European Spine Journal (2019) 28:1480–1490
https://doi.org/10.1007/s00586-018-05872-4

ORIGINAL ARTICLE

# Prognostic significance of pretreatment plasma D-dimer levels in patients with spinal chordoma: a retrospective cohort study

Bo Li[1] · Hao Zhang[1] · Pingting Zhou[2] · Jiaxiang Yang[1,3] · Haifeng Wei[1] · Xinghai Yang[1] · Cheng Yang[1] · Zhipeng Wu[1] · Jianru Xiao[1]

Received: 20 August 2018 / Revised: 22 November 2018 / Accepted: 22 December 2018 / Published online: 25 January 2019


## Abstract

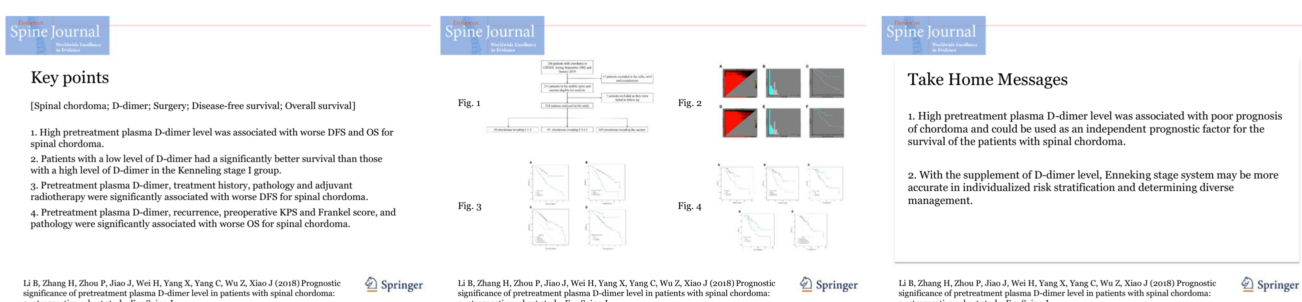
**Purpose** Plasma D-dimer levels, a marker of hypercoagulation, have not only been used as an indicator for cascaded reaction in the coagulation process but are also reported to be an underlying biomarker in several types of cancers. This retrospective cohort study was designed to evaluate the prognostic value of preoperative plasma D-dimer level in patients with spinal chordoma.

**Methods** We enrolled 224 patients who underwent surgery for spinal chordoma between 2002 and 2015 at Changzheng Orthopedic Oncology Center. Preoperative clinical parameters were recorded and evaluated by univariate and multivariate Cox regression models. The correlation between preoperative plasma D-dimer levels and survival was assessed using the Kaplan–Meier method.

**Results** The optimal cutoff value of pretreatment D-dimer was 840 μg/L determined by X-tile. DFS (disease-free survival) was 64.7% and OS (overall survival) was 75% in the cohort. Multivariate Cox regression model identified D-dimer level as an independent prognostic factor of DFS and OS, as well as treatment history, preoperative Karnofsky Performance Scale, preoperative Frankel score, pathology classification and adjuvant radiotherapy ($p < 0.05$). In addition, D-dimer level may also be an effective supplement for defining tumor Enneking staging ($p < 0.05$).

**Conclusions** Higher pretreatment plasma D-dimer level was associated with a poor prognosis in chordoma and could be used as an independent prognostic factor for the survival of the patients with spinal chordoma. With supplementation of D-dimer level, Enneking stage may be more able to accurate stratify individualized risk and determine clinical management.

**Graphical abstract** These slides can be retrieved under Electronic Supplementary Material.




**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00586-018-05872-4) contains supplementary material, which is available to authorized users.

Bo Li, Hao Zhang, Pingting Zhou and Jiaxiang Yang have contributed equally to this work.

Extended author information available on the last page of the article

**Keywords** Spinal chordoma · D-dimer · Surgery · Disease-free survival · Overall survival

## Introduction

Chordoma is a relatively rare primary malignant bone tumor that exclusively invades the axial skeleton, accounting for about 1–4% of all primary malignancies of the spine [1–3]. This disease can occur at any age, with a peak occurrence at 50–60 years of age [4]. It is generally believed that the name "chordoma" was derived from undifferentiated notochordal remnants [5], but some scholars think that the name chordoma originated from vagal chordal tissue [6].

Chordoma is an insidious disease [7] that grows slowly and is histologically considered to be a low-grade neoplasm [8]. It exhibits strong local aggressiveness, invasiveness, sarcomatoid changing potential and high recurrence, making clinical management difficult [9–11]. Currently, almost no treatment has any obvious effect on chordoma except surgery due to its resistance to radiotherapy and unresponsiveness to chemotherapy [12, 13]. In recent years, arterial embolization technology has continued to advance [14], and orthopedic oncologists use wide or marginal resection to treat chordoma. However, the effect of surgery is still unsatisfactory due to the complicated anatomic structures surrounding the spine. Therefore, precise prognostic assessment is crucial for chordoma patients.

A relevant study of 153 chordoma surgery recipients at our center was published in 2015 [15]. Independent prognostic variables were distinguished on the basis of traditional clinical features and neurological status. Remarkably, inflammatory biomarkers such as D-dimer, NLR and CRP in malignant tumors have been widely investigated, although their exact mechanism is still unclear [16–19]. We considered inflammatory biomarkers to be powerful supplements of prediction, which could provide guidance for clinical management of cancer patients across a range of malignancies.

