The prognostic significance of hypertension at diagnosis in children with Wilms tumor

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Objectives: To determine the prognostic effect of hypertension at diagnosis on outcomes of children with Wilms tumor (WT).

Methods: A single center retrospective analysis was conducted on 85 consecutive children with WT diagnosed between January 2000 and August 2013. Patients were classified as hypertensive or normotensive at diagnosis. Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan-Meier method. Cox regression was used to determine the predictive significance of hypertension and other clinical factors.

Results: Seventy-one patients had complete data. Of this, 25 (35.2%) were hypertensive and 46 (64.8%) normotensive with corresponding remission rates of 56.0% versus 82.6%, \( p = 0.032 \); and death as first event of 7% versus 0%, \( p = 0.004 \). The 5-year OS in the hypertensive versus normotensive patients were (67.1 ± 10.3% versus 89.6 ± 4.9%, \( p = 0.009 \)) and the corresponding 5-year PFS were (53.4 ± 10.4% versus 79.1 ± 6.2%, \( p = 0.007 \)). With univariate analysis, hypertension and local stage were predictors of OS (\( p = 0.012 \) and \( p = 0.029 \)) and PFS (\( p = 0.030 \) and \( p = 0.008 \)). In the multivariate analysis, hypertension, local stage, and histopathology were identified as independent prognostic factors of OS (\( p = 0.004 \), \( p = 0.034 \), and \( p = 0.038 \)); and hypertension and local stage as prognostic for PFS (\( p = 0.010 \) and \( p = 0.012 \)).

Conclusion: Hypertension at diagnosis is a prognostic predictor of poor outcome in WT and may signify tumor resistance.

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Wilms tumor (WT) is the most common form of childhood kidney cancer. It accounts for 6% of all pediatric cancers, represents more than 95% of all kidney tumors in children and commonly seen in children younger than 5 years. Over the past few decades, considerable progress has been made in the treatment of WT, and it is one of the great success stories in oncology. Currently, the 5-year overall survival (OS) exceeds 90%. This outstanding outcome was achieved through the multicenter collaboration of several groups such as the International Society of Pediatric Oncology (SIOP) and the Children’s Oncology Group (COG). Many clinical variables including: tumor histopathology, tumor stage, molecular and genetic markers, and age at presentation have been investigated in the past as prognostic indicators of outcome in patients with WT. Currently, the COG risk-grouping stratifies WT patients to different treatment intensities based on age, tumor weight, histology, stage, tumor cytogenetics (loss of heterozygosity of chromosomes 1p and 16q), and the rapidity of response of metastatic lung nodules to chemotherapy. In contrast, the SIOP risk-stratification is based on stage, histology, tumor volume, and the response of the tumor to preoperative chemotherapy. Despite the fact that hypertension is reported in up to 55% of children with WT at diagnosis, its prognostic significance on survival outcome has never been studied. Thus, we hypothesized that WT patients with hypertension at diagnosis would have poor survival outcomes compared to normotensive patients.

Methods. This is a retrospective single-center study that included all consecutive pediatric patients aged 14 years or younger with histologically confirmed WT, newly diagnosed between January 2000 and August 2013, at the Princess Noorah Oncology Center, King Abdulaziz Medical City, Jeddah, Saudi Arabia. Data on demographics, blood pressure at diagnosis, histopathology, stage (I, II, III, IV or V), chemotherapy, radiotherapy, complications, and treatment outcomes were collected. Only patients with a documented diagnosis of “hypertension that required treatment with antihypertensive therapy” were included in the hypertensive group. Patients with incomplete data and/or without any documentation to indicate normal blood pressure and/or treated in institutions other than the Princess Noorah Oncology Center were excluded. The Institutional Research and Ethics Review Committee of the King Abdullah International Medical Research Center (KAIMRC) approved the study and was conducted in accordance with the Declaration of Helsinki.

Definitions and statistical analysis. Descriptive statistics was used to summarize patient demographics and clinical information. Chi-square or Fisher’s exact test was used as appropriate to compare categorical variables. Hypertension in our center followed the published standard definition of a systolic and/or diastolic blood pressure ≥95th percentile for age, gender, and height. Based on the documented blood pressure at diagnosis, patients were classified into normotensive and hypertensive groups. Patients with documentation indicating normal blood pressure were classified as normotensive and patients with a documented diagnosis of hypertension that required antihypertensive therapy on presentation were classified as hypertensive.

