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CONTENTS

Editorial

Childhood Cancer Registry in Bangladesh: A Call to Action 1
Sabina Karim

Original Articles

Primary School Teachers as Potential First Responders to Childhood Cancer Warning Signs in a Referral-Dependent Region of Bangladesh 7
Renesha Islam, ATM Atikur Rahman, Tandra Chakma, Yesmin Tanjin Jahan, Wahida Nargis, Momtahina Mou, Md. Nazrul Islam Mondal, Majeda Khanam

Clinical-Pathological Profiles and Risk-Stratified Remission Outcomes of Pediatric Rhabdomyosarcoma in a Resource-Limited Setting 13
Ferdousi Begum, SM Rashed Zahangir Kabir, Mamtaz Begum, Mehnaz Akter, Shahinoor Akter Soma, Farida Yasmin, Marufa Akter Panna, Rezwana Rahman

Variation of Vitamin D Level with Induction Chemotherapy in Acute Lymphoblastic Leukemia in Children- A Prospective Observational Study 20
Mubina Nuzhat Chowdhury, Md. Anwarul Karim, Ferdousi Begum, Olivia Akter, Ainaeek Zaman, Tasnuva Khan, Nazia Khan Majlish

Clinical Presentation and Early Treatment Outcomes of Childhood Wilms Tumor at a Tertiary Referral Center in Bangladesh: A Retrospective Cohort Study 27
Momena Begum, Md. Abdul Khaleque, Helena Begum, Md. Anwarul Karim

Systemic Fungaemia among Pediatric Oncology Patients in a Tertiary Care Hospital of Bangladesh 33
S.M. Rezanur Rahman, Yesmin Tanjin Jahan, Md. Lutfor Rahman Molla, Mehnaz Akter, Amirul Al Rafi, Sumaya-E-Noor Ety, Md. Imran Habib, Md. Bani Yeamin, Hosna Jhahan

Case Report

Metastatic Neuroblastoma in a Child at a Non-Transplant Setting: Experience with Chemo-differentiation Therapy 38
Eshita Reza Khan, Ferdousi Begum, Sabina Karim

Review Article

Prevention of High-Dose Methotrexate-Induced Mucositis in Pediatric Malignancies: Resource-Limited Approaches 42
Eshita Reza Khan, Ferdousi Begum, Sabina Karim

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Editorial

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Childhood Cancer Registry in Bangladesh: A Call to Action

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Abstract

Each year, an estimated 400,000 children and adolescents aged 0–19 years develop cancer worldwide. Although childhood cancer is uncommon compared with adult cancer, its rarity, biological diversity and distinctive age distribution make accurate registration particularly important. Childhood cancers include leukaemias, lymphomas, central nervous system tumours, embryonal tumours, sarcomas and other uncommon malignancies. High-quality population-based registration is therefore essential to measure incidence, describe geographical and demographic patterns, identify inequities, plan services and support population-based survival assessment.

International efforts to standardize childhood-cancer incidence reporting have developed over several decades. The first volume of the International Incidence of Childhood Cancer (IICC) series was published in 1988 using data mainly from the 1970s, followed by a second volume in 1998. IICC-3, published in 2025, extends coverage to adolescents aged 15–19 years and includes high-quality data from 308 population-based cancer registries in 82 countries and territories.

Bangladesh has generated valuable childhood-cancer evidence through pioneering hospital-based and institutional initiatives, including studies involving Bangladesh Medical University (BMU), the National Institute of Cancer Research and Hospital (NICRH), and ASHIC Foundation. These studies demonstrate both the burden encountered by major centres and the feasibility of systematic data collection. However, hospital-based datasets cannot provide a complete population-level picture because children who are diagnosed or treated elsewhere, never reach specialist centres, remain undiagnosed, or die before referral may not be recorded.

Bangladesh now needs a coordinated and sustainable population-based childhood and adolescent cancer registration system, progressively expanding toward national coverage. Such a system would transform fragmented institutional information into actionable evidence and provide a foundation for measuring incidence, monitoring survival through appropriate follow-up, identifying inequities, planning services and assessing progress toward the WHO Global Initiative for Childhood Cancer target of at least 60% survival by 2030.

Introduction

Childhood cancer remains a major global public-health concern, with substantial disparities in outcomes across countries. An estimated 400,000 children and adolescents aged 0–19 years develop cancer globally each year. In high-income countries, where comprehensive services are generally accessible, more than 80% of children with cancer are cured, whereas in many low- and middle-income countries fewer than 30% are cured. To address this inequity, the World Health Organization (WHO), together with St. Jude Children's Research Hospital and other global partners, launched the Global Initiative for Childhood Cancer (GICC) in 2018, with the goal of achieving at least 60% survival globally by 2030 and reducing suffering among children with cancer.[1]

Reliable cancer data are central to this effort. Childhood cancers differ substantially from adult cancers in biology, clinical presentation, age distribution and classification. They include leukaemias, lymphomas, central nervous system tumours, embryonal tumours, germ-cell tumours, bone and soft-tissue sarcomas and other rare malignancies. Because individual tumour types are uncommon, incomplete registration can substantially distort estimates of disease burden and trends.

Hospital-based cancer data are valuable for describing patients who reach particular institutions, treatment patterns and service workload, but they are influenced by referral pathways, access to care and institutional catchment. In contrast, a population-based cancer registry aims to identify all eligible cancer cases occurring among residents of a clearly defined population, irrespective of where diagnosis or treatment takes place. A defined population denominator allows valid calculation of incidence rates, while complete case ascertainment, linkage and reliable follow-up are necessary for population-based survival analysis and evaluation of cancer-control programmes.[2]

The International Evolution of Childhood Cancer Registration

The International Incidence of Childhood Cancer series was established with the publication of IICC-1 in 1988. That first volume primarily presented incidence data from the 1970s and introduced a standardized approach to reporting childhood cancers according to diagnostic groups relevant to paediatric populations.[3]

IICC-2 followed in 1998, expanding international coverage and presenting data mainly from the 1980s. IICC-3 was published in 2025 and represents a further major expansion: it includes adolescents aged 15–19 years for the first time in the series and presents high-quality data from 308 population-based cancer registries in 82 countries and territories. The data are classified using the International Classification of Childhood Cancer, third edition, 2017 update. [4,5]

This progression—from IICC-1 in 1988, to IICC-2 in 1998, and IICC-3 in 2025—is directly relevant to Bangladesh. Population-based childhood-cancer registration is a well-established component of cancer surveillance, and Bangladesh now has an opportunity to build on existing institutional experience and contribute systematically to this international evidence base.

Survival Disparities and the Need for Reliable Cancer Data

The large survival gap between high-income and many low- and middle-income countries is associated with delayed or missed diagnosis, limited diagnostic capacity, barriers to accessing care, treatment abandonment, treatment-related toxicity, inconsistent availability of essential medicines and avoidable relapse.[1] For Bangladesh, addressing these challenges requires reliable answers to basic questions: How many children and adolescents develop cancer? Where do they live? What cancers do they have? Where are they diagnosed and treated? Do they complete treatment? What are their outcomes after diagnosis?

At present, Bangladesh does not have sufficiently complete population-based childhood-cancer data to answer these questions with adequate precision. Strengthening cancer registration is therefore essential not only for estimating disease burden but also for identifying gaps in diagnosis and care, supporting health-service planning and evaluating progress over time.

Bangladesh Has Evidence—but Predominantly Hospital-Based Evidence

Bangladesh should not be described as a country without childhood-cancer data. Important evidence

has already been generated through several pioneering hospital-based and institutional initiatives. Presented chronologically, these studies also show how data collection has evolved over time.

In 2013, Islam and Eden provided an important overview of paediatric oncology in Bangladesh. At BMU, the number of children with cancer presenting to the service increased from 280 in 2010 to 400 in 2011 and 455 in 2012. Among malignancies seen at BMU in 2012, acute lymphoblastic leukaemia accounted for 58%, followed by non-Hodgkin lymphoma (11%), acute myeloid leukaemia (10%) and neuroblastoma (5%). The authors also documented the establishment of the web-based Pediatric Oncology Networked Database (POND) in June 2012, demonstrating the feasibility of systematic electronic collection of paediatric-oncology data and outcomes.[6]

In 2016, Hossain et al. analysed 3,143 malignant neoplasms among individuals younger than 20 years diagnosed during 2001–2014 using data collected from NICRH and ASHIC Foundation. For 2011–2014, they reported an age-standardised incidence estimate of 7.8 per million person-years among children aged 0–14 years. Retinoblastoma and leukaemia were the leading childhood cancers. Among adolescents aged 15–19 years, the reported age-specific incidence estimate was 2.1 per million person-years, with malignant bone tumours, germ-cell and gonadal tumours, and epithelial tumours predominating. Importantly, the authors highlighted incomplete recording of cases, limited diagnostic capacity, inadequate access to health care and low awareness as likely explanations for the lower-than-expected observed rates. The study therefore provided valuable epidemiological information while also illustrating the limitations of the available registration framework.[7]

In 2022, Begum et al. reported a 12-year experience from the Paediatric Haematology and Oncology Department of NICRH. Their retrospective review covered 4,458 paediatric patients who attended the department between January 2008 and December 2019. The records were grouped using the International Classification of Childhood Cancer, third edition; the dataset also included cases that were not confirmed and a small number classified as other than malignancy. The study described the pattern of childhood malignancies encountered at a major tertiary cancer hospital and demonstrated the feasibility of sustained long-term hospital-based data collection.[8]

These contributions are important not because they constitute a national population-based registry, but because they show that Bangladesh already has clinicians, researchers, institutions and data systems capable of generating meaningful childhood-cancer information. They should be viewed as important building blocks for a coordinated national registration programme.

The Limitations of Hospital-Based Data in Estimating Childhood Cancer Incidence

The distinction between hospital-based and population-based data is fundamental in childhood-cancer epidemiology. Hospital-based data describe patients diagnosed or treated within a particular institution or network. They are useful for understanding disease patterns among patients who reach care, diagnostic workload, treatment practices and outcomes. However, they may exclude children who live far from specialist centres, receive care elsewhere, are not referred, remain undiagnosed or die before reaching a specialist facility.

This limitation is particularly relevant in Bangladesh, where specialist childhood-cancer services are concentrated mainly in major urban and tertiary centres. Children living in rural or underserved areas may therefore be less likely to appear in hospital datasets. The relatively low incidence estimates reported in the Bangladeshi study by Hossain et al. should consequently be interpreted cautiously. They may reflect true differences in disease occurrence, but underdiagnosis, referral barriers, limited access to care and incomplete case ascertainment are also plausible explanations identified by the authors.[7]

The central problem is therefore not simply a lack of data, but the absence of a sufficiently complete population-based framework to measure the burden of childhood cancer. Without population-based registration, Bangladesh cannot accurately determine incidence or geographical patterns, and cannot

confidently evaluate whether cancer-control services are reaching all children who need them. High-quality population-based registration is therefore essential for evidence-based health-service planning, resource allocation and cancer-control evaluation.[2]

Why Bangladesh Needs Population-Based Childhood Cancer Registration

Bangladesh has a large population of children and adolescents and a growing need for organized childhood-cancer services. A reliable registration system is essential to determine how many children develop cancer, where they live, and whether patterns of diagnosis and outcomes differ across regions and population groups.

A nationally coordinated population-based childhood-cancer registration system should aim to identify all eligible childhood and adolescent cancer cases among residents of clearly defined geographic populations, regardless of where diagnosis or treatment occurs. Standardized diagnostic terminology and coding based on the International Classification of Childhood Cancer would improve consistency and international comparability. The programme should begin with a core minimum dataset, clear case definitions, trained registry personnel, electronic case notification and active or mixed-source case ascertainment. Hospitals, paediatric oncology units, pathology and haematology laboratories, diagnostic centres, radiotherapy services and mortality records can serve as complementary sources for identifying cases and improving completeness.[2]

The core population-based registry should first prioritize complete and high-quality ascertainment of incident cases. Where resources permit, enhanced clinical modules or linkage with treatment databases can capture treatment initiation, treatment completion, treatment abandonment, relapse and long-term outcomes. Reliable follow-up and linkage with mortality data are particularly important for estimating survival at the population level. This phased approach would allow Bangladesh to establish a robust surveillance foundation without overburdening the registry at the outset.

Population-Based Registration for Measuring Inequalities in Childhood Cancer Care

One of the greatest values of population-based childhood-cancer registration is its ability to reveal inequalities that may be invisible in individual hospital datasets. Bangladesh needs to determine whether children living outside major urban centres have the same opportunity for timely diagnosis and treatment as those living near specialist facilities. It is also important to examine whether access to care differs by sex, geography or socioeconomic circumstances and whether treatment abandonment and survival vary across population groups.

Population-based data, especially when appropriately linked with clinical and outcome information, can help identify areas where new diagnostic or treatment services are needed, estimate workforce and medicine requirements, strengthen referral pathways and assess whether investments in childhood-cancer care are improving outcomes. Cancer registration is therefore not only an epidemiological activity; it is also a mechanism for health-system planning, equity and accountability.

Building on Existing Capacity for a National Childhood Cancer Registry

Bangladesh already has important foundations for developing a national childhood-cancer registration programme. In chronological order, Islam and Eden documented the feasibility of electronic paediatric-oncology data collection at BMU in 2012; Hossain and colleagues subsequently analysed childhood and adolescent cancer patterns using data collected by NICRH and ASHIC Foundation; and Begum and colleagues later demonstrated sustained hospital-based data collection over 12 years at NICRH. [6–8]

These initiatives should not simply be merged and labelled population-based. Instead, they should become major case-notification and data sources within a coordinated registry system governed by common definitions, standardized coding, interoperable electronic systems, deduplication procedures, quality assurance and clearly defined geographic coverage. A phased strategy could begin in selected population areas with reliable case ascertainment and then expand progressively toward broader national coverage.

International collaboration could support this development. In May 2020, IARC and St. Jude Children's Research Hospital launched the targeting Childhood Cancer through the Global Initiative for Cancer Registry Development (ChildGICR) collaboration to improve the quality and availability of childhood-cancer data, particularly in resource-limited settings. Its work in implementation, education and research provides a relevant model for countries seeking to strengthen childhood-cancer registration.[9]

A National Call to Action

Bangladesh should establish a National Childhood Cancer Registry programme as a coordinated, government-led initiative involving the Ministry of Health and Family Welfare, national cancer-control authorities, NICRH, paediatric oncology centres, medical universities, existing cancer registries, pathology and diagnostic services, professional organizations and relevant international partners.

