ORIGINAL ARTICLE

Evaluation of Inpatient Mortality in Pediatric Non-Hodgkin Lymphoma and Lessons Learnt at a Tertiary Care Hospital in Pakistan

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ABSTRACT

Objective: Non-Hodgkin Lymphoma (NHL) is an aggressive pediatric malignancy that carry dismal prognoses in developing countries. A mortality audit was done to identify causes of inpatient mortality in children with NHL at a tertiary care hospital.

Study Design: Descriptive study

Place and Duration of Study: Pediatric Hematology Oncology Department at The Children's Hospital, Lahore from 1st January 2020 till June 2022.

Material and Methods: Mortality analysis was done of pediatric NHL patients retrospectively. Demographics, clinical, and epidemiological features, histopathology, stage, and causes of death were analyzed. Mortality cause was categorized as treatment-related or disease-related mortality.

Results: There were 42 mortalities out of 205 NHL patients. Thirteen patients (31%) had very early deaths. Thirty-eight percent were between 5 -10 years of age, 81% were boys and 81% were from other cities. Predominant symptoms were fever (52%), abdominal pain/distension (38%), respiratory distress (33%) palpable mass (21%), and lymphadenopathy (21%). Histopathology was T Lymphoblastic Lymphoma (22%), Burkitt's Lymphoma and High-grade B cell NHL (34%). Common causes of mortality were infection (57%), tumor lysis syndrome (19%), disease progression/resistance (10%), Superior vena cava syndrome (7%) and COVID infection (4%). Twenty-seven (64%) patients had treatment-related mortality while 15(36%) had disease-related mortality.

Conclusion: Infection-related mortality was the most common cause of mortality. Febrile neutropenia and sepsis were still the most common causative factors. A significant number of Pediatric NHL patients presented with an Oncological emergency and had significant diagnostic delays. Many of these deaths are preventable by better infection control practices, early diagnosis, recognition, and management of oncological emergencies.

Key Words: *Non-Hodgkin Lymphoma, Children, Mortality, Sepsis, Oncological emergency*

Abbrevations: *NHL = Non-Hodgkin lymphoma; BL = Burkitt's lymphoma; ALCL = Anaplastic large cell lymphoma; T LL = T cell lymphoblastic lymphoma; LMIC'S = Lower middle-income countries; TLS = T Lysis syndrome; SVC = Superior vena cava syndrome; TRM = Treatment related mortality; DRM = Disease related mortality; PICU = Pediatric intensive care unit*

INTRODUCTION

Non-Hodgkin lymphoma (NHL) consists of a diverse group of malignant neoplasms of the lymphoid tissue derived from B or T cell progenitors, mature B or T cells. Pediatric NHL is usually high-grade and has aggressive clinical behavior.[1] It's the fifth commonest pediatric cancer in children under the age of 15 years, and accounts for approximately 7% of childhood cancers in the developed world.[2] Common subtypes are Burkitt lymphoma (BL), diffuse large B cell lymphoma (DLBCL), T cell lymphoblastic lymphoma (T LL), and anaplastic large cell lymphoma (ALCL).[3] Children with NHL carry a much better prognosis than adolescents and adults. The prognosis though is variable for different types and stages of NHL but generally, the 5-year survival rate for children ages 0 to 14 with NHL is 91%, and for teens ages 15 to 19 is 89%.[4] in the developed world. The prognosis for pediatric NHL in developing countries varies from 60-70% due to delayed diagnosis, heterogenicity of care, and resources available.[5] The mortality rate due to NHL has decreased significantly in developed countries due to therapy improvement and better supportive care, while it's still high in many developing countries primarily due to infection and limited supportive care.[6]. There is little in-depth analysis mainly focusing on causes of mortality in pediatric non-Hodgkin lymphoma patients in developing countries. This mortality analysis aims to identify the causes of inpatient mortality of pediatric NHL in a tertiary care setting.

