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Correlation between monocyte and length of in-hospital stay in patients with allergic rhinitis: data from the MIMIC-IV database

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Abstract

Background This study aimed to explore the factors associated with the length of in-hospital stay (LOS) in allergic rhinitis (AR).

Methods Patients with AR and related data were identified from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database. The influencing factors of LOS were determined by correlation analysis and linear regression. We ranked the importance of significant variables. Finally, mediation analysis was performed to explore the potential mediating factors associated with LOS.

Results This retrospective study enrolled 937 patients diagnosed with AR. Correlation analysis showed that 10 variables were closely correlated with the LOS. Linear regression further showed that albumin, white blood cell (WBC), red blood cell (RBC), red cell distribution width (RDW), total Ca, and monocyte were independently related to the LOS (all $P < 0.05$). After considering comorbidities, monocyte, albumin, WBC, RBC, total Ca, and Charlson comorbidity index were independent factors for LOS (all $P < 0.05$). The permutation importance exhibited that monocyte was the most important variable. Finally, mediation analysis demonstrated that WBC played a mediating role in the relationship between monocytes and LOS.

Conclusion Monocyte level is related to the LOS of patients with AR, and their relationship can be mediated by WBC. Medical and nursing staff can stratify AR management according to monocyte levels to make crucial clinical decisions and shorten LOS.

Clinical trial Not applicable.

Keywords Allergic rhinitis, MIMIC IV, Length of stay, Monocyte

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Introduction

Allergic rhinitis (AR) is a common chronic disease caused by the immune response to inhaled allergens mediated by immunoglobulin E [1]. AR has aroused widespread concern worldwide with an elevated incidence [2]. In some countries, the incidence of AR is beyond 50% [2]. AR, like other allergic inflammatory diseases, is viewed to be intricately affiliated with genetic and some external factors, including environmental exposures, climate changes, and lifestyle, in its etiology [3, 4]. Besides, air pollution and airborne pollen caused the increased incidence and deterioration of AR [5, 6].

The allergic inflammation of rhinitis can be divided into two phases: the early phase and the late phase [7, 8]. The early phase response occurs within minutes of being exposed to the allergen, and immunoglobulin E (IgE) binds to the high-affinity IgE receptor on tissue mast cells, followed by the release of inflammatory mediators, promoting symptoms of immediate type I hypersensitivity [9, 10]. After exposure to allergens, the early-phase allergic response is followed by the late-phase allergic response, which takes place within 4 to 12 h and is characterized by the increasing number of Th2 lymphocytes, eosinophils, basophils, and neutrophils [8, 11]. As inflammation progresses, monocytes play a major role [12]. Human monocytes are a heterogeneous cell population in circulation and are classified as classical, intermediate, and nonclassical monocytes, which contribute differently to inflammatory responses [13]. Previous studies identified that monocytes were recruited during the inflammation and infection processes [14]. Moniuszko et al. found that AR is associated with several phenotypic alterations of circulating monocytes [15]. Besides, the high infiltration level of monocytes was a characteristic of the late-phase allergic response, and it was also a biomarker for inflammation [16]. However, little is known about the relationship between admission monocyte level and the prognosis of patients with AR.

Currently, many therapies have been developed for the treatment of AR patients, including pharmacotherapy, immunotherapy, and biologics [4]. Moreover, these therapies, especially allergen-specific immunotherapy have shown a great effect on the AR treatment [17–19]. However, the effectiveness of immunotherapy might be affected by individual differences due to the complexity of patient constitution, allergen type, and symptomatology [20]. Thus, in this study, we tried to determine the clinical factors involved in the recovery of AR and initially explore the potential mechanism of AR development.

Methods

Study population

This retrospective cohort study was carried out based on MIMIC IV (v2.2), a large and public database, including demographics, vital signs, laboratory test results, procedures, medications, and microbiology events. To access this database, the first author of this study, completed the Collaborative Institutional Training Initiative course and passed both the "Conflicts of Interest" and "Data or Specimens Only Research" exams. The research team was finally qualified to use the database and extract data.

We estimated the sample size by the G*Power software (version 3.1.9.7) with the following parameters: the statistical test was two-tailed, the significance level was set at $\alpha = 0.05$, the effect size was set to 0.3, and the power to 0.95, yielding a minimal sample size of 580. In this study, by searching the keyword "rhinitis" in the MIMIC IV database, 2246 patients aged > 18 years old were diagnosed with rhinitis. First, 210 samples diagnosed with chronic rhinitis (it is not clear whether AR or non-allergic rhinitis) were excluded and 2036 samples diagnosed with definite AR were included. Second, 393 samples without admission information were excluded. Third, 706 samples lacking demographics or laboratory information were excluded. Finally, 937 samples were enrolled.

