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ORIGINAL ARTICLE

Inflammatory and traditional risk factors associated with the progression of chronic kidney disease in patients with rheumatoid arthritis

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Abstract

Background Chronic kidney disease (CKD) is a significant comorbidity in patients with rheumatoid arthritis (RA). The relative contributions of inflammatory and traditional renal risk factors to CKD progression remain unclear.

Methodology We retrospectively analyzed 601 RA patients. Renal function and urinary abnormalities were assessed using creatinine-based estimated glomerular filtration rate (eGFR) and urinary albumin. We examined the factors associated with high or very high CKD risk in KDIGO heatmap and progression of CKD stage over five years using two models: logistic regression and Cox proportional hazards models. Furthermore, Propensity score methods were used to assess the association between methotrexate (MTX) use and CKD stage progression**.**

Results CKD stage progression occurred in 106 patients. Both inflammatory and traditional renal risk factors were associated with high or very high CKD risk. In Cox analyses, age, lower baseline eGFR, anemia, and CRP ≥0.5 mg/dL were associated with CKD stage progression. In patients with baseline eGFR ≥60 mL/min/1.73 m^2, CRP ≥0.5 mg/dL was independently associated with progression, whereas proteinuria and albuminuria were more relevant in patients with baseline eGFR <60 mL/min/1.73 m^2. After adjusting for confounding variables using propensity score matching, there was no association between MTX use and an increased risk of kidney stage progression.

Conclusions Risk factors for CKD progression in RA may differ according to baseline eGFR. In patients with preserved eGFR, residual inflammation appears to be a relevant factor. In contrast, proteinuria, albuminuria, and anemia are more significant in patients with reduced eGFR.

Keywords Rheumatoid arthritis · Chronic kidney disease · Inflammatory factor · Proteinuria

Introduction

Rheumatoid arthritis (RA) is a representative rheumatic disease characterized by positive autoantibodies, such as rheumatoid factor (RF), and anti-cyclic citrullinated peptide (anti-CCP) antibody, leads to joint destruction [1]. However, various organ lesions may appear as extra-articular symptoms [2]. It has long been reported that RA patients are prone to renal impairment, and in the past, secondary amyloidosis was a common RA complication when disease activity could not be adequately controlled [3]. Nevertheless, recent advances in RA treatment have been reported to change clinical presentation of RA-associated conditions [4].

Meanwhile, chronic kidney disease (CKD) is widely recognized in the general population and is significantly associated with cardiovascular events and all-cause mortality [5]. CKD is defined by a decline in estimated glomerular filtration rate (eGFR) and proteinuria [6]. Recently, in RA, CKD comorbidity is becoming more prevalent [7]. In

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previous RA and CKD studies, findings based on eGFR are well documented, but urine protein and urinary albumin quantification are rarely performed [8]. However, proteinuria is closely associated with renal prognosis and cardiovascular events [9], so its assessment is important in RA.

Furthermore, It has also been reported that persistently elevated levels of inflammation are a risk factor for the development of CKD in patients with RA [10]. Treatment strategies for RA may also need to be tailored to each stage of CKD.

In this study, we analyzed our cohort of RA patients to compare the association between eGFR stage progression and various clinical factors, and to assess proteinuria. We also investigated treatment strategies to suppress CKD progression in RA patients.

Materials and methods

Patient inclusion

This retrospective observational study comprises cross-sectional and longitudinal analyses of patients with RA who were treated at the Department of Rheumatology at Kindai University Nara Hospital and the Department of Nephrology/Rheumatology at Hashima Municipal Hospital between April 2021 and March 2025. Patients were included if they met the 1987 American College of Rheumatology (ACR) or the 2010 European League Against Rheumatism (EULAR)/ACR classification criteria for RA. Cases of end-stage renal failure requiring renal replacement therapy, hereditary diseases that could lead to impaired renal function and primary glomerular disease diagnosed by renal biopsy were excluded.

Clinical background factors

Clinical background factors, such as age at the time of renal function assessment, sex and duration of RA, were tabulated. In addition, the following immunological findings were measured: RF, ACPA, C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR). To assess RA disease activity, we calculated the Disease Activity Score (DAS) 28-ESR and Clinical Disease Activity Index (CDAI) scores. CRP, ESR, hemoglobin, DAS28-ESR, and CDAI were assessed at least annually during the observation period, and the median values of available measurements were used for analysis. Furthermore, we analyzed factors associated with CKD, including hypertension, type 2 diabetes and dyslipidemia (confirmed by a history of medication use for at least six months), alongside hemoglobin (Hb) levels, current smoking status and Body Mass Index (BMI). The use of medications, including MTX, was assessed as treatment exposure at the conclusion of the follow-up period, as appropriate. To assess changes in MTX exposure during follow-up, MTX use was additionally classified into four patterns according to MTX use at baseline eGFR assessment and at the end of follow-up: continued use, discontinuation, initiation and continued non-use.

Assessment of renal function

Renal function was assessed by measuring serum creatinine (Cr), serum cystatin C (Cys-C) and calculating estimated glomerular filtration rates (eGFR Cr and eGFR Cys-C) using the Japanese Society of Nephrology's formulae based on these values [11, 12]. Furthermore, changes in renal function were observed by looking back five years from the time of assessment in the longitudinal study, and the presence or absence of progression in CKD stage was examined. Progression of CKD stage was defined as deterioration of at least one stage based on eGFR Cr within the past five years, confirmed on at least two consecutive occasions without subsequent recovery to the original stage. Analyses were performed in cases with at least two years of data on renal function trends based on eGFR Cr. The frequency and interval of serum creatinine measurements were also calculated.

