Prognostic Value of Preoperative Systemic Immune-Inflammation Index in Non-Metastatic Paediatric Wilms' Tumour Patients Undergoing Upfront Radical Nephrectomy

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ABSTRACT

Objective: To analyse the relationship between the preoperative systemic immune-inflammation index (SII) and the relapse-free survival (RFS) of paediatric patients with Wilms' tumour (WT) after radical surgery, and to establish and validate a prognostic survival model.

Study Design: Observational study.

Place and Duration of the Study: Department of Oncologic Surgery, Anhui Children's Hospital of Fudan University, Hefei, China, from January 2013 to August 2023.

Methodology: A retrospective analysis was conducted on 79 WT patients treated with radical resection, with their preoperative SII values computed. The best cut-off for SII was determined through the ROC curve, categorising patients into high and low SII groups. The Kaplan-Meier method and Cox-regression were used for survival analysis. A survival prognostic model was constructed and its predictive capability gauged (AUC of the ROC).

Results: The study included 79 WT patients with a median RFS of 65 months and an average of 75.5 ± 3.4 months. The optimal cut-off value for SII was 534.95. The low SII group had a higher RFS (Log-rank: χ^2 = 9.380, p = 0.002). Preoperative SII (HR = 3.277, 95% CI: 1.167 - 9.200, p = 0.024), clinical staging (HR = 8.408, 95% CI: 2.604 - 27.147, p <0.001), and tissue differentiation (HR = 2.237, 95% CI: 1.043 - 5.828, p = 0.039) were independent risk factors for RFS. The model's diagnostic performance was 0.749 (95% CI: 0.636 - 0.861). Internal validation showed an AUC of 0.723 (95% CI: 0.608 - 0.838).

Conclusion: Lower preoperative SII suggests a more favourable prognosis. The SII-based nomogram efficiently forecasts post-radical surgery prognosis for WT.

Key Words: *Wilms' Tumour, Systemic immune-inflammation index, Relapse-free survival, Nomogram.*

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INTRODUCTION

Wilms' Tumour (WT) stands as the second most prevalent extracranial solid malignancy in paediatric cases and is the predominant malignant renal tumour. It comprises 5% of paediatric malignancies and signifies 80% of kidney cancers diagnosed in children and adolescents.[1] Even with the improvement with contemporary medicine pushing the overall survival rate of WT beyond 90%, there remains a segment of patients prone to relapse or disease progression, profoundly impacting their life quality and outlook.[2]

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Hence, evaluating prognosis and stratifying risks hold paramount significance for therapeutic choices and ameliorating survival in WT patients. At present, prognostic evaluations for WT predominantly hinge on factors such as the age of the patient, the staging of the tumour, the histological type, and genetic mutations.[3] Yet, these elements still possess constrained predictive capabilities for prognosis, particularly when assessing recurrence and metastatic risks.

In recent years, the crucial roles of immunity and inflammation in the initiation, progression, metastasis, and prognosis of tumours have gained increasing attention. The preoperative systemic immune-inflammation index (SII) is a convenient indicator based on peripheral blood lymphocyte, neutrophil, and platelet counts and has demonstrated significant prognostic value in various malignancies.[4-6] However, for WT, there has been no research so far focusing on the impact of SII on prognosis. Additionally, a nomogram is a graphical tool that quantifies individual patient characteristics and predicts the likeli-

hood of a certain outcome, and it has been widely used in the prognostic assessment of cancer diseases.[7,8] This study aimed to explore the relationship between the preoperative SII and the relapse-free survival (RFS) of WT patients after radical surgery and to attempt to construct a prognostic nomogram model based on SII, hoping to provide a more precise basis for the individualised treatment and risk stratification of WT.

METHODOLOGY

This observational study was conducted retrospectively at the Oncology Department of Anhui Children's Hospital of Fudan University, from January 2013 to August 2023. The inclusion criteria consisted of newly diagnosed cases of Wilms' tumour confirmed on histology pre-surgery radiological evaluations along with baseline tests such as the complete blood count, and the availability of exhaustive postoperative follow-up details. The exclusion criteria included patients at an elevated risk for renal failure, individuals with distant metastasis before the operation, those presenting with significant anaesthesia risk due to the severity of their condition, and those with a heightened risk of surgical complications. Patients whose legal guardians refused to give consent to this research were also excluded. The study was conducted with the approval of the Hospital's Medical Ethics Committee.

