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# Wilms Tumor in Children: Results from A Large Indonesian Referral Hospital's Experience Over 5 Years

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## ABSTRACT

***Introduction:*** *Wilms tumor also known as nephroblastoma, first described by Thomas F. Rance in 1.814 is one of the most common solid malignant neoplasms in children. Therapy modalities for Wilms tumor are surgery, chemotherapy, and radiotherapy. We want to evaluate the disease characteristics and treatment outcome of a patient with Wilms tumor over for 5 years.*

***Methods:*** *We retrospectively reviewed the Wilms Tumor patient who had undergone surgery and other therapy in our national referral hospital in the interval between January 2013 and December 2018. Demographic features, obstetric history, tumor stage, histopathologic and radiographic results, therapy and outcome were evaluated. Descriptive analysis using frequencies was used to describe the study variables.*

***Result:*** *A total of 50 patients (54% female) with Wilms tumor with a median age of 56 months were identified. The stage frequencies of our cases were: stage I (24%), stage II (12%), stage III (28%) and stage IV (36%). Nephrectomy was performed in 16 patients (32%). The majority of parents (72%) have a low educational level. Sixty-eight percent of parents attended antenatal care less than four times during pregnancy. The mean of pregnancy age from the mother is 24.96 ± 4.370. The average birth weight and birth length were within the normal range; 2878±415, 50.32±3.50 respectively. Significant correlations were found between tumor stage educational level (p=0.002), and antenatal care (p=0.011). While other factors such as age, gender, treatment of choice, mother's age at delivery, birth weight, and birth length failed to show any significant correlations.*

***Conclusion:*** *The outcome in our center was poorer than worldwide Wilms Tumor, even in Asia. Our study showed that maternal educational background and antenatal care were the only two factors significantly associated with tumor stage in our study.*

## Keyword

Tumor Wilms, Children, Characteristic tumor.

## Introduction

One of the most common malignancy occurred in children was nephroblastoma or well known as Wilms tumor, was first described by Thomas F. France in 1814. Wilms tumor was accounted for 95% of all kidney cancer in children under the age of 15 in United Stade and it is 6 – 7% accounted for all of the childhood cancer [1]. Most of the patients were diagnosed before 5 years of age, with 3.5 years old as the median age. There is no specific male to the female predilection of the disease, but Wilms tumor can manifest at an earlier age among males rather than females both unilateral and bilateral tumors. In East Asia, however, 25-40% of the total incidence occurred in infants aged under 1 year, compared with around 15% in many Western series [1].

It is about 10% of children with Wilms tumor have congenital anomalies and syndromes, there are number of genes that have been identified as the culprit of the development of Wilms tumor such as WT1 that was considered to be a classic tumor suppressor gene that mutation in this gene will result in Wilms tumor growth, WTX act as another tumor suppressor gene and also the most common mutation type of pediatric kidney cancer, and others gene

like 11p15 and TP53 may play a role in Wilms tumor development [2,3].

Most of the patients, approximately 90% of them were diagnosed accidentally. If we take a look back at the epidemiological data of Wilms tumor, stated that most of the patients were diagnosed before age 5, this means that children on that group of age couldn't communicate well enough to tell their parents about the symptoms. Other than large mass relative to children's body size, the most common complaint is hematuria (20%) and hypertension (25%). Is not necessary to take operative action immediately, since a patient with Wilms tumor should be evaluated thoroughly by laboratory analysis such as complete blood count, liver enzymes, serum electrolytes, BUN, creatinine, and calcium [4,6].

The current Wilms tumor staging system that has been used is the Children's Oncology Group (COG). For stage I, described as a tumor that still confined to the kidney and completely resected, the renal capsule is intact, and the tumor was not ruptured before removal, no renal sinus extension, and there is no residual tumor. Stage II described as extracapsular penetration, but the tumor is completely resected, renal sinus extension or extra-renal vessels may contain tumor thrombus or be infiltrated by tumor. Stage III residual nonhematogenous tumor confined to the Abdomen, lymph node involvement, any tumor spillage, peritoneal implants, tumor beyond surgical margin either grossly or microscopically, or tumor not completely removed. Stage IV, hematogenous metastases to lung, liver, bone, brain and so on. Stage V, bilateral renal involvement at diagnosis [7]. Staging the Wilms tumor was one of the important steps other than determined tumor histopathology because it can determine the outcome of the disease [8].

Several cooperative groups and individual institutions have made important contributions to the optimization of Wilms' tumor therapy. Because the NWTSG and SIOP studies have included the largest number of patients, this review focuses on their findings. Since the NWTSG and SIOP nephroblastoma studies began more than three decades ago, there has been a philosophical difference of opinions about the administration of preoperative chemotherapy [8].

