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Original Article

Long-term efficacy of adalimumab in elderly patients with rheumatoid arthritis and associated risk factors

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Abstract: Objective: To evaluate the long-term efficacy of adalimumab (ADA) combined with methotrexate (MTX) in elderly patients with rheumatoid arthritis (RA) and to identify risk factors associated with therapeutic efficacy. Methods: This retrospective study enrolled 320 RA patients aged ≥60 years, divided into a control group (MTX monotherapy, n=157) and a combination group (MTX plus ADA, n=163), with a 24-month follow-up. Primary endpoints included improvements in disease activity and functional status, while secondary endpoints comprised changes in inflammatory markers and safety outcomes. Multivariate regression analysis was conducted to determine predictors of efficacy. Results: The overall response rate was significantly higher in the combination group than that in the control group (P<0.05). After 24 months, reductions in Disease Activity Score (DAS) in 28 joints based on erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and tumor necrosis factor-α were all significantly greater in the combination group (all P<0.001). Combination therapy markedly reduced the risk of treatment failure (odds ratio [OR]=0.296, P=0.001). High baseline disease activity (DAS in 28 joints based on CRP≥5.1, OR=2.568) and elevated ESR (≥40 mm/h, OR=1.082) were independent predictors of poor efficacy. Injection-site reactions occurred more frequently in the combination group (P<0.05). Conclusion: ADA combined with MTX significantly improves disease activity and functional outcomes in elderly patients with RA, demonstrating sustained long-term efficacy and acceptable safety. For patients with a high baseline inflammatory burden, combination therapy should be prioritized, with individualized management guided by risk stratification.

Keywords: Rheumatoid arthritis, adalimumab, methotrexate, risk factors

Introduction

With the aging of the global population, the incidence of rheumatoid arthritis (RA) among older adults has risen markedly [1]. RA is a systemic autoimmune disease characterized by chronic synovial inflammation that, if uncontrolled, leads to progressive joint destruction, deformity, and functional impairment, thereby severely diminishing quality of life and imposing a substantial public health and economic burden [2, 3]. In elderly patients with RA, age-related immune dysregulation and the presence of multiple comorbidities further complicate diagnosis and management [4, 5]. Therefore, clinicians must not only aim to suppress inflammation and relieve joint pain and stiffness but also ensure treatment safety and tolerability in this vulnerable population.

Traditional disease-modifying antirheumatic drugs, such as methotrexate (MTX) and hydroxychloroquine, remain the cornerstone of early RA management. However, in elderly patients, age-related decline in hepatic and renal function, along with polypharmacy, often increases the risk of adverse drug reactions and may attenuate therapeutic efficacy [6, 7]. Moreover, a subset of patients exhibits an inadequate response to conventional disease-modifying antirheu-

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matic drugs, leading to persistent disease activity, uncontrolled symptoms, and progressive joint destruction [8]. The introduction of biologic therapies, particularly tumor necrosis factor-α (TNF-α) inhibitors, has transformed the treatment landscape of RA by providing substantial anti-inflammatory benefits and delaying structural joint damage [9].

Adalimumab (ADA), a fully human monoclonal antibody targeting TNF-α, binds to TNF-α and prevents its interaction with cell surface receptors, thereby inhibiting downstream inflammatory signaling pathways [10]. Numerous clinical studies have demonstrated that ADA significantly reduces disease activity, alleviates morning stiffness, and delays radiographic joint damage progression [11]. Across multiple randomized controlled trials, ADA has shown both robust efficacy and acceptable safety, establishing it as one of the preferred biologic agents recommended in RA treatment guidelines [12]. However, most existing evidence has been derived from middle-aged or younger cohorts, and data on its long-term efficacy in elderly patients remain limited.

Evaluating the long-term efficacy of biologic agents is particularly important in elderly populations. Previous studies have indicated that baseline disease activity, body mass index (BMI), and comorbidities such as chronic pulmonary disease and diabetes may influence therapeutic outcomes of biologic treatments [13, 14]. However, these findings are predominantly derived from short-term studies with limited sample sizes, and comprehensive analyses focusing specifically on elderly patients with RA remain scarce. Furthermore, older adults frequently present with multiple comorbidities, including osteoporosis and hypertension, which necessitate additional consideration of treatment tolerability and safety. Therefore, developing a risk prediction model and identifying key determinants of long-term ADA efficacy in elderly RA patients may provide valuable guidance for individualized treatment strategies.

