–1.106)	
Tumor size (cm)		0.209	NA	
<6	47 (56.6)			
≥6	36 (43.4)			
Location		0.629	NA	
Cervical spine	20 (24.1)			
Thoracic spine	15 (18.1)			
Lumber spine	27 (32.5)			
Sacral spine	21 (25.3)			
Involved segment		0.506	NA	
Monosegment	23 (27.7)			
Multisegment	60 (72.3)			
Enneking stage		0.161	NA	
II	71 (85.5)			
III	12 (24.5)			
PFS		0.023*	NA	
A–C	49 (59)			
D–E	34 (41)			
Resection mode		0.002		0.018†
Subtotal	19 (22.9)		1.000	
Piecemeal	41 (49.4)		0.594 (0.386–0.914)	
En bloc	23 (27.7)			
D-dimer (μg/mL)		<0.001*		0.009†
<0.3	36 (43.4)		1.000	
≥0.3	47 (56.6)		2.589 (1.266–5.294)	
NLR		0.205		
<3.2	47 (56.6)			
≥3.2	36 (43.4)			
PLR		0.011*	NA	
<168	40 (48.2)			
≥168	43 (51.8)			
CAR		<0.001*		0.037†
<1.5	43 (51.8)		1.000	
≥1.5	40 (48.2)		1.930 (1.040–3.579)	
LMR		0.431	NA	
<2.2	51 (61.5)			
≥2.2	32 (38.5)			
AGR		0.099*	NA	
<1.4	37 (44.6)			
≥1.4	46 (55.4)			

HR, hazard ratio; CI, confidence interval; NA, not applicable; PFS, preoperative Frankel score; NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; CAR, C-reactive protein/albumin ratio; LMR, lymphocyte/monocyte ratio; AGR, albumin/globulin ratio.

*$P < 0.1$.

†$P < 0.05$.

Nomogram-Based Model for Predicting the Prognosis of Patients with Spinal ESFTs

To predict the DFS and OS for patients with spinal ESFTs, 2 nomograms were established using multivariate Cox proportional hazards with all statistically significant independent factors for DFS and OS (Figure 4). The nomograms were interpreted by summing the points assigned to each variable, indicated at the top scale. The top points were converted to predict the 2-year probability of death and recurrence for a patient with points in the lowest scale. The Harrell C-index for DFS and OS prediction was 0.698 (95% confidence interval [CI], 0.686–0.710) and 0.708 (95% CI, 0.694–0.722), respectively. In addition, the calibration plots showed good agreement between the nomogram prediction and actual observation for 2-year DFS and 2-year OS.

DISCUSSION

As the second most common primary malignant tumor, ESFTs generally occur in the bones, especially the long bones of the lower limbs, followed by the pelvis and spine.[24] With the development of multidisciplinary treatment, DFS and OS have significantly improved. However, given the rarity of the disease,

