Online ISSN: 2682-2628
Print ISSN: 2682-261X

IJCBR

International Journal of Cancer and Biomedical Research

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International Journal of Cancer & Biomedical Research
(IJCBR) https://jcbr.journals.ekb.eg

IJCBR is an Int. journal published by the Egyptian Society of Cancer Research (EACR, established in 2014, http://eacr.tanta.edu.eg) and sponsored by the Egyptian Knowledge Bank (EKB: www.ekb.eg).

IJCBR has been approved by the Supreme Council of Universities, Egypt with score 7 (http://egjournal.scu.eg). The journl is cited by google scholar and registered by Publons (https://publons.com). The journal has recently been evaluated in 2020 by Nature Springer with a good standing.

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INTERNATIONAL JOURNAL OF CANCER AND BIOMEDICAL RESEARCH (IJCBR)

RESEARCH ARTICLE

The association of adiponectin polymorphism (rs2241766) with susceptibility and prognosis of Egyptian patients with haematological malignancies: A case-control study

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ABSTRACT

Background: Haematological malignancies are ranked as the highest in incidence. Adiponectin (ADIPOQ), the most abundant circulating adipocytokine, plays a major role in the regulation of insulin sensitivity, metabolism, and hematopoiesis. Various ADIPOQ gene polymorphisms are associated with an increased risk of different cancers. However, to the best of our knowledge, the association between ADIPOQ T45G (rs2241766) single nucleotide polymorphism (SNP) and leukemia is unknown. **Aim**: This study aimed to investigate the association between ADIPOQ (rs2241766) and the clinicopathological status of Egyptian leukemia patients. **Materials and Methods**: A case-control design was used, including 80 leukemia patients and 70 healthy controls. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used for genotyping. Survival analysis and biochemical investigations including hematological and lipid profiles, liver and kidney functions in addition to anthropometric measurements were also determined. **Results**: A significant positive correlation between ADIPOQ gene T45G (rs2241766) SNP and leukemia incidence was detected. The G allele was more frequent in leukemia patients compared to the T allele. Kaplan-Meier analysis revealed that the SNP rs2241766was associated with the patient's event-free survival but not the overall survival. In addition, G carriers, hyperglycemia, and hyperuricemia patients had a significantly shorter median EFS compared with T carriers, normoglycaemia, and normoglycemia patients. **Conclusion**: The current study shows an association between the SNP (rs2241766) and leukemia incidence and prognosis in Egyptian patients. Furthermore, an association between the rs2241766 and high prevalence of hyperglycemia and dyslipidemia in the G allele carrier's leukemia patients was also evident.

Keywords: Adiponectin, Polymorphism; rs2241766; Leukemia; Prognosis

Editor-in-Chief: Prof. M.L. Salem, PhD - Article DOI: 10.21608/JCBR.2020.25954.1014

ARTICLE INFO

Article history

Received: March 15, 2020
Revised: April 11, 2020
Accepted: April 13, 2020

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INTRODUCTION

According to the Globocan 2018 worldwide cancer statistics, leukemia was ranked as the 1st and 4th most prevalent cancer in individuals with the ages of 0-29 and 0-49, respectively. It causes the highest mortality rate up to the age of 44 with the highest incidence rates registered in industrialized followed by developing countries (Bray *et al.*, 2018). There are differences in incidence, risk factors, response to treatment, and overall survival (OS) of patients in different countries. In Egypt, recent

studies indicated that almost half of Egyptian children suffering from cancer were diagnosed with leukemia (Elmetwaly *et al.,* 2019; Khaled *et al*., 2019, Safinaz *et al.*, 2019).

Adiponectin is a *multifunctional* 244 amino-acid protein, the most abundant circulating adipocytokine that is encoded by the ADIPOQ gene located on human chromosome 3q27 (Vionnet *et al*., 2000). Adiponectin plays a major role in the regulation of insulin sensitivity, lipid metabolism, and hematopoiesis. *It is* synthesized by many tissues but mainly the white adipose tissue. It reduces the hepatic glucose production, increases the utilization of glucose and fatty acids by skeletal muscles, lowers blood glucose levels, and exerts its anti-diabetic action via protectingβ-cell and regulating the pathogenesis of the metabolic syndrome. Also, it has anti-inflammatory, anti-atherosclerotic and apoptotic effects besides a possible role in the regulation of blood cell proliferation (Barbe *et al.,*2019; Pasha *et al.,* 2019). Various single nucleotide polymorphisms in *ADIPOQ* gene was suggested to be associated with alterations of adiponectin levels and genetic susceptibility and progression of different types of diseases such as diabetes (Karimi *et al.,* 2018), hypertension (Jhuo*et al.,* 2019), as well as many solid tumors including breast (Geriki *et al.,* 2019), pancreatic (Mohamed *et al.,* 2019), and lung cancer (Li *et al.,* 2015). A meta-analysis suggested that serum *ADIPOQ* levels may be inversely correlated with leukemia (Ma *et al.* 2016). Moreover, a significant decrease in adiponectin levels was observed in relapsed acute and lymphoblastic leukemia patients (El-Baz *et al*., 2013).

