Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/x9gzvz57

CORRELATION BETWEEN PRETEXT STAGING AND POST OPERATIVE OUTCOME OF HEPATIC RESECTION IN CHILDREN WITH HEPATOBLASTOMA ACCORDING TO SIOPEL PROTOCOL

Dr. Mahfuz Alam Khan[1*], Prof A.K.M. Zahid Hossain[2], Dr. AKM Anwar Hossain[3], Dr. Abdullah All Mahmud[4], Dr. Umme Habiba Dilshad Munmun[5], Dr. Syeda Sushmita Zafar[6], Dr. Tanjirul Islam[7], Dr. Sheikh Jakia Billah[8]

[1*]Resident Surgeon, Department of Paediatric Surgery, Mymensingh Medical College Hospital, Mymensingh, Bangladesh, email: ratulszmc13@gmail.com, orcid id: 0000-0001-6858-2711
[2]Professor, Department of Paediatric Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, email: drzahidps@gmail.com
[3]Assistant Professor, Department of Radiology & Imaging, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, email: drakmanowar@gmail.com, orcid id:0009-0003-3300-3291
[4]Assistant Registrar, Department of Paediatric Surgery, Shaheed Suhrawardy Medical College Hospital, Dhaka, Bangladesh, email: hemelrpmc37@gmail.com, orcid id: 0009-0009-2162-2849
[5]Medical Officer, Department of Paediatric surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, email: dilshadmunmun@gmail.com, orcid id: 0009-0004-2212-6816
[6]Assistant Professor, Community Medicine, Saic College of Medical Science and Technology, Dhaka, Bangladesh, email: sushmitazafar@gmail.com, orcid id: 0009-0004-2462-7956
[7]Paediatric surgeon, Medical officer, Bhanga upazila Health complex, Faridpur, email: maaamunn@gmail.com, orcid id: 0009-0000-9266-7264
[8]Medical Officer, Upazilla Health Complex, Tarakanda, Mymensingh, Bangladesh, email: sheikhjakia09@gmail.com, orcid id: 0009-0004-8428-9119

***Corresponding Author:** Dr. Mahfuz Alam Khan
*Resident Surgeon, Department of Paediatric Surgery, Mymensingh Medical College Hospital, Mymensingh, Bangladesh, email: ratulszmc13@gmail.com

Abstract

Background:

Hepatoblastoma, the most frequent paediatric malignant hepatic tumor, relies on cisplatin-based chemotherapy followed by complete surgical removal. Pretreatment evaluation by imaging is crucial to defining the extent of the disease, risk stratification, and treatment planning process, which directly affect surgical outcomes and patient survival (short and long term). This study evaluates the relationship between the postoperative outcome of hepatic resection and PRETEXT staging according to the SIOPEL protocol.

Aim of the study:

The study aims to evaluate the correlation between PRETEXT Staging and postoperative outcomes in children with hepatoblastoma according to the SIOPEL protocol.

Methods:
This prospective observational study was conducted in the Department of Paediatric Surgery, BSMMU, Dhaka, Bangladesh, from August 2021 to August 2023. A total of 12 children were enrolled in this study. Study variables were PRETEXT staging and annotation factors, pre and postoperative S. Alfa fetoprotein level, and sonographic estimation of local recurrence. Proper clinical history, physical examination and initial investigations were recorded, and all cases were staged according to pretreatment extent of disease (PRETEXT) system. They all received neoadjuvant chemotherapy according to SIOPEL protocol, followed by surgical resection and adjuvant chemotherapy. Statistical results were analysed using window-based computer software devised with Statistical Packages for Social Sciences (SPSS-22).

Results:
The median age was 22.50 months, with ranged from 10 to 75 months. Two-thirds (66.7%) of subjects were male. PRETEXT II comprises 66.7% of study subjects, whereas PRETEXT III was found 33.3%. No cases of PRETEXT I & IV were recorded. 66.7% of subjects had a positive annotation factor. The median S. alfa fetoprotein was 900.0 (ng/ml), 100.9 (ng/ml) and 4.2 (ng/ml) in preoperative, post operative 14 days and post operative three months respectively. Both the differences were statistically significant ($p<0.05$) with preoperative value. The median S. alfa fetoprotein found 1.65(ng/ml) in 6 months postoperative period which was statistically non-significant with preoperative value. Among cases with local recurrence median S. alfa fetoprotein at diagnosis, preoperative, 14 days postoperative, three months postoperative and six months postoperative period were 400000 ng/ml, 8249 ng/ml, 2000 ng/ml, 1000 ng/ml and 300000 ng/ml respectively. Among cases without local recurrence median S. alfa fetoprotein at diagnosis, preoperative, 14 days postoperative, three months postoperative, and six months postoperative period were 2000 ng/ml, 93.5 ng/ml, 8.5 ng/ml, 2.3 ng/ml and 1.3 ng/ml respectively. One-fourth (25.0%) of subjects had focal lesions at six months postoperative sonographic estimation. One-fourth (25.0%) of subjects had multifocality. Half of the subjects were involved in the caudate lobe. 12.5% of subjects had a recurrence in PRETEXT II with a 95% CI was 0 to 31.6. 50% of PRETEXT III cases were found with recurrence with a 95% CI of 1-99. 50% of multifocal cases were found with recurrence with 95% CI of 1-99. Only one case of multiple positive annotation factor (CF) was observed, and it experienced local recurrence with a 95% CI of 100. The mean postoperative hospital stay was 8.50±1.31 days.

