ORIGINAL RESEARCH

The Prognostic Significance of C-Reactive Protein to Albumin Ratio in Newly Diagnosed Acute Myeloid Leukaemia Patients

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Background: The ratio of C-reactive protein to albumin (CAR) is an inflammatory marker that has been demonstrated to be a simple and reliable prognostic factor in several solid tumours and chronic lymphocytic leukaemia (CLL). However, no studies have investigated the prognostic value of the CAR in patients with acute myeloid leukaemia (AML).

Objectives and Methods: We retrospectively analysed 212 newly diagnosed non-M3 AML patients. Using the receiver operating characteristic curve (ROC) method, the optimal cut-off value for CAR was determined. We investigated the correlations of the pretreatment CAR levels with clinical characteristics, treatment response of induction chemotherapy, overall survival (OS) and event-free survival (EFS). We also assessed the prognostic value of the CAR compared with other inflammation-based prognostic parameters by the area under the curve (AUC).

Results: According to the ROC curve, the optimal cut-off value of CAR was 1.015. CAR was associated with age, C-reactive protein (CRP) levels, albumin levels, ferritin levels, bone marrow blast percentage, French-American-British (FAB) classification, immuno-phenotype and 2017 European Leukemia Net (2017 ELN) risk stratification. Importantly, we found that high CAR was a powerful indicator of a lower complete remission (CR) rate ($p<0.001$), worse OS ($p<0.001$) and worse EFS ($p<0.001$). Subgroup analysis showed that a high CAR was associated with shorter OS and EFS in patients with intermediate risk stratification or those aged ≤65 years or those without haematopoietic stem cell transplantation (HSCT). In the multivariate analysis, the CAR was an independent prognostic factor for OS and EFS. Furthermore, the predictive value of CAR for OS is superior to that of CRP, albumin and GPS in de novo AML patients aged ≤65 years old.

Conclusion: CAR is a simple and effective prognostic marker in patients with AML. It could be an additional prognostic factor that help further precise the current risk stratification of non-M3 AML, particularly for patients in intermediate risk stratification and those aged ≤65 years and those who did not undergo HSCT.

Keywords: acute myeloid leukaemia, C-reactive protein to albumin ratio, prognosis

Introduction

Acute myeloid leukaemia (AML) is an aggressive haematological malignancy with a high degree of heterogeneity.[1] Although advances in treatment have been made in recent years, the long-term survival remains relatively unsatisfactory, with more than 50% of patients eventually dying from the disease.[2] Currently, the choice of the best treatment option for AML patients relies on the prognostic risk stratification of the most widely used 2017 European Leukemia Net (2017 ELN), which is mainly based on cytogenetic risk factors and molecular markers.[3] Although the relationship between some molecular abnormalities and the prognosis of AML has been identified, there remain many molecular abnormalities with relationships with the prognosis of AML that are unclear. This classification does not completely reflect the heterogeneity within each subgroup, especially for AML in the intermediate risk stratification. Therefore, a vital step

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to improve risk stratification is to identify additional prognostic markers that can contribute to clinical decision-making and help to individualize treatments for AML patients.

It has long been recognized that systemic inflammation is associated with tumorigenesis, progression and metastasis.[4] Although some AML patients have severe infections at the time of presentation, few data are available to assess whether prior infections play a role in the pathogenesis and prognosis of AML. C-reactive protein (CRP) is an acute phase protein produced in the liver following stimulation by cytokines, especially IL-6, and it plays a regulatory role in the inflammatory response by enhancing the function of phagocytes and activating complement.[5] Investigators have revealed that elevated CRP levels were associated with worse survival outcomes in patients with various types of cancer, including haematologic malignancies.[6–8] Serum albumin is a measure of an individual's nutritional status. Systemic inflammation can reduce serum albumin concentrations by increasing capillary permeability.[9] Notably, more than half of cancer patients will develop malnutrition at some point during their illness. The levels of inflammatory factors in malnourished patients are significantly elevated, which could place the body in a state of chronic immunosuppression and ultimately lead to a poor prognosis in cancer patients.[10] Recently, several studies have shown that hypoalbuminemia is an important independent risk factor for treatment-related morbidity and mortality and inferior survival in AML.[11–13]

The ratio of CRP to albumin (CAR) is a useful score based on inflammation and nutrition, reflecting not only systemic inflammation status but also nutritional status. CAR has recently been proved to be a prognostic marker for various solid tumours[14–16] and haematologic malignancies, such as chronic lymphocytic leukaemia.[17] Similarly, the Glasgow prognostic score (GPS) and modified GPS (mGPS), determined by the serum CRP and albumin levels, have been proposed as prognostic indicators for AML patients.[18] However, the clinical correlations of CAR and its prognostic value in AML patients have not yet been clarified. Therefore, we retrospectively investigated whether CAR has prognostic potential in patients with newly diagnosed non-M3 AML. We also compared the prognostic value of CAR with other established prognostic parameters based on inflammation.

Patients and Methods
Patients

This retrospective, single-centre study enrolled 212 newly diagnosed non-M3 AML patients. De novo and secondary AML were included. The samples were collected from January 2017 to December 2020 at Zhengzhou University People's Hospital. The last follow-up occurred in July 2021. Patients who had received prior chemotherapy, had an Eastern Cooperative Oncology Group (ECOG) performance score of >3 and were intolerant of chemotherapy, or did not receive induction chemotherapy for other reasons were excluded. All baseline characteristics were collected from the medical records, including age, sex, frequent comorbidities (including hypertension, diabetes mellitus and cardiac-cerebral vascular disease), haemoglobin (HB), white blood cell count (WBC), platelet (PLT) count, lactate dehydrogenase (LDH) (normal ranges: 120–250 U/L), ferritin (normal ranges: 11–306 ng/mL), CRP (normal ranges: 0–10 mg/L), albumin (normal ranges: 40–55 g/L), peripheral blood blast percentage, bone marrow blast percentage, immunophenotype and French-American-British (FAB) subtypes. It is worth noting that laboratory data were collected within 24 hours after the first admission.