D-dimer is a degradation product of cross-linked fibrin that is generated during the progression of coagulation [20]. D-dimer is closely associated with cardio-cerebrovascular events [21], and in recent years, D-dimer has been shown to have prognostic value in a range of malignancies including lung cancer, gastrointestinal cancer and gynecological cancer. Furthermore, elevated levels of D-dimer were demonstrated to be associated with a poor malignancy prognosis [22–26], and plasma D-dimer level is therefore considered a promising prognostic factor. No previous study has reported on the clinical significance of D-dimer in patients with chordoma. Our study aims to elucidate the prognostic significance of pretreatment plasma D-dimer levels in patients with spinal chordoma and details the correlation between pretreatment plasma D-dimer levels and survival.

## Materials and methods

### Study design and patients

In total, 224 patients who underwent operation for spinal chordoma between September 2002 and January 2016 at our hospital were enrolled. All patients underwent surgical resection and were pathologically diagnosed with chordoma. The following inclusion criteria were applied: (1) patients who had received spinal chordoma resection surgery at our center; (2) patients who had more than 12 months of follow-up or cancer-related death or recurrence; (3) patients without homeostasis disorders, thrombosis disorders including pulmonary embolism and vein embolism, and chronic inflammatory diseases; (4) patients who had not received anti-inflammatory treatment or immunosuppressive therapy in the past 3 months. A typical case treated in our center is illustrated in Supplementary Figure.

### Data extraction

Data were extracted from the retrospective spinal tumor databases in our center according to our inclusion criteria. Electronic medical records and surgery notes were both used as reference materials. All clinicopathological factors were assessed at baseline. Clinical characteristics and tumor factors are listed in Table 1. Inflammatory biomarker was D-dimer tested preoperatively.

The endpoints analyzed in this study were chordoma-related recurrence and death. We documented each discharged patient, and clinical follow-ups were conducted in the outpatient department at 3 months and 6 months after discharge, every 6 months for the next year and then once every year from then on. If patients failed to attend scheduled follow-up, they were contacted by telephone and e-mail.

### Statistical methods

Disease-free survival (DFS) was defined as the time from surgery to recurrence with the evidence of clinical manifestations and imaging findings on follow-up or pathological evaluation of re-operation. Overall survival (OS) was defined as the interval from tumor resection to death or to the last day of follow-up. Data analysis was carried out by using SPSS version 23.0 (SPSS, Inc. Chicago, IL, USA). X-tile 3.6.1 software (Yale University, New Haven, CT, USA) was used to determine the optimal cutoff value for D-dimer by dividing all the original data into training and validating groups for P value estimation [27]. The Cox proportional hazard model was employed to identify univariate factors and multivariate factors from all

**Table 1** Clinical characteristics of patients with spinal chordoma

| Parameters | Total | D-dimer (μg/L) | | *p* |
|---|---|---|---|---|
| | *N* (%) | < 840 | ≥ 840 | |
| Overall | 224 | 130 | 94 | |
| Age | | | | 0.491 |
| < 40 years | 90 (40.2) | 55 | 35 | |
| ≥ 40 years | 134 (59.8) | 75 | 59 | |
| Gender | | | | 0.771 |
| Male | 155 (69.2) | 91 | 64 | |
| Female | 69 (30.8) | 39 | 30 | |
| Treatment history | | | | 0.886 |
| Primary | 150 (67.0) | 88 | 62 | |
| Recurrent | 74 (33.0) | 42 | 32 | |
| Preoperative KPS | | | | 0.075 |
| < 80 | 129 (57.6) | 68 | 61 | |
| ≥ 80 | 95 (42.4) | 62 | 33 | |
| Preoperative Frankel score | | | | 0.011* |
| A–C | 54 (24.1) | 23 | 31 | |
| D–E | 170 (75.9) | 107 | 63 | |
| Tumor size | | | | 0.210 |
| < 6 cm | 138 (61.6) | 85 | 53 | |
| ≥ 6 cm | 86 (38.4) | 45 | 41 | |
| Location | | | | 0.225 |
| C1–2 | 20 (8.9) | 8 | 12 | |
| C3–L5 | 95 (42.4) | 56 | 39 | |
| S1–5 | 109 (48.7) | 66 | 43 | |
| Enneking stage | | | | 0.136 |
| I | 189 (84.4) | 114 | 75 | |
| II–III | 35 (15.6) | 16 | 19 | |
| Tomita classification | | | | 0.139 |
| I–III | 111 (49.6) | 70 | 41 | |
| IV–VII | 113 (50.4) | 60 | 53 | |
| Pathology | | | | 0.150 |
| Classical | 183 (81.7) | 110 | 73 | |
| Chondroid | 16 (7.1) | 10 | 6 | |
| Dedifferentiated | 25 (11.2) | 10 | 15 | |
| Resection mode | | | | 0.080 |
| Piecemeal | 106 (47.3) | 55 | 51 | |
| En bloc | 118 (52.7) | 75 | 43 | |
| Preoperative embolization | | | | 0.321 |
| No | 132 (58.9) | 73 | 59 | |
| Yes | 92 (41.1) | 57 | 35 | |
| Intraoperative chemotherapy | | | | 0.075 |
| No | 78 (34.8) | 39 | 39 | |
| Yes | 146 (68.2) | 91 | 55 | |
| Operative blood loss | | | | 0.734 |
| < 1000 mL | 169 (75.4) | 97 | 72 | |
| ≥ 1000 mL | 55 (24.6) | 33 | 22 | |
| Adjuvant radiotherapy | | | | 0.392 |
| No | 190 (84.8) | 108 | 82 | |
| Yes | 34 (15.2) | 22 | 12 | |

*KPS* Karnofsky performance status

* $p \leq 0.05$

potential predictors of survival. Kaplan–Meier survival analyses were used to evaluate DFS and OS. The significance level was set at $p < 0.1$ for the univariate screen and $p < 0.05$ for the multivariate screen. Confidence intervals (CIs) were all set at the 95% confidence level.