Data collection

The raw data were extracted by employing structure query language with Navicat. To avoid possible bias, variables were excluded if they had more than 20% missing values [21]. Variables with less than 20% missing data were processed by multiple imputations using a random forest algorithm (trained by other non-missing variables) by the "mice" package of R software.

The extracted data included: [1] demographics, such as age (years), gender (female and male), race (American-African, Asian, and White), weight (lbs), body mass index (BMI, kg/m^2); [2] vital signs, blood pressure on admission (mmHg); [3] the length of in-hospital stay (LOS, days). The LOS ≤ 7 days was considered as short LOS, while the LOS > 7 days was considered as long LOS [3]. laboratory indicators, including blood platelet (K/μL), albumin (g/dL), red blood cells (RBC, m/μL), white blood cells (WBC, K/μL), hemoglobin (g/dL), red cell distribution width (RDW, %), anion gap (mEq/L), free Ca (mmol/L), total Ca (mg/dL), chloride (mEq/L), blood urea nitrogen (BUN, mg/dL), glucose (mg/dL), alanine transaminase (ALT, IU/L), aspartate aminotransferase (AST, IU/L), international normalized ratio (INR), prothrombin time (PT, sec), partial thromboplastin time (PTT, sec), sodium (Na, mEq/L), potassium (K, mEq/L), magnesium (Mg, mg/dL), lymphocyte (%), neutrophil (%), monocyte (%), basophils (%); [4] comorbidity, including asthma. Besides, a 17-item Charlson comorbidity index (CCI) was adopted to describe the patients' baseline comorbidities [22]. The 17 comorbidities included myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, pulmonary disease, rheumatic disease,

peptic ulcer disease, mild liver disease, diabetes without complications, diabetes with complications, paraplegia, renal disease, malignant cancer, severe liver disease, metastatic solid tumor, and acquired immunodeficiency syndrome (AIDS).

Statistical analysis

Continuous variables were presented as mean ± SD or median (interquartile range) according to data distribution, whereas categorical variables were expressed as frequency and proportions. The Kolmogorov-Smirnov test was employed to evaluate the normality of continuous parameters. The difference of continuous variables between the two groups was compared using a t-test if they presented a normal distribution and using the Mann–Whitney U-test if they conformed to non-normal distribution, while the chi-square test was applied to compare the differences of categorical variables in two LOS groups. We also used the Spearman and Kendall analyses to analyze the correlation between variables and LOS. Further, linear regression analysis was performed to explore the independent factors associated with LOS, and then the importance of the identified independent factors was ranked. Finally, a mediation analysis was carried out to examine the mediating effect of related variables on the LOS using the r package "lavaan". Mediation analysis was done through the establishment of three pathways (a, b and c). For this purpose, we set three pathways: [1] exposure to mediator; [2] mediator to outcome (direct effect); and [3] exposure to outcome (total effect). The total effect reflected the sum of a direct effect and a mediated (indirect) effect. The percentage of the mediated effect was calculated using the following formula: (mediated effect/total effect) × 100%. Bootstrapping was used for significance testing for mediation analysis. All statistical analysis was performed by the R software (version 4.0.2) and SPSS 22.0 (IBM SPSS Statistics, Armonk, NY, USA). $P<0.05$ was considered as the statistical significance.

Results

Baseline clinical characteristics and comorbidities

The baseline clinical characteristics of patients with AR are shown in Table 1 stratified by LOS (<7 or ≥7 days). According to the chi-square test, most patients with long LOS were male (52.381% vs. 43.693%) ($P=0.040$). Additionally, patients with long LOS usually have higher weight, WBC, RDW, anion gap, BUN, glucose, INR, PT, and neutrophil, while patients with short LOS have higher albumin, RBC, hemoglobin, total Ca, chloride, Mg, lymphocyte, and basophils (all $P<0.05$). As for comorbidities, a higher proportion of congestive heart failure cases in the long LOS group (7.143% vs. 4.681%) ($P<0.05$). The proportion of malignant cancers was 26.190% in the long LOS group, higher than the short LOS group (10.533%) ($P<0.05$). There were no significant differences in the other comorbidities. Besides, the CCI value was significantly higher in the long LOS group compared with the short LOS group ($P<0.05$) (Table 2). To avoid multi-collinearity, the CCI value was included but the specific comorbidities in the CCI were not included in the subsequent analyses.

