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# The prognostic and predictive value of plasma D-dimer in children with neuroblastoma: a 7-year retrospective analysis at a single institution

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**Purpose:** Elevated plasma D-dimer level is a poor prognostic factor for many solid tumors. However, limited research has been conducted on D-dimer in children with neuroblastoma (NB), and its clinical significance remains unclear. The present study investigated the clinical and prognostic significance of D-dimer in pediatric NB patients.
**Methods:** A retrospective analysis of all newly admitted NB patients was conducted from January 2014 to December 2020. Baseline clinicopathological features, preoperative laboratory parameters, and follow-up information were collected. Univariate and multivariate analyses were performed to determine the relationship between D-dimer level, clinical features, and the prognostic value.
**Results:** Among 266 patients, the median value of D-dimer was 2.98 ng/mL, of which 132 patients showed elevated D-dimer levels before surgery (>2.98 ng/mL). Univariate analysis revealed that elevated D-dimer was significantly associated with age, hemoglobin, neutrophil-to-lymphocyte ratio, neuron-specific enolase, 24-hour vanillylmandelic acid, overall survival, and so on ($P < 0.05$). Patients with elevated D-dimer levels had shorter median overall survival time when compared with normal D-dimer levels ($P = 0.01$). The prognosis was better in patients with normal D-dimer levels when combined with lower age, ganglioneuroblastoma tumor type, lower stage on International Neuroblastoma Staging System, low-risk group, and without bone metastasis or bone marrow metastasis. The continuous increase of D-dimer level after treatment indicated tumor recurrence or progression.
**Conclusion:** A high D-dimer level is associated with low overall survival, and an elevated D-dimer level after treatment indicates tumor recurrence and progression. D-dimer can be used as one of the evaluation factors for NB treatment or prognosis.
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**Key Words:** Child, D-dimer, Neuroblastoma, Prognosis

## INTRODUCTION

Neuroblastoma (NB) is the most prevalent and lethal extracranial solid tumor in children, accounting for 8%–10% of childhood malignancies but 15% of the overall risk of death from childhood cancer [1-4]. It is an embryonic-derived tumor

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that could either rapidly progress or spontaneously regress [2,5,6]. Approximately 85% of the children were younger than 5 years old at the time of diagnosis. The long-term survival rate for the low-medium risk group was more than 90%, whereas it was less than 50% for the high-risk group [7,8]. Although neuron-specific enolase (NSE), 24-hour vanillylmandelic acid (VMA), lactate dehydrogenase, and ferritin have been widely used as biomarkers for poor prognosis of NB, the sensitivity and specificity are still unsatisfactory [9-11]. The heterogeneity of prognostic outcomes highlights the urgent need for more reliable biomarkers to identify high-risk patients and guide individual treatment strategies.

In 1865, Trousseau first reported the relationship between tumors and thromboembolism. Almost all types of tumors may activate the coagulation system through host-tumor interaction, resulting in hypercoagulation and elevated D-dimer. D-dimer is routinely used in clinical screening for deep vein thrombosis, disseminated intravascular coagulation, and pulmonary embolism and plays an essential role in patients with malignant tumors [12]. Previous studies have shown that elevated D-dimer is associated with the stages, recurrence, and metastasis of malignant tumors, such as gastric cancer [13], lung cancer [14], liver cancer [15], breast cancer [16], colorectal cancer [17], prostate cancer [18], and cervical cancer [19].

However, there are few reports on the relationship between D-dimer and NB in children. Therefore, this retrospective study investigated the clinical and prognostic significance of D-dimer in pediatric NB.

## METHODS

This study was approved by the Review Committee of the Children's Hospital of Chongqing Medical University (No. 202553), and informed consent was exempted according to the committee's regulations.

### Study subject inclusion criteria

A retrospective analysis was conducted for all NB patients who underwent surgery in the Department of Pediatric Surgical Oncology, Children's Hospital of Chongqing Medical University, from January 2014 to December 2020. Inclusion criteria were as follows: (1) pathologically confirmed NB or bone marrow examination indicates NB accompanied with elevated 24-hour urinary VMA; (2) complete clinical follow-up data; (3) no history of other malignant tumors; (4) no acute inflammatory diseases; and (5) no anticoagulant therapy was performed before surgery. Exclusion criteria were as follows: (1) non-neuroblastoma histologically, (2) complicated with hematological diseases, (3) combined with immune system diseases, or (4) long-term treatment with hormonal drugs.

