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Assessment of minimal residual disease in patients with B-cell acute lymphoblastic leukemia using EuroFlow: Relation to other prognostic factors

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ABSTRACT

Purpose: Presence of post-therapeutic leukemia cells in the bone marrow is defined as minimal residual disease (MRD) in acute lymphoblastic leukemia. Purpose of monitoring MRD is to determine the response to treatment and the risk of leukemia relapses.

Materials and methods: This is a retrospective study of 66 B-cell acute lymphoblastic leukemia patients treated at King Fahad Specialist Hospital-Dammam from November 2018 to December 2020. We tested MRD results on day-29 of treatment from bone marrow aspiration and correlated the relationship of MRD found to other prognostic factors such as patient age, gender, hematological parameters at diagnosis such as white blood count (WBC), hemoglobin level, absolute neutrophil count, platelets, percent blast cell in the bone marrow and blast cell in peripheral blood at diagnosis, aberrant markers of immunophenotype of blasts at diagnosis, and cytogenetic abnormalities.

Results: On day 29, a significant correlation between WBC and MRD status was discovered. Also, a significant correlation between peripheral blood blast percentage and MRD status was determined on day 29. Also, hemoglobin, neutrophils, and platelets are not significantly associated with MRD status. Similarly, cytogenetic variables and risk stratification are not significantly associated with MRD status. Furthermore, CDw65+ and CD15+ are the only aberrant markers significantly associated with MRD status, even though they are not commonly expressed in patients.

Conclusion: CD22, TdT, cyCD79a, CD81, and CD9 were other immunophenotype markers expressed by most participants. Hyperdiploidy was the most common karyotype.

Keywords: minimal residual disease, B-cell acute lymphoblastic leukemia, EuroFlow

INTRODUCTION

At least 25% of BM is dedicated to the B-cell lineage [1]. Almost 85% of B-cell acute lymphoblastic leukemia (B-ALL) cases can be treated successfully, but there is a need for continuous monitoring. This results from the probability of relapses in leukemia cases, and thus, minimal residual disease (MRD) is the most sensitive test that can detect these minimal residues. A malignant blast rate higher than 0.01% in the bone marrow is considered MRD positive and has a high chance of relapse [2-5]. MRD is a powerful predictor of acute leukemia relapses. It helps with therapeutic stratification for acute lymphoblastic leukemia (ALL) protocols [1]. A measurable residual disease refers to the number of leukemic cells in the patient's BM during or after treatment and accounts for more than 0.01%. These cells can recur and cause relapses [6]. Over the last two decades, it has been proven that MRD has prognostic importance in the treatment of ALL. MRD results are critical for stratifying patients based on the type of disease they have. It ensures the best decision is made on the therapeutic type and improves the patient's condition [7]. The MRD tests are highly effective since they are very sensitive. Some of these tests that are commonly used to identify the level of MRD include second-generation flow cytometry (EuroFlow), polymerase chain reaction (PCR) tests, and next-generation sequencing [8, 9]. An MRD positive test means the presence of a residual aberrant clone at a level of 0.01 [10]. An MRD negative result implies a residual clone below the cut-off value of 0.01% [11]. This article investigated the correlation between MRD status at day-29 in B-ALL patients and other prognostic factors considered, including demographic characteristics, hematological parameters, karyotype, cytogenetic abnormalities, aberrant markers, and immunophenotype of blasts at diagnosis. Therefore, this study analyzed the correlation between MRD status on day-29 and other

prognostic factors in patients who have undergone treatment for B-ALL.