The correlation analysis between LOS and related factors

Then, we further explored the correlation between potential clinical factors and LOS. As shown in Fig. 1A-B, the LOS of AR patients was negatively related to albumin, WBC, RBC, hemoglobin, RDW, total Ca, BUN, glucose, lymphocyte, and monocyte (all $P<0.05$).

Next, the ten factors related to LOS were screened out for further univariate linear regression analysis. The significant variables with $P<0.05$ in univariate analysis were then enrolled into the multivariate analysis to explore the independent variables. According to the univariate and multivariate analysis results (Table 3), albumin, WBC, RBC, RDW, total Ca, and monocyte were independent influencing factors of LOS (all $P<0.05$). Subsequently, permutation importance was performed on the six independent factors, and the results exhibited that monocyte was the most important factor among the six independent factors (Fig. 2A).

After taking comorbidities into consideration, we conducted a multivariate linear regression analysis by including the above-identified influencing factors (albumin, WBC, RDW, total Ca, and monocyte) and CCI. As shown in Table 4, monocyte, albumin, WBC, RBC, total Ca, and CCI were independently related to LOS in AR (all $P<0.05$). Then, the importance of these six factors was ranked and monocytes still ranked first, followed by total Ca, albumin, RBC, CCI, and WBC (Fig. 2B). These results indicated the vital role of monocytes in AR prognosis.

The mediation analysis in AR

Our study initially found no difference in the monocytes between LOS > 7 and LOS ≤ 7 groups. However, the independent role of monocytes on LOS was significant. Besides, monocytes showed the highest importance in AR as above mentioned, which triggers us to speculate that the influence of monocytes on the LOS may be affected by other variables. Previous studies identified that monocytes played a major role in the improvement of AR [23, 24], and the function of monocytes may be affected by WBC and albumins [25, 26]. Therefore, we tried to explore the potential mediating effect of other variables on the correlation between monocytes and LOS. As shown in Fig. 3A and E; Table 5, WBC served as a mediator in the relationship between monocyte and LOS; however, albumin, RDW, total Ca, and RBC did not

Table 1 The baseline clinical characteristics of the patients with allergic rhinitis

