

Research Article

Spectrum and Outcome of Intra-abdominal Tumors in children Under-five in a Pediatric Critical Care Unit of a Tertiary Care Center of Pakistan

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Abstract:

Objective: To determine the spectrum and outcome of intra-abdominal tumors in children less than five years admitted in the critical care unit of a tertiary care center of Pakistan.

Methodology: This retrospective study included children less than five years with malignant abdominal mass admitted in the pediatric critical care unit of the tertiary care center of Pakistan from July 2015 to June 2019. Undiagnosed patients or with relapsed or benign abdominal tumors managed in an outpatient or admitted in the critical care for post-operative care only were excluded from the study. Data was entered and analyzed by using SPSS version 21.0.

Result: Total 55 patients were included with 69% boys and median age three years (IQR – 2 years). Abdominal distention was the commonest complain (100%). Only 42% children survived (n=23/55). High grade mature B-cell Non Hodgkin Lymphoma was the most common (45%) diagnosis. Advance Stage III/IV was seen in 94%. Combined multiple site metastasis was most common (45.4%). Sepsis (OR-5.30, 95% CI-1.24-22.65, p-0.024), inotropic use (OR-9.00, 95% CI-1.33-60.92, p-0.024) and malnutrition (OR-4.85, 95% CI-1.08-21.63, p-0.039) were identified as the most significant prognostic factors related to high mortality.

Conclusion: B-cell Non-Hodgkin Lymphoma was the most common histopathological diagnosis, while sepsis was the commonest reason for admission in critical care unit. Majority presented with advanced stages (stage III/IV) with poor outcome(58% mortality). Sepsis, malnutrition and need of inotropes were found to be the independent risk factors contributing to this high mortality. We recommend for early recognition of abdominal distention as an important sign of cancer with prompt referral to pediatric oncology unit which would definitely decrease the upfront critical care requirement and improve survival.

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Introduction:

Abdominal mass presentation in children are often shocking and of great concern for both parents and the primary caregivers. The diagnosis of these masses may range from inflammatory/infective etiology like abscess or mesenteric lymphadenopathy to benign

pathology such as hydronephrosis, hemangiomas or choledochal cyst to life threatening malignant conditions including Wilms tumor, Neuroblastoma and germ cell tumors^{1,2}. These abdominal malignancies are not un-common with Neuroblastoma comprising 7.6% and renal (mainly Wilms) 5.6% of the entire childhood cancer³. These malignant masses require combination

of treatment depending on their diagnosis including surgery, neoadjuvant or adjuvant chemotherapy or irradiation. Over the years, the survival of the children with these tumors has increased dramatically to 70 - 90% in developed countries depending on stage and *treatment risk group*⁵. This has been achieved due to better understanding of tumors, improved surgical expertise and superior supportive care.

In Pakistan, there are limited studies on pediatric malignant abdominal tumors. These studies had primarily focused on their histopathological diagnosis and outcome. They included all abdominal tumors whether benign or malignant and patients with age less than 16 years admitted in either critical or non-critical area or treated in an outpatient setting⁶⁻⁷. So we aimed to fill this gap in knowledge and intended to assess the demographic data, clinical presentation, histopathological diagnosis and short-term outcome of intra-abdominal malignant tumors in children less than five years of age in the critical care department of the tertiary care center of Pakistan and identify factors for their outcome.

Methods:

This was a retrospective, observational study. It was conducted after the approval of institutional IRB with this number IRD_IRB_2019_08_007 and dated 3rd September 2019. A minimum sample size of 53 children was calculated using Open Epi software through formula for single proportion taking 12.7% frequency of non-Hodgkin lymphoma⁴, confidence level of 95% and 9% margin of error. All children from one month to five years of age with intra-abdominal malignant tumors being admitted in pediatric critical care of tertiary care center of Pakistan from July 2015 to June 2019 for their initial diagnostic work up, stabilization and monitoring, or critical care management were consecutively included in the study. Patients with relapsed abdominal malignancies, whose histopathological diagnosis was not confirmed, had benign abdominal tumors, admitted in the critical care for post-surgical observation or children with abdominal tumor not admitted in the pediatric critical care and being diagnosed on an outpatient basis or in the pediatric oncology ward were excluded.

