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Synovial Fluid White Blood Cell Count as a Potential Biomarker for the Clinical Severity of Knee Osteoarthritis: A Prospective Study

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Abstract: Knee osteoarthritis is categorized classically as a non-inflammatory arthropathy. However, there has been increasing evidence regarding the supplementary role of inflammation in the pathogenesis and disease progression of knee osteoarthritis. This study aims to identify a potential correlation between synovial fluid white blood cell (SF WBC) count and the severity of knee osteoarthritis clinical presentation. 200 knees (200 patients) were assessed through SF aspiration and cytology analysis for WBC count. All patients have filled out the Knee Injury and Osteoarthritis Outcome Score for clinical correlation. For the 200 knees, there was a statistically significant positive correlation between the severity of osteoarthritis clinical presentation as expressed by the Knee Injury and Osteoarthritis Outcomes Score (KOOS) and the synovial white blood cell count among the studied cases (p-value < 0.001). There was no statistically significant correlation found between the patient's age, sex, or side and KOOS or SF white cell count. The clinical severity of knee osteoarthritis is directly correlated with increased SF white cell count, and hence, SF WBCs may play a role in identifying and grading osteoarthritis clinical severity. This may raise the interest in identifying the role of using specific disease-modifying drugs that deal with the WBC function in cases of osteoarthritis along with other modalities.

Keywords: knee osteoarthritis, synovial fluid, white blood cell count, Oxford Knee Score

1. Introduction

Being the most common type of arthritis [1, 2], osteoarthritis (OA) has been an important focus of research, and several studies and updates continuously emerge to further understand its pathogenesis and the mechanism of disease progression. Despite being considered classically as a non-inflammatory, degenerative joint disease, based on the amount of synovial fluid WBC (SF WBC) count that falls below 1000–2000 WBCs/mm^3 [3, 4], many recent studies have shown that inflammation and local immune reaction have been partially implicated in the pathogenesis of OA [4–14]. For instance, compared to non-OA controls, it was discovered that individuals with symptomatic knee OA had considerably higher levels of plasma, leukocyte-based inflammatory mediators like 15-hydroxyeicosatetraenoic acid. Additionally, individuals with radiographic advancement indicated by joint space narrowing (JSN) had enhanced baseline expression of Interleukin-1β, tumor necrosis factor α (TNF-α), and cyclooxygenase 2 messenger RNA, according to transcriptome analysis of peripheral blood leucocytes [5]. In a separate study that utilized microscopic analysis of the knee synovium in patients with both early and late OA, it was discovered that over 50% of the patients with early OA exhibited synovitis lesions characterized by the presence of mononuclear infiltrates, diffuse fibrosis, thickening of the lining layer, the appearance of macrophages, and the development of new blood vessels [6]. Given that integrating clinical information with cellular and molecular studies is crucial for comprehending the pathogenesis of OA [7], there is a growing interest in finding biomarkers that can be used to diagnose OA sooner, predict its progression, and identify medications that can modify the condition. Among all biomarkers, synovial local interleukins [10, 11, 15] and synovial white blood cell count were proposed as potential biomarkers in osteoarthritic knees [13, 16].

Identifying and effectively addressing important elements of synovial inflammation have the potential to greatly improve pain relief and promote structural changes [17, 18]. Although many research studies investigated different biomarkers that are found in association with osteoarthritic knees [4, 5, 7, 9, 10, 13], fewer studies have focused on a link between these biomarkers and the clinical severity of the disease [6, 15, 16]. In this prospective study, we aimed to identify the relation between a simple, readily available biomarker, the SF WBC count, and the severity of knee OA as represented by the patients' reported Knee Injury and Osteoarthritis Outcomes Score

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(KOOS) [19, 20]. We hypothesized that the clinical severity may be directly related to the amount of synovial WBC count. Such correlation may allow for early control of the disease and prevention of irreversible progression upon utilization of immunomodulator drugs in symptomatic patients with early radiological OA.