### Data collection

Data were derived from the hospital's electronic medical record and hospital information system. Clinical and demographic variables included age, sex, leukocyte, platelet, hemoglobin, lymphocyte, monocyte, neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), disease diagnosis, D-dimer, urinary VMA, NSE, α-FP, *MYCN* amplification, and follow-up time. The patients were regularly followed up at the clinic and through Internet hospital, WeChat, or telephone. All laboratory parameters were analyzed during routine examinations before surgery. Plasma D-dimer levels were determined through immunoturbidimetry. The normal reference values of plasma D-dimer, 24-hr urine VMA, and serum NSE at our institution were lower than 0.91 mg/L, 13.6 ng/mL, and 16.3 ng/mL, respectively. Disease staging was performed according to International Neuroblastoma Staging System (INSS) and risk classification by Children's Oncology Group stratification. Overall survival (OS) was calculated from the date of diagnosis to the date of death or the last follow-up. The last follow-up was on November 30, 2022.

### Statistical analysis

IBM SPSS Statistics ver. 22.0 (IBM Corp.) was used for statistical analysis. The Shapiro-Wilk test was used to check normality; measurement data are expressed as mean and standard deviation ($X \pm S$); count data are expressed as percentages; count data were compared using the chi-square test or Fisher exact test; the least significant difference test was used for comparison between two groups. The Kruskal-Wallis test was used for measurement data with nonnormal distribution, and binary logistic regression analysis was used for multivariate analysis. Preoperative D-dimer levels were divided into two parts around the median number, and survival curves from the time of operation to the time of death or the last follow-up were plotted according to the Kaplan-Meier method. The logarithmic rank test was used for comparison. Cox proportional hazard regression models were used for univariate and multivariate analyses. Significant statistical variables ($P < 0.05$) were included in the univariate analysis to determine independent prognostic factors for survival, with $P < 0.05$ (on both sides) considered statistically significant.

## RESULTS

### Patient data

This study enrolled 266 NB patients who underwent surgery. There were 116 female (43.6%) and 150 male patients (56.4%) with a median age of 28 months (1–167 months). More than half of the patients with advanced disease (147, 55.3%) were in stage IV, whereas 168 (63.2%) were at high risk. The median follow-

up time was 38.45 months. During the entire follow-up period of 1.5–99.0 months, 113 patients (42.5%) died during the follow-up period. The 1-, 2-, and 3-year OS rates were 97.4%, 77.8%, and 57.5%, respectively.

Preoperative D-dimer levels were elevated (>2.98 mg/L) in 132 patients (49.6%). Table 1 analyzes the relationship between D-dimer and clinicopathological factors. Elevated D-dimer levels were significantly correlated with age, hemoglobin, NLR, NSE, 24-hr VMA, tumor size, bone metastasis, bone marrow metastasis, tumor type, tumor stage, Shimada classification, risk group, treatment response, and OS ($P < 0.05$). However, no significant difference was found between sex, *MYCN* amplification, leukocytes, platelets, neutrophils, monocytes, lymphocytes, the scope of surgical resection, tumor location,