Overall survival (OS) was defined as the time elapsed from diagnosis of WT to time of death from any cause or last follow-up. Progression free survival (PFS) was defined as the time from diagnosis to date of first event: relapse, progressive disease, or death. Patients without events were censored at the last date of follow-up. The Kaplan-Meier method was used to estimate OS and PFS probabilities. The log-rank test was used for group comparisons. Univariate and multivariate Cox proportional hazard models were used to determine potential predictors of survival. Predictive factors significant at p<0.10 in the univariate analysis were entered simultaneously into a multivariate analysis. All other tests were considered statistically significant if p<0.05. Statistical computations were performed using the Statistical Package for Social Sciences Software Package (SPSS Inc, Chicago, IL, USA) for Windows.

Results. A total of 85 patients were reviewed. Of this, 14 were excluded due to undocumented blood pressure and 71 qualified for the final analysis. Patients were then classified at diagnosis into hypertensive (n=25) and normotensive (n=46) groups. The demographic features of these patients are reported in Table 1. The clinical stage distribution was similar in the 2 groups (p=0.631). In addition, no significant difference was observed between patient groups in terms of histopathological risk (p=0.894). Complete remission was achieved more frequently in the hypertension group compared with the normotensive group. The difference was statistically significant (p=0.032). Relapse rates were similar between patient groups (p=0.146) (Table 1).
Eleven (15.5%) patients died, 7 in the hypertensive and 5 in the normotensive group representing a significant statistical difference between the 2 groups, \( p=0.043 \). Death as first event occurred in 5 (7%) patients. It should be noted that 5 out of 25 (20%) of hypertensive patients experienced death as a first event compared to none in the normotensive group and the difference was statistically significant, \( p=0.004 \). The median time to death as first event was 6.4 months (range 4 days to 7.1 months) with a median age at diagnosis of 12 months (range 7 to 36 months). Tumor stage distribution for patients who had death as a first event was 2 in stage V, 2 in stage IV, and one in stage III. Except for one patient, who died of tumor rupture at day 4 of presentation, the remaining patients died of progressive disease following at least 8 weeks of preoperative chemotherapy. A detailed description of these patients including: age, gender, histology, time to death as first event, and the causes of death is summarized in Table 2.

**Influence of hypertension on survival.** For the 71 patients, the 5-year OS was 82.3±4.9%. The OS rates were inversely proportional to tumor stage with 5-year OS rates of 84.6±5.4% for localized versus 76.0±10.5% for metastatic stage IV disease \( p=0.462 \). Furthermore, the 5-year OS rates by local stage were 94.4±5.4% for local stage I, 94.1±5.7% for local stage II, and 68.7±8.8% for local stage III disease \( p=0.046 \). In contrast, the 5-year OS in the hypertensive group was 67.1±10.3% and in the normotensive group was 89.6±4.9% \( \text{Figure 1B} \). In addition, hypertensive patients with local stage I/II disease had significantly lower 5-year OS rates of 81.6±11.6% compared with 100% for normotensive patients \( p=0.032; \text{Figure 2} \). Similarly, a significantly lower 5-year OS rate was observed among hypertensive patients with local stage III disease compared with normotensive patients \( p=0.035; \text{Figure 2} \).

**Determinants of survival.** Univariate and multivariate analyses were conducted to assess the prognostic significance of hypertension at diagnosis on

### Table 1 - Demographics at diagnosis and treatment outcomes (hypertensive versus normotensive patients).

| Category       | Hypertensive n (%) | Normotensive n (%) | P-value |
|----------------|--------------------|--------------------|---------|
| Number (%)     | 25 (35.2)          | 46 (64.8)          | 1.000   |
| Age (median in years) | 2.5                | 3.6                | 0.015   |
| Gender         | Male               | Female             |         |
| Male           | 17 (68.0)          | 16 (34.8)          |         |
| Female         | 8 (32.0)           | 30 (65.2)          |         |
| Stage          |                    |                    | 0.631   |
| I              | 5 (20.0)           | 13 (28.3)          |         |
| II             | 3 (12.0)           | 7 (15.2)           |         |
| III            | 5 (20.0)           | 12 (26.1)          |         |
| IV             | 8 (32.0)           | 11 (23.9)          |         |
| V              | 4 (16.0)           | 3 (6.5)            |         |
| Histopathology*| Favorable          | Unfavorable        | 0.894   |
| Favorable      | 21 (84.0)          | 40 (87.0)          |         |
| Unfavorable    | 2 (8.0)            | 6 (13.0)           |         |
| Remission      |                    |                    | 0.032   |
| Yes            | 14 (56.0)          | 38 (82.6)          |         |
| No             | 11 (44.0)          | 8 (17.4)           |         |
| Relapse        |                    |                    | 0.146   |
| Yes            | 1 (4.0)            | 8 (17.4)           |         |
| No             | 24 (96.0)          | 38 (82.6)          |         |

*Number do not add up to 100% due to missing data or not applicable.

