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The role of miRNA- 96 and miRNA-150 between different BCR-ABL p210 transcript levels and between different levels of imatinib optimal response in CML patients

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ABSTRACT

Background: Dysregulation of miRNA expression patterns is one of the **several** effects developments of cancer. MiRNA has been found to express abnormally in hematological neoplasia such as chronic myeloid leukemia and solid malignancies. Resistance and the degree of response following tyrosine kinase inhibitor (TKI (treatment are correlated with miRNA expression. Hence this study has evaluated the correlation between miRNA- 96 and miRNA-150 with different p210 BCR-ABL transcript levels and the role of miRNA- 96 and miRNA-150 at different levels of imatinib optimal response in CML patients.

Method: This study is based on 60 CML patients divided into two groups based on response to imatinib therapy. 30 samples have the optimal molecular response of CML patients. The other 30 samples that have failed molecular response CML patients, which were compared to 30 samples of healthy volunteers as control by depending on the results of CBC film and PCR. BCR-ABL 210 transcript, which was used in this study, is obtained from the patient's file.

Results: The results based on the comparison of transcript levels showed that there was a significant difference between the positive response and failed response of CML patients ($P \leq 0.0001$). The result of miRNA-96 showed that there was no noteworthy difference within both CML patients ($P \geq 0.5030$), while miRNA-150 results exhibited a high significant difference ($P \leq 0.0001$). The miRNA-96 and miRNA-150 expression levels in all responses of CML patients demonstrated a highly significant difference with $P = 0.0134$ and $P = 0.0002$, respectively. The cut-off value of response against failure response of miRNA-96 and miRNA-150 with *P* value of 1.691 and 1.784, respectively with high sensitivity is a diagnostic value of the difference between the response and failure response.

Conclusion: modulating gene expression with different of miRNAs expression has an impact on drug-gene interactions, with consequences for cell growth and death. The gene expression that shows the different level miRNAs (miRNA- 96 and miRNA-150) among of CML patients of imatinib therapy exhibited high expression in response patients than that of the failure response of patients. The gene expression level of miRNA- 96 and miRNA-150 was differed between through different response CML patients.

1. Introduction

Hematopoiesis is described as the ability of self-renewing cells to form mature blood cells, (Aïnseba and Benosman, 2011). The increase of immature cells in the bone marrow and abnormal hematopoiesis defined leukemia is a highly diverse hematological malignancy (Xu et al., 2016). Between January 2018 and December 2019, the Iraqi Center for Hematology in the Medical City Complex of Baghdad recorded 3102 eligible leukemia cases. For all types of cancer, 1402 cases were registered in 2018 and 1700 in 2019 (Abdulridha, Jawad et al., 2021). Chronic myeloid leukemia (CML) is a rare disease worldwide. Its incidence is estimated to be 1–2 cases / 100,000 presence of people, accounting for around 15% of newly diagnosed adult leukemia cases (Alves et al., 2021). CML has been diagnosed in 8450 persons in the United States in 2020, with 1130 people dying from the disease (Deininger et al., 2020). Men are more likely than women to be diagnosed

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with CML, and the disease usually occurs in their sixth or seventh decade of life (Sampaio et al., 2021). Agranulocytosis, marrow hypercellularity, and splenomegaly are all symptoms of CML, which is caused by a mutation in a pluripotent stem cell (Matti et al., 2013). This myeloproliferative neoplasm is a clonal hematopoietic stem cell (HSC) neoplasm marked by an increase in myeloid linage cells at all stages of development (Alves et al., 2021). The increase of Philadelphia chromosome-positive (Ph+) myeloid cells is a defining feature of CML patients. A reciprocal translocation between the Abelson (ABL) protooncogene on chromosome 9 and the breakpoint cluster area (BCR) on chromosome 22 results in the Ph chromosome, t (9;22) (q34; q11). (Mohamad and Elias, 2021). As a result, p210 BCR-ABL a fusion protein constitutive is produced with ABL tyrosine kinase (TK) activity an abnormal (Khoshnaw et al., 2014). This kinase regulates several downstream substrates, including A serine threonine kinase also known as protein kinase B (Akt), Myelocytomatosis MYC and c-Jun N-terminal kinase (JNK), which are all required for normal cell proliferation and survival. The hyperactivity of the BCR-ABL kinase, on the other hand, breaks this delicate balance and drives cells to uncontrolled proliferation and survival, both of which provide a growth advantage to malignant cells with this mutation, ultimately leading to CML pathogenesis (Jabbour et al., 2010). For the efficient treatment of CML, tyrosine kinase inhibitors (TKIs) are required to suppress the kinase activity of the BCR-ABL protein (Di Stefano et al., 2016). Imatinib mesylate is a tyrosine kinase inhibitor TKI that inhibits downstream BCR-ABL signaling by blocking the ATP binding site of the protein (Jabbour et al., 2010). Although imatinib, a tyrosine kinase inhibitor TKI, works for the great majority of CML patients, resistance can develop either spontaneously or during treatment (Alves et al., 2021). MicroRNAs (miRNAs) are short noncoding RNAs that affect cell survival and development after transcription. Overexpression of oncogenic miRNAs (oncomiRs) or reduced expression of tumor suppressor miRNAs have been found in malignancies, and miRNAs have been proven to induce carcinogenesis (Abd-Aziz et al., 2020). Over 30% of specific genes, which are involved in key biological processes such as proliferation, differentiation, survival, invasion, and programmed cell death, are found in the human genome, have been demonstrated to be regulated by miRNAs (Hosseinahli et al., 2018). Although the role of miRNA in leukemia pathogenesis remained unclear, some research has suggested that miRNA expression profiles could be used as biomarkers for leukemia diagnosis, prognosis, and treatment response (Anelli et al., 2021). Lineage commitment and differentiation are influenced by a set of miRNAs present in hematopoietic cells (Bartel, 2018). In hematological malignancies, aberrant miRNA expression has been reported, with distinct expression patterns compared to normal equivalents (Di Stefano et al., 2016). Changes in transcription regulation may potentially cause changes in microRNA expression during carcinogenesis. Transcription factors encoded by oncogenes or suppressor genes regulate some microRNAs (Szymczyk et al., 2018). For numerous miRNAs, functional validation of unregulated miRNAs in hematopoiesis has been demonstrated and linked to the leukemogenesis and have been implicated in important hematological processes (Starczynowski et al., 2016).