The CAR was calculated using CRP and albumin concentrations. GPS and mGPS were calculated as previously described.[19] The GPS values were defined as CRP ≤10 mg/L and albumin ≥35 g/L, scoring 0 point; CRP >10 mg/L or albumin <35 g/L, scoring 1 point; and CRP >10 mg/L and albumin <35 g/L, scoring 2 points. The mGPS was derived from GPS, and the main difference between mGPS and GPS was that only patients with albumin <35 g/L had a score of 0. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Medical Ethical Committee of Zhengzhou University People's Hospital. Each participant signed a written informed consent before enrolment, and patients younger than 18 years of age were provided with informed consent by their parents or legal guardian.

Treatment and Follow-Up

Induction chemotherapy regimens included IA (idarubicin 8–12 mg/m^2 for 3 days combined with cytarabine 100–200 mg/m^2 for 7 days), DA (daunorubicin 40–60 mg/m^2 for 3 days combined with cytarabine 100–200 mg/m^2 for 7 days), MA

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(mitoxantrone 6–8 mg/m^2 for 3 days combined with cytarabine 100–200 mg/m^2 for 7 days) or CAG±D (aclarubicin mg/m^2/d for 4 days, cytarabine 10 mg/m^2 /q12h for 14 days, G-CSF 300 µg/d for 14 days with/without decitabine 20 mg/m^2/d for 5 days). Patients with complete remission (CR) continued consolidation chemotherapy with medium-dose or high-dose cytarabine. Haematopoietic stem cell transplantation (HSCT) was performed in patients with moderate or poor prognosis with suitable donors.

Definitions of Treatment Response and Survival Time

The response criteria were defined as recommended by the international panel of experts on behalf of the 2017 ELN.[3] Complete remission (CR) was defined as less than 5% bone marrow blasts, no extramedullary disease, absolute neutrophil count $>1.0 \times 10^9$/L, platelet count $>100 \times 10^9$/L, and independence from red cell transfusions. CR with incomplete haematologic recovery (CRi) was defined as meeting all of the CR criteria except for residual neutropenia $<1.0 \times 10^9$/L or thrombocytopenia $<100 \times 10^9$/L. Treatment-related mortality (TRM) was defined as death during disease treatment period due to various complications, such as infection, bleeding and organ dysfunction. The endpoints of this study included overall survival (OS), which was calculated from the date of diagnosis to the date of death or the last follow-up, and event-free survival (EFS), which was calculated from the date of diagnosis to the date of primary refractory disease, or relapse from CR, or CRi, or death or the last follow-up.

Statistical Analysis

All statistical analyses were completed using SPSS software, version 22.0. Categorical variables were compared using the chi-square test or Fisher's exact test. Continuous variables following a normal distribution are expressed as the mean ± standard deviation (SD), and nonnormally distributed variables are expressed as the median and quartile. The independent-samples t-test or Wilcoxon's rank sum test was used for comparisons between consecutive data groups. The cut-off value of CAR was determined using the receiver operating characteristic curve (ROC) method, and the area under the curve (AUC) was calculated to evaluate the discriminatory ability of each prognostic parameter. The Kaplan–Meier method was used to analyse OS and EFS, and the Log rank test was used to compare the differences between groups. Univariate and multivariate Cox proportional hazards regression was used to analyse factors affecting OS and EFS. The statistical significance level was 0.05 for a two-tailed test.

Results

Baseline Characteristics

We enrolled 212 patients with newly diagnosed non-M3 AML receiving at least two cycles of induction chemotherapy, of which cases 91.5% were identified as de novo and 8.5% as secondary. The baseline characteristics are summarized in Table 1. Among the 212 patients, 120 (56.6%) were men. The median age at diagnosis was 49 years old (range 7–82 years). All patients were tested for cytogenetic and molecular abnormalities of bone marrow blasts, including *NPM1, CEBPA, FLT3-ITD, KMT2A, GATA2, ASXL1, RUNX1 and TP53* at diagnosis. According to the risk stratification based on the 2017 ELN, 20.3%, 45.8%, and 33.9% of the patients had a risk status of favourable, intermediate, and adverse, respectively. The median follow-up time from diagnosis was 25 months (range 1–52 months). During this period, a total of 68 patients (31.6%) experienced relapse, and 90 patients (42.4%) died. A total of 212 eligible patients were divided into the high CAR group and the low CAR group based on the optimal cut-off value of CAR.

The Optimal Cut-off Values of CAR and Associations with Clinicopathologic Variables

According to ROC curve analysis, the optimal cut-off value for CAR to predict treatment response after two cycles of induction chemotherapy (CR1 or non-CR1) was 1.015, and the AUC was 0.690 (95% CI: 0.525–0.699, $p<0.001$). A total of 114 patients (53.8%) with CAR ≤1.015 at diagnosis were defined as the low CAR group, and 98 patients (46.2%) with CAR >1.015 at diagnosis were defined as the high CAR group. There were no significant differences in sex, frequent comorbidities, WBC, HB levels, PLT count, LDH levels, peripheral blood blast percentage or TRM between the two groups. Patients in the low CAR group were younger ($p<0.001$), had lower CRP levels ($p<0.001$) and had higher albumin

