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Original Article

Prognostic significance of CD56 and CD7 in acute myeloid leukaemia and their outcome

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Abstract: Background: The expression of CD7 and CD56 in Acute Myeloid Leukaemia was considered to be a poor prognostic factor for overall survival, complete remission but the result were limited and more prognostic parameter need to study. The importance of validating new prognostic parameters in acute myeloid leukaemia was the reason to investigate the prognostic significance of CD7 and CD56. Material and methods: Study involving patients who had newly diagnosed AML. Imunophenotyping was carried out at diagnosis and after induction therapy also compared with molecular and cytogenetics studies. End points were the leukaemia free survival, relapse-free survival, and overall survival. Result: All 87 patients that were included in the study were divided into 4 groups based on expression of CD56 and CD7 as Group 1 (CD7+, CD56+), group 2 (CD7-, CD56+), group 3 (CD7+, CD56-) and group 4 (CD7-, CD56-) and were compared clinically and immunophenotypically. The clinical parameters that were correlated were age, sex, LFS (leukaemia free survival), Overall survival (OS) and Relapse Free survival (RFS) and were followed up with MRD at day 30 along with Molecular abnormalities and cytogenetic karyotyping. Conclusion: The study data suggest that prognostic significance of CD7 and CD56 expression in patients of acute myeloid leukaemia could be indicative of poor prognosis as it was also associated with the adverse prognostic parameter (Minimal Residual Disease, high risk, shorter overall survival).

Keywords: Acute myeloid leukaemia, minimal residual disease, overall survival, relapse free survival, leukaemia free survival, leukaemia-associated immunophenotypes

Introduction

Acute myeloid leukaemia (AML) is heterogeneous disorders which have different morphological, immunophenotypic and cytogenetic patterns [1, 2]. The AML was previously classified by French-American-British (FAB) system, based on morphologic and cytochemical aspects. [2] Immunophenotypic methods were later introduced as part of the diagnostic criteria. AML can be divided into different categories by their aberrancies, which are asynchronous antigen expression, lineage infidelity, antigen over expression, aberrant light-scatter properties and absence of lineage-specific antigens [4]. Lineage infidelity is the expression of lymphoid markers (CD2, CD3, CD5, CD7, CD10, and CD19) in AML and represent important independent prognostic factors that affect the clinical outcome of these patients [5].

Immunophenotyping is widely used and complementary to morphological, cytochemical and cytogenetics studies, allowing a more precise diagnosis and classification of AML. Minimal residual disease (MRD) denotes the presence of leukemic cells down to levels of $1:10^4$ to $1:10^6$ as compared with 1:20 in morphology-based assessments, therefore multiparameter flow cytometry are increasingly applied to quantify the degree of both response to therapy and MRD [3].

CD56 and CD7 expression in AML and MRD can be used for prognostication of AML. CD56 antigen [6] is a NK cell marker, which expressed in several lymphohematopoietic neoplasms including acute myeloid leukaemia (AML). The presence of CD56 antigen on blast cells may influence complete remission (CR) duration and survival also associated with short overall survival, lower CR rates and shorter duration of CR [7, 8].

CD7 is Lymphoid marker, which expressed in 30% of AML cases and linked with poor progno-

sis in myeloid malignancies [9]. The prognosis of prognostic group of CD7 and CD56 are correlated with their MRD status, Post induction status, molecular status and their cytogenetic prognosis also OS, RFS and LFS were plotted by Kaplan-Meier method.

Material and methods

Patients

It was an observational study carried out in the cancer department of AIIMS, New Delhi, during year 2013-2016. Fresh bone marrow samples of AML patients were used in the study. Bone marrow obtained from 100 newly diagnosed AML patients (Study included all age group and excluding cases without MRD studies and also Acutepromyelocyticleukeima cases). Routine diagnostic flow cytometer experiment was performed on bone marrow samples. The study was done on the 87 patients as the 13 cases did not receive any form of treatment. Diagnosis of patients was based on immunophenotyping which was later correlated to the other prognostic parameters. The WBC count, FAB diagnosis, gender, age, clinical and outcome data were collected for each patient from the records section of department. Cytogenetic and molecular abnormality analysis was done on the same samples in other lab and correlated. MRD data for all patients was received as a part of routine diagnostic protocol. No additional tests were performed for this study. Response to therapy was assessed according to standardized criteria.