MATERIALS AND METHODS

Retrospective research was structured to deal with objectives directly. In this research, the quasi-experimental research design was used to analyze and understand the correlation between B-ALL patients' MRD at day-29 status and the patients' prognostic factors. This study's population consists of patients already diagnosed and treated for B-ALL at King Fahad Specialist Hospital-Dammam. The patients were treated between the stipulated dates of November 2018 and December 2020. The patients included also need to have been tested for MRD status using the second-generation flow cytometry method (EuroFlow). The study used primary data collection methods based on analyses of recorded results. The research process sought the IRB's consent to conduct the study at the King Fahad Specialist Hospital-Dammam on November 25, 2020 (IRB study number LAB0316). The permission included a request to access the relevant databases since the information would consist of sensitive patient data. However, the patient information's sensitivity and the data's security were addressed below. After obtaining permission, the researcher went over the inclusion and exclusion criteria to ensure they were verified before entering them into the database in the form of a query. The researcher then applied the data analysis software and analyzed it to get the results. The patient exclusion criteria include patients who have not been diagnosed with B-ALL by flow cytometry, bone marrow morphology, or cytogenetics. Patients who do not have CD19+ ALL, as confirmed by flow cytometry at the King Fahad Specialist Hospital-Dammam between the stipulated dates of 2018 and 2020, Patients who have not been tested for MRD status using the second-generation flow cytometry method are excluded. Data analysis involves the process of converting data into more reliable information for inferencing. The right tools are needed to conduct data analysis for the statistical data; in this case, statistical software. The statistical software used was the SPSS statistical package analysis, which provided results in tabulated forms that are easy to interpret. The SPSS tool also accommodated large data sets and carried out many analyses. This study conducted a correlation analysis by relating the MRD status to the various variables. A statistical test's choice depends on the researcher's desired objective and the available variable type. The study's aim is correlation analysis, but the research team had different forms of variables in the data set. More specifically, categorical variables represent the majority of the variables in the data set, while continuous variables, notably age, white blood count (WBC), etc. For the first objective, the dependent variable was categorical, while the independent variable was a mixture of continuous and categorical variables. Therefore, to analyze continuous independent and continuous variables, the research team first used the independent t-test to compare means and then used the point-biserial correlation, a special case of the Pearson product-moment correlation coefficient, to estimate the correlation between the two variables. For categorical independent variables, the Pearson Chi-square test was utilized to test for the association. Simultaneously, the phi coefficient was used to determine the strength and direction of the correlation between the two variables. For the second objective, a case study approach was used for the patients that experienced relapse. The test results at the different stages were analyzed and a conclusion was drawn.

Table 1. Correlations between MRD on day 29 and hematology/demographic characteristics

Variable		Value
Gender	Male: n (%)	34 (51.5)
	Female: n (%)	32 (48.5)
Age (years)	Mean (SD)	11.08 (13.16)
WBC ($\times 10^9$/L)	Mean (SD)	25.26 (41.01)
PB blast cell (%)	Mean (SD)	43.85 (35.84)
BM blast cell (%)	Mean (SD)	75.05 (26.67)
Hemoglobin (g/dL)	Mean (SD)	8.53 (1.48)
Neutrophils %	Mean (SD)	7.91 (9.46)
Platelets ($\times 10^9$/L)	Mean (SD)	79.82 (81.22)

Table 2. Immunophenotyping at time of diagnosis

Markers	n (%)			
	Positive	Negative	NA	Dim
CD 9	54 (81.8)	5 (7.6)	7 (10.6)	0 (0.0)
CD38	56 (84.8)	8 (12.1)	2 (3.0)	0 (0.0)
CD22	64 (97.0)	1 (1.5)	1 (1.5)	0 (0.0)
CD24	54 (81.8)	5 (7.6)	7 (10.6)	0 (0.0)
TdT	61 (92.4)	3 (4.5)	2 (3.0)	0 (0.0)
CD123	46 (69.7)	13 (19.7)	7 (10.6)	0 (0.0)
CD81	55 (83.3)	4 (6.1)	7 (10.6)	0 (0.0)
CD19	100 (66.0)	0 (0.0)	0 (0.0)	0 (0.0)
cyCD79a	63 (95.5)	2 (3.0)	1 (1.5)	0 (0.0)
CD45	2 (3.0)	12 (18.2)	0 (0.0)	52 (78.8)
CD34	49 (74.2)	17 (25.8)	0 (0.0)	0 (0.0)
CD10	65 (98.5)	1 (1.5)	0 (0.0)	0 (0.0)
CD20	24 (36.4)	39 (59.1)	3 (4.5)	0 (0.0)
CD58	63 (95.5)	2 (3.0)	1 (1.5)	0 (0.0)
CD66c	34 (51.5)	30 (45.5)	2 (3.0)	0 (0.0)
CDw65 & CD15	2 (3.0)	60 (90.9)	4 (6.1)	0 (0.0)
cyIgM	6 (9.1)	53 (80.3)	7 (10.6)	0 (0.0)
CD33	6 (9.1)	57 (86.4)	3 (4.5)	0 (0.0)
CD13	2 (3.0)	60 (90.9)	4 (6.1)	0 (0.0)
CD21	1 (1.5)	58 (87.9)	7 (10.6)	0 (0.0)
CD13	5 (7.6)	59 (89.4)	2 (3.0)	0 (0.0)

