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Associations between age, red cell distribution width and 180-day and 1-year mortality in giant cell arteritis patients: mediation analyses and machine learning in a cohort study

Si Chen[1], Rui Nie[1], Xiaoran Shen[1], Yan Wang[1], Haixia Luan[1], Xiaoli Zeng[1], Yanhua Chen[2*] and Hui Yuan[1*]

Abstract

Objective The aim of this study was to investigate the correlation between age, red cell distribution width (RDW) levels, and 180-day and 1-year mortality in giant cell arteritis (GCA) patients hospitalized or admitted to the ICU.

Methods Clinical data from GCA patients were extracted from the MIMIC-IV (3.0) database. Logistic and Cox regression analyses, Kaplan–Meier (KM) survival analysis, restricted cubic spline (RCS) analysis, and mediation effect analysis were employed to investigate the association between age, RDW levels, and 180-day and 1-year mortality in GCA patients hospitalized or admitted to the ICU. Predictive models were constructed using machine learning algorithms, and SHapley Additive exPlanations (SHAP) analysis was applied to evaluate the contributions of age and RDW levels to mortality in this patient population.

Results A total of 228 GCA patients were eligible for analysis. Our study identified both age and RDW levels (both with OR > 1, $P < 0.05$) as significant predictors of 180-day and 1-year mortality in GCA patients hospitalized or admitted to the ICU using multivariate logistic regression analysis. In multivariate Cox regression analysis, both age and RDW (both with HR > 1, $P < 0.05$) also emerged as prognostic risk factors for 180-day and 1-year mortality in this patient population. KM survival analysis further showed that GCA patients hospitalized or admitted to the ICU with higher age or elevated RDW levels had significantly lower survival rates compared to younger patients or those with lower RDW levels ($P < 0.0001$). Moreover, RCS analysis indicated a strong nonlinear relationship between RDW levels (threshold: 17.53%) and 1-year mortality in this population. Additionally, RDW levels were found to modestly mediate the relationship between age (per 10-year increase) and 180-day or 1-year mortality in GCA patients hospitalized or admitted to the ICU. The results of the machine learning analysis indicated that the model built using the random forest algorithm performed the best, with an area under the curve of 0.879. Furthermore, SHAP analysis revealed that both age and RDW levels made significant contributions to the prediction of mortality in GCA patients hospitalized or admitted to the ICU.

*Correspondence:
Yanhua Chen
ieyanhuachen@zzu.edu.cn
Hui Yuan
18911662931@189.cn

Conclusions Older age and higher RDW levels were identified as independent risk factors for increased 180-day and 1-year mortality in GCA patients hospitalized or admitted to the ICU. Furthermore, elevated RDW levels modestly mediated the relationship between age and 180-day or 1-year mortality in this patient population.

Keywords Giant cell arteritis, Age, Red cell distribution width, Mediation analyses, Machine learning

Introduction

Giant cell arteritis (GCA) was recognized as the most common form of vasculitis affecting large and medium-sized arteries, predominantly in individuals over the age of 50. This condition primarily involved the cranial arteries, especially the temporal artery, but could also extend to other major vessels such as the aorta, leading to complications like aneurysms and stenosis. Patients often presented with symptoms such as headache, jaw claudication, and visual disturbances due to arterial inflammation and tissue ischemia [1]. A study conducted in Olmsted County, Minnesota, reported an incidence rate of 19.8 cases per 100,000 people for GCA from 2000 to 2009, with the rate remaining relatively stable since 1970 [2]. Another study from southern Sweden found an annual incidence rate of 14.1 per 100,000 people, with significantly higher rates in women. The study also observed that incidence increased with age [3]. A population-based study covering 1987 to 2012 found that patients with GCA were at a slightly higher risk of hospitalization compared to the general population, with a rate ratio of 1.13 [4]. Glucocorticoids (GC) had long been the standard treatment to manage inflammation, although their extended use was associated with significant side effects. More recently, advancements in treatment included the use of biologic agents like Tocilizumab, offering an effective steroid-sparing option [5]. Early and accurate diagnosis were critical to minimizing the risk of serious complications and improving patient outcomes.

Research on the mortality associated with GCA showed that the causes of death varied depending on the stage of the disease. Studies indicated that GCA was linked to increased mortality, particularly in the early stages after diagnosis, where complications such as large-vessel vasculitis, cardiovascular events, and infections were more prevalent [6]. In contrast, deaths occurring in the later stages of the disease were often attributed to chronic complications or comorbidities, such as long-term corticosteroid use or underlying cardiovascular conditions. Further exploration of the specific causes of mortality in these different stages provided a clearer understanding of the overall impact of GCA on patient survival. A systematic review suggested that it was elevated in hospital-based cohorts, indicating higher mortality in patients with severe disease [7]. Research indicated that red cell distribution width (RDW) might be a significant predictor of mortality in various clinical settings. Elevated RDW levels had been associated with increased all-cause and cause-specific mortality. For instance, a study involving a large cohort from the Malmö Diet and Cancer cohort found that higher RDW levels significantly correlated with an increased risk of mortality from all causes, cancer, cardiovascular diseases, and respiratory diseases [8]. No literature has reported a relationship between RDW and mortality in autoimmune diseases. However, studies generally suggest that RDW, as a marker of inflammation and oxidative stress, may serve as an indicator for predicting mortality in diseases with systemic inflammatory components, which are commonly present in autoimmune diseases. Research suggested that age significantly influenced mortality in patients with GCA and the conclusions were inconsistent. A population-based cohort study found that patients diagnosed with GCA at the age of 70 or younger had a higher mortality risk than those diagnosed at older ages [9]. Another study found that GCA patients aged 85 and older had a higher mortality rate, more ischemic complications, and were more likely to develop permanent visual loss compared to younger patients [10].

To date, there has been a notable gap in the literature regarding the relationship between the prognosis of GCA and factors such as age and RDW. This research aimed to fill this gap by examining whether RDW mediates the relationship between age and 180-day or 1-year mortality in GCA patients admitted to the hospital or ICU. This study sought to contribute to a better understanding of the underlying mechanisms linking these variables, which could have important implications for predicting GCA outcomes and guiding future research directions.

Methods

Data source

In this study, we utilized data from version 3.0 of the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database [11], which is an extensive, deidentified collection of health records. This dataset includes information from over 65,000 intensive care unit (ICU) patients and more than 200,000 emergency department visits at the Beth Israel Deaconess Medical Center in Boston, Massachusetts, USA, covering the years 2008 to 2022 [12]. Access to the MIMIC-IV database was granted to the first authors (Si Chen) upon successful

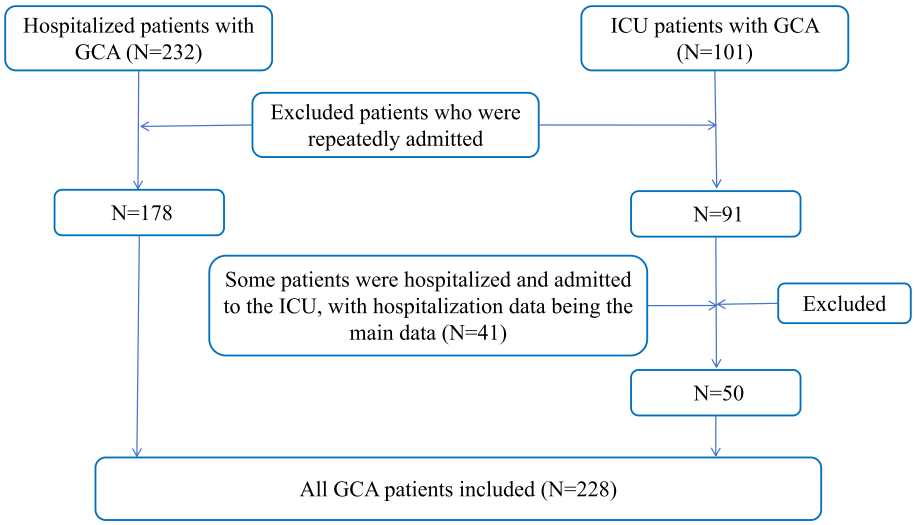

Fig. 1 Flowchart of patient inclusion and exclusion from the MIMIC-IV database. Abbreviations: GCA: giant cell arteritis; ICU: intensive care unit; MIMIC-IV: Medical Information Mart for Intensive Care-IV

completion of the Collaborative Institutional Training Initiative program (certification number: 64388854). This research complied with the Declaration of Helsinki, and the need for informed consent was waived due to the use of anonymized data. The institutional review board at Beth Israel Deaconess Medical Center provided ethical approval for the study.

