

Abdominal tumors in children: A comprehensive study on the diagnosis, management, and clinical outcome of pediatric patients with lymphoma in Kashmir



Zahida Akhtar¹, Zahid Kaleem², Showkat Majeed Kakroo³

¹Associate Professor, ²Senior Resident, Department of General Surgery, SKIMS Medical College and Hospital, Sri Nagar, Jammu and Kashmir, ³Medical Officer, Health and Medical Education, Department of General and Laparoscopic Surgery, SKIMS Medical College and Hospital, Sri Nagar, Jammu and Kashmir

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ABSTRACT

Background: Although primary abdominal tumors are rare but their diagnosis, high-cost treatment and psychological instability among both patients and parents are challenging. There are several types of abdominal tumors in pediatric age group which include neuroblastoma, Wilm's tumor, hepatoblastoma, lymphomas, soft-tissue sarcomas, and germ cell tumors. **Aims and Objectives:** The present study was objectively conducted to identify Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) tumors among all patients presented with abdominal tumors. In addition to this, histopathological profile, clinical profile and disease prognosis among such patients has also been analyzed. **Materials and Methods:** A total of 64 pediatric patients presented with primary abdominal tumors were included in the study but only 20 patients with lymphoma were identified. The study was conducted at the Department of Pediatric Division, SMHS Hospital Srinagar with effect from 2005 to 2008. **Results:** The Majority of NHL patients were found to have Stage II and Stage IV. Moreover, all the four cases of Hodgkins lymphoma had Stage IV. Out of the 20 patients with Lymphoma six died, of them five had NHL and one patient had HL, thus placing the overall survival rate as 70%. **Conclusion:** The present study demonstrated that both NHL and HL tumors may develop to advanced stage and even patient may die if the timely diagnosis and proper management is not there. We recommend collective team work of medicos from various departments for the precise diagnosis and optimal management of such patients.

Key words: Abdominal tumours; Hodgkin lymphoma; Lymphoma; Non-Hodgkin lymphoma

INTRODUCTION

Abdominal tumors among children include diverse forms of lesions that can occur from the new born baby through adolescence.¹ Of all the forms of cancers, the proportion of pediatric tumors is relatively low and in developing countries the incidence of childhood cancers appears lower, some five-fold to six-fold. The majority of children present with cancer each year are from developing countries and as such developing countries are immensely contributing toward the increased proportion of world's childhood cancers.^{2,3} Even though primary abdominal tumors are rare

but their diagnosis, high-cost treatment and psychological instability among both patients and parents are challenging. Some abdominal tumors are tangibly located and few are identified because of pain; however, in most of the cases, there is complete absence of peculiar signs and patient's symptomatic response and as such delay in the timely diagnosis often results in vulnerabilities. By the time, tumor is clinically diagnosed; its development has already resulted into tumor metastasis. Therefore, orchestrated team work of pediatric oncologist, radiologists, pathologists, and surgeons is all the more important and essential for the optimal management of tumors. Not only the

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Address for Correspondence:

Dr. Showkat Majeed Kakroo, Medical Officer, Department of General and Laparoscopic Surgery, SKIMS Medical College and Hospital, Sri Nagar, Jammu and Kashmir. **Mobile:** 7006140182, **E-mail:** i.showket.sk.sk@gmail.com

radiological examination through computed tomography and ultrasonography (USG) play a significant role in the identification and location of tumors but the pathological evaluation of tumor tissue is equally important because it has been seen that DNA of the tumor is not as same as DNA of non-malignant cells.⁴ There are several types of abdominal tumors in pediatric age group which include neuroblastoma, Wilm's tumor, hepatoblastoma, lymphomas, soft-tissue sarcomas, and germ cell tumors. However, in the present paper, we will objectively focus on lymphomas tumors that account for about 10% of cancers diagnosed <20 years of age. Lymphomas are essentially lymphocyte-driven malignancy that results in solid tumors in peripheral lymphoid tissues.^{5,6} Broadly lymphomas have been divided into two categories: Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), the latter of which also includes Burkitt lymphoma. HL is composed of Reed-Sternberg cells derived from mature B-cells while as NHL is composed of numerous subtypes with 85–90% derived from B-cells and the remaining from T-cells.^{6,7}

Aims and objectives

The present study was objectively conducted to identify Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL) tumors among all patients presented with abdominal tumors. In addition to this, histopathological profile, clinical profile and disease prognosis among such patients has also been analyzed.

