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Research Article

Estimation of Serum Beta 2-microglobulin among newly diagnosed children with cancer in Basra

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Abstract

Background: Beta 2- micro globulin (β2-MG) is involved in human malignancies. Increased synthesis and release of β2-MG, as indicated by elevated serum, plasma, or urine β2-MG concentration, occurs in several malignant diseases,

Objective: The study was designed to assess the role of serum Beta2- micro globulin in the support of the diagnosis of different types of pediatric malignancies.

Subjects and Methods: This case - control study was carried out on 137 children and adolescents with newly diagnosed pre-treated malignant diseases who were admitted to pediatric oncology center at Basra Children's Specialty Hospital, their ages ranged from 3 months to 15 years, during the period from the 1st of November 2014 till the end of October 2015, 71 were males and 66 were females and 148 healthy children and adolescents (83 were males and 65 were females) matched for age and sex regarded as control group. Cases and control characteristics were assessed from data collection by special questionnaire. All patients and control group were investigated for Beta2- microglobulin by the enzyme-linked immunosorbent assay.

Results: The study had revealed that level of Beta2-microglobulin was significantly higher in patients with malignancy in comparison to control group, P value < 0.001.Also the serum Beta2- microglobulin level for both hematological malignancies and solid malignancies was assessed and it was found that significantly higher percentage of elevated serum Beta2- microglobulin level was present in patients with hematological malignancies in comparison to solid malignancies, P value <0.01.The study also had revealed that there was a significant correlation between the initial white blood cells count ≥ 50000 cells/ml and abnormal serum Beta2-microglobulin level, P value < 0.01,but there was no significant differences in serum Beta2- microglobulin level in relation to risk groups and immunophynotypes of acute lymphoblastic leukemia ,morphological subtypes of acute myloid leukemia, stages of each type of lymphoma (Hodgkin lymphoma and non-Hodgkin lymphoma) and the histopathological subtypes of non-Hodgkin lymphomas. After subjecting variables (specific to acute lymphoblastic leukemia) to logistic regression analysis, the significant independent risk factor that associated with abnormal serum Beta2- microglobulin level was high initial white blood cells count (≥50000 cells/ml).

Conclusion: Serum Beta2- microglobulin level is significantly higher in patients with hematological malignancies and high initial white blood cells count(≥50000cells/ml) .From this study, serum Beta2-microglobulin could be recommended in the initial work up for diagnosis of childhood malignancy.

Introduction

Although childhood cancer is rare, accounting for less than 1 per cent of all cancer in industrialized countries, it is of great scientific interest for a number of reasons. Several types of cancer are actually unique to childhood, whereas the carcinomas most frequently seen in adults, those of lung, female breast, stomach, large bowel, and prostate, are extremely rare among children [1]. Beta 2- microglobulin (β2-MG) is involved in cancer and other human malignancies. Increased synthesis and release of β2-MG , as indicated by elevated serum, plasma, or urine β2-MG concentration, occurs in several malignant diseases, including prostate cancer, lung cancer, breast cancer, renal cell carcinoma (RCC), gastrointestinal and nasopharyngeal cancers, hepatocellular

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carcinoma, ovarian cancer, multiple myeloma, and lymphocytic malignancies such as non-Hodgkin's lymphoma [2].

Risk factors for childhood cancer are numerous. Examples are genetic diseases like Down syndrome and Klinefelter syndrome, accidental radiation exposure, radiation therapy and chemotherapy, immune system suppression, certain chemicalsd [3]. Every year 130–140 children per million under the age of 16 years, or around 1 out of 500 children, are diagnosed with childhood cancer[4], 80% of children diagnosed with cancer will survive at least 5 years, 70% will be cured. However, cancer continues to be the leading causes of no accident-related deaths in children [5]. In Iraq ,it is one of leading cause of morbidity and mortality and second cause of death according results of Iraqi registry in 2011.The distribution of common ten cancer in Iraqi children is classified according to frequency up to fourteen of age, leukemia is diagnosed in about 33.11% of all childhood cancer, 26.8% of children are from Basra [6]. Central nervous system (CNS) cancers are the second most frequent in Iraqi pediatric oncology, accounting for about 17.34% of childhood cancer. Lymphomas represent the next most common type of Iraqi childhood cancer, Hodgkin's lymphoma (HL) accounts for 6.89% of all childhood cancers and non- Hodgkin's lymphomas (NHL) account for 13.92% of all childhood malignancies. Bone cancers (including osteosarcoma and Ewing's sarcoma) account for 5.26%, kidney cancer is 4.85%, soft tissues cancer is 3.62%, eye cancer is 2.46%, adrenal gland cancer is 1.64% and liver cancer is 1.16% from all Iraqi pediatric cancers[6]. A relatively wide age range exists in pediatric age group, with 2 peaks: the 1st in early childhood and the 2nd in adolescence [7,8].

