

**HEPATIC SINUSOIDAL OBSTRUCTION SYNDROME IN SOUTH AFRICAN
CHILDREN TREATED FOR WILMS TUMOUR: PREVALENCE, RISK
FACTORS AND OUTCOMES**

Anabela De Sousa Andrade

A research report submitted to the Faculty of Health Sciences, University of the
Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of
Master of Medicine in the branch of Paediatrics.

Johannesburg, 2013

DECLARATION

I, Anabela De Sousa Andrade declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics, in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

.....

.....day of, 2013

DEDICATION

For

Daniela and Joshua,

My niece and nephew.

ABSTRACT

Wilms Tumour (WT) is one of the commonest tumours in children. Hepatic Sinusoidal Obstruction Syndrome (HSOS) is a documented complication following treatment of WT.

The role of malnutrition in the development of HSOS has not been studied. Malnutrition reduces tolerance to chemotherapy and shows increased risk for toxicity.

Purpose of study

To determine the prevalence of HSOS in children with WT, as well as its predisposing factors and outcomes.

Method

A descriptive retrospective analysis of medical records of children treated for WT, who developed HSOS, at the Paediatric Haematology/Oncology Unit, Chris Hani Baragwanath Hospital.

Results

82 patients were evaluated. 19 (23%) showed features compatible with HSOS. Younger age, irradiation and a right-sided WT predicted the development of HSOS but were not statistically significant. Serum albumin levels were lower in the affected group ($P = 0.02$). Apart from 2 deaths, outcomes were good, with patients showing full resolution of symptoms.

Conclusion

A higher prevalence of HSOS was shown than previously reported. Low serum albumin levels points to the role of malnutrition. Effort needs to be put into the various methods of identifying malnutrition. Long term follow-up is needed.

ACKNOWLEDGEMENTS

Dr G. Naidu MBChB, FCPaed(SA), MMed(Paed)

My co-supervisor, for her guidance, assistance and support at all times

Dr R. Wainwright MBBCh, FCPaed(SA)

My co-supervisor, for her guidance, assistance and support at all times

Esnat Chirwa and Dickman Gareta

For their assistance with the statistical methods

TABLE OF CONTENTS

	Page
Declaration	2
Dedication	3
Abstract	4
Acknowledgements	5
Table of contents	6
List of tables	9
List of abbreviations	10
1.0 Introduction	12
2.0 Study objectives	16
3.0 Methods	18
3.1 Study design and population	18
3.2 Sample size	18
3.3 Exclusion criteria	18
3.4 Inclusion criteria	18
3.4.1 Diagnosis of WT	18
3.4.2 Diagnosis of HSOS	19
3.4.3 Diagnosis of malnutrition	20
3.5 Data analysis	21
3.6 Ethical clearance	22

3.7 Study limitations	22
4.0 Results	23
4.1 Prevalence of HSOS	23
4.2 Episodes of HSOS	23
4.3 Patient characteristics	24
4.4 Potential risk factors	27
4.5 Anthropometry	32
5.0 Discussion	34
5.1 Prevalence	34
5.2 Patient characteristics	34
5.2.1 Timing	34
5.2.2 Anthropometry	35
5.2.3 Clinical	35
5.2.4 Biochemical	36
5.2.5 Sepsis	37
5.3 Potential risk factors	37
5.3.1 Age	37
5.3.2 Lower body weight and nutritional status	38
5.3.3 High doses of ACD	39
5.3.4 Abdominal irradiation	39
5.3.5 Right sided WT	40
5.4 Outcomes	41
5.4.1 Management	41
5.4.2 Changes in the SIOP-9 protocol	42
6.0 Conclusion	43

7.0 Appendix 1	45
8.0 Appendix 2	46
9.0 Appendix 3	47
10.0 Appendix 4	50
11.0 References	52

LIST OF TABLES

	Page
4.1 Prevalence of HSOS	23
4.2 Episodes of HSOS	23
4.3 Patient characteristics	24
4.4 Potential risk factors	27
4.5 Anthropometry	32

LIST OF ABBREVIATIONS

ACD	Actinomycin D
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
FNA	Fine needle aspiration
CMP	Calcium magnesium phosphate
CRP	C-reactive protein
CT	Computer tomography
CTCAE	Common terminology criteria for adverse events
HB	Haemoglobin
HSOS	Hepatic sinusoidal obstruction syndrome
INR	International normalised ratio
LLN	Lower limit of normal
NHLS	National health laboratory service
PAI	Plasminogen activator inhibitor
PLTS	Platelets
PTT	Partial thromboplastin time
SCT	Stem cell transplantation

SIOP	Société Internationale d'oncologie Pédiatrique
ULN	Upper limit of normal
WCC	White cell count
WT	Wilms tumour
WHO	World Health Organisation

1.0 INTRODUCTION

Renal tumours comprise 7-8% of all tumours in the first 15 years of life, of which Wilms tumour (WT) or nephroblastoma is the most common (85%) [1]. The incidence of WT is around 4-10 per year per one million children under fifteen years of age worldwide [2]. In Europe and the USA, overall long-term survival is now 85-90% [3]. However, 80% of children with WT live in countries with limited resources where survival is lower [4].

Reported survival rates for patients with a WT in Africa range between 11% (Sudan) and 70% (French-African Pediatric Oncology group) [5, 6]. In a South African centre, Davidson et al. [7] found the estimated 5-year overall survival in their study to be 80.5%.

Pathological staging of a WT is determined using the Société Internationale d'oncologie Pédiatrique (SIOP) WT 2001 staging criteria for renal tumours of childhood (Appendix 1). The revised SIOP working classification of renal tumours in childhood is used to assist in classifying the tumour histology as being either low risk, intermediate risk or high risk (Appendix 2). Histology is also reviewed at the time of the nephrectomy i.e.: after the course of preoperative chemotherapy is completed. The SIOP Nephroblastoma Treatment Protocol (Appendix 3) consists of a course of preoperative chemotherapy, followed by surgery and postoperative chemotherapy and sometimes radiotherapy according to histology and stage. [3,8].

The various SIOP trials, which commenced in 1971, saw preoperative radiotherapy being replaced by chemotherapy, and then optimal duration of both pre- and post-operative treatment being adjusted. The SIOP-9 nephroblastoma protocol showed that there was no significant change in survival between 4 and 8 weeks of preoperative treatment in children with non-metastatic disease [3]. The SIOP Committee then amended this protocol, changing the dose of Actinomycin D (ACD) from 0,45mg/m² to 15µg/kg once it was

suspected as a cause for hepatotoxicity in some cases. Children under 1 year and/ or less than 12 kg were recommended to have 2/3 of the dose of all drugs for the same reason [9,10].

Hepatic sinusoidal obstruction syndrome (HSOS), formerly known as hepatic veno-occlusive disease, has been described after haematopoietic stem cell transplantation (SCT) as well as after chemotherapy for WT, the incidence being 10-20% and 1.2-8% respectively [11,12]. It has also been described in other solid tumours such as rhabdomyosarcomas and neuroblastomas [20]. In South Africa, Davidson et al [7] showed only a 0.5% incidence of HSOS [7]. In other studies, De Kraker et al reported an incidence of 2.9% [8], Ludwig et al 4.8% [10], and Bisogno et al 8% [21].

Risk factors for developing HSOS have included a younger age/lower body weight, administration of ACD, administration of ACD in combination with, or directly following radiotherapy, and right-sided WT [10,12,13]. The administration of abdominal irradiation has been shown to double the occurrence of overall hepatotoxicity [10, 21]. Cytoreductive therapy has been shown to cause vascular changes in the liver, affecting small hepatic venules, sinusoids and the portal veins at its branches. Sinusoidal blood flow is reduced after administration of hepatotoxic substances; slowing of the circulation generates microthrombi and consequently obstruction of the sinusoidal pores [14].

Another important risk factor that needs to be considered in the developing world is malnutrition [15, 22]. It has been reported that malnutrition reduces tolerance to chemotherapy and has been associated with decreased survival and/or increased toxicity [16]. In South Africa, a retrospective study by Wessels et al. [17] described that 35% of children with WT presenting to Tygerberg Hospital, were found to be malnourished at presentation. This study did not include the incidence of toxic events. Also in South Africa,

a study by Davidson et al [7] in The Red Cross Children's Hospital, found that 20.7% of their patients were malnourished. They found only one case of HSOS. In Malawi, Israels et al. [18] found an even higher rate (55%) of malnourishment, but no cases of HSOS. The two South African studies however, did not adjust the patients weight according to the tumour burden, thus the degree of malnourishment may have been underestimated.

Diagnosis of HSOS is primarily clinical, based on criteria defined by McDonald et al. [23] i.e.: the presence of at least two of the following signs or symptoms: hepatomegaly or right upper quadrant pain, unexplained weight gain (of >5%) and/or ascites, and hyperbilirubinaemia (>2mg/dL). When only one of the criteria was present, McDonald et al placed patients in the 'uncertain' category [23]. This set of criteria, was used in the diagnosis of HSOS post-SCT but has been extended to include non- SCT patients, allows a diagnosis of HSOS with a good specificity and negative predictive value but a modest sensitivity [12].

Several reports have looked for other biochemical markers besides hyperbilirubinaemia to assist in making the diagnosis of HSOS more sensitive. HSOS is associated with several alterations of the haemostatic profile, for example, thrombocytopenia refractory to platelet transfusions, increase of von Willebrand factor, thrombomodulin and clotting activation parameters, decrease of factor VII, natural clotting inhibitors and plasminogen [20].