Understanding the intersections between metabolism and cancer genetics remains an open challenge. So that studying *ADIPOQ*SNP and its potential consequences on the metabolism of glucose, lipids, and proteins in hematopoietic *malignancies* and correlating the role of both genetic and metabolic alterations with the response to therapy may add benefits in limiting the relapse. Therefore, *the current study aimed to investigate the association between* ADIPOQ T45G (rs2241766) SNP *with the risk* (OS) and event-free survival (EFS) and clinicopathological status of Egyptian leukemia patients.

2. SUBJECTS AND METHODS

2.1. Subjects and sampling:

A total of 150 subjects were enrolled for this study (80 newly diagnosed leukemia patients and 70 healthy controls). Patients were admitted to the Hematology unit at the medical research institute and Faculty of Medicine Hospital, Alexandria University. All subjects signed a written informed consent before participation and the study was approved by the ethics committee of the Medical Research Institute (code: IORG 0008812). The patients' follow-up continued for two years after treatment, starting from 1 Jan. 2017 to 30 Dec. 2018. The study included any confirmed newly diagnosed leukemia Egyptian patients within this period and excluded any patient who received treatments before the study or having another type of cancer. Among the leukemia patients, 46 were males and 34 were females while the control group had 53 males and 17 females. A total of 5mL peripheral venous blood was collected from each participant at presentation and after the first cycle of chemotherapy (for patients) and divided into two parts: 2mL were allowed to clot and serum was isolated and stored at -20^{o}C until assayed for biochemical investigations. The other 3mL of blood was collected into EDTA-containing plexiglass tube and was used for genotyping analysis.

2.2. Treatment regimens:

Thirty-one patients diagnosed with acute lymphoblastic leukemia. (ALL) were treated with Hyper-CVAD, which consists of two courses:(A) Cyclophosphamide, vincristine, dox orubicin and dexamethasone, and
(B) Methotrexate, leucovorin, and cytarabine were given in an alternating fashion (Garcia-Manero and Kantarjian 2000). Twenty-eight acute myeloid leukemia (AML) patients were treated with different protocols including 3+7 protocol (Daunorubicin for 3 days followed by Cytosar for 7 days) (Yates *et al.*,1982)or Larson protocol (cyclophosphamide-daunorubicin-vincristine-prednisone-L-asparaginase)
(Larson *et al*., 1995) or Linker protocol (Daunorubicin-Vincristine-Prednisone-

Asparaginase) (Linker *et al*., 1991). Seventeen chronic myeloid leukemia (CML) patients were mainly treated with Imatinib or Nilotinib and four patients with chronic lymphoblastic leukemia (CLL) were treated with FCR protocol (Fludarabine, Cyclophosphamide, and Rituximab) (Rossi *et al*., 2015). A representation of the treatment protocols used and patient response is summarized in (Figure 1).

2.3. Anthropometric and Biochemical Studies

Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared. Biochemical investigations included: (1) fasting blood glucose samples were collected after 8 hours fasting and measured using the glucose oxidase method; (2) lipid profile including total cholesterol (TC), high-density lipoproteins (HDL) and triglycerides (TrG) were measured by an enzymatic assay using an autoanalyzer (Hitachi, Tokyo, Japan); (3) low-density lipoproteins (LDL) cholesterol was calculated by the Friedewald's equation; (4) liver function tests (alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin and albumin, kidney function tests (urea and creatinine) and uric acid (UA) were determined by standard laboratory procedures(Burtis *et al.,* 2007).

2.4. Genotyping and PCR-RFLP analysis

Genomic DNA extraction was carried out by the QIAamp DNA mini kit (cat # 51104, Qiagen Hilden, Germany) according to the manufacturer's recommendations. DNA concentration was measured using NanoDrop™ 2000c spectrophotometer (Thermo Scientific, USA). The PCR was performed using Taq PCR Master Mix Kit (Cat # 201443) (Qiagen, Applied Biosystems). The PCR thermal protocol was: initial denaturation at 95°C for 3 min followed by 35 cycles of denaturation at 94°C for 35 Sec, 60°C for 40 sec, 72°C for 45 sec and a final extension at 72°C for 7 min (Takahashi *et al.,* 2000). The used ADIPOQ primers were as follows: forward 5'-GAAGTAGACTCTGCTGAGATGG–3'and reverse 5'-TATCAGTGTAGGAGGTCTGTGATG-3' (Takhshid et al., 2015). The amplified PCR products (10 – 12 µL) were directly digested with 0.5 µL of *SmaI* (10U/µL) restriction enzyme (Cat: ER#0665) (Thermo-Fischer Scientific, USA)at 30°C for 5 hours and then analyzed by electrophoresis on a 2% agarose gel stained with ethidium bromide for band molecular weight determination and restriction fragment analysis as described previously (Hu et al., 2013).