For Normal control 10 bone marrow samples obtained from patients with solid tumors and lymphoma, uninvolved by disease and post-induction regenerating marrows from patients with acute lymphoblastic leukaemia, were used as controls to obtain the normal expression pattern of the markers used in the study.

Morphological analysis

The morphological analysis was performed using a bone marrow smear or a peripheral blood smear after anticoagulation with EDTA stained with May Grunwald-Giemsa. The diagnostic bone marrow cytological exam subjectively assessed the cellularity, hematopoiesis, and myeloid blasts percentage. Post induction bone marrow slide was also seen for remission status for correlation.

Immunophenotyping

The bone marrow or peripheral blood samples were collected in EDTA. The sample was processed by standard stain-lyse-wash method. The instrument aligment was done by Flow Check fluorospheres (BC, Hialeah, FL, USA). Flow Set beads (BC, Hialeah, FL, USA) was used for voltage standardization and compensation. For flow cytometric analysis experiment was perform on Coulter FC500 instrument [Beckman Coulter (BC), Hialeah, FL, USA]. 200,000 events were acquired at follow up in all cases and data were stored as list mode file. Different antibodies with CD34 and CD45 as backbone markers in each tube were run for the test. The antibodies used were MPO, 79a, CD13, CD33, CD117, CD7 CD56, HLA-DR from Beckman Coulter (BC), Hialeah, FL, USA. Gating strategy include the debris exclusion by time gate (for taking continuous sample stream). On CD45/SS plot at intermediate/low side scatter region a gate was formed, followed by back gating on the CD34+ population and removal of CD19+ hematogones from analysis. These cells were used to identify LAIP in each case.

Risk status (molecular abnormalities and cytogenetic)

Bone marrow (BM) or peripheral blood sample was used. Three to five milliliters samples were collected in ethylenediaminetetraacetic acid vials for performing molecular mutations and in heparinized syringes for conventional karyotyping and processed within 6-24 h of collection. Molecular abnormality experiment was done as per standard procedure with PCR. Mutation analysis was done for Nucleophosphomin (NPM1), FMS-like tyrosine kinase 3 (FLT3), AML ETO and Core binding factor (CBF genes). Cytogenetic analysis was performed on metaphases from bone marrow aspirates taken at diagnosis with the use of standard procedures. Patients could be separated into three categories: favourable cytogenetics include nv(16) or t(8;21), t(15;17) or t(16;16) and inv(16), Intermediate cytogenetics includes Normal cytogenetics, +8 alone, t(9;11), Other non-defined and poor cytogenetics include Complex (3 clonal chromosomal abnormalities), Monosomal karyotype, -5, 5q-, -7, 7q-, 11q23, non t(9;11), inv(3), t(3;3), t(6;9), t(9;22). The information on cytogenetic and molecular genetic abnormalities was used to determine the risk

category the patient mentioned below in **Table 1**.

Statistical analysis

A log binomial model was used to analyse the data. The outcomes of interest were the response of induction and relapse after achieving CR. Whether the patient was LAIP positive or negative was included in each model as a predictor. A number of potential confounders were identified (age at diagnosis, gender, MRD, cytogenetic risk group and molecular abnormalities). The Kaplan-Meier methods, log rank test and Cox's proportional hazards model were used and only those with a *p*-value of less than 0.25 in univariate analyses were included in the model. Both unadjusted and adjusted risk ratios were calculated to compare prognostic group with MRD and risk.

OS was measured from the date of diagnosis until date of death or last date available and RFS for patients who achieved CR was measured from the date of diagnosis to relapse while LFS for patients who achieved CR was measured from the date of CR to relapse. OS, RFS and LFS were plotted by Kaplan-Meier method and differences between curves were analysed by the log-rank test. The log-rank test was used to validate equality of the survival distributions. This analysis was performed in STATA 11.1. A p-value ≤ 0.05 was required for statistical significance.

