GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

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Evaluation of serum taurine level as a biomarker for early diagnosis and follow up of chronic myeloid leukemia

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GSC Biological and Pharmaceutical Sciences, 2023, 25(02), 411–433

Publication history: Received on 10 October 2023; revised on 24 November 2023; accepted on 27 November 2023

Article DOI: https://doi.org/10.30574/gscbps.2023.25.2.0501

Abstract

Objective: Investigate serum taurine level as a biomarker for early diagnosis and follow up of chronic myeloid leukemia, find correlation between serum taurine level in different phases of Chronic Myeloid Leukemia and number of blast cells in each phase, find correlation between serum taurine level and the percentage of BCR-ABL gene in body which is the diagnostic biomarker for chronic myeloid leukemia.

Method: One Hundred and thirty eight chronic myeloid leukemia patients (male and female) were chosen from National Cancer Institute after their approval, patients classified into four groups (Chronic Phase (CP) of CML group, Accelerated Phase (AP) of CML group, Blast Phase (BP) of CML group& after Treatment group (Healing Patients from CML)) according to their Complete clinical examination, investigation and biochemical analysis. Thirty frank healthy control persons enrolled as volunteers. Complete clinical examination, investigation and biochemical analysis (liver and kidney functions, complete blood pictures, Cytology analysis), and the recent biomarker taurine, was measured for all patient and volunteers.

Results: The data showed that, according to age, there were statistically significant difference between control group and after treatment group. We did not find a significant difference between gender in different groups (P=0.942).by comparing family history between groups we found that 62.5% of AP group had positive family history, 50% of BP group had positive family history, 44.3% of CP group had positive family history, 33.3% of controls had positive family history while no patients in after treatment group had positive family history .we found that median hemoglobin level were statistically significant differ between groups. By doing pairwise comparison we found that median HB level in AP group is differ from this in CP, after treatment and control group (P=0.027, 0.028, <0.001 respectively). In addition, this in control group is statistically differ from this in BP and CP groups (P=0.002 and <0.001 respectively). That median WBCS level were statistically significant differ between groups. By doing pairwise comparison we found that median WBCS level in after treatment group were differ from CP,AP groups(P=0.012,<0.001 respectively). Also control group differ from CP and AP groups (P=<0.001, <0.001 respectively) .we found that median ALT level were statistically significant differ between groups. By doing pairwise comparison we found that median ALT level in control group is differ from CP and AP (P=0.17, 0.21 respectively).also, median AST level were statistically significant differ between groups. By doing pairwise comparison we found that median AST level in control group is differ from CP and AP and after treatment groups (P=<0.001, <0.001 and 0.034 respectively). Bilirubin and urea were not statistically differ between groups. Creatinine were statistically significant differ between groups. By doing pairwise comparison we found that median creatinine level in control group is differ from AP, BP and CP group (P=<0.001, 0.034, <0.001 respectively).

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Alkaline phosphatase were statistically significant differ between groups. By doing pairwise comparison we found that median alkaline phosphatase level in control group is differ from AP and CP (P=0.008, <0.001).we found that median blast cells level were statistically significant differ between groups. By doing pairwise comparison we found that median blast cells level in CP group is differ from AP and BP(P=<0.001,<0.001 respectively). Median BCR-ABL level were statistically significant differ between groups. By doing pairwise comparison we found that median BCR-ABL level in CP group is differ from AP and BP (P=<0.001, <0.001 respectively). The most interesting thing that the Median serum taurine level were statistically significant differ between groups. By doing pairwise comparison we found that median taurine level in BP group is differ from CP and after treatment group(P=<0.001,<0.001 respectively) and in AP group is differ from CP, after treatment and control(P=<0.001,<0.001 respectively).we found that there is correlation between taurine level and different numeric variables , we found that age has fair negative correlation with taurine level meaning that for each year increase in age taurine level will decrease .also WBCS has good negative correlation with taurine level meaning that for each increase in in WBCS taurine level will decrease. In addition, RBCS and HB have good positive correlation with taurine level meaning that for each increase in RBCS or HB taurine level will increase. Platelets, neutrophils, bilirubin and urea show no significant correlation with taurine level. ALT and AST show week to fair negative correlation with taurine level. Creatinine has good negative correlation with taurine level. Number of Blast cells and BCR-ABL ratio show excellent negative correlation with taurine level meaning that when they increase taurine level decrease and vice versa .

Conclusion: Serum taurine level is statistically significant differ between groups ,that decrease with the increase of the chronicity of disease and the number of blast cells , increase in normal frank control volunteers and after treatment patients which make it possible to be used as a pre biomarker for early diagnosis and follow up of chronic myeloid leukemia disease.

Keywords: Taurine(Tau); Chronic Myeloid Leukemia(CML); Chronic Phase(CP) of CML; Accelerated Phase(AP) of CML; Blast Phase(BP) of CML; Blast Cells; BCR-ABL gene(Philadelphia gene)

1. Introduction

Chronic myeloid leukemia (CML) has a long history as a model disease, dating back to the initial identification of the Philadelphia chromosome and the discovery of leukemia ending with the current goal of finding treatment-free remission after targeted therapies and find a new types of diagnosis for disease as fast as possible which may prevent complications of disease (1).

Leukemia is a class of blood cancers described as an oligoclonal expansion of hematopoietic cells that invades the bone marrow and can also invade the blood and other extramedullary tissues (2).The proliferation of leukemic cells causes the expulsion of the normal hematopoietic cells and the loss of their functions, leading to severe symptoms, including thrombocytopenia, anemia, and immunodeficiency. Hematological cancers are ranked as the 11th common type of cancer and the 10th common cause of cancer-related death. More than 350,000 new leukemia cases and 265,000 leukemia death were estimated to have occurred in 2012(3). In The United States, leukemia accounts for approximately 4% of cancer-derived mortalities and 3.5% of all cancer cases. , The incidence, mortality, and survival of leukemia depends on the diagnosis, prognosis, as well as natural history of neoplasms arising from the malignant transformation of hematopoietic stem cells of progenerator cells in the bone marrow (4).

Leukemia can be classified according to its progression pattern (acute or chronic) and affected lineage (lymphoid or myeloid).The four major subtypes are acute myeloid leukemia (AML),acute lymphoblastic leukemia(ALL), chronic lymphoblastic leukemia(CLL) and chronic myeloid leukemia (CML) (5,6). ALL is one of the most common types of malignancy in children worldwide (7), while the other subtypes are more common in adults. In all types of leukemia, the abnormal proliferation of bone marrow and blood cells disrupt the production of functionally healthy cells and crowd this healthy cells. Thus, anemia ensues in people with leukemia, increase abnormal WBCs resulting in reduced ability to fight infections and dereased number of functionally platelets causes clotting disorders for most patients, the causes of leukemia and its subtypes are unclear partly due to diverse abnormalities and multiple risk factors. However, the genetic background interacting with environmental factors including exposure to high doses of radiation or carcinogenic agents, such as benzene; parental occupational exposures; and infections all led to a higher risk and possibilty of developing leukemia (8).

Chronic myeloid leukemia (CML) is a myeloproliferative tumor originating from hematopoietic stem cells, characterized by the formation of the BCR-ABL1 fusion gene (9).

The BCR-ABL1 protein enhances tyrosine kinase activity and contribute to uncontrolled proliferation and apoptosis inhibition (10). As first- line drugs, tyrosine kinase inhibitors (11) have significantly improved the prognosis of CML, but their clinical application is limited by drug intolerance and drug resistance (12-13). Therefore, it is of great significance to find novel anti-CML compounds, Nature products are an essential resource of anti-tumor drugs (14).

CML is associated with a cytogenetic abnormality known as Philadelphia(Ph) chromosome(BCR-ABL1 fusion gene).this is one of the definitive diagnostic markers for CML (15) Ph chromosome arises from a reciprocal translocation t(9;22) between chromosome 9 and 22 (2,3). The Philadelphia chromosome is found in approximately 95% of patients with CML (16). However, few CML patients do not have Ph chromosome or might have normal karyotype, but even in one third of these patients, there is occult BCR-ABL fusion gene (Ph chromosome negative and BCR-ABL positive) (17). Molecular analysis confirms presence of BCR-ABL in these patients (18).

CML affects the bone marrow and peripheral blood and is classified into three phases, the blast crisis, accelerated, or the most common, chronic phase (90%-95%) from patients present in CML-CP. (19).

About 50% of patients diagnosed with CML are asymptomatic and are often diagnosed accidently in a routine physical examination or blood tests, typical symptoms of CML if present may include fatigue, night sweats, malaise, splenomegaly, hepatomegaly, weight loss, low fever, weakness, and left upper quadrant discomfort. (20,21), less frequently symptoms, leukemic retinopathy, secondary to choroidal and retinal vascular disturbances, can lead to neovascularization. Retinal detachment, retinal hemorrhage, and direct leukemic infiltration of the retina, few cases have reported bilateral blurry vision as the primary presenting symptoms of CML in a young adults. (22, 23).

The diagnosis of CML is simple and consists of documenting, in the setting of persistent unexplained leukocytosis (or occasionally thrombocytosis), the presence of Philadelphia (Ph) chromosome abnormality, the t(9;22)(q34;q11), by routine cytogenetics, or the Ph-related molecular BCR-ABL1 abnormalities by fluorescence in situ hybridization (FISH) or by molecular studies like Reverse transcriptase- polymerase chain reaction(RT-PCR).(24-26). Bone marrow aspiration is mandatory for all patients in whom CML is suspected, as it will complete and make the diagnosis sure (eg, cytogenetic analysis), and provide information needed for staging in terms of the blast and basophil percentages. Baseline cytogenetic analysis allows the detection clonal evolution (27).

