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ORIGINAL ARTICLE

Absolute Monocyte Count is Superior than Absolute Lymphocyte Count at Day 28 as an Independent Prognostic Factor in Acute Myeloid Leukemia

Manar M. Ismail[1,3] · **Nahla A. B. Abdulateef**[1,2]

Abstract Leukemia is one of leading causes of death despite the significant improvement of survival. This study aimed at assessing the impact of absolute monocytic count (AMC), and absolute lymphocytic count (ALC) recovery on overall survival (OS) and leukemia free survival (LFS) in AML. 83 de novo AML cases were enrolled in this study. The hemogram parameters including differential leukocyte counts were determined and collected sequentially at days 1, 14, 21 and 28. There was no significant difference regarding AMC or ALC at any time points in relation to the cytogenetics prognostic groups. High AMC $\geq 0.8 \times 10^9$/L at day 28 was associated with shorter OS and LFS, P value 0.012 and 0.003 respectively. On multivariate models, high AMC was shown as an independent prognostic factor associated with poor OS and LFS (HR 3, 95% CI 1.1–8.1 and P value 0.02) and (HR 5, 95% CI 1.5–17.4 and P value 0.01) respectively. High ALC-D28 ($\geq 0.35 \times 10^9$/L) was associated with prolonged OS and LFS survival, P value 0.032 and 0.016 respectively. However, it failed to prove the same significance using multivariate analysis. It was concluded that low AMC is an emerging independent predictor of better outcome in AML.

Keywords Acute myeloid leukemia · Absolute monocyte count · Absolute lymphocyte count · Induction chemotherapy · Overall survival · Leukemia free survival · Prognostic factors

Introduction

Acute leukemia is a disease characterized by uncontrolled clonal expansion of progenitor cells of the hematopoietic system [1]. Acute myeloid leukemia (AML) has a reasonable complete remission rate with standard induction chemotherapy that ranges from 60 to 80%. However, poor treatment outcome is a well-known feature of the disease where the majority of patients will relapse and die within 2 years after remission [2].

Most of the available prognostic factors for AML patients include patient clinical data e.g. age and tumor biological features e.g. initial white blood cell (WBC) count, time to achieve complete remission, immunophenotype, cytogenetics and molecular features [3, 4]. However, scant data are available on the contribution of the immune system and tumor microenvironment to the patients' biological and clinical diversity [5].

Minimal residual disease (MRD) evaluation is a direct measurement of the chemosensitivity of the blasts and it is essential for early identification of the high-risk patient [6]. However, MRD is detected by quantitative polymerase chain reaction (PCR) and flow cytometry-based MRD that may not be technologically and/or economically feasible in some circumstances e.g. developing countries or recently established oncology centers. In these circumstances,

✉ Manar M. Ismail
mmismail@uqu.edu.sa

Nahla A. B. Abdulateef
AbdAlltif.N@kamc.med.sa

1 Laboratory Medicine Department, Faculty of Applied Medical Science, Umm Al Qura University, Al-Abdya, Makkah, Kingdom of Saudi Arabia

2 Laboratory and Blood Bank Department, King Abdullah Medical City, Makkah, Kingdom of Saudi Arabia

3 Clinical Pathology Department, National Cancer Institute, Cairo University, Giza, Egypt

extraction of critical data from a simple test such as complete blood count (CBC) with differential may help in risk stratification of AML cases for better treatment optimization and improvement of patient remission durability [7]. Data obtained from CBC including absolute monocytic count (AMC), absolute lymphocytic count (ALC) and absolute neutrophilic count (ANC) reflect the status of the tumor microenvironment especially the immune status that facilitates evasion from immune surveillance and affects patient outcome [6]. These items were studied in different hematological malignancies but still not clinically appreciated.

AMC showed a relation to survival in different types of lymphoma [8–10], and chronic lymphocytic leukemia [11]. However, their role in myeloid malignancies not clearly studied. ALC emerges as a host factor with a predictive ability after autologous hematopoietic stem cell transplantation for AML [12]. It was speculated that these lymphocytes may represent an effective front line in the host's immune response to leukemic blasts [13].

Objectives

This study aimed to assess the impact on leukemia free survival and overall survival based on AMC, and ALC recovery following induction chemotherapy in patients with AML.