MATERIAL AND METHODS

A descriptive study based on mortality audit of pediatric NHL patients was conducted retrospectively in the inpatient unit of the pediatric hematology oncology ward at The Children's Hospital, University of Child Health Sciences (UCHS), from 1st January 2020 till July 2022. Inpatient Mortality data was retrieved from the patient's medical record files and entered into proforma. Children less than 18 years of age who expired due to any cause with a histopathologically confirmed diagnosis of NHL were included in the analysis. Patients with relapse NHL or who partially received treatment at another center were excluded. Exemption was taken from the institutional review board (IRB) to conduct the mortality audit study. Two of the three study investigators conducted a detailed chart review of each death. The reviewer assigned the presenting signs and symptoms as per the complaints documented by the hematology-oncology ward pediatric resident or hematology oncology fellow or consultant. In case of a discordant finding, further review was undertaken by all three investigators. One to two most likely cause of death determination was based on a retrospective chart review and the investigator's best judgment. One to two most likely causes of death were noted. Sepsis was defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection and labeled as clinical or laboratory evidence of infection with systemic inflammatory response syndrome.[7] TLS was defined as per Cairo-Bishop's classification.[8] Death not directly due to cancer has been termed treatment-related mortality.[9] Lymphoblastic Lymphoma patients were treated according to the UKALL 2011 Protocol while BL, DLBCL, High-grade B cell NHL, and T cell Histiocyte Rich B Cell Lymphoma were treated according to UKCCSG Guidelines for Mature B cell Lymphoma 2020 without Rituximab. Patient with ALCL was treated according to CCLG Guidelines for management of ALCL 2022. Mortality was primarily categorized as disease-related mortality (DRM) or treatment-related mortality (TRM). Patients who died within forty-eight hours of admission were considered very early deaths.

Data was entered and analyzed by SPSS 22. Data analyzed included age, gender, primary diagnosis, distance from the treatment center, presenting complaints, stage of disease,

histopathology, treatment received, duration of last stay as an inpatient, and cause of mortality. Baseline and demographic characteristics were summarized by descriptive statistics. Frequency and percentages were calculated for quantitative variables like gender, diagnosis, and cause of mortality. Chi-square tests were used to evaluate significant differences between categorical data of each demographic characteristic. A P-value of <0.05 was taken as significant.

RESULTS

There were 205 newly diagnosed pediatric patients with non-Hodgkin lymphoma during the study period. There were 46 patients mortality with suspected NHL but histopathological diagnosis was not available for 3 patients and one took treatment before presentation to our hospital so they were not included in the study. Forty-two NHL patient mortalities fulfilled the inclusion criteria. The mortality rate was 20.4%. Mortality analysis showed patients' ages ranged from 1 1/2 years to 16 years (mean 9 yrs, SD 3.28). Eight (19%) patients were from the local city while 34 (81%) of patients were from other cities. The longest travel distance to the hospital was 834 Km. Fever (52%), respiratory distress (33%), abdominal pain (16.6%), and distension (28%) were predominant symptoms (table 1). Duration of symptoms before presentation with the malignancy ranged from 1 day to 6 months. T Lymphoblastic Lymphoma (22%) was the predominant histological diagnosis followed by Burkitt's Lymphoma and High-Grade B cell NHL (16% each). The causes of mortality were treatment-related in 27 (64%) while disease-related in 15 (36%) of patients. There were 34 treatment-related and 24 disease-related events observed in patients identified as a cause of mortality. Few patients had more than one cause identified as a cause of death. Two patients died of COVID-related complications (4%). Infection was a major cause of treatment-related mortality (57%). Tumor lysis syndrome was a major cause of disease-related mortality (fig 1).

Thirteen patients had very early deaths within 48 hrs of presentation. Out of these patients, five patients died before a full staging workup can be retrieved. Four patients presented with tumor lysis syndrome out of which 03 had acute renal failure. Two patients had mediastinal mass and had SVC syndrome along with FN, sepsis, and pleural effusions requiring chest intubation and the cause of death was concomitant sepsis along with SVC in these patients and they stayed in the ward for 1 and 5 days respectively. One expired due to sepsis and intracranial bleeding (table 1). Steroids alone were started in those patients whose histopathological diagnosis was not confirmed at admission being very sick and with disease complications.