2. Methods

The prevalence of knee OA is known to be 10–13% of the population above 60 years old [21]. Simple random sample method for sample size calculation with a margin of error of ±0.05% and an expected sample proportion of 0.13 called for enrollment of at least 174 cases to obtain statistically significant values that have a confidence interval of 95%. To account for the potential loss of samples, three hundred patients with clinical and radiological findings of OA were initially enrolled in this study. All the patients have given consent, and IRB approval has been obtained from our institution's ethics committee. Patients were selected from the outpatient clinic of our university hospital, based on the clinical examination. Before recruitment, all the patients underwent full history taking and clinical examination to confirm the diagnosis. All the recruited patients had baseline CBC and serum uric acid analysis before tapping to exclude gout or any presence of leukocytosis.

Inclusion criteria for selected patients included the following:

1) The American College of Rheumatology criteria for OA [22], which included the presence of knee pain in association with three of the following criteria: morning stiffness of less than 30 min duration, crepitus on motion, no palpable knee warmth, bony tenderness, and bony enlargement; and
2) The presence of any of OA's clear radiological features [23] such as JSN, sub-chondral sclerosis, sub-chondral cysts, and bony osteophytes.

The exclusion criteria comprised patients with a known history of any knee injury within the past six months, as well as those who had undergone knee tapping, injections, surgeries (including arthroscopy), or had experienced septic arthritis. Additionally, patients with contraindications for tapping—such as nearby infections, bleeding disorders, or those on anticoagulant medications—were excluded. Those with known rheumatological conditions, gouty arthritis, leukocytosis, or elevated serum uric acid levels were also not considered. Furthermore, cases involving unsuccessful knee tapping or inadequate laboratory assessment of the synovial fluid sample were excluded from the study.

Simple measures were undertaken to standardize the clinical and radiographic assessment for the patients' recruitment. Before starting the study, the study protocol was discussed and agreed upon between the researchers involved in the study. The investigations have been performed at a single institution outpatient clinic. A summary of the study protocol regarding the clinical and radiographic parameters for patient inclusion was placed in the clinic until the required cohort size was fulfilled.

Each patient has filled out KOOS forms for each knee before knee tapping. The KOOS form questions were translated and printed in a single, uniform document that was presented to all patients. Either a physician or an experienced nurse who had knowledge of the study helped with questionnaire interpretation for the patients, without interference with the scoring. All the KOOS subscales were reported individually to support the clinical interpretation. All the patients underwent SF tapping using a 10 cm sterile syringe under local sterilization with alcohol 70% and Betadine, as an outpatient procedure. On all occasions, knee tapping was performed in the same setting as a planned knee local injection (hyaluronic acid or steroids), and tapping was performed just before the injection. A sample of 2–3 ml of SF was obtained from the knee and examined in the laboratory for synovial WBC count. Both cytometer and microscopy were used to perform white cell counting, and the same laboratory was used for all patients. Figure 1 highlights the study protocol process.

