RISK FACTORS OF MORTALITY IN CHILDREN WITH WILMS' TUMOR AT SOETOMO HOSPITAL SURABAYA

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ABSTRACT

Objective: *Wilms' tumor is the most common childhood renal tumor for about 6% of pediatric malignant disease. The 5-year survival rate in United States increased from approximately from 70% (1970-1973) to 92% (1989-1996). This study was aim to analyze the risk factors of mortality in children with Wilms' tumor.* ***Material & Methods:*** *A cross-sectional study was conducted in children with Wilms' tumor at Soetomo Hospital during 2006-2011. The data of demographic, clinical profile, complete blood count, blood urea nitrogen, glomerular filtration rate, histological type, disease stage, metastases and relapse were analyzed as risk factors of mortality using logistic regression.* ***Results:*** *There were 37 Wilms' tumor children and 5 children were excluded because of incomplete data. The mean age was 3.0 (SD 2.6) years, and male-to-female ratio was 2.5 : 1. There were 5/32 children in stage I, 7/32 children in stage II, 8/32 children in stage III, 11/32 children in stage IV, and 1/32 children in stage V. There were 15/32 children underwent operation. Complete remission occurred in 12/32 children and 1/32 children relapsed. There were 20/32 children died, associated with anemia (P=0.033, OR=6.111, 95% CI=1.056-35.352) and advanced stage (P=0.021, OR=8.000, 95% CI=1.575-40.632). The risk of mortality increased 3.284 folds with every increased stage (P=0.007, 95% CI=1.338-7.775).* ***Conclusion:*** *Disease stage is the significant risk factor of mortality in children with Wilms' tumor.*

Keywords: *Wilms' tumor, risk factor, mortality, children.*

ABSTRAK

Tujuan: *Tumor Wilms merupakan tumor ginjal yang paling sering pada anak, didapatkan sekitar 6% dari penyakit keganasan anak. Angka kesintasan 5 tahun semakin meningkat dari 70% (1970-1973) menjadi 92% (1989-1996) di Amerika Serikat. Penelitian ini bertujuan untuk menganalisis faktor risiko mortalitas pada anak dengan tumor Wilms.* ***Bahan & Cara:*** *Penelitian potong lintang telah dilaksanakan pada pasien anak dengan tumor Wilms di RSUD Dr. Soetomo selama tahun 2006-2011. Beberapa faktor risiko mortalitas yaitu kondisi demografi, profil klinis, pemeriksaan darah lengkap, blood urea nitrogen, laju filtrasi glomerulus, tipe histologi, stadium penyakit, metastasis dan kekambuhan, dianalisis menggunakan regresi logistik.* ***Hasil:*** *Didapatkan 37 pasien anak dengan tumor Wilms, 5 diantaranya dieksklusi karena data tidak lengkap. Rerata usia adalah 3.0 (SD 2.6) tahun, dan rasio laki-laki dan perempuan 2.5 : 1. Didapatkan 5 dari 32 anak dengan stadium I, 7 anak dengan stadium II, 8 anak stadium III, 11 anak stadium IV dan 1 anak dengan stadium V. Terapi pembedahan dilakukan pada 15 anak. Remisi komplit didapatkan pada 12 dari 32 anak dan 1 anak mengalami kekambuhan. Dua puluh anak meninggal dengan kondisi anemia (P=0.033, OR=6.111, 95% CI=1.056-35.352) dan menjadi stadium lanjut sebanyak 20 anak (P=0.021, OR=8.000, 95% CI=1.575-40.632). Risiko mortalitas meningkat 3.284 kali pada setiap peningkatan stadium (P=0.007, 95% CI=1.338-7.775).* ***Simpulan:*** *Stadium penyakit merupakan faktor risiko mortalitas pada anak dengan tumor Wilms.*

Kata kunci: *Tumor Wilms, faktor risiko, mortalitas, anak.*

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INTRODUCTION

Wilms' tumor is the most common childhood renal tumor for about 6% of pediatric malignant disease.[1] Wilms' tumor originates in the developing renal tissue, the metanephrogenic blastema, and also found in combination with congenital anomalies. The firm irregular abdominal mass is the most common presentation. Other presenting symptoms are abdominal pain, hematuria, fever, and gastrointestinal symptoms. Histological classifications are either favorable histology (FH) or unfavorable histology (UH). Significant advances have been made in the treatment of children with Wilms' tumor. This progress has been made possible with the current chemotherapy, surgery and radiotherapy.[2] The 5-year survival rate in United States increased from approximately from 70% (1970-1973) to 92% (1989-1996).[3,4]

OBJECTIVE

The aim of this study was to analyze the risk factors of mortality in children with Wilms' tumor at Soetomo Hospital Surabaya.

