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Article

Nutritional Risk in Older Adults with Rheumatoid Arthritis: Sex-Specific Patterns and Clinical Implications of the Prognostic Nutritional Index

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Abstract

Background/Objectives: Nutritional risk is increasingly recognized as a relevant but under-assessed dimension of rheumatoid arthritis (RA), particularly in older adults managed in outpatient settings. Simple nutritional indices such as the Prognostic Nutritional Index (PNI) may help identify individuals at increased nutritional risk beyond conventional disease activity measures. This study aimed to characterize nutritional risk in older adults with RA using the Prognostic Nutritional Index, explore sex-specific patterns, and identify clinical associations of PNI variability, with complementary analyses focusing on high nutritional risk. **Methods:** We conducted an observational cross-sectional study including 275 consecutive adults aged ≥ 50 years with RA attending routine follow-up at a tertiary rheumatology clinic. Nutritional risk was assessed using the PNI, calculated from serum albumin and total lymphocyte count, and analyzed primarily as a continuous variable and secondarily using established cut-off values. Clinical characteristics, inflammatory markers, body mass index, laboratory parameters, and patient-reported outcomes were recorded. Analyses were stratified by sex. Multivariable linear regression models were used to identify factors associated with PNI variability, and complementary logistic regression analyses were performed to explore factors independently associated with high nutritional risk ($\text{PNI} < 40$). **Results:** More than half of the cohort (53.3%) exhibited PNI values compatible with nutritional risk. Men showed significantly lower PNI values than women, with a higher frequency of nutritional risk (61.5% vs. 49.7%, $p < 0.01$) and a markedly greater prevalence of high nutritional risk (18.0% vs. 5.0%, $p < 0.001$). Sex-specific association patterns were observed. In women, PNI showed only a weak inverse association with age. In contrast, in men, lower PNI values were associated with higher inflammatory burden, greater disease activity, lower body mass index, poorer mental health-related quality of life, and lower hemoglobin levels. In multivariable linear regression models restricted to men, hemoglobin emerged as the principal independent correlate of PNI. In complementary logistic regression analyses focusing on high nutritional risk ($\text{PNI} < 40$), hemoglobin remained the sole independent predictor (OR = 0.94, 95% CI 0.91–0.98; $p < 0.01$), supporting a robust association with clinically relevant nutritional risk. **Conclusions:** Nutritional risk assessed by the PNI is common among older adults with RA and displays pronounced sex-specific patterns, with men showing a substantially higher burden of nutritional risk. The PNI captures a clinically relevant dimension of disease burden that extends beyond joint inflammation and traditional activity indices, supporting its use as a pragmatic nutritional screening tool in routine rheumatology practice.

Keywords: rheumatoid arthritis; nutritional risk; prognostic nutritional index; sex-specific patterns

Introduction

Rheumatoid arthritis (RA) is a chronic immune-mediated disease characterized by persistent joint and systemic inflammation [1]. This persistent inflammatory state accelerates biological ageing of the immune system and contributes to premature immune senescence [2].

Sustained immune-metabolic activation promotes a chronic low-grade inflammatory state, termed inflammaging, which drives oxidative stress, mitochondrial dysfunction and early cellular ageing [3]. In older adults, this inflammatory burden interacts with age-related metabolic changes and a progressive reduction in nutritional reserve, contributing to sarcopenia, metabolic dysfunction, anemia of chronic disease and loss of homeostatic reserve [4,5]. Together, these processes erode integrative physiological capacity in ways not captured by conventional disease activity indices and help explain the emergence of nutritional vulnerability in older adults with RA.

Nutritional status has growing relevance in RA because it reflects the intersection of inflammation, metabolic resilience and host immune competence. Understanding nutritional risk in RA is clinically important, as reduced nutritional reserve may affect treatment tolerance, increase susceptibility to infection and impair physical functioning, in line with robust evidence on disease-related malnutrition in chronic conditions [6]. Moreover, malnutrition appears to be highly prevalent among patients with RA and has been independently associated with increased all-cause mortality, thereby revealing an additional layer of disease burden beyond joint inflammation [7].