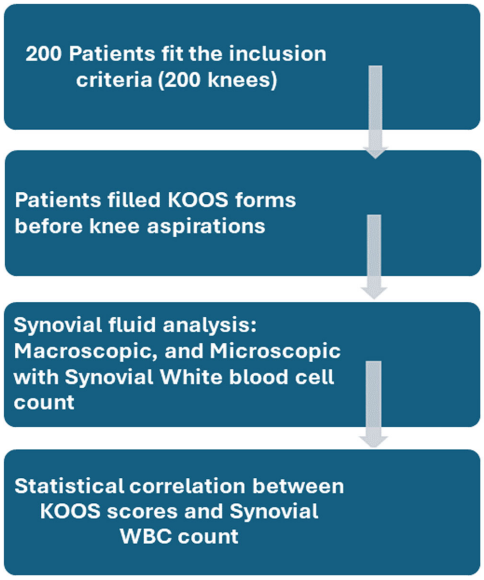

Figure 1. Flowchart of the study methodology

2.1. Statistical analysis

Using SPSS software, version 25 (SPSS Inc., PASW Statistics for Windows version 25, The SPSS Inc., Chicago.), the gathered data were updated, coded, tabulated, and imported into a PC. Numbers and percentages were used to describe the qualitative data. Median, range, mean, and SD were used to characterize quantitative data. The normality of the data distribution was examined using the Kolmogorov-Smirnov test. A p-value of less than 0.05 was used to determine the significance of the obtained results. Data were shown, and appropriate analysis was carried out in accordance with the kind of data found for each parameter.

1) **Descriptive statistics:**
   - Mean, range, and standard deviation (± SD) for numerical data.
   - Frequency and percentage of non-numerical data.
2) **Analytical statistics:**
   - **Chi-square T-test** was used to assess the statistical significance of the difference between different groups.
   - **ANOVA test** was used to assess the statistical significance of the difference between the study group mean values.
   - **Spearman's Rate Correlation Coefficient** was utilized to assess and summarize the strength and direction (positive or negative) of the link between the various components of KOOS and the synovial WBC count for all cases.

3. Results

Two hundred patients (200 knees, 119 males and 81 females, 131 left, and 69 right) met the selection criteria and were included in the study. Patients with bilateral knee OA had only their more symptomatic knee included in this study. The mean age of patients

Table 1. Demographic data side, appearance, and synovial fluid white cell count among the studied cases

		No. = 200
Age	Mean ± SD	58.42 ± 5.65
	Range	47 – 69
Sex	Female	81 (40.5%)
	Male	119 (59.5%)
BMI	Mean ± SD	29.05 ± 6.81
	Range	17 – 40
Side	Right	69 (34.5%)
	Left	131 (65.5%)
Appearance	Yellow Viscous	144 (72.0%)
	Bloody Viscous	20 (10.0%)
	Clear Viscous	24 (12.0%)
	Turbid Viscous	12 (6.0%)
Synovial fluid white cell count	Mean ± SD (cells/mm^3)	209.97 ± 76.55
	Range	78 – 381

Table 2. KOOS score for the studied cases

		No. = 200
KOOS Pain	Mean ± SD	27.78 ± 11.11
	Range	8.33 – 75
KOOS Symptom	Mean ± SD	27.68 ± 11.24
	Range	7.14 – 78.57
KOOS ADL	Mean ± SD	28.41 ± 8.87
	Range	11.76 – 67.65
KOOS Sport/Rec	Mean ± SD	27.65 ± 12.71
	Range	5 – 80
KOOS QOL	Mean ± SD	28.75 ± 12.44
	Range	6.25 – 81.25

was 58.42 ± 5.65 (range 47–69). Demographic data are summarized in Table 1. Most cases had a clear viscous SF sample (72%). The mean synovial WBC count for all cases was 209.97 ± 76.55 cells/mm^3.

The average KOOS pain, symptoms, activities of daily life, sports, and quality of life for all the included cases were 27.78, 27.68, 28.41, 27.65, and 28.75 cells/mm^3, respectively (Table 2). As for the side of the examined knee, the mean synovial WBC count was 217.84 ± 74.03 and 205.82 ± 77.81 for the right and left knees, respectively, which was not statistically significant. Similarly, there was no statistically significant difference between the side of the examined knee and each of the KOOS score results (Table 3). As for the patients' gender, no statistically significant differences were found between the patient's sex, and the synovial WBC count or the KOOS scores (Table 4). Likewise, there was no statistically significant correlation between the appearance of SF, and the synovial WBC count or the KOOS scores (Table 5). On the other hand, there was a highly statistically significant inverse correlation between the SF white cell count and all the elements of the KOOS ($p < 0.001$ for all of the KOOS elements, r = −0.4, −0.46, −0.58, −0.58, and −0.48 for KOOS pain, symptoms, ADL, Sports, and QOL respectively), indicating increased SF WBC count in more symptomatic patients (Table 6, Figure 2).