Assessment of urinary protein

Urinary protein was quantified using a colorimetric method and urinary albumin using an immunoturbidimetric method. The urinary protein-to-creatinine ratio (UPCR) (g/g creatinine) and the urinary albumin-to-creatinine ratio (UACR) (mg/g creatinine) were calculated from the creatinine measured simultaneously in the urine. Qualitative assessment of urinary protein was also performed using the dipstick method.

To minimize the impact of transient urine findings, UPCR and UACR were measured at least three times during the observation period, and the median value was used for analysis to reduce the influence of transient urinary abnormalities. Furthermore, agreement between the dipstick method and UPCR/UACR was evaluated for all cases. In accordance with the CKD Clinical Practice Guide 2024, UACR was classified as follows: A1 (<30 mg/g Cr), A2 (30–299 mg/g Cr) and A3 (≥300 mg/g Cr). For UPCR, the classification was as follows: <0.15 g/g Cr and ≥0.5 g/g Cr. Dipstick method results were categorized as negative, trace, or ≥1(+).

Classification of CKD and clinical comparisons were made between the high- or very high-risk groups and the other groups in the chronic kidney disease heatmap

CKD risk was classified using eGFR Cr and UACR, comparisons were made on the KDIGO CKD heatmap [6] between groups classified as G3b or higher, G3a and A2 or higher, or A3 or higher — that is, those in the 'high risk' or 'very high risk' categories — and the remaining groups, with regard to clinical background. Furthermore, logistic regression analyses were performed to identify factors associated with RA disease activity that are independent of traditional renal risk factors. The cut-off values for CRP were set at 0.15 mg/dL (the upper limit of normal in our hospital laboratory) and 0.5 mg/dL (corresponding to the upper quartile of the data in this study).

Factors associated with progression of CKD Stage

Furthermore, we compared the following factors between the group that progressed by one or more CKD stages within 5 years and the group that did not. Furthermore, a Cox proportional hazards model was constructed to calculate the respective risk coefficients. UPCR and UACR were entered separately, considering potential confounding factors, and UPCR and UACR models were calculated separately. Furthermore, analyses were performed separately for two stages: baseline eGFR $\geq$ 60 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2. In these Cox proportional hazards models, clinically significant covariates were selected for use in the analysis. In a subsequent subgroup analysis, which was based on a limited case number, the number of covariates was restricted in order to avoid overfitting.

Analysis of the association between MTX administration and progression of CKD stage

The association between MTX administration and progression of CKD stage was examined in all patients and in those with a baseline eGFR of $\geq$60 mL/min/1.73 m^2. Furthermore, propensity scores were calculated using logistic regression analysis incorporating covariates related to MTX administration. As the primary analysis, we used inverse probability of treatment weighting (IPTW), and propensity score matching (PSM) was performed as a sensitivity analysis. We confirmed that the clinical backgrounds were well balanced, with a standardized mean difference (SMD) <0.1.

Statistical analysis

Continuous variables were summarized as the median (interquartile range) and categorical variables as the number (proportion). For comparisons between groups, we used the Mann–Whitney U test for continuous variables and the chi-squared test or Fisher's exact test for categorical variables, as appropriate.

The results of the logistic regression analysis are presented as odds ratios and 95% confidence intervals, and the results of the Cox proportional hazards model are presented as hazard ratios and 95% confidence intervals. A complete case analysis was performed, and missing data were not imputed. P-values were calculated to compare the clinical characteristics of patients, with a two-sided p-value of less than 0.05 being considered statistically significant. Model assumptions were verified by visual inspection of residual plots. All results were analyzed using EZR [13] (version 1.70, Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R software (The R Foundation for Statistical Computing, Vienna, Austria) and IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA).

Results

Of the 748 cases included, one case was excluded as the patient was already undergoing peritoneal dialysis; two cases were excluded as the patients had been diagnosed with autosomal dominant polycystic kidney disease; and three cases were excluded as the patients had been diagnosed with primary glomerular disease following renal biopsy. Furthermore, 141 cases were excluded due to insufficient data, such as an incomplete clinical background or insufficient follow-up. This left 601 cases for analysis. During the clinical observation period, seven patients progressed to end-stage renal failure and commenced renal replacement therapy. The cohort was predominantly female and elderly, with a median disease duration of eight years. Table 1 summarizes baseline renal function, urinary findings, RA-related variables, and comorbidities.

