

Analysis of prognostic factors and development of a predictive model following radical nephrectomy for Wilms tumor in children

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Abstract. Wilms tumor (WT) is a common pediatric renal malignancy that poses significant challenges in clinical management and prognosis. The aim of the present study was to identify prognostic factors affecting outcomes in pediatric patients with WT following radical nephrectomy, to stratify high-risk groups for recurrence, and to develop a predictive model to support clinical decision-making and research in Chinese pediatric WT populations. The present retrospective, single-center study included clinical data from 180 pediatric patients with WT who underwent radical nephrectomy at the Baoding Branch of Beijing Children's Hospital (Baoding, China) between January 2015 and January 2019. Univariate and multivariate analyses were performed to identify prognostic factors, and a prediction model was constructed and validated. Progression-free survival (PFS) and overall survival (OS) were analyzed for all patients. The final follow-up was in July 2024. The results demonstrated that the 5-year OS and PFS rates were 99.6 and 94.3%, respectively. The median OS was 76.9 months (range, 30-101 months) and the median PFS was 75.5 months (range, 29-101 months). During follow-up, 25 patients experienced recurrence and 16 died. Univariate analysis revealed that clinical stage, histological subtype and tumor thrombus were significantly associated with prognosis

($P<0.05$). Multivariate Cox regression analysis identified advanced clinical stage [stage III-IV; hazard ratio (HR), 4.151; 95% confidence interval (CI), 1.440-11.922; $P=0.009$] and unfavorable histology (HR, 3.842; 95% CI, 1.592-9.283; $P=0.002$) as independent prognostic factors. A predictive model incorporating these two variables was established, yielding an area under the receiver operating characteristic curve of 0.755 (95% CI, 0.685-0.816; $P<0.001$). In conclusion, clinical stage and histological subtype are independent predictors of prognosis in children with WT after radical surgery. A predictive model based on these factors may help estimate individual prognosis and guide clinical management strategies.

Introduction

Wilms tumor (WT), also known as nephroblastoma, is one of the most common malignant renal tumors in children, with an incidence rate of ~7.1 cases per 100,000 children in the US (1). In Asian populations, the incidence is slightly lower, with China reporting an incidence rate of approximately 2.5 cases per million children (2), accounting for >90% of all pediatric renal malignancies (3). It may affect a single kidney or occur bilaterally (4). Based on histological classification, WT is divided into favorable histology (FH) WT, which comprises ~90% of cases, and anaplastic WT. The typical age of onset is between 2-3 years, although it can occur in infants and in children aged >10 years old (5). With advances in imaging technologies and the adoption of multidisciplinary treatment strategies, the survival rate of WT has markedly improved, with a 5-year survival rate of >90% (6). However, a subset of patients still experiences recurrence or metastasis after radical surgery, leading to a poor prognosis and compromised long-term survival and quality of life (7-9). Therefore, identifying prognostic factors and establishing effective prediction models is essential to improving treatment outcomes and long-term prognosis in pediatric WT.

Over the past decades, research on WT has focused primarily on genetics, molecular biology and clinical management. Studies have reported that WT is closely associated with aberrant expression of genes such as WT1, catenin $\beta 1$ and WNT signaling components (10,11). In addition, clinical stage, tumor size, histological subtype and preoperative chemotherapy have been identified as important prognostic factors (12-15). Although numerous studies have explored the

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Abbreviations: WT, Wilms tumor; FH, favorable histology; UHF, unfavorable histology; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival; HR, hazard ratio; CI, confidence interval; ROC, receiver operating characteristic; AUC, area under the curve; COG, Children's Oncology Group; SIOP, International Society of Paediatric Oncology; CCCG, Chinese Children Cancer Group; EE4A, vincristine + actinomycin D regimen; DD4A, vincristine + actinomycin D + doxorubicin regimen

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impact of these factors, the findings remain inconsistent due to differences in study populations, sample sizes and methodologies (16,17). Therefore, further research is needed to clarify the prognostic significance of these variables across diverse populations and to develop multifactorial prognostic models that can guide clinical decision-making more accurately and comprehensively.

The present study retrospectively analyzed the clinical data of 180 pediatric patients with WT who underwent radical nephrectomy at the Department of Surgical Oncology, Baoding Branch of Beijing Children's Hospital (Baoding, China). The study aimed to identify prognostic factors and to construct a predictive model based on these variables, with the ultimate goal of providing clinicians with valuable evidence to support more precise treatment strategies and improve survival outcomes and quality of life for children with WT.

