Clinical and Experimental Medicine (2025) 25:165
https://doi.org/10.1007/s10238-025-01652-9

RESEARCH

Complex association of mean corpuscular volume and outcomes in patients with aplastic anemia treated with cyclosporine A plus androgen or cyclosporine A alone

Li Han[1] · XueDong Shi[1] · ShuQi Wang[1] · QiuShuang Wang[1] · AnQi Xia[1] · Jiang Cao[2,3,4] · KaiLin Xu[2,3,4] · Hai Cheng[2,3,4]

Received: 29 January 2025 / Accepted: 26 March 2025

Abstract

The aim of this study was to explore the prognostic value of mean corpuscular volume (MCV) in newly diagnosed aplastic anemia (AA) patients treated with cyclosporine A (CsA) plus androgen or CsA alone. The clinical data of 181 newly diagnosed patients with aplastic anemia from April 2008 to September 2020 in the Affiliated Hospital of Xuzhou Medical University were retrospectively analyzed. According to the MCV levels, the patients were divided into a high-MCV group (107/181) and a normal-MCV group (74/181). We investigated the effect of MCV outcomes in patients with AA. Between the high-MCV and normal-MCV groups, neutrophil count, red blood cell count, platelet count, reticulocyte count, disease severity, lymphocytes, and granulocytes were significantly different ($P < 0.05$). The overall response rates (CR + PR) were 69.16% and 59.46% in the high-MCV and normal-MCV groups, respectively. The duration of response was not significantly different between MCV groups. The high-MCV patients had an improved 5-year overall survival and progression-free survival compared to the normal-MCV patients (94.40% vs. 68.10%; 71.80% vs. 60.30%, $P < 0.001$). Regarding hemogram restoration, the leukocyte, neutrophil, hemoglobin, and platelet recovery was accelerated in the high-MCV group ($P < 0.05$). Furthermore, MCV levels were positively correlated with reticulocyte count, reticulocyte percentage, high-fluorescence reticulocyte, medium-fluorescence reticulocyte, and immature reticulocyte fraction; on the other hand, MCV levels were negatively correlated with low fluorescent reticulocyte. In conclusion, aplastic anemia patients with a high MCV were a better prognostic factor, and the patients with high MCV may have better residual bone marrow hematopoietic function than those with normal MCV.

Keywords Aplastic anemia · Prognostic factor · Mean corpuscular volume · Reticulocyte

Introduction

Aplastic anemia is a syndrome of bone marrow failure caused by various etiological factors, characterized by a decrease in bone marrow function resulting in progressive pancytopenia. The clinical manifestations mainly include anemia, hemorrhage, and infections [1]. The incidence of AA in Europe is 2–3 per 1 million population, while the incidence in China is 2–3 times higher than that in the West, about 7.4 per 1 million population, which can occur in all ages, and the incidence of young and old people is higher, showing a double peak; there was no significant difference in incidence between men and women [2–4]. It is currently believed that T cell function is abnormal, $CD8^+$T cells increase, regulatory T cells decrease. The increased secretion of cytokines interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) leads to the injury of hematopoietic stem

Li Han, XueDong Shi, ShuQi Wang, and QiuShuang Wang have contributed equally and cofirst authors to this work.

✉ KaiLin Xu
lihmd@163.com

✉ Hai Cheng
hai_cheng@xzhmu.edu.cn

1 Faculty of Clinical Medicine, Xuzhou Medical University, Xuzhou, China

2 Department of Hematology, The Affiliated Hospital of Xuzhou Medical University, 99 Huaihai West Road, Quanshan District, Xuzhou City 221002, Jiangsu Province, China

3 Blood Diseases Institute, Xuzhou Medical University, Xuzhou, China

4 Jiangsu Key Laboratory of Bone Marrow Stem Cells, Xuzhou, China

Published online: 16 May 2025

and progenitor cells (HSPCs), a mechanism that plays an important role in the pathogenesis of AA [1, 5]. It also provides a theoretical basis for immunosuppressive treatment (IST) of AA. Due to the significant individual differences in the form of onset, response to treatment, and prognosis of AA, the treatment outcome of this disease has received increasing attention from clinicians. Kao et al. [6] showed that the early treatment effect of patients with AA was closely related to the prognosis, and effective early treatment predicted a better prognosis. Therefore, predicting early treatment outcomes is crucial to developing a precise treatment plan.

Anemia is one of the common clinical manifestations of AA and, like many other diseases. MCV is a key indicator to assess the size of an individual's red blood cells and is often used to classify the cell morphology of anemia types [7]. Normally, the size of red blood cells in the blood ranges from 80 to 100 fL, and according to this size range, anemia can be classified as macrocytic, normocytic, or microcytic anemia [8, 9]. However, clinical testing has revealed that some patients with AA may have macrocytic anemia, which is inconsistent with the previously perceived normocytic anemia, as confirmed by the study of Young et al. [10]. By analyzing the causes of macrocytic anemia in 628 patients, Natsuko et al. found that some AA patients showed macrocytic anemia, and its frequency was significantly higher than that of megaloblastic anemia [11]. Currently, the mechanism of elevated MCV levels in AA patients is not fully understood. Although the mechanism of macrocytic anemia in AA patients is not clear, related studies suggest that it may be related to the increased levels of EPO and cell-stimulating factor in AA patients, which can stimulate the rapid proliferation and maturation of the remaining erythroblasts and release into the blood, leading to the macrocytic anemia in AA patients [12, 13]. Some scholars also believe that it is related to the reduction of the number of hematopoietic stem cells or poor development during maturation [14]. The residual hematopoiesis in the bone marrow of AA patients is mainly manifested as mild megaloblastic erythropoiesis and nuclear and plasma imbalance [14]. The dysplastic hematopoiesis of AA patients can be manifested in the morphology of bone marrow erythroblasts and indirectly manifested as the volume of red cells and the increase of MCV in peripheral blood.

Recent studies have found that elevated MCV levels are associated with a variety of poor outcomes, including diabetes, acute kidney injury, cerebral hemorrhage, cardiovascular disease, esophageal cancer, and other malignancies [15–22]. The role of MCV in the hematological system has also been validated, and high MCV is considered to be a good indicator of prognosis in patients with myelodysplastic syndrome (MDS), which differs from its prognostic value in other systems [23–27]. Marsh et al. [28] found that MCV is a useful early response indicator in AA patients after antilymphocyte globulin (ALG) treatment; however, there has been no clear report on the correlation between MCV and AA prognosis. Therefore, the purpose of this study was to investigate the relationship between MCV levels and prognosis in AA patients, to determine whether MCV can be used as an effective indicator for the prognosis of AA.

Materials and methods

Patients

We retrospectively collected 181 newly AA patients diagnosed in the Department of Hematology, the Affiliated Hospital of Xuzhou Medical University, from April 2008 to September 2020. Using the normal reference range of MCV (80–100 fl), the patients were divided into a high-MCV group and a normal-MCV group. The diagnosis of AA, disease severity, and response to IST refer to the criteria developed by the British Committee For Standards In Hematology [29]. Exclusion criteria included: age < 18 years; very severe aplastic anemia; hepatitis with AA; pregnant women with AA; positive Ham's test or paroxysmal nocturnal hemoglobinuria (PNH) at initial diagnosis; patients who had been treated with cyclosporine or combined androgens; and patients undergoing hematopoietic stem cell transplantation.

Collection of specimens

Bone Marrow Cell Morphology Analysis: Bone marrow was obtained from the iliac bone of all patients. Smears were prepared using specimens with abundant bone marrow particles and optimal preparation quality, followed by staining with Wright–Giemsa staining method. The distribution of bone marrow smear cells, bone marrow cellularity, and the counts of lymphocytes, granulocytes, erythrocytes, and megakaryocytes were observed under a microscope for each specimen. Hematological Analysis: 2 mL of peripheral venous blood was drawn from each patient in the fasting state in the morning and collected in EDTA-anticoagulated vacuum tubes for complete blood cell analysis.

