



# Elderly Patients Exhibit Stronger Inflammatory Responses during Gout Attacks

Jae Hyun Lee,<sup>1\*</sup> Ji Ae Yang,<sup>1\*</sup>  
Kichul Shin,<sup>2</sup> Ga Hye Lee,<sup>3,4</sup>  
Won-Woo Lee,<sup>3,4</sup> Eun Young Lee,<sup>1</sup>  
Yeong Wook Song,<sup>1,5</sup> Eun Bong Lee,<sup>1</sup>  
and Jin Kyun Park<sup>1,5</sup>

<sup>1</sup>Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea; <sup>2</sup>Department of Internal Medicine, Seoul Metropolitan Government-Seoul National University Boramae Medical Center, Seoul, Korea; <sup>3</sup>Department of Microbiology and Immunology, Seoul National University College of Medicine, Seoul, Korea; <sup>4</sup>Department of Biomedical Sciences, Seoul National University College of Medicine, Seoul, Korea; <sup>5</sup>WCU Department of Molecular Medicine and Biopharmaceutical Sciences, Medical Research Institute, Seoul National University College of Medicine, Seoul, Korea

\*Jae Hyun Lee and Ji Ae Yang contributed equally to this work.

Received: 23 June 2017

Accepted: 16 September 2017

Address for Correspondence:

Jin Kyun Park, MD  
Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea  
E-mail: jinkyunpark@gmail.com

Funding: This research was supported in part by a grant from Korea Healthcare Technology R & D Project, Ministry for Health and Welfare Affairs, Republic of Korea (HI13C0715).

## INTRODUCTION

Gout is an inflammatory arthritis that is caused by the crystallization of uric acid in the joints and periarticular tissue and subsequent inflammation. When serum uric acid concentration exceeds the solubility limit of approximately 6.8 mg/dL, crystal formation begins. Therefore, persistent hyperuricemia is an important risk factor for developing a gout arthritis (1), and lowering serum uric acid levels below 6 mg/dL is crucial to prevent further gout flares (2,3).

The monosodium urate (MSU) crystals activate innate immune cells, which then secrete pro-inflammatory cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)- $\alpha$  (4-7). These cytokines recruit and activate other immune cells, thereby generating a self-perpetuating inflammatory cascade in the joint. This leads to the sudden onset of excruciatingly painful arthritis, characteristic of a gout attack. Once

Gout attacks are often accompanied by systemic inflammatory response. The aim of the retrospective study was to compare gout patients in different age groups in terms of their clinical features at gout attacks. Patients, who were treated for gout attack in two tertiary medical centers between January 2000 and April 2014, were divided into young ( $\leq 50$  years), middle-aged, and elderly ( $> 65$  years) groups. Patients in three age groups were compared in terms of presence of fever ( $> 37.8^{\circ}\text{C}$ ), C-reactive protein (CRP) levels, and erythrocyte sedimentation ratio (ESR) at the gout attacks. Monocytes, which were isolated from 10 consecutive patients who previously experienced gout attacks, were stimulated with monosodium urate (MSU) crystals and cytokine production was measured by flow cytometry. Among 254 patients analyzed in this study, 48 were young, 65 were middle-aged, and 141 were elderly. The elderly patients were more likely to have fever (51.1%) during the attack than the young (20.8%) and middle-aged (30.8%) patients ( $P < 0.001$  by  $\chi^2$  test). They were also more likely to have higher ESR and CRP levels than the young patients ( $P = 0.002$  for ESR,  $P < 0.001$  for CRP). Patients' age correlated significantly with CRP and ESR levels (both  $P < 0.001$ ). After stimulation with MSU, the production of interleukin-1 $\beta$  by monocytes increased with patients' age ( $r = 0.670$ ,  $P = 0.03$ ). In conclusion, gout attacks in elderly patients are associated with fever and higher ESR and CRP levels, often resembling a septic arthritis.

**Keywords:** Gout; Aging; Fever; C-reactive Protein; Inflammation

released into bloodstream, inflammatory cytokines can induce a febrile response and drive the hepatic production of acute phase reactants, which cause C-reactive protein (CRP) levels and erythrocyte sedimentation ratios (ESRs) to rise (8).

