SURVIVAL ANALYSIS OF PEDIATRIC WILMS TUMOR BASED ON RISK STRATIFICATION

[1]Andy, [2]Yacobda Hamonangan Sigumonrong.

[1] Department of Urology, Faculty of Medicine/Universitas Indonesia, H. Adam Malik Hospital, Medan.
[2] Department of Urology, Faculty of Medicine/Universitas Sumatera Utara, H. Adam Malik Hospital, Medan.

ABSTRACT

Objective: *This study aims to determine prognostic factors of WT patient in Adam Malik Hospital, Medan.* ***Material & Methods:*** *A total of 21 WT patients diagnosed from 2003-2019 were taken from medical records at Adam Malik Hospital, Medan. Univariate and multivariate Cox regression analyses were performed to determine independent prognostic factors for WT. The primary endpoint of this study were patients' overall survival (OS) obtained by performing 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) with males have a higher hazard ratio. The multivariate Cox regression analysis yielded age of diagnosis (HR = 13.860, p = 0.014) and incomplete tumor removals (HR = 0.056, p = 0.008). Kaplan-Meier analysis were performed on three significant variables mentioned before. Only gender yielded a significant Mantel-Cox log-rank score (p = 0.002) with male patients were found to have better survivability (which median survival 476 days compared to females' 11 days). The survival of the boys was 45.45% while all of the girls did not survive until the cut-off.* ***Conclusion:*** *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.*

Keywords: *Wilms tumor, prognostic factors, Indonesia, survival, mortality.*

ABSTRAK

Tujuan: *Penelitian ini bertujuan untuk mengetahui faktor prognostik pasien WT di RS Adam Malik Medan.* ***Bahan & Cara****: Sebanyak 21 pasien WT yang terdiagnosis dari tahun 2003-2019 diambil dari rekam medis di RS Adam Malik Medan. Analisis regresi Cox univariat dan multivariat dilakukan untuk menentukan faktor prognostik independen untuk WT. Titik akhir utama dari penelitian ini adalah kelangsungan hidup pasien secara keseluruhan (OS) yang diperoleh dengan melakukan analisis Kaplan-Meier pada variabel yang signifikan.* ***Hasil:*** *Dari analisis regresi Cox univariat, jenis kelamin ditemukan sebagai satu-satunya faktor yang signifikan (HR = 0.218, p = 0.005) dengan laki-laki memiliki rasio hazard yang lebih tinggi. Analisis regresi Cox multivariat menghasilkan usia diagnosis (HR = 13.860, p = 0.014) dan pengangkatan tumor yang tidak lengkap (HR = 0.056, p = 0.008). Analisis Kaplan-Meier dilakukan pada tiga variabel signifikan yang disebutkan sebelumnya. Hanya jenis kelamin yang menghasilkan skor log-rank Mantel-Cox yang signifikan (p = 0.002) dengan pasien pria yang ditemukan memiliki kemampuan bertahan hidup yang lebih baik (dengan median kelangsungan hidup 476 hari dibandingkan dengan wanita 11 hari). Kelangsungan hidup anak laki-laki adalah 45.45% sementara semua anak perempuan tidak bertahan sampai cut-off.* ***Simpulan:*** *Tiga faktor prognostik, termasuk jenis kelamin anak, usia diagnosis, dan status pengangkatan tumor, dipastikan menjadi faktor prognostik untuk kelangsungan hidup keseluruhan anak-anak dengan WT. Studi lebih lanjut yang mencakup area demografis yang lebih luas disarankan untuk mengkonfirmasi hasil yang signifikan.*

Kata Kunci*: Tumor Wilms, faktor prognostic, Indonesia, kelangsungan hidup, kematian.*

Correspondence: Andy, c/o: Department of Urology, Faculty of Medicine/Universitas Indonesia, H. Adam Malik Hospital, Jl. Bunga Lau No.17, Kemenangan Tani, Medan Tuntungan, Medan, Sumatera Utara 20136, Indonesia. Email: andy.andy.2590@gmail.com.

INTRODUCTION

Wilms tumor (WT) or nephroblastoma is the most common primary malignant tumor of the kidney found on children (comprising about > 95% of all kidney tumor). WT is the fifth most frequent tumor of all abdominal tumors found on pediatric patients. Around 75% of WT cases were found on children aged under 5 years old with a peak incidence of 2-3 years old.[1] Worldwide, low-income

countries were found having higher number of WT incidence and mortality rates compared to middle-income and high-income countries.[2] WT patients usually came with an asymptomatic abdominal mass which was 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 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 approach.[5]

Therefore, it is important to determine the prognostic factors on the patients with WT in an attempt to give the precise therapy regimen.[6] Until previous studies that studied 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 chromosome 1p and 16q.[5,7-9]

Different studies showed that diffuse anaplasia,[8] surgery, radiation,[9] microscopic residual disease, and lymphatic involvement[10] were related to WT prognosis. Another study created a nomogram that confirm 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. The study by Hartono (2007) showed some prognostic factors of WT in RS Sardjito, Yogyakarta, which were nutritional status, histopathological findings, regional lymph node, preoperative chemotherapy, and surgery types.[11] This study intended to explore Adam Malik Hospital WT patients' clinical characteristics, describe patients' survivability, and determine those prognostic factors.