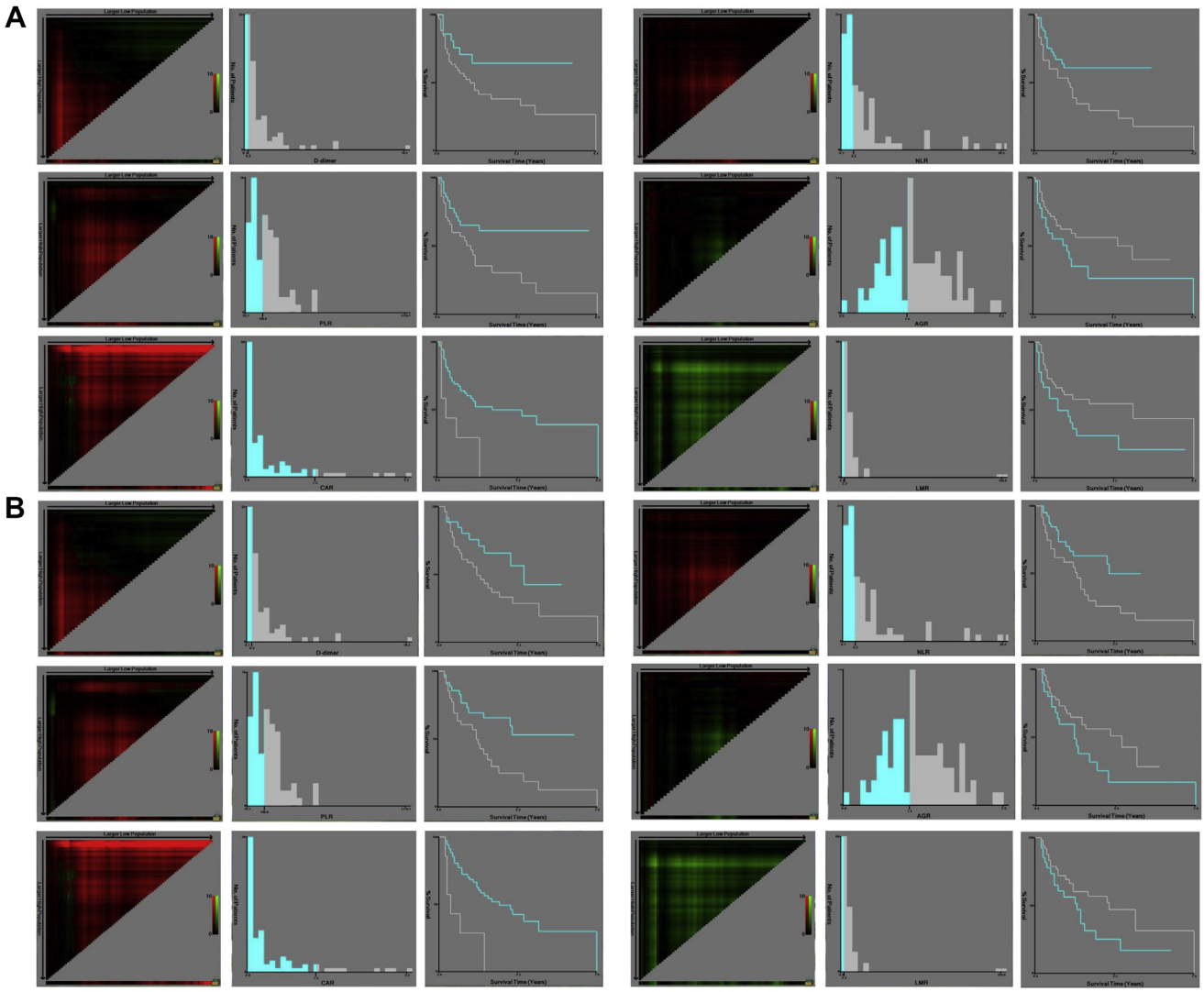

Figure 3. X-tile analysis of (**A**) disease-free survival and (**B**) overall survival was performed using the patients' data to determine the optimal cutoff values for D-dimer, neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, albumin/globulin ratio, C-reactive protein/albumin ratio, and lymphocyte/monocyte ratio, which were 0.3, 3.2, 168, 1.4, 1.5, and 2.2, respectively. The sample of patients with Ewing's sarcoma family tumors was equally divided into training and validation sets. (**Left**) X-tile plots of the training sets, with plots of matched validation sets shown in the small inset. (**Middle**) Optimal cutoff values shown in histograms of the entire cohort. (**Right**) Kaplan-Meier plots. *P* values were determined using the cutoff values defined in the training sets and applying them to the validation sets.

the favorable prognostic factors for DFS and OS for spinal ESFTs remain controversial. Our former retrospective study[8] of 63 patients showed that age >25 years and receipt of neoadjuvant chemotherapy were favorable independent prognostic factors for recurrence-free survival and OS. Also, en bloc spondylectomy, postoperative chemotherapy, postoperative radiotherapy, and no metastases were significantly related to OS. In the present study, to the best of our knowledge, we have for the first time used inflammatory biomarkers and the preoperative D-D level to perform a prognostic analysis of spinal ESFTs. The results suggested that age, resection mode, and preoperative D-D level are favorable prognostic factors for DFS and OS. In addition, metastasis and CAR were significantly associated with OS.