Since both MSU crystals and bacteria activate innate immune cells via similar pathogen-associated molecular receptors, gout attacks are often indistinguishable from acute septic arthritis, especially when there are strong extra-articular symptoms such as fever, leukocytosis, and CRP elevation (9-11). There is some evidence that the clinical characteristics of gout attack differ between older and younger patients. Even though elderly patients often fail to mount systemic inflammatory response during bacterial infection, unlike younger patients (perhaps as a result of immune aging) (12,13), they seem to present more often with fever in gout attacks (14). The prevalence of gout in Korea increased sharply from 0.35% in 2007 to 0.76% in 2015 with a higher prevalence among the elderly (2). With aging society

and rising gout prevalence in Korea, differentiating a gouty arthritis from a septic arthritis will be a clinical challenge in elderly patients who present with fever and inflammatory arthritis. Therefore, the present study was performed to investigate the association between inflammatory response and patients' age during gout attacks.

## MATERIALS AND METHODS

### Patients

All patients who were treated for an acute gout attack at Seoul National University Hospital and Seoul Metropolitan Government-Seoul National University Boramae Medical Center between January 2000 and April 2014 were included. In initial step, all patients with International Classification of Disease (ICD) code for gout (ICD M10), which was entered for billing and reimbursement purpose, were selected in the electronic medical record system. The medical records of those selected patients were extensively reviewed. Gout was diagnosed by consulting rheumatologists according to 1977 American College of Rheumatology criteria (15). Patients with uncertain gout diagnosis or concurrent infection were excluded from this study. The patients were divided into young (age  $\leq 50$  years), middle-aged (age  $> 50$  and  $\leq 65$  years), and elderly patient groups (age  $> 65$  years), similar to the age classification used the previous studies (2,16). Information on the presence of fever ( $\geq 37.8^{\circ}\text{C}$ ), the number of involved joints, the presence of MSU crystals if joint fluid analysis was done, and the laboratory findings at the time of the gout attack were retrieved from the medical records. All body temperatures were measured and documented by health care providers.

### Stimulation of monocytes

The laboratory personnel, who performed the cytokine assay, were blinded to clinical characteristics of the 10 gout patients. Purified monocytes were stimulated for 4 hours with 10 ng/mL lipopolysaccharide (LPS) or 200  $\mu\text{g/mL}$  MSU (InvivoGen, San Diego, CA, USA) in the presence of brefeldin A (BFA; BD Biosciences, San Jose, CA, USA). The cells were fixed and permeabilized using Cytofix/Cytoperm kit (BD Biosciences) and stained for 30 minutes at 4 degrees with antibodies to CD14, TNF- $\alpha$  (both from BD Biosciences), IL-1 $\beta$  (BioLegend, San Diego, CA, USA), IL-6 (eBiosciences, San Diego, CA, USA). Stained cells were acquired on a BD LSRFortessa (BD Biosciences) and analyzed using Flowjo software (Tree star, Ashland, OR, USA).

### Statistical analysis

The three groups were compared in terms of categorical variables by  $\chi^2$  tests and in terms of continuous variables by analysis of variance (ANOVA) or Kruskal-Wallis test with Dunn's multiple comparison test, as appropriate. The correlation between

age and CRP, ESR, and white blood cell (WBC) counts was assessed by Spearman's rank correlation. A sensitivity analysis was performed with patients of whom MSU crystals in joint fluid were confirmed. The cytokine production was compared using Mann-Whitney test. The correlation between the cytokine production and age was assessed by Spearman's correlation.  $P < 0.05$  was considered to indicate statistical significance. All analyses were performed by using IBM SPSS statistics version 21 (SPSS Inc., Chicago, IL, USA).

### Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board and Ethics Committee at Seoul National University Hospital (IRB No. H-1504-030-662). The requirement for informed consent was waived since the study involved a minimum risk to the enrolled patients in this retrospective cohort and no identifiable information was used. For monocyte stimulation assay, 10 consecutive gout patients without active gout were enrolled after obtaining an informed consent.

