RESEARCH ARTICLE

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Monocytic Myeloid-Derived Suppressor Cells But Not Monocytes Predict Poor Prognosis of Acute Myeloid Leukemia

Akut Myeloid Lösemide Kötü Prognoz Belirteci Monositler Değil Monositik Myeloid Süpresör Hücrelerdir

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Abstract

Objective: Some reports suggest that high absolute monocyte count (AMC) at diagnosis is an independent predictor of poor prognosis in acute myeloid leukemia (AML), but others disagree. Monocytic myeloid-derived suppressor cells (Mo-MDSCs) are immature monocytes. This study aimed to compare the value of monocytes and Mo-MDSCs in predicting the prognosis of AML.

Materials and Methods: Peripheral blood samples from 107 newly diagnosed patients with AML and 47 healthy controls (HCs) were collected. We validated the clinical significance of AMC, monocyte count ($CD14^+CD45^{++}$), and Mo-MDSC count ($CD14^+$HLA-DRlow/-$CD45^{++}$) for initial induction therapy response, maintenance of treatment effects, and long-term survival.

Results: Compared with HCs, the levels of AMC, monocyte count, and Mo-MDSC count were all significantly higher among patients with AML. However, only elevated Mo-MDSC count was significantly associated with lower complete remission rate, higher relapse/refractory rate, and poorer long-term survival.

Conclusion: Mo-MDSCs but not monocytes predict the poor prognosis of AML.

Keywords: Acute myeloid leukemia, Absolute monocyte count, Monocytic myeloid-derived suppressor cells, Prognosis

Öz

Amaç: Bazı yayınlara göre tanıda yüksek mutlak monosit sayısı (AMC) akut myeloid lösemi (AML) olgularında bağımsız kötü prognoz belirtecidir, ama bazı yayınlar bu sonucu desteklememektedir. Monositik myeloid süpresör hücreler (Mo-MDSCs) olgunlaşmamış monositlerdir. Bu çalışmadaki amacımız AML'de prognozu belirlemek adına monositlerin ve Mo-MDSC'lerin değerini tespit etmektir.

Gereç ve Yöntemler: Yüz yedi yeni tanı AML hastasından ve 47 sağlıklı kontrolden (HC) periferik kan örneği alındı. AMC, monosit sayısı ($CD14^+CD45^{++}$), ve Mo-MDSC sayısını ($CD14^+$HLA-DRlow/-$CD45^{++}$) indüksiyon tedavisine yanıtta, tedavi yanıtının idamesi üzerine etkisinde ve uzun dönem sağkalım için değerlendirdik.

Bulgular: HC ile karşılaştırıldığında, AMC sayısı, monosit sayısı ve Mo-MDSC sayısı AML hastalarında anlamlı düzeyde daha yüksek saptanmıştır. Fakat, sadece Mo-MDSC sayısı daha düşük tam remisyon oranları, daha yüksek relaps/refrakterlik oranları ve uzun dönem olumsuz sağkalım süresi ile ilişkili bulundu.

Sonuç: Monositler yerine Mo-MDSC'ler AML'de kötü prognoz için belirteçtirler.

Anahtar Sözcükler: Akut myeloid lösemi, Mutlak monosit sayısı, Monositik myeloid süpresör hücreler, Prognoz

Introduction

Acute myeloid leukemia (AML) is a cytogenetically, molecularly, and clinically heterogeneous malignant clonal disease originating from hematopoietic stem cells [1]. The 5-year overall survival (OS) rate for AML is only 29.5%. Efforts have been made to find reliable clinical indicators to identify prognostic outcomes at an early stage. In recent years, some studies have shown that the initial absolute monocyte count (AMC) can predict clinical response and survival outcome [2,3]. Ismail and Abdulateef [4] focused on different time intervals and proposed AMC as an independent prognostic factor superior to absolute lymphocyte count at day 28 of induction chemotherapy. However, Merdin et al. [5] concluded that AMC is not associated with several prognostic gene mutations in AML. Moreover, the monocyte-to-neutrophil ratio (MNR) has been shown to predict the outcome

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of initial induction therapy for AML [6]. Therefore, it seems inaccurate to take AMC as an independent factor for assessing the prognosis of AML. With that in mind, the present study was undertaken to explore a new indicator of AML prognosis.