Variables	Total (*n* = 937)	Long LOS (*n* = 168)	Short LOS (*n* = 769)	*P*
Gender, n (%)				
Female	513(54.749)	80(47.619)	433(56.307)	0.040
Male	424(45.251)	88(52.381)	336(43.693)	
Age, n (%)				
Older (> 30)	898(95.838)	164(97.619)	734(95.449)	0.202
Younger (≤ 30)	39(4.162)	4(2.381)	35(4.551)	
Race, n (%)				
American-African	152(17.491)	25(17.241)	127(17.541)	0.794
Asian	39(4.488)	5(3.448)	34(4.696)	
White	678(78.021)	115(79.310)	563(77.762)	
Body mass index, n (%)				
> 28	416(51.232)	72(52.174)	344(51.039)	0.425
18.5 ~ 28	378(46.552)	61(44.203)	317(47.033)	
< 18.5	18(2.217)	5(3.623)	13(1.929)	
Asthma, n (%)				
No	712(75.987)	129(76.786)	583(75.813)	0.789
Yes	225(24.013)	39(23.214)	186(24.187)	
Systolic blood pressure, median [IQR]	131.000[120.140,138.510]	131.180[121.085,138.510]	131.000[120.000,138.510]	0.879
Diastolic blood pressure, median [IQR]	73.077[70.000,78.000]	74.000[70.360,78.230]	73.000[70.000,78.000]	0.567
Weight, median [IQR]	187.000[154.000,205.400]	189.720[160.000,213.800]	184.000[152.600,204.200]	0.025
Blood platelet, median [IQR]	225.000[175.000,285.000]	209.000[164.000,287.000]	228.000[177.000,284.000]	0.095
Albumin, median [IQR]	3.756[3.545,3.834]	3.600[3.200,3.877]	3.756[3.583,3.829]	< 0.001
White blood cell, median [IQR]	8.200[6.200,11.100]	9.100[6.500,12.800]	8.100[6.200,10.800]	0.011
Red blood cell, median [IQR]	4.040[3.590,4.480]	3.980[3.400,4.420]	4.050[3.650,4.490]	0.020
Hemoglobin, median [IQR]	12.100[10.900,13.400]	11.800[10.300,13.400]	12.200[11.000,13.400]	0.043
RDW, median [IQR]	13.700[13.000,14.600]	14.000[13.100,15.200]	13.600[12.900,14.500]	0.004
Anion gap, median [IQR]	14.000[12.000,16.000]	14.000[12.000,17.000]	14.000[12.000,16.000]	0.026
Free Ca, median [IQR]	8.900[8.400,9.200]	8.900[8.200,9.300]	8.900[8.400,9.200]	0.660
Total Ca, median [IQR]	1.152[1.138,1.157]	1.143[1.119,1.156]	1.152[1.142,1.157]	< 0.001
Chloride, median [IQR]	103.000[100.000,106.000]	103.000[99.000,106.000]	104.000[101.000,106.000]	0.031
Blood urea nitrogen, median [IQR]	15.000[11.000,20.000]	17.000[13.000,23.000]	14.000[11.000,19.000]	< 0.001
Glucose, median [IQR]	114.290[112.720,127.450]	123.000[113.630,133.310]	113.630[112.420,125.000]	< 0.001
Alanine transaminase, median [IQR]	28.270[21.610,30.470]	25.000[20.000,32.000]	28.270[22.180,30.320]	0.092
Aspartate aminotransferase, median [IQR]	24.380[22.940,34.630]	27.000[22.000,42.170]	24.020[22.940,33.330]	0.113
INR, median [IQR]	1.100[1.072,1.200]	1.130[1.100,1.300]	1.100[1.072,1.200]	< 0.001
PT, median [IQR]	12.400[12.048,13.500]	12.800[12.000,14.500]	12.300[12.048,13.427]	0.017
PTT, median [IQR]	29.100[27.528,33.187]	29.500[27.300,33.531]	28.949[27.528,33.000]	0.675
Sodium, median [IQR]	138.609[137.000,139.689]	138.589[136.000,140.000]	138.609[137.000,139.688]	0.711
Potassium, median [IQR]	4.000[3.800,4.300]	4.100[3.800,4.400]	4.000[3.725,4.300]	0.070
Magnesium, median [IQR]	2.000[1.800,2.100]	1.900[1.800,2.100]	2.000[1.800,2.100]	0.048
Lymphocyte, median [IQR]	23.428[18.700,26.185]	21.604[10.000,25.442]	23.882[21.000,26.315]	< 0.001
Neutrophil, median [IQR]	66.302[64.414,71.800]	69.229[64.510,82.600]	65.319[64.400,70.422]	< 0.001
Monocyte, median [IQR]	5.809[5.715,5.890]	5.793[5.100,6.200]	5.809[5.724,5.883]	0.876
Basophils, median [IQR]	0.353[0.318,0.364]	0.350[0.200,0.368]	0.354[0.322,0.364]	0.016

Long LOS: LOS > 7 days, Short LOS: LOS ≤ 7 days

Abbreviations LOS, length of in-hospital stay; RDW, red cell distribution width; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time

Table 2 The comorbidities of the patients with allergic rhinitis

Variables	Total (*n* = 937)	Long LOS (*n* = 168)	Short LOS (*n* = 769)	*P*
Myocardial infarct, n(%)	70(7.471)	17(10.119)	53(6.892)	0.150
Congestive heart failure, n(%)	108(11.526)	33(19.643)	75(9.753)	**< 0.001**
Peripheral vascular disease, n(%)	41(4.376)	8(4.762)	33(4.291)	0.787
Cerebrovascular disease, n(%)	48(5.123)	12(7.143)	36(4.681)	0.190
Dementia, n(%)	10(1.067)	3(1.786)	7(0.910)	0.317
Pulmonary disease, n(%)	231(24.653)	49(29.167)	182(23.667)	0.134
Rheumatic disease, n(%)	34(3.629)	5(2.976)	29(3.771)	0.618
Peptic ulcer disease, n(%)	16(1.708)	2(1.190)	14(1.821)	0.568
Mild liver disease, n(%)	65(6.937)	16(9.524)	49(6.372)	0.145
Diabetes without cc, n(%)	165(17.609)	36(21.429)	129(16.775)	0.151
Diabetes with cc, n(%)	54(5.763)	9(5.357)	45(5.852)	0.803
Paraplegia, n(%)	10(1.067)	3(1.786)	7(0.910)	0.317
Renal disease, n(%)	114(12.166)	27(16.071)	87(11.313)	0.087
Malignant cancer, n(%)	125(13.340)	44(26.190)	81(10.533)	**< 0.001**
Severe liver disease, n(%)	13(1.387)	5(2.976)	8(1.040)	0.052
Metastatic solid tumor, n(%)	31(3.308)	11(6.548)	20(2.601)	**0.010**
AIDS, n(%)	7(0.747)	2(1.190)	5(0.650)	0.461
CCI, median[IQR]	4.000[2.000,6.000]	5.000[3.000,6.000]	4.000[2.000,5.000]	**< 0.001**