Testing indicators

The complete blood counts were obtained before and after treatment, reticulocyte index, sex, age, disease severity, bone marrow cell morphology, and other related clinical data of AA patients were collected.

Disease severity of aplastic anemia

Severe AA (SAA): Marrow cellularity < 25% (or 25–50% with < 30% residual hematopoietic cells), plus at least 2 of: (i) neutrophils $< 0.5 \times 10^9$/L, (ii) platelets $< 20 \times 10^9$/L, (iii) reticulocyte count $< 20 \times 10^9$/L (see diagnostic section for automated reticulocyte count); Very Severe AA (VSAA): As for SAA but neutrophils $< 0.2 \times 10^9$/L; Non-severe AA (NSAA): AA not fulfilling the criteria for SAA or VSAA [29].

Clinical outcomes and follow-up

The efficacy was evaluated according to the criteria developed by the British Committee For Standards In Hematology [29], Severe Aplastic Anemia (SAA): Complete Response (CR): Hemoglobin concentration normal for age and gender, Neutrophils $> 1.5 \times 10^9$/L and Platelets $> 150 \times 10^9$/L; Partial Response (PR): Transfusion independent and no longer meet criteria for severe disease; No Response (NR): Still fulfill severe disease criteria. Non-Severe Aplastic Anemia (NSAA): Complete Response (CR): Same criteria as for severe disease; Partial Response (PR): Transfusion independence (if previously dependent) or doubling or normalization of at least one cell line or increase of baseline [hemoglobin concentration of > 30 g/L(if initially < 60), neutrophils of $> 0.5 \times 10^9$/L(if initially < 0.5), or platelets of $> 20 \times 10^9$/L (if initially < 20)].

Statistical methods

SPSS 25.0 and GraphPad Prism 9 were used for statistical analysis and graphics drawing. Measurement data are expressed as the median (range), and comparisons between groups were performed using the Mann–Whitney *U* test or independent samples t-test. Categorical data are presented as the number of cases (percentage) [n,(%)], and comparisons between groups were performed using the χ^2 test or Fisher's exact test. Spearman correlation was used to measure the correlation between two continuous variables. The Kaplan–Meier (K-M) method was used for descriptive analysis and survival analysis, and the log-rank test was used to compare the OS and PFS between the two groups. Univariate and multivariate Cox regression models were used to analyze factors associated with survival. A two-sided P-value < 0.05 was considered statistically significant.

Results

Patient characteristics

The median age of all AA patients was 43 years (range, 18–97), and there were 109 male patients and 72 female patients. There were 107 patients (59.12%) in the high-MCV group and 74 patients (40.88%) in the normal-MCV group, including 125 patients (69.06%) in the NSAA group and 56 patients (30.94%) in the SAA group. Among the participants, 165 (91.16%) were initially treated with cyclosporine A plus androgen, and fewer were treated with cyclosporine A alone. The differences in clinical characteristics between the two groups were compared and analyzed. There were statistically significant differences in neutrophil count, red blood cell count, mean corpuscular volume, platelet count, reticulocyte count, and disease severity between the two groups ($P < 0.05$) (Table 1).

Meanwhile, the results showed that the average MCV levels of NSAA patients and SAA patients were 104.63 fl and 98.13 fl, respectively, and the difference was statistically significant ($P < 0.001$). Moreover, the MCV level of NSAA patients was significantly higher than that of SAA patients (Fig. 1A).

Comparison of bone marrow cell morphology at initial diagnosis

Of the 181 overall patients, 1.66% had significantly active bone marrow cellularity (II), 23.20% had active bone marrow cellularity (III), 69.61% had reduced bone marrow cellularity (IV), and 5.52% had extremely reduced bone marrow cellularity (V) (Fig. 1B). Between the two groups of patients, the proportion of bone marrow lymphocytes in the high-MCV group was lower than that in the normal-MCV group, and the difference was statistically significant ($P = 0.016$, Fig. 2A). At the same time, the average proportion of bone marrow granulocytes in the high-MCV group was significantly higher than that in the normal-MCV group ($P = 0.027$, Fig. 2B), and there was no significant difference in other indicators between the two groups ($P > 0.05$, Fig. 2C, D). In addition, the results showed that the average proportion of lymphocytes in NSAA patients was lower than that in SAA patients, while the average proportion of granulocytes was higher than that in SAA patients ($P < 0.05$, Fig. 2E, F). There was no significant difference in the level of the other two lines between the disease types ($P > 0.05$ Fig. 2G, H).

MCV and ORR or DOR

By treatment with cyclosporine A plus androgen or cyclosporine A alone, there were 160(88.40%) surviving patients and 21(11.60%) deaths out of 181 patients. Remission occurred in 74 high-MCV patients, and the ORR was 69.10%, including 19 patients (17.76%) with a CR, and 55 patients (51.40%) with a PR. Remission occurred in 44 normal-MCV patients, with an ORR of 59.46%, including 19 patients with a CR (25.68%), and 25 patients with a PR (33.78%). There were significant differences in the

Table 1 The characteristics of the 181AA patients

Characteristics	High-MCV($n=107$)	Normal-MCV($n=74$)	χ^2	P
Sex [n(%)]			0.030	0.862
Male	65 (60.748%)	44 (59.460%)		
Female	42 (39.252%)	30 (40.541%)		
Age [year, M (range)]	35 (18–97)	48 (18–86)		0.108
WBC [$\times 10^9$/L, M(range)]	2.400 (0.890–7.300)	2.260 (0.600–6.610)		0.434
NE [$\times 10^9$ /L, M (range)]	0.820 (0.270–5.880)	0.675 (0.010–4.820)		**0.001**
LY [$\times 10^9$ /L, M (range)]	1.300 (0.300–3.100)	1.400 (0.200–3.600)		0.350
EO[$\times 10^9$ /L, M (range)]	0.010 (0–0.210)	0.010 (0–0.070)		0.785
MO [$\times 10^9$ /L, M (range)]	0.110 (0–0.390)	0.120 (0–0.430)		0.266
RBC [$\times 10^9$/L, M(range)]	1.710 (0.540–3.790)	2.035 (0.660–4.030)		**0.001**
HB [g/L, M (range)]	63 (19–142)	66 (21–120)		0.564
HCT [%, M (range)]	19 (5.500–41.800)	18.600 (5.800–84.800)		0.566
MCV [fl, M (range)]	108.300 (100.700–129)	93.500 (80.100–100)		**< 0.001**
RDW-SD [%, M (range)]	60.900 (13.600–85.900)	50.350 (36.300–75.500)		**< 0.001**
RDW [%, M (range)]	15.500 (0–23.400)	15.950 (11.600–24.400)		0.690
PLT[$\times 10^9$ /L, M (range)]	20 (2–118)	13 (1–86)		**0.003**
Ret [$\times 10^9$ /L, M (range)]	35.400 (5.300–87.300)	19.150 (1.900–78)		**< 0.001**
Diagnostic type [n (%)]			18.374	**< 0.001**
NSAA	87 (81.308%)	38 (51.351%)		
SAA	20 (18.692%)	36 (48.649%)		

Percentages may not total 100% because of rounding. P-value < 0.05 was considered statistically significant and is indicated in bold. Abbreviations: WBC, white blood cell; NE, neutrophil; LY, lymphocyte; EO, eosinophils; MO, monocytes; RBC, red blood cell; HB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; RDW-SD, red blood cell distribution width standard deviation; RDW, red blood cell distribution width; PLT, platelet; Ret reticulocyte, NSAA, non-severe aplastic anemia; SAA, severe aplastic anemia