2.5. Statistical analysis

The analysis was done using the statistical package for social sciences (SPSS/version 21.0) software. Hardy-Weinberg equilibrium of genotype frequencies distribution was used for comparing cases against the controls. The differences in frequencies of individual polymorphisms were assessed by frequent analysis, Fisher's exact tests, and Chi-square tests. Kaplan-Meier curves were utilized to test associations of the SNP with survival time. OS was estimated from the date of diagnosis to the date of death while the endpoint of EFS was estimated at the time of relapse, resistance, or death.

3. RESULTS

3.1. Demographic analysis

There was no significant difference regarding the age or gender of both groups (p= 0.153 and 0.151 respectively). The mean BMI was significantly lower (p = 0.0003) in patients (26.83±3.16) compared to the controls (29.56±2.81)(Table 1).

3.2. Biochemical Investigations

Fasting blood sugar (FBS) was significantly higher in leukemia patients compared to the controls. Lipid profile showed a significant increase (p = 0.024) in TrG levels in patients compared to the controls and a significant decrease in HDL-C, TC/HDL ratio, and LDL/HDL ratio in patients compared to controls (p = 0.001, 0.001 and 0.002), respectively. A significant decrease in hemoglobin level and platelet count was detected in leukemia patients compared to the controls while the white blood cells and blast cell counts were significantly higher. On the other hand, there was no significant difference in any of the kidney or liver function tested parameters between patients and controls except for uric acid and albumin (Table 1).

Table 1: Demographic, clinical and biochemical characteristics of patients and controls.

characteristic	Patients	Control	P
Gender			

Male (%)	46 (57.5)	53(75)	X^2 =
Female (%)	34 (42.5)	17 (25)	0.151
Age (years)	37.6±15.1	33.9±13.9	0.153
BMI (Kg/m²)	26.8±3.16	29.5±5.3	0.0003
Hb (mg/dl)	9.13±7.7	12.16±2.4	0.002*
WBCs(x1000 cells/	20.18±23.6	5.3±2.48	0.0001
Platelets(x1000(cells	127.93±120	270±89.4	0.0001
Blast Cells %	40.62±30.3	2.00±1.00	0.0001
FBS (mg/dl)	105.2±25.0	87.57±13.	0.0001
Urea (mg/dl)	26.58±10.8	4.04±1	0.0001
ALT (U/L)	33.81±26.2	21.82±6.2	0.0003
AST (U/L)	28.02±14.6	20.85±6.1	0.0002
Total Bilirubin	0.69±0.5	0.55±0.3	0.047*
Albumin (g/dl)	3.1±0.5	4.04±1	0.0001
Creatinine (mg/dl)	3.1±0.5	4.04±1	0.062
Uric acid (mg/dl)	3.65±1.45	2.13±0.58	0.0001
TC (mg/dl)	119.75 36.1	122.91	0.554
TrG (mg/dl)	123.19±78.	85.98±25.	0.0002
HDL (mg/dl)	30.70±12.0	47.39±13.	0.0001
LDL (mg/dl)	62.94 29.9	61.87 20.4	0.84
TC/HDL	4.26±1.5	2.69±0.5	0.0001
LDL/HDL	2.22±1.09	1.4±0.6	0.0001

Data are given as mean ± SD. * Statistically significant at (P < 0.05) compared to control.BMI, Body mass index. Hb, Hemoglobin. WBCs, white blood cells. FBS, Fasting blood sugar.ALT, alanine transaminase. AST, aspartate transaminase.TC, total cholesterol. TrG, Triglycerides.HDL, high-density lipoproteins.LDL, low-density lipoproteins.

3.3. Genotype and allele frequencies analysis

Following PCR-RFLP and the *SmaI* enzyme digestion, the ADIPOQ wild-type TT homozygous yielded a single 372 bp uncut fragment while the heterozygous TG mutant resulted in a digestion profile of 372, 219 and 153bp fragments. Finally, the homozygous G/G alleles resulted in a digestion profile of 219 and 153bp fragments (Figure 2).

