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Risk factors for mortality in children with Wilms tumor

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Abstract

Background Wilms tumor is the most common renal malignancy in children (95%) and one of the leading causes of death in children, with high mortality rates in developing countries. Identifying risk factors for mortality is important in order to provide early intervention to improve cure rates.

Objective To identify risk factors for mortality in children with Wilms tumor.

Methods We performed a case-control study of children (0-18 years of age) with Wilms tumor admitted to Dr. Sardjito Hospital between 2005 and 2012. The case group consisted of children who died of Wilms tumor, whereas the control group were children who survived. Data were collected from medical records. Statistical analyses using Chi-square and logistic regression tests were done to determine odds ratios and 95% CI of the potential risk factors for mortality from Wilms tumor.

Results Thirty-five children with Wilms tumor were admitted to Dr. Sardjito Hospital during the study period. Nine (26%) children died and 26 survived. Stage ≥III was a significant risk factor for mortality in chidren with Wilms tumor (OR 62.8; 95%CI 5.6 to 70.5). Age ≥2 years (OR 1.4; 95%CI 0.1 to 14.3) and male sex (OR 1.2; 95%CI 0.1 to 10.8) were not significant risk factors for mortality.

Conclusion Stage ≥III is a risk factor for mortality in children with Wilms tumor. **[Paediatr Indones. 2016;56:226-9. doi: 10.14238/pi56.4.2016.226-9]**.

Keywords: *Wilms tumo;, risk factors for mortality; children*

Approximately 250,000 new cases of pediatric malignancy are identified globally every year, and about 200,000 cases occur in developing countries.[1] Wilms tumor is the fourth most common malignancy after leukemia, retinoblastoma, and neuroblastoma, and is the most common renal malignancy in children (95%).[2,3] Its incidence increases every year.[4] Wilms tumor remains one of the leading causes of death in children with high mortality rates in developing countries.[5,6]

Risk factors for mortality in children with Wilms tumor may include tumor factors (stage or metastasis status) and patient factors (age at diagnosis and sex).[7,8] Wilms tumor stage ≥III is aggressive (through hematogenic and lymphogenic routes) and can metastasize to various organs (lymph nodes, liver, lungs, brain, bones, and others), but shows good response to combination therapy (chemotherapy, surgery, and radiotherapy). Anaplasia in children with Wilms tumor over 2 years of age is often resistant to chemotherapy.

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[9] Male sex is believed to influence mortality of children with Wilms tumor due to its relationship with a pre-zygotic (germinal) mutation in the Wilms tumor 1 gene (WT1) needed for genitourinary system development.

Early diagnosis and treatment of Wilms tumor has been associated with higher cure rates.[10] Identification of risk factors for mortality is important to determine early interventions that can lead to higher cure rates. This study aimed to assess tumor stage ≥III, age at diagnosis of ≥2 years, and male sex as possible risk factors for mortality in children with Wilms tumor.

Methods

We conducted an observational, case-control study in children with Wilms tumor who were admitted to Dr. Sardjito Hospital from 2005 to 2012. Data were taken from medical records. The study was conducted in the Child Health Department of Dr. Sardjito Hospital in April to May 2013, after obtaining approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Gadjah Mada and Dr. Sardjito Hospital.

Subjects in the case group were patients with Wilms tumor, aged 0 – 18 years, who died during their last hospital admission. Subjects in the control group were patients with Wilms tumor, aged 0 – 18 years who survived their last hospital admission. Patients with congenital anomalies such as WAGR syndrome, Denys-Drash syndrome, or Beckwith-Wiedemann syndrome, as well as incomplete data in their medical records were excluded from the study. Evaluated risk factors for mortality from Wilms tumor were stage ≥III, age at diagnosis of ≥2 years, and male sex. Data [name, sex, age at diagnosis, developmental history, physical examination, location of tumor, stage, supporting examinations such as computed tomography scan (CT scan), chest x-ray, ultrasonography, tumor histopathology, and most recent condition (died or survived)] were obtained retrospectively from medical records.

Diagnosis of Wilms tumor was established by history-taking, physical examination, CT scan, chest x-ray, and tumor histopathology. Stage of Wilms tumor was classified by CT scan and chest x-ray findings. According to the *2002 Nephroblastoma Protocol*, patients were classified stage <III or stage ≥ III, where stage ≥ III was considered to be a risk factor for mortality in Wilms tumor.[11] Age at diagnosis was classified as <2years and ≥2 years, where age ≥2 years was considered to be a risk factor for mortality. Gender was classified as female or male, where male sex was potentially a risk factor for mortality. The WAGR syndrome is a condition consisting of Wilms tumor, aniridia, genitourinary malformation, and mental retardation. Denys-Drash syndrome is a condition consisting of Wilms tumor and genital ambiguity. Beckwith-Wiedemann syndrome is a condition consisting of Wilms tumor, hemihypertrophy, omphalocele, macroglossia, and organomegaly.

The minimum required sample size of the case group was 16, as calculated for a case-control study with α=0.05, power 80%, and proportion of children with Wilms tumor stage ≥III who died 94%. Likewise, the minimum required sample size of the control group was 16 subjects, with an assumed 1:1 proportion of case to control.

