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The Epidemiological Study of Children with Malignant Disorders in the Pediatric Department at Menoufia University Hospital, Menoufia, Egypt during the Last Fifteen Years

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Abstract

Background: This study aims to assess the epidemiological, clinical, and paraclinical characteristics and survival of childhood with malignant disorders in the pediatrics department, menoufia University Hospital.

Methods: A retrospective study with clinical and epidemiological data from patients was conducted on 314 children who attended Pediatric Department, Haematology-Oncology Unit, Menoufia University Hospital during the last fifteen years.

Results: 314 children were assessed, their ages ranged from 2 months-18 years with mean 5.96±3.79 years. Also, 252 (80.3%) were diagnosed with hematological malignancies, and 62 (19.5%) were diagnosed with solid tumors. Among hematological malignancies, 186 were diagnosed with acute leukemia, 158 (49.7%) with acute lymphoblastic leukemia (ALL), and 28 (8.8%) with acute myeloid leukemia (AML). The most frequent clinical presentations were fever in 95.24% in hematological malignancies vs 48.4% in solid ($p<0.001$),, pallor in 92.5% in hematological malignancies vs 69.4% in solid ($p<0.001$), hepatomegaly in 81.3% in hematological malignancies vs 37.1% in solid ($p<0.001$),, lymphadenopathy in 77.6 % in hematological malignancies vs 24.2% in solid ($p<0.001$), and splenomegaly in 76.3% of hematological malignancies vs 12.9% in solid ($p<0.001$),The majority of the patients 64.15% had white blood cells (WBCs) less than 50,000/mm³, while 35.85% had WBCs more or equal to 50,000/mm³ with significant relation with risk stratification ($p=0.001$). The survivors who finished their treatment course were 31.8% and the recurence patients were 9%.

Conclusion: Acute lymphoblastic leukemia is the most frequent childhood hematological neoplasm. Various clinical and laboratory features present at the time of initial diagnosis can predict the likelihood that a patient will remain in remission or not including age: under 1 and over 10 years, gender: male sex, WBCS more than 50,000/mm³ at presentation.

Keywords: Acute lymphoblastic leukemia, Cancer, Children, Epidemiology, Malignant disorders

Introduction

Cancer in children becomes more prevalent. (1) It is one of the leading causes of death among children. (1, 2) Leukemia represents the most frequent pediatric malignancies (about 28%) followed by tumors of the central nervous system (CNS) (about 26%) followed by lymphoma (about 8%), less frequent neuroblastoma (8%), nephroblastoma (5%), malignant bone tumors (5%), soft tissue tumors (7%), germ-cell tumors (about 4%). (3-6).

Brain and CNS tumors are the most common solid tumor and the second leading cause of cancer death in individuals aged 0–19 years in the United States (US) and Canada. (7, 8) The main subtype of brain and CNS tumors in children are astrocytoma, brain stem glioma, medulloblastoma, craniopharyngioma, high risk glioma, atypical teratoid rhabdoid, ependymoma and desmoplastic infantile ganglioglioma (1, 9).

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Acute leukemias represent a clonal expansion and arrest at a specific stage of normal myeloid or lymphoid hematopoiesis (10, 11). Leukemias may be defined as a group of malignant diseases in which hematopoietic cells' genetic abnormalities give rise to cells of unregulated clonal proliferation. (12) The progeny of these cells has a growth advantage over normal cellular elements because of their increased rate of proliferation and a decreased rate of spontaneous apoptosis. The result is a disruption of normal marrow function and, ultimately, marrow failure. (13). Leukemia of childhood is the most common cancer affecting children representing about 32% of malignancies in children younger than 15 years old. (14) Approximately 3280 new cases of childhood leukemia occur annually in the U.S 80% of which are acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML) for approximately 12%, chronic myelogenous leukemia (CML) for 2-3 %, and juvenile myelomonocytic leukemia (JMML) for 1-2% (14, 15). In Egypt, the total diagnosed new cases with cancer below 20 years were 58.2% were males, and 41.8% were females (16, 17), About 34% of males and 33% of females were diagnosed with leukemia. Acute leukemia is the first ranked in pediatric cancer and the fifth in the adult group (16, 17, 18, 19). Therefore, this research goal was to assess the epidemiological, clinical and paraclinical characteristics and survival of childhood with malignant disorders in the Pediatric Department, Menoufia University Hospital in fifteen years (2002- 2017).

Materials and Methods

Study design & patients

A retrospective study was implemented on 314 patients (183 males and 131 females) presented with different types of malignancy recruited from the Pediatric Hematology-Oncology Unit, Menoufia University Hospital during fifteen years from February 2002 to February 2017. The data of these patients were abstracted from patient's medical records of each participant. The study design was conducted between July 2019 and February 2022. The study protocol was approved by the Menoufia University Faculty of Medicine's ethical committee by IRB approval number 19819PEDI28. All children underwent entire medical history, general and local examination, routine peripheral blood, bone marrow cytological examination, lumbar puncture (LP) and flow cytometric immunophenotyping after admission for a confirmed diagnosis. Further molecular and cytogenetic investigations were performed. Each patient was assessed for the presence or absence of mediastinal mass through chest X-ray and/or computed tomography (CT) scan. Initial echocardiography for all patients and testicular ultrasound for male patients were performed.