Acute lymphoblastic leukemia (ALL) is diagnosed in approximately 2,400 children <15 yr of age in the United States of America (USA) each year and accounts for approximately 77% of cases of childhood leukemia. ALL has a striking peak incidence at 2-3 yr of age and occurs more in boys than girls at all ages [9]. The incidence of ALL: 3–4 cases per 100,000 white children, and accounts for 25–30% of all childhood cancer [10]. The incidence of ALL varies significantly throughout the world and it is different in relation to the sex with the rates ranging from 9 to 47 per million for male children, and from 7 to 43 per million for females [11]. In virtually all cases, the etiology of ALL is unknown, although several genetic and environmental factors are associated with childhood leukemia. Exposure to medical diagnostic radiation both in utero and in childhood has been associated with an increased incidence of ALL [9,12]. In certain developing countries, there has been an association between B-cell ALL and Epstein-Barr viral infections [9,13].

Immunophenotyping of blast cells by flow cytometric analysis (FCM) in suspected cases of ALL is essential in making the correct diagnosis [9,10,12]. Phenotypically, surface markers show that about 85% of cases of ALL are derived from progenitors of B cells, about 15% are derived from T cells, and about 1% are derived from B cells. A small percentage of children with leukemia has a disease characterized by surface markers of both lymphoid and myeloid derivation. Immunophenotypes often correlate to disease manifestations [9,10].

Eighty-five percent of children with common ALL are HLA DR and CD10-positive, which indicates a good prognosis. Children with T-cell ALL are characterized by: older age (peak at 8 years of age), with a ratio of boys to girls of 4:1; high initial leukocyte count, Mediastinal enlargement, high proliferation rate and/or frequent extramedullary manifestation (initially and at relapse) [14]. Since many of the CD antigens are not lineage specific, the immunophenotypic classification is based on the combination of CD antigen expression, and at least 95% of all leukemias can be classified as lymphoid or myeloid with or without co-expression of myeloid or lymphoid CD antigens [15].

Acute myloid leukemia (AML) accounts for 11% of the cases of childhood leukemia in the USA; it is diagnosed in approximately 370 children annually [9]. The incidence of

pediatric AML is estimated to be between 5to7 cases per million people per year [16]. One subtype, with acute promyelocytic leukemia being three times more common in Latin than non-Latin countries , and also higher in Hispanic and Mediterranean populations , but incidence of the other types is generally uniform [17,9]. AML may either arise de novo or occur following underlying diseases such as myelodysplastic syndrome, which is much more frequent in elderly patients with AML than in children. Other underlying diseases may be chromosomal-breakage syndromes like Fanconi anemia [18]. The British Committee for Standards in Hematology (BCSH) recommends a standardized panel of monoclonal antibodies. This includes B-lymphoid (CD79a, CD22, CD19, CD10), T-lymphoid (CD3, CD2), myeloid (CD117, anti MPO, CD13), and non-specific (TdT) [19].

The clonal origin of AML has been demonstrated by several methods including cytogenetic analysis and assay using x-linked polymorphism .The karyotype of a remission bone marrow returns to normal .At relapse, the original clone reappears, indicating that the leukemic clone was suppressed but not eliminated by chemotherapy [20].

Hodgkin lymphoma (HL) is a B-cell lymphoid malignancy that occurs in 2 per 100,000 children before the age of 15 years in the USA. In the USA and other developed nations, HL is primarily a disease of adolescence and young adults with a second peak in older adulthood (>50 years). In the developing world, the age distribution is shifted toward younger children.HL is diagnosed from a lymph node biopsy and requires the demonstration of the classic Reed-Sternberg (RS) cells in a background of lymphocytes, histiocytes, eosinophils, and plasma cells [21]. Non-Hodgkin lymphoma (NHL) is about 1.5 times as common as Hodgkin lymphoma. The incidence is low in children less than 5 year of age, but from that point it increases steadily with age throughout life. In all age groups, there is a significant male predominance, particularly among patients with Burkitt's lymphoma (BL). The incidence of different histologic subtypes is variable in children and adults. There are four major histologic subtypes of NHL that occur commonly in children (in order of frequency): diffuse large B-cell lymphoma (DLBCL), lymphoblastic lymphoma (LL), Burkitt 's lymphoma (BL), and anaplastic large cell lymphoma (ALCL) [22].