2. Materials and method

2.1. Subjects

This study was carried out during period between September 2021–July 2022 at Baghdad Teaching Hospital/ Medical City. Sixty patients with CML were enrolled in the current study, and their age were over the age of 18, and had been on imatinib mesylate therapy for more than a year. Patients were divided into groups based on treatment response and BCR-ABL transcript levels according to q PCR results. The European Leukemia-Net (ELN) guidelines were used to define treatment response criteria (Hochhaus et al., 2020). Thirty samples were classified as optimal responders (p210 BCR-ABL transcript levels <0.1%) and thirty samples as failure molecular responders (p210 BCR-ABL transcript levels >1%). Thirty samples' volunteers were used as controls. Blood count indices were obtained and calculated by an automated blood count analyzer at the time of sampling. This study was approved by the scientific ethics committee/ All the study experiments were performed at performed at AL- Mustansiriyah University - College of Science - Department of biology. Exclusion criteria: <12-month treatment, CML on other TKI, Chronic illness and malignance, Chronic illness, and malignance. Inclusion criteria: Age ≥ 18-year-old, CML patients on imatinib therapy for at level 12 month, No other malignance, No other Chronic diseases.

2.2. Statistical analysis

GraphPad Prism 7.0 was used for achieving the statistical analysis in order to detect the effect of different parameters in study, where discrete variables presented using their number and percentage. Chi square test was used for analyzing. The non-parametric data such variables were analyzed by Kruskal-Wallis test for comparison between different groups (response, and failure response and control). The probability was calculated for variables that followed normal distribution One way ANOVA that used for their analysis. For post Hoc analysis, Tukey *U* test was used for those analyzed by One way ANOVA, while Dunn's multiple comparison test was used for those analyzed by Kruskal-Wallis test. The receiver operator curve (ROC) was used to examine the expression of the level miRNA regards the recognizing failure response cases from optimal response, and (P 0.05) were considered such statistically significant.

3. Results

Out of 60 CML patients on imatinib therapy, patients were divided into two groups based on response to therapy, thirty samples were with optimal response with (mean age 45.97 ± 2.23 years, M:F ratio was 12: 18) and thirty samples were with failure response with (mean age 49.87 ± 2.25 years, M:F ratio was 18: 12)and thirty samples of healthy volunteers were included and evaluated as control with (mean age 30.93 ± 1.75 years, M:F ratio 24 : 6).

The following patient characteristics were included based on a complete blood count the median white blood cells count (cell/ cm^3) for the response, failure response CML patients and control group was 6.6×10^3 (3.9–15.3), 7.05×10^3 (3.1–12.6), 6.15×10^3 (0.8–18.3), respectively they showed no significant difference between all studied groups as shown in Fig. 1(A). While the median hemoglobin level g/dl to μL for the response, failure response CML patients and control group was (12.15 g/dl) (6.8–15.3), (13.1 g/dl) (9.6–15.9), (15.8 g/dl) (10.2–17.3), respectively also showed no significant difference ($P = 0.5386$) for both patients CML groups, but showed a significant difference among patients groups and control group according to the hemoglobin level ($P \leq 0.0001$) showed which demonstrated a reduced hemoglobin levels than the control, as shown in Fig. 1(B). The median platelets count $\times 10^3/\mu L$ for the response, failure response CML patients and control group was (235×10^3) (17–391), (210.5×10^3) (48–1237), (237×10^3) (159–450) respectively also showed no significant difference between all student groups, as shown in Fig. 1 (C).

The results for p210 BCR-ABL transcripts level showed a significant difference between both CML patients groups ($P \leq 0.0001$) with a highest transcript level in failure responder CML group with mean (7.463 ± 3.345%) and optimal response group with mean (0.0145 ± 0.03%) in relation to BCR-ABL transcript levels as shown in Fig. 2.

The result mean ± SE BCR-ABL p-210 transcript level among different responses of CML patients groups <0.0032, 0.01–0.0032, 0.1–0.01 and > 1 = 0.0019 ± 0.0005, 0.0056 ± 0.0007, 0.0271 ± 0.0036, 7.463 ± 3.345, respectively shown high significant difference between all studied patients ($p \leq 0.0001$) based on the Table 1.