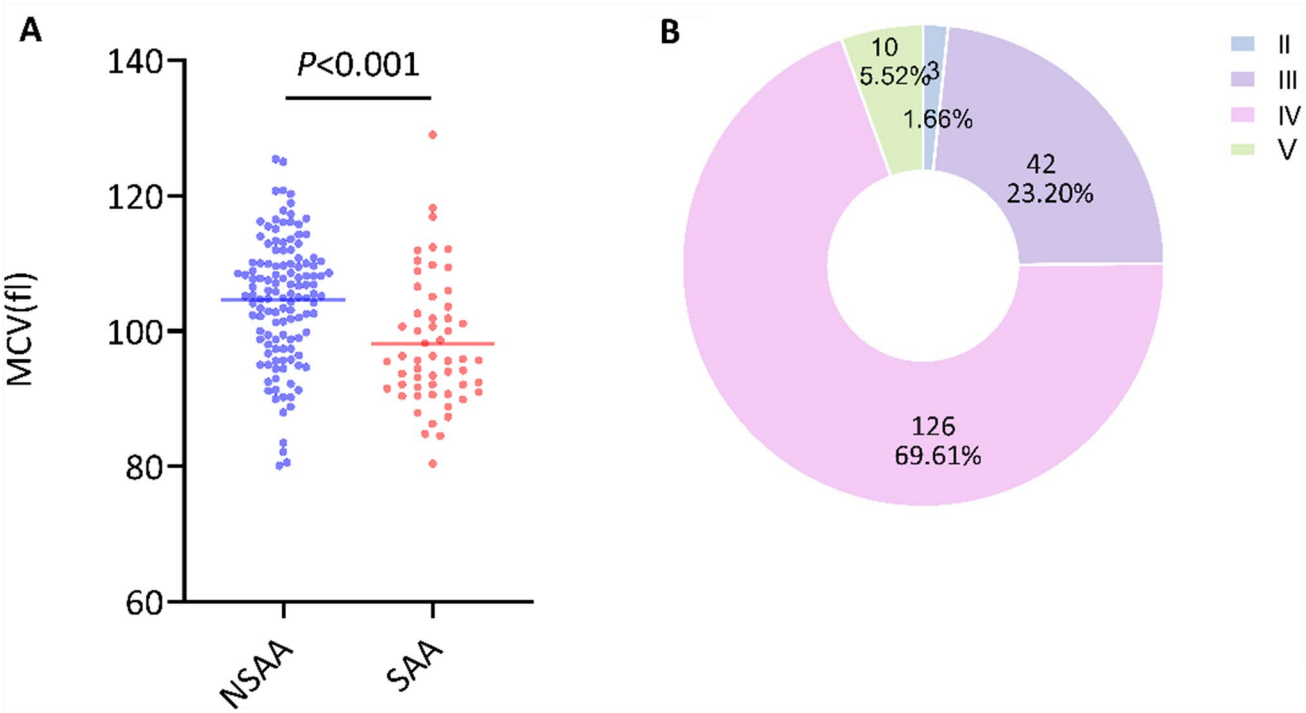

Fig. 1 Mean corpuscular volume (MCV) level according to disease severity at diagnosis (non-severe and severe AA) (**A**). The degree of bone marrow cellularity in all AA patients. (II: significantly active; III: active; IV: reduced; V: extremely reduced) (**B**)

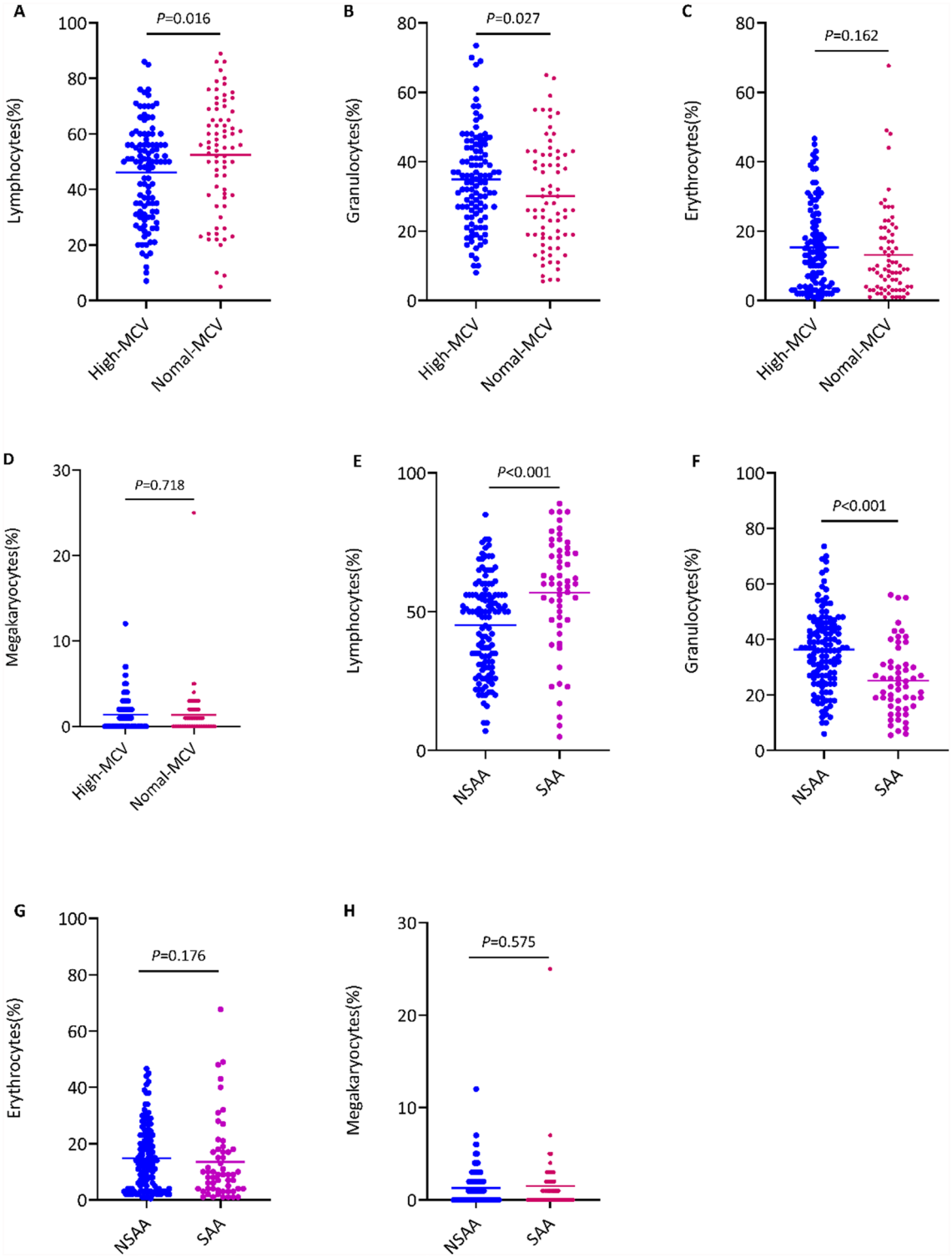

Fig. 2 Baseline bone marrow cell morphology comparison of lymphocytes, granulocytes, erythrocytes, and megakaryocytes in MCV subgroups (**A**–**D**), in disease severity at diagnosis (non-severe and severe AA, **E**–**H**)

ORR between the two groups ($P = 0.049$)(Fig. 3A). Furthermore, in the high-MCV group, the median DOR was 48 months, and in the normal-MCV group, the median DOR was 34.5 months. There were no significant differences in the DOR between the high-MCV and normal-MCV groups (P = 0.482)(Fig. 3B).

MCV and OS or PFS

The overall median follow-up time was 50 months (95%CI 22–82.5). The median OS and PFS in the high-MCV group have not yet been obtained. In the normal-MCV group, the median OS was not yet obtained, and the median PFS was 63 months (95%CI: 23.91–102.09). The 5-year OS of AA patients in the high-MCV group was higher than that in the normal-MCV group (96.99%, 76.23%, $P<0.001$) (Fig. 4A), and the 5-year PFS of the former was also better than that of the latter (77.39%, 50.68%, $P<0.001$) (Fig. 4B). At the same time, according to the results of univariate analysis and clinical experience, age, disease severity, white blood cell count, neutrophil count, platelet count, and reticulocyte count were included in Cox regression analysis, and normal MCV and SAA were independent risk factors for poor survival (Table 2).