Results

Group criteria

All 87 patients that were included in the study were divided into 4 groups based on expression of CD56 and CD7 as Group 1 (CD7+, CD56+), Group 2 (CD7-, CD56+), Group 3 (CD7+, CD56-) and Group 4 (CD7-, CD56-) (**Figure 1**). Most abundant immunophenotypic group was group 4 (CD7- CD56-) with 47 cases (54.02%) followed by group 2 (CD7- CD56+) with 21 cases (24.14%), group 1 (CD7+ CD56+) with 10 cases and group 3 (CD7+ CD56-) with 9 cases respectively. The clinical parameters correlated in study, were age, sex, LFS (leukaemia free survival), Overall survival (OS) and Relapse Free survival (RFS) and followed up with MRD at day 30 along with Molecular abnormalities namely NPM1, CBF, AML-ETO and FLT3 and cytogenetic karyotyping. The observations were noted in groups having either one or both aberrant phenotype at diagnosis namely groups 1-3 and compared with that of group 4 with both markers were negative. This was used to predict the overall prognosis and outcome of patients in these groups (**Table 2**). Male female ratio were 9:1, 1.4:1, 8:1 and 1.9:1 in Group 1, 2, 3 and 4 respectively.

Minimal residual disease studies

The incidence of MRD positivity was shown in every group but Group 1 had reported 70% of it cases as MRD positive while the lowest cases of MRD positivity was reported in Group 4, which was 31.9%. Other Group also showed MRD positivity, which were 61.9% and 55.5% for Group 2 and Group 3 respectively. This result was similar to the morphological remission. Group 4 with both markers negative showed the highest remission rates at Day 28 with 74.4% and group 1 with the maximum incidence of Non remission marrows 50%.

Molecular abnormalities

Molecular abnormalities were analysed for NPM1, FLT3, AML ETO and CBF genes. Their presence or absence in each group indicates the risk factor for the group. NPM1 presence had the favourable prognosis, if not present with FLT3. NPM1+ and FLT3+ had the highest incidence in Group 1 with 1 (10%) cases while other group were negative for dual positivity. NPM1- FLT3+ were higher in the group 1 with 2 (20%) cases while group 3 and group 4 had 1 (11.1%), 3 (6.38%) respectively. AML-ETO was expressed at higher rate in group 2 and group 3 with 8 (38%) and 3 (33.3%) cases respectively while group 1 had just one case as positive (*p* value 0.45). CBF was positive in group 1 and group 3 with 1 (10%) and 1 (11.1%) cases respectively while group 2 was shown less frequently with *p* value 0.88.

Cytogenetics

Cytogenetic was evaluated in the group for different criteria, which is Favourable, intermediate and unfavourable. The favourable cytogenetics was more in Group 2, with 13 (61.9%) while the least favourable Group was 1, with 3 (30%). The unfavourable cytogenetics incidence was mostly seen in Group 4, with 9 (19.1) while least incidence was in Group 1, which is 1 (10%). The results were statistically insignificant.

Table 1. Risk status based on validated cytogenetics and molecular abnormalities NCCN Guidelines version 2.2014 acute myeloid leukaemia

RISK STATUS	CYTOGENETICS	MOLECULAR ABNORMALITIES
low-risk	nv(16) 2, 3 or t(8;21) 2 t(15;17) 2 or t(16;16)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD, or isolated biallelic CEBPA mutation
Intermediate-risk	Normal cytogenetics, +8 alone, t(9;11), Other non-defined	(8;21), inv(16), t(16;16): with c-KIT5 mutation
high-risk	Complex (3clonalchromosomal abnormalities), Monosomal karyotype, -5, 5q-, -7, 7q-, 11q23 - non t(9;11), inv(3), t(3;3), t(6;9), t(9;22)4	Normal cytogenetics: with FLT3-ITD mutation

