

# The Role of Inflammatory Cytokine and Inflammatory Regulator Protein Related to Severity of Joint Effusion in Osteoarthritis

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# The Role of Inflammatory Cytokine and Inflammatory Regulator Protein Related to Severity of Joint Effusion in Osteoarthritis

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## Abstract

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**BACKGROUND:** Osteoarthritis (OA) is an inflammatory degenerative articular disease characterized by damage narrowing the joint gap, pain, and loss of joint function. Joint effusion is a clinical feature often found in OA patients and believed to be directly proportional to the levels of pro-inflammatory cytokine, tumor necrosis factor (TNF)-alpha, and interleukin 1B (IL-1B), and various other regulatory proteins such as transcription factor proteins, nuclear factor of activated T-cells 1 (NFATC1), and chromosome 1 open reading frame 38 (C1orf38).

**AIM:** The aim of the study was to explore the role of pro-inflammatory cytokine expression (TNF-alpha and IL-1B) and transcription regulatory proteins (NFATC1 and C1orf38) with the severity of joint effusion in OA patients.

**METHODS:** This study was an observational study with a case series study approach. A total of 80 study subjects with OA joint effusions were included in the study. The diagnosis of OA was based on clinical and radiologic assessment from American College of Rheumatology. Data of clinical severity were assessed with Kellgren-Lawrence criteria, Tegner Lysholm Knee Scoring Scale. Random blood examination was performed to obtain erythrocyte sedimentation rate (ESR) and qualitative C-reactive protein to evaluate the level of inflammation in the body. TNF-alpha, IL-1B, NFATC1, and C1orf38 levels were assessed in joint fluid using the enzyme-linked immunosorbent assay method. The correlation was analyzed with the Pearson correlation test (p = 0.05).

**RESULTS:** The severity of OA joint effusion was not correlated to ESR (p adjusted = 0.169; r = 0.078), TNF-alpha (p adjusted = 0.112; r = -0.087), IL-1B (p adjusted = 0.136, r = -0.078), C1orf38 (p adjusted = 0.121; r = -0.088), and NFATC1 (p adjusted = 0.102; r = -0.08).

**CONCLUSION:** Pro-inflammatory cytokines of TNF-alpha and IL-1B, and the transcription factors of pro-inflammatory cytokines gene expression, NFATC1, and C1orf38, did not correlate with the severity of joint effusion in OA.

## Introduction

Osteoarthritis (OA) is an inflammatory degenerative articular disease of the joints common in elderly patients older than 50 years. This disorder is characterized by damage narrowing the joint gap, pain, and loss of joint function [1]. OA is one of the disorders with the highest morbidity in elderly patients, which will cause disability and require substantial funds in management and rehabilitation. As the degree of health and advancement in the medical world increases, it causes an increase in life expectancy which leads to an increase in elderly population. Radiography is an important investigation used to diagnose OA, although this examination is unable to detect and monitor biochemical and molecular changes that occur in joint tissues long before the onset of symptoms from OA or the appearance of disabilities due to OA [2].

In the management of OA, the modulation the specific mechanisms of the immune systems plays a role, such as tumor necrosis factor-α (TNF-α), Interleukin 1 (IL-1), and IL-6 signaling, or lymphocyte activation [2].

Joint effusion is a clinical feature often found in OA patients. Apart from joint pain and radiologic osteophytes, nine out of ten people with OA exhibit a clinical picture of joint effusion. Joint effusion is a condition that precedes damage to the joints which will lead to osteophyte formation and narrowing of the joints resulting in pain and movement disorders in OA patients. Joint effusion is an initial pathological condition of OA that needs to be explored to obtain novel biological markers that are expected to be developed into predictors in diagnosis, prognosis, and management of OA [3], [4].

Joint effusion is believed to be closely related to joint inflammation. Inflammation is a pathological condition that forms the basis of joint effusion. Inflammatory conditions of the joints will cause pro-inflammatory cytokine activation, TNF-alpha, and IL-1B. TNF-alpha and IL-1B will initiate the activation of reactive oxygen species, an oxidant, which will lead to the activation of proteolytic enzymes in the joints. Proteolytic enzymes will yield in matrix degradation of the cartilage and lead to joint cartilage damage and hence impaired joint mobility. The severity of joint

effusion was hypothesized to be directly proportional to the levels of pro-inflammatory cytokine, TNF-alpha, and IL-1B. The more severe the joint effusion, the pro-inflammatory cytokine levels will increase [2], [5], [6].