In our series, the mean patient age was 25.8 years, male gender predominated, and the peak incidence was in patients aged <25 years. Our findings differ from those from previous reports,[25,26] probably owing to racial differences between Asians and whites. The results of the multivariate analysis suggested that age >25 years is a favorable prognostic factor for DFS and OS, in contrast to Cotterill et al.[27] They reported that age >15 years was related to unsatisfactory outcomes. Arpaci et al.[28] also reported that age was not a favorable prognostic factor.

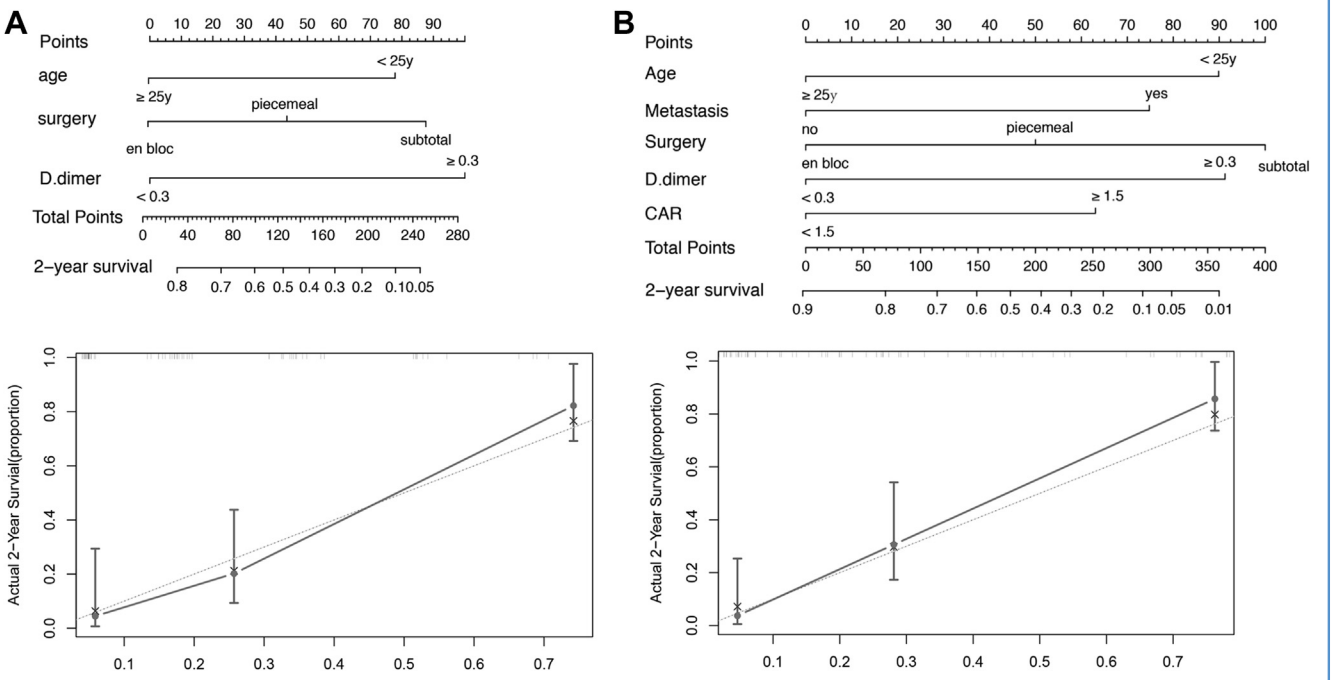

Figure 4. Nomograms convey the outcomes of prognostic models using inflammatory biomarkers, preoperative D-dimer level, and clinical parameters to predict disease-free survival (DFS) and overall survival (OS) of patients with Ewing's sarcoma family tumors. The nomograms can be interpreted by summing the points assigned to each variable, indicated at the top of the scales. The total points can be converted to predict the probability of recurrence and death for a patient with points at the lowest scale. (**A**) Nomogram predicting the risk of recurrence and calibration curves for DFS using nomograms with favorable prognostic factors. (**B**) Nomogram predicting the probability of death and calibration curves for OS using nomograms with independent prognostic factors. Harrell's concordance index for DFS and OS prediction was 0.698 (95% confidence interval, 0.686–0.710) and 0.708 (95% confidence interval, 0.694–0.722), respectively. The x-axis shows the nomogram-predicted probability of survival and the y-axis, the actual survival. The reference line is 45° and indicates perfect calibration.

ESFTs have a strong potential to metastasize, mostly to the lungs and bones. More than 10% of patients will present with multiple bone metastasis at the initial diagnosis. Nine patients (10.8%) in our series presented with metastasis. Metastasis usually predicts for a worse prognosis, because a metastatic lesion is more difficult to control and more likely to quickly progress. Our study showed that metastasis was a useful prognostic indicator of OS for patients with spinal ESFTs.

