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Survival Analysis of Pediatric Wilms Tumor Based on Risk Identification

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ABSTRACT

Background: Wilms Tumor (WT) or nephroblastoma is the most common primary malignant tumor of the kidney found in children (comprising about > 95% of all kidney tumors). The study of WT prognostic factors has not been elaborated enough in Indonesia. This study aimed to determine the prognostic factors of WT patients in Adam Malik Hospital, Medan.

Methods: This study was conducted with a retrospective design due to the rarity of WT cases. A total of 21 WT patients diagnosed from 2003 to 2019 were taken from medical records at Adam Malik Hospital, Medan. Univariate and multivariate Cox regression analyses were performed to determine the independent prognostic factors of WT. The primary endpoint of this study was patients' overall survival (OS) obtained by the Kaplan-Meier analysis on significant variables.

Results: From the univariate Cox regression analysis, gender was found to be the sole significant factor (HR = 0.218, p = 0.005) where males have a lower hazard ratio. The multivariate Cox regression analysis yielded an age of diagnosis (HR = 13.860, p = 0.014) and complete tumor removals (HR = 0.056, p = 0.008). The Kaplan-Meier analysis was performed on three significant variables mentioned before. Only gender yielded a significant Mantel-Cox log-rank score (p = 0.002) with male patients found to have better survivability with a median survival of 476 days compared to that of females of 11 days. The three-year survival of males was 45.45% while all females did not survive until the cut-off.

Conclusions: Three prognostic factors, including children's gender, age of diagnosis, and tumor removal status, were confirmed to be prognostic factors for the overall survival of children with WT. Further studies covering broader demographic areas were suggested to confirm significant results.

INTRODUCTION

Wilms Tumor (WT) is the fifth most frequent tumor of all abdominal tumors found in pediatric patients. Around 75% of WT cases were found in children aged under 5 years with a peak incidence in children aged 2-3 years [1]. Worldwide low-income countries were found to have high WT incidence and mortality rates compared to middle-income and high-income countries [2]. WT patients usually come with an asymptomatic abdominal mass which is noticed by their caregiver or pediatrician [3]. Today, the survival rate of WT has increased significantly due to advances in therapy modalities. In 2005, the survival rate increased dramatically to > 90% compared to < 30% in the 1930s [4].

There are two different recommendations for WT treatment. Children's Oncology Group (COG) recommends surgery before initiating therapy. On the other hand, the International Society of Pediatric Oncology (SIOP) recommends preoperative chemotherapy [1]. In the context of selecting the best therapy regiment for WT patients, prognostic factors are of vital importance to be acknowledged. A predictive prognostic factor to one therapy approach does not imply the same level of prediction for the other approaches [4]. Therefore, it is important to determine the prognostic factors in the patients with WT to give the precise therapy regimen [5]. Previous studies on the prognostic factors of WT children only used tumor stages and histological findings to determine the treatment of choice. However, in

clinical practice, a lot of other clinical and biological factors were also applied, such as age, drug sensitivity, tumor size, and loss of heterozygosity on chromosomes 1p and 16q [5–9]. Different studies showed that diffuse anaplasia [7], surgery, radiation [8], microscopic residual disease, and lymphatic involvement were related to WT prognosis. Another study created a nomogram that confirmed five independent prognostic factors of WT, which were age, tumor size, tumor laterality, surgery, and tumor stage [6].

There have not been a lot of studies on WT prognostic factors in Indonesia. A study by Hartono [10] showed some prognostic factors of WT in Sardjito Hospital Yogyakarta, which were nutritional status, histopathological findings, regional lymph node, preoperative chemotherapy, and surgery types. This study intended to explore Adam Malik Hospital WT patients' clinical characteristics, describe patients' survivability, and determine those prognostic factors.

METHODS

Patients selection

This study was conducted with a retrospective design. All the samples in this study were taken from medical records at Adam Malik Hospital, Medan. Patients with the following criteria were included in the study: (1) patients diagnosed with WT; (2) patients under 18 years old; (3) patients diagnosed from 2003 to 2019; (4) patients with intact follow-up. The histological examination of the surgical specimens was carried out by the institutional pathologist according to the guidelines of SIOP. Twenty-one patients were traced retrospectively. The information was extracted from the medical records and included gender, age, status (alive or deceased), time of death, time of diagnosis, laterality, tumor size, tumor removal status, distance, histopathological findings, tumor stage, and recurrence. Patients with the following conditions were excluded: (1) patients without the stage, laterality, and surgery information; (2) patients without a definite tumor size, survival time, and status; (3) patients diagnosed at >18 years of age.