## RESULTS

### Clinical characteristics of the three age groups

During the study period, 423 patients were treated for gout attack. Patients with missing demographic or laboratory values (including the CRP and uric acid levels at the time of the gout attack) were excluded, resulting in a final cohort of 254 patients. Of those patients, 48 were young (age  $\leq 50$  years), 65 were middle-aged ( $> 50$  and  $\leq 65$  years), and 141 were elderly (age  $> 65$  years) (Table 1). The elderly patients were more likely to be female than the other two groups ( $P = 0.007$ ). They also had a lower body mass index ( $P < 0.001$ ), a longer duration of gout disease ( $P = 0.015$ ), and more comorbidities, including diabetes mellitus, hypertension, chronic kidney disease, anemia, coronary artery disease, cerebrovascular disease, and malignancy. The elderly patients had lower hemoglobin level and lower glomerular filtration rate than the other two groups (both  $P < 0.001$ ) (Table 1).

### Elderly patients exhibit greater inflammatory responses than the other age groups

The proportion of patients with more than one joint involvement did not differ significantly between age groups (37.5% in the young, 43.1% in the middle-aged, and 52.5% in elderly patients,  $P = 0.388$ ). However, the older patients were more likely to present with fever (51.1%) than the young (20.8%) and middle-aged (30.8%) patients ( $P < 0.001$ ) (Fig. 1A). The CRP levels in the elderly (9.42 [3.53–16.08] mg/dL) were also significantly higher than those of the middle-aged (3.64 [0.72–7.28] mg/dL,  $P < 0.001$ ) and young (2.83 [0.87–5.59] mg/dL,  $P < 0.001$ ) patients. In addition, the elderly patients had significantly higher

**Table 1.** Baseline clinical characteristics of patients at gout attack according to age groups

Characteristics	Age groups			P*
	Age ≤ 50 (n = 48)	50 < Age ≤ 65 (n = 65)	Age > 65 (n = 141)	
Age at attack, yr	40.9 (34.5–46.6)	58.6 (54.7–62.3)	74.1 (69.7–78.9)	< 0.001
Male	47 (97.9)	60 (92.3)	116 (82.3)	0.007
BMI	25.7 ± 4.5	24.4 ± 3.2	23.5 ± 3.1	< 0.001
Disease duration, yr	0.2 (0–3.2)	2.2 (0–7.8)	3.9 (0–8.3)	0.015
Presence of tophus	6 (12.5)	12 (18.5)	26 (18.4)	0.618
<b>Comorbidities</b>				
Diabetes mellitus	6 (12.5)	12 (18.5)	49 (34.8)	0.003
Hypertension	17 (35.4)	30 (46.2)	97 (68.8)	< 0.001
Chronic kidney disease	12 (25.0)	14 (21.5)	61 (43.3)	0.003
Coronary artery disease	3 (6.3)	7 (10.8)	25 (17.7)	0.098
Cerebrovascular disease	3 (6.3)	3 (4.6)	28 (19.9)	0.003
Liver disease	4 (8.3)	5 (7.7)	8 (5.7)	0.654
Cancer	3 (6.3)	9 (13.8)	35 (24.8)	0.009
Renal stone	0 (0)	1 (1.5)	6 (4.3)	0.368
<b>Gout medication</b>				
Allopurinol	7 (14.6)	9 (13.8)	25 (17.7)	0.740
Febuxostat	1 (2.1)	0 (0.0)	5 (3.5)	0.401
Benzbromarone	1 (2.1)	0 (0.0)	2 (1.4)	0.766
Colchicine	3 (6.3)	5 (7.7)	5 (3.5)	0.386
NSAID	4 (8.3)	5 (7.7)	12 (8.5)	0.980
Prednisolone	3 (6.3)	2 (3.1)	5 (3.5)	0.668
Hemoglobin, g/dL	13.8 (11.2–15.4)	12.1 (10.0–14.2)	10.9 (9.9–12.3)	< 0.001
Uric acid, mg/dL	8.2 (6.8–9.5)	7.0 (5.0–8.4)	7.5 (5.7–9.0)	0.014
Creatinine, mg/dL	1.1 (0.9–1.9)	1.2 (1.0–1.5)	1.5 (1.1–1.9)	0.002
GFR, mL/min/1.73 m <sup>2</sup>	70.0 (40.7–93.3)	60.6 (46.4–74.4)	44.8 (29.7–59.7)	< 0.001

All data are presented as mean ± standard deviation, median (interquartile range), or number (%).

BMI = body mass index, NSAID = nonsteroidal anti-inflammatory drug, GFR = glomerular filtration rate, ANOVA = analysis of variance.