Following endothelial damage, the release of endothelial von Willebrand factor and cytokines stimulate platelet adhesion and aggregation, thus leading to thrombocytopenia. The cytokines released (tumour necrosis factor [TNF]- α and interleukin [IL]-1 β) further mediate liver and multi-organ impairment [21].

The natural history of HSOS is characterised by the appearance of laboratory alterations suggestive of liver dysfunction, with a peak occurrence approximately 10 days from onset,

combined with symptoms as described in the McDonalds criteria. Non- SCT-HSOS is less common than SCT-HSOS, and is mild to moderate in terms of severity; the clinical picture resolves spontaneously in the majority of cases (mild), but severe cases may occur. If HSOS continues to progress, multi-organ failure develops. The level of hyperbilirubinaemia and the severity of fluid retention predict the subsequent occurrence of pleural effusion, pulmonary infiltrates, heart failure, bleeding, acute renal failure, and neurological impairment due to encephalopathy [21].

After observation of an apparent increase in the numbers of patients being diagnosed and treated for HSOS in our centre, this study thus set out to establish the prevalence and outcomes of HSOS in patients with WT. The study also aimed to identify predisposing factors for HSOS especially looking at the role of nutrition.

2.0 STUDY OBJECTIVES

Wilms Tumour (WT) is the one of the commonest tumours diagnosed in children. In high income countries WT carries a good prognosis in all stages, and low stage (I and II) should portend a good prognosis even in low income countries. Therefore interest continues in decreasing any toxicity that develops as a consequence of therapy.

Hepatic sinusoidal obstruction syndrome (HSOS) is a well documented complication of treatment of WT, which can at times be fatal. Known risk factors of HSOS include administration of high doses of Actinomycin D (ACD), ACD in combination with radiotherapy, patients of a younger age/ lower body weight, and a right-sided WT.

It is of interest to note which other risk factors may play a role in HSOS, in low income countries. Of particular interest is the role of malnutrition, the incidence of which remains high in South Africa. Malnutrition is known to reduce tolerance to chemotherapy and has an increased risk for toxicity. Seeing that nutritional status may have a prognostic effect on outcome, its early identification and early treatment, using a multi-disciplinary approach, can only be of benefit to the patients.

The aims of this study are to:

1. Determine the prevalence of HSOS in patients with WT
2. Identify the potential risk factors for the development of HSOS and,
3. Describe the patient outcomes following treatment.

The objectives of this study are:

1. To identify patients who developed HSOS using the McDonald's criteria
2. To appreciate the clinical/ laboratory parameters that often accompanies the standard diagnosis of HSOS.

3. To evaluate the established risk factors (administration of high doses of ACD, ACD in combination with radiotherapy, patients of a younger age/ lower body weight, and a right-sided WT) for HSOS and explore possible risk factors which may be pertinent to low income countries particularly the role of nutrition.
4. To review the outcomes and adjustments made to patient management in the face of HSOS.

3.0 METHODS

3.1 Study Design and Population

The study was based at the Paediatric Haematology/Oncology Unit, Chris Hani Baragwanath Hospital. It was a descriptive retrospective analysis of all children diagnosed with Wilms Tumour (WT), who subsequently developed Hepatic Sinusoidal Obstruction Syndrome (HSOS). It included all children admitted to the above unit and treated with the SIOP-9 nephroblastoma protocol, from the period 1st January 2002 to 31st December 2011.

3.2 Sample size

95 patients were diagnosed with WT during the above study period. 3 presented as relapsed disease and 8 patients did not commence treatment (3 defaulted and 5 died before commencement of treatment). 2 patients were not treated using the SIOP-9 protocol (due to initial incorrect diagnosis). Thus 82 patients were included in the study.

3.3 Exclusion Criteria

The following patients were excluded from the study: if histology was not compatible with WT, if they were treated for WT at another institution and presented to the above unit with relapsed disease, if they were not treated with the SIOP-9 nephroblastoma protocol.

3.4 Inclusion Criteria

3.4.1 Diagnosis of Wilms Tumour

Radiology: Computed Tomography (CT) Scan of the abdomen; CT Chest assisted with staging by identifying the presence/absence of metastasis to the lungs.

Histology: Fine needle aspirate (FNA) of the abdominal mass was done under sonar guidance and histology reviewed by a cytologist; histology was reviewed at nephrectomy.

Treatment was based on the stage and histology at nephrectomy.

3.4.2 Diagnosis of Hepatic Sinusoidal Obstruction Syndrome

Using McDonald's criteria, two of the following symptoms or signs were necessary to diagnose HSOS: jaundice or bilirubin >2mg/dL, painful hepatomegaly (>3cm below costal margin), weight gain (>5%) with or without ascites. A concurrent sepsis was excluded by recording patient's temperature at the time of confirmed/suspected HSOS. Weight and height was measured and recorded by nursing staff. The assessment of hepatomegaly and ascites was assessed clinically.

As McDonald et al placed patients in the 'uncertain' category when only 1 of the 3 criteria were met, this study will classify these patients as 'Suspected HSOS'; laboratory values as mentioned below will also assist with placing patients into this category.

Laboratory (NHLS paediatric normal reference ranges; abnormal values defined using the Common Terminology Criteria for Adverse Events [CTCAE] Version 4.0).

- White Cell Count: leucopenia graded as: Grade I: $3.0 \times 10^9/L$ - < age-dependant lower limit of normal (LLN); Grade II: $2.0-3.0 \times 10^9/L$; Grade III: $1.0-2.0 \times 10^9/L$; Grade IV: $<1.0 \times 10^9/L$
- Haemoglobin: anaemia graded as: Grade I: $10.0g/dL$ - < age-dependant LLN; Grade II: $8.0-10.0g/dL$; Grade III: $6.5-8.0g/dL$; Grade IV: $<6.5g/dL$
- Platelets : thrombocytopenia graded as: Grade I: $75.0 \times 10^9/L$ - < age-dependant LLN; Grade II: $50.0-75.0 \times 10^9/L$; Grade III: $25.0-50.0 \times 10^9/L$; Grade IV: $<25.0 \times 10^9/L$
- INR/PTT: increased Grade 1: $>1-1.5 \times$ age-dependant upper limit of normal (ULN); Grade 2: $1.5-2.5 \times$ ULN; Grade 3: $> 2.5 \times$ ULN

- D-dimers: Normal range <224ng/mL
- Fibrinogen: Normal range 2.0- 4.0 g/L
- CRP and Blood Culture (to exclude concurrent sepsis)
- Serum Bilirubin: increased Grade 1: > age-dependant ULN - 1.5 x ULN; Grade 2 : 1.5-3.0 x ULN; Grade 3: 3.0-10.0 x ULN; Grade 4: >10.0 x ULN
- Transaminases:
 - Increased AST and ALT: Grade 1: > age-dependant ULN – 3.0 x ULN; Grade 2: 3.0-5.0 x ULN; Grade 3: 5.0-20.0 x ULN; Grade 4: > 20.0 x ULN
 - Hepatotoxicity defined as: Grade I: transaminases > age-dependant ULN – 3.0 x ULN; Grade II: 3.0-5.0 x ULN; Grade III: 5.0-20.0 x ULN; Grade IV: >20.0 x ULN

Suspected HSOS: Cefalo et al [20] considered some combinations of haemoglobin, leukocytes and platelets as possibly related to HSOS. A thrombocytopenia level of at least Grade III combined with a normal or Grade I leukocytopenia, and an Hb level of either Grade I or II suggested HSOS. A transaminitis of at least Grade II was considered as indicative of a liver disease of uncertain kind. When the blood results were suggestive, the patient was considered to have a “suspected” episode of HSOS.

Where necessary, viral studies were performed to exclude other causes of liver dysfunction (CMV, EBV, Hepatitis studies). Serum albumin levels as well as INR/PTT levels assisted in identification of liver dysfunction.

3.4.3 Diagnosis of Malnutrition (WHO International Growth Curves)

- WHO Anthro and Anthro Plus Calculators were used for accurate Z-scores

- Weight (Low-weight-for-age): Z-score <-2: underweight; Z-score <-3: severely underweight
- Height (Low height-for-age): Z-score <-2: stunted; Z-score <-3: severely stunted
- <5yrs: Low-weight-for-height: Z-score <-2: moderate malnutrition/wasted; Z-score <-3: severe malnutrition/ severely wasted
- >5yrs: Low BMI-for –age: Z-score <-2: wasted; Z-score <-3: severely wasted

Radiology assisted in correcting body weight for tumour mass (body weight – estimated tumour weight). Tumour size determined using the formula: volume (ml) = length (cm) x width (cm) x height (cm) x 0.523. The weight of 1 litre of tumour as measured by CT equated to 1kg.

Laboratory (as an indication for micronutrient deficiency): Calcium, Magnesium, Phosphate (CMP); Serum Albumin (done at diagnosis of WT and again at diagnosis of HSOS).

A data collection sheet was designed to record the above variables (Appendix 4).

3.5 Data Analysis

Data from the questionnaire was coded and entered into the MS Excel 2007 database and analysed by the STATA 10.0 software. A descriptive analysis was carried out to determine the risk of HSOS. HSOS was identified using the McDonalds criteria (at least two of the following: painful hepatomegaly [$>3\text{cm}$], weight gain [$>5\%$] and/or ascites and hyperbilirubinaemia of $>2\text{mg/dL}$). Chi-square test and Fischer's exact test was used to examine the association between categorical values (gender, laterality, tumour stage, histology, ACD dose, irradiation [including site of administration], jaundice, hepatomegaly, ascites, weight gain and viral serology). The Student's t-test was used to

test continuous variables (age, anthropometry, laboratory results). All assumptions were tested. The Kruskal Wallis test was used for variables that are continuous but that did not obey all the assumptions. The logistic regression model and odds ratio was used to describe the strength of the association of these variables versus HSOS. All estimates were reported with 95% Confidence Intervals. Logistic equation (where P is the probability of the outcome and β_0 is a constant):

$$\log\left(\frac{P}{1-P}\right) = \beta_0 + \beta_{\text{age}} + \beta_{\text{tumour laterality}} + \beta_{\text{irradiation}} + \beta_{\text{serum albumin level}}$$

All statistical analyses were done by the author after explanation and demonstration by a statistician.