Table 1 Patient Demographics and Baseline Characteristics

Characteristics	All Patients	Low CAR	High CAR	P value
Number of patients, n	212	114	98	–
Age (years)	49 (7–82)	46 (7–82)	54 (10–82)	<0.001
Gender, n (%)				0.327
Male	120 (56.6%)	61 (53.5%)	59 (60.2%)	
Female	92 (43.4%)	53 (46.5%)	39 (39.8%)	
Type of AML, n (%)				0.021
De novo AML	194 (91.5%)	109 (95.6%)	85 (86.7%)	
Secondary AML	18 (8.5%)	5 (4.4%)	13 (13.3%)	
HB (g/L)	77.9±21.2	79.1±21.4	76.4±20.9	0.358
WBC (×10^9/L)	12.03 (3.4–41.7)	10.9 (4.0–34.0)	13.9 (2.6–55.2)	0.764
PLT Count (×10^9/L)	36.0 (19.3–72.8)	34.0 (18–74.5)	37.0 (20.0–70.5)	0.765
LDH (U/L)	389 (99–6318)	387 (133–2989)	417 (99–6318)	0.837
CRP (mg/L)	30.5 (9.4–78.7)	10.4 (2.8–21.5)	84.1 (52.4–134.1)	<0.001
Albumin (g/L)	35.9±5.5	38.6±4.7	32.8±4.6	<0.001
Ferritin (ng/mL)	439.7 (250.6–761.7)	338.6 (122.1–632.5)	518.9 (414.9–1154.9)	0.001
Bone Marrow Blasts (%)	59.2 (40.4–76.0)	50.8 (25.6–71.6)	66.6 (42.0–79.)	0.026
Peripheral Blood Blasts (%)	43.0 (13.0–76.0)	35 (10.5–73.0)	47.0 (17.0–79.6)	0.428
Comorbidities, n (%)				
Hypertension	19 (9.0%)	7 (6.1%)	12 (12.2%)	0.416
Diabetes mellitus	8 (3.8%)	4 (3.5%)	4 (4.2%)	1.0[a]
Cardiac-cerebral vascular disease	11 (18.9%)	3 (2.7%)	8 (8.2%)	0.308[a]
Two or more comorbidities	14 (6.7%)	9 (7.9%)	5 (5.1%)	0.077
FAB Classification, n (%)				
M0	4 (1.9%)	2 (1.7%)	2 (2.0%)	1.0[a]
M1	8 (3.3%)	3 (2.6%)	5 (4.1%)	0.482[a]
M2	117 (50.5%)	71 (57.9%)	46 (41.8%)	0.025
M4	32 (15.1%)	15 (13.2%)	17 (17.4%)	0.444
M5	32 (14.6%)	17 (14.9%)	15 (14.3%)	0.936
M6	1 (0.5%)	0 (0)	1 (1.0%)	1.0[a]
M7	1 (0.5%)	1 (0.9%)	0 (0)	1.0[a]
Unclassifiable	17 (8%)	5 (4.4%)	12 (12.2%)	0.036
ELN risk stratification, n (%)				
Favorable	43 (20.3%)	33 (28.9%)	10 (10.2%)	0.001
Intermediate	97 (45.8%)	49 (43.0%)	48 (49.0%)	0.409
Adverse	72 (33.9%)	32 (28.1%)	40 (40.8%)	0.08
CR1, n (%)	160 (75.5%)	98 (86.0%)	62 (63.3%)	<0.001
Relapse, n (%)	68 (42.5%)	36 (36.7%)	32 (51.6%)	0.064
HSCT, n (%)	40 (18.9%)	27 (23.7%)	13 (13.3%)	0.053
TRM, n (%)				
Infection	28 (13.2%)	13 (11.4%)	15 (15.3%)	0.102
Bleeding	12 (5.7%)	5 (4.4%)	7 (7.1%)	0.685
Organ dysfunction	5 (2.6%)	3 (2.6%)	2 (2.0%)	0.652[a]

Note: [a]Fisher's exact test, $p<0.05$ is considered significant.
Abbreviations: CAR, C-reactive protein to albumin ratio; HB, hemoglobin; WBC, white blood cell count; PLT, platelets; LDH, lactate dehydrogenase; CRP, C-reactive protein; FAB, French-American-British; ELN, European Leukemia Net; CR1, first complete remission after two cycles of induction therapy; HSCT, hematopoietic stem cell transplantation; TRM, treatment-related mortality.

levels ($p<0.001$). The comparison between the two groups showed obvious differences in ferritin levels and bone marrow blast percentage, which were higher in the high CAR group ($p=0.001$ and $p=0.026$). Additionally, we also observed statistically significant differences in the type of AML, French-American-British (FAB) classification and 2017 ELN risk stratification between the low and high CAR groups, and the proportions of de novo AML ($p=0.021$), AML-M2 ($p=0.025$) and favourable risk stratification ($p=0.001$) were higher in the low CAR group.

Relationship Between CAR and Immunophenotype

In our study, the immunophenotyping of bone marrow blast samples at diagnosis was evaluated in 194 patients. The immunophenotypic results are listed in Table 2. In particular, 60 of 108 patients (55.6%) in the low CAR group were CD15 positive. In contrast, 31 of 86 patients (36%) were CD15 positive in the high CAR group, and the expression of CD15 was significantly higher in the low CAR group than in the high CAR group ($p=0.007$). Similarly, we observed that patients in the low CAR group were more likely to have higher expression of CD33 ($p=0.046$). However, the expression of other markers, such as CD34, CD38, CD117, HLA-DR, CD13, CD123, CD7, CD11b, CD56, CD64 and CD71, was not significantly different between the two groups (all $p>0.05$).

Relationship Between CAR and Treatment Response of Induction Chemotherapy

For the entire cohort of 212 patients, 160 patients (75.5%) achieved CR (CR/CRi) after two cycles of induction chemotherapy. Ninety-eight patients (86.0%) achieved CR in the low CAR group compared to 62 patients (63.3%) in the high CAR group, and the CR rate in the low CAR group was remarkably higher than that in the high CAR group ($p<0.001$). Among the 160 patients who experienced CR, 68 patients suffered disease relapse, including 36 in the low CAR group (36.7%) and 32 in the high CAR group (51.6%). Patients in the high CAR group presented a trend towards a greater risk of relapse ($p=0.064$).

Relationship Between CAR and Clinical Outcomes

The CRP blood concentration that distinguished CR1 from non-CR1 was 19.92 mg/L (ROC analysis). We verified the association of high CRP and low albumin levels with worse OS and EFS in AML by Kaplan–Meier survival curve analysis (Figure 1A–D). By the end of the follow-up visit, the median follow-up time for the whole cohort was 25

Table 2 Immunophenotypic Analysis of Bone Marrow Blasts Between the Two Groups

Immunophenotype	Low CAR (n=108)	High CAR (n=86)	χ^2	P value
CD34	84 (77.8%)	61 (70.9%)	1.189	0.276
CD38	100 (92.6%)	77 (89.5%)	0.560	0.454
CD117	99 (91.7%)	73 (84.9%)	2.191	0.139
HLA-DR	98 (90.7%)	71 (82.6%)	2.855	0.091
CD33	107 (99.1%)	80 (93.0%)	–	0.046
CD13	104 (96.3%)	82 (95.3%)	–	0.349
CD123	94 (87.0%)	80 (93.0%)	1.855	0.173
CD7	41 (37.9%)	32 (37.2%)	0.012	0.914
CD11b	30 (27.8%)	20 (23.3%)	0.628	0.428
CD15	60 (55.6%)	31 (36.0%)	7.317	0.007
CD56	40 (37.0%)	30 (34.9%)	0.096	0.756
CD64	69 (65.1%)	49 (60.0%)	0.960	0.327
CD71	11 (10.4%)	13 (15.1%)	1.074	0.3