The programme should begin with clearly defined population coverage, a standardized minimum dataset, common diagnostic and coding standards, trained registry staff, electronic case notification and systematic case ascertainment. Over time, linkage with pathology, haematology, hospital, treatment and mortality records can improve completeness and enable more reliable follow-up and survival analysis. Governance, data confidentiality, sustainable financing and routine data-quality assessment should be integral to the programme from the beginning.[2]

Importantly, the registry should ultimately support more than case counting. Through appropriate linkage and follow-up, it should help Bangladesh assess access to diagnosis and treatment, treatment continuity, population-based survival and inequities across regions and population groups. Reliable baseline and follow-up data are essential for monitoring progress toward the WHO GICC target of at least 60% survival by 2030.[1]

Conclusion

The international history of childhood-cancer registration provides a clear lesson. IICC-1 was published in 1988, IICC-2 in 1998 and IICC-3 in 2025, progressively expanding the availability and comparability of population-based childhood-cancer incidence data. IICC-3 further reinforces the value of standardized childhood and adolescent cancer surveillance across diverse settings.[3–5]

Bangladesh has already made important contributions through studies and data systems at NICRH, ASHIC Foundation, BMU and other institutions. These initiatives have generated valuable knowledge, documented the burden encountered by major centres and shown that systematic data collection is feasible. The next step is to move beyond fragmented institutional evidence toward a coordinated population-based registration system.

Bangladesh needs a National Childhood Cancer Registry programme. Population-based registration would provide the defined denominator required to measure incidence, identify geographical and socioeconomic inequities, guide resource allocation and service planning, and—when combined with reliable follow-up—provide the evidence required to measure survival and monitor progress.

A registry is therefore not simply a database. It is an instrument of visibility, accountability and action.

Every child with cancer should count—not only as a patient who reaches a hospital, but as a child within a defined population whose access to diagnosis, treatment and survival should be measurable. For Bangladesh, establishing a National Childhood Cancer Registry is not merely an academic exercise or an optional future project. It is a necessary step toward closing the survival gap and translating the goals of the Global Initiative for Childhood Cancer into measurable national progress.

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Original Article

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Primary School Teachers as Potential First Responders to Childhood Cancer Warning Signs in a Referral-Dependent Region of Bangladesh

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Abstract

Background: *Early diagnosis is a major determinant of childhood cancer survival. Despite substantial improvements in high-income countries, outcomes remain poor in Bangladesh because of delayed diagnosis and limited access to specialised paediatric oncology services. Primary school teachers may facilitate earlier recognition of warning signs for childhood cancer through regular contact with children.* **Objective:** *To assess primary school and kindergarten teachers' knowledge and attitudes regarding childhood cancer warning signs and identify factors associated with such knowledge in Gopalganj, Bangladesh.* **Methods:** *A cross-sectional study was conducted involving 200 primary school and kindergarten teachers from five upazilas of Gopalganj district, between November 2025 and April 2026, after obtaining ethical clearance. A structured questionnaire containing 12 childhood-cancer warning-sign items derived from International Society of Paediatric Oncology (SIOP) materials was used. Knowledge scores (0–12) were categorised as good (9–12), fair (5–8), or poor (0–4).* **Results:** *The mean knowledge score was 6.52±2.08. Good, fair, and poor knowledge was observed in 24.0%, 43.0%, and 33.0% of the participants, respectively. Recognition of individual warning signs varied from 11.0% for leukocoria to 81.5% for persistent fever. Teachers working in urban schools and those who had received previous childhood cancer training had significantly higher knowledge scores and were independently associated with good knowledge (both p<0.001). Although attitudes toward teachers' involvement in early recognition were highly positive, 25.5% incorrectly believed paediatric cancer is contagious. Face-to-face workshops were the preferred training modality.* **Conclusions:** *The awareness of childhood cancer warning signs among primary school and kindergarten teachers was insufficient, especially concerning the less common yet highly specific indicators. Targeted training, especially for rural teachers, and stronger collaboration between the education and health sectors may improve early recognition and timely referral of children with suspected malignancies.*

Keywords: *Childhood cancer; Early diagnosis; Primary school teachers; Childhood cancer warning signs; Diagnostic delay.*

Introduction:

Globally, paediatric cancer is a major cause of disease-related mortality among children and adolescents, with nearly 400,000 cases diagnosed annually—approximately 90% in Low- and Middle-Income Countries (LMICs)[1]. While survival exceeds 80% in high-income countries, it remains below 30% in many LMICs due to late diagnosis, limited access to specialised care, treatment abandonment, and health-system inequities[2-5]. To bridge these disparities, the World Health Organisation Global Initiative for Childhood Cancer (WHO GICC) aims to achieve at least 60% worldwide survival by 2030 through the CureAll framework, which emphasises early diagnosis, timely referral, standardised treatment, and strengthened health systems[1,4,6].

In Bangladesh, childhood malignancies remain an under-recognised public health challenge. The first nationwide epidemiological study reported a lower-than-expected incidence, driven by limited public awareness, inadequate diagnostic facilities, poor access, and incomplete registration[7]. Furthermore, the WHO South-East Asia Regional Office identified delayed diagnosis and unequal access to specialised services as primary barriers to survival in the region[8]. In referral-dependent rural districts like Gopalganj, secondary care is available via 250 Bedded General Hospital and Gopalganj Medical College Hospital, but children with suspected malignancies require referral outside the district, prolonging diagnostic timelines through transportation and financial hurdles[9-11].

Primary school teachers spend substantial time with children and are ideally positioned to identify early physical or behavioural changes. The International Society of Paediatric Oncology (SIOP) Childhood Cancer Early Diagnosis and Appropriate Referral (CEDAR) initiative aims to strengthen early recognition among healthcare providers[6]. Given the scarcity of data on teacher awareness in Bangladesh, this study aimed to assess knowledge and attitudes regarding childhood cancer warning signs and identify associated factors among primary school and kindergarten teachers in Gopalganj.

Methods:

Following ethical approval, a cross-sectional study was conducted from November 2025 to April 2026 among primary school and kindergarten teachers in Gopalganj district (comprising Gopalganj Sadar, Kotalipara, Tungipara, Kashiani, and Muksudpur upazilas). Children with suspected malignancies in this referral-dependent region are routinely referred to tertiary hospitals outside the district.

Eligible participants included government and non-government teachers educating children aged 3–12 years attending Gopalganj Medical College Hospital, for personal or family medical care, with ≥1 year of teaching experience and written informed consent. Non-teaching personnel, administrative staff, teachers on extended leave (>3 months), and pilot study participants were excluded. A total of 200 teachers were recruited using snowball-augmented convenience sampling, balanced across all five upazilas.

Data were collected using a structured, pre-tested Bangla questionnaire incorporating 12 warning-sign items derived from SIOP childhood cancer warning-sign materials, the Childhood Cancer Early Diagnosis and Appropriate Referral (CEDAR) initiative, and relevant literature[4,6,8]. The questionnaire comprised five domains: sociodemographic characteristics, access to health information and media, knowledge of the 12 childhood-cancer warning-sign items, attitudes toward childhood cancer and early referral, and previous childhood cancer training and information sources. Knowledge was assessed using 12 dichotomous items (score range: 0–12) and categorised as good (9–12), fair (5–8), or poor (0–4). Attitudes were assessed using five statements on a five-point Likert scale.

Data were analysed utilising SPSS Statistics version 26.0. Independent t-tests, ANOVA, and multivariable logistic regression (adjusting for age, sex, school location, training, and experience) were performed. Statistical significance was set at $p < 0.05$.

Results:

In all, 200 kindergarten and primary school teachers took part in this study. Most participants were female (71.0%), aged 31-40 years (45.0%), worked in government primary schools (70.5%), and had 6–10 years of teaching experience (61.0%) (Table I).

Table I: *Sociodemographic Characteristics of the Study Participants (N=200)*

Variable	Category	n (%)
Age (years)	20–30	68 (34.0)
	31–40	90 (45.0)
	>40	42 (21.0)
Sex	Female	142 (71.0)
	Male	58 (29.0)
School Location	Rural	70 (35.0)
	Peri-urban	96 (48.0)
	Urban	34 (17.0)
School Type	Government Primary	141 (70.5)
	Non-Govt / Kindergarten	59 (29.5)
Teaching Experience	1–5 years	50 (25.0)
	6–10 years	122 (61.0)
	>10 years	28 (14.0)

The mean knowledge score was 6.52 ± 2.08 (median: 6; IQR: 5–8; range 1-12). Overall, 24.0% had good knowledge, 43.0% fair, and 33.0% poor. Recognition of the 12 childhood-cancer warning-sign items varied substantially (Figure 1). Persistent fever (81.5%), persistent pallor (73.0%), and unexplained weight loss (69.5%) were the most frequently recognised warning signs, whereas leukocoria (11.0%), progressive visual changes (15.5%), persistent bone pain or limping (19.5%), and persistent enlarged lymph nodes (27.0%) were the least recognised.

Only 13.0% previously received childhood cancer-related training. Doctors and medical personnel (32.0%) were the main information sources, and face-to-face workshops (44.0%) were the preferred training format (Table II).

In the multivariable logistic regression analysis (Table III), urban school location (AOR 16.84, 95% CI 5.24–54.11; $p < 0.001$) and previous childhood cancer training (AOR 12.52, 95% CI 4.02–38.98; $p < 0.001$) were independently associated with good knowledge. In contrast, age and teaching experience were not significant predictors.

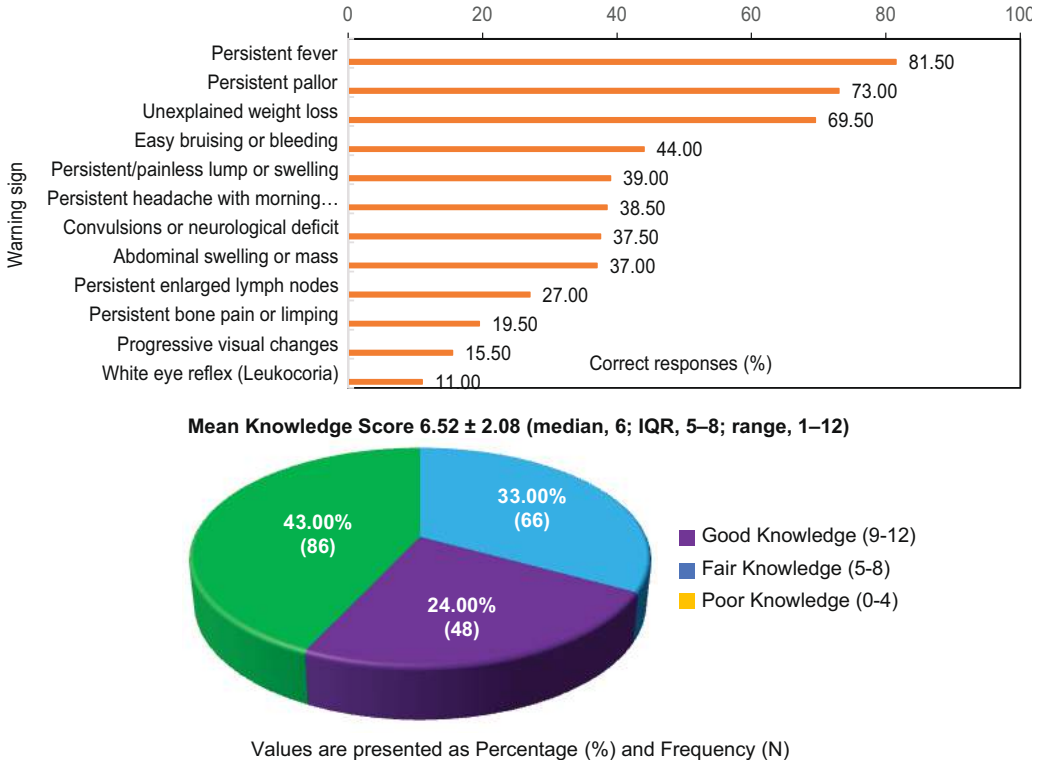


Figure 1. *Recognition of 12 SIOP-derived childhood-cancer warning-sign items (N=200)*

Table II: Training and Information Characteristics of the Study Participants (N=200)

Variable	Category	n (%)
Prior Cancer Training	No	174 (87.0)
	Yes	26 (13.0)
Primary Info Source	Doctor / Medical Personnel	64 (32.0)
	Nurse	35 (17.5)
	Internet / Social Media	31 (15.5)
	Friends / Relatives / Media	52 (26.0)
	None	18 (9.0)
Preferred Training Modality	Face-to-face workshop	88 (44.0)
	Hospital outreach	60 (30.0)
	Online webinar / App	42 (21.0)
	Printed booklet / TV	10 (5.0)

Table III: U*nivariable and multivariable logistic regression analysis of factors associated with good knowledge of childhood cancer warning signs among primary school teachers (N = 200)*

Variable	Good knowledge n (%)	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	*p*-value
Age group (years)					
20–30	16 (26.7)	1.00	–	1.00	–
31–40	21 (23.3)	0.84 (0.40–1.78)	0.652	0.91 (0.41–2.03)	0.819
>40	11 (22.0)	0.77 (0.31–1.91)	0.575	0.82 (0.31–2.18)	0.694
School location					
Rural	9 (11.8)	1.00	–	1.00	–
Peri-urban	18 (18.8)	1.73 (0.72–4.14)	0.217	1.61 (0.63–4.09)	0.316
Urban	21 (75.0)	22.20 (7.80–63.18)	<0.001	16.84 (5.24–54.11)	<0.001
Previous childhood cancer training					
No	28 (16.1)	1.00	–	1.00	–
Yes	20 (76.9)	17.34 (6.21–48.43)	<0.001	12.52 (4.02–38.98)	<0.001
Teaching experience					
≤5 years	10 (20.0)	1.00	–	1.00	–
6–10 years	29 (23.8)	1.25 (0.53–2.94)	0.612	1.12 (0.45–2.80)	0.804
>10 years	9 (32.1)	1.89 (0.67–5.32)	0.228	1.46 (0.47–4.57)	0.512

Table IV: *Attitudes Toward Childhood Cancer Early Recognition (N=200)*

Statement	Strongly Agree n (%)	Agree n (%)	Neutral n (%)	Disagree n (%)	Strongly Disagree n (%)
Teachers should receive training	187 (93.5)	2 (1.0)	11 (5.5)	0 (0)	0 (0)
Teachers can contribute to early recognition	186 (93.0)	3 (1.5)	8 (4.0)	3 (1.5)	0 (0)
Early diagnosis improves survival	127 (63.5)	3 (1.5)	42 (21.0)	21 (10.5)	7 (3.5)
Teachers should advise prompt medical evaluation	160 (80.0)	5 (2.5)	28 (14.0)	3 (1.5)	4 (2.0)
Childhood cancer is contagious (Misconception)	46 (23.0)	5 (2.5)	9 (4.5)	23 (11.5)	117 (58.5)

The participants showed generally positive attitudes toward childhood cancer awareness (Table IV). Most strongly agreed that teachers should receive childhood cancer training (93.5%) and could contribute to early recognition (93.0%). However, 25.5% incorrectly believed that childhood cancer is contagious.