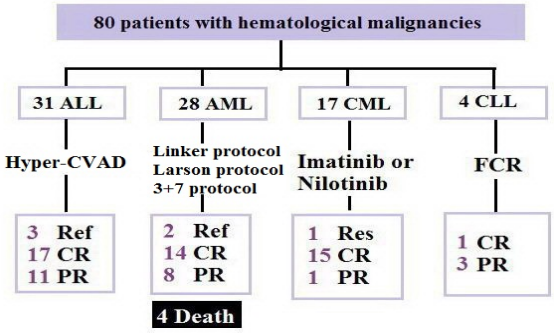

Figure 1. Flow chart representing recruited Leukemia patient's subtypes, treatment protocols and patient response. FCR (fludarabine, cyclophosphamide, rituximab), Ref: refractory, CR: complete remission, PR: partial remission, Res: resistance.

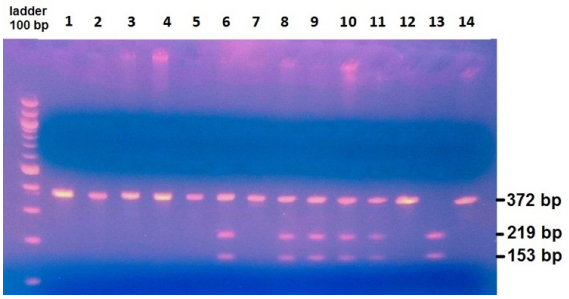

Figure 2. Representative agarose gel electrophoresis showing the PCR-RFLP analysis for ADIPOQ T45G (rs2241766) SNP with the 3 genotypes detected; Lanes 1-5, 7, 12 and14: wild-type (TT); Lanes 6, 8-11: heterozygous (TG); Lane 13: homozygous (GG). A 100 bp ladder is used as a DNA molecular weight marker.

Genotype and allele frequency distribution data are shown in (Table 2); the mutated variants TG, GG of ADIPOQ (rs2241766) were significantly higher in leukemia patients compared to controls (p=0.001). The homozygous wild type TT was the most frequent in patients and controls with 45 (56.2%) and 63 (90%) respectively. Interestingly, the mutant heterozygous TG variant was found in 34 (42.5%) of patients compared to only 5 (7.1 %) of the controls. Finally, the mutant homozygous variant GG was the least frequent in both groups, found in only 1 patient (1.2%) and 2 controls (2.9%).

Table 2: Genotype and allele frequencies of ADIPOQ (rs2241766) polymorphism among patients and controls.

ADIPOQ T45G (rs2241766)	**Patients n=80 (%)**	**Control n=70 (%)**
Genotype		
TT(%)	45 (56.2%)	63 (90.0%)
GG(%)	1 (1.2%)	2 (2.9%)
TG(%)	34 (42.5%)	5 (7.1%)
Hardy-Weinberg	0.98	0.601
X^2, (P-value)	14.0 (0.001*)	
Allele type		
T (%)	124 (77.5)	131 (93.6)
G (%)	36 (22.5)	9 (6.4)
X^2 (p-value)	15.1, (0.001*)	
OR (95.0% CI)	5.11 (2.621-13.11)	
RR (95.0% CI)	4.52 (1.58-8.22)	

Frequency of genotypes was compared by Chi-square test (χ2). Odd ratios (ORs) and Risk ratio (RR), 95% confidence intervals (CI) were calculated by logistic regression analysis.* Statistically significant at (P < 0.05).

The G allele frequency was significantly higher in patients (22.5%) compared to controls (6.4 %, p=0.001) and under the Hardy–Weinberg equilibrium was associated with a higher risk of leukemia [OR (95 % CI) 5.11 (2.621 –13.11) and RR (95 % CI) 4.52 (1.58 –8.22)].

There were no significant genotype-related differences associated with anthropometric parameters, leukemia subtypes, BMI, hemoglobin (Hb), Platelets, white blood cells (WBCs), Blast cells, kidney function, liver function, TC, TrGand LDL-C levels. However, a significant elevation of FBS level, LDL/HDL, TC/HDL ratios, and a significant decrease in HDL levels were observed in G carriers (Table 3).

3.4. Kaplan Meier analysis of overall survival (OS) and event-free survival (EFS)

Association between the clinical patient's outcome including OS and EFS and ADIPOQ (rs2241766) was investigated after2 years of follow up of patients. There was no significant difference in the OS in relation to rs2241766 polymorphism (Table 4). However, patients with mutated heterozygous TG or homozygous GG rs2241766 variants showed poor prognosis (partial remission, relapse or death) and a statistically significant (P= 0.027) shorter EFS compared to those with the wild type TT genotype (median EFS=12 and 17 months, respectively, HR=0.457; 95% CI 0.223 – 0.937) (Table 4 and Figure. 3A). Moreover, survival analysis indicated that 21% of leukemia patients with hyperglycemia (FBS>120 mg/dl) showed significantly shorter median EFS of 12 months compared with *19* for normoglycaemia patients (HR=2.588; 95% CI 1.195 – 5.60, p=0.012) (Figure 3B). Similarly, 16 % of patients with hyperuricemia (>5mg/dl) showed significantly worse outcomes with median EFS of 11 months compared to 17 for normoglycemia patients (HR=3.207; 95% CI 1.437–7.15, p=0.003) (Figure 3C). AML patients showed an increased death rate (p=0.041) while CML was associated with a good prognosis and longer EFS (mean 19.35months, p=0.006). Finally, patients treated with Imatinib or Nilotinib exhibited a good prognosis and longer EFS (mean 19.2months, p=0.021) (Figure 3D-F).