Conclusion:
In children with hepatoblastoma, PRETEXT staging, along with annotation factors (CF and F), strongly predicted postoperative outcomes, particularly local recurrence.

Keywords: Hepatoblastoma, PRETEXT staging, Postoperative outcome, SIOPEL Protocol

INTRODUCTION

Hepatoblastoma (HB) comprises slightly >1% of all childhood malignancies, yet it is the most common primary malignant liver tumour in children [1] and the third most common intra-abdominal malignancy. It is thought to result from the unregulated proliferation of transformed hepatic stem cells or hepatic progenitor cells [2]. HB most often occurs within the first two years of life. Most cases of hepatoblastoma present with an asymptomatic upper abdominal (right upper quadrant or epigastric) mass palpated by parents or physicians [3]. Sometimes, patients may have fever, anorexia, weight loss, and fatigue. Rarely, it may present with pain and haemorrhage [4,5]. HB are chemosensitive tumors with an overall excellent prognosis. With the introduction of a cisplatin-based chemotherapy regime, overall survival of hepatoblastoma has increased from 35% to 70% and increased even further up to 80% in the most recent trials [6]. SIOPEL introduced the concept of primary chemotherapy and delayed surgery. The most significant benefit of preoperative chemotherapy in treating HB is that approximately two-thirds of the initially unresectable tumors became resectable. Moreover, neoadjuvant chemotherapy leads to fewer surgical complications due to the shrinking of the tumor

before surgery, and it exerts an antitumor effect on overt or cryptic metastasis from the initial phase of treatment. In the SIOPEL-1 trial, patients received four preoperative chemotherapy courses: cisplatin and doxorubicin (PLADO) and two additional courses of PLADO postoperatively. The outcome of the patients improved with a 5-year overall survival of 75 % and event-free survival of 66 %. Cisplatin monotherapy for standard-risk disease was tested in the SIOPEL-2 trial. In the subsequent SIOPEL-3 trial, standard-risk patients were randomized to receive cisplatin alone versus PLADO after an initial course of cisplatin. The current strategy for high-risk HB will be considered based on the results from SIOPEL-4 [7]. The European SIOPEL group has developed a pre-surgical staging system based on the pretreatment extent of disease in imaging studies (PRETEXT) [8]. It also has some limitations as PRETEXT relies on radiographic imaging that is difficult to reliably distinguish the mass effect of tumor compression from actual tumor ingrowth hence PRETEXT has a tendency to over stage [6]. PRETEXT is assigned based on the number of contiguous liver sections utterly free of tumor. PRETEXT was revised in 2005 with added annotations [6]. PRETEXT I: Three contiguous hepatic sections are accessible from the tumor. PRETEXT II: Two contiguous hepatic sections are accessible from the tumor. PRETEXT III: One contiguous hepatic section is accessible from the tumor. PRETEXT IV: No tumor-free section. Annotation factors include vascular involvement (V-hepatic vein/inferior venacava; P-portal vein), extrahepatic tumor extension (E), multifocality (F), tumor rupture (R), caudate lobe involvement (C), lymph node metastasis (N) and distant matastases (M) [8]. AFP is the most important marker for hepatoblastoma; it is increased in 90% of patients with the tumor [1]. In neonates, the interpretation of AFP measurements is more difficult because of infants' naturally high serum levels. After chemotherapy, most patients experience a significant decline in AFP level [9]. To evaluate the intrahepatic extent of the tumor and the patency of the portal hepatic veins, liver ultrasonography with Doppler is an essential tool. Abdominal CT demonstrates the PRETEXT of disease [10]. HB is life-threatening for some patients due to the recurrence or progression of the disease. Prognosis is based on numerous factors, including the age of diagnosis, PRETEXT group, metastases, alfa fetoprotein (AFP) levels, histologic subtype, tumour response to chemotherapy, completeness of resection, and clinical stage of the disease [8]. This study evaluated the relationship between PRETEXT staging and post-operative outcome according to SIOPEL protocol.