Discussion:

To our knowledge, this is the first study to evaluate primary school teachers' awareness of childhood cancer warning signs in Bangladesh. Although teachers interact with children daily, only 24% demonstrated good knowledge, indicating a substantial awareness gap consistent with reports of gaps in cancer awareness among parents in other settings[12]. Given that early diagnosis determines survival, limited awareness among frontline educators contributes to delayed referrals where specialised oncology services are concentrated in distant tertiary centres[2,3,13,14].

Recognition varied significantly across warning signs. While common systemic symptoms like persistent fever (81.5%), pallor (73.0%), and weight loss (69.5%) were widely recognised, specific signs such as leukocoria (11.0%), visual changes (15.5%), bone pain/limping (19.5%), and lymphadenopathy (27%) were poorly recognised. These findings are clinically crucial because subtle, specific signs correspond to malignancies such as retinoblastoma and bone tumors, where diagnostic delays severely impact visual, functional, and survival outcomes[14-16]. Continued dissemination of the International Society of Paediatric Oncology (SIOP) warning signs may improve awareness among non-healthcare professionals[17].

Teachers from urban schools achieved significantly higher knowledge scores ($p < 0.001$) than those from rural schools, and urban schools' location remained an independent predictor of good knowledge ($p < 0.001$). Similar disparities have been reported in other LMICs, reflecting unequal access to health information and educational opportunities[3,13]. Previous childhood cancer training was also strongly associated with better knowledge, highlighting the value of structured educational programs. Comparable improvements in cancer awareness following educational interventions have been reported in prior research. These findings support integrating childhood cancer awareness into both pre-service and in-service teacher training programs in line with the World Health Organisation Global Initiative for Childhood Cancer (WHO GICC)[13,18,19].

Participants showed positive attitudes toward childhood cancer awareness, with most agreeing that teachers should receive training (93.5%) and could contribute to early recognition (93.0%). However, one-quarter (25.5%) incorrectly believed that childhood cancer is contagious, indicating persistent misconceptions that should be addressed through future educational interventions[12]. Doctors and other healthcare professionals (32.0%) were the most common sources of information, and face-to-face workshops (44.0%) and hospital outreach programmes (30.0%) were the preferred training methods. Strengthening teamwork between the education and health services can enhance community awareness,

promote earlier referrals, and ultimately contribute to better outcomes for paediatric malignancies, as supported by previous studies[3,12,13,17].

Targeted lessons on childhood cancer awareness should be incorporated into pre-service and in-service training programmes for teachers, notably those in rural areas. Enhancing cooperation between the education and health fields could lead to prompt recognition and timely referral of children with suspected malignancies.

Conclusion:

Teachers demonstrated inadequate knowledge of childhood cancer warning signs despite positive attitudes. Urban location and prior training independently predicted higher knowledge. Targeted training for rural teachers and education-health sector collaboration is essential to support early diagnosis and ultimately improve outcomes of paediatric malignancies in Bangladesh.

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Conflict of interest statement

No potential conflicts of interest relevant to this article were reported.

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Original Article

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Clinical-Pathological Profiles and Risk-Stratified Remission Outcomes of Pediatric Rhabdomyosarcoma in a Resource-Limited Setting

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Abstract:

Background: *Rhabdomyosarcoma (RMS) is the most common soft-tissue sarcoma in children and requires multimodal treatment using a risk-stratified approach. Risk group stratification based on clinicopathological profiles is crucial for determining prognosis and optimizing treatment intensity. The National Institute of Cancer Research and Hospital (NICRH), Bangladesh, is a tertiary cancer hospital providing comprehensive multimodal oncology care. This study aimed to characterize the clinicopathological profiles of pediatric RMS and evaluate remission rates by risk group in a resource-limited setting using a risk-adapted multimodal treatment approach.* **Materials and Methods:** *This prospective observational study included children with RMS who attended the Pediatric Hematology and Oncology Department of the NICRH between January 2016 and December 2020. Children of both sexes aged ≤ 18 years with a definitive diagnosis of RMS were included consecutively. Each child was thoroughly evaluated clinically, and their imaging, surgical, and pathological reports were reviewed carefully. Based on their clinical and pathological profiles, children with RMS were stratified into risk groups. Treatment was assigned to each risk group according to the Children's Oncology Soft-Tissue Sarcoma (COG-STS). The overall outcome was measured according to the risk group in December 2025. Data were analyzed using SPSS version 23.* **Results:** *This study enrolled 130 children with RMS. Males were predominant (n=77; M: F = 1.5), and the age ranged from 0.33 to 17 years, with a mean of 6.3 ± 4.8 y. Favorable histology, ERMS constitutes 79.2% of cases, but unfavorable (UF) sites (76.9%), size ≥5 cm (86.9%), and CG groups III and IV (77.6%) were present in most cases. Moreover, nodal involvement and metastatic disease were present in 33.1% and 14.6% of the children, respectively. Based on the clinicopathological profiles, the low-risk group accounted for 15.4%, the intermediate-risk group for 70.0%, and the high-risk group for 14.6% of the children studied. The remission rate was found in only 23.1%, and the majority (76.9%) experienced death and relapse. The remission rate varied, with 55.0% in the low-risk group and 20.9% in the intermediate-risk group. In contrast, no remission was observed in the high-risk group.* **Conclusion:** *The study found that most children in the low-risk group achieved remission, whereas no remission was observed in the high-risk group. Most children belonged to the intermediate-risk group, which had a low remission rate and a high rate of mortality and relapse.*

Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma, accounting for 3.5% of all malignant neoplasms in children aged 0–14 years and 2% in those aged 15–19 years.[1,2] The remission rate of localized rhabdomyosarcoma has improved dramatically with combined-modality treatment, with more than 70% of patients surviving five years after diagnosis.[3,4]

Clinical-pathological profiles are the prime component for risk group stratification in children with RMS in both the Children's Oncology Group (COG) and European Pediatric Soft Tissue Sarcoma Study Group (EPSSG). Risk groups determine prognosis, treatment duration, and intensity.

The most common primary sites of Rhabdomyosarcoma include the head and neck region (Parameningeal), the genitourinary tract, and the extremities, with less common primary sites including the trunk, chest wall, perineal/anal region, abdomen, the retroperitoneum, and biliary tract.[3-5] A favorable prognosis is observed in cases involving the orbital and non-para-meningeal head and neck sites. Improved survival is found in children with tumors ≤5 cm compared to those with tumors > 5 cm.[3] In the IRS-I and IRS-II studies, the histological subtype, alveolar variety, was associated with less favorable outcomes, even in patients whose primary tumors were completely resected (Group I).[4] The FOXO1 gene fusion status, which is associated with poor prognosis, typically occurs only in tumors with alveolar histology.[5]

The extent of the disease after the primary surgical procedure (surgical-pathological or clinical group) correlated with the outcome. Relapses are more common in patients who have unresectable disease, tumor in an unfavorable site at diagnosis, or metastatic disease at diagnosis.[5] The best prognosis was observed in children aged 1–9 years.[6] In contrast, prognosis is poor for children below 1 year of age, often because of the need for treatment modifications. In infants, chemotherapy doses are reduced by 50% to avoid chemotherapy-related toxicities, and infants are less likely to receive radiation therapy for local control because of the high incidence of late effects.[1,2,3]

RMS management is complex and challenging because of its aggressive growth pattern, high metastatic potential, disease heterogeneity, and the need for evolving treatment regimens. Moreover, the lack of molecular testing facilities, limited investigation capacity, and advanced-stage disease make the situation more challenging for resource-constrained countries such as Bangladesh.

All RMS children require multimodal treatment, including systemic chemotherapy (CT) along with either surgery or radiation therapy (RT) to maximize local tumor control.[6,7,8] Multimodal treatment is determined based on prognostic factors and risk groups. Risk-group stratification is defined based on pre-treatment TNM staging, surgical-pathological Group (CG), and tumor histology (/* FOXO1 fusion status).[4,9,10] Risk-directed multimodality therapy reduces treatment-related morbidity by tailoring chemotherapy and radiotherapy doses without compromising the outcome for low-risk patients and reducing the risk of complications related to chemotherapy and radiotherapy. Moreover, the remission rate in high-risk patients should be improved with more intensive therapy.

The National Institute of Cancer Research and Hospital (NICRH) is a tertiary hospital in Bangladesh, where RMS is a common malignancy in children. Each year, 30-35 children usually attend the Pediatric Hematology and Oncology Department (PHO) of the NICRH. Multimodal treatment can be applied in a one-stop setting, but with diverse obstacles. We face diverse challenges, such as debulking surgery at presentation, advanced-stage disease, failure to receive the scheduled dose and time of radiotherapy, treatment irregularities, chemotherapy-related toxic death, refractoriness, and early dropout in children with RMS. To improve the outcomes of children with RMS, there is a need to identify the most favorable group. Hence, it is mandatory to understand the various clinicopathological profiles and risk groups of children with RMS.

This study aimed to determine the clinicopathological profiles and risk-group-based remission rates in children with RMS treated with multimodal therapy at a resource-limited center in Bangladesh.

Patients and Methods

This prospective observational study was conducted on children with RMS who attended the Pediatric Hematology and Oncology Department of the NICRH, Bangladesh, between January 2016 and December 2020. Children of both sexes aged ≤ 18 years with a definitive diagnosis of RMS were included consecutively. Informed consent was obtained from the guardians of the children before their inclusion in the study. Information related to the

clinical profile, imaging reports, histopathological reports, immunohistochemistry, and postsurgical status was gathered in a pre-formed data sheet. Magnetic resonance imaging (MRI) or computed tomography (CT) scans of the primary sites were performed for all patients. For metastatic work-up, chest X-ray or CT, bone scan, CSF study, and bilateral bone marrow aspiration and biopsy were performed when indicated.

After gathering all clinical and pathological profiles, the stage was determined based on the primary site, tumor size, and presence or absence of regional lymph nodes and/or distant metastases.[11,12] The Clinical Group (CG) was determined by postsurgical resection status/biopsy, with a pathological assessment of the tumor margin and lymph node disease.[4,13] Risk stratification was performed using histopathological subtype, tumor stage, and postsurgical status.[3,11,12] Due to a lack of facilities, gene fusion status was not assessed. The study followed the risk-stratified Children Oncology Group (COG) treatment protocol for each risk group. The dose and timing of radiation therapy were determined according to the Rhabdomyosarcoma Group, Histology, and Site of Disease (COG) using 3-dimensional conformal RT.[14]

Evaluation was performed before radiotherapy, after each 6-week chemotherapy cycle, and before any definitive surgical measure if gross tumour residue was found at presentation. Follow-up was given after treatment completion four monthly in 1st two years, six-monthly afterwards. The last follow-up was given on 30th December 2025.

Statistical Analysis

Outcomes were measured as remission, relapse, refractoriness with progressive disease, death, and dropout rates. Outcome status was determined during the treatment period as well as after treatment. The updated disease status was collected from follow-up records and from telephone interviews with guardians. Data were analyzed using SPSS version 23.

Results

Of the 146 enrolled children, 16 were dropped out. Among the 130 children studied, the ages ranged from 0.33 to 17.0 years, with a mean of 6.3 years ± SD 4.8. The median age was 5.0 years. The study population was predominantly male (n=77), with a male-to-female ratio of 1.5. The clinical and pathological profiles are described in Table 1.

Table 1. *Clinical-pathological profiles of studied children (n=130)*

Variable	Number (N)	Percentage (%)
Age in years		
<1	12	9.2
1 to <10	83	63.9
10 to <19	35	26.9
Sex		
Male	77	59.2
Female	53	40.8
Primary site of the tumor		
Orbital	15	11.5
Head-Neck NPM	06	4.6
Head-Neck PM	42	32.3
Trunk and Extremity	26	20.0
Genito-urinary (non-bladder/ non-prostate)	09	6.9
Genito-urinary (bladder/ Prostate)	08	6.2
Abdominal Cavity	17	13.1
Perineal and perianal area	07	5.4
Type of sites		
Favorable sites (F)	30	23.1
Unfavorable sites (UF)	100	76.9
Tumor Size		
≤5 cm (a)	17	13.1
> 5 cm (b)	113	86.9
Nodal status(N)		
N0	05	3.8
N1	43	33.1
NX	82	63.1
Metastases(M)		
M0	111	85.4
M1	19	14.6
Histology subtype		
Embryonal	103	79.2
Alveolar	23	17.7
Undifferentiated	04	3.1
TNM staging		
Stage 1	18	13.8
Stage 2	10	7.7
Stage 3	83	63.8
Stage 4	19	14.6
Post-surgical pathological status of tumor (Clinical Group-CG)		
CGI	02	1.5
CGII	27	20.8
CG III	83	63.8
CG IV	18	13.8

Using the COG-Risk stratification, based on the clinicopathological characteristics, low-risk was 15.4%; intermediate-risk, 70.0%; and high-risk, 14.6% among the studied children [Figure 1].

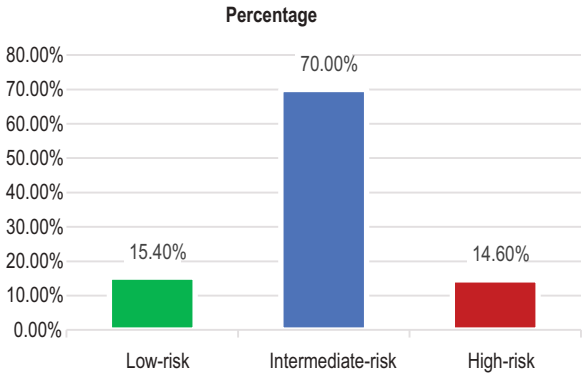


Figure 1: *COG-Risk group distribution of the studied children.*

Outcome: Initially, 83.1 % (n = 108) of the studied children showed an excellent response to chemotherapy; 16.9% (n=22) had disease progression. From the 83.1% responsive cases, only 23.1% achieved complete remission, 42.3% relapsed, and 17.7% died due to chemotoxicity and/or disease progression after responding for a period. From the relapse cases, 35.5% ultimately died, and only 3.8% were alive at the last follow-up.

