

Elevation of Serum Immunoglobulin Free Light Chains During the Preclinical Period of Rheumatoid Arthritis

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ABSTRACT. Objective. Immunoglobulin free light chains (FLC) represent biomarkers of B cell activity in rheumatoid arthritis (RA) and are associated with all-cause mortality in the general population. Our objective was to evaluate the relationships of serum FLC to preclinical disease, RA characteristics, and mortality in RA compared to non-RA subjects.

Methods. A population-based study in Olmsted County, Minnesota, USA, was performed by crosslinking a large cohort in the general population having available serum FLC measurements with established RA incidence and prevalence cohorts. Serum κ , λ , and total FLC and their trends relative to RA incidence were compared between RA and non-RA subjects. Regression models were used to determine the associations between FLC, disease characteristics, and mortality, testing for differential effects of FLC on mortality in RA.

Results. Among 16,609 subjects, 270 fulfilled the criteria for RA at the time of FLC measurement. Mean total FLC were significantly higher in RA compared to non-RA subjects (4.2 vs 3.3 mg/dl, $p < 0.001$). FLC became elevated 3–5 years before the clinical onset of RA and remained elevated during followup. Polyclonal FLC were found to predict higher mortality in persons with RA, though elevation to the highest decile had a relatively lower effect on mortality in RA compared to non-RA subjects.

Conclusion. Elevation of serum FLC precedes the development of RA and may be useful in monitoring B cell activity and disease progression. FLC are associated with mortality among patients with RA as well as the general population. (First Release Jan 15 2015; *J Rheumatol* 2015;42:181–7; doi:10.3899/jrheum.140543)

Key Indexing Terms:

B CELL

BIOMARKERS

AUTOIMMUNITY

MORTALITY

B lymphocytes are fundamental to the pathogenesis of rheumatoid arthritis (RA) and other autoimmune rheumatic diseases. Activation of autoreactive B cells, differentiation into plasma cells, and production of autoantibodies are hallmarks of many of these diseases. Prognosis and RA susceptibility are associated with the development of serum

rheumatoid factor (RF) or anticitrullinated protein antibodies (ACPA) in a subset of seropositive patients^{1,2}, which can be detected > 10 years before the onset of clinical disease³. Accumulation of specific ACPA against certain peptides, such as citrullinated α -enolase, fibrinogen, or vimentin, often occurs during the evolution from preclinical

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autoimmunity to clinically overt RA^{4,5}. Confirmation of the central role of B cells in RA is evident in the proven efficacy of B cell depletion therapy^{6,7,8}.

However, only limited data exist on the relationship between B cell immunoglobulin production and disease course and prognosis. Excess immunoglobulin free light chains (FLC) are produced by terminally differentiated B cells and plasma cells during activation and are released into the blood. Elevated concentrations of FLC in the serum and urine have been reported in case series of patients with RA^{9,10} and systemic lupus erythematosus^{11,12,13}. A hospital-based correlative study has reported significant elevations of serum FLC in patients with RA compared to controls with a normal ratio of κ -to- λ FLC, indicating a polyclonal process¹⁴. Other studies have suggested that serum FLC correlate with disease activity and with the clinical response to B cell depletion therapy with rituximab (RTX)^{15,16}. Considering that ACPA can be detected before the onset of clinical RA, we hypothesized that polyclonal elevation of serum FLC could also be detected during the preclinical period.

The objectives of our study were to evaluate trends in serum FLC concentrations before and after the clinical onset of RA relative to non-RA subjects, and to determine the significance of these trends in terms of clinical disease characteristics and longterm mortality. We took advantage of a unique opportunity to crosslink the dataset of our population-based RA incidence cohort with a longterm study of the prevalence of monoclonal gammopathy of undetermined significance (MGUS) conducted at our institution.

MATERIALS AND METHODS

Study design. The previous studies on the prevalence of MGUS^{17,18} used the resources of the Rochester Epidemiology Project (REP)^{19,20} to enumerate individuals who were ≥ 50 years of age and living in Olmsted County, Minnesota, USA, as of January 1, 1995. The sample consisted of 28,038 enumerated individuals, including 75% of subjects in this demographic of the county population. Serum samples were previously obtained from 21,463 of these individuals between January 1995 and November 2003, with 86% of the acquisitions from January 1995 through December 1997. The frequency of MGUS among subjects who gave permission to perform serum studies was the same as that among subjects who did not give permission. The characteristics of the final study population of 16,609 were similar to those of the total enumerated population¹⁷. Thus, this cohort was considered representative of the general population living within Olmsted County²¹.