Materials and methods

Study population. Clinical data were retrospectively collected from pediatric patients with WT who underwent radical nephrectomy at Baoding Branch of Beijing Children's Hospital between January 2015 and January 2019. Data sources included electronic medical records and handwritten treatment documentation. To ensure data integrity and consistency, all handwritten treatment records were independently reviewed and cross-checked against corresponding entries in the electronic medical record system by two trained clinical researchers. Discrepancies, if identified, were resolved through consensus review and, when necessary, verification with the original source documents or consultation with treating physicians. For cases with missing or incomplete data, predefined exclusion criteria were applied to maintain the accuracy and completeness of the dataset; patients with notable missing data were excluded from the final analysis. The inclusion criteria were as follows: i) Age of <18 years; ii) histopathology-confirmed diagnosis of WT; iii) radical nephrectomy performed; and iv) complete clinical data available. The exclusion criteria included the following: i) No pathological diagnosis or unclear pathology; ii) presence of a second primary malignancy or hematologic disease; iii) notable comorbid injury to other organs; and iv) incomplete medical records.

The present study was approved by the Ethics Committee of the Baoding Branch of Beijing Children's Hospital (approval no. H-BDETKJ-SOP006-03-A/2; project no. 2341ZF378). Informed consent was obtained from the guardians of all patients prior to treatment.

Postoperative adjuvant therapy. Diagnosis, staging and treatment for all patients were performed in accordance with the guidelines of the Children's Oncology Group (COG)-Renal Tumor Committee and national protocols developed by the Chinese Children Cancer Group (CCCG), including CCCG-WT-2003 (18), CCCG-WT-2009 (19) and CCCG-WT-2015 (20). Stages I-II were defined as early stage and stages III-IV as advanced stage. All patients received standard postoperative therapy. The early-stage group was treated with the vincristine + actinomycin D (EE4A) regimen. Vincristine was administered via intravenous bolus on day 1 only, at a dosage of 0.025 mg/kg for patients aged

<1 year, 0.05 mg/kg for those aged 1-3 years, and 1.5 mg/m² (maximum 2.0 mg) for those aged >3 years. Actinomycin D was administered via intravenous infusion on day 1 only, at a dosage of 0.023 mg/kg for patients aged <1 year and 0.045 mg/kg (maximum 2.3 mg) for those aged >1 year. The total treatment duration was 19 weeks. The advanced-stage group received the vincristine + actinomycin D + doxorubicin (DD4A) regimen for 25 weeks, combined with radiotherapy (180 cGy/day; 5 days/week). Vincristine was administered via intravenous bolus on day 1 only, at a dosage of 0.025 mg/kg for patients aged <1 year, 0.05 mg/kg for those aged 1-3 years and 1.5 mg/m² (maximum 2.0 mg) for those aged >3 years. Actinomycin D was administered via intravenous infusion on day 1 only, at a dosage of 0.023 mg/kg for patients aged <1 year and 0.045 mg/kg (maximum 2.3 mg) for those aged >1 year. Doxorubicin was administered via intravenous infusion on day 1 only, at a dosage of 1 mg/kg for patients aged ≤1 year and 30 mg/m² for those aged >1 year.

Follow-up and outcome evaluation. Patients who completed WT treatment were followed up every 3 months during the first and second postoperative years, every 4 months in the third year, every 6 months in the fourth year, and once in the fifth year. Follow-up frequency was further individualized based on clinical stage at diagnosis. Specifically, patients with advanced-stage disease (stage III-IV) underwent more intensive monitoring during the first 2 postoperative years, including clinical evaluations and imaging every 2 months during the first year, and every 3 months during the second year. This stage-adapted surveillance strategy was intended to facilitate early detection of recurrence or metastasis. Follow-up examinations included abdominal ultrasonography of the kidney, liver, spleen and gallbladder, and chest X-rays (anteroposterior and lateral views). Follow-up beyond the fifth year was not mandatory. Progression-free survival (PFS) was defined as the interval from the date of radical nephrectomy to the date of tumor recurrence or last follow-up. Overall survival (OS) was defined as the time from surgery to death from any cause or last follow-up. The median follow-up duration was 67 months (range, 29-101 months), with the cutoff date of follow-up in July 2024.

Statistical analysis. All data were analyzed using SPSS version 27.0 (IBM Corp.). Categorical variables were compared using the χ^2 test or Fisher's exact test, depending on the expected count in the contingency table. PFS was used as the primary survival endpoint in the present study, as it captures the time from treatment to disease progression, recurrence or death. Moreover, whilst OS is an important outcome, the small number of deaths (n=16) in the present study limited the ability to performed an extensive OS analysis. Therefore, PFS was used as the main survival measure. Survival analyses were performed using the Kaplan-Meier method, and differences between groups were assessed using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model. Receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) was calculated to evaluate model performance. All tests were two-sided, and P<0.05 was considered to indicate a statistically significant difference. Variables with

$P < 0.05$ in the univariate analysis were prioritized for multivariate modeling; however, tumor thrombus was intentionally retained due to its clinical relevance despite its nonsignificant multivariable P -value.