Supplementary Figure S1 shows the agreement rates for UACR, UPCR and qualitative urine protein testing based on the measurement method. The highest UPCR agreement rate was observed in Group A1, although 12% of dipstick results were discordant. In Group A2, 40% of dipstick results and 30% of UPCR results were discordant. In Group A3, the agreement rates were nearly equivalent. In Groups A1 and A2, the semi-quantitative dipstick method exhibited lower agreement rates compared to UPCR. Regarding the association between UPCR and UACR classification and CKD

Table 1 Patient characteristics

Variables	Overall $n = 601$
Age (years) (median [IQR])	71 (60–78)
Sex (Female), n (%)	443 (73.7%)
Disease duration (years) (median [IQR])	8 (3–16)
ACPA positive (%)	433 (72.0%)
ACPA titer IU/mL (median [IQR])	52.9 (2.0–276.4)
RF positive, n (%)	461 (76.7%)
RF titer IU/mL (median [IQR])	56 (17–155.5)
ESR (mm/h) (median [IQR])	19 (9–33.75)
CRP (mg/dL) (median [IQR])	0.13 (0.04–0.37)
Hb (g/dL) (median [IQR])	12.8 (11.8–13.6)
Pt VAS-GH (mm) (median [IQR])	20 (7–41)
Ph VAS-GH (mm) (median [IQR])	15 (5–30)
DAS 28-ESR (median [IQR])	2.38 (1.74–2.98)
DAS 28-ESR remission, n (%)	483 (81.2%)
CDAI (median [IQR])	4.0 (1.42–7.77)
CDAI remission, n (%)	232 (38.7%)
MTX use, n (%)	281 (46.8%)
MTX dose (mg/week) (median [IQR])	0 (0–8)
b/tsDMARDs use, n (%)	328 (54.6%)
TNFi/IL-6Ri/ABT/JAKi, n (%)	103 (17.1)/76 (12.6)/57 (9.5)/92 (15.3)
GC use, n (%)	58 (9.7%)
NSAIDs use, n (%)	108 (18.0%)
Serum Creatinine (mg/dL)	0.7 (0.6–0.85)
eGFR Creatinine (mL/min/1.73m^2)	67.7 (55.4–80.3)
eGFR Creatinine <60 (mL/min/1.73m^2)	185 (30.8%)
Serum Cystatin C (mg/L)	1.01 (0.84–1.23)
eGFR Cystatin C (mL/min/1.73m^2)	67.1 (51.4–81.3)
eGFR Cystatin C <60 (mL/min/1.73m^2)	229 (38.1%)
Urinary Protein/Creatinine ratio (g/g creatinine)	0.11 (0.11–0.11)
Previous eGFR Creatinine (mL/min/1.73m^2)	72 (63–83.1)
Urinary Protein ≥0.15 g/g creatinine n (%)	89 (14.8%)
Urinary Albumin/Creatine ratio (mg/g creatinine)	18.0 (12.5–18.0)
Urinary Albumin≥30 mg/g creatinine, n (%)	94 (15.6%)
Type 2 diabetes, n (%)	56 (9.3%)
Hypertension, n (%)	237 (39.4%)
Dyslipidemia, n (%)	132 (22.0%)
Body Mass Index ≥25, n (%)	89 (14.8%)
Smoking, n (%)	47 (7.8%)

ACPA anti-cyclic citrullinated peptide antibodies; *b/ts DMARDs* biological/targeted synthesized Disease Modifying Anti Rheumatic Drugs; *CDAI* clinical disease activity index; *CRP* C-reactive protein; *DAS28-ESR* disease activity score 28-joint count using ESR; *eGFR* estimated glomerular filtration rate; *ESR* erythrocyte sedimentation rate; *GC* glucocorticoid; *IQR* interquartile range; *MTX* Methotrexate; *NSAIDs* non-steroidal anti-inflammatory drugs; *Pt VAS-GH* patient's visual analogue scale assessing global health; *Ph VAS-GH* physician's visual analogue scale assessing global health; *RF* rheumatoid IgM factor; *TNFi* anti-tumor necrosis factor-alpha inhibitor; *IL-6Ri* interleukin- 6 receptor inhibitor; *ABT* abatacept; *JAKi* Janus Kinase inhibitor; Numbers are median; *p*-Values were calculated to compare patient's clinical background with several DMARDs were determined using Mann–Whitney test of Fisher's exact test

stage progression, UPCR positivity was associated with a higher risk; however, a stepwise increase, as seen with UACR, was not evident. (See Supplementary Figure S2.)

Table 2 shows a comparison of the clinical characteristics of the high- or very high-risk groups and the other groups within the CKD severity classification. The high- or very high-risk group was characterized by older age, longer disease duration, higher CRP levels, lower Hb and lower baseline eGFR, hypertension, type 2 diabetes and dyslipidemia were also more prevalent in this group. Additionally, logistic regression analysis indicated that, in the clinical background of the high- or very high-risk group, only CRP ≥0.5 mg/dL was associated with RA disease activity (Table 3). Other factors did not constitute independent risk factors.

Table 4 shows a comparison of the clinical background between the CKD Group G progression group and the non-progression group. The progression group showed trends similar to those observed in the CKD risk classification analysis. Furthermore, strong correlations were observed between urinary protein and both UACR and UPCR. The median change in eGFR was −12 mL/min/1.73 m^2 in patients with CKD stage progression and −3 mL/min/1.73 m^2 in those without progression. The frequency and interval of serum creatinine measurements are shown in Supplementary Table S1.