Data on the age, gender, weight, site of disease onset, initial symptoms, tumour size (largest diameter of the excised specimen), lymph node metastasis status (N status), pathological type, and deformities of hospitalised paediatric patients were collected. Preoperative peripheral blood test results included neutrophil count (NEUT), platelet count (PLT), lymphocyte count (LY), and white blood cell count (WBC). The SII was calculated using the formula SII = PLT×NEUT / LY. The follow-up began at the time of histopathological diagnosis. RFS was defined as the period from the histopathological diagnosis date to the first recurrence, death from any cause, or the end of the follow-up in August 2023.

Data analysis was conducted using IBM SPSS 26.0 and the R programming language (v4.1.3). The normality of data was tested using the Kolmogorov-Smirnov method. Data were considered to follow a normal distribution when $p \geq 0.05$. Measurements that followed a normal distribution were represented as $\bar{x} \pm s$. The Student's t-test was used for statistical analysis between two independent samples. Data that did not follow a normal distribution were described using $[M(P_{25}, P_{75})]$ and were statistically analysed using the Mann-Whitney U test. Categorical variables were expressed as n%, and the Chi-square test (χ^2 test) was used for between-group comparisons. By analysing the ROC curve of SII, the optimal cut-off value (corresponding to the maximum Youden's index) was determined, and patients were categorised into high SII and low SII groups. The relationship between SII and various clinical pathological features was analysed using the Chi-square test (χ^2 test). The relationship between SII groups and RFS was analysed using the Kaplan-Meier method, and differences were assessed using the Log-rank test. Factors significant in univariate analysis ($p < 0.05$) were subjected to multivariate Cox-regression analysis, reporting hazard ratios (HR) and their 95% confidence intervals (95% CI). Based on the results, a nomogram was constructed using R to predict the 3-year postoperative RFS probability for WT patients. The diagnostic performance of the model was evaluated using the receiver operating characteristic (ROC) curve, and its accuracy was assessed using the calibration curve. Internal validation was carried out using the calibration curve with 1,000 bootstrap resampling. Unless specifically stated, otherwise, all tests were two-tailed with a significance level of $\alpha = 0.05$, and a value of $p < 0.05$ was considered statistically significant.

RESULTS

This study analysed a cohort of 79 paediatric patients, comprising 46 males and 33 females, with tumour histological types including 33 cases of epithelial cell type, 11 cases of blastemal type, 20 cases of stromal cell type, and 15 cases of mixed type. Their ages ranged from 3 to 119 months, with a median age of 36 months (interquartile range: 15-49 months). Regarding tumour location, there were 41 cases with tumours in the left kidney and 38 in the right kidney, with no instances of bilateral renal tumours. The maximum tumour diameter varied from 4.5 cm to 10.5 cm, averaging 6.5 ± 1.8 cm. Radical surgery was successfully performed on all 79 paediatric patients, and typical cases can be seen in Figure 1. For all the paediatric patients in this study, the median RFS spanned 65 months, with an average of 75.5 ± 3.4 months.

After completing the necessary evaluations, the paediatric patients underwent laparoscopic radical nephrectomy for WT. All patients received standard chemotherapy postoperatively according to clinical staging.[9] With the occurrence of relapse within 3 years in WT paediatric patients as the endpoint, the AUC of the ROC for SII was recorded as 0.885 (95% CI: 0.797 - 0.974, $p < 0.001$, Figure 1A). When SII equals 534.95, the Youden index peaks. At this point, the sensitivity predicted by SII is 0.826, and the specificity is 0.893.

Using an SII cut-off of 534.95, patients were divided into a high SII group (SII ≥534.95, n = 36) and a low SII group (SII <534.95, n = 43). The average RFS for all 79 paediatric patients was 75.5 ± 3.4 months. The RFS for the high SII group was 63.8 ± 5.5 months, whereas for the low SII group, it was 83.8 ± 3.4 months, significantly longer than that of the high SII group (Log-rank: $\chi^2 = 9.380$, $p = 0.002$, Figure 1B).