Gender was defined as either male or female. The age of diagnosis was calculated by the difference between dates of birth and dates of diagnosis. A previous study used an optimal age of diagnosis cut-off (using X-tile program from Yale University) of 3 years [6]. Therefore, this study classified the children into two age diagnosis groups (0-3 years and 3-18 years). Based on the side of which WT grew, tumor laterality was classified as left and right laterals; no bilateral tumors were found. Tumor staging was defined as stages 1, 2, 3, and 4. The patients' tumor size was determined from intraoperative reports combined with CT imaging. The researcher categorized tumor size into two groups < 7 cm and > 7 cm based on the longest axis of the tumor [11]. Tumor distance from the original site was classified as localized, regional, and distant metastasis. After surgery, tumor status was grouped as free or remained. Recurrence was described in a yes/no variable.

Statistical analysis

The researcher defined overall survival (OS) as the primary endpoint of the current study. OS was defined as the survival time calculated from cancer confirmed to mortality from all probable clinical characteristics. Survival was defined as the difference between the time of diagnosis and death in days. Patients still alive during the period of data cleaning were censored and given survival values equivalent to the longest survival time of the deceased patients of 692 days. Three-year survivability was defined as the number of patients in each group or category that remained alive after three years. Proportions for that parameter were calculated by dividing the number of survivors by the number of deceased patients of the same category.

Univariate Cox regression was performed to determine hazard ratios (HR) for all the variables (age of diagnosis, gender, laterality, tumor size, tumor removal status, tumor stage, distance, and recurrence). Regardless of the significance in univariate analysis, multivariate Cox regression analysis was performed for statistically ($p < 0.25$) or theoretically significant variables to further refine the results. Kaplan-Meier survival analysis was performed on the variables yielding significant HR ($p < 0.05$). Univariate and multivariate Cox regression analyses were carried out using SPSS software (version 24.0 by IBM corp.).

RESULTS

A total of twenty-one WT patients aged under 18 years at diagnosis from 2003 to 2019 at Adam Malik Hospital were enrolled in the present study. The demographic and clinical characteristics of these patients were listed in **Table 1**. Among the patients, 11 patients (52.4%) were male, and 10 patients (47.6%) were female. Of all patients, 11 patients (52.4%) were 0-3 years old, and 10 patients (47.6%) were 4-10 years old. In terms of tumor laterality, a total number of 9 patients (42.9%) had left lateral and 11 patients (57.1%) had right lateral. Based on the tumor size, 3 patients (14.3%) had below 7 cm-sized tumor while the other 18 patients (85.7%) had above 7 cm-sized tumor. After surgery, 11 patients (52.4%) were free of the tumor while the other 10 (47.6%) had remains of the tumor. The regional tumor was the most common (11 (52.4%)) while localized and distant metastatic tumors were found with equal prevalence (5 (23.8%) each). According to the tumor stage present when the patients were diagnosed with WT, 5 patients (23.8%) were in stage 1, 4 (19.0%)

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in stage 2, 7 (33.3%) in stage 3, and 5 (23.8%) in stage 4. Most patients (16 (76.2%)) did not experience recurrence while the other 5 patients (23.8%) did. Finally, most of the patients (16 (76.2%)) died while 5 patients (76.2%) survived. The parameter used to determine the prognostic factors in this study is days of survival since the patient is diagnosed with Wilms Tumor.

The survival rate of male patients had a median of 476 days (2-692) after diagnosis while female patients had a shorter survival rate with a median of 18 days (1-692). Besides, none of the females survived 3 years from the dates of diagnosis while 5 males (45.5%) did. Children diagnosed above 3 years of age had a higher median survival of 360 days (7-692). Only 3 patients (30%) diagnosed at > 3 years of age and 2 patients (18.12%) diagnosed at ≤ 3 years of age survived three years from diagnosis. Patients with left-lateral tumors had higher 3-year survivability (33.3%) (N = 4) compared to patients with right-lateral tumors (N = 1). Patients with smaller tumor size (< 7 cm) had longer median survival (692 (42-892)) days and higher 3-year survivability (66.7%) than those with tumors larger than 7 cm (16.7%).