Data collection

The clinical data of the included children were collected from the hospital medical records, including age, sex, chief complaint, white blood cells (WBC) at initial diagnosis, bone marrow cytology, flow cytometric immunophenotyping, molecular and cytogenetic characteristics, treatment regimens, complications during treatment and treatment outcome.

Statistical analysis

The results were collected, tabulated, and statistically analyzed by SPSS version 22.0 on IBM compatible computer. Descriptive statistics were calculated as percentage (%), mean and standard deviation (SD) for each variable. Analytic statistics using *Chi-squared test* (χ^2) to study the association between two qualitative variables, *Fisher's exact test* to study the association between two qualitative variables, and at least one expected cell was less than 5, *Student t-test* for comparison between two groups having normally distributed quantitative variables, and *Mann-Whitney test (U)* (non-

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parametric test) for comparison between two groups having not normally distributed quantitative variables. Relapse-free survival (RFS) and Overall Survival (OS) rate curves were computed using the *Kaplan-Meier estimator*. P <0.05 was considered statistically significant.

Results

A flowchart of the study population is shown in Figure 1. Of the 330 children with malignant disorders, patients were admitted to the Pediatrics Department, Haematology-Oncology Unit, Menoufia University Hospital during the last fifteen years. 16 patients were excluded from the study (7 patients declined consent and 9 patients did not meet the inclusion criteria). 314 patients participated in the study and a written informed consented from their parents and care givers after explaining the aim of study. The studied patients were divided into two groups according to type of malignancy as 252 children with hematological malignancies (Group I), and 62 children with solid tumors (Group II), (Figure 1). During this retrospective study, 314 children were assessed. Sociodemographic data was illustrated in Table I. Among the studied cases, the most frequent clinical presentations were fever in 91.4% of them followed by pallor in 87.8%, hepatomegaly in 72.3 %, lymphadenopathy in 66.7 %, splenomegaly in 63.4 %, abdominal enlargement in 14.6%, mediastinal involvement in 7.3 %, pleural effusion in 7.0 %, inability to walk in 6.9 %, tumor lysis in 3.6 %, skin lesions in 1.7 %, proptosis in 1.7%, intestinal obstruction in 1.3 %, facial edema in 1.3%, facial palsy in 1.0%, CNS involvement in 1.0 %, parotid involvement in 0.3 %, testicular swelling in 0.3%, and lastly bilateral raccoon eye in 0.3 %. Fever, pallor, hepatomegaly, lymphadenopathy, and splenomegaly were significantly more common ($p<0.001$) in hematological malignancies than in solid tumors. At the same time, abdominal enlargement was significantly common ($p<0.001$) in solid tumors than in hematological malignancies. Other clinical presentations showed no statistically significant difference between both types of malignancies (Table II). The majority of the patients 64.15% had WBCs less than 50,000/mm^3, while 35.85% had WBCs more or equal to 50,000/mm^3. The hemoglobin (Hb) levels, platelets, and WBCs counts were significantly lower ($p<0.001$) in hematological malignancies compared with solid tumors cases. In contrast, the other laboratory data, serum alanine transaminase (ALT), aspartate transaminase (AST), serum urea, serum creatinine, serum sodium (Na), serum potassium (K), uric acid and lactate dehydrogenase (LDH) showed no statistically significant difference between the two types of malignancies (Table III). Of the 314 studied children, 252 (80.3%) were diagnosed with hematological malignancies, 186 of them were diagnosed with acute leukemia, 49.7% with acute lymphoblastic leukemia (80.4% had precursor-B and 19% whad T-cell), and 8.8% with acute myeloid leukemia (25% of them were M3). Regarding the other hematological malignancies, 14.5% were diagnosed with Non-Hodgkin lymphoma and 7.3% with Hodgkin lymphoma. Regarding solid tumors, 9.9% were diagnosed with neuroblastoma, 0.6% with Burkitt's lymphoma, and 0.8% with Wilms tumor. The outcome of the study, the survivors who finished their treatment course were 31.8%, 15% were referred to other hospitals for treatment, 1% did not complete follow-up, 43.6% of cases died, and the relapsed cases were 9%. Of these relapses, 51.8% were medullary, 37% extramedullary, and 11.1% combined relapses. Extramedullary relapse mostly affected the CNS in 80% then testicular