At the last follow-up in December 2025, the remission rate was 23.1% (n=30) among the 130 children [Figure 2].

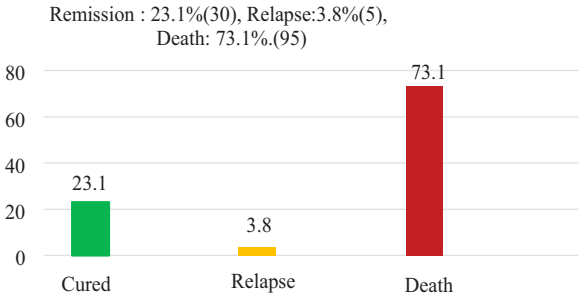


Figure 2: Overall outcome of enrolled (n=*130) children*

From the low-risk group, 55.0% achieved remission, and from the intermediate-risk group, only 20.9 % achieved remission. In contrast, no remission was observed in the high-risk group (Table II).

Table II: Outcome by Risk Group (n=130)

Outcome/ Risk group	Remission Number (%)	Relapse Number (%)	Death Number (%)	Total/ Percentage
Low risk	11 (55%)	01 (5%)	8 (40%)	20(100%)
Intermediate risk	19 (20.9%)	04 (4.4%)	68 (74.7%)	91 (100%)
High risk	00 (00%)	00 (00%)	19 (100%)	19(100%)
Total/Percentage	30(23.1%)	05(3.8%)	95(73.1%)	130 (100%)

Discussion

The recent NICRH study identified various clinical-pathological characteristics among the 130 children studied. The majority of the children (63.9%) were in the favorable age group (1 to <10 years), and most (79.2%) had favorable histology (embryonal). Different studies reported better outcomes in children aged 1–9 years than in those younger than 1 year or older than 10 years [6, 15,16]. This is because embryonal histology is common in this age group. Male patients were predominant(n=77) among the studied children. Male patients have a higher incidence of embryonal tumors than female patients.[4] This reflects the male-dominant variables in this observational study.

The prognosis of children with RMS is also influenced by tumor site and size, resectability, metastases at diagnosis, nodal involvement, response to therapy, and gene fusion status.[4,17-25] According to the studies mentioned, the majority of the clinicopathological profiles of the recently studied children were associated with poor prognosis, despite the favorable age group and histological subtype. In most cases, tumors were in unfavorable sites (76.9%), and size was >5 cm (86.9%). Moreover, nodal involvement (33.1%),

metastatic disease (14.6%), alveolar histology (17.7%), and advanced clinical group (III and IV; 84.6%) were unfavorable prognostic factors for the studied children. Gene fusion status and other biological characteristics were not studied because of a lack of facilities for such analyses.

With the mentioned clinicopathological profiles, the low-risk group accounted for only 15.4% among the studied children, with the majority (70%) in the intermediate-risk group and less common (14.6%) in the high-risk group. The remission rate varied by risk group among the studied children.

In the COG studies, approximately 25% of newly diagnosed patients were low risk. COG studies proved that highly tailored, less intense therapies can maintain excellent survival rates while successfully minimizing toxic burdens in children with low-risk rhabdomyosarcoma. The 5-year overall survival (OS) rate was 97%, and 93% in a different subset of the low-risk group.[26] The COG-STS study found estimated 5-year FFS rates were 89% (95% CI, 84% to 92%) for subgroup A patients (n = 264) and 85% (95% CI, 74% to 91%) for subgroup B patients (n = 78).[27] Our study found a remission rate of 55% in the low-risk group, far lower than in the COG studies.[26,27]

In the COG studies, approximately 50% of newly diagnosed patients were in the intermediate-risk category. But our study found that 70% of children were in the intermediate-risk group. The study faced challenges with the majority of children in the intermediate-risk group, who achieved a very low remission rate (20.9%). On the contrary, in different COG studies, the 4-year OS was 73% for the VAC regimen.[28,29]

The high-risk group of patients continues to have a relatively poor prognosis with current therapy (5-year survival rate of ≤50%). Our study had 14.6% of children in the high-risk group, who were treated with the COG-STS protocol, with no one achieving remission. COG-STS had experience with outcomes of 109 patients with metastatic disease, with 3-year OS and EFS of 34% (SE, 1.7) and 27% (SE, 1.6), respectively. The intensive protocol did not appear to improve outcomes for the highest-risk patients.[30,31]

In high-income countries, an overall remission rate of 70–80% was observed in RMS with current treatment regimens, with significant variability among various risk groups.[32,33] In contrast, low- and middle-income countries report a suboptimal overall survival (OS) rate of less than 50%.[34,35]

In the existing settings of Bangladesh, with various challenges, our study found only a 23.1 % (n=23) complete remission rate, which is far below the above-mentioned studies.[32,33,34,35] The poor outcome, with a low remission rate (23.1%) and high rates of death and relapse (65.1%) among the studied children, was a challenging and painful journey for both children and treating physicians.

Conclusion

The study found a majority remission among the children in the low-risk group, but none were in the high-risk group. In the intermediate risk group, the remission rate was low, with a high rate of mortality and relapse.

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Variation of Vitamin D level with Induction Chemotherapy in Acute Lymphoblastic Leukemia in Children- A Prospective Observational Study

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Abstract

Background: *Vitamin D deficiency is common in children with acute lymphoblastic leukemia (ALL) and may worsen during chemotherapy. Deficiency has been associated with impaired bone health, immune dysfunction, and unfavourable clinical outcomes.* **Objectives:** *This study aimed to evaluate serum vitamin D levels at diagnosis and after completion of induction chemotherapy in children with acute lymphoblastic leukemia.* **Methods:** *This prospective observational study was conducted in the Department of Pediatric Hematology and Oncology at Bangladesh Medical University from July 2023 to June 2024. Thirty newly diagnosed children with ALL were enrolled. Serum 25-hydroxyvitamin D [25(OH)D] levels were measured at diagnosis and after induction chemotherapy using the LIASON® Analyser. Patients received chemotherapy according to the UK-ALL 2019 protocol. Clinical and laboratory data were recorded. Paired t-test, Wilcoxon signed-rank test, and chi-square test were used; $p \leq 0.05$ was considered statistically significant.* **Results:** *Most participants were aged 1–6 years, and 80% were male. At the time of diagnosis, 83.3% had vitamin D insufficiency or deficiency. Mean serum vitamin D decreased significantly from 21.04 ± 8.77 to 14.36 ± 7.49 ng/mL after induction chemotherapy ($p=0.002$), representing a 32% reduction. Haematological parameters and peripheral blood blast percentage also improved significantly after induction ($p \leq 0.028$). No significant differences in vitamin D status were observed between chemotherapy regimens or immunophenotypic subtypes.* **Conclusion:** *Vitamin D insufficiency was highly prevalent among children with ALL at diagnosis and worsened significantly after induction chemotherapy. Routine screening and appropriate vitamin D supplementation should be considered during induction therapy to reduce deficiency-related complications and improve supportive care. Larger multicenter studies are recommended to evaluate the impact of vitamin D supplementation on treatment outcomes and long-term prognosis.*

Keywords: *Acute lymphoblastic leukemia, vitamin D, induction chemotherapy*

Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy worldwide.[1] It accounts for approximately 75–80% of childhood leukemias[3] and has a peak incidence between 1 and 4 years of age.[4] It is more common in boys[5], and the 5-year survival rate in developed countries is approximately 90%.[6] However, outcomes in Bangladesh remain poorer, potentially due to delayed diagnosis, infections, limited resources, and nutritional deficiencies.

Vitamin D is a hormone essential for bone metabolism and growth.[7] Sunlight exposure and dietary sources are its main sources[8], and it undergoes hepatic and renal hydroxylation to its active form.[9] In addition to maintaining bone health, vitamin D has anti-inflammatory, immunomodulatory, and proapoptotic effects.[10] Vitamin D deficiency is common among children with cancer at diagnosis and during treatment[11-14] and may result from reduced sunlight exposure, inadequate intake, mucositis, and impaired absorption[15]. It may contribute to reduced bone mineral density and is an important risk factor for poor bone health in children receiving high-dose methotrexate and prolonged corticosteroid therapy.[1-17]

Previous studies have reported a high prevalence of vitamin D deficiency in children with acute leukemia, with lower vitamin D levels potentially associated with poorer outcomes.[18] However, data on changes in vitamin D levels during induction chemotherapy in children with ALL are limited, particularly in Bangladesh. Therefore, this study aimed to evaluate serum vitamin D levels at diagnosis and after completion of induction chemotherapy in children with ALL.

Materials and Methods

This is a prospective observational study conducted in the department of Pediatric Hematology and Oncology of Bangladesh Medical University from July 2023 to June 2024. A total of 30 children diagnosed with acute lymphoblastic leukemia who were admitted into the department were enrolled in this study. Patients on a vitamin D supplement or suffering from concomitant diseases like Rickets, Chronic Liver Disease, Chronic Kidney Disease, Celiac Disease, Cystic fibrosis, Short Bowel Disease, Inflammatory bowel disease, Chronic Pancreatitis, Hyperparathyroidism were excluded. Moreover, patients who had a history of chronic steroid use or patients on phenytoin therapy were not included as potential confounders.

Before the commencement of this study, the thesis protocol was approved by the Institutional Review Board of BMU, Dhaka. All patients diagnosed with ALL by standard diagnostic methods (Bone marrow morphology and immunophenotyping) who were admitted to the ward for induction chemotherapy were screened to ensure they met the inclusion and exclusion criteria. Informed written consent from the parent or guardian was obtained at the time of study enrollment. Data were collected using a pre-formatted data collection sheet (questionnaire). Demographic data, including age, sex, and socio-economic status, were collected from guardians or parents. Medical data on initial presentation at diagnosis, risk stratification, treatment protocol type, number of days in hospital, complications during treatment, and number of days to complete induction chemotherapy were compiled. Clinical information on pallor, temperature, pulse, blood pressure, respiratory rate, bleeding manifestations, and other systemic parameters was recorded. After that, blood samples of a least 2 mL were collected from participating patients. Samples were meticulously carried to the institute's biochemistry department. The patients' vitamin D levels were measured in the supplied specimens using the LIASON® Analyser**.** All patients received chemotherapy according to the UK-ALL 2019 protocol: regimen A for standard-risk patients and regimen B for high-risk patients. After completion of chemotherapy, vitamin D levels of the same patients were measured in the same manner. Along with serum vitamin D, other routine investigations were performed in all patients, including a Complete blood count on alternate days, which was sent to the Department of Pediatric Hematology and Oncology, BSMMU, for analysis. Routine investigations for metabolic workup (SGPT, S. Creatinine, S. Electrolytes, PT, APTT) were also sent to the same laboratory. The results of investigations were collected and correlated with the respective clinical outcomes.

Data were collected on proposed data sheets (Appendices) and also recorded in digital formats for security and convenience for analysis. Statistical analysis was performed using SPSS version 26. Data were tabulated in percentage and frequency tables. Quantitative variables were analysed by paired Student t-tests and the Wilcoxon signed-rank test. Qualitative Variables were analysed by the chi-square test. A p-value ≤ 0.05 was considered statistically significant.

Results

This prospective observational study was conducted in the Department of Pediatric Hematology and Oncology of Bangladesh Medical University from July 2023 to June 2024. Thirty pediatric patients diagnosed with Acute Lymphoblastic Leukemia based on clinical features, physical findings, and investigations were enrolled in this study. Patients were assessed at the start and followed up after completion of the induction phase.

Table I: *Clinical, Physical, and Treatment Features of the Study Participants (N=30)*

Parameter	No of Patients	Percentage
General Condition		
Well	5	16.7
Sick	25	83.3
Toxic	0	0.0
Maintenance of Oral Hygiene		
Knows and applies	15	50.0
Does not know	5	16.7
Does not apply	10	33.3
Pallor		
Mild	20	66.67
Moderate	9	30.0
Severe	1	3.33
Bony Pain		
Present	14	46.7
Absent	16	53.3
Bleeding Manifestation		
Present	9	30.0
Absent	21	70.0
Nutritional Status		
Under nutrition	14	46.6
Normal	16	53.3
Treatment Regimen Used		
Regimen A	14	46.7
Regimen B	16	53.3

Table I shows the clinical, physical, and treatment features of the study participants. Among the 30 patients, 25 (83.33%) were sick, and 5 (16.67%) were well-alert. Half of the patients maintained oral hygiene, while one-third did not. A total of 20 (66.67%) patients had mild pallor, 9 (30%) patients had moderate pallor, and 1 (3.33%) had severe pallor. 14 (46.7%) patients complained of bony pain, while 16 (53.3%) had none. Bleeding manifestations were observed in 9 (30%) patients, and 21 (70%) had none. Of the 30 patients, 46.6% were undernourished, while 53.3% had a normal nutritional status. UK ALL Protocol 2019 regimen A was used in 14 (46.7%) patients and regimen B in 16 (53.3%) patients.

Table II: *Comparison of Mean Vitamin D Level before & after Induction of Chemotherapy (N=30)*

Parameter	Before Induction	After Induction	*p*-value
Mean Vitamin D level	21.04±8.77	14.36±7.49	0.002

Paired t-test was used

Table II compares mean Vitamin D levels before and after chemotherapy induction among study participants. The mean vitamin D level before chemotherapy was 21.04±8.77, and 14.36±7.49 after completion of the induction phase. The comparison was statistically significant (p= 0.002).

Laboratory data were collected at baseline. Then, the same parameters were rechecked after the induction phase of chemotherapy was completed. Comparisons between initial and post-induction therapy mean hemoglobin level, median white blood cell count, median platelet count, and median blast% in PBF were found to be statistically significant (p value 0.028, 0.006, 0.002, <0.001, respectively). However, comparisons between the initial and post-induction mean SGPT and creatinine levels were not statistically significant (p values of 0.381 and 0.182, respectively).