Multidisciplinary treatment of ESFTs usually consists of 3–6 cycles of neoadjuvant chemotherapy after diagnosis by biopsy, followed by surgery and/or local therapy and 6–10 cycles of chemotherapy.[29] Neoadjuvant chemotherapy provides a new method for the treatment of ESFTs, which is conducive to reducing the tumor size, eliminating micrometastasis, and facilitating en bloc resection. Furthermore, surgery is a standard treatment of spinal ESFTs, with the aim of removing the tumor, preserving or even improving functionality, relieving pain, and controlling local recurrence and the promise of prolonging survival. It has been reported that total en bloc spondylectomy to remove spinal ESFTs can result in a better prognosis.[30] Our study has demonstrated that the risk of recurrence and death for patients who underwent total en bloc spondylectomy was lower than that for patients who had undergone subtotal and total piecemeal spondylectomy. Postoperative radiotherapy is usually given to patients with inadequate surgical margins and no response or a low response to chemotherapy. However, because the primary aim of our study was to identify the prognostic significance of inflammatory biomarkers and the preoperative D-D level, we did not focus on the clinical outcomes of patients who had undergone neoadjuvant chemotherapy and radiotherapy.

Some recent studies[31] have indicated that the risk of malignancy increased in patients with inflammatory disease, suggesting that the inflammatory response could play a critical role in tumor invasion, progression, and metastasis. The cutoff value for the NLR, PLR, CAR, LMR, and AGR was determined using the X-tile program (Yale University). Our study demonstrated that the CAR is significantly associated with OS in patients with spinal ESFTs. CRP is frequently used as a serum marker to assess the inflammatory status of a patient and has been discussed as a prognostic factor in patients with Ewing's sarcoma. Li et al.[2] reported that the CAR was an ideal prognostic indicator for patients with Ewing's sarcoma, consistent with our findings. However, their study mainly focused on Ewing's sarcoma in the limb, and our study discussed the prognostic significance of inflammatory biomarkers and the preoperative D-D level in patients with

spinal ESFTs. The mechanism of inflammatory response in tumorigenesis has been reported to be associated with the release of inflammatory cytokines, including interleukin-1, interleukin-6, and tumor necrosis factor from leukocytes, triggered by tumor progression, which further induces homeostasis and activates an acute phase response.[2,32] Our results have demonstrated that other inflammatory biomarkers, including the NLR, PLR, LMR, and AGR, were not related to the prognosis of patients with spinal ESFTs.