Table 3: Association between ADIPOQ (rs2241766), anthropometric and biochemical parameters in Leukemia patients.

characteristic	TT "n=45"	TG+GG "n=35"	P
Age (years)	35.60±14.47	37.27±13.75	0.608
BMI (Kg/m²)	27.16±2.88	26.50±3.48	0.35
Hb (mg/dl)	8.39±1.79	8.16±2.33	0.61
WBCs(x1000 cells/ µl)	18.20±19.51	22.73±30.41	0.74
Platelets(x1000(cells/ µl)	112.11±94.95	148.28±145.7	0.184
Blast Cells %	39.64±30.59	41.88±30.41	0.74
FBS (mg/dl)	95.84±18.24	117.2±27.61	0.0001*
Urea (mg/dl)	24.93±7.62	28.71±13.18	0.120
ALT (U/L)	34.13±29.35	33.4±22.46	0.90
AST (U/L)	26.08±9.94	30.51±18.89	0.18
Total Bilirubin (mg/dl)	0.66±0.44	0.73±0.57	0.53
Albumin (g/dl)	3.07±0.51	3.14±0.61	0.57
Creatinine (mg/dl)	0.83±0.45	0.86±0.5	0.77
Uric acid (mg/dl)	3.48±1.05	3.86±1.83	0.24
Cholesterol (mg/dl)	114.9±35.15	127.4±36.97	0.12
TrG (mg/dl)	124.6±77.45	121.2±81.67	0.84
HDL-C (mg/dl)	34.5±14.18	25.81±5.98	0.001*
LDL-C (mg/dl)	59.62±30.52	67.21±28.99	0.26
TC/HDL	3.71±1.39	4.96±1.35	0.0001*
LDL/HDL	1.923±1.03	2.64±1.06	0.003*

Data are given as mean ± SD; * statistically significant (P < 0.05) compared to control.BMI, Body mass index. Hb, Hemoglobin. WBCs, white blood cells. FBS, Fasting blood sugar.ALT, alanine transaminase.AST, aspartate transaminase. TrG, Triglycerides. HDL, high-density lipoproteins. LDL, low-density lipoproteins. TC, total cholesterol.

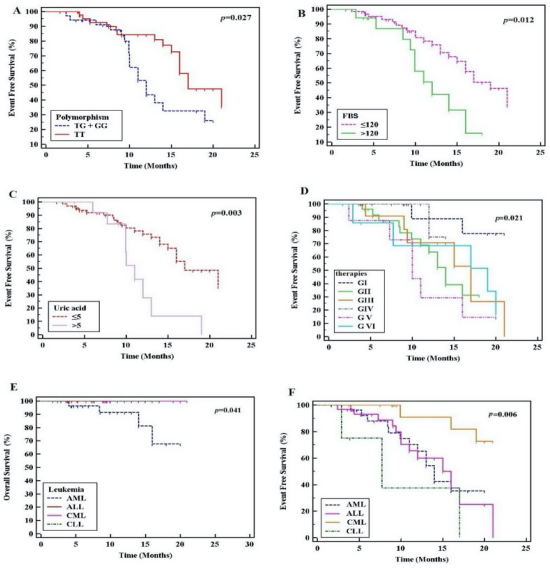

Figure 3. Kaplan-Meier survival curves: (A) EFS in relation to T45G polymorphism; (B) EFS in relation to blood glucose level; (C) EFS in relation to Uric acid level; (D) EFS in relation to therapeutic protocols: Imatinib or Nilotinib (Group I), Daunorubicin for 3 days followed by Cytosar for 7 days (Group II), Larson protocol (Group III), Linker protocol (Group IV), Hyper-CVAD (Group V), Others (Group VI); (E) OS in relation to leukemia subtypes; (E) EFS in relation to leukemia subtypes, the significance is considered at p<0.05.