Table III: *Comparison of Laboratory Parameters before and after induction of chemotherapy (N=30)*

Parameter	Value (Mean/Median)	*p*-value
Mean Hemoglobin level		
Initial	7.46±2.23	0.028[a]
After Induction	8.51±0.91	
Median White Blood Cell Count		
Initial	37000 (747600-1500)	0.006[b]
After Induction	9000 (142000-3000)	
Median Total Platelet Count		
Initial	48500 (312000-6000)	0.002[b]
After Induction	100000 (325000-25000)	
Median Blast% in PBF		
Initial	37.5% (85%-0%)	<0.001[b]
After Induction	0% (10%-0%)	
Mean SGPT		
Initial	26.47±10.58	0.381[a]
After Induction	28.87± 12.94	
Mean Creatinine		
Initial	0.44±0 .18	0.182[a]
After Induction	0.40± 0.12	

Paired T-test (a) and Wilcoxon Signed Rank test (b) were used

Table IV: *Comparison of Vitamin D Level between Patients Receiving Different Regimens of Chemotherapy (N=30)*

Protocol	Vitamin D level	No. of Patients Before Induction (N=30)	No. of Patients After Induction (N=30)	*p*-value
	Sufficient	1 (7.1%)	1 (7.1%)	
Regimen- A	Insufficient	12 (85.7%)	8 (57.1%)	0.177
	Deficient	1 (7.1%)	5 (35.7%)	
Total		14	14	
	Sufficient	2 (12.5%)	2 (12.5%)	
Regimen-B	Insufficient	13 (81.3%)	11 (68.8%)	0.537
	Deficient	1 (6.3%)	3 (18.8%)	
Total		16 (100%)	16 (100%)	

Chi-square test was used

Table IV shows a stratified comparison of vitamin D levels before and after chemotherapy induction according to treatment regimen. Within Regimen-A and Regimen-B, the pre- versus post-induction distributions of vitamin D status were not statistically significant (*p*values of 0.177 and 0.537, respectively).

Table V: C*omparison of Mean/ Median of Ordinal Vitamin D level before and after the induction phase of Chemotherapy (N=30)*

Vitamin D level	Mean/ Median Value Before Induction	Mean/ Median Value After Induction	*p*-value
Deficient	8.235± 0.26	17.7 ± 0.42	0.98[a]
Insufficient	19.25 (28.7-11.0)	12.8 (61.8-4.0)	0.07[b]
Sufficient	35.96± 5.18	13.47±4.97	**0.02[a]**

Paired t-test (a) and Wilcoxon Signed Rank test (b) were used

Table V shows the comparison of mean/ median ordinal vitamin D levels before and after the induction phase of chemotherapy. The comparison of the mean deficient vitamin D level and the median insufficient vitamin D level before and after the induction phase of chemotherapy was not statistically significant (*p* values of 0.98 and 0.07, respectively). However, the comparison of mean sufficient vitamin D levels before and after the induction phase of chemotherapy was statistically significant (*p*=0.02).

Discussion

This prospective observational study evaluated serum vitamin D levels before and after induction chemotherapy in 30 children with acute lymphoblastic leukemia (ALL). The principal finding was a significant reduction in serum vitamin D levels following induction chemotherapy.

In our study, 80% of participants were male, with a male-to-female ratio of 4:1. Male predominance in childhood ALL has also been reported in previous studies, although the degree of predominance varies between populations[19–21]. Most patients (66.67%) were aged 1–6 years, which is consistent with the recognized peak incidence of childhood ALL[22].

The common presenting features were pallor (66.67%), bony pain (46.7%), and bleeding manifestations (30%). Bony pain is a recognized presentation of childhood ALL and may occasionally be the predominant symptom[23]. Nearly half of our patients (46.6%) were undernourished at diagnosis, which is comparable to findings from a previous study conducted at BMU[24].

The most important finding was the significant decline in mean serum vitamin D from 21.04 ± 8.77 ng/mL before induction to 14.36 ± 7.49 ng/mL after induction chemotherapy (p=0.002), representing an approximately 32% reduction. This finding is consistent with previous reports demonstrating reduced vitamin D levels following treatment in children with ALL. Simmons et al. reported a 15% decrease in vitamin D levels among childhood ALL survivors[25], while another study reported a reduction of approximately 27%[26]. The greater reduction observed in our study may reflect differences in patient characteristics, treatment duration, nutritional status, or timing of vitamin D assessment.

At diagnosis, 83.3% of our patients had insufficient or deficient vitamin D levels. A similarly high prevalence of inadequate vitamin D levels (90%) was reported among patients with acute leukemia in Pakistan[30]. The high prevalence in our population may be related to nutritional, environmental, and socioeconomic factors.

We also observed significant improvements in hemoglobin, white blood cell count, platelet count, and peripheral blood blast percentage following induction chemotherapy. These changes reflect hematological response to treatment. However, as these parameters were not the primary outcomes of this study, their detailed interpretation is beyond the main scope of the present discussion.

The comparison of vitamin D status according to treatment regimen and immunophenotypic subtype showed no statistically significant differences. Similarly, vitamin D levels within the deficient and insufficient groups did not show significant changes, whereas a significant change was observed among

patients with sufficient vitamin D levels. These subgroup findings should be interpreted cautiously because of the small sample size, particularly the limited number of patients in the T-ALL subgroup.

The observed decline in vitamin D during induction chemotherapy highlights the importance of monitoring vitamin D status in children with ALL. Potential contributing factors include reduced dietary intake, decreased sunlight exposure, treatment-related gastrointestinal problems, and the effects of corticosteroids and other chemotherapeutic agents. Larger prospective studies are needed to determine the mechanisms responsible for this decline and whether vitamin D supplementation can improve bone health and other treatment-related outcomes.

Overall, our findings demonstrate that vitamin D insufficiency or deficiency is common at diagnosis and that serum vitamin D levels decline significantly during induction chemotherapy in children with ALL. These findings support consideration of routine assessment of vitamin D status and appropriate supplementation as part of supportive care, particularly in children at increased risk of deficiency.

Conclusion

Vitamin D insufficiency or deficiency was common at diagnosis and serum vitamin D levels decreased significantly after induction chemotherapy in children with acute lymphoblastic leukemia. Routine assessment of vitamin D status and appropriate supplementation may be considered as part of supportive care. Further multicenter studies are needed to determine the clinical impact of vitamin D supplementation.

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Clinical Presentation and Early Treatment Outcomes of Childhood Wilms Tumor at a Tertiary Referral Center in Bangladesh: A Retrospective Cohort Study

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Abstract

Background: *The most frequent malignant renal tumor in children is Wilms tumor (nephroblastoma) which is responsible for about 6-7% of all childhood cancers. In high-income countries, survival of over 90%, but in low- and middle-income countries, the rate of survival is less, as a result of delayed diagnosis, advanced disease at presentation and resource limitation. The data on published work in Bangladesh are limited.* **Objective:** *To depict clinical presentation, treatment features and early outcome of Wilms tumor among children in tertiary care hospital in Bangladesh.* **Methods:** *The Department of Pediatric Hematology and Oncology, Bangladesh Medical University (BMU), Dhaka, Bangladesh carried out a retrospective cohort study. Records of children diagnosed with Wilms tumor from July 2023 to June 2025 were extracted. Demographic parameters, clinical presentation, tumor stages, pathological examination, therapeutic approach and prognosis were evaluated. Follow-up continued until June 2026.* **Results:** *Twenty children aged 0-10 years were included; 13 (65%) were male and 7 (35%) were female. Sixty percent of children (12) were under three years old. Abdominal swelling was the most frequent presenting symptom (100%), followed by mild-to-moderate abdominal pain (90%), nausea and vomiting (50%), microscopic hematuria (40%) and low-grade fever (25%). The tumours were more commonly on the left side of the body (60%) than on the right (35%) and one child (5%) had bilateral disease. The most common presentation was stage III (50%), stage II (30%), and stage IV (20%). Favorable histology was seen in 55% of patients and 15% had diffuse anaplastic Wilms tumor. Twenty (100%) underwent surgery, 20 (100%) received chemotherapy in accordance with the COG protocols and five (25%) received radiotherapy. At follow-up, two of the patients (10%) relapsed, one patient died (5%), and nineteen patients (95%) were alive.* **Conclusion:** *Most children that were referred with advanced-stage disease had received standardized multimodal treatment. To further improve outcomes in Bangladesh, early diagnosis, prompt referral and multidisciplinary management is key. Nephroblastoma (Wilms tumor) is the most common form of kidney cancer in children. Treatment outcome refers to the chances of a child's survival after nephroblastoma treatment.*

Keywords: *Wilms tumor, nephroblastoma, pediatric oncology, childhood cancer, treatment outcome, Bangladesh*

Introduction

Wilms tumor (nephroblastoma) is the most common primary malignant renal tumor in children, making up about 85–90% of all kidney cancers in children and 6–7% of all childhood cancers worldwide.[1] The tumor is most frequently seen in children less than 5 years of age, and with a peak incidence of 2 to 4 years. The disease predominantly affects children younger than five years of age and usually presents as a painless abdominal mass. Other clinical manifestations include abdominal pain, hematuria, hypertension, fever, anorexia, and respiratory symptoms when metastatic disease is present.[2] The etiology remains unclear, but Wilms tumor is known to be related to abnormalities of renal embryogenesis and to some genetic syndromes, such as WAGR syndrome, Denys–Drash syndrome and Beckwith–Wiedemann syndrome.[3]

In the last 50 years, great progress has been made in multidisciplinary treatment to make Wilms tumor one of the most successfully treated cancers in children.[4] Through multimodal treatment consisting of surgery, chemotherapy, and selective radiotherapy, five-year overall survival now exceeds 90% in high-income countries. These achievements are largely attributed to collaborative treatment protocols developed by the Children's Oncology Group (COG) and the International Society of Paediatric Oncology (SIOP).[5,6]

Despite these advances, results in low- and middle-income countries (LMICs) are not as promising. High morbidity and mortality rates remain due to delayed diagnosis, presentation at late stage of the disease, lack of access to specialized paediatric oncology services, financial limitations, treatment dropout and poor supportive care.[7] However, significant differences between survival reported in sub-Saharan Africa and high-income settings have been reported, suggesting that there are still inequalities in the care of childhood cancer.[8]

The services of pediatric oncology have grown significantly in Bangladesh in the last 2 decades, with the creation of specialized treatment centers and the establishment of standardized treatment protocols. Bangladesh Medical University (BMU), a tertiary care facility, was one of the top hospitals in Bangladesh offering multi-disciplinary comprehensive care of children with cancer. However, little information is available on the clinical presentation, histopathological features, treatment trends and prognosis of Wilms tumor in children in Bangladesh. Local evidence is crucial to help clarify disease trends, assess current treatment, and uncover ways to enhance patient outcomes.

This was aimed at describing demographical characteristics, clinical presentation, stage of the disease, histopathological findings, treatment modalities and early treatment outcome of children diagnosed with Wilms tumor in the Department of Pediatric Hematology and Oncology, Bangladesh Medical University, from July 2023 till June 2025. We also aimed to obtain baseline information which could be used for future multicenter studies and help build pediatric oncology services in Bangladesh.

Materials and Methods

This was a retrospective cohort study conducted at the Department of Pediatric Hematology and Oncology of Bangladesh Medical University (BMU), Dhaka, Bangladesh, a tertiary referral centre for all paediatric cancers. Children were identified with Wilms tumor by histopathology between July 2023 and June 2025 and their medical records and follow-up data were reviewed up to June 2026. Children (0-10 years) attending BMU for definitive treatment were included and those with incomplete records, other renal malignancies, or treatment elsewhere were excluded.

Medical records were reviewed by using a standardized data collection form to extract demographic, clinical presentation, laterality of the tumor, stage of the disease, histopathological findings, treatment details, relapse, mortality, and follow-up information. Clinical presentation consisted of abdominal swelling or mass, abdominal pain, hematuria, fever, hypertension, nausea and vomiting, associated with weight loss, and respiratory symptoms.

Diagnosis was made by clinical examination, radiographs and histopathology. Tumors were staged by the Children's Oncology Group (COG) staging system and classified as favorable histology, unfavorable histology or diffuse anaplastic Wilms tumor depending upon pathological findings.

All patients received treatment following the COG treatment protocol using multimodal therapy (surgery and multi-agent chemotherapy). If possible, radical nephrectomy was offered for unilateral tumours and the patient with bilateral disease had individualized multidisciplinary treatment. Selected patients were treated by radiotherapy depending on the stage of the disease and the histopathological results. Supportive care was provided as appropriate such as transfusion of blood, antimicrobial therapy, nutrition, pain management and psychosocial counseling.

Patients were followed up until June 2026. Early treatment outcome was the primary outcome (death vs. alive at the last follow-up). Secondary outcomes were relapse, mortality, stage distribution, histopathological subtype and characteristics of treatment.

The data analyzed and entered in the Microsoft Excel and analyzed by SPSS Statistics version 23.0. Categorical variables were presented as frequencies and percentages. There were only limited numbers for analysis so a descriptive analysis was used.

Since this was a retrospective study of anonymous medical records, informed consent was not required. The anonymity of the patients was ensured during the study by the elimination of personal data from the analysis.

Results

Between July 2023 and June 2025, 20 children were treated for Wilms tumor in the Department of Pediatric Hematology and Oncology of Bangladesh Medical University with confirmed diagnosis of Wilms tumor from the histopathology section. All patients went through the treatment, and their follow-up was conducted until June 2026. Most patients (12, 60%) were less than 3 years old, 6 (30%) were between the ages of 3–5 years and 2 (10%) were 5–10 years old. There was a male predominance with 13 males (65%) and 7 females (35%) with a ratio of males to females of 1.9:1. In terms of tumor side, 60% of patients had left-sided tumours, 35% had right-sided tumours and 5% had bilateral Wilms tumor. As a result, 95% of the cases were unilateral.

All patients (100%) presented with abdominal swelling or with a palpable abdominal mass. 18 children (90%) complained of mild to moderate abdominal pain while 2 children (10%) complained of severe abdominal pain. Ten patients (50%) developed nausea and vomiting and microscopic hematuria was noted in 8 (40%). Five children (25%) had a low grade fever, and each of three (15%) had hypertension and loss of appetite with weight loss. 2 (10%) patients had gross hematuria. Respiratory symptoms with a diagnosis of pulmonary metastasis was found in one patient (5%).All the children had a large firm smooth, non tender abdominal mass on physical examination. In 19 patients (95%), the mass did not cross the midline.

The most common presentation per Children's Oncology Group (COG) staging system was Stage III (10 patients, 50%), followed by Stage II (6 patients, 30%) and Stage IV (4 patients, 20%). The 11 patients had favorable histology, 6 were unfavorable, and 3 were diffuse anaplastic Wilms tumor. Favorable histology =11 patients (55%), unfavorable histology = 6 patients (30%), and diffuse anaplastic Wilms tumor = 3 patients (15%).