In clinical practice, comprehensive nutritional assessment is often complex and time-consuming, particularly in outpatient settings. In this context, the Prognostic Nutritional Index (PNI) [8], based exclusively on serum albumin and total lymphocyte count, provides a simple, pragmatic and readily accessible surrogate of nutritional risk. The PNI offers an interpretable estimate of protein reserve and systemic vulnerability and has demonstrated consistent prognostic value across a wide range of chronic diseases [9–11].

Nevertheless, evidence regarding its clinical role in RA remains limited and fragmented. Previous studies have mainly focused on specific outcomes such as disease activity [12], sarcopenia [13], infection risk [14] or mortality [15], rather than on the overall prevalence and clinical correlates of nutritional risk assessed by the PNI in well-characterized clinical cohorts. Consequently, data remain scarce on how frequently nutritional risk occurs in routine rheumatology practice and how PNI values relate to broader dimensions of disease burden beyond joint inflammation. Further studies are therefore needed to clarify the utility of the PNI for estimating nutritional risk, contextualizing disease impact and supporting patient stratification.

RA is also increasingly recognized as a disease characterized by relevant sex-related biological and clinical differences. Beyond prevalence, accumulating evidence indicates that immune responses, inflammatory burden, body mass index (BMI) and metabolic adaptations vary between men and women, highlighting the importance of a sex-informed perspective when interpreting clinical and biological indices in this disease [16–18].

In this context, we aimed to characterize the prevalence and clinical impact of nutritional risk in a cohort of older adults with RA, using the PNI as the primary analytic tool. We examined the distribution of PNI values, assessed their clinical and biochemical correlates, and identified factors independently associated with higher nutritional risk through multivariable modelling. This approach provides new insights into the burden of nutritional risk in RA and its potential relevance for patient stratification and clinical management.

Methods

Study Population

We conducted an observational cross-sectional study including 275 consecutive adults aged 50 years or older, of either sex, with RA attending routine follow-up visits at a tertiary university hospital rheumatology clinic. All participants fulfilled the 2010 ACR/EULAR classification criteria. The study was conducted within the framework of the Bellvitge Rheumatoid Arthritis–Life Impact

and Comorbidity Evaluation cohort (BELL-RA-LIFE), a single-center observational cohort specifically designed to include middle-aged and older adults with RA followed under routine clinical care. The cohort was conceived to characterize the global impact of the disease across ageing, with a particular focus on comorbidity burden, nutritional status, physical function, patient-reported outcomes, and health-related quality of life in real-world settings.

Patients with conditions that could substantially confound the assessment of nutritional status or disease-related outcomes, including active malignancy, advanced heart or respiratory failure, chronic liver disease, or advanced chronic kidney disease, were excluded.

All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Hospital Universitari de Bellvitge (protocol PR057/20).

Study Variables

Sociodemographic Characteristics

Recorded sociodemographic variables included age, sex and body mass index (BMI). Lifestyle-related variables comprised smoking status (never, former, current) and self-reported physical activity, categorized as none, sporadic, regular low-intensity or regular high-intensity activity.

Disease-Related Variables

- Clinical History and Serology

Key disease-related characteristics were documented, including disease duration, seropositivity for rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA), with their respective titers. Current pharmacological treatment was recorded and categorized as glucocorticoids, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic DMARDs, or Janus kinase inhibitors.

- Disease Activity

Disease activity was assessed using the Disease Activity Score in 28 joints (DAS28) [19], calculated from tender and swollen joint counts, patient global assessment and inflammatory markers, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Laboratory Parameters

Laboratory measurements included hemoglobin concentration, total lymphocyte count and serum albumin levels, obtained from routine blood analyses performed in proximity to study inclusion.

Assessment of Nutritional Risk

The PNI was calculated as follows [8]:

$$\text{PNI} = (10 \times \text{serum albumin [g/dL]}) + (0.005 \times \text{total lymphocyte count [per mm}^3\text{]}).$$

Lower values indicate poorer nutritional status. Commonly used interpretative thresholds were applied: (a) ≥ 45 , adequate nutritional status; (b) 40–44.9, mild nutritional risk; and (c) < 40 , high nutritional risk.