Results

Baseline clinical characteristics. A total of 180 pediatric patients with WT were included in the present study, comprising 114 male (63.3%) and 66 female (36.7%) patients. A total of 74 patients (41.1%) were aged ≤ 2 years and 106 (58.9%) were aged > 2 years. The median age of the patients was 3.3 years, with an age range of 0.5–8.5 years. Clinical manifestations included abdominal mass in 107 (59.4%) cases, hematuria in 34 (18.9%) cases and other symptoms in 39 (21.7%) cases. Clinical staging revealed 62 (34.4%) patients in stage I, 53 (29.4%) patients in stage II, 61 (33.9%) patients in stage III and 4 (2.2%) patients in stage IV. Histologically, 158 patients (87.8%) had FH, whilst 22 patients (12.2%) had unfavorable histology (UFH). Additional clinical details are presented in Table I.

Univariate and multivariate analysis of prognostic factors. To identify prognostic factors following radical surgery, univariate analysis was performed which revealed that clinical stage, lymph node metastasis, histological subtype and the presence of tumor thrombus were significantly associated with prognosis ($P < 0.05$; Table I). Furthermore, multivariate Cox regression analysis demonstrated that advanced clinical stage [stage III–IV; hazard ratio (HR), 4.151; 95% confidence interval (CI), 1.440–11.922; $P = 0.009$] and UFH (HR, 3.842; 95% CI, 1.592–9.283; $P = 0.002$) were independent risk factors for adverse outcomes (Table II). Notably, tumor thrombus demonstrated the highest univariate HR of 5.332 ($P < 0.001$) among all variables, although its effect size decreased after adjustment for stage and histology in the multivariate analysis ($P > 0.05$).

Prognostic outcomes. By the end of follow-up, 25 patients (13.9%) experienced recurrence and 16 patients (8.9%) had died. The 5-year OS rate was 99.6% and the 5-year PFS rate was 94.3%. The median OS was 76.9 months (range, 30–101 months) and the median PFS was 75.5 months (range, 29–101 months) (Figs. 1 and 2). Further stratified analysis revealed that patients with stage I–II WT had significantly longer PFS than those with stage III–IV WT ($P < 0.001$; Fig. 3). Additionally, despite more frequent follow-up in patients with advanced-stage disease (stage III–IV), these patients still experienced significantly lower PFS compared to those with early-stage disease ($P < 0.001$). This suggests that while increased surveillance may facilitate earlier detection, it does not fully mitigate the impact of more aggressive disease biology in advanced-stage Wilms tumor. Similarly, patients with FH demonstrated significantly longer PFS compared with those with UFH ($P < 0.001$; Fig. 4).

Development of the predictive model. A prognostic model was developed based on clinical stage and histological subtype. The discriminative performance of the model was evaluated using ROC analysis, which yielded an AUC of 0.755 (95%

CI, 0.685–0.816; $P < 0.001$), indicating good predictive accuracy (Fig. 5).

Discussion

WT is a common malignant renal tumor in children. With the refinement of risk-adapted diagnostic and treatment protocols developed by the COG and the International Society of Paediatric Oncology (SIOP) (3,21), long-term survival outcomes for WT have steadily improved, with current 5-year OS rates reaching $\sim 90\%$ (6,22). Nevertheless, $\sim 15\%$ of patients with FHWT still experience recurrence or metastasis, leading to disease progression (13,23). Accordingly, the present study aimed to analyze the clinical characteristics and prognostic factors in patients with WT treated at the Baoding Branch of Beijing Children's Hospital.

The present study primarily focused on PFS due to its ability to comprehensively reflect disease progression, recurrence, and death. The 5-year PFS rate was 94.3%, with a median PFS of 75.5 months. Continued follow-up and expanded sample sizes will be necessary to investigate factors influencing long-term survival.