Among 79 WT patients, 16 (20.25%) had recurrences within a 3-year period. Patients were categorised based on relapse within 3 years into a good prognosis group (no relapse, n = 63) and a poor prognosis group (relapsed, n = 16). A comparative analysis of the clinical characteristics and pathological outcomes of the two groups showed notable differences in clinical stages, pathological types, tissue differentiation, and lymph node metastasis (all with $p < 0.05$, Table I).

Table I: Clinical characteristics and pathological differences between two patient groups [M(P25, P75), n (%), (x ± s)].

Parameters	Prognostically Favourable Group (n = 63)	Prognostically Unfavourable Group (n = 16)	Z/t/χ^2-value	p-value
Age (months)	38 (18.51)	32 (11.46)	-1.458	0.145
Gender			0.251	0.616
Male	35 (55.56)	10 (62.50)		
Female	28 (44.44)	6 (37.50)		
Weight (kg)	19.37 ± 2.70	18.69 ± 2.65	0.899	0.371
Tumour diameter (cm)	6.16 ± 1.33	6.63 ± 1.86	-1.148	0.255
Initial symptoms			0.638	0.727
Abdominal mass	29 (46.03)	9 (56.25)		
Haematuria	17 (26.98)	4 (25.00)		
Other	17 (26.98)	3 (18.75)		
Clinical staging			5.124	0.024
Stage I-II	43 (68.25)	6 (37.50)		
Stage III-IV	20 (31.75)	10 (62.50)		
Pathological type			7.524	0.006
Mixed type	36 (57.14)	3 (18.75)		
Non-mixed type	27 (42.86)	13 (81.25)		
Associated malformation			<0.001	1.000
Yes	16 (25.40)	4 (25.00)		
No	47 (74.60)	12 (75.00)		
Tissue differentiation			6.618	0.010
Medium-high differentiation	53 (84.13)	8 (50.00)		
Poorly differentiated	10 (15.87)	8 (50.00)		
Lymph node metastasis			4.908	0.027
Yes	15 (23.81)	9 (56.25)		
No	48 (76.19)	7 (43.75)		

Note: Age was analysed using the Mann-Whitney U test, weight and tumour diameter were analysed using the Independent samples t-test; other parameters were analysed using the Chi-square test.

Table II: Factors influencing the prognosis of WT paediatric patients after radical surgery and their assignments.

Parameters	Variable	Description of the assignment
SII	X1	≤534.95 = 0, >534.95 = 1
Clinical staging	X2	I ~ II stage = 0, III ~ IV stage = 1
Pathological type	X3	Hybrid = 0, non-hybrid = 1
Lymph node metastasis	X4	Yes = 0, No = 1
Tissue differentiation	X5	Medium-high differentiated = 0, poorly differentiated = 1

Table III: Multifactorial regression analysis of COX affecting RFS in children with WT.

Parameters	B	SE	Wald χ^2	p	HR	95% CI
Clinical staging	2.129	0.598	12.678	<0.001	8.408	2.604 - 27.147
Tissue differentiation	0.805	0.389	4.282	0.039	2.237	1.043 - 5.828
SII	1.187	0.527	5.076	0.024	3.277	1.167 - 9.200
Lymph node metastasis	0.568	0.552	1.058	0.304	1.764	0.598 - 5.202
Pathological type	0.946	0.548	2.981	0.084	2.576	0.080 - 7.542

