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Original article

Clinical Significance of Fibroblast Growth Factor 2 in Chronic Myeloid Leukaemia Patients

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ABSTRACT

Background: Fibroblast Growth Factor 2 (FGF2) is involved in different stages of haematopoiesis, inducing stem cell proliferation and differentiation, suggesting that its dysregulation can result in haematological malignancies. Its level was significantly increased in CML patients. The aim was to evaluate the clinical significance of FGF2 in CML patients.

Methods: 20 newly diagnosed CML patients and 20 apparently healthy sex and age matched subjects considered as a control group were included. Conventional karyotyping for detection of Philadelphia chromosome, Quantitative real time PCR for detection of BCR – ABL fusion gene at time of diagnosis and after 3 months of treatment and measurement of serum FGF2 by ELISA were performed.

Results: There was a statistically significant increase in the serum FGF2 level among the CML patient group compared to the control group. 25% of CML patients were treated with Imatinib alone, and 75% were treated with both hydra and Imatinib. About 15% of patients did not respond to treatment. There was no difference between CML patients treated with hydra and Imatinib and those treated with Imatinib only concerning FGF2 levels. However, there was a statistically significant increase in the median FGF2 level among resistant patients compared to non-resistant ones.

FGF2 at a cut-off >83.8 ng/mL exhibited a sensitivity of 66.7%, specificity of 94.1%, and accuracy of 90% in predicting the response to treatment among the patient group. An FGF2 level less than 83.8 ng/mL significantly increased the chance of an optimal response of CML patients to treatment by 32 folds

Conclusions: Our data suggest an important biological role of FGF2 in pathogenesis and prognosis of CML.

Keywords: Chronic myeloid leukemia; Fibroblast growth factor 2; Prognosis

INTRODUCTION

Chronic myeloid leukemia (CML) is a chronic myeloproliferative disorder characterized by excessive expansion of myeloid series, with accumulation of immature granulocytic precursors and terminally differentiated cells leading to the characteristic clinical features at diagnosis of marked granulocytosis of the peripheral blood, together with basophilia, eosinophilia, thrombocytosis, anemia and splenomegaly. The defining molecular pathogenetic event, which is well established in CML patients, is a reciprocal chromosomal translocation t(9:22) that results in the formation of an oncogenic fusion gene BCR-ABL. The fusion of BCR with ABL results in constitutive activation of the ABL kinase,

which is responsible for the transforming properties of BCR-ABL. subsequently, this kinase activity induces the activation of many anti-apoptotic and proliferation signaling cascades that promotes leukemogenesis [1].

Fibroblast growth factor 2 (FGF-2) belongs to the FGF family. Twenty-two members of the FGF family have been identified in humans, that are structurally related molecules. The main function of FGF2 is to promote endothelial cell proliferation and its organization into tube-like structures. They induce growth of new blood vessels and angiogenesis from the pre-existing vasculature. FGF2 is more potent than platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) as an angiogenic factors [2].

A clinical challenge for therapy of CML is the development of resistance to kinase inhibitors drugs. Mutations of kinase domain are a common mechanism of resistance to treatment in CML patients, yet, in the absence of mutations, the mechanism of resistance remains unclear [3].

FGF2 was capable of promoting growth of cells in bone marrow microenvironment in both short - and long-term assays through the FGF receptors via activation of RAS/mitogen-activated protein kinase pathway. Previous study was reported that there was an association between elevated plasma FGF2 and Imatinib resistant CML patients [4].

The aim of our work is to evaluate the clinical significance of FGF2 in CML patients.

METHODS

Our study was performed in Clinical Pathology, and Hematology unit of Internal Medicine departments. Faculty of Medicine, Zagazig University Hospitals, during the period from October 2021 to March 2022. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Our study groups were not exposed to any risk or harm and the data of the patient were confidential. The investigated groups were informed about the purpose and nature of the study and an informed written consent, for the required investigations, was taken from all the patients. Moreover, an approval from the institutional review board (IRB) in Faculty of Medicine, Zagazig University was obtained.

In this study, we included 20 newly diagnosed CML patients. They were 15 females and 5 males. Their ages ranged from 23 to 72 years. Also, we investigated 20 apparently healthy, sex and age matched subjects that considered as control group. They were 17 females and 3 males, their ages ranged from 20 to 75 years.