Monocytic myeloid-derived suppressor cells (Mo-MDSCs) mainly consist of pathologically activated monocytes with potent immunosuppressive activity and are closely associated with poor clinical outcomes in cancer [7,8,9]. However, the roles of Mo-MDSCs in hematopoietic malignancies, and especially AML, remain unclear, in contrast to knowledge of their multiple roles in cases of solid tumors [10]. Contrary to some views that AMC is related to the prognosis of AML, this study examines the hypothesis that AMC and monocyte count are irrelevant to the prognosis of AML while Mo-MDSC count is significant.

Materials and Methods

Patients

We evaluated a total of 107 patients with AML who were newly diagnosed from 2013 to 2019. Forty-seven age- and sex-matched healthy controls (HCs) were also recruited. The diagnosis and classification of AML were based on French-American-British (FAB) and World Health Organization criteria. All patients were treated according to their own diagnostic stratification and received standard induction chemotherapy composed of anthracyclines for 3 days and cytarabine for 7 days, followed by either chemotherapeutic consolidation therapy or allogeneic hematopoietic stem cell transplantation in accordance with the Chinese guidelines for the diagnosis and treatment of adult AML [11]. Complete remission (CR) was defined according to European LeukemiaNet (ELN) consensus guidelines. The collected baseline data included age, sex, FAB classification, white blood cell count, cross linage expression, extramedullary infiltration, leukemic blast percentage, chromosome karyotype, fusion genes, gene mutations, ELN risk classification, AMC, monocyte count, and Mo-MDSC count.

Absolute Monocyte Count (AMC)

Peripheral blood was obtained from all patients at the time of diagnosis. AMC values were obtained from routine blood examinations based on clinical laboratory records as determined with a Sysmex XE2100 hematology analyzer (Sysmex Corporation, Kobe, Japan).

Monocytes and Mo-MDSCs

Following previously described protocols, peripheral blood mononuclear cells were collected from 107 patients with AML and the cells were then stained. Monocytes were gated as $CD14^{+}CD45^{++}$ cells. Mo-MDSCs were gated as $CD14^{+}HLA\text{-}DR^{low/-}CD45^{++}$ cells (Figure 1) [12,13]. The following monoclonal antibodies were purchased from Beckman Coulter (Miami, FL, USA): FITC-labeled CD14 (clone RMO52), PE-labeled HLA-DR (clone Immu-357), and PC5-labeled CD45 (clone J.33).