MCV of diverse population and OS or PFS

We further compared the results in subgroups of MCV across different populations (disease severity, sex, age). The results showed that the OS of the high-MCV group was better than that of the normal-MCV group in SAA patients, male patients, and patients younger than 35 years or aged 35–55 years ($P<0.05$). In NSAA, SAA, male, female, and 35–55-year-old patients, the high-MCV group had better PFS than the normal-MCV group ($P<0.05$). There was

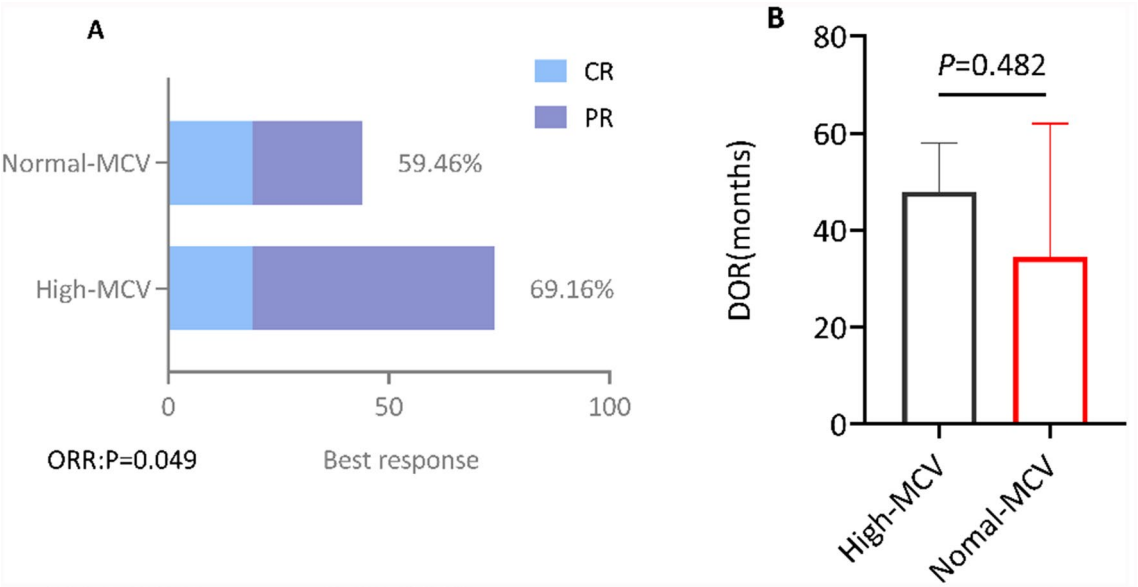

Fig. 3 The rates of best response in MCV subgroups (**A**). The DOR in MCV subgroups (**B**)

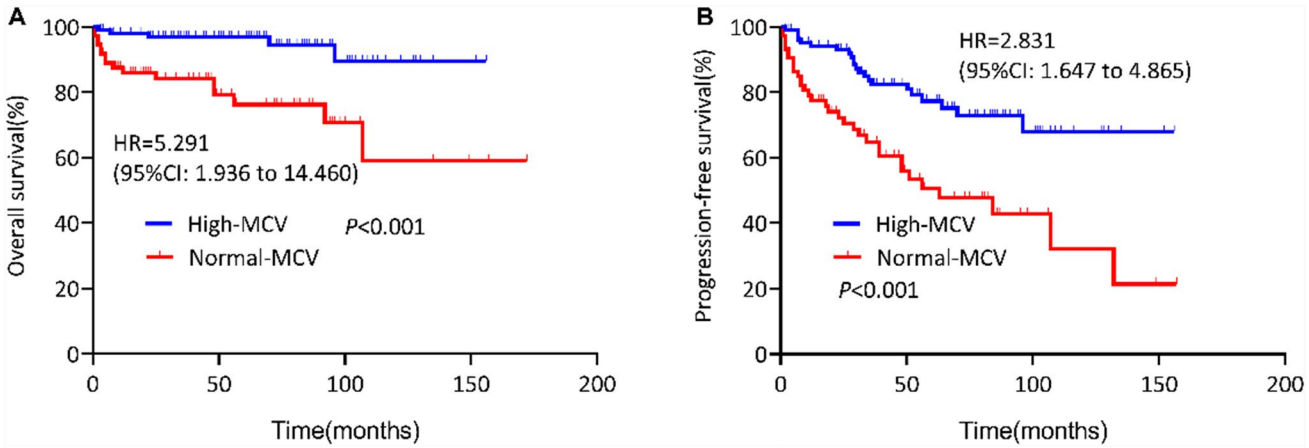

Fig. 4 Overall survival and progression-free survival in MCV subgroups (**A** and **B**)

no significant difference in OS and PFS between MCV subgroups in other populations ($P > 0.05$)(Fig. 5A–N). Subgroup analysis of MCV according to disease severity showed that OS in male patients with high MCV was better than that in the normal-MCV group ($P < 0.05$), and PFS in male patients or patients aged 35–55 years was better than that in the normal-MCV group ($P < 0.05$). There was no significant difference in OS and PFS between the other groups ($P > 0.05$) (Supplementary information—Fig. S1).

MCV and hemogram restoration

We compared the blood cell counts between the two MCV groups after treatment. In our study, The results showed that white blood cell (WBC) count, neutrophil (NE) count, hemoglobin (Hb) level, and platelet (PLT) count were significantly higher than before treatment, and the high-MCV group was higher than the normal-MCV group, among which Hb increased most significantly. The difference was statistically significant ($P < 0.05$) (Fig. 6).

MCV and reticulocyte parameters

In the results of the study comparing the levels of reticulocytes and their related parameters between the two groups, the relative and absolute reticulocyte counts, high-fluorescence reticulocyte (HFR), medium-fluorescence reticulocyte (MFR), and immature reticulocyte fraction (IRF) in the high-MCV group were significantly higher than those in the normal-MCV group ($P < 0.001$). At the same time, the low-fluorescence reticulocyte (LFR) was significantly lower in patients with high MCV than in those with normal MCV ($P < 0.001$) (Fig. 7).

To explore the association between reticulocyte parameters and MCV, this study further analyzed the correlation between reticulocyte and its parameters and MCV. The results showed that there was a positive correlation between MCV level and absolute reticulocyte count, relative reticulocyte count, high-fluorescence reticulocyte (HFR), medium-fluorescence reticulocyte (MFR), and immature reticulocyte fraction (IRF) ($r = 0.384$, $r = 0.300$, $r = 0.430$, $r = 0.447$, $r = 0.507$, respectively). At the same time, MCV level was negatively correlated with low-fluorescence reticulocyte (LFR) ($r = -0.514$). All correlation analyses reached statistical significance ($P < 0.001$) (Fig. 8).