Assessed of mean miRNA expression level among response group and failure response group of CML patients, the mean folding miRNA-96

expression for response and failure response was = 25.72 ± 11.69 and 4.442 ± 1.482, respectively. Although the results showed an increase in the expression level in response group against failure response group, it was found that there is no significant difference between both groups of CML patients, as shown in Fig. 3(A). Additionally, there was no significant difference between responders CML patients and the control studied group. The mean folding miRNA-150 expression was 391.8 ± 349.3 and 1.919 ± 0.4081 for both response and failure response, respectively. The result showed high significant difference between both patients groups ($P \leq 0.0001$), as shown in Fig. 3(B).

Assessed of mean miRNA-96 expression level among different responses groups and failure response group of CML patients showed significant difference in the mean BCR-ABL1 0.0032, 0.01–0.0032, 0.1–0.01 and > 1, were expression 16.68 ± 4114, 2.439 ± 228.5, 43.17 ± 1941 and 4.442 ± 7.637, respectively as shown in Fig. 4(A).

As for of miRNA- 150 showed significant differences result in the mean BCR-ABL1 < 0.0032, 0.01–0.0032, 0.1–0.01 and > 1, were expression 1203 ± 1164, 14.17 ± 8.502, 59.16 ± 24.35 and 1.919 ± 0.4081, respectively as shown in Fig. 4(B).

Based on Tables 3 and 4, a receiver operating characteristic (ROC) curve analysis was used to determine the cut-off value of miRNA-96 and miRNA-150 with *P* value1.691 and 1.784, respectively differentiate between response and failure response, as shown in Figs. 5 and 6. (See Figs. 1–3.) (See Table 1.)

4. Discussion

In chronic myeloid leukemia (CML), abnormal expressions of miRNAs have been described, the goal is to identify the miRNAs as predictive biomarkers of TKI sensitivity in addition to aid in the investigation of potential miRNA-mediated TKI resistance mechanisms for therapeutic use (Ghazaryan et al., 2020). MiRNA levels in the blood were shown alter considerably in newly diagnosed CML patients before and throughout the first two weeks of Imatinib treatment, suggesting the possibility of identifying easily detectable biomarkers to monitor TKI response. These findings showed that there is a great possibility to use miRNA signatures as biomarkers in CML research, allowing for CML staging and predicting patient response to TKI therapy (Kotagama et al., 2015). In this study, 60 patients of CML with mean age was (45.97 ± 2.23, 49.87 ± 2.25, 30.93 ± 1.75) years for both response, failure response CML patients and control group, respectively, without significant statistical differences between both patients groups. This is comparable to ELN 2020 review as among Asian population was the median age at diagnosis was <50 years, which reflects the population's lower median age (Hochhaus et al., 2020). The results also showed a significant difference of age between different groups of CML patients ($P \leq 0.0001$). Chronic myeloid leukemia (CML) affects people of all ages,

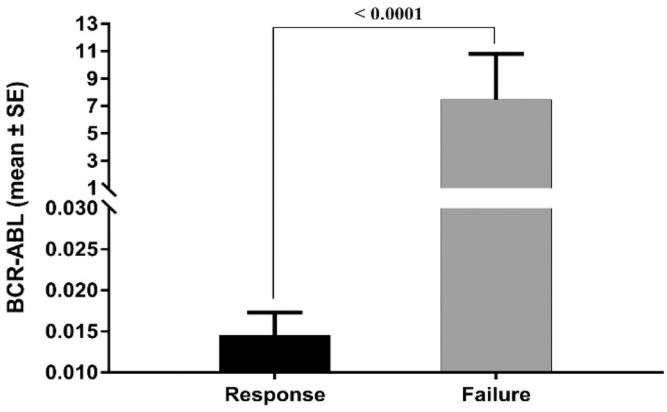

Fig. 2. BCR-ABL P-210 transcript level between response and failure response of CML patients.

and its prevalence increases with age. Prior to the introduction of imatinib, older age was a risk factor. The outcomes of CML patients have improved, and older age appears to have lost its risk factor status (Kalmanti et al., 2014). Early studies reveal that imatinib mesylate has a high efficacy in CML, the activity of this drug leads in the transcriptional manipulation of many genes involved in the control of the cell cycle, cell adhesion, and cytoskeleton organization, resulting to the apoptotic death of Ph-positive cells via blocking the ATP-binding site of the kinase domain of ABL(Mojtahedi, Yazdanpanah et al., 2021). For white blood cells, they showed no significant difference between both patients group. It is also shown that there was no significant difference between both patients CML groups and control group. While the median hemoglobin level g/dl to μL showed no significant difference for both patients CML groups and showed a significant difference among patients groups and control group ($P \leq 0.0001$) that reflect a reduced hemoglobin levels than the control, reduced hemoglobin levels which might be related to the long-term use of imatinib treatment (Sabir et al., 2021). Anemia increase gradually with the prolongation of medication (Liu et al., 2020). This could lead to anemia due to the related effect of in renal function because kidney produces a hormone erythropoietin that helps to make red blood cells (Sakurai et al., 2016). The median platelet count among all studied groups was within the normal range, but this does not rule out the presence of various stages of CML in this study. According to European Leukemia Net recommendations, achieving complete hematological response CHR within 3 months of starting therapy is an optimal response. Nearly all patients with chronic CML achieve a CHR with TKI therapy (Cortes et al., 2011). In this study, the expression level of miRNAs was compared with the degree of response achieved after treatment for CML patients with failure response. Through assessment