Study Design and Methodology

In this retrospective study, a total of 83 de novo AML cases presented to King Abdullah Medical City-Holly Capital, KSA from October 2010 to April 2015 were enrolled in the study. All patients were in the adult age group; 18 years or older. Secondary AML cases or cases with history of previous hematological diseases (e.g. MDS or PNH) were excluded from the study. The diagnosis and classification of the AML subtypes were based on the morphological, immunophenotypic, and cytogenetic features of leukemic blasts according to WHO 2008 criteria [14] and FAB classification [15].

Medical records were reviewed to determine age, gender, white blood cell (WBC) count, absolute monocyte count (AMC), absolute lymphocyte count (ALC), absolute neutrophile count (ANC), platelet count, and the proportion of peripheral blood (PB) and bone marrow (BM) blast cells. Blast cell distribution ratio (BCDR); the ratio between PB blasts and BM blasts was calculated. AMC, ALC, and ANC were recorded during induction therapy at the following time points: days 1, 14, 21 and 28. The values of the hemogram including WBC and differential count were determined by hematology automatic analyzer (Sysmex XN, 1000) and confirmed by manual differential in cases of abnormal values or very low count.

Cytogenetic Analysis

Conventional karyotype analysis was performed on BM samples obtained at diagnosis. At least 20 metaphase cells were analyzed using standard culturing and R- and/or G-banding techniques. The results were reported according to the International System for Human Cytogenetics Nomenclature [16]. Cytogenetic failures were observed in seven (8.4%) patients. NCCN guidelines were followed for risk stratification of AML [17].

Therapy and Complete Remission Achievement

All AML cases underwent induction protocol 7 + 3, which consisted of idarubicin 12 mg/m^2 from day 1 to day 3 and cytarabine 100 mg/m^2/days from day 1 to day 7. All patients who achieved complete remission (CR) underwent high dose Ara-C protocol as a part of their post-remission consolidation for 3–4 cycles [18, 19]. Patients who achieved CR received high-dose cytarabine-based consolidation, while the patients who failed to achieve CR after at least two cycles of induction therapy received salvage therapy [20]. All APL cases received ATRA 45 mg/m^2 (days 1–36, divided) and arsenic trioxide 0.15 mg/kg (days 9–26) in addition to idarubicin as an induction therapy and consolidation therapy was ATRA and arsenic trioxide based [19, 21].

Statistical Analysis

Data were analyzed using SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL, USA) version 20 for Microsoft Windows. Quantitative data were presented as the mean ± SD or median (min–max) as appropriate. Categorical data were presented as frequency and percentage. Comparison between two groups was conducted using Student's t test, and nonparametric Mann–Whitney U and Kruskal–Wallis tests were used according to data distribution. Comparisons between more than two groups were conducted using ANOVA (ANALYSIS OF VARIANCE), paired comparisons were conducted using Bonferroni's test. Survival analysis was done using Kaplan–Meier method. Survival curves were compared with log-rank test. Univariate analysis using Cox proportional hazards regression model was conducted to calculate hazard ratios (HRs) with its 95% confidence intervals. Variables that were statistical significant in the univariate analysis were included in the multivariate Cox proportional hazards model. Overall survival (OS) was calculated from the date

of initial diagnosis to the date of death or last follow-up. Leukemia free survival (LFS) was calculated from the date of CR to the time of relapse or death. For all comparisons, a two-sided alpha value was set at 0.05. Probability (P value) < 0.05 and < 0.001 were considered significant and highly significant, respectively.

Results

This study included 83 cases, 50 male and 33 female. There median age was 41.7 years ranged from 18 to 60. The hemogram parameters at the studied time points were shown in Table 1.

FAB Classifications

According to the FAB classification, the study group was classified as follow: two cases M0 (2.4%), 22 (26.5%) M1, 18 (21.7%) M2, 11 (13.3%) M3, 18 (21.7% M4), 9 (10.8%) M5, one M6 (1.2%), and 2 (2.4%) M7. For simplification of data analysis, we grouped the cohort into myeloid (M1 and M2), M3 and monocytic (M4 and M5). There was no significant difference between the different FAB subtypes regarding the studied parameters during induction therapy.