Central dogma states that every expression of a protein is preceded by a process of transcription and translation, as well as in the expression of TNF-alpha and IL-1B proteins in joint inflammation. TNF-alpha and IL-1B protein expression is regulated by various other regulatory proteins such as transcription factor proteins that play a role in initiating the expression of a particular protein gene. Transcription factor proteins are hypothesized to regulate the expression of pro-inflammatory proteins. Nuclear factor of activated T-cells 1 (NFATC1) and chromosome 1 open reading frame 38 (C1orf38) are transcription factors that play a role in the expression of pro-inflammatory cytokine protein. NFATC1 will mediate the activation of TNF-alpha and IL-1B transcription genes, which will cause expression of pro-inflammatory proteins [7]. C1orf38 is an open reading frame factor group, which plays a role in the initiation of transcription of pro-inflammatory cytokine genes, TNF-alpha, and IL-1B [8], [9]. The presence of NFATC1 transcription factors must be accompanied by the presence of C1orf38 transcription factors in initiating transcription of the pro-inflammatory cytokine gene. Therefore, these two transcription factors are very important regulatory proteins in the expression of pro-inflammatory cytokine protein [10], [11], [12].

This study aimed to explore the role of the expression of pro-inflammatory cytokine (TNF-alpha and IL-1B) and transcription regulatory proteins (NFATC1 and C1orf38) with the severity of joint effusion in OA patients.

## Methods

### Study design

This study was an observational study with a case series study approach. In this study, observations of the expression of pro-inflammatory cytokine (TNF-alpha and IL-1B) and transcriptional regulatory proteins (NFATC1 and C1orf38) were then correlated with clinical, laboratory, and severity joint effusion features in OA patients.

### Study subjects

A total of 80 study subjects who met the inclusion criteria (age >40 years; OA was diagnosed; joint effusion feature was present; and agreed to participate in the study by signing informed consent) were included in this study. The OA subjects were the

patients that visited Dr. Moh Hoesin General Hospital and Su'adah Clinic, Palembang, Indonesia within the period of January–June 2019. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya/Dr. Moh Hoesin General Hospital (No.021/kptfkunsri-rsmh/2019).

### Physical and blood examination

Subjects basic data were obtained with age and body mass index (BMI) being emphasized. BMI mean in this study was assessed with the category suggested for Asians: <18.5 kg/m<sup>2</sup> (underweight); 18.5–23 kg/m<sup>2</sup> (normal); 23–27.5 kg/m<sup>2</sup> (overweight); and 27.5 kg/m<sup>2</sup> or higher (obesity) [13]. Random blood examination was performed to obtain erythrocyte sedimentation rate (ESR) and qualitative C-reactive protein (CRP) to evaluate the level of inflammation in the body. ESR mean value was assessed with normal value below 20 mm/h [14]. CRP was presented in negative or positive results.

### OA examination

The diagnosis of OA was based on clinical and radiologic assessment from American College of Rheumatology, namely, knee pain with osteophytes plus one of three criteria: Age over 40 years, joint stiffness in the morning <30 min, and/or crepitus. In radiologic examination, the Kellgren-Lawrence criteria were used. Score 0: Normal: (1) narrowing of the joint gap is doubtful and can be accompanied by osteophytes; (2) osteophytes are clear and can be accompanied by narrowing of the joint gap; (3) multiple moderate osteophytes with clear narrowing of joint gaps, sometimes with sclerosis and may also be accompanied by bone contour deformity; and (4) osteophytes are large and are characterized by narrowing of the joint gap, severe sclerosis and clear deformity of the bone contour. OA was radiologically enforced when the Kellgren-Lawrence score ≥2 [15]. Tegner Lysholm knee scoring scale was used to assess how OA condition affected the patients' ability to manage in daily living, with score >90 as excellent, 84–90 good, 65–83 fair, and <65 poor [16].