Peripheral blood (PB) and bone marrow (BM) samples were collected from all patients at diagnosis before initiation of therapy. Venous blood samples were aseptically taken from each patient. One ml of the blood was delivered into a sterile vacutainer containing EDTA for CBC examination. 0.5 ml of the sample was delivered into a sterile vacutainer containing EDTA for molecular detection of BCR – ABL fusion gene by quantitative real-time PCR and, 1.5 ml was delivered into a plan vacutainer tube for detection of serum FGF2 level by ELISA technique. 1.5 ml of the BM were aspired from each patient and delivered in lithium heparin vacutainer for cytogenetic analysis. Only peripheral blood samples were obtained from healthy control.

Participants included in our study were subjected to the following: complete history taking, clinical examination, radiological examination includes abdominal ultrasonography, complete blood count was identified by cell counter (Sysmex XN1000, Japan), bone marrow aspiration and examination, conventional karyotyping, using G banding technique, for detection of Philadelphia chromosome was done and, quantitative real time polymerase Chain Reaction (PCR) for detection of BCR – ABL fusion gene was performed on gene expert genetic analyser (Novartis, USA) at time of diagnosis and after 3 months of treatment to evaluate response to treatment. Also, measurement of serum FGF2 by ELISA (Enzyme linked immunosorbent assay) was done.

Measurement of serum FGF2 by ELISA using FGF2 kit (cloud _clone crop) company. This assay employs the competitive inhibition enzyme immunoassay technique. A microplate was precoated with a monoclonal

antibody specific to FGF2. A reaction of competitive inhibition is occurred between unlabelled FGF2 (Standards or samples) and biotin labelled FGF2 with the pre-coated FGF2 antibody. Washing off the unbound conjugate is done after incubation. Next, we added avidin which is conjugated to horse radish peroxidase (HRP) to each microplate well and incubated. The amount of bound HRP conjugate is inversely proportionated to the FGF2 concentration in the sample. The intensity of color developed, after addition of the substrate solution, is inversely proportionated to the FGF2 concentration in the sample.

Statistical analysis:

Analysis of data was performed using SPSS computer program (version 20; SPSS Inc. Chicago, Illinois, USA). Qualitative data were compared by $\chi 2$-test. While, quantitative data were compared by Mann–Whitney and t tests. The receiver operating characteristic curve (ROC) analysis was used to detect a best cut-off value. Odds ratio (OR) with its 95% confidence interval (CI) was used for risk estimation. Moreover, Spearman rank correlation test had been done to analyse correlation between FGF2 level and other laboratory parameters. A P value less than 0.05 was considered statistically significant, and P<0.001was highly significant.

RESULTS

Regarding demographic, clinical and laboratory data, there were no statistically significant differences between the CML patients and control groups in age and sex distribution. While, there was a statistically significant increase in frequency of hepatomegaly and splenomegaly, WBCs count, platelets count and BCR-ABL fusion gene as well as statistically significant decrease in Hb level among the CML patients group compared to control group. Moreover, there was a statistically significant increase in serum FGF2 level among CML patients group compared to control group (P=<0.001) (table 1).

There was a statistically significant decrease in WBCs count, platelets count and BCR-ABL% among post treatment CML patients group compared to pre-treatment one. No significant difference was found between both groups regarding Hb level pre & post treatment (table 2).

Among CML patients group, 25% treated with Imatinib only and 75% (17/20) treated with hydra and Imatinib. 15% (3/20) of CML patient were not responded to treatment and 85% (17/20) of Patients were responded to treatment (table 3) and (figure 1).

There was no significant difference in FGF2 Level regarding sex (male vs. female), hemoglobin level (≤10.5 vs >10.5 g/dl), WBCs count (≤110 vs. >110 103/dl), platelet count (≤405 vs. >405 103/dl), BCR-ABL% (≤57% vs. >57%), and presence or absence of splenomegaly and hepatomegaly in the CML patients' group. While, there was a statistically significant difference in FGF2 level regarding age of CML patients (It is significantly higher in those ≤50 years) (P=0.041). Also, there was no difference in FGF2 level between cases treated with both hydra and Imatinib and cases treated with Imatinib only (P=0.57). However, there was a statistically significant increase in median FGF2 level among resistant CML patients who did not respond to treatment compared to those who respond (P= 0.03) (table 4).