This study retrospectively analyzed long-term follow-up data of elderly patients with RA treated with ADA at Shangluo Central Hospital, focusing on changes in disease activity, functional status, and radiographic outcomes. Multivariate regression analysis was performed to identify factors associated with treatment efficacy.

Methods

Study population

This retrospective study included 320 elderly patients with RA who received treatment at Shangluo Central Hospital and Tianshui Hospital of Integrated Traditional Chinese and Western Medicine between January 2021 and February 2023. Patients were divided into two groups: the control group (n=157), which received MTX monotherapy, and the combination group (n=163), which received MTX plus ADA. The inclusion criteria were as follows: (1) age ≥60 years; (2) diagnosis of RA; (3) completion of at least 12 weeks of treatment; and (4) availability of complete clinical and follow-up data. Exclusion criteria included: (1) presence of malignancy, severe cardiovascular disease, hepatic or renal failure, or other major comorbidities; (2) autoimmune or infectious diseases; and (3) discontinuation or change of treatment due to allergy, intolerance, or poor adherence.

This study was conducted in accordance with the Declaration of Helsinki (1964) and its subsequent amendments and was approved by the Ethics Committee of Tianshui Hospital of Integrated Traditional Chinese and Western Medicine.

Data collection

Baseline clinical data were extracted from patients' electronic medical records. Demographic parameters included age, sex, BMI, and disease duration. Comorbidities such as hypertension, diabetes, osteoporosis, and cardiovascular disease were documented. Medication history was reviewed, including recent use of corticosteroids and immunosuppressive agents (e.g., MTX). Joint involvement was assessed by recording the baseline tender joint count, swollen joint count, and duration of morning stiffness. Disease activity was evaluated using the following indices: DAS28-ESR (Disease Activity Score in 28 joints based on erythrocyte sedimentation rate), DAS28-CRP (based on C-reactive protein), VAS (Visual Analog Scale for self-reported pain), CDAI (Clinical Disease Activity Index), and SDAI (Simplified Disease Activity Index). Inflammatory markers, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), interleukin-1β (IL-1β), TNF-α, and interleukin-6 (IL-6).

Treatment regimen and follow-up

In the control group, patients received MTX monotherapy, whereas those in the study group were treated with a combination of MTX and ADA. MTX tablets (10 mg once weekly) were provided by Shanghai Sine Pharmaceutical Laboratories Co., Ltd., and ADA injections (40 mg twice weekly, subcutaneous) were supplied by Suzhou Innovent Biologics, Inc. All patients also received intra-articular methylprednisolone acetate injections (5 mg weekly during the first 4 weeks), with dosage adjustments every 2 weeks thereafter according to clinical response. Both groups adhered to their assigned regimens for 12 weeks.

Patients were followed up at 6, 12, and 24 months in the outpatient department. For those unable to attend in person, follow-up was conducted within two weeks via telephone, supplemented with results from local laboratory tests. During each follow-up visit, disease activity, joint symptoms, inflammatory markers, functional status, and quality of life were assessed. The following parameters were recorded: disease activity scores (DAS28-ESR, DAS28-CRP, VAS, CDAI, and SDAI), joint assessments (tender joint count, swollen joint count, and duration of morning stiffness), and inflammatory markers (ESR, CRP, RF, IL-1β, TNF-α, and IL-6). Adverse events, including infections, injection-site reactions, gastrointestinal disturbances, hepatic dysfunction, and hematologic abnormalities, were monitored throughout the study. Venous blood samples were collected from all participants in the early morning after overnight fasting. Approximately 5 mL of peripheral venous blood was drawn using sterile, heparinized vacuum tubes and mixed gently. Each sample was divided into two aliquots: one used for ESR and RF testing, and the other centrifuged at 3000 rpm for 10 minutes to obtain serum, which was stored at -80°C for subsequent measurement of CRP, IL-1β, TNF-α, and IL-6 levels.

ESR was determined using an automated ESR analyzer (Monitor-100, Vital Scientific, Italy) under anticoagulant conditions. RF levels were measured by immunoturbidimetry using commercial kits from Shanghai Gaozong Medical Device Technology Co, Ltd. Concentrations of CRP, IL-1β, TNF-α, and IL-6 were quantified by enzyme-linked immunosorbent assay kits (Shanghai Enzyme-linked Biotechnology Co., Ltd.).