Study population

Since the clinical data of GCA patients in outpatient clinics were incomplete, this study only included patients hospitalized and admitted to the ICU. From the MIMIC-IV database, we retrospectively selected hospitalized and ICU patients diagnosed with GCA using the International Classification of Diseases (ICD) codes: ICD-9 code 446.5 and ICD-10 code M31.6. It is important to note that the included GCA patients were not necessarily newly diagnosed at the time of their hospitalization, and GCA was not always the primary cause for their admission. Some patients may have been admitted for other reasons and were diagnosed with GCA during their hospital stay. As detailed on the MIMIC website, MIMIC-IV is divided into two primary modules: 'hosp' and 'ICU.' The 'hosp' module contains data from the hospital-wide electronic health records, whereas the 'ICU' module includes data from the ICU-specific clinical information systems. Some patients initially presented to the emergency department and were subsequently transferred to the ICU without being admitted to the hospital. Therefore, our cohort of GCA patients was drawn from both hospitalized and ICU settings. For patients with both hospital and ICU admissions, only data from the first hospitalization were used for analysis. In instances where multiple hospitalizations or ICU admissions occurred, we analyzed only the data from the first admission. Patients were excluded based on the following criteria: age under 18, missing pertinent records, or a simultaneous diagnosis of polymyalgia rheumatica (PMR). The final study cohort comprised 228 GCA patients. Figure 1 illustrates the patient selection process.

Data extraction and definitions

PostgreSQL software was utilized to extract data on demographic characteristics, medication use, prognostic indicators, and laboratory measurements. For laboratory data, the initial recorded measurements following hospital admission or ICU entry were used for analysis. RDW is determined by dividing the standard deviation of red blood cell (RBC) volume by the mean corpuscular volume (MCV) and then multiplying by 100. This calculation reflects the variability in RBC size, indicating the heterogeneity of RBC volume within a blood sample. Stroke, limb ischemia, vision loss, and aortic aneurysm are the primary complications associated with GCA. However, due to the limited number of GCA patients exhibiting these complications as identified through ICD-9/ICD-10 codes, the current analysis didn't consider the associated risks of these complications. Mortality was calculated starting from the first day of hospitalization or ICU admission, and the primary endpoints of this study were the 180-day and 1-year mortality rates among GCA patients.

Statistical analysis

Categorical variables are presented as percentages, while continuous variables are initially tested for normality. Data that conform to a normal distribution are represented as mean ± standard deviation. In contrast, data that do not follow a normal distribution are described using the median and interquartile range to convey central tendency and variability. To compare groups, appropriate statistical tests such as the Student's t-test, Mann–Whitney U test, chi-squared test, and Fisher's exact test were employed. Logistic regression analysis and Cox proportional hazards regression analysis were used to examine the relationships between age, RDW, and mortality. Initially, univariate analyses were conducted for each potential factor. The univariate analysis conducted in this study was subjected to Bonferroni correction, and the variables with significant differences and clinical significance after correction were subsequently included in the multivariate analysis. The least absolute shrinkage and selection operator (LASSO) regression method was employed to identify factors significantly associated with mortality outcomes in GCA patients. The factors identified by LASSO regression were then used as independent variables in multivariable logistic and Cox proportional hazards regression models. The performance of these two multivariable models was evaluated using receiver operating characteristic (ROC) curves. For survival analysis, Kaplan–Meier (KM) curves were plotted, and log-rank tests were conducted. Restricted cubic spline (RCS) curves were utilized to examine possible nonlinear relationships between age, RDW, and mortality. Mediation analysis was carried out to determine whether RDW acted as a mediator in the relationship between the exposure variable (age) and the outcome (GCA). To enhance the robustness of our analysis, we employed a thousand bootstrap samples. The results display the size of the indirect pathway effect, the proportion of the mediating effect, and the associated p-value. Given the presence of minor missing values in certain variables and the non-normal distribution of many variables, median imputation was used to handle missing data. Variables with more than 20% missing data were excluded from the analysis. All statistical analyses were conducted using R software (version 4.4.1) and DecisionLinnc1.0 software [13]. A *P*-value of less than 0.05 (two-tailed) was considered statistically significant, and the results of multivariate logistic and Cox regression analysis were presented as odds ratios (OR)/hazard ratios (HR) and their 95% confidence intervals (CI).

Machine learning

The variables selected through a combination of LASSO and Logistic regression were incorporated into machine learning algorithms. The dataset was divided into training and testing sets in a 7:3 ratio. The training set was used to build the models, and the testing set was used for evaluation. Decision tree (DT), random forest (RF), extreme gradient boosting survival learner (XGBoost), and support vector machine (SVM) algorithms were applied to analyze the selected variables and predict the one-year mortality risk of GCA patients. During model development, optimal hyperparameters were set. Model performance was assessed using ROC curves and the corresponding area under the curve (AUC). Clinical utility was evaluated using decision curve analysis (DCA). The best-performing model on the testing set was further interpreted using SHapley Additive exPlanations (SHAP) values, which provided insights into the importance and ranking of each variable. SHAP values provided a clear visualization of the positive or negative impact of each variable on model predictions, with a screening threshold of 0.05 [14]. Additionally, the bootstrap method was applied to evaluate the performance of the best model, with performance metrics including ROC and DCA. The bootstrap process involved 5 cycles, with a training sample ratio of 0.7, and the random seed set to 123.

Results

Baseline characteristics

A total of 228 GCA patients were included in this study based on the screening criteria (Fig. 1). The baseline characteristics of the participants at the 180-day and 1-year follow-ups are presented in Table 1. The median age of the cohort was 81 years, with 30.70% of the participants being male, and the majority identifying as white. Non-survivors, compared to survivors, exhibited significantly higher levels of RDW, creatinine (Cr), and blood urea nitrogen (BUN), as well as older age and higher glucocorticoid use. In contrast, non-survivors had significantly lower levels of RBC, hemoglobin (Hb), and hematocrit (HCT) than survivors.

Primary outcomes of logistic regression analyses

To identify factors associated with 180-day and 1-year mortality in GCA patients, univariate and multivariate logistic regression analyses were conducted (Table 2). Multivariate analysis identified both age and RDW as significant predictors of 180-day and 1-year mortality in GCA patients. For 180-day mortality, age had an OR of 1.10 (95% CI: 1.04 to 1.16; $P=0.0008$) and RDW had an OR of 1.27 (95% CI: 1.04 to 1.57; $P=0.023$). For 1-year mortality, age had an OR of 1.12 (95% CI: 1.07 to 1.18; $P<0.0001$) and RDW had an OR of 1.30 (95% CI: 1.06 to 1.61; $P=0.015$).

Given the potential intercorrelations among the 14 variables, dimensionality reduction was performed

Table 1 Characteristics of study participants

Variables	180-day follow-up			1-year follow-up		
	Survivors ($n=194$)	Non-survivors ($n=34$)	*P*-value	Survivors ($n=183$)	Non-survivors ($n=45$)	*P*-value
Age, years	79 (72–85)	86.5 (84–91)	***<0.0001***	78 (72–84.5)	88 (84–91)	***<0.0001***
Male, n (%)	61 (31.44)	9 (26.47)	0.56	57 (31.15)	13 (28.89)	0.77
Race, n (%)						
White	158 (81.44)	30 (88.24)	0.20	148 (80.87)	40 (88.89)	0.10
Black	17 (8.76)	0 (0.00)		17 (9.29)	0 (0.00)	
Other	19 (9.80)	4 (11.76)		18 (9.84)	5 (11.11)	
GC, n (%)	117 (60.31)	23 (67.65)	0.42	107 (58.47)	33 (73.33)	0.07
Immunosuppressants, n (%)	5 (2.58)	1 (2.94)	0.90	5 (2.73)	1 (2.22)	0.85
RBC, m/uL	3.68 (3.3–4.22)	3.37 (2.96–3.72)	***0.0009***	3.68 (3.31–4.21)	3.47 (3.12–3.85)	***0.016***
Hb, g/dL	11.21 ± 1.98	10.1 ± 1.86	***0.003***	11.22 ± 1.93	10.31 ± 2.13	***0.011***
HCT, %	34.37 ± 5.87	31.22 ± 5.45	***0.004***	34.36 ± 5.72	32.03 ± 6.35	***0.028***
RDW, %	14.8 (13.5–15.8)	15.9 (14.83–17.58)	***<0.0001***	14.5 (13.4–15.7)	15.9 (14.9–17.5)	***<0.0001***
WBC, K/uL	9.3 (7.4–11.67)	10 (7.05–13.25)	0.63	9.3 (7.4–11.55)	10.1 (7.1–13.4)	0.76
PLT, K/uL	221 (182.75–306.25)	215.5 (155–248.25)	0.13	221 (186–311)	212 (162–255)	0.07
Glu, mg/dL	116 (97–146)	108 (89.25–144)	0.36	116 (95.5–144)	114 (94–155)	0.98
Cr, mg/dL	0.9 (0.7–1.1)	1.1 (0.9–1.4)	***0.006***	0.9 (0.7–1.1)	1 (0.9–1.4)	***0.010***
BUN, mg/dL	19 (14–24)	26 (19.75–39.5)	***0.0001***	19 (14–23.5)	24 (17–38)	***0.0003***