Central nervous system tumors: Central nervous system tumors are the most common type of solid tumor in children, and the second childhood cancer, close to 55% of these tumors originate in the posterior fossa or infratentorial and 45% are supratentorial [23]. They are the leading cause of death from solid tumors in children. They account for approximately 25% of pediatric cancer [24]. Medulloblastoma is one of the more common brain tumors in childhood, accounting for about 20% of CNS tumors in children. While it does occur in adults, the peak incidence is in early childhood. Gliomas constitute over 50% of CNS tumors in children, and most are low grade. The high grade glioma category of brain tumors includes anaplastic astrocytoma (AA), glioblastoma multiforme (GBM), high grade mixed glioma, anaplastic oligodendroglioma and high grade glioma not otherwise specified (NOS). They occur in any location in the CNS [25]. Neuroblastoma (NB): is the most common extra cranial solid tumor in infants and children. It originates from primitive sympathetic ganglion cells and may be present prenatally. Children may present with an adrenal, abdominal, thoracic, cervical or pelvic mass. NB commonly spreads to cortical bone, bone marrow, skin, lymph nodes and the liver [26].

Fifty percent of children with NB present with high risk disease at diagnosis, with 5-year survival below 40%, even with intensive multimodal therapy [27]. Wilms tumor: is the second most common retroperitoneal tumor in children, accounting for approximately 6% of childhood malignancies. A tumor of the developing kidney, it typically occurs in young children between the ages of 1 and 5 years, with equal

incidence among boys and girls (though interestingly occurs at earlier ages in boys). Most cases of Wilms tumor are sporadic, with approximately 1% being familial and 2% to 4% associated with rare congenital syndromes. Familial cases are more likely to present with bilateral tumors and occur at a younger age. Congenital anomalies occur in 12% to 15% of cases, the most common being hemi hypertrophy, aniridia, and genitourinary tract anomalies such as cryptorchidism, hypospadias, horseshoe kidney, ureteral duplication, and polycystic kidney [28].

Retinoblastoma is the primary intraocular cancer in children. It is either unilateral or bilateral, main clinical features are leukocoria in 60%, strabismus is the second manifestation, the remaining 20% of cases of retinoblastoma present with atypical signs and symptoms [29]. Rhabdomyosarcoma (RMS) represents approximately 5% of all cancers among children. Two thirds of patients are 10 years or younger [30]. It is a common soft-tissue sarcoma in children, most often originates from mesenchymal cells that are committed normally to skeletal muscle formation, Primary head and neck tumors are most common in children younger than 8 years of age [23]. Bone cancers, Osteosarcoma (60%) and Ewing sarcoma (30%) are common Pediatric bone tumors, about 3% of all osteosarcomas are secondary to therapeutic irradiation [31]. Ewing's sarcoma is characterized by molecular alterations that most commonly involve the EWS gene on chromosome 22. It is an aggressive tumor, with metastases present at diagnosis in 20–25% of cases [32]. It is neuroectodermal in origin; it tends to occur in the diaphysis (shaft) of a long bone rather than the metaphysis [26].

Beta 2 microglobulin (β2-MG) a nonglycosylated protein of molecular mass 11,800 Da , is synthesized by all nucleated cells and forms a small invariable light-chain moiety of the human leukocyte antigen(HLA) (-A, -B, -C) through noncovalent linkage on cell surfaces [33]. It consists of 99 amino acids and belongs to the immunoglobulin superfamily with a primary and secondary structure simulating IgGs. Half of the plasma β2-MG originates daily from lymphocytes [34]. The classical HLA class I genes HLA-A, B and Cw code for heterodimers formed by a heavy (α) chain of approximately 43 kDa , non-covalently linked to the β2-MG light chain .The latter is coded for by a gene located outside the HLA region on chromosome 15. The extracellular portion of the α chain has three domains (α1, α2 and α3) encoded by exons 2, 3 and 4, respectively. The transmembrane and cytoplasmic domains are encoded by exons 5, 6 and 7, respectively.

The β2-MG, which confers stability on the molecule, is non-covalently linked to the α3 domain [35]. Major histocompatibility complex (MHC) class I antigen presentation begins with the intracellular breakdown of proteins by a multi-molecular proteolytic complex known as a proteasome. These peptides are actively transported by TAP (transporter associated with antigen processing) proteins into the endoplasmic reticulum, where empty MHC class I molecules are being assembled .This complex is then stabilized by the association of β2-MG before being transported to the cell surface. In this way, the cells are continuously advertising the peptide composition of the proteins that they are producing [36].

The reference range of β2-MG in serum or plasma samples is 0-3 μg/mL, while in urine samples is 0-0.3 μg/mL [37]. The production rate of β2-MG varies from 2-4 mg/kg/day, with a half-life of 2.5 hours. Ninety percent of β2-MG is eliminated via glomerular filtration and almost completely reabsorbed by the proximal tubules. Thus, in individuals with chronic kidney disease, especially end-stage renal disease, β2-MG can increased in the blood [38]. β2-MG also regulates the expression of hormone/ growth factor receptors, such as, androgen receptors (AR), epidermal growth factor receptor, insulin receptor, and insulin-like growth factor receptor, on cell surfaces,

indicating that β2-MG mediated signaling may be transmitted through these receptors [39,40]. Elevated plasma β2-MG is a result of decreased glomerular filtration or increased synthesis. It is the most effective test for the detection of proximal tubular dysfunction. The determination of urinary β2-MG is important for monitoring renal transplant patients [41].