The results of the Cox regression hazard analysis regarding progression to CKD Group G are presented in Table 5 for all cases, while Table 6 shows the results of the analysis stratified into two groups based on an eGFR of 60 ml/min/1.73 m^2. The analysis of all cases identified age, baseline eGFR, Hb levels and CRP ≥0.5 mg/dL as independent risk factors, while positive UPCR and UACR or CDAI remission did not reach statistical significance. The subgroup analysis of patients with eGFR ≥60 ml/min/1.73 m^2 showed finding consistent with the analysis of the overall cohort. However, in the analysis of cases with eGFR <60 ml/min/1.73 m^2, CRP ≥0.5 mg/dL was not a significant independent risk factor. Instead, positive urine protein was identified as an independent risk factor, and the risk associated with UACR was found to be greater than that associated with UPCR. In these cases, Hb levels remained a significant independent risk factor. Furthermore, propensity score-weighted survival curves showing the effect of MTX administration on the progression of CKD stage are presented in Figs. 1 and 2.

In patients with an eGFR of ≥60 mL/min/1.73 m^2, the MTX group showed a tendency towards less progression of CKD stage compared with all cases. However, as shown in Table 7, the difference between the two groups was not statistically significant in either the propensity score matching analysis or the inverse probability weighting analysis. The

Table 2 Comparison of the clinical background of patients with CKD category between Green or Yellow and Orange or Red

Variables	CKD low risk and moderately increased risk *(n*=512)	CKD high risk and very high risk (*n*=89)	*p*-Value
Age (years) (median [IQR])	70 (58–77)	79 (73–83)	<0.001
Sex (male), n (%)	132 (25.8%)	26 (29.2%)	0.515
Disease duration (years) (median [IQR])	8 (3.0–15.0)	10 (4.0–20)	0.032
ACPA positive, n (%)	363 (70.9%)	70 (78.7%)	0.159
ACPA titer (IU/mL) (median [IQR])	53.25 (1.8–277)	51.5 (10.3–213.3)	0.652
RF positive, n (%)	388 (75.8%)	73 (82.0%)	0.223
RF titer (IU/mL) (median [IQR])	55 (16–145.5)	80 (23–177)	0.156
Baseline eGFR Creatinine (mL/min/1.73m^2) (median [IQR])	75.0 (66.0–86.0)	51.0 (42.0–59.0)	<0.001
eGFR Creatinine (mL/min/1.73m^2) (median [IQR])	71 (62–82.43)	41.5 (35–48.6)	<0.001
eGFR Cystatin C (mL/min/1.73m^2) (median [IQR])	70.8 (57.48–84.6)	37.7 (29.9–49.2)	<0.001
CRP (mg/dL) (median [IQR])	0.11 (0.04–0.31)	0.22 (0.07–0.60)	0.001
ESR (mm/h) (median [IQR])	18 (8–30)	31 (18.25–55)	<0.001
Hb (g/dL) (median [IQR])	12.9 (12.1–13.7)	11.6 (10.5–12.8)	<0.001
DAS 28-ESR (median [IQR])	2.31 (1.69–2.9)	2.83 (2.13–3.46)	0.001
DAS 28-ESR remission	324 (63.8)	36 (41.4)	<0.001
CDAI (median [IQR])	3.9 (1.3–7.5)	5.25 (2.28–9.7)	0.027
CDAI remission	211 (41.3%)	25 (28.4%)	0.025
MTX use, n (%)	266 (52.0%)	15 (16.9%)	<0.001
b/tsDMARDs use, n (%)	277(54.1%)	51(57.3%)	0.645
TNFi/IL-6Ri/ABT/JAKi	235 (45.9)/97 (18.9%)/67 (13.1%)/43 (8.4%)/70 (13.7%)	38 (42.7%)/6 (6.7%)/9 (10.1%)/14 (15.7%)/22 (24.7%)	0.001
GC use, n (%)	42 (8.2%)	16 (18.0%)	0.01
NSAIDS use, n (%)	91 (17.8%)	17 (19.1%)	0.765
Type 2 Diabetes Mellitus, n (%)	41 (8.0%)	15 (16.9%)	0.016
Hypertension, n (%)	179 (35.0%)	58 (65.2%)	<0.001
Dyslipidemia, n (%)	101 (19.7%)	31 (34.8%)	0.002
Body Mass Index ≥25, n (%)	94 (18.4%)	11 (12.4%)	0.225
Smoking, n (%)	40 (7.8%)	7 (7.9%)	1.00

ACPA anti-cyclic citrullinated peptide antibodies; *b/tsDMARDs* biological targeted synthesized disease modifying antirheumatic drugs; *CDAI* clinical disease activity index; *CRP* C-reactive protein; *DAS28-ESR* disease activity score 28-joint count using CRP; *eGFR* estimated glomerular filtration rate; *ESR* erythrocyte sedimentation rate; *GC* glucocorticoid; *IQR* interquartile range; *MTX* methotrexate; *NSAIDs* non-steroidal anti-inflammatory drugs; *RF* rheumatoid IgM factor; *TNFi* anti-tumor necrosis factor-alpha inhibitor; *IL-6Ri* interleukin- 6 receptor inhibitor; *ABT* abatacept; *JAKi* Janus Kinese inhibitor; *p*-Values were calculated to compare patients with CKD category green and yellow or orange and red using Mann-Whitney test of Fisher's exact test

Table 3 Effect of predictive factors on CKD high risk and very high-risk group logistic regression multivariate models

	Odds ratio (*95% CI*)	*p*-value
ACPA positive	1.8 (0.855–3.81)	0.121
RF positive	1.22 (0.545–2.72)	0.632
CRP≥0.15	1.77 (0.916–3.43)	0.089
CRP≥0.5	1.98 (1.13–3.47)	0.0171
DAS28-ESR remission	1.29 (0.669–2.48)	0.45
CDAI remission	0.956 (0.49–1.86)	0.894

Results were obtained from multivariate linear regression models with adjusting traditional renal predictive factors, age sex, HTN, NIDDM, DL, BMI≥25

changes in MTX use during follow-up are shown in Supplementary Table S2.