\*P values were generated by using ANOVA, Kruskal-Wallis test, or  $\chi^2$  test. P values less than 0.05 are shown in Bold.

ESR levels (54 [38–88] mm/hr) than the young patients (27 [13.5–53.0] mm/hr,  $P = 0.002$ ); a significant difference from the middle-aged patients was not observed (54 [38–88] mm/hr vs. 51 [28.5–72.8] mm/hr,  $P = 0.288$ ). The three groups did not differ in terms of WBC counts (Fig. 1B). Moreover, all three groups had less than 50% leukocytosis (defined as WBC > 10,000/ $\mu$ L) and did not differ in terms of leukocytosis frequency ( $P = 0.569$  by  $\chi^2$  test) (Data not shown). Furthermore, age at attack correlated significantly with ESR (Spearman's rank correlation coefficient  $r = 0.327$ ,  $P < 0.001$ ) and CRP ( $r = 0.329$ ,  $P < 0.001$ ) but not with WBC counts ( $r = 0.005$ ,  $P = 0.942$ ) (Fig. 1C).

### Sensitivity analysis

In 75 (29.5%) of 254 patients, MSU crystals were detected in the synovial fluid during their gout attack. Baseline characteristics of these patients were similar to those of whole patients (Table 2). The CRP levels of elderly patients (13.82 [8.71–23.07] mg/dL) were also significantly higher than those of the young patients (5.14 [2.77–15.29] mg/dL,  $P = 0.012$ ) and the middle-aged patients (5.02 [2.98–15.86] mg/dL,  $P = 0.018$ ). The percentage of patients with fever and the levels of ESR were higher in the elderly group but did not reach statistical significance (Table 3).

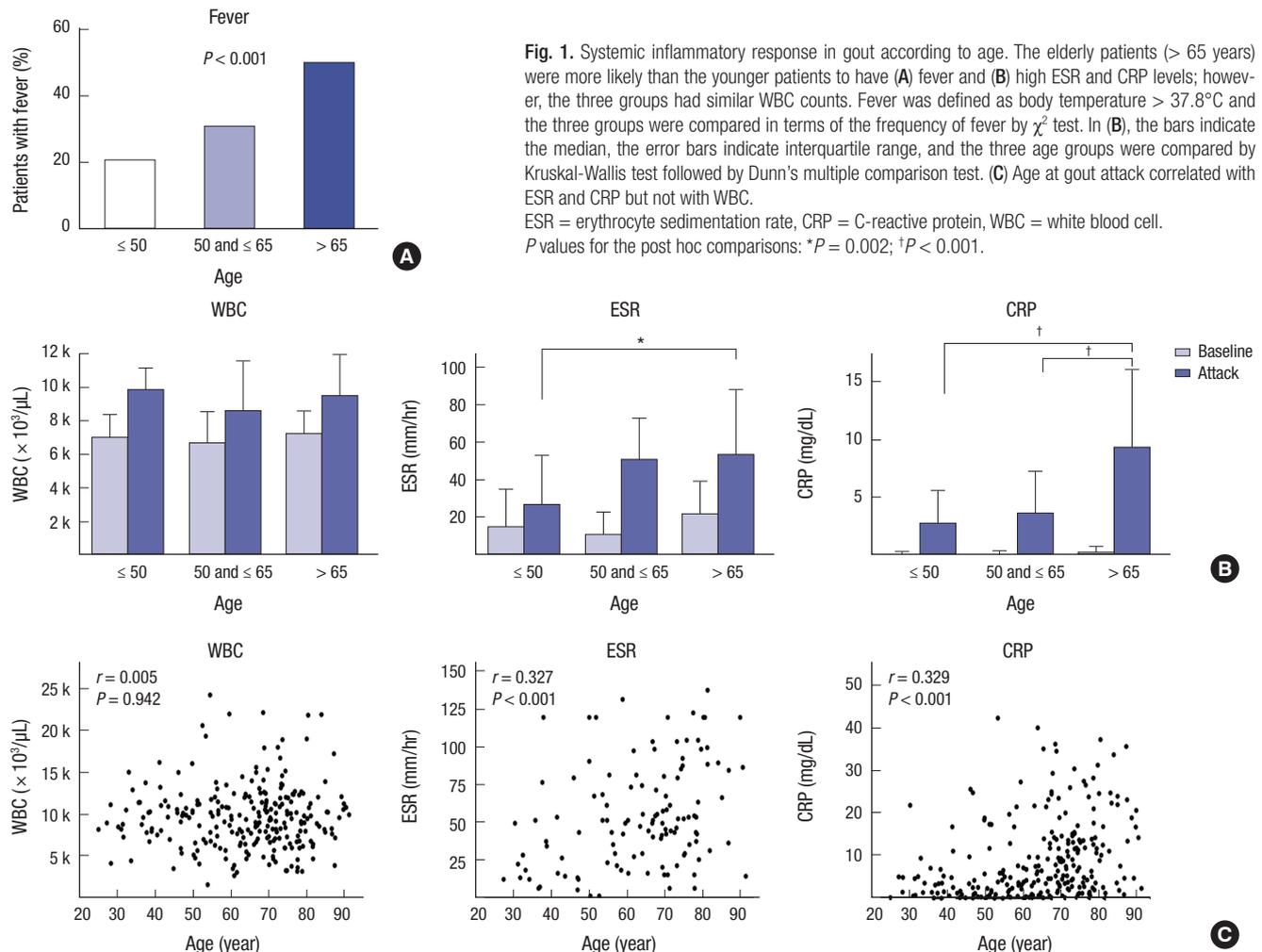
### Production of inflammatory cytokines correlates with age