Physical Performance Measures

Handgrip strength was measured using a Jamar[®] dynamometer in the dominant hand. Three attempts were performed, and the highest value was recorded. Low grip strength was defined using EWGSOP2 [20] sex- and age-specific thresholds: a) < 27 kg in men, b) < 16 kg in women. Gait speed was measured over a 4-meter course at the participant's usual walking pace. A gait speed < 0.8 m/s was classified as slow.

Fatigue

Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale [21]. Lower scores indicate greater fatigue; scores <30 were considered indicative of clinically relevant fatigue.

Health-Related Quality of Life

Health-related quality of life (HRQoL) was evaluated using the 12-Item Short Form Survey (SF-12) [22]. Two summary measures were analyzed: a) the Physical Component Score (PCS), reflecting physical functioning and perceived physical health, and b) the Mental Component Score (MCS), reflecting emotional well-being and mental health.

Higher scores indicate better perceived health status in both components.

Statistical Analysis

Descriptive statistics were used to summarize sociodemographic, clinical, laboratory and nutritional characteristics. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR) according to their distribution, assessed using the Shapiro–Wilk test. Categorical variables are presented as frequencies and percentages. Comparisons between men and women were performed using the chi-square test or Fisher’s exact test for categorical variables and Student’s t-test or Mann–Whitney U test for continuous variables, as appropriate.

The PNI was analyzed both as a continuous variable and as a categorical variable according to established cut-offs (adequate, mild risk, high risk). Given the observed differences in PNI between men and women, all analyses were stratified by sex.

Associations between PNI values and clinical or laboratory parameters were examined using Pearson or Spearman correlation coefficients, depending on data distribution.

To identify independent factors associated with PNI variability, multivariable linear regression models were constructed with PNI as the dependent variable, including as covariates all variables that were significantly associated with PNI in the univariate analyses.

In addition, a complementary multivariable logistic regression analysis was performed restricted to men to identify factors independently associated with high nutritional risk, defined as PNI < 40.

All statistical tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Results

Baseline sociodemographic and clinical characteristics of RA patients are summarized in Table 1. Within the cohort, 69.5% (n = 191) were women and 30.5% (n = 84) were men.

Table 1. Characteristics of the 275 RA patients, stratified by sex into men (n = 84) and women (n = 191).

	Men	Women	p-value
Age (years)	71.9 ± 8.5	67.5 ± 8.8	<0.001
BMI (kg/m²)	27.5 ± 3.5	27.9 ± 5.4	ns
Underweight (n, %)	1 (1.2%)	0	ns
Normal range (n, %)	18 (21.4%)	64 (33.5%)	-
Overweight (n, %)	49 (58.3%)	72 (37.5%)	<0.01
Obese (n, %)	16 (19.1%)	55 (29%)	-
Smoking			
Never (n, %)	72 (85.7%)	164 (87.2%)	ns
Former (n, %)	1 (1.2%)	2 (1.1%)	
Current (n, %)	11 (13.1%)	22 (11.7%)	
Physical activity			
None (n, %)	31 (37%)	94 (50.3%)	ns