The selection of clinical stage and histological subtype as core predictors was driven by three main criteria: i) Statistical strength: Both factors demonstrated the highest HRs in univariate analysis (stage III–IV HR, 4.981 and UFH HR, 5.658; both $P < 0.001$) and retained independence in multivariate modeling. Other variables, such as tumor thrombus, became non-significant when adjusted (adjusted $P = 0.154$); ii) clinical feasibility: These parameters are routinely confirmed within 48 h post-nephrectomy, enabling rapid risk stratification according to COG/SIOP guidelines (24); and iii) biological relevance: Advanced stage reflects metastatic potential, whilst anaplasia is associated with tumor protein P53-mediated treatment resistance, which has been validated in prior studies (25–27). Additionally, other clinical factors, such as tumor size and lymph node involvement, were considered in the multivariate analysis. Lymph node involvement showed statistical significance in the univariate analysis and was therefore included in the multivariate model. Whilst excluding these factors may limit the sensitivity of the model in certain patient subgroups, focusing on clinically relevant and easily obtainable variables allows for more practical application in routine clinical settings.

In the present study, univariate factors significantly associated with PFS included clinical stage, histological subtype and tumor thrombus ($P < 0.05$). Multivariate Cox regression confirmed that stage III–IV disease (HR, 4.151; 95% CI, 1.440–11.922; $P = 0.009$) and UFH (HR, 3.842; 95% CI, 1.592–9.283; $P = 0.002$) were independent risk factors for PFS. However, as PFS was the primary endpoint, competing risks, such as death from causes other than WT or comorbid conditions, were not explicitly accounted for, which may affect survival outcomes. Whilst the small number of deaths ($n = 16$) limited the ability to perform detailed competing risk analysis, it is acknowledged that such factors should be considered in future studies. A more comprehensive survival analysis, incorporating competing risks, would provide a clearer picture of the influence of several factors on patient survival and help refine prognostic models.

Table I. Univariate analysis of prognostic factors in patients with pediatric Wilms tumor.

Variable	Cases, n (%)	Recurrence cases, n (%)	Total recurrence rate, %	HR (95% CI)	χ^2	P-value
Age, years						
≤2	74 (41.1)	10 (40.0)	13.5	1.000		
>2	106 (58.9)	15 (60.0)	14.2	1.253 (0.527-3.657)	0.190	0.663
Sex						
Male	114 (63.3)	15 (60.0)	13.2	1.000		
Female	66 (36.7)	10 (40.0)	15.2	1.051 (0.489-3.527)	0.008	0.929
Clinical presentation						
Abdominal mass	107 (59.4)	15 (60.0)	14.0	1.000		
Hematuria	34 (18.9)	8 (32.0)	23.5	1.124 (0.639-4.021)		
Other	39 (21.7)	2 (8.0)	5.1	1.405 (0.695-3.963)	-	0.104 ^a
Hypertension						
No	136 (75.6)	20 (80.0)	14.7	1.000		
Yes	44 (24.4)	5 (20.0)	11.4	1.090 (0.578-2.957)	0.012	0.912
Tumor laterality						
Left	86 (47.8)	13 (52.0)	15.1	1.000		
Right	94 (52.2)	12 (48.0)	12.8	0.954 (0.698-4.538)	0.292	0.589
Clinical stage						
I-II	115 (63.9)	5 (20.0)	4.4	1.000		
III-IV	65 (36.1)	20 (80.0)	30.8	4.981 (2.515-9.634)	20.852	<0.001
Tumor diameter						
≤5 cm	72 (40.0)	9 (36.0)	12.5	1.000		
>5 cm	108 (60.0)	16 (64.0)	14.8	1.263 (0.602-3.451)	0.378	0.539
Tumor volume						
≤1,000 ml	121 (67.2)	16 (64.0)	13.2	1.000		
>1,000 ml	59 (32.8)	9 (36.0)	37.3	1.327 (0.581-3.036)	0.508	0.476
Tumor rupture						
No	166 (92.2)	22 (88.0)	1.8	1.000		
Yes	14 (7.8)	3 (12.0)	7.1	1.871 (0.723-5.063)	-	0.443 ^a
Lymph node metastasis						
No	172 (95.6)	24 (96.0)	14.0	1.000		
Yes	8 (4.4)	1 (4.0)	12.5	1.682 (0.762-6.309)	-	0.032 ^a
Tumor thrombus						
No	173 (96.1)	21 (84.0)	12.1	1.000		
Yes	7 (3.9)	4 (16.0)	57.1	5.332 (2.354-9.658)	-	0.032 ^a

Table I. Continued.