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relapse in 20% of extramedullary relapses**.** The majority of patients died during the consolidation or maintenance phases 66.4%, followed by the induction phase 24% (Table IV). The majority of ALL patients (76.6%) were between 1 and 9 years, and the mean age± SD was 6.16± 3.71. One patient (0.6%) was less than one year old and 36 (22.8%) were more than nine years old at the initial diagnosis. The majority of ALL patients were males (58.2%), while females were 41.8%. At the time of initial diagnosis, there was testicular involvement in 0.6%, CNS involvement in 1.3%, and mediastinal involvement in 0.6%. The majority of the ALL patients had WBCs less than 50,000/mm³ 57.0%, while those with WBCs were more or equal to 50,000/mm³ composed about 43.0% of patients with a mean ± SD of 62.38 ± 87.29. The distribution of the ALL cases according to the risk stratification showed that 104 (65.8%) patients were stratified as standard risk and 54 (34.2%) were low risk. The age increased significantly in standard and high-risk ALL cases (p=0.001) than in low-risk cases. The CNS and mediastinal involvement showed a statistically significant difference (p<0.001) between standard and high-risk ALL cases compared to low-risk cases. The WBCs count showed a statistically significant increase (p<0.001) in the standard and high-risk cases compared to low-risk ALL cases. The standard and high-risk ALL cases showed significantly worse outcomes than low-risk ALL cases (Table V). In our study, the overall survival (OS) of the studied patients was 51.3 % in five years. The relapse-free survival (RFS) was 46.2 % in 5 years (Tables VI, Figures 2, 3).

Table I: Socio-demographic data of all studied cases.

Socio-demographic data	***No.***	***%***
Sex		
Male	183	58.3
Female	131	41.7
Age at diagnosis (years)	314	100.0
Min. – Max.	0.20 – 18.0	
Mean ± SD.	5.96 ± 3.79	
Median (IQR)	5.0(3.0 – 9.0)	
Age at remission (years)	156	49.7
Min. – Max.	0.42 – 16.0	
Mean ± SD.	6.25 ± 3.65	
Median (IQR)	5.0(3.50 – 9.0)	
Age at finished chemotherapy (years)	100	31.8
Min. – Max.	0.42 – 19.0	
Mean ± SD.	8.64 ± 3.87	
Median (IQR)	8.0(6.0 – 11.0)	
Age at referred Cases (years)	47	15
Min. – Max.	0.50 – 18.0	
Mean ± SD.	7.07 ± 4.35	
Median (IQR)	6.0(4.0 – 10.0)	
Age at loss Follow up (years)	3	1.0
Min. – Max.	2.0 – 15.0	
Mean ± SD.	7.60 ± 5.78	
Median (IQR)	5.0(3.50 – 12.50)	
Age at Death (years)	137	43.6
Min. – Max.	0.42 – 18.0	
Mean ± SD.	6.44 ± 4.15	
Median (IQR)	5.50(3.0 – 10.0)	

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Age at Relapse (years)	27	9.0
Min. – Max.	2.0 – 21.0	
Mean ± SD.	10.0 ± 4.75	
Median (IQR)	9.0(7.0 – 13.0)	

SD: Standard deviation, **IQR:** Interquartile range, **Min.:** minimum, **Max:** maximum

Table II: Relation between the types of malignancy and clinical data.

Clinical Presentations	Type of Malignancy				χ^2	*P value*
	Hematological (n = 252)		Solid (n = 62)			
	No.	%	No.	%		
Fever	240	95.24	30	48.4	24.919*	<0.001*
Pallor	223	92.5	43	69.4	24.709*	<0.001*
Hepatomegaly	196	81.3	23	37.1	48.148*	<0.001*
Lymphadenopathy	187	77.6	15	24.2	63.279*	<0.001*
Splenomegaly	184	76.3	8	12.9	85.512*	<0.001*
Abdominal Enlargement	3	1.2	41	66.1	166.627*	<0.001*
Mediastina involvement	17	7.1	5	8.1	0.070	FEp=0.786
Pleural effusion	16	6.7	5	8.1	0.149	FEp=0.779
Inability To Walk	20	8.3	1	1.6	3.417	FEp=0.089
Tumor lysis	11	4.6	0	0.0	2.936	FEp=0.128
Skin lesion	3	1.2	2	3.2	1.192	FEp=0.272
Proptosis	4	1.7	1	1.6	0.001	FEp=1.000
Intestinal Obstruction	2	0.8	2	3.2	2.158	FEp=0.188
Facial edema	3	1.3	1	1.6	0.050	FEp=1.000
Facial palsy	3	1.2	0	0.0	0.780	FEp=1.000
CNS involvement	3	1.3	0	0.0	0.780	FEp=1.000
Bilateral Raccoon Eye	0	0.0	1	1.6	3.884	FEp=0.205
Parotid involvement	1	0.4	0	0.0	0.260	FEp=1.000
Testicular involvement	1	0.4	0	0.0	0.260	FEp=1.000

CNS: central nervous system, **χ^2:** Chi-square test, **FE:** Fisher Exact test, **p:** p-value for comparing different parameters, ***:** Statistically significant at $p \leq 0.05$

Table III: Comparison between the types of malignancy regarding the laboratory data.