Children's Oncology Group (COG) protocol multimodal treatment was used for all patients. 100% of 20 patients received chemotherapy and surgical treatment. 25% (5 patients) needed radiotherapy according to the stage of the tumor and the postoperative histopathological diagnosis.

Patients were followed up to June 2026. In the follow-up period, 2 patients (10%) had disease relapse and 1 patient (5%) died. At the last follow-up, 19 children (95%) were alive.

Table I : *Demographic and Clinical Characteristics of the Study Population (N = 20)*

Characteristic	Number (%)
Age group	
<3 years	12 (60.0)
3–5 years	6 (30.0)
5–10 years	2 (10.0)
Sex	
Male	13 (65.0)
Female	7 (35.0)
Tumor laterality	
Left kidney	12 (60.0)
Right kidney	7 (35.0)
Bilateral kidneys	1 (5.0)

Demographic profile of children with Wilms tumor, including age distribution, sex, and tumor laterality, treated at the Department of Pediatric Hematology and Oncology, Bangladesh Medical University, between July 2023 and June 2025.

Table II: *Clinical Presentation of Children with Wilms Tumor (N = 20)*

Clinical feature	Number (%)
Abdominal swelling/mass	20 (100)
Mild–moderate abdominal pain	18 (90)
Severe abdominal pain	2 (10)
Nausea and vomiting	10 (50)
Microscopic hematuria	8 (40)
Low-grade fever	5 (25)
Hypertension	3 (15)
Loss of appetite/weight loss	3 (15)
Gross hematuria	2 (10)
Respiratory symptoms	1 (5)
Large, firm, smooth abdominal mass	20 (100)
Mass not crossing the midline	19 (95)

Frequency of presenting symptoms and physical examination findings among children with Wilms tumor at the time of diagnosis.

Table III: *Tumor Stage and Histopathological Findings (N = 20)*

Variable	Number (%)
Tumor stage	
Stage II	6 (30)
Stage III	10 (50)
Stage IV	4 (20)
Histopathology	
Favorable histology	11 (55)
Unfavorable histology	6 (30)
Diffuse anaplastic Wilms tumor	3 (15)

Distribution of disease stage according to the Children's Oncology Group (COG) staging system and histopathological classification of Wilms tumor.

Table IV: *Treatment Modalities (N = 20)*

Treatment	Number (%)
Chemotherapy	20 (100)
Surgery	20 (100)
Radiotherapy	5 (25)

Treatment modalities administered to children with Wilms tumor, including chemotherapy, surgery, and radiotherapy, according to the Children's Oncology Group (COG) treatment protocol.

Table V: *Clinical Outcomes at Last Follow-up*

Outcome	Number (%)
Alive	19 (95)
Death	1 (5)
Relapse	2 (10)

Early treatment outcomes of children with Wilms tumor, including survival status, relapse, and mortality, at the last follow-up (June 2026).

Discussion

This is a retrospective cohort study which reports clinical presentation, treatment features and early outcome of children with Wilms tumor treated in this tertiary care center in Bangladesh. The study represents a small number of patients, but this is useful background information from a resource-poor environment where published information about the management of childhood Wilms tumor is sparse. Most children seen were under 5 years of age and the most frequent symptom at presentation was abdominal swelling; at presentation, most children were diagnosed with Stage III disease. Although many were advanced stages of disease, early treatment results were good after multimodal therapy according to Children's Oncology Group (COG) protocol.[9,10]

The age distribution of the children in our study is like that reported for the epidemiology of Wilms tumor. Most patients (90%) were younger than 5 years of age and 60% were diagnosed prior to 3 years. Wilms tumor is known to occur in a highly embryonal age group, the National Wilms Tumor Study (NWTS) and International Society of Paediatric Oncology (SIOP) reported children ages two to five years accounted for most cases (65%).[11] While Wilms tumor seems not to

have any significant sex predilection, some hospital-based studies in low and middle-income countries (LMICs) have reported a male predominance.[12]

All children had abdominal swelling, and it continues to be the most characteristic clinical symptom of Wilms tumor. Mild-to-moderate abdominal pain was reported in 90% of patients, while severe abdominal pain occurred in 10%. Nausea and vomiting, microscopic hematuria, and low-grade fever were reported in 50%, 40%, and 25% of patients, respectively. Less common were gross hematuria and hypertension. A previous report reported that hematuria and hypertension occur in a smaller proportion of patients, with the most common presentation being an asymptomatic abdominal mass, which may suggest a delay in the presentation of larger tumors that cause stretching of the renal capsule or compression of surrounding organs.

One of the major findings of this study was that 70% of the patients had advanced disease at diagnosis, 50% had Stage III and 20% had Stage IV disease. Such a pattern is not seen in countries with high incomes where most children are diagnosed at an early stage by better awareness and prompt referrals.[13,14] This highlights the need to raise public awareness and improve referral systems in Bangladesh.

The histology was favorable in 55% and unfavorable or diffuse anaplastic in 45% of the patients. The higher percentage of unfavorable histology in our study is noteworthy and should be taken with a grain of salt due to the small study size and single center study design.[15] However, these patients were treated more intensively including in selected cases, postoperative radiotherapy, demonstrating the need for accurate pathological assessment for risk stratification.

In the current study, multimodal treatment (surgery and COG protocol-based chemotherapy) was given to all children, and 25% of them received radiotherapy. Two patients had relapse and one patient was dead after standard multidisciplinary management, leading to a 95% observed survival at last follow-up.[16,17] While the follow-up period was brief, long-term overall survival could not be obtained, these results suggest promising early results, even though many of the patients had advanced stage disease.

The main strengths of this study are that it brings up to date information regarding the presentation and management of childhood Wilms tumor from one of the best pediatric oncology centers in Bangladesh. The results are however limited to the single center and the small sample size, and the follow-up is relatively short, however, limiting the generalizability of the results and not allowing long-term survival analysis. Longer follow-up periods in larger multicenter prospective studies are required to more fully define the treatment outcome and prognostic factors seen in children with Wilms tumor in Bangladesh.

Finally, when considering the outcome of early treatment, most children with Wilms tumor in this series were at diagnosis with advanced disease, but with good outcome after a standard multimodal approach. To further enhance the outcomes of children with Wilms tumor in Bangladesh, earlier diagnosis, timely referral and ongoing development of multidisciplinary services for children with oncology is essential.

Conclusion

Although abdominal swelling was the most common symptom, the majority of children with Wilms tumor were diagnosed with advanced disease in this retrospective cohort study. All the patients were treated in a standard multimodal fashion and the early outcomes were good with low relapse and mortality during follow-up. Continuous strengthening of MDO services, timely referral and early diagnosis are crucial to further enhance the outcomes of children with Wilms tumor in Bangladesh. There is a need for larger, multicenter studies with longer follow up to assess long-term survival and prognosis.

Strengths and Limitations

This study is one of the few studies to report clinical presentation and early treatment outcome of Wilms tumor in children in Bangladesh. All the patients received treatment in a specialized tertiary Centre of Paediatric Oncology following a standard treatment protocol developed by COG group and were followed up till June 2026.

The retrospective nature of the study with its single-centre design, small number of patients, and relatively short follow-up time, limit the generalizability of the results and make it impossible to evaluate long-term survival. These results should be confirmed in larger multicenter prospective studies with longer follow-up to assess long-term results.

Conflict of Interest

The authors declare that they have no competing interests.

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Original Article

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Systemic Fungaemia among Pediatric Oncology Patients in a Tertiary Care Hospital of Bangladesh

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Abstract

Background: *Systemic fungi are among the leading causes of morbidity in pediatric cancer patients, in part due to neutropenia and immunosuppression from chemotherapy. The identification of fungaemia early is very important in improving clinical outcomes.* **Objective:** *To determine clinical and hematological features of systemic fungaemia in oncology patients.*

Methods: *A descriptive observational study was conducted primarily on pediatric oncology patients diagnosed with a confirmed fungal infection of the bloodstream. The correct information was retrieved from clinical records and laboratory reports and was analyzed with the help of descriptive statistical tools.*

Results: *Total ninety-three patients' specimen were collected. Of them thirty-four (36.6%) blood culture-positive pediatric cancer patients were analyzed. Among them eight patients (23.5%) who had a positive blood culture on fungal growth mostly Candida albicans were involved in the study. The majority (87.5%) were aged between 1 and 10 years. Males constituted 75% of the cases. Acute lymphoblastic leukemia (ALL) was the most common underlying malignancy (87.5%). Leukopenia (<3000/mm³) was observed in 37.5% of patients, while severe neutropenia (ANC <100/mm³) was present in 37.5% of cases.*

Conclusion: *Candida albicans was the most common cause of systemic fungaemia in pediatric oncology patients and was most common in younger children, patients who have ALL, and neutropenic patients.*

Key words: *Systemic fungaemia; Pediatric cancer; Candida albicans; Neutropenia; Leukemia; Bloodstream infection*

Introduction

Systemic fungal infections have come to be considered one of the leading causes of morbidity and mortality in pediatric cancer patients. Although there is an increase in chemotherapy and other support modalities that result in increased survival rates with childhood cancers, the treatment is characterized by extensive immunosuppression that exposes them to opportunistic infections and, in particular, invasive fungal infections (IFIs).[1]

Candida species are the most frequent bloodstream Candida infection in immunocompromised persons and are responsible for a large percentage of nosocomial infections in the world.[2] Candidemia, defined as the presence of *Candida* organisms in the bloodstream, is associated with high mortality, particularly in patients with underlying malignancies [3]. Though non-albicans Candida infections have increased worldwide, Candida albicans is the most frequently identified species in most health care facilities, especially in developing nations.[4]

The risk of candidemia is particularly augmented among patients with hematological diseases, prolonged neutropenia, concentrated chemotherapy contact, central venous catheterization, broad-spectrum antibiotic usage, and prolonged hospitalization.[5] Hematological malignancies, especially acute lymphoblastic leukemia (ALL), are susceptible factors to invasive fungal infections because of the severity and duration of immunosuppression.[5]

Neutropenia is one of the most hazardous risk factors for fungi. Neutrophils play an essential role in host defense against fungal pathogens and the severity of neutropenia as well as the duration of neutropenia is significant in increasing the risk of invasive candidiasis. [6] Patients with an absolute neutrophil count (ANC) of less than 500/mm^3, and even lower, of less than 100/mm^3, are highly vulnerable to systemic fungal infection.[7]

In addition to hematological parameters, demographic factors such as age and sex, and such clinical factors as the kind of malignancy can also affect the incidence and the outcome of fungaemia. In order to initiate the treatment using antifungal drugs and to attain a higher survival rate, the high-risk patients need to be identified at an early stage.[5]

As opposed to patients with cancerous conditions whose chances of having fungal bloodstream infection are quite high because of the risk of invasive fungal infection, patients with cancers who are in pediatric oncology are also not at risk of having fungal bloodstream infections as compared to bacterial bloodstream infections. The most commonly isolated pathogens that are isolated in immunocompromised patients are Candida species. However, they have been reported to constitute a low proportion of bloodstream infections in cancer groups, approximately 3% in some studies.[8] Although with low frequency, they are associated with high morbidity and mortality, with late identification and therapy resulting in mortality of up to 25-40%.[8] Thus, early diagnosis and timely antifungal treatment are crucial to the treatment of pediatric cancer patients.

Although the clinical importance of systemic fungaemia has been established, there is limited data from resource-limited countries like Bangladesh. The diagnosis, prevention and early treatment of invasive fungi in pediatric cancer patients of pediatric age are significant according to the international guidelines because the morbidity and mortality rates of the disease are high.[9]

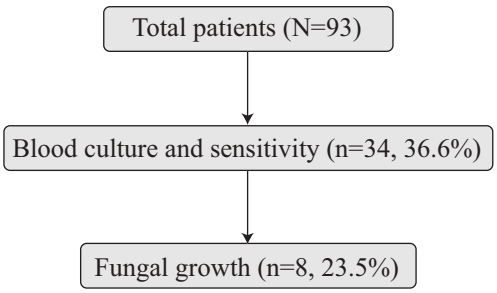
Therefore, the present study was conducted to identify the clinical and hematological characteristics of systemic fungaemia in a variety of oncology patients in a tertiary care unit among children.

Methods

This descriptive observational study was carried out from July 2020 to April 2023 in the Department of Pediatric Hematology and Oncology, Dhaka Medical College Hospital (DMCH), a tertiary care hospital, among pediatric oncology patients with systemic fungal infection during the study period. It involved the inclusion of patients whose diagnosis had to be confirmed as cancerous and a positive blood culture of fungal organisms, as well as the exclusion of patients based on the absence of fungus organism. The culture was given during patient's febrile illness within one hour of prophylactic antibiotics start. Due to the limited number of culture-positive cases, all eligible patients identified during the study period were included using purposive sampling. The limited sample size reflects

the low frequency of fungal bloodstream infections encountered in routine oncology practice rather than selective recruitment or exclusion of cases. Data were collected retrospectively from clinical records, laboratory reports, and blood culture findings using a structured data collection form. The study variables included age, sex, type of malignancy, total leukocyte count, absolute neutrophil count, and microbiological characteristics among pediatric oncology patients with confirmed systemic fungaemia. Fungaemia was defined as the presence of fungal organisms in blood culture. Neutropenia, severe neutropenia, and profound neutropenia were defined as ANC <1500/mm³, <500/mm³, and <100/mm³, respectively. Data were reviewed for completeness and accuracy and analyzed using descriptive statistical methods. The findings were presented as tables, figures, and percentages.

Results



A total of eight pediatric oncology patients with systemic fungaemia were included in the study.

Table 1: *Age Distribution of study subjects*

Age Group (years)	Number of Patients	Percentage (%)
1–10	7	87.5
>10	1	12.5
Total	8	100

Table 1 indicates that, of the patients taking part in the study, 7 (87.5%) were aged between 1–10 years, and 1 (12.5%) patient was above 10 years. These were between 1 to 11 years old.

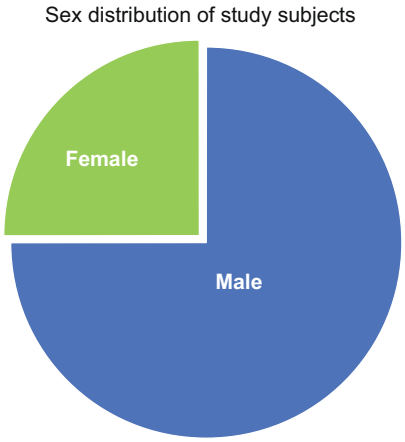


Figure 1: Sex Distribution of study subjects

In Figure 1, 6 (75%) out of 8 patients were males and 2 (25%) females; hence, male-dominated with a female-to-male ratio of 1:3.