4. Discussion

This study aimed to identify a potential correlation between the clinical severity of knee OA and the SF white blood cell count. The results of this study found a highly statistically significant inverse correlation between the KOOS scores and SF WBC count, indicating increased SF WBC in association with the severity of knee OA symptoms. Although it is unlikely that a single biomarker could offer a broad description of a complex disease such as OA, given that OA affects multiple tissues in the joints, our study supports that combinations of clinical and biological markers may enhance the predictive capacity of individual biomarkers. Also, the results of this study support the role of local immunological processes in OA disease progression and/or exacerbation.

OA arises from a combination of several causes, which might involve both systemic and local biomechanical aspects. Age, sex, estrogen levels, racial and genetic vulnerability, bone density, and nutritional considerations are examples of systemic influences. Trauma or other localized events can cause gradual chondral injury and synovitis. Apart from trauma, synovial inflammation is becoming more widely acknowledged as a factor in the development and manifestation of OA [2, 3]. Histological changes in OA-associated synovitis include synovial hypertrophy and hyperplasia with an increased number of lining cells often accompanied by infiltration with lymphocytes. A degree of synovial

Table 3. Relation of the side of the knee examined with KOOS score and synovial fluid white cell count

		Right No. = 69	Left No. = 131	Test value•	P-value	Sig.
KOOS Pain	Mean ± SD	27.33 ± 10.71	28.01 ± 11.34	−0.408	0.683	NS
	Range	8.33 – 72.22	11.11 – 75			
KOOS Symptom	Mean ± SD	27.69 ± 12.59	27.67 ± 10.50	0.012	0.991	NS
	Range	7.14 – 78.57	7.14 – 75			
KOOS ADL	Mean ± SD	27.24 ± 8.19	29.03 ± 9.17	−1.361	0.175	NS
	Range	11.76 – 52.94	14.71 – 67.65			
KOOS Sport/Rec	Mean ± SD	27.97 ± 12.14	27.48 ± 13.04	0.259	0.796	NS
	Range	10 – 80	5 – 75			
KOOS QOL	Mean ± SD	27.99 ± 11.02	29.15 ± 13.15	−0.627	0.531	NS
	Range	12.5 – 68.75	6.25 – 81.25			
Synovial fluid white cell count	Mean ± SD	217.84 ± 74.03	205.82 ± 77.81	1.056	0.292	NS
	Range	78 – 345	78 – 381			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value< 0.01: highly significant (HS); •: Independent t-test

Table 4. Relation of sex of the studied cases with KOOS score and synovial fluid white cell count

		Female No. = 81	Male No. = 119	Test value•	P-value	Sig.
KOOS Pain	Mean ± SD	28.98 ± 11.86	26.96 ± 10.54	1.263	0.208	NS
	Range	11.11 – 72.22	8.33 – 75			
KOOS Symptom	Mean ± SD	27.51 ± 11.17	27.79 ± 11.32	−0.171	0.864	NS
	Range	7.14 – 75	7.14 – 78.57			
KOOS ADL	Mean ± SD	27.92 ± 7.98	28.74 ± 9.45	−0.642	0.522	NS
	Range	13.24 – 51.47	11.76 – 67.65			
KOOS Sport/Rec	Mean ± SD	26.36 ± 12.87	28.53 ± 12.58	−1.187	0.237	NS
	Range	5 – 75	5 – 80			
KOOS QOL	Mean ± SD	26.93 ± 12.17	29.99 ± 12.52	−1.717	0.088	NS
	Range	6.25 – 81.25	12.5 – 75			
Synovial fluid white cell count	Mean ± SD	216.75 ± 72.06	205.35 ± 79.43	1.034	0.302	NS
	Range	79 – 337	78 – 381			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value <0.01: highly significant (HS); •: Independent t-test