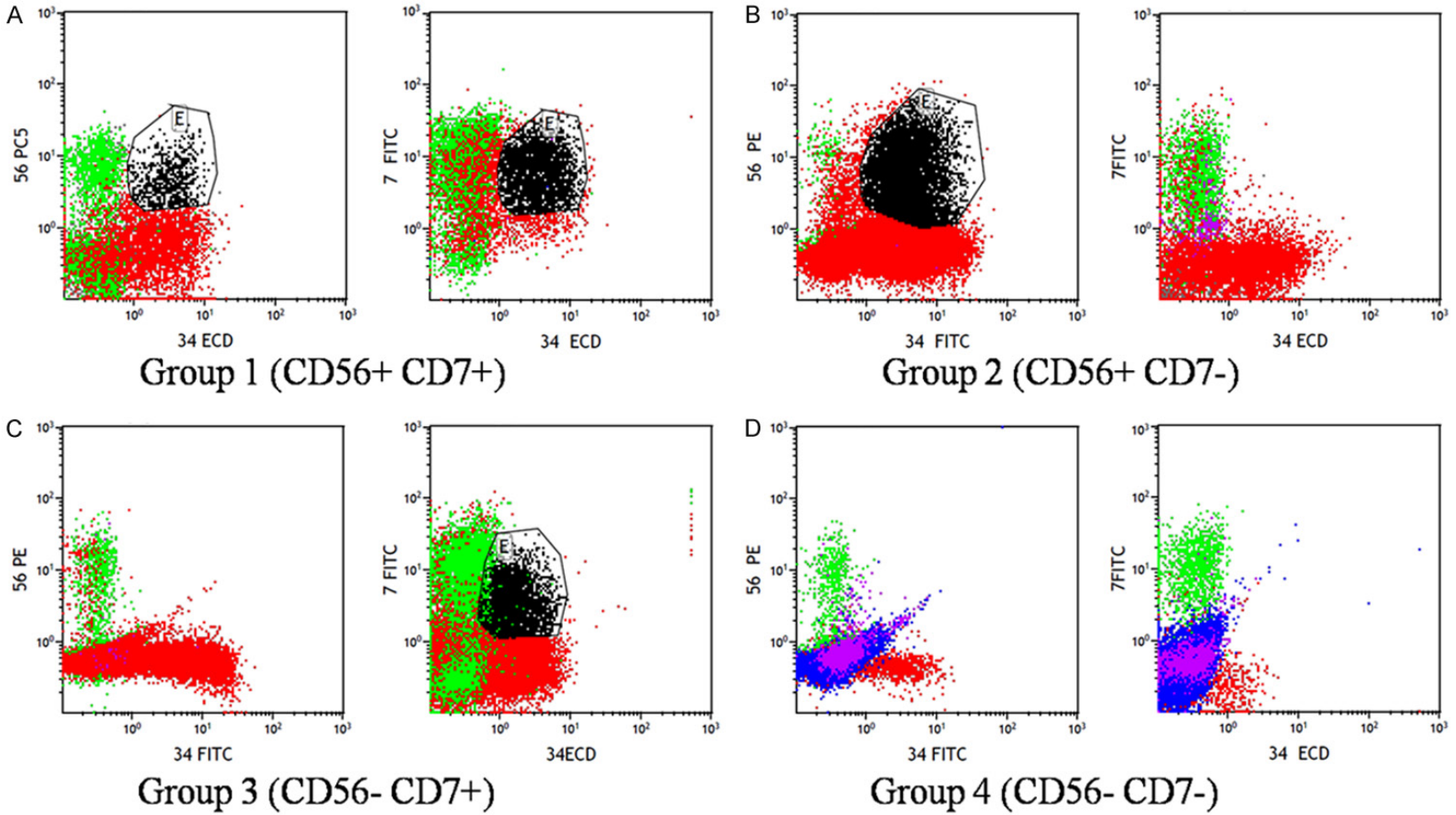

Figure 1. Flow cytometry plots showing the expression of CD7 and CD56 in four immunophenotypic categories of acute myeloid leukaemia Plot (A) illustrates the co-expression of CD7 and CD56 in blast populations. Plot (B) illustrates the positivity for CD56 and no expression of CD7. Plot (C) shows blast cells expressing CD7 but not CD56. Plot (D) shows the negative expression of both CD7 and CD56.