Statistical methods

All statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Data from all 320 elderly patients with RA were included in the full analysis. Microsoft Excel (Microsoft Corp., Redmond, WA, USA) was used for data organization and figure preparation. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Comparisons between groups were conducted using the chi-square test for categorical variables and the independent samples t-test for continuous variables. Repeated-measures analysis of variance was employed to assess longitudinal data across multiple time points, followed by Bonferroni post hoc tests for pairwise comparisons. Multivariate logistic regression analysis was performed to identify independent risk factors associated with treatment failure. A two-sided *P* value <0.05 was considered statistically significant.

Results

Comparison of baseline characteristics between the groups

Baseline characteristics were well balanced between the two groups. No significant differences were observed in demographic variables (age, sex distribution, BMI, disease duration), comorbidities or medication history (hypertension, diabetes, osteoporosis, cardiovascular disease, and recent glucocorticoid use), or baseline clinical parameters (tender joint count, swollen joint count, and duration of morning stiffness) (all P>0.05; **Table 1**).

Comparison of clinical efficacy between the groups

The overall treatment response differed significantly between the two groups. The rate of nonresponse was significantly lower, and the total effective rate was significantly higher in the study group compared with the control group, indicating a superior therapeutic outcome in the study group (both P<0.05; **Table 2**).

Comparison of changes in mobility between the groups

At baseline, no significant differences were observed between the control and study groups

Table 1. Baseline characteristics of elderly patients with RA in the control and study groups

Variable	Control group (n=157)	Study group (n=163)	t/χ^2	P
Age (years)	69.35±5.81	69.85±5.46	0.786	0.432
Sex (male/female)	42/115	47/116	0.173	0.678
BMI (kg/m^2)	23.67±3.09	24.23±3.26	1.576	0.116
Disease duration (years)	7.96±2.51	8.18±2.82	0.766	0.444
Comorbidities and medication history				
Hypertension (yes/no)	49/108	51/112	0.000	0.988
Diabetes (yes/no)	30/127	34/129	0.153	0.696
Osteoporosis (yes/no)	39/118	36/127	0.338	0.561
Cardiovascular disease (yes/no)	27/130	30/133	0.080	0.778
Glucocorticoid use within 3 months (yes/no)	49/108	55/108	0.234	0.629
Tender joint count	12.48±3.55	11.93±3.39	1.405	0.161
Swollen joint count	8.53±2.64	8.28±2.48	0.882	0.378
Morning stiffness duration (min)	59.79±10.12	61.26±12.61	1.157	0.248

Note: Data are presented as mean ± standard deviation or number of cases. P>0.05 indicates no statistically significant difference between the groups. BMI, body mass index; RA, rheumatoid arthritis.

Table 2. Comparison of clinical efficacy between the control and study groups

Treatment outcome	Control group (n=157)	Study group (n=163)	Z/χ^2	P
Significant improvement, n (%)	51 (32.48)	71 (43.56)		
Effective, n (%)	61 (38.85)	66 (40.49)		
Ineffective, n (%)	45 (28.66)	26 (15.95)	2.731	0.006
Total effective rate, n (%)	112 (71.34)	137 (84.05)	7.485	0.006

Note: Data are presented as the number of cases and corresponding percentages. P<0.05 indicates a statistically significant difference between the groups.

in any disease activity indices or clinical measures (all P>0.05). During treatment, both groups demonstrated improvements across all parameters; however, the study group showed significantly greater reductions in disease activity scores and joint assessment measures at 6, 12, and 24 months (all P<0.001; **Table 3**).

Comparison of changes in inflammatory indices between the groups

At baseline, no significant differences were observed between the control and study groups in any of the inflammatory markers (all P>0.05). During treatment, the study group exhibited significantly greater reductions in ESR, CRP, IL-1β, TNF-α, and IL-6 at 6, 12, and 24 months compared with the control group (all P<0.05). In particular, CRP levels were significantly lower in the study group at 12 months (P=0.016). Although RF showed no significant difference between the two groups at 6 months (P>0.05), it was significantly reduced in the study group at 12 months (P=0.028) and 24 months (P<0.001) (**Table 4**).

Comparison of adverse events between the groups

The overall incidence of adverse events did not differ significantly between the two groups (P>0.05). Infection-related events (including upper respiratory tract and other site infections), gastrointestinal disturbances, hepatic dysfunction, hematologic abnormalities (leukopenia and thrombocytopenia), and fatigue were comparable between the two groups (all P>0.05). However, injection-site reactions occurred significantly more frequently in the study group (P=0.002) (**Table 5**).