Monocytes from 10 consecutive gout patients currently not on acute gout attack were activated with MSU crystals or LPS. MSU induced the monocytes to preferentially secrete IL-1 $\beta$  as compared to LPS, suggesting IL-1 $\beta$  as the key cytokine in the gout flare (Fig. 2A). The production of IL-1 $\beta$  significantly correlated with age of patients, whereas there was no correlation between production of IL-6 and TNF- $\alpha$  and patients' age (Fig. 2B).

### DISCUSSION

To the best of our knowledge, our study is the first to show that gout attacks in elderly patients are accompanied by stronger systemic inflammatory responses than those in younger patients. This contradicts the general assumption that elderly patients might not be able to mount appropriate inflammatory responses due to immune aging.

The inflammatory responses that are raised during gout attack are largely driven by immune cells that recognize MSU crystals as a danger signal and thereafter secrete pro-inflammatory cytokines such as IL-1 $\beta$ , IL-6, and TNF- $\alpha$  (4–7). Those cytokines ultimately induce a febrile response and hepatic synthesis of acute phase reactants with subsequent elevation of



**Fig. 1.** Systemic inflammatory response in gout according to age. The elderly patients (> 65 years) were more likely than the younger patients to have (A) fever and (B) high ESR and CRP levels; however, the three groups had similar WBC counts. Fever was defined as body temperature > 37.8°C and the three groups were compared in terms of the frequency of fever by  $\chi^2$  test. In (B), the bars indicate the median, the error bars indicate interquartile range, and the three age groups were compared by Kruskal-Wallis test followed by Dunn's multiple comparison test. (C) Age at gout attack correlated with ESR and CRP but not with WBC. ESR = erythrocyte sedimentation rate, CRP = C-reactive protein, WBC = white blood cell. *P* values for the post hoc comparisons: \**P* = 0.002; †*P* < 0.001.

ESR and CRP. Since the specialized receptors of T and B lymphocytes cannot recognize MSU crystals, their role in gout attack may be trivial. This means that the higher inflammatory responses of elderly patients during gout attack are due to augmentation of their innate immune responses to MSU crystals, increased formation of "reactive" MSU crystals, or both.

It seems less likely that increased reactive MSU crystal formation alone explains the more pronounced inflammatory profile of the elderly patients with gout attack: although the elderly patients did have a significantly longer disease duration than the other groups (*P* = 0.015, Table 1), and gout disease duration correlates positively with total body crystal burden (17), large tophi in the joints and periarticular tissue might not necessarily induce severe gout flares. Moreover, the different age groups in the present study did not differ in terms of the presence of tophi (Table 1). Thus, the alternative explanation, that elderly patients have augmented innate immune responses to MSU crystals, may be more likely.