3.6 Ethical Clearance

Ethical clearance was obtained from the Ethics Committee for Research on Human Subjects (Medical) of the University of Witwatersrand (Number M120220).

3.7 Study Limitations

This is a retrospective study of a relatively rare phenomenon in a fairly small cohort which limits the evaluation of the risk factors.

Estimation of tumour burden from the CT scans was done using values provided by different radiologists over the years, and not by a single dedicated radiologist. Also, these values were not always provided.

Patients were weighed by different nurses in the unit thus accuracy cannot be guaranteed. They were also not weighed on a daily basis during the presentation of HSOS, thus making determination of significant weight gain difficult.

4.0 RESULTS

The following tables show the variable analysis between the 2 groups of patients, and univariate P values as measured by the Pearson Chi-square and Student's t-test/ Kruskal Wallis test. Where continuous variables were not normally distributed, they were described as median and range. Categorical values have been described as proportions. A logistic regression model was used to analyse the known risk factors. The STATA 10.0 statistical package was used.

4.1 Prevalence of HSOS

Table 4.1 Prevalence of HSOS

HSOS		
Present N (%)	Not Present N (%)	Total N (%)
19 (23)	63 (77)	82 (100)

82 patients were enrolled in the study. Of those, 19 (23%) developed HSOS during the treatment period and 63 (72%) did not develop HSOS, as diagnosed using McDonalds criteria.

4.2 Episodes of HSOS

Table 4.2 Episodes of HSOS

McDonalds Criteria	HSOS	
	First Episode N (%)	Second Episode N (%)
Fulfilled	14 (61)	7 (64)
Not Fulfilled	9 (39)	4 (36)
Total	23	11

Of the 19 patients who developed true HSOS, there were 21 episodes amongst them (2 patients developed 2 episodes of true HSOS). 14 of these episodes were first presentation,

and 7 were 2nd presentation, i.e.: 2 patients developed a second episode of true HSOS whilst 5 developed true HSOS after an initial presentation of suspected HSOS.

There were 13 suspected episodes of HSOS amongst 12 patients; 9 were initial presentations (5 of which went onto develop an episode of true HSOS at a later stage) and 4 were 2nd presentations (1 patient had 2 suspected episodes of HSOS, 3 had had a previous episode of true HSOS). Of these 13 suspected episodes, there were 4 patients whom did not develop a true case of HSOS at all (i.e.: neither a first nor second episode was ever confirmed as true HSOS).

4.3 Patient Characteristics

Table 4.3 Patient Characteristics

Patient Characteristics	True HSOS	Suspected HSOS
Time to HSOS days median [IQR]	158 [81- 186]	126 [33- 165]
When HSOS Developed Pre-op N (%) Post-op N (%)	5 (24) 16 (76)	3 (23) 10 (77)
Week of chemotherapy Pre-op week median [IQR] Post-op week mean [SD]	6 [5- 6] 8 [4]	4 [2- 6] 8 [5]
Total dose Actinomycin D (µg/kg) mean [SD]	274 [134]	255 [147]
Weight-for-age Z Score mean [SD] Normal N (%) Underweight N (%) Severely underweight N (%)	-1.38 [0.95] 14 (66.7) 6 (28.5) 1 (4.8)	-0.89 [0.75] 13 (100) 0 (0) 0 (0)
Weight-for-height Z Score mean [SD] Normal N (%) Wasted N (%)	-0.6 [1.11] 17 (94.4) 1 (5.6)	-0.08 [1.08] 11 (92) 1 (8)
BMI-for-age Z Score mean [SD] Normal N (%) Wasted N (%)	-0.64 [1.22] 19 (90.5) 2 (9.5)	0.01 [1.11] 12 (92) 1 (8)
Hepatomegaly >3cm Yes N (%) No N (%) Size cm median [IQR]	21 (100) 0 (0) 6 [4- 6]	9 (69) 4 (31) 4 [3- 6]

Ascites		
Yes N (%)	5 (24)	0 (0)
No N (%)	16 (76)	13 (100)
Weight gain >5%		
Yes N (%)	20 (95)	1 (8)
No N (%)	1 (5)	12 (92)
% gain median [IQR]	8.9 [6.9- 12.5]	1.2 [0- 2]
Hyperbilirub >2mg/dL		
Yes N (%)	3 (14)	0 (0)
No N (%)	18 (86)	13 (100)
Serum level median [IQR]	0.82 [0.47- 1.17]	0.7 [0.47- 0.82]
Normal N (%)	16 (76)	13 (100)
Grade 1 N (%)	1 (5)	(0)
Grade 2 N (%)	4 (19)	(0)
White Cells		
Count x10 ⁹ /L median [IQR]	2.5 [0.7- 4.5]	2.8 [1.7- 3.6]
Normal N (%)	4 (19)	0 (0)
Grade 1 N (%)	6 (28.6)	4 (31)
Grade 2 N (%)	3 (14.3)	5 (38.5)
Grade 3 N (%)	2 (9.5)	3 (23)
Grade 4 N (%)	6 (28.6)	1 (7.5)
Haemoglobin		
Level g/dL mean [SD]	7.1 [1.4]	8.3 [1.5]
Normal	0 (0)	1 (7.7)
Grade 1 N (%)	1 (4.8)	1 (7.7)
Grade 2 N (%)	6 (28.6)	7 (54)
Grade 3 N (%)	5 (23.8)	3 (23)
Grade 4 N (%)	9 (42.8)	1 (7.7)
Platelets		
Count x 10 ⁹ /L median [IQR]	20 [9-36]	28 [14- 35]
Normal N (%)	1 (4.8)	0 (0)
Grade 1 N (%)	2 (9.5)	0 (0)
Grade 2 N (%)	1 (4.8)	1 (7.5)
Grade 3 N (%)	3 (14.3)	7 (54)
Grade 4 N (%)	14 (66.7)	5 (38.5)
AST		
Level median [IQR]	134 [72-372]	150 [126 -320]
Normal N (%)	1 (5)	0 (0)
Grade 1 N (%)	10 (50)	8 (61.5)
Grade 2 N (%)	2 (10)	2 (15.5)
Grade 3 N (%)	5 (25)	1 (7.5)
Grade 4 N (%)	2 (10)	2 (15.5)
ALT		
Level median [IQR]	88 [32- 252]	127 [90- 222]
Normal N (%)	8 (40)	1 (8)
Grade 1 N (%)	4 (20)	6 (46)
Grade 2 N (%)	2 (10)	3 (23)
Grade 3 N (%)	5 (25)	2 (15)
Grade 4 N (%)	1 (5)	1 (8)
Grade Transaminitis		
Normal N (%)	1 (5)	0 (0)
Grade 1 N (%)	10 (50)	6 (46)
Grade 2 N (%)	0 (0)	3 (23)
Grade 3 N (%)	7 (35)	2 (15.5)

Grade 4 N (%)	2 (10)	2 (15.5)
INR		
Level median [IQR]	1.17 [1.1- 1.25]	1.05 [0.98- 1.21]
Normal N (%)	9 (53)	9 (75)
Grade 1 N (%)	7 (41)	2 (17)
Grade 2 N (%)	1 (6)	0 (0)
Grade 3 N (%)	0 (0)	1 (8)
PTT		
Level median [IQR]	49.8 [38- 60.1]	38.8 [33.9- 45.5]
Normal N (%)	5 (29.4)	8 (67)
Grade 1 N (%)	10 (58.8)	3 (25)
Grade 2 N (%)	2 (11.8)	1 (8)
D Dimers		
Level median [IQR]	3.6 [0.36- 7.15]	0.66 [0.45- 1.65]
Fibrinogen		
Level median [IQR]	4.68 [3.7- 5.7]	4.4 [4.1- 9.2]
Albumin		
Level median [IQR]	38 [32-39]	37 [35-38]
Normal N (%)	15 (71.5)	11 (85)
Grade 1 N (%)	4 (19)	1 (7.5)
Grade 2 N (%)	2 (9.5)	1 (7.5)
Calcium		
Level mean [SD]	2.2 [0.16]	2.1 [0.21]
Normal N (%)	17 (81)	8 (67)
Grade 1 N (%)	2 (9.5)	1 (8)
Grade 2 N (%)	2 (9.5)	2 (17)
Grade 3 N (%)	0 (0)	1 (8)
Magnesium		
Level median [IQR]	0.75 [0.73- 0.78]	0.76 [0.71- 0.81]
Normal N (%)	19 (90.5)	9 (75)
Grade 1 N (%)	2 (9.5)	1 (8.3)
Grade 2 N (%)	0 (0)	1 (8.3)
Grade 3 N (%)	0 (0)	1 (8.3)
Phosphate		
Level mean [SD]	0.96 [0.36]	1.03 [0.4]
Normal N (%)	7 (33.3)	5 (42)
Grade 1 N (%)	8 (38.1)	4 (33)
Grade 2 N (%)	2 (9.5)	2 (17)
Grade 3 N (%)	4 (19.1)	1 (8)
Sepsis		
Fever		
Yes N (%)	12 (57)	7 (54)
No N (%)	9 (3)	6 (46)
CRP		
Level median [IQR]	72 [21- 115]	31 [20- 94]
Normal N (%)	4 (22)	2 (15)
Increased N (%)	14 (78)	11 (85)
Blood Culture		
Positive N (%)	6 (30)	4 (31)
Negative N (%)	14 (70)	9 (69)
Outcomes		
Resolved N (%)	20 (95)	12 (92)
Death N (%)	1 (5)	1 (8)