Discussion

In recent years, the prognostic value of MCV levels in myelodysplastic syndromes has been demonstrated [23–27]. The elevated MCV level at diagnosis is an indicator of good prognosis in patients with bone marrow blasts < 5% of myelodysplastic syndromes. Holtan et al. reported that lower MCV level was an independent risk factor for OS in patients with 5q- syndrome [25]. Subsequently, Wang et al. conducted multivariate analysis on 164 MDS patients with abnormal chromosome karyotypes and found that MCV ≤ 100 fl was an independent adverse prognostic factor for MDS patients with chromosomal karyotype abnormalities [26]. Recently, Shi et al. also analyzed the effect of MCV level on overall survival (OS) and overall survival

Table 2 Logistic regression analysis of influencing factors of overall survival in AA patients

	Univariate COX regression		Multivariate COX regression	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age				
< 35	1			
35 ≤ ~ < 55	2.287 (0.697 ~ 7.498)	0.172		
≥ 55	3.183 (1.085 ~ 9.366)	**0.035**		
WBC	0.685 (0.413 ~ 0.1.134)	0.141		
NE	0.348 (0.119 ~ 1.023)	**0.055**		
PLT	0.962 (0.923 ~ 1.002)	0.063		
RET	0.964 (0.935 ~ 0.994)	**0.018**		
MCV				
High-MCV	1			
Normal-MCV	5.291 (1.936 ~ 14.46)	**0.001**	4.196 (1.500 ~ 11.736)	**0.006**
Disease severity				
NSAA	1			
SAA	4.432 (1.833 ~ 10.715)	**0.001**	3.404 (1.368 ~ 8472)	**0.008**

WBC, white blood cell; NE, neutrophil; PLT, platelet; Ret reticulocyte, MCV, mean corpuscular volume; NSAA, non-severe aplastic anemia; SAA, severe aplastic anemia; HR, hazard ratios; CI, confidence intervals. *P*-value < 0.05 was considered statistically significant and is indicated in bold

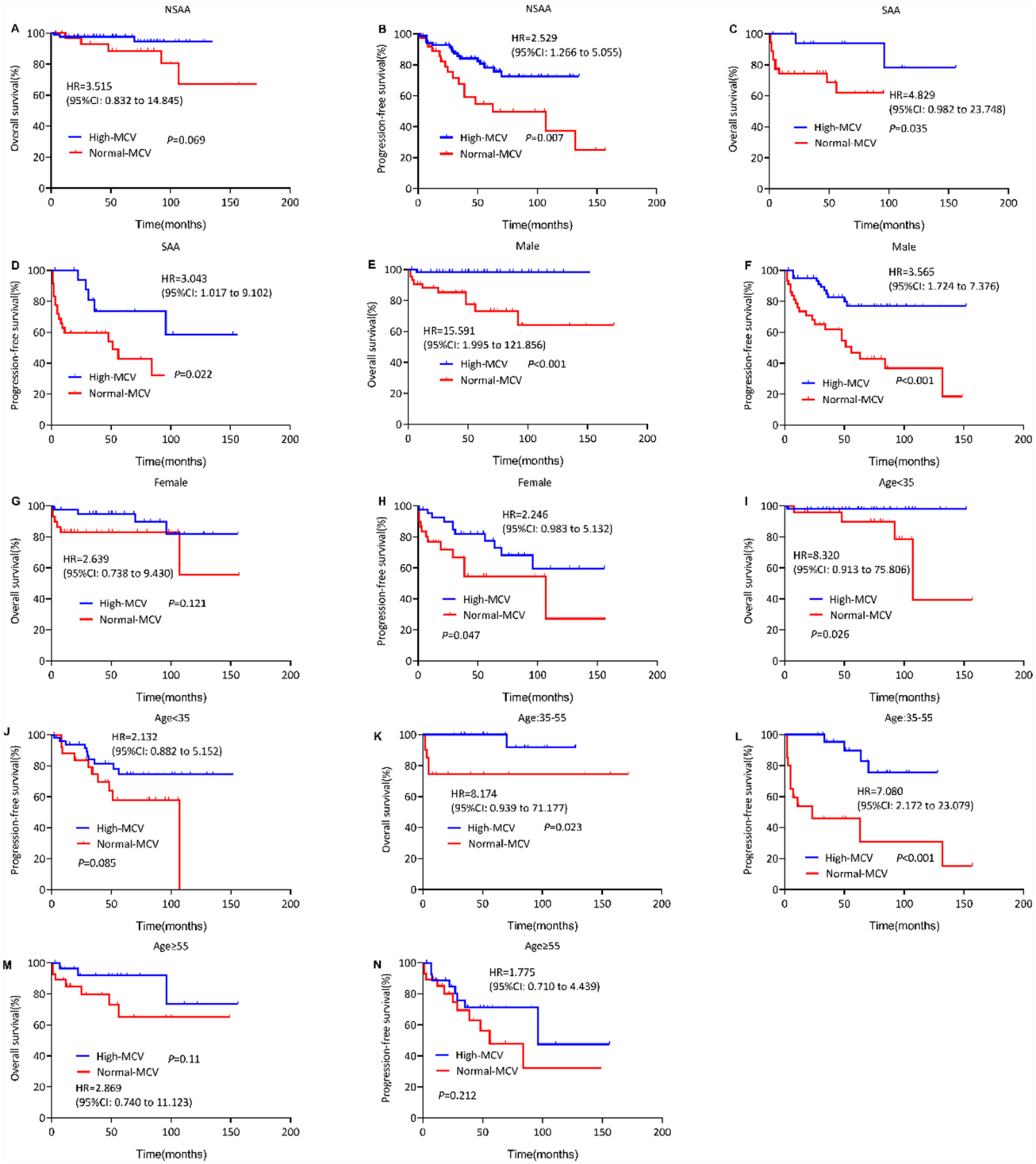

Fig. 5 Long-term outcomes between MCV groups in diverse populations. **A**–**D** The OS and PFS between MCV subgroups in NSAA and SAA. **E**–**H** The OS and PFS between MCV subgroups in male and female. **I**–**N** The OS and PFS between MCV subgroups in the populations of age of < 35, age of 35–55, and age of ≥ 55 (year)

(OS) in MDS patients with different bone marrow blasts levels and confirmed that MCV ≤ 100 fl was an adverse prognostic factor independent of gene mutation and other clinical indicators in MDS patients with bone marrow blasts < 5% [27]. Many studies have shown that elevated MCV levels indicate better bone marrow compensatory response, so