**Table 1.** Correlation between D-dimer and clinicopathological features of patients

| Variable | D-dimer (ng/mL) | | $\chi^2$/Z | P-value |
|---|---|---|---|---|
| | ≤2.98 (n =134) | >2.98 (n =132) | | |
| Age, ≥18 mo | 84 (62.7) | 102 (77.3) | 6.73 | 0.012 |
| Male sex | 68 (50.7) | 82 (62.1) | 3.50 | 0.061 |
| *MYCN* gene amplification | 22 (16.4) | 33 (25.0) | 3.42 | 0.060 |
| WBC ($\times10^9$/L) | 7.39 ± 2.86 | 7.29 ± 2.91 | 0.55 | 0.593 |
| Platele ($\times10^9$/L) | 354.66 ± 142.12 | 329.46±155.20 | 1.76 | 0.782 |
| Hemoglobin (g/L) | 110.40 ± 17.47 | 93.07±27.43 | 7.80 | <0.001 |
| Neutrophil ($\times10^9$/L) | 3.71 ± 2.24 | 3.91±2.10 | 1.40 | 0.162 |
| Lymphocyte ($\times10^9$/L) | 3.13 ± 1.89 | 2.92±1.77 | 0.95 | 0.341 |
| Monocyte ($\times10^9$/L) | 0.3 ± 0.18 | 0.28±0.15 | 0.14 | 0.890 |
| NLR | 1.14 (0.63–2.21) | 1.52 (0.875–2.375) | 2.01 | 0.040 |
| PLR | 118.89 (83.58–176.67) | 118.56 (68.52–222.37) | 0.26 | 0.802 |
| LMR | 10.73(6.46–18.1) | 11 (6.65–14.95) | 0.56 | 0.581 |
| Tumor size (cm) | | | 13.80 | 0.001 |
| ≤5 | 37 (27.6) | 20 (15.2) | | |
| 5–10 | 55 (41.0) | 42 (31.8) | | |
| ≥10 | 42 (31.3) | 70 (53.0) | | |
| Shimada classification | | | 20.15 | <0.001 |
| FH | 61 (45.5) | 26 (19.7) | | |
| uFH | 73 (54.5) | 106 (80.3) | | |
| Serum NSE (μg/L) | 32 (18.7–97.6) | 187.4 (74.7–537.5) | 6.96 | <0.001 |
| 24-hr VMA (μg/L) | 9.38 (3.28–22.48) | 19.51 (3.45–52.19) | 2.11 | 0.035 |
| Serum α-FP (μg/L) | 2.21 (1.37–5.53) | 2.13 (1.29–4.17) | 0.79 | 0.431 |
| Tumor type | | | 14.80 | <0.001 |
| NB | 93 (69.4) | 117 (88.6) | | |
| GNB | 41 (30.6) | 15 (11.4) | | |
| Scope of surgical resection | | | | |
| Microscopic negative | 52 (38.8) | 48 (36.4) | 0.17 | 0.713 |
| No microscopic negative | 82 (61.2) | 84 (63.6) | | |
| Tumor location | | | | |
| Retroperitoneal or adrenal | 109 (81.3) | 112 (84.8) | 0.58 | 0.521 |
| Others | 25 (18.7) | 20 (15.2) | | |
| Bone metastasis | | | 4.70 | 0.030 |
| Positive | 21 (15.7) | 35 (26.5) | | |
| Negative | 113 (84.3) | 97 (73.5) | | |
| Bone marrow metastasis | | | 21.50 | <0.001 |
| Positive | 33 (24.6) | 69 (52.3) | | |
| Negative | 101 (75.4) | 63 (47.7) | | |
| Lymph node metastasis | | | 0.59 | 0.442 |
| Positive | 33 (24.6) | 38 (28.8) | | |
| Negative | 101 (75.4) | 94 (71.2) | | |
| INSS stage | | | 14.21 | <0.001 |
| I + II + IVs | 36 (26.9) | 12 (9.1) | | |
| III + IV | 98 (73.1) | 120 (90.9) | | |

**Table 1.** Continued

| Variable | D-dimer (ng/mL) | | $\chi^2$/Z | P-value |
|---|---|---|---|---|
| | ≤2.98 (n =134) | >2.98 (n =132) | | |
| Treatment response | | | 16.51 | <0.001 |
| Survival | 69 (51.5) | 38 (28.8) | | |
| Recurrence | 24 (17.9) | 22 (16.7) | | |
| Death | 42 (31.3) | 71 (53.8) | | |
| Risk group | | | 33.41 | <0.001 |
| Low | 30 (22.4) | 9 (6.8) | | |
| Intermediate | 42 (31.3) | 17 (12.9) | | |
| High | 62 (46.3) | 106 (80.3) | | |

Values are presented as number (%), mean ± standard deviation, or median (interquartile range).
NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; FH, favorable histology; uFH, unfavorable histology; NSE, neuron-specific enolase; VMA, vanillylmandelic acid; NB, neuroblastoma; GNB, ganglioneuroblastoma; INSS, International Neuroblastoma Staging System.