Discussion

The present study demonstrated that factors associated with CKD progression in RA differed according to baseline renal function.

In Japan, it is difficult to perform urinary albumin quantification on all patients due to health insurance coverage issues [14]. However, the prevalence of CKD in RA patients is significantly higher than in the general population [15]. In our study of RA patients, discrepancies were observed between the proteinuria stage determined by UACR and the

Table 4 Comparison of the clinical background of patients with eGFR G progressed or not progressed

Variables	eGFR G not progressed (*n=495*)	eGFR G progressed (*n*=106)	*p*-Value
Age (years) (median [IQR])	69 (57–76.5)	77.5 (72–81.75)	<0.001
Sex (male), n (%)	129 (26.1%)	29 (27.4%)	0.808
Disease duration (years) (median [IQR])	7 (3–15)	12 (5–20)	<0.001
ACPA positive, n (%)	348 (70.3%)	85 (80.2%)	0.043
ACPA titer (IU/mL) (median [IQR])	51.5 (1.1–276.7)	53.25 (10.15–243.75.3)	0.499
RF positive, n (%)	375 (75.8%)	86 (81.1%)	0.257
RF titer (IU/mL) (median [IQR])	51 (16–143.5)	81 (25–165.75)	0.053
Baseline eGFR Creatinine (mL/min/1.73m^2) (median [IQR])	75 (66.0–86.5)	62 (54–66)	<0.001
eGFR Creatinine (mL/min/1.73m^2) (median [IQR])	71.9 (63.1–83.45)	48.45 (41.58–54.92)	<0.001
eGFR Cystatin C (mL/min/1.73m^2) (median [IQR])	70.9 (56.8–85.35)	47.85 (37.32–59.58)	<0.001
Baseline eGFR Creatinine − GFR Creatinine (mL/min/1.73m^2) (median [IQR])	3.0 (−0.7–8.0)	12.0 (9.13–16.98)	<0.001
CRP (mg/dL) (median [IQR])	0.12 (0.04–0.32)	0.17 (0.04–0.62)	0.127
CRP≥0.5 mg/dL, n (%)	84 (17)	29 (27.4)	0.019
ESR (mm/h) (median [IQR])	18 (7–29)	30 (15.75–48)	<0.001
Hb (g/dL) (median [IQR])	12.9 (12.1–13.7)	11.85 (10.8–12.8)	<0.001
Hb≥11 g/dL, n (%)	447 (90.3%)	75 (70.8%)	<0.001
DAS 28-ESR (median [IQR])	2.31 (1.67–2.9)	2.83 (2.17–3.47)	<0.001
DAS 28-ESR remission, n (%)	314 (64.1)	46 (43.8)	<0.001
CDAI (median [IQR])	3.9 (1.4–7.5)	6 (1.87–9.53)	0.014
CDAI remission, n (%)	201 (40.6%)	35 (33.7%)	0.225
MTX use, n (%)	253 (51.1%)	28 (26.4%)	<0.001
Urinary Protein/Creatinine ratio (g/g creatinine)	0.11 (0.10–0.11)	0.11 (0.11–0.16)	<0.001
Urinary Protein≥0.15 g/g creatinine n (%)	57 (11.5)	32 (30.2)	<0.001
Urinary Protein≥0.5 g/g creatinine n (%)	21 (4.2)	12 (11.3)	0.008
Urinary Albumin/Creatine ratio (mg/g creatinine)	18 (12.5–18)	18 (15–40.08)	<0.001
Urinary Albumin≥30 mg/g creatinine, n (%)	58 (11.7)	38 (34.0)	<0.001
Urinary Albumin≥300 mg/g creatinine, n (%)	15 (3.0)	14 (13.2)	<0.001
b/tsDMARDs use, n (%)	269 (54.3%)	59 (55.7%)	0.830
TNFi/IL-6Ri/ABT/JAKi, n (%)	93 (18.8%)/67 (13.5%)/42 (8.5%)/67 (13.5%)	10 (9.4%)/9 (8.5%)/15 (14.2%)/25 (23.6%)/	0.005
GC use, n (%)	41 (8.3%)	17 (16.0%)	0.019
NSAIDS use, n (%)	84 (17.0%)	24 (22.6%)	0.166
Type 2 Diabetes Mellitus, n (%)	43 (8.7%)	13 (12.3%)	0.269
Hypertension, n (%)	178 (36.0%)	59 (55.7%)	<0.001
Dyslipidemia, n (%)	91 (18.4%)	41 (38.7%)	<0.001
Body Mass Index ≥25, n (%)	87 (17.6%)	18 (17.0%)	1.000
Smoking, n (%)	37 (7.5%)	10 (9.4%)	0.549