Until 2000, drug therapy for CML was limited to nonspecific agents such as busulfan, hydroxyurea, and interferon-alfa (IFN-a). (28). IFN-a led to disease regression and improved survival but was hindered by its modest efficacy and associated significant toxicities. Allogeneic stem cell transplantation (allo-SCT) is curative, but carries risks of morbidity and mortality. More than this, allo-SCT is an option only for patients with good performance status and organ functions, and who have an appropriate donor. The CML therapeutic landscape changed dramatically with the production of the small molecule tyrosine kinase inhibitors (TKIs) such (imatinib, dasatinib, nilotinib and ponatinib) that potently interfered with the interaction between the BCR-ABL1 oncoprotein and adenosine triphosphate (ATP), preventing cellular proliferation of the malignant clone. This "targeted" approach altered the natural history of CML improving the 10-year survival rate from approximately 20% to 80%-90%.(29,30,31).

Taurine is a sulfuric amino acid with the chemical formula $NH_2CH_2CH_2SO_3H$ that is common in mammalian tissues. This semi-essential amino acid is obtained in the body from food consumption as well as the reaction of methionine with cysteine in the liver [32]. Evidence suggests that taurine may be a conditionally necessary amino acid in disorders like diabetes, obesity, metabolic syndrome, and atherosclerosis, which are all linked to increased oxidative stress and inflammation [32].

Taurine administration reduced oxidative stress in the brain, increase and improve hormonesecretion, and prevent diabetic neuropathy, retinopathy, and nephropathy. Taurine has been shown to be useful in the treatment of diabetic hepatotoxicity, vascular issues, and heart injury. Taurine has been found to be helpful in the treatment of oxidative stress [33].

Taurine has been used as an antipyretic and anti-inflammatory mediator, to treat liver and gall bladder diseases [34] and modulate inflammation [35].

Tau, as an effective antioxidant may hinder the increase of reactive oxygen species (ROS) in tumors, causing a delay in the development of cancer [36].Also, Tau can play a role in the process of anti-tumors by down-regulating matrixmetalloproteinase-2 (MMP-2), up-regulating N-acetylgalactosaminyltransferase, and temporarily inhibiting potential invasion and metastasis made by ionizing radiation [37].

Many Previous studies have shown that changes in systemic taurine levels can be used to predict the formation and malignant transformation of individual tumors [38].

Tau can be used as an early biomarker as in breast cancer, the evaluation of serum Tau level in highly susceptible patients for breast cancer is helpful in early detection of malignant changes in the breast [39].Also, in uterus cancer, its level in women with abnormal uterine bleeding might detect any malignancy change of the endometrial wall [36].

Taurine levels in patients leukemic cells were reported to be abnormally low in patients with AML, CML and CLL [40, 41]

2. Material and methods

2.1. Patients

The study include One hundred and thirty eight patients (male and female) were chosen from National Cancer Institute after their approval. Beside Thirty healthy volunteers enrolled as frank control group. The study protocol was approved by Institutional Review Board, National Cancer Institute, Cairo University.

The patients will be divided into four groups beside frank control group.

- Group (1): frank control group (n = 30)
- Group (2): Chronic phase of CML patients group (n=88).
- Group (3): Accelerated phase of CML patients group (n=24).
- Group (4): Blast phase of CML patients group (n=6).
- Group (5) : After treatment (healing patient from CML) group (n=10)

2.2. Sample collections and tests

A portion of the blood was collected on EDTA for the determination of complete blood picture and to determine BCR-ABL by PCR. The other portion left to clot for 2 hours, at 4 °C without shaking, then centrifuged at 3000 r.p.m. for 20 min. The blood which collected was separated and divided into two parts. The 1st part was used to measure blood urea, serum creatinine, AST, ALT, Alkaline phosphatase, Bilirubin total . The 2nd part was stored in a deep freezer at -20°C till used for the assay of taurine. Serum taurine was measured using High Performance Liquid Chromatography (HPLC) according to pre-column extraction and derivatization methodology.

2.3. Statistical analysis

Data was analyzed using IBM SSPS statistics version 22. Data was tested for normality using Kolmogrov-Smirnov test and Shapiro-Wilk test. Quantitative data was presented as mean and standard deviation or median and range while qualitative data was presented as number and percentage. Analysis of variance test was used to compare normally distributed numerical variables between different groups while Man Whiney test was used to compare not normally distributed numerical variables between two groups or more than two groups respectively. Chi Square or Fisher exact as appropriate was used to compare categorical variables between groups. Spearman correlation coefficient was used to compare taurine level with different numeric variables. P value set significant at 0.05 levels. All tests were two tailed.

3. Results

This study include 168 participant (138 cases and 30 control). According to age, there were statistically significant difference between AP, BP, CP groups and control while there were not a difference between control group and after treatment group. We did not find a significant difference between gender in different groups (p=0.942). By comparing family history between groups we found that 62.5% of AP group had positive family history, 50% of BP group had positive family history, 44.3% of CP group had positive family, 33.3% of controls had positive family history while no patients in after treatment group had positive family history (Table 1)

Table 1 Relation between different groups of patients and their characteristics

Variables		CP	AP		BP		After treatment		Control		Test *	P value
		N=88 %	N=24	%	N=6	%	N=10	%	N=30	%		
Age		41.42±13.62	43.92±14.52		48.17±17.50		38.70±12.22		27.83±9.91		29.053**	<0.001
Gender	Male	49 55.7	15	62.5	3	50.0	5	50.0	16	53.3	0.891	0.942
	Female	39 44.3	9	37.5	3	50.0	5	50.0	14	46.7		
Family history	Negative	38 43.2	9	37.5	3	50.0	10	100.0	20	66.7	17.566	0.001
	Positive	50 56.8	15	62.5	3	50.0	0	0.0	10	33.3		

(*) Analysis of variance test, (**) Chi square test, p value set significant at ≤0.05

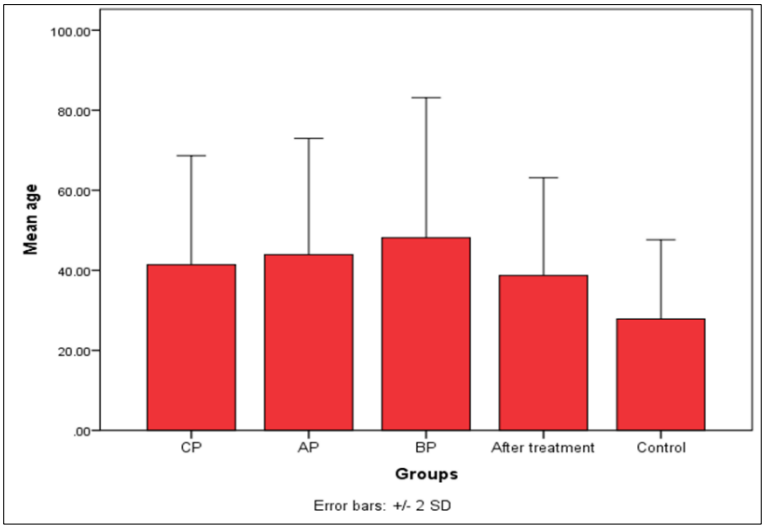

Figure 1 Mean age in different study groups

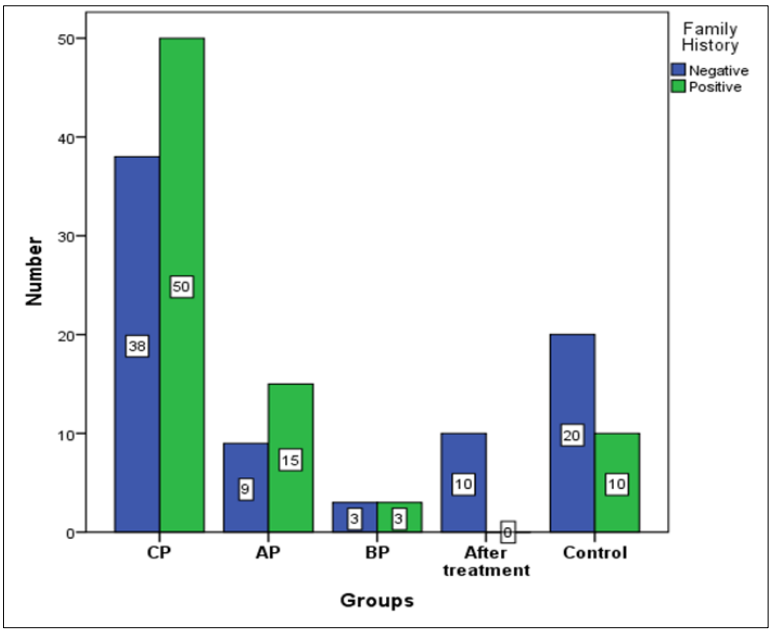

Figure 2 Family history in different study groups

Table 2 Relation between Blood picture parameters and study groups

Variables	**CP**	**AP**	**BP**	**After treatment**	**Control**	Test *	P value
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)		
HB	10.85 (4.70-16.20)	9.06 (4.80-13.30)	8.9 (8.60-13.80)	12.30 (9.20-14.60)	13.45 (11.80-14.80)	49.95	<0.001
WBCS	47.05 (2.58-605.77)	221.24 (5.30-505.0)	14.50 (1.88-249.82)	5.94 (3.60-10.30)	6.53 (4.40-9.40)	49.62	<0.001
RBCS	3.92 (1.96-6.27)	3.45 (1.90-4.69)	3.01 (2.42-3.72)	4.40 (2.92-6.27)	5.06 (4.10-6.27)	53.03	<0.001
PLT	287.00 (49.00-927.00)	150.00 (18.00-866.0)	112.50 (45.00-604.0)	262.50 (172.00-460.0)	279.00 (153.00-382.0)	7.55	0.110
Neutrophils	54.00 % (3.60%-290.0%)	44.70% (22.00%-300.0%)	301.50% (11.00%-539.0%)	56.50 % (37.40%-67.0%)	50.00% (40.00%-66.10%)	6.05	0.196

(*) Kruskal wallis test, p value set significant at ≤0.05

Table 2 shows that median hemoglobin level were statistically significant differ between groups. By doing pairwise comparison we found that median HB level in AP group is differ from this in CP, after treatment and control group (p=0.027, 0.028, <0.001 respectively). In addition, this in control group is statistically differ from this in BP and CP groups (p=0.002 and <0.001 respectively). That median WBCS level were statistically significant differ between groups. By doing pairwise comparison we found that median WBCS level in after treatment group were differ from CP,AP groups (p=0.012,<0.001 respectively).also control group differ from CP and AP groups (p=<0.001,<0.001 respectively). Platelets and neutrophils were not statistically differ between groups.