Treatment		
FFP mean N [SD]	5 [3]	3 [2]
PLT mean N [SD]	3 [1]	2 [1]
VIT K mean N [SD]	4 [2]	4 [3]
SIOP Protocol Adjustments		
Chemo stopped		
Yes N (%)	16 (76)	2 (15)
No N (%)	4 (19)	10 (77)
Death N (%)	1 (5)	1 (8)
Restarted weeks median [IQR]	3 [2-4]	2 [1- 2]
Dose adjusted		
Yes N (%)	9 (43)	5 (38)
No N (%)	9 (43)	5 (38)
RIP N (%)	1 (4.5)	1 (8)
Changed Adriamycin N (%)	2 (9.5)	1 (8)
ACD stopped N (%)	0 (0)	1 (8)
Dose		
25% N (%)	1 (11)	0 (0)
33% N (%)	0 (0)	1 (20)
50% N (%)	7 (78)	2 (40)
75% N (%)	1 (11)	2 (40)
Resolution days		
Liver Enzymes median [IQR]	10 [2-40]	10 [4-14]
Platelet Count median [IQR]	7 [4-23]	5 [3- 7]
Hepatomegaly median [IQR]	30 [15- 55]	6 [0- 19]

Table 5 shows the differences between the episodes that fulfilled McDonald's criteria and those that were suspected cases of HSOS. Not much difference is noted except in the number of patients that developed a significant hepatomegaly (100% vs. 69%), as well as the detection of significant weight gain (95% vs. 8%) and ascites (24% vs. 0%). This is expected by definition. By commenting on episodes rather patients, anthropometrical abnormalities could be overestimated i.e.: there were 7 episodes (not 7 patients) classified as underweight in the true HSOS group.

4.4 Potential risk Factors

Table 4.4 Potential Risk Factors

Factor	HSOS		P value	Odds Ratio (95% CI)
	Present N (%)	Not Present N (%)		
Age months median [IQR]	37 [18-48]	42 [22-64]	0.24	0.98 (0.96- 1.0)

Gender			0.25	
Male	8 (42)	36 (57)		
Female	11 (58)	27 (43)		
Tumour Laterality			0.73	0.65 (0.21- 1.9)
Right	9 (47)	24 (38)		
Left	8 (42)	33 (52)		
Bilateral	2 (11)	6 (10)		
Tumour size grams median [IQR]	870 [497- 1300]	890 [472- 1240]	0.72	
Tumour Stage			0.3	
I	2 (11)	11 (19)		
II	3 (17)	14 (24)		
III	7 (39)	12 (20)		
IV	4 (22)	18 (31)		
V (I)	1 (5.5)	2 (3)		
V(III)	0 (0)	2 (3)		
V(IV)	1 (5.5)	0 (0)		
Histology Risk Group			0.6	
Low	3 (16.5)	6 (10)		
Intermediate	14 (78)	47 (78)		
High	1 (5.5)	7 (12)		
Histological Subtype			0.4	
Mixed	13 (72)	45 (75)		
Blastemal predominant	1 (5.5)	3 (5)		
Diffuse Anaplasia	0 (0)	3 (5)		
Cystic	0 (0)	2 (3)		
Completely necrotic	3 (17)	4 (7)		
Epithelial predominant	0 (0)	2 (3)		
Focal Anaplasia	1 (5.5)	0 (0)		
Stromal predominant	0 (0)	1 (2)		
ACD Dose			0.8	
15µg/kg	16 (84)	56 (89)		
50% dose	0 (0)	1 (2)		
75% dose	2 (11)	4 (6)		
0.45mg/m ²	1 (5)	2 (3)		
SIOP Protocol			0.5	
Adjusted	6 (32)	25 (40)		
Not adjusted	13 (68)	38 (60)		
Irradiation			0.5	0.5 (0.25- 1.98)
Yes	11 (58)	31 (49)		
No	8 (42)	32 (51)		
Dose Gy [IQR]	12 [10.8-20]	10.8 [10.8-12]	0.68 (Dose)	

Irradiation Site			0.86	
Chest	6 (27)	13 (28)		
Abdomen	5 (23)	16 (35)		
Right Flank	5 (23)	6 (13)		
Left Flank	3 (13.5)	5 (11)		
IVC	2 (9)	3 (6.5)		
Liver	1 (4.5)	3 (6.5)		
Abdominal irradiation			0.2	
Yes	11 (100)	26 (87)		
No	0 (0)	4 (13)		
Admission Serum Albumin				
Level mean [SD]	35 [5]	39 [6]	0.02 (level)	0.9
Normal	9 (47)	46 (73)	0.09 (grade)	(0.83 – 0.99)
Grade 1	8 (42)	12 (19)		
Grade 2	2 (11)	5 (8)		
Admission Serum Calcium				
Level mean [SD]	2.38 [0.12]	2.36 [0.23]	0.76 (level)	
Normal	18 (100)	60 (95.2)	0.83 (grade)	
Grade 1	0 (0)	1 (1.6)		
Grade 2	0 (0)	1 (1.6)		
Grade 4	0 (0)	1 (1.6)		
Admission Serum Magnesium				
Level mean [SD]	0.95 [0.26]	0.92 [0.18]	0.67 (level)	
Normal	17 (94.5)	62 (98)	0.15 (grade)	
Grade 1	1 (5.5)	0 (0)		
Grade 2	0 (0)	1 (2)		
Admission Serum Phosphate				
Level mean [SD]	1.45 [0.25]	1.55 [0.3]	0.19 (level)	
Normal	16 (89)	61 (97)	0.15 (grade)	
Grade 1	2 (11)	1 (1.5)		
Grade 2	0 (0)	1 (1.5)		

On the univariate analysis age, gender, tumour laterality, tumour size, tumour stage, histology (risk group and subtype), Actinomycin D Dose, completion of the SIOP Protocol, irradiation (dose and site), and admission serum Calcium, Magnesium and Phosphate levels did not show a statistically significant difference between the group of patients affected by HSOS and the group not affected.

There was a statistical significance between the 2 groups (P value 0.02) with regards to the mean serum albumin level, with the affected group showing lower admission serum albumin levels.

The logistic regression model showed the following:

- Age: for every 1 month increase in age, the odds of developing HSOS decreased by 0.02 (2%)
- Tumour laterality: The odds of developing HSOS decreased by 0.35 (35%) in patients with a left sided tumour. However the line of no effect is crossed and the Confidence Interval is wide
- Irradiation: The odds of a patient developing HSOS after irradiation increased by 0.5 (50%). However the line of no effect is crossed and the Confidence Interval is wide
- Serum albumin level: For every unit increase in the albumin level, the odds of developing HSOS decreased by 0.1 (1%)

Tumour size was calculated using, where available, measurements estimated from abdominal CT scans. Where a child did not receive pre-operative chemotherapy, tumour weight at histology post-nephrectomy was used. This value was only available for 5 of the 19 affected patients, and 33 of the 63 unaffected patients.

There were 5 patients who died towards the end of their preoperative chemotherapy course, thus were not assigned a tumour stage. 4 patients died before nephrectomy and thus before accurate histological risk group and subtype could be available.

Overall, the Actinomycin D dose was adjusted to 50% in 1 patient who was 8 months old. 75% of the dose was given to 6 patients- 3 who were less than 12 months of age, and 3

who had weights below 12kg. 3 patients followed the previous SIOP- protocol and had received an Actinomycin D dose of 0.45mg/m². Of the 19 patients who developed HSOS, 13 followed the recommended SIOP-9 nephroblastoma protocol to completion. The remaining patients had an adjustment made to the original protocol. 1 had 2 courses of preoperative chemotherapy, 1 had no preoperative chemotherapy, and 1 died at the end of preoperative chemotherapy, the option to palliate was made for 1 patient after week 8 of postoperative chemotherapy, and 2 patients were changed to a different protocol during postoperative chemotherapy following poor treatment response.

Of the 63 patients that did not develop HSOS, 38 followed the recommended SIOP-9 nephroblastoma protocol to completion. The remaining 25 patients had an adjustment made to the original protocol. 1 patient had 2 courses of preoperative chemotherapy, 9 had no preoperative chemotherapy, 1 only had 3 weeks preoperative chemotherapy after which tumour rupture occurred requiring an urgent nephrectomy, 8 were changed to a different protocol postoperatively, 3 died at the end of preoperative chemotherapy, 1 was transferred to another institution after 2 weeks of postoperative chemotherapy, 1 patient defaulted therapy after 4 weeks postoperative chemotherapy, and 1 patient had 2 courses of preoperative chemotherapy and was also changed to a high risk protocol postoperatively after histology was found to be of a high risk subtype.

Of the 42 patients that received irradiation, 6 areas were irradiated amongst them (chest, abdomen, right flank, left flank, IVC and liver). Patients had different combinations of areas irradiated (1 patient's irradiation site was unknown). All 11 affected patients that received irradiation had irradiation to an area of the abdomen. Whether the different areas were analysed separately or whether they were grouped into abdominal versus non-abdominal irradiation, a statistical significance was not shown in the development of HSOS.

In the group that developed HSOS, 1 patient's serum Calcium, Magnesium and Phosphate level was unknown.