Laboratory Data	Malignancy		t	*P value*
	Hematological (n = 252)	Solid (n = 62)		
Hb (gm/dl)				
Min. – Max.	2.70 – 14.80	3.90 – 13.70	8.680*	<0.001*
Mean ± SD.	6.44 ± 2.18	9.09 ± 1.97		
Platelet count (×10³/ul)				
Min. – Max.	3.0 – 432.0	20.0 – 888.0	8.970*	<0.001*
Mean ± SD.	91.21 ± 85.72	275.98 ± 156.27		
WBCs (×10³/ul)				
Min. – Max.	0.60 – 585.0	2.50 – 140.0	7.323*	<0.001*
Mean ± SD.	52.35 ± 75.43	13.37 ± 17.11		
Serum ALT (IU/L)				
Min. – Max.	6.0 – 164.0	8.0 – 250.0	0.785	0.435
Mean ± SD.	21.73 ± 14.58	25.02 ± 32.06		
Serum AST (IU/L)				
Min. – Max.	8.0 – 86.0	8.0 – 370.0	1.614	0.112

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Mean ± SD.	22.51 ± 11.79	32.73 ± 49.50		
Serum Urea (mg⁄dl)				
Min. – Max.	1.20 – 197.0	8.0 – 142.0	0.432	0.666
Mean ± SD.	17.48 ± 14.0	18.39 ± 17.30		
Serum creatinine (mg⁄dl)				
Min. – Max.	0.20 – 198.0	0.20 – 3.80	0.913	0.362
Mean ± SD.	2.70 ± 18.38	0.57 ± 0.46		
Serum Na (mEq⁄L)				
Min. – Max.	0.25 – 145.0	130.0 – 145.0	0.179	0.858
Mean ± SD.	134.07 ± 9.49	134.29 ± 3.11		
Serum K (mEq⁄L)				
Min. – Max.	0.50 – 8.0	0.20 – 5.0	0.576	0.565
Mean ± SD.	4.16 ± 0.70	4.11 ± 0.69		
Uric acid (mg /dl)			8.956	0.452
Min. – Max.	2.4 – 10.5	3.2 – 12.5		
Mean ± SD.	6.45 ±2.0	7.67 ± 3.1		
LDH (IU/L)				
Min. – Max.	210-3120	456-4139	7.560	0.153
Mean ± SD.	1356±2315.2	817.2±161.5		

Hb: hemoglobin, WBC: white blood cells, AST: aspartate transaminase, ALT: alanine transaminase, Na: sodium, K: potassium, lactate dehydrogenase, t: Student t-test, *: Statistically significant at $p \leq 0.05$

Table IV: Type of hematological malignancy and outcome of all studied cases.

Type of malignancy	**No.**	**%**
ALL	158	62.6
Precursor-B	127	80.4
T cell	30	19
Undifferentiated	1	0.6
AML	28	11.1
Mo – M1	4	14.3
M1	2	7.1
M1– M2	3	10.7
M2	4	14.3
M3	7	25
M4	6	21.5
M5	2	7.1
Non Hodgkin Lymphoma (NHL)	46	18.3
Hodgkin lymphoma	20	7.9
Burikitt's lymphoma	2	0.6
Neuroblastoma	31	9.9
Wilms tumor	3	0.8
Outcome	**No.**	**%**
Finished (survivor)	100	31.8
Referred	47	15
Loss of follow up	3	1.0
Died	137	43.6
Relapsed	27	9
Time of death	**No.**	**%**
Before starting treatment	12	8.75
During induction	33	24
During consolidation or maintenance	91	66.4
After finishing treatment	1	7.3
Site of relapse in relapsed patient	**No.**	**%**
CNS	8	29.6
Testicular	2	7.4
Medullary	14	51.8
Combined	3	11.1

ALL: acute lymphoid leukemia, **AML:** acute myeloid leukemia, **NHL:** non-Hodgkin Lymphoma **CNS:** central nervous system

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Table V: Relation between risk stratification and different parameters in all cases.

	Risk stratification				Test of sig.	*P value*
	Low-risk (n= 54)		Standard + High-risk (n= 104)			
	No.	%	No.	%		
Age (years) at diagnosis						
<1	0	0.0	0	0.0	χ^2= 11.026*	0.001*
1 – 9	50	92.6	72	69.2		
>9	4	7.4	32	30.8		
Min. – Max.	1.0 – 16.0		1.20 – 17.0			
Mean ± SD.	4.29 ± 3.03		7.13 ± 3.68		U= 1426.5*	<0.001*
Median	3.50		6.0			
Sex						
Male	29	53.7	63	60.6	χ^2= 0.690	0.406
Female	25	46.3	41	39.4		
Remission						
No	12	22.2	26	25.0	χ^2= 0.150	0.698
Yes	42	77.8	78	75.0		
Testicular involvement						
No	54	100.0	103	99.0	χ^2= 0.523	FEp= 1.000
Yes	0	0.0	1	1.0		
CNS involvement						
No	54	100.0	102	98.1	χ^2= 1.052	FEp= 0.001*
Yes	0	0.0	2	1.9		
Mediastinal involvement						
No	54	100.0	103	99.0	χ^2= 0.523	FEp= 1.000
Yes	0	0.0	1	1.0		
WBCs (×10³)						
<50,000/mm³	47	87.0	43	41.3	χ^2= 30.269*	<0.001*
>50,000/mm³	7	13.0	61	58.7		
Min. – Max.	1.10 – 381.0		0.60 – 585.0			
Mean ± SD.	34.52 ± 60.82		76.85 ± 95.36		U= 1577.5*	<0.001*
Median	22.0		56.50			
Favorable outcome						
No	35	64.8	97	93.3	χ^2= 20.933	<0.001*
Yes	19	35.2	7	6.7		