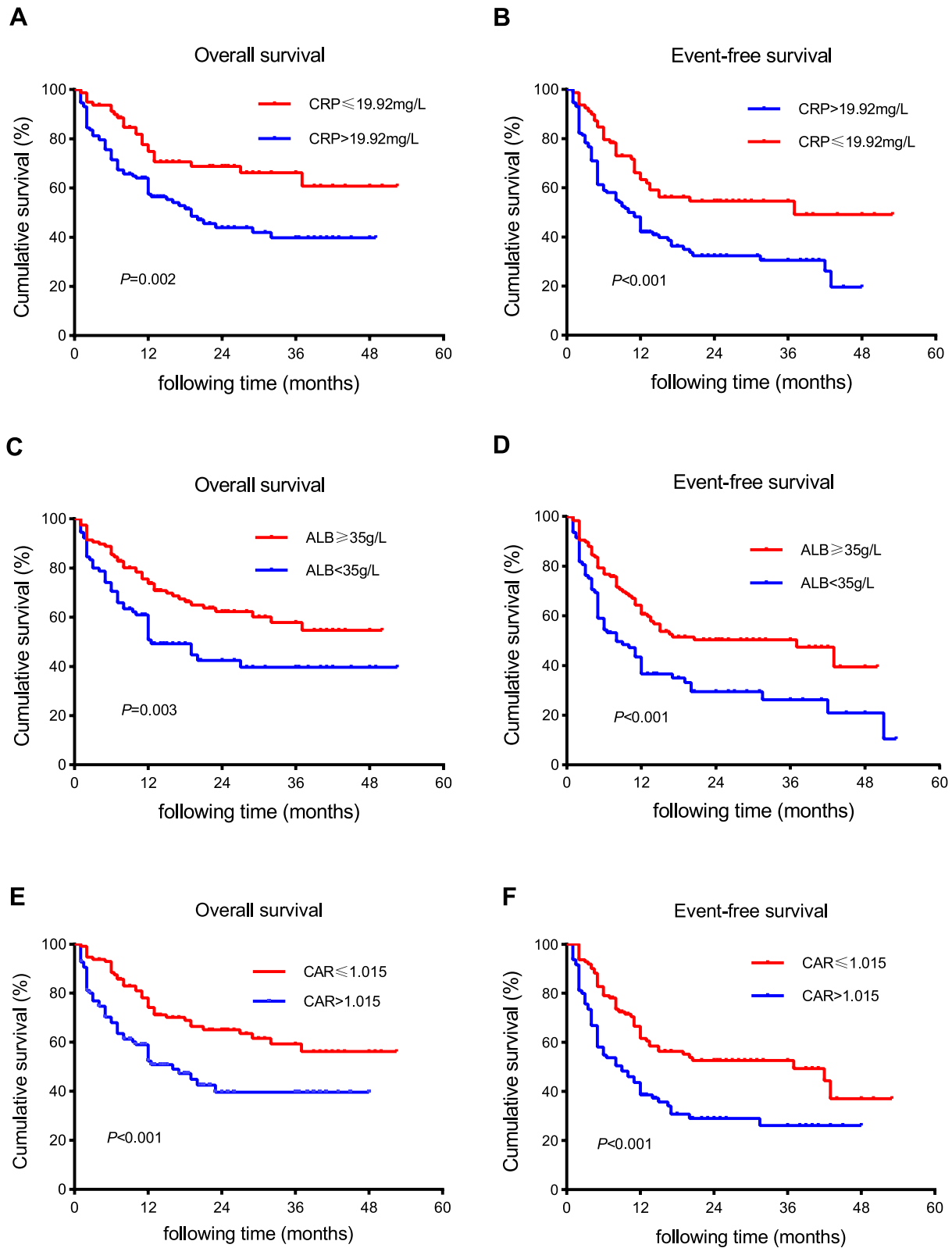**Abbreviation**: CAR, C-reactive protein to albumin ratio.

Figure 1 Kaplan–Meier curves of overall survival (OS) and event-free survival (EFS) for different CRP (**A** and **B**), ALB (**C** and **D**) and CAR (**E** and **F**) levels in AML patients.
Abbreviations: CRP, C-reactive protein; ALB, albumin; CAR, C-reactive protein to albumin ratio.

months (range 1–52 months), the median OS time in the high CAR group was 16 months, and the median OS time in the low CAR group was not reached (*p*<0.001). Similarly, patients in the high CAR group demonstrated a significantly shorter median EFS (10 vs 37 months; *p*<0.001) (Figure 1E and F).

Furthermore, we investigated the relevance of CAR to survival in different subgroups. We investigated whether CAR could further risk stratify patients in each 2017 ELN risk stratification. For patients in the intermediate risk stratification, better median OS (37 versus 16 months; *p*=0.032) and median EFS (37 versus 9 months; *p*=0.034) were observed in the low CAR group (Figure 2C and D). However, there were no significant prognostic effects of CAR in patients with favourable and adverse risk stratification (Figure 2A, B, E and F). Additionally, we divided patients into two groups depending on age. Among patients ≤65 years old, we observed that the median OS (not reached vs 20 months; *p*=0.003) and median EFS (42 vs 12 months; *p*=0.005) were significantly longer in the low CAR group than in the high CAR group (Figure 3A and B). In patients >65 years old, CAR had no significant effect on prognosis (Figure 3C and D). We also divided patients into two groups based on whether they underwent HSCT. Among patients without HSCT, the median OS (not reached vs 12 months; *p*=0.003) and median EFS (20 months vs 8 months; *p*<0.001) were significantly better in the low CAR group (Figure 4A and B). However, CAR has no effect on prognosis in patients who underwent HSCT (Figure 4C and D).