Variable	Cases, n (%)	Recurrence cases, n (%)	Total recurrence rate, %	HR (95% CI)	χ^2	P-value
Histological type						
FH	158 (87.8)	14 (56.0)	8.9	1.000		
UFH	22 (12.2)	11 (44.0)	50.0	5.658 (3.064-10.325)	34.221	<0.001
Number of lymph nodes dissected						
<7	13 (7.2)	2 (8.0)	15.4	1.000		
≥7	167 (92.8)	23 (92.0)	13.8	1.136 (0.581-4.964)	-	0.795 ^a
Postoperative chemotherapy						
No	4 (2.2)	1 (4.0)	25.0	1.000		
Yes	176 (97.8)	24 (96.0)	13.6	0.857 (0.519-3.725)	-	0.482 ^a
Postoperative radiotherapy						
No	114 (63.3)	15 (60.0)	13.2	1.000		
Yes	66 (36.7)	10 (40.0)	15.2	0.986 (0.693-3.928)	0.334	0.564

^aFisher's exact test. HR, hazard ratio; CI, confidence interval; FH, favorable histology; UFH, unfavorable histology.

Table II. Multivariate cox regression analysis of prognostic factors in pediatric Wilms tumor.

Variable	HR	95% CI	P-value
Clinical stage (III-IV vs. I-II)	4.151	1.440-11.922	0.009
Histological type (UFH vs. FH)	3.842	1.592-9.283	0.002
Tumor thrombus	2.284	0.731-7.186	0.156
Lymph node metastasis	1.568	0.624-6.81	0.339

HR, hazard ratio; CI, confidence interval; FH, favorable histology; UFH, unfavorable histology.

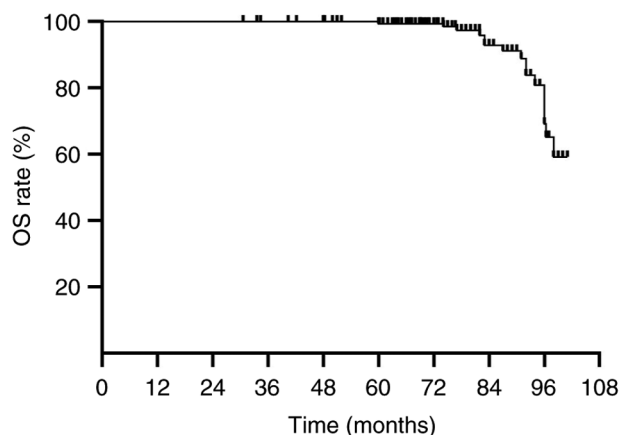


Figure 1. Kaplan-Meier OS curve for 180 pediatric patients with Wilms tumor after radical nephrectomy. OS, overall survival.

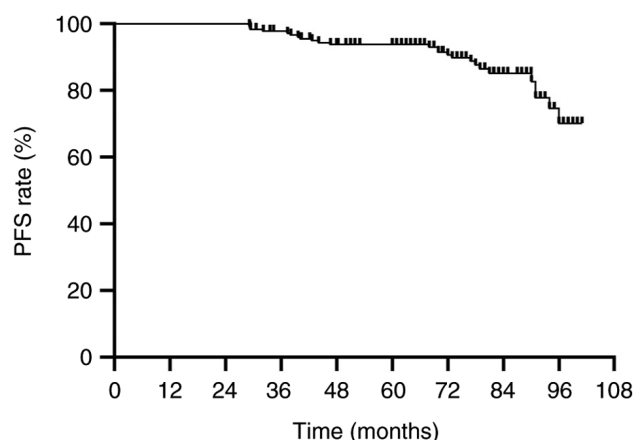


Figure 2. Kaplan-Meier PFS curve for 180 pediatric patients with Wilms tumor after radical nephrectomy. PFS, progression-free survival.

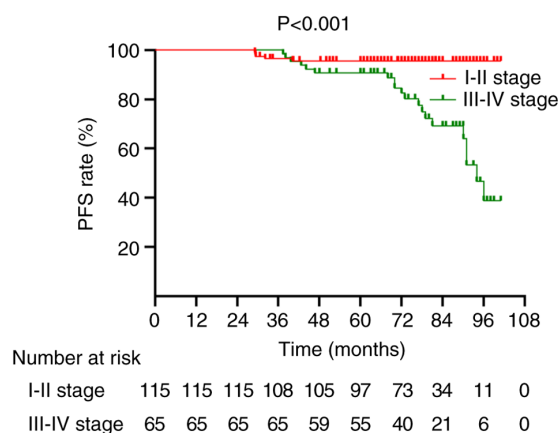


Figure 3. Comparison of PFS between patients with early-stage (I-II) and advanced-stage (III-IV) Wilms tumor. PFS, progression-free survival.