METHODOLOGY

This prospective observational study was conducted at the Department of Paediatric Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Twelve children with upper abdominal mass were evaluated in this study during two years, from August 2021 to August 2023. All these children underwent hepatic resection for hepatoblastoma after receiving neo-adjuvant chemotherapy according to SIOPEL protocol, and Patients with lung metastasis were excluded from the study. A detailed history was taken, and clinical examinations were done for each patient and recorded in a designed data collection sheet. After pre-procedure evaluation/investigations, diagnosis was confirmed by complete blood count, liver function tests, tumour marker (serum alfa-fetoprotein), radiological evaluation (sonographic evaluation, CT scan), and image-guided core biopsy. Information about several cycles of neo-adjuvant chemotherapy was noted. Ethical clearance for the study was taken from the Institutional Review Board (IRB) of BSMMU prior to the commencement of this study.

PRETEXT assessment was done by radiological evaluation. Then the patient was referred to the Department of Paediatric Hemato-oncology, and 4-6 cycles of neoadjuvant chemotherapy were received according to SIOPEL protocol. Flowing Exclusion criteria, the rest were admitted to the Department of Paediatric Surgery. Proper counselling of the parents were done. After obtaining consent and fitness for general anaesthesia from the Department of Anaesthesia, Analgesia and Intensive Care Medicine, operative procedure (hepatic resection) was performed. Close monitoring was done during postoperative hospital stay.

After post-operative recovery, they were again referred to the Department of Paediatric Hemato-oncology for adjuvant chemotherapy. Post-operative (14 days, three months, six months) follow-ups were done. Operative findings, complications with their management, and standardization of

operative techniques to different types of hepatic resections were done. Standardization of post-operative management was made up to the mark. Any change for the benefit of the patient could be made and noted. Standard discharge criteria and management were followed.

Operational definition:

Hepatoblastoma: It is a malignant liver tumor occurring in infants and children. It is composed of tissue resembling fetal liver cells or bile duct cells.

Surgical margin: It is the margin of apparently non-tumorous tissue around a tumor that has been surgically removed.

Local recurrence: It means the cancer has returned to the same place it first started.

PRETEXT: It is a staging system done by radiological imaging (CT scan) to assess the pretreatment (before chemotherapy) extent of hepatic malignancy in children.

SIOPEL: It is an international childhood liver tumor strategy group.

Data collection and analysis:

The pretested data collection sheet recorded the demographic information, relevant history, PRETEXT staging, examination findings, and investigation reports of all the study subjects. Complications during follow-up with the patient were recorded. All the data was compiled and appropriately sorted, and the numerical data was analyzed using standard statistical tools: percentage, proportion, ratio, mean±SD, median and P value of <0.05 considered significant. Statistical analysis of the results was done using computer-based statistical software, statistical package for social sciences (SPSS), and the standard statistical tool application.

RESULT

The sample size of this study was 12. The median age of the study cohort was 22.5 months, spanning from 10 to 75 months. Most of the children (58.33%) were between 13 and 24 months of age. The sex distribution shows a higher prevalence of males (66.67%) compared to females (33.33%) (Table 1). Table 2 reveals that the most common PRETEXT stage among the subjects was IIC, accounting for 33.3% of the cases. Other PRETEXT stages were less frequent, with stages II, IIF, and III representing 16.7% of the subjects. The least common stages were IIIC and IIICF, each observed in 8.3% of the subjects. 66.7% of participants were positive for annotation factors (Table 3). The mean serum bilirubin level significantly increased from the preoperative value of 100.0±0.0 to 441.25±524.45 at 14 days post-operation (P = 0.041s). However, it showed a non-significant decline at three months (P = 0.074ns) and fluctuated by six months (P = 0.132ns). There was a significant rise of S. Transaminase at 14 days post-operation (P = 0.034s), reflecting hepatic injury, followed by a non-significant reduction at three months (P = 0.143ns) and near normalization by six months (P = 0.501ns). A significant drop of AFP level was observed at 14 days (P = 0.003s) and three months (P = 0.015s), indicating adequate tumor resection. However, a non-significant increase at six months (P = 0.105ns) may require further investigation (Table 3). The mean prothrombin time showed slight variations postoperatively, decreasing to 93.46 at 14 days, 92.31 at three months, and 93.95 at six months with non-significant change. The INR values remained unchanged, slightly increasing to 101 at 14 days and decreasing to 96.62 at three months, returning to 100 by six months (Table 4). Median AFP levels were very high at diagnosis (400,000) for the recurrence group and decreased to 8249 preoperatively. Although AFP levels continued to drop postoperatively at 14 days (2000) and three months (1000), they spiked again to 300,000 at six months. For the non-recurrence group, median AFP levels were much lower, starting at 2000 at diagnosis, and showed a consistent decrease to 93.5 preoperatively and further down to 8.5 at 14 days, 2.3 at three months, and 1.3 at six months post-operation (Table 5). Patients with PRETEXT stage II had a low recurrence rate, with only 1 out of 8 patients (12.5%) experiencing recurrence, while the majority (87.5%) had no recurrence. In contrast, PRETEXT stage III was associated with a higher recurrence rate, with 50% of patients (2 out of 4) showing recurrence. Among the annotation factors, factor C was present in 5 patients, with a recurrence rate of 20%, while factor F was associated with a 50% recurrence rate (1 out of 2 patients). In case of presence of multiple annotation factors together(C&F), the recurrence rate is maximum (100%) (Table 6). Table 7 exhibits