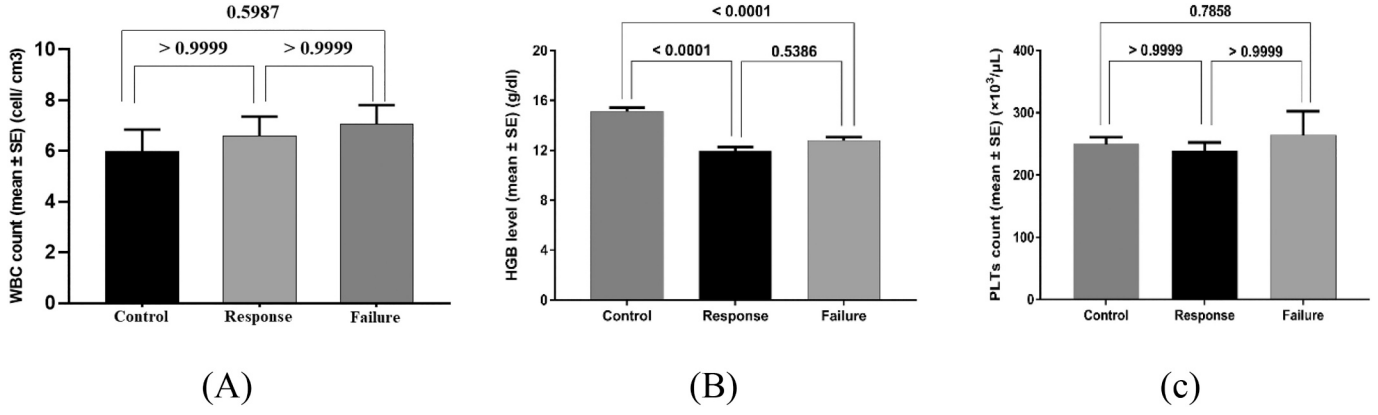

Fig. 1. Patients characteristics according to complete blood count among both CML groups and control group. (A) white blood cells count (B) hemoglobin level (C) Platelet count.

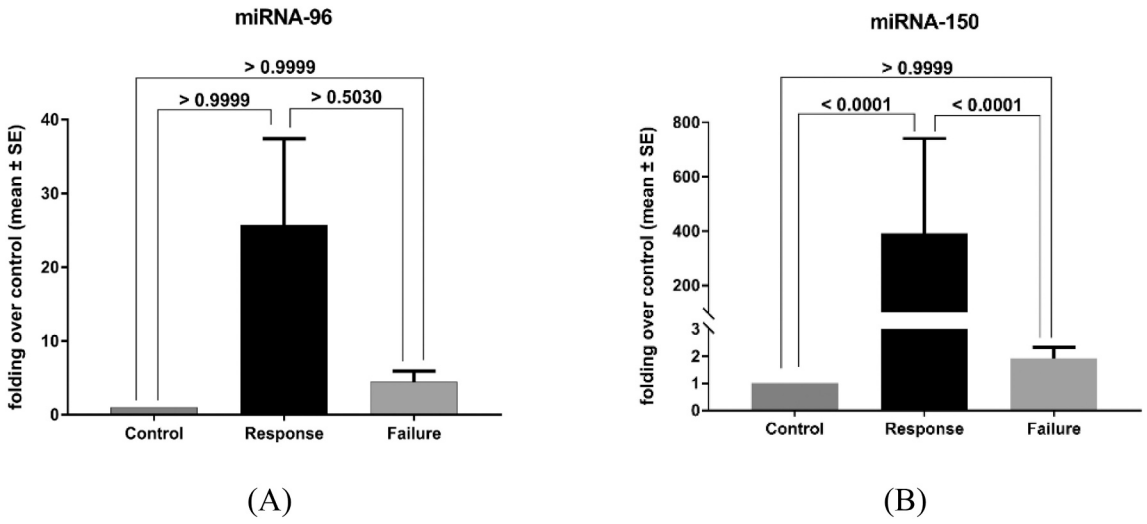

Fig. 3. (A) MiRNA-96 expression with BCR-ABL transcript level through response and failure response of CML patients (B) MiRNA-150 expression with BCR-ABL transcript level through response and failure response of CML patients.

Table 1
Distribution of mean BCR-ABL p-210 transcript level and frequency among different responses of CML patients groups.