4.5 Anthropometry

Table 4.5: Anthropometry

Anthropometry	HSOS		P Value
	Present N (%)	Not Present N (%)	
Weight-for-age uncorrected			
Z Score mean [SD]	-0.28 [0.72]	-0.62 [1.06]	0.2 (Z Score)
Normal	19 (100)	54 (91.5)	0.42 (Classification)
Underweight	0 (0)	4 (7)	
Severely underweight	0 (0)	1 (1.5)	
Weight- for-age corrected			
Z Score mean [SD]	-1.25 [1.02]	-1.34 [1.33]	0.88 (Z Score)
Normal	4 (80)	24 (77.5)	0.4 (Classification)
Underweight	1 (20)	2 (6.5)	
Severely underweight	0 (0)	5 (16)	
Height-for-age			
Z Score mean [SD]	-1.05 [1.2]	-1.13 [1.26]	0.81 (Z Score)
Normal	15 (79)	52 (82.5)	0.92 (Classification)
Stunted	2 (10.5)	6 (9.5)	
Severely stunted	2 (10.5)	5 (8)	
Weight-for-height uncorrected			
Z Score median [IQR]	0.48 [0.21- 0.76]	-0.05 [-0.55 – 1.03]	0.3 (Z Score)
Normal	17 (100)	40 (87)	0.48 (Classification)
Wasted	0 (0)	1 (2)	
Severely wasted	0 (0)	2 (4)	
Overweight	0 (0)	3 (7)	
Weight-for-height corrected			
Z Score median [IQR]	-0.9 [-1.1- 0.3]	-0.49 [-1.67- 0.36]	0.8 (Z Score)
Normal	5 (100)	20 (80)	0.55 (Classification)
Wasted	0 (0)	2 (8)	
Severely wasted	0 (0)	3 (12)	
BMI-for-age uncorrected			
Z Score mean [SD]	0.53 [0.7]	0.2 [1.41]	0.34 (Z Score)
Normal	19 (100)	55 (87.5)	0.6 (Classification)
Wasted	0 (0)	1 (1.5)	
Severely wasted	0 (0)	1 (1.5)	
Overweight/obese	0 (0)	6 (9.5)	
BMI-for-age corrected			
Z Score median [IQR]	-0.76 [-1.05- 0.13]	-0.16 [-1.35- 0.51]	0.5 (Z Score)
Normal	5 (100)	28 (85)	0.65 (Classification)

Wasted	0 (0)	1 (3)	
Severely wasted	0 (0)	4 (12)	
Weight-for-age Post-nephrectomy			
Z Score mean [SD]	-1.16 [1.1]	-1.38 [1.03]	0.9 (Z Score)
Normal	13 (72)	38 (72)	0.7 (Classification)
Underweight	5 (28)	13 (24.5)	
Severely underweight	0 (0)	2 (3.5)	
Weight-for-height Post-nephrectomy			
Z Score median [ISQ]	-0.72 [-1.41 - 0.14]	-0.72 [-1.56 - 0.16]	0.87 (Z Score)
Normal	14 (87.5)	33 (82.5)	0.52 (Classification)
Wasted	2 (12.5)	4 (10)	
Severely wasted	0 (0)	3 (7.5)	
BMI Post- nephrectomy			
Z Score mean [SD]	-0.57 [1.09]	-0.83 [1.5]	0.48 (Z Score)
Normal	16 (89)	47 (82.5)	0.68 (Classification)
Wasted	2 (11)	8 (14)	
Severely wasted	0 (0)	2 (3.5)	
Weight-for-age prior to Irradiation			
Z Score mean [SD]	-1.41 [0.8]	-1.47 [0.95]	0.85 (Z Score)
Normal	8 (67)	20 (71.5)	0.5 (Classification)
Underweight	4 (33)	6 (21.5)	
Severely underweight	0 (0)	2 (7)	
Weight-for-height prior to Irradiation			
Z Score median [ISQ]	-0.88 [-1.08 - -0.53]	-1.63 [-2.3 - -0.15]	0.58 (Z Score)
Normal	9 (90)	11 (58)	0.2 (Classification)
Wasted	1 (10)	7 (37)	
Severely wasted	0 (0)	1 (5)	
BMI-for-age prior to Irradiation			
Z Score median [ISQ]	-0.78 [-1.46 - -0.4]	-1.05 [-2.14 - -0.03]	0.82 (Z Score)
Normal	10 (83)	21 (70)	0.61 (Classification)
Wasted	2 (17)	8 (27)	
Severely wasted	0 (0)	1 (3)	

Where an anthropometrical variable is described as ‘uncorrected’ it describes a patient weight that has not been corrected for tumour volume. The WHO Anthro Calculator does not calculate weight-for-age in children over 10 years of age nor weight-for-height in children older than 5 years. There was no statistical significance between the 2 groups on analysis of their anthropometry.

5.0 DISCUSSION

5.1 Prevalence

Our data reveals that of the 82 patients diagnosed with Wilms Tumour in the study period, 19 (23%) developed HSOS. There were 4 patients who were suspected of having HSOS; however they did not go on to develop it. If they were to be grouped together, it would mean that 23 (28%) patients had varying degrees of hepatotoxicity.

A study by Bisogno et al. showed that 64 (12.5%) out of 511 patients had evidence of various degrees of hepatotoxicity, of which 41 (8%) showed clinical features compatible with HSOS [21]. Ludwig et al. showed that 72 (15%) of their 481 patients suffered at least 1 episode of hepatotoxicity and the criteria for HSOS were satisfied in 23 (4.8%) patients [10].

Our study shows a much higher prevalence of both true and suspected HSOS.

5.2 Patient Characteristics

In our study, the patient characteristics at the diagnosis of HSOS, is a description of the 21 episodes recorded rather than of the 19 patients affected. The characteristics of the suspected episodes are placed alongside for comparison.

5.2.1 Timing

The median number of days to the development of HSOS was 158 [81- 186]. 5 (24%) episodes of HSOS developed during preoperative chemotherapy and 16 (76%) developed post-operatively. Preoperatively, the median week in which HSOS developed was during week 6 [5- 6], and during week 8 [SD 4] when developed post-operatively. The median total accumulative dose of ACD at diagnosis of HSOS was 274 μ g/kg [134].

The suspected cases of HSOS developed slightly earlier, and after slightly lower doses of ACD than the true cases. This may show that suspected cases were acted on immediately rather than by waiting for them to progress to true cases of HSOS.

5.2.2 Anthropometry

Considering that a poorer nutritional status [22] is considered a risk factor for HSOS and increases the risk for toxicity, anthropometry as well as the patients' serum albumin, calcium, magnesium and phosphate levels were measured at diagnosis of HSOS. The weight-for-height showed that there was only 1 episode where a patient was classified as wasted; the serum albumin level was normal in 15 episodes with a median level of 38 [32-39]; the serum calcium level was normal in 17 episodes with a mean serum level of 2.2 [0.16]; the serum magnesium level was normal in 19 episodes with a median serum level of 0.75 [0.73- 0.78]; the serum phosphate level was only normal in 7 episodes with a mean serum level of 0.96 [0.36]- most of the episodes were classified as a Grade I hypophosphataemia. Similar results were seen in the suspected group.

Since weight gain and/or ascites is one of the McDonald's criteria in the diagnosis of HSOS, assessment of weight at this point may mask an underlying nutritional deficit.

5.2.3 Clinical

HSOS is primarily a clinical diagnosis, based on criteria defined by McDonald et al. [21]. i.e.: at least 2 of the following is required: jaundice or bilirubin >2mg/dL, painful hepatomegaly (>3cm below costal margin) and/ or weight gain (>5%) with or without ascites [12]. These symptoms however, may only arise in advanced stages of HSOS [14].

In our study, patients were not weighed on a daily basis, thus documentation of the weight gain was difficult. The identification of ascites and measurement of the hepatomegaly was

made by different clinicians over the years. Thus McDonald's criteria were subject to a practitioners' clinical acumen.

In our study, all the true episodes of HSOS presented with a significant hepatomegaly (median size of 6cm [4- 6]). Only 5 (24%) had documented ascites, and 20 (95%) had a weight gain of >5%. Of interest, our suspected cases (i.e.: not fulfilling McDonald's criteria) were largely without ascites and/or weight gain. Whether this was because the unit had not allowed them to progress to a more severe episode of HSOS or whether it was missed by the clinician were 2 considerations. Hyperbilirubinaemia was only detected in 3 (14%) episodes, with a median level of 0.82mg/dL [0.47- 1.17].

5.2.4 Biochemical

Various studies have tried to look at other biochemical markers (excluding hyperbilirubinaemia) in assisting with the diagnosis of HSOS [12]. Increase in transaminases is not necessarily characteristic of HSOS [21]. Alterations of the haemostatic profile (thrombocytopenia, deranged clotting parameters) is not specific enough and is merely indicative of endothelial damage and/or impaired liver function, which may occur in other therapy-related complications [12].

In our study we looked at:

- White cell count (WCC): median count of $2.5 \times 10^9/L$ [0.7- 4.5]; WCC was normal in only 4 episodes; the commonest grade of leucopenia was Grade I and IV
- Haemoglobin (Hb): The mean Hb was 7.1g/dL [SD 1.4] with the commonest grade of anaemia being Grade IV. Only 1 episode showed a normal Hb level

- Platelets (Plts): the median Plt count was $20 \times 10^9/L$ [9- 36] with the commonest grade of thrombocytopenia being Grade IV. Only 1 episode showed a normal platelet count
- Transaminases (AST/ALT): median AST level was 134 [72- 372] (1 episode had normal levels) and ALT level was 88 [32- 252] (8 episodes had normal levels). The commonest presentation was of a Grade I transaminitis
- INR/PTT: The median INR level was 1.17 [1.1- 1.25] (9 episodes had normal levels), and PTT level 49.8 [38- 60.1] (5 episodes had normal levels); the commonest derangement was a Grade I level for both parameters
- D-dimers, fibrinogen: The median ranges were raised in both parameters. D-dimers: 3.6 [0.36- 7.15]; fibrinogen 4.68 [3.7- 5.7]

The suspected group showed similar results.