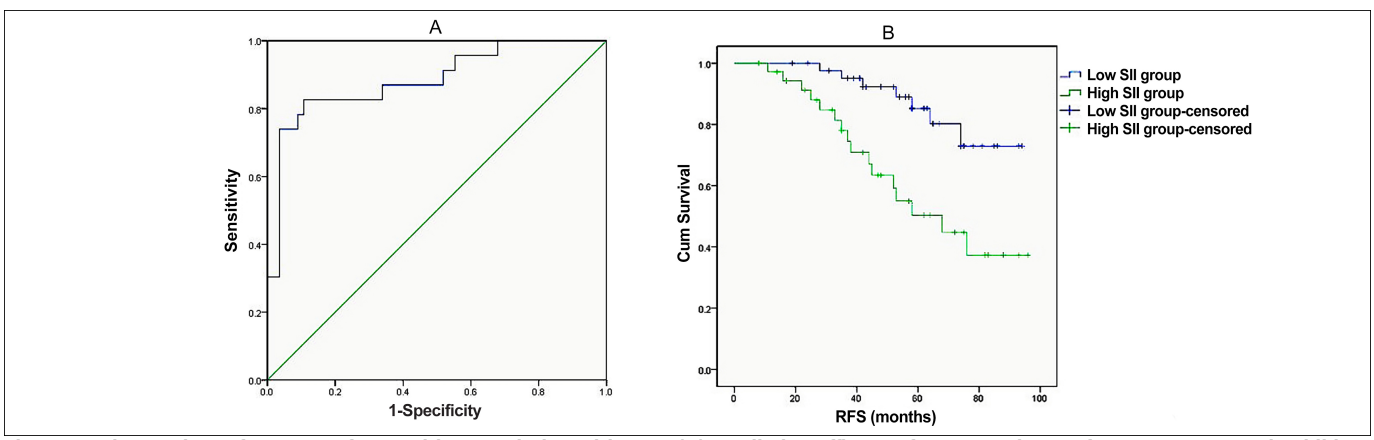

Figure 1: Diagnostic performance of SII and its correlation with RFS. (A) Predictive efficacy of preoperative SII for RFS at 3 years in children with WT. (B) Survival curves of patients in the high SII and low SII groups.

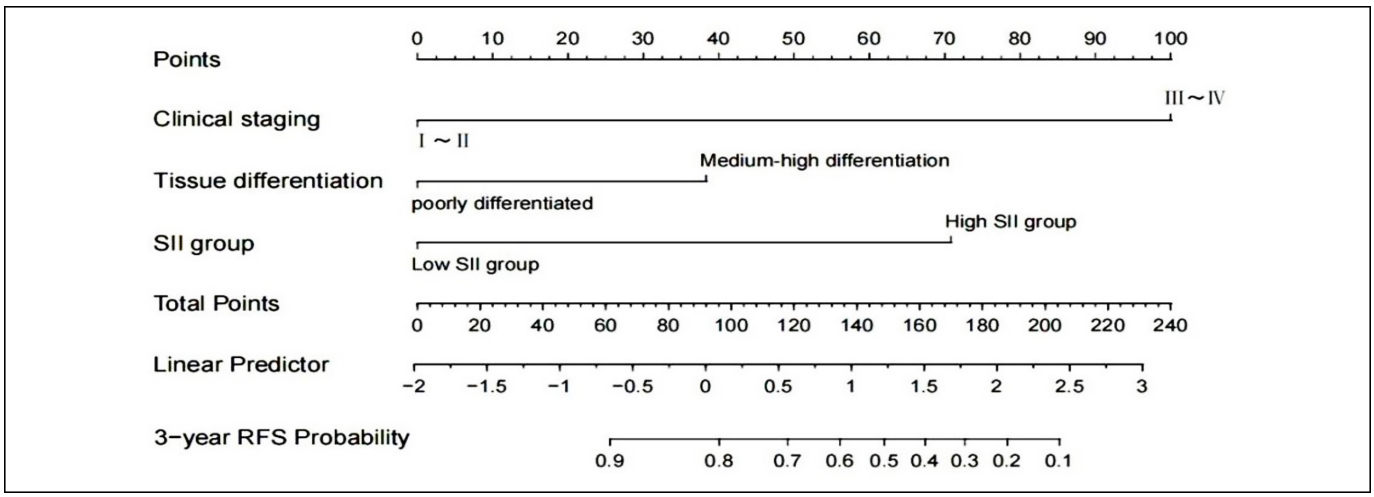

Figure 2: Nomogram of the RFS prediction model for children with WT.