	BCR-ABL p-210 transcript level among the responders CML patients			BCR-ABL in failure response group	P value
	< 0.0032	0.01–0.0032	0.1–0.01	> 1	
Frequency (%)	9 (15)	7 (11.66)	14 (23.33)	30 (50)	
BCR-ABL mean ± SE	0.0019 ± 0.0005	0.0056 ± 0.0007	0.0271 ± 0.0036	7.463 ± 3.345	< 0.0001

miRNA-96 expression levels in different responses and failure response of CML patients, the date showed significant difference result in the mean BCR-ABL1 < 0.0032, 0.01–0.0032, 0.1–0.01 and > 1, was 16.68 ± 4114, 2.439 ± 228.5, 43.17 ± 1941 and 4.442 ± 7.637, respectively as shown in Table 2. Among different responses of CML patients there was a significant difference ($P = 0.0201$) between (0.01–0.0032) against (0.1–0.01) only, without significant difference among other studied patients groups, as shown in Fig. 4(A). MicroRNA-96 is a member of the

Table 2
The mean miRNA expression level and *P*-value through different responses groups and failure response group of CML patients.

mean ± SE miRNA folding	BCR-ABL (< 0.0032)	BCR-ABL (0.01–0.0032)	BCR-ABL (0.1–0.01)	BCR-ABL (>1)	P value
miRNA-96 folding over control (mean ± SE)	16.68 ± 4114	2.439 ± 228.5	43.17 ± 1941	4.442 ± 7.637	0.0134
miRNA-150 folding over control (mean ± SE)	1203 ± 1164	14.17 ± 8.502	59.16 ± 24.35	1.919 ± 0.4081	0.0002

miR-183-96-182 family, which governs cell motility and tumor progression by targeting numerous genes as an oncogene or tumor suppressor (Rahimi et al., 2022). MiR-96 suppressed protein translation, phosphorylation, and downstream signaling pathway activity of BCR-ABL1 by directly binding to its 3'UTR, according to the mechanism and function of miR-96 in the blastic transformation of CML when compared to CML chronic phase patients and cell lines, miR-96 is downregulated in CML blast crisis (CML-BC) patients and cell lines (CML-CP) miR-96 expression was shown to be low in CML-BC cells, which promoted cell proliferation and hampered cell differentiation. By targeting the fusion oncogene BCR-ABL1, miR-96 serves as a tumor suppressor against CML blast crisis, potentially providing a new therapy option for CML blast crisis (Huang et al., 2019). MiR-96 can restore TKI sensitivity in resistant CML cell lines by inhibition of BCR-ABL and results in reduced leukemic cell (Gao and Wang, 2015). As for miRNA-150 expression levels in different responses and failure response of CML patients, the results of date showed significant difference in the mean BCR-ABL1 < 0.0032, 0.01–0.0032, 0.1–0.01 and > 1, was 1203 ± 1164, 14.17 ± 8.502, 59.16 ± 24.35 and 1.919 ± 0.4081, respectively as shown in Fig. 4 (B). The results between (< 0.0032 against >1) and (0.1–0.01 against >1), showed significant differences ($P = 0.0471$) and ($P = 0.0001$), respectively.MYB has been shown to be a top predicted target of miR-150, furthermore, miR-150 can target MYB in chronic myeloid leukemia (CML) and limit the production of a number of oncogenes, preventing CML cells from proliferating (Hu et al., 2021). MYB expression was dramatically enhanced at Dg in AP/BC, with a significant negative association of MYB with miR150 expression and a significant positive correlation between MYB expression and BCR-ABL transcript level (Poláková et al., 2011). BCR-ABL suppresses miR-150 expression, which leads to the overexpression of its target MYB, and hence plays an important role in the pathogenesis of CML (He et al., 2014). At the molecular level, BCR-ABL and miR-150 had a positive connection, this means that once patients on imatinib have achieved molecular remission from chronic myeloid leukemia, miR-150 can be used to predict remission outcome (Ezeanosike and Afonne, 2017).According to several studies, decreased miR-150 expression indicates a poor prognosis and a more advanced stage of CML, in cell lines, however, restoration of miR-150 alleviates symptoms (Kotagama et al., 2015). MiR-150 levels in BC have dropped dramatically but have returned to normal in patients taking imatinib, for diagnosis and advanced stages of CML, significant down-regulation of the miRNA in contrast to healthy controls was confirmed. In 67% of hematological relapses, the level of MiR-150 dropped by more than twofold (Srutova et al., 2018).