Table 2: *Underlying Disease of study participants*

Diagnosis	Number of Patients	Percentage (%)
ALL	7	87.5
AML	1	12.5
Total	8	100

In Table II, it is observed that 7 (87.5%) patients had acute lymphoblastic leukemia (ALL), and 1 (12.5%) patient had acute myeloid leukemia (AML).

Table 3: *Total Leukocyte Count among study subjects*

TC of WBC (cells/mm³)	Number of Patients	Percentage (%)
<3000	3	37.5
3000–11000	5	62.5
Total	8	100

Table 3 shows that the total leukocyte count was within the range of 3000–11000/mm³ in 5 (62.5%) patients, while 3 (37.5%) patients had leukopenia (<3000/mm³).

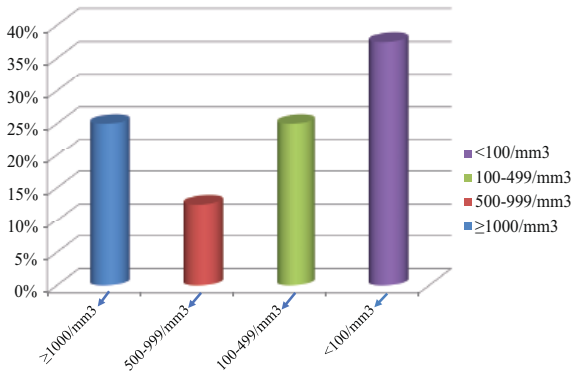


Figure 2: *Absolute Neutrophil Count (ANC) among study subjects*

Figure 2 shows that the ANC distribution showed profound neutropenia (<100/mm³) in 3 (37.5%) patients, severe neutropenia (100-499/mm³) in 2 (25.0%), ANC 500-999/mm³ in 1 (12.5%), and ANC ≥1000/mm³ in 2 (25.0%) patients.

Discussion

This paper demonstrates that it is systemic fungaemia, which is a leading complication of pediatric oncology patients, and that it is Candida albicans is able to cause the condition in all patients. The present study is consistent with the existing literature that C. species are among the most prevalent causes of invasive C. infections in immunocompromised children, particularly during chemotherapy.[1,2]

Despite the trends suggesting increased prevalence of non-albicans Candida species in the global environment, *C. albicans* continues to be one of the major Candida pathogens in the environment of the present study, especially in bloodstream infections.[2,4] This study may be limited by local trends or the small sample size.

The small number of patients used in the current study is in line with the epidemiology of fungal bloodstream infections across the globe. The number of culture-proven cases in the study period (8) is not unexpected as previous studies have suggested that the contribution of Candida spp. to bloodstream infections in oncology patients is relatively small.[4,8] In addition, the estimated incidences of candidemia in cancer units are around 0.5-1.6 cases per 1000 admissions or patient-days.[5,8] This finding supports the inclusion of all cases that qualified in the study period, and the moderate number of cases in this study. Although fungal bloodstream infections are uncommon, they are clinically significant because of their potential for morbidity and mortality when not diagnosed and treated early, and continuous monitoring and early treatment of patients with pediatric oncology are essential.[2,3]

Most of the patients were 1-10-years and this is within the highest incidence of childhood malignancies, and acute lymphoblastic leukemia (ALL) in particular. This age group may be highly susceptible to invasive fungal infections due to the effects of their intensive chemotherapy and immunosuppression from treatments.[1,9]

The high proportion (87.5%) of patients with ALL supports the previous data that hematological malignancies are highly interconnected with a high risk of acquiring invasive fungal infections.[5,8] Prolonged neutropenia, mucosal injury, corticosteroid exposure, and intensive chemotherapy have been closely associated with the predisposition.[1,5,9]

A significant feature of this study and most patients was neutropenia which was acute and profound in most patients. This has been a long-recognized risk factor in invasive fungal infection since neutrophils make an important contribution to host control of fungal infections. [6,9] Previous studies already demonstrated that the duration and the intensity of neutropenia are predisposing factors to invasive fungal infection and candidemia.[5,6]

It was also observed that leukopenia progressed in a large group of patients and acted as a confirmatory sign of the strength of immunosuppression produced by chemotherapy in the emergence of systemic fungal infections.[6,9] The correlation between low circulatory leukocyte levels and susceptibility to infection has been defined particularly in patients with acute leukemia.[6]

The female predominance observed is contrasted with some studies which show male predominance or no significant difference in gender among candidemia and cancer patients.[8] This difference can be attributed to the small sample size and should thus be viewed cautiously.

In the current study, blood cultures identified all cases, which highlights the importance of candidemia

as a form of invasive candidiasis.[2,3] Bloodstream infections due to Candida spp. are associated with high morbidity and mortality without good treatment.[2,3]

Systemic candidiasis has continued to pose a significant healthcare-associated infection in immunocompromised patients that causes lengthy hospitalization, high healthcare costs, and high mortality rates. [2,4] Among children with cancer, other risk factors that predispose them to invasive fungal infection include neutropenia, exposure to broad-spectrum antibiotics, persistent neutropenia, and intensive chemotherapy.[1,4,9]

The consistent result of C. albicans in this study could be compared to local epidemiology or low sample diversity.[2,4,8]. Larger studies have indicated an increasing role of non-albicans Candida species, with the necessity to identify species and evaluate antifungal susceptibility correctly.[2,3]

These results underscore the need to diagnose and administer antifungal drugs early in the course of the disease. Recent guidelines advocate early detection and treatment of suspected fungal infection in high-risk children with oncology, and especially those with persistent and severe neutropenia, which could lead to poorer outcomes with delays in microbiological diagnosis and antifungal treatment.[1,3,9] Delayed treatment may be associated with inferior outcomes, mainly in harshly immunocompromised patients.[2,3] Clinicians are therefore advised to maintain a high level of suspicion of fungal infection in pediatric oncology patients, especially those with persistent and profound neutropenia, and should consider timely microbiological investigation and antifungal therapy in case of clinical suspicion.[1,3,9]

Conclusion

Systemic fungaemia is a serious complication in pediatric oncology patients, with Candida albicans being the most common pathogen. Younger children, particularly those with acute lymphoblastic leukemia (ALL) and neutropenia, appear to be at higher risk. Early diagnosis and prompt antifungal treatment are essential to improve outcomes. This study highlights the importance of vigilant monitoring and infection control measures in high-risk patients. Further multicenter studies are needed to better define the epidemiology and risk factors of systemic fungal infections in pediatric oncology.

Limitations

1. The sample used was very small, due to the fact that systemic fungaemia is a rare complication and few cases were culture-confirmed during the time frame of the study.
2. This was a single-center study; therefore, the findings might not be applicable to other hospitals and geographical regions.

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Case Report

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Metastatic Neuroblastoma in a Child at a Non-Transplant Setting: Experience with Chemo-differentiation Therapy

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Abstract:

Neuroblastoma is a highly aggressive childhood malignancy accounting for 8-10% of childhood malignancies and approximately 15% of pediatric cancer-related mortality. Metastatic neuroblastoma in children above 18 months, regardless of other features belongs to high-risk group, which requires intensive chemo-induction, surgery, myeloablative therapy with autologous stem cell rescue, radiation therapy and maintenance therapy with anti-GD2 (Dinutuximab), GM-CSF and isotretinoin. In developing countries with non-transplant setting, the outcome of metastatic neuroblastoma is dismal. Isotretinoin is a vitamin A derivative which causes differentiation of malignant neuroblastoma cell into mature cells and can be used with or without stem cell transplant. Here, we describe a successfully managed case of a 2-year-old child with metastatic neuroblastoma, with conventional chemotherapy followed by oral metronomic chemo-differentiation therapy in Bangladesh at a non-transplant setting.

Key words: *High-risk Neuroblastoma Isotretinoin Bangladesh Non-transplant*

Introduction:

Neuroblastoma accounts for 8-10% of childhood malignancies and approximately 15% of pediatric cancer-related mortality.[1] According to the Childhood Oncology Group (COG) classification system, risk stratification of neuroblastoma depends on age, stage, histology, *MYCN* amplification, ploidy and segmental chromosomal aberration. Metastatic neuroblastoma in children above 18 months, regardless of other features belongs to high-risk group.[2] Pulmonary metastasis is usually associated with *MYCN* amplification, elevated LDH levels and an unfavorable outcome.[3]

High-risk neuroblastoma requires treatment with intensive induction chemotherapy and surgical resection, consolidation with of myeloablative therapy and autologous HSCT and radiation therapy to the site of the primary tumor and residual metastatic sites followed by post-consolidation with anti-GD2 (Dinutuximab) immunotherapy with GM-CSF and isotretinoin therapy.[4-5]

In developing countries with non-transplant setting, the outcome of metastatic neuroblastoma is dismal. In two large Indian studies, 2-year overall survival of neuroblastoma were found to be 7.1- 8.7% only.[6-7] In

another study in Argentina, 5-year overall survival of high-risk neuroblastoma was 24%.[8] In a recent study in Bangladesh, metastatic neuroblastoma was treated conventional chemotherapy followed by one year of metronomic chemotherapy (propranolol, vinblastine, cyclophosphamide, etoposide and an NSAID, if pain). In this study, 10 children out of total 55 study population (18%) survived, although 4 of children later had recurrences. Among the survived group, 6 were <18 months of age and no child had pulmonary metastasis.[9]

Isotretinoin (13-cis-retinoic acid) is a derivative of vitamin A, which causes arrest of cell growth and morphologic differentiation of human neuroblastoma cell lines.[10-12] High-dose pulse therapy with 13-cis-RA given after completion of intensive chemo-radiotherapy (with or without autologous bone marrow transplantation) significantly improves event-free survival in high-risk neuroblastoma.[13] Current treatment protocol of high risk neuroblastoma includes isotretinoin in post-transplant maintenance therapy with Anti-GD2.[5] A recent study in USA showed that, in patients with high-risk neuroblastoma with poor response to initial therapy, long-term isotretinoin therapy after autologous HSCT was well tolerated and may have contributed to long-term survival.[14]

There is currently no published study or case report on outcome of high-risk neuroblastoma patients with isotretinoin maintenance therapy in non-transplant setting.

Here, we describe a successfully managed case of a 2-year-old child with metastatic neuroblastoma, with conventional chemotherapy followed by oral metronomic chemo-differentiation maintenance therapy in Bangladesh at a non-transplant setting.

Case summary:

A 2-year-old girl from a North-Eastern district of Bangladesh presented with progressive distension and pain of abdomen and constipation for 3 weeks and vomiting for 5 days. She was admitted in a private hospital in Dhaka and was treated conservatively for 6 days without any significant improvement.

CT scan of abdomen showed extensive abdominal lymphadenopathy involving mesenteric, para-aortic and retro-peritoneal nodes. CT scan of chest showed mediastinal lymphadenopathy with right-sided pleural effusion with inhomogeneous pulmonary opacities and also mild pericardial effusion. There were no clinical features of skin infiltration like blue-berry muffin rash, subcutaneous nodule or raccoon-eye.

Hemoglobin was 6.8 gm/dl, WBC-12.8 $x10^9$/L, neutrophil-92%, platelet-500 x 10^9/L, LDH- 2008 U/L, S. ALT-10 U/L, S. Creatinine- 0.27 mg/dl, S. Electrolytes showed mild hyponatremia, Echocardiography: LVEF- 64%. As her condition was progressively deteriorating, emergency laparotomy was done with debulking surgery of huge tumor mass and sample was sent for histopathology and immunohistochemistry.

Histopathology report was suggestive of malignant small round cell tumor, most likely metastatic neuroblastoma. In immunohistochemistry, S100, Chromogranin, NSE, Synaptophysin and CD56 all were positive, confirming metastatic neuroblastoma (Fig: 1).

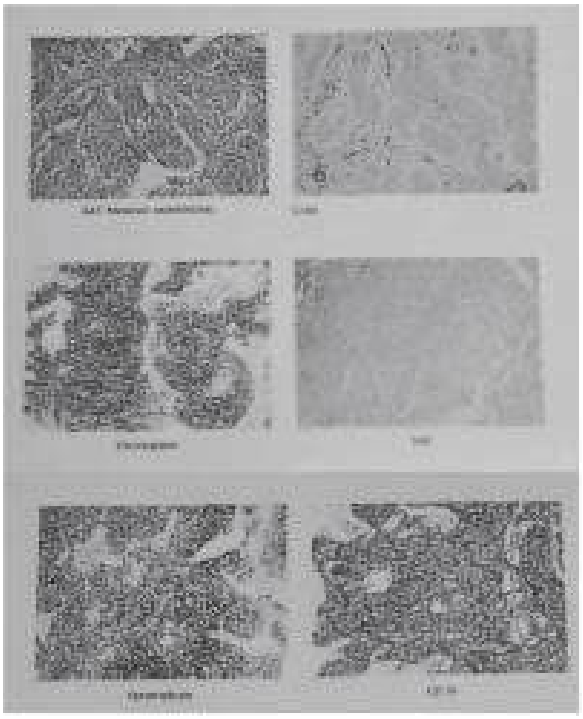


Fig 1: *Immunohistochemistry report suggestive of metastatic neuroblastoma*

Then the child was referred to the Pediatric Hematology and Oncology department of National Institute of Cancer Research and Hospital (NICRH) in Dhaka. MIBG scan was not done due to lack of availability. Urine for Vanillylmandelic acid (VMA)

was not done as patient presented to us after surgery with immuno-histochemistry report.

From all above clinical findings and investigations, the child was diagnosed as a case of Neuroblastoma Stage 4. After initial supportive investigations and management, conventional intermediate risk chemotherapy was started with a palliative intention as it is a non-transplant institution. Chemotherapy included carboplatin, cyclophosphamide, etoposide and doxorubicin.

At the end of this 3-weekly 8 cycle chemotherapy, there was persistent abdominal mass and pediatric surgery consultation was taken for a 2nd look surgery. But, according to pediatric surgeons, it was unresectable. Therefore, we started palliative chemotherapy and isotretinoin and advised for an FDG PET scan.

The FDG PET scan after 1 months of palliative chemotherapy showed that, there were low FDG avid (SUVMAX:1.5) enlarged matted nodular lesions (94 x 66 mm) in the abdomen from D9-L3 vertebrae encasing the aorta and multiple FDG avid mesenteric lymph nodes. Deauville score was 4/5 which was suggestive of active residual disease. There was also an incidental finding of a non FDG avid contrast enhanced hyperdense SOL (44 x 28 mm) with calcification in right parietal region of brain suggestive of meningioma. (Fig:2).