Cytogenetic Analysis

Chromosomal analysis revealed that 24 (28.9%) patients had favorable cytogenetic profile that included [t (8;21), t (15;17), and inv 16] and 52 (62.7%) had either intermediate [normal karyotype, + 8, + 4, + 11q23, t (9;11)] or unfavorable cytogenetics [complex abnormality, inv 17, t (7;11), monosomy 7, monosomal karyotype and t (9;22)] [22]. No significant difference regarding the studied white blood cells parameters could be detected between the favorable group compared to the intermediate and unfavorable groups, P value > 0.05.

Remission Induction

Sixty-six (79.5%) patients achieved CR, eight (9.6%) patients did not achieve CR after at least two cycles of induction therapy and nine patients (10.8%) died early in the first 14 days of induction therapy. The group of patients that achieved CR showed significant low levels of AMC at day 14, 21 and 28, P value < 0.001.

Disease Outcome

On following up the cases that achieved CR, 19/66 cases relapsed. There was no significant difference in AMC, ALC or ANC at any time point and the development of relapse, P value > 0.05.

According to the overall patients' status, 43 (51.8%) cases were alive without disease until the end of the study. This group showed a significant higher ALC-D28 ($1.05 \pm 0.91 \times 10^9$/L) than the dead group ($0.62 \pm 0.49 \times 10^9$/L), P value = 0.023. Also, there was a significant low ANC-D28 in the favorable outcome group (0.7 ± 1.30 vs $2.41 \pm 3.48 \times 10^9$/L), P value = 0.016. Otherwise, no significant relation could be detected with other parameters.

Overall Survival

The median OS was 34.9 weeks ranged from 1 to 234 weeks. According to age, we classified the study group into < 40 years and ≥ 40 years where we found significant prolonged survival in the younger age group, P value 0.043. Additionally, favorable cytogenetic profile and lower values of BCDR at diagnosis were associated with longer OS, P value 0.04 and 0.02 respectively. Data are shown in Table 2 and Fig. 1.

Following the cutoffs previously used by many researchers; 0.35×10^9/L for ALC [7], 1.5×10^9/L for ANC [23] and 0.8×10^9/L AMC [5], these factors were analyzed as a predictor of survival. At day 1, 14 or 21 none of these factors had any effect on OS, while at day 28, high ALC ≥ 0.35×10^9/L and ANC ≥ 0.5×10^9/L were

Table 1 Hemograme parameters at different time points

	Day 1 no = 83	Day 14 no = 79	Day 21 no = 77	Day 28 no = 74
TLC × 10⁹/L	20.4 (0.8–397)	0.5 (0.1–20.68)	0.5 (0.07–19.0)	1.9 (0.1–19.4)
HB g/dl	8.2 (4.1–13.1)	8.2 (6.2–11.4)	8.4 (6.7–11.0)	8.6 (1.7–10.6)
ALC × 10⁹/L	3.0 (0.3–39.7)	3.7 (0.03–3.22)	0.41 (0.0–4.6)	0.68 (0.05–5.1)
AMC × 10⁹/L	1.34 (0.0–19.3)	0.1 (0.0–2.7)	0.02 (0.0–8.8)	0.41 (0.0–9.9)
ANC × 10⁹/L	1.2 (0.0–59.4)	0.05 (0.0–13.5)	0.03 (0.0–12.4)	0.44 (0.0–15.5)
Platelets × 10⁹/L	44 (7–329)	20 (3–166)	25 (1–403)	72 (1–747)

Data presented as median (min–max)

Table 2 Significant parameters that affected overall survival (OS)