Moreover, by application of Spearman rank correlation test, there were no statistically significant correlation between FGF2 level and any of the laboratory parameters including hemoglobin, platelets, WBCs, and BCR-ABL fusion gene percentage (table 5).

The cut-off value of FGF2 for prediction of response to treatment was determined using the receiver operating characteristic curve. The optimal cut-off value we used was >83.8 ng/ml, which had sensitivity of 66.7%, specificity of 94.1% and accuracy of 90% for the prediction of treatment response among the CML Patient group (table 6) and (figure S1).

There was a statistically significant association between response of CML patients to treatment and level of FGF2. FGF2 less than 83.8 ng/mL significantly increases opportunity of optimal response by 32 folds. There was association of FGF2 level and response to therapy in CML patient group.

Response of CML patients to treatment was significantly better when level of FGF2 less than 83.8 ng/mL (table S1).

Table (1): Demographic, clinical and laboratory data of CML patients and control group:

Variable		Cases (n=20)		Control (n=20)		P
Sex: *	Female Male	No 15 5	% 75 25	No 17 3	% 85 15	0.43
Age:# (years)	Mean ± SD. Range	49.8 ± 13.89 23- 72		45.85 ± 14.58 20 – 75		0.39
Splenomegaly: Size: # (cm)	Mean ± SD Range	18.96 ± 3.05 15 – 24		12.03 ± 2.64 9.6-15.8		**<0.001**
Hepatomegaly: Size: # (cm)	Mean ± SD Range	16.59 ± 0.85 15 - 18.1		11.01 ± 1.34 8.5-16		**<0.001**
Hb: #(gm/dl)	Mean ± SD Range Median (IQR)	10.7 ± 2.02 7.2 – 15.2 10.55 (9.45 – 12.08)		12.9 ± 1.79 12.5 – 16.5 12.8 (12.67 – 14.3)		**<0.001**
WBCs:** ($x10^3/mm^3$)	Mean ± SD Range Median (IQR)	143.78 ± 100.34 31.4 – 435 110.7(72.03-202.33)		8.85 ± 2.16 4.6-11.5 8.85 (6.9-10.65)		**<0.001**
Platelets:** ($x10^3/mm^3$)	Mean ± SD Range Median (IQR)	619.9 ± 927.14 154 – 4488 405(285-619.5)		304 ± 81.86 150-412 304 (233.25-352.59)		**0.009**
BCR_ABL:** (%)	Mean ± SD Range Median (IQR)	57.53 ± 16.56 27.9 – 85.94 57 (43.53-69.4)		2 ± 1.75 0 – 6 2 (1-4)		**<0.001**
FGF2:** (ng/ml)	Mean ± SD Range Median (IQR)	63.94 ± 72.89 14.5 – 320 40.75(31.15-54.05)		14.62 ± 4.67 5 – 22 13.9 (11.95-19.28)		**<0.001**

*, χ^2 test; #, t test; **, Mann Whitney test

P>0.05, non-significant; P<0.05, significant; P<0.001, highly significant

Table (2): Laboratory findings among CML patients pre and post treatment

Variable		Initial (n=20)	After 3 m (n=20)	P
Hb:* (gm/dl)	Mean ± SD Range	10.7 ± 2.02 7.2 – 15.2	11.27 ± 1.3 8.2 – 13.9	0.24
WBCs:# ($x10^3/mm^3$)	Mean ± SD Range Median (IQR)	143.78 ± 100.34 31.4 – 435 110.7(72.03-202.33)	8.91 ± 7.1 4 -30.37 6.95(4.86-8.16)	**<0.001**
Platelets:# ($x10^3/mm^3$)	Mean ± SD Range	619.9 ± 927.14 154 – 4488	270.25 ± 196.69	**0.01**

	Median (IQR)	405(285-619.5)	48 – 926 221.5(163.25-301.5)	
BCR_ABL:# (%)	Mean ± SD Range Median (IQR)	57.53 ± 16.56 27.9 – 85.94 57 (43.53-69.4)	4.35 ± 8.74 0 – 27.4 0.07(0.02-3.76)	**<0.001**

*, Paired: t test; #,Wilcoxon test

IQR, interquartile range (range between 25th and 75th quartiles); SD: Standard deviation

P>0.05, non-significant; P<0.05, significant; P<0.001, highly significant

Table (3): Treatment response data among the studied CML patients group:

Variable		**Cases (n=20)**	
		No	**%**
Type:	**Hydra and Imatinib** **Imatinib**	15 5	75 25
Response to treatment:	**Yes** **No**	17 3	85 15

Table (4): Comparison between FGF2 level among the CML patients group regarding clinical and laboratory data:

Variable		N	FGF 2(ng/ml)		**P**
			Median	IQR	
Sex:*	Male Female	5 15	54.9 35.1	71-77.5 27.75-45.83	0.09
Age:*	≤50 years >50 years	10 10	50.25 35.1	38.3 – 80.65 24.46 – 40.95	0.041
Splenomegaly:*	No Yes	1 19	14.5 41	14.5 34.5-53.2	0.10
Hepatomegaly:*	No Yes	4 16	47.7 40.6	27.5-72.5 32.1-50.25	**0.78**
Hemoglobin:*	≤10.5 g/dl >10.5 g/dl	10 10	41.56 40.35	33.88 – 119.45 25.28 – 52.35	**0.45**
WBCs:*	≤110 (10^3/dl) >110 (10^3/dl)	10 10	40.35 41.83	28.98 – 60.55 32.63 – 61.15	**0.65**
Platelet:*	≤405 (10^3/dl) >405 (10^3/dl)	10 10	37.65 45.83	25.28 – 53.28 33.88 – 60.55	**0.241**
BCR_ ABL%:*	≤57% >57%	10 10	41.83 37.8	28.98 – 110 31.06 – 52.35	**0.45**
Type of treatment:*	Hydra+Imatinab Imatinib	15 5	40.2 42.3	30.2-51.5 27.5-142.5	0.57
Response to treatment:*	Yes No	17 3	40.5 90.1	30.2-49 65.15-205.05	**0.03**

IQR, Inter quartile range *, Mann Whitney test

P>0.05, non-significant; P<0.05, significant

Table (5): Correlation analysis between FGF2 and laboratory parameters:

Parameter	r	P
Age	-0.407	0.075
Haemoglobin	0.029	0.902
WBCs	-0.053	0.826
Platelet	0.314	0.178
BCR-ABL%	-0.029	0.902

r, Spearman rho correlation coefficient; P>0.05, non-significant

Table (6): Validity of FGF2 level in prediction of response to treatment among the CML patients group:

Cut off	AUC (95%CI)	P	Sensitivity	Specificity	PPV	NPV	Accuracy
>83.8 ng/ml	0.80 (0.51-1)	0.01	66.7%	94.1%	66.7%	94.1%	90%

AUC, Area under curve; PPV, +ve predictive value; NPV, -ve predictive value. P<0.05, significant

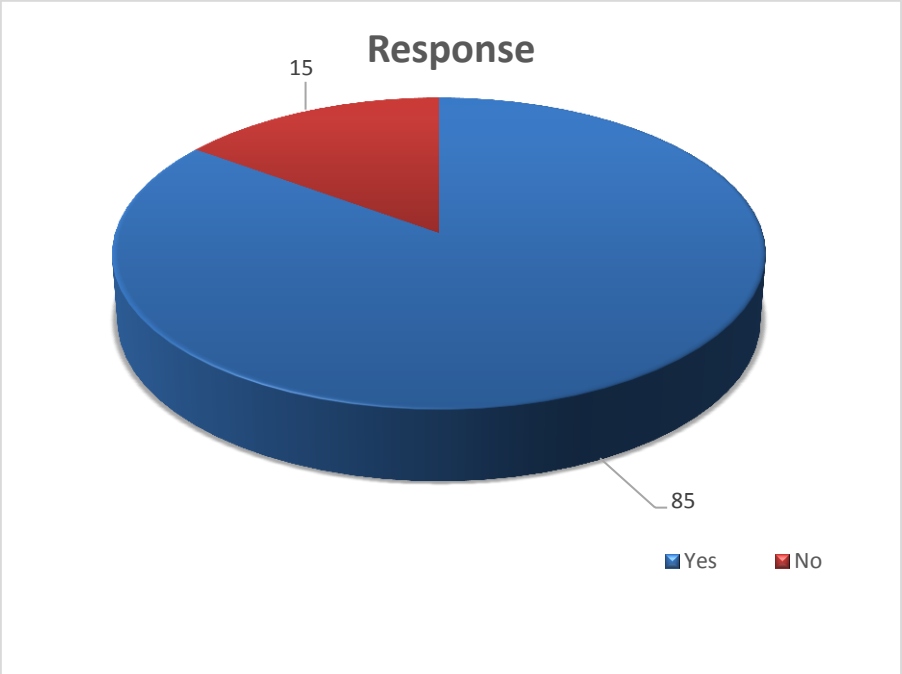

Fig. (1): Response to treatment among the CML patients group.