GC glucocorticoids, *RBC* red blood cells, *Hb* hemoglobin, *HCT* hematocrit, *RDW* red cell distribution width, *WBC* white blood cells, *PLT* platelets, *Glu* Glucose, *Cr* Creatinine, *BUN* blood urea nitrogen. Significant *P* values are in bold

Table 2 Logistic analyses: risk factors of mortality

Variables	Univariate logistic analysis		Multivariate logistic analysis		LASSO-logistic analysis	
	OR (95% CI)	*P*-value*	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
180-day follow-up						
Age	1.11 (1.06–1.17)	***0.0001***	1.10 (1.04–1.16)	***0.0007***	1.10 (1.04–1.16)	***0.0006***
RBC	0.36 (0.19–0.64)	***0.0007***	0.21 (0.04–0.89)	0.05	0.54 (0.28–0.99)	0.05
Hb	0.74 (0.60–0.90)	***0.0034***	1.42 (0.85–2.51)	0.20		
HCT	0.91 (0.85–0.97)	0.0048				
RDW	1.38 (1.18–1.64)	***0.0001***	1.31 (1.08–1.60)	***0.0072***	1.23 (1.03–1.49)	***0.0266***
PLT	0.997 (0.992–1.00)	0.08				
BUN	1.03 (1.01–1.05)				1.01 (0.99–1.04)	0.34
1-year follow-up						
Age	1.13 (1.08–1.20)	***<0.0001***	1.12 (1.07–1.19)	***<0.0001***	1.12 (1.07–1.19)	***<0.0001***
RBC	0.48 (0.28–0.78)	***0.0041***	0.48 (0.12–1.81)	0.29	0.74 (0.41–1.28)	0.28
Hb	0.78 (0.65–0.93)	***0.0067***	1.18 (0.73–1.93)	0.50		
HCT	0.93 (0.88–0.99)	0.0188				
RDW	1.42 (1.22–1.69)	***<0.0001***	1.34 (1.10–1.66)	***0.0045***	1.31 (1.09–1.59)	***0.0046***
PLT	0.996 (0.992–0.999)	0.0306				
BUN	1.03 (1.01–1.05)	***0.0038***	1.01 (0.99–1.04)	0.27	1.02 (0.99–1.04)	0.23

RBC red blood cells, *Hb* hemoglobin, *HCT* hematocrit, *RDW* red cell distribution width, *PLT* platelets, *BUN* blood urea nitrogen; **P*-value was Bonferroni corrected; Significant *P* values after Bonferroni correction are shown in bold

using LASSO regression to identify the most representative predictors of 180-day and 1-year mortality in GCA patients (Supplementary Fig. 1A-1D). The LASSO regression analysis identified age, RBC, RDW, and BUN as significant predictors for 180-day and 1-year mortality. Following this, a multivariate logistic regression model

Table 3 The association between RDW levels and mortality by logistic regression analyses

		Medel 1		Medel 2		Medel 3	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
180-day follow-up							
RDW		1.38 (1.18–1.64)	***0.0001***	1.33 (1.13–1.59)	***0.0009***	1.27 (1.04–1.57)	***0.023***
RDW (quartile)							
Q1	13.2 (12.9–13.6)	reference		reference		reference	
Q2	14.8 (14.5–15)	4.49 (1.33–20.52)	***0.026***	3.75 (1.08–17.40)	0.05	3.80 (1.07–17.88)	0.05
Q3	16.9 (16–18.2)	9.05 (2.92–39.75)	***0.0006***	7.79 (2.43–34.89)	***0.0018***	6.52 (1.74–32.38)	***0.01***
P for trend		***0.0002***		***0.0008***		***0.0086***	
1-year follow-up							
RDW		1.42 (1.22–1.69)	***< 0.0001***	1.39 (1.18–1.67)	***0.0002***	1.30 (1.06–1.61)	***0.015***
RDW (quartile)							
Q1	13.2 (12.9–13.6)	reference		reference		reference	
Q2	14.8 (14.5–15)	4.85 (1.66–17.71)	***0.007***	4.13 (1.35–15.59)	***0.02***	3.84 (1.24–14.61)	***0.029***
Q3	16.9 (16–18.2)	9.75 (3.54–34.56)	***0.0001***	9.03 (3.10–33.28)	***0.0002***	6.84 (2.02–28.05)	***0.004***
P for trend		***< 0.0001***		***0.0001***		***0.0031***	

95% CI 95% confidence interval

Model 1: no covariates were adjusted

Model 2: adjusted for age

Model 3: adjusted for age, RBC, Hb, HCT, PLT, BUN

RBC red blood cells, *Hb* hemoglobin, *HCT* hematocrit, *RDW* red cell distribution width, *PLT* platelets, *BUN* blood urea nitrogen. Significant *P* values are in bold

was developed using these four variables selected by the LASSO model. As shown in Table 2, age and RDW were confirmed as significant predictors of both 180-day and 1-year mortality in GCA patients. For 180-day mortality, age had an OR of 1.10 (95% CI: 1.04 to 1.16; $P=0.0006$) and RDW had an OR of 1.23 (95% CI: 1.03 to 1.49; $P=0.0266$). For 1-year mortality, age had an OR of 1.12 (95% CI: 1.07 to 1.19; $P<0.0001$) and RDW had an OR of 1.31 (95% CI: 1.09 to 1.59; $P=0.0046$).

As shown in Table 3, RDW levels were significantly associated with both 180-day and 1-year mortality in GCA patients. Model 1 did not adjust for any covariates, Model 2 adjusted for age, and Model 3 adjusted for age, RBC, Hb, HCT, platelets (PLT), and BUN. The analysis revealed that in Model 3, RDW levels remained positively correlated with 180-day mortality (OR: 1.27, 95% CI: 1.04 to 1.57, $P=0.023$) and 1-year mortality (OR: 1.30, 95% CI: 1.06 to 1.61, $P=0.015$) in GCA patients. Subsequently, RDW levels were divided into three quantiles, with Q1 serving as the reference group. The analysis showed that the OR for 180-day and 1-year mortality in GCA patients were significantly higher in the highest quantile (Q3) compared to Q1 (OR: 9.05, 95% CI: 2.92 to 39.75, $P=0.0006$ for 180-day mortality; OR: 9.75, 95% CI: 3.54 to 34.56, $P=0.0001$ for 1-year mortality). After adjusting for multiple covariates in Model 3, GCA patients in the highest RDW tertile had a substantially higher risk of 180-day and 1-year mortality compared to those in the lowest tertile (OR: 6.52, 95% CI: 1.74 to 32.38, $P=0.01$ for 180-day mortality; OR: 6.84, 95% CI: 2.02 to 28.05, $P=0.004$ for 1-year mortality).

Primary outcomes of Cox regression analyses

To identify prognostic indicators for 180-day and 1-year mortality, univariate and multivariate Cox regression analyses were initially performed. The multivariate Cox analysis revealed that both age (HR: 1.08, 95% CI: 1.03 to 1.13; $P=0.001$ for 180-day mortality; HR: 1.09, 95% CI: 1.05 to 1.14; $P<0.0001$for 1-year mortality) and RDW levels (HR: 1.19, 95% CI: 1.04 to 1.37; $P=0.01$ for 180-day mortality; HR: 1.18, 95% CI: 1.04 to 1.34; $P=0.008$ for 1-year mortality) were independent risk factors for mortality in GCA patients (Table 4).