that focal lesions were present after 6 months postoperative period in 25% of the patients, while 75% had no focal lesions. Similarly, multifocality was observed in 25% of the cases, with the majority (75%) showing no multifocality. Involvement of the caudate lobe was evenly split, with 50% of the patients having caudate lobe involvement and 50% without. Regarding postoperative recovery, most patients (75%) had a hospital stay of less than ten days, while 25% stayed for ten days or more, with a mean hospital stay of 8.50±1.31 days and a range of 7 to 11 days.

Table 1: Distribution of the study subjects by demographic profile (n=12)

Demographic profile	Frequency (n)	Percentage (%)
Age (in months)		
≤12	1	8.33
13-24	7	58.33
25-36	1	8.33
37-48	0	0.00
49-60	1	8.33
>60	2	16.67
Median	22.5	
Range (min-max)	10-75	
Sex		
Male	8	66.67
Female	4	33.33

Table 2: Distribution of the study subjects by PRETEXT staging with annotation factors (n=12)

Stage	Frequency (n)	Percentage (%)
II	2	16.7
IIC	4	33.3
IIF	2	16.7
III	2	16.7
IIIC	1	8.3
IIICF	1	8.3
Annotation factor positive	8	66.7

Table 3: Serum profile of the study populations (n=12)

Variable	Preoperative	Post-operative					
		14 days	P value	3 months	P value	6 months	P value
S. Bilirubin							
Mean±SD	100.0±0.0	441.25±524.45	0.041 s	142.78±69.85	0.074 ns	595.83±1061.38	0.132 ns
S. Transaminase							
Mean±SD	100.0±0.0	195.15±135.76	0.034 s	168.96±151.41	0.143 ns	106.48±32.21	0.501 ns
S. Alfa fetoprotein (AFP)							
Mean±SD	2544.7±4448.7	690.4±10709	0.003 s	624.1±1547.8	0.015 s	66668.01±137068.2	0.105 ns

Table 4: Prothrombin time and INR status of the study populations (n=12)

Variable	Preoperative	Post-operative					
		14 days	P value	3 months	P value	6 months	P value
Prothrombin time							
Median	100	93.46	0.936ns	92.31	0.211ns	93.95	0.538ns
INR							
Median	100	101	0.590ns	96.62	0.148ns	100	0.746ns

- Preoperative mean value of s. bilirubin, s. transaminase, prothrombin time & INR as a constant 100.0

Table 5: S. Alfa fetoprotein (AFP) level at different time period (n=12)

Local recurrence		AFP at diagnosis	Preoperative AFP	AFP at post operative		
				14 days	3 months	6 months
Recurrence (n=3)	Median	400000	8249	2000	1000	300000
	Mean± SD	329266.7±298258.3	7949.7±6804.9	2069.3±1326.4	2134.5±2871.6	266666.7±152752.5
No recurrence (n=9)	Median	2000	93.5	8.5	2.3	1.3
	Mean± SD	30932.8±64539.4	743.1±1014.2	230.7±431.7	120.6±303.2	1.8±0.99

Table 6: Correlation of PRETEXT staging and annotation factors with local recurrence (n=12)

Stage	Recurrence (n=3)		No recurrence (n=9)		Total		95% CI
	n	%	n	%	n	%	
II	1	12.50	7	87.50	8	66.67	0-31.6
III	2	50.00	2	50.00	4	33.33	1-99.0
C	1	20.00	4	80.00	5	41.67	0-86.0
F	1	50.00	1	50.00	2	16.67	1-99.0
CF	1	100.00	0	0.00	1	8.33	100.0-100.0

Table 7: Outcome of the study population (n=12)

Variables	Frequency (n)	Percentage (%)
Focal lesion		
Present	3	25
Absent	9	75
Multifocality		
Yes	3	25
No	9	75
Involvement of caudate lobe		
Yes	6	50
No	6	50
Post operative hospital stay		
<10	9	75
≥10	3	25
Mean±SD	8.50±1.31	
Range (min - max)	7-11	