Univariate and Multivariable Analyses of Clinical Prognostic Factors

We analysed various prognostic factors for OS and EFS. The results of the univariate Cox regression analysis are shown in Table 3. In addition to higher CAR (OS: *p*=0.001; EFS: *p*=0.002), factors associated with shorter OS and EFS in univariate analysis included age >65 (OS: *p*<0.001; EFS: *p*<0.001), higher WBC (OS: *p*=0.007; EFS: *p*=0.008), higher LDH (OS: *p*=0.004; EFS: *p*=0.006) and non-HSCT (OS: *p*=0.002; EFS: *p*=0.004). Patients with adverse risk stratification showed inferior OS (*p*=0.019) and EFS (*p*=0.009). We further investigated the prognostic impact of CAR in the multivariate Cox regression analysis model. In multivariate Cox regression analysis sequentially adjusted for age, WBC count, LDH and adverse risk stratification, a higher CAR remained significantly associated with shorter OS (*p*=0.023) and EFS (*p*=0.034) (Table 4).

Comparison of the Prognostic Value of CAR with Other Established Prognostic Parameters in De Novo AML Patients Aged ≤65 Years

Because of the significant correlations among CRP, albumin, CAR, GPS and mGPS, we further investigated the prognostic significance of CAR compared to other established prognostic parameters. ROC curves for OS were constructed in de novo AML patients aged ≤65 years, and AUC values were compared to assess the discriminatory ability of each prognostic parameter. The AUC value for OS was 0.612 (95% CI: 0.525–0.699) for the CAR, which was equal to that for mGPS (AUC = 0.612, 95% CI: 0.525–0.700) but was higher than those for CRP (AUC = 0.578, 95% CI: 0.487–0.669), albumin (AUC = 0.531, 95% CI: 0.438–0.624) and GPS (AUC = 0.604, 95% CI: 0.515–0.693). This result suggested that CAR is a more powerful predictor than CRP, albumin or GPS in de novo non-M3 AML patients aged ≤65 years (Figure 5).

Discussion

As a sensitive but nonspecific marker of systemic inflammatory markers, serum C-reactive protein (CRP) is affected by a variety of factors, such as infection, injury, and tumours. In contrast, serum albumin concentration is relatively stable and does not vary with short-term changes in nutrient intake or malnutrition status. Previous studies showed that high serum CRP levels and hypoalbuminemia are associated with poor prognosis in AML patients.[11,12,20] Therefore, we hypothesized that their combination might be a better prognostic factor than CRP or albumin alone in AML patients.

CAR, as a new and stable prognostic marker, has attracted much attention recently. To our knowledge, this study was the first to explore the CAR in newly diagnosed non-M3 AML patients. As the data showed, a high CAR was associated with unfavourable clinical characteristics and adverse risk stratification, such as older age, higher CRP levels, lower albumin levels and higher bone marrow blast percentage. In addition, we also observed that a high level of ferritin led to
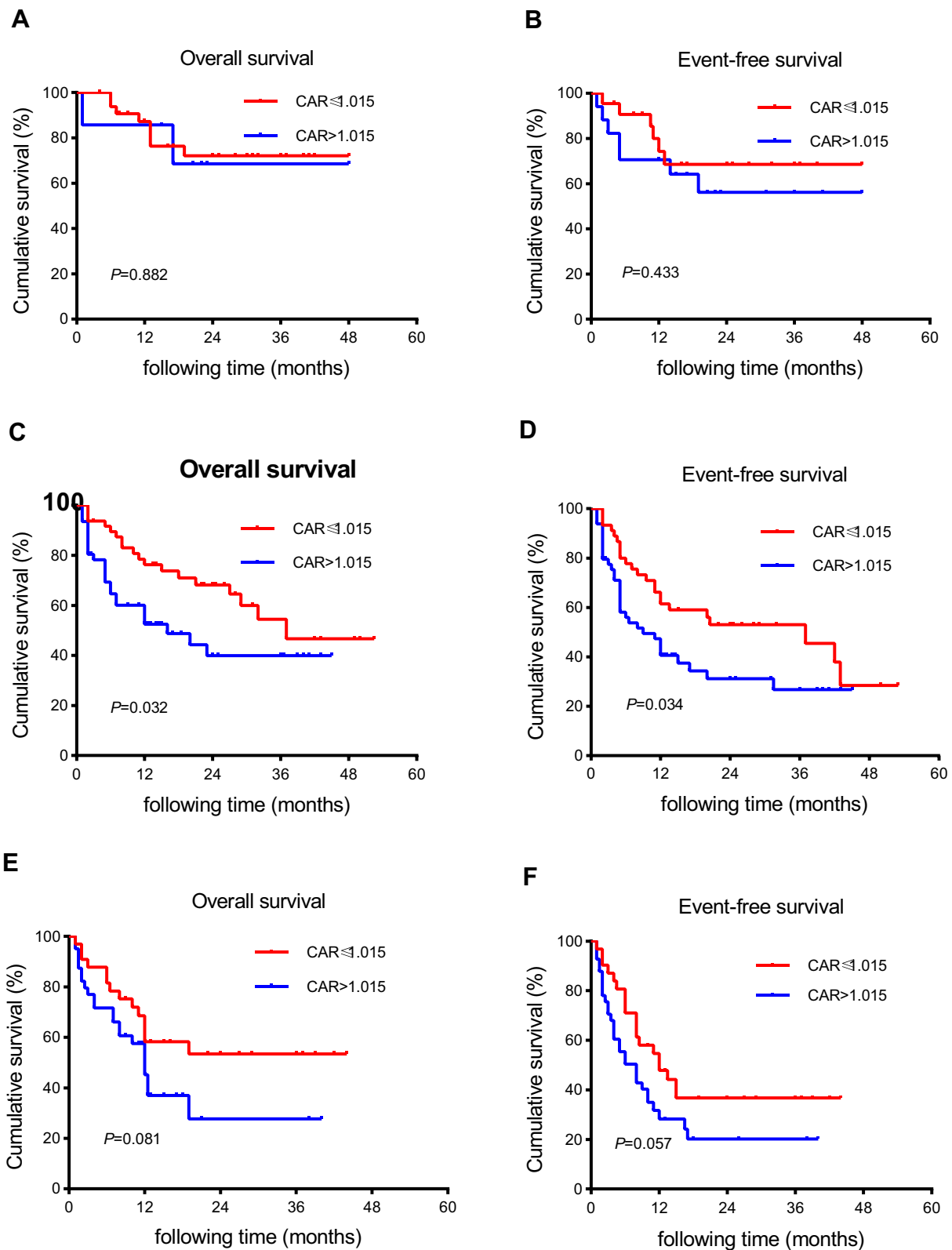
Figure 2 Kaplan–Meier curves of overall survival (OS) and event-free survival (EFS) according to different CAR levels in AML patients with favourable risk (**A** and **B**), intermediate risk (**C** and **D**), and adverse risk (**E** and **F**) stratified by 2017 ELN risk classification.
Abbreviation: CAR, C-reactive protein to albumin ratio.