Table 5. Relation of appearance of synovial fluid aspirate samples with KOOS score and synovial fluid white cell count

		Yellow viscous No. = 144	Bloody viscous No. = 20	Clear viscous No. = 24	Turbid viscous No. = 12	Test value	P-value	Sig.
KOOS Pain	Mean ± SD	28.59 ± 11.43	23.75 ± 6.34	27.55 ± 12.66	25.23 ± 9.13	1.353	0.259	NS
	Range	11.11 – 75	16.67 – 38.89	8.33 – 72.22	13.89 – 38.89			
KOOS Symptom	Mean ± SD	28.35 ± 11.73	25.18 ± 7.98	28.13 ± 12.07	22.92 ± 6.18	1.236	0.298	NS
	Range	7.14 – 78.57	7.14 – 39.29	17.86 – 75	10.71 – 32.14			
KOOS ADL	Mean ± SD	28.83 ± 9.19	25.44 ± 9.14	28.43 ± 7.95	28.31 ± 5.40	0.853	0.466	NS
	Range	14.71 – 67.65	11.76 – 44.12	14.71 – 45.59	19.12 – 35.29			
KOOS Sport/Rec	Mean ± SD	27.95 ± 13.63	27.25 ± 10.70	27.50 ± 10.43	25.00 ± 8.53	0.206	0.892	NS
	Range	5 – 80	10 – 45	10 – 45	10 – 40			
KOOS QOL	Mean ± SD	29.60 ± 12.95	26.25 ± 13.08	27.60 ± 10.08	25.00 ± 8.43	0.924	0.430	NS
	Range	6.25 – 81.25	12.5 – 50	12.5 – 50	12.5 – 37.5			
Synovial fluid white cell count	Mean ± SD	207.26 ± 76.90	214.60 ± 76.92	203.96 ± 80.61	246.75 ± 60.34	1.058	0.368	NS
	Range	78 – 337	87 – 317	79 – 381	135 – 345			

P-value >0.05: Non-significant (NS); P-value <0.05: Significant (S); P-value <0.01: highly significant (HS); •: One Way ANOVA test

Table 6. Correlation of synovial fluid white cell count (cells/mm^3) with KOOS score

	Synovial fluid white cell count (cells/mm^3)	
	r	P-value
KOOS Pain	−0.403**	<0.001
KOOS Symptoms	−0.461**	<0.001
KOOS ADL	−0.589**	<0.001
KOOS Sport/Rec	−0.582**	<0.001
KOOS QOL	−0.480**	<0.001

**Spearman's correlation coefficients

inflammation has been noticed in both early and late OA, although being more relevant in advanced stages and accompanied by more profound chondral and sub-chondral damage [3].

Although a clinically relevant number of OA patients present with signs of inflammation, e.g., joint swelling and effusion, these inflammatory processes were interpreted classically as a bystander, not as a driving force in OA pathogenesis [4, 18]. While SF analysis classically designates OA as a non-inflammatory process [3, 4], a set of more recent studies have increasingly recognized OA as a disease with a significant inflammation component [5–7, 24]. Many studies further aimed to map the associated inflammatory processes more precisely, both in human and animal models [10–16]. Among all, SF WBC count and analysis have long been recognized to have a role in the assessment and diagnosis of arthritis [6, 7, 13, 16].