A retrospective review of NWTS-4 found that age at diagnosis less than 24 months and tumor weight less than 550 g were correlated with the absence of relapse-associated variables previously described in patients with stage I favorable histology tumors. Based on these findings, NWTS-5 prospectively treated 75 children younger than 24 months with small (<550 g) stage I favorable histology tumors with nephrectomy only. The study closed early according to predefined stopping rules because the risk of relapse at 2 years was 13.5%; however, all patients were successfully salvaged with standard therapy [9,10].

The activity of dactinomycin and vincristine against Wilms' tumor was shown in the 1950s and 1960s, and these drugs have served as the cornerstone of Wilms' tumor therapy ever since. Doxorubicin was added to the Wilms' tumor treatment armamentarium in the 1970s. Radiation therapy, although still an important component of Wilms' tumor therapy, is restricted to the treatment of stage III or IV disease.

## Methods

Wilms' tumor patients from this study were collected retrospectively from the medical record at Adam Malik General Hospital. The inclusion criteria were all the patients with the diagnosis of Wilms Tumor patient who had undergone surgery and other therapy in our national referral hospital in the interval between January 2013 and December 2018. Medical records of these patients were evaluated for demographic feature, obstetric history, tumor stage, histopathologic and radiographic results, therapy and outcome were evaluated. Clinical stage of renal tumor patients was classified and treatment protocol was devised according to the National Wilms Tumor.

Descriptive analysis using frequencies was used to describe the study variables. The analysis in this study was performed with SPSS version 20.0. We calculated the statistical analysis with the independent T-test for the parametric continuous variables and chi-square for categoric variables. P-value $< 0.05$ was considered as significant result. All procedures performed in studies involving human participants were in complied with the guidelines of the Local Review Board and Ethics Committee and data were obtained with patient consent at the time of procedure/data collection.

## Results

Our study documented about 50 patients diagnosed with Wilms tumor within 5 years of urology practice in H Adam Malik Hospital from 2013 to 2018. Among the patients, about 46% were male, while the other 54% were female. The tumor stage upon diagnosis was equally distributed with stage IV Wilms tumor showing the highest number of occurrences (36%). Maternal education was mostly at senior high and followed by elementary school. Furthermore, antenatal care visits were mostly done below 4 visits (68%) with only 32% of patients who have done above 5%. The age of pregnancy was in the mean age of 24.96 ± 4.370, with a birth weight of 2878 ± 415 gr and birth height of 50.32 ± 3.50 cm (Table 1).

| Patient Characteristics | | N (n=50) | Percentage (n=50) |
|---|---|---|---|
| Gender | Male | 23 | 46% |
| | Female | 27 | 54% |
| Stage | I | 12 | 24% |
| | II | 6 | 12% |
| | III | 14 | 28% |
| | IV | 18 | 36% |
| Therapy | Chemotherapy | 34 | 68% |
| | Surgery | 16 | 32% |
| Maternal Education | Uneducated | 8 | 16% |
| | Elementary | 13 | 26% |
| | Senior High | 15 | 30% |
| | University | 8 | 16% |

| | | | |
|---|---|---|---|
| ANC | <4 | 34 | 68% |
| | ≥4 | 16 | 32% |
| Age of Pregnancy | | 24.96 ± 4.370 | |
| Weight | | 2878 ± 415 | |
| Height | | 50.32 ± 3.50 | |

**Table 1:** Study Demographics.

Among the 50 Wilms tumor patients, about 36 (72%) patients were with low educational background, while the other 14 patients were with non-low educational background. From 36 patients with a low educational background, 6 (16%) patients were at stage I, 2 (5.55%) patients at stage II, 12 (33.33%) at stage III, and 16 (44.44%) stage patients were at stage IV of tumor Wilms. Out of the 14 patients with non-low educational background, 6 (42.85%) patients were at stage I, 4 (28.57%) at stage II, 2 (14.28%) at stage III and 2 (14.28%) at stage IV. Statistical analysis showed a significant (p=0,002) association between the educational status of the patients with the stage of Wilms tumor upon diagnosis (Table 2).

| Education | Stage I | Stage II | Stage III | Stage IV | P-Value* |
|---|---|---|---|---|---|
| Low Education | 6 | 2 | 12 | 16 | 0.002 |
| Non Low Education | 6 | 4 | 2 | 2 | |
| Total | 12 | 6 | 14 | 18 | |

**Table 2:** Maternal Education Profile and Tumor Wilms Stages upon Diagnosis.
Low Education: No education – Junior High School.
Non-low education: Senior High School – College.
*Tested using Chi-Square.