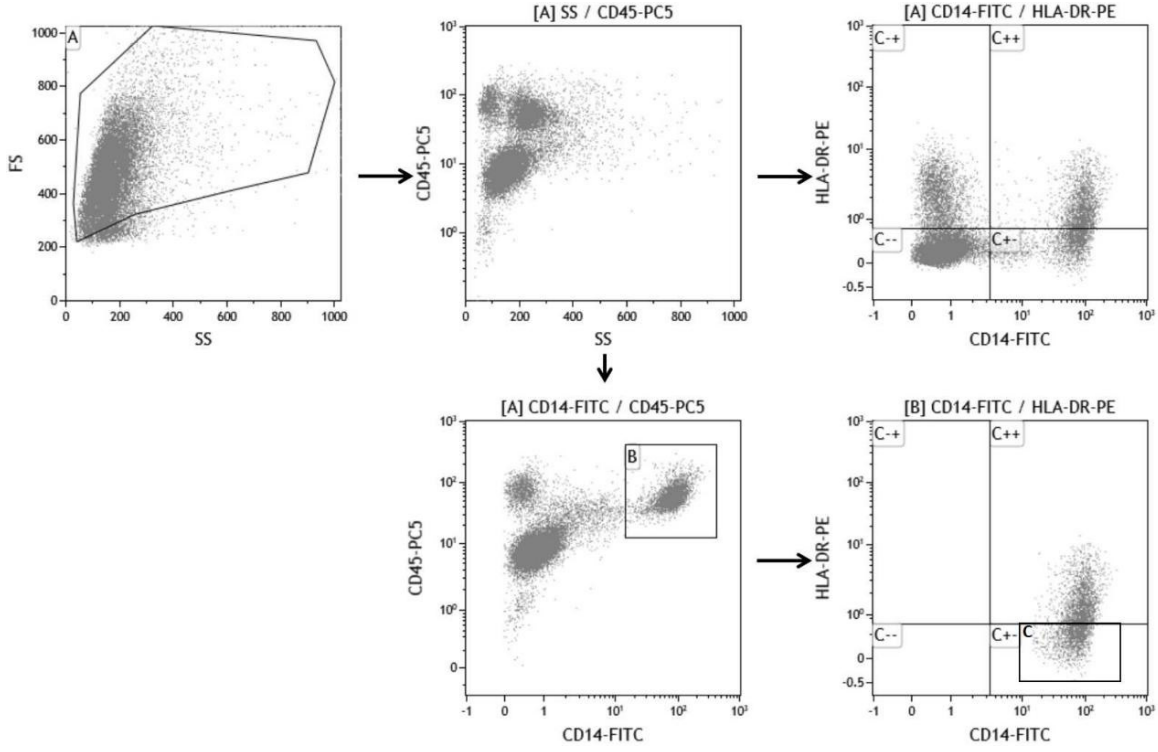

Figure 1. Analysis process of flow cytometric dot plots demonstrated the frequencies of $CD14^{+}$monocytes (gate B) and $CD14^{+}HLA\text{-}DR^{LOW/-}$ Mo-MDSCs (gate C).

Statistical Analysis

Categorical variables were compared using the chi-square test or Fisher exact test, and numerical variables were compared using the Wilcoxon rank-sum test. Monocyte and Mo-MDSC counts of the HC group were utilized to calculate the upper limit of the 95% confidence interval of the mean values as cut-offs. The cut-off values for monocytes and Mo-MDSCs were 8.0396% and 0.2321%, respectively. For AMC, we chose the upper limit of the normal range ($1x10^9$/L) as the direct cut-off value. The high group included individuals with levels greater than the cut-off value; the remainder of participants were in the low group. OS was defined as the time from date of diagnosis until the date of death. The survival curve was estimated using the Kaplan-Meier method and comparisons were made using the log-rank test. All tests were two-sided and $p<0.05$ was considered to reflect statistical significance.

Results

Patient Characteristics

A total of 107 patients and 47 HCs were enrolled in the present study. The clinical characteristics of patients at diagnosis are provided in Table 1. Approximately half (52%) of the patients were younger than 60 years old, and 47 patients did not receive treatment in our department or died untreated. According to the results of the initial induction chemotherapy, the remaining patients were divided into two groups, with 35 in the complete response (CR) group and 25 in the non-complete response (non-CR) group. According to the curative effect, they were regrouped as the continuous CR (CCR) group (27 cases) and the refractory recurrence/relapse (R/R) group (33 cases).

Comparisons of AMC, Monocyte Count, and Mo-MDSC Count

Data about AMC were available for 92 of 107 patients with AML. These patients had significantly increased levels of AMC

Table 1. Characteristics of healthy controls and 107 patients with AML [median (range) or (n, %)].

Characteristics	Healthy controls	AML patients	p
Gender	Male (26, 55.3%) Female (21, 44.7%)	Male (62, 58%) Female (45, 42%)	0.762
Age, years	52 (21-89)	57 (14-91)	0.158
FAB classification	- - - - - - - -	M0 (1, 0.9%) M1 (4, 3.7%) M2 (32, 29.9%) M3 (19, 17.8%) M4 (19, 17.8%) M5 (9, 8.2%) M6 (1, 0.9%) Mu (22, 20.6%)	- - - - - - - -
ELN risk classification	- - - -	Low risk (27, 25%) Medium risk (46, 43%) High risk (15, 14%) No data (19, 18%)	- - - -
Fusion gene	- - - -	*RUNX1-RUNX1T1* (8, 7%) *PML/RARα* (16, 15%) *CBFβ-MYH11* (5, 5%) Others (78, 73%)	- - - -
Gene mutation	- - - - -	*FLT3-ITD* (9, 8%) *CEBPA* (5, 5%) *NMP1* (2, 2%) *C-kit* (3, 3%) Others (73, 68%)	- - - - -
First induction	- -	CR (35, 58.3%) Non-CR (25, 41.7%)	- -
Curative effect	- -	CCR (27, 45%) R/R (33, 55%)	- -
Blasts in peripheral blood (%)	-	60 (0.3-99)	-

FAB: French-American-British; ELN: European LeukemiaNet; CR: complete response; CCR: continuous complete response; R/R: recurrence/relapse.