RESULTS

The study included 66 subjects. Of these, males constituted 51.5%, while females comprised 48.5% of the participants. The average age of participants was 11.08 years (standard deviation [SD] = 13.16). The average WBC was 25.26 (SD = 41.01). The average percentage of the blast in the bone marrow was 43.85%, while the peripheral blood was 75.05% (SD = 26.67). The average hemoglobin count was 8.53 (SD = 1.48), while the neutrophil count was 7.91 (SD = 9.46) and the platelet count was 79.82 (SD = 81.22) (**Table 1**).

The results presented in **Table 2** indicated in CD9 was expressed in 81.8% of the participants, while no expression was expressed in 7.6% of the participants. CD38 is expressed in 84.8% of the patients but not expressed in 12.1% of the participants. Unfortunately, data on CD38 was not available. 97% of patients tested positive for CD22 at diagnosis, while 1.5% tested negative, although data was not available for 1.5% of the patients. 81.8% of the patients expressed CD24, while 92% expressed TdT. 7.6% and 4.5% of patients did not express CD24 and TdT, respectively. CD123 was positive for 69.7% of the patients and negative for 19.7% of the patients. CD81 is present in 83.3% of the patients, while it is negative for 6.1%

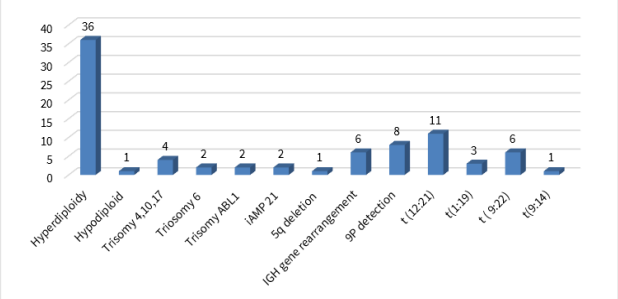

Figure 1. Frequency of cytogenetic abnormalities at diagnosis (Source: Authors' own elaboration)

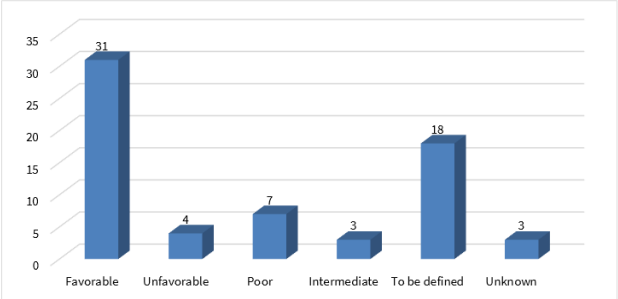

Figure 2. Frequency cytogenetic risk stratification at diagnosis (Source: Authors' own elaboration)

Table 3. Correlations between MRD on day 29 and aberrant immunophenotype

Aberrant marker	MRD status on day 29			Chi (p)	r
	Positive: n (%)	Negative: n (%)	Total		
CD 9 bright	1 (5)	19 (95)	20	4.063 (0.051)[a]	-0.250
CD123 Bright	3 (14)	18 (86)	21	0.012 (0.990)	0.014
CD66c +	4 (12)	30 (88)	34	3.022 (0.121)	0.820
CDw65, CD15 +	1 (50)	1 (50)	2	8.254 (0.037)	0.356
CD33 +	3 (50)	3 (50)	6	4.244 (0.074)	0.258
CD13 +	0 (0)	2 (100)	2	0.516 (0.990)	0.089
NG2 +	0 (0)	1 (100)	1	0.254 (0.990)	0.063