**Table 2.** Univariate and multivariate Cox proportional risk regression analysis of overall survival in children with NB

| Variable | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age (mo), ≥18 *vs.*<18 | 0.43 (0.27–0.69) | <0.001 | 1.41 (0.69–2.87) | 0.352 |
| Sex, male *vs.* female | 1.30 (0.89–1.89) | 0.172 | | |
| *MYCN* amplification, (–) *vs.* (+) | 1.85 (1.20–2.86) | 0.005 | 0.96 (0.53–1.71) | 0.880 |
| Plasma D-dimer (ng/mL), <2.98 *vs.* ≥2.98 | 2.09 (1.43–3.06) | <0.001 | 1.00 (0.55–1.85) | 0.991 |
| WBC ($\times 10^9$/L), ≥6.95 *vs.* <6.95 | 1.31 (0.90–1.89) | 0.160 | | |
| Platelet ($\times 10^9$/L), ≥300 *vs.* <300 | 2.08 (0.51–8.48) | 0.311 | | |
| Hemoglobin (g/L), ≥100 *vs.* <100 | 2.47 (1.67–3.64) | <0.001 | 1.18 (0.69–2.01) | 0.562 |
| NLR, ≥1.36 *vs.* <1.36 | 0.95 (0.65–1.37) | 0.782 | | |
| PLR, ≥118.89 *vs.* <118.89 | 1.02 (0.70–1.47) | 0.932 | | |
| LMR, ≥10.83 *vs.* <10.83 | 1.04 (0.72–1.50) | 0.850 | | |
| Tumor size (cm), ≤5 *vs.* >5 | 1.43 (0.86–2.36) | 0.171 | | |
| Tumor microscopic negative, yes *vs.* no | 1.51 (0.98–2.33) | 0.073 | | |
| Tumor location, retroperitoneal or adrenal *vs.* others | 1.22 (0.75–2.01) | 0.434 | | |
| Shimada classification, FH *vs.* uFH | 0.31 (0.19–0.51) | <0.001 | 0.73 (0.33–1.58) | 0.423 |
| Serum NSE (μg/L), ≥87.9 *vs.* <87.9 | 0.38 (0.24–0.60) | <0.001 | 0.52 (0.32–0.86) | 0.010 |
| 24-hr VMA (μg/L), ≥13.6 *vs.* <13.6 | 0.89 (0.61–1.32) | 0.572 | | |
| Tumor types, NB *vs.* GNB | 0.51 (0.29–0.91) | 0.023 | 1.00 (0.51–2.13) | 0.913 |
| Bone metastasis, (–) *vs.* (+) | 0.52 (0.35–0.78) | 0.001 | 0.92 (0.53–1.59) | 0.764 |
| Bone marrow metastasis, (–) *vs.* (+) | 0.47 (0.32–0.68) | <0.001 | 0.79 (0.47–1.33) | 0.381 |
| Lymph node metastasis, (–) *vs.* (+) | 0.57 (0.39–0.84) | 0.004 | 0.91 (0.56–1.49) | 0.713 |
| INSS stage, I+II+IVs *vs.* III+IV | 7.38 (2.72–20.03) | <0.001 | 2.63 (0.83–8.33) | 0.102 |
| Differentiation degree, low + intermediate *vs.* high | 0.17 (0.09–0.29) | <0.001 | 0.32 (0.15–0.67) | <0.001 |

NB, neuroblastoma; HR, hazard ratio; CI, confidence interval; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio; FH, favorable histology; uFH, unfavorable histology; NSE, neuron-specific enolase; VMA, vanillylmandelic acid; GNB, ganglioneuroblastoma; INSS, International Neuroblastoma Staging System.

PLR, LMR, α-FP, and lymph node metastasis.