As a marker of high coagulation and the fibrinolytic state, plasma D-D has gained considerable attention with respect to the relationship between activation of the hemostatic system and tumor progression.[33,34] Thus, the plasma D-D level might be, not only a mediator of thrombosis, but also a biomarker for tumor angiogenesis, metastasis, and invasion. To the best of our knowledge, no study has reported on the prognostic role of the preoperative plasma D-D level in patients with spinal tumors. In the present study, we first evaluated whether the plasma D-D level could be used as an independent prognostic factor for DFS and OS of patients with spinal ESFTs. The result showed that patients with greater preoperative D-D levels might indicate worse surgical outcomes.

Nomograms have been used as a reliable tool to identify possible risk factors and predict the prognosis of oncology patients.[35,36] The accuracy of nomograms can be confirmed using the C-index and calibration curve. Compared with other staging systems, nomograms offer prognostic information for individuals and groups and can be used to visualize all quantified possible variables, allowing doctors and patients to clearly understand the possible outcomes of the disease.[37,38] In our study, we addressed the prognostic role of inflammatory biomarkers and the preoperative D-D level in patients with spinal ESFTs and established a nomogram-based model to predict the outcomes of these patients. This method could provide us with a novel promising tool for predicting the prognosis of patients with spinal ESFTs.

To the best of our knowledge, our study had the largest sample of patients with spinal ESFTs to date and was a highly homogeneous study involving patients from a single center. However, our study still had some limitations. First, the analysis was retrospective. Second, we only evaluated the DFS and OS of patients who had undergone surgical treatment. Finally, the follow-up duration was not long enough.

CONCLUSIONS

The results from the present study have indicated that the preoperative D-D level is an effective prognostic factor with discriminatory ability for the DFS and OS of patients with spinal ESFTs. In addition, CAR was an independent and robust prognostic indicator for OS. This nomogram-based model could be used as a practical tool for predicting the prognosis of patients with spinal ESFTs in terms of DFS and OS.

REFERENCES

1. Gaspar N, Hawkins DS, Dirksen U, Lewis IJ, Ferrari S, Le Deley MC, et al. Ewing sarcoma: current management and future approaches through collaboration. *J Clin Oncol*. 2015;33:3036-3046.

2. Li YJ, Yang X, Zhang WB, Yi C, Wang F, Li P. Clinical implications of six inflammatory biomarkers as prognostic indicators in Ewing sarcoma. *Cancer Manag Res*. 2017;9:443-451.

3. Burchill SA. Ewing's sarcoma: diagnostic, prognostic, and therapeutic implications of molecular abnormalities. *J Clin Pathol*. 2003;56:96-102.

4. Lee CY, Yen CC, Yen HJ, Shiau C-Y, Chao T-C, Wu P-K, et al. Outcomes of 50 patients with Ewing sarcoma family of tumors treated at a single institution in Taiwan. *Medicine (Baltimore)*. 2016;95:e3830.

5. Ahmed SK, Randall RL, DuBois SG, Harmsen WS, Krailo M, Marcus S, et al. Identification of patients with localized Ewing sarcoma at higher risk for local failure: a report from the Children's Oncology Group. *Int J Radiat Oncol Biol Phys*. 2017;99:1286-1294.

6. Li JXJ, Phan K, Tran TM, Mobbs RJ, Stanford R. Image-guided lateral mass osteotomy for en bloc resection of cervical Ewing sarcoma: a technical note. *World Neurosurg*. 2017;104:628-633.

7. Hobusch GM, Noebauer-Huhmann I, Krall C, Holzer G. Do long term survivors of Ewing family of tumors experience low bone mineral density and increased fracture risk? *Clin Orthop Relat Res*. 2014;472:3471-3479.

8. Wan W, Lou Y, Hu Z, Wang T, Li J, Tang Y, et al. Factors affecting survival outcomes of patients with non-metastatic Ewing's sarcoma family tumors in the spine: a retrospective analysis of 63 patients in a single center. *J Neurooncol*. 2017;131:313-320.