ACPA anti-cyclic citrullinated peptide antibodies; *b/tsDMARDs* biological targeted synthesized disease modifying antirheumatic drugs; *CDAI* clinical disease activity index; *CRP* C-reactive protein; *DAS28-ESR* disease activity score 28-joint count using CRP; *eGFR* estimated glomerular filtration rate; *ESR* erythrocyte sedimentation rate; *GC* glucocorticoid; *IQR* interquartile range; *MTX* methotrexate; *NSAIDs* non-steroidal anti-inflammatory drugs; *RF* rheumatoid IgM factor; *TNFi* anti-tumor necrosis factor-alpha inhibitor; *IL-6Ri* interleukin- 6 receptor inhibitor; *ABT* abatacept; *JAKi* Janus Kinese inhibitor; *p*-Values were calculated to compare patients with eGFR progressive or not progressive in CKD grade G using student t test for continuous value and Mann–Whitney test of Fisher's exact test for categorized value

dipstick method, particularly in stages A1 and A2. Discrepancies were also observed between the UACR and UPCR methods in stage A2. Similar issues regarding discrepancies in the assessment of proteinuria have been reported previously in patients without RA [16]. Although this was a univariate analysis, UACR was superior to UPCR in predicting CKD stage progression. The current KDIGO classification of CKD is based on urinary albumin, and it is well established that albumin quantification is more useful than urine protein quantification for predicting CKD progression and cardiovascular events [9, 17, 18]. Furthermore, it has recently been reported that even extremely low levels of UACR are

Table 5 Effect of predictive factors on CKD progression on Cox hazard multivariate models in all cases

	Coefficient (*95% CI*)	*p*-value
UPCR model		
Age	1.033 (1.003–1.065)	0.034
Sex (Male)	0.678 (0.363–1.266)	0.223
HTN	1.385 (0.807–2.376)	0.237
NIDDM	1.047 (0.458–2.340)	0.913
BMI≥25	0.954 (0.488–1.864)	0.890
Baseline eGFR	0.839 (0.796–0.885)	<0.0001
Hb (g/dL)	0.782 (0.646–0.946)	0.011
UPCR≥0.15 g/g creatinine	1.830 (0.984–3.400)	0.056
CRP≥ 0.5 mg/dL	2.027 (1.09–3.77)	0.026
CDAI remission	0.832 (0.485–1.430)	0.506
UACR model		
Age	1.032 (1.001–1.063)	0.041
Sex (Male)	0.706 (0.382–1.305)	0.266
HTN	1.408 (0.821–2.416)	0.214
NIDDM	1.021 (0.447–2.334)	0.960
BMI≥25	0.953 (0.487–1.865)	0.889
Baseline eGFR	0.840 (0.800–0.886)	<0.0001
Hb (g/dL)	0.776 (0.642–0.939)	0.009
UACR≥30 mg/g creatinine	1.65 (0.890–3.061)	0.0892
CRP≥ 0.5 mg/dL	2.014 (1.083–3.748)	0.027
CDAI remission	0.845 (0.491–1.454)	0.544

Results were obtained from multivariate Cox hazard models adjusted with traditional renal predictive factors, age, sex, HTN, NIDDM, BMI ≥25, Baseline eGFR, Hb, UPCR, UACR and inflammatory factors, CRP≧ 0.5 mg/dL CDAI remission, respectively

Table 6 Effect of background clinical factors on CKD progression on COX hazard multivariate models between eGFR≥60 and <60 mL/min/1.73m^2

	Coefficient (*95% CI*)	*p*-value
eGFR≥60 mL/min/1.73m^2		
UPCR model		
Age	1.032 (1.003–1.063)	0.032
Baseline eGFR	0.844 (0.801–0.889)	<0.0001
Hb (g/dL)	0.766 (0.640–0.916)	0.0036
UPCR≥0.15 g/g creatinine	1.693 (0.940–3.073)	0.084
CRP≥ 0.5 mg/dL	1.99 (1.12–3.540)	0.019
UACR model		
Age	1.031(1.002–1.062)	0.037
Baseline eGFR	0.844 (0.801–0.888)	<0.0001
Hb (g/dL)	0.763 (0.648–0.913)	0.0032
UACR≥30 mg/g creatinine	1.559 (0.856–2.840)	0.146
CRP≥0.5 mg/dL	1.998 (1.122–3.560)	0.018
eGFR<60 mL/min/1.73m^2		
UPCR model		
Age	0.963 (0.925–1.003)	0.071
Baseline eGFR	0.981 (0.950–1.014)	0.258
Hb (g/dL)	0.690 (0.541–0.881)	0.0029
UPCR≥0.15 g/g creatinine	2.417 (1.085–5.382)	0.031
CRP≥ 0.5 mg/dL	0.788 (0.377–1.649)	0.528
UACR model		
Age	0.954 (0.914–0.997)	0.034
Baseline eGFR	0.985 (0.955–1.017)	0.365
Hb (g/dL)	0.686 (0.537–0.876)	0.0025
UACR≥30 mg/g creatinine	3.715 (1.704–8.098)	<0.0001
CRP≥ 0.5 mg/dL	0.769 (0.356–1.616)	0.488

Results were obtained from multivariate Cox hazard models adjusted with age, Baseline GFR, Hb, UPCR or UACR, CRP ≥0.5 mg/dL

strongly associated with the prognosis of RA patients [19]. In future RA management, the objectives are anticipated to extend beyond merely suppressing RA disease activity to include preventing organ complications and cardiovascular events in the long term. In particular, measuring UACR may be useful for various risk assessments in cases of reduced eGFR [20].