As previously noted, LASSO regression was utilized to identify the most representative risk factors for 180-day and 1-year mortality in GCA patients (Supplementary Fig. 2A-2D). The LASSO regression identified age, RBC, RDW, and BUN as significant risk factors, indicated by the number of non-zero regression coefficients. A multivariate Cox regression model was then developed using these four variables. As shown in Table 4, both age and RDW levels remained independent risk factors for 180-day and 1-year mortality in GCA patients. For 180-day mortality, age had a HR of 1.08 (95% CI: 1.03 to 1.13; $P=0.001$), and RDW had an HR of 1.18 (95% CI: 1.03 to 1.35; $P=0.016$). For 1-year mortality, age had an HR of

Table 4 Cox analyses: risk factors of mortality

Variables	Univariate Cox analysis		Multivariate Cox analysis		LASSO-Cox analysis	
	HR (95% CI)	*P*-value*	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
180-day follow-up						
Age	1.10 (1.05–1.15)	***< 0.0001***	1.08 (1.03–1.13)	***0.001***	1.08 (1.03–1.13)	***0.001***
RBC	0.42 (0.25–0.68)	***< 0.0001***	0.17 (0.03–0.96)	0.05	0.60 (0.35–1.02)	0.06
Hb	0.77 (0.65–0.92)	***0.003***	1.21 (0.50–2.94)	0.68		
HCT	0.92 (0.87–0.98)	***0.005***	1.10 (0.78–1.55)	0.61		
RDW	1.30 (1.16–1.45)	***< 0.0001***	1.20 (1.04–1.37)	***0.01***	1.18 (1.03–1.35)	***0.016***
PLT	0.997 (0.993–1.00)	0.08				
BUN	1.02 (1.01–1.04)	***0.003***	1.01 (0.99–1.03)	0.36	1.01 (0.991–1.03)	0.31
1-year follow-up						
Age	1.11 (1.07–1.16)	***< 0.0001***	1.10 (1.05–1.14)	***< 0.0001***	1.09 (1.05–1.14)	***< 0.0001***
RBC	0.51 (0.33–0.79)	***0.002***	0.45 (0.14–1.42)	0.17	0.76 (0.49–1.20)	0.24
Hb	0.81 (0.69–0.94)	***0.005***	1.23 (0.82–1.83)	0.31		
HCT	0.94 (0.89–0.99)	0.016				
RDW	1.30 (1.18–1.43)	***< 0.0001***	1.21 (1.08–1.36)	***0.001***	1.20 (1.06–1.34)	***0.003***
PLT	0.996 (0.993–1.00)	0.031				
BUN	1.02 (1.01–1.03)	***0.001***	1.01 (0.995–1.03)	0.19	1.01 (1.00–1.03)	0.16

GC glucocorticoids, *RBC* red blood cells, *Hb* hemoglobin, *HCT* hematocrit, *RDW* red cell distribution width, *WBC* white blood cells, *PLT* platelets, *Glu* Glucose, *Cr* Creatinine, *BUN* blood urea nitrogen; **P*-value was Bonferroni corrected; Significant *P* values after Bonferroni correction are shown in bold

1.09 (95% CI: 1.05 to 1.14; $P<0.0001$), and RDW had an HR of 1.20 (95% CI: 1.06 to 1.34; $P=0.003$).

KM survival analyses

KM survival analyses were performed to assess 180-day and 1-year mortality in GCA patients based on age and RDW levels. The analysis identified an optimal cut-off point of 83 years for both 180-day and 1-year mortality, categorizing 97 patients as having high age and 131 as having low age. For RDW levels, the best cut-off for 180-day mortality was 16.8%, with 42 patients classified as having high RDW levels and 186 as having low RDW levels. The optimal RDW cut-off for 1-year mortality was 14.8%, with 125 patients classified as having high RDW levels and 103 as having low RDW levels. Additionally, patients with either advanced age or elevated RDW levels had significantly lower survival rates compared to those with younger age or lower RDW levels ($P<0.0001$) (Fig. 2A-D).

Non-linear analyses

RCS analysis revealed a strong nonlinear relationship between RDW levels and 1-year mortality in GCA patients (Fig. 3A). Threshold effect analysis identified a critical RDW level of 17.53%, indicating that when RDW levels are below this threshold, the risk of mortality is relatively low. However, once RDW levels exceed this point, the mortality risk increases significantly. In contrast, no nonlinear relationship was observed between RDW levels and 180-day mortality in GCA patients (Fig. 3B). Additionally, no evidence of a nonlinear relationship was found between age and either 180-day or 1-year mortality in GCA patients (Fig. 3C-D).

Mediating effect of RDW on age and the mortality of GCA patients

Our research demonstrated that age, RDW levels, and 180-day or 1-year mortality in GCA patients were pairwise correlated (Fig. 4A, Supplementary Fig. 3A-3B). To make the mediation effect estimates more interpretable, we divided the age variable by 10. This allowed us to express the impact of age in terms of a 10-year increase, providing effect estimates that were less numerically small and easier to interpret. After scaling age by a factor of 10, we found that RDW mediated the relationship between age (per 10-year increase) and 180-day or 1-year mortality in GCA patients. Specifically, the average causal mediation effect (ACME) was statistically significant ($P<0.0001$), indicating that a 10-year increase in age had a small but meaningful indirect effect on mortality in GCA patients through its impact on RDW levels. The average direct effect (ADE) was also statistically significant, indicating a substantial direct influence of age (per 10-year increase) on both 180-day (estimate: 0.0003; 95% CI: 0.0000 to 0.0023; $P=0.002$) and 1-year (estimate: 0.0001; 95% CI: 0.0000 to 0.0007; $P<0.0001$) mortality. The total effect was statistically significant as well, reflecting a significant overall impact of age (per

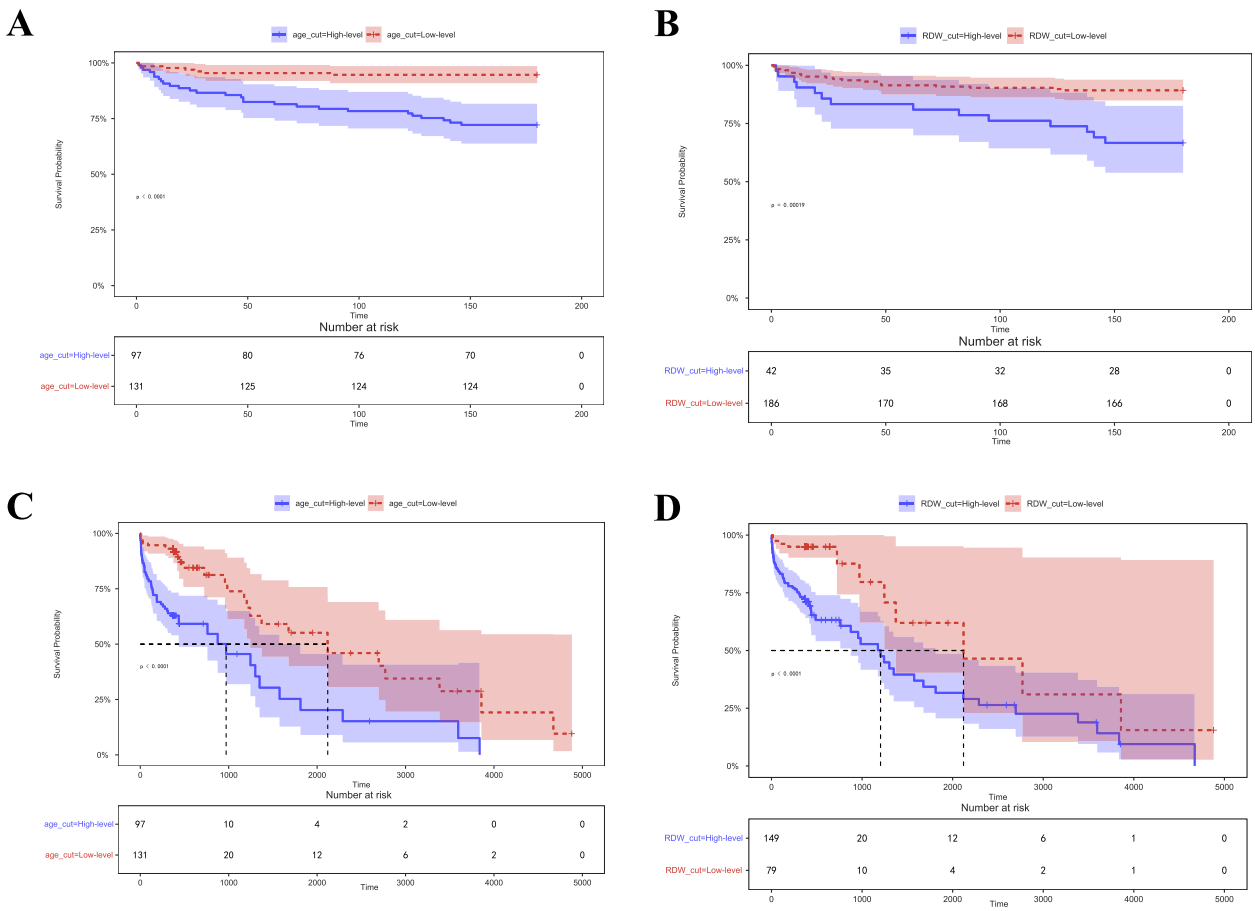

Fig. 2 KM survival curves of age and RDW levels for 180-day and 1-year mortality in GCA patients hospitalized or admitted to the ICU. **A** age for 180-day mortality in GCA patients hospitalized or admitted to the ICU; (**B**) RDW levels for 180-day mortality in GCA patients hospitalized or admitted to the ICU; (**C**) age for 1-year mortality in GCA patients hospitalized or admitted to the ICU; (**D**) RDW levels for 1-year mortality in GCA patients hospitalized or admitted to the ICU; Abbreviations: GCA: giant cell arteritis; KM: Kaplan–Meier; RDW: red cell distribution width