Table 2. Immunophenotypic groups and their prognostic characteristics

Groups	CD7+ CD56+ (1) n=10	CD7- CD56+ (2) n=21	CD7+ CD56- (3) n=9	CD7- CD56- (4) n=47	*P* value
F, Prevalence (95% CI)	10, 11 (0.5, 0.2)	21, 24 (0.15, 0.34)	9, 10 (0.04, 0.1)	47, 54 (0.42, 0.64)	
Sex ratio (%)					
Male	9 (15)	12 (20)	8 (13.3)	31 (51.6)	0.15
Female	1 (3.7)	9 (33.3)	1 (3.7)	16 (59.2)	
Male female ratio	9:01	1.4:1	8:01	1.9:1	
MRD					
MRD+ f (%)	7 (70)	13 (61.9)	5 (55.5)	15 (31.9)	0.034
MRD- f (%)	3 (30)	8 (38.1)	4 (44.5)	32 (68.1)	
Ratio	2.3:1	1.6:1	1.2:1	0.46:1	
Cytogenetics					
Favorable	3 (30)	13 (61.9)	3 (33.4)	15 (31.9)	0.267
Intermediate	6 (60)	5 (23.8)	5 (55.5)	23 (48.9)	
Unfavorable	1 (10)	3 (14.2)	1 (11.1)	9 (19.1)	
Molecular abnormality					0.67
NPM1+ FLT3+	1 (10%)	0	0	0	
NPM1+ FLT3-	0	1 (4.7%)	1 (11.1%)	3 (6.38%)	
NPM1- FLT3+	2 (20%)	0	1 (11.1%)	3 (6.38%)	
NPM1- FLT3-	6 (60%)	20 (95.2%)	7 (77.7%)	41 (87.23%)	
AML-ETO					
Positive	1 (3.8)	8 (30.7)	3 (11.5)	14 (53.8)	0.45
negative	9 (96.2)	13 (69.3)	6 (89.5)	33 (46.2)	
CBF					
Positive	1 (12.5)	1 (12.5)	1 (12.5)	5 (62.5)	0.88
negative	9 (87.5)	20 (87.5)	8 (87.5)	42 (37.5)	
Mean survival (Days)					
OS	399+179	462+125	409+139	521+96	0.005
LFS (days)	220.5+180	361.5+141	300.2+177	381.4+151	0.024
RFS (Days)	249+178	407+144	311+164	424+177	0.015
Median survival (Days)					
OS (Days)	374 (167, 593)	527 (223, 621)	511 (208, 534)	534 (171, 871)	0.005
LFS (days)	185 (14, 505)	462 (103, 513)	255 (64, 483)	433 (96, 703)	0.024
RFS (Days)	228 (48, 541)	511 (139, 586)	289 (127, 534)	515 (172, 871)	0.015
Overall survival					
Death	4 (40)	6 (28)	3 (33.3)	7 (14.8)	0.043
Survival prob. (455 days)	0.56 (0.20-0.80)	0.71 (0.47-0.86)	0.74 (0.28-0.33)	0.93 (0.80-0.97)	
Incidence rate (per 1000)	1	0.61	0.81	0.28	
Leukemia free survival					
Relapse	6 (60)	6 (28.5)	5 (55.5)	11 (23.4)	0.005
Survival prob. (455 days)	0.30 (0.04-0.61)	0.70 (0.45-0.85)	0.44 (0.13-0.71)	0.75 (0.59-0.85)	
Incidence rate (per 1000)	2.7	0.7	1.8	0.6	
Relapse free survival					
Relapse	6 (60)	6 (28.5)	5 (55.5)	11 (23.4)	0.002
Survivalprob. (455 days)	0.32 (0.58-0.63)	0.70 (0.45-0.85)	0.44 (0.13-0.71)	0.81 (0.66-0.90)	
Incidence rate (per 1000)	2.4	0.6	1.6	0.51	