Nevertheless, fewer studies have discussed the relation between OA clinical severity and the quantity of tested biomarkers or SF WBC count especially [6, 16]. To our knowledge, the current study is one of very few studies that solely assess the direct correlation between the clinical severity of OA and a biomarker level. Ene et al. [6] found that when the severity of OA increased, so did the cellular infiltrate and synovial fibrosis. They haven't, however, established precise guidelines for how they will clinically distinguish between early and late OA cases. McCabe et al. [16] discovered that SF WBC count was shown to be greater in instances with increased synovial thickness on MRI in osteoarthritic patients, and hence, they suggested that SF WBC may be a possible biomarker for synovitis in osteoarthritic patients. Furthermore, they discovered that in patients with

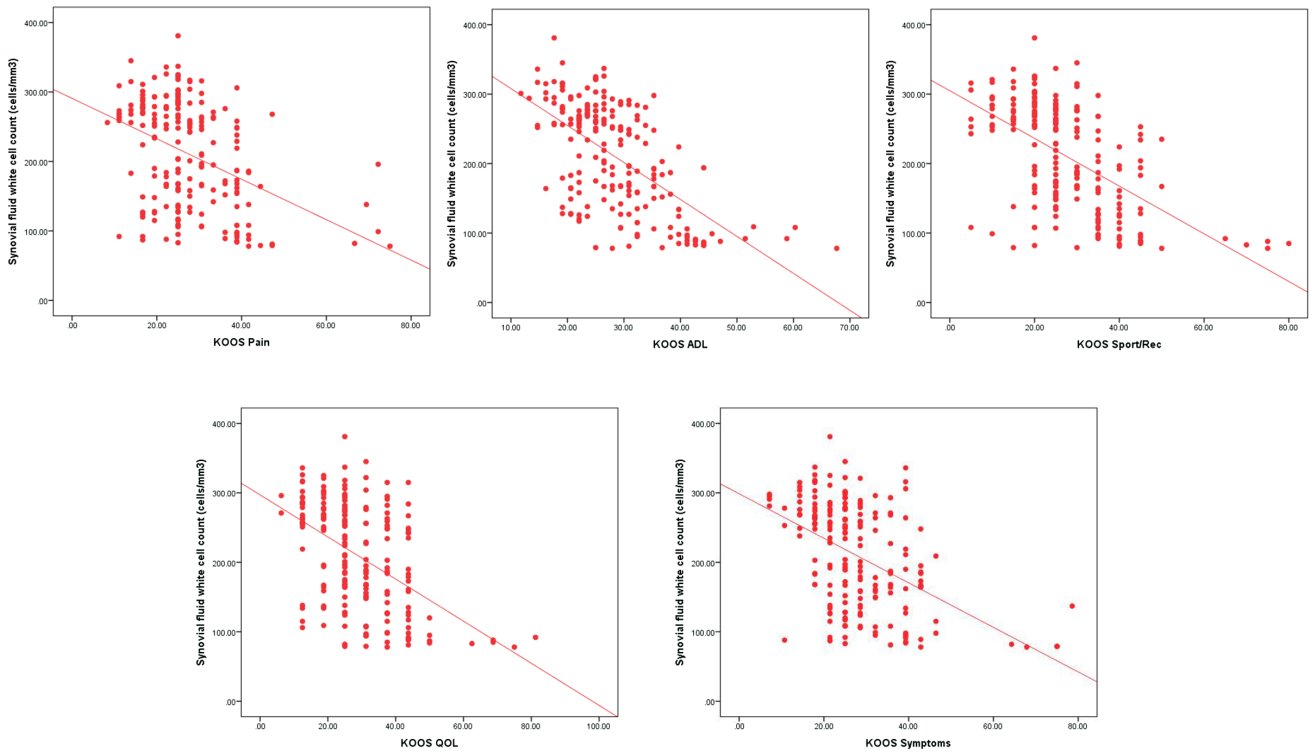

Figure 2. Correlation of synovial fluid white cell count (cells/mm^3) with KOOS scores

pretreatment elevated SF WBC count, the KOOS decreased following intra-articular steroid injection, indicating that the SF WBC count can predict the response to anti-inflammatory therapy. However, they did not assess the correlation between the clinical severity and SF WBC count. Haraden et al. [25] discovered six SF biomarkers associated with OA that were correlated with synovial inflammation, radiographic features, and the intensity of OA symptoms. These biomarkers were particularly connected to markers of active macrophages and neutrophils. However, the suggested biomarkers required special analytical methods for assessment that may not be readily available in ordinary labs. On the other hand, several other studies mentioned the role of WBCs in the pathogenesis of OA, in association with specifically associated syndromes, or in association with increased OA radiographic severity [7, 13, 26–28]. These studies, however, have not correlated their results with the patient's subjective clinical data.