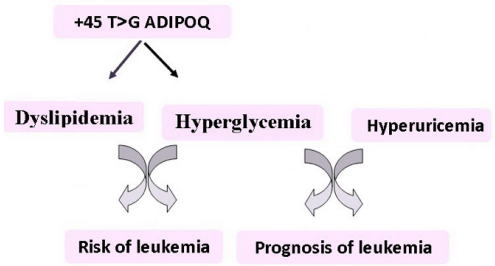

Figure 4. Graphical abstract representing the suggested interconnection between ADIPOQ (rs2241766) SNP and leukemia through metabolic reprogramming of Glucose, lipids and as uric acid levels.

Table 4: Kaplan-Meier analysis for leukemia patients.

	N	Mean	Median	Hazard	95% C.I	%	Log-rank	
Polymorphism								
TG + GG	**32**	17.75	-	-	-	75.0	0.005	0.945
TT	**48**	20.00	-	1.087	0.103 – 11.5	89.7		
FBS(mg/dl)								
≤120	**66**	20.21	–	-	-	91.3	0.421	0.516
>120	**14**	17.0	–	2.089	0.215 – 20.3	75.0		
Uric acid (mg/dl)								
≤5	**69**	20.01	–	-	-	88.3	0.404	0.525
>5	**11**	–	–	0.041	0.0 - 173743	100.0		
Subtypes of leukemia								
AML	**28**	17.69	-	–	–	67.8	8.236*	0.041*
ALL	**30**	-	-	0.006	0.0 – 4511.6	100.0		
CML	**18**	-	-	0.005	0.0 – 2703	100.0		
CLL	**4**	-	-	0.005	0.0 – 1.44	100.0		
Polymorphism								
TG + GG	**35**	13.17	12.0	-	-	26.1	4.897*	0.027*
TT	**45**	16.75	17.0	0.457	0.223 – 0.937	35.7		
FBS (mg/dl)								
≤120	**57**	16.35	19.0	-	-	34.7	6.375*	0.012*
>120	**23**	11.96	12.0	2.588*	1.195 – 5.60	15.8		
Uric acid (mg/dl)								
≤5	**64**	16.27	17.0	-	-	36.3	9.121*	0.003*
>5	**16**	11.50	11.0	3.207*	1.437 – 7.15	0.0		
Subtypes of								
AML	**28**	14.18	14.0	–	–	–	12.454*	0.006*
ALL	**30**	14.39	16.0	0.904	0.420	1.94		
CML	**18**	19.35	-	0.163	0.044	0.598		
CLL	**4**	9.99	7.70	2.227	0.631	7.866		
Therapeutic								
Group I(R)	**16**	19.21	-	–	–	77.8	13.272*	0.021*
Group II	**27**	13.23	14.0	7.75*	1.64 – 36.6	31.3		
Group III	**12**	14.99	17.0	6.16*	1.22 – 30.98	0.0		
Group IV	**10**	13.50	-	2.26	0.195 – 26.3	75.0		
Group V	**8**	11.14	10.0	11.62*	2.24 – 60.14	14.6		
Group VI	**7**	14.76	19.0	6.60*	1.23 – 35.3	17.1		

* Statistically significant at (P < 0.05). Therapeutic protocols: Imatinib orNilotinib (Group I), Daunorubicin for 3 days followed by Cytosar for 7 days (Group II), Larson protocol (Group III), Linker protocol (Group IV), Hyper-CVAD (Group V), Others (Group VI).Acute myeloid leukemia (AML), Acute lymphoblastic leukemia (ALL), Chronic myeloid leukemia (CML), Chronic lymphoblastic leukemia (CLL).

4. DISCUSSION

As a result of the global continuous increase in air pollution and other environmental factors, there is an increasing incidence of leukemia worldwide as well as among the Egyptian population (Filippini *et al*., 2019). Adiponectin has been shown to play a crucial role in obesity-associated tumors (Parida *et al*., 2019). On the other hand, there is increasing evidence that obesity is associated with an increased risk as well as worst prognosis for leukemia patients (Larsson *et al*., 2008, Castillo *et al*., 2016).

Among the different ADIPOQ SNPs reported, T45G ADIPOQ has been suggested to decrease serum levels of ADIPOQ protein and to be associated with many metabolic disorders and solid tumors (Smetnev *et al.,* 2019). The impact of serum ADIPOQ levels on hematological malignancies was investigated in a single study showing that serum ADIPOQ levels were significantly lower in acute leukemia (Aref *et al.,* 2013). Moreover, among the many research articles emphasizing both the metabolic reprogramming "Warburg effect" and somatic gene mutation theories for cancer, only a few have investigated both theories in hematopoietic malignancies and mostly were done at the experimental level (Gottschalk *et al.,* 2004, Poljsak *et al.,*2019). Therefore the present study aimed to investigate the association between Adiponectin polymorphism (rs2241766) in relation to the susceptibility and prognosis of Egyptian leukemia patients, in addition, to analyze its effect on the hematological profile and metabolic parameters including blood glucose level, plasma proteins, lipid profile, uric acid as well as liver and kidney functions.