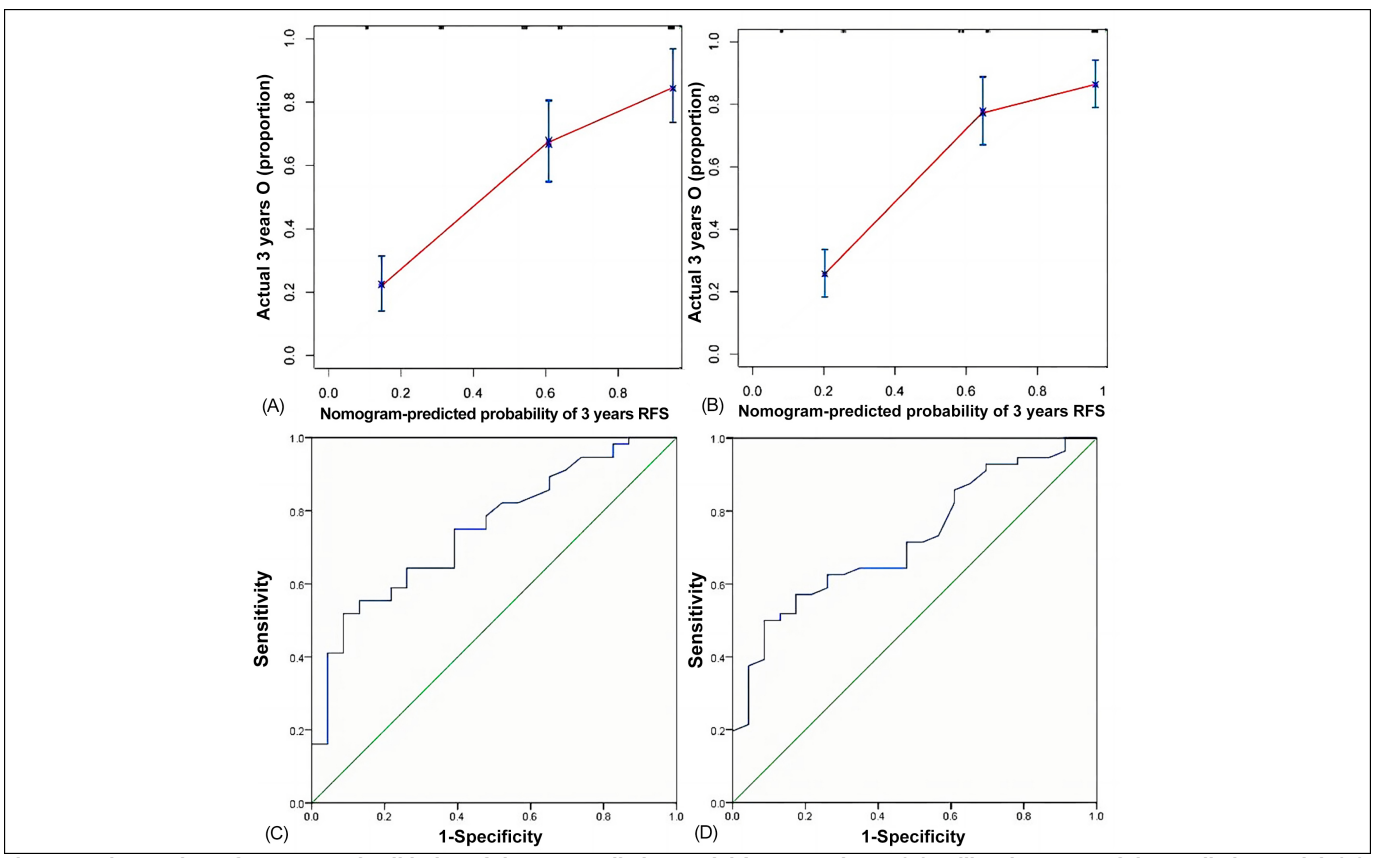

Figure 3: Diagnostic performance and validation of the RFS prediction model for WT patients. (A) Calibration curve of the predictive model. (B) Calibration curves for internal validation of predictive model using the Bootstrap method. (C) Receiver operating characteristic curve of the RFS prediction model for WT patients. (D) Diagnostic efficacy during internal validation of RFS prediction models for children with WT.

Using the Cox proportional hazards regression model with a forward method based on partial maximum likelihood estimation, a multivariate analysis was conducted on prognostic influencing factors after radical surgery in WT paediatric patients. The results showed that SII (HR = 3.277, 95%CI: 1.167-9.200, p = 0.024), clinical staging (HR = 8.408, 95%CI: 2.604 - 27.147, p <0.001), and tissue differentiation (HR = 2.237, 95%CI: 1.043 - 5.828, p = 0.039) are independent factors affecting RFS post-radical surgery in WT paediatric patients (Table II and III).