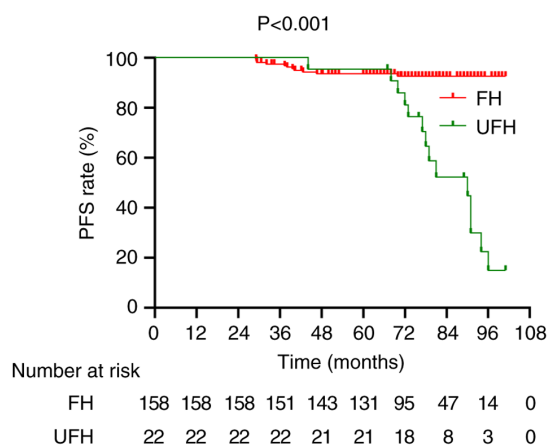


Figure 4. Comparison of PFS between FH and UFH subtypes. PFS, progression-free survival; FH, favorable histology; UFH, unfavorable histology.

Tumor stage has been consistently identified as a major prognostic determinant in WT. As all cases in the present study underwent upfront surgery, clinical staging was defined according to COG guidelines, where stage I-II is considered early stage and stage III-IV as advanced stage. A national registry by the Japan Wilms Tumor Study Group reported relapse-free survival (RFS) rates of >90% for stages I-III but markedly worse outcomes for stage IV (RFS, 66.2%) (28). Similarly, combined analyses of the SIOP 93-01 and 2001 studies reported that patients with

stage III WT had a higher risk of recurrence than those with stage I (29). In general, patients with advanced-stage disease (III-IV) present with more extensive tumor burden and consequently worse prognosis than those diagnosed at earlier stages (30). Therefore, early detection and accurate staging are critical to improving outcomes in pediatric WT. Even in patients who undergo radical nephrectomy, those with advanced-stage disease should receive timely postoperative adjuvant therapy and close follow-up to prevent recurrence. Whilst all patients in the present

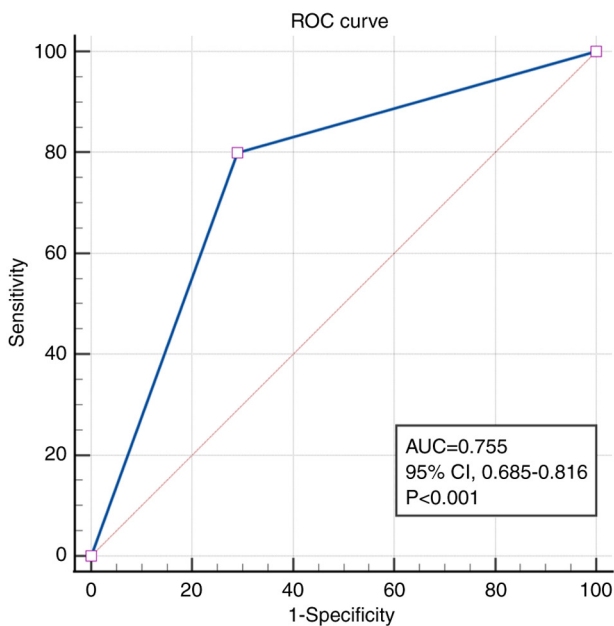


Figure 5. ROC curve of the prognostic model based on clinical stage and histological type. ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

study received standard postoperative therapy, treatment regimens varied slightly based on individual patient characteristics, such as disease stage, histological subtype and tumor size. Specifically, patients with advanced-stage disease (stage III-IV) received the more intensive DD4A regimen combined with radiotherapy, whereas those with early-stage disease (stage I-II) were treated with the EE4A regimen. These regimens differ in both the number of drugs and the inclusion of radiotherapy, which was administered to advanced-stage patients to address the higher risk of recurrence. However, the potential impact of these differences on survival outcomes was not fully analyzed in the present study. In future studies, it would be valuable to explore how the interaction between different treatment modalities (chemotherapy compared with radiotherapy) and clinical variables, such as tumor size, stage or histological subtype, influences survival outcomes. This could help identify which patient subgroups benefit most from specific treatment strategies and guide personalized treatment approaches. Further analyses may also provide insight into whether certain treatment regimens could be more effective for specific histological types or tumor sizes, potentially improving patient outcomes.

Histological subtype was also demonstrated to be a crucial prognostic factor in the present study. Previous studies have reported that patients with FHWT have notably improved survival outcomes compared with those with UFH (31-33). In the present study, patients with UFH had notably higher recurrence and mortality rates. These tumors are typically more aggressive and prone to relapse, potentially due to underlying immunological and biochemical alterations such as oxidative and glycoxidative stress responses (34).