Univariate analysis of factors associated with treatment nonresponse

Table 6 summarizes the univariate analysis of factors associated with treatment efficacy. A higher swollen joint count, longer duration of morning stiffness, elevated baseline DAS28-ESR, DAS28-CRP, ESR, and CRP, as well as MTX monotherapy or Methotrexate + adalimumab

Table 3. Changes in disease activity and clinical measures at baseline and during follow-up

Variable	Time point	Control group (n=157)	Study group (n=163)	t	P
DAS28-ESR	Baseline	5.48±1.18	5.69±1.10	1.601	0.11
	6 months	4.21±1.14[a]	3.17±0.78[a]	9.458	<0.001
	12 months	3.79±1.05[a,b]	2.75±0.74[a,b]	10.175	<0.001
	24 months	3.64±1.18[a,b]	2.70±0.63[a,b]	8.833	<0.001
	F	67.324	176.255		
	P	<0.001	<0.001		
DAS28-CRP	Baseline	5.37±0.79	5.26±0.90	1.140	0.255
	6 months	4.35±1.00[a]	3.02±0.69[a]	13.828	<0.001
	12 months	3.90±0.91[a,b]	2.71±0.57[a,b]	14.016	<0.001
	24 months	3.72±1.00[a,b]	2.57±0.48[a,b]	12.951	<0.001
	F	74.851	201.62		
	P	<0.001	<0.001		
Tender joint count	Baseline	12.48±3.55	11.93±3.39	1.418	0.157
	6 months	8.45±3.05[a]	6.26±2.44[a]	7.067	<0.001
	12 months	7.23±3.03[a,b]	4.73±2.09[a,b]	8.555	<0.001
	24 months	6.75±3.31[a,b]	3.80±1.74[a,b,c]	9.951	<0.001
	F	78.655	231.41		
	P	<0.001	<0.001		
Swollen joint count	Baseline	8.53±2.64	8.28±2.48	0.882	0.378
	6 months	6.13±2.48[a]	3.94±1.76[a]	9.059	<0.001
	12 months	5.75±2.41[a]	3.29±1.40[a,b]	11.13	<0.001
	24 months	4.69±2.03[a,b,c]	2.39±0.88[a,b,c]	13.073	<0.001
		51.463	150.74		
		<0.001	<0.001		
VAS	Baseline	7.54±1.18	7.30±1.24	1.731	0.084
	6 months	5.23±1.77[a]	4.07±1.37[a]	6.515	<0.001
	12 months	5.08±1.59[a]	3.50±1.16[a,b]	10.159	<0.001
	24 months	4.62±1.61[a,b]	2.81±1.00[a,b,c]	11.996	<0.001
		86.214	194.320		
		<0.001	<0.001		
CDAI	Baseline	31.76±8.44	30.40±10.90	1.252	0.212
	6 months	24.73±8.04[a]	19.65±6.94[a]	6.032	<0.001
	12 months	22.30±7.51[a]	15.00±4.86[a,b]	10.284	<0.001
	24 months	19.33±7.71[a,b,c]	11.94±4.61[a,b,c]	10.359	<0.001
		53.210	97.626		
		<0.001	<0.001		
SDAI	Baseline	37.64±9.66	36.26±10.45	1.226	0.221
	6 months	26.94±9.37[a]	21.40±7.65[a]	5.791	<0.001
	12 months	24.49±8.57[a,b]	15.49±5.84[a,b]	10.932	<0.001
	24 months	19.76±8.56[a,b,c]	13.93±5.77[a,b,c]	7.123	<0.001
		92.643	187.846		
		<0.001	<0.001		

Note: Data are expressed as mean ± standard deviation. DAS28-ESR, Disease Activity Score in 28 joints based on erythrocyte sedimentation rate; DAS28-CRP, based on C-reactive protein; VAS, visual analog scale; CDAI, clinical disease activity index; SDAI, simplified disease activity index. [a]P<0.05 vs. baseline; [b]P<0.05 vs. 6 months; [c]P<0.05 vs. 12 months.

combination therapy, were all significantly associated with treatment nonresponse (all P< 0.01). No significant associations were observed for other variables (all P>0.05).