A

Overall survival

B

Event-free survival

C

Overall survival

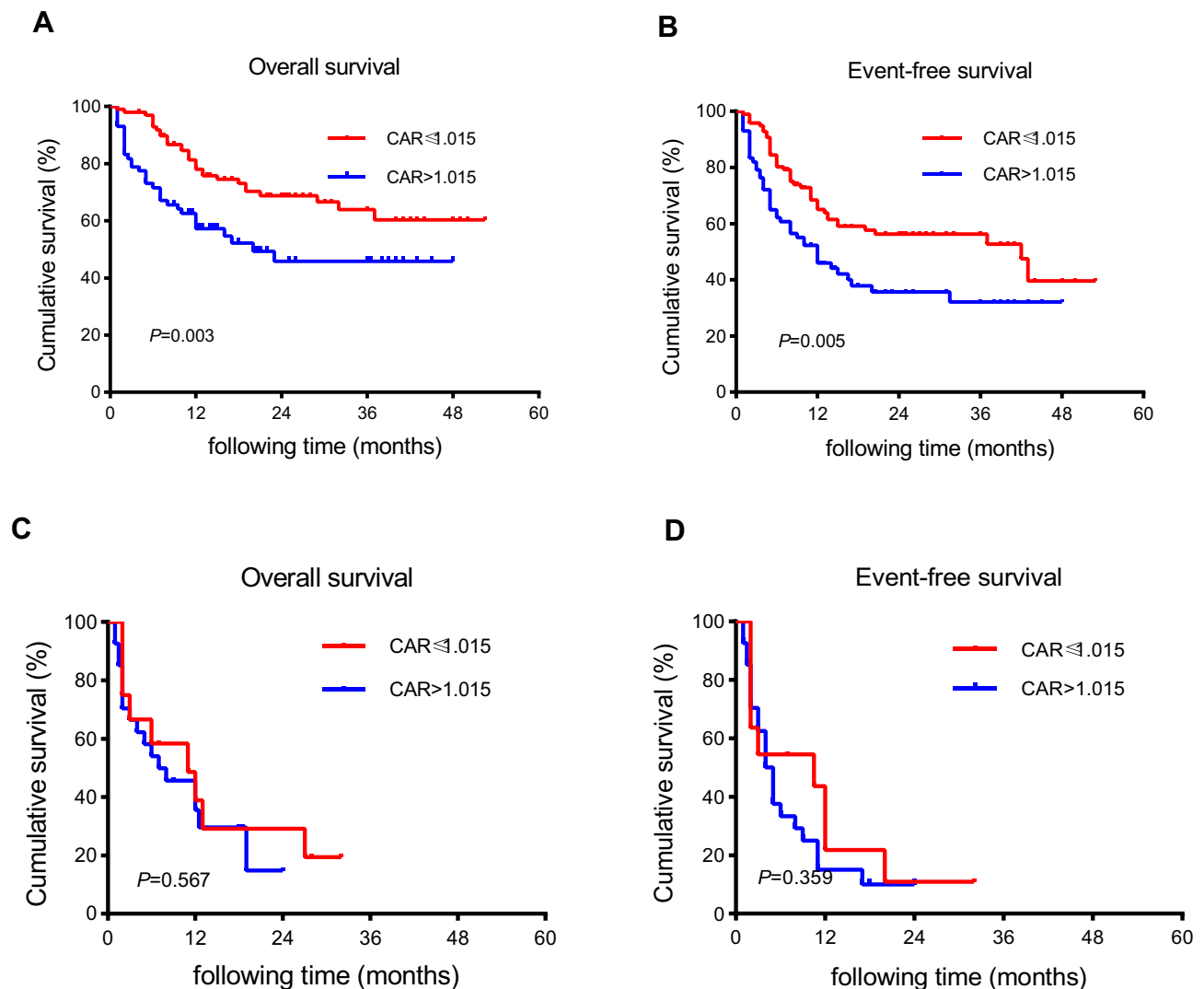**D**

Event-free survival

Figure 3 Kaplan–Meier curves of overall survival (OS) and event-free survival (EFS) according to different CAR levels in AML patients ≤65 years old (**A** and **B**) and patients >65 years old (**C** and **D**) stratified by age.
Abbreviation: CAR, C-reactive protein to albumin ratio.

a high CAR since ferritin also reflects the levels of inflammation.[21,22] Previous studies have demonstrated that AML patients with high levels of ferritin were associated with higher tumour burden, chemoresistance, relapse and poor prognosis.[23–25]