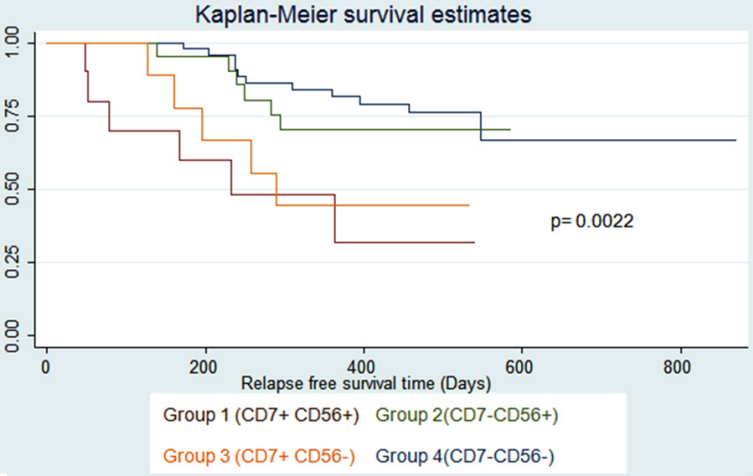

Figure 2. Kaplan-Meier Relapse Free survival analysis also shows a similar trend on survival analysis group 4 had the highest overall survival whereas group 1 had the lowest survival curve while group 2 and group 3 had intermediate survival curves when followed overall period of 1 and a half year.

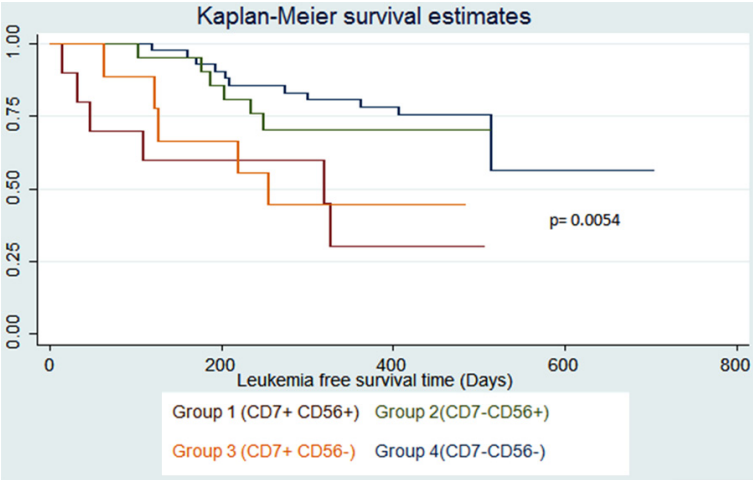

Figure 3. Kaplan-Meier Leukaemia Free survival analysis also shows a similar trend on survival analysis group 4 had the highest overall survival whereas group 1 had the lowest survival curve while group 2 and group 3 had intermediate survival curves when followed overall period of 1 and a half year.

Survival analysis

Survival analysis showed that group 1 had the lowest mean as well as lowest median overall survival, Leukaemia free survival, and relapse free survival days (Mean-399, 220, 249 and Median-374, 185, 228 respectively) while that of group 4 had the highest mean and median for overall survival, Leukaemia free survival and relapse free survival (mean-521, 381, 424 and median-533, 433, 515 days respectively). Group 2 and group 3 were having intermediate mean overall, leukaemia free and relapse free survival.

Relapse free survival

The relapse free survival analysis showed that Group 1 had the highest incidence rate (0.0024) of deaths with 60% of patients and also the least survival probability of 0.32. The Least incidence rate (0.00051) of death was seen in group 4 (23.4%) and survival probability was 0.81 (**Figure 2**).

Leukaemia free survival

Group 1 had the highest incidence rate of leukaemia free survival (0.0027) of deaths with 60% of patients and also the least survival probability of 0.30. The Least incidence rate (0.0006) of death was seen in group 4 (23.4%) and survival probability was 0.75 (**Figure 3**).

Overall survival

In overall survival analysis Group 1 had the highest incidence rate (0.0010) of deaths with 40% of patients and also the least survival probability of 0.56. The Least incidence rate (0.00028) of death was seen in group 4 (14.8%) and survival probability was 0.66 (**Figure 4**).