## Results

### Patients and clinicopathological characteristics

A total of 224 patients with spinal chordoma treated at our center between September 2002 and January 2016 were enrolled in the cohort (Fig. 1). Mean follow-up time was 45.1 months for DFS and 53.9 months for OS. The male-to-female ratio was 2.24:1 (155: 69) with a mean age of 43.6 years (range 18–72 years). Plasma D-dimer levels in these patients ranged from 100 to 6400 μg/L with an average value of 872 μg/L. Of these patients, 109 (48.7%) had chordoma located in the sacrum, 20 (8.9%) in C1–2 and 95 (42.4%) in C3–L5. The tumor size was smaller than 6 cm for 138 (61.6%) patients and larger than 6 cm for the remaining 86 (38.4%).

Enneking stage and Tomita classification were both recorded to describe patient tumor characteristics. Specifically, 189 (84.4%) patients were in the Enneking stage I, and nearly half of the patients (49.5%) had I–III Tomita classification.

All 224 patients underwent surgical treatment: 150 (67.0%) patients received primary surgery, and 74 (34.4%) received the revision operation after primary surgery at other centers. Total *en bloc* spondylectomy was performed in 118 (52.7%) cases, and total piecemeal resection was performed in 106 (47.3%) cases.

### Optimal cutoff values for D-dimer and patient outcomes

The optimal cutoff values of D-dimer as determined by X-tile program were 840 μg/L and 830 μg/L for DFS and OS, respectively (Fig. 2). These values were so close to each other that we choose 840 μg/L as a unified value. Before multivariate analysis, baseline and homogeneity of patients in different cutoff value-based groups were checked. Except for preoperative Frankel score ($p = 0.011$), all other factors showed no significant difference between two groups.

### Univariate and multivariate analysis of predictive factors for DFS and OS

In Table 2, we evaluated the association between clinicopathological characteristics and prognosis. Univariate Cox proportional hazards regression was used to screen

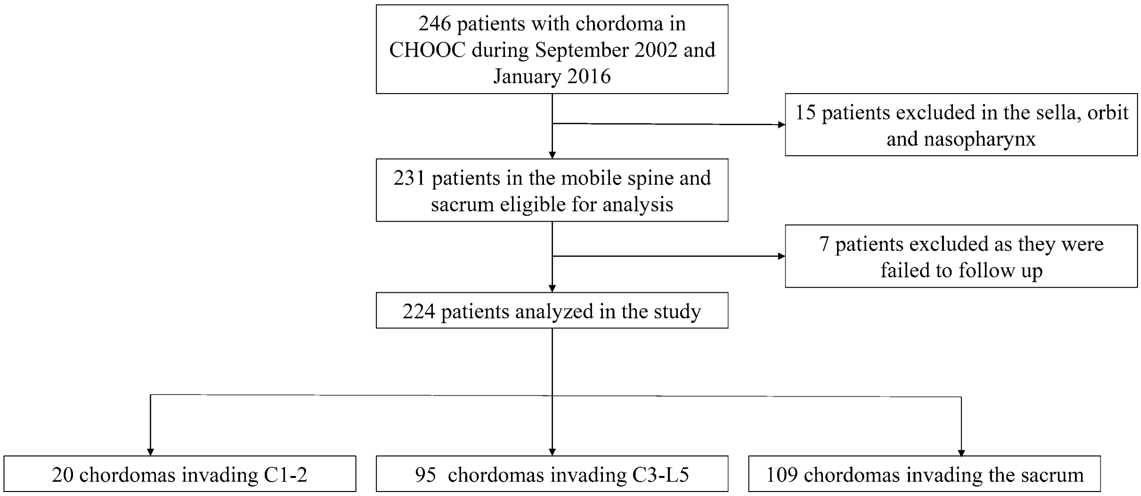



**Fig. 1** Patients flow diagram. In total, 246 consecutive patients were included originally, 15 patients were excluded for the chordoma in orbit, sella and nasopharynx, and 7 patients were excluded for failing to follow-up. In total, 224 evaluable patients remained