It is possible that these augmented responses are the result of pro-inflammatory hyperactivity of the innate immune system in older people that serves to compensate for the aging-associated

impaired dysfunction of the adaptive immune cells: the physiological thymus involution that occurs with age is known to lead to relative immunodeficiency of adaptive immunity (18, 19). This notion is supported by the observation that CD16-positive monocytes, which are also called pro-inflammatory monocytes, increase with age and secrete higher amounts of TNF- $\alpha$  when activated (20,21). In vitro, when monocytes isolated from gout patients were stimulated with MSU crystals, they produced preferentially IL-1 $\beta$  rather than IL-6 and TNF- $\alpha$  and the IL-1 $\beta$  production correlated with patient's age (Fig. 2). The importance of IL-1 $\beta$  production during gout attack is supported by the successful efficacy of IL-1 $\beta$  inhibitor such as canakinumab in gout (4). Interestingly, since production of TNF- $\alpha$  and IL-6 by monocytes was not age-dependent, one might speculate that function of inflammasome, which is the intracellular site of IL-1 $\beta$  production, increases with age as a compensatory mechanism.

Colchicine is widely used to treat a gout attack. It decreases production of IL-1 $\beta$  in monocytes and neutrophils by interfering with inflammasome function (22). Recently colchicine has been shown to reduce risk of a cardiovascular disease in gout patients (23-25). Therefore, colchicine might an attractive treat-

**Table 2.** Baseline clinical characteristics of patients of the sensitivity analysis cohort

Characteristics	Age groups			P*
	Age ≤ 50 (n = 16)	50 < Age ≤ 65 (n = 16)	Age > 65 (n = 43)	
Age at attack, yr	38.9 (33.9–16.1)	57.7 (52.1–62.6)	75.9 (70.1–80.0)	< 0.001
Male	16 (100.0)	15 (93.8)	36 (83.7)	0.160
BMI	25.9 ± 4.8	24.4 ± 3.6	23.2 ± 3.7	<b>0.072</b>
Disease duration, yr	0.4 (0–4.8)	1.3 (0–9.3)	3.0 (0–8.1)	0.661
Presence of tophus	0 (0.0)	5 (31.3)	4 (9.3)	<b>0.017</b>
Comorbidities				
Diabetes mellitus	0 (0)	3 (18.8)	13 (30.2)	<b>0.040</b>
Hypertension	5 (31.3)	8 (50.0)	28 (65.1)	0.062
Chronic kidney disease	2 (12.5)	4 (25.0)	11 (25.6)	0.548
Coronary artery disease	1 (6.3)	1 (6.3)	5 (11.6)	0.731
Cerebrovascular disease	1 (6.3)	0 (0)	9 (20.9)	0.071
Liver disease	2 (12.5)	0 (0)	3 (7.0)	0.363
Cancer	1 (6.3)	3 (18.8)	13 (30.2)	0.135
Renal stone	0 (0)	0 (0)	1 (2.3)	0.686
Gout medication	5 (31.3)	3 (18.8)	13 (30.2)	0.648
Allopurinol	3 (18.8)	1 (6.3)	7 (16.3)	0.547
Febuxostat	0 (0)	0 (0)	1 (2.3)	0.686
Benzbromarone	0 (0)	0 (0)	0 (0)	
Colchicine	2 (12.5)	2 (12.5)	2 (4.7)	0.464
NSAID	2 (12.5)	1 (6.3)	5 (11.6)	0.808
Prednisolone	0 (0)	1 (6.3)	2 (4.7)	0.630
Hemoglobin, g/dL	13.9 (11.8–14.8)	12.7 (10.5–13.4)	11.4 (9.6–12.3)	<b>0.001</b>
Uric acid, mg/dL	8.0 (6.5–8.9)	7.3 (5.7–8.6)	7.7 (5.9–8.9)	0.656
Creatinine, mg/dL	1.0 (0.9–1.2)	1.4 (1.0–1.9)	1.4 (1.2–1.8)	<b>0.007</b>
GFR, mL/min/1.73 m <sup>2</sup>	86.1 (70.0–96.6)	54.6 (37.3–72.9)	42.0 (30.6–59.1)	< 0.001

All data are presented as mean ± standard deviation, median (interquartile range), or number (%).

BMI = body mass index, NSAID = nonsteroidal anti-inflammatory drug, GFR = glomerular filtration rate, ANOVA = analysis of variance.