CNS: central nervous system, white blood cells, SD: Standard deviation, X^2: Chi-square test, U: Mann whiteny test, *Significant

Table VI: Kaplan-Meier survival curve for Overall Survival and for relapse-free survival.

	Mean (months)	% End Study
Overall Survival (OS)	36.135	51.3
Relapse-free survival (RFS)	34.938	46.2

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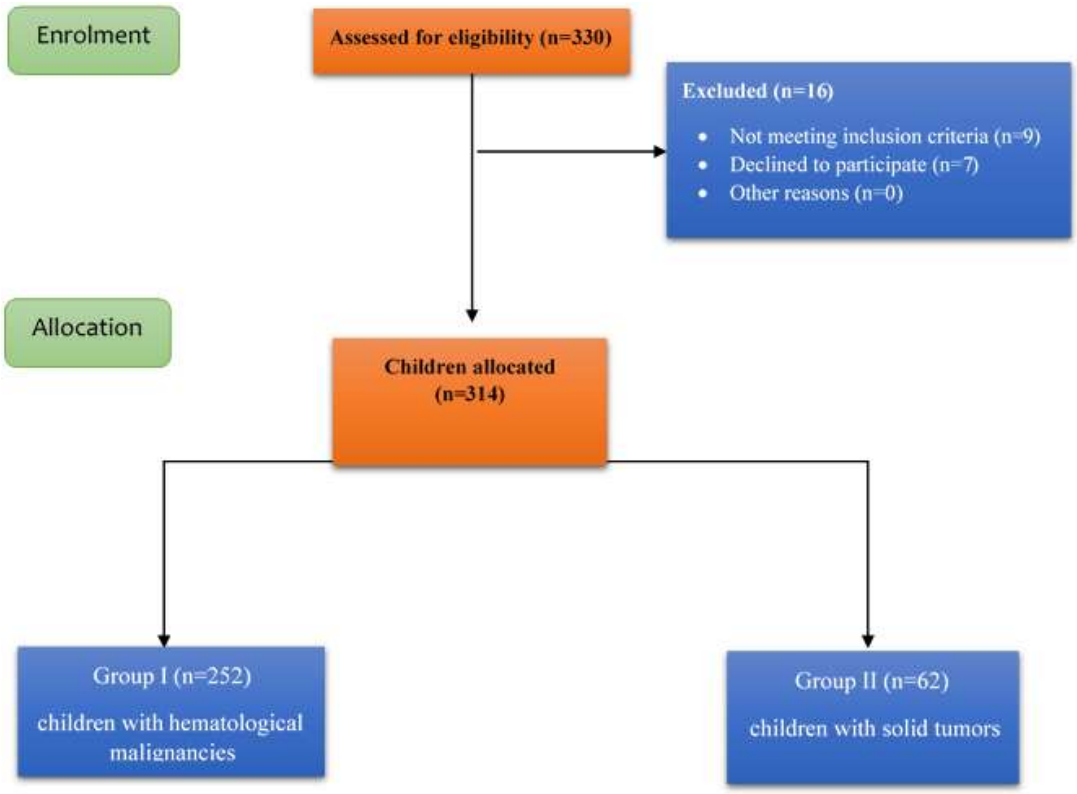

Figure 1. Flowchart of the studied groups.