9. Li J, Li B, Zhou P, Zhao J, Wu Z, Yang X, et al. Nomograms for prognostic factors of spinal giant cell tumor combining traditional clinical characteristics with inflammatory biomarkers after gross total resection. *Oncotarget*. 2017;8:86934-86946.

10. Wang Y, Li J, Xia Y, Gong R, Wang K, Yan Z, et al. Prognostic nomogram for intrahepatic cholangiocarcinoma after partial hepatectomy. *J Clin Oncol*. 2013;31:1188-1195.

11. Hirahara N, Matsubara T, Mizota Y, Ishibashi S, Tajima Y. Prognostic value of preoperative inflammatory response biomarkers in patients with esophageal cancer who undergo a curative thoracoscopic esophagectomy. *BMC Surg*. 2016;16:66.

12. Suega K, Bakta IM. Correlation between clinical stage of solid tumor and D dimer as a marker of coagulation activation. *Acta Med Indones*. 2011;43:162-167.

13. Batschauer AP, Figueiredo CP, Bueno EC, Ribeiro MA, Dusse LM, Fernandes AP, et al. D-dimer as a possible prognostic marker of operable hormone receptor-negative breast cancer. *Ann Oncol*. 2010;21:1267-1272.

14. Mbeutcha A, Shariat SF, Rieken M, Rink M, Xylinas E, Seitz C, et al. Prognostic significance of markers of systemic inflammatory response in patients with non-muscle-invasive bladder cancer. *Urol Oncol*. 2016;34:483.e17-483.e24.

15. Caceres S, Peña L, Silvan G, Illera MJ, Woodward WA, Reuben JM, et al. Steroid tumor environment in male and female mice model of canine and human inflammatory breast cancer. *Biomed Res Int*. 2016;2016:8909878.

16. Raj SD, Zhou X, Bueso-Ramos CE, Ravi V, Patel S, Benjamin RS, et al. Prognostic significance of elevated D-dimer for survival in patients with sarcoma. *Am J Clin Oncol*. 2012;35:462-467.

17. Kaseda K, Asakura K, Kazama A, Ozawa Y. Prognostic significance of preoperative plasma D-dimer level in patients with surgically resected clinical stage I non-small cell lung cancer: a retrospective cohort study. *J Cardiothorac Surg*. 2017;12:102.

18. Hong T, Shen D, Chen X, Wu X, Hua D. Preoperative plasma fibrinogen, but not D-dimer might represent a prognostic factor in non-metastatic colorectal cancer: a prospective cohort study. *Cancer Biomark*. 2017;19:103-111.

19. Li Y, Jia H, Yu W, Xu Y, Li X, Li Q, et al. Nomograms for predicting prognostic value of inflammatory biomarkers in colorectal cancer patients after radical resection. *Int J Cancer*. 2016;139:220-231.

20. Tomás I, Arias-Bujanda N, Alonso-Sampedro M, Casares-de-Cal MA, Sánchez-Sellero C, Suárez-Quintanilla D, et al. Cytokine-based predictive models to estimate the probability of chronic

periodontitis: development of diagnostic nomograms. *Sci Rep*. 2017;7:11580.

21. Dihge L, Bendahl PO, Rydén L. Nomograms for preoperative prediction of axillary nodal status in breast cancer. *Br J Surg*. 2017;104:1494-1505.

22. Shen J, He L, Li C, Wen T, Chen W, Lu C, et al. Nomograms to predict the individual survival of patients with solitary hepatocellular carcinoma after hepatectomy. *Gut Liver*. 2017;11:684-692.

23. Frankel HL, Hancock DO, Hyslop G, Melzak J, Michaelis LS, Ungar GH, et al. The value of postural reduction in the initial management of closed injuries of the spine with paraplegia and tetraplegia. I. *Paraplegia*. 1969;7:179-192.