## Prognostic factors associated with neuroblastoma overall survival

Log-rank analysis showed that OS was correlated with age, tumor type, *MYCN* amplification, plasma D-dimer, hemoglobin, NSE, INSS stage, risk group, bone metastasis, bone marrow metastasis, lymph node metastasis, and Shimada classification but not with sex, neutrophils, platelets, scope of surgical resection, tumor location, NLR, PLR, LMR, tumor size, and 24-hr VMA. In univariate analysis, an elevated D-dimer level was found to be an adverse prognostic factor for OS (hazard ratio, 2.09; 95% confidence interval, 1.43–3.06) (Table 2). Patients with elevated D-dimer levels had a shorter OS time than those

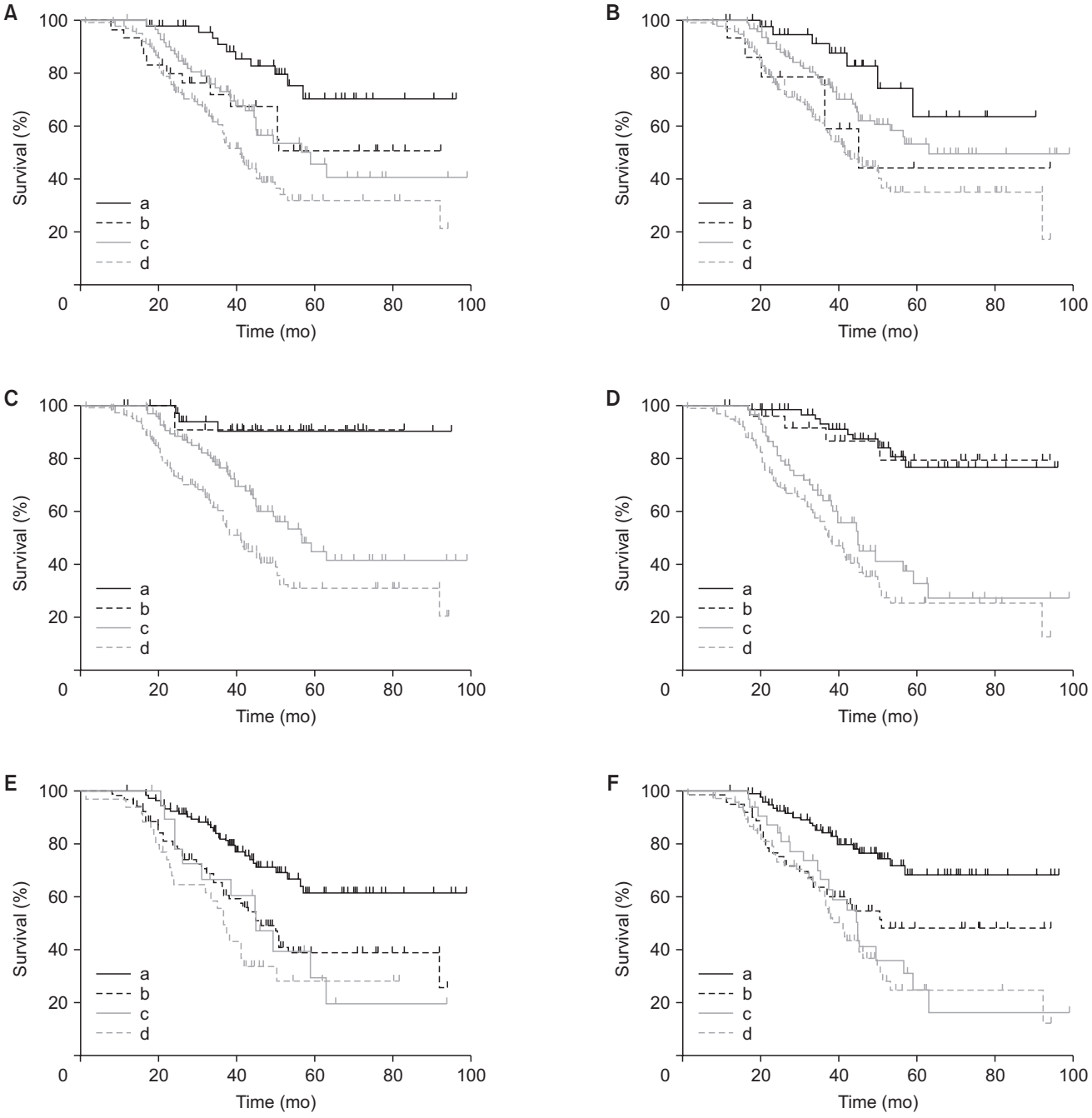


**Fig. 1.** Kaplan-Meier survival curves of plasma D-dimer and neuroblastoma (NB) subgroup. (A) Survival curve of plasma D-dimer with age. a, D-dimer ≤2.98 ng/mL + age <18 months; b, D-dimer >2.98 ng/mL + age <18 months; c, D-dimer ≤2.98 ng/mL + age ≥18 months; and d, D-dimer >2.98 ng/mL + age ≥18 months. (B) Survival curve of plasma D-dimer by tumor class. a, D-dimer 2.98 ng/mL + ganglioneuroblastoma (GNB); b, D-dimer >2.98 ng/mL + GNB; c, D-dimer ≤2.98 ng/mL + NB; and d, D-dimer >2.98 ng/mL + NB. (C) Survival curve of plasma D-dimer with tumor stage (International Neuroblastoma Staging System). a, D-dimer ≤2.98 ng/mL + stage I + II + IVs; b, D-dimer >2.98 ng/mL+ stage I + II + IVs; c, D-dimer ≤2.98 ng/mL + stage III + IV; and d, D-dimer >2.98 ng/mL + stage III + IV. (D) Survival curve of plasma D-dimer with tumor risk group. a, D-dimer ≤2.98 ng/mL + low risk; b, D-dimer >2.98 ng/mL + low risk; c, D-dimer ≤2.98 ng/mL + high risk; and d, D-dimer >2.98 ng/mL + high risk. (E) Survival curve of plasma D-dimer with bone metastasis. a, D-dimer ≤2.98 ng/mL + no bone metastasis; b, D-dimer >2.98 ng/mL + no bone metastasis; c, D-dimer ≤2.98 ng/mL + bone metastasis; and d, D-dimer >2.98 ng/mL + bone metastasis. (F) Survival curve of plasma D-dimer with bone marrow metastasis. a, D-dimer ≤2.98 ng/mL + no bone marrow metastasis; b, D-dimer >2.98 ng/mL + no bone marrow metastasis; c, D-dimer ≤2.98 ng/mL + bone marrow metastasis; and d, D-dimer >2.98 ng/mL + bone marrow metastasis.

with normal D-dimer levels (36.75 months *vs.* 41.05 months, P = 0.01). However, only the disease risk group and NSE were independent predictors of OS in multivariate analysis.

### Prognostic analysis of preoperative plasma D-dimer in different subgroups of neuroblastoma

As displayed in Fig. 1, among different types of NB subgroups, the prognosis was better in patients with lower age, ganglioneuroblastoma (GNB), earlier tumor stage, low-risk group, and without bone metastasis/bone marrow metastasis. Among these patients with better prognoses, patients with normal D-dimer levels have even better prognoses (P < 0.05) (Fig. 1).

### Relationship between pre-/posttreatment D-dimer levels and prognosis

The D-dimer levels before and after treatment were divided into normal (N) or high (H) using the median value of 2.98 ng/mL. The results showed that prognosis was favorable in patients with normal plasma D-dimer levels before and after treatment (N-N) or decreased D-dimer levels after treatment (H-N). In addition, the survival time of those with increased D-dimer levels after treatment (N-H) and those with continuously rising D-dimer levels (H-H) was shorter; the difference was statistically significant (P < 0.05) (Table 3, Fig. 2). The plasma D-dimer levels in surviving children were decreased; by contrast, the D-dimer of relapsed and deceased patients did not decrease significantly or even increased after treatment; the difference was statistically significant (P < 0.05) (Table 4, Fig. 3).