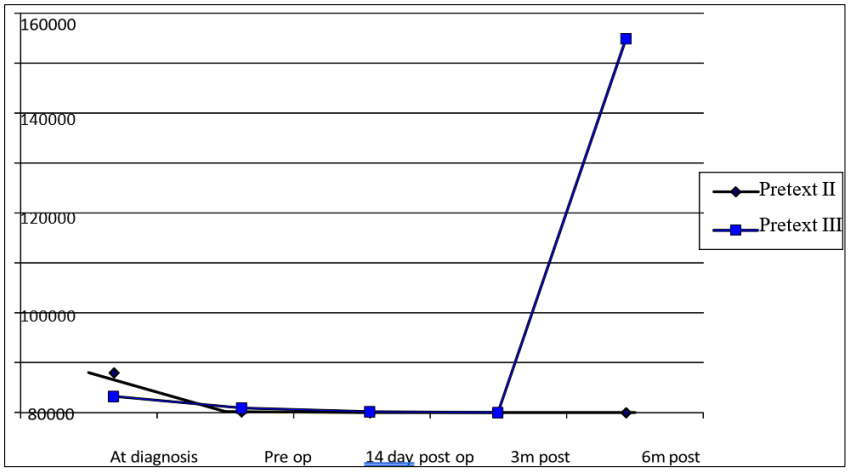

Figure 1: Correlation curve showing median S. alfa fetoprotein level at differenttime period with PRETEXT staging

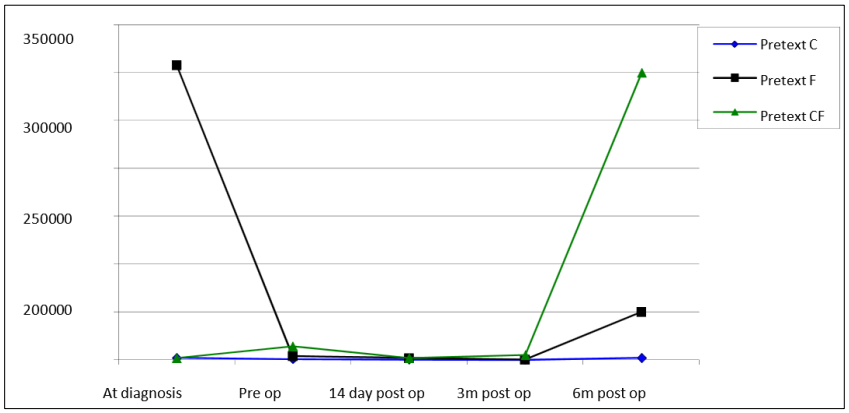

Figure 2: Correlation curve showing median S. alfa fetoprotein level at differenttime period with annotation factors

DISCUSSION

This prospective type of observational study aimed to assess PRETEXT staging and annotation factors and determine postoperative local recurrence by ultrasonography and serum alfa fetoprotein level. Hepatoblastoma is predominantly a disease of early childhood, with a peak incidence between 12 and 24 months of age. In this present study, it was observed that 58.33% of subjects belonged to ages 13-24 months. The median age was 22.50 months, with ranged from 10 to 75 months. This age distribution aligns with the existing body of knowledge regarding hepatoblastoma, also obtained by Yoon et al., Santini et al. and Koh et al. [8,11,12]. Sunil et al. conducted a comprehensive analysis of paediatric hepatoblastoma cases and concluded that almost similar age groups at diagnosis [13]. Age is a crucial factor in the prognosis and management of hepatoblastoma but its role is intricate and influenced by various clinical variables. One of the key demographic findings in this study was the distribution of male and female subjects with 66.7% male and 33.3% female. Several studies have reported a higher incidence of hepatoblastoma in males compared to females, as reported by Santini et al., Koh et al., and Aronson et al. [11,12,14]. A study conducted by Sunil et al. found that 66.7% of their hepatoblastoma cases were male which is consistent with the present study findings [13]. This consistent gender bias suggests that there may be underlying genetic or hormonal factors contributing to the development of hepatoblastoma which warrants further investigation. According to our study 33.3% of the subjects had PRETEXT IIC followed by 16.7% with PRETEXT II, PRETEXT IIF and PRETEXT III and 8.3% with PRETEXT IIIC and IIICF respectively. Furthermore two-thirds (66.7%) of the subjects had a positive annotation factor. In the study of Schnater et al., it was noted that a substantial proportion of patients presented with PRETEXT II disease a finding consistent with our findings [15]. According to Santini et al., among all patients 6% had a PRETEXT score of I, 16% scored II, 58% scored III, and 19% scored IV [11]. In this study as we have population of different age group and liver maturation & function varies in different subject. So, we undertook preoperative

mean value of s. bilirubin, s. transaminase, prothrombin time & INR as a constant 100.0 and values of different time period was calculated according to the preoperative value of each subject.