(Figure 2A), monocyte counts (Figure 2B), and Mo-MDSC counts (Figure 2C) in comparison to the HC group. There was no difference in the distributions of AMC (Figure 2D) or monocyte count (Figure 2E) between the CR group and non-CR group, but a statistically significant elevation of Mo-MDSC count was observed in the non-CR group compared to the CR group (Figure 2F). Similarly, considering the long-term curative effect, no significant differences in AMC (Figure 2G) or monocyte count (Figure 2H) were detected between the CCR and R/R groups. However, the Mo-MDSC counts of the R/R group were statistically significantly higher than those of the CCR group (Figure 2I, Table 2).

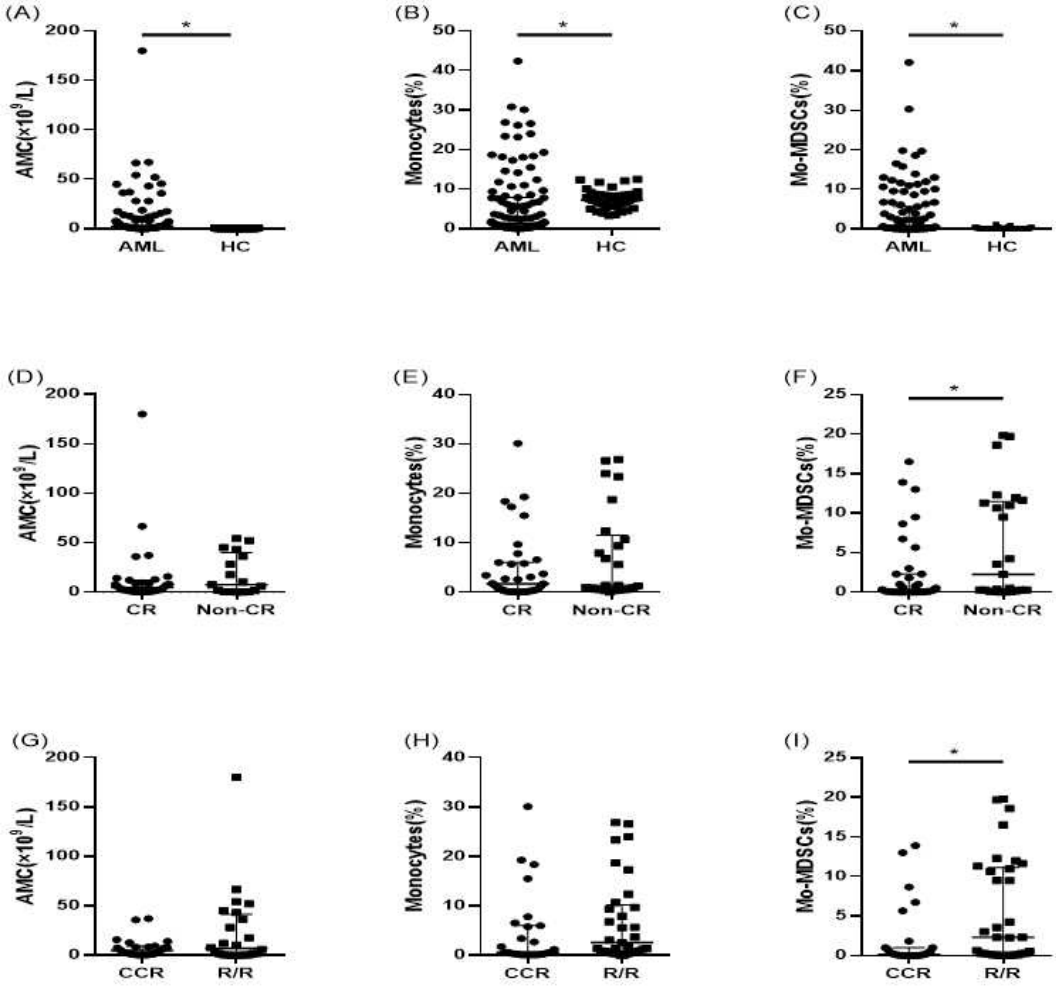

Figure 2. Differences in the absolute monocyte count (AMC), monocyte count, and monocytic myeloid-derived suppressor cell (Mo-MDSC) count were compared among different groups of patients with AML. (A-C) Differences in AMC, monocyte count, and Mo-MDSC count, respectively. (D) Differences in AMC for patients with complete response (CR) vs. non-CR. (E) Differences in monocyte count for CR vs. non-CR. (F) Differences in Mo-MDSC count for CR vs. non-CR. (G) Differences in AMC for patients with continuous complete response (CCR) vs. recurrence/relapse (R/R). (H) Differences in monocyte count for CCR vs. R/R. (I) Differences in Mo-MDSCs for CCR vs. R/R.