β2-MG amyloidosis also known as dialysis-related amyloidosis (DRA), occurs due to the accumulation of β2-MG in renal failure and predominantly affects articular and periarticular structures in patients with end-stage renal failure who have been on dialysis for at least 7–10 years [42]. Substantial changes of CSF β2-MG concentrations in purulent meningitis, leptomeningeal metastasis,viral meningitis/encephalitis,and neuroborreliosis, while in multiple sclerosis these changes are not significant. Intrathecal synthesis and immune activation are present in these clinical entities, also significantly elevated CSF β2-MG values in neonates with cytomegalovirus infection, by reason of an intrathecal synthesis [43]. Serum β2-MG levels are an important prognostic factor in lymphoid malignancies, including non-Hodgkin's lymphoma, Hodgkin's disease, acute lymphocytic leukemia, multiple myeloma, and chronic lymphocytic leukemia , also its serum levels are an important, and probably independent, prognostic factor for patients with chronic myloid leukemia (CML) in early chronic phase treated with interferon (IFN) - based Therapy [44]. β2-MG, a MHC class I subunit, is found to act as a prototypical oncogenic factor capable of stimulating growth and progression of various cancers and plays a key regulatory role in inducing cancer metastasis[45].

It is also known to stimulate the growth and survival of stromal cells, such as mesenchymal stem cells (MSCs), osteoblasts and osteoclasts supporting cancer bone metastasis [46,47]. It has been shown that some tumors demonstrate decreased expression of β2-MG. This may serve as one of the mechanisms of escaping immune surveillance and progressing to metastases. However, significantly elevated serum β2MG levels have been observed in numerous neoplasms, especially of the lymphoproliferative type, correlating with tumour mass, stage and prognosis [48]. In multiple myeloma serum β2-MG is often increased and is a useful indicator of prognosis, levels less than 4 mg/L imply a relatively good prognosis. An international prognostic index has been used based on serum β2-MG and albumin levels in multiple myeloma , patients with serum β2-MG >5.5 mg /L and an albumin <35 g /L have a poor survival as do those with frequent circulating plasma cells [49]. Elevated concentrations of β2-MG in cerebrospinal fluid have been used to detect central nervous system involvement with metastatic cancer ,although the value of increased β2-MG levels in CSF is less clearly defined than in serum [2,43,50,].

In neuroblastoma, N-myc expression is variably correlated with low levels of β2-MG and Class I MHC antigen expression. β2-MG is a marker of differentiated adrenal medullary cells, expressed late during the third trimester of development. By using morphological and immunological criteria, found that β2-MG is expressed in differentiated tumor cells of neuroblastoma and the expression of β2-MG in neuroblastoma is associated with the stage of differentiation of the tumor cell and not N-myc expression [51]. Monoclonal antibodies (mAbs) specific to human β2-MG stimulate apoptosis in vitro and are therapeutic in animals models of myeloma and other hematological tumor cells. Cell death occurs rapidly without the need for exogenous immunological effectors mechanisms. Although the expression of β2-MG on normal hematopoietic cells is a potential safety concern, the mAbs are selective to tumor-transformed cells and do not induce apoptosis of normal cells. Therefore, such mAbs offer the potential for a therapeutic approach to hematological malignancies [50]. Also the antibodies targeting β2-MG have tumoricidal activity through interference with the β2-MG-Hemochromatosis (HFE) protein complex .The β2-MG-HFE complex defends against the influx and accumulation of intracellular iron and negatively regulates

intracellular iron concentration in cancer cells, mediated by β2-MG - HFE complex interaction with transferrin receptor (TFR). Anti- β2-MG monoclonal antibodies appear to be favorably selective for tumor cells, in part because of the presence of higher levels of transferrin (TF) - transferrin receptor (TFR) complex facilitating active iron transport in tumor but not normal cells when treated with anti-β2-MG monoclonal antibodies [52]. Aim of this study to estimate serum β2-MG in children with malignant disease and its assistance as a marker for initial work up and any correlation to the type and stage of each cancer.

Subjects and Methods

Subjects

Patients: A case - control study has been carried out on 137 children and adolescents with newly diagnosed cancer who were admitted to Pediatric Oncology Center at Basrah Children's Specialty Hospital, their ages ranged from 3 months - 15 years, during the period from the 1st of November 2014 till the end of October 2015. Seventy one were males and 66 were females.