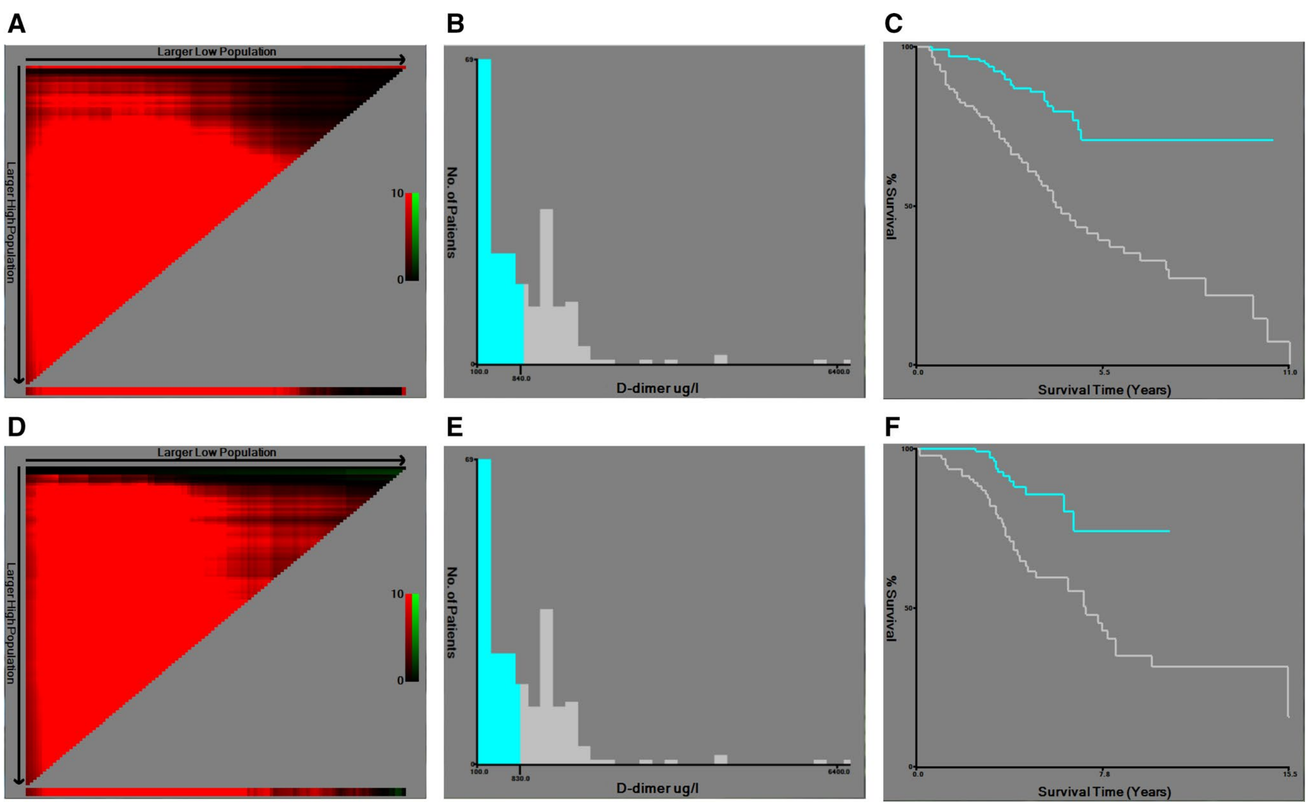



**Fig. 2** The optimal cutoff value for D-dimer is determined by X-tile. Spinal chordoma was divided into training and validation sets equally. The left panel shows X-tile plots of training sets, and plots of matched validation sets are shown in the smaller inset (**a**, **d**). The middle panels show the optimal cutoff values in histograms of the entire cohort (**b**, **e**). Kaplan–Meier plots are displayed in right panels (**c**, **f**). *p* value was determined by using the cutoff value defined in training sets and applying it to validation sets. The cutoff values for D-dimer of DFS and OS were 840 μg/L ($\chi^2 = 25.1571$, $p < 0.001$) and 830 μg/L ($\chi^2 = 15.5543$, $p < 0.001$), respectively

**Table 2** Univariate and multivariate survival analyses of DFS and OS in patients with spinal chordoma

| | DFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* |
| D-dimer | | < 0.001* | | < 0.001# | | < 0.001* | | < 0.001# |
| < 840 μg/L | 1.000 | | 1.000 | | 1.000 | | 1.000 | |
| ≥ 840 μg/L | 3.255 (2.004–5.287) | | 2.678 (1.577–4.550) | | 3.516 (1.870–6.610) | | 3.701 (1.814–7.549) | |
| Age | | 0.010* | | 0.208 | | 0.003* | | 0.092 |
| < 40 year | 1.000 | | 1.000 | | 1.000 | | 1.000 | |
| ≥ 40 year | 1.880 (1.164–3.036) | | 1.414 (0.825–2.425) | | 2.398 (1.333–4.312) | | 1.773 (0.911–3.451) | |
| Gender | | 0.769 | – | – | | 0.478 | | |
| Male | 1.000 | | | | 1.000 | | | |
| Female | 1.073 (0.669–1.723) | | | | 0.813 (0.459–1.441) | | | |
| Treatment history | | < 0.001* | | < 0.001# | | < 0.001* | | < 0.001# |
| Primary | 1.000 | | 1.000 | | 1.000 | | 1.000 | |
| Recurrent | 3.429 (2.174–5.408) | | 2.707 (1.583–4.630) | | 3.619 (2.120–6.178) | | 3.159 (1.675–5.958) | |
| Preoperative KPS | | 0.015* | | 0.738 | | 0.001* | | 0.018# |
| < 80 | 1.000 | | 1.000 | | 1.000 | | 1.000 | |
| ≥ 80 | 0.543 (0.331–0.889) | | 0.913 (0.533–1.561) | | 0.314 (0.158–0.623) | | 0.412 (0.198–0.861) | |
| Preoperative Frankel score | < 0.001* | | 0.140 | | < 0.001* | | 0.011# | |
| A–C | 1.000 | | 1.000 | | 1.000 | | 1.000 | |
| D–E | 0.412 (0.262–0.647) | | 0.676 (0.402–1.137) | | 0.358 (0.211–0.608) | | 0.460 (0.252–0.839) | |
| Tumor size | | 0.006* | | 0.297 | | 0.005* | | 0.085 |
| < 6 cm | 1.000 | | 1.000 | | 1.000 | | 1.000 | |
| ≥ 6 cm | 1.869 (1.195–2.926) | | 1.297 (0.796–2.114) | | 2.139 (1.258–3.637) | | 1.731 (0.927–3.234) | |
| Location | | 0.386 | – | – | | 0.817 | – | – |
| C1–2 | 1.000 | | | | 1.000 | | | |
| C3–L5 | 1.875 (0.734–4.789) | | | | 1.351 (0.511–3.571) | | | |
| S1–5 | 1.585 (0.615–4.080) | | | | 1.362 (0.507–3.660) | | | |
| Enneking stage | | 0.007* | | 0.861 | | 0.020* | | 0.515 |
| I | 1.000 | | 1.000 | | 1.000 | | 1.000 | |
| II–III | 2.055 (1.223–3.453) | | 1.056 (0.574–1.941) | | 2.039 (1.121–3.708) | | 0.791 (0.390–1.603) | |
| Tomita classification | | 0.110 | – | – | | 0.670 | – | – |
| I–III | 1.000 | | | | 1.000 | | | |
| IV–VII | 1.443 (0.920–2.264) | | | | 1.121 (0.663–1.894) | | | |
| Pathology | | < 0.001* | | 0.006# | | < 0.001* | | 0.038# |
| Classical | 1.000 | | 1.000 | | 1.000 | | 1.000 | |
| Chondroid | 1.480 (0.632–3.467) | | 2.381 (0.963–5.884) | | 3.330 (1.983–6.391) | | 0.510 (0.067–3.866) | |
| Dedifferentiated | 4.207 (2.508–7.058) | | 2.490 (1.347–4.605) | | 3.560 (1.983–6.391) | | 2.358 (1.165–4.773) | |
| Resection mode | | 0.002* | | 0.187 | | 0.004* | | 0.068 |
| Piecemeal | 1.000 | | 1.000 | | 1.000 | | 1.000 | |