Table 4. Comparison of inflammatory markers between the control and study groups at baseline during follow-up

Variable	Time point	Control group (n=157)	Study group (n=163)	t	P
ESR (mm/h)	Baseline	40.32±14.47	39.88±14.69	0.273	0.785
	6 months	28.49±12.53[a]	19.90±9.25[a]	6.958	<0.001
	12 months	25.48±12.33[a,b]	14.54±6.74[a,b]	9.798	<0.001
	24 months	21.61±9.61[a,b,c]	9.90±4.43[a,b,c]	13.905	<0.001
		57.483	184.324		
		<0.001	<0.001		
CRP (mg/L)	Baseline	33.94±17.61	32.20±18.47	0.862	0.39
	6 months	28.00±11.84[a]	23.09±10.36[a]	3.939	<0.001
	12 months	22.20±8.15[a,b]	19.89±8.89[a,b]	2.422	0.016
	24 months	16.81±6.07[a,b,c]	12.56±5.49[a,b,c]	6.561	<0.001
		50.346	64.563		
		<0.001	<0.001		
RF (IU/mL)	Baseline	149.15±53.32	146.12±54.63	0.501	0.617
	6 months	133.86±42.74[a]	125.62±43.00[a]	1.72	0.086
	12 months	123.54±42.04[a]	113.72±37.01[a,b]	2.214	0.028
	24 months	115.33±36.99[a,b]	101.92±31.24[a,b,c]	3.497	<0.001
	F	17.689	30.592		
	P	<0.001	<0.001		
IL-1β (pg/mL)	Baseline	12.48±4.49	11.78±4.20	1.444	0.150
	6 months	9.84±3.48[a]	7.87±2.48[a]	5.827	<0.001
	12 months	8.77±3.29[a,b]	6.44±2.30[a,b]	7.311	<0.001
	24 months	8.10±2.77[a,b]	6.10±2.03[a,b]	7.347	<0.001
		36.784	101.357		
		<0.001	<0.001		
TNF-α (pg/mL)	Baseline	19.71±4.93	20.64±4.45	1.774	0.077
	6 months	16.73±4.45[a]	12.89±3.50[a]	8.548	<0.001
	12 months	15.00±3.88[a,b]	10.03±3.49[a,b]	12.036	<0.001
	24 months	12.27±3.83[a,b,c]	8.92±2.77[a,b,c]	8.958	<0.001
		72.620	153.157		
		<0.001	<0.001		
IL-6 (pg/mL)	Baseline	21.95±5.64	21.42±5.87	0.819	0.414
	6 months	15.55±4.53[a]	12.16±4.35[a]	6.815	<0.001
	12 months	14.59±4.24[a]	9.22±3.28[a,b]	12.655	<0.001
	24 months	13.49±4.05[a,b]	9.73±3.40[a,b]	8.981	<0.001
		86.154	164.322		
		<0.001	<0.001		

Note: Data are expressed as mean ± standard deviation (SD). ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; RF, rheumatoid factor; IL-1β, interleukin-1 beta; TNF-α, tumor necrosis factor-alpha; IL-6, interleukin-6. [a]P<0.05 vs. baseline; [b]P<0.05 vs. 6 months; [c]P<0.05 vs. 12 months.

Multivariate analysis of independent risk factors for treatment nonresponse in patients with RA

Table 7 presents the independent predictors of treatment nonresponse identified by multivariate logistic regression analysis. A higher swollen joint count (P=0.008), longer duration of morning stiffness (P=0.001), elevated baseline disease activity (DAS28-ESR and DAS28-CRP, both P<0.001), and higher baseline inflammatory markers (ESR and CRP, both P<0.001) were independently associated with increased odds of treatment nonresponse. The treatment regimen also remained a significant factor (P=0.001), with MTX monotherapy conferring high-

Table 5. Comparison of treatment-emergent adverse events between the control and study groups

Adverse event category	Control group (n=157)	Study group (n=163)	χ^2	P
Overall adverse events	65 (41.40)	82 (55.78)	2.554	0.110
Infection-related				
Upper respiratory tract infection	15 (9.55)	20 (12.27)	0.606	0.437
Other site infections	5 (3.18)	9 (5.52)	1.044	0.307
Non-infection-related				
Injection-site reaction	2 (1.27)	15 (9.20)	9.994	0.002
Gastrointestinal disturbance	20 (12.74)	17 (10.43)	0.417	0.518
Hepatic dysfunction	12 (7.64)	15 (9.20)	0.252	0.616
Hematologic abnormalities				
Leukopenia	3 (1.91)	5 (3.07)	0.439	0.508
Thrombocytopenia	3 (1.91)	2 (1.23)	0.243	0.622
Other				
Fatigue	10 (6.37)	12 (7.36)	0.123	0.726

Note: Data are presented as number of patients (%). P<0.05 indicates a statistically significant difference between the groups.

er risk of nonresponse, whereas combination therapy with ADA significantly reduced that risk.