10-year increase) on 180-day (estimate: 0.0004; 95% CI: 0.0000 to 0.0032; $P<0.0001$) and 1-year (estimate: 0.0001; 95% CI: 0.0000 to 0.0008; $P<0.0001$) mortality. The proportion mediated by RDW was statistically significant, mediating approximately 5.61% of the total effect for 180-day mortality (95% CI: 0.011 to 0.222; $P=0.004$, Fig. 4B) and 4.25% for 1-year mortality (95% CI: 0.010 to 0.144; $P<0.0001$, Fig. 4C). These findings suggest that RDW has a significant, albeit modest, indirect mediating effect on the relationship between age (per 10-year increase) and mortality in GCA patients at both 180-day and 1-year intervals.

Establishment and validation of the prediction models

We applied machine learning techniques to predict the 1-year mortality in GCA patients. Supplementary Table 1 outlined the optimal hyperparameters for the four models. Figure 5 presented the ROC curves for both the training and testing sets, with model performance indicated by AUC values. In the testing set, the AUC for the DT was 0.791, for RF 0.879, for XGBoost 0.864, and for the SVM 0.824. Supplementary Fig. 4A and 4B showed the DCA curves for both the training and testing sets, with all models demonstrating substantial net benefit, indicating strong clinical validity. Based on the AUC results from the testing set, the RF model was identified as the best-performing model. SHAP analysis applied to the RF model highlighted age and RDW as the most critical variables, as shown in Fig. 6A (dual-coordinate line plot), 6B (heatwave plot), and 6C (bar plot), which consistently emphasize their significant contribution to the model's predictive outcomes. The RF model's performance was further evaluated using the bootstrap method. Supplementary Fig. 4C showed the DCA curves for the bootstrap analysis. Figure 7A demonstrated that the AUC values for all models exceeded 0.7, and Fig. 7B showed that the 95% CI was 0.728–0.807, indicating that they outperformed random guessing. Notably, the

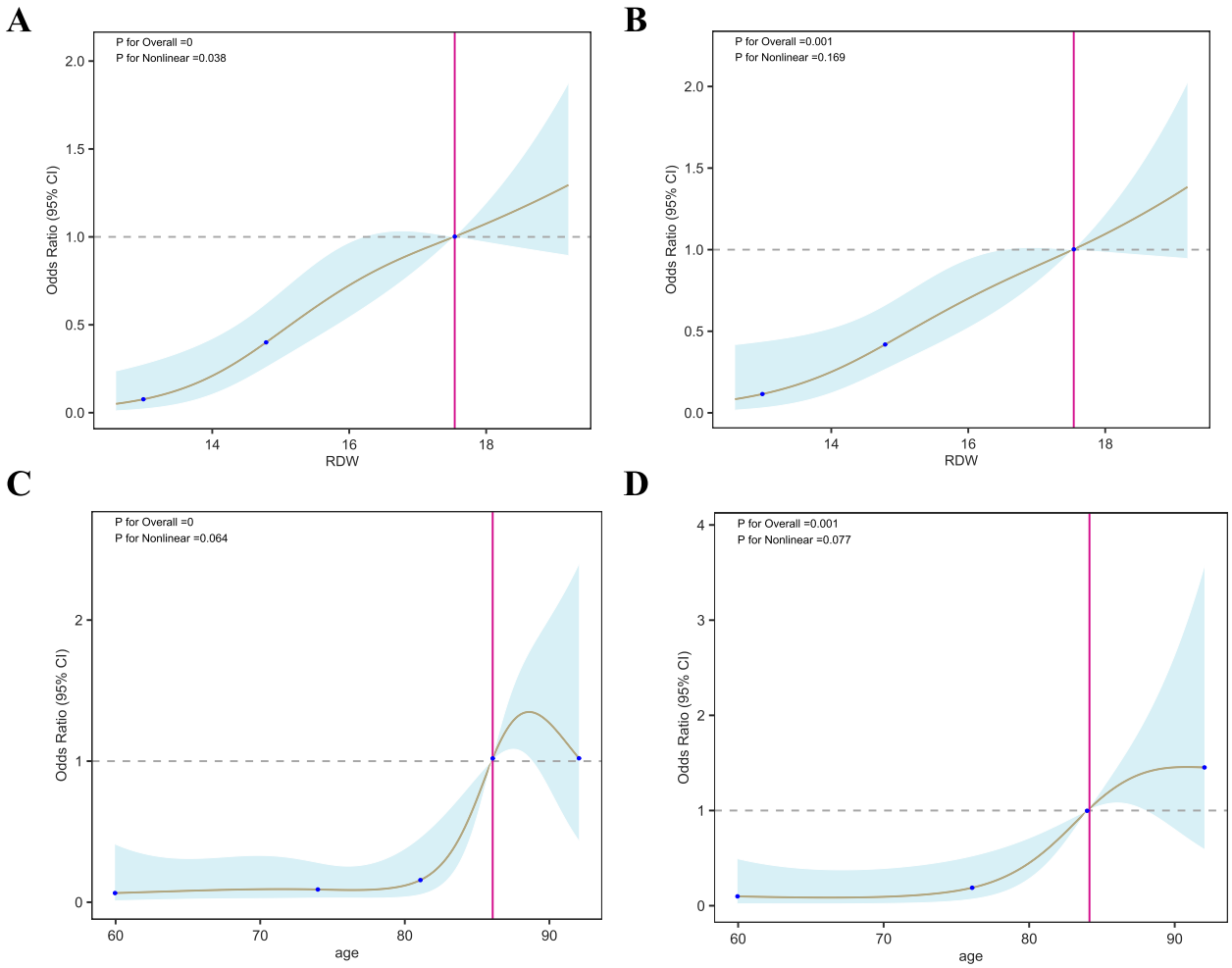

Fig. 3 RCS analysis of age and RDW levels for 180-day and 1-year mortality in GCA patients hospitalized or admitted to the ICU. **A** RDW levels for 1-year mortality in GCA patients hospitalized or admitted to the ICU; (**B**) RDW levels for 180-day mortality in GCA patients hospitalized or admitted to the ICU. **C** age for 1-year mortality in GCA patients hospitalized or admitted to the ICU; (**D**) age for 180-day mortality in GCA patients hospitalized or admitted to the ICU. Abbreviations: GCA: giant cell arteritis; RCS: Restricted cubic spline; RDW: red cell distribution width

RF_BR1TEST and RF_BR5TEST models exhibited the best performance, achieving relatively high AUC values.

Discussion

This study marked a pioneering effort to examine the relationship between 180-day or 1-year mortality and relevant laboratory biomarkers in GCA patients hospitalized or admitted to the ICU. The primary aim was to explore whether RDW mediates the relationship between age and 180-day or 1-year mortality in GCA patients hospitalized or admitted to the ICU. The results of this investigation provided several compelling insights into the potential mechanisms linking these factors, offering valuable implications for clinical practice and patient management.