**Table 2** (continued)

| | DFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate analysis | | Multivariate analysis | | Univariate analysis | | Multivariate analysis | |
| | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* | HR (95% CI) | *p* |
| En bloc | 0.475 (0.297–0.758) | | 0.709 (0.426–1.181) | | 0.444 (0.255–0.773) | | 0.555 (0.295–1.045) | |
| Preoperative embolization | | 0.017* | | 0.772 | | 0.150 | – | – |
| No | 1.000 | | 1.000 | | 1.000 | | | |
| Yes | 0.551 (0.337–0.901) | | 0.919 (0.520–1.625) | | 0.659 (0.373–1.163) | | | |
| Intraoperative chemotherapy | 0.003* | | 0.563 | | 0.309 | – | – | |
| No | 1.000 | | 1.000 | | 1.000 | | | |
| Yes | 0.511 (0.327–0.800) | | 0.854 (0.501–1.457) | | 0.755 (0.439–1.298) | | | |
| Operative blood loss | | 0.260 | – | – | | 0.151 | – | – |
| < 1000 mL | 1.000 | | | | 1.000 | | | |
| ≥ 1000 mL | 1.352 (0.800–2.285) | | | | 1.678 (0.847–2.940) | | | |
| Adjuvant radiotherapy | | 0.011* | | 0.006# | | 0.934 | – | – |
| No | 1.000 | | 1.000 | | 1.000 | | | |
| Yes | | | 0.273 (0.100–0.747) | 0.236 (0.083–0.666) | 1.032 (0.487–2.188) | | | |
| DFS | | – | | – | | 0.001* | | 0.058 |
| No | | | | | 1.000 | | 1.000 | |
| Yes | | | | | 2.618 (1.501–4.566) | | 0.477 (0.222–1.024) | |

*KPS* Karnofsky performance status, *DFS* disease-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval

* $p<0.1$; # $p<0.05$

predictive factors for DFS and OS, as was the base of the multivariate Cox proportional hazards regression analysis.

DFS was 64.7% in this cohort. In univariate analysis, twelve parameters, including D-dimer, age, treatment history, preoperative KPS and Frankel score, tumor size, Enneking stage, pathology, resection mode, preoperative embolization, intraoperative chemotherapy and adjuvant radiotherapy, as screened out by Kaplan–Meier survival analysis, had a significant association with DFS ($p<0.1$). Filtered factors were submitted to Cox proportional hazards analysis and multivariate analysis. The prognostic significance of D-dimer, as well as treatment history, pathology and adjuvant radiotherapy was confirmed ($p<0.05$). High plasma D-dimer level remained significantly associated with worse DFS (HR 2.678, 95% CI 1.577–4.550, $p<0.001$). The Kaplan–Meier survival analyses of the four factors are shown in Fig. 3.

OS reached 75% in this cohort. In univariate analysis, the Cox regression model revealed that ten parameters, including D-dimer, age, treatment history, preoperative KPS and Frankel score, tumor size, Enneking stage, pathology, resection mode and DFS, had a correlation with OS in spinal chordoma ($p<0.1$). These factors were all further included in multivariate analysis. The multivariate analysis demonstrated that D-dimer level ≥ 840 μg/L (HR 3.701, 95% CI 1.814–7.549, $p<0.001$), recurrent case, KPS score < 80, Frankel score A-C, dedifferentiated isoform and chondroid isoform were strongly associated with worse OS ($p<0.05$). All the Kaplan–Meier survival analyses are shown in Fig. 4.