Primary Outcome was defined as patient alive and discharged from critical care area or expired during the

admission. Reasons for admission to critical care included respiratory distress or failure, sole critical care monitoring, sepsis or combination of these. Sepsis was defined as Presumed or proven infection with systemic inflammation (SIRS) as per guidelines of International Pediatric Sepsis Conference⁸. Patients with weight for age less than 3rd centile according to World Health Organization criteria were labelled as malnourished.

The data was extracted from the electronic medical record of pediatric oncology data base and collected in the pre-designed case report form. This included age, gender, date of admission, discharge/death and histopathological diagnosis, presenting symptoms with their duration of onset, relevant abdominal examination findings with all vital signs. Investigations including full blood count, coagulation profile, serum creatinine, liver function tests, tumor markers if done [Lactate dehydrogenase (LDH), Erythrocyte sedimentation rate(ESR), Alpha fetoprotein (AFP), Beta human chorionic gonadotrophin (β -HCG), Metanephrine, Vanillyl Mandelic acid (VMA)] were documented. Relevant imaging and their findings such as ultrasound, Computed tomography scan and Magnetic Resonance Imaging findings were collected. Final diagnosis with mode of biopsy either radiological guided trucut core biopsy or laparotomy/open biopsy and tissue source were collected. Stage of the disease and in case of stage IV or metastatic, site of metastasis was documented. The details of critical care treatments including use of mechanical ventilator for respiratory failure, inotropes for circulatory compromise, dialysis or insertion of pigtail were collected.

Data was entered and analyzed by using SPSS version 21.0. Descriptive statistics including mean, standard deviation (median, range where applicable) were computed for age, duration of hospital stay and symptoms (in days). Frequency and percentages were calculated for qualitative variables like gender, disease stages, diagnosis, and the outcome.

Pearson Chi-square test and Fisher Exact test were applied to find out the significant difference between the categorical data. Independent sample t test was also applied to find the mean difference between the outcome and quantitative variables. Adjusted logistic regression model was applied to find the independent risk

factor for death. A p-value < 0.05 was considered significant.

Results:

Total 55 patients were enrolled in the study and 69% (n=38) were male, median age was three years (Interquartile range 2 years) and 49%(n=27) were malnourished. Median duration of symptoms including abdominal distention with pain and fever was 45 days (range 5 – 180 days) and hospital stay was 14 days (range 2 – 384 days). Most common histopathological diagnosis was B-cell Non-Hodgkin Lymphoma (BNHL) (n=25, 45%) followed by Neuroblastoma (n=10, 18%) and hepatoblastoma (n=8, 15%). Majority patients (n=46, 94%) presented in advanced stages - Stage III (n=24, 49%) and IV(n=22, 45%). Stages of six patients were not assessed as they expired before staging workup. Combined multiple site metastasis i.e. lymph nodes, peritoneum, liver and brain was most common (n=10, 45.4%) followed by bone marrow (n=8, 36%). Sepsis was the top primary reason of admission in critical care area (n=31, 56.4%) although combination of respiratory distress with sepsis and monitoring was seen in 32 children (58%). Overall mortality was 58% (n/N – 32/55) (**Table 1**).

Table 1: Demography and Outcome of children with Intra-abdominal tumors admitted in a Pediatric Critical Care Unit (N=55)

Age	
Median, range	3, 0.3 – 5
Sex	
Male	38 (69%)
Female	17 (31%)
Malnourished (weight for age < 3rd centile)	
Yes	27 (49.1%)
No	28 (50.9%)
Duration of days (Hospital stay)	
Median (range)	14 (2-384)
Duration of days (Symptoms)	
Median (range)	45 (5-180)
Stages*	
I	2 (4%)
II	1 (2%)
III	24 (49%)
IV	22 (45%)
Diagnosis	
B-NHL	25 (45%)
Neuroblastoma	10 (18%)