DISCUSSION

Chronic myeloid leukemia is a chronic myeloproliferative disorder characterized by excessive myeloid proliferation with accumulation of immature granulocytic series [5]. The Philadelphia chromosome (Ph) is a hallmark of CML [6]. FGF2 promotes proliferation of bone marrow stromal cells in adult haematopoiesis. Moreover, FGF2 counteracts the suppressive effect of transforming growth factor beta (TGF-β) on myeloid progenitor cells and induces the production of interleukin-6 (IL-6). The involvement of FGF2 in different stages of

haematopoiesis suggests that its dysregulation can result in haematological malignancy [7].

The present study was designed to evaluate the clinical significance of FGF2 in CML patients. In our study, the median percentage of BCR-ABL1 at diagnosis was 57% and after 3 months' therapy was 0.07%, which corresponds with reports of Zhang et al [8], who stated that, BCR-ABL1 median percentage at presentation was 43.20% and after 3-month was 3.55%.

In this study, about 25% of the CML patients were treated with Imatinib only and 75% treated with hydra and Imatinib with 85% of patient were responded to treatment with optimal molecular response. This data is in agreement with reports of Abdulrahman [9] (85%) and Hoch Haus et al. [10] (82.8%). While, it was higher than that reported by Bileni and Erdem et al. [11] (71%) and lower than that reported by Samrat et al, [12] (97%). However, this is not in agreement with Nasser et al. [13], who found that only 23.4% of CML patients who received imatinib, achieved optimal molecular response.

The current study revealed a statistically significant increase in serum FGF2 level among CML patients compared to the control group with a mean value ± SD of 63.94 ± 72.89 ng/ml & 14.62+4.67 ng/ml, respectively. That corresponds with the reports of Krejci et al. [14] and Bieker et al. [15] who stated that the level of serum FGF2 is increased in CML patients.

The elevated level of FGF2 in peripheral blood is considered to play a role in regulating the growth of leukemic cells [14]. Moreover, several studies have shown that FGF2 is a key tumor -promoting factor in tumor micro environment [16].

By the same manner, circulating FGF2 levels are elevated in myeloid leukaemia patients [17] and in several human cancers [18]. Serum level of FGF2 strongly elevated in Hairy cell leukaemia [19], multiple myeloma [20], Hodgkin's [21] and non -Hodgkin's lymphoma [22].

In the present study, as regard response to therapy, patients with failure of response to treatment revealed a statistically significant increase in median level of FGF2 as compared to those with overall response (90.1 ng/ml VS 40.5 ng/ml), respectively. While, no significant differences were observed as regard other parameters including sex, splenomegaly, hepatomegaly, haemoglobin, WBCs, platelets, BCR-ABL, and type of treatment. On the other hand, a significant difference was noted regarding age. Different studies have been reported that ageing could be a negative independent factor for response in the category of elderly patients due to consequent increased toxicity of available agents and concomitant comorbidities [23]. Moreover, there were no statistically significant correlation between FGF2 level and any of the laboratory parameters including hemoglobin, platelets, WBCs, and BCR-ABL fusion gene percentage, which is in agreement with those reported in numerous studies [14, 24].

Similar results were reported by Traer et al. [24] who stated that FGF2 promotes resistance to imatinib. FGF2 is produced by bone marrow stromal cells and plays an active role in haematopoiesis and is thought to be secreted from stromal cells into the extramedullary matrix. FGF2 has an effect on cell cycle and chemo-sensitivity of leukaemia cells on stromal layers. FGF2 treatment attenuated the viability of human technology readiness level (TRL-01) stromal-dependent leukaemia cells and this suggest that FGF2 enhanced the chemo-sensitivity of leukaemia cells growing on stromal layers by inhibiting stromal functions to induce cell cycle arrest [25].