Discussion

This study assessed 87 patients, diagnosed as having AML and treated with standard chemotherapy protocols of the institution. The diagnosis was made based on clinical, cytomorphological, cytochemical and immunophenotypic data according to the FAB classification.

The most common prognostic group was Group 4 (CD56- and CD7-), which was expected based on incidence of LAIP. The second most common group was Group 2 (CD56+ CD7-) with 21

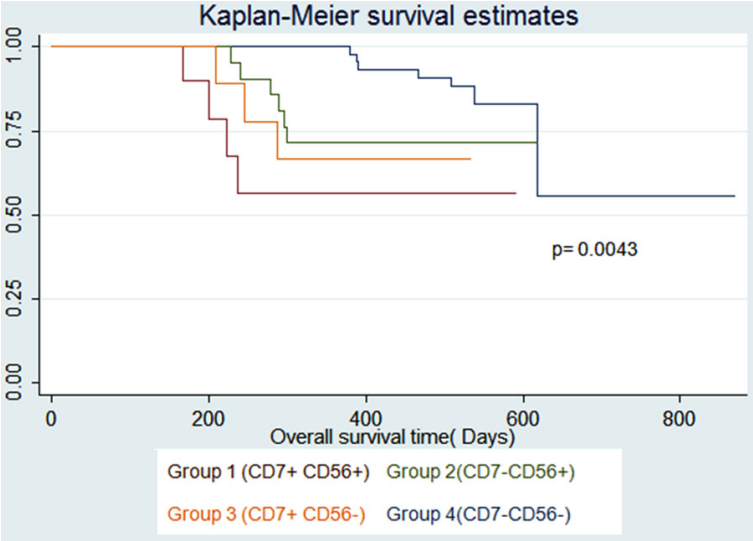

Figure 4. Kaplan-Meier Overall Survival analysis also shows similar trend on survival analysis group 4 had the highest overall survival whereas group 1 had the lowest survival curve while group 2 and group 3 had intermediate survival curves when followed overall period of 1 and a half year.

cases, which was similar to the result seen by Nahla Ahmad [11] while seen higher earlier by Suzuki [12] and Cruse JM [13] This difference could be explained on the basis of regional variability or sampling error.

Our study had the sex ratio or male predominance were seen more in Group 1 and Group 3, 9:1 and 8:1 respectively while other group have equal sex ratio. These outcomes were similar to the result of Suzuki [14] that CD7+ CD56+ had higher male predominance (male:female ratio 15:2/53:23, P=0.09 for CD7+ CD56+ with M0 and other than M0) while Eros di bona [15] stated that CD56+ population did not have male predominance which was similar to our observation (1.4:1).

Group 4 had the highest CR (complete remission) rate (74%, P=0.255) while the group 1 had the lowest remission rate (50%, P=0.255). CR's rate for CD56+ or CD7+ was higher in our study, in comparison to the previous studies by Suzuki [14] (CR rate 68%, P=0.12 for AML other than M0 and 78%, P=0.02 for AML M0), Eros di bona [15], D Raspadori [20] (CD56+ CR rate 36%, P=0.035). The result however was not significant statistically.

In our study MRD positivity was found more in Group 1, while it was least found in group 4, which was our control group (70% P=0.034). These findings were comparable with the study of Cao H [16] that high frequency of CD7 and CD56 in the CD34+ CD38- Lin- stem cell subpopulation predicts a high frequency of positive MRD in later detection.

In our study cytogenetic analysis was done in prognostic group. Cytogenetic abnormalities associated with unfavourable prognosis in group 2 (P=0.267, 14.2%) and group 3 (P=0.267, 11.1%) and this result was similar to those reported by Raspadori D [20] where a cytogenetic analysis was associated with a significant correlation between CD56 or CD7 expression and cytogenetic abnormalities associated with unfavourable prognosis was documented both in univariate and multivariate analysis. Similarly, Ogata [24] also found that CD7 positivity did not adversely affect the OS or DFS in the favourable or intermediate cytogenetic category. In support of our study, Ana Paula Alegretti [22] found a significant correlation between CD56 expression and cytogenetic abnormalities associated with unfavourable prognosis was documented both in univariate and multivariate analysis.