### Joint effusion examination

Joint effusion clinical enforcement was based on a physical examination of the balloon sign and a positive stroke sign. Balloon sign examination was performed on the patient in a supine position and knee extension, where one of the examiner hands was on the suprapatellar part and the other hand held the lateral and medial side of the patella. The examiner's hand on the suprapatellar part pushed the fluid and the other examiner's hand sensed the fluid push. A stroke test was performed at the supine

position with knee extension and maximum relaxation. Examination started from the medial tibiofemoral joint line, examiners pushed up 2–3 times toward the suprapatellar gap in an attempt to move the swelling in the joint capsule to the suprapatellar gap. The examiner then pushed down on the lateral distal thigh, just above the suprapatellar gap, toward the lateral joint line. Fluid waves could be observed in seconds on the medial side of the knee.

The degree of joint effusion was assessed in semi-quantitative and quantitative. Semi-quantitative assessment was done based on a stroke test and quantitative assessment was based on the volume of joint aspiration obtained in milliliters (ml). A stroke test was assessed as "trace" if a small wave appeared on the medial side with push down; +1 if there was a large protrusion on the medial side with downward push; +2 if effusion spontaneously returned to the medial side after upward pushing (no downward pushing needed); and +3 excessive fluid, was not possible to move the effusion outside the medial aspect of the knee.

#### Pro-inflammatory cytokine and regulator protein assay

TNF-alpha, IL-1B, NFATC1, and C1orf38 levels were assessed in joint fluid using the enzyme-linked immunosorbent assay (ELISA) method (Cloud-Clone®). Obtained joint fluid was put into a 1.5 mL centrifuge tube (Eppendorf®), and then a centrifuge (Bio-Rad®) was carried out at a speed of 5000 rpm, at 25°C, for 20 min. Centrifugation supernatant was separated from the pellet, then stored at -20°C. A total of 10 µL supernatants from each sample was put into each ELISA well microplate, and then incubated for 30 min, at 37°C. After washing with washing liquid with immune washer (Bio-Rad®), horseradish peroxidase-link was administered, followed by incubation and washing, then adding of chrome A and B to each well. After incubation, a stop solution was added and a microplate was immediately inserted into the ELISA reader (Bio-Rad®) to measure optical density (OD) of each well at a wavelength of 450 nm. Subsequent analysis, the conversion of OD values to levels (pg/mL), was performed using a standard curve equation.

#### Statistical analysis

Data processing of the results of the study was carried out using SPSS 24, with a significance of  $p < 0.05$ . Data were presented as mean  $\pm$  SD (standard deviation). Univariate analysis was presented in the form of frequency tabulations. Bivariate analysis that presented correlations between variables was performed by correlation analysis using the Pearson correlation test.

## Results

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### Baseline characteristics of study subjects

As shown in Table 1, BMI mean value was at the category of overweight. A total of 80 subjects of

**Table 1: Baseline characteristics of OA subjects with effusion**

S. No	Baseline characteristics	OA subjects with effusion (n=80)
1.	Age (years), mean $\pm$ SD	59.4 $\pm$ 13.4
2.	BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	24.9 $\pm$ 6.2
3.	Effusion volume (ml), mean $\pm$ SD	14.9 $\pm$ 5.3
4.	ESR (mm/hour), mean $\pm$ SD	10.2 $\pm$ 2.1
5.	Kellgren-Lawrence score, percentage	
	Grade 3	45
	Grade 4	55
6.	Stroke test score, percentage	
	Score 1	25
	Score 2	62.5
	Score 3	12.5
7.	Qualitative CRP, percentage	
	Positive	0
	Negative	100
8.	Tegner-Lysholm score, mean $\pm$ SD	62.5 $\pm$ 11.3
9.	TNF-alpha (pg/ml), mean $\pm$ SD	74.6 $\pm$ 13.5
10.	IL-1B (pg/ml), mean $\pm$ SD	78.6 $\pm$ 14.8
11.	C1orf38 (pg/ml), mean $\pm$ SD	65.2 $\pm$ 11.5
12.	NFATC1 (pg/ml), mean $\pm$ SD	67.8 $\pm$ 12.8

OA: Osteoarthritis; SD: Standard deviation; BMI: Body mass index; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; TNF: Tumor necrosis factor; IL-1B: Interleukin 1B; C1orf38: Chromosome 1 open reading frame 38; NFATC1: Nuclear factor of activated T cells 1.