### Table 2 - Causes of death as first event.

| SN | Age | Gender | Stage | Histology | Blood pressure* | Time to first event* | Cause of death                                      |
|----|-----|--------|-------|-----------|-----------------|----------------------|-----------------------------------------------------|
| 1  | 36 m | Male   | IV    | Unfavorable | HT              | 7 m                  | Progressive disease/died of respiratory failure     |
| 2  | 32 m | Male   | IV    | Favorable  | HT              | 7 m                  | Progressive disease/died of progressive refractory disease |
| 3  | 12 m | Male   | V     | Unfavorable | HT              | 6 m                  | Tumor progression and rupture preoperatively, died intra-operatively from uncontrolled bleeding |
| 4  | 7 m  | Male   | III   | Favorable  | HT              | 4 d                  | Progressive disease/intra-operative tumor bleeding   |
| 5  | 8 m  | Female | V     | Favorable  | HT              | 2 m                  | Progressive disease/renal failure that led to cardiac failure |

HT - hypertension, m - month, d - day
outcome. In a univariate analysis; age, gender, metastatic disease, local stage, histopathology, and hypertension at diagnosis were considered. Hypertension and local stage were found to be significant predictors for OS (Table 3). Other factors did not show statistically significant differences. However, histopathology was forced into the multivariate models due to clinical importance. Therefore, using multivariate analysis hypertension, local stage, and unfavorable histopathology were identified as independent predictors of OS (Table 3).

The potential predictors for PFS were also assessed using univariate and multivariate models in a similar manner as for the OS. At a univariate level, hypertension, and local stage were significant predictors of PFS; however, at multivariate analysis, hypertension and local stage were detected as predictors of PFS (Table 4).

**Discussion.** Twenty to 55% of children with WT reportedly present with hypertension at diagnosis.7-9 Despite this knowledge, tumor histopathology, stage, molecular and genetic markers, tumor weight/volume, rapidity of response to chemotherapy, and age at diagnosis are the most widely studied prognostic factors of outcome in WT patients.5,6 The present study evaluates the prognostic significance of hypertension at presentation on survival outcomes of children with WT. Our findings demonstrate that hypertension at diagnosis is a predictor of poor outcome in patients with WT. In this study, 35.2% of patients were hypertensive at diagnosis, which is consistent with rates reported in children with WT in other studies.7-9 Furthermore, no statistically significant differences were observed between the 2 patient groups in relation to age, tumor stage, or histopathology. Despite these similarities, patients with hypertension at diagnosis had inferior OS and PFS compared with normotensive patients.

To further illustrate the causes for poor outcomes in hypertensive patients, we examined events of treatment failure such as tumor relapse, progression, and death between the study groups. Relapse rates were similar in both patient groups. However, hypertensive patients had significantly higher incidence of tumor progression and death as first event. In fact, 20% of our patients
diagnosed with hypertension experienced death as first event compared with none in the normotensive group. Thus, the significantly worse OS and PFS among hypertensive patients were closely associated with death as first event. In the hypertensive group, tumor progression was the main cause of death as the first event. Therefore, the inferior OS and PFS may be explained by the higher rate of tumor progression leading to high incidence of death as the first event.