Receiver operating characteristic curve analysis of independent predictors for treatment nonresponse

Receiver operating characteristic curve analysis was conducted to assess the discriminative performance of each independent predictor for treatment nonresponse (**Figure 1**). Baseline DAS28-CRP exhibited the highest predictive value (area under the curve [AUC]=0.73), followed closely by baseline ESR (AUC=0.73). Baseline DAS28-ESR demonstrated moderate discriminative ability (AUC=0.66), as did baseline CRP (AUC=0.67) and the duration of morning stiffness (AUC=0.65). The swollen joint count and treatment regimen showed relatively lower predictive performance, with AUCs of 0.61 and 0.59, respectively.

Discussion

In elderly patients with RA, the treatment process is often complicated by immune system dysfunction and the presence of chronic comorbidities [15]. Therefore, identifying effective therapeutic strategies, optimizing efficacy, and minimizing treatment-related risks are crucial to improving clinical outcomes and long-term prognosis in this population. The results of our study demonstrated that the combination of ADA with MTX produced significantly better outcomes than MTX monotherapy, with marked improvements in disease activity, joint symptoms, and functional status. These findings provide robust evidence supporting the use of ADA plus MTX combination therapy in elderly patients with RA.

A key finding of this study is that combination therapy with ADA and MTX produced superior treatment responses across multiple efficacy measures compared with MTX monotherapy. At 6, 12, and 24 months of follow-up, patients in the combination group exhibited significant improvements in disease activity scores (DAS28-ESR and DAS28-CRP), joint symptoms (tender and swollen joint counts), functional outcomes (VAS, CDAI, SDAI), and radiographic progression. These results are consistent with the findings of Emery et al. [16], who reported that ADA reduced relapse rates following dose reduction in patients with sustained remission (36% vs. 45%), aligning with the 24-month DAS28 improvements observed in our cohort. Furthermore, previous studies have suggested that ADA modulates the Treg/Th17 immune balance through inhibition of TNF-α signaling, thereby mitigating immunosenescence in elderly RA patients [17]. This mechanism may partially explain the gradual reduction in RF levels observed in this study.

Compared with MTX monotherapy, ADA not only provides superior disease control but also alleviates morning stiffness and joint pain, thereby improving patients' overall quality of life [18, 19]. In the oral rheumatoid arthritis trial, Fleis-

Table 6. Univariate analysis of factors associated with treatment nonresponse

Variable	OR (95% CI)	P
Age (years)	1.013 (0.967-1.061)	0.581
Sex		0.939
Male	1.023 (0.569-1.840)	
Female	0.978 (0.544-1.758)	
BMI (kg/m^2)	1.052 (0.968-1.143)	0.236
Disease duration (years)	1.039 (0.941-1.146)	0.453
Hypertension		0.226
Yes	0.692 (0.381-1.256)	
No	1.446 (0.796-2.625)	
Diabetes mellitus		0.788
Yes	1.093 (0.571-2.094)	
No	0.915 (0.478-1.752)	
Osteoporosis		0.454
Yes	1.259 (0.688-2.303)	
No	0.794 (0.434-1.452)	
Cardiovascular disease history		0.354
Yes	0.705 (0.336-1.477)	
No	1.419 (0.677-2.975)	
Glucocorticoid use within 3 months		0.983
Yes	0.994 (0.566-1.746)	
No	1.006 (0.573-1.767)	
Baseline tender joint count	1.004 (0.931-1.084)	0.913
Baseline swollen joint count	1.178 (1.056-1.314)	0.003
Morning stiffness duration (min)	1.038 (1.014-1.063)	0.002
Baseline DAS28-ESR	1.645 (1.279-2.117)	<0.001
BaselineDAS28-CRP	2.889 (1.994-4.185)	<0.001
Baseline VAS	1.071 (0.859-1.335)	0.543
Baseline CDAI	0.989 (0.962-1.016)	0.414
Baseline SDAI	0.975 (0.950-1.002)	0.066
Baseline ESR (mm/h)	1.066 (1.043-1.090)	<0.001
Baseline CRP (mg/L)	1.034 (1.018-1.050)	<0.001
Treatment modality		0.007
Methotrexate monotherapy	2.117 (1.229-3.646)	
Methotrexate + adalimumab combination	0.472 (0.274-0.813)	