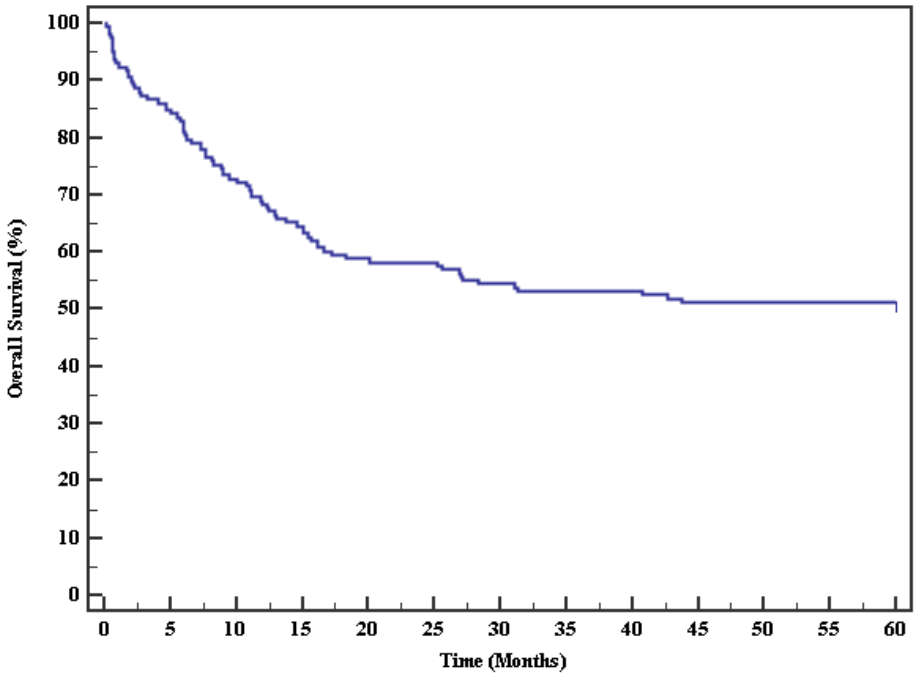

Figure 2. Kaplan-Meier survival curve for overall survival (OS).

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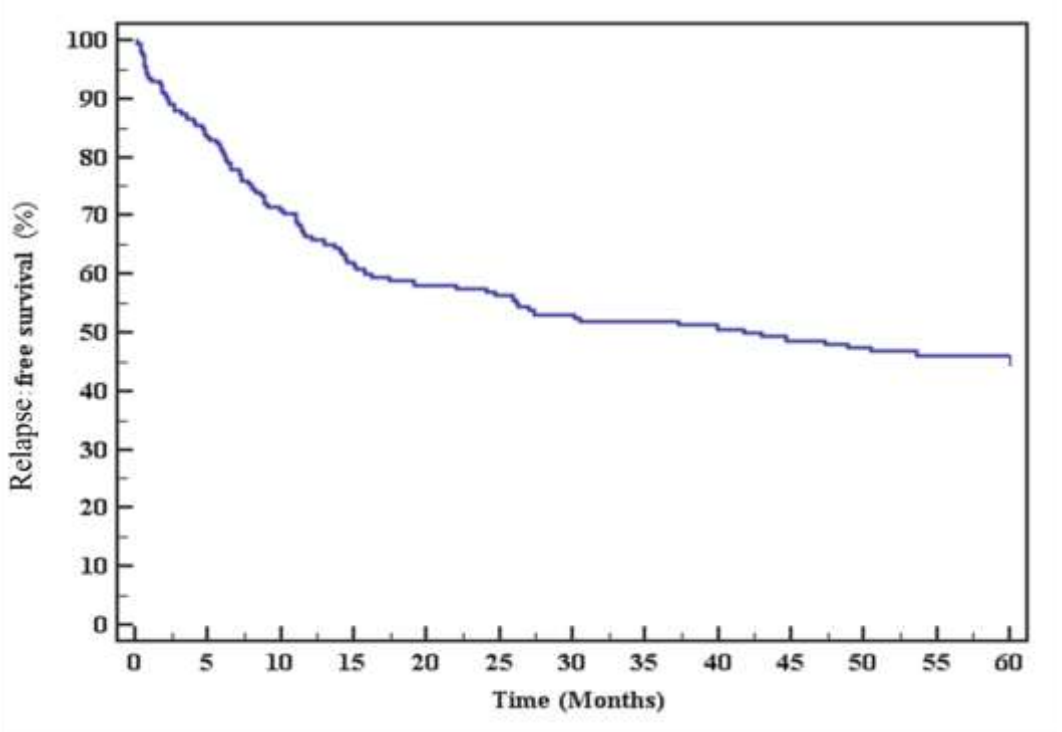

Figure 3. Kaplan-Meier survival curve for relapse-free survival (RFS).

Discussion

In the current study, 186 patients with acute leukemia, 49.7% with ALL, and 8.8% with AML. 14.5% non-hodgkin lymphoma (NHL) and 7.3% with hodgkin lymphoma (HL). Regarding solid tumors, 9.9% with neuroblastoma, 0.6% with Burkitt's Lymphoma, 0.8% with Wilms tumor and other solids were 8.2%. Our results were inconsistent with the study by Ward *et al.*, who stated that ALL is considered the most common cancer in children in the USA and accounts for 26%, followed by Non-Hodgkin's Lymphoma, 6% and Hodgkin's Lymphoma 4 % for estimated cases of childhood cancer. (17)

Our study also agrees with the study of cancer incidence of the Middle East Cancer Consortium (MECC), (20) reported in Egypt, from 1996 to 2001, showed that the total number of people diagnosed with new cases of childhood cancer below the age of 20 years was 1813. Males were 1063 (58.6%), and 750 (41.4%) were females.