Long LOS: LOS > 7 days, Short LOS: LOS ≤ 7 days

Abbreviations LOS, length of in-hospital stay; Diabetes without cc, diabetes without complications; diabetes with cc, diabetes with complications; AIDS, acquired immunodeficiency syndrome; CCI, Charlson comorbidity index

play a mediating role in the association of monocyte and LOS.

Discussion

Herein, we conducted a retrospective study with a large-scale dataset to explore the factors related to the LOS of patients with AR. After an integrative analysis, the monocyte was identified as a core LOS-related factor and enrolled for further mediation analysis to reveal its potential regulatory path in AR.

AR is a common inflammatory disease of the nasal mucosa caused by an immunologic response to an allergen in a sensitized individual [27]. It has been revealed that the interactions of mast cells with other inflammatory cells such as eosinophils via cell-cell contact and soluble mediators promote allergic inflammation [28, 29]. In the immunopathogenesis of AR, the dendritic cells captured the allergens and presented them to CD4 T cells, resulting in the activation and maturation of dendritic cells [30]. During this process, exosomes are secreted, which carry and transmit signaling molecules to mediate intercellular communication [31]. These exosomes can induce Th2 cytokine production in allergic donors, which may be important immunostimulatory factors in allergic immune responses [32]. For AR patients, the release of mediators by inflammatory cells, including monocytes, basophils, and eosinophils, enhances and sustains the inflammation, leading to more persistent symptoms [33]. Upon the correlation analysis, univariate and multivariate linear regression analyses were employed to identify independent risk factors for LOS in patients with AR, among which monocyte was the most important variable. The authors speculated that high levels of monocytes may suggest the deterioration of inflammation, thereby leading to longer LOS.

Subsequently, the mediation analysis results showed that WBC served as a mediator in the relationship between monocyte and LOS. WBC count is an inexpensive, simple biomarker of systemic inflammations and includes several cell subtypes, such as neutrophils, monocytes, lymphocytes, basophils, and eosinophils [34]. Besides, the lymphocytes contain T cells, B cells, and natural killer cells, which play a vital role in inflammation [35]. Some studies showed that lymphocyte level was increased upon inflammation, and its elevation was closely related to a favorable prognosis [36, 37]. However, Valero et al. claimed that the low lymphocyte count, high neutrophil, and monocyte counts were related to the poor outcomes [38]. Further experiments identified that the increase of monocytes inhibited the activation and cytotoxicity of T cells [39, 40]. Additionally, Rojas-Dotor et al. determined that the inhibition of monocytes could induce pro- and anti-inflammatory cytokine production in CD4 + T lymphocytes in AR patients [41]. It suggested that monocytes may affect the function of lymphocytes. Our results revealed that WBC was negatively related to the monocyte counts, indicating that the monocyte cells may deteriorate AR by inhibiting the recruitment of WBC.

In clinical use, monocyte level may be used as a reference index to evaluate the severity of the disease and LOS of patients with AR. High levels of monocyte predict