To identify patients with RA, the general population sample (MGUS study) was crosslinked to a population-based RA inception cohort consisting of adult residents of Olmsted County who first fulfilled the 1987 American College of Rheumatology (ACR) classification criteria²² from January 1, 1955, through December 31, 2009¹⁹. The date of RA incidence was defined as the earliest date of fulfillment of 4 of the 7 classification criteria. A total of 806 subjects were alive in 1995. Additionally, 349 patients with prevalent RA on January 1, 1995, were identified by screening the same list of diagnostic codes used to identify the incident cases. Prevalent patients were included on the basis of physician diagnosis when the ACR criteria at the time of RA diagnosis were not available. Among these 1155 patients with incident or prevalent RA who were alive

in 1995, only 731 were eligible for the MGUS study (i.e., age ≥ 50 years in 1995).

Using the resources of the REP, all subjects were followed similarly over time until death, migration, or January 1, 2010. Ascertainment of death, identical for RA and non-RA subjects, was based on the Olmsted County and Minnesota electronic death certificates and the National Death Index. The institutional review boards of the Mayo Clinic and the Olmsted Medical Center approved our study. All subjects provided written informed consent to participate in our research.

Data collection. Medical records were abstracted to define RA clinical characteristics, as previously described²³. The duration of RA was calculated from the RA incidence date. Smoking was categorized as current, ever, or never. Body mass index was defined as kg/m². Extraarticular manifestations, including the presence of rheumatoid nodules, secondary Sjögren syndrome, pulmonary fibrosis, and vasculitis, were ascertained. Severe extraarticular manifestations were defined according to the Malmö criteria and included scleritis/retinal vasculitis, Felty syndrome, glomerulonephritis, major cutaneous vasculitis, neuropathy, pericarditis/pleuritis, or vasculitis involving other organs²⁴. Radiographic erosive/destructive changes were based on the review of radiologic reports. Coronary heart disease was defined by angina pectoris, coronary artery disease, myocardial infarction (including silent events), and coronary revascularization procedures. Exposure to RA medications was ascertained, including corticosteroids (oral or parenteral), disease-modifying antirheumatic drugs (methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, or azathioprine), and biologic agents (including tumor necrosis factor inhibitors, anakinra, abatacept, and RTX), all of which were available during the period of our study.

The results of testing for antinuclear antibodies (positive vs negative), serum creatinine (mg/dl), erythrocyte sedimentation rate (ESR, mm/h), and RF (\geq upper limit of normal) were ascertained from laboratory records. Persistent ESR elevation was defined as ≥ 3 ESR measurements of ≥ 60 mm/h in the first year of RA incidence. The estimated glomerular filtration rate was calculated using the chronic kidney disease-epidemiology collaboration equation formula.

The concentrations of serum immunoglobulin FLC were measured using a commercial immunonephelometric assay (Binding Site) as previously described¹⁷. The assay reported κ and λ FLC concentrations and the κ -to- λ ratio²⁵. We defined a result indicative of an FLC MGUS as an FLC ratio outside the normal diagnostic range (0.26–1.65). The reference ranges for κ -FLC and λ -FLC were 0.33–1.94 mg/dl and 0.57–2.63 mg/dl, respectively²⁵.

Statistical analysis. Characteristics of the patients with and without RA were compared using rank sum or chi-square tests, and also linear or logistic regression models, adjusting for age and sex, as appropriate.

Trends in FLC values, according to time since RA incidence, were examined using linear regression models of the log-transformed FLC values depicted using smoothing splines. Trends in the percentages of patients with FLC ≥ 4.72 mg/dl, the cutoff for the highest decile in our previous publication¹⁷, were obtained using generalized additive models with smoothing splines. The non-RA reference lines were age- and sex-adjusted to the RA population.