Our study has several limitations: First, we did not perform differential WBC count analysis to identify whether a dominating cell type was present to further specify the responsible cells and categorize the patients. Studies by Sakkas and Platsoucas [29] implied that the primary cell type in the OA synovium is T helper type 1 polarized cells. Conversely, Bondeson et al. [30] stated that OA synovitis is primarily caused by synovial macrophages and their primary pro-inflammatory cytokines, TNF-α, and interleukin. We could not add support to either of the findings. The second limitation is that we did not consider the radiological findings in grading OA, as we depended only on KOOS as an indicator of the OA clinical severity. However, we considered the patients' symptoms to be the main identifying parameter, since radiological findings can be numerous and different and may not necessarily correlate with the clinical picture [31, 32]. Third, we solely depended on a single clinical scoring system (KOOS). Ideally, other scores such as the Oxford Knee Score and the Western Ontario and McMaster Universities Arthritis Index may be additionally utilized to increase the accuracy of the clinical picture interpretation. Another limitation is that other parameters of SF analysis, such as biochemical components, and other cellular components were not examined nor compared. Finally, other confounding factors and associated conditions or diseases that we have not accounted for may have played a role in the presentation of our patients.

Currently, the US Food and Drug Administration considers slowing of JSN as an outcome for trials of disease-modifying OA drugs [33]. To date, no drugs have been approved in the US or Europe to achieve this purpose [34]. As radiographic findings occur well after histological and biochemical changes in the joint [35, 36], future development of specific disease-modifying drugs that are aided by consideration of validated potential diagnostic and prognostic biomarkers, such as synovial white cell count, synovial C reactive protein [37], synovial Alarmins [38], and serum collagen II fragment [39], in combination with simple clinical outcome measures such as the pain scale or the Oxford knee score may be helpful in early control of the OA upon an early start of disease-modifying agents and immunomodulators. 10 Early diagnosis of OA, before radiographic damage has occurred, would require collaboration between improved diagnostic imaging and biomarkers [10, 40–43]. Recently, there has been an increasing interest in disease-modifying OA drugs such as monoclonal antibodies, enzyme inhibitors, growth factors, nucleic acids, and peptides, which were designed based on OA biomarkers, in the early control of OA before the occurrence of significant joint damage [44].

5. Conclusion

Our study identified a highly statistically significant correlation between the clinical severity of OA, as represented by the patient-reported KOOS, and SF white blood cell count. The clinical

severity of OA could be potentially linked to the presence of a high amount of synovial white blood cells, and hence, further research is required to identify the specific white cell inflammatory mediators that are mostly associated with increased OA symptoms and consequently develop disease-modifying drugs that specifically counteract such mediators or biomarkers.

Conflicts of Interest

The authors declare that they have no conflicts of interest to this work.

Data Availability Statement

The data that support this work are available upon reasonable request to the corresponding author.

Author Contribution Statement

Hesham El-khodary: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Resources, Data curation. **Ahmed Nageeb Mahmoud:** Software, Writing – original draft, Writing – review & editing, Visualization. **Daniel S. Horwitz:** Writing – review & editing, Visualization. **Elzaher Hassan Elzaher:** Resources, Writing – review & editing, Visualization. **Mostafa Aly Elabd:** Software, Resources, Writing – review & editing. **Mariia Sovalkina:** Software, Formal analysis. **Ahmed Samy Kamel:** Conceptualization, Methodology, Investigation, Resources, Data curation, Supervision, Project administration. **Ahmed Mohasseb:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Resources, Data curation, Supervision, Project administration.

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