Hypertension at diagnosis is a known complication of childhood cancer and is mainly observed in the context of Wilms tumor, neuroblastoma, brain tumors, and pheochromocytoma.7 The cause of hypertension in children with cancer can be multifactorial and due to renin secretion by the tumor, mechanical mass effect causing renal vascular compression or thrombosis, hormonal secretion of glucocorticoids or catecholamines, cancer-related pain, secondary to treatment with steroid chemotherapy, or a result of increased intracranial pressure.7,9 In WT patients, hypertension results from increased renin production secondary to intra-renal vascular compression. Alternatively, renin may be produced by the tumor cells.12,13 Increased plasma renin concentration has been reported in approximately 80% of hypertensive WT children at diagnosis and relapse was observed in 3 out of 4 patients with increased plasma prorenin/renin concentrations.8,14 Renin production is controlled by the renin-angiotensin system (RAS), which plays a decisive role in maintaining blood pressure homeostasis. Renin-angiotensin system activation promotes cell proliferation, angiogenesis, and tumor progression.15-17 Therefore, we hypothesize that the observed inferior outcomes might be the result of progressive/refractory disease in relation to the effects of RAS activation. However, our study is limited by the fact that renin levels were not assessed; and further studies are required to test this hypothesis. If RAS activation can be established as pathogenic in WT, then inhibiting the RAS could induce apoptosis and hinder tumor growth.18-20 Indeed, blocking RAS activity using angiotensin I and II inhibitors in combination with chemotherapy has been shown to improve survival in adult patients with bladder, gastric, and pancreatic cancers.16,21,22 However, currently, no studies have investigated the effect of RAS inhibitors on the treatment outcomes in WT. The use of RAS inhibitors to treat hypertension in WT may present a reasonable therapeutic option to control hypertension and may potentially have the added benefit of improving the overall response to therapy.8 Based on the results of the present study, we believe that improving survival outcomes among hypertensive WT patients is needed. Therefore, we postulate that adding RAS inhibition to conventional chemotherapy regimens may have a synergistic effect in improving the outcomes of hypertensive WT children. We believe that this hypothesis merits further study.

**Study limitation.** The present study has several limitations that should be acknowledged. First, this

| Table 3 - Prognostic factors for overall survival (OS). |
|---------------------------------------------------------|
| Prognostic variables for OS | Estimate | HR | 95% CI | P-value |
|----------------------------|----------|----|--------|---------|
| Univariate analysis        |          |    |        |         |
| Age ≥2 years               | 0.917    | 0.195-4.323 | 0.913 |
| Gender Male                | 1.045    | 0.319-3.428 | 0.942 |
| Stage Local vs. metastatic | 1.687    | 0.494-5.763 | 0.404 |
| Stage Local stage          | 5.503    | 1.187-25.502 | 0.029 |
| Histopathology Unfavorable | 3.400    | 0.898-12.871 | 0.072 |
| Hypertension Yes           | 4.804    | 1.402-16.328 | 0.012 |
| Multivariate analysis      |          |    |        |         |
| Histopathology Unfavorable | 5.053    | 1.097-23.265 | 0.038 |
| Hypertension Yes           | 8.055    | 1.976-32.837 | 0.004 |
| Local stage Stage III vs. I/II | 5.353 | 1.138-25.179 | 0.034 |

| Table 4 - Prognostic factors for progression free survival (PFS). |
|---------------------------------------------------------------|
| Prognostic variables for PFS | Estimate | HR | 95% CI | P-value |
|----------------------------|----------|----|--------|---------|
| Univariate analysis       |          |    |        |         |
| Age ≥2 years               | 1.030    | 0.293-3.618 | 0.963 |
| Gender Female              | 1.366    | 0.529-3.527 | 0.520 |
| Stage Local vs. metastatic | 1.957    | 0.758-5.050 | 0.165 |
| Stage Local Stage          | 4.486    | 1.473-13.661 | 0.008 |
| Histopathology Unfavorable | 2.584    | 0.849-7.868 | 0.095 |
| Hypertension Yes           | 2.798    | 1.107-7.686 | 0.030 |
| Multivariate analysis      |          |    |        |         |
| Hypertension Yes           | 3.738    | 1.366-10.231 | 0.010 |
| Local stage Stage III vs. I/II | 4.241 | 1.371-13.121 | 0.012 |

vs. - versus, HR - hazard ratio, 95%CI - 95% confidence interval
study is retrospective, with a relatively small patient population in each group. Second, data regarding the duration of hypertension were not available to assess its impact on outcome. Third, renin levels were not assessed. Thus, our findings should be interpreted in light of these limitations. Despite these limitations, our study shows for the first time that hypertension at presentation is a significant predictor of poor survival in WT patients.

In conclusion, our findings call attention to the importance of recognizing hypertension at diagnosis in WT patients and highlight the need to consider this factor in prognostic risk stratification. This area merits further studies to better define the impact of hypertension at diagnosis on the treatment outcome of children with WT.