Control group: Control group included 148 children, they were matched for age and sex with patients group, their ages distribution <5 year was 79 and >5 year was 69, sex distribution was 83 males and 65 females had visited AL-Razi primary health center during same period of the study, all had no fever or any acute or chronic illness, they attended health centers for vaccination or they came with their families and the other from 2 primary schools that included Wasit and Beirut primary schools after formal permission was taken from health and education directorates.

Exclusion criterias

- Any patient who had received chemotherapy
- Any patient with renal function impairment
- Infection

Data collection

A special questionnaire (**Appendix 1 and 2**) was designed to collect data about the following:

Patients

Name, sex, age according to date of birth, date of diagnosis, type of cancer. They were segregated according to the type of cancer .The leukemia were classified to acute lymphoblastic leukemia (ALL) and acute myloid leukemia(AML).The acute lymphoblastic leukemia cases were sub-classified to standard and high risk groups. The lymphomas were classified to Hodgkin (HL) and non-Hodgkin lymphomas (NHL), the stage of lymphoma were determined in each type. Other solid tumor were classified according to the type of cancer included CNS tumors, Neuroblastomas, Wilms tumors, Retinoblastomas, Rhabdomyosarcomas, Osteosarcomas, Ewing sarcomas and Germ cell tumors.

Classification of some variables:

- Risk group (standard risk, high risk) [9].
- Initial WBC (<50000 cells/ml, ≥50000 cells/ml) [10].
- Immunophenotype of acute lymphoblastic leukemias (early pre-B cell ALL, pre-B cell ALL, common B-cell ALL, T- cell ALL) [12].
- Morphological subtypes of acute myloid leukemias (M0, M1, M2, M3, M4, M5, M6, M7) [16].

- Stages of lymphoma (HL and NHL): I, II, III, IV [53].
- Histopathological types of non-Hodgkin lymphomas (Burkitt ’s lymphomas (BL), Lymphoblastic lymphomas (LL), diffuse large B cell lymphoma (DLBCL), anaplastic large cell lymphoma (ALCL) [53].

Control

Information related to the control group were collected included:

Name, sex, age, date of the sample, serum β2-MG values.

Methods

Five milliliters of venous blood were withdrawn from each patient and control, in supine position, without application of tourniquet.Samples were transferred into clean blood collection tube that contain gel and clot activator, centrifuged for 15 minutes at 4000×g to separate serum .The separated serum was transferred into a new plane tube. Serum samples were stored frozen at -50°C until assayed within one month fom the freezing. Measurements of β2-MG levels were performed with the enzyme-linked immunosorbent assay (ELISA). The results were expressed in µg/mL.

Investigations

- Initial white blood cells (WBC) for cases of acute lymphoblastic leukemias
- Immunophenotype for cases of acute leukemias by flow cytometry.
- NHL histopathology.
- Serum β2-MG values were measured for all cases and compared with that of control group.

β2-MG measurements

β2-MG was estimated once the diagnosis had been established, depending on immunometric enzyme immunoassay for the quantitative determination of β2-MG in the serum, β2-MG enzyme linked immunosorbant assay (ELISA). The principle of the test depends on highly purified anti-human β2MG antibodies are bound to microwells. β2-MG, if present in diluted serum ,bind in the microwells . Washing of the microwells removes unreactive serum components. Horseradish peroxidase (HRP) conjugated anti- human β2MG immunologically bind to the bound patient β2-MG forming a conjugate/β2-MG/Ab-complex. Washing of the microwells removes unbound conjugate .An enzyme substrate in the presence of bound conjugate hydrolyzes to form a blue color .The addition of an acid stops the reaction forming a yellow end – product. The intensity of this yellow color is measured photometrically at 450 nm. The amount of color is directly proportional to the concentration of β2-MG present in the original sample. The upper normal value was considered 3.0 mg/L according to mean ± standard deviation of control group, cases were segregated into those with normal and those with elevated levels. Then serum β2-MG was studied in relation to many variables.

Statistical analysis

Statistical analysis was done using Statistical Packages for Social Sciences(SPSS) software version 18. Data were expressed and comparisons of proportions were performed using chi square test, Fisher exact test, T- test and ANOVA test, P-value of <0.05 was considered as statistically significant. Logistic regression analysis was also done for the analysis of different potential risk factors, and for each variable the odd ratio (OR) and 95% confidence interval (CI) were assessed.

Results

Age and sex distribution of patients and control group

A total of 285 children and adolescents were included in the study, 137 with newly diagnosed malignancy and 148 as a control group. The mean age of patients was 5.8 ± 3.8 years, while in control group the mean age was 6.07 ± 3.7 years (Tables 1-10).

Table 1: Distribution of cases and control according to age and sex.