Note: Data were analyzed using univariate logistic regression. OR, odds ratio; CI, confidence interval; BMI, body mass index; DAS28, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CDAI, clinical disease activity index; SDAI, simplified disease activity index; VAS, visual analog scale.

chmann et al. [20] reported that ADA in combination with MTX achieved a higher American College of Rheumatology 50% improvement response rate (46%) compared with either agent alone, supporting our finding that combination therapy significantly reduces the risk of treatment failure (OR=0.296). Furthermore, previous studies [17, 18] have suggested that MTX may enhance the efficacy of biologic agents by suppressing the formation of anti-drug antibodies, which could explain the sustained reduction in inflammatory markers such as TNF-α and IL-6 observed in the combination group of the present study.

Regarding inflammatory markers, patients in the combination therapy group exhibited significant reductions in CRP, ESR, IL-1β, TNF-α, and IL-6 levels following ADA treatment. Notably, CRP and ESR levels were markedly lower in the

Table 7. Multivariate logistic regression analysis of independent predictors for treatment nonresponse

Variable	OR (95% CI)	P
Swollen joint count	1.209 (1.050-1.392)	0.008
Morning stiffness duration (min)	1.054 (1.021-1.088)	0.001
Baseline DAS28-ESR	2.073 (1.461-2.943)	<0.001
Baseline DAS28-CRP	2.568 (1.660-3.972)	<0.001
Baseline ESR (mm/h)	1.082 (1.052-1.113)	<0.001
Baseline CRP (mg/L)	1.039 (1.018-1.061)	<0.001
Treatment modality		0.001
Methotrexate monotherapy	2.117 (1.229-3.646)	
Methotrexate + adalimumab combination	0.296 (0.143-0.614)	

Note: Data were analyzed using multivariate logistic regression. OR, odds ratio; CI, confidence interval; DAS28, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

study group at 12 and 24 months, reflecting effective suppression of systemic inflammation. Smolen et al. [21] reported that baseline DAS28-ESR serves as a strong predictor of the therapeutic response to TNF inhibitors, consistent with our finding that baseline DAS28-CRP was a key predictor of treatment efficacy. Furthermore, previous evidence [17] indicated that elevated baseline CRP levels (>40 mg/L) were associated with an increased risk of ADA treatment failure, emphasizing the predictive value of CRP in assessing therapeutic outcomes.

Although ADA demonstrated strong efficacy in elderly patients with RA, adverse reactions remain an important consideration. In this study, injection site reactions occurred more frequently in the combination therapy group than those in the control group, although the overall incidence of adverse events did not differ significantly between the groups. Jani et al. [17] reported a negative correlation between anti-ADA antibody levels and serum drug concentrations, suggesting that optimizing injection techniques may help local immune responses - findings that align with our observations. Notably, most injection site reactions were transient and did not necessitate treatment discontinuation, consistent with previous literature [16], which also emphasized that rotating injection sites effectively mitigates such reactions.

This study also identified several independent risk factors for treatment failure through univariate and multivariate regression analyses. High baseline DAS28 scores, greater joint swelling, prolonged morning stiffness, and elevated CRP and ESR levels were all significant predictors of poor ADA efficacy. Taylor et al. [22] reported that baricitinib, a Janus kinase inhibitor, achieved a superior American College of Rheumatology 20% improvement response rate compared with ADA, suggesting that biologic agents with alternative mechanisms of action may be more suitable for elderly patients with high baseline disease activity. Furthermore, the non-inferiority of TNF inhibitors and IL-6 inhibitors (e.g., olokizumab) in elderly RA patients has also been demonstrated [23], although their long-term safety profiles require further confirmation.

While this study provides valuable insights into the therapeutic efficacy of ADA in elderly patients with RA, several limitations should be acknowledged. First, the retrospective design may not- fully account for interindividual variability and potential confounding factors. Second, the follow-up duration of 24 months is relatively short, and a more comprehensive evaluation of long-term efficacy and safety is warranted. Future prospective studies should explore the feasibility of ADA dose reduction strategies for maintaining remission, including the potential benefits of extending the dosing interval to every three weeks, which may be more suitable for elderly patients. Moreover, integrating therapeutic drug monitoring with imaging-based assessments may help to further optimize individualized treatment regimens.