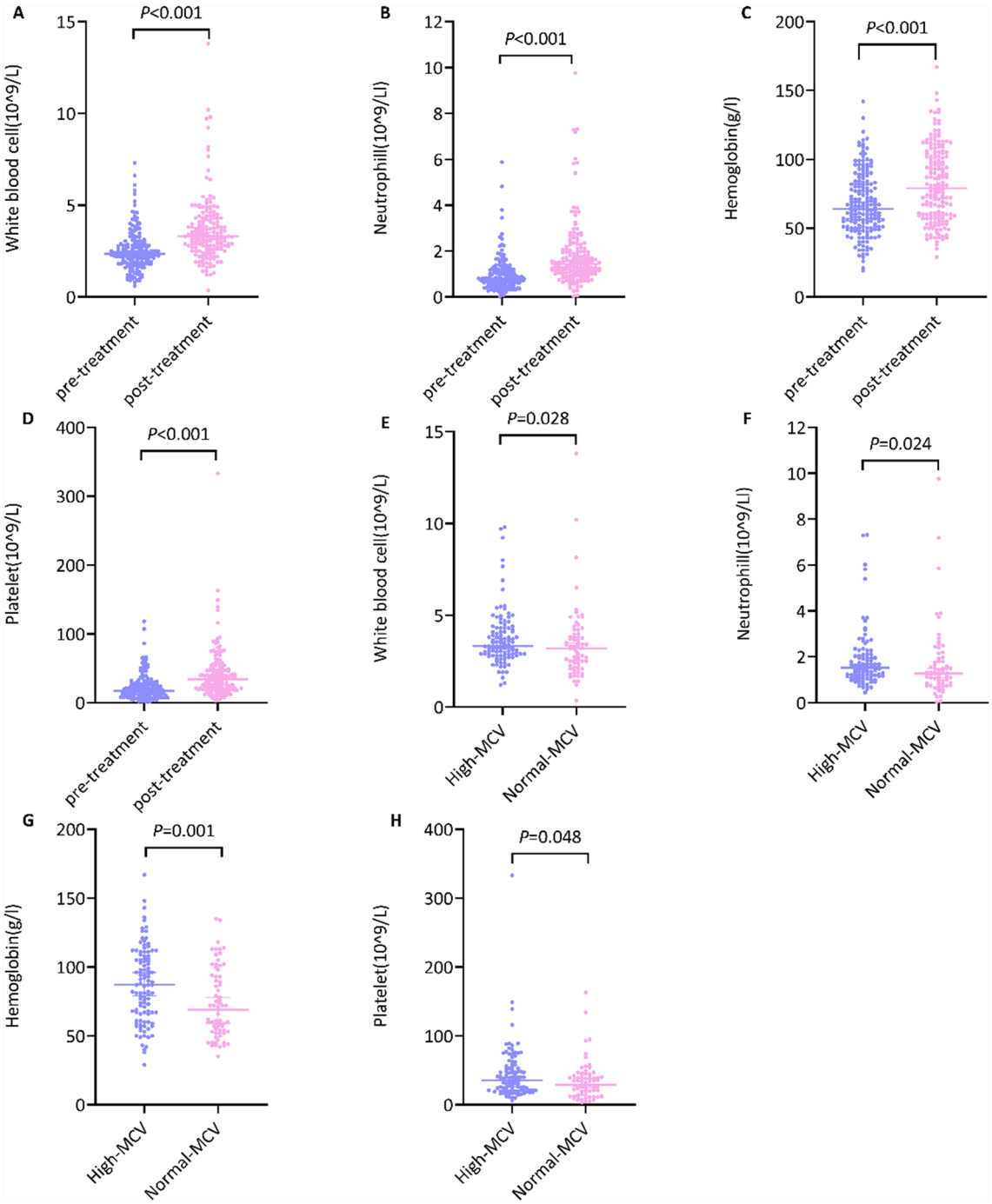

Fig. 6 Hemogram restoration, comparison with the recovery of blood routine pre-treatment and post-treatment (**A**–**D**), the recovery of blood routine between two groups of patients (**E**–**H**)

MDS patients with elevated MCV have a better prognosis. In addition, high MCV may lead to poor prognosis, such as coronary artery disease, esophageal squamous cell carcinoma end-stage renal disease, acute pancreatitis, and other diseases [15, 17, 18, 30].

To the best of our knowledge, this report is the first study of the prognostic value of MCV level in patients with aplastic anemia. The report clearly indicates that MCV elevation is closely related to the prognosis of patients with aplastic anemia, especially when MCV exceeds 100 fl, which significantly affects the prognosis of aplastic anemia. In this study, we observed that patients with high MCV had higher 5-year overall survival (OS) and 5-year progression-free survival (PFS) than those

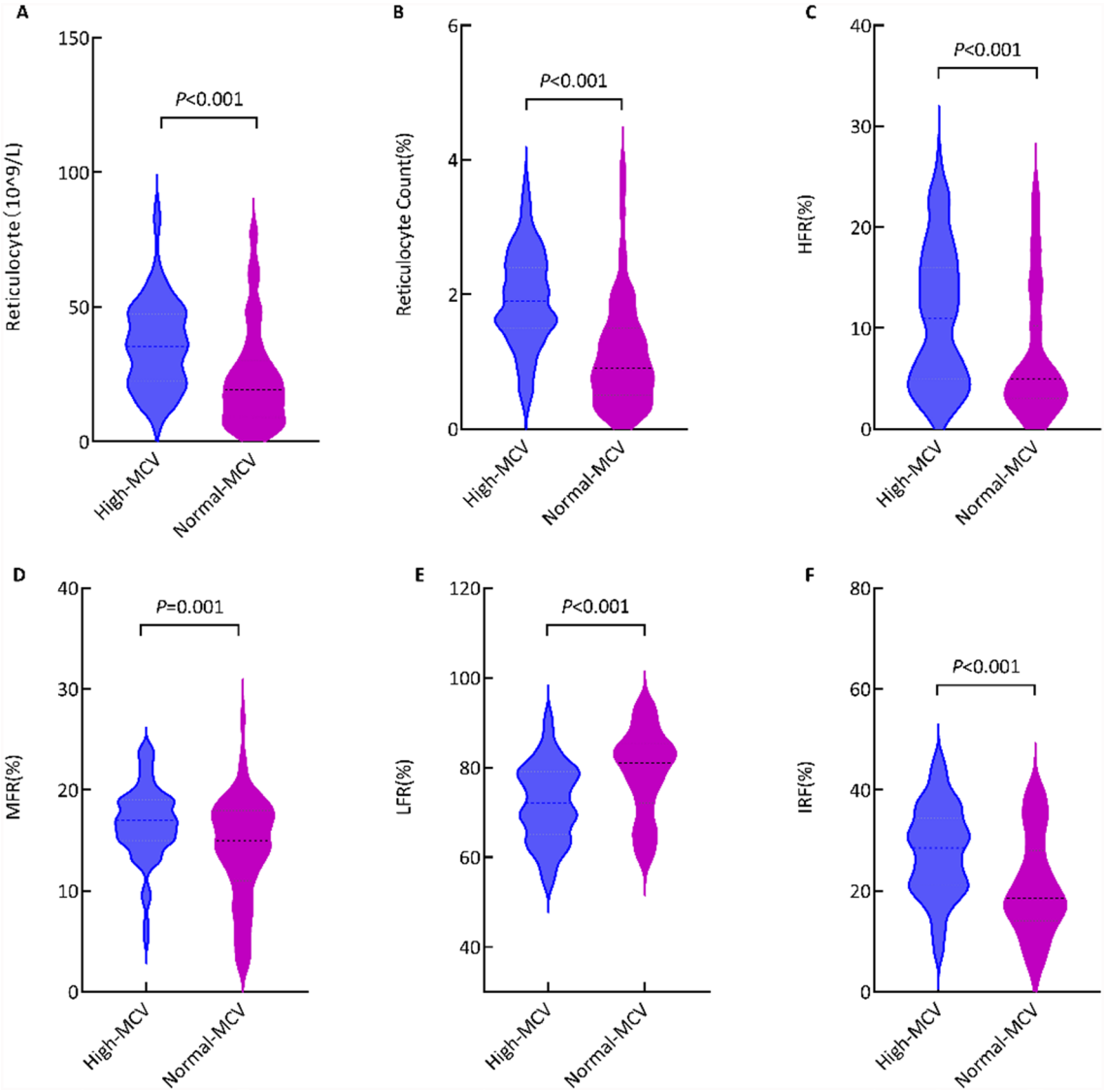

Fig. 7 Reticulocyte parameters were stratified by MCV. The reticulocyte, reticulocyte percentage, HFR, MFR, LFR, IRF in the High-MCV subgroup compared with those in the Normal-MCV subgroup (**A**–**F**). (HFR: high-fluorescence reticulocyte; MFR: medium-fluorescence reticulocyte; LFR: low-fluorescence reticulocyte; IRF: immature reticulocyte fraction; MCV mean corpuscular volume)

with normal MCV, which may partly be due to the higher proportion of NSAA patients in patients with high MCV, leading to better OS and PFS results. Therefore, the patients were further divided into the NSAA group and SAA group, and the OS and PFS between the different groups were compared. The results showed that the 5-year OS and PFS of the high-MCV group were better than that of the normal-MCV group in both NSAA and SAA groups. The effect of MCV on NSAA is more obvious than that of SAA, which may be related to its unique pathological characteristics. NSAA has milder bone marrow failure and still retains some erythroid activity. Data analysis showed that 81.308% of the NSAA patients had macrocytic anemia (MCV > 100 fL), which was significantly higher than that of the SAA group (18.692%), and the median MCV of the NSAA group (105.50 fL) was significantly higher than that of the SAA group (95.70 fL) ($P < 0.001$). The analysis of prognostic factors in these patients showed that normal MCV and SAA were independent influencing factors for the poor prognosis of AA patients. The results showed that the ORR of patients with high MCV was higher than that of patients with normal MCV ($P < 0.05$). There was no significant difference in the duration of treatment effect between the two groups ($P > 0.05$). The results showed that the recovery of white blood cell count, neutrophil count, hemoglobin level, and platelet count in the high-MCV