OBJECTIVE

This study aims to determine prognostic factors of WT patient in Adam Malik Hospital, Medan.

MATERIAL & METHODS

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) diagnosed with WT; (2) aged under 18 years old; (3) diagnosed from 2003 to 2019; and (4) intact follow-up. Histological examination of the surgical specimens was carried out by the institutional pathologist according to the guidelines of the International Society of Pediatric Oncology (SIOP). Twenty-one patients were traced retrospectively.

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; and (3) patients were 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 cutoff (using X-tile program, Yale University) of 3.0 years old.[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 stages were defined as stadium 1, stadium 2, stadium 3, and stadium 4.

The patients' tumor size was determined from intraoperative reports combined with CT imaging. The researcher categorized into two groups < 7 cm and > 7 cm based on the longest axis of tumor. Tumor distance from the original site was classified as localized, regional, and distant metastasis. After surgery, tumor status was grouped as free or remains. Recurrence was described in a yes/no variable.

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: 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 each variable, which were the 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 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; IBM corp.).

RESULTS

A total of twenty-one WT patients aged under 18 years old at diagnosis from 2003-2019 at Adam Malik Hospital were rolled 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 boys and 10 patients (47.6%) were girls. 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 tumor size, 3 patients (14.3%) had below 7 cm sized tumor, while 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 tumor distance found (11 (52.4%)), while

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)	4 (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

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%) in stage 2, 7 (33.3%) in stage 3, and 5 (23.8%) in stage 4. The majority of the 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 survival rate of boy patients had a median of 476 days (2-692) after diagnosis, while girls had a lower median of 18 days (1-692). Besides, none of the girls survived 3 years from the dates of diagnosis, while 5 boys (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 (18.12%) patients diagnosed at ≤ 3 years of age survived for three years from diagnosis. Patients with left-lateral tumors had higher 3-year survivability (33.3%) (N=4) survival compared to patients with right-lateral tumors (N=1). Patients with smaller tumor size (< 7 cm) have higher 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 better prognosis. Patients declared free from tumors after surgery had median survival of 430 (2-692) with 3-year survivability of 36.36%. Patients presenting with stage 1, stage 2, stage 3, and stage 4 tumors had three-year survivabilities 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 2. Univariate Cox regression analysis for OS in WT Patients at H. Adam Malik Hospital.

Variables	HR	Overall Survival 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
Laterality			
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

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

Variables	HR	Overall Survival 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

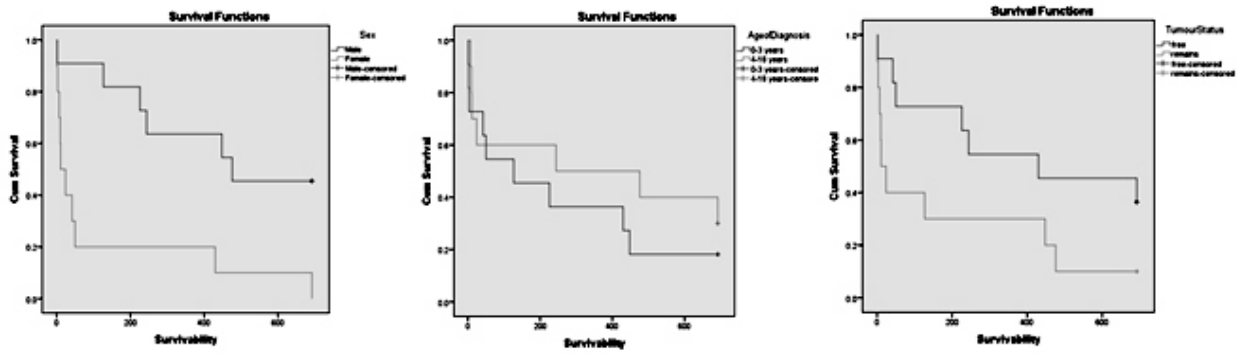

Figure 1. Kaplan-Meier survival functions for gender, age of diagnosis, laterality, and tumour removal status.

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 higher hazard ratio. Multivariate Cox regression analysis were then performed to determine each factor's independence which was presented in Table 3. Earlier age of diagnosis (HR = 13.860, p = 0.014) and incomplete tumor removals (HR = 0.056, p = 0.008) were groups associated with greater hazard.