In addition to histological factors, molecular markers such as WT1 mutations and loss of heterozygosity at 1p/16q, have emerged as notable prognostic indicators in WT. Although

these molecular data were not included in the present study due to data limitations, future studies should explore their potential role in refining prognostic models. The incorporation of genetic and molecular data could enhance prognostic accuracy, provide a more comprehensive understanding of tumor biology, and offer insights into personalized treatment strategies. For example, WT1 mutations, which are frequently associated with UFH and poor prognosis (35), could serve as a powerful predictor for treatment response and long-term outcomes. Therefore, pathological assessment serves a pivotal role in risk stratification and treatment planning.

Furthermore, individualized therapeutic approaches based on histological subtype may improve patient outcomes. Whilst the COG and SIOP risk stratification systems for WT are well-established and widely used, the present study provided important new insights that may enhance current risk stratification and inform treatment strategies. Specifically, the following three clinically actionable findings of the present study from a cohort treated at a single center in China suggest the need for further refinement of existing protocols. i) Higher incidence of stage III disease: A total of 33.9% of patients presented with stage III disease, compared with 28% reported in the SIOP 2001 trials (36). This finding suggests potential regional differences in disease aggressiveness, which may influence the choice of treatment regimens and surveillance strategies in different populations. ii) Tumor thrombus as a prognostic factor: Although tumor thrombus was present in only 3.9% of cases, it demonstrated a strong univariate association with recurrence (57.1 vs. 12.1%; $P<0.001$). This highlights that the presence of tumor thrombus, although rare, should be considered a notable prognostic factor, particularly in cases of recurrence risk. Whilst its prognostic significance was reduced after adjusting for stage and histology, it still warrants consideration in clinical decision-making. iii) Interaction between stage III-IV and tumor thrombus: The data also suggested that the interaction between stage III-IV disease and the presence of tumor thrombus accounts for ~75% of thrombus-associated recurrences. This finding indicates a synergistic risk escalation, suggesting that a more personalized approach may be needed for patients with these combined factors. These findings underscore the need for a more nuanced approach to risk stratification for WT, one that considers both regional differences in disease presentation and additional prognostic factors not fully captured in existing models. Although COG and SIOP provide robust guidelines, the findings from the present study indicate that further refinements may be needed to improve the accuracy of recurrence prediction and optimize treatment strategies, particularly in populations with unique disease patterns.

Based on clinical stage and histology, the present study developed a predictive model for postoperative prognosis in children with WT. The model demonstrated good discriminatory power, with an area under the ROC curve of 0.755 (95% CI, 0.685-0.816; $P<0.001$), supporting its clinical utility in forecasting recurrence risk and guiding personalized management strategies. From a clinical perspective, the predictive model based on clinical stage and histological subtype offers a practical tool for early postoperative risk stratification. Both variables are readily available within 48-72 h following radical nephrectomy, allowing clinicians to implement early decisions

regarding surveillance intensity and adjuvant treatment. For example, patients identified as high-risk by the model (namely, stage III-IV and/or UFH) may benefit from intensified imaging surveillance during the first 2 postoperative years, earlier initiation or escalation of chemotherapy, or closer multidisciplinary follow-up. Notably, this model complements, rather than replaces, existing risk stratification systems such as those established by the COG. Whilst COG guidelines provide protocol-driven treatment based on operative and pathological findings, the model in the present study serves to refine prognostic predictions post-surgery, particularly in settings where clinical discretion is allowed (such as borderline stage II/III cases or histologically ambiguous presentations). Thus, integration of this model into routine clinical practice could enhance individualized care by aligning early prognostic assessment with standardized treatment protocols.

Further refinement of the model could include additional clinical, molecular and genetic factors such as WT1 mutations, loss of heterozygosity at 1p/16q or other emerging biomarkers. Incorporating these factors could potentially improve the accuracy of the model and broaden its applicability, particularly in genetically heterogeneous populations. Furthermore, external validation was not performed using independent cohorts, which is a crucial step to assess the robustness and generalizability of the model in diverse clinical settings. Future studies should aim to perform internal validation (such as bootstrapping or k-fold cross-validation) as well as external validation to refine and validate the predictive power of the model in different clinical environments.