References

1. Horner MJ, Ries LA, Krapcho M, Neyman N, Aminou R, Howlader N, et al. SEER Cancer Statistics Review, 1975-2006. Bethesda (MD): National Cancer Institute; 2009. Available from URL: http://seer.cancer.gov/archive/csr/1975_2006/.
2. Scott RH, Stiller CA, Walker L, Rahman N. Syndromes and constitutional chromosomal abnormalities associated with Wilms' tumour. J Med Genet 2006; 43: 705-715.
3. Smith MA, Seibel NL, Altekruse SF, Ries LA, Melbert DL, O'Leary M, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. J Clin Oncol 2010; 28: 2625-2634.
4. Metzger ML, Dome JS. Current therapy for Wilms' tumor. Oncologist 2005; 10: 815-826.
5. Breslow N, Sharpes K, Beckwith JB, Takashima J, Kelalis PP, Green DM, et al. Prognostic factors in nonmetastatic, favorable histology Wilms' tumor: Results of the Third National Wilms' Tumor Study. Cancer 1991; 68: 2345-2353.
6. Dome JS, Perlman EJ, Graf N. Risk stratification for Wilms tumor: current approach and future directions. Am Soc Clin Oncol Educ Book 2014: 215-23.
7. Madre C, Orbach D, Baudouin V, Brisse H, Bessa F, Schleiermacher G, et al. Hypertension in childhood cancer: a frequent complication of certain tumor sites. J Pediatr Hematol Oncol 2006; 28: 659-664.
8. Maas MH, Cransberg K, van Grotel M, Pieters R, van den Heuvel-Eibrink MM. Renin-induced hypertension in Wilms tumor patients. Pediatr Blood Cancer 2007; 48: 500-503.
9. Szych E, Apps J, Pritchard-Jones K. Wilms' tumor: biology, diagnosis and treatment. Transl Pediatr 2014; 3: 12-24.
10. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. Pediatrics 2004; 114: 555-576.
11. Al Salloum AA, El Mouzan MI, Al Herbish AS, Al Omar AA, Qurashi MM. Blood pressure standards for Saudi children and adolescents. Ann Saudi Med 2009; 29: 173-178.
12. Steinbrecher HA, Malone PS. Wilms tumour and hypertension: incidence and outcome. Br J Urol 1995; 76: 241-243.
13. Spahr J, Demers LM, Shochat SJ. Renin producing Wilms' tumor. J Pediatr Surg 1981; 16: 32-34.
14. Leckie BJ, Birnie G, Carachi R. Renin in Wilms’ tumor: prorenin as an indicator. J Clin Endocrinol Metab 1994; 79: 1742-1746.
15. Ager EI, Neo J, Christophi C. The renin-angiotensin system and malignancy. Carcinogenesis 2008; 29: 1675-1684.
16. Khakoo AY, Sidman RL, Pasqualini R, Arap W. Does the renin-angiotensin system participate in regulation of human vasculogenesis and angiogenesis? Cancer Res 2008; 68: 9112-9115.
17. Kim ST, Park KH, Oh SC, Seo JH, Kim JS, Shin SW, et al. How does inhibition of the renin-angiotensin system affect the prognosis of advanced gastric cancer patients receiving platinum-based chemotherapy?. Oncology 2012; 83: 354-360.
18. Noguchi R, Yoshiji H, Ikenaka Y, Namisaki T, Kitade M, Kaji K, et al. Synergistic inhibitory effect of gemcitabine and angiotensin type-1 receptor blocker, losartan, on murine pancreatic tumor growth via antiangiogenic activities. Oncol Rep 2009; 22: 355-360.
19. Amaya K, Ohba T, Kitagawa H, Kayahara M, Takamura H, Fujimura T, et al. Prognostic value of renin-angiotensin system blockade in non-muscle-invasive bladder cancer. Int J Oncol 2004; 25: 849-856.
20. Gong Q, Davis M, Chipitsyna G, Yeo CJ, Arafat HA. Blocking angiotensin II type 1 receptor triggers apoptotic cell death in human pancreatic cancer cells. Pancreas 2010; 39: 595-603.
21. Yuge K, Miyajima A, Tanaka N, Shirotake S, Kosaka T, Kikuchi K, et al. Renin-angiotensin system participate in regulation of human vasculogenesis and angiogenesis. Cancer Res 2008; 68: 9112-9115.
22. Kim ST, Park KH, Oh SC, Seo JH, Kim JS, Shin SW, et al. How does inhibition of the renin-angiotensin system affect the prognosis of advanced gastric cancer patients receiving platinum-based chemotherapy?. Oncology 2012; 83: 354-360.