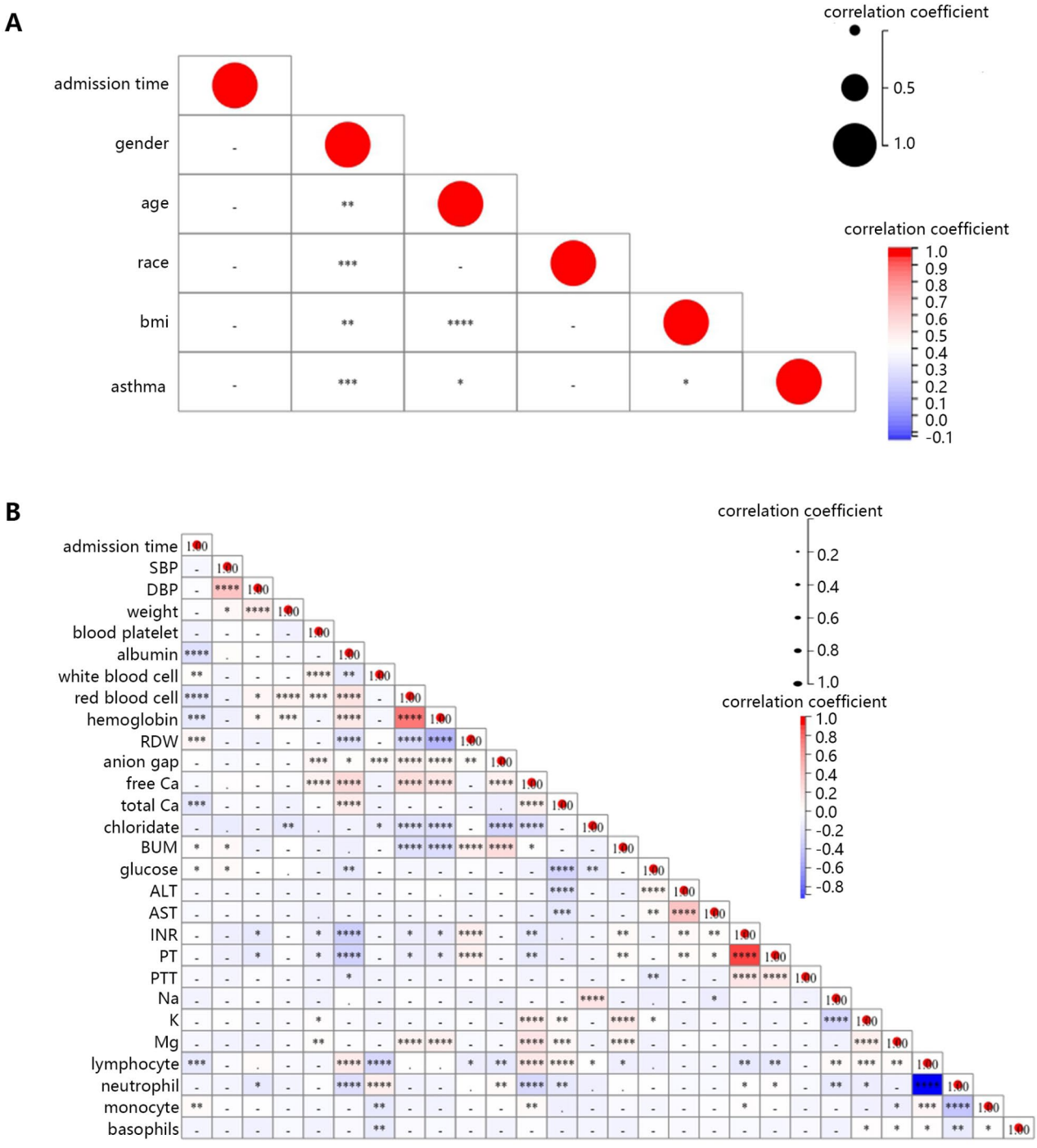

Fig. 1 The correlation analysis by Spearman and Kendall methods. (**A**) The correlation between categorical variables and LOS. (**B**) The correlation between continuous variables and LOS. **Abbreviations** LOS, length of in-hospital stay; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; RDW, red cell distribution width; BUN, blood urea nitrogen; ALT, alanine transaminase; AST, aspartate aminotransferase; international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; Na, sodium; K, potassium; Mg, magnesium

a longer LOS, suggesting that the clinical staff should monitor monocyte levels in time and stratify AR management according to monocyte levels. Those with high levels of monocyte should be given closer attention and immediate intervention. Based on the existing treatment regimen, the medication may be adjusted based on the monocyte level, thereby reducing the LOS. Due to the regulatory relationship among monocytes, WBC, and LOS, the imbalance between monocytes and WBC can

Table 3 The univariate and multivariate linear regression analysis associated with the LOS

	Univariate				Multivariate			
Variables	**β**	**P**	**95% lower**	**95% upper**	**β**	**P**	**95% lower**	**95% upper**
Albumin	-0.172	< 0.001	-3.990	-1.847	-0.116	**0.001**	-3.088	-0.834
WBC	0.085	0.009	0.021	0.144	0.077	**0.017**	0.013	0.134
RBC	-0.128	< 0.001	-1.896	-0.634	-0.076	**0.023**	-1.406	-0.107
Hemoglobin	-0.109	0.001	-0.598	-0.156				
RDW	0.124	< 0.001	0.221	0.684	0.083	**0.011**	0.069	0.534
Total Ca	-0.125	< 0.001	-42.555	-13.808	-0.091	**0.005**	-34.807	-6.088
BUN	0.071	0.029	0.004	0.069				
Glucose	0.069	0.034	0.001	0.038				
Lymphocyte	-0.108	0.001	-0.137	-0.035				
Monocyte	0.091	0.006	0.087	0.503	0.091	**0.004**	0.093	0.502