Using the independent influencing factors identified in the aforementioned multivariate analysis (SII, clinical staging, and tissue differentiation), a predictive model for RFS was established and a Nomogram was constructed (Figure 2). The AUC of this model is 0.749 (95CI: 0.636 - 0.861, p =

0.001), with a sensitivity and specificity of 0.554 and 0.870, respectively (Figure 3C).

This nomogram was applied to paediatric patients (aged 0 - 18 years) with newly diagnosed, non-metastatic Wilms' tumours who were candidates for upfront radical nephrectomy. To use the nomogram, each patient's SII value, clinical stage, and tissue differentiation grade were located on their respective axes. Vertical lines up to the points axis were drawn to determine how many points are attributed to each variable; these points were summed and located on the total points axis. A vertical line was drawn down from this point to estimate the 3-year RFS probability. It is important to note that this tool should be used as an adjunct to clinical judgement, not as a sole determinant of treatment decisions. The nomogram may assist in risk stratification, potentially guiding decisions on postoperative surveillance intensity and adjuvant therapy considerations.

The calibration curve of this predictive model was plotted (Figure 3A), using the Bootstrap method with 1,000 resamples for internal validation of the model. The results showed an AUC of 0.723 (95CI: 0.608~0.838, p = 0.002), suggesting that the model still possesses a high discriminative ability (Figure 3D). There is good consistency between the predicted and actual prognostic value curves for post-radical surgery in WT paediatric patients (Figure 3B).

DISCUSSION

This study conducted an in-depth analysis of 79 paediatric WT patients. All patients successfully underwent radical surgery, with an RFS of 75.5 ± 3.4 months for these patients. Through ROC curve analysis, it was found that the predictive effect of SII is significant, with an area under the curve (AUC) as high as 0.885. Moreover, when SII = 534.95, its predicted sensitivity and specificity reached 0.826 and 0.893, respectively. Notably, there is a significant correlation between the SII values of patients and RFS. The average RFS of the high SII group is significantly lower than that of the low SII group. Multivariate regression analysis further confirmed that SII, clinical staging, and tissue differentiation are independent influencing factors affecting RFS after radical surgery in paediatric nephroblastoma patients. Based on this, the authors also successfully constructed a predictive model, which has high sensitivity, specificity, accuracy, and reliability, providing a powerful tool for clinicians to predict the prognosis of WT patients.

The immune-inflammatory status of patients is reflected by SII. In recent years, the association between inflammation and tumour progression has received widespread attention. Inflammation may promote tumour development by inducing DNA damage, stimulating tumour growth and metastasis, and suppressing cellular immune responses. A high SII value may imply a more active inflammatory response, which might be associated with more malignant tumour biological behaviour.[10,11] The systemic effects of inflammation include changes in peripheral blood cell counts, further promoting tumour growth. Tumour cells release various inflammation-related substances, leading to cell damage and DNA mutations, thereby altering the tumour microenvironment and enhancing the proliferation and invasion capabilities of tumour cells. Inflammatory cells interact with the extracellular matrix in the tumour microenvironment, affecting the occurrence and development of tumours.[12] Therefore, the inflammatory response of tumours may become a potential target for treatment. Researchers can reflect the inflammatory status of various malignant cells by detecting peripheral blood markers. High SII may manifest as elevated platelet levels, increased neutrophil levels, and decreased lymphocyte levels.

Investigating the role of these cells in tumour progression helps to understand the relationship between SII and WT prognosis and further studying the interactions between inflammation, immunity, and WT. The blood of cancer patients is usually in a hypercoagulable state. Platelets can produce platelet-derived endothelial growth factor and transforming growth factor-β, and form aggregates with circulating tumour cells, enabling them to evade immunity, and thus promote tumour metastasis.[13] Neutrophils can produce matrix metalloproteinase (MMP)-9, interleukin-8 (IL-8), and vascular endothelial growth factor (VEGF), inducing angiogenesis, which is conducive to tumour differentiation and invasion.[14] The serum concentration of cytokines released by neutrophils in cancer patients is higher.[15] Additionally, tumour-associated macrophages and other white blood cells may promote carcinogenesis by inducing remodelling of the extracellular matrix in the tumour microenvironment.[16]

Lymphocytes are an essential component of tumour-specific immune responses, inhibiting tumour development by enhancing cancer immune surveillance and stimulating related cells to release lymphocyte-associated cytokines.[17] Systemic chronic inflammation may lead to a reduction in lymphocyte counts, thereby weakening the cytotoxic immune response. Therefore, if a patient has a higher SII, the tumour microenvironment of the body may be more conducive to tumour invasion, metastasis, and recurrence. However, as a non-specific parameter, SII may be influenced by factors such as age, infection, hypertension, inflammatory diseases, and medicines. Further research is needed to explore whether preoperative SII can serve as a specific prognostic marker in clinical settings to differentiate high-risk and low-risk groups.