Table 4. Correlations between MRD on day 29 and cytogenetics abnormalities

Aberrant marker	MRD status on day 29			Chi (p^b)	r^c
	Positive: n (%)	Negative: n (%)	Total		
Hyperdiploidy	5 (14)	31 (86)	36	1.883 (0.170)[a]	-0.170
Hypodiploid	0 (0)	1 (100)	1	0.254 (0.990)	-0.063
Trisomy 4, 10, 17	0 (0)	4 (100)	4	0.786 (0.990)	-0.110
Triosomy 6	0 (0)	2 (100)	2	1.161 (0.363)	0.134
Trisomy ABL1	1 (50)	1 (50)	2	1.161 (0.363)	0.134
iAMP 21	1 (50)	1 (50)	2	1.161 (0.363)	0.134
5q deletion	1 (100)	0 (0)	1	4.063 (0.200)	0.250
IGH gene rearrangement	0 (0)	6 (100)	6	1.653 (0.335)	-1. 159
9P detection	1 (13)	7 (87)	8	0.321 (0.685)	-0.070
t (12:21)	2 (18)	9 (82)	11	0.027 (0.990)	-0.021
t(1:19)	0 (0)	3 (100)	3	0.786 (0.605)	-0.110
t (9:22)	2 (33)	4 (67)	6	1.354 (0.574)	0.144
t(9:14)	1 (100)	0 (0)	1	4.063 (0.200)	0.250
Hyperdiploidy	5 (14)	31 (86)	36	1.883 (0.170)[a]	-0.170
Hypodiploid	0 (0)	1 (100)	1	0.254 (0.990)	-0.063

and not available for 10.6%. CD19 is expressed in all patients, making it an important B-ALL marker. CyCD79a is positive for 95.5% of the participants, but negative for 3% of them. CD45 is positive for 3% of participants, negative for 18.2% of participants, and dim to negative for 78.8% of the participants. 74.2% of the participants expressed CD34 compared to 25.8% who were negative for CD34. Similarly, 98.5% of participants are positive on CD10, but 1.5% are negative. 95.5% of participants tested positive for CD58, with 3% testing negative. 51.5% were positive on CD66c, while 30% were negative on CD66c. 3% of the patients expressed CDw65 and CD13, while 90.9% did not express CDw65 and CD13. 9.1% of the patients were positive for cylgM and CD33, but as 80.3% were negative for cylgM, 86.4% were negative for CD33. 1.5% of patients expressed CD21, while 87.9% did not express CD21.

Figure 1 showed that hyperdiploidy was present in 36% of patients, while hypodiploidy was present in 1% of patients. Moreover, trisomy 4, 10, and 17 were found in 4% of the respondents, while trisomy 6, trisomy ABL1, and iAMP-21 were found in 2% of the patients. IGH rearrangement was present in 6%, with 9p detection in 8% of patients. t (12; 21) was found in 11% of the respondents, t (1; 19) was found in 3% of the respondents, t (9; 22) in 6% of the respondents, and t (9; 14) in 1% of the respondents.

Figure 2 represents the frequency of cytogenetic risk stratification at diagnosis. The result showed that 31% of the participants were considered favorable risks, 18% were to be defined as risks, 4% were unfavorable risks, 7% were poor risks, 3% were intermediate risks, and 3% were unknown risks as shown in **Figure 2**.

The results for the test of association between aberrant immunophenotype and MRD status on day 29 found that CDw65, CD15+ were significantly associated with MRD status (r = 0.356), as shown in **Table 3**.

Table 4 presents the association between cytogenetic abnormalities and MRD status on day 29. The result showed that none of the cytogenetic abnormalities were significantly associated with MRD status on day 29, as shown in **Table 4**.