Sporadic (n, %)	16 (19%)	36 (19.3%)	
Regular with low intensity (n, %)	33 (39.2%)	55 (29.4%)	
Regular with high intensity (n, %)	4 (4.8%)	2 (1.1%)	
Hemoglobin (g/dL)	14.2 ± 1.5	13.3 ± 1.2	<0.001
Serum albumin (g/L)	42.9 ± 4.7	44.3 ± 3.5	< 0.01
Total lymphocyte count	2.1 ± 1.2	2.4 ± 1.0	ns
Disease duration (years)	12.5 ± 9.6	16.8 ± 10.3	<0.01
RF + (n, %)	50/83 (60.2%)	123/168 (73%)	ns
RF titer (UI/L)	175 ± 224	208 ± 415	ns
ACPA + (n, %)	52/83 (62.6%)	115/167 (69%)	ns
ACPA titer (U/L)	571 ± 1040	369 ± 672	ns
Current medication			
Glucocorticoids (n, %)	46 (54.7%)	89 (46.5%)	ns
cDMARDs (n, %)	73 (86.9%)	172 (90%)	ns
bDMARDs (n, %)	20 (23.8%)	68 (36%)	<0.001
Jak inhibitors (n, %)	2 (2.4%)	10 (5%)	ns
ESR (mm/h)	24.3 ± 26.2	24.8 ± 20.8	ns
CRP (mg/dL)	10.1 ± 18.3	5.2 ± 6.1	<0.05
DAS28	2.5 ± 1.2	2.9 ± 1.1	<0.01
Remission (n, %)	49 (58.3%)	77 (40.5%)	ns
LDA (n, %)	16 (19%)	47 (24.5%)	ns
MDA (n, %)	15 (17.9%)	61 (32%)	<0.01
HDA (n, %)	4 (4.8%)	6 (3%)	ns
SF-12			
Mental health	51.5 ± 10.0	45.1 ± 11.4	<0.001
Physical health	42.5 ± 9.6	36.8 ± 9.5	<0.001
Low grip strength (n, %)	36 (42.9%)	108 (56.8%)	<0.05
Low gait speed (n, %)	12 (14.3%)	50 (26.5%)	<0.05
PNI median, [IQR] (*)	44.0 [40.0–46.0]	45.0 [43.0–46.0]	
Adequate nutritional status (n, %)	32 (38.5%)	96 (50.3%)	< 0.01
Mild nutritional risk (n, %)	36 (43.4%)	86 (45.0%)	< 0.01
High nutritional risk (n, %)	15 (18.1%)	9 (4.7%)	

(*) PNI could be calculated in 83 men and 191 women due to one missing albumin count. BMI, body mass index; RF, rheumatoid factor; ACPA, anti-citrullinated peptides antibodies; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; cDMARDs, conventional disease-modifying antirheumatic drugs; bDMARDs; biological disease-modifying antirheumatic drugs; DAS28, Disease Activity Score 28; LDA, low disease activity; MDA, moderate disease activity; HDA: high disease activity; RAPID3, Routine Assessment of Patient Index Data 3; SF-12: Short Form Health Survey-12. IQR, interquartile range.

Men were older than women (71.9 ± 8.5 vs. 67.5 ± 8.8 years, $p < 0.001$) but had shorter disease duration (12.5 ± 9.6 vs. 16.8 ± 10.3 years, $p < 0.01$). No sex differences were observed in ESR, CRP, or autoantibody status. Women showed higher disease activity, reflected by higher DAS28 scores (2.9 ± 1.1 vs. 2.5 ± 1.2, $p < 0.01$), and poorer HRQoL in both the physical and mental components of the SF-12.

In the overall series, according to PNI values, 53.3% of patients exhibited nutritional risk, which was mild in 44.5% and high in 8.8%.

PNI values were lower in men than in women (44.0 [40.0–46.0] vs. 45.0 [43.0–46.0], $p < 0.05$). The frequency of nutritional risk was significantly higher in men compared with women (61.5% vs. 49.7%, $p < 0.01$), and a markedly higher proportion of men presented high nutritional risk (18.1% vs. 4.7%, $p < 0.001$).

In women, PNI was only associated with age, showing a weak inverse correlation ($r = -0.169$, $p < 0.05$).

In men, PNI showed multiple significant associations. It was inversely correlated with age ($r = -0.339$, $p < 0.01$), CRP ($r = -0.287$, $p < 0.01$), and DAS28 ($r = -0.307$, $p < 0.01$), and positively correlated with BMI ($r = 0.267$, $p < 0.05$) and hemoglobin levels ($r = 0.389$, $p < 0.01$).

Progressive multivariable linear regression models identified hemoglobin as the principal independent factor associated with PNI variability (Table 2). In the first model, hemoglobin alone accounted for 15.2% of the variance in PNI ($R^2 = 0.152$; adjusted $R^2 = 0.141$), with a significant positive association ($\beta = 0.389$, $p < 0.001$). The addition of the SF-12 mental component score in Model 2 increased the explained variance to 20.3% (adjusted $R^2 = 0.182$), with both hemoglobin ($\beta = 0.364$, $p = 0.001$) and mental health ($\beta = 0.228$, $p = 0.029$) remaining independently associated with PNI.