Children who successfully got tumors fully removed have a better prognosis. Patients declared free from tumors after surgery had a median survival of 430 (2-692) with 3-year survivability of 36.36%. Patients presenting with tumors stages 1, 2, 3, and 4 had three-year survivability of respective stages of 20% (N = 1), 50% (N = 2), 28.6% (N = 2), and 0 in the same order. None of the patients with distant metastases survived over 3 years. Two patients (40%) with localized tumors survived three years after diagnosis. The 3-year survivability of recurring patients was 31.25% (N = 5). No patients with recurrent tumors lived for three years after diagnosis.

Table 1. Demographic and clinical characteristics of WT patients at H. Adam Malik Hospital

Characteristics	N (%)	Survival in Days	3-Year Survivability N (%)
Gender			
Male	11(52.4)	476 [2-692]	5 (45.5)
Female	10(47.6)	18 [1-692]	0
Age			
< 3	11(52.4)	127 (1-692)	2 (18.2)
3–18	10(47.6)	360 (7-692)	3 (30)
Laterality			
Left	9 (42.9)	439 (1-692)	(33.3)
Right	12 (57.1)	42 (2-692)	1 (11.1)
Tumor Size			
< 7 cm	3 (14.3)	692 (42-692)	2 (66.7)
> 7 cm	18 (85.7)	177 (1-692)	3 (16.7)
Tumor Removal Status			
Free	11 (52.4)	430 (2-692)	4 (36.4)
Remains	10 (47.6)	18 (1-692)	1 (10)
Stages			
Stage 1	5 (23.8)	42 (1-692)	1 (20)
Stage 2	4 (19)	561 (2-692)	2 (50)
Stage 3	7 (33.3)	448 (3-692)	2 (28.6)
Stage 4	5 (23.8)	226 (7-692)	0
Distance			
Localized	5 (23.8)	50 (1-692)	2 (40)
Regional	11 (52.4)	430 (1-692)	3 (27.3)
Distant	5 (23.8)	226 (7-692)	0
Recurrence			
No	16 (76.2)	244 (127-692)	5 (31.2)
Yes	5 (23.8)	46 (1-692)	0

Table 2. Univariate Cox regression analysis for OS in WT Patients at H. Adam Malik Hospital

Variables	Overall Survival		
	HR	95% CI	*p*
Gender			
Male	Reference		
Female	4.590	1.594–13.214	0.005
Age of Diagnosis			
0–3	Reference		
>3	0.654	0.241–1.778	0.405
Side			
Right	Reference		
Left	0.503	0.186–1.361	0.176
Tumor Size			
≤ 7 cm	Reference		
> 7 cm	3.790	0.497–28.881	0.199
Tumor Removal Status			
Free	Reference		
Remains	2.442	0.894–6.673	0.082
Stages			
Stage 1	Reference		
Stage 2	0.361	0.065–2.015	0.246
Stage 3	0.568	0.150–2.156	0.406
Stage 4	1.018	0.270–3.835	0.979
Distance			
Localized	Reference		
Regional	1.304	0.343–4.951	0.697
Distant	2.025	0.480–8.551	0.337
Recurrence			
No	Reference		
Yes	1.140	0.390–3.330	0.811

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Table 3. Multivariate Cox regression analysis for OS in WT patients at H. Adam Malik Hospital

Variables	Overall Survival		
	HR	95% CI	*p*
Gender			
Male	Reference		
Female	5.022	0.868–29.050	0.072
Age of Diagnosis			
0–3	Reference		
>3	0.072	0.009–0.584	0.014
Laterality			
Right	Reference		
Left	0.139	0.017–1.165	0.069
Tumor Size			
≤ 7 cm	Reference		
> 7 cm	10.333	0.415–0.584	0.154
Tumor Removal Status			
Free	Reference		
Remains	17.894	2.156–148.536	0.008

The results of the univariate Cox regression are shown in **Table 2**. Gender was the only variable that yielded significant results (HR = 0.218, p = 0.005) with males having a lower hazard ratio. Multivariate Cox regression analysis was then performed to determine each factor's independence which is presented in **Table 3**. Earlier age of diagnosis (HR = 13.860, p = 0.014) and complete tumor removals (HR = 0.056, p = 0.008) were groups associated with greater hazard. Kaplan-Meier survival analysis was performed on these three significant variables. Of these variables, only gender yielded a significant Mantel-Cox log-rank score (p = 0.002). Male patients were found to have better survivability with a median survival of 476 days compared to that of females (11 days). The survival of the male patients was 45,45% while all the female patients did not survive until the cut-off. The survival function for those three variables can be seen in **Figure 1**.