Table 2. AMC, monocytes, and Mo-MDSCs in each group of patients [n (median)].

	AML	HC	p	CR	Non-CR	p	CCR	R/R	p
AMC (x10⁹)	92 (2.61)	47 (0.44)	0.0001	32 (4.55)	22 (7.44)	0.504	25 (4.8)	29 (6.8)	0.409
Monocytes (%)	107 (1.4)	47 (7.2)	0.0001	35 (1.7)	25 (1.4)	0.239	27 (0.6)	33 (2.6)	0.051
Mo-MDSCs (%)	107 (0.42)	47 (0.088)	0.0001	35 (0.23)	25 (2.26)	0.028	27 (0.16)	33 (2.3)	0.015

AMC: Absolute monocyte count; Mo-MDSC: monocytic myeloid-derived suppressor cell; AML: acute myeloid leukemia; HC: healthy control group; CR: complete response; CCR: continuous complete response; R/R: recurrence/relapse.

Impacts of AMC, Monocyte Count, and Mo-MDSC Count on Diagnostic Stratification

Stratified analyses of AMC, monocyte count, and Mo-MDSC count were performed for AML considering common clinical risk groups and cytogenetic molecular risk groups. Combining the present results with those of our previous study [13], the main statistical differences in the three considered indices occurred between the M4/M5 subtypes and the other FAB subtypes. However, there were no statistical differences in AMC, monocyte count, or Mo-MDSC count between different groups of white blood cell counts, cross-linage expressions, extramedullary infiltration statuses, leukemic blast percentages, chromosome karyotypes, fusion genes, gene mutations, or ELN risk categories.

Impacts of AMC, Monocyte Count, and Mo-MDSC Count on Chemotherapy Response

According to the above results, only Mo-MDSC count had a statistically significant difference between various disease states. Next, we evaluated the impact of the three indicators of AMC, monocyte count, and Mo-MDSC count from the perspective of chemotherapy response. There was no correlation between therapeutic response and the increase or decrease of AMC (Figures 3A and 3D) and monocyte count (Figures 3B and 3E) for either the initial induction chemotherapy results or long-term efficacy. With increased Mo-MDSC count, the CR rate after initial induction decreased (Figure 3C), and the CCR rate also decreased (Figure 3F), indicating that increased Mo-MDSC counts had a negative impact on the efficacy of chemotherapy.

Impacts of AMC, Monocyte Count, and Mo-MDSC Count on Survival Outcomes

Based on the finding that elevated Mo-MDSC counts were associated with lower CR and higher R/R rates, we further verified the survival value of the three indicators of AMC, monocyte count, and Mo-MDSC count. Kaplan-Meier analysis showed no difference in OS between the low AMC group and high AMC group (Figure 4A) or for monocyte counts (Figure 4B). However, patients with higher Mo-MDSC counts had a significant survival disadvantage compared to those with lower Mo-MDSC counts (Figure 4C).

Discussion

According to a previous report, high AMC at diagnosis constitutes an independent predictor of poor survival in AML [3]. Especially in M4 and M5, monocytopenia is significantly associated with higher CR rates and lower rates of death, relapse, and early relapse together with longer disease-free survival [2]. In multivariate models, elevation of AMC at day 28 of induction chemotherapy has been shown to be an independent prognostic factor associated with poor OS and leukemia-free survival [4]. However, such studies have not considered monocytes themselves. The present study has explored the influence of