Our observation showed that the preoperative mean serum bilirubin level was 100.0±0.0. At 14 days postoperatively the mean serum bilirubin level significantly rises to 441.25±524. At three months postoperatively there is a decrease in the mean serum bilirubin level to 142.78±69.85, though it remains elevated compared to the preoperative baseline. Surprisingly at six months postoperatively the mean serum bilirubin level rises significantly to 595.83±1061.38. The statistical significance of these differences is highlighted ($p<0.05$). Needham et al. mentioned in this study that plasma bilirubin levels exhibited a notable peak on the second day following surgery, followed by a gradual decline toward the normal range [16]. However it is important to note that the true baseline values were not reestablished until a period ranging from 3 to 6 weeks following the resection procedure. Post-hepatectomy bilirubin took approximately two weeks to return to normal [17-19]. The results of this study revealed that the mean S. transaminase levels increased sharply (195.15±135.7) at 14 days after surgery, reached a peak, and then gradually decreased at 3 and 6 months postoperative to 168.96±151.41 and 106.48±32.21. The statistically significant difference ($p<0.05$) in S. transaminase levels between the preoperative and postoperative 14-day periods underscores the importance of monitoring liver function after hepatic resection in children with hepatoblastoma. Lin et al. found S. transaminase rose immediately postoperatively and fell rapidly to normal within a week [17]. Needham et al. found that S. transaminase was maximum on the first postoperative day but values had fallen to normal within the 14^{th} postoperative day [16]. Transaminase values were significantly greater and took longer to normalize among children who had received chemotherapy which correlates with our study. Prothrombin time (PT) indicates the coagulation profile, essential for minimizing intraoperative and postoperative bleeding complications. The preoperative mean PT was 100.0±0.0, which was set as a constant. At 14 days postoperative the mean PT increased to 99.6±16.82. The mean PT values at three months and six months postoperative continued to show slight fluctuations, with means of 94.6±14.0 and 97.01±16.33 respectively. The differences were not statistically significant. Zoli et al. found in their research that prothrombin activity was slightly reduced soon after surgery and returned to normal within 14 days [20]. Yildirim et al. describe the rapid fall of the prothrombin index as caused by decreased hepatic synthesis of coagulation factors, peripheral degradation, or both [21]. We found that the mean INR level preoperatively was set at 100.0±0.0. After 14 days the mean INR increased to 105.8±14.0. At three and six months the mean INR levels were 95.59±9.82 and 101.58±16.44 respectively. There was no significant correlation between preoperative INR values and postoperative outcomes in children undergoing hepatic resection for hepatoblastoma. This is a reassuring outcome, as maintaining stable clotting function is crucial in the postoperative period to prevent complications such as bleeding. A study showed that the international normalized ratio (INR) is directly associated with prothrombin time, exhibited its greatest prolongation during the first two postoperative days [16]. By the seventh day INR values had returned to within the normal range. Our findings reveal that the reduction in S. Alpha-fetoprotein levels is statistically significant at the 14-day and 3-month postoperative periods ($p<0.05$). The reduction at the 6-month postoperative mark was insignificant ($p>0.05$). These results suggest that hepatic resection in children with hepatoblastoma can effectively reduce S. Alpha-fetoprotein levels in the short term (14 days and three months). This reduction may indicate successful tumor removal and a positive early postoperative outcome. However the lack of significance in the 6-month postoperative period may be due to some extreme values, especially in those three recurrent cases. According to Sunil et al., having an AFP level lower than 100 ng/ml and being diagnosed with small cell undifferentiated histology were statistically significant factors predicting worse outcomes [13]. Towu et al. study observed a wide range of serum alpha-fetoprotein levels from 49,000 to 3,500,000 ku/L with a median value of 172,714 ku/L [22]. The present study highlights a significant correlation between S. Alfa fetoprotein levels and the recurrence of hepatoblastoma. The results indicate that in cases of local recurrence, there is a notable elevation in S. Alfa fetoprotein levels at the time of diagnosis (median: 400,000.0 ng/ml) which decreases postoperatively but remains elevated compared to cases with no recurrence. In contrast in cases with no recurrence, S. Alfa fetoprotein levels are comparatively lower at diagnosis (median: 2,000.0 ng/ml) and remain low postoperatively. The decrease in S. Alfa fetoprotein levels

over time in patients without recurrence is a promising indicator of a successful surgical outcome. Regular monitoring of S. Alfa fetoprotein levels can aid in the early detection and management of recurrence in paediatric hepatoblastoma cases. In this study we found the correlation of median S.AFP level at different time period with PRETEXT staging shows a better outcome tendency of PRETEXT II over PRETEXT III. Among annotation factors multifocality (F) and presence multiple annotation factors (CF) shows worse outcome tendency.