Moreover, the present study has several limitations. First, it was a single-center retrospective analysis with a relatively limited sample size, which may reduce the statistical power and generalizability of the findings. An important consideration for future studies is the potential impact of postoperative complications, such as renal insufficiency, infections or other treatment-related side effects. These complications may negatively affect prognosis and overall survival outcomes, particularly in children with WT who may experience long-term treatment-related toxicities. Whilst these factors were not specifically addressed in the current study due to data limitations, future research should aim to evaluate the role of postoperative complications in survival outcomes. Including such factors in prognostic models could provide a more comprehensive assessment of patient risk and guide individualized treatment approaches. Whilst this approach ensures consistency in data collection, the results may not fully reflect the broader pediatric WT population, particularly with respect to regional or demographic differences. For instance, variations in treatment protocols, patient characteristics and disease prevalence across different regions or institutions could influence outcomes. Therefore, the external validity of these findings could be limited. To confirm and validate the results of the present, future multicenter studies, incorporating diverse patient populations from several geographic regions, would be valuable. A larger and more heterogeneous cohort would enhance the generalizability of the model and improve its applicability to different clinical settings. Second, the prognostic value of tumor thrombus requires cautious interpretation due to small event numbers ($n=7$), although its univariate significance aligns with emerging evidence

from AREN03B2 trial sub-studies (37). Third, an important aspect to consider in future studies is the use of biomarkers in postoperative follow-up. Biomarkers such as circulating tumor DNA, WT1 mutations, 1q gain and microRNAs have shown promise as early indicators of recurrence or metastasis (38,39). For example, 1q gain is associated with more aggressive disease and worse prognosis in patients with WT, making it an important biomarker for risk stratification (40). Similarly, microRNA expression changes can help predict disease progression and outcomes (41,42). Additionally, prohibitin levels have been reported to be associated with relapse in WT, highlighting its potential as a non-invasive biomarker for monitoring recurrence (43). Incorporating these biomarkers into routine postoperative surveillance could improve the accuracy of recurrence prediction and allow for more personalized treatment strategies. Future research should focus on validating the reliability and feasibility of these biomarkers in clinical practice. Additionally, certain clinical variables, such as tumor rupture timing and long-term treatment-related complications (for example, cardiac or renal dysfunction), were not fully captured. The reliance on a single data source may also introduce selection and information biases, which are inherent in retrospective studies and single-center data collection. Another limitation is the potential for follow-up loss, as not all patients could be consistently monitored for the entire follow-up period. Additionally, variability in protocol adherence could affect the consistency of treatment and outcomes. Furthermore, the study did not incorporate genetic or molecular biomarkers, such as WT1, 1p/16q LOH and 1q gain, which have been identified as important prognostic indicators in WT. The absence of these markers in the current study was due to data limitations, including the unavailability of genetic profiling for certain patients. Future research should aim to include these molecular markers to improve the prognostic accuracy of the model and improve the stratification of patient risk. Finally, internal cross-validation (such as bootstrapping or k-fold cross-validation) was not performed and external validation cohorts were not used in the development of the predictive model. This limitation may affect the robustness and generalizability of the model. Future studies should incorporate internal validation techniques and use independent cohorts to enhance the accuracy and applicability of the model.

In conclusion, the present study primarily focused on PFS as the key prognostic indicator, as it provides a useful reflection of the risk of recurrence, progression and death in patients with WT. Nevertheless, the findings of the present study provide meaningful guidance for clinicians and offer a foundation for future research. Future studies should incorporate additional clinical and genetic factors to refine the predictive model further. For instance, integrating molecular markers such as WT1 mutations, 1p/16q loss of heterozygosity or other genetic alterations could markedly improve the accuracy of the model. Furthermore, additional cohort studies, especially multicenter or international studies, would help validate the findings of the study and assess the robustness of the model across diverse populations. Incorporating data from different clinical settings and populations may enhance the generalizability of the model, ensuring its applicability in routine clinical practice. Furthermore, another important

aspect that should be considered in future studies is the assessment of long-term quality of life in pediatric patients with WT. Whilst the present study focused on PFS and OS, the impact of postoperative treatments, recurrence and treatment-related side effects on the physical function, mental health and social adaptation of patients is also crucial. Incorporating quality of life assessments into future research would provide a more comprehensive understanding of the treatment impacts on the overall well-being of patients and help guide personalized and holistic care. Through early diagnosis, accurate staging, individualized treatment and comprehensive perioperative management, the prognosis of children with WT can be substantially improved. Moreover, the development of a multifactorial prognostic model may facilitate more precise and evidence-based clinical decision-making, ultimately enhancing survival and quality-of-life in this patient population.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HT and DM conceived and designed the study. HT collected clinical data, performed the statistical analysis and drafted the manuscript. BH, KS, HL, JW and JS contributed to data interpretation and literature review. DM critically revised the manuscript for important intellectual content and supervised the overall project. HT and DM confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Baoding Branch of Beijing Children's Hospital, Baoding Children's Hospital (approval no. H-BDETKJ-SOP006-03-A/2). Written informed consent was obtained from the legal guardians of all participating patients prior to enrollment.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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