Data was analyzed using *SPSS for Windows*. Crude OR (COR) and adjusted OR (AOR) were calculated using logistic regression test to obtain the risk for mortality from Wilms tumor. Statistical significance was confirmed by 95% confidence intervals.

Results

Thirty-five children with Wilms tumor were admitted to Dr. Sardjito Hospital during the period of study. We did not have the minimum required number in the case group, nine children (26%) who died were included in the case group and 26 children who survived were included in the control group. The mean age of subjects was 36 months, with approximately equal ratio of males to females (1:0.9). None of the subjects had congenital anomalies such as WAGR, Denys-Drash, or Beckwith-Wiedemann syndrome. Characteristics of subjects are displayed in **Table 1**.

Multivariate analysis (AOR) showed that stage ≥III was a significant risk factor for mortality in children with Wilms tumor, with a 63 times higher risk of mortality than stage <III.

Table 1. Characteristics of subjects

Characteristics	N=35
Gender, n	
Male	18
Female	17
Age at diagnosis, n	
<2 years	12
≥2 years	23
Location of tumor, n (%)	
Unilateral	35
Bilateral	0
Stage, n	
I	3
II	21
III	2
IV	9
V	0

spread of tumor cells, due to the relative thinness and penetrability of newly formed vessels formed as a response to angiogenesis.[12] for these reasons, stage ≥ III increases the mortality risk of Wilms tumor in children.

The age of ≥2 years at the time of diagnosis is believed to be a risk factor for mortality because of its relationship with anaplasia. Anaplasia is a regression in differentiation, from well differentiated to poorly differentiated, a condition that limits functionality of the cancer cells. Anaplasia was found in 14% of Wilms tumor cases, causing 60% mortality. Anaplasia causes resistance to chemotherapy, due to a mutation on the p53 gene that eliminates the cells' ability to undergo

Table 2. Risk factors for mortality in children with Wilms tumor

Variables	Died (n=9)	Survived (n=26)	COR	AOR	95%CI
Stage, n					
≥ III	9	3	61.3	62.8	5.6 to 70.5#
< III	1	23			
Age at diagnosis, n					
≥ 2 years	6	17	1.1	1.4	0.1 to 14.3
< 2 years	3	9			
Gender, n					
Male	5	13	1.2	1.2	0.1 to 10.8
Female	4	13			

#statistically significant

Discussion

We found that Wilms tumor stage ≥III is a significant risk factor for mortality Wilms tumor stage ≥III is indicative of tumor spread and is believed to be a risk factor for mortality due to angiogenesis, invasion, and dissemination to distant organs. Tumor angiogenesis is the formation of new vessels in response to substances secreted by the tumor, to accomodate the growth of tumor cells. Metastasis is the spread of tumor cells from their origin (primary) site through lymphatic or blood vessels to other new (secondary) sites. In order to metastasize, tumor cells must be released from their origin site. At the time of release, tumor cells invade the basal membrane of the blood or lymphatic vessels to be disseminated. This process involves secretion of collagenase type IV enzyme that attacks tissue integrity, enabling tumor cells to invade the basal membrane of lymphatic or blood vessels and enter the circulation. This enzyme enables the effective apoptosis.[13] Anaplasia starts to occur at the age of 2 years (2%) and increases seven-fold by the age of > 5 (14%) years.[9] However, we found that the age of diagnosis was not a predictive factor for mortality, because the mean age of our subjects was 36 months, an age at which anaplasia is rarely seen (2%), before significant increases at the age of >5.

Male sex is believed to be a risk factor of mortality since it is related to a pre-zygotic (germinal) mutation on the WT1 gene that is needed for genitourinary development. The mutation of the WT1 gene leads to the mutation of the sex-determining region Y (SRY) gene, located in the short arm of Y chromosome band 11.3 (Y p11.3). The SRY gene serves as a testis-determining factor (TDF). Mutation of the SRY gene renders Sertoli cells unable to secrete mullerian inhibiting substance (MIS) hormone, leading to testicle dysgenesis related to genital ambiguity (Denys-Drash syndrome) and genitourinary anomaly (WAGR and Beckwith-Wiedemann syndrome). This

condition increases the likelihood of renal failure and its development to end-stage renal disease increases mortality in children with Wilms tumor. WAGR, Denys-Drash, and Beckwith-Wiedemann syndromes are more commonly found in children with bilateral Wilms tumor. We found no relationship between male sex and mortality, since none of our subjects suffered from congenital anomalies such as WAGR, Denys-Drash, Beckwith-Wiedemann syndrome, or bilateral Wilms tumor.

A limitation of our study was the imbalanced proportion of subjects in the case and control groups, and also did not have the minimum required number in the case group, due to the limited number of cases in Dr. Sardjito Hospital. As such, a longer period of prospective study is necessary.

In conclusion, stage ≥III is a significant risk factor for mortality in children with Wilms tumor, however, age ≥2 years at the time of diagnosis and male sex are not significant risk factors for mortality. A prospective study is necessary to identify risk factors and outcomes in children with Wilms tumor other than mortality, such as relapse and survival rate. Early detection and establishing a diagnosis at an early stage are vital to increase cure rates of children with Wilms tumor.

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Conflict of interest

None declared.

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