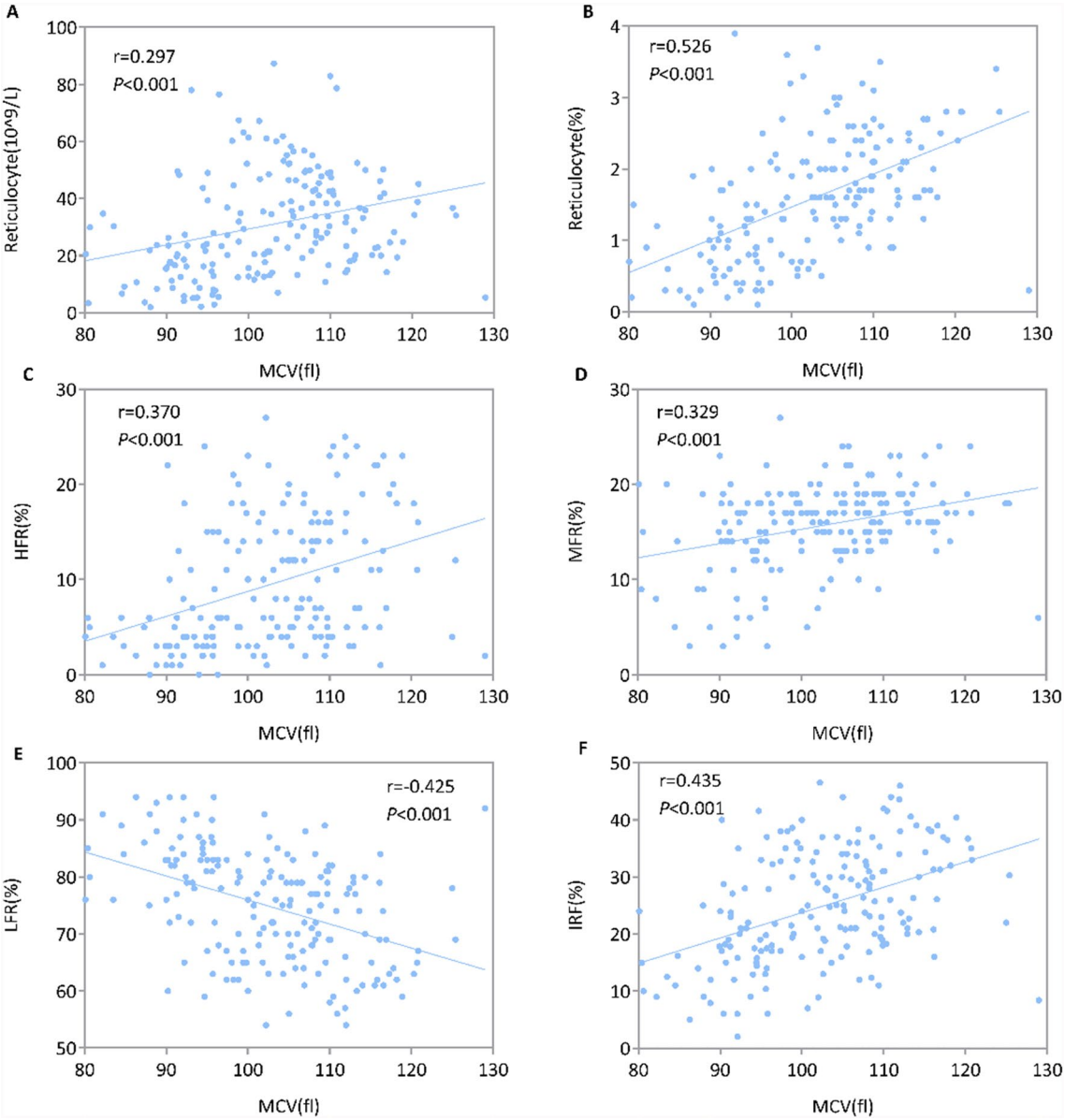

Fig. 8 Correlation between reticulocyte, reticulocyte percentage, HFR, MFR, LFR, IRF, and MCV (**A**–**F**). (HFR: high-fluorescence reticulocyte; MFR: medium-fluorescence reticulocyte; LFR: low-fluorescence reticulocyte; IRF: immature reticulocyte fraction; MCV mean corpuscular volume)

group was significantly higher than that in the normal-MCV group ($P < 0.05$). The reason may be that the degree of residual hematopoiesis in the bone marrow of patients with high MCV is higher, which improves the blood cells and has a better response to drug treatment. Therefore, it can be inferred that MCV can become an independent factor for judging the prognosis of AA patients, and high MCV can be considered a positive prognostic factor in hematological diseases, which is consistent with the results of previous studies [31]. However, the limitation of this study is that it could not monitor the MCV level after treatment and study the correlation between the elevated MCV level and the treatment response, and the patients need to be followed up for a longer time.

The mechanism of the correlation between high MCV and good prognosis in patients with aplastic anemia is still unclear, and it may be related to the different degrees of residual hematopoiesis in bone marrow. The different degrees of residual hematopoiesis in the bone marrow of AA patients will significantly affect the hematological response and survival rate after immunosuppressive treatment [32–34]. A large number of studies have shown that reticulocyte and their parameters can reflect erythropoiesis and maturity in bone marrow, which

is an early indicator of bone marrow hematopoietic function recovery. AA patients with high reticulocyte have a better treatment effect [35, 36]. If the patient's baseline reticulocyte count is high, it may indicate that the remaining bone marrow function is relatively good, and it also indicates that there are enough stem cells to support hematopoiesis after immunosuppressive treatment [37]. When the hematopoietic system is stimulated, more reticulocytes, even naive erythrocytes, are released from the bone marrow into the peripheral blood. As a result, MFR, HFR, and IRF were significantly increased, while LFR was decreased [38], which was consistent with the results of this study. The relative and absolute reticulocyte count, HFR, MFR, and IRF in AA patients with high MCV were higher than those in AA patients with normal MCV ($P < 0.001$). However, LFR was significantly lower than that of AA patients in the normal-MCV group ($P < 0.001$). Currently, the reticulocyte count and its related parameters are considered the preferred index for assessing the recovery of bone marrow erythrocytes. These parameters can more accurately and comprehensively reflect the production of red blood cells, more truly reflect the hematopoietic level of bone marrow erythrocytes, and more effectively evaluate the hematopoietic function of bone marrow. The correlation analysis between MCV level and reticulocyte parameters showed that MCV was positively correlated with reticulocyte count, HRF, MRF, and IRF, but negatively correlated with LRF. On the one hand, it is confirmed that there is a causal relationship between MCV level and reticulocyte-related parameters. On the other hand, it has also been confirmed that patients with elevated MCV can show good residual bone marrow hematopoietic function. Therefore, MCV can reflect the hematopoietic function of the erythroid lineage of bone marrow and also reflect the residual hematopoietic function of bone marrow to a certain extent. This has a certain reference value for evaluating the prognosis of patients with aplastic anemia, which is consistent with the results of our study.

In conclusion, AA patients with high MCV at initial diagnosis have better prognosis and response to drug treatment. AA is a bone marrow failure disease, and the residual normal bone marrow hematopoiesis is of great significance for the prognosis. The patients with elevated MCV have better bone marrow compensatory function and better prognosis. Therefore, MCV can indirectly evaluate the prognosis of patients by assessing the residual normal hematopoiesis in the bone marrow. Moreover, the most important feature of MCV is that it is an inexpensive and readily available prognostic factor that can be obtained from an automated blood count at the time of diagnosis.

In general, this study is a retrospective, single-center study, which inevitably has some limitations. Moreover, the median follow-up time in this study was short, and further multicenter, prospective studies with long-term follow-up are needed to verify the results of this study.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10238-025-01652-9.

Acknowledgements The authors thank the study participants and their families and the staff of the Department of Hematology at the Affiliated Hospital of Xuzhou Medical University.