Molecular mutations in AML are considered to be major determinants of the patient response to therapy and outcome. Since both FLT3 and NPM1 mutations were common in AML patients. Clinical outcome was evaluated according to the presence or absence of these mutations in AML patients, by dividing them into FLT3-ITD+/NPM1-, FLT3-ITD-/NPM1+, FLT3-ITD+/NPM1+ and FLT3-ITD-/NPM1- groups. In our study the molecular abnormalities like NPM1, FLT3, AML-ETO and CBF was correlated in the prognostic group considering Group 4 as a control group. NPM1+ and FLT3+ cases were more profoundly present in Group 1 (10%) while other group didn't have any dual positive case. our study suggest that patients belonging to both FLT3-ITD+/NPM1- as well as the FLT3-ITD+/NPM1+ groups had poor CR rates which is similar to other studies by Thiede and Schnittger [25, 26] signifying the fact that NPM1 muta-

tion confers favourable prognosis only in the absence of a co-existing FLT3/ITD mutation. NPM1 does not have any impact on the adverse prognosis conferred by FLT3/ITD. Similar results were also seen by Paietta E [18] and Pradeepsinghchauhan [17]. Harry Dang [19] also reported same result that CD56 and CD7 both are equally express FLT3 and NPM1 mutations proving it to high risk group with unfavourable prognosis. AML-ETO was highly express in Group 4 (53.8%) and least express in group 1(3.8%) as FLT3/ITD mutation was found to be inversely associated with AML/ETO fusion gene suggested by Pradeepsinghchauhan [17]. CBF was less frequently seen in the all groups (12.4% P=0.88) as it expressed favourable prognosis as reported by C Sinha [21].

Our study showed that Group 3 had the highest number of high risk patients based on NCCN Guidelines (22.2%, P=0.039) followed by Group 2 (19%, P=0.039), Group 1 (CD56+ CD7+, 10%, P=0.039) while Group 4 had the least number of high risk patients (6.38%, P=0.039), which was considered statistically significant. Similar result was observed by Ana Paula Alegretti [22] which confirmed that CD56 is a risk factor. Djunic I [23] also demonstrated that CD56+ was the most significant risk factor for OS: P=0.05 and disease-free survival (P=0.005).

In our study survival analysis was done to found out OS, RFS and LFS of each group. Group 1 (CD56+ and CD7+) had the least mean, median and survival probability (OS-399, 374 and 0.56, RFS-249, 228 and 0.32, LFS-220, 185 and 0.30 respectively) but higher incidence rate (1/1000, 2.4/1000 and 2.7/1000 respectively), which was similar to those seen by Suzuki [12], they found out the overall survival (OS) for CD7+ CD56+ AML subtype M0 was poor with no statistical difference in survival among those groups however, leukemia-free survival (LFS) of the CD7+ CD56+ M0 CR cases showed a significantly poorer prognosis than for M0. Also in another study by Suzuki [14] in AML other than M0 the overall survival (OS) and disease-free survival (DFS) prognosis of the CD7+ CD56+ patients was also poor in all type of AML cases, their result however were not significant. In a study the Ana Paula Alegretti [7], found out that CD56 expression in the blasts of AML patients is indicative of shorter OS and also CD7 positivity influenced the response to therapy. Similar conclusion was found by Raspadori D [20] that CD56 antigen reduced probability of achieving CR and had a shorter survival with respect to CD56 negative patients which correlated with our results.

Conclusion

Our study finding suggest that Group 1 with CD56 and CD7 positivity had the highest relapse rates, MRD positivity and death rate, while group 4 with CD56 and CD7 negativity had the least. Thus, it can be concluded that clinical outcome of CD56 and CD7 positivity indicated a very poor prognosis in patients of AML and also associate with the high risk molecular and cytogenetic abnormality. These markers should be incorporated in diagnostic panels of AML to predict response of treatment and survival. More study need to be done as clinical outcome in AML could be evaluated.

Disclosure of conflict of interest

None.

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