24. Galyfos G, Karantzikos GA, Kavouras N, Sianou A, Palogos K, Filis K. Extraosseous Ewing sarcoma: diagnosis, prognosis and optimal management. *Indian J Surg*. 2016;78:49-53.

25. Venkateswaran L, Rodriguez-Galindo C, Merchant TE, Poquette CA, Rao BN, Pappo AS. Primary Ewing tumor of the vertebrae: clinical characteristics, prognostic factors, and outcome. *Med Pediatr Oncol*. 2001;37:30-35.

26. Ilaslan H, Sundaram M, Unni KK, Dekutoski MB. Primary Ewing's sarcoma of the vertebral column. *Skeletal Radiol*. 2004;33:506-513.

27. Cotterill SJ, Ahrens S, Paulussen M, Jürgens HF, Voûte PA, Gadner H, et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's sarcoma study group. *J Clin Oncol*. 2002;18:3108-3114.

28. Arpaci E, Yetisyigit T, Seker M, Unca D, Uyeturk U, Oksuzoglu B, et al. Prognostic factors and clinical outcome of patients with Ewing's sarcoma family of tumors in adults: multicentric study of the Anatolian Society of Medical Oncology. *Med Oncol*. 2013;30:469.

29. Womer RB, West DC, Krailo MD, Dickman PS, Pawel BR, Grier HE, et al. Randomized controlled trial of interval-compressed chemotherapy for the treatment of localized Ewing sarcoma: a report from the Children's Oncology Group. *J Clin Oncol*. 2012;30:4148-4154.

30. Samartzis D, Marco RA, Benjamin R, Vaporciyan A, Rhines LD. Multilevel en bloc spondylectomy and chest wall excision via a simultaneous anterior and posterior approach for Ewing sarcoma. *Spine (Phila Pa 1976)*. 2005;30:831-837.

31. Jess T, Simonsen J, Jørgensen KT, Pedersen BV, Nielsen NM, Frisch M. Decreasing risk of colorectal cancer in patients with inflammatory bowel disease over 30 years. *Gastroenterology*. 2012;143:375-381.

32. McCourt M, Wang JH, Sookhai S, Redmond HP. Activated human neutrophils release hepatocyte growth factor/scatter factor. *Eur J Surg Oncol*. 2009;27:396-403.

33. Liu Z, Guo H, Gao F, Shan Q, Li J, Xie H, et al. Fibrinogen and D-dimer levels elevate in advanced hepatocellular carcinoma: high pretreatment fibrinogen levels predict poor outcomes. *Hepatol Res*. 2017;47:1108-1117.

34. Watanabe A, Araki K, Hirai K, Kubo N, Igarashi T, Tsukagoshi M, et al. A novel clinical factor, D-dimer platelet multiplication, may predict postoperative recurrence and prognosis for patients with cholangiocarcinoma. *Ann Surg Oncol*. 2016;23(suppl 5):886-891.

35. He C, Mao Y, Wang J, Duan F, Lin X, Li S. Nomograms predict long-term survival for patients with periampullary adenocarcinoma after pancreatoduodenectomy. *BMC Cancer*. 2018;18:327.

36. Bobdey S, Balasubramaniam G, Mishra P. Nomogram prediction for survival of patients with oral cavity squamous cell carcinoma. *Head Neck*. 2016;38:1826-1831.

37. Gu L, Ma X, Li H, Chen L, Xie Y, Zhao C, et al. Prognostic value of preoperative inflammatory response biomarkers in patients with sarcomatoid renal cell carcinoma and the establishment of a nomogram. *Sci Rep*. 2016;6:23846.

38. Song SH, Ahn JH, Lee HY, Lee G, Choi JY, Kang J, et al. Prognostic impact of nomogram based on whole tumour size, tumour disappearance ratio on CT and SUV max on PET in lung adenocarcinoma. *Eur Radiol*. 2016;26:1538-1546.

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