DISCUSSION

The research team expected that the minimum residual disease was significantly higher in men than in women. However, the research team found that both gender and age do not significantly affect MRD status after 29 days of treatment. This result is consistent with the findings in [12] that found no significant association of age and gender with MRD status in a sample of 362 pediatric patients at the Indus Hospital. However, some hematological factors are paramount for MRD negativity, namely WBC and PB blast cells. Moreover, white blood cells and PB blast cells are significantly higher for positive MRD participants than for negative ones. Both variables are also significantly correlated with MRD status on day 29. Conversely, other factors such as BM blast cells, hemoglobin, neutrophils, and platelets count. The most commonly expressed aberrant markers, namely CD81+, CD10 bright, and others, were not significantly associated with MRD status at day 29. The significantly associated aberrant markers are CD58-and CDw65, CD15+, and both were expressed in only two patients each, and both have a medium-positive association with MRD status. Neither the cytogenetic factors nor the cytogenetic risk stratification are significantly associated with MRD status. Similarly, the study in [7] also found that cytogenetic factors are not associated with MRD status. However, the insignificant association between risk stratification and MRD status contradicts the result in [13, 14] that found that high-risk patients were significantly more likely to be MRD positive than standard-risk patients and also found significant evidence for an association between MRD status and cytogenetic abnormalities. Besides, it was found that cytogenetic abnormalities like t (9; 22) and t (1; 19) are significantly correlated with MRD status in childhood B-ALL for an Egyptian sample. This result is in contrast with the findings of this study. The results point out the fact that the methods should be used to complement one another, but not as substitutes [15-19]. Turning to the correlation between MRD status by EuroFlow and cytogenetic follow-up, there was a significant association between three to five times. There is sufficient data to calculate Chi-square statistics between EuroFlow's MRD status and morphological relapse incidence. Fortunately, there was sufficient data to calculate Chi-square statistics. The correlation of MRD status with disease relapses was the strongest for a cytogenetic follow-up than for all others, except for the fifth time when EuroFlow was strongest. The result implies that none of the MRD techniques is a direct substitute for another but should complement one another. The case study analysis of the patients who suffered relapses confirms that relapse is associated with blast cell resurgence in the bone marrow and peripheral blood cells in some cases. This finding is supported by [8], which found that patients who had no detectable blood blasts by flow cytometry on day 8 were rarely MRD positive on day 29.

CONCLUSION

This research sets out to assess the minimum residual disease in patients with B-ALL in relation to other risk factors. The data was collected from the medical histories and laboratory tests of B-ALL patients from the King Fahad Specialists Hospital-Dammam, Saudi Arabia. The analysis of the data revealed that CD19 was the only immunophenotype marker expressed by all the patients. CD22, TdT, cyCD79a, CD81, and CD9 were other immunophenotype markers expressed by most participants. Hyperdiploidy was the most common karyotype. The study showed that demographic characteristics are not significant for MRD status as there was no significant relationship between MRD status on day 29 and age or gender. On the other hand, WBC, and PB blast were significantly associated with MRD status on day 29. Also, CDw65 and CD15 aberrant markers were significantly associated with MRD status on day 29. However, more experiments need to be carried out to substantiate this claim. None of the cytogenetic factors or the cytogenetic risk stratification is significantly associated with MRD status. Given this study's findings, there is a need to investigate some aberrant markers more closely. These markers were found in a lower proportion of participants but were found to be significantly related to MRD status. There is a need for a detailed analysis of whether they are specific markers for B-ALL or can be found in other ALL categories. Their prognosis needs to be entirely determined in a setting where patients who express these markers are followed over time needs to be carried out to substantiate this claim.

Author contributions: FMA & SMA: conceptualization; **FMA:** supervision; **SMA:** investigation and writing–original draft preparation; **SSA & FMH:** methodology; **HNR:** validation; **SA:** writing–review and editing; **SSAK:** project administration; & **AMA:** funding acquisition. All authors have agreed with the results and conclusions.

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Ethical statement: The authors stated that the study was approved by the King Fahad Specialist Hospital-Dammam on 25 November 2020 with IRB study number LAB0316. Written informed consents were obtained from the participants.

AI statement: The authors stated that no generative AI or AI-based tools were used in any part of the study, including data analysis, writing, or editing.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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