TABLE 1: Clinical characteristics

Category	Subcategory (Total 42);	Number (%)
Fever	present	22 (52.4)
	Absent	20 (47.6)
Lymphadeno-pathy	present	9 (21.4)
	Absent	33 (78.6)
Abdominal Symptoms	Abdominal Pain	7 (16.6)
	Abdominal mass	9 (21.4)
	Abdominal Distension	9 (21.4)
	Urinary Retention	1 (2.3)
	Vomiting	2 (4.8)
	No abdominal symptom	21 (50.0)
Respiratory Symptom	Respiratory Distress	14 (33.3)
	Cough	02 (4.8)
	No resp symptoms	29 (61.9)
Other	bleeding	02
	Failure to thrive	01
	fits	01
	Joint pain	01
	Cheek/face swelling	02
	pallor	01
Inpatient Stay	<48hours	12 (13.0)
	2days-1week	7 (30.4)
	1week-1 month	18 (46.0)
	>1month	05 (11.9)
Surgical Intervention	Chest Intubation	03 (7.1)
	Laparotomy for intussusception	01 (2.0)
	Laparotomy for diagnostic biopsy	03 (7.1)
	Left maxillary sinus biopsy	01 (2.4)
	Pericardial Tap	01 (2.4)

TABLE 2: Factors associated with mortality

	Characteristic	Total (%)	Disease Related Mortality (%)	Treatment Related Mortality (%)	p value
Gender	Female	08(19.0)	2	6	0.494
	male	34(81.0)	13	21	
Distance from Treatment Centre	Local city	8(19.0)	1	7	0.272
	Out of station	34(81.0)	14	20	
Age	1-5yrs	13(31.0)	3	10	0.08
	5-10 yrs	16(38.0)	9	7	
	>10yrs	13(31.0)	8	5	
Histopathology	Burkitt's Lymphoma	07(16.7)	1	6	0.02
	High Grade B cell NHL	07(16.7)	1	6	
	T Lymphoblastic Lymphoma (T LL)	10(22.0)	4	6	
	Diffuse large B cell Lymphoma (DLBCL)	04(9.5)	1	3	
	Anaplastic Large Cell Lymphoma (ALCL)	02(4.8)	0	2	
	T cell histiocyte rich B cell Lymphoma	01(2.4)	1	0	
	B NHL	04(9.5)	3	1	
	B Lymphoblastic Lymphoma	01(2.4)	1	0	
	NHL*	06(14.3)	3	3	
Length of hospital stay	<48hrs	12(29.0)	9(80.0)	3(80.0)	0.04
	48 hrs -1 wk	7(16.0)	2(80.0)	5(80.0)	
	1wk-1month	18(43.0)	5(43.0)	13(80.0)	
	>1month	5(12.0)	0(0.0)	5(100.0)	
Stage	1	0	0	0	0.87
	2	0	0	0	
	3	33(78.6%)	12	21	
	4	9(21.4%)	6	3	
Very early death	Within 48 hrs	13(31.0)	9(69.0)	04(31.0)	0.002
Cause of death		42(20.0)	15(36.0)	27(64.0)	0.001

* FNA confirmed NHL and advised excisional biopsy of mass but the patient was sick and died before that.