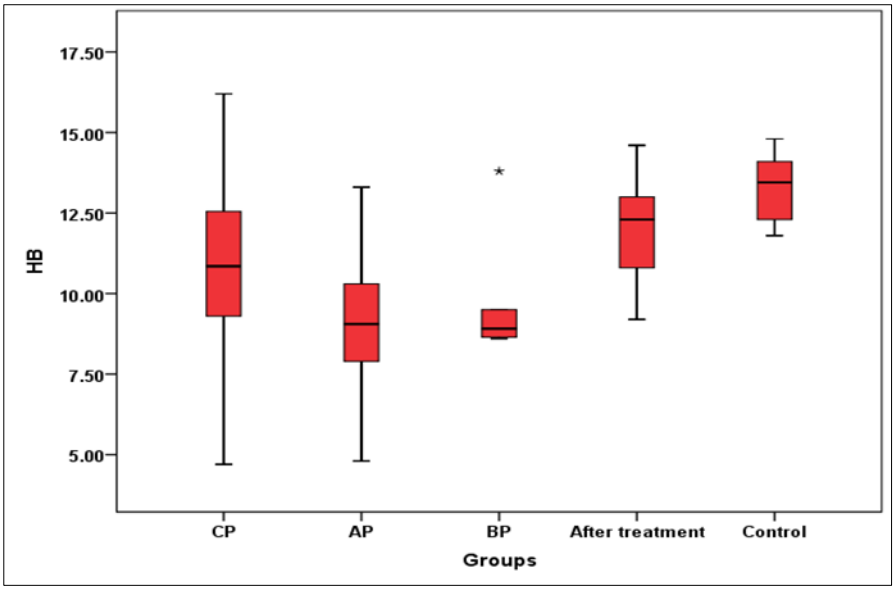

Figure 3 Median HB level between groups

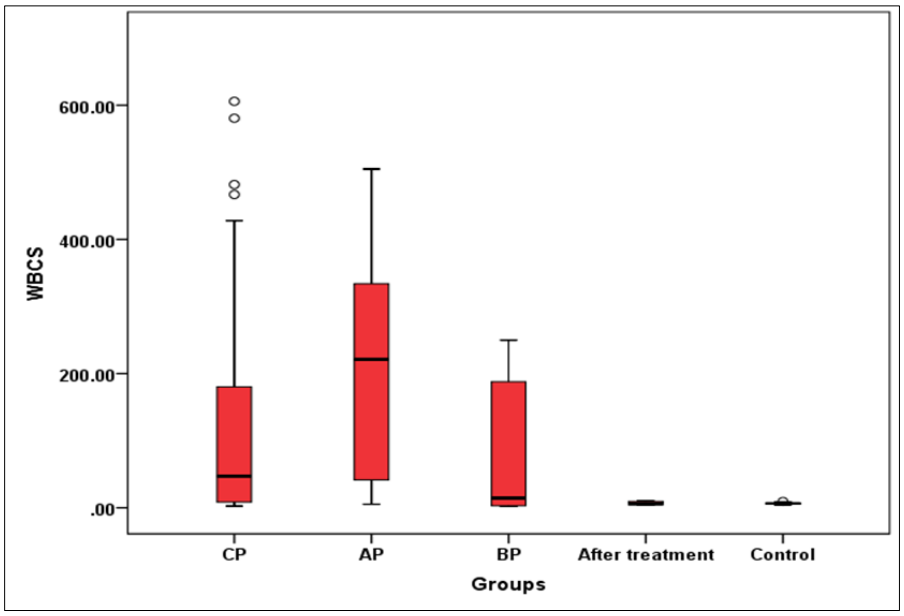

Figure 4 Median WBCS level between groups

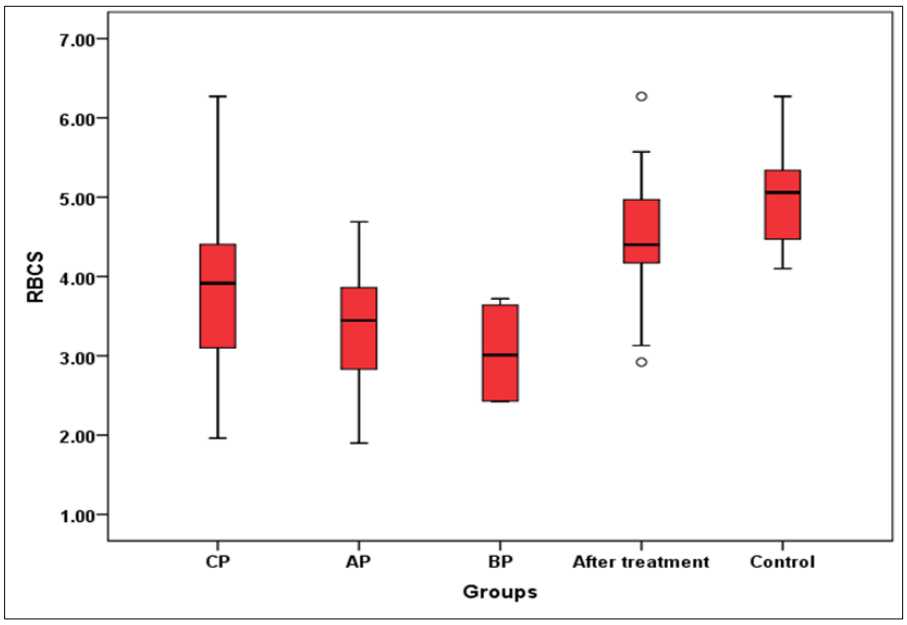

Figure 5 Median RBCS level between groups

Table 3 shows that median ALT level were statistically significant differ between groups. By doing pairwise comparison we found that median ALT level in control group is differ from CP and AP (P= 0.17, 0.21 respectively).also, median AST level were statistically significant differ between groups. By doing pairwise comparison we found that median AST level in control group is differ from CP and AP and after treatment groups (P=< 0.001, <0.001 and 0.034 respectively).Bilirubin and urea were not statistically differ between groups. Creatinine were statistically significant differ between groups. By doing pairwise comparison we found that median Creatinine level in control group is differ from AP, BP and CP group (P=< 0.001, 0.034, <0.001 respectively). Alkaline phosphatase were statistically significant differ between groups. By doing pairwise comparison we found that median alkaline phosphatase level in control group is differ from AP and CP (p=0.008, <0.001).

Table 3 Relation between liver and kidney function test and study groups

	CP	AP	BP	After treatment	Control	Test *	P value
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median	Median		
ALT	17.00 (7.0-177.0)	19.00 (7.0-36.0)	15.50 (8.0-50.0)	20.00 (10.0-29.0)	12.00 (7.0-33.0)	13.88	0.008
AST	20.50 (10.0-68.0)	25.50 (12.0-41.0)	27.00 (12.0-33.0)	23.50 (12.0-28.0)	13.75 (9.0-32.0)	28.09	<0.001
Bilirubin	0.60 (0.10-9.60)	0.55 (0.20-1.30)	0.55(0.40-0.80)	0.52 (0.30-0.70)	0.55 (0.20-0.98)	2.065	0.724
Creatinine	0.90(0.50-10.29)	0.90 (0.58-5.40)	0.89 (0.60-1.60)	0.88 (0.56-0.99)	0.54(0.21-1.00)	45.95	<0.001
Urea	27.50 (6.80-138.0)	26.00(15.0-138.0)	32.00 (27.0-41.0)	22.00 (10.0-45.0)	28.50 (11.40-44.0)	5.72	0.221
Alkaline phosphatase	84.50 (28.0-490.0)	89.00 (32.0-208.0)	83.50 (53.0-798.0)	72.50 (58.0-104.0)	58.00 (29.0-88.0)	23.99	<0.001