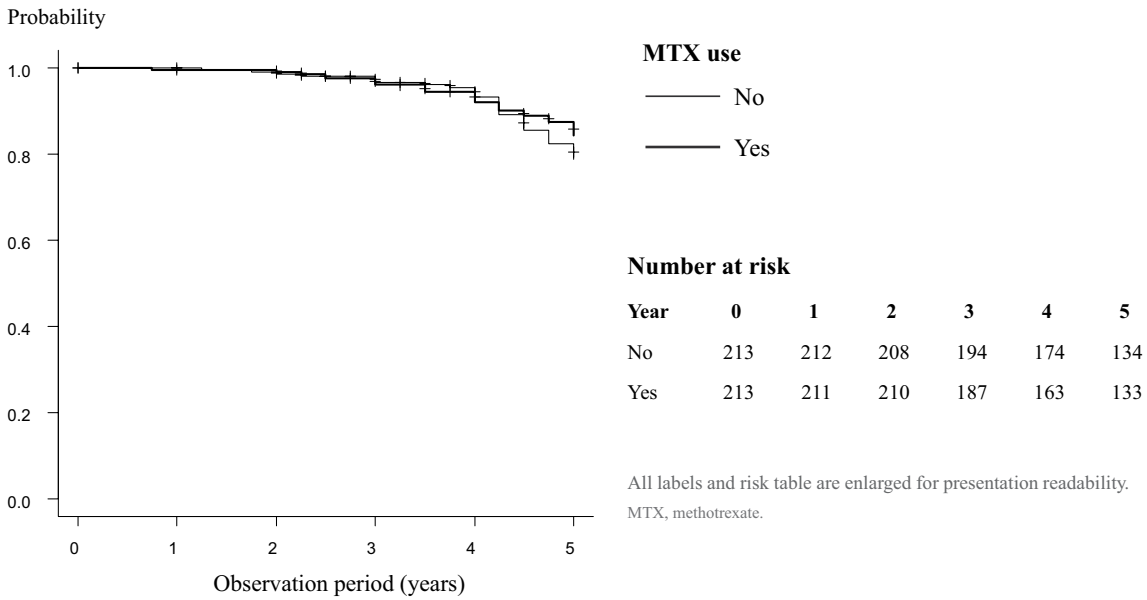


Fig. 1 CKD G progression of Propensity score-weighted survival curves according to MTX use

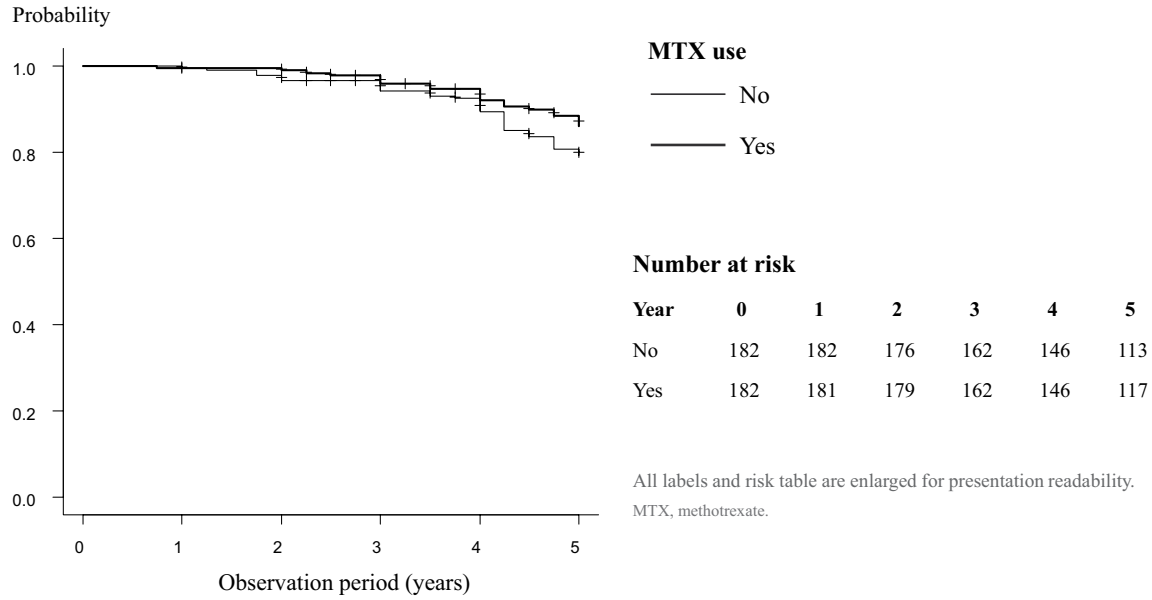


Fig. 2 CKD G progression of Propensity score-weighted survival curves according to MTX use (Baseline eGFR≥60 mL/min/1.73 m^2)

Table 7 MTX on CKD progression analyzed with COX hazard multivariate survival model adjusted propensity score matching (PSM) and inverse probability weighting (IPTW)

	Hazard ratio (*95% CI*)	*p*-value
MTX use (PSM) (all cases)	0.7791 (0.473–1.283)	0.3268
MTX use (IPTM) (all cases)	0.8474 (0.5396–1.331)	0.4721
MTX use (PSM) (Baseline eGFR≥60 mL/min/1.73m^2)	0.655 (0.3777–1.136)	0.1319
MTX use (IPTW) (Baseline eGFR≥60 mL/min/1.73m^2)	0.7126 (0.4295–1.182)	0.1897

