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Serum Soluble ST2 and IL–33 Levels in Finnish Patients With Juvenile Idiopathic Arthritis

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ABSTRACT

Johanna Teräsjärvi (J.T.T.), Milja Möttönen (M.M), Heidi Rahikkala (H.R.), Sonja Kvist (S.K.), Denise Anabe (D.A.), Jussi Mertsola (J.M.), and Qiushui He (Q.H.)*. In this study, we aimed to investigate whether the levels of serum soluble stimulation 2 (sST2) and interleukin (IL) –33 correlate with Juvenile Idiopathic Arthritis (JIA) subtypes and disease activity, and whether there are differences between sexes. Ninety-four patients under 16 years of age who fulfilled the International League of Associations for Rheumatology (ILAR) classification criteria for JIA were recruited. The control samples included baseline sera collected from healthy Finnish children participating in a vaccine study conducted in Turku, Finland. Serum sST2 and IL–33 levels were measured using ELISA, and the detailed clinical data/parameters were compared. No significant difference was found in serum sST2 levels between male and female controls. A higher level of serum sST2 was observed in male patients with oligoarthritis (median: 33,000 pg/mL) compared to male controls (median 21,600 pg/mL) ($p = 0.03$), whereas no such difference was found between female patients and controls. Further, a positive correlation between age and sST2 levels was observed in male patients. Notably, no significant correlation was found between serum sST2 or IL–33 levels and disease activity parameters or therapy used. Our findings provide valuable insights in the sex/gender-specific role of sST2 in nonsystemic JIA and warrant further studies of sST2 in children with oligoarthritis in different populations.

1 | Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatological autoimmune and inflammatory disorder in children under 16 years of age, causing joint and extra-articular inflammation [1]. It is divided into seven subtypes: systemic onset JIA (so-JIA), oligoarticular JIA (o-JIA), rheumatoid factor (RF)-negative polyarthritis (p-JIA), RF-positive polyarthritis (RF+ *p*-JIA), enthesitis-related JIA (ERA), psoriatic JIA and undifferentiated JIA, which differ from each other in terms of pathogenesis. The exact mechanisms of JIA remain unclear, but the pivotal role of immune cell imbalances and cytokine signaling has been recognized [2]. An imbalance among type 1 T helper (Th1), Th17, and regulatory T (Treg) cells plays a key role in the development of nonsystemic JIA subgroups [3]. Cytokines such as tumor necrosis factor (TNF) α, IL-17, IL-10, [3, 4] and IL-33 [5] are involved in these processes. ERA differs from o-JIA and p-JIA, in which human leukocyte antigen (HLA)-B*27 plays a central role [5] by activating T-cells, inducing endoplasmic reticulum stress, and promoting disease progression. IL-17,

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IL-23, and TNFα are major cytokines involved in the inflammatory response in ERA [5].

IL–33 is an alarmin cytokine whose binding to ST2 [6, 7] activates the myeloid differentiation primary response (MyD) 88 pathway and promotes Th2 and Treg responses [6]. Soluble form (sST2) is found to be elevated in patients with cardiovascular disorders, as well as in atopic and inflammatory diseases [8–10]. Soluble ST2 acts as a decoy receptor, inhibiting IL–33 function and shifting the response toward Th1 activation, leading to the release of inflammatory cytokines (e.g.,TNF-a) and inflammation [10]. Under normal conditions, serum sST2 and IL–33 levels are low [11, 12].

Previous studies have shown that elevated sST2 levels correlate with disease activity in so-JIA [13] and rheumatoid arthritis (RA) [14], but its role in nonsystemic JIA remains unclear. Noor-eldeen et al. found that, serum IL–33 levels and its relative mRNA expression were significantly higher in patients with JIA than in healthy controls [15]. In addition, they found that the serum and synovial fluid (SF) levels of IL–33 significantly correlated with disease activity markers [15].

The role of sST2 and IL–33 in the pathogenesis of nonsystemic JIA remains poorly understood. This study investigates whether serum sST2 and IL–33 levels correlate with disease activity in nonsystemic JIA subtypes.