(*) Kruskal Wallis test, p value set significant at ≤0.05

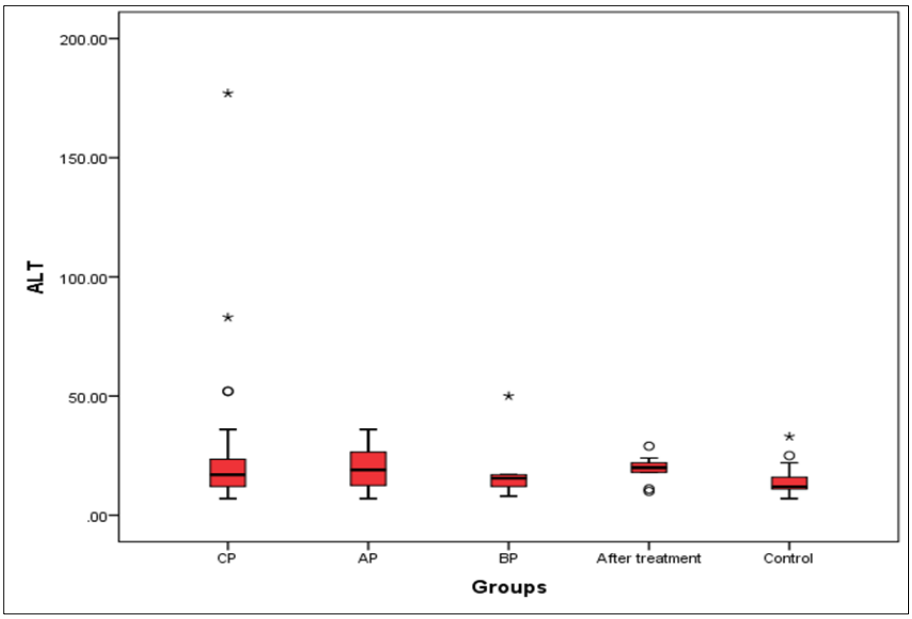

Figure 6 Median ALT level between groups

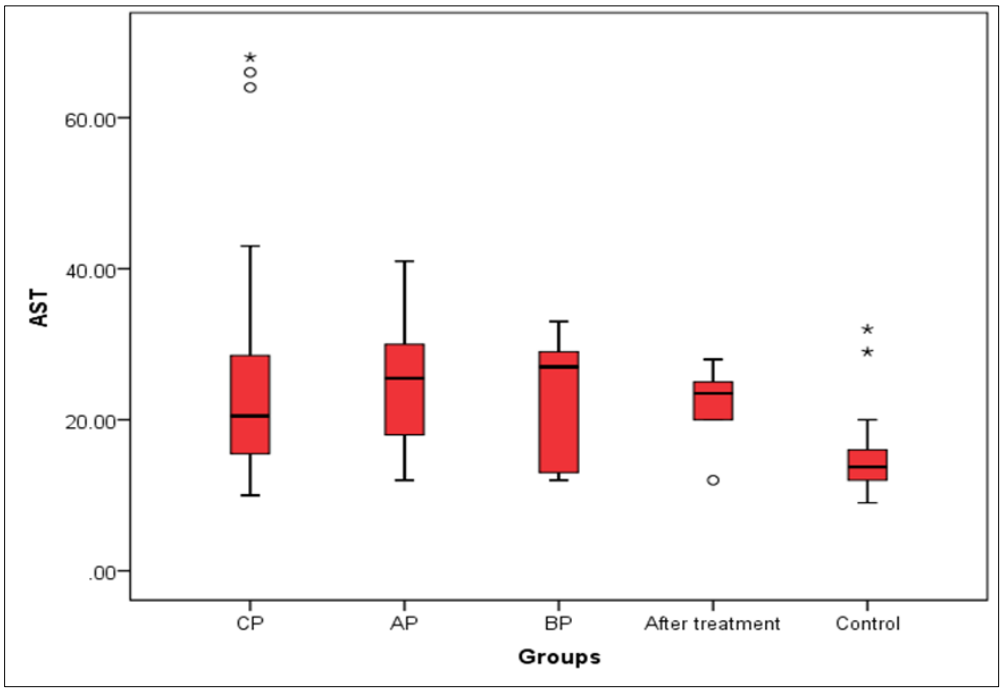

Figure 7 Median AST level between groups

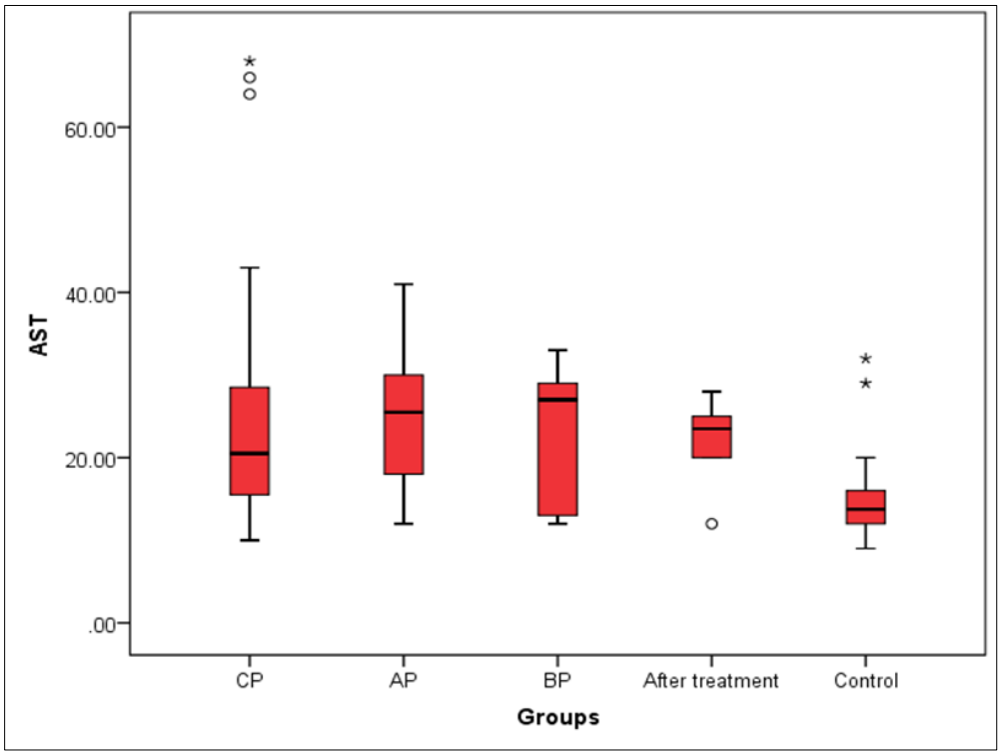

Figure 8 Median creatinine level between groups

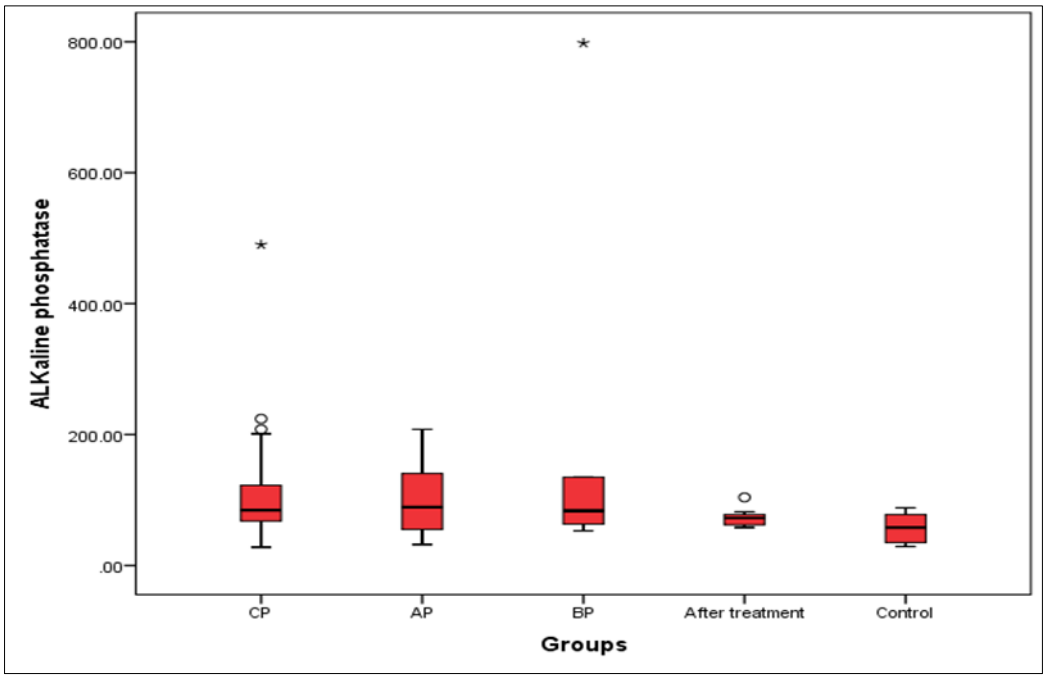

Figure 9 Median alkaline phosphatase level between groups

Table 4 Relation between Blast cells, BCR ABL and taurine level between study groups

Variables	CP	AP	BP	After treatment	Control	Test*	P value
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)		
Blast cells	2.00 (0.0-10.00)	14.00 (10.0-19.0)	37.50 (20.0-55.0)	ND	NA	95.748	<0.001
BCR ABL	0.00 (0.0-0.10)	6.35 (0.17-52.0)	159.00 (80.0-440.0)	ND	NA	68.665	<0.001
Taurine	35.20 (20.30-39.90)	17.20 (3.15-20.10)	0.58 (0.12-1.39)	51.30 (40.50-57.0)	78.20 (70.0-86.0)	128.28	<0.001

(*) Kruskal Wallis test, p value set significant at ≤0.05, (NA): Not applicable, (ND): Not Detected

Table 4 shows that median Blast cells level were statistically significant differ between groups. By doing pairwise comparison we found that median Blast cells level in CP group is differ from AP and BP (P= <0.001, <0.001 respectively). Median BCR ABL level were statistically significant differ between groups. By doing pairwise comparison we found that median BCR ABL level in CP group is differ from AP and BP (P= <0.001, <0.001 respectively). Median Taurine level were statistically significant differ between groups. By doing pairwise comparison we found that median Taurine level in BP group is differ from CP and in treatment (P= <0.001, <0.001 respectively) and in AP group is differ from CP, after treatment and control (P= <0.001, <0.001 respectively).