In this study, it was observed that there were 8 cases in PRETEXT II, and 87.5% did not experience local recurrence, while 12.5% developed local recurrence with 95% CI for recurrence in this stage, ranging from 0% to 31.6%. In PRETEXT III there were 4 cases and 50.0% had no recurrence while the other 50.0% did experience recurrence. The confidence interval for recurrence in this stage spans from 1% to 99.0%. Among 5 cases in which the annotation factor C was positive 80.0% had no local recurrence and 20.0% did have recurrence. The 95% confidence interval for recurrence in this stage ranges from 0% to 86.0%. There were 2 cases in annotation F positive and both were divided equally between no recurrence (50.0%) and recurrence (50.0%). The confidence interval for recurrence in this stage spans from 1% to 99.0%. Only 1 case was observed where multiple annotations (CF) were present and it experienced local recurrence (100.0%). The confidence interval for recurrence in this stage is narrow, indicating a 100% recurrence rate with no variation. The relationship between different PRETEXT stages and the likelihood of local recurrence. PRETEXT II and annotation C have higher percentages of cases with no recurrence (87.5% and 80.0% respectively). In contrast, PRETEXT III and annotation F have an equal distribution of cases with and without recurrence. Multiple annotation is positive (CF) in only one case and has a 100.0% recurrence rate. Schneller et al. study found that among the cohort of patients examined, ten individuals (8%) experienced a recurrence of their disease [15]. These recurrences were categorized based on the PRETEXT classification system, with three patients having PRETEXT II tumors (3 of 55), five patients having PRETEXT III tumors (5 of 47), and two patients having PRETEXT IV tumors (2 of 6). The primary finding of this study was that 25.0% of the subjects experienced focal lesions at six months postoperative sonographic estimation following hepatic resection for hepatoblastoma. In a study, Sunil et al. noted that recurrence rates following liver resection spanned from 8.0% to 25.0% across different case series [13], which supports the present study. We found that 25.0% of the subjects had multifocality. According to Yoon et al., recommended that patients diagnosed with multifocal tumors undergo rigorous chemotherapy [8]. These findings align with prior research and emphasize that the presence of microscopic residual tumor tissue in apparently clear liver imaging can potentially result in relapse following the sole resection of multifocal tumors [23,24]. In a Maibach et al. (2012) study, approximately 20.0% of hepatoblastoma patients exhibit multifocal tumors. Various studies consistently indicate that individuals with multifocal disease experience more unfavourable outcomes than those with a single focal point of the disease [11,25]. The caudate lobe (Couinaud segment 1) is considered an important annotation factor in the revised PRETEXT classification system. The tumour is considered PRETEXT II if it only involves the caudate lobe [26]. One of the notable findings from the present study was the observation that 25.0% of the subjects had involvement of the caudate lobe. One of the key findings in this study was the distribution of patients based on their postoperative hospital stay. The mean postoperative hospital stay was 8.50±1.31 days, varying from 7 to 11 days. Zwintscher et al. demonstrated that the typical hospital stay duration averaged 10.04 days, comparable with the present study [27].

Limitations of the study:

- There was no PRETEXT stages I and IV patient within this study population.
- The study's sample size is too small; it may not represent the larger population, potentially limiting the generalizability of the results.

CONCLUSION AND RECOMMENDATIONS

The study concluded that PRETEXT staging, along with annotation factors, is a good predictor and has a positive correlation with postoperative outcomes in children with hepatoblastoma. PRETEXT II tends to have a better outcome than PRETEXT III. The less the annotation factor is involved, the

better the outcome is anticipated. To stratify risk, plan treatment, and anticipate post-operative outcomes in children with hepatoblastoma, appropriate assessment of PRETEXT staging with annotation factors should be done. A multidisciplinary approach is critical to achieving a better outcome.