MATERIALS AND METHODS

The present study was objectively conducted to identify HL and NHL tumors among all patients presented with abdominal tumors. The clinical profile, efficacy of various investigations for early diagnosis, and multimodality treatment protocols in the management of these tumors were comprehensively assessed. A total of 64 pediatric patients presented with primary abdominal tumors were included in the study conducted at the Department of Pediatric division, SMHS Hospital Srinagar with effect from 2005 to 2008. However, after proper investigation, we identified only 16 patients with NHL tumor classification and four patients with HL type tumor classification. Records of all the patients admitted and operated were analyzed and were advised to attend the follow-up clinic. Patients were followed throughout the study period. While evaluating the results of the study, relevant history was taken and examination was done. Routine investigations such as hematological, blood bio-chemistry, urine analysis, and chest and abdominal radiographs were performed. Specific investigations included USG abdomen, fine needle aspiration cytology (FNAC) of the swelling, contrast-enhanced computed tomography abdomen and chest when

required, magnetic resonance imaging, tumor markers, bone marrow biopsy, and bone scan. Post-operative follow-up of the patients was done in all patients. The treatment was planned according to stage of disease, clinical examination, and investigative workup.

RESULTS

In the present study, we will present the results of the study comprehensively. Out of 64 patients, we identified only 20 (33.33%) patients with lymphomas tumors. Of them, NHL was accounting for 16 (25%) and HL was 4 (6.25%) tumors.

We observe that the most of the patients with NHL tumor accounting for (37.5%) belong to the age group (4–6) years followed by (25%) belonging to age group of (12–14) years. As reflected in Table 1; out of four patients with HL tumors, 2 (50%) patients were falling in the age group of (4–6) years and 2 (50%) had their age (6–8) years.

We observed that out of 16 patients with NHL tumors, 75% were males and 25% were females and majority of patients with NHL tumors, constituting about (66.66%) patients were belonging to rural area and 33.33% were belonging to urban area. Moreover, from a total of four patients with HL tumors, 50% were male and 50% were females and half of the patients with HL tumors were belonging to rural area and 50% were belonging to urban area.

The most of the patients with NHL in pediatric age group had intestinal obstruction (62.5%), swelling abdomen (50%), vomiting (43.75%), and the proportion of patients with other presenting feature is displayed in Table 2. In case of HL tumors, all the patients had swelling abdomen, (75%) had fever, (75%) had generalized weakness, and the proportion of patients with other symptoms is displayed in Table 2. The incidence of physical signs such as pallor, cervical LAP, axillary LAP, and inguinal LAP was observed in (43%), (25%), 18.75%, and 18.75% of NHL patients, respectively. Among four patients with Hodgkins disease, physical signs such as pallor, jaundice, edema, cervical

Table 1: Age distribution of studied patients

| Age (Years) | NHL, n1=16 | | HL, n2=4 | |
|-------------|------------|-------|----------|-------|
| | No. | % age | No. | % age |
| 4–6 | 6 | 37.5 | 2 | 50 |
| 6–8 | 2 | 12.5 | 2 | 50 |
| 8–10 | 2 | 12.5 | - | - |
| 10–12 | 2 | 12.5 | - | - |
| 12–14 | 4 | 25 | - | - |
| Total | 16 | 100 | 4 | |

HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma

Table 2: Incidence of various symptoms among studied patients

| Symptoms | NHL, n1=16 | | HL, n2=4 | |
|--------------------------|------------|-------|----------|-------|
| | No. | % age | No. | % age |
| Intestinal obstruction | 10 | 62.5 | 0 | 0 |
| swelling abdomen | 8 | 50 | 4 | 100 |
| Pain abdomen | 6 | 37.5 | 2 | 50 |
| Fever | 6 | 37.5 | 3 | 75 |
| Generalized weakness | 6 | 37.5 | 3 | 75 |
| Vomiting | 7 | 43.75 | 0 | 0 |
| Altered bowel habits | 5 | 31.25 | 0 | 0 |
| Weight loss | 3 | 18.75 | 3 | 75 |
| Anemia | 4 | 25 | 4 | 100 |
| Metastatic manifestation | 2 | 12.5 | 1 | 25 |

HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma

LAP, and axillary LAP were, respectively, observed in 100%, 50%, 50%, 100%, and 100% patients of HL disease. Routine KFT, LFT, and CBC were performed and the most of the patients revealed normal reports; however, Hb level was observed below 6 g% in one patient of NHL and 2 (50%) patients with HL disease.