Varaibles	Groups	Cases No. (%)	Control No. (%)	Total No (%)	P-value
	3 - 12M	7 (5.1)	9 (6.1)	16 (5.6)	
Age	>1 - 5yr	74 (54)	70 (47.3)	144 (50.5)	
(years)	>5 - 10yr	34 (24.8)	44 (29.7)	78 (27.4)	0.571*
	>10 - 15yr	22 (16.1)	25 (16.9)	47 (16.5)	
	Mean ± SD	5.838 ± 3.854	6.035 ± 3.764		0.663**
	Male	71 (51.8)	83 (56.1)	154 (54)	
Sex	Female	66 (48.2)	65 (43.9)	131 (46)	0.478 *
	Total	137	148	285 (100)	

*Chi-quare test was used to measure P- value
**T- test was used to measure P- value
Table (1) reveals that both cases and control were matched for age and sex, most ages were between >1 and 5 yr. The male to female ratio is 1.07:1 in cases and 1.2:1 in control group.

Table 2: Distribution of cases in relation to the type of cancer.

Type of cancers	Cases No. (%)
ALL	38 (27.73)
AML	17 (12.40)
HL	10 (7.29)
NHL	20 (14.59)
Other solid tumors	52 (37.95)
Total	137 (100)

Table 2 illustrates that 37.95% of them are other solid tumors, while the percentage of acute leukemias (ALL and AML) are 40.1% and lymphomas (HL and NHL) are 21.9%.

Table 3: Distribution of cases and control according to the serum β2-MG level.

β2-MG level	Cases No. (%)	Control No. (%)	P-value
≤ 3 µg/mL >3 µg/mL	99 (72.26) 38 (27.73)	130 (87.83) 18 (12.16)	<0.001*
Mean ± SD (µg/mL)	3.080 ± 1.108	2.212 ± 0.839	<0.001**
Total	137	148	

*Chi-quare test was used to measure P- value
**T- test was used to measure P- value
Table (3) shows the number and percentage of patients with malignancy who have serum β2-MG level < 3 µg/mL is 38 (27.7%) ,while in control group is 18 (12.2%) ,which is statistically extremely significant result(p value < 0.001).The mean of serum β2-MG for patients is slightly higher than control, (P value < 0.001).

Table 4: Serum β2-MG level in relation to the hematological malignancies and solid malignancies.

Variables	β2-MG level ≤ 3 µg/mL No. (%)	β2-MG level <3 µg/mL No. (%)	P-value	Mean ±SD(µg/mL)	P-value
Hematological malignancies	54 (63.5)	31 (36.5)	0.003*	3.354 ± 1.231	0.002**
Solid malignancies	45 (86.5)	7 (13.5)		2.632 ± 0.669	
Total	99 (72.3)	38 (27.7)		3.080 ± 1.108	

* Chi-quare test was used to measure P- value
**T- test was used to measure P- value
Table (4) shows that higher number and percentage of patients with hematological malignancies 31 (36.5%) who have serum β2-MG level <3µg/mL in comparison to solid malignancies 7 (13.5%) with statistically highly significant result (p value < 0.01) and the mean of serum β2-MG for hematological malignancies is more than that of solid malignancies with statistically highly significant result (P value < 0.01).

Table 5: Distribution of serum β2-MG level in relation to the risk groups of ALL.

Variable Risk groups	β2-MG level ≤ 3 µg/mL No. (%)	β2-MG level <3 µg/mL No. (%)	P-value	Mean ± SD (µg/mL)	P-value
Standard risk	13 (76.5)	4 (23.5)	0.181*	2.823 ± 1.029	0.167**
High risk	11 (52.4)	10 (47.6)		3.352± 1.237	
Total	24 (63.2)	14 (36.8)		3.115 ± 1.165	

*Fisher exact test was used to measure P-value
**T- test was used to measure P- value
Table (5). There was no significant difference regarding the risk groups of ALL and Serum β2-MG level (p value > 0.05).

Table 6: Distribution of serum β2-MG level in relation to the initial WBCs count in patients with ALL.

Variable initial WBCs count	β2-MG level ≤ 3 µg/mL No. (%)	β2-MG level <3 µg/mL No (%)	P-value	Mean±SD(µg/mL)	P-value
< 50000 cells/mm^3	21 (77.8)	6 (22.2)	0.008*	2.707 ± 0.871	0.004**
≥ 50000 cells/mm ^{3}	3 (27.3)	8 (72.7)		4.118 ± 1.221	
Total	24 (63.2)	14 (36.8)		3.115 ± 1.165	

*Fisher exact test was used to measure P-value
**T- test was used to measure P- value
Table (6) shows that higher number and percentage of patients with initial WBCs count of ≥ 50000 cells/ml who have serum β2-MG level < 3 µg/mL 8 (72.7%) in comparison to initial WBCs count of < 50000 cells/ml 6 (22.2%) with statistically highly significant result (p value < 0.01) and the mean of serum β2-MG for initial WBCs count of ≥ 50000 cells/ml is more than that of initial WBCs count of < 50000 cells/ml, (P value < 0.01).