## Subdivision of the Enneking staging system according to pretreatment plasma D-dimer levels

Enneking staging system is widely used in the assessment of tumors, including chordoma. However, this biomarker does not always reflect tumor severity. In multivariate

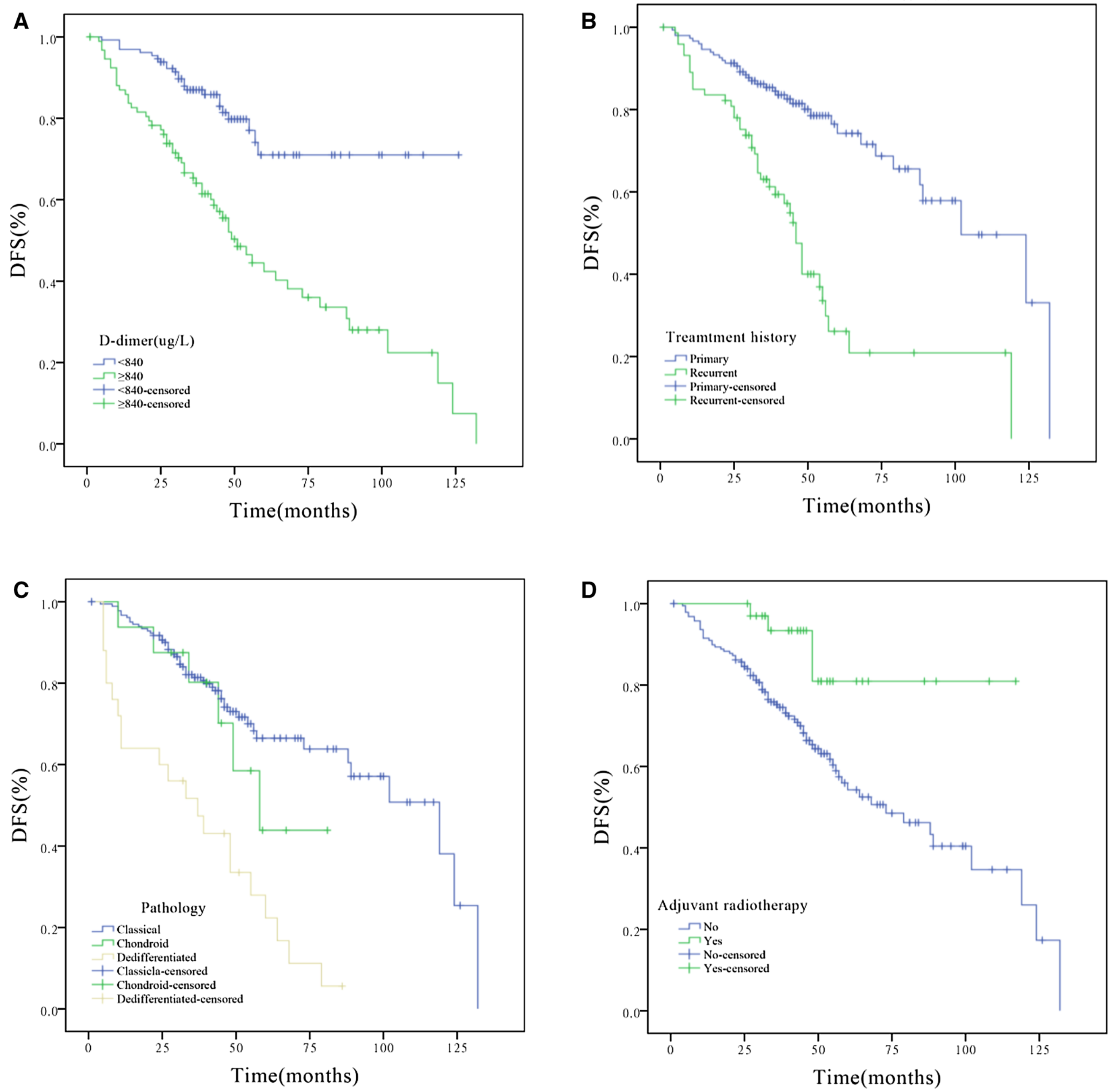



**Fig. 3** K–M survival curves revealing impacts of independent prognostic factors of DFS. **a** K–M survival curves of all patients according to the different levels of D-dimer. **b** K–M survival curves of all patients according to treatment history. **c** K–M survival curves of all patients according to pathology. **d** K–M survival curves of all patients according to adjuvant radiotherapy

analysis, Enneking stage was not an independent prognostic factor for DFS or OS. Generally, patients in stage II–III groups have a worse OS than those in group I, as the tumor at Enneking stage I is considered to have a low potential for malignancy. Enneking staging was further subdivided (stage I) within this analysis of D-dimer level. According to the optimal cutoff, stage I was divided into two parts: I–D-dimer low level (< 840 μg/L) and I–D-dimer high level (≥ 840 μg/L). In subgroup analysis, 75 out of 190 patients in stage I had a D-dimer level ≥ 840 μg/Land were regrouped into I–D-dimer high level. The remaining 115 patients belonged to the I–D-dimer low level. According to Kaplan–Meier survival analysis, patients at the I–D-dimer low level had significantly better survival than those at the I–D-dimer high level, as well as the patients at stage II–III ($p < 0.001$), as given in Table 3. In addition, survival of the I–D-dimer high-level group was similar to that of stage II–III groups.