OA patients with effusion obtained Kellgren-Lawrence score of Grade 3–4, stroke test score 2–3, and Tegner Lysholm mean score of 62.5 (poor condition), where these parameters indicated that the patients were in severe clinical conditions. It was quite surprising to observe the qualitative CRP and ESR values did not support that the state of OA with effusion was caused by chronic inflammation. The ESR result in this study was normal and CRP was 100% negative in all study subjects.

### Correlation between effusion volume and inflammation

This study inhibited interesting and quite surprising results, as displayed in Table 2 and Figure 1.

**Table 2: Correlation between effusion volume and inflammation**

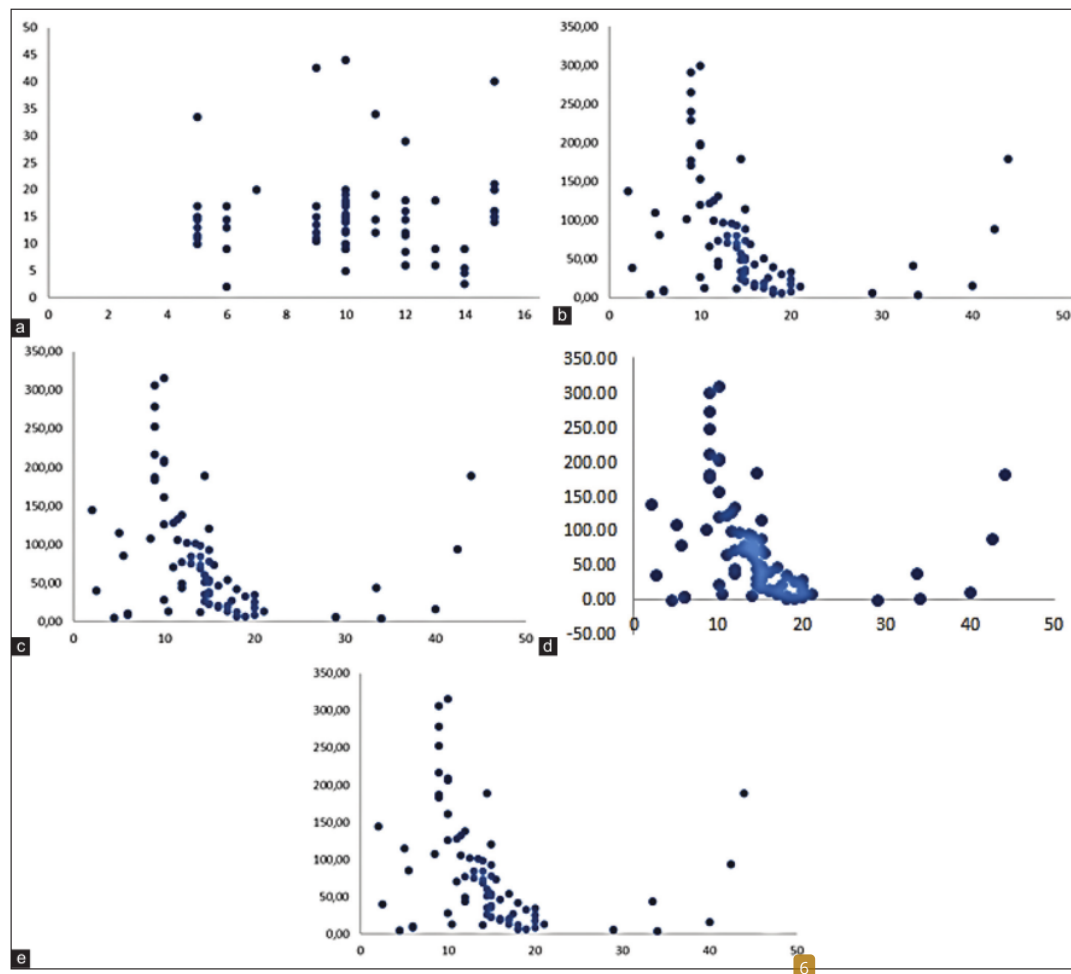
Inflammatory markers	r	p
ESR	0.078	0.169
TNF-alpha	-0.087	0.112
IL-1B	-0.078	0.136
C1orf38	-0.088	0.121
19 C1	-0.081	0.102

ESR: Erythrocyte sedimentation rate; TNF: Tumor necrosis factor; IL-1B: Interleukin 1B.