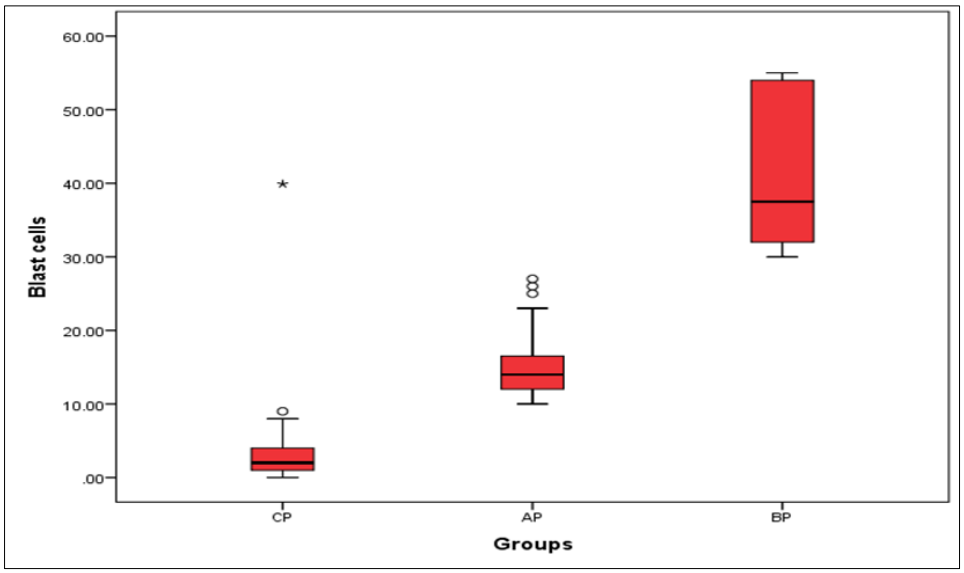

Figure 10 Median Blast cells level between groups

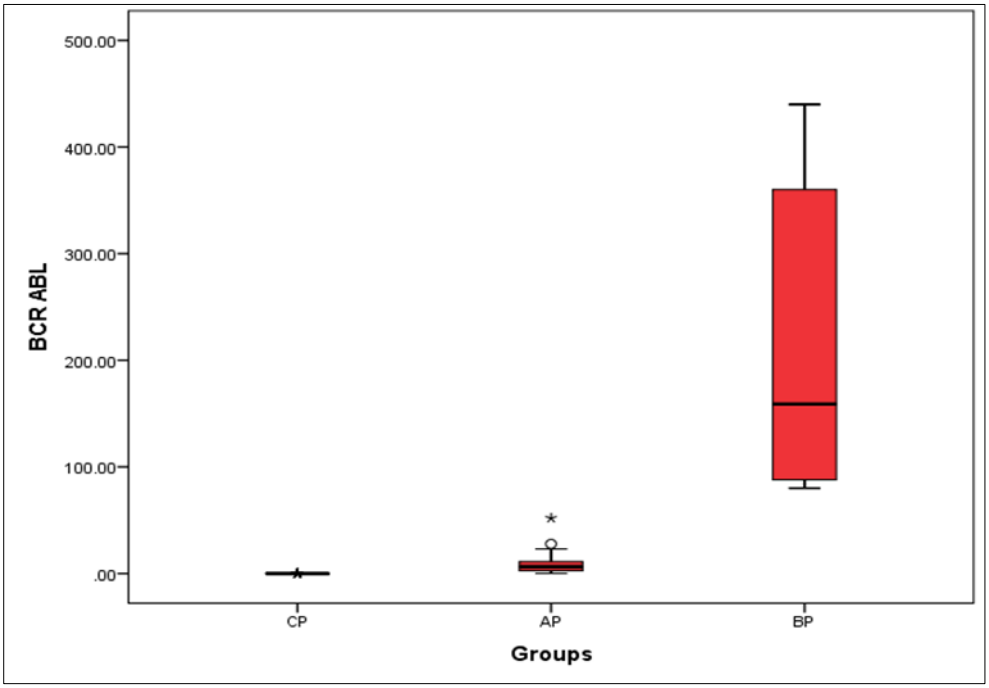

Figure 11 Median BCR ABL level between groups

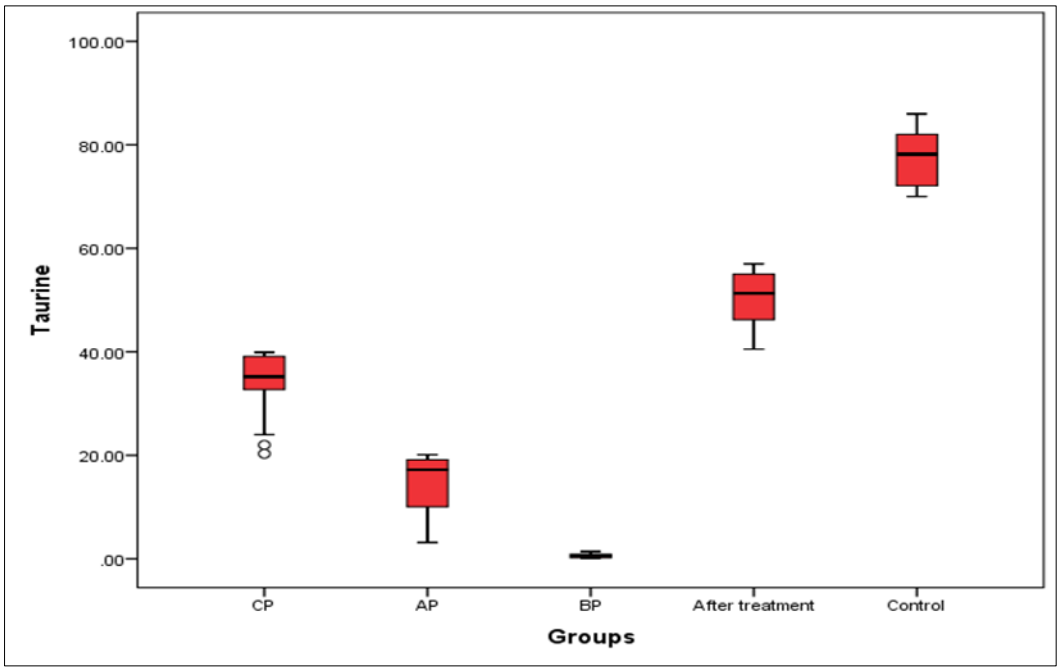

Figure 12 Median Taurine level between groups

Table 5 Correlation between taurine and different numeric variables

Variables	r*	P
Age	-0.371	<0.001
WBCs	-0.471	<0.001
RBCs	0.534	<0.001
HB	0.523	<0.001
PLT	0.103	0.199
Neutrophils	0.015	0.855
ALT	-0.203	0.010
AST	-0.375	<0.001
Bilirubin	-0.085	0.288
Creatinine	-0.407	<0.001
Urea	-0.047	0.557
Alkaline phosphatase	-0.248	0.002
Blast cell	-0.944	<0.001
BCR- ABL	-0.971	<0.001

(*) Spearman correlation coefficient, p value set significant at ≤0.05

Table 5 shows correlation between taurine level and different numeric variables, we found that age has fair negative correlation with taurine level meaning that for each year increase in age taurine level will decrease. Also WBCS has good negative correlation with taurine level meaning that for each increase in WBCS taurine level will decrease. In addition, RBCS and HB have good positive correlation with taurine level meaning that for each increase in RBCS or HB taurine level will increase. Platelet, neutrophils, bilirubin and urea show no significant correlation with taurine level. ALT and

AST show week to fair negative correlation with taurine level. Creatinine has good negative correlation with taurine level. Blast cell and BCR ABL show excellent negative correlation with taurine level meaning that when they increase taurine level decrease and vice versa.