Table 7: Serum β2-MG level in relation to the each immunophenotypes of ALL and morphological subtypes of AML.

Type of cancer	Immunophenotypes of ALL and morphological subtype of AML	β2-MG level ≤ 3 µg/mL No. (%)	β2-MG level <3 µg/mL No. (%)	P-value	Mean±SD (µg/mL)	P-value
	Early pre- B cell ALL	2 (100)	0 (0)		2.550	
ALL	Pre -B cell ALL	7 (70)	3 (30)	0.366*	3.380 ± 1.301	0.803**
	Common B-ALL	13 (65)	7 (35)		2.550 ± 0.212	
	T-cell ALL	2 (33.3)	4 (66.7)		3.066 ± 1.137	
	Total	24 (63.2)	14 (36.8)		3.115 ± 1.165	
	M0,M1,M2	2 (40)	3 (60)		4.150 ± 1.466	
AML	M3	2 (66.7)	1 (33.3)	0.280*	3.633 ± 1.184	0.580**
	M4	2 (50)	2 (50)		3.350 ± 0.842	
	M5	2 (66.7)	1 (33.3)		3.266 ± 0.635	
	M6	1 (50)	1 (50)		2.300	
	Total	9 (52.9)	8 (47.1)		3.605 ± 1.134	

*Fisher exact test was used to measure P-value,**ANOVA was used to measure P- value
Table (7) reveals that there was no statistical difference in serum β2-MG level among patients with different immunophenotypes of ALL and morphological subtype of AML (p value <0.05).Multiple comparison of mean using scheffe post hoc significant difference test(ANOVA) showed there was no statistically significant difference in mean serum β2-MG level in any specific immunophenotypes of ALL or morphological subtype of AML in relation to other subtypes.

Table 8: Serum β2-MG level in relation to the stages of lymphoma.

Type of lymphoma	Stage and Total no.	β2-MG level ≤ 3 µg/mL No. (%)	β2-MG level <3 µg/mL No. (%)	P-value	Mean±SD (µg/mL)	P-value
	I 5	4 (80)	1 (20)		2.833 ± 0.631	
HL	II 3	2 (66.7)	1 (33.3)	1.00*	3.300 ± 0.888	0.684**
	III 2	2 (100)	0 (0)		2.850	
	Total 10	8 (80)	2 (20)		2.990 ± 0.667	
	I 4	3 (75)	1 (25)		3.650 ± 1.569	
	II 7	6 (85.7)	1 (14.3)	0.083*	3.514±1.763	0.361**
NHL	III 7	4 (57.1)	3 (42.9)		3.571 ± 1.025	
	IV 2	0 (0)	2 (100)		5.650	
	Total 20	13 (65)	7 (35)		3.775 ± 1.529	

*Fisher exact test was used to measure P-value, ** ANOVA was used to measure P- value
Table (8) illustrates that there was no statistical difference among the stages of HL in relation to the serum β2-MG level (p value < 0.05) and the stages of NHL in relation to the serum β2-MG levels (p value < 0.05).Multiple comparison of mean using scheffe post hoc significant difference test (ANOVA) showed there was no statistically significant difference in mean serum β2-MG level in any specific stage of HL or NHL in relation to other stages.

Table 9: Serum β2-MG level in relation to the histopathological subtypes of non-Hodgkin lymphomas.

Variable NHL–histopathological subtypes and total No.	β2-MG level ≤3µg/mL No. (%)	β2-MGlevel <3µg/mL No. (%)	P-value	Mean±SD (µg/mL)	P-value
BL 12	7 (58.3)	5 (41.7)	0.611*	3.907 ± 1.712	0.662**
LL 4	4 (100)	0 (0)		2.925 ± 0.095	
DLBCL 2	1 (50)	1 (50)		4.400	
ALCL 2	1 (50)	1 (50)		4.200	
Total 20	13 (65)	7 (35)		3.775 ± 1.529	

*Fisher exact test was used to measure P-value
**ANOVA was used to measure P- value
Table (9) illustrates that there was no statistical difference among the histopathological subtypes of NHL in relation to the serum B2-MG levels (p value < 0.05). Multiple comparison of mean using scheffe post hoc significant difference test (ANOVA) showed there was no statistically significant difference in mean serum β2-MG level in any specific histopathological subtypes NHL in relation to other subtypes.

Table 10: Logistic regression analysis of the variables that are related to ALL.