In the current study, no significant association between T45G ADIPOQ genotypes with age or gender was observed. This agrees with a previous study that revealed the absence of association between T45G ADIPOQ genotypes and age or gender (Awede *et al.,* 2018). However, a significant decrease in BMI in leukemia patients compared to controls was observed. Another study revealed that lower BMI together with diabetes is significantly associated with the incidence of leukemia in Egypt (El-Koofy *et al.,* 2020). In contrast, a recent meta-analysis study reported that among the 20 most populous countries, Egypt had the highest level of adult obesity that is associated with the incidence and mortality from leukemia (GBD, 2017).

Our fundamental ADIPOQ genotyping analysis indicated an association between rs2241766 polymorphism and the risk of developing leukemia since the mutated genotypes TG/GG as well as the G allele frequency were significantly higher in Leukemia patients compared to controls. This may be explained as the G allele exerts its effect by negatively influencing the stability of ADIPOQ mRNA, subsequently interfering with the anti-proliferation, anti-angiogenic and pro-apoptotic effects of ADIPOQ, as well as resistance to chemotherapy (Takhshid *et al.,* 2015, Tumminia *et al.,* 2019). The lack of association between the G allele and OS of patients in the current study might be attributed to the small sample size where only 4 patients with AML out of 80 patients died within the 2 years follow-up period, a number that could not segregate leukemia patients according to the SNP T45G ADIPOQ.

Our data revealed that among all biochemical parameters, hyperglycemia was associated with both G allele and poor prognosis in leukemia patients compared to those with normoglycemia without a notable effect on OS. consistent with our data, another study showed evidence of a susceptibility locus for type 2 diabetes in French whites on chromosome 3q27 supporting the relationship between the gene locus of ADIPOQ on human chromosome 3q27and hyperglycemia (Vionnet *et al.*, 2000; Dorajoo *et al*., 2015; Rashkovan et al., 2019).

Our data showed that dyslipidemia was associated with the G allele, while hyperuricemia was associated with worse clinical outcomes in patients compared to those with normouricemia. These results are in accordance with another study showing that the G carriers had dyslipidemia (Foucan *et al.,* 2018). This supports the crosstalk between ADIPOQ and HDL where ADIPOQ induces HDL production and vice versa (Ge *et al.,* 2015). Besides the genetic effect, we cannot ignore the role of malnutrition on the production of HDL where it has been reported

that low protein and fruit consumption were observed in leukemia patients during radio-or chemotherapy (Bahgat *et al.,* 2013). Moreover, hyperglycemia accelerates lipolysis and subsequently, leads to decreased HDL levels. Our data match a previous study that pointed to the role of the genetic alterations and dietary pattern in dyslipidemia via interference with HDL-induced anti-oxidative, anti-proliferative and anti-inflammatory properties (Christou *et al.,* 2013). Regarding the hyperglycemia, Motawi *et al*. (2015) reported the association between G allele frequency with Diabetes Mellitus (DM) in Egyptians via reducing the level of ADIPOQ, besides, Castillo *et al*. (2012) highlighted the role of DM in increasing the risk of leukemia (Castillo *et al.,* 2012, Motawi *et al.,*2015).

Many mechanisms were proposed to explain the association between ADIPOQ, hyperglycemia, and leukemia. Firstly, as mentioned above, ADIPOQ exerts its anti-diabetic action via protecting β-cell, reducing the hepatic glucose production, increasing the utilization of glucose and regulating the insulin sensitivity (Motawi *et al*., 2015), thus its deficiency as expected in G carriers may be attributed to the notable hyperglycemia. Secondly, oncogenes such as BCR-Abl, a mutated gene resulting from *t*(9;22) chromosomal translocation in 25% of leukemia cells, promotes the glucose uptake via trafficking of glucose transporter (Glut1) to the cell surface and promoting glycolysis, lipid and nucleotide biosynthesis (Liu *et al*., 2014). Thirdly, over-expression of free insulin-like growth factor (IGF-1), an enhancer of hyperglycemia and cell transformation, increases the glucose uptake by leukemic cells to support their proliferation as well as chemotherapy resistance (Casellas *et al*., 2015, Ye *et al*., 2018). Finally, hyperglycemia was strongly correlated with infection-induced death in leukemia patients as the notable poor prognosis in G carriers and hyperglycaemic patients (Matias *et al.,* 2013, Xu *et al.,* 2018) and since hyperglycemia is known to impair ADIPOQ production via the oxidative stress (Li *et al.,* 2019), therefore, it is suggested that (rs2241766) SNP of ADIPOQ together with hyperglycemia might have an impact on the worst clinical outcome for leukemia patients.