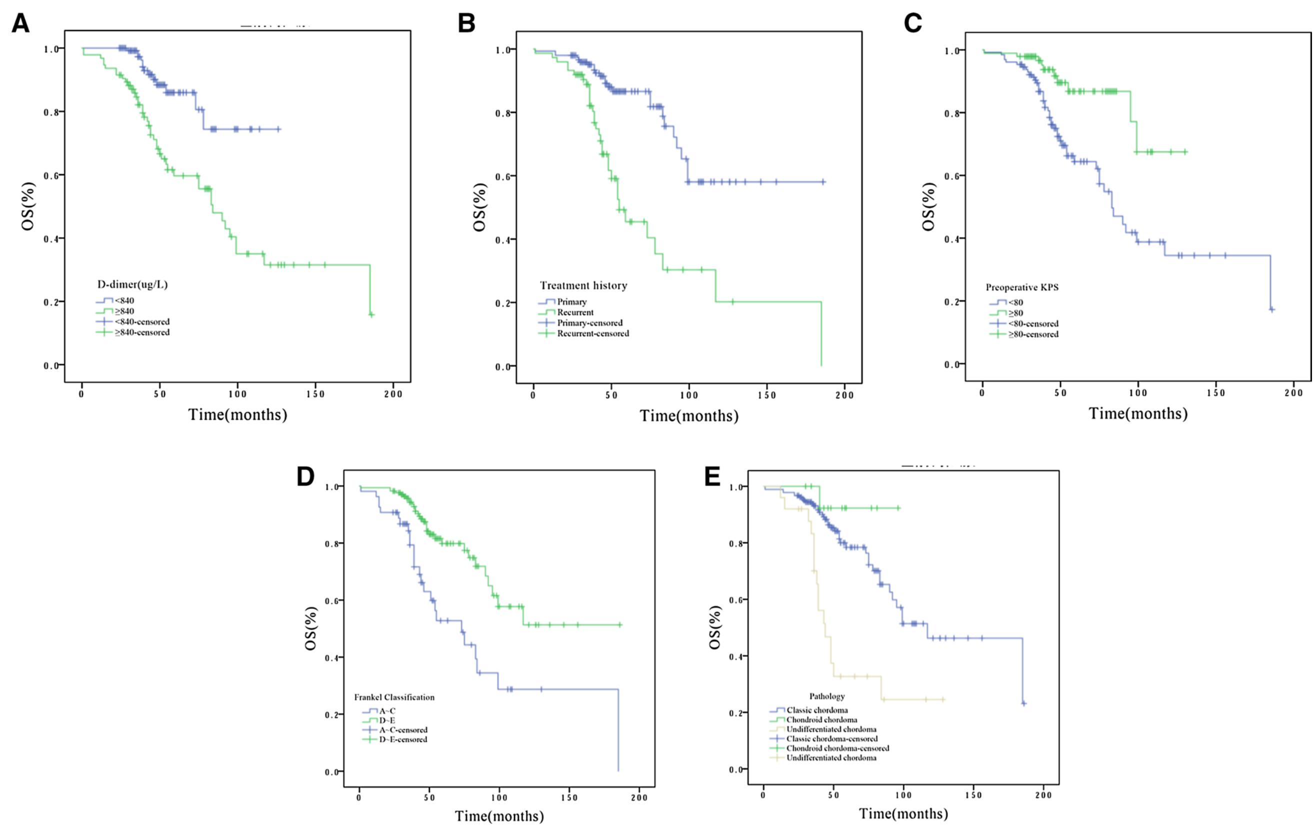



**Fig. 4** K–M survival curves revealing impacts of independent prognostic factors of OS. Kaplan–Meier curves of OS for **a** D-dimer, **b** treatment history, **c** preoperative KPS, **d** Frankel classification and **e** pathology

**Table 3** Survival analysis according to Enneking stage and D-dimer levels

| | DFS | | OS | |
|---|---|---|---|---|
| | HR (95%) | *p* | HR (95%) | *p* |
| Enneking stage | | < 0.001* | | < 0.001* |
| I–D-dimer low level | 0.245 (0.128–0.467) | < 0.001* | 0.178 (0.075–0.421) | < 0.001* |
| I–D-dimer high level | 0.866 (0.501–1.497) | 0.606 | 0.853 (0.460–1.582) | 0.614 |
| II–III | 1.000 | – | 1.000 | – |

*DFS* disease-free survival, *OS* overall survival, *HR* hazard ratio, *CI* confidence interval

* $p < 0.05$

## Discussion

Treatment of spinal chordoma is a difficult clinical challenge for orthopedic oncologists. This condition is a relatively rare low-grade malignant tumor that always occurs at both ends of the axial skeleton: cervical spine and sacrum. This intricate anatomic position presents a unique challenge to surgeons [10, 28]. Additionally, local recurrence is a common characteristic of spinal chordoma and must be addressed to reduce the high recurrence rate. Above all, prognostic prediction of chordoma is of primary issue and requires a more effective evaluation methodology. This study analyzed the prognostic significance of D-dimer in a cohort of 224 patients with spinal chordoma and serves as a reference for clinical management.

D-dimer is a small protein fragment found in the plasma after degradation of the cross-linked fibrin [29, 30]. It is generally considered to be a sensitive biomarker to aid in the diagnosis of thrombotic disorders [29]. In recent years, a series of studies have demonstrated that D-dimer may be a potential prognostic factor for common malignancies, such as lung cancer, prostate cancer, colorectal cancer and cervical cancer [22–25]. D-dimer level can be quantitatively measured by blood routine examination. Compared with other prognostic methods, it is convenient and economical with potential to be widely applied in clinical situations. In the chordoma area, the study of prognostic significance of D-dimer is still unknown. We aimed to investigate the association between D-dimer level and the outcome of spinal chordoma patients. Finally, we demonstrated that high pretreatment D-dimer levels correlate with adverse clinical profiles. We enrolled 224 chordoma patients, which is one of the largest in the study of spinal chordoma so far.