Kaplan-Meier survival analysis were performed on these three significant variables. Of these three variables, only gender yielded a significant Mantel-Cox log-rank score (p = 0.002). Male patients were found to have better survivability with median survival of 476 days compared to that of females (11 days). The survival of the boys was 45.45% while all of the girls did not survive until the cut-off. The survival function for those three variables can be seen in Figure 1.

DISCUSSION

Wilms tumor survival still varies in every country, especially the differences images from high-income countries that the survival rate has increased significantly above 90%, for example in Europe and North America. However, inverse for low and middle-income countries, that the survival rate is lower, with a various range from 11% until 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, and males, the survival of 3 years 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 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 for confounding variables while identifying the prognostic factors.

Of all 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.'s study which contained 1613 children, as none of them indicates 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. Learned from the previous study using X-tile to determine the optimal cut-point of WT patients' age at diagnosis as 3 years old based on status and survival time, this study found that the patients who were diagnosed at age ≥ 3 years old survived slightly better than patients who were younger (< 3 years old). D'Angelo et al. also reported that children under 2 years old at diagnosis had better prognosis.[10] In contrast, Tang et al. found that increased age was indicated as a poorer prognosis,[6] as well as Dome et al. who found children younger than 2 years old, had the best outcome compared to older children.[5]

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 Tang et al. who showed that patients who had received surgery had a better 3- and 5-year survival.[6] Although Tang et al. did not specifically mention the tumor status after surgery, it could be implied that children who underwent surgery probably would be free of tumors. In terms of the laterality, studies found there were significant between unilateral and bilateral diseases.[6] Bilateral WT was a challenge and had a worse prognosis. The issue was to completely resect bilateral tumors, yet maintain 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 statements from tumor removal status findings, although, in terms of tumor stage, the researchers statistically did not find it as a prognostic factor. Pritchard-Jones and Davidoff's 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.[4,9]

The Children's Oncology Group (COG) 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, while the International Society of Pediatric Oncology (SIOP) uses staging, histology, tumor volume, and responsiveness to initial chemotherapy as the prognostic factors for WT risk stratification schema.[5]

Following up in the low and middle countries is challenging, some other priorities like funds, lack of home address, phone number not always available, and others are the factors that returning to the hospital for follow up become not priority, the condition in which will affect the results of survival. Even, in our province government hospital, WT cases were 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. Even 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).

CONCLUSION

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.

REFERENCE

1. Daw NC, Huff V, Anderson PM. Wilms tumour. In: Kliegman RM, Stanton BF, Schor NF, St. Gemme III

JW, Behrman RE, eds. Nelson textbook of pediatrics. 20th ed. Philadelphia: Elsevier Saunders; 2016. p. 2465.
2. Cunningham ME, Klug TD, Nuchtern JG, et al. Global Disparities in Wilms Tumour. J Surg Res. 2020; 247: 34?51
3. Friedman AD. Wilms tumour. Pediatr Rev. 2013 Jul; 34(7): 328-30.
4. Davidoff AM. Wilms' tumour. Curr Opin Pediatr. 2009 Jun; 21(3): 357-64.
5. Dome JS, Perlman EJ, Graf N. Risk stratification for Wilms tumour: current approach and future directions. Am Soc Clin Oncol Educ Book. 2014; 215?23.
6. Tang F, Zhang H, Lu Z, Wang J, He C, He Z. Prognostic Factors and Nomograms to Predict Overall and Cancer-Specific Survival for Children with Wilms' Tumour. Dis Markers. 2019; 2019: 1092769.
7. Dome JS, Graf N, Geller JI, et al. Advances in Wilms Tumour Treatment and Biology: Progress Through International Collaboration. J Clin Oncol. 2015; 33(27): 29993007.
8. Dome JS, Fernandez CV, Mullen EA, et al. Children's Oncology Group's 2013 blueprint for research: renal tumours. Pediatr Blood Cancer. 2013; 60(6): 9941000
9. Pritchard-Jones K, Kelsey A, Vujanic G, et al. Older age is an adverse prognostic factor in stage I, favorable histology Wilms' tumour treated with vincristine monochemotherapy: a study by the United Kingdom Children's Cancer Study Group, Wilm's Tumour Working Group. J Clin Oncol. 2003; 21(17): 326975.
10. D'Angelo P, Di Cataldo A, Terenziani M, et al. Factors possibly affecting prognosis in children with Wilms' tumour diagnosed before 24 months of age: A report from the Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) Wilms Tumour Working Group. Pediatr Blood Cancer. 2017; 64(12): 10.1002/pbc.26644.
11. Hartono S. Hubungan faktor-faktor Prognosis dan ketahanan hidup penderita Tumour Wilms di RS Dr. Sardjito tahun 2002-2006 (Doctoral dissertation, Universitas Gadjah Mada).
12. Israels T, et al. Survival of children with a wilms tumor in Blantyre, Malawi. Pediatric hematology and oncology. 2018; 35(3): 196-202.