CKD progression between MTX user or not user with propensity score matching and IPTW COX hazard multivariate models adjusted with age, sex, HTN, NIDDM, BMI≥25, Baseline eGFR, Hb, UPCR, ACPA, RF, GC use, CRP≥0.5 mg/dL, CDAI. Each clinical background factors SMD were confirmed below 0.1

Regarding reduced eGFR, i.e. progression of CKD stage, our study identified CRP ≥0.5 mg/dL as a risk factor, as mentioned earlier. Elevated CRP levels have already been reported [21]. However, a subgroup analysis for eGFR <60 in this study revealed no significant association between elevated CRP and progression of CKD stage. Although the small sample size may have been a limiting factor, the association between CKD progression and elevated CRP was not evident in cases where eGFR was already reduced. Ausserwinkler et al. suggested that the association between RA and CKD is primarily due to metabolic comorbidities [15]. As for the reasons for the differences from our results, variations in inflammatory parameters, the frequency of proteinuria measurements, and unknown clinical background factors—such as disease severity and treatment exposure—may have contributed to these differences. Therefore, the contribution of inflammation should be interpreted as potentially varying depending on the definition of baseline renal function and renal outcomes.

Our study demonstrated that low Hb is strongly associated with the progression of CKD. It is already widely recognized that anemia is a major risk factor for the progression of CKD [22]. Even in cases where eGFR is only slightly reduced, renal anemia may be present [23]. Therefore, close attention must be paid to erythropoietin deficiency and iron metabolism.

In rheumatoid arthritis (RA) patients whose renal function has not deteriorated, methotrexate (MTX) should be the first-line disease-modifying antirheumatic drug (DMARD) of choice [24]. MTX is the anchor drug for RA treatment; it is expected to suppress the production of inflammatory cytokines, including interleukin-6 (IL-6), and lymphocyte function [25], thereby leading to low CRP levels [26]. Regarding the association between methotrexate (MTX) and chronic kidney disease (CKD), some reports suggest that it inhibits CKD progression [27], while others indicate that high-dose administration leads to a decline in estimated glomerular filtration rate (eGFR) [28]. The findings of this study indicated an absence of correlation between the administration of MTX and the progression of CKD. Despite the inability to analyze the MTX dosage, or its effect on proteinuria, the findings indicate that, when administered appropriately regardless of baseline eGFR, MTX is not a major cause of renal function decline. However, the interpretation of MTX use requires caution because MTX exposure changed during follow-up in some patients and may have been influenced by renal function and clinical judgment. Therefore, the use of MTX at the conclusion of follow-up should not be interpreted as a fixed baseline exposure, and the propensity

score analysis of MTX use should be considered exploratory rather than causal. On the other hand, as UACR and UPCR were significantly associated with CKD progression in the group with an eGFR of less than 60 ml/min/1.73 m^2, it is considered particularly important in these groups not only to suppress RA disease activity, but also to screen for concomitant primary renal disease and consult a nephrologist. Efforts should also be made to reduce urinary protein, for example through intensified antihypertensive therapy and strategies to inhibit the renin–angiotensin–aldosterone system [29].

Our study has several limitations. First, its retrospective design precludes causal inference. Second, the study did not thoroughly evaluate changes in CRP, proteinuria, albuminuria, and treatments over time. DAS28-ESR, CDAI and CRP strictly time-averaged or cumulative disease activity could not be evaluated. Third, detailed information on antihypertensive, antidiabetic, and lipid-lowering therapies was unavailable. The number of patients with baseline eGFR <60 mL/min/1.73 m^2 was limited. Fourth, eGFR based on creatinine has the potential to overestimate renal function in patients with RA. This study evaluated the progression of CKD using eGFR based on creatinine, which may result in an inaccurate estimation of renal function. Finally, it is important to note that selection bias related to UACR measurement, and the possibility of unrecognized kidney disease cannot be excluded.

Conclusion

This study suggests that factors associated with CKD progression in RA patients may differ depending on baseline eGFR. In the group with a baseline eGFR of ≥60 mL/min/1.73 m^2, elevated C-reactive protein (CRP) levels were associated with progression to a higher CKD stage. In the group with a baseline eGFR of <60 mL/min/1.73 m^2, Hb, and proteinuria were strongly associated with progression. These results suggest that, while assessing residual inflammation is important in the earlier stages of RA, cases of impaired renal function require a focus on assessing and managing classical chronic kidney disease prognostic factors such as urinary protein, urinary albumin, anemia, and hypertension.

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Author contributions MS conceived and designed the study, collected the data, performed the statistical analysis, interpreted the results and wrote the first draft of the manuscript. SM, TT, ST and CM contributed to the collection of data and the verification of clinical information. KK contributed to the statistical analysis and interpretation of the results. SR supervised the study. All authors critically revised the manuscript for important intellectual content, reviewed it, and approved the final version.

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Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval This study was conducted in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Review Committee of Kindai University Nara Hospital (No.833). As this was a retrospective observational study, the Ethics Review Committee waived the requirement for obtaining individual written consent.

Consent to participate in the study As this is a retrospective observational study, the Ethics Review Committee waived the requirement to obtain individual written consent.

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