Table 2. Multivariable linear regression models identifying factors associated with the PNI in men with RA.

	Constant	Coefficient	p	Adjusted R ²
Model 1				
Hemoglobin	25.013	0.389	< 0.001	0.141
Model 2				
Hemoglobin	20.623	0.364	< 0.01	0.182
SF12 MH		0.228	< 0.05	
Model 3				
Hemoglobin	12.532	0.333	< 0.01	0.231
SF12 MH		0.242	< 0.05	
BMI		0.241	< 0.05	
Model 4				
Hemoglobin	15.154	0.295	< 0.05	0.263
SF12 MH		0.235	< 0.05	
BMI		0.236	< 0.05	
CRP		-0.205	< 0.05	

Model 3 showed that BMI contributed further to PNI variability, increasing R^2 to 0.260 (adjusted $R^2 = 0.231$). Hemoglobin ($\beta = 0.333$, $p = 0.001$), the SF-12 mental component score ($\beta = 0.242$, $p = 0.017$) and BMI ($\beta = 0.241$, $p = 0.018$) were all independently associated with PNI.

In the final model (Model 4), CRP added a modest but significant negative contribution ($\beta = -0.205$, $p = 0.040$), increasing the explained variance to 30.0% (adjusted $R^2 = 0.263$). Overall, in men, higher hemoglobin levels, better mental health status and higher BMI were independently associated with higher PNI values, whereas higher CRP levels were associated with lower PNI. The proportion of explained variance remained moderate.

A complementary logistic regression analysis was performed in men to explore factors independently associated with high nutritional risk (PNI < 40). Hemoglobin was the only variable that remained significantly associated, showing an inverse relationship with the odds of high nutritional risk (OR = 0.94, 95% CI 0.91–0.98; $p < 0.01$). Thus, lower hemoglobin levels were associated with a higher probability of high nutritional risk.

Discussion

In this cross-sectional study of predominantly older adults with RA, nutritional risk assessed by the PNI was common and showed clear sex-related differences. More than half of the cohort exhibited PNI values compatible with nutritional risk, with men displaying significantly lower PNI values, a higher frequency of nutritional risk and a markedly greater prevalence of high nutritional risk compared with women.

Importantly, the clinical correlates of PNI differed substantially by sex. In women, despite slightly higher disease activity, high nutritional risk was uncommon and PNI showed only a weak

association with age, with no meaningful relationships with inflammatory markers, disease activity or patient-reported outcomes. This pattern suggests a more gradual, age-related decline in nutritional reserve, largely independent of RA-specific clinical features. In contrast, in men, nutritional risk emerged as a clinically meaningful dimension of disease burden, associated with systemic inflammation, higher disease activity, lower BMI and poorer mental HRQoL. In multivariable analyses, hemoglobin emerged as the principal independent factor associated with PNI variability, reflecting the close relationship between nutritional risk and systemic vulnerability in older men with RA.

Taken together, these results support the use of simple laboratory-based indices such as the PNI to capture dimensions of disease impact that are not adequately reflected by conventional measures of inflammatory activity alone.

The clinical context of RA has evolved substantially over recent decades. Treat-to-target strategies [23], earlier diagnosis, and the widespread use of biologic and targeted synthetic DMARDs have reduced severe inflammatory complications and hospitalizations [24]. Consequently, most patients are now managed in outpatient settings with satisfactory control of synovitis. This therapeutic progress has shifted attention toward less visible domains of disease impact, including functional decline, fatigue and nutritional vulnerability, which are incompletely captured by conventional disease activity indices and may persist despite low or moderate inflammatory activity [25].

In this ambulatory setting, tools capable of identifying patients at increased nutritional risk are particularly relevant. Our findings support the use of nutritional risk assessment in routine RA care not as a marker of acute illness or disease severity, but as an indicator of underlying vulnerability that may influence long-term outcomes and overall disease impact. Accordingly, the PNI may be considered a pragmatic screening tool to identify patients who could benefit from closer nutritional evaluation or targeted interventions, rather than a diagnostic instrument per se [26,27]. Notably, in our cohort, a substantial proportion of older adults with RA—particularly men—exhibited PNI values compatible with nutritional risk despite the absence of overt malnutrition or severe disease activity, suggesting that this vulnerability may remain clinically silent unless actively screened for [14].