MATERIAL & METHODS

Medical records of all pediatric patients diagnosed as Wilms' tumor at the Division of Pediatric Hematology Oncology from 2006 to 2011 were retrospectively reviewed.

Risk factors were evaluated for demographic (age, gender, ethnicity), clinical profile, nutrition status, complete blood count, blood urea nitrogen (BUN), initial glomerular filtration rate (GFR), histological type, disease stage, metastasis and relapse.

Clinical profile was defined by clinical manifestation, laboratory and radiological findings. Clinical manifestations included abdominal mass, abdominal pain, hematuria (tea-colored or cola-colored urine) and genitourinary anomalies (hypospadias, cryptorchidism and varicocele). Laboratory findings such as complete blood count, azotemia (BUN ≥ 20 mg/dL) and reduced GFR (GFR ≤90 ml/minute/1.73 m^2 by Steward Formula).[5]

Based on histological type, Wilms' tumor can be separated into two groups on the basis of histopathology: favorable histology when histology mimics development of a normal kidney consisting of 3 components: blastema, epithelium (tubules) and stroma without any anaplasia; unfavorable histology, characterized by anaplasia (extreme cellular pleomorphism and atypia, diffuse). Focal anaplasia may not confer nearly as poor a prognosis as diffuse anaplasia.[6,7]

The staging system is in accordance to the National Wilms' Tumor Study (NWTS), which is based on the extent of disease at the time of surgery, whether immediate or delayed (Table 1).[6]

Wilms' tumor metastases location site are the lungs, liver, bones, brain or lymph node metastases.[3] Relapse defined as recurrence in the original tumor bed, in the retroperitoneum, or within the abdominal cavity or pelvis, but does not include children with hematogenous hepatic metastases only.[8]

For nutrition status, weight, height and mid-upper arm circumference were recorded. Nutritional status of the children was evaluated using the

Table 1. Children's oncology group Wilms' tumor staging system.

Stage	Description
I	Tumor confined to kidney and completely resected; no capsular breach, tumor spillage or renal sinus extension.
II	Extracapsular penetration (including iatrogenic via biopsy prior to resection) or renal sinus extension with vascular involvement; complete resection with negative margins and no lymph node involvement.
III	Non-hematogenous spread beyond the kidney (abdominal lymph nodes, transected renal vein, IVC tumor thrombus); macroscopic/ microscopic residual tumor after resection; peritoneal spillage during resection.
IV	Hematogenous metastases (lung, liver, bone, brain) or extra abdominal lymph node spread.
V	Bilateral renal involvement at diagnosis.

following scheme: Moderate malnutrition: <2 standard deviation (SD) Z score value and severe malnutrition: < 3 SD Z score value.[9,10]

Data analysis was performed using the SPSS statistical package (SPSS for Windows Version 23). Risk factor analysis used the chi-square test, Fisher's exact test, and binary logistic regression. Variables with p<0.25 in the bivariate analysis were analyzed further with the logistic regression model (p<0.05).

RESULTS

There were 37 Wilms' tumor children and 5 children were excluded because of incomplete data. The mean age was 3.0 (SD 2.6) years, and male-to-female ratio was 2.5 : 1. Approximately two-third of the participants was malnourished. Patient characteristics are shown in table 2.

The common clinical presentations were abdominal mass and abdominal pain, followed by hematuria. In this study, there was no sign of genitourinary anomalies (Table 3).

According NWTS staging, there were 5/32 children in stage I, 7/32 children in stage II, 8/32 children in stage III, 11/32 children in stage IV, and 1/32 children in stage V. There were 14/32 children underwent operation. The pathologic types of the surgically resected tumor were FH in 11 patients and UH in 3 patients. Complete remission occurred in 12/32 children with 1/32 children relapsed (Table 4). There were 20/32 children died, associated with anemia (P=0.033, OR=6.111, 95% CI=1.056-35.352) and advanced stage (P=0.021, OR=8.000, 95% CI=1.575-40.632) (Table 5). The risk of mortality increased 3.284 folds with every increased stage (P=0.007, 95% CI=1.338-7.775).

Surgery, chemotherapy, and radiotherapy were the three major modalities of treatment in our study patients. Chemotherapy comprised of vincristine, actinomycin D, and adriamycin.

Table 2. Patient characteristics.