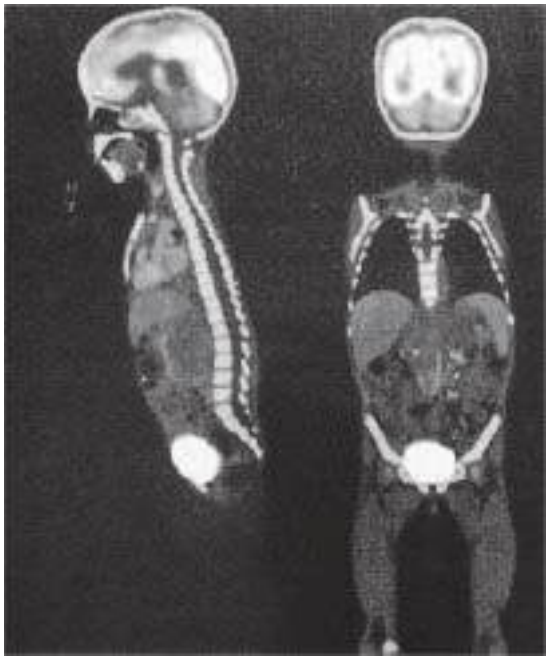


Fig:2: *FDG PET scan at the end of initial chemotherapy*

As there was FDG-avid residual disease, the oral palliative/ metronomic chemotherapy was rescheduled with addition of isotretinoin as a differentiating agent, along with previous agents (cyclophosphamide, etoposide, sodium valproate, prednisolone). The dosage were the following:

Tab. Cyclophosphamide- 50 mg/m^2/day- 21 days

Cap. Etoposide- 50 mg/m^2/day- 21 days

Syrup. Valproate- 200 mg/m^2/day- continued

Syrup. Prednisolone- 20 mg/m^2/day for 5 days, then 10 mg/m^2/day for next 5 days (along with oral famotidine)

Cap. Isotretinoin- 5 mg/kg/day-14 days (after 1 cycle, this dose was reduced to 70% for cheilitis and skin rash)

This was a 28-days' cycle, which was continued for 12 months.

There was one episode of neutropenic fever during therapy which was successfully managed. At the end of 12 months of this oral chemo-differentiation treatment, the therapy was stopped.

At 14th month, FDG-PET scan was done and showed there is no FDG-avid disease anywhere in the body. MRI of abdomen showed residual mass, which was then resected by laparotomic surgery. The histopathology of the residual mass showed fibrotic and necrosed tissue and no evidence of malignancy.

Currently at 18th month of follow-up, the child is gaining weight and height with a catch-up growth. The child is now under close follow up and monitoring under the primary physician with informed verbal and written consent from the parents.

Discussion:

The usual dose of isotretinoin in post-HSCT patients is 160 mg/m^2/day, 14 days in each 28 days' cycle.[5] But at this dose, many adverse events are common such as cheilitis, dry skin, anorexia, nausea, vomiting, and most alarmingly idiopathic intracranial hypertension which might present as headache or might be diagnosed in routine ophthalmologic assessment for papilloedema.[15] Besides, isotretinoin has been also found to cause premature epiphyseal arrest, especially in pre-pubertal age group.[16] Therefore close follow up and monitoring is required during isotretinoin

therapy. Here, as the weight of the child was below 12 kg, weight-based dosing (5 mg/kg) was used. This dosing is safe and effective in high risk neuroblastoma patients according to a previously published study.[17]

Limitations:

There are many limitations in the management in this patient, such as not assessing the *MYCN* status, ploidy and segmental chromosomal aberration for risk stratification at the initial diagnosis and inability to provide involved-site radiotherapy (age below 3 years are usually not considered for radiotherapy due to institutional limitations).

Conclusion:

Managing high risk metastatic neuroblastoma in resource-constraint setting is very challenging. Chemo-differentiating therapy might be used instead of palliative metronomic therapy at non-transplant settings with a hope for more sustained response.

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Review Article

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Prevention of High-Dose Methotrexate-Induced Mucositis in Pediatric Malignancies: Resource-Limited Approaches

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Abstract:

High dose methotrexate (HD-MTX) is an integral component of treatment of a variety of pediatric malignancies. It may cause potentially life-threatening oro-intestinal mucositis in 14-47% pediatric patients along with other serious adverse events. In resource-constraint settings, HD-MTX therapy is specially challenging due to limited availability of timely serum serum methotrexate level monitoring and therefore, pharmacokinetically guided folinic acid rescue therapy. This review article explores recent updates regarding prophylactic measures to prevent MTX-induced mucositis and scope of these measures at low-resource settings.

Keywords: *Methotrexate Mucositis Prevention Low-Resource*

Introduction:

High dose Methotrexate (HD-MTX) is defined as intravenous methotrexate at a dose of 500 mg/m2 or more which was first introduced in the treatment of pediatric cancer in 1975.[1] HD-MTX is used in various Highly curable paediatric haematological malignancies, such as in Non Hodgkin lymphoma (BFM-95 protocol for lymphoblastic lymphoma, LMB-96 protocol for mature B-cell lymphoma and ALCL-99 protocol for Anaplastic Large Cell Lymphoma).[2-5] It is also used in pediatric osteosarcoma as MAP protocol (methotrexate, Adriamycin and Cispaltin) which is still the most preferred treatment protocol.[6]

At low-resource setting, HD-MTX therapy requires more cautious approach to balance between efficacy to kill malignant cells and risk of life-threatening adverse events, specially oro-intestinal mucositis. This review article explores recent updates regarding preventing MTX-induced mucositis and feasibility these prophylactic measures in resource-constraint settings.

Toxicities of HD-MTX:

HD-MTX may cause several adverse events including mucositis, myelosuppression, hepatotoxicity, acute kidney injury and dermatologic toxicity. In various studies, severe neutropenia has been reported in 76-79%, febrile neutropenia in 21%, mucositis in 14-47%, thrombocytopenia in 13-58%, raised creatinine in 1.9-8%, hepato-toxicities in 1.9%. dermatitis in 1.9%, neuro-toxicities in 1% cases.[7-10]

A study conducted in Bangladesh involving 12 pediatric patients who received a total of 48 cycles of HD-MTX reported mucositis in 56% of treatment cycles. This incidence was considerably higher than that reported in several studies from other settings.[11]

Mucositis after HD-MTX:

Oral and intestinal mucositis due to chemotherapy such as HD-MTX usually develops within several days of treatment. It starts as erythema in the mucosa, which subsequently becomes eroded and ulcerated. A white fibrinous pseudo-membrane may cover the ulcerations. The location of ulcers is usually limited to non-keratinized surfaces of the mouth (buccal mucosa, lateral tongue, ventral tongue, and soft palate). chemotherapy causes death of the basal epithelial cells and induces formation of reactive oxygen species which causes cellular death directly and via up regulating the inflammatory pathways including TNF-alpha.[12,13]

Severe mucositis can be associated with uncontrollable pain, local and systemic superinfection, bleeding, dehydration, poor nutrition, poor quality of life, interruptions or de-escalation in anticancer treatment, resulting in worse oncologic outcomes.[14]

Evaluation of oral mucositis is dependent upon clinical history and physical findings. If there are ulcers, samples should be sent for culture, preferably including viral or fungal etiology. The severity of mucositis is measured with several well-defined scales (Table).[12,15]

Table-I: *Different grading scales for oral mucositis**

	Functional classification	Clinical classification	WHO classification
Grade 1	Asymptomatic or mild symptoms, and intervention is not indicated as well as the patient maintains a normal diet.	Mucosal erythema	Erythema and soreness, no ulcers, can maintain a normal diet.
Grade 2	Moderate pain or ulcer that does not interfere with oral intake, and the patient requires a modified diet.	patchy ulceration or pseudo-membranes	Ulcers, can tolerate solid food.
Grade 3	Severe pain which interferes with oral intake	Minor trauma resulting in bleeding, confluent ulcers, or pseudomembranes.	Ulcers, can not tolerate solid food, restricted to a liquid diet.
Grade 4	Life-Threatening consequences that require urgent intervention	Tissue necrosis, spontaneous bleeding, life-threatening events.	Oral nutrition is impossible.
Grade 5	Death	Death	

*Lalla et al 2008, Bell et al 2023

Identifying and managing predictors of severe toxicity:

Delayed clearance of methotrexate:

Delayed clearance of methotrexate may occur in 24-27% of infusions of HD-MTX.[9,16] Raised 24-hour methotrexate concentration (64 μmol/L) is an independent risk factors for adverse events like fever, infection, mucositis and thrmbocytopenia.[17]

Renal function and hydration:

Baseline normal renal function, more specifically, glomerular filtration rate (GFR) ≥ 60 ml/min/1.73m² and pre-infusion hydration (≥2.5 L/m²/day) are prerequisites for HD-MTX.[18,19,]

rising serum creatinine concentration or decreased urine output after HDMTX indicates a medical emergency, requiring urgent hyper-hydration, high-dose folinic acid, and glucarpidase (if available).[20]

Baseline urine pH are significant predictors of HD-MTX-related severe nephrotoxicity in children. Therefore, urinary alkalinization (pH > 7.0) are consistently recommended to prevent methotrexate crystallization.[18-21] For some children, oral sodium bicarbonate is a feasible alternative to intra-venous medication which shows similar efficacy in attaining desired urine pH and adequate methotrexate clearance.[22]

Hypoalbuminemia:

Serum albumin levels should be checked before starting HD-MTX cycles, especially in resource-limited settings where malnutrition is common, and serum MTX monitoring may not be available. Optimizing serum albumin levels before HD-MTX may help decrease the possibility of HD-MTX toxicities.[23]

Third space accumulation:

In patients with malignant ascites or pleural effusion, methotrexate may accumulate in the third space fluid, which might cause delayed clearance of the drug and subsequent toxicities.[24]

Timing of Folinic acid rescue:

After HD-MTX therapy, folinic acid rescue at 42–48 hours results in considerable toxicity in comparison to toxicities when rescue starts at 30–36 hours.[25] Therefore, folinic acid rescue should be started within 24-36 hours from the start of high dose MTX. Folinic acid rescue timing and dosing should be guided by serum MTX levels.[19]

Drug interaction:

a. **Tazobactum/piperacillin** with HD-MTX may result in delayed renal clearance of MTX resulting in severe toxicities.[26]

b. **Proton pump inhibitor**s (omeprazole, lansoprazole, rabeprazole and pantoprazole) are also risk factor for delayed elimination of plasma MTX in HDMTX therapy for malignant diseases. On the other hand, no methotrexate toxicity was found when a histamine H2 blocker was substituted for a PPI.[27-28]

Low-resource setting measures:

High dose methotrexate 3 g/m²/cycle is feasible in low-resource settings where routine MTX monitoring is unavailable[29]. In centers lacking access to MTX levels, administration of HD-MTX at full doses, with extended hydration, additional doses of folinic acid and monitoring of serum creatinine and urine pH, is feasible with manageable toxicities.[30]

Preventive agents/interventions:

a. **Chlorhexidine mouth wash** along with oral and general asepsis measures might be helpful prophylactically in alleviating mucositis in children on chemotherapy.[31]

b. **Cryotherapy is** an established prophylactic option against chemo-induced mucositis.[32] It is especially appropriate for older co-operative pediatric patients. In a randomized controlled trial, children aged 5-18 years receiving high dose methotrexate-based chemotherapy were asked to suck on ice cubes /lollies for 1hour during the initial bolus infusion and then every 6-8 h till the beginning of folinic acid rescue. The incidence of oral mucositis was significantly low in the intervention arm.[33]

c. **Palifermin,** a recombinant keratinocyte growth factor which promotes thickening of the mucosa, may prevent and reduce severity of mucositis caused by chemotherapy in up to 30 % iof the patients. Palifermin might reduce the severity, duration and clinical sequelae of oral mucositis in HD-MTX-based chemotherapy.[34-35]

d. **Hyaluronic acid** is an important glycosaminoglycan produced by fibroblasts which is widely used in clinical practice to accelerate skin wound repair and may act in preventing oxidative stress-induced mucosal damage. It is found to be an effective option for prophylaxis and treatment of oral mucositis in a randomized control trial.[36] High molecular weight hyaluronic acid drastically reduces chemotherapy-induced mucositis and apoptotic cell death.[37]

e. **Glutamine** acts to accelerate the division of leukocytes along with macrophages in the immune system. Glutamine stimulates the synthesis of hexosamine as a mucin-forming material that lines the mucosa and as a barrier in preventing bacterial translocation. It was also found to be effective as oral supplement and/or mouthwash in reducing the incidence and overall duration of severe mucositis in children receiving HDMTX.[38-39]

f. **Combination of L-glutamine and hyaluronic acid** is found to be associated with less severe oral mucositis in a randomized clinical trial.[40]

g. **Sucralfate** is effective in protecting the gastro-intestinal mucosa against injury through various mechanisms like: adsorption of pepsin and bile acids, stimulating mucus production, releasing bicarbonate and prostaglandin and protecting vascular integrity.[41-42] It also enhances of epithelial proliferation through the stimulation growth factor receptors.[43] It was also found effective as prophylaxis in patients receiving bone marrow transplantation.[44] In a systematic meta-analysis, sucralfate was found to be the most effective intervention due to its cyto-protective action, low cost, good compliance and safety[45]

Newer agent: Glucarpidase is a recombinant bacterial enzyme that rapidly disintegrates methotrexate from circulation into its non-toxic metabolites. It is found to be effective in minimizing toxicities in patients with delayed MTX clearance with renal dysfunction. But, it is still being used in selective cases and should not be included as a routine preventive measure. [46]

Recommendations:

In low-resource setting where serum methotrexate level can not be monitored due to financial constraint, HD-MTX should be administered cautiously with extended hydration (2.5L/m^2/day), urine alkalinization, strict monitoring of renal function, serum albumin and urine pH, improved local care, early (24-36 hours) and extended folinic acid rescue and avoidance of possible drug interactions.

However, timing of folinic acid rescue and methotrexate level monitoring should be protocol-specific, especially designed for the specific primary diagnosis.

Further randomized controlled trial should be considered to evaluate the cost-effectiveness of various therapies like: cryotherapy, glutamine, hyaluronic acid and sucralfate. Cryotherapy is currently appearing to be the most promising prophylactic intervention.

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