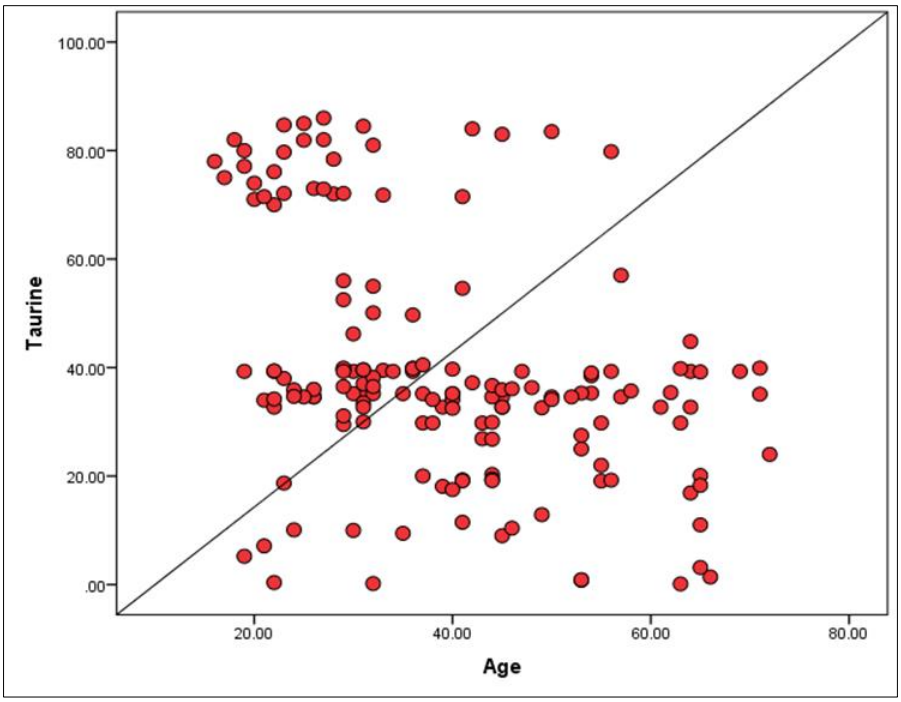

Figure 13 Scatter plot shows correlation between taurine level and age

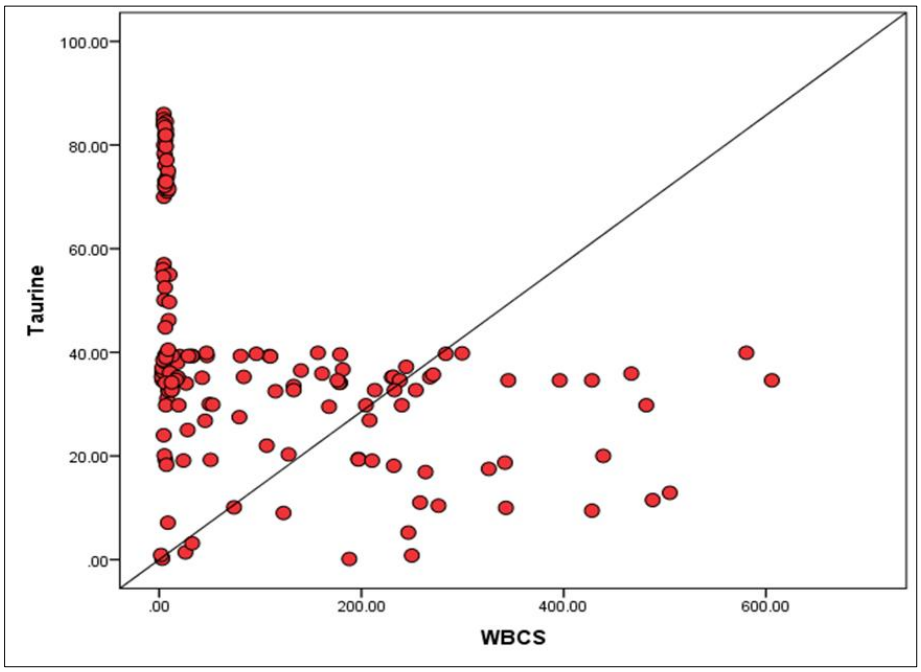

Figure 14 Scatter plot shows correlation between taurine level and WBCS

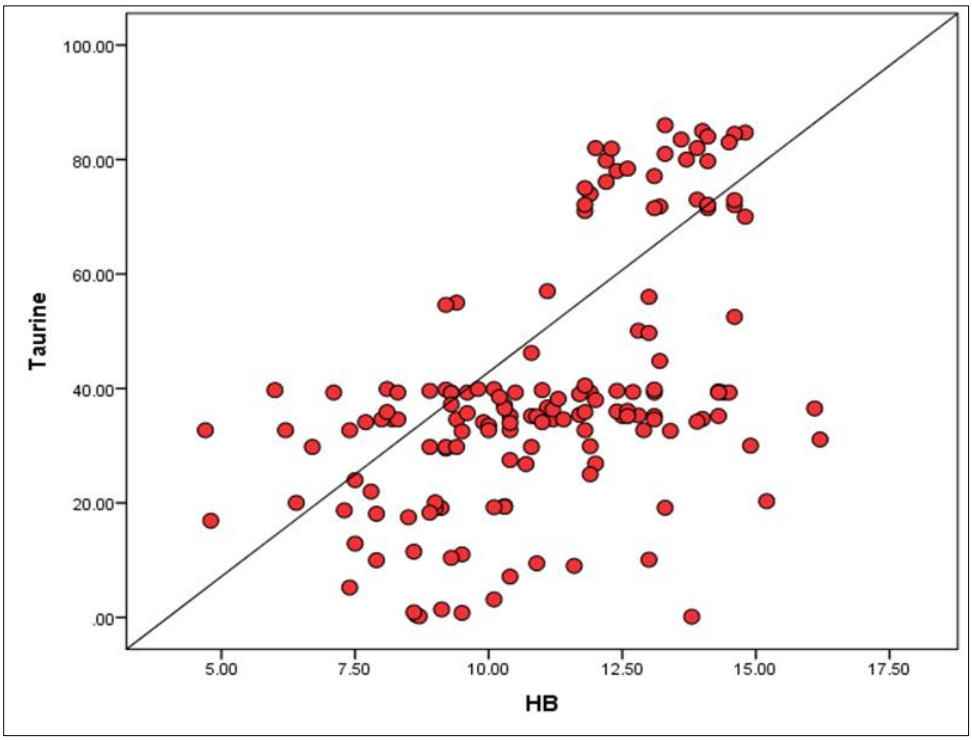

Figure 15 Scatter plot shows correlation between taurine level and HB

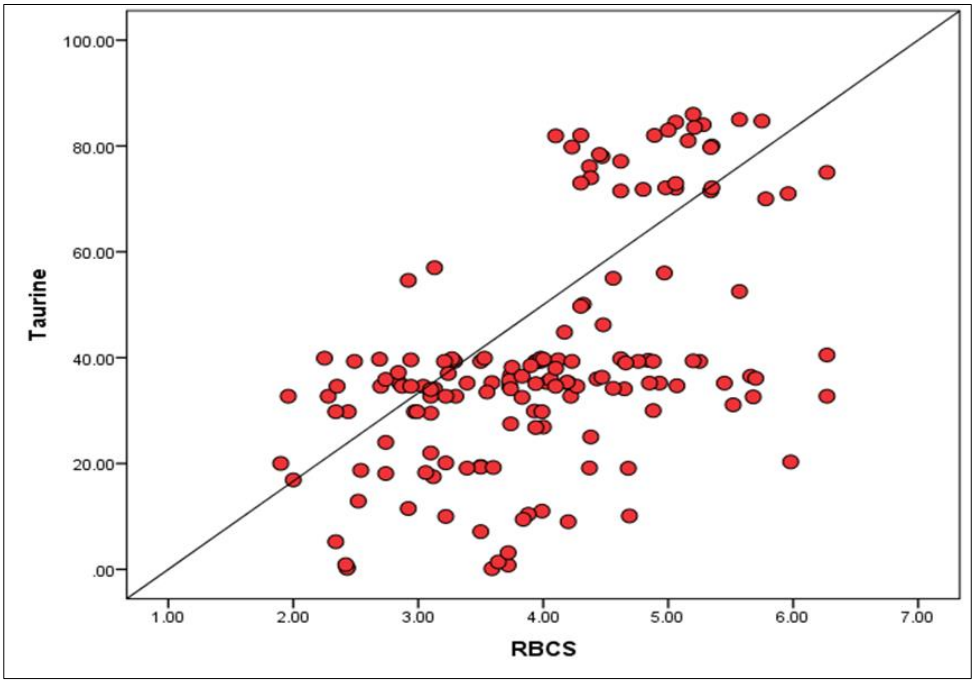

Figure 16 Scatter plot shows correlation between taurine level and RBCS

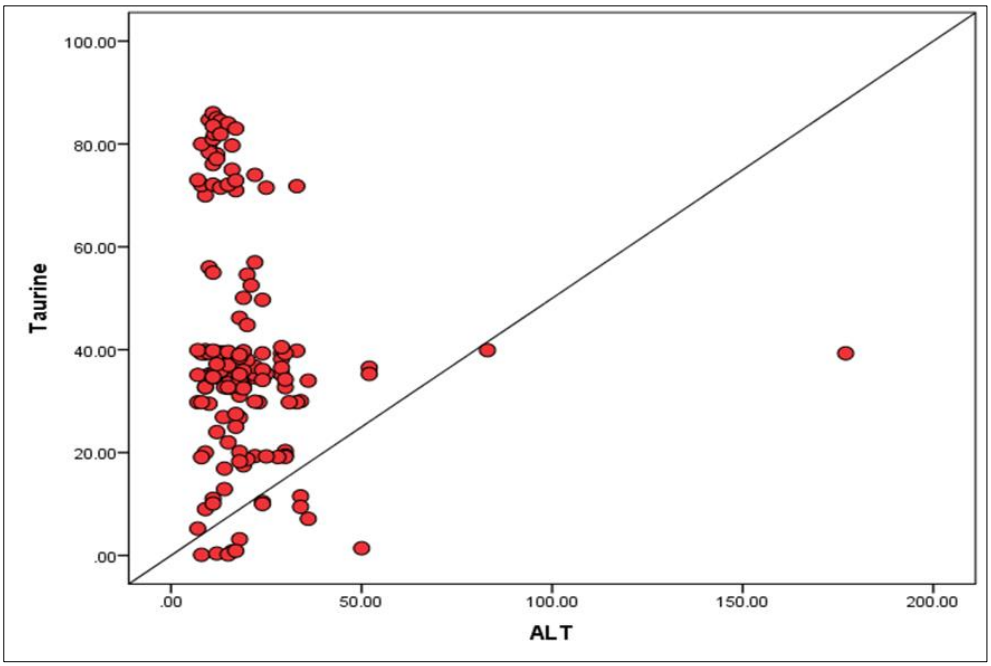

Figure 17 Scatter plot shows correlation between taurine level and ALT

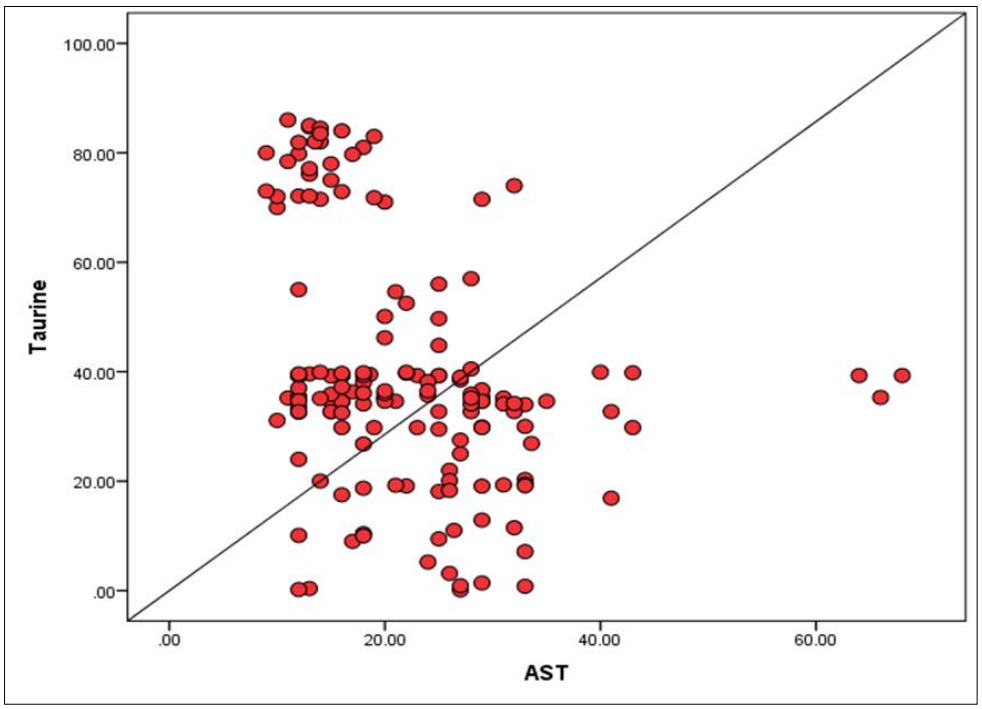

Figure 18 Scatter plot shows correlation between taurine level and AST

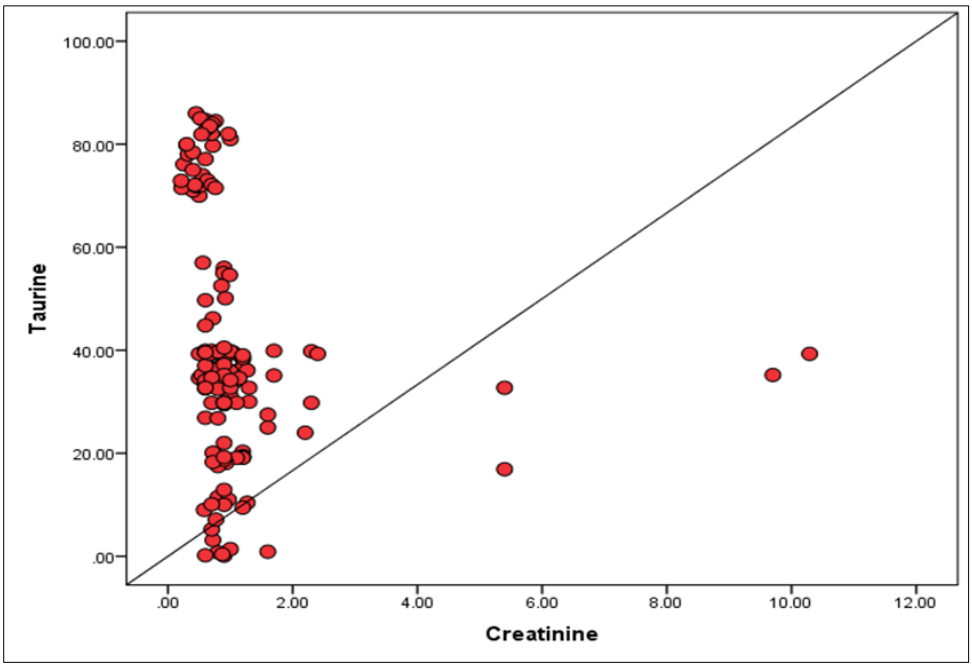

Figure 19 Scatter plot shows correlation between taurine level and Creatinine

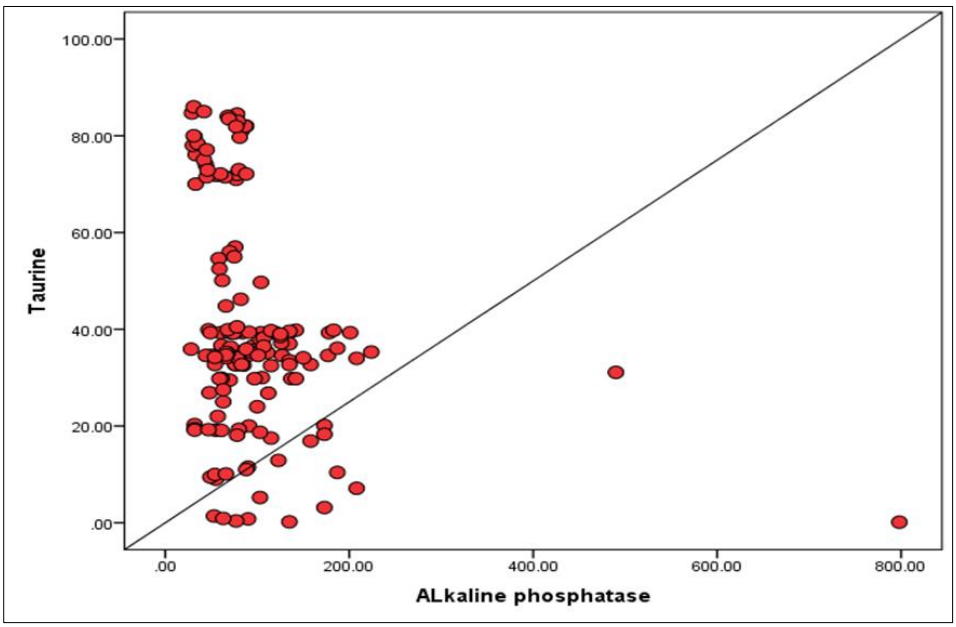

Figure 20 Scatter plot shows correlation between taurine level and alkaline phosphatase

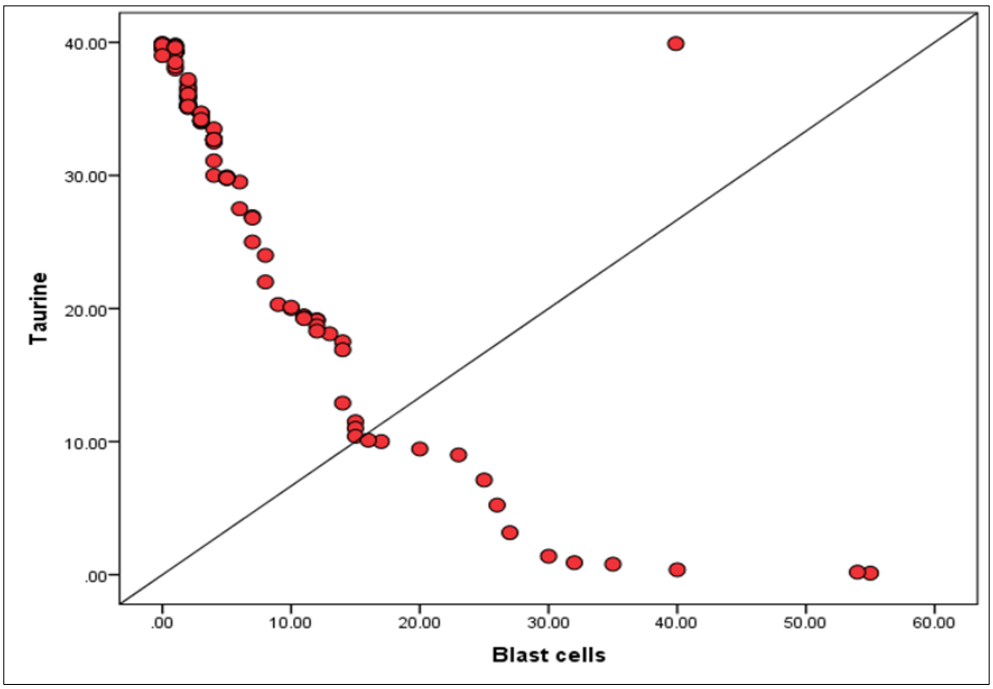

Figure 21 Scatter plot shows correlation between taurine level and Blast cells

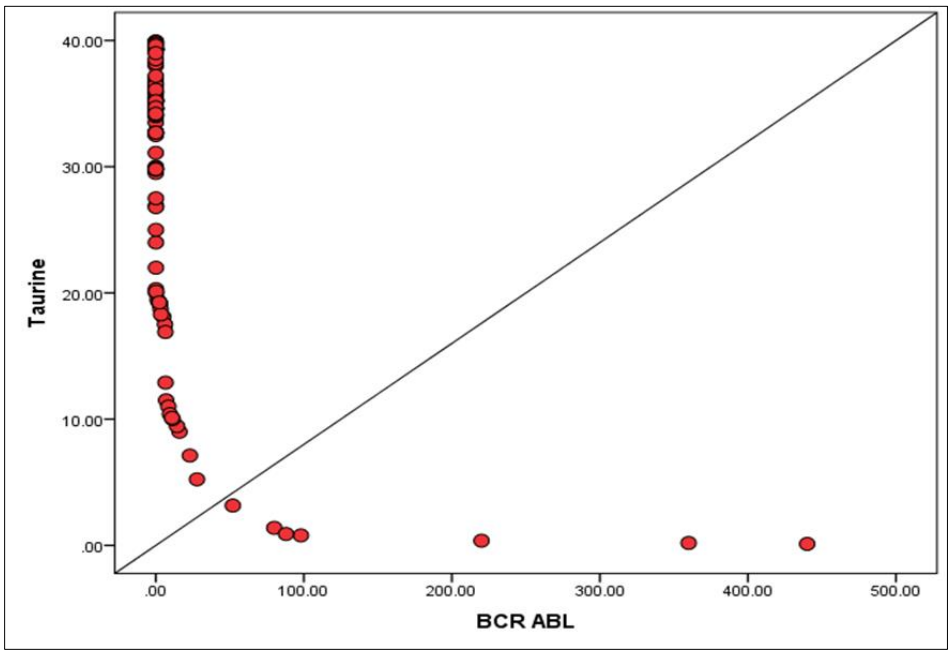

Figure 22 Scatter plot shows correlation between taurine level and BCR ABL

Table 6 Relation between taurine level and gender

	Gender		**Test**	**P value**
	Male	**Female**		
	Median (Min-Max)	**Median (Min-Max)**		
Taurine	35.23 (0.12-86.0)	35.35 (0.20-83.50)	-0.382	0.703

(*) Man Whitney test, p value set significant at ≤0.05

Table 7 Relation between of taurine level and family history in all study groups

	FH		**test**	**P value**
	Negative	**Positive**		
	Median (Min-Max)	**Median (Min-Max)**		
Taurine	38.75 (0.12-86.0)	34.60 (0.20-73.0)	-2.870	0.004

(*) Man Whitney test, p value set significant at ≤0.05

Table 8 Relation of taurine level and family history in controls

	Family history in control		test	P value
	Negative	Positive		
	Median (Min-Max)	Median (Min-Max)		
Taurine	81.45 (74.0-86.0)	71.90 (70.0-73.0)	55.0	<0.001

(*) Man Whitney test, p value set significant at ≤0.05

Table 6 shows that gender has no significant effect on taurine level. Although family history has significantly affect taurine level as participant has positive family history (in all groups or in control only) show lower level of taurine than those who don't have positive family history (table 7 and 8)