Characteristic	Patients (Total = 32) n (%)
Age	
0 - 2 years	15 (46.9)
2 - 5 years	14 (43.8)
5 - 10 years	2 (6.3)
>10 years	1 (3.1)
Gender	
Male	23 (71.9)
Female	9 (28.1)
Nutritional status	
Normal	4 (12.5)
Moderate malnutrition	18 (56.3)
Severe malnutrition	10 (31.3)

Table 3. Clinical profiles of patients.

Clinical profile	Patients (Total = 32) n (%)
Clinical manifestation	
Abdominal mass	32 (100)
Abdominal pain	32 (100)
Hematuria	23 (71.9)
Genitourinary anomalies	0 (0)
Laboratory finding	
Anemia	13 (40.6)
Azotemia	0 (0)
GFR<90 ml/minute/1.73 m^2	12 (37.5)
GFR<60 ml/minute/1.73 m^2	4 (12.5)

Table 4. Staging of the patients according to NWTS.

Staging	Number n (%)	Complete remission	Number of relapse	Outcome died
I	5 (15.6)	4	-	1
II	7 (21.9)	4	-	3
III	8 (25)	3	-	5
IV	11 (34.4)	1	1	10
V	1 (3.1)	-	-	1
Total	32	12	1	20

Table 5. The result of univariate chi-square test for risk factors.

Variable	Category	Died n (%)	P
Gender	Male	15 (65.2)	0.612
	Female	5 (55.5)	
Age	<2 years	10 (66.7)	0.647
	>2 years	10 (58.8)	
Nutritional status	Malnutrition	14 (50)	0.844
	No malnutrition	6 (21.4)	
Hematuria	yes	15 (65.2)	0.612
	no	5 (55.5)	
Abdomen mass	yes	20 (100)	-
	no	-	
Abdomen pain	yes	20 (100)	-
	no	-	
Anemia	yes	11 (84.6)	0.033*
	no	9 (47.3)	
Azotemia	yes	-	-
	no	20 (100)	
GFR <90	yes	6 (50%)	0.258
	no	14 (70%)	
GFR <60	yes	2 (50%)	0.620
	no	18 (64.3%)	
Relapse	yes	1 (100%)	1.000
	no	19 (61.3%)	
Disease stage	Stage >2	16 (80%)	0.021*
	Stage ≤2	4 (33.3%)	
Metastase	yes	6 (50%)	0.262
	no	14 (70%)	

Table 6. Multivariate logistic regression analysis of risk factor.

Parameter	P	OR	95% CI	
			Lower	Upper
Anemia	.033	6.111	1.056	35.352
Disease stage	.021	8.000	1.575	40.632

Table 7. Risk of mortality with disease stage.

Parameter	P	OR	95% CI	
			Lower	Upper
Disease stage	.007	3.284	1.338	7.775

DISCUSSION

The main clinical presentations in our study were abdominal mass and abdominal pain followed by hematuria. No patient presented with hypertension and/or genitourinary abnormalities. Over 90% of children will present with an asymptomatic abdominal mass. Most Wilms' tumors are solitary lesions, although 6% present with bilateral disease and 12% may present with multifocal disease within a single kidney. Presenting symptoms can include abdominal pain that should alert the surgeon to the risk of preoperative rupture and bleeding. Gross hematuria may be a sign of tumor extension into the collecting system or ureter. Atypical presentations occur in less than 10% of patients. They are a result of compression of surrounding organs or vascular invasion. Vascular extension into the renal vein or inferior vena cava occurs in up to 4% of Wilms' tumor patients. Patients with vascular extension can present with ascites, congestive heart failure, hepatomegaly and varicocele. Paraneoplastic syndromes can result from tumor production of hormonal substances, and include hypertension, hypercalcemia, erythrocytosis and von Willebrand's disease.[6] Occasionally, fever, malaise and anemia occur as a result of tumor necrosis with intraparenchymal bleeding.[11] Wilms' tumor is associated with congenital anomalies in 10-13% of cases. Aniridia is present in 10% of children; hemihypertrophy is noted in 2-3%. Other genitourinary malformations are present is 5% of cases mainly cryptorchidism, hypospadias, double collecting system or fused kidney. Rarely, Wilms' tumor has been found in a horseshoe kidney. Congenital abnormalities are seen more commonly is bilateral tumors. The "Denys-Drash Syndrome" is a combination of Wilms' tumor, male pseudo-hermaphroditism and glomerulonephritis. The "WAGR Syndrome" is a combination of Wilms' tumor with aniridia, genitourinary malformations and mental retardation. Wilms' tumor also occurs with increased frequency in the "Beckwith - Wiedemann syndrome" which includes macrosomia, hemihypertrophy, and macroglossia. Hemihypertrophy is extremely rare and normally seen in only 3 per 100.000 children. Other associated malformations include septal defects, microcephalus, hyperinsulinism, and von Willebrand's disease (8%).[7]