Hepatoblastoma	8 (15%)
Wilms Tumor	6 (11%)
Germ Cell Tumor	4 (7%)
LCH	1 (2%)
Rhabdomyosarcoma	1 (2%)
Metastatic Sites - Stage IV	22
Bone Marrow	8 (36.4%)
Lungs	4 (18.2%)
Others in combination (Distant nodes, peritoneum, liver, brain)	10 (45.4%)
Reason of Critical Care admission	
Respiratory Distress	28(51%)
Sepsis	31 (56.4%)
Monitoring	23 (42%)
Combination of above	32 (58%)
ICU Therapies	
Mechanical Ventilation	13 (23.6%)
Inotropic use	16 (29%)
Dialysis	1 (1.8%)
Pigtail insertion	8 (14.5%)
Outcome	
Alive	23 (42%)
Expired	32 (58%)

*Disease stage of 6 patients were not assessed

B-NHL=B cell Non-Hodgkin lymphoma, LCH= Langerhans cell histiocytosis

The most common presenting symptoms were abdominal distention (100%) followed by fever 56.36% (n=31) and pain in abdomen and generalized body weakness in 47.27% (n=26) cases. The most prevalent examination findings were palpable abdominal mass 61.82% (n=34) followed by pallor 32.73% (n=18) and hepatomegaly 21.82% (n=12) (**Fig. 1**).

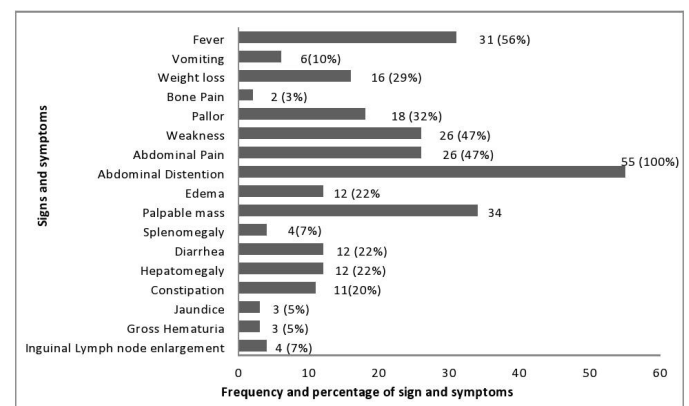


Figure 1: Presenting Signs and symptoms of children with intraabdominal tumors admitted in a Pediatric Critical Care Unit (N=55)

At univariate logistic regression analysis, malnutrition (OR-6.03, 95% CI-1.87-19.44), sepsis (OR-13.03,95%

CI-3.56-47.61), use of inotropes (OR-11.2, 95% CI-2.23- 56.36), and need of mechanical ventilation (OR-18.75, 95% CI-2.21- 158.46), were found to be substantial contributors ($p < 0.05$) leading to mortality. Age, gender, disease diagnosis and stage of the disease were not statistically significant factors of mortality (p -value > 0.05) (Table - 2). However, sepsis (OR-5.30, 95% CI-1.24-22.65, p - 0.024), inotropic use (OR-9.00, 95% CI-1.33-60.92, p - 0.024) and malnutrition (OR-4.85, 95% CI-1.08-21.63, p - 0.039) remained only the independent risk factor of mortality in the adjusted logistic regression model (Table - 3).

Table 2: Determinants of mortality in patients with intra-abdominal tumors (N=55)

Determinant	Odds Ratio	95% CI	p-value
Age	1.05	0.73 – 1.55	0.77
Gender			
Female (Ref)	1		
Male	1.39	0.44 – 4.38	0.57
Malnutrition			
No (Ref)	1		
Yes	6.03	1.87 – 19.44	0.003
Diagnosis			
Others	1		
NHL	0.59	0.11 – 3.20	0.54
Wilms tumor	0.19	0.013 – 2.66	0.22
Neuroblastoma	1.5	0.19 – 11.53	0.70
Hepatoblastoma	2.63	0.30 – 23.00	0.38
Stage of the disease			
Stage I / II	1		
Stage III	0.36	0.05 – 2.34	0.28
Stage IV	1.07	0.16 – 7.31	0.94
Sepsis			
No	1		
Yes	13.03	3.56 47.61	< 0.001
Inotrope use			
No	1		
Yes	11.2	2.23 – 56.36	0.003
Mechanical Ventilation			
No	1		
Yes	18.75	2.21 – 158.46	0.007

Table 3: Adjusted logistic regression model– Determinants of mortality in patients with intra-abdominal tumors (N=55)