## DISCUSSION

In this study, the data from 266 NB cases were retrospectively analyzed. The results indicated that high D-dimer levels (>2.98 ng/mL) were associated with low OS, and elevated D-dimer levels after treatment indicate tumor recurrence and progression. Univariate analysis revealed that elevated D-dimer was significantly correlated with age, hemoglobin, NLR, NSE, 24-hr VMA, tumor size, bone metastasis, bone marrow metastasis, tumor type, INSS stage, Shimada classification, treatment response, risk group, and OS. Patients with abnormal D-dimer levels had shorter survival time, and the prognosis was better in patients with normal D-dimer accompanied by lower age, earlier INSS stage, lower risk stratification, and absence of bone/bone marrow metastasis. Patients with normal D-dimer

**Table 3.** Relationship between plasma D-dimer level and overall survival time before and after treatment

| D-dimer level after treatment | Number | Overall survival (mo), mean ± SEM | P-value |
|---|---|---|---|
| N-N | 78 | 48.02 ± 19.16 | <0.001 |
| H-N | 90 | 43.08 ± 20.91 | <0.001 |
| N-H | 53 | 35.00 ± 15.29 | 0.041 |
| H-H | 45 | 29.75 ± 14.97 | Reference |

SEM, standard error of mean; N, normal; H, high.

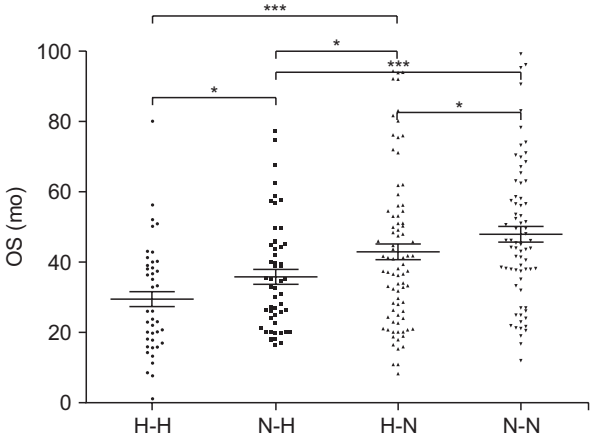


**Fig. 2.** The relationship between plasma D-dimer and overall survival (OS) before and after treatment. N, normal; H, high. *P < 0.05, ***P < 0.001.

**Table 4.** D-dimer levels (mean±sem) and treatment response

| Treatment response | D-dimer level (ng/mL), mean ± SEM | P-value |
|---|---|---|
| Preoperative | 6.22 ± 0.60 | Reference |
| Survival | 1.79 ± 0.28 | <0.001 |
| Recurrence | 8.51 ± 1.76 | 0.043 |
| Death | 9.27 ± 1.34 | <0.001 |

SEM, standard error of mean.

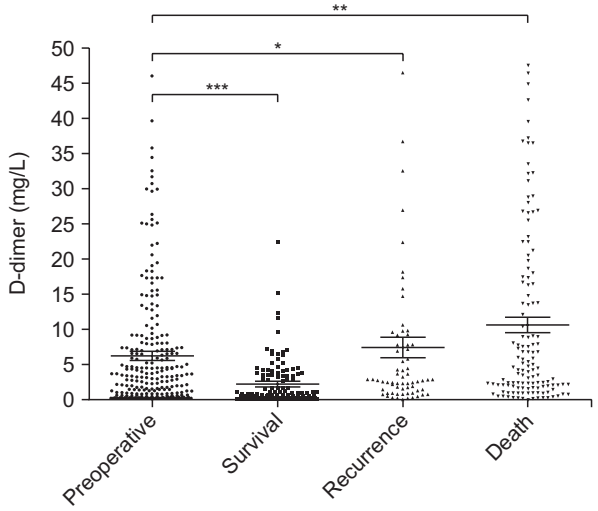


**Fig. 3.** Plasma D-dimer level and prognosis after treatment. *P < 0.05, **P < 0.01, ***P < 0.001.

levels before and after treatment had the best prognosis. The continuous increase of D-dimer after treatment indicated tumor recurrence or progression.