RA is increasingly recognized as a disease with relevant sex-specific biological and clinical differences [16]. In the present study, these differences extended beyond disease activity and patient-reported outcomes to nutritional risk, as reflected by distinct PNI profiles in men and women. Notably, men exhibited lower PNI values and a disproportionately higher prevalence of high nutritional risk, despite the common perception of greater overall disease burden in women. These findings suggest that nutritional vulnerability in RA does not simply parallel inflammatory activity or patient-reported burden, but may reflect sex-related immune and metabolic trajectories that are insufficiently captured by conventional clinical assessment [14,28–30].

In this context, the strong association between hemoglobin levels and PNI is particularly informative. Anemia of chronic disease, a frequent consequence of chronic inflammation and ageing-related processes, reflects alterations in iron handling, erythropoiesis and metabolic efficiency [5,30]. Hemoglobin may therefore act as an integrative marker linking inflammatory burden, nutritional reserve and systemic vulnerability in older adults with RA.

Across multivariable analyses, hemoglobin emerged as the factor most consistently associated with PNI variability and the only variable independently associated with high nutritional risk (PNI < 40) in both linear and logistic models, supporting the robustness of this finding. Given the cross-sectional design, hemoglobin should be interpreted as a marker of nutritional vulnerability rather than a causal determinant, likely reflecting the integrated effects of chronic inflammation, metabolic adaptation and reduced physiological reserve rather than isolated dietary insufficiency [31].

Other variables, including BMI, CRP and the mental component of HRQoL, showed weaker and less consistent independent associations with PNI. These factors likely capture complementary dimensions influencing nutritional reserve in chronic inflammatory disease—such as systemic

inflammation, body composition and psychological well-being—suggesting a contextual rather than primary role in driving nutritional risk [32,33].

Beyond biological mechanisms, social and behavioral factors may also contribute to the observed sex-related patterns of nutritional vulnerability [34,35]. In older adults, nutritional status is shaped not only by inflammatory and metabolic processes but also by living conditions, dietary behaviors and social support. Older men, particularly those living alone, have been shown to exhibit poorer diet quality and lower engagement in nutritional self-care [34,35]. Although not directly assessed in the present study, these factors may partially modulate the nutritional risk captured by the PNI and should be considered when interpreting sex-specific differences.

Several strengths of this study deserve emphasis. The analysis was conducted within a well-characterized, real-world cohort of older adults with RA, with comprehensive clinical, laboratory, functional and patient-reported data collected under routine care conditions. This setting enhances the clinical relevance of the findings and reflects contemporary outpatient management of RA. Importantly, the sex-stratified analytical approach allowed the identification of distinct patterns of nutritional risk that would likely have been obscured in pooled analyses.

Nevertheless, certain limitations should be acknowledged. The cross-sectional design precludes causal inference and limits conclusions regarding temporal relationships between nutritional risk and clinical outcomes. Although the PNI provides a pragmatic and accessible screening measure, it does not replace comprehensive nutritional assessment and does not capture all dimensions of malnutrition, including dietary intake, micronutrient status or body composition. Finally, the single-center nature of the cohort may limit generalizability, although it also ensures methodological consistency and uniform clinical assessment.

In conclusion, nutritional risk assessed by the PNI is common among older adults with RA and shows marked sex-specific patterns, with men exhibiting a greater burden of nutritional vulnerability. The PNI captures a clinically relevant dimension of disease impact that extends beyond joint inflammation and conventional activity indices, reflecting aspects of physiological and nutritional reserve not routinely assessed in clinical practice. These findings support the integration of simple nutritional screening tools into routine RA care to improve risk stratification and promote a more holistic, patient-centered approach to disease management. Longitudinal studies are needed to determine whether trajectories of nutritional risk predict clinical outcomes and to clarify the role of targeted nutritional and multidisciplinary interventions in RA.

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Data Availability Statement: The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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