2 | Material and Methods

A total of 94 patients under 16 years of age who fulfilled the ILAR classification criteria for JIA, were recruited from the Pediatric Rheumatology Clinic at Turku University Hospital in Turku, Finland, between November 2020 and September 2023. The mean age of patients at sampling was 10.4 years (range: 2.2–16.9 years), and the median disease duration was 3.9 years (range: 0–13.6 years). The cohort included 48 (51.1%) with o-JIA, 33 (35.1%) with p-JIA, 10 (10.6%) with ERA, and three patients with rarer subtypes. No patients with so-JIA or RF+ *p*-JIA were included. Final analyses included patients with o-JIA, p-JIA and ERA ($n = 91$). Most of the patients were females (72.3%), except in ERA group, where males predominated (90.0%). Detailed patient characteristics were previously described by Möttönen et al. [16]. The control samples used in this study were baseline specimens collected from healthy Finnish individuals participating in a vaccine study conducted in Turku, Finland [17]. Altogether, 73 participants (age range: 7–15 years; male $n = 36$; female $n = 37$) were included. The exclusion criteria for both JIA patients and controls have been described previously [16, 17].

Before enrollment in the study, the patients and their guardians were informed about the procedures and the aim of the study, and they provided written informed consent in accordance with the principles of the Declaration of Helsinki. The study was approved by the Ethics Committee of Turku University and the Hospital District of Southwest Finland (ETMK 31/1801/2020, 16 June 2020).

Sera from patients with JIA were collected during routine clinical visits [16], while control samples were obtained at the same hospital using an identical protocol [17]. Blood samples were promptly transported to the research laboratory, where serum was isolated following a standardized protocol. Samples were allowed to clot for 60 min at room temperature, then centrifuged at 2000 × g for 10 min at +4°C. The resulting serum was aliquoted into cryovials and stored at −20°C until used for analyses. Soluble ST2 and IL–33 levels were measured using ELISA (E-EL-H6082 and E-EL-H2402, Elabscience Biotechnology, Houston, Texas, US) according to the manufacturer's instructions. The detection ranges for sST2 and IL–33 were 310–20,000 pg/mL and 15.63–1000 pg/mL, with sensitivities of 190 pg/mL and 9.38 pg/mL, respectively. The same ELISA kits with the same LOT numbers (sST2 AK05RRRJ9217 and IL–33 AK07V6203124) were used to analyze samples from both controls and JIA patients. Values below the limit of detection (LOD) were substituted with half of the lowest limit of detection in the analyses.

Levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured at the laboratory of Clinical Chemistry at the University Hospital of Turku.

Disease activity was assessed using the Juvenile Arthritis Disease Activity Score (JADAS) 10, total active joints count (incl. the sacroiliac joint [SI]), Child Health Assessment Questionnaire (CHAQ), patient/parent global assessment, and pain assessment.

Categorical data were compared using the Chi-square test or Fisher's exact test. Nusing on-normally distributed data were compared using Mann–Whitney U test. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated. Multiple regression analysis was performed to investigate the association between clinical and demographic variables and serum sST2 concentrations in JIA. The dependent variable was sST2 (pg/mL), and the model included age at sampling, JADAS10, JIA subtypes, and sex. Two-tailed $p < 0.05$ was considered statistically significant. This study was exploratory and focused on clinically relevant variables. Due to the relatively small number of patients in the subgroups, formal adjustments for multiple comparisons were not applied.

3 | Results

All participants in the healthy control group had detectable sST2 (median: 21,200 pg/mL; IQR: 57.9), and almost all tested serum samples ($n = 50$) had undetectable levels of IL–33 (median: 7.82 pg/mL; IQR: 0.00). In patients with JIA, the median sST2 level was 20,000 pg/mL; (IQR: 20.3) and median IL–33 level 7.82 pg/mL; (IQR: 0.58). Within this group, male patients exhibited higher median serum sST2 levels (25,300 pg/mL; IQR: 32.3) compared to female patients (18,800 ng/mL; IQR: 16.4). However, this difference did not reach statistical significance ($p = 0.085$). Male JIA patients showed a weak positive correlation between age and sST2 levels ($r = 0.39$, $p = 0.03$) (Figure 1). No statistically significant differences were observed in serum IL–33 levels between sexes or in relation to age.