Among the 50 Wilms tumor patients, there were 34 (68%) patients whose parents had ANC visits below four times, while the other 16 (32%) patients had ANC above four times during pregnancy. From 34 patients with ANC below 4 times, the highest number of IV stage Wilms tumor was obtained with 16 (47%) patients followed by 5 (14.7%), 1 (2.9%), 12 (35.2%) patients in stage I, II, and III respectively. Out of 16 patients with ANC above four times, 7 (43.75%) patients were at stage I which is the highest number, followed by 5 (31.25%) patients at stage II, and 2 (12.5%) patients in the 3rd and 4th stages respectively (Table 3). When T-test was done, there is a significant (p=0.011) relationship between the ANC status of the patients with the stage of Wilms tumor.

| Education | Stage I | Stage II | Stage III | Stage IV | P-Value* |
|---|---|---|---|---|---|
| ANC <4 | 5 | 1 | 12 | 16 | 0.011 |
| ANC ≥ 4 | 7 | 5 | 2 | 2 | |
| Total | 12 | 6 | 14 | 18 | |

**Table 3:** Maternal Antenatal Visits and Tumor Wilms Stages upon Diagnosis.
*Tested using Chi-Square.

## Discussion

Global epidemiological data shows that Wilms tumor or nephroblastoma affects approximately 10 children and adolescents per 1 million before age 15 years and accounts for 6-7% of all childhood cancers [11]. Since the epidemiological data shows a similar number and incidence rate in different countries, with exception of higher rate in Africa and a low rate in East Asia [12], we are expecting the same incidence rate occurs in North Sumatra. The Current estimate of the North Sumatra population number is 14.26 million people [13]. Exact number of children and adolescents under 15 years of age in North Sumatra is not available but we can infer this number from Indonesia national data which estimates around 27.3 percent of population under 15 years old [14]. By combining both numbers, it can be estimated that there are 3.9 million children under 15 years old in North Sumatra. Since global epidemiological data estimated 10 out of 1 million children and adolescents under 15 years old will suffer from Wilms tumor and we should see around 39 to 40 children with this case in North Sumatra. From our data, we successfully gathered around 50 Wilms tumor patients from the beginning of our study in 2013 to 2018 with almost 50-50 ratio of male to female cases, which number exceeds the global prevalence by 25%. But compared to global incidence of 6-9 cases per million person-years [12], we should expect around 84 to 126 cases which could indicate that the detection rate of Wilms tumor in North Sumatra is lacking beyond the global detection rate which will be explained further.

When compared between staging groups, more than 50% of Wilms tumor cases included in this study can be categorized as advanced (stage III and IV). This number is different from global data which suggests that around 60-65% of Wilms tumor cases fall between stage I and II [12]. Compared to global age mean when the disease is detected (around 3.5 years or 42 months) [12], our data suggest that detection of Wilms tumor in North Sumatra happens when the children have grown older to around 56 months or almost 5 years old. These discrepancies should support our initial idea that the detection of Wilms tumor cases in North Sumatra occurs later when the disease course had been advancing.

Several factors such as the age of the pregnancy, birth weight, and birth height fail to show any significant correlation to tumor severity since Wilms tumor is mostly affected by genetics (familial history of Wilms tumor, and mutation to several genes such as WT1, WT2, or CTNNB1) [15]. This should indicate that babies with WT1, WT2, or CTNNB1 mutations may have normal pregnancy and birth history comparable to normal population although further study is needed to confirm this idea. On the contrary, mother education level and compliance to antenatal care show significant correlations to disease severity. It should be clear and well known that education level positively affects health-seeking behavior [16,17]. Mothers with higher education levels may have better insights and tend to seek medical care more frequently when realizing a difference in child growth, development, or behavior as opposed to mothers with lower education. This health-seeking behavior, in turn, decreases the detection time of Wilms tumor while in the lower stage compared to mothers with lower education groups with longer detection time coupled with higher tumor staging [18]. It is unclear from our data whether frequent antenatal care correlates with lower tumor severity due to the increased rate of detection or caused by higher health-seeking behavior in

the first place. But other studies also showed that mothers with higher educational level had better compliance to antenatal care compared to mothers with lower educational history [19].

We are aware of our limitations regarding this study. A bigger number of samples should enable our further analysis and evaluation regarding the characteristic of patients with Wilms Tumor. The sample size could be increased by including more centers in Indonesia. However, centers in Indonesia which can detect, diagnose, and treat Wilms tumor are still limited. This, in turn, becoming the biggest reason that studies regarding Wilms tumor in Indonesia are still limited. Furthermore, the distribution of cases in Indonesia is still low and further investigation in the distribution and registration of cases as such in Indonesia is a need for future studies on this matter. Besides the lack of data required for this study, the lack of resources and distance from other centers may also be a limitation for the study.

## Conclusion

The outcome of Wilms tumor in our center was poorer than worldwide Wilms Tumor, even in Asia. Furthermore, our study showed that maternal educational background and antenatal care were the only two factors significantly associated with tumor stage in our study.

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