5.2.5 Sepsis

By causing endothelial damage, sepsis may cause biochemical and clinical changes synonymous with HSOS. A patient with HSOS may well also have a concurrent sepsis, thus confusing the diagnosis. In our study, 12 episodes had documented fever, 14 had an elevated CRP level, however only 6 had positive blood cultures. The suspected group showed similar results.

5.3 Potential risk Factors

5.3.1 Age

Although not statistically significant, probably as a result of a small sample size, our affected patients are younger, with a median age of 37 months [18- 48] as compared to the unaffected group with a median age of 42 months [22- 64]. The logistic regression model

shows that for every 1 month increase in age, the odds of developing HSOS decrease by 0.02 (2%).

Age is a well documented risk factor, in that the younger the patient, the higher the risk of developing HSOS [12, 14]. Ludwig et al. again showed that affected patients were significantly younger (P value 0.0003).

Another point to note is that patients less than 12 months of age will have their dose of ACD adjusted. This again might explain the insignificant statistical significance detected between our 2 groups.

5.3.2 Lower body weight and nutritional status

Patients of a lower body weight are considered to be more at risk of developing HSOS [13, 14, 21]. Anthropometrical measurements taken from our patients at various points during their course of chemotherapy (on admission, post nephrectomy, at irradiation, on diagnosis of HSOS) do not show any significance between the 2 groups.

Malnutrition can affect tolerance of therapy, increase the risk of co-morbidities, and influence the overall survival [22]. However, weight by itself is not a very sensitive or reliable indicator of nutritional status and in a small child a large tumour may influence body weight and therefore anthropometric classification (17). An attempt to correct body weight for tumour size was made, however the abdominal CT measurements was only available for 36 of the 82 patients. Perhaps other measures such as arm anthropometry would have been of more assistance.

Biochemical tests have limited usefulness in the determination of nutritional status. Some studies have shown prealbumin levels to be of significance in malnourished children [22]. Our study looked at serum albumin levels; however it is an acute-phase reactant, therefore, its levels may be altered by other factors, such as fever and infection [21]. Merrit et al [24]

commented that a low serum albumin in the absence of abnormal nutritional parameters is a finding that has been documented previously, and that it is often seen in the face of sepsis. However on admission, patients with WT are not generally ill making these statements irrelevant. A statistical significance is noted between the 2 groups, (P value 0.02), with the affected group showing lower admission serum albumin levels. The logistic regression model shows that for every unit increase in the albumin level, the odds of developing HSOS decrease by 0.1 (1%). Serum calcium, magnesium and phosphate levels were not statistically significant between the 2 groups.

5.3.3 High doses of ACD

Previous SIOP Protocols used a higher dose of ACD and it was only after ACD was recognised as an important risk factor for the development of HSOS that the dose was reduced for patients less than 10kg. This recommendation was then increased to 12kg [10]. Our unit took into consideration patient age and weight, and the ACD dose was adjusted accordingly. The previous SIOP protocol was followed for 3 patients (ACD dose of 0.45mg/m²), of which only one developed HSOS.

Of interest is that 31 of the 82 patients did not follow the SIOP-9 protocol to completion. i.e.: some were changed to a high risk protocol, some received 2 courses of preoperative chemotherapy (e.g.: Stage V patients, where an attempt for maximal tumour shrinkage was made), some had no preoperative chemotherapy (e.g.: Stage I), some defaulted therapy or were transferred to another unit etc. All of this meant fewer patients received full courses of ACD and thus had a lower risk for developing HSOS.

5.3.4 Abdominal Irradiation

Administration of abdominal radiotherapy is a well documented risk factor for the development of HSOS [10, 12, 13, 14]. A study by Bisogno et al. [21] showed that 68 of

their 511 patients underwent radiotherapy. Of the 11 patients with HSOS who had also had irradiation, 10 developed hepatotoxicity either during (2 cases) or after radiotherapy.

Although our data is not statistically significant, the logistic regression model shows that the odds of a patient developing HSOS after irradiation increased by 0.5 (50%). However the line of no effect is crossed and the Confidence Interval is wide. Reasons for an insignificant statistical significance may be due to a small sample size, but also may be explained by our practice of omitting ACD from the SIOP-9 protocol as a protective measure until the irradiation course is completed.

The amount of liver included in the radiotherapy target field as well as the radiation dose received has been implicated in the development of HSOS [21]. In our study, both radiation site and irradiation dose does not show a statistical significance between the 2 groups. Again, it is probably as a result of a small sample size.

5.3.5 Right Sided WT

A right sided Wilms Tumour is a well documented risk factor in the development of HSOS [13, 14, 21]. Our study does not show a statistically significant difference probably as a result of a small sample size. Also, the group with bilateral tumour were grouped separately making the sample size even smaller. The logistic regression model shows that the odds of developing HSOS decreased by 0.35 (35%) in patients with a left sided tumour. However the line of no effect is crossed and the Confidence Interval is wide.

Gender, tumour stage, tumour histology and tumour size are not significant risk factors in our study. There is no documentation to date showing them to be significant [10].

5.4 Outcomes

Considering that HSOS following chemotherapy is of a ‘milder’ form than HSOS following stem cell transplantation, outcomes are usually good [21]. Bisogno et al. showed an overall survival of 94% [21]. In our study, 2 patients demised- 1 following a true case of HSOS and a 2nd following a suspected case of HSOS; the remainder (91%) all had resolution of their symptoms. Liver enzymes usually took a median of 10 days [2- 40] to normalise; platelet count improved after a median of 7 days [4- 23]; the median number of days to reduction of the hepatomegaly to < 3cm was 30 [15- 55].

Following an episode HSOS, chemotherapy would be interrupted and ACD doses adjusted, thus it would be interesting to know the long term outcomes of these patients. In brief, of the 18 patients who developed HSOS and had resolution of their symptoms, there were 5 (3 initially staged as SIOP stage IV, 1 as SIOP stage II and 1 as SIOP stage III) who ultimately relapsed, requiring further cytoreductive therapy, of which 1 demised.

5.4.1 Management

Patients were treated symptomatically, with the administration of fresh frozen plasma (mean of 5 units [SD 3]), platelet infusions (mean of 3 units [SD 1]) and daily Vitamin K therapy (over a mean of 4 days [SD 2]). It was usually stopped once the patient had clinically improved and clotting parameters had normalised. Cesaro et al [12] saw a potential role of defibrotide in the therapy of HSOS however they had a limited number of patients in their study. There are however limited reports on the use of defibrotide [12] and it is currently unavailable in our unit.

5.4.2 Changes in SIOP-9 protocol

Chemotherapy was stopped in 16 (76%) of the episodes (this excluded the patient who died). Chemotherapy was restarted over a median of 3 weeks [2-4]. ACD was changed to Adriamycin in 2 episodes. In the suspected group, ACD was stopped completely in 1 patient, but overall, chemotherapy was not interrupted in 10 (77%) of the cases, perhaps as the episodes of suspected HSOS were not severe.

When restarted, the dose of ACD was adjusted in 9 episodes to: 25% (1 episode), 50% (7 episodes) and 75% (1 episode). Most of them had a gradual increase in the dose of ACD over the next few weeks. One of the suspected cases of HSOS had an initial reduction to 33% of the dose.

Although fewer patients were observed, a study by Cesaro [12] saw chemotherapy being resumed after a median of 16 days [10- 46]; doses of ACD were also reduced (two-thirds in 2 patients, 50% in 1 patient and stopped completely in 1 patient) and then slowly increased after 3- 4 courses of chemotherapy. Studies have shown it unnecessary to withhold chemotherapy after the signs of HSOS have disappeared, however the clinician needs to beware recurrence [21].

6.0 CONCLUSION

This study illustrates a much higher prevalence of HSOS than previously reported. This is found despite the documented risk factors being accounted for, i.e.: patients under 12 months of age and /or with a body weight of less than 12kg had their dose of ACD adjusted; ACD was omitted in patients receiving irradiation and only restarted once the course of irradiation was complete; changes in the SIOP-9 nephroblastoma protocol saw doses of ACD being adjusted from 0.45mg/m² to 15µg/kg.

The most significant result that emerges from this study is the lower levels of serum albumin found in our affected group. This indirectly indicates that malnutrition may have a role to play in the development of HSOS. Anthropometry however is not a significant factor in our study, however a body weight corrected for tumour size in all our patients would have been ideal.

HSOS is a clinical disease based on criteria defined by McDonald et al. These criteria were initially developed to describe HSOS after stem cell transplantation but then adapted to include HSOS following chemotherapy [12]. Seeing that HSOS following chemotherapy is often of a milder form, and that it has a gradual onset, the application of McDonald's criteria is a difficult one: i.e.: waiting for a patient to develop significant hyperbilirubinaemia or significant ascites before being active in its treatment perhaps would not be in the patient's best interests.

Our study attempts to look for other laboratory features that would suggest HSOS. Most patients show varying degrees of leukocytopenia, anaemia, thrombocytopenia, transaminitis and clotting profile abnormalities. However these results could be explained by other factors such as sepsis, liver disease from other causes and even the effects of

chemotherapy itself. Cesaro et al [12] showed plasminogen activator inhibitor type 1 (PAI-1) to be a specific marker of HSOS; however this is not available in our unit.