In our study, a high CAR was significantly associated with worse OS and EFS in the univariate analysis and multivariate analysis, suggesting that CAR was independent of classical prognostic factors, such as age, WBC count, and adverse risk stratification. The present study is consistent with previous studies showing that a high CAR was associated with poor survival.[14–16,26] Notably, the subgroup analysis that we performed showed that a high CAR was associated with shorter OS and EFS for AML patients in the intermediate risk group. The same result was observed in AML patients aged ≤65 years and who did not undergo HSCT. These results implied that CAR could be an additional prognostic factor that help to further precise the current risk stratification for non-M3 AML, particularly for patients in the intermediate risk group and those aged ≤65 years and those who did not undergo HSCT. To understand which inflammation parameter was more valuable in predicting the survival of de novo non-M3 AML patients ≤65 years old, we directly compared CRP, albumin, GPS and mGPS with CAR by ROC curve analysis. The ROC analysis for OS demonstrated that the AUC value for CAR was higher than those for CRP, albumin and GPS, and it was equal to that for
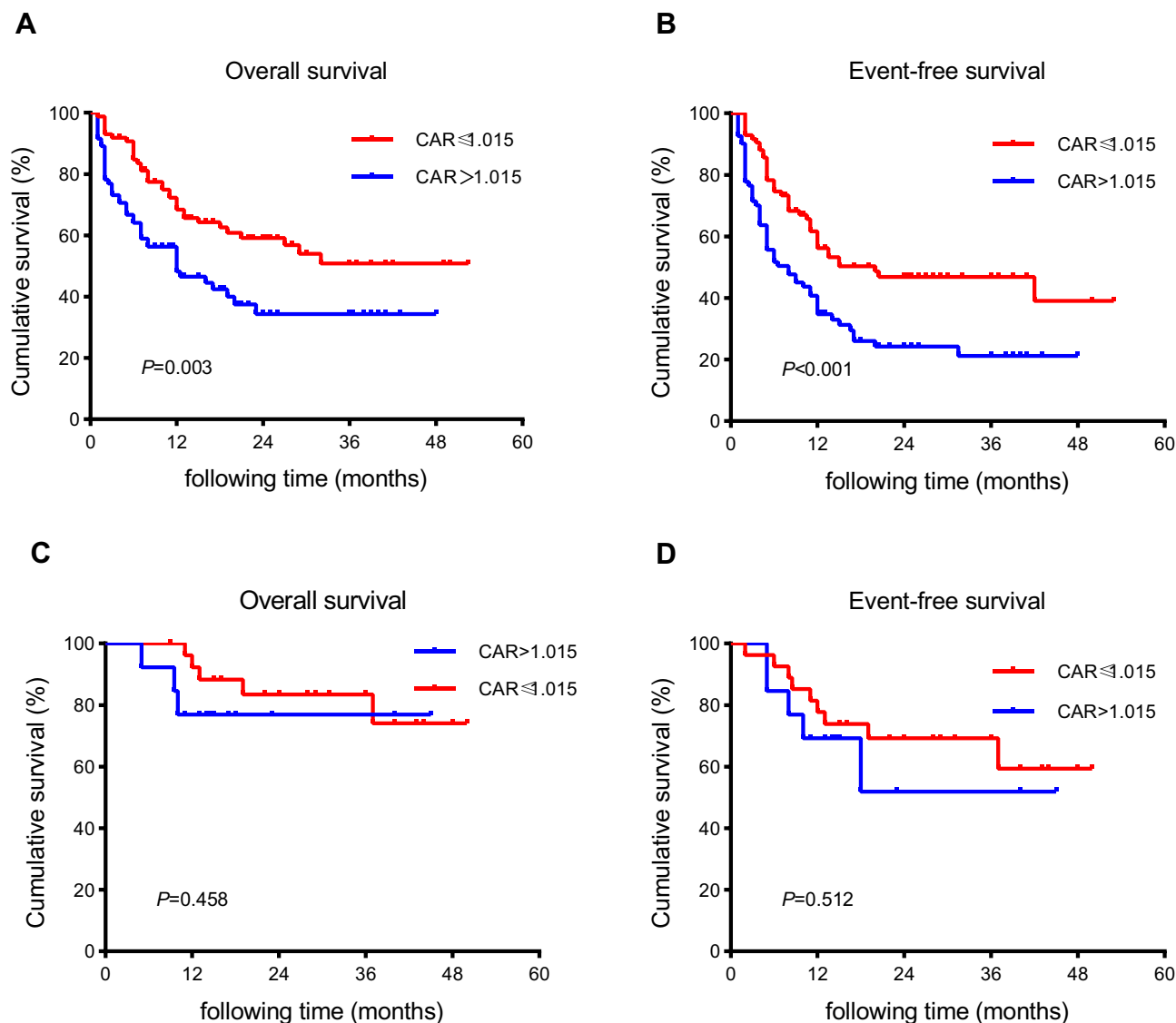
Figure 4 Kaplan–Meier curves of overall survival (OS) and event-free survival (EFS) according to different CAR levels in AML patients without HSCT (**A** and **B**) and patients with HSCT (**C** and **D**).
Abbreviations: CAR, C-reactive protein to albumin ratio; HSCT, haematopoietic stem cell transplantation.

mGPS, indicating that the predictive value of CAR and mGPS for OS is superior to that of CRP, albumin and GPS in de novo AML patients aged ≤65 years.

In addition, we also observed that patients in the low CAR group had significantly higher CD15 and CD33 expression. The CD15 antigen, a member of the cell adhesion molecule family, is normally expressed on neutrophils.[27] Previous studies have shown that CD15 expression was associated with a high CR rate[28–30] and long OS duration.[31] Repp et al reported that CD33 expression was associated with long OS.[32] Derolf et al analysed the different expression patterns of CD33 and CD15 in AML patients to predict the clinical outcomes and showed that patients who expressed both CD15 and CD33 had better survival.[31] We first reported that a low CAR was correlated with the expression of CD15 and CD33, however, the potential association requires further study.

Inflammatory mediators are important components of the tumour local microenvironment and play an important role in the development, chemotherapy resistance and disease progression of AML patients.[33,34] Inflammatory cytokines, such as IL-6, are able to induce CRP production while suppressing the synthesis of albumin. The levels of IL-6 in peripheral

Table 3 Univariate Analysis of Overall Survival (OS) and Event-Free Survival (EFS) in AML Patients

Variables	Overall Survival (OS)			Event-Free Survival (EFS)		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age >65 years	3.092	1.952–4.898	<0.001	3.082	1.996–4.758	<0.001
WBC ≥100 ×10^9/L	2.204	1.240–3.918	0.007	2.078	1.215–3.553	0.008
HB <100 g/L	1.701	0.851–3.400	0.133	1.605	0.879–2.932	0.123
PLT count <20 ×10^9/L	1.000	0.630–1.588	1.000	1.264	0.813–1.964	0.298
LDH ≥700 U/L	1.905	1.232–2.946	0.004	1.741	1.170–2.591	0.006
ELN risk stratification (adverse vs others)	1.654	1.087–2.516	0.019	1.658	1.133–2.428	0.009
CAR	2.030	1.335–3.086	0.001	1.816	1.247–2.645	0.002

Abbreviations: WBC, white blood cell count; HB, hemoglobin; PLT, platelets; LDH, lactate dehydrogenase; ELN, European Leukemia Net; HSCT, hematopoietic stem cell transplantation; CAR, C-reactive protein to albumin ratio.