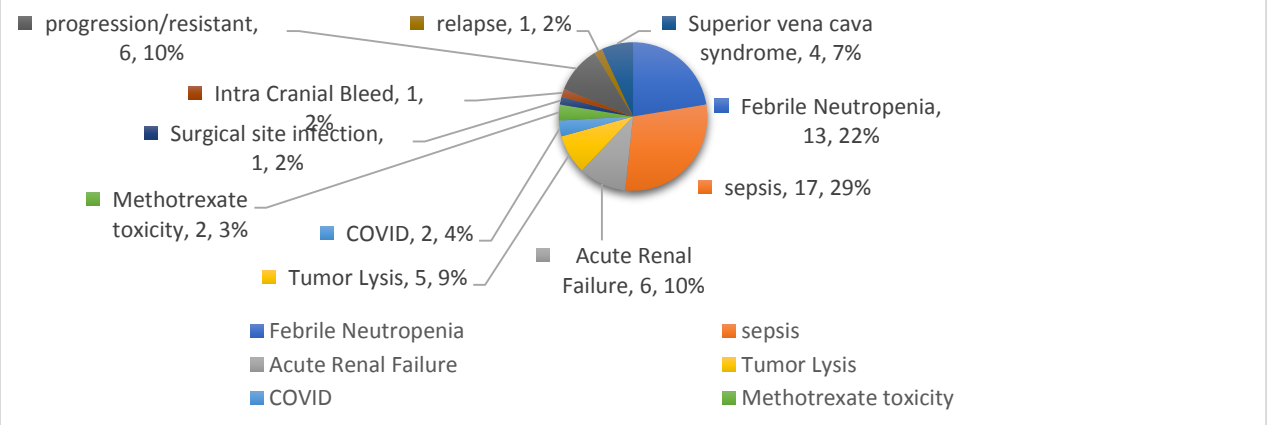

Fig 1: Causes of mortality

DISCUSSION

Treatment-related mortality (p-value <0.05) is the most common cause of mortality in pediatric NHL patients in this study. Infection remains the predominant cause (57%). There are very few studies from low and lower-middle-income countries (LMICs) analyzing causes of mortality in pediatric NHL.[10] Our study cohort has an almost similar incidence of Infection-related and disease-related mortality as seen in other developing countries.[11,12] The majority of our patients had multiple factors predisposing them to mortality. In the current study, COVID-19 has been the cause of mortality in two patients. Appreciating the differences between TRM and disease-related death is critical in directing strategies to improve supportive care, interventions delivered, or disease progression.[13].

Thirty-four (81%) of patients were referred from outside the city, which, though is statistically not significant in this study but more studies recruiting a large number of patients need to be carried out to see the exact significance of travel distance from the hospital. Thirteen (31%) of the NHL patients in our study were very unstable and expired within 48 hrs of admission and the majority of these were with disease-related complications (p-value 0.002). The maximum duration of illness was 6 months. This signifies a significant diagnostic delay before they reach an oncology center. A delay in diagnosis adversely affects the prognosis[14]. The majority of these patients present first at primary care centers near their hometowns, which are often not well-equipped to recognize and deal with these emergencies. The detailed analysis of factors responsible for delay in seeking care is beyond the scope of this article but the limited number of pediatric oncology centers and lack of trained pediatric oncologist near their home towns can be a contributing factor. This creates a huge gap that can be addressed by training district pediatricians in the early diagnosis and treatment of pediatric cancers and oncologic emergencies.

Confirming the histological diagnosis is another challenge for these patients. Three of our patients underwent laparotomy for biopsy before referral to our center and one of them died due to severe septicemia secondary to surgical site infection. Multidisciplinary teams need to be trained to do ultrasound-guided Trucut biopsy. It's a relatively simple procedure that needs diagnostic equipment, a trained radiologist, and a histopathologist at each district-level hospital to avoid diagnostic delay and unnecessary major surgical procedures.

Our study highlights significant differences (p-value <0.05) between treatment-related and disease-related mortality in terms of histopathology, length of last inpatient stay, cause of death, and very early deaths. Very early deaths were more in patients who presented with a disease-related complication, especially T lysis syndrome. The causes of mortality were significantly different between the two groups. The length of inpatient hospital stay was more for patients with treatment-related mortality. The clinical characteristics of the patient cohort in our study are comparable to data from other centers[15] but mortality is higher in comparison to data from high-income countries that have achieved better prognoses and reduced mortality rates by better supportive care and robust research.[16,17] The results of a large study evaluating outcomes for pediatric NHL by Attarbachie et al[18] show a five-year cumulative incidence of progression/ relapse and treatment-related death as a first event as 22% ± 4% and 24% ± 4% with inferior survival rate in patients having preexisting conditions. One of the major limitations of our study is that it's a retrospective single-center mortality audit recruiting a limited number of patients. There is a need to collect multi-institutional mortality data prospectively on a large number of patients for in-depth analysis.

International pediatric oncology leaders have summarized key elements of successful cancer treatment in LMICs through local need assessment, community mobilization, twinning, multidisciplinary teams, better supportive care, social support (subsidized travel and housing), and the development of locally adapted treatment protocols.[19] It is estimated that over 90% of paediatric NHL worldwide occur in LMIC; therefore, even modest improvements in outcome would have a significant impact in reducing the burden of paediatric NHL globally.[20] Strict infection prevention and control measures are the key to preventing such high infection-related

mortality, while early diagnosis and management of oncologic emergencies can prevent disease-related mortality. Developing more pediatric oncology centers with trained staff and multidisciplinary teams is the ultimate solution that requires local team ownership, public-private partnership, and strong Government support.[21]

CONCLUSION

Infection-related mortality is the predominant cause of mortality in pediatric NHL, followed by mortality due to an oncological emergency. Many of these deaths are preventable. There is a need for better infection control practices, early recognition of oncological emergencies, expedited diagnosis, and multidisciplinary care to improve prognosis.

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