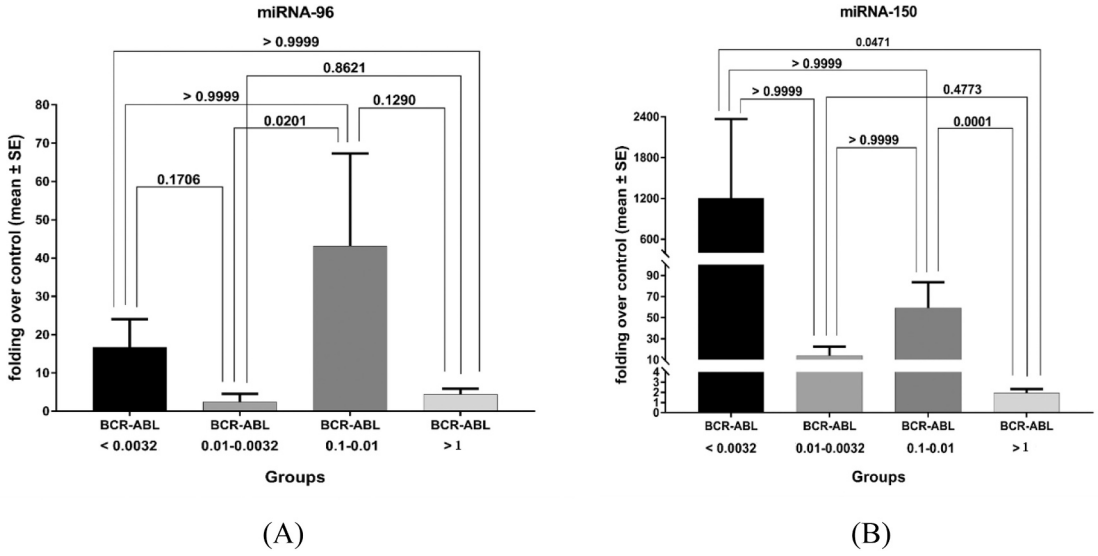

Fig. 4. (A) MiRNA −96 expression level through different responses groups and failure response of CML patients (B) MiRNA −150 expression level through different responses groups and failure response of CML patients.

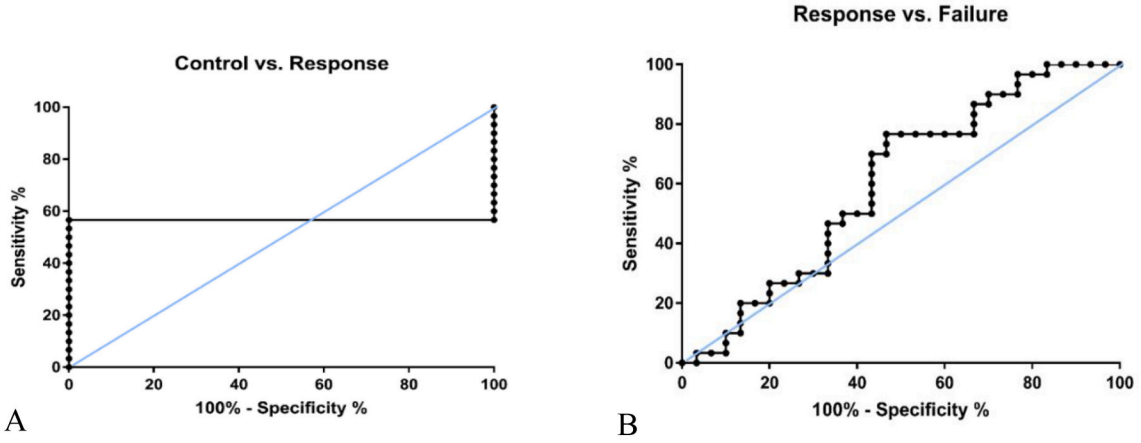

Fig. 5. ROC analysis for miRNA-96 expression (A) for control against a response (B) for response against failure response.

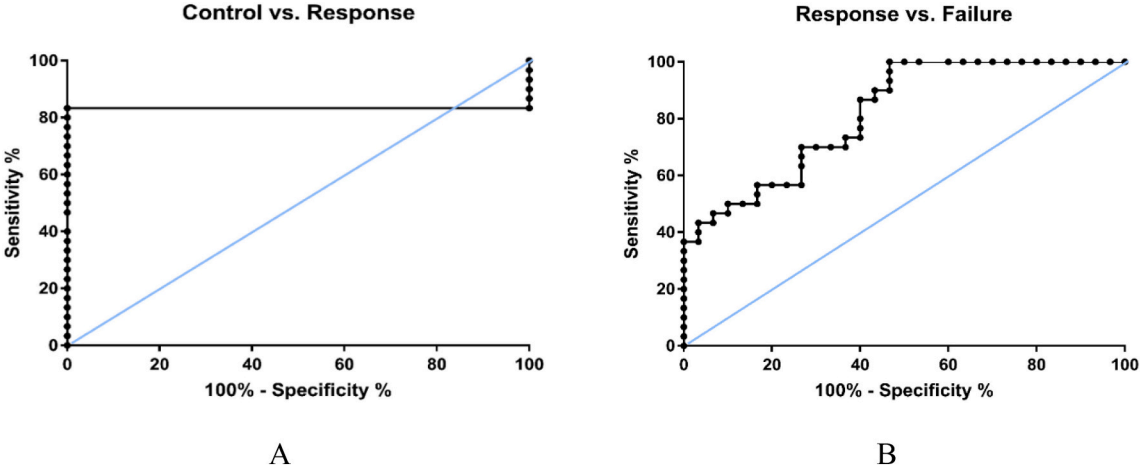

Fig. 6. ROC analysis for miRNA-150 expression (A) for control against a response (B) for response against failure response.

Table 3
The ROC analysis for miRNA-96 expression.

Comparison groups	AUC	95% CI of AUC	P-value	Optimum cut off value	SN (%)	SP (%)
Control vs. Response	0.567	0.389–0.744	0.375	1.4	56.7	100
Response vs. Failure response	0.602	0.456–0.748	0.174	1.691	70	56.7

ROC: Receiver operating characteristic AUC: area under curve SN: sensitivity SP: specificity.

Table 4
The ROC analysis for miRNA-150 expression.