Firstly, our results showed that age was associated with 180-day and 1-year mortality in GCA patients. However, we acknowledged that age is a well-known risk factor for increased mortality across many populations, independent of GCA status. Therefore, it was possible that part of the observed association between age and mortality in our study may reflect the broader trend that older adults generally faced higher mortality rates. Additionally, previous research indicated that age uniquely affected mortality in GCA patients, although findings have been inconsistent. A population-based cohort study reported that patients diagnosed with GCA at 70 years of age or younger had a higher risk of mortality compared to those diagnosed at older ages, with mortality rates peaking during the first two years following diagnosis and then again more than ten years later [9]. Conversely, another study highlighted that GCA patients aged 85 and older exhibited higher mortality rates, experienced more ischemic complications, and were more prone to permanent visual

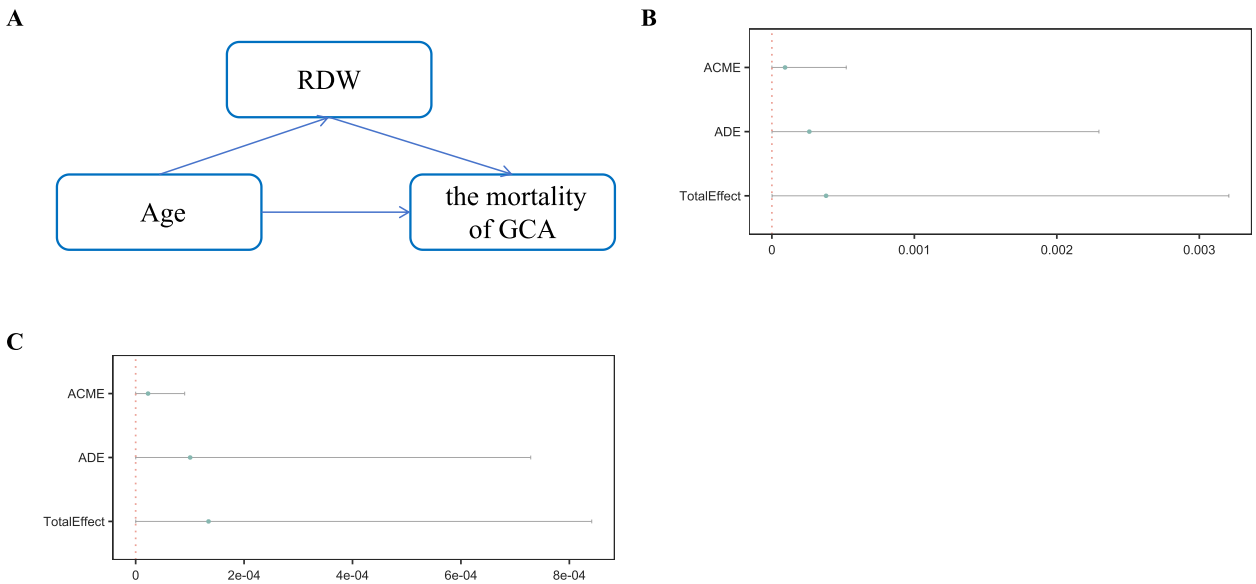

Fig. 4 Mediating effect of RDW on age (per 10-year increase) and the mortality of GCA patients hospitalized or admitted to the ICU. **A** Mediational models; (**B**) Mediating effect of RDW on age and the 180-day mortality of GCA patients hospitalized or admitted to the ICU; (**C**) Mediating effect of RDW on age and the 1-year mortality of GCA patients hospitalized or admitted to the ICU. Abbreviations: GCA: giant cell arteritis; RDW: red cell distribution width; ACME: average causal mediation effects; ADE: average direct effect

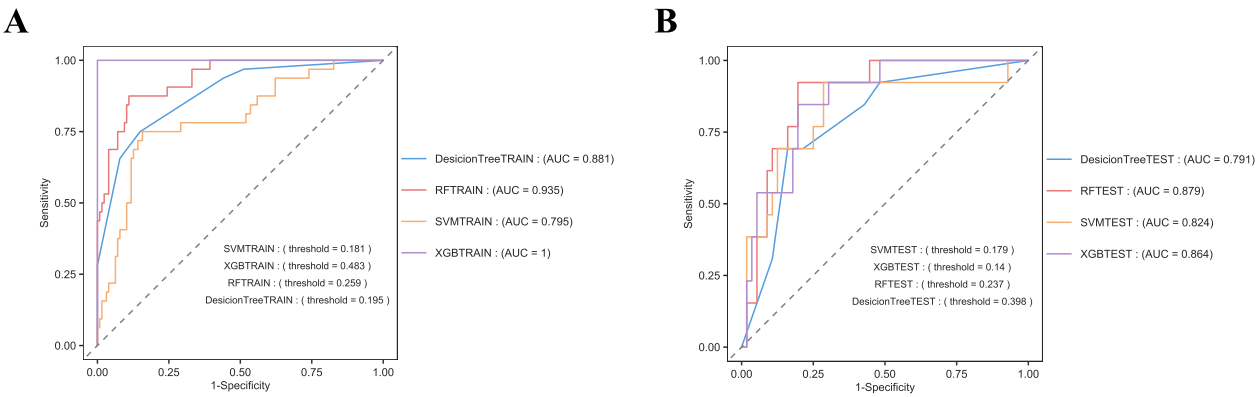

Fig. 5 The ROC curves for the four models. **A** The training sets; (**B**) The testing sets. Abbreviations: ROC: receiver operating characteristic; AUC: area under the curve; RF: random forest, XGB: extreme gradient boosting survival learner; SVM: support vector machine

loss compared to their younger counterparts. This underscored the importance of early diagnosis and vigilant monitoring, especially in older patients [10]. These findings suggested that age significantly impacted both short-term and long-term mortality in GCA patients. Younger patients (≤70 years) might face heightened mortality risks shortly after diagnosis and later in life, more than a decade after diagnosis. Meanwhile, older patients diagnosed with GCA tend to experience immediate increased mortality risks, although their long-term mortality patterns might differ [15]. Consequently, age emerged as a critical factor in understanding mortality risk in GCA, with both younger and older patients facing unique challenges at different stages of their illness. Our study identified age as a significant predictor of 180-day and 1-year mortality in GCA patients hospitalized or admitted to the ICU through logistic regression analysis. In Cox regression analysis, age emerged as a prognostic risk factor for 180-day and 1-year mortality in GCA patients hospitalized or admitted to the ICU. KM survival analysis further demonstrated that GCA patients hospitalized or admitted to the ICU with higher age had significantly reduced survival rates compared to those who were younger. In the RF machine learning model, SHAP analysis identified

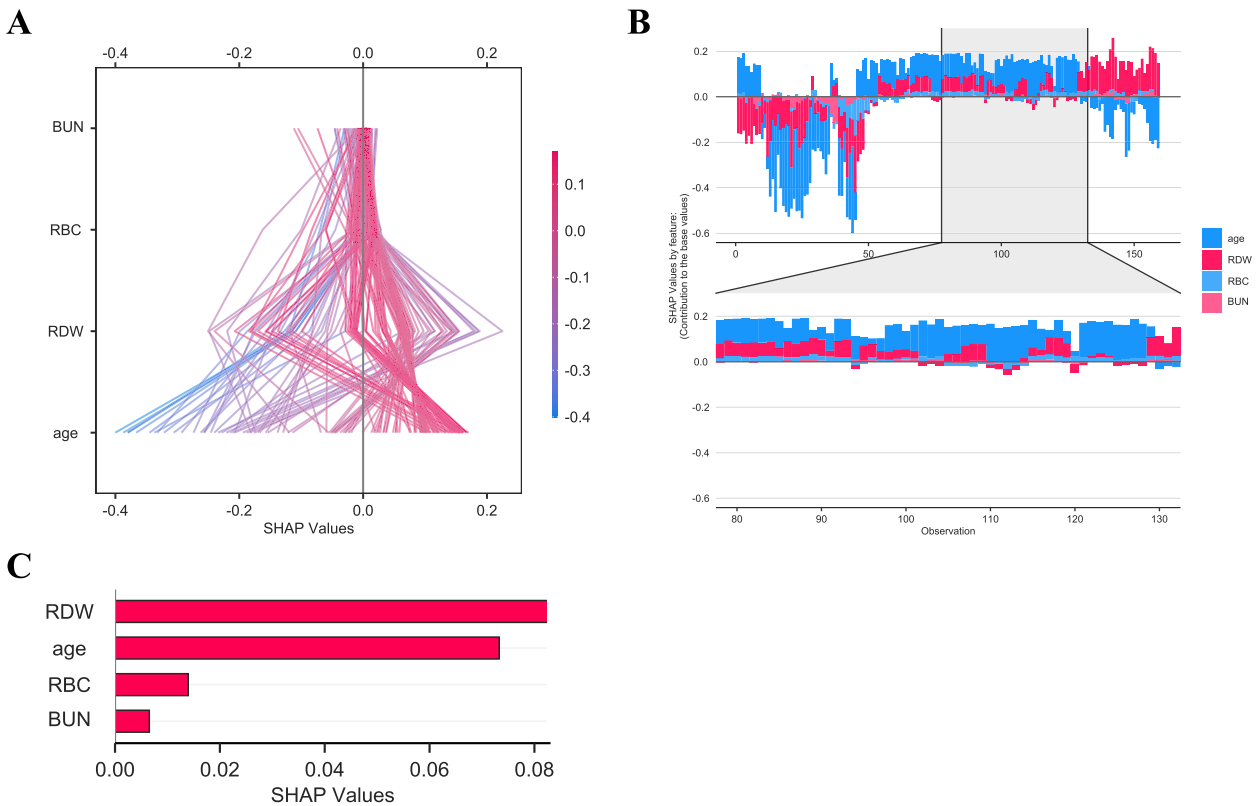

Fig. 6 The results of SHAP analysis. **A** Dual-coordinate line plot; (**B**) Heatwave plot; (**C**) Bar plot. Abbreviations: RDW: red cell distribution width; RBC: red blood cells; BUN: blood urea nitrogen