In the present study, most patients were in the age group less than nine years, and the majority were males. These results were inconsistent with Jawass *et al*. (21) who reported that a male to female ratio was 1.4:1. The predominant age group was 5-9 years 35%, followed by 10-14 years 33.7%, and 0-4 years group 31% and consistent with other the study which reported that the childhood malignancy in younger than 20 years of age, with the peak incidence occurring at 3 to 5 years of age and diagnosed more males than females. (22) Another study found the mean age was 6.1±3.9 years, and 59.2% were boys. (23), on the other study, on 300 children with malignancy, reported that 57.7% of patients were males and 127 (42.3%) were females. The median age at diagnosis was 5 years. (24) The study by Hussein *et al.* showed that the median age of the patients was 5 years ranging from 1 to 16 years. Of 150 patients 75% of them were less than 10 years old. Male

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predominance of 60% was noted with a male: female ratio of 1.5:1. (25)

In our study, children older than nine years accounted only for 22.8%, and this was consistent with one study which showed that 22-29% of patients their ages were around this age group. (25) In contrast, the frequency of patients in this age group older than nine years was slightly lower at 18.4%. (26)

In the current study, the most frequent clinical presentations were fever in 91.4% followed by pallor in 87.8%, hepatomegaly in 72.3 %, lymphadenopathy in 66.7 %, splenomegaly in 63.4%, abdominal enlargement in 14.6%, mediastinal involvement in 7.3 %. Clarke *et al.* (26) identified 95 presenting signs and symptoms, Five features present in >50% of children: hepatomegaly 64%, splenomegaly 61%, pallor 54%, fever 53% and bruising 52%. An additional eight features were present in a third to a half of children: recurrent infections 49%, fatigue 46%, limb pain 43%, hepatosplenomegaly 42%, bruising/petechiae 42%, lymphadenopathy 41%, the bleeding tendency 38% and rash 35%.

In hematological malignancies, fever, pallor, hepatomegaly, lymphadenopathy, and splenomegaly were significantly different than in solid tumors. At the same time, abdominal enlargement was significantly different in solid tumors than in hematological malignancies. This coincides with another study which showed that the most frequently observed clinical features were hepatomegaly, splenomegaly and lymphadenopathy. (27) Another study by Khazaei *et al.* (28) showed that fatigue, fever, bleeding, chest pain, and splenomegaly were often seen in children with leukemia. (28)

In the present study, CNS involvement and mediastinal involvement were seen in 1.0 % and 7.3 %, respectively, which coincides with one study which showed that CNS involvement and mediastinal mass were observed in 2.4% and 6.3%, respectively (29), but lower than another study which showed that CNS involvement and mediastinal mass were observed in 6.6% and 11.8%, respectively. (27)

High WBCs at diagnosis (more than or equal to 50,000/mm³) in our study was present in 54.1% of patients which is consistent with a study which showed that 50% of patients had WBC more than or equal to 50,000/mm³ at diagnosis (30) but lower than another study that showed that 69.6% of patients had WBC at diagnosis more than or equal to 50,000/mm³ (31) and higher than other studies which showed that the patients had WBC at diagnosis more than or equal to 50,000/mm³ was in a frequency of (21-24.6%). (23, 27)

The uric acid level is important in terms of increased tumor load, increased white blood cells, stage of disease and renal function. During induction therapy, many patients are lost due to electrolyte and renal dysfunction. Uric acid is also important because it is part of the tumor lysis syndrome. In 40.7% of our patients, uric acid levels were above the normal level. Bassan *et al.* (32) reported that patients with creatinine > 1.6 mg/dl and uric acid > 8 mg/dl were at risk for renal failure. Crews *et al*. (33) showed that low uric acid levels in ALL patients were associated with less dialysis and less nephrotoxicity.

In this study (51.3%) of patients presented LDH levels >1000 U/L. The elevated LDH up to 4139 IU/L which is higher as compared to another study which showed LDH levels up to 1292 IU/L. (34)

In the present study, Hb levels, platelets, and WBCs count significantly decreased in hematological malignancies compared with solid tumors cases. In contrast, the other laboratory data showed no statistically significant difference between the two types of malignancies. The survivors who finished their treatment course were 31.8%, 15% referred to other

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hospitals for treatment, 1% did not complete follow-up, 43.6% died, and 9% the relapsed. Relapse was documented in 9 % of patients, which is consistent with study that showed the relapse was in 7 to10% among ALL patients. (24) In contrast to other different studies the relapse rate was 19.3% and 20%. (29)

Of these relapses, the most common relapse site was medullary in 51.8%, followed by extramedullary in 37% and 11.1% was a combined relapse. Extramedullary relapse mostly affects the CNS in 80% then testicular relapse in 20% of extramedullary relapses. This is similar to studies which showed that medullary relapse was detected in (59.3%, 71.4%), CNS relapse in (29.6%, 17.8%) and combined relapse in (11.1%, 3.6%), respectively. (34) Whitlock *et al.* (35) showed that 59.9% of relapsed patients had CNS relapse while systemic relapse observed in 26.6% of patients. Testicular relapse observed in 13.3% of patients. Other study by Sarper *et al.* (29) found 72.5% isolated bone marrow relapse, 5% had isolated CNS relapse, 5% isolated testicular relapse, 7.5% had a combined relapse (bone marrow and CNS), and 10% had bone marrow and testicular relapses.