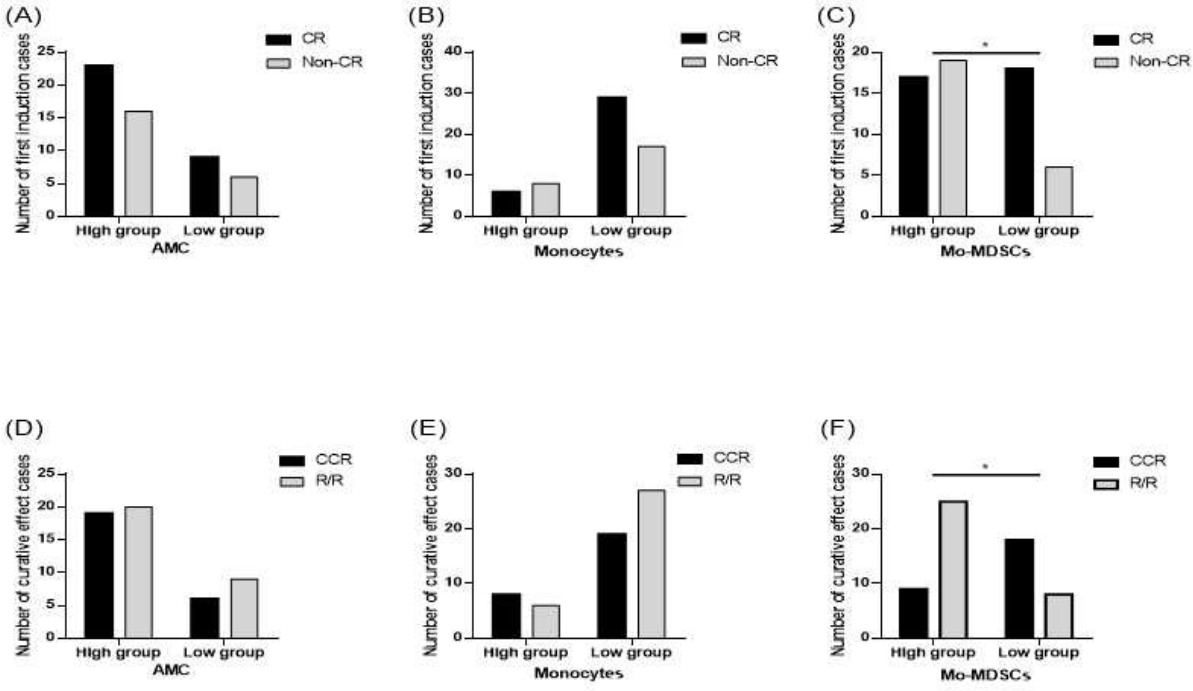

Figure 3. Chemotherapy response according to absolute monocyte count (AMC), monocyte count, and monocytic myeloid-derived suppressor cell (Mo-MDSC) count at the time of diagnosis of AML. Results of initial chemotherapy: (A) High AMC group vs. low AMC group. (B) High monocyte count vs. low AMC. (C) High Mo-MDSC count vs. low AMC. Results of long-term efficacy: (D) High AMC vs. low AMC. (E) High monocyte count vs. low AMC. (F) High Mo-MDSC count vs. low AMC.

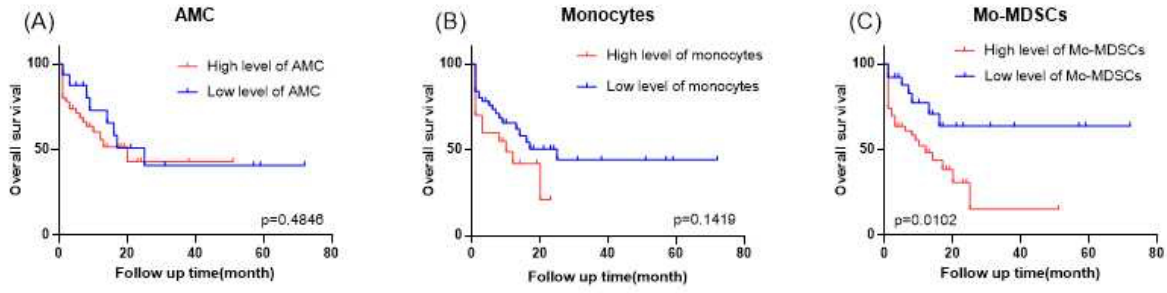

Figure 4. Survival outcomes according to absolute monocyte count (AMC), monocyte count, and monocytic myeloid-derived suppressor cell (Mo-MDSC) count at the time of diagnosis of AML. Overall survival after diagnosis: (A) Low AMC vs. high AMC. (B) Low monocyte count vs. high monocyte count. (C) Low Mo-MDSC count vs. high Mo-MDSC count.

monocyte and Mo-MDSC counts on the prognosis of AML and has found that the relationship between monocytes and the prognosis of AML is unclear. Our results showed that neither the increase of AMC nor the levels of circulating monocytes affected the prognosis of AML. However, elevations in the levels of circulating Mo-MDSCs was found to be an unfavorable factor and a poor prognostic biomarker in AML.