Table 4 Multivariate Analysis of Overall Survival (OS) and Event-Free Survival (EFS) in AML Patients

Variables	Overall Survival (OS)			Event-Free Survival (EFS)		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age >65 years	3.553	2.089–6.042	<0.001	3.732	2.273–6.127	<0.001
WBC ≥100 ×10^9/L	2.312	1.186–4.508	0.014	2.441	1.310–4.551	0.005
LDH ≥700 U/L	2.051	1.235–3.406	0.006	1.851	1.169–2.930	0.009
ELN risk stratification (adverse vs others)	1.119	0.701–1.786	0.638	1.162	0.760–1.778	0.488
CAR	1.729	1.079–2.770	0.023	1.575	1.035–2.398	0.034

Abbreviations: WBC, white blood cell count; LDH, lactate dehydrogenase; ELN, European Leukemia Net; CAR, C-reactive protein to albumin ratio.

blood and bone marrow are significantly elevated in adult AML patients due to autocrine IL-6 secretion by AML cells or IL-6 production by normal stromal cells or monocytes in the bone marrow.[35,36] STAT3 signalling is known to regulate antiapoptotic gene expression, and IL-6 can promote chemoresistance and relapse through the STAT3 signalling pathway and support leukaemia stem cells.[34] Importantly, IL-6 is associated with emotional health of patients, and its levels are closely related to the severity of depression.[37]

However, this study was a single-centre, retrospective study, and the sample size was relatively small in the subgroup analysis. In addition, the heterogeneity of treatment regimens might have confounded the results of this study. AML is a complex and dynamic disease, while our study only involved the association between CAR and the prognosis of AML at the time of diagnosis. Therefore, to further validate the prognostic value of CAR, prospective studies involving large-scale and multi-centre studies should be conducted, and CAR should be monitored dynamically at various time points.

Conclusion

In conclusion, our results implied that CAR is a simple and effective prognostic marker in patients with AML. It could be an additional prognostic factor that help further precise the current risk stratification of non-M3 AML, particularly for patients in the intermediate risk stratification and those aged ≤65 years and those who did not undergo HSCT.
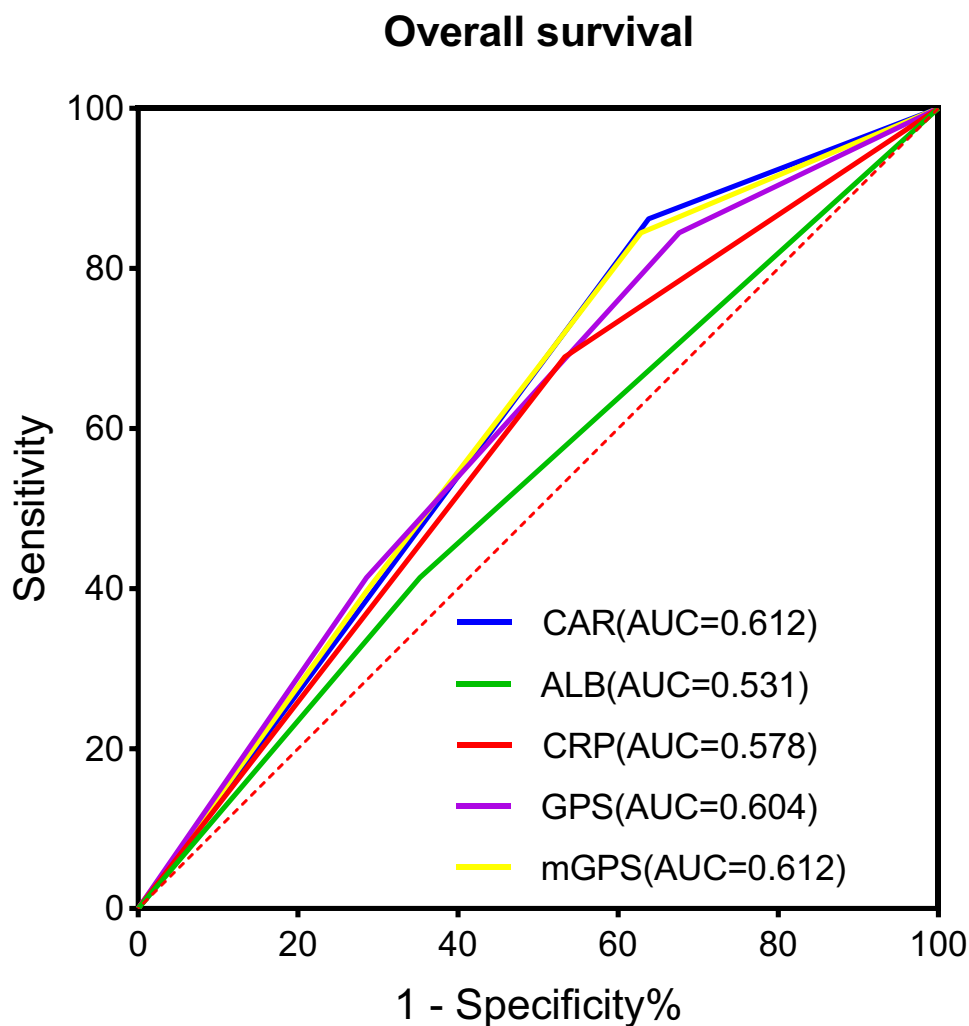
Figure 5 Comparison of the prognostic value of CRP, ALB, GPS, and mGPS with CAR by ROC curves in de novo non-M3 AML patients ≤65 years old.
Abbreviations: CRP, C-reactive protein; ALB, albumin; GPS, Glasgow prognostic score; mGPS, modified GPS; CAR, C-reactive protein to albumin ratio.

Ethics Approval and Consent to Participate

The study protocol was approved by the research ethics committees of Zhengzhou University People's Hospital. Each participant signed a written informed consent form before enrolment, and a parent or legal guardian of patients younger than 18 years of age provided informed consent.

Acknowledgments

We would like to express our gratitude to all of the doctors, nurses and pathologists of all of the hospitals and haematology departments who participated in this survey. Our manuscript has been edited in English to correct the grammar or style.

Author Contributions

All of the authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis or interpretation or in all of these areas; participated in drafting, revising or critically reviewing the article; gave final approval of the version to be published; agreed on the journal to which the article has been submitted; and agreed to be accountable for all aspects of the work.

Funding

This study was partially supported by the National Natural Science Foundation of China (No. 81971508, No. 81471589) and the Foundation and Frontier Research Grant of Henan Provincial Science and Technology Bureau, PR China (No. 112300410027).

Disclosure

The authors report no conflicts of interest in this work.

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