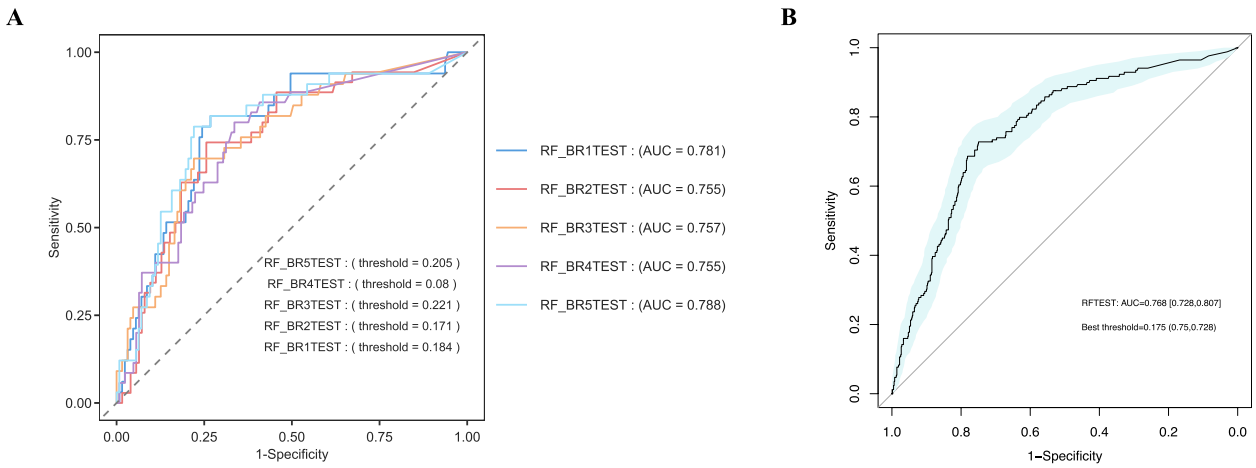

Fig. 7 The results of bootstrap analysis. **A** ROC curves after 5 cycles; (**B**) ROC curve with 95% CI. Abbreviations: RF: random forest

age as a highly important variable influencing the mortality of GCA patients hospitalized or admitted to the ICU. The SHAP values demonstrated that age significantly contributed to the model's predictions, underscoring its critical impact on outcomes for GCA patients hospitalized or admitted to the ICU.

Secondly, this study's findings demonstrated a clear association between age and elevated RDW levels, indicating that the variation in red blood cell size increases with advancing age. The relationship between age and elevated RDW levels is well known. Supporting this, a study involving 116,666 participants from the UK

Biobank revealed that RDW levels not only rose with age but also predicted several adverse health outcomes, such as mortality, coronary heart disease, and cancer. This study further highlighted those genetic factors accounted for a significant portion of RDW variability, particularly among older individuals [16]. Additionally, research has shown that RDW levels increase consistently across the entire adult age range, emphasizing that this trend is a universal biological feature rather than being influenced by the type of hematology analyzer used. Both RDW and MCV exhibited age-related increases, indicating that future investigations into RDW's prognostic value should take these age-related changes into account [17].

Thirdly, we found that RDW levels were associated with 180-day or 1-year mortality in GCA patients hospitalized or admitted to the ICU. Recent research indicated that RDW was associated with the activity and severity of various autoimmune diseases. Elevated RDW levels had been observed in conjunction with increased disease activity in conditions such as rheumatoid arthritis, systemic lupus erythematosus (SLE), primary biliary cholangitis, dermatomyositis, and polymyositis, suggesting its utility as a marker for assessing disease activity in these disorders [18, 19]. One study demonstrated a positive correlation between RDW and markers of inflammation and disease activity in SLE patients, including serum IgM, C-reactive protein (CRP), and the SLE disease activity index. Additionally, treatment with GC was associated with a decrease in RDW levels, highlighting its responsiveness to changes in disease activity [20]. Other studies have found that RDW levels were significantly elevated in patients with autoimmune liver diseases compared to healthy controls, correlating with inflammatory markers such as aspartate transaminase and CRP, which pointed to RDW's potential as a diagnostic and monitoring tool for the severity of these conditions [21]. In Takayasu arteritis, RDW was shown to correlate with inflammatory activity, with higher levels observed in patients experiencing active disease compared to those in remission, even in the absence of anemia, reinforcing its role as an inflammatory marker in vascular autoimmune disorders [22]. Furthermore, research had identified higher RDW levels in patients with relapsing PMR compared to those without relapse, with elevated RDW serving as an independent predictor for early relapse, underscoring its value in forecasting disease recurrence [23].

RDW had been extensively studied as a predictor of mortality across diverse patient populations. A meta-analysis demonstrated that, among patients with chronic kidney disease, a 1% increase in RDW was linked to a 47% higher risk of all-cause mortality, underscoring RDW's potential as a marker for mortality risk in this group [24]. In the Malmö Diet and Cancer cohort study, elevated RDW levels were significantly associated with increased all-cause mortality, as well as mortality specifically due to cancer, cardiovascular, and respiratory diseases, supporting RDW's role as a non-specific mortality risk marker in the general population [8]. Research conducted in ICU settings found that higher RDW levels upon admission were significantly correlated with 30-day mortality in COVID-19 patients, with RDW's predictive power for mortality being comparable to established severity scores such as APACHE II and SOFA [25]. In critically ill patients with acute kidney injury, elevated RDW was independently associated with higher mortality rates, with those in the highest RDW categories facing a significantly greater risk of death compared to patients with lower RDW levels [26]. Analysis of data from the MIMIC-III database consistently showed that higher RDW levels were linked to increased short-term and long-term mortality among unselected critically ill patients, suggesting that RDW is a reliable mortality predictor in these settings [27]. Among patients with hemophagocytic lymphohistiocytosis, a condition marked by severe immune system activation, RDW was strongly associated with mortality, with higher RDW values correlating with an increased risk of death. This highlights RDW's potential utility in predicting outcomes in severe immune-related conditions [28]. Although specific data on autoimmune diseases was less emphasized, existing research suggested that RDW, as a marker of inflammation and oxidative stress, might serve as an indicator for mortality prediction in diseases characterized by systemic inflammation, common in autoimmune conditions. Our study was the first to identify RDW levels as a significant predictor of 180-day and 1-year mortality in GCA patients hospitalized or admitted to the ICU using logistic regression analysis. Similarly, Cox regression analysis confirmed RDW levels as a prognostic risk factor for both time-frames. KM survival analysis further demonstrated that GCA patients hospitalized or admitted to the ICU with higher RDW levels had significantly lower survival rates compared to those with lower RDW levels. Additionally, RCS analysis revealed a strong nonlinear relationship between RDW levels and 1-year mortality in GCA patients hospitalized or admitted to the ICU, showing that mortality risk remains relatively low when RDW is below 17.53%, but increases sharply beyond this threshold. Elevated RDW was consistently associated with increased mortality risk across various clinical scenarios, particularly those involving inflammatory and immune responses. In the RF machine learning model, SHAP analysis identified RDW levels as a highly important variable influencing mortality in GCA patients hospitalized or admitted to the ICU. SHAP values showed that RDW significantly contributed to the model's

predictions, underscoring its critical impact on outcomes for GCA patients hospitalized or admitted to the ICU. These findings highlight the need for further research to explore RDW's prognostic value in autoimmune diseases and its broader application as a tool for risk stratification and prognosis in both general and specialized patient populations.