Cox models were used to examine the associations between FLC variables and mortality in the RA and non-RA cohorts. Patients with MGUS were excluded from this analysis. The presence of RA was treated as a time-dependent covariate, meaning that patients who developed RA during followup were counted in the non-RA group prior to development of RA, and in the RA group after development of RA. Interactions between cohort and FLC variables were assessed to determine whether the associations of FLC variables with mortality differed between the RA and non-RA groups. Kaplan-Meier methods were used to estimate the survival curves among subjects with and without RA who did and did not have FLC values ≥ 4.72 mg/dl. The RA status was assessed at the time of FLC measurement for this survival analysis.

RESULTS

Comparison of the RA and non-RA cohorts. As shown in Figure 1, 16,609 subjects were enrolled in our study. At the time of the FLC measurement, 16,339 subjects had no history of inflammatory arthritis, and 270 subjects had RA (195 from our RA inception cohort plus 75 prevalent cases). In addition, 127 subjects developed RA after FLC measurement.

As shown in Table 1, the RA group was slightly older than the non-RA group (67 vs 65 yrs, respectively, $p < 0.001$). The percentage of females was higher among the RA subjects than among the non-RA subjects (68% vs 55%, $p < 0.001$). For patients who developed RA before the FLC assay, the median RA disease duration was 12.2 years (range 0.0–39.3 yrs); for patients who developed RA after the FLC assay, the median time to development of RA was 5.4 years (range 0.0–16.1 yrs). The mean followup was similar between the RA and non-RA groups at about 10 person-years.

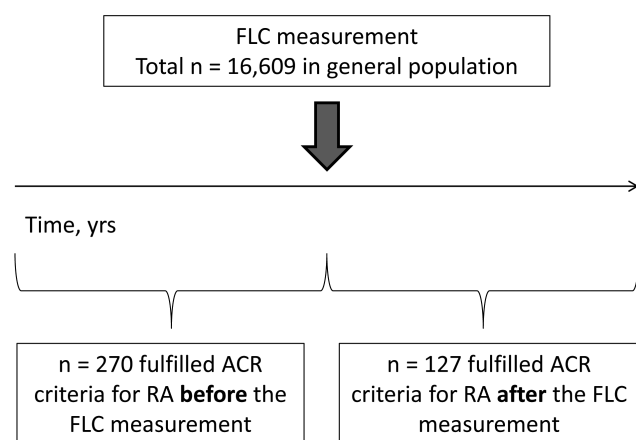


Figure 1. Study design illustrating the identification of subjects with RA with onset either before or after the FLC measurement. ACR: American College of Rheumatology; RA: rheumatoid arthritis; FLC: free light chain.

Table 1. Characteristics of patients with and without RA at the time of FLC measurement. Serum creatinine was available for 13,562 non-RA subjects and 182 RA subjects at the time of the FLC assay. eGFR was estimated using the CKD-EPI formula. Values are mean (SD) or n (%) unless otherwise specified.

Characteristics	Non-RA, n = 16,339	RA, n = 270	Crude p	p, Adjusted for Age and Sex
Age, yrs	64.5 (10.5)	67.3 (10.0)	< 0.001	—
Female sex	8947 (54.8)	184 (68.1)	< 0.001	—
Followup, yrs	10.2 (4.2)	9.6 (4.5)	—	—
Total FLC	3.3 (4.1)	4.2 (3.7)	< 0.001	0.003
Total FLC \geq 4.72 mg/dl	1816 (11.1)	64 (23.7)	< 0.001	< 0.001
κ FLC, mg/dl	1.6 (3.2)	2.0 (2.4)	< 0.001	0.07
λ FLC, mg/dl	1.8 (2.2)	2.2 (1.6)	< 0.001	0.005
κ -to- λ FLC ratio	1.0 (5.2)	1.0 (1.4)	0.34	0.90
Light chain MGUS	537 (3.3)	11 (4.1)	0.47	0.48
MGUS, intact Ig	517 (3.2)	12 (4.4)	0.24	0.34
Serum creatinine, mg/dl	1.1 (0.5)	1.1 (0.7)	< 0.001	0.69
eGFR, ml/min/1.73 m ²	64.8 (15.7)	65.2 (17.7)	0.56	< 0.001

RA: rheumatoid arthritis; FLC: free light chains; eGFR: estimated glomerular filtration rate; CKD-EPI: chronic kidney disease–epidemiology collaboration equation; MGUS: monoclonal gammopathy of undetermined significance; Ig: immunoglobulin.