Tumor characteristic with the help of USG was explored and all the (100%) patients reflected solid mass and lymph node status both in NHL and HL tumor type patients and the proportion of patients with liver involvement, spleen involvement, and ascites is reflected in Table 3. The CT investigation on patients with HL tumors revealed disease localized status in 2 (100%) patients, extent demarcated in 2 (100%) patients, and lymph nodes in 2 (100%) patients. We performed FNAC analysis among patients with accessible masses and observed that out of 10 patients of NHL with accessible mass, 5 (50%) are positive and 5 (50%) are negative, similarly, out of all four patients of HL with accessible mass, 2 (50%) were positive and 2 (50%) were negative. However, bone marrow aspiration cytology performed on 10 NHL patients revealed 6 (60%) positive malignant cells and 4 (40%) negative results.

From the above Table 4; we observe that the incidence of different staging among NHL patients was performed according to St. Jude Children Research Hospital staging scheme (Murphy) and the majority of patients were found to have Stage II observed in (37.5%) and Stage IV observed in (37.5%) followed by 25% with Stage II. Among four cases of Hodgkins lymphoma, we explored Ann Arbor staging scheme and found that all the 04 (100%) patients had Stage IV.

In the present study, only 6 (37.5%) patients with NHL were operated who had not responded to conservative management and rest of the patients were adjuvant therapy. In all the operated patients; ileum, ascending colon, or mesentery was involved. The right

Table 3: Tumor characteristics among study subjects on the basis of USG

| Tumor characteristics | NHL, n1=16 | | HL, n2=4 | |
|-----------------------|------------|-------|----------|-------|
| | No | % age | No | % age |
| Solid | 16 | 100 | 4 | 100 |
| Liver involvement | 9 | 56.25 | 3 | 75 |
| Spleen involvement | 9 | 56.25 | 4 | 100 |
| Lymph node status | 16 | 100 | 4 | 100 |
| Ascites | 9 | 56.25 | 3 | 75 |

USG: Ultrasonography, HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma

Table 4: Incidence of patients as per staging of patients

| Stage | NHL, n1=16 | | HL, n2=4 | |
|-----------|------------|-------|----------|-------|
| | No. | % age | No. | % age |
| Stage I | 0 | 0 | 0 | 50 |
| Stage II | 6 | 37.5 | 0 | 25 |
| Stage III | 4 | 25 | 0 | 0 |
| Stage IV | 6 | 37.5 | 4 | 50 |

HL: Hodgkin lymphoma, NHL: Non-Hodgkin lymphoma

hemicolectomy surgery was performed in all the six cases followed by chemotherapy COPP and in remaining 10 NHL patients who were not operated received combination of chemotherapy COPP and radiotherapy (2000–2500 rads) and out of 16 patients with NHL, five patients died. Among non-operated HL patients, manifestations were wide spread and hence they were put on a combination of chemo-radio therapy; methotrexate, oncovin (vincristine) methyl prednisolone, procarbazine (MOPP) six cycles radiotherapy 3500–400 rads at a rate of 1000–1100 rads per week. Out of four patients, three were alive and scummed to disease on chemotherapy as shown in Table 5.