Abbreviations LOS, length of in-hospital stay; WBC, White blood cell; RBC, red blood cell; RDW, red cell distribution width; BUN, blood urea nitrogen

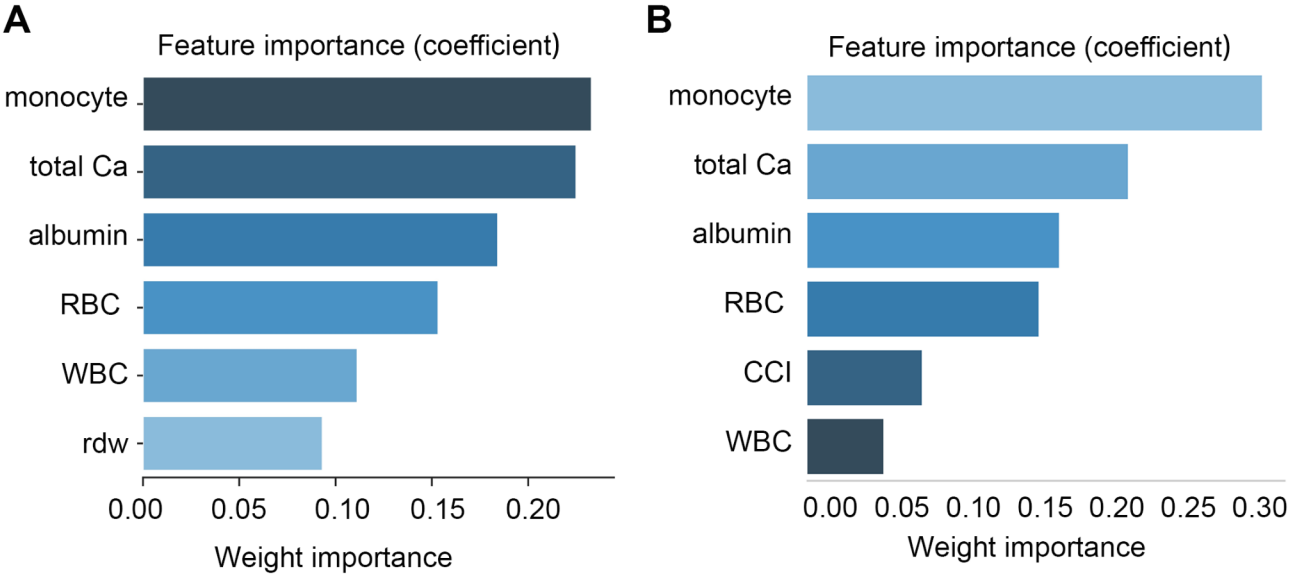

Fig. 2 The importance of independent variables. (**A**) Feature importance of monocyte, total Ca, albumin, RBC, WBC, and RDW. (**B**) Feature importance of monocyte, total Ca, albumin, RBC, CCI, and WBC. **Abbreviations** RBC, red blood cell; WBC, white blood cell; RDW, red cell distribution width; CCI, Charlson comorbidity index

Table 4 Multivariable linear regression analysis associated with the LOS

Variables	**β**	**95% lower**	**95% upper**	***P***
Monocyte	0.277	0.073	0.480	**0.008**
Albumin	-1.76	-2.89	-0.630	**0.002**
White blood cell	0.072	0.012	0.132	**0.019**
Red blood cell	-0.674	-1.323	-0.025	**0.042**
RDW	0.216	-0.023	0.455	0.077
Total Ca	-20.506	-34.793	-6.219	**0.005**
Charlson comorbidity index	0.244	0.075	0.413	**0.005**

Abbreviations LOS, length of in-hospital stay; RDW, red cell distribution width

also be corrected through immunoregulatory treatment to achieve a more effective therapeutic purpose.