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Comparison of FLC levels between patients with RA and non-RA subjects. The patients with RA had significantly higher mean concentrations of total, κ , and λ FLC as compared to non-RA subjects in the general population (Table 1). The differences between the groups in these FLC concentrations were not explained by age, sex, or kidney function.

Trends in serum FLC levels relative to RA incidence. Although FLC were only measured once per individual, by identifying patients with RA before ($n = 270$) and after FLC measurement ($n = 127$) as shown in Figure 1, it was possible to examine trends in serum FLC levels occurring before the development of RA. The mean concentration of serum total FLC appeared to be elevated in subjects with RA compared to the non-RA subjects in the preclinical period, about 5 years before the RA incidence date (Figure 2). A test for trend, applied to the log-transformed total FLC values, revealed that total FLC increased over time by 1% per year ($p < 0.001$), and a test for change in slope at the time of RA incidence revealed a significantly steeper rate of increase (from 1% per yr to 3% per yr) beginning at RA incidence ($p = 0.008$). Additionally, the percentage of patients with RA who had a total FLC concentration of ≥ 4.72 mg/dl was higher than among non-RA subjects beginning at least 5 years before RA incidence (Figure 2). The higher elevation of serum FLC in patients with RA compared to non-RA was found to persist for the duration of followup. The results separately for κ and λ FLC were similar (data not shown). In the general population, serum FLC have been shown to increase with age, as well as with declining renal function¹⁷.

Predictors of elevated serum FLC in RA. Data on RA disease characteristics were available for the 195 subjects with RA incidence before FLC measurement. Because the RF is associated with B cell autoimmunity, we analyzed the association between the RF and FLC among patients with

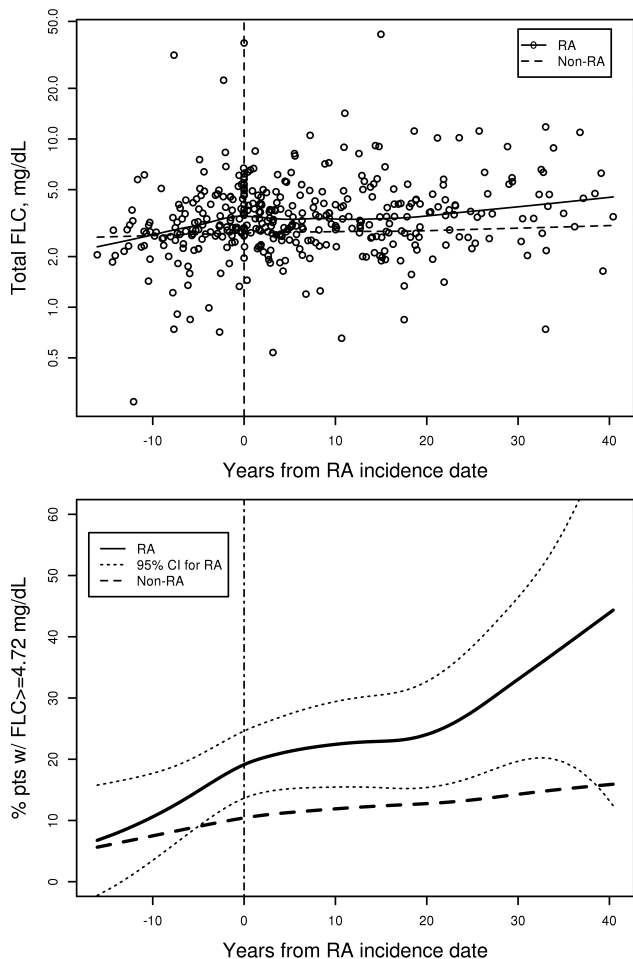


Figure 2. Evidence of preclinical activation of B cell immunity in patients with RA compared to subjects in the general population. The graphs display trends in the concentration (mg/dl) of total FLC (top panel) and in the percentage of patients with total FLC ≥ 4.72 mg/dl (bottom panel), both relative to time from the RA incidence date. In the top panel, the FLC data points for RA are shown along with a smooth line for trend in the 270 patients with RA (solid line) and a reference line for the 16,339 age- and sex-matched trend in the non-RA group (dashed line). A test for trend revealed that total FLC increased over time ($p < 0.001$), and a test for change in slope at the time of RA incidence among the patients with RA revealed a significant change with a steeper rate of increase following RA incidence ($p = 0.035$). In the bottom panel, the percentage of patients with RA with total FLC ≥ 4.72 mg/dl increased over time (solid line with 95% CI depicted as dashed lines) and exceeded the age- and sex-matched trend in the non-RA group (solid line). FLC: free light chains; RA: rheumatoid arthritis.