The regression analysis showed that sex was significantly associated with sST2 levels (B = −11,378.9, $p = 0.018$, 95% CI [−20,784.8, −1973.1]). The negative coefficient reflects the coding of the

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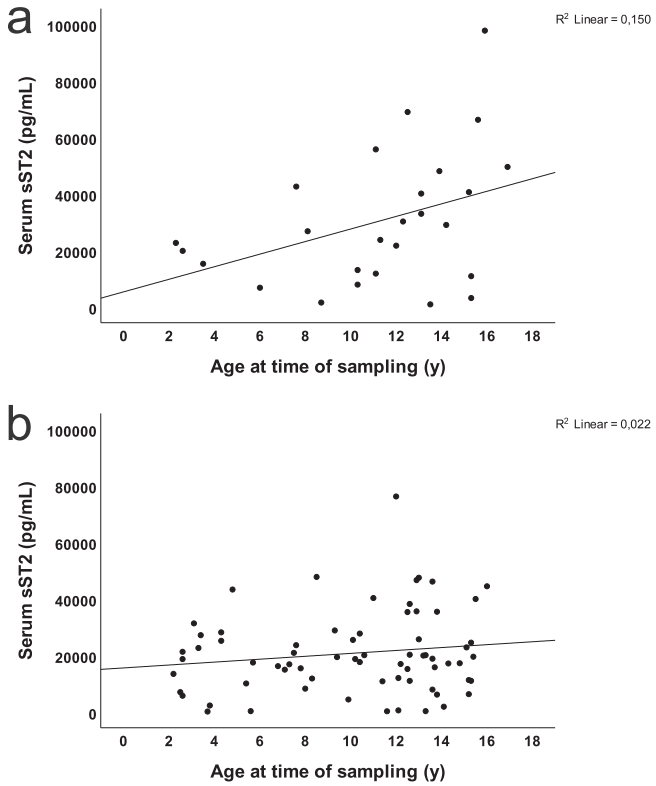

FIGURE 1 | Serum sST2 levels and their correlation with age in male (a) and female (b) patients with JIA.

gender variable, where female was the reference category. Age at sampling showed a borderline association with sST2 levels (B = 928.0, $p = 0.053$, 95% CI [−13.7, 1869.8]), suggesting a possible trend toward higher sST2 with increasing age; however this did not reach statistical significance. Other variables, including JADAS10 and JIA subtypes, were not significantly associated with sST2 levels. The coefficient of determination (R^2) for the model was 0.154, indicating that approximately 15.4% of the variation in sST2 levels could be explained by the included variables. The remaining 84.6% of the variation is likely attributable to other factors not captured in the model.

Serum sST2 and IL–33 levels were correlated only in the ERA group (Pearson correlation = 0.69, $p = 0.028$). Male o-JIA patients (median: 33,000 pg/mL) had higher serum sST2 levels than male controls (21,600 pg/mL, $p = 0.03$) (Figure 2a). Median serum sST2 levels did not differ significantly between controls and JIA patients ($p = 0.763$) (Figure 2b).

Serum sST2 and IL–33 correlations were analyzed with CRP, ESR, JADAS10, active joint count, CHAQ, patient/parent global assessment, and pain assessment. Significant correlations were found only in the ERA group (sST2 with JADAS10: $r = 0.75$, $p = 0.03$), and in the p-JIA group (IL–33 with pain assessment: $r = 0.38$, $p = 0.03$).

Disease activity was available for 83 patients, categorized as inactive (CID, $n = 41$), low (LDA, $n = 13$), moderate (MDA, $n = 12$), or high disease activity (HAD, $n = 17$). Serum sST2 levels were