In conclusion, the combination of ADA and MTX significantly improves disease activity, allevi-

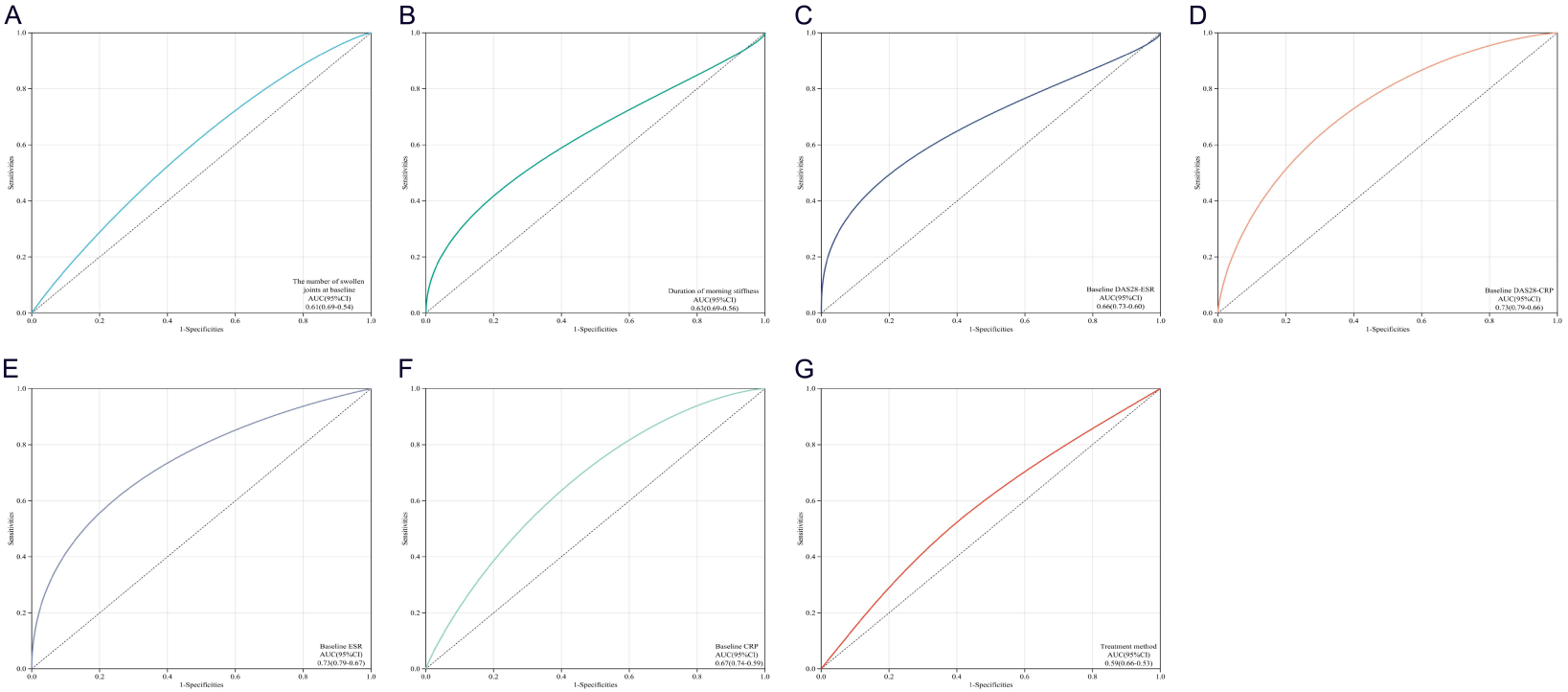

Figure 1. ROC curves for independent predictors of treatment nonresponse. A. Swollen joint count (AUC=0.61, 95% CI: 0.56-0.64); B. Duration of morning stiffness (AUC=0.65, 95% CI: 0.60-0.68); C. Baseline DAS28-ESR (AUC=0.66, 95% CI: 0.63-0.70); D. Baseline DAS28-CRP (AUC=0.73, 95% CI: 0.70-0.76); E. Baseline ESR (AUC=0.73, 95% CI: 0.70-0.67); F. Baseline CRP (AUC=0.67, 95% CI: 0.64-0.69); G. Treatment regimen (AUC=0.59, 95% CI: 0.56-0.63). Note: ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; DAS28-ESR, disease activity score in 28 joints based on erythrocyte sedimentation rate; DAS28-CRP, disease activity score in 28 joints based on C-reactive protein; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

ates joint symptoms, and enhances functional outcomes in elderly patients with RA, demonstrating favorable long-term efficacy and an acceptable safety profile.

Disclosure of conflict of interest

None.

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