RA, of whom 128 (66%) were known previously to be RF-positive. No statistically significant differences between RF-positive and RF-negative patients were observed in the mean concentrations of total FLC (4.3 vs 4.1 mg/dl, $p = 0.72$), κ FLC (mean 2.0 vs 1.8 mg/dl, $p = 0.65$), or λ FLC (mean 2.2 vs 2.3 mg/dl, $p = 0.77$). Further analysis considered the relationships of serum FLC to other inflammatory disease characteristics, adjusting for age and sex (Table 2). Strong associations were detected between the

highest decile of serum FLC and the presence of rheumatoid lung disease (OR 8.53, $p = 0.013$) or severe extraarticular manifestations (OR 3.64, $p = 0.017$). A nonsignificant trend was observed between higher serum FLC and disease duration (OR 1.03 per yr, $p = 0.09$). No other significant associations were detected. Results of linear regression for the associations between the RA disease characteristics and log-transformed total FLC were similar (data not shown).

Association of FLC with mortality in RA. Next, we examined the association between serum FLC levels and mortality among the 252 patients with RA and 15,431 non-RA subjects in the general population without MGUS. A total of 4896 patients died during followup (3725 non-RA with FLC < 4.72 mg/dl, 1043 non-RA with FLC ≥ 4.72 mg/dl, 92 RA with FLC < 4.72 mg/dl, and 36 RA with FLC ≥ 4.72 mg/dl).

Total κ and λ FLC were observed to predict higher mortality in patients with RA (Table 3). The HR for the association between total serum FLC and mortality was lower in patients with RA (HR 1.07, 95% CI 1.03–1.11) compared to subjects in the general population (HR 1.14, 95% CI 1.13–1.16), adjusting for age, sex, serum creatinine, and the RA \times FLC interaction term above.

The interaction between RA and total FLC was statistically significant (HR 0.93, 95% CI 0.90–0.97, $p < 0.001$). Unexpectedly, the mortality risk of the highest decile of serum total FLC (≥ 4.72 mg/dl) appeared to be attenuated in patients with RA (HR 1.25, 95% CI 0.88–1.80) compared to the general population (HR 2.04, 95% CI 1.89–2.20). This same statistically significant interaction (≥ 4.72 mg/dl) was also detected between RA status and total FLC (HR 0.62, 95% CI 0.43–0.89, $p = 0.009$), after adjusting for age, sex, serum creatinine, the total FLC, and the RA/non-RA indicator variable (Table 3). The results were similar for κ and λ FLC. However, as shown in Figure 3, the CI of the survival curves for subjects with RA with high FLC (≥ 4.72 mg/dl) and subjects in the general population with high FLC were overlapping. Taken together, the findings suggested that the seemingly lower relative effect of serum FLC on mortality in RA relative to the general population reflected the higher mortality of patients with RA in general.

DISCUSSION

In our study, we first explored a unique population-based dataset to test the hypothesis that elevation of serum FLC precedes the onset of clinical RA. By analyzing trends in serum FLC concentrations relative to the date of RA incidence in patients compared to non-RA subjects, we have shown that elevated concentrations of serum FLC become detectable 5–10 years before the diagnosis of RA. Of relevance, the results of a nested case-control study in Finland performed by Aho, *et al* showed an elevation of serum immunoglobulin G levels > 10 years before the clinical development of RA²⁶. A study of the ESPOIR

Table 2. Association between RA disease characteristics and elevation of serum total FLC to the highest overall population decile (≥ 4.72 mg/dl) at the time of the FLC assay in 195 patients with incident RA. Results of logistic regression models adjusted for age and sex. Values represent the mean (SD) or n (%) unless otherwise specified.