Our findings suggested that RDW modestly mediate the association between age (per 10-year increase) and 180-day or 1-year mortality in GCA patients hospitalized or admitted to the ICU. In a study focusing on super-elderly patients (aged 90 and above) diagnosed with community-acquired pneumonia, RDW levels were found to be significantly associated with mortality. Higher RDW, along with advanced age, increased the risk of death, suggesting that RDW may play a role in mediating age-related mortality in critical illness settings [29]. A meta-analysis of community-based studies involving older adults showed that RDW is a strong predictor of mortality, with each 1% increase in RDW associated with approximately a 14% increase in the risk of death. This study emphasized RDW's effectiveness as a mortality predictor across various demographic and health subgroups, highlighting its potential as an indicator of biological aging [30]. Another study examining immunohematologic profiles found that RDW, along with other blood count parameters, varied with age and was linked to an increased mortality risk. This research suggests that RDW is a component of the immuno-hematologic system that reflects aging and its associated health outcomes [31]. Consistent with our study, a small mediating effect of RDW was found in the relationship between age and 180-day or 1-year mortality in GCA patients hospitalized or admitted to the ICU. The association between elevated RDW and increased mortality risk, particularly in older populations, indicates that RDW could mediate the relationship between age and disease mortality. Therefore, RDW could serve as a valuable biomarker for assessing aging-related health risks and mortality.

The application of machine learning in the clinical prediction of autoimmune diseases has gained significant traction due to its ability to process complex datasets and uncover patterns beyond human capacity. One critical advancement in this field was the incorporation of SHAP to enhance the interpretability of these models. SHAP is a game-theoretic approach that assigns importance scores to each feature in a machine learning model, allowing clinicians to understand the contribution of various factors to model predictions. For example, a study applying machine learning models to predict remission in rheumatoid arthritis patients treated with biologics used SHAP to identify key clinical features like age, rheumatoid factor, and CRP as significant predictors of treatment response [32]. Another study predicting immunotherapy efficacy in non-small cell lung cancer patients leveraged SHAP to highlight the neutrophil-to-lymphocyte ratio as a critical variable influencing outcomes [33]. These examples underscored how SHAP helped demystify the "black box" nature of machine learning, offering more transparent and actionable insights for clinical decision-making in autoimmune diseases. This study employed machine learning techniques to predict mortality in GCA patients hospitalized or admitted to the ICU, with the RF model emerging as the best-performing model based on both the training and testing sets. SHAP analysis of the RF model identified age and RDW levels as the most critical variables, highlighting their substantial contributions to the model's predictions of mortality in GCA patients hospitalized or admitted to the ICU.

This study is the first to investigate the role of RDW as a mediator in the relationship between age and 180-day or 1-year mortality in a large, diverse cohort of hospitalized, multi-ethnic patients with GCA. A primary strength of this study is that it utilized data from the extensive, publicly available MIMIC-IV database, which allowed for a comprehensive analysis. However, several limitations should be noted. First, the external validity of our findings is limited by the retrospective and single-center nature of the study, underscoring the need for further prospective, multi-center research to confirm our results. Second, due to the study design, we were unable to establish a causal relationship among age, RDW, and 180-day or 1-year mortality in GCA patients, highlighting the need for additional research in this area. Third, due to incomplete outpatient data, this study only included GCA patients who were hospitalized or admitted to the ICU. Consequently, some patients may have been excluded, potentially introducing a degree of bias. Fourth, this study focused on GCA patients with severe disease requiring hospital or ICU admission, which may limit the generalizability of our findings to the broader GCA population, particularly those seen in outpatient or fast-track clinic settings with milder disease. Future studies should include outpatient cohorts to compare outcomes and better understand mortality risks across different care settings. Fifth, the lack of a non-GCA comparison cohort limited our ability to isolate the mortality risk specifically attributable to GCA from age-related mortality risks seen in the general population. We recommend that future studies incorporate a non-GCA cohort to more accurately assess the impact of GCA on mortality relative to age-related trends, providing a clearer understanding of how GCA may amplify age-related mortality risks. Sixth, this study did not investigate the factors influencing RDW; future studies are recommended to further explore these relevant factors. Lastly, although we accounted for

numerous potential confounders, the possibility of residual confounding cannot be entirely excluded.

Conclusions

Our findings indicated that older age and elevated RDW levels were independent risk factors for increased 180-day and 1-year mortality in GCA patients hospitalized or admitted to the ICU. Additionally, RDW partially mediated the relationship between age and mortality, suggesting a role for RDW in explaining age-related mortality risk in this patient population.

Abbreviations

ACME	Average causal mediation effect
ADE	Average direct effect
Cr	Creatinine
GCA	Giant cell arteritis
GC	Glucocorticoids
Glu	Glucose
RDW	Red cell distribution width
MIMIC-IV	Medical Information Mart for Intensive Care-IV
ICU	Intensive care unit
ICD	International Classification of Diseases
PMR	Polymyalgia rheumatica
RBC	Red blood cell
MCV	Mean corpuscular volume
Hb	Hemoglobin
HCT	Hematocrit
BUN	Blood urea nitrogen
WBC	White blood cells
PLT	Platelets
LASSO	Least absolute shrinkage and selection operator
ROC	Receiver operating characteristic
KM	Kaplan-Meier
RCS	Restricted cubic spline
DT	Decision tree
RF	Random forest
XGBoost	Extreme gradient boosting survival learner
SVM	Support vector machine
AUC	Area under the curve
DCA	Decision curve analysis
SHAP	SHapley Additive exPlanations
OR	Odds ratio
CI	Confidence interval
HR	Hazard ratio
SLE	Systemic lupus erythematosus
CRP	C-reactive protein

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-025-03477-z.

Supplementary Material 1. Supplementary Figure 1. Screening the factors affecting the mortality of GCA patients hospitalized or admitted to the ICU using LASSO binary regression. (A) Lasso regression lambda value mean square error plot for 180-day mortality in GCA patients hospitalized or admitted to the ICU; (B) Lasso regression lambda value coefficient plot for 180-day mortality in GCA patients hospitalized or admitted to the ICU; (C) Lasso regression lambda value mean square error plot for 1-year mortality in GCA patients hospitalized or admitted to the ICU; (D) Lasso regression lambda value coefficient plot for 1-year mortality in GCA patients hospitalized or admitted to the ICU.

Supplementary Material 2. Supplementary Figure 2. Screening the factors affecting the mortality of GCA patients hospitalized or admitted to the ICU using LASSO survival regression. (A) Lasso regression lambda value mean square error plot for 180-day mortality in GCA patients hospitalized or admitted to the ICU; (B) Lasso regression lambda value coefficient plot for 180-day mortality in GCA patients hospitalized or admitted to the ICU; (C) Lasso regression lambda value mean square error plot for 1-year mortality in GCA patients hospitalized or admitted to the ICU; (D) Lasso regression lambda value coefficient plot for 1-year mortality in GCA patients hospitalized or admitted to the ICU.

Supplementary Material 3. Supplementary Figure 3. Linear regression between age (per 10-year increase) and RDW levels. (A) Linear regression for 180-day mortality in GCA patients hospitalized or admitted to the ICU; (A) Linear regression for 1-year mortality in GCA patients hospitalized or admitted to the ICU.

Supplementary Material 4. Supplementary Figure 4. The DCA curves for the four models. (A) The training sets; (B) The testing sets; (C) The bootstrap analysis. Abbreviations: DCA: decision curve analysis; RF: random forest, XGB: extreme gradient boosting survival learner; SVM: support vector machine.

Supplementary Material 5.

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Authors' contributions

Si Chen and Rui Nie conceptualized and designed this study. Xiaoran Shen, Yan Wang, and Haixia Luan performed data extraction and initial analysis. Si Chen, Xiaoli Zeng, Yanhua Chen, and Hui Yuan assisted in the data cleaning, data proofreading, and statistical analysis. Rui Nie and Yanhua Chen contributed to figure plotting. Si Chen prepared the initial manuscript draft. Xiaoli Zeng and Hui Yuan participated in the critical revision of the manuscript. Hui Yuan supervised the study. All authors participated in editing, reviewing, and approving the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Clinical Laboratory, Beijing Anzhen Hospital, Capital Medical University, Anzhen Road No. 2, Chaoyang District, Beijing 100029, China. [2]School of Computer and Artificial Intelligence, Zhengzhou University, No. 100, Science Avenue, High-Tech Zone, Zhengzhou, Henan 450001, China.

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