Comparison groups	AUC	95% CI of AUC	P-value	Optimum cut off value	SN (%)	SP (%)
Control against Response	0.833	0.7–0.967	<0.0001	1.197	83.3	100
Response against Failure response	0.819	0.715–0.922	<0.0001	1.784	70	73.3

ROC: Receiver operating characteristic AUC: area under curve SN: sensitivity SP: specificity.

5. Conclusion

Currently impossible to predict whether a patient will develop resistance to imatinib mesylate, this makes identification of predictors of resistance to imatinib an important goal in management of patients with chronic myeloid leukemia (CML). In chronic myeloid leukemia (CML), abnormal expressions of miRNAs have been described, miRNA expression patterns can be used to predict outcome which can be remission or relapse. Regular monitoring is required to detect inadequate TKI response or resistance in a timely manner.

Author contributions

All authors contributed equally to writing—original draft preparation, All authors have read and agreed to the published version of the manuscript.

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Ethical approval

The Ethics Committee of the Mustansiriyah University approved and oversaw this study.

Research involving human participants

No human sample was used.

Declaration of Competing Interest

The authors declare no conflict of interest.

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References

Abd-Aziz, N., Kamaruzman, N.I., Poh, C.L., 2020. Development of MicroRNAs as potential therapeutics against Cancer. J. Oncol. 2020, 8029721.
Abdulridha, R.H., Jawad, N.K., A. T. Numan and Toxicology, 2021. Prevalence and risk of leukemia reported cases, observational descriptive statistic from Iraqi Center for Hematology in Baghdad Province. Indian J. Forens. Med. 15 (1), 2429.
Aïnseba, B.E., Benosman, C., 2011. Global dynamics of hematopoietic stem cells and differentiated cells in a chronic myeloid leukemia model. J. Math. Biol. 62 (6), 975–997.
Alves, R., Gonçalves, A.C., Rutella, S., Almeida, A.M., De Las Rivas, J., Trougakos, I.P., Sarmento Ribeiro, A.B., 2021. Resistance to tyrosine kinase inhibitors in chronic myeloid leukemia-from molecular mechanisms to clinical relevance. Cancers 13 (19), 4820.
Anelli, L., Zagaria, A., Specchia, G., Musto, P., Albano, F., 2021. Dysregulation of miRNA in leukemia: exploiting miRNA expression profiles as biomarkers. Int. J. Mol. Sci. 22 (13), 7156.
Bartel, D.P., 2018. Metazoan micrornas. Cell 173 (1), 20–51.
Cortes, J., Quintás-Cardama, A., Kantarjian, H.M., 2011. Monitoring molecular response in chronic myeloid leukemia. Cancer Cell 117 (6), 1113–1122.
Deininger, M.W., Shah, N.P., Altman, J.K., Berman, E., Bhatia, R., Bhatnagar, B., DeAngelo, D.J., Gotlib, J., Hobbs, G., Maness, L., 2020. Chronic myeloid leukemia, version 2.2021, NCCN clinical practice guidelines in oncology. J. Natl. Compr. Cancer Netw. 18 (10), 1385–1415.
Di Stefano, C., Mirone, G., Perna, S., Marfe, G., 2016. The roles of microRNAs in the pathogenesis and drug resistance of chronic myelogenous leukemia. Oncol. Rep. 35 (2), 614–624.
Ezeanosike, O.B., Afonne, O., 2017. Prognostic significance of micro RNA 150 marker in BCR-ABL positive chronic myeloid leukaemia patients on imatinib mesylate. Int. J. Contemp. Pediatr. 4 (5), 1557.
Gao, F., Wang, W., 2015. MicroRNA-96 promotes the proliferation of colorectal cancer cells and targets tumor protein p53 inducible nuclear protein 1, forkhead box protein O1 (FOXO1) and FOXO3a. Mol. Med. Rep. 11 (2), 1200–1206.
Ghazaryan, A., Goodwin, C.B., O'Connell, R.M., 2020. A microRNA prevents resistance to targeted therapy in chronic myeloid leukemia. 2020 Non-coding RNA Investigation.
He, Y., Jiang, X., Chen, J., 2014. The role of miR-150 in normal and malignant hematopoiesis. Oncogene 33 (30), 3887–3893.
Hochhaus, A., Baccarani, M., Silver, R.T., Schiffer, C., Apperley, J.F., Cervantes, F., Clark, R.E., Cortes, J.E., Deininger, M., Guilhot, F., 2020. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia 34 (4), 966–984.
Hosseinahli, N., Aghapour, M., Duijf, P.H., Baradaran, B., 2018. Treating cancer with microRNA replacement therapy: a literature review. J. Cell. Physiol. 233 (8), 5574–5588.
Hu, D., Shao, W., Liu, L., Wang, Y., Yuan, S., Liu, Z., Liu, J., Zhang, J., 2021. Intricate crosstalk between MYB and noncoding RNAs in cancer. Cancer Cell Int. 21 (1), 1–15.
Huang, T., Fu, Y., Wang, S., Xu, M., Yin, X., Zhou, M., Wang, X., Chen, C., 2019. miR-96 acts as a tumor suppressor via targeting the BCR-ABL1 oncogene in chronic myeloid leukemia blastic transformation. Biomed. Pharmacother. 119, 109413.
Jabbour, E., Hochhaus, A., Cortes, J., La Rosée, P., Kantarjian, H., 2010. Choosing the best treatment strategy for chronic myeloid leukemia patients resistant to imatinib: weighing the efficacy and safety of individual drugs with BCR-ABL mutations and patient history. Leukemia 24 (1), 6–12.
Kalmanti, L., Saussele, S., Lauseker, M., Proetel, U., Müller, M.C., Hanfstein, B., Schreiber, A., Fabarius, A., Pfirrmann, M., Schnittger, S., Dengler, J., Falge, C., Kanz, L., Neubauer, A., Stegelmann, F., Pfreundschuh, M., Waller, C.F., Spiekermann, K., Krause, S.W., Heim, D., Nerl, C., Hossfeld, D.K., Kolb, H.J., Hochhaus, A., Hasford, J., Hehlmann, R., 2014. Younger patients with chronic myeloid leukemia do well in spite of poor prognostic indicators: results from the randomized CML study IV. Ann. Hematol. 93 (1), 71–80.
Khoshnaw, N., Francis, B., Safar, B.M., Mahmood, S.S., Nore, B.F., 2014. Cytogenetic response in chronic myeloid leukaemia patients treated with imatinib mesylate homolog-drugs: 6 year's transitional study. J. Cancer Ther. 2014.
Kotagama, K., Chang, Y., Mangone, M., 2015. miRNAs as biomarkers in chronic myelogenous leukemia. Drug Dev. Res. 76 (6), 278–285.
Liu, Z., Shi, Y., Yan, Z., He, Z., Ding, B., Tao, S., Li, Y., Yu, L., Wang, C., 2020. Impact of anemia on the outcomes of chronic phase chronic myeloid leukemia in TKI era. Hematology 25 (1), 181–185.
Matti, B.F., Alwan, A.F., Alwan, A.F., 2013. Evaluation of the safety of imatinib mesylate in 200 Iraqi patients with chronic myeloid leukemia in the chronic phase: single-center study. Turkish J. Hematol. 30 (4), 387.
Mohamad, S.F.S., Elias, M.H., 2021. Potential treatment for chronic myeloid leukemia using microRNA: in silico comparison between plants and human microRNAs in targeting BCR-ABL1 gene. Egypt. J. Med. Human Genet. 22 (1), 1–8.
Mojtahedi, H., Yazdanpanah, N., Rezaei, N.J.S.C.R., Therapy, 2021. Chronic myeloid leukemia stem cells: targeting therapeutic implications, 12 (1), 1–27.
Poláková, K.M., Lopotová, T., Klamová, H., Burda, P., Trněný, M., Stopka, T., Moravcová, J., 2011. Expression patterns of microRNAs associated with CML phases and their disease related targets. Mol. Cancer 10 (1), 1–13.
Rahimi, H.R., Mojarad, M., Moghbeli, M., 2022. MicroRNA-96: A therapeutic and diagnostic tumor marker. Iran. J. Basic Med. Sci. 25 (1), 3.