Characteristics	Value	OR (95% CI)	p
RA lung disease	8 (4)	8.53 (1.57–46.34)	0.013
Severe extraarticular manifestations	17 (9)	3.64 (1.26–10.58)	0.017
Sjögren syndrome	15 (8)	1.66 (0.52–5.28)	0.39
Rheumatoid nodules	53 (27)	1.65 (0.80–3.41)	0.18
Hydroxychloroquine, current use	33 (17)	1.58 (0.68–3.69)	0.29
ANA, positive (> ULN)	70 (36)	1.41 (0.70–2.83)	0.33
Radiographic erosive/destructive changes	99 (51)	1.13 (0.58–2.22)	0.72
Smoking, current at RA incidence	53 (27)	1.08 (0.50–2.31)	0.85
Disease duration, yrs	12.2 \pm 10.1	1.03 (1.00–1.06)	0.09
Body mass index at RA incidence, kg/m ²	26.7 \pm 5.2	0.97 (0.90–1.04)	0.41
Persistent ESR elevation in first yr of RA incidence	35 (18)	0.88 (0.36–2.18)	0.79
RF, positive (> ULN)	128 (66)	0.83 (0.41–1.70)	0.61
Smoking, ever	127 (65)	0.82 (0.39–1.73)	0.60
Other DMARD, current use	58 (30)	0.75 (0.35–1.62)	0.47
Methotrexate, current use	46 (24)	0.75 (0.32–1.75)	0.50
Coronary heart disease	44 (23)	0.65 (0.28–1.50)	0.31
Prednisone, current use	89 (46)	0.59 (0.30–1.19)	0.14

RA: rheumatoid arthritis; FLC: free light chains; ULN: upper limit of normal; ANA: antinuclear antibody; ESR: erythrocyte sedimentation rate; RF: rheumatoid factor; DMARD: disease-modifying antirheumatic drugs.

Table 3. Association of serum polyclonal FLC variables with mortality among 15,431 non-RA subjects and 252 patients with RA, considering potential interaction between RA and serum FLC variables.

FLC Variable	Non-RA		RA		RA \times Variable Interaction		
	HR	95% CI	HR	95% CI	HR	95% CI	p
Total FLC	1.14	1.13–1.16	1.07	1.03–1.11	0.93	0.90–0.97	< 0.001
Total FLC ≥ 4.72	2.04	1.89–2.20	1.25	0.88–1.80	0.62	0.43–0.89	0.009
κ FLC, mg/dl	1.30	1.27–1.33	1.11	1.03–1.19	0.85	0.80–0.91	< 0.001
λ FLC, mg/dl	1.24	1.22–1.26	1.10	1.02–1.18	0.91	0.85–0.98	0.008
Log, κ -to- λ ratio	1.10	1.001–1.21	0.96	0.57–1.63	0.88	0.51–1.49	0.62

The results of Cox regression analysis are shown; models contain age, sex, creatinine, RA/non-RA status, variable of interest, and the RA \times variable interaction term. For this analysis, RA is a time-dependent covariate, meaning that subjects are counted in the non-RA group until the time at which they developed RA during followup. The interaction term tests the hypothesis that FLC have a different effect on mortality among the patients with RA compared to patients without RA. The HR for the interaction is the differential effect of FLC (per 1 mg/dl of FLC) on mortality among patients with RA. A total of 18 RA and 908 non-RA subjects with abnormal κ -to- λ ratio or detectable monoclonal heavy chains were excluded from this mortality analysis. FLC: free light chains; RA: rheumatoid arthritis; log: natural logarithm.

cohort reported higher concentrations of serum κ and λ FLC in patients with early RA compared to patients with undifferentiated arthritis after 1 year of followup¹⁶. Although caution is warranted, considering we were unable to perform serial FLC measurements before and after the onset of RA, the strengths of our study design underscore the significance of our inferences from this trends analysis.

The second part of our study was to determine the significance of serum FLC in terms of their relationships to clinical disease characteristics and outcomes in people with RA. It is interesting that we did not observe any differences in serum FLC between RF-positive and RF-negative patients. This contrasts with the reported association of both RF and ACPA with serum FLC by Gottenberg, *et al*¹⁴. Our

study was not designed to evaluate the association between RF and serum FLC with 4 key limitations. First, RF testing was not done at the time of FLC measurement. Second, there were no remaining sera from these patients at the time of the FLC assays to test for RF or ACPA. Third, the method of RF measurement varied over the time period of our study, precluding analysis of the titers and diagnostic cutoffs. Fourth, association between serum FLC and RF positivity could have been confounded by the level of disease activity at the time of testing, which was unmeasured in our study. Future studies are needed to address this specific question.