Our study shows good outcomes and relatively rapid resolution of symptoms of HSOS; however seeing that Wilms Tumours generally has a good prognosis, interest continues in decreasing toxicity as a consequence of its therapy. The use of PAI-1 in assisting in making the diagnosis needs to be considered, taking into account resource limitation in our setting. The risk of malnutrition needs to be explored further; early identification is important and other means such as arm anthropometry and prealbumin levels may be of assistance. Other important aspects which need to be explored are the long term outcomes, considering that treatment is often interrupted and adjusted, as well as long term effects of toxicity.

7.0 APPENDIX 1

SIOP WT 2001 Staging Criteria for Renal Tumours of Childhood

Stage I

- The tumour is limited to kidney or surrounded with a fibrous (pseudo)capsule if outside of the normal contours of the kidney. The renal capsule or pseudocapsule may be infiltrated by the tumour but it does not reach the outer surface
- The tumour may be protruding (“bulging”) into the pelvic system and “dipping” into the ureter but it is not infiltrating their walls
- The vessels or the soft tissues of the renal sinus are not involved
- Intrarenal vessel involvement may be present

Notes: Fine needle aspiration or percutaneous core needle (“tru-cut”) biopsy does not upstage the tumour but the size of the needle gauge should be mentioned to the pathologist. The presence of necrotic tumour or chemotherapy-induced change in the renal sinus and/or within the perirenal fat should not be regarded as a reason for upstaging a tumour providing it is completely excised and does not reach the resection margins

Stage II

- a) Viable tumour penetrates through the renal capsule and/or fibrous pseudocapsule into perirenal fat but is completely resected (resection margins “clear”)
- b) Viable tumour infiltrates the soft tissues of the renal sinus
- c) Viable tumour infiltrates blood and lymphatic vessels of the renal sinus or in the perirenal tissue but it is completely resected
- d) Viable tumour infiltrates the renal pelvic or ureter’s wall
- e) Viable tumour infiltrates adjacent organs or vena cava but it is completely resected

Stage III

- Viable or non-viable tumour extends beyond resection margins
- Any abdominal lymph nodes are involved
- Tumour rupture before or intraoperatively (irrespective of other criteria for staging)
- The tumour has penetrated through the peritoneal surface
- Tumour implants are found on the peritoneal surface
- The tumour thrombi at resection margins of vessels or ureter, are trans-sected or removed piecemeal by surgeon
- The tumour has been surgically biopsied (wedge biopsy) prior to preoperative chemotherapy or surgery

Note: The presence of necrotic tumour or chemotherapy-induced changes in a lymph node or at the resection margins is regarded as proof of previous tumour with microscopic residue and therefore the tumour is assigned stage III (because of the possibility that some viable tumour is left behind in the adjacent lymph node or beyond resection margins)

Stage IV

- Haematogenous metastasis (lung, liver, bone, brain, etc) or lymph node metastases outside the abdomino-pelvic region

Stage V

- Bilateral tumours at diagnosis. Each side should be substaged according to the above criteria

8.0 APPENDIX 2

The Revised International Society of Paediatric Oncology (SIOP) Working

Classification of Renal Tumours of Childhood (2001)

I Low risk tumours <ul style="list-style-type: none">• Mesoblastic nephroma• Cystic partially differentiated nephroblastoma• Nephroblastoma- completely necrotic (following preoperative chemotherapy)
II Intermediate risk tumours <ul style="list-style-type: none">• Nephroblastoma- epithelial type• Nephroblastoma- stromal type• Nephroblastoma- mixed type• Nephroblastoma- regressive type• Nephroblastoma- focal anaplasia type
III High risk tumours <ul style="list-style-type: none">• Nephroblastoma- blastemal type• Nephroblastoma- diffuse anaplasia type• Clear cell sarcoma of the kidney• Rhabdoid tumour of the kidney

9.0 APPENDIX 3

Society of Paediatric Oncology (SIOP) Nephroblastoma Treatment Protocol

Preoperative chemotherapy (Stages I, II and III)	
Week 1	Vincristine 1.5mg/m ² IVI (Day 1) Actinomycin D 15µg/kg/day IVI (Days 1-3)
Week 2	Vincristine 1.5mg/m ² IVI day 1 (Day 1)
Week 3	Vincristine 1.5mg/m ² IVI (Day1) Actinomycin D 15µg/kg/day IVI (Days 1-3)
Week 4	Vincristine 1.5mg/m ² IVI (Day 1)
Week 5	Vincristine 1.5mg/m ² IVI (Day 1) Actinomycin D 15µg/kg/day IVI (Days 1-3)
Week 7	Vincristine 1.5mg/m ² IVI (Day 1) Actinomycin D 15µg/kg/day IVI (Days 1-3)
Week 8	Vincristine 1.5mg/m ² IVI (Day 1)
Week 9	Surgery
Post-operative chemotherapy (Stage I)	
Week 1	Vincristine 1.5mg/m ² IVI (Day 1)
Week 2	Vincristine 1.5mg/m ² IVI (Day 1) Actinomycin D 15µg/kg/day IVI (Days 1-5)
Week 3	Vincristine 1.5mg/m ² IVI (Day 1)
Week 4	Vincristine 1.5mg/m ² IVI (Day 1)
Week 10	Vincristine 1.5mg/m ² IVI (Day 1) Actinomycin D 15µg/kg/day IVI (Days 1-5)
Week 17	Vincristine 1.5mg/m ² IVI (Day 1) Actinomycin D 15µg/kg/day IVI (Days 1-5)
Week 18	Vincristine 1.5mg/m ² IVI (Day 1)
Post-operative chemotherapy (Stage II and III)	
Week 1	Vincristine 1.5mg/m ² IVI (Day 1))
Week 2	Vincristine 1.5mg/m ² IVI (Day 1)) Actinomycin D 15µg/kg/day IVI (Days 1-5)) DXT to abdomen,
Week 3	Vincristine 1.5mg/m ² IVI (Day 1)) Stage II nodes +
Week 4	Vincristine 1.5mg/m ² IVI (Day 1)) and Stage III Adriamycin 30mg/m ² IVI (Day 1))
Week 5	Vincristine 1.5mg/m ² IVI (Day 1)
Week 6	Vincristine 1.5mg/m ² IVI (Day 1) Actinomycin D 15µg/kg/day IVI (Days 1-5)
Week 7	Vincristine 1.5mg/m ² IVI (Day 1)
Week 8	Vincristine 1.5mg/m ² IVI (Day 1) Adriamycin 30mg/m ² IVI (Day 1)
Week 11	Vincristine 1.5mg/m ² IVI (Day 1) Actinomycin D 15µg/kg/day IVI (Days 1-5)
Week 12	Vincristine 1.5mg/m ² IVI (Day 1)
Week 14	Vincristine 1.5mg/m ² IVI (Day 1) Adriamycin 30mg/m ² IVI (Day 1)

Week 15	Vincristine 1.5mg/m ² IVI (Day 1)	
Week 17	Vincristine 1.5mg/m ² IVI (Day 1)	
	Actinomycin D 15µg/kg/day IVI (Days 1-5)	
Week 18	Vincristine 1.5mg/m ² IVI (Day 1)	
Week 20	Vincristine 1.5mg/m ² IVI (Day 1)	
	Adriamycin 30mg/m ² IVI (Day 1)	
Week 21	Vincristine 1.5mg/m ² IVI (Day 1)	
Week 23	Vincristine 1.5mg/m ² IVI (Day 1)	
	Actinomycin D 15µg/kg/day IVI (Days 1-5)	
Week 24	Vincristine 1.5mg/m ² IVI (Day 1)	
Week 26	Vincristine 1.5mg/m ² IVI (Day 1)	
	Adriamycin 30mg/m ² IVI (Day 1)	
Week 27	Vincristine 1.5mg/m ² IVI (Day 1)	
Preoperative chemotherapy (Stage IV)		
Week 0	Vincristine 1.5mg/m ² IVI (Day 1)	
	Adriamycin 30mg/m ² /day IVI (Days 1 and 2)	
	Actinomycin D 15ug/kg/day (Days 1-3)	
Week 1	Vincristine 1.5mg/m ² IVI (Day 1)	
Week 2	Vincristine 1.5mg/m ² IVI (Day 1)	
	Actinomycin D 15ug/kg/day (Days 1-3)	
Week 3	Vincristine 1.5mg/m ² IVI (Day 1)	
Week 4	Vincristine 1.5mg/m ² IVI (Day 1)	
	Adriamycin 30mg/m ² /day IVI (Days 1 and 2)	
	Actinomycin D 15ug/kg/day (Days 1-3)	
Week 5	Vincristine 1.5mg/m ² IVI (Day 1)	
Week 6	Surgery	
Post-operative chemotherapy (Stage IV)		
Week 0	Vincristine 1.5mg/m ² IVI (Day 1))
	Actinomycin D 15µg/kg/day IVI (Days 1-5))
Week 1	Vincristine 1.5mg/m ² IVI (Day 1)) DXT to abdomen
Week 2	Vincristine 1.5mg/m ² IVI (Day 1)) and lungs
Week 3	Vincristine 1.5mg/m ² IVI (Day 1))
	Adriamycin 30mg/m ² IVI (Day 1)	
Week 4	Vincristine 1.5mg/m ² IVI (Day 1)	
Week 5	Vincristine 1.5mg/m ² IVI (Day 1)	
	Actinomycin D 15µg/kg/day IVI (Days 1-5)	
Week 6	Vincristine 1.5mg/m ² IVI (Day 1)	
Week 7	Vincristine 1.5mg/m ² IVI (Day 1)	
	Adriamycin 30mg/m ² IVI (Day 1)	
Week 8	Vincristine 1.5mg/m ² IVI (Day 1)	
Week 10	Vincristine 1.5mg/m ² IVI (Day 1)	
	Actinomycin D 15µg/kg/day IVI (Days 1-5)	
Week 11	Vincristine 1.5mg/m ² IVI (Day 1)	
Week 13	Vincristine 1.5mg/m ² IVI (Day 1)	
	Adriamycin 30mg/m ² IVI (Day 1)	
Week 14	Vincristine 1.5mg/m ² IVI (Day 1)	
Week 16	Vincristine 1.5mg/m ² IVI (Day 1)	
	Actinomycin D 15µg/kg/day IVI (Days 1-5)	