Sabir, S., Alwatar, W.M. Ali, Matti, B.F., 2021. Characteristic of CD4+ CD25+ T cells in chronic myeloid leukemia patients treated with Imatinib Mesylate with different BCR-ABL transcripts levels response. Medico-Legal Update 21 (1).
Sakurai, M., Mori, T., Karigane, D., Kasahara, H., Tozawa, K., Matsuki, E., Kikuchi, T., Kato, J., Shimizu, T., Okamoto, S., 2016. Long-term treatment with imatinib is associated with decreased estimated glomerular filtration rate and hemoglobin level in patients with chronic myelogenous leukemia. Blood 128 (22), 1888.
Sampaio, M.M., Santos, M.L.C., Marques, H.S., de Souza Gonçalves, V.L., Araújo, G.R.L., Lopes, L.W., Apolonio, J.S., Silva, C.S., de Sá Santos, L.K., Cuzzuol, B.R., 2021. Chronic myeloid leukemia-from the Philadelphia chromosome to specific target drugs: a literature review. World J. Clin. Oncol. 12 (2), 69.
Srutova, K., Curik, N., Burda, P., Savvulidi, F., Silvestri, G., Trotta, R., Klamova, H., Pecherkova, P., Sovova, Z., Koblihova, J., 2018. BCR-ABL1 mediated miR-150 downregulation through MYC contributed to myeloid differentiation block and drug resistance in chronic myeloid leukemia. Haematologica 103 (12), 2016.
Starczynowski, D.T., Morin, R., McPherson, A., Lam, J., Chari, R., Wegrzyn, J., Kuchenbauer, F., Hirst, M., Tohyama, K., Humphries, R.K., 2016. Genome-wide identification of human microRNAs located in leukemia-associated genomic alterations. Blood J. Am. Soc. Hematol. 117 (2), 595–607.
Szymczyk, A., Macheta, A., Podhorecka, M., 2018. Abnormal microRNA expression in the course of hematological malignancies. Cancer Manag. Res. 10, 4267.
Xu, L.-H., Guo, Y., Zhang, X.-L., Chen, J.-J., Hu, S.-Y., 2016. Blood-based circulating microRNAs are potential diagnostic biomarkers for leukemia: result from a meta-analysis. Cell. Physiol. Biochem. 38 (3), 939–949.