The finding of a strong association of serum FLC with rheumatoid lung disease is of interest and deserves further evaluation in a larger cohort of patients with lung disease.

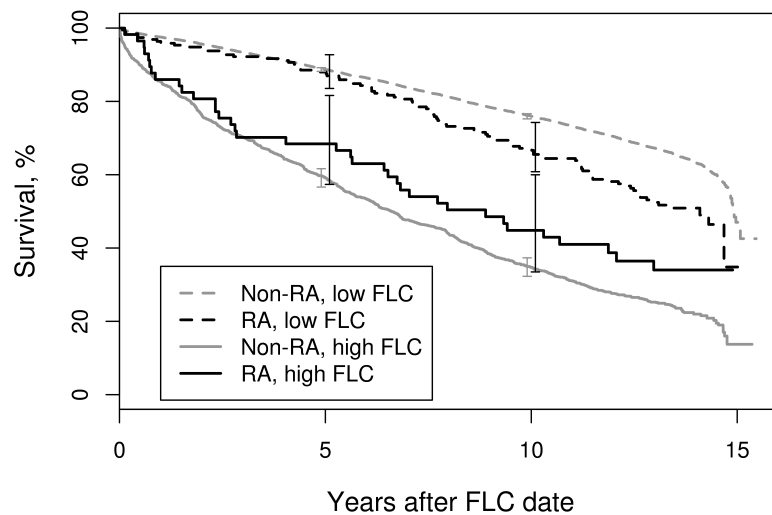


Figure 3. Effect of the highest decile of polyclonal total FLC on mortality in patients with RA compared to non-RA subjects. Shown are Kaplan-Meier curves comparing the survival experience between 15,431 non-RA subjects without (black dashed line) and with total FLC ≥ 4.72 mg/dl (black solid line), and 252 patients with RA without and with serum FLC in the highest decile (gray dashed and solid lines, respectively). Vertical bracketed lines at the 5- and 10-year timepoints represent 95% CI. All curves are age- and sex-adjusted to the age/sex distribution of the RA cohort. FLC: free light chains; RA: rheumatoid arthritis.

B cell autoimmunity and generation of autoantibodies to citrullinated proteins, especially citrullinated heat shock protein 60 isoforms, have been postulated to be central to the pathogenesis of RA-associated interstitial lung disease^{27,28}. Our data highlight a relationship between polyclonal B cell activation and the pathogenesis of parenchymal lung disease in RA.

A study by Dispenzieri, *et al* showed that individuals in the highest overall decile for total serum FLC had significantly increased mortality (HR 4.38, 95% CI 4.08–4.70), which remained significant after adjusting for age, sex, and kidney function¹⁷. Of note, the HR for the association between the highest decile of total FLC and mortality was lower in our current study than in the Dispenzieri, *et al* study, probably because of the differences in our statistical approach and covariates. This compelled us to determine how the presence of rheumatoid disease modifies the effect of serum FLC on mortality. Our results confirm that serum total FLC are significant predictors of increased mortality in patients with RA. Initially, we were surprised to observe a seemingly lower effect of high serum FLC on mortality in patients with RA relative to the general population. Based on our data, we believe the correct interpretation is that the apparently lower effect of serum FLC on mortality in RA is simply a reflection of the known significantly increased mortality of patients with RA relative to the general population. Further research is necessary to understand the prognostic value of serum FLC in managing early RA.

As discussed above, a significant limitation of our study

is the lack of data on ACPA. Because ACPA serological status has been associated with serum FLC in previous studies, as well as with increased risk of rheumatoid lung disease, other extraarticular manifestations, and mortality, we cannot exclude confounding of the results by this unmeasured factor in our study. Further research is necessary to determine whether elevation of serum FLC have prognostic value beyond standard ACPA detection.

Our population-based study comparing serum FLC in patients with RA to non-RA subjects reveals evidence of polyclonal elevation in the preclinical period prior to the onset of overt clinical disease. The presence of RA lung disease was observed to predict serum FLC levels. Increased serum FLC were shown to predict a greater risk of mortality in persons with RA, though the effect of the highest levels of total FLC on mortality was lower among individuals with established RA than with subjects in the general population. The findings highlight the fundamental role of B cells in the pathogenesis of RA and inform future studies of preclinical progression of the disease. Clinically, serum FLC may be helpful in monitoring the disease course in persons with RA.

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