\*P values were generated by using ANOVA, Kruskal-Wallis test, or  $\chi^2$  test. P values less than 0.05 are shown in Bold.

**Table 3.** Characteristics of gout attack in the sensitivity analysis cohort

Characteristics	Age group			P*
	Age ≤ 50 (n = 16)	50 < Age ≤ 65 (n = 16)	Age > 65 (n = 43)	
Fever (> 37.8°C)	7 (43.8)	9 (56.3)	29 (67.4)	0.241
Leukocytosis	10 (62.5)	5 (31.3)	24 (55.8)	0.156
Oligoarticular gout	4 (25.0)	7 (43.8)	21 (48.8)	0.257
During attack				
WBC, × 10 <sup>3</sup> /μL	10.23 (8.79–12.67)	9.03 (6.78–11.51)	10.20 (8.02–12.35)	0.361
CRP, mg/dL	5.14 (2.77–15.29)	5.02 (2.98–15.86)	13.82 (8.71–23.07)	<b>0.009</b>
ESR, mm/hr	50.00 (24.00–98.50)	54.00 (51.00–72.25)	58.00 (43.50–99.50)	0.520
At baseline				
WBC, × 10 <sup>3</sup> /μL	6.76 (6.01–9.35)	6.58 (5.01–8.09)	7.60 (6.10–9.57)	0.210
CRP, mg/dL	0.22 (0.12–0.57)	0.09 (0.02–0.37)	0.55 (0.19–1.12)	<b>0.028</b>
ESR, mm/hr	25.00 (13.25–45.00)	10.00 (8.00–30.25)	31.00 (11.50–52.50)	0.296

All data are presented as mean ± standard deviation, median (interquartile range), or number (%).

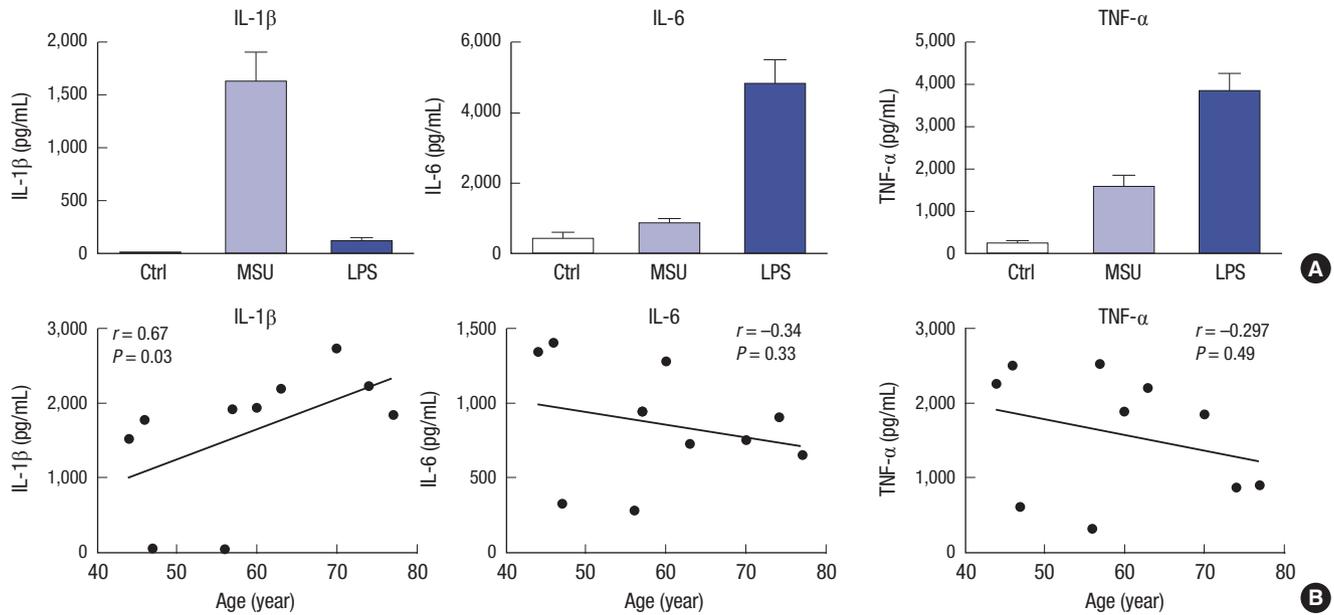
WBC = white blood cell, CRP = C-reactive protein, ESR = erythrocyte sedimentation ratio.