For strengths, the sample size of this study is considerable and reliable since we have calculated the minimal sample size through G*Power software. Besides, statistical analyses were all appropriately used to identify the independent risk factors of AR and validate the importance of monocytes. Moreover, the mediating role of WBC in the relationship between monocytes and LOS provides new directions and clues for in-depth study of the AR pathogenesis as well as the cellular mechanisms of AR in inflammatory response and immune regulation. Whereas, these mechanisms require in vitro and in vivo experiment validation in the future. For limitations, the retrospective study design only reveals the relationship between monocyte and LOS rather than causality. Second, the study relies on data from a single database, which may limit the generalizability of the findings. Therefore, the results should be verified by using another independent cohort. Third, some confounding variables were not included due to a lack of data in the database, which should also be considered in the future.

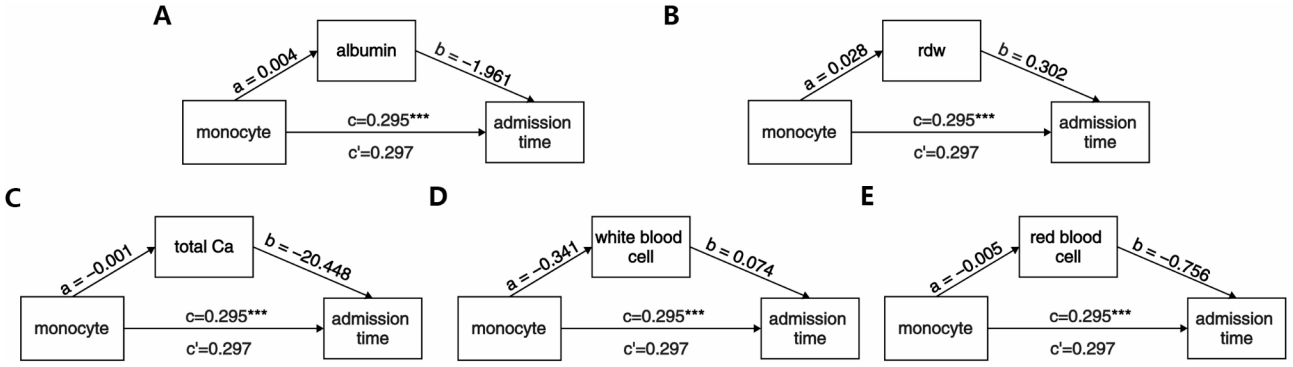

Fig. 3 The mediation association between monocyte and LOS. (**A**) The mediation correlation among monocyte, LOS, and albumin. (**B**) The mediation correlation among monocyte, LOS, and RDW. (**C**) The mediation correlation among monocyte, LOS, and total Ca. (**D**) The mediation correlation among monocyte, LOS, and white blood cell. (**E**) The mediation correlation among monocyte, LOS, and red blood cell. **Abbreviations** LOS, length of in-hospital stay; RDW, red cell distribution width

Table 5 The mediation analysis

	c	a	a(*p*)	b	b(*p*)	a*b	a*b (Boot SE)	a*b (z)	a*b (*p*)	a*b (95%Boot CI)	c'
Monocyte = > albumin = > LOS	0.295	0.004	0.559	-1.961	0.001***	-0.007	0.016	-0.457	0.648	-0.067	0.297
Monocyte = > RDW = > LOS	0.295	0.028	0.340	0.302	0.011**	0.008	0.013	0.654	0.514	-0.053	0.297
Monocyte = > total Ca = > LOS	0.295	-0.001	0.068	-20.448	0.005***	0.018	0.020	0.892	0.373	-0.086	0.297
Monocyte = > white blood cell = > LOS	0.295	-0.341	0.002***	0.074	0.017**	-0.025	0.025	-1.01	0.313	-0.105	0.297
Monocyte = > red blood cell = > LOS	0.295	-0.005	0.644	-0.756	0.023**	0.004	0.011	0.346	0.729	-0.047	0.297

*$P < 0.05$; **$P < 0.01$, and ***$P < 0.001$

Abbreviations LOS, length of in-hospital stay; RDW, red cell distribution width

In conclusion, several independent factors were identified for LOS in patients with AR, among which monocyte was the most important predictor. Moreover, WBC mediated the relationship between monocytes and LOS. Therefore, the clinical staff should monitor the monocyte levels and take immediate interventions for those with high monocyte levels. The treatment regimen may be modified by considering monocyte and WBC levels to reduce the LOS in patients with AR.

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Author contributions
DF, JL and PF contributed to the conception and design. DF, ZQM and HJH contributed to the collection and assembly of data. YS, GPQ and JZ analyzed and interpreted the data. All authors wrote and approved the final manuscript.

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Data availability
The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The Ethics Committee of Hangzhou First People's Hospital deemed that this research is based on open-source data, so the need for ethics approval was waived.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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