Malignant tumors are always characterized by hypercoagulability, thrombosis and embolism [31]. However, the underlying mechanism of this condition is still unclear. The escalating tumor burden including large tumor size, advanced tumor stage and distant metastasis is a prevalent conjecture, which elevates plasma D-dimer levels, and in turn, D-dimer could promote proliferation, adhesion and metastasis in tumor [32, 33]. Another possible explanation is that cancer cells may release tissue factors and cytokines, which activate the coagulation cascade [34]. Subsequently, D-dimer accumulates due to the degeneration of cross-linked fibrin. In several studies, the connection between cytokines and status of chordoma has been proved [32], although the relevant underlying molecular mechanism requires further exploration.

In this study, we investigated the prognostic significance of plasma D-dimer levels in chordoma with univariate and multivariate analysis. Our cohort contained 224 cases of spinal chordoma treated between September 2002 and January 2016 with more comprehensive data compared to former studies of chordoma. The cutoff value for D-dimer, 840 μg/L, was determined by X-tile, although this value was different from values used in previous studies. In the study, we demonstrated that:

1. High plasma D-dimer levels were associated with worse DFS and OS.
2. Patients with a low level of D-dimer had a significantly better survival than those with a high level of D-dimer within Enneking stage I group. The survival of the I–D-dimer low-level group was similar to that of stage II–III groups.

KPS score is a widely used metric to stratify the patient viability and determine appropriate case management with a connection with adverse events in malignancies [35]. In our study, KPS score was proved to be a prognostic factor for DFS and OS in chordoma. Patients with a KPS score $< 80$ had a worse DFS and OS. In this study, three histopathological subtypes of chordoma were included. In total, 183 out of 224 (81.7%) cases of chordoma belonged to the conventional subtype, 16 (7.1%) to chondroid subtype, and the remaining 25 (11.2%) were dedifferentiated subtype. In the univariate and multivariate analyses, pathology type was identified as a prognostic factor in DFS and OS.

Patient treatment history shows a theoretical significance in the prognosis of chordoma. Orthopedic oncologists often perform surgical excision with wide margins as a crucial aspect of chordoma surgeries, although high-dose radiotherapy is also regarded as an alternative therapy when surgery resection is unfeasible or margin-negative resection is unavailable. Compared with metastasis, local progression is a much more severe issue. The peculiar anatomic structures around the tumor had been altered in the first surgery, and it seemed impossible to achieve complete resection for the recurrent disease. With such a clinical situation, poor outcomes may be inevitable. Statistical analysis reached a similar conclusion that treatment history was a prognostic factor for DFS and OS.

The Enneking staging is a simple, convenient system widely used to regulate the therapeutic regimens of tumor patients; however, this system has also been shown to be imprecise. A tumor patient at Enneking stage I is considered to have a better OS and DFS than later stages. Remarkably, Enneking stage was not a prognostic factor in this study, contrary to what was expected. Here, we explored the connection between D-dimer level and Enneking staging system. The spinal chordoma patients in stage I were subdivided into two groups according to the plasma D-dimer value. Patients at stage I with low D-dimer level had a better DFS and OS. The patients at stage II–III had a similar DFS and OS with those stage I patients with high D-dimer levels. This finding demonstrated that therapeutic regimen cannot be determined just based on the tumor morphology. D-dimer may be considered to be a feasible supplement to optimize the Enneking staging system. The prognostic significance of D-dimer levels in cancer still needs to be verified in the future. High-risk patients could be distinguished, and individualized treatment will be more accurate if new biomarkers are identified.

We have to acknowledge the limitations of this retrospective analysis when compared with the prospective one, although the electronic databases and medical records were reviewed prospectively. Additionally, we only collected the preoperative D-dimer value to analyze the impact on DFS and OS. The optimal mode for analyzing prognostic role of D-dimer is dynamic observation. If the postoperative values of D-dimer can be consistently recorded, the association described in this study may be more convincing. However, it was not a routine for operative and postoperative examination of D-dimer in our center, and only preoperative level of D-dimer indicating patients' coagulation was observed in our center to exclude surgical contraindications. Therefore, it still appeals for well-designed prospective research focusing on continuous level of D-dimer during perioperative period for spinal chordoma in future. In addition, the databases came from one center, so we suggest further validation with other datasets from multiple centers. Despite this, our results were convincing due to a large scale and a long follow-up of spinal chordoma.

**Funding** This study is supported by the National Natural Science Foundation of China (Grant No. 81702659).

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflicts of interest.

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## Affiliations

**Bo Li[1] · Hao Zhang[1] · Pingting Zhou[2] · Jiaxiang Yang[1,3] · Haifeng Wei[1] · Xinghai Yang[1] · Cheng Yang[1] · Zhipeng Wu[1] · Jianru Xiao[1]**

✉ Cheng Yang
ddyc2001@163.com

✉ Zhipeng Wu
eaglewzp@163.com

✉ Jianru Xiao
liliunit@163.com

[1] Department of Orthopedic Oncology, Changzheng Hospital, Second Military Medical University, 415 Fengyang Road, Shanghai 200003, China

[2] Department of Radiation Oncology, Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

[3] Anhui University of Chinese Medicine, 103 Meishan Road, Hefei 230038, Anhui, China