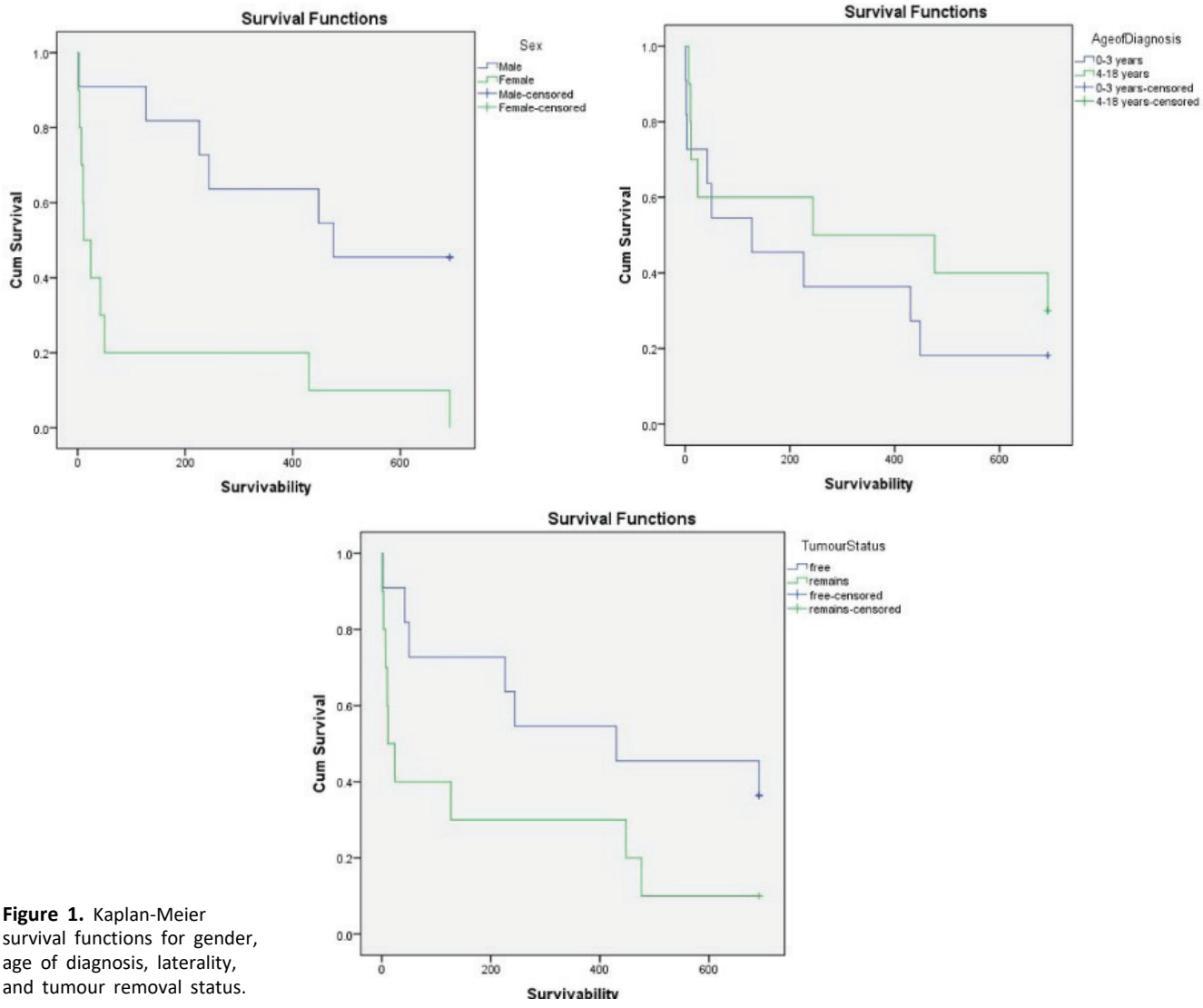

Figure 1. Kaplan-Meier survival functions for gender, age of diagnosis, laterality, and tumour removal status.

DISCUSSION

WT survival still varies in every country, especially the difference from developed countries where the survival rate has increased significantly above 90%, for example, in Europe and North America. Inversely, the survival rate in developing countries is lower with a various range from 11 to 46% [12]. Therefore, studies for evaluating the long-term survival need to be conducted for evaluation and prognosis of this disease. From this study, the researcher had likely 24% for 3 years of free survival, which is still low and in range, for low and middle-income countries. For males, the survival of a 3-year follow-up for free survival is 45%. Other countries came with various numbers. For instance, a study in Sudan reported 11% of survival at the end of treatment, but for Africa, for two-year, the event rate free survival was 73-87% [12].