Regarding the observed hyperuricemia, our results are in agreement with a previous report showing that uric acid exerts many pro-inflammatory effects that contribute to the progression and aggressiveness of cancer (Fini *et al.,* 2012). The interconnection between hyperuricemia, hyperglycemia in leukemia patients might be explained by different mechanisms. Firstly, the high rate of cell lysis in leukemia patients results in releasing of purines, accumulation of uric acid, and increasing the risk of insulin resistance (Furuhashi *et al.,* 2018). Secondly, the production of UA is accompanied by the generation of reactive oxygen species which have an inhibitory effect on ADIPOQ production (Washio *et al.,* 2017). Overall, our data suggest that ADIPOQ (rs2241766) SNP might center the association between dyslipidemia, hyperglycemia, and leukemia as emphasized and represented in Figure 4.

The four death cases during our study were diagnosed with AML; this is consistent with a previous report which revealed that AML patients display the poorest survival rate (Bhayat *et al.,* 2009). Several reports have revealed that despite advances in the therapy of lymphoid and myeloid leukemia and achievement of complete remission(CR), higher relapse and death rate due to infection and hemorrhage are recorded (El-Zawahry *et al.,* 2007; Abdelmabood *et al.,* 2018).

Our Kaplan-Meier analysis of EFS indicated that ALL patients who were treated with Linker protocol showed a better prognosis compared to the Larson protocol and Hyper CVAD regimen. This is consistent with a previous study indicating that hyperglycemia is associated with recurrence in ALL treated with the hyper-CVAD regimen (Vu *et al.,* 2012). Moreover, our data show that CML patients who were treated with Imatinib or Nilotinib, tyrosine kinase inhibitors (TKIs), showed a good prognosis. It was reported that treatment of CML patients with imatinib results in the increase of ADIPOQ levels as well as improving the glucose and lipid metabolism as it enhances the adipocytes differentiation in bone marrow (Fitter *et al.,* 2010).

Since deaths during induction therapy in acute leukemia remain a major challenge in developing countries, using enhanced supportive care is effective to improve the survival outcome (Hafez *et al.,*2019). A recent study showed that resistance to Imatinib and nilotinib are attributed mainly to genetic mutation and suggested that the outcomes may be improved by supportive therapy as those enhanced ADIPOQ productions. Many natural therapies that enhance the production of ADIPOQ such as l-cysteine, garlic, manganese, cobalt, and phytochemicals including astragaloside II, isoastragaloside I, Zatariamultiflora and temocapril extracts may be effective in improving the clinical outcomes (Achari*et al.,* 2017).

Collectively, our data agree with the metabolic reprogramming theory for cancer, reflected by biochemical differences associated with the rs2241766 as well as the genetic theory confirmed by the significant differences observed in the genotype distribution and allele frequency between leukemia patients and controls. Besides, it is confirming its role in response to different therapeutic protocols.

Our data implicate that adiponectin single nucleotide polymorphism (rs2241766) might be used as a prognostic factor for leukemia patients. It is recommended to use supportive therapies that enhance ADIPOQ production and action, as well as, counteracting of hyperglycemia and dyslipidemia in leukemia patients having T45G genotype. This may improve the efficacy of chemotherapy and clinical outcomes. Also, the implication of ADIPOQ in improving Imatinib and Nilotinib actions should be taken into consideration.

In conclusion, we may suggest more research on supportive therapy enhancing ADIPOQ production and action which might lead to improving the efficacy of chemotherapy and therefore the patient's clinical outcome. Moreover, ADIPOQ rs2241766 SNP may be used as a prognostic factor for leukemia patients treated with different chemotherapeutic regimens.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENT

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Egyptian Association for Cancer Research (EACR)
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EACR is an NGO society that was declared by the Ministry of Social Solidarity (Egypt) No. 1938 in 19/11/2014 based on the initiative of Prof. Mohamed Labib Salem, the current Chairman of EACR. EACR aims primarily to assist researchers, in particular young researchers in the field of cancer research through workshops, seminars and conferences. Its first international annual conference entitled "Anti-Cancer Drug Discovery" was successfully organized in April 2019 (http://acdd.tanta.edu.eg). Additionally, EACR aims to raise the awareness of the society about the importance of scientific research in the field of cancer research in prediction, early diagnosis and treatment of cancer. EACR is also keen to outreach the scientific community with periodicals and news on cancer research including peer-reviewed scientific journals for the publication of cutting-edge research. The official scientific journal of EACR is "International Journal of Cancer and biomedical Research (IJCBR: https://jcbr.journals.ekb.eg) was successfully issued in 2017 and has been sponsored by the Egyptian Knowledge Bank (EKB: www.ekb.eg).

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International Journal of Cancer & Biomedical Research
(IJCBR) Online ISSN 2682-2628

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