Surgery and chemotherapy were the main modalities of treatment in our study. Radiotherapy was used only in few cases because the facilities for radiotherapy are not optimal. But one of the main controversies in the treatment of children with Wilms' tumor is whether or not to administer preoperative chemotherapy, as suggested by the International Society of Pediatric Oncology (SIOP). The surgeon considering the use of preoperative chemotherapy should realize that there can be significant adverse affects on staging and histological evaluation in children who receive preoperative chemotherapy which could lead to either over treatment or under treatment. Evidence to support the dangers of under treatment is a SIOP study that showed an increased incidence of infradiaphragmatic relapses in patients who did not receive postoperative radiation therapy. Likely, patients with lymph node involvement were missed due to preoperative chemotherapy. Proponents of preoperative therapy suggest that the tumor is easier to resect with a decreased incidence of tumor spill and a lower mortality and morbidity. However, the morbidity and mortality following tumor resection in NWTS is extremely low, and the incidence of tumor spill was less than ten percent. Despite the arguments given above against the use of preoperative therapy, specific patient groups can be identified who would seem to benefit from preoperative chemotherapy.[3,12]

One child aged three year with Wilms' tumor stage III was treated successfully with the management included pre-operative chemotherapy, nephrectomy, followed by chemotherapy and radio therapy to the tumor bed. Unfortunately, the child relapsed later on and died because of the progressive disease. The largest relative risks for local recurrence were observed in patients with stage III disease,

those with unfavorable histology (especially diffuse anaplasia), and those reported to have tumor spillage during surgery. Surgical rupture of the tumor must be prevented by the surgeon, because spills produce an increased risk of local relapse.[8]

Twelve patients in our study had metastases when diagnosis, commonly in the lung. The primary distant site for Wilms' tumor metastases is the lungs; hepatic metastases are much less common. Approximately 12 percent of Wilms' tumor patients will have evidence of hematogenous metastases at diagnosis, with 80% having pulmonary metastases. Patients with stage IV FH tumors at diagnosis still have a good prognosis while UH patients and patients who relapse with metastatic disease have a grave prognosis. Approximately 20% of favorable histology patients will relapse following therapy with a majority of relapses being in the lungs. Patients with pulmonary metastases usually can be managed by combined chemotherapy and radiation therapy; pulmonary resection is rarely indicated because chemotherapy is extremely effective. Although histologic confirmation of pulmonary relapse may be indicated, complete removal of pulmonary metastases at relapse does not increase survival.[3,7]

In our study, the logistic regression model analysis showed disease stage (P=0.021, OR=8.000, 95% CI=1.575-40.632) was the only significant risk factor. The risk of mortality would increase 3.284 folds with every increased stage (P=0.007, 95% CI=1.338-7.775). Historically, the most important prognostic variables for patients with Wilms' tumor have been the histopathologic tumor classification and surgical stage. Since appropriate therapy, as well as prognosis, is based on tumor stage, accurate staging of patients with Wilms' tumor at the time of diagnosis is imperative and includes histologic assessment of regional lymph node involvement. There are two distinct histopathologic types of Wilms' tumor, favorable and unfavorable. The unfavorable group comprises Wilms' tumors with anaplasia (extreme nuclear and cytologic atypia). Anaplasia is present in about 5 percent of Wilms' tumor and is more common in older children, reaching a peak at approximately five years of age. There are two additional, distinct renal tumors that can occur in children, each characterized by sarcomatous stroma and a poor outcome. They are clear cell sarcoma of the kidney and malignant rhabdoid tumor of the kidney.[3]

Unfortunately, in our study the underlying cause of death was not complete recorded because of incomplete data in medical records. However, almost all studies revealed that underlying cause of death is usually a result of progressive disease or acute effects of treatment.[4,13] The analysis was limited by relatively small numbers of cause-specific deaths, and the fact that the length of follow-up for patients diagnosed in recent periods was short. Additional studies and continued follow-up of the cohort will be needed to confirm that currently observed trends persist.

CONCLUSION

Disease stage is the significant risk factor of mortality in children with Wilms' tumor.

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