It is universally acknowledged that diverse factors affect tumor development and patients' prognosis. Most previous studies focused on a single aspect of the prognosis of children with WT. Undoubtedly, judging a patient's prognosis through just a single variable may contribute to deviation [6]. To maximize the accuracy, the researcher performed univariate and multivariate Cox regression analyses and controlled the confounding variables while identifying the prognostic factors.

Of all the variables analyzed by univariate Cox regression analysis (**Table 2**), gender was considered significant even though it could not be the single risk factor. The possible reason might be the limitation of the small sample size. This was found against Tang et al. [6] study which involved 1,613 children as none of them indicated that gender was a prognostic factor for WT survival as mentioned above [5,6].

On the contrary, after conducting multivariate Cox regression analysis on all variables, the variables found to be significant were the age of diagnosis and tumor removal status. From the previous study using X-tile to determine the optimal cut-point of WT patients' age at diagnosis as 3 years based on the status and survival time, this study found that the patients who were diagnosed at the age of ≥ 3 years survived slightly better than younger patients (< 3 years). D'Angelo et al. [11] reported that children under 2 years old at diagnosis had a better prognosis. In contrast, Tang et al. [6] found that increased age was indicated as a poorer prognosis. Dome et al. [5] also found that children younger than 2 years old had the best outcome compared to older children.

For tumor size, this study demonstrated it wasn't a prognostic factor. This study found intraoperative tumor removal status as the prognostic factor. Children free of tumors had better survivability than children who had remains of tumors. This finding was in line with that of Tang et al. [6] study showing that patients who had received surgery had a better 3- and 5-year survival. Although Tang et al. [6] did not specifically mention the tumor status after surgery, it could be implied that children who underwent surgery probably would be free of tumors. Studies found significant results between unilateral and bilateral diseases [6]. Bilateral WT was a challenge and had a worse prognosis. The issue was to completely resect bilateral tumors while maintaining adequate nephrons to prevent renal failure. There were no data about bilateral disease in our institution.

Surgery was generally acknowledged as the most critical part of the therapy of WT. Several groups concluded that surgery played a paramount part in the therapy of WT [4,7]. This study has also confirmed a statement from tumor removal status findings although, in terms of tumor stage, the researcher statistically did not find it as a prognostic factor. Pritchard-Jones et al. [9] and Davidoff [4] studies reported that distant tumor was associated with tumor metastases, and the most frequent distant site for WT metastases was pulmonary metastases; liver metastases were less common. The COG's study of WT currently uses patient age, histology, tumor stage, tumor weight, rapidity of lung nodule response, and loss of heterozygosity (LOH) at chromosome 1p and 16q [4–9] while SIOP uses staging, histology, tumor volume, and responsiveness to initial chemotherapy as the prognostic factors for WT risk stratification schema [5].

Follow-up in the low- and middle-income countries is challenging. Some other priorities like funds, lack of home address, phone number not always available, and others are the factors that make returning to the hospital for follow-up, not a priority. This will affect the results of survival. In addition, in our province government hospital, WT cases are still rare. Proper statistical analyses to determine each variable's significance as a prognostic factor could not be conducted. A future study is expected to incorporate a larger number of samples to assess WT patients' clinicopathologic factors into the risk stratification. Chromosomal studies, like 1p and 16q, should scheme for favorable histology of WT. Chemotherapy and radiotherapy were not included in the present study due to inhomogeneous data (each patient received different doses and types of drugs in their respective chemotherapy regiment). However, this study provides important information and finding. It could be the groundbreaking finding that gender might be used as a prognostic factor to determine survivability in WT patients.

CONCLUSIONS

Three prognostic factors, including children's gender, age of diagnosis, and tumor removal status, were confirmed to be the prognostic factors for the overall survival of children with WT. Further studies covering broader demographic areas were suggested to confirm significant results.

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DECLARATIONS

Ethics Approval

The authors were given ethical clearance by Universitas Sumatera Utara Research Committee for this research. The necessary document is provided in a separate file. The ethical clearance letter number is 195/KEP/USU/2020.

Competing of Interest

The authors declare no competing interest in this study.

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