Author contributions Hai Cheng and KaiLin Xu diagnosed the AA patients and designed the research study. Li Han, XueDong Shi, ShuQi Wang, and QiuShuang Wang analyzed the results and wrote the manuscript; AnQi Xia followed up with the patients; Jiang Cao reviewed and critically edited the manuscript.

Funding This work was supported by grants from the National Natural Science Foundation of China (82070127 and 82470140) and the Science and Technology Project of Xuzhou Health Commission (XWKYSL20220264).

Data availability The data of the current study can be requested via email from the corresponding author.

Declarations

Conflict of interests No relevant conflicts of interest are related to this study.

Ethical approval This retrospective investigation fully followed the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2023-KL449-01).

References

1. Lucio L, Risitano AM. Advances in understanding the pathogenesis of acquired aplastic a-naemia. Br J Hematol. 2018;182(6):758–76.
2. Liu C, Shao Z. Aplastic anemia in China. J Transl Intern Med. 2018;6(3):134–7.
3. Montane E, Ibanez L, Vidal X, et al. Epidemiology of aplastic anemia: a prospective multicenter study. Haematologica. 2008;93(4):518–23.

4. Killick SB, Bown N, Cavenagh J, et al. Guidelines for the diagnosis and management of adult aplastic anemia. Br J Hematol. 2016;172(2):187–207.
5. Wang P, Cai Q, Peng X, et al. Increased co-expression of CTLA4/LAG3 predicted adverse clinical outcomes in patients with T-cell malignancies. Cell Investig. 2025;1(1):100004.
6. Kao SY, Xu W, Brandwein JM, et al. Outcomes of older patients ([or = 60 years) with acquired aplastic anemia treated with immunosuppressive therapy. Br J Haematol. 2008;143(5):738–43.
7. Yavorkovsky LL. Mean corpuscular volume, hematocrit and polycythemia. Hematology. 2021;26(1):881–4.
8. Capps JA. A Study of Volume Index. Observations upon the volume of erythrocytes in various disease conditions. J Med Res. 1903;10(3):367–401.
9. Maner BS, Moosavi L. Mean corpuscular volume. Treasure Island (FL): StatPearls Publishing; 2022.
10. Young NS, Calado RT, Scheinberg P. Current concepts in the pathophysiology and treatment of aplastic anemia. Blood. 2006;108(8):2509–19.
11. Takahashi N, Kameoka J, Takahashi N, Tamai Y, Murai K, Honma R, Noji H, Yokoyama H, Tomiya Y, Kato Y, Ishizawa K. Causes of macrocytic anemia among 628 patients: me-an corpuscular volumes of 114 and 130 fL as critical markers for categorization. Int J Hematol. 2016;104(3):344–57.
12. Rowley PT. Williams hematology. Am J Hum Genet. 1995;57(2):514.
13. Kojima S, Matsuyama T, Kodera Y. Circulating erythropoietin in patients with acquired aplastic anemia. Acta Haematol. 1995;94(3):117–22.
14. Lee JJ, Kook H, Chung IJ, et al. Telomere length changes in patients with aplastic anemia. Br J Hematol. 2001;112(4):1025–30.
15. Zheng YZ, Dai SQ, Li W, et al. Prognostic value of preoperative mean corpuscular volume in esophageal squamous cell carcinoma. World J Gastroenterol WJG. 2013;19(18):2811.
16. Yoon HJ, Kim K, Nam YS, et al. Mean corpuscular volume levels and all-cause and liver cancer mortality. Clin Chem Lab Med (CCLM). 2016;54(7):1247–57.
17. Hsieh YP, Chang CC, Kor CT, et al. Mean corpuscular volume and mortality in patients with CKD. Clin J Am Soc Nephrol CJASN. 2017;12(2):237–44.
18. Kor CT, Hsieh YP, Chang CC, et al. The prognostic value of interaction between mean corpuscular volume and red cell distribution width in mortality in chronic kidney disease. Sci Rep. 2018;8(1):11870.
19. Nagai H, Yuasa N, Takeuchi E, et al. The mean corpuscular volume as a prognostic factor for colorectal cancer. Surg Today. 2018;48:186–94.
20. Ueda T, Kawakami R, Horii M, et al. High mean corpuscular volume is a new indicator of prognosis in acute decompensated heart failure. Circ J. 2013;77(11):2766–71.
21. Jomrich G, Hollenstein M, John M, et al. High mean corpuscular volume predicts poor outcome for patients with gastroesophageal adenocarcinoma. Ann Surg Oncol. 2019;26:976–85.
22. Zhang L, Yin J, Sun H, et al. Relationship between mean corpuscular volume and 30-day mortality in patients with intracerebral hemorrhage: evidence from the MIMIC-III database. Medicine. 2022;101(44):e31415.
23. Tennant GB, Al-Sabah AI, Burnett AK. Prognosis of myelodysplasic patients: non-parametric multiple regression analysis of populations stratified by mean corpuscular volume and marrow myeloblast number. Br J Hematol. 2002;119(1):87–96.
24. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. Clin Oncol. 2007;25:3503–10.
25. Holtan SG, Santana-Davila R, Dewald GW, et al. Myelodysplastic syndromes associated with interstitial deletion of chromosome 5q: clinicopathologic correlations and new insights from the prelenalidomide era. Am J Hematol. 2008;83(9):708–13.
26. Wang H, Wang XQ, Xu XP, et al. Mean corpuscular volume predicts prognosis in MDS patients with abnormal karyotypes. Ann Hematol. 2010;89:671–9.
27. Shi ZX, Qin TJ, Xu ZF, et al. Mean corpuscular volume ≤ 100 fl was an independent prognostic factor in patients with myelodysplastic syndrome and bone marrow blast<5 percent. Zhonghua Xueyexue Zazhi. 2020;41(1):28–33.
28. Marsh JC, Hows JM, Bryett KA, Al-Hashimi S, Fairhead SM, Gordon-Smith EC. Survival after antilymphocyte globulin therapy for aplastic anemia depends on disease severity. Blood. 1987;70(4):1046–52.
29. Killick SB, Bown N, Cavenagh J, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. Br J Haematol. 2016;172(2):187–207.
30. Tennankore KK, Soroka SD, West KA, et al. Macrocytosis may be associated with mortality in chronic hemodialysis patients: a prospective study. BMC Nephrol. 2011;12:1–7.
31. Ballas SK, Smith ED. Red blood cell changes during the evolution of the sickle cell painful crisis. Blood. 1992;79(8):2154–63.
32. Scheinberg P, Young NS. How I treat acquired aplastic anemia. Blo-od. 2012;8(9):1185–96.
33. Kojima S, et al. Immunosuppressive therapy for aplastic anemia: anti-thymocyte globulin and cyclosporine versus cyclophosphamide. Blood. 2003;101.7:2896–901.
34. Marsh JC, Bacigalupo A, Schrezenmeier H, et al. Prospective study of rabbit antithy-mocyte globulin and cyclosporine for aplastic anemia from the EBMT severe aplastic anaemia working party. Blood. 2012;119(23):5391–6.
35. Marković M, Majkić-Singh N, Subota V, Mijusković Z. Reticulocyte hemoglobin content in the diagnosis of iron deficiency anemia. Clin Lab. 2004;50(7–8):431–6.
36. Noronha JFA, De Souza CA, Vigorito AC, et al. Immature reticulocytes as an early predictor of engraftment in autologous and allogeneic bone marrow transplantat-ion. Clin Lab Haematol. 2003;25(1):47–54.
37. Piva E, Brugnara C, Chiandetti L, et al. Automated reticulocyte counting: state of the art and clinical applications in the evaluation of erythropoiesis. Clin Chem Lab Med. 2010;48(10):1369–80.
38. Rosenfeld S, Follmann D, Nunez O, et al. Antithymocyte globulin and cyclosporine for severe aplastic anemia: association between hematologic response and long-term outcome. JAMA. 2003;289(9):1130–5.