\*P values were generated by using Kruskal-Wallis test, or  $\chi^2$  test. P values less than 0.05 are shown in Bold.

ment option in elderly patients with cardiovascular risk factors (Table 1).

Since both gouty and septic arthritis are characterized by intense arthritis with a sudden onset, a gout attack is often clinically indistinguishable from a septic arthritis attack, especially when extra-articular features (including fever, high leukocytosis, and CRP elevation) are dominant. The present study showed

that as many as 50% of the gout attacks in elderly patients involved fever. The elderly patients also had significantly higher CRP levels and ESR than the other groups of patients (both  $P < 0.001$ ) (Fig. 1). In addition, CRP and ESR, but not WBC counts, correlated significantly with patients' age at attack (Fig. 1). As a result, the elderly patients were more likely than the younger patients to be misdiagnosed with septic arthritis and to undergo joint



**Fig. 2.** Age-dependent IL-1 $\beta$  production by monocytes following activation with urate crystal. **(A)** Monocytes from 10 consecutive gout patients were stimulated with MSU crystals or LPS as described in Materials and Methods. MSU induced the monocytes to preferentially secrete IL-1 $\beta$  as compared to LPS. The bars indicate the mean, and the error bars indicate standard error. **(B)** The IL-1 $\beta$  production but not that of IL-6 or TNF- $\alpha$  correlated with patients' age. Correlation between cytokine production and age was assessed using Spearman's correlation.

MSU = monosodium urate, LPS = lipopolysaccharide, IL = interleukin, TNF = tumor necrosis factor.

lavage (data not shown), which often associates with pain and a considerable hospital stay after the procedure. These observations suggest that elderly patients who present with fever and joint pain should be suspected of gout attack. If they lack obvious risk factors of septic arthritis (i.e., no history of trauma or other infection), it may be preferable to administer empirical antibiotics and observe them watchfully until the microbial culture result of joint fluid is available before proceeding with more invasive procedures such as joint lavage.

A major limitation of this study is that arthrocentesis was not performed in all patients. As a result, it remains possible that some of the patients had a pseudogout or another crystal-induced arthropathy. However, in a sensitivity analysis with patients with proven MSU crystal during their gout attack, CRP were still higher in the elderly than in the younger patients (Table 3). Further prospective studies are needed to identify clinical and laboratory features that might help differentiate a gout attack from septic arthritis. Furthermore, since neutrophils contribute to the inflammatory response during gout attack, their response to MSU crystals in different age groups needs further investigations (1).

In conclusion, gout attacks in elderly patients are commonly accompanied by strong systemic inflammatory responses with fever and higher CRP levels and ESRs, resembling a septic arthritis. To avoid unnecessary invasive procedures or prolonged treatment with antibiotics, it is crucial that gout attacks be diagnosed and treated correctly in elderly patients.

## DISCLOSURE

The authors have no potential conflicts of interest to disclose.

## AUTHOR CONTRIBUTION

Conceptualization: Lee JH, Yang JA, Park JK. Data curation: Lee JH, Yang JA, Shin K, Lee GH, Lee WW. Formal analysis: Lee EY, Park JK. Writing - original draft: Lee JH, Yang JA. Writing - review & editing: Shin K, Lee EY, Song YW, Lee EB, Park JK.

## ORCID

Jae Hyun Lee <https://orcid.org/0000-0002-5668-4793>  
 Ji Ae Yang <https://orcid.org/0000-0003-1620-0376>  
 Kichul Shin <https://orcid.org/0000-0002-6749-7598>  
 Ga Hye Lee <https://orcid.org/0000-0002-5909-7471>  
 Won-Woo Lee <https://orcid.org/0000-0002-5347-9591>  
 Eun Young Lee <https://orcid.org/0000-0001-6975-8627>  
 Yeong Wook Song <https://orcid.org/0000-0002-5384-3437>  
 Eun Bong Lee <https://orcid.org/0000-0003-0703-1208>  
 Jin Kyun Park <https://orcid.org/0000-0003-2167-9393>

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