C1orf38: Chromosome 1 open reading frame 38; NFATC1: Nuclear factor of activated T cells 1.

Inflammation has been believed to play a major role in the severity of effusion in patients with OA. Otherwise in this study, ESR did not correlate with the severity of OA joint effusion ( $p$  adjusted = 0.169;  $r = 0.078$ ). Pro-inflammatory cytokine level of TNF-alpha did not correlate with the severity of OA joint effusion ( $p$  adjusted = 0.112;





**Fig. 33** 1: Correlation of effusion volume to LED (a), tumor necrosis factor-alpha (b), interleukin 1B (c), chromosome 1 open reading frame 38 (d), and nuclear factor of activated T cells 1 (e)

$r = -0.087$ ). The result of correlation between IL-1B level to the severity of OA joint effusion was in line with the previous results of TNF-alpha and ESR, where there was no correlation between IL-1B level with severity of OA joint effusion ( $p$  adjusted = 0.136,  $r = -0.078$ ). OA joint effusion severity was not in line with an increase in C1orf38 level ( $p$  adjusted = 0.121;  $r = -0.088$ ) and NFATC1 level ( $p$  adjusted = 0.102;  $r = -0.081$ ).

## Discussion

This study was an exploratory study conducted in the context of exploring the role of the inflammatory pathway on joint effusion severity in OA cases. Inflammation is a pathogenesis that is widely believed to play a role related to severity joint effusion in OA [7], [17], [18], [19], [20].

However, this study revealed other results related to joint effusion in OA. Inflammation did not play a role as the pathogenesis that underlay the severity of effusion. This study stated that there was no correlation between inflammatory markers with effusion volume in OA patients. Transcription factor proteins, NFATC1 and C1orf38 did not correlate with severity of joint effusion in OA. Efforts of upstream to downstream exploration in the pathway of this inflammation, yielded similar results, that the inflammatory pathway did not correlate with the severity of joints effusion in OA patients. Synovia [36] id is a result of filtration from blood plasma, which plays a role in lubricating and maintaining the ability of the joints to be able to carry out physiological movements. Synovial fluid is rich in protein, especially hyaluronic acid, which is a protein that plays a role in the regulation of water retention in synovial fluid [3], [21], [22].

Micro trauma that occurs in OA underlies the occurrence of chronic inflammation, which results in

damage to the joint cartilage. This causes a decrease in hyaluronic acid<sup>31</sup> in synovial fluid. Researchers hypothesized that the concentration of hyaluronic acid in synovial fluid might play a major role<sup>40</sup> the process of joint effusion in OA. The decrease of hyaluronic acid concentration in synovial fluid will cause transudation of water to the synovial which results in joint effusion. Hyaluronic acid exploration is suggested for further study to uncover the factors that play a role in the severity of joint effusion in OA. In addition, the exploration of synovial joint protein, plasma protein, is also suggested. A decrease in plasma protein is believed to reduce the concentration of protein in the synovial joint, decreasing the synovial fluid oncotic pressure, hence leading to massive transudation of water from extra synovial into the joint. This is believed to be one of the alleged factors that influence the severity of joint effusion in OA [23], [24], [25]. The limitation of this study was the absence of a control group. Further studies could be conducted to explore this topic.

## Conclusion

Pro-inflammatory cytokines of TNF-alpha and IL-1B, and the transcription factors of pro-inflammatory cytokines gene expression, NFATC1 and C1ORF38, did not correlate with the severity of joint effusion in OA.

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## Authors' Contributions

The authors equally contributed in design, data compiling and analysis, and the composing of the manuscript.

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