	N	One year OS%	Five years OS%	Mean OS time ± SE (weeks)	95% confidence interval	P value
Age						
< 40	35	75.8	50.8	138.4 ± 20.5	98.3–178.6	0.04*
≥ 40	48	54.1	24.8	77.8 ± 13.4	51.4–104.2	
Blast cell distribution ration (BCDR)						
< 1	58	67.6	42.1	120.7 ± 15.3	90.7–5.7	0.02*
≥ 1	25	0.00	0.00	44.2 ± 7.6	29.2–59.3	
Cytogenetics						
Favourable	24	77.8	57.4	135 ± 19.9	96.3–174.6	0.04*
Unfavorable	52	54.6	26.6	88.3 ± 15.4	58.0–118.6	
Absolute lymphocyte count (day 28)						
< 0.35×10^9/L	19	65.2	9.1	64.7 ± 13.9	37.3–92.1	0.032*
≥ 0.35×10^9/L	54	71	54.3	144.7 ± 16.5	112.4–177.1	
Absolute neutrophile count (day 28)						
< 1.5×10^9/L	39	65%	18.6	82.69 ± 15.8	51.7–113.7	0.014*
≥ 1.5×10^9/L	34	74.3	64.8	154.2 ± 17.6	119.6–188.7	
Absolute monocyte count (day 28)						
≤ 0.8×10^9/L	47	81.1	73	167.9 ± 20.1	128.6–207.2	0.012*
> 0.8×10^9/L	26	67.2	22.5	89.7 ± 15.1	59.9–119.4	

*Significant

associated with prolonged survival, P value 0.032 and 0.014 respectively. On the other hand, high AMC ≥ 0.8×10^9/L was associated with shorter OS, P value 0.012. Data are shown in Table 2 and Fig. 2.

Multivariate analysis was done including all the significant predictor factors for OS in univariate. AMC continued to be a significant prognostic factor for OS in AML (HR3 and P value 0.02) on the same hand the cytogenetics still keeping its place as an independent prognostic factor in this cohort, HR 2.8 and P value 0.04. Data are shown in Table 4.

Leukemia Free Survival (LFS)

The median duration of LFS was 37.7 weeks, ranged from 1 to 215 weeks. Prolonged LFS was significantly linked to favorable cytogenetics profile, high ALC D-28 and high ANC D-28, P value 0.02, 0.016, and 0.01 respectively. On the other hand, high AMC-D28 was significantly associated with shorter LFS, P value 0.003. Data are shown in Table 3 and Fig. 3.

Using multivariate model after adjusting for the other significant parameters in univariate analysis revealed that high AMC D-28 remained strongly associated with poor LFS (HR 5, P value 0.01). This high HR implies that a patient with an AMC ≥ 0.8×10^9/L has 5 times higher probability of recurrence compared with a patient with AMC < 0.8×10^9/L. Data are shown in Table 4.

Discussion

With the advent of chemotherapy and immunotherapy for the treatment of AML, the host immune status becomes more important in these treatment modalities. AMC at diagnosis was recently reported to be an independent prognostic marker for survival in AML [5]. The ALC recovery was reported to be a surrogate marker of immune status and a significant prognostic factor for survival. Therefore, we set out to investigate whether these hematological parameters at day 28 of induction chemotherapy affects clinical outcome in the setting of AML.

In this study low AMC ≤ 0.8×10^9/L detected during remission induction (day 14, 21 and 28) was associated with achievement of complete remission. Moreover, high AMC at day 28 appeared as a poor prognostic factor for both OS and LFS and proved to be independent prognostic factor after multivariate analysis. Also, the same results were obtained after exclusion of APL cases (data are not shown). Despite no matched results is available, Feng et al. [5] identified high initial AMC as an independent prognostic factor for OS in AML.
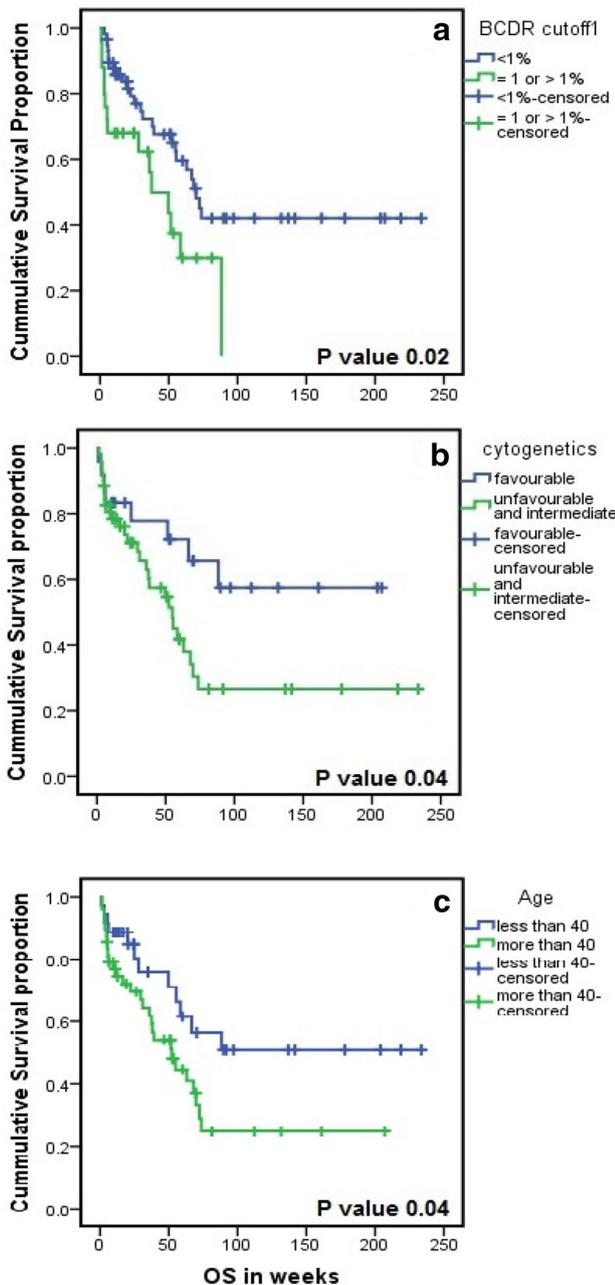
Fig. 1 Kaplan–Meier estimates of Leukemia free survival analysis of the studied AML patients in relation to: **a** blast cell distribution ratio, **b** cytogenetic, **c** age

Fig. 2 Kaplan–Meier estimates of overall survival analysis of the studied AML patients in relation to: **a** absolute neutrophile count at day 28 (ANC-D28), **b** absolute lymphocyte count at day 28 (ALC-D28), **c** absolute monocyte count at day 28 (AMC-D28)

Monocytes are a key component of inflammatory response and a major source of the inflammatory cytokines e.g. IL-1, IL-6, and TNF-α. Generally, prolonged inflammatory response boosts the proliferation of the malignantly transformed cells by induction of death of the normal cells. Hence, giving a space for proliferation of cancer cells [24, 25]. Tumor-derived cytokines and growth factors induce an altered hematopoiesis that modifies the myeloid cell differentiation process, promoting the proliferation and
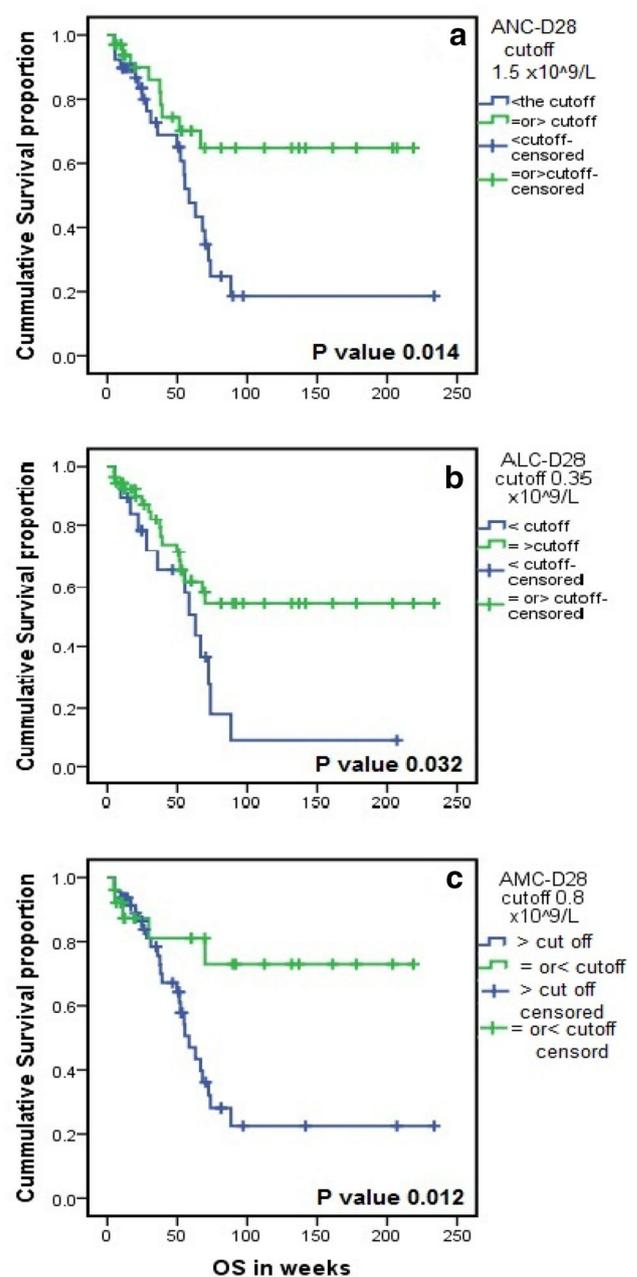
expansion of myeloid-derived suppressor cells (MDSCs) that are closely related to monocyte phenotype but with immunosuppressive skills [26]. MDSCs can suppress T-cells and NK cells, as well as antigen-presenting cells end in frustration of the advantageous immune response [27] and promotion of tumor growth [28].

Furthermore, inflammatory cytokines released from monocytes promotes recruitment of MDSCs with their mentioned inhibitory properties [29]. Sun et al., reported

Table 3 Significant parameters that affected leukemia free survival (LFS)

|	N	One year LFS %	Five years LFS %	Mean LFS time ± SE (weeks)	95% confidence interval	P value
Cytogenetics						
Favorable	20	80	72	157.5 ± 19.5	119.3–195.6	0.024*
Unfavorable	40	51.6	36.9	99.4 ± 17.7	64.6–134.2	
Absolute lymphocyte count (ALC)						
$< 0.35 \times 10^9/L$	17	58.8	12.6	62.0 ± 17.4	27.8–96.2	0.016*
$\geq 0.35 \times 10^9/L$	47	64.2	64.2	148.8 ± 15.3	118.8–178.9	
Absolute neutrophile count (ANC)						
$< 1.5 \times 10^9/L$	34	49	23.8	42.1 ± 14.2	44.1–100.1	0.01*
$\geq 1.5 \times 10^9/L$	30	75.7	69.4	159.4 ± 17.7	124.6–194.2	
Absolute monocyte count (AMC)						
$\leq 0.8 \times 10^9/L$	43	86.5	56.8	188.6 ± 17.1	155.1–222.3	0.003*
$> 0.8 \times 10^9/L$	21	52.1	26.1	82.4 ± 15.2	52.6–112.2	

*Significant
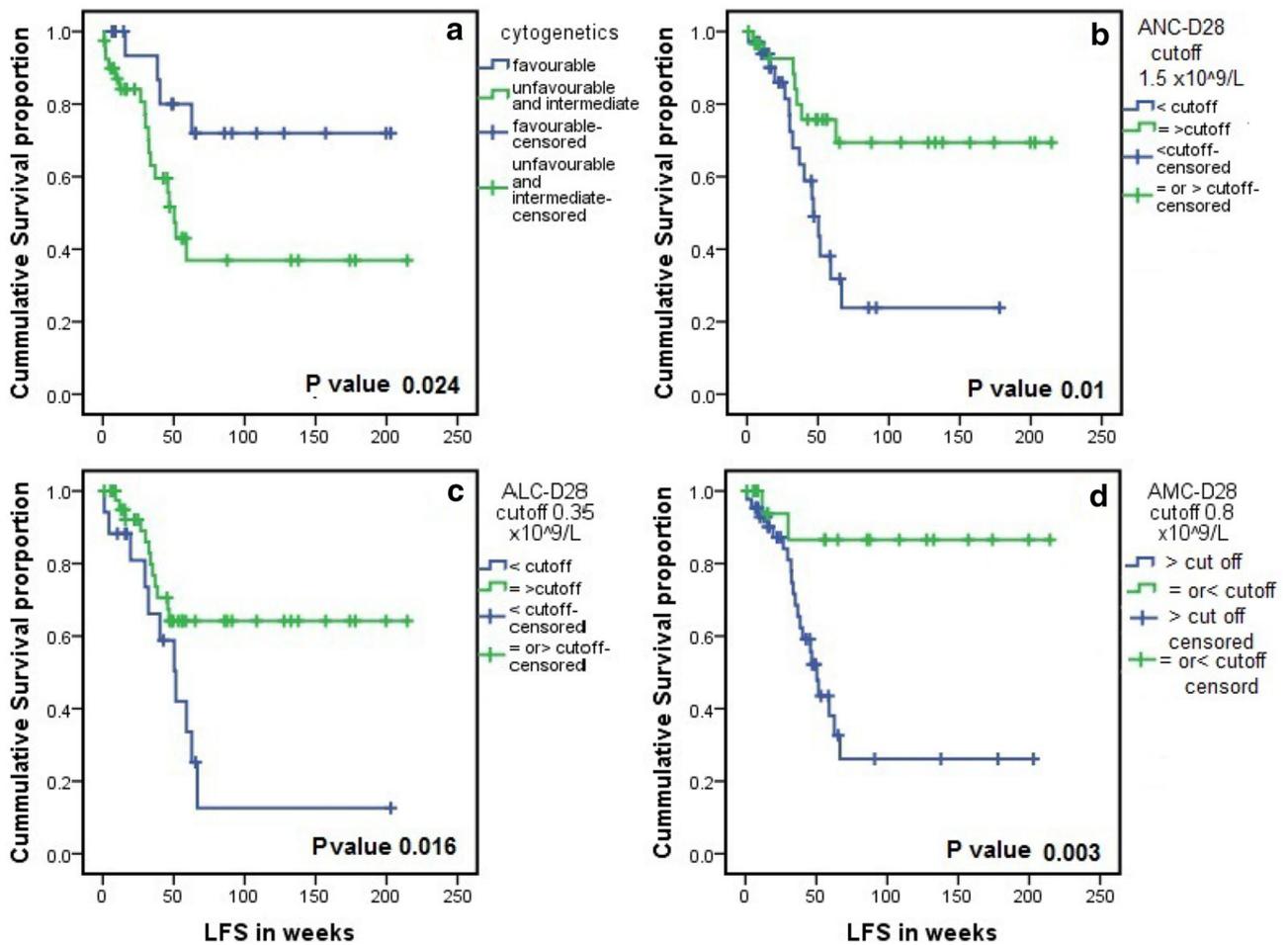
Fig. 3 Kaplan–Meier estimates of Leukemia free survival analysis of the studied AML patients in relation to: **a** cytogenetics, **b** absolute neutrophile count at day 28 (ANC-D28), **c** absolute lymphocyte count at day 28 (ALC-D28), **d** absolute monocyte count at day 28 (AMC-D28)

Table 4 Univariate and multivariate analysis of the significant factors that affected survival

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Overall survival						
Age	2.0	1.0–3.9	0.044*	1.5	0.9–5.1	0.067
BCDR	2.11	1.1–4.1	0.023*	1.6	0.7–4.9	0.136
Cytogenetics	2.17	0.9–4.8	0.050*	2.8	1.1–7.5	0.040*
ALC at day 28	4.62	0.2–0.9	0.037*	1.4	0.6–3.3	0.305
ANC at day 28	3.87	0.2–0.8	0.018*	1.4	0.5–3.9	0.434
AMC at day 28	3.08	0.1–0.8	0.018*	3.0	1.1–8.1	0.028*
Leukemia free survival						
Cytogenetics	3.29	1.1–9.8	0.033*	2.4	0.8–7.1	0.100
ALC at day 28	3.80	0.2–0.9	0.021*	1.3	0.6–3.5	0.331
ANC at day 28	3.25	0.1–0.8	0.014*	1.5	0.5–4.2	0.370
AMC at day 28	1.42	0.1–0.6	0.009*	5.0	1.5–17.4	0.010*

HR hazard ratio, *CI* confidence interval

*Significant

that, in the BM of newly diagnosed adult AML, MDSCs were found to be increased and correlated with poor remission rate and extramedullary spread [30], this could be one of the explanation for the association of increased AMC and poor prognosis in AML. Moreover, tumor cell-derived cytokines and chemokines, such as monocyte chemoattractant protein-1 (MCP-1) and vascular endothelial growth factor (VEGF), could trigger differentiation of monocytes into tumor-associated macrophages (TAMs) [31, 32] that contribute to systemic immunosuppression and have an important role in tumor angiogenesis, invasion, and migration [33, 34]. Accordingly, elevated peripheral blood monocyte count reflects a high tumor burden in patients with cancer, which in turn correlates with poor clinical outcome.

In this study, we found that an ALC $\geq 0.35 \times 10^9$/L at day 28 predicts good OS and LFS in adults' acute myeloid leukemia patients. We demonstrate that univariate analysis of ALC has prognostic significance for LFS and OS. This result was in accordance to previous study done by Guillermo and colleagues [7]. However, they demonstrated ALC as an independent prognostic factor in multivariant analysis but we did not reach such a result in our studied cohort. In our study, we had more unfavorable cytogenetics profile in the low ALC group that could have affected the multivariate analysis and patient outcome. Our data were also comparable to Behl et al. [23], who reported that ALC is a predictive of disease outcome in adults with AML. In the same context, early ALC regeneration after induction chemotherapy (at day 28) correlates with improved OS and LFS in pediatric AML [35]. Additionally, higher ALC recovery after autologous stem cell transplantation experienced superior survival [12].

These data proving the predictive significance of ALC points to the important role of lymphocyte in AML patients. ALC may be linked to the characteristics of both host and leukemia itself; patients with better ALC recovery are usually presented with a lower leukemic burden at diagnosis which would lead to improved immune reconstitution following therapy and prolonged survival [7]. Furthermore, ALC could be considered as a host factor that represents the immune status of the patients. In malignant diseases, the immune system tries to perform its normal function in destruction of tumor cells versus the virulent malignant cells that try to evade the immune response. ALC constitute all the lymphocytes lineage; B cell, T cell and their different subsets (mainly T helper, T cytotoxic and T regulatory) and NK cells. Concerning immune surveillance function, both T cytotoxic (Tc) and NK cells play the starring roles while T regulatory cells are inhibitory for their function.

Many researchers were anxious about the regeneration of Tc and NK cells after complete remission and they demonstrated their valuable role after administration of chemotherapy [13]. Also, it was found that even if the overall lymphocyte counts are depressed, the percentages of Tc cells are increased after remission induction [36]. Furthermore, the number of NK cells after repeated cycles of chemotherapy has been observed to be normalized irrespective to the number of T or B cells [12]. On the same scientific background, the NK cell number was observed to be correlated with ALC after autologous transplantation [37], and the leukemia cytolytic activity offered by the NK cell were associated with prolonged remission [6]. It was claimed that the NK cells play a key role after remission induction based on their rapid recovery even in the absence

of a functional thymus [38, 39]. Additionally, the maintenance of remission was assumed to count on the immune response rather than the chemotherapy administrated to the patient [6]. Collectively, these prior observations and the present results highlight the supporting anti-leukemia immune surveillance role of the reconstituting lymphocytes after standard induction therapy in AML [40].

Concerning the prognostic significance of absolute neutrophilic count during remission induction, we detected that ANC showed a significant prognostic value in univariate analysis but not after multivariate analysis. However, ANC $\geq 1.5 \times 10^9$ is an indication of BM regeneration after chemotherapy rather than a component of immune surveillance process [23].

In this study we had some limitation, being a retrospective study, non randomized and included a relatively small number of cases. We did not evaluate the recovery of the individual lymphocyte subsets or their function or detected the percentage of MDSCs in the BM. Nevertheless, we could detect a significant prognostic value of the studied parameters.

Conclusion and Recommendations

Low AMC emerges as an unconventional significant independent predictor of better outcome in this AML cohort. To solidify this result, we recommend analysis of MDSCs in the BM and correlate them with the AMC.

ALC was shown to be a prognostic factor in univariate analysis, which is auspicious result. To get a reliable opinion about ALC, it is needed to be studied in large numbers and multiple centers with evaluation of the lymphocyte subsets after induction therapy.

However, these parameters deserves appreciations being cheap and easily obtained for most patients and if confirmation by multicenter studies is obtained, would provide a helpful tool in risk stratification of AML patients specially in developing countries and recently established oncology centers.

Compliance with Ethical Standards

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

Ethical Approval The study was approved by the Institutional Ethics Committee IRB13-057. All procedures performed in this study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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