FGF2 has a role as a prognostic factor for different types of malignancy [26] and can promote progression of cancer through alternative mechanism [27]. FGF2 may induce MEK signalling to upregulate antiapoptotic proteins and subsequently enhance chemoresistance [28].

To address the significance of elevated plasma FGF2 in CML patients and to what extent the high-level affect response to therapy, we assess cut off level of FGF2 in prediction of treatment response. We found a statistically significant association between the level of FGF2 and response to therapy. FGF2 level less than 83.8ng/mL significantly increase opportunity of optimal response by 32 folds.

Validity of FGF2 level in prediction of response among the CML patients group revealed that FGF2 at cut off >83.8 ng/ml had a sensitivity of 66.7%, specificity of 94.1% with accuracy of 90% in prediction of response among the studied cases group.

The leukemic cells are able to use FGF2 to counteract the effects of the kinase inhibitors drugs. However, yet it still not clear how the FGF2 signal reaches the leukemia cells from the bone marrow stromal cells. Leukemic cells which had taken up FGF2 were more resistant to kinase inhibitor drugs than leukemia cells which had not [29]. Moreover, FGF2 can affect the bone marrow stromal cells by making them grow faster, producing more FGF2 and release more exosomes. So, if the effect of FGF2 is blocked on the stromal cells, their growth will be slower and will induce less release of exosomes. This suggests that usage of drugs that prevent the release of FGF2 in exosomes by bone marrow stromal cells might improve leukemia treatment [30].

Taken together, our data suggest an important role of FGF2 as a potential predictive prognostic biomarker for response to therapy in CML patients.

CONCLUSIONS

We concluded that, serum FGF2 level significantly increased among CML patients versus controls, supporting its role in the pathogenesis of CML. The levels of FGF2 are higher in non-responders who didn't respond to treatment than responders. This indicate that FGF2 may act as prognostic marker. Response of CML patients to treatment is significantly better when level of FGF2 less than 83.8 ng/ml. Taken together, our data suggest an important biological role of FGF2 in pathogenesis and prognosis of CML.

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SUPPLEMENTARY FILES

Table (S1): Odds ratio of a high FGF2 level in predicting response to treatment of CML patients' group:

	Response		P	COR (95% CI)
	YES N=17 (%)	NO N=3 (%)		
<83.8 ng/mL	16 (94.1%)	1 (33.3%)	0.045*	32 (1.39 – 737.5)
≥83.8 ng/mL	3 (5.9%)	2 (66.7%)		

COR, crude odds ratio; CI, confidence interval

P<0.05, significant

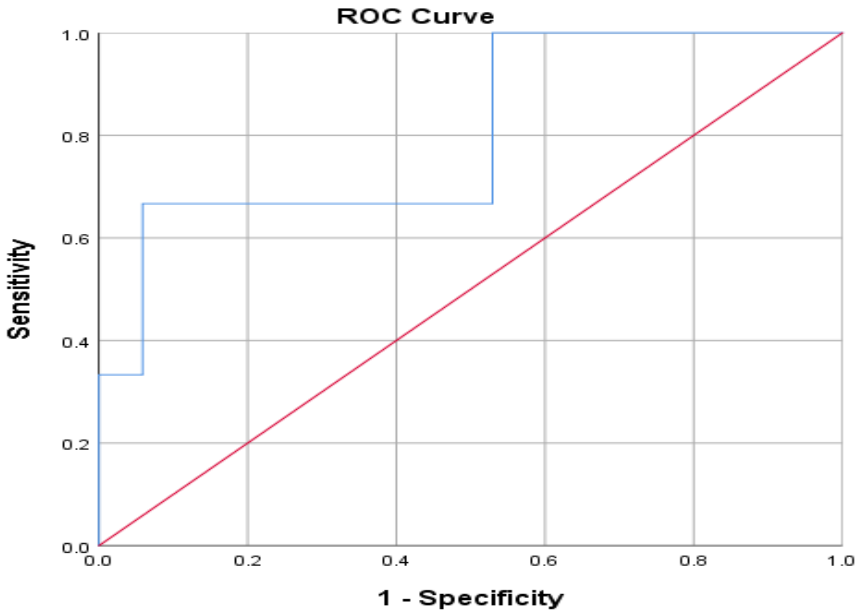

Fig. (S1): Roc curve for Validity of FGF2 Level in prediction of response to treatment among the CML patients' group.