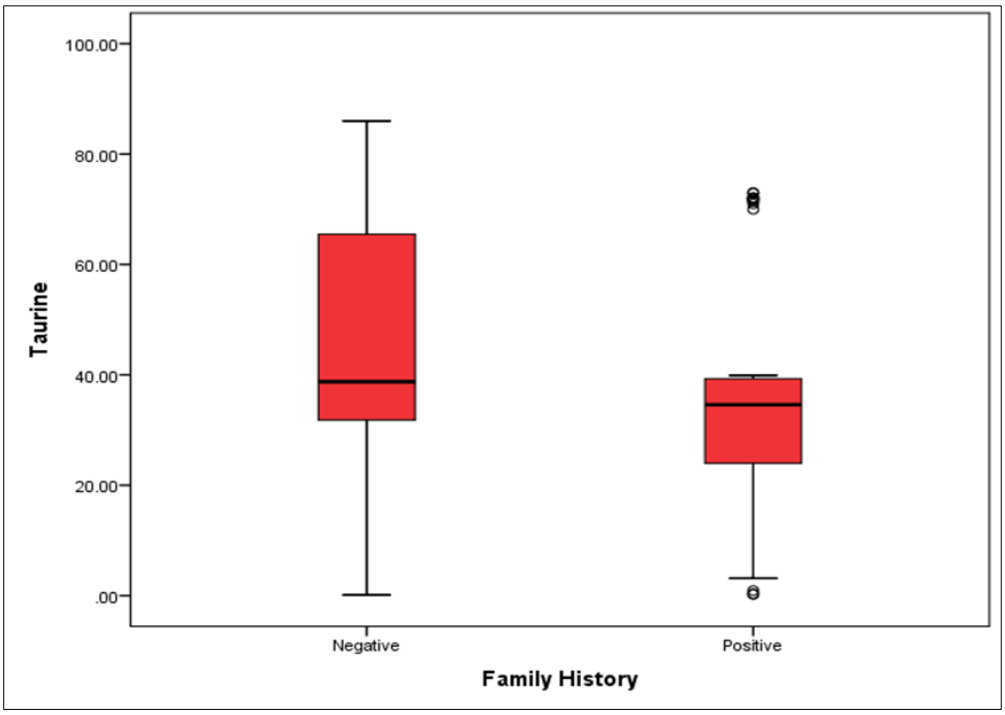

Figure 23 Box plot show relation between family history in all groups and taurine level

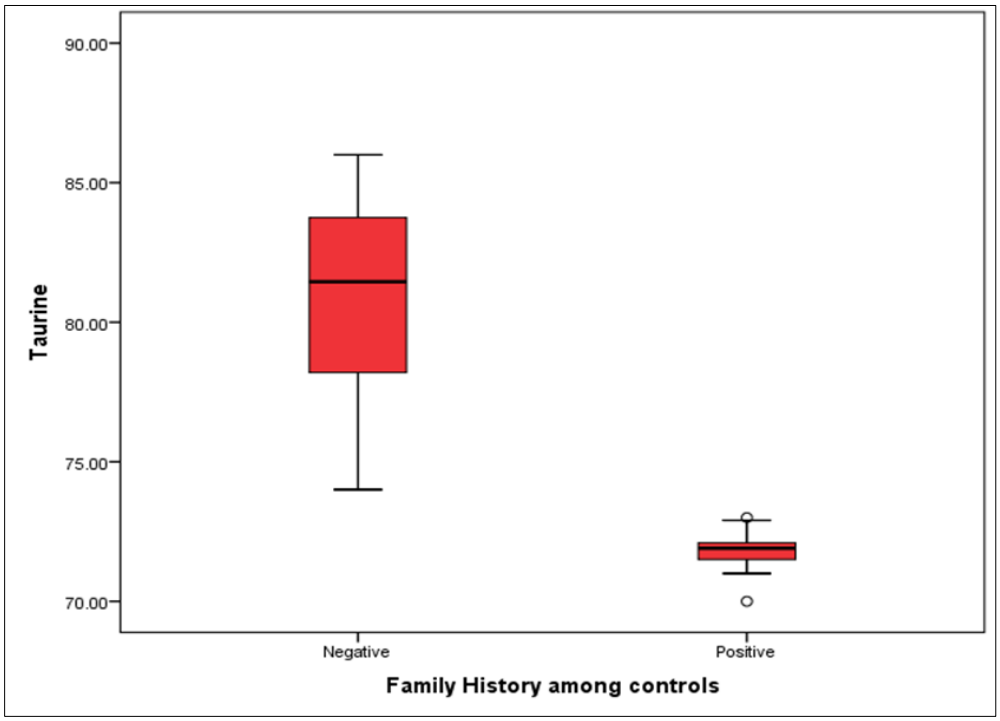

Figure 24 Box plot show relation between family history in controls and taurine level

4. Discussion

According to clinical pathology department in National Cancer Institute, the number of CML patients who attend to National Cancer Institute arise every year that from January 2020 to december2020 there were 102 new cases of CML in NCI, when in 2021 from January to December there were 178 new cases diagnosed while from January to December 2022 there were 247 new cases. [42]

Chronic myeloid leukemia: is a myeloproliferative neoplasm with an incidence of 1-2 cases per 100.000 adults. It accounts for approximately 15% of newly diagnosed cases of leukemia in adults. [43]

Chronic myeloid leukemia affect bone marrow which produce blood cells (19) so its diagnosis depends on complete blood picture to examine the blood cells (RBCS, WBCS, Platelets), bone marrow biopsy to examine the number of blast cells which determine the stage of disease and the final diagnostic biomarker for CML is cytogenetic examinations to examine the presence and amount of Philadelphia chromosome (BCR-ABL gene) which is found specially in CML disease.

Chronic myeloid leukemia divided into 3 clinical phases:

- Chronic phase: 90%-95% diagnosed patients, few blasts (>10%) in peripheral film, slightly elevated eosinophils and basophils, no significant symptoms (19).
- Accelerated phase: impaired neutrophil differentiation, circulating blasts(10%-19%)with increasing peripheral basophils(pruritus), CBC show (thrombocytopenia), cytogenetic evidence of clonal evolution, worsening constitutional symptoms and splenomegaly (extramedullary hematopoiesis).(19)
- Blast crisis: more aggressive course, blasts fall to differentiate, blasts (<20%) in peripheral blood or bone marrow; reflective of acute leukemia (1\3 ALL, 2\3 AML) which is difficult to be treated so that it is very important to find a new type of diagnosis to predict this disease and control complications.(19)

Chronic myeloid leukemia can be classified as a long term disease with several complications which may affect kidneys, liver, spleen, lymphs ,brain and all body organs depending on the chronicity of disease , the time of diagnosis and the type of treatment so that our research aims to find a new type of diagnosis which may help in treatment, follow up and recovery of patients .

The goal of our study is to investigate the correlation between serum taurine level and stages of chronic myeloid leukemia after full clinical examination, biochemical analysis and investigation for all patients. We selected 138 patients with CML from National Cancer Institute after their agreement beside thirty healthy volunteers, find relationship between serum taurine level and number of blast cells which determine the stage of disease in each case and find a relationship betwwen serum tauine level and percentage of BCR-ABL1 gene in body which is the diagnostic marker for CML. In our research we found that 90% of healing patients from CML disease were treated with imatinib drug and had no family history for CML, they took care for their life style which help them to control this disease.

From the result of our research we found that:

- Median Blast cells level were statistically significant differ between groups. By doing pairwise comparison we found that median Blast cells level in CP group is differ from AP and BP (P= <0.001, <0.001 respectively). Median BCR ABL level were statistically significant differ between groups. By doing pairwise comparison we found that median BCR ABL level in CP group is differ from AP and BP (P= <0.001, <0.001 respectively). Median Taurine level were statistically significant differ between groups. By doing pairwise comparison we found that median Taurine level in BP group is differ from CP and in treatment (P= <0.001, <0.001 respectively) and in AP group is differ from CP, after treatment and control (P= <0.001, <0.001 respectively).
- There is correlation between taurine level and different numeric variables, we found that age has fair negative correlation with taurine level meaning that for each year increase in age taurine level will decrease. Also WBCS has good negative correlation with taurine level meaning that for each increase in WBCS taurine level will decrease. In addition, RBCS and HB have good positive correlation with taurine level meaning that for each increase in RBCS or HB taurine level will increase. Platelet, neutrophils, bilirubin and urea show no significant correlation with taurine level. ALT and AST show week to fair negative correlation with taurine level. Creatinine has good negative correlation with taurine level. Blast cell count and BCR ABL1 percentage in body show excellent negative correlation with taurine level meaning that when they increase taurine level decrease and vice versa.

- The most important point we found, that gender has no significant effect on taurine level. Although family history has significantly affect taurine level as participant has positive family history (in all groups or in control only) show lower level of taurine than those who don't have positive family history and the most impressive observation in our work is the result of taurine which showed significant decrease in its serum level in after treatment patients when compared to frank group and with the other stages of CML disease, taurine level decrease parallel to the severity and chronicity of disease which is very high significance between each other .

We suggest a new classification for stages of CML disease according to serum taurine level. the taurine level may represent another real evaluation of the possibility of patients deterioration as shown in this study. It has been shown that the taurine level can detect any change from normal case which may anticipate any future change and control it so that Taurine may be useful as a biochemical marker in diagnosis as well as for prediction of relapse and effectiveness of chemotheraby, radiotheraby and drug theraby on patients with chronic myeloid leukemia.

We suggest that all CML patients must measure taurine regularly at least every three months to guard against most common complications and control chronicity of CML as it is a simple test done on blood serum sample. We finally suggest regular measure for all persons have positive family history of chronic myeloid leukemia to guard against most common complications of CML and to predict any future possibility of disease and take special dose of taurine to protect and raise the immunity of their body.

Abbreviations

- Tau: Taurine;
- CML: Chronic myeloid leukemia;
- ALP: Alkaline phosphatase;
- AST: Aspertat transmenase;
- ALT: Alanin transmenase;
- RT-PCR: Reverse Transcriptase –Polymerase Chain Reaction;
- FISH :Flourescence In Situ Hybridization ;
- CP :Chronic phase of CML ;
- AP :Accelerated phase of CML ;
- BP: Blast phase of CML.

5. Conclusion

Serum taurine level is statistically significant differ between groups, that decrease with the increase of the chronicity of disease and the number of blast cells, increase in normal frank control volunteers and after treatment patients which make it possible to be used as a pre biomarker for early diagnosis and follow up as well as for prediction of relapse of chronic myeloid leukemia disease.

Compliance with ethical standards

Acknowledgments

The authors thank all patients in the Study for their generous participation and expresses his sincere gratitude to the collaborators and the staff in National Cancer Institute, Egypt for their support.

Disclosure of conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Statement of ethical approval

Ethical approval was obtained from Institutional Review Board with IRB Approval number- 2303-405-0014.

Statement of informed consent

This manuscript is being submitted after consent was obtained from all authors, and all authors are aware of this manuscript submission.

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