The mortality among our patients was 43.6%. Most patients died during the consolidation or maintenance phases of chemotherapy in 66.4%, followed by the induction phase in 24%. The most common cause of death was infection in 37.9% followed by unknown causes with sudden arrest in 24%. This is consistent with Shibl *et al.* (36) who showed that 53% of patients died during the consolidation or maintenance phases of chemotherapy and also found the most common cause of death was infection in 40.3% of them and Mushtaq *et al.* (34) study which showed that there were 17% deaths, the 55% of them died during the consolidation or maintenance phases of chemotherapy. 45% of them died during the induction phase. The most common cause of death was infection in 71.4%, and hemorrhage in 14.3% of patients.

Various clinical and laboratory features present at the time of initial diagnosis can predict the likelihood that a patient will remain in remission or not. Unfavorable prognostic factors in ALL include age under 1 and over 10 years, males sex, WBCS more than 50,000/mm^3 at presentation, mediastinal lymphadenopathy, CNS involvement, testicular involvement, failure to achieve remission at the end of induction, immunophenotype and cytogenetic characteristics. (37) The distribution of the ALL cases according to the risk stratification of the tumor, 65.8% of patients stratified as standard risk and 34.2% had low risk. This classification depends on clinical prognostic factors (age, WBCs, CNS involvement, early response to induction therapy, biological, genetic feature and minimal residual disease).

Also, in the present study the age increased significantly in standard and high-risk ALL cases than low-risk cases. The CNS and mediastinal involvements significantly different among high-risk ALL cases than low-risk cases. The WBCs count significantly increased in the standard and high-risk cases than low-risk ALL cases. The standard and high-risk ALL cases showed significantly worse outcomes than low-risk ALL cases.

It was also observed in this study that age at diagnosis has been recognized as an important prognostic factor of both incidence and survival of pediatric ALL, the lowest survival is observed among patients diagnosed during infancy, followed by children who are diagnosed between 15 and 19 years of age, this may be due to the presence of other unfavorable presenting features in this age group such as hyperleukocytosis, CNS disease. In contrast, ALL patients in ages from 1 to 9-

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years found to have the highest chance of survival among all age groups. This is in concordance with many studies which found age to be a strong prognostic factor in childhood ALL. (37-39)

The other factor which emerged as an important prognostic factor with ALL in our study was immunophenotyping which showed that T-cell phenotype of blast cells continued to have a poorer outcome than those with Pre-B phenotype and this agree with other studies. (25,38) Regarding gender, it has been reported in various studies that females have superior survival than males of the same age group having ALL. (40)

Also, CNS status and mediastinal involvement at presentation considered to be important features that can predict the outcome in patients with ALL. (41) It has been reported that early response to induction therapy is also important for determining the prognosis in patients with ALL. (25) The WBC count-prognosis relationship has been established in many studies on pediatric ALL and it has been observed that a count of more than 50,000/mm³ at presentation is associated with adverse outcome. (38)

In the present study using the Kaplan Meier method for 5-year the overall survival (OS) found in 51.3 % patients, 5-year relapse-free survival (RFS) in 46.2 %. This is in agreement with Mushtaq *et al.* (34) who reported that the RFS and OS were 63% and 65% respectively. Sarper *et al.* (29) showed that 7-year EFS and OS increased to 78.9% and OS to 84.2% respectively. Sousa *et al.* (27) showed that RFS was 71.2 ± 5.2% and 5-year OS was 72 ± 5.24%. Also, Halalsheh *et al.* (24) estimated 5-year RFS and OS in 80% and 89%, respectively. Pui *et al.*(42) found 5-year RFS in 79.1% boys, and 83.3% girls. Schrappe *et al.* (43) showed that the 6-year RFS rate in 75% boys, and 82% girls. The impressive development in cancer research, screening, diagnosis and therapy over the past 30 years has led to markedly improved patient outcomes. (33) Finally, there were some limitations of the current study included small sample size and incomplete data in some files, missed follow up during and after the end of chemotherapy for some patients, also, MRD and cytogenetics investigations were analyzed at different hospitals because they aren't available in our hospital. Also, some relapsed patients in the current study referred to other hospitals for bone marrow transplantation because isn't available at our unit of Menoufia university hospital. So, we hope for more development and progress of our unit and the establishment of bone marrow transplantation unit in our Menoufia university hospital.

Conclusion

Lymphoblastic leukemia is the most frequent childhood hematological neoplasm. Various clinical and laboratory features present at the time of initial diagnosis can predict the likelihood that a patient will remain in remission or not including age: under 1 and over 10 years, gender: male sex, WBCS more than 50,000/mm³ at presentation.

Ethical Consideration

The study protocol was approved by the Menoufia University Faculty of Medicine's ethical committee by IRB approval number 19819PEDI28.

Our local Ethics Committee approved our study and a written consent for participation was obtained from all patients. No animals were used for studies that are the basis of this research. All the humans were used in accordance with the Helsinki Declaration of 1975.

Author’s contiributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took

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part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Conflicts of interests

The authors declare no competing interests in this work.

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