DISCUSSION

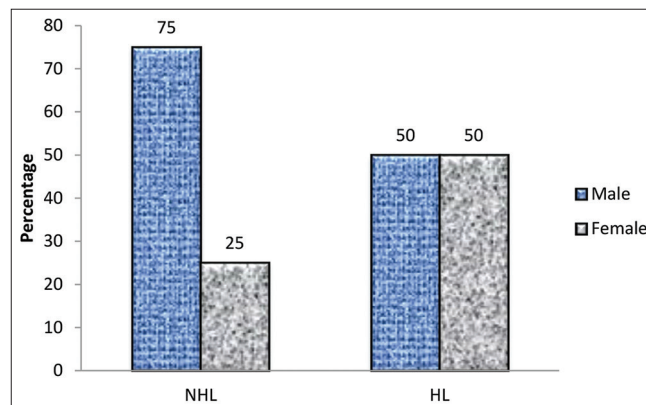
In the present study on the diagnosis, management, and clinical outcome of patients with NHL and HL tumors; we thoroughly analyzed patients data based on demographic, clinical, radiological, surgical, histopathological aspects, and follow-up data. Out of 64 patients, we identified only 20 (33%) patients with lymphomas tumors. Of them, NHL was accounting for 16 (25%) and HL was 4 (6.25%) tumors. Among all 16 patients of NHL, we observed a male dominance; out of 16 patients with NHL tumors, 75% were males and 25% were females and majority of patients with NHL tumors, constituting (as shown in Figure 1) about (66.66%) patients were belonging to rural area and 33.33% were belonging to urban area. Moreover, from a total of four patients with HL tumors, 50% were male and 50% were females and half of the patients with HL tumors were belonging to rural area

Table 5: Histopathological findings in 16 NHL patients

| Histopathology | No. | % age |
|---|-----|-------|
| Diffuse lymphocytic poorly differentiated | 8 | 50 |
| Diffuse lymphocytic well differentiated | 4 | 25 |
| Burkitts lymphoma | 4 | 25 |

NHL: Non-Hodgkin lymphoma

and 50% were belonging to urban area. In the present study, the overall male to female ratio was 2.3:1, which is comparable to 2.87:1 and 2.5:1 in the two other studies reported from India.^{8,9} Wright et al., (1997) and Pedrosa et al., (2007) also reported likewise male to female ratio of 2.7:1 and 2.4:1, respectively.^{10,11} We observed that most of the patients with NHL tumor accounting for (37.5%) belong to the age group (4–6) years followed by (25%) belonging to age group of (12–14) years and out of four patients with HL tumors, 2 (50%) patients were falling in the age group of (4–6) years and 2 (50%) had their age (6–8) years. Contrary to this, a study from Brazil reported that 48.2% patients are below 5 years of age.¹² Bharatnur et al., (2016) reported in their study that the most of patients with lymphomas accounting for 59.2% belong to age group of (6–15) years with 16% of their patients belong to 2–5 years and 24.8% belonged to the age group of 16–19 years.¹³ In the present study, the most of the patients with NHL had intestinal obstruction (62.5%), swelling abdomen (50%), and vomiting (43.75%). In case of HL tumors, all the patients had swelling abdomen, (75%) had fever, and (75%) had generalized weakness. Tumor characteristic with the help of USG was explored and all the (100%) patients reflected solid mass and lymph node status both in NHL and HL tumor type patients and the proportion of patients with liver involvement, spleen involvement, and ascites is reflected in Table 3. Likewise, results were reported by the previous Indian study in which peripheral nodes were involved in 48% of cases and GIT and intrabdominal/retroperitoneum were involved in 18.2% of cases.¹⁴ The incidence of different staging among NHL patients was performed according to St. Jude Children Research hospital staging scheme (Murphy) and the majority of patients were found to have Stage II observed in (37.5%) and Stage IV (37.5%) followed by 25% with Stage II. In the present study, out of 16 NHL tumors, only 6 (37.5%) patients were operated because 10 patients had either reached Stage III or IV. In all the operated patients; ileum, ascending colon, or mesentery were involved. The right hemicolectomy surgery was performed in all the six cases followed by chemotherapy COPP and in the remaining 10 NHL patients who were not operated received combination of chemotherapy COPP and radiotherapy (2000–2500 rads). Out of 10 operated patients, four patients succumbed

**Figure 1: Sex distribution among studied subjects**

to disease which make 60% survival rate. These survival rates are in conformity with the observations reported by Woolmer (1977) and Wataru et al., (1973).^{15,16} These results are also in consonance with the study of South West Oncology group who reported 53% survival in all NHL tumors and Murphy et al., (1980) who reported 55% survival rate among such type of patients.¹⁷ Among non-operated HL patients, manifestations were wide spread. These patients were diagnosed by lymph node biopsy. All these four patients were put on a combination of chemo radio therapy; methotrexate, oncovin (vincristine) MOPP six cycles radiotherapy 3500–400 rads at a rate of 1000–1100 rads/week. Out of four HL patients, three were alive and one succumbed to disease on chemotherapy which makes the survival rate among HL patients as 75%. In a study at Sydney-Faser Cancer Centre, 90% survival rate was reported in HL disease patients on chemoradiation which is more than what we observed;¹⁸ the reason for slightly lower survival rate among HL patients on chemoradiation may be ascribed to the lack of advanced laboratory system and supportive therapy. However, contemporary to our observation, 84% survival rate was reported in a joint study conducted at MD Anderson Hospital, USA which is almost comparable with our study.¹⁹