Variable	Odd Ratio	95%confidance intervals	P-value
ALL risk groups	0.855	(0.124 - 5.872)	0.873
Initial WBCs count	9.863	(1.262 - 77.080)	0.029
ALL immunophenotypes	1.245	(0.626 - 2.473)	0.532

(10) Logistic regression analysis
Three variables in relation to the ALL cancer type were evaluated to look for the independent risk factors associated with elevated serum β2-MG level. Table (3-10).
Table (10) shows that the independent risk factor for elevated serum B2-MG level in patients with ALL is high initial WBCs count of < 50000 cells/ml.

Discussion

Beta2- microglobulin has been reported to be a growth-stimulating factor and cell signaling molecule in several types of cancer cells and has multiple roles in cancer development and induces tumor genesis and angiogenesis [46]. It is well known that cancer growth is accompanied by the elevated serum concentrations of many different soluble factors released into the circulation directly from the neoplastic cells or indirectly from non-neoplastic immune or inflammatory cells activated in response to the tumor, in this study we have focused in investigation of the clinical utility of serum β2-MG measurements in pediatric malignancies. This study reported that mean pretreatment serum level of β2-MG was significantly higher in children with malignancy than in healthy Controls, the same result was reported by other studies that were done by Al-Rubaye et al in Al-Kadhimiya Teaching Hospital [45] and Martincu et al. in Timisoara [54]. This can be explained by the fact that presence of β-2MG on the surface of all nucleated cells, as a component of the HLA class I molecule, may be associated with the theory of histocompatibility and with the immune response, the presence of β-2MG on the surface of the numerous tumor cell lines identifies it with the theory of tumor mass. A structural defect of the HLA complex tumor cells may also result in changes in epitope expression and increased release of β2-MG in serum.

This mechanism is consistent with the observation that serum β2-MG level reflect tumor burden and cell turnover [45]. The current study also reported that pre-treatment serum β2-MG level in children with hematological malignancies was significantly higher than in solid malignancies, the same result was reported by other studies that were done by Bien et al in Medical University of Gdansk, Poland [48] and Balcerska et al. in Poland [55]. This may be explained by the fact that in leukemias and lymphomas it may result from the relative increase in production of the β2-MG chains or it may reflect the increased turnover of tumor cells as lymphoid cells release more β2-MG during cell division stimulation with various cytokines [33,34]. It also has been suggested, that such different behavior of serum β2-MG concentration in hematological and solid malignancies may be caused by different biological sources of this protein [48].

This study reported that mean pretreatment serum level of β2-MG was significantly

higher with high initial WBCs count in patients with ALL. This can be explained by the fact that β2-MG is especially plenteous on the surface of white blood cells, and white blood cell membrane turnover is the principal source of serum β2-MG and upon metabolism and degradation of HLA, β2-MG is dissociated from the heavy chain and is released in its free form into the extracellular fluids [56]. In regard to the immunophynotypes of ALL and morphological subtypes of AML, this study had not found any significant association with abnormal serum β2-MG level, which was different from the result of other study that was done by Tsimberidou et al. in Texas, U.S.A, [57], which had revealed there was statistically significant relation between the abnormal serum β2-MG level and M4 and M5 morphological subtypes of AML and elevated β2-MG level was correlated with increased numbers of monocytes. Several of the correlations, such as those between β2-MG level and leukocyte counts, circulating blasts or monocytes, indicate that β2-MG level is a marker of increased turnover. This difference can be related to type and sensitivity of test detecting the β2-MG and small sample size of each type of acute leukemias in this study compared to the other studies.

This study had not reported significant association in mean pretreatment serum level of β2-MG among the stages of lymphomas and histopathological subtypes of non-Hodgkin lymphomas, which was different from the results of other studies that were done by Bien et al. in Poland [58] and by Mazher N in Lahore, [59] which had shown that advancing stages of lymphomas were statistically significant in relation to serum B2-MG level, reflect tumor burden of malignant cells and β2-MG level was high with progression of disease [59]. Also was different from the result of other study that was done by Al-Barazanchi et al. in Basra, [60] which had found there was statistically significant relation between the abnormal serum B2-MG level and histopathological subtypes of non-Hodgkin lymphomas (Burkitt's lymphomas & lymphoblastic lymphomas) , because in both BL and LL, bone marrow involvement of ≥ 25% is consistent with acute leukemia and patients with BL have a significantly worse prognosis if there is bone marrow involvement [53]. In conclusion hematological malignancies, serum β2-MG level is significantly higher than solid malignancies So serum β2-MG level need to be assessed in all newly diagnosed children with cancer especially hematological malignancies as an important supporting marker in diagnosis In conclusion Serum Beta2- microglobulin level is significantly higher in patients with hematological malignancies serum So Beta2- microglobulin could be recommended in the initial work up for diagnosis of childhood malignancy.

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