Determinant	Adjusted Odds Ratio	95% CI	p-value
Sepsis (Yes)	5.30	1.24 – 22.65	0.024
Inotrope use (Yes)	9.00	1.33 – 60.92	0.024
Malnutrition (Yes)	4.85	1.08 – 21.63	0.039

Discussion:

This retrospective study showed dismal prognosis (58% mortality) of our cohort of abdominal malignancies that required upfront critical care admission. Similar high mortality rate was also observed in the pediatric oncology patients admitted in the intensive care unit of other Pediatric Oncology Unit (POU) of Pakistan⁹. This can be attributed to multifactorial reasons present in the resource limited settings like delayed and advanced disease presentation and high rate of septicemia. One factor related to poor survival could be lack of a dedicated pediatric critical care setup as shown by Khan et al⁹. But this was not the case in our setting as we have a specialized pediatric critical care. High fatality rate in our children could be due to increase number of children in sepsis (95% CI 1.24-22.65, adjusted OR 5.30) with respiratory and circulatory failure (95% CI 1.33-60.92, adjusted OR 9.0).

Dursun et al from Turkey also reported 55% PICU mortality in children with malignancies, higher than their general pediatric annual mortality of 12%¹⁰. Although improved PICU survival of these pediatric oncology children with septic shock have been documented in other parts of the world¹¹⁻¹². This can be due to their inclusion of only septic shock patients during the chemotherapy. Patients with these abdominal tumors do have good prognosis even in Pakistan if they don't directly land in PICU on their initial presentation to hospital. Survival of 67- 80% have been documented by Halepota et al and Anwar et al¹³⁻¹⁴. So early referral is the key to improve the survival in these patients.

In our cohort, three factors were identified to be the most significantly associated with poor survival. These were clinical sepsis, malnutrition and the use of inotropes during the hospital stay. These prognostic factors along with mechanical ventilation need, high PRISM III score and organ dysfunction have also been proven to be directly related to increase deaths in multiple studies^{9,10,15}. We had limitation to assess the PRISM score or organ dysfunction due to the retrospective nature of our study. Malnutrition was significant factor contributing to mortality in our study. This is in concordance with other studies which also showed strong relationship between malnutrition and poor PICU outcome and even high treatment related mortality and

decreased survival^{9,16-17}.

The most common histopathological diagnosis in our study was High grade mature B-cell Non Hodgkin Lymphoma including Burkitts and Diffuse large cell B cell lymphoma. This is in contrast to majority studies which showed Wilms tumor or Neuroblastoma as the most frequent abdominal malignancy in children^{4,18-20}. This difference might be due to the reason that BNHL patients are generally sick and require extensive clinical and laboratory monitoring for tumor lysis syndrome in the critical area. Though Blevrakis et al looked at the histopathological diagnosis of abdominal malignancies in children less than sixteen years age admitted in specially critical care but still reported Neuroblastoma as the commonest tumor²¹.

Delay in presentation leads to late diagnosis, advance stage disease and poor survival²². Although our patients had median duration of symptoms of 45 days before coming to our POU and majority had advanced stage on presentation but these two factors had no significant prognostic implication at least on their short term outcome in the critical care. This can be due to limited sample size of our study. Further prospective studies are needed to document if any relationship exists.

Our study limitations included retrospective data analysis from a single institution and a small sample size of 55 patients. The scarcity of data on this cohort of patients requires an extensive prospective study, correlating various factors to form an efficient clinical approach to improve outcomes in these patients.

Conclusion:

B-cell Non-Hodgkin Lymphoma was the most common histopathological diagnosis. Majority presented with advanced stages (stage III/IV) resulting in poor outcome with 58% mortality. Sepsis was the most frequent reason of admission in the critical care area. Sepsis, malnutrition and need of inotropes were found to be the independent risk factors contributing to high mortality. We recommend for early recognition of abdominal distention as an important sign of cancer with prompt referral to pediatric oncology unit which would definitely decrease the upfront critical care requirement and improve survival. In conclusion, early suspicion of malignancy by healthcare workers especially general

practitioners, pediatricians and pediatric surgeons along with public awareness regarding signs and symptoms of cancer is of utmost significance. This will lead to early referral of patients to Pediatric oncology units with fewer complications, decreasing the need for critical care admissions and hence improve their survival.

Ethical Approval: Given

Conflict of Interest: The authors declare no conflict of interest.

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