Even for children with advanced disease, the prognosis for NHL is reported as being very good. The prognosis for children diagnosed with this type of tumor has significantly improved over the past few decades as a result of advancements in the management of these cases. According to studies done on kids under the age of 15, the survival rate at the ages of 5–10 years increased from 76.6% to 73%, respectively, between 1990 and 1994 to 87.7% and 86.9%, respectively, between 2000 and 2004. Even better, the 10-year survival rate for kids who were diagnosed between 2005 and 2009 increased to 90.6%.²⁰ Despite all of these statistics, only four of our patients who had been diagnosed with NHL lived past the 2-year

mark. The possibility that elevated LDH levels may be a risk factor for a poor prognosis in these patients was raised in some of the studies that tried to identify the factors that influence prognosis.²¹ However, in our series of cases; only one of the five patients who passed away had a noticeably elevated level of LDH. Since the survival rate can be high even in cases of advanced stages at onset, the tumor stage does not always affect the prognosis of these tumors. Despite all of these facts, childhood NHL is still a fatal condition.

Limitations of the study

The limitation of the study was that the studied patients constituted a small sample and therefore a large sample studies are warranted.

CONCLUSION

Even though the prevalence of pediatric lymphoma is low but due to their complicated pathogenesis, they cannot be ignored. The present study demonstrated that both NHL and HL tumors may develop to advanced stage and even patient may die if the timely diagnosis and proper management is not there. We recommend collective team work of medicos from various departments for the precise diagnosis and optimal management of such patients.