REFERENCES

1. Hager J, Sergi CM. Hepatoblastoma. Exon Publications. 2021 Apr 6:145-64.
2. Yang T, Whitlock RS, Vasudevan SA. Surgical management of hepatoblastoma and recent advances. Cancers. 2019 Dec 4;11(12):1944.
3. Litten JB, Tomlinson GE. Liver tumors in children. The oncologist. 2008 Jul 1;13(7):812-20.
4. Musick SR, Smith M, Rouster AS, Babiker HM. Hepatoblastoma. InStatPearls [Internet] 2023 Jul 17. StatPearls Publishing.
5. DeRenzi AD, Bowen A. A Case Report and a Review of Pediatric Hepatoblastoma. HCA Healthcare Journal of Medicine. 2023;4(5):377.
6. Meyers RL, Czauderna P, Otte JB. Surgical treatment of hepatoblastoma. Pediatric blood & cancer. 2012 Nov;59(5):800-8.
7. Aronson DC, Czauderna P, Maibach R, Perilongo G, Morland B. The treatment of hepatoblastoma: Its evolution and the current status as per the SIOPEL trials. Journal of Indian Association of Pediatric Surgeons. 2014 Oct 1;19(4):201-7.
8. Yoon HM, Hwang J, Kim KW, Namgoong JM, Kim DY, Koh KN, Kim H, Cho YA. Prognostic factors for event-free survival in pediatric patients with hepatoblastoma based on the 2017 PRETEXT and CHIC-HS systems. Cancers. 2019 Sep 18;11(9):1387.
9. Spyridakis I, Kepertis C, Lampropoulos V, Mouravas V, Filippopoulos A. Embryonal/Fetal subtype hepatoblastoma: A case report. Journal of clinical and diagnostic research: JCDR. 2014 Sep;8(9):ND01. Emre S et al. 2012
10. El-Nakeep S, Ziska SK. Doppler liver assessment, protocols, and interpretation of results. InStatPearls [Internet] 2023 Aug 13. StatPearls Publishing.
11. Saettini F, Conter V, Provenzi M, Rota M, Giraldi E, Foglia C, Cavalleri L, D'Antiga L. Is multifocality a prognostic factor in childhood hepatoblastoma?. Pediatric Blood & Cancer. 2014 Sep;61(9):1593-7.
12. Koh KN, Park M, Kim BE, Bae KW, Kim KM, Im HJ, Seo JJ. Prognostic implications of serum alpha-fetoprotein response during treatment of hepatoblastoma. Pediatric Blood & Cancer. 2011 Oct;57(4):554-60.
13. Sunil BJ, Palaniappan R, Venkitaraman B, Ranganathan R. Surgical Resection for Hepatoblastoma—Updated Survival Outcomes. Journal of gastrointestinal cancer. 2018 Dec;49:493-6.
14. Aronson DC, Schnater JM, Staalman CR, Weverling GJ, Plaschkes J, Perilongo G, Brown J, Phillips A, Otte JB, Czauderna P, MacKinlay G. Predictive value of the pretreatment extent of disease system in hepatoblastoma: results from the International Society of Pediatric Oncology Liver Tumor Study Group SIOPEL-1 study. Journal of clinical oncology. 2005 Feb 20;23(6):1245-52.
15. Schnater JM, Aronson DC, Plaschkes J, Perilongo G, Brown J, Otte JB, Brugieres L, Czauderna P, MacKinlay G, Vos A. Surgical view of the treatment of patients with hepatoblastoma: Results from the first prospective trial of the International Society of Pediatric Oncology Liver Tumor Study Group (SIOPEL-1). Cancer. 2002 Feb 15;94(4):1111-20.
16. Needham P, Dasgupta D, Davies J, Stringer MD. Postoperative biochemical liver function after major hepatic resection in children. Journal of pediatric surgery. 2008 Sep 1;43(9):1610-8.
17. Lin TY, Chen CC. Metabolic function and regeneration of cirrhotic and non-cirrhotic livers after hepatic lobectomy in man. Annals of Surgery. 1965 Dec;162(6):959.
18. Yamanaka N, Okamoto E, Kawamura E, Kato T, Oriyama T, Fujimoto J, Furukawa K, Tanaka T, Tomoda F, Tanaka W. Dynamics of normal and injured human liver regeneration after hepatectomy as assessed on the basis of computed tomography and liver function. Hepatology. 1993 Jul 1;18(1):79-85.

19. Schaffner F. Structural and functional aspects of regeneration of human liver. Digestive diseases and sciences. 1991 Sep;36:1282-6.
20. Zoli M, Marchesini G, Melli A, Viti G, Marra A, Marrano D, Pisi E. Evaluation of liver volume and liver function following hepatic resection in man. Liver. 1986 Oct;6(5):286-91.
21. Yildirim SI, Poulsen HE. Quantitative liver functions after 70% hepatectomy. European journal of clinical investigation. 1981 Dec;11(6):469-72.
22. Towu E, Kiely E, Pierro A, Spitz L. Outcome and complications after resection of hepatoblastoma. Journal of pediatric surgery. 2004 Feb 1;39(2):199-202.
23. Czauderna P, Otte JB, Aronson DC, Gauthier F, Mackinlay G, Roebuck D, Plaschkes J, Perilongo G. Guidelines for surgical treatment of hepatoblastoma in the modern era–recommendations from the Childhood Liver Tumour Strategy Group of the International Society of Paediatric Oncology (SIOPEL). European Journal of Cancer. 2005 May 1;41(7):1031-6.
24. D'Antiga L, Vallortigara F, Cillo U, Talenti E, Rugge M, Zancan L, Dall'Igna P, Salvo GL, Perilongo G. Features predicting unresectability in hepatoblastoma. Cancer. 2007 Sep 1;110(5):1050-8.
25. Meyers RL, Maibach R, Hiyama E, Häberle B, Krailo M, Rangaswami A, Aronson DC, Malogolowkin MH, Perilongo G, von Schweinitz D, Ansari M. Risk-stratified staging in paediatric hepatoblastoma: a unified analysis from the Children's Hepatic tumors International Collaboration. The Lancet Oncology. 2017 Jan 1;18(1):122-31.
26. Towbin AJ, Meyers RL, Woodley H, Miyazaki O, Weldon CB, Morland B, Hiyama E, Czauderna P, Roebuck DJ, Tiao GM. 2017 PRETEXT: radiologic staging system for primary hepatic malignancies of childhood revised for the Paediatric Hepatic International Tumour Trial (PHITT). Pediatric radiology. 2018 Apr;48(4):536-54.
27. Zwintscher NP, Azarow KS, Horton JD. Morbidity and mortality associated with liver resections for primary malignancies in children. Pediatric surgery international. 2014 May;30:493-7.