For high-risk groups, earlier therapeutic intervention and closer postoperative monitoring may be required.

The significance of SII in the prognosis of WT has not been widely reported in the existing literature, possibly due to different tumour types and research methods. Previous literature mainly focused on the application of SII as a single indi-

cator in certain malignant tumours, and some research results remain somewhat controversial. For example, most studies have confirmed that inflammation and cell-mediated immune functions have been found to be related to the efficacy of PD-1 blockade therapy.[18,19] Fornarini *et al.* found that in patients with advanced urothelial cancer, higher levels of SII were associated with better survival outcomes.[20] However, Chen *et al.* found that when SII exceeded the cut-off value, it was not significantly related to the RFS of immunotherapy for advanced gastric cancer.[21] Qi *et al*. indicated that SII is not an important prognostic factor for the overall survival rate of extensive-stage small cell lung cancer.[22]

In this study, two key indicators were also identified as closely related to the prognosis of paediatric WT patients: Clinical staging and tissue differentiation. Clinical staging is a standardised method to assess tumour size, depth, and whether it has metastasised to other parts. A higher clinical stage is usually associated with more extensive disease spread, which may lead to more complications and a worse prognosis. Additionally, tumours with a higher stage might be more challenging to completely remove, and the remaining tumour residue could lead to recurrence and progression.[23] Tissue differentiation reflects the degree to which tumour cells resemble the original tissue. Tumour cells with low differentiation are usually more uncontrolled, grow faster, and are more prone to metastasis. Furthermore, they might exhibit resistance to therapeutic interventions, subsequently impacting the prognosis.[24]

While this study offers valuable insights into the prognosis of paediatric nephroblastoma, there are still some limitations. Firstly, the sample size of this study is relatively small, which might affect the robustness and generalisability of the statistical results. Future research should consider increasing the sample size to obtain more convincing conclusions. Secondly, this study is retrospectively designed, which might introduce selection bias and information bias. Prospective, randomised controlled studies might yield more accurate results. Additionally, even though the authors discussed some key factors affecting prognosis, there might still be other confounding factors not considered. Future research can consider more potential influencing factors, such as genetic mutations, lifestyle, and other biomarkers. Lastly, this study mainly focused on the biological characteristics of patients, overlooking the potential impact of treatment strategies on prognosis. Future research might explore the effects of different treatment methods on WT prognosis and how to best combine these treatments.

The nomogram developed in this study offers a visual tool for clinicians to estimate individual patient prognosis based on preoperative SII, clinical staging, and tissue differentiation. This could aid in patient counselling, treatment planning, and risk-adapted follow-up strategies. However, it is crucial to recognise that while this nomogram showed good predictive performance in the cohort, external validation in larger, diverse populations is necessary before widespread clinical adoption. Furthermore, as the understanding of Wilms' tumour biology evolves, the integration of molecular markers could potentially enhance the predictive accuracy of future iterations of this tool.

CONCLUSION

This study demonstrated the prognostic significance of preoperative SII, clinical staging, and tissue differentiation in predicting relapse-free survival in paediatric Wilms' tumour patients. The SII-based nomogram provides a valuable tool for risk stratification, which can guide clinical decision-making. However, while these indicators offer important prognostic information, further research is needed to explore the underlying biological mechanisms of Wilms' tumour.

ETHICAL APPROVAL:
This study was conducted with the approval of the Medical Ethics Committee of Anhui Children's Hospital Affiliated to Fudan University, Hefei, China.

PATIENTS' CONSENT:
Written informed consent was taken from all the patients.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
KS, QG: Concept of the study, design, data analysis, and data interpretation.
YBD: Revision of the manuscript for important intellectual content.
All authors approved the final version of the manuscript to be published.

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