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REFERENCES

- Willi UV. Imaging the child with an abdominal mass. In: Hodler J, Von Schulthess GK and Zollikofer CL, editors. *Diseases of the Abdomen and Pelvis*. Milano: Springer; 2006. https://doi.org/10.1007/88-470-0508-6_31
- Rodriguez-Galindo C, Friedrich P, Alcasabas P, Antillon F, Banavali S, Castillo L, et al. Toward the cure of all children with cancer through collaborative efforts: Pediatric oncology as a global challenge. *J Clin Oncol*. 2015;33(27):3065-3073. <https://doi.org/10.1200/JCO.2014.60.6376>
- Bhakta N, Force LM, Allemanni C, Atun R, Bray F, Coleman MP, et al. Childhood cancer burden: A review of global estimates. *Lancet Oncol*. 2019;20(1):e42-e53. [https://doi.org/10.1016/S1470-2045\(18\)30761-7](https://doi.org/10.1016/S1470-2045(18)30761-7)
- Surgery of Infants and Children: Scientific Principles and Practice*, Editor-Keith T., M.D. Oldham; Editor-Paul M. Colombani; Editor-Robert P., M.D. Foglia ISBN 10: 0397514174/ ISBN 13: 9780397514175, Published by Lippincott Williams & Wilkins, 1997 Keith TO, Paul MC and Robert PG. *Surgery of Infants and Children* 537-548, 549-565.
- Shanbhag S and Ambinder RF. Hodgkin lymphoma: A review and update on recent progress. *CA Cancer J Clin*. 2018;68(2):116-132. <https://doi.org/10.3322/caac.21438>
- Siegel RL, Miller KD and Jemal A. *Cancer statistics, 2017*. *CA Cancer J Clin*. 2017;67(1):7-30. <https://doi.org/10.3322/caac.21387>
- Allen CE, Kelly KM and Bollard CM. Pediatric lymphomas and histiocytic disorders of childhood. *Pediatr Clin North Am*. 2015;62(1):139-165. <https://doi.org/10.1016/j.pcl.2014.09.010>
- Jaffe ES, Harris NL, Stein H and Isaacson PG. Classification of lymphoid neoplasms: The microscope as a tool for disease discovery. *Blood*. 2008;112(12):4384-4399. <https://doi.org/10.1182/blood-2008-07-077982>
- Sandlund JT, Downing JR and Crist WM. Non-Hodgkin's Lymphoma in Childhood. *N Engl J Med*. 1996;334(19):1238-1248. <https://doi.org/10.1056/NEJM199605093341906>
- Wright D, McKeever P and Carter R. Childhood non-Hodgkin lymphomas in the United Kingdom: Findings from the UK Children's cancer study group. *J Clin Pathol*. 1997;50(2):128-134. <https://doi.org/10.1136/jcp.50.2.128>
- Pedrosa MF, Pedrosa F, Lins MM, Neto NT and Falbo GH. Non-Hodgkin's lymphoma in childhood: Clinical and epidemiological characteristics and survival analysis at a single center in Northeast Brazil. *J Pediatr (Rio J)*. 2007;83(6):547-554. <https://doi.org/10.2223/JPED.1726>
- Percy CL, Smith MA, Linet M, Ries LA and Friedman DL. Lymphoma and reticuloendothelial neoplasms. In: Ries LA, Smith MA, Gurney JG, Linet M, Tamra T and Young JL and Bunin GR, editors. *Cancer Incidence and Survival among Children and Adolescents: United States SEER Program 1975-1995*. Bethesda: ICCCI; 1999. p. 35-50.
- Bharatnur SS, Amirtham U, Premalata CS and Kumar RV. Distribution of Non-hodgkin Lymphoma in Children and Adolescents. A Study from a Regional Cancer Centre in South India. *IOSR J Dent Med Sci* 2016; 15:712.
- Sherief LM, Elsafy UR, Abdelkhalek ER, Kamal NM, Yousesef DM and Elbehedy R. Disease patterns of pediatric non-Hodgkin lymphoma: A study from a developing area in Egypt *Mol Clin Oncol* 2015;3(1):139-144. <https://doi.org/10.3892/mco.2014.425>
- Karales JH. *Memorial Sloan-Kettering Cancer Center Annual Report*; 1977. p. 22.
- Wataru WS, Teresa JV and Donald JF. *Clinical Pediatric Oncology*. St Louis: CV Mosby; 1973.
- Murphy SB, Dahl GV, Look AT, Ochs J, Abromowitch M, Pui CH, et al. Recent results from total therapy study X for standard and high risk acute lymphoblastic leukemia in children: Recognition of new clinical and biologic risk features. *Haematol Blood Transfus*. 1985;29:78-81. https://doi.org/10.1007/978-3-642-70385-0_19
- Schellong G, Pötter R, Brämwig J, Wagner W, Prott FJ, Dörfel W, et al. High cure rates and reduced long-term toxicity in pediatric Hodgkin's disease: The German-Austrian multicenter trial DAL-HD-90. The German-Austrian Pediatric Hodgkin's Disease Study Group. *J Clin Oncol*. 1999;17(12):3736-3744. <https://doi.org/10.1200/JCO.1999.17.12.3736>
- Wataru WS, Donal JF and Terasaj V. *Clinical Pediatric Oncology*. 3rd ed., Ch. 19. Mosby, United States; 1984, p. 416-451.
- Pulte D, Gondos A and Brenner H. Trends in 5- and 10-year survival after diagnosis with childhood hematologic malignancies

- in the United States. *J Natl Cancer Inst.* 2008;100(18):1301-1309.
<https://doi.org/10.1093/jnci/djn276>
21. Burkhardt B, Zimmermann M, Oschlies I, Niggli F, Mann G, Parwaresch R, et al. The impact of age and gender on biology, clinical features and treatment outcome of non-Hodgkin lymphoma in childhood and adolescence. *Br J Haematol.* 2005;131(1):39-49.
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Authors Contribution:

ZA- Designed the study and prepared the draft of manuscript; **ZK-** Performed review literature; and **SMK-** Performed the statistical analysis and wrote discussion.

Work attributed to:

General and Laparoscopic Surgery Department, SKIMS Medical College and Hospital, Sri Nagar, Jammu and Kashmir, India.

Orcid ID:

Dr. Zahida Akhtar - <https://orcid.org/0000-0002-6892-2613>

Dr. Zahid Kaleem - <https://orcid.org/0000-0003-3640-4640>

Dr. Showkat Majeed Kakroo - <https://orcid.org/0000-0002-9706-6692>

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