Week 17	Vincristine 1.5mg/m ² IVI (Day 1)
Week 19	Vincristine 1.5mg/m ² IVI (Day 1)
	Adriamycin 30mg/m ² IVI (Day 1)
Week 20	Vincristine 1.5mg/m ² IVI (Day 1)
Week 22	Vincristine 1.5mg/m ² IVI (Day 1)
	Actinomycin D 15µg/kg/day IVI (Days 1-5)
Week 23	Vincristine 1.5mg/m ² IVI (Day 1)
Week 25	Vincristine 1.5mg/m ² IVI (Day 1)
	Adriamycin 30mg/m ² IVI (Day 1)
Week 26	Vincristine 1.5mg/m ² IVI (Day 1)
Week 28	Vincristine 1.5mg/m ² IVI (Day 1)
	Actinomycin D 15µg/kg/day IVI (Days 1-5)
Week 29	Vincristine 1.5mg/m ² IVI (Day 1)
Week 31	Vincristine 1.5mg/m ² IVI (Day 1)
	Adriamycin 30mg/m ² IVI (Day 1)
Week 32	Vincristine 1.5mg/m ² IVI (Day 1)

10.0 APPENDIX 4

Data Collection Sheet

CASE NUMBER			
Age (months)			
Gender (M/F)			
	Uncorrected	Corrected	Post nephrectomy
Weight-for-age + Z Score			
Height-for-age + Z Score		-----	-----
Weight-for-height + Z-score			
BMI-for-age + Z Score			
Laterality (R/L/Bilat)			
Tumour Stage (1-5)			
Histology risk group + subtype			
Tumour Volume (grams)			
Actinomycin D dose			
SIOP protocol adjusted			
Irradiation (Y/N)			
Irradiation site and dose			
Weight at DXT			
	At dx of WT	Dx of HSOS	2nd episode HSOS
Weight gain + percentage	-----		
Time to HSOS days	-----		
Week of chemo + pre/post op	-----		
Total dose ACD	-----		
Jaundice			
Hepatomegaly (cm)			
Ascites			
Fever			
White cell count + grade			
Hb + grade			
Platelets + grade			
AST/ALT + grade			
Grade transaminitis			
Bilirubin + grade			
INR/PTT + grade			
D-dimers + fibrinogen	-----		
Albumin + grade			
CMP + grade			
CRP + Blood culture result	-----		
Viral serology			
Treatment of HSOS	Chemo stopped		

	Adjusted dose		
	Week restarted		
	FFPs (no.)		
	Platelets (no.)		
	Vit K (doses)		
Outcomes: Died (Y/N)	-----		
Resolution (days)	Liver enzymes		
	Platelets		
	Hepatomegally		

11.0 REFERENCES

- 1) Birch JM, Breslow N. Epidemiologic features of Wilms tumor. *Hematol Oncol Clin North Am* 1995 Dec;9(6):1157-1178.
- 2) Stiller CA, Parkin DM. Geographic and ethnic variations in the incidence of childhood cancer. *Br Med Bull* 1996 Oct;52(4):682-703.
- 3) Tournade MF, Com-Nougue C, de Kraker J, Ludwig R, Rey A, Burgers JM, et al. Optimal duration of preoperative therapy in unilateral and nonmetastatic Wilms' tumor in children older than 6 months: results of the Ninth International Society of Pediatric Oncology Wilms' Tumor Trial and Study. *J Clin Oncol* 2001 Jan 15;19(2):488-500.
- 4) United Nations. "The state of the world's children." 2006.
<http://www.unicef.org/sowc06/fullreport/full_report.php> [Accessed 1 Dec 2011].
- 5) Abuidris DO, Elimam ME, Nugud FM, Elgaili EM, Ahmed ME, Arora RS. Wilms tumour in Sudan. *Pediatr Blood Cancer* 2008 Jun;50(6):1135-1137.
- 6) Harif M, Barsaoui S, Benchekroun S, Boccon-Gibod L, Bouhas R, Doumbe P, et al. Treatment of childhood cancer in Africa. Preliminary results of the French-African paediatric oncology group. *Arch Pediatr* 2005 Jun;12(6):851-853.
- 7) Davidson A, Hartley P, Desai F, Daubenton J, Rode H, Millar A. Wilms tumour experience in a South African centre. *Pediatr Blood Cancer* 2006 Apr;46(4):465-471.
- 8) de Kraker J, Graf N, van Tinteren H, Pein F, Sandstedt B, Godzinski J, et al. Reduction of postoperative chemotherapy in children with stage I intermediate-risk and anaplastic Wilms' tumour (SIOP 93-01 trial): a randomised controlled trial. *Lancet* 2004 Oct 2-8;364(9441):1229-1235.

- 9) Corn BW, Goldwein JW, Evans I, D'Angio GJ. Outcomes in low-risk babies treated with half-dose chemotherapy according to the Third National Wilms' Tumor Study. *J Clin Oncol* 1992 Aug;10(8):1305-1309.
- 10) Ludwig R, Weirich A, Abel U, Hofmann W, Graf N, Tournade MF. Hepatotoxicity in patients treated according to the nephroblastoma trial and study SIOP-9/GPOH. *Med Pediatr Oncol* 1999 Nov;33(5):462-469.
- 11) Helmy A. Review article: updates in the pathogenesis and therapy of hepatic sinusoidal obstruction syndrome. *Aliment Pharmacol Ther* 2006 Jan 1;23(1):11-25.
- 12) Cesaro S, Spiller M, Sartori MT, Alaggio R, Peruzzo M, Saggiorato G, et al. Venooclusive disease in pediatric patients affected by Wilms tumor. *Pediatr Blood Cancer* 2011 Aug;57(2):258-261.
- 13) Flentje M, Weirich A, Potter R, Ludwig R. Hepatotoxicity in irradiated nephroblastoma patients during postoperative treatment according to SIOP9/GPOH. *Radiother Oncol* 1994 Jun;31(3):222-228.
- 14) Jagt CT, Zuckermann M, Ten Kate F, Taminiau JA, Dijkgraaf MG, Heij H, et al. Venooclusive disease as a complication of preoperative chemotherapy for Wilms tumor: A clinico-pathological analysis. *Pediatr Blood Cancer* 2009 Dec 15;53(7):1211-1215.
- 15) Israels T, Molyneux EM, Caron HN, Jamali M, Banda K, Bras H, et al. Preoperative chemotherapy for patients with Wilms tumor in Malawi is feasible and efficacious. *Pediatr Blood Cancer* 2009 Oct;53(4):584-589.
- 16) Israels T, van de Wetering MD, Hesselink P, van Geloven N, Caron HN, Molyneux EM. Malnutrition and neutropenia in children treated for Burkitt lymphoma in Malawi. *Pediatr Blood Cancer* 2009 Jul;53(1):47-52.

- 17) Wessels G, Hesselning PB, Van Ommeren KH, Boonstra V. Nutrition, morbidity, and survival in South African children with Wilms' tumor. *Pediatr Hematol Oncol* 1999 Jul-Aug;16(4):321-327.
- 18) Israels T, Borgstein E, Jamali M, de Kraker J, Caron HN, Molyneux EM. Acute malnutrition is common in Malawian patients with a Wilms tumour: A role for peanut butter. *Pediatr Blood Cancer* 2009 Dec 15;53(7):1221-1226.
- 19) Sartori MT, Spiezia L, Cesaro S, Messina C, Paris M, Pillon M, et al. Role of fibrinolytic and clotting parameters in the diagnosis of liver veno-occlusive disease after hematopoietic stem cell transplantation in a pediatric population. *Thromb Haemost* 2005 Apr;93(4):682-689.
- 20) Cefalo MG, Maurizi P, Arlotta A, Scalzone M, Attina G, Ruggiero A, et al. Hepatic veno-occlusive disease: a chemotherapy-related toxicity in children with malignancies. *Paediatr Drugs* 2010 Oct 1;12(5):277-284.
- 21) Bisogno G, de Kraker J, Weirich A, Masiero L, Ludwig R, Tournade MF, et al. Veno-occlusive disease of the liver in children treated for Wilms tumor. *Med Pediatr Oncol* 1997 Oct;29(4):245-251.
- 22) Sala A, Pencharz P, Barr RD. Children, cancer, and nutrition--A dynamic triangle in review. *Cancer* 2004 Feb 15;100(4):677-687.
- 23) McDonald GB, Sharma P, Matthews DE, Shulman HM, Thomas ED. Venocclusive disease of the liver after bone marrow transplantation: diagnosis, incidence, and predisposing factors. *Hepatology* 1984 Jan-Feb;4(1):116-122.
- 24) Merritt RJ, Kalsch M, Roux LD, Ashley-Mills J, Siegel SS. Significance of hypoalbuminemia in pediatric oncology patients--malnutrition or infection? *JPEN J Parenter Enteral Nutr* 1985 May-Jun;9(3):303-306.