NB is a complex disease in biology, morphology, and clinical heterogeneity. However, current diagnosis and treatment methods include surgery, chemotherapy, radiotherapy, bone marrow transplantation, immunotherapy, and other therapeutic means. The prognosis of high-risk patients was still poor; the 5-year OS rate was less than 50% [20]; half of all high-risk patients developed relapse and progression within 18 months of diagnosis [21,22]; the 5-year survival rate after progression was less than 20%. Therefore, it is necessary to explore the prognostic methods further.

D-dimer has been strongly related to clinical stage, metastasis, and poor prognosis in various types of tumor patients, such as lung cancer [14], gastric cancer [13], and breast cancer [16]. D-dimer is a product of fibrin degradation, and its elevation indicates a hypercoagulable state and secondary hyperfibrinolysis in the body. There is a very complex interaction between coagulation and tumor. First, tumor hypercoagulation is caused by various potential mechanisms, including stasis (direct pressure of tumor mass on blood vessels), bed rest after surgery, poor physical status, iatrogenic hypercoagulation caused by chemotherapy and targeted therapy, and degradation of endogenous heparin caused by the secretion of heparin by malignant tumor [23]. Second, fibrinolysis and coagulation activation systems can promote tumor growth and distant metastasis through various mechanisms, including promoting angiogenesis and inhibiting tumor cell apoptosis [24]. For instance, the platelet-fibrin axis promotes metastasis by preventing natural killer cells from eliminating tumor cells [25]. Platelet and coagulation proteins promote the survival of circulating tumor cells by influencing epithelial-mesenchymal transition, promoting the expression of protumor survival genes, and helping to escape immune cell destruction, thereby promoting tumor metastasis [26]. Tumor-induced coagulation is essentially related to tumor growth, angiogenesis, and metastasis [27]. Previous studies have reported that higher D-dimer (≥0.72 mg/L) has shorter 3-year OS, and elevated D-dimer levels may help to predict the prognosis of NB patients [28]. Our study demonstrated that D-dimer was significantly correlated with age, hemoglobin, NLR, NSE, 24-hr VMA, tumor size, bone metastasis, bone marrow metastasis, tumor type, INSS stage, Shimada classification, risk group, and OS. Higher OS was observed in patients with lower age, GNB tumor type, I + II + IVs INSS stage, low-risk group, and absence of bone or bone marrow metastasis. Moreover, we found that the D-dimer level was decreased obviously in survived patients after treatment; by contrast, the D-dimer of relapsed and deceased patients did not decrease significantly or even increase after treatment, suggesting that D-dimer can be used as an indicator of the therapeutic effect.

Nowadays, studies have focused on biomarkers requiring complex molecular and genetic tests to predict tumor prognoses, such as minimal residual lesions, circulating tumor cells, DNA methylation, and programmed cell death 1/programmed cell death ligand [29,30]. However, the cost and complexity of these examinations limited their large-scale practical application. By contrast, our study used conventional biochemical tests as a prognostic factor for clinical monitoring, which is low-cost, highly maneuverable, without requiring much-specialized equipment or expertise, and yields more reliable results. Studies have demonstrated that hematological indicators, such as CA125, NSE, and 24-hr urinary VMA, can be used to monitor tumor prognosis, which could be used to evaluate the disease condition and predict the therapeutic effect of NB patients. Our study's univariate analysis revealed that OS was associated with age, *MYCN* amplification, plasma D-dimer, hemoglobin, NSE, type, INSS stage, risk group, bone metastasis, bone marrow metastasis, and lymph node metastasis. In multivariate analysis, only the risk group and NSE (≥87.9 μg/L) were independent predictors of OS. This finding is consistent with that of other reports that NSE can be used as a prognostic factor for NB.

This study has several limitations. First, this study has the inherent bias of retrospective study. Second, the D-dimer threshold was greater than 2.98 ng/mL in this study, far higher than the clinical critical point of 0.91 ng/mL, which may have influenced our findings. Third, D-dimer is not a specific biomarker for NB or for tumors, which may have affected our findings. Therefore, a further large-scale prospective study will be required on the prognostic value of D-dimer in NB.

In conclusion, high plasma D-dimer level is associated with low OS, and an elevated level of D-dimer after treatment indicates tumor recurrence and progression. D-dimer can be used as one of the evaluation factors for NB treatment or prognosis.

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None.

### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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