First of all, the levels of AMC in comparisons between the HC group and AML patients showed significant differences, in marked contrast to previous findings. Although blood cell analyses are based on cell data such as size, distribution, proportions, and other such indicators, these analyses cannot completely accurately identify all cells in the blood. However, leukemia cells have elevated heterogeneity and morphological diversity, so the combination of peripheral hematological analysis, bone marrow morphology, and flow cytometry immunotyping has become an important means of comprehensive analysis in cases of leukemia. Primitive or immature nuclei are easily classified as monocytes due to their large size and high lateral fluorescence intensity. In patients with leukemia, there are many immature cells among the peripheral white blood cells, so AMC is often elevated in routine blood tests [14]. At the same time, there may be confounding factors affecting AMC in AML patients, meaning that AMC cannot accurately and truly reflect the actual level of monocytes. Therefore, exploring the difference in AMC distributions in various disease states and even the relationship between AMC and AML prognosis on this basis may not reflect the real situation even if the results are statistically significant. In addition, AMC data are insufficient when the patient's white blood cell levels are too high to obtain AMC values. In the present study, after the real total monocytes ($CD14^{+}CD45^{++}$) were identified and analyzed by flow cytometry, there was still no statistical difference in their distribution among the groups. This might be due to the fact that the population of $CD14^{+}$ monocytes includes both mature and immature monocytes. All these findings suggested that the elevation of immature monocytes represented by Mo-MDSCs but not total monocytes was the real cause of poor AML prognosis, and this finding was significantly more common in the non-CR group after initial treatment and the R/R group with statistical significance. Subsequently, we further compared the survival of patients with different Mo-MDSC counts and found that patients with higher Mo-MDSC counts had a significant survival disadvantage, which reaffirmed our initial conclusions.

Monocytes and Mo-MDSCs both originate as common myeloid progenitors and monocytic precursors. Classical myeloid cell activation takes place in response to strong signals of pathogens and tissue damage and is mainly driven via danger-associated molecular patterns, pathogen-associated molecular patterns, and Toll-like receptor activation, leading to the rapid mobilization of neutrophils and monocytes from the bone marrow. On the other hand, pathological activation results from the persistent stimulation of the myeloid cell compartment on account of the prolonged presence of myeloid growth factors and inflammatory signals in the settings of cancer, chronic infections or inflammation, and autoimmune diseases [15]. It has been shown that the pathogenesis of AML is related to immunological disorders of several individual immune cell subsets and immune molecules [16]. This is consistent with the pathological state of immune activation required for the appearance of Mo-MDSCs, which may be the cause of elevated Mo-MDSCs in AML patients. On the other hand, Mo-MDSCs utilize immunosuppressive mechanisms to suppress host immune functions, including the production of regulatory T cells and the mediation of the secretion of various cytokines such as arginase-1, interleukin-10, cyclooxygenase 2, and indoleamine 2 [7,15]. Accumulating evidence suggests that Mo-MDSCs participate in immunosuppressive responses to both solid tumors [17,18] and hematological malignancies [19,20]. Tumors promote the production of Mo-MDSCs, and Mo-MDSCs promote the development and drug resistance of tumors in turn, leading to poor prognosis.

Conclusion

Mo-MDSCs but not monocytes predict poor prognosis in cases of AML. This study has contributed data to the literature on the roles of the immune system in the biological and clinical diversity of AML with the aim of supporting the development of new immune-based strategies in the treatment of AML.

Ethics

Ethics Committee Approval: Biomedical Ethics Committee of Anhui Medical University (no:20131030).

Authorship Contributions

Concept: X.R., Q.T., H.W., Q.Z., M.Z., L.L., Z.Z.; Design: X.R., Q.T., H.W., Q.Z., M.Z., L.L., Z.Z.; Data Collection or Processing: X.R., Q.T., H.W., Q.Z., M.Z., L.L., Z.Z.; Analysis or Interpretation: X.R., Q.T., H.W., Q.Z., M.Z., L.L., Z.Z.; Literature Search: X.R., Q.T., H.W., Q.Z., M.Z., L.L., Z.Z.; Writing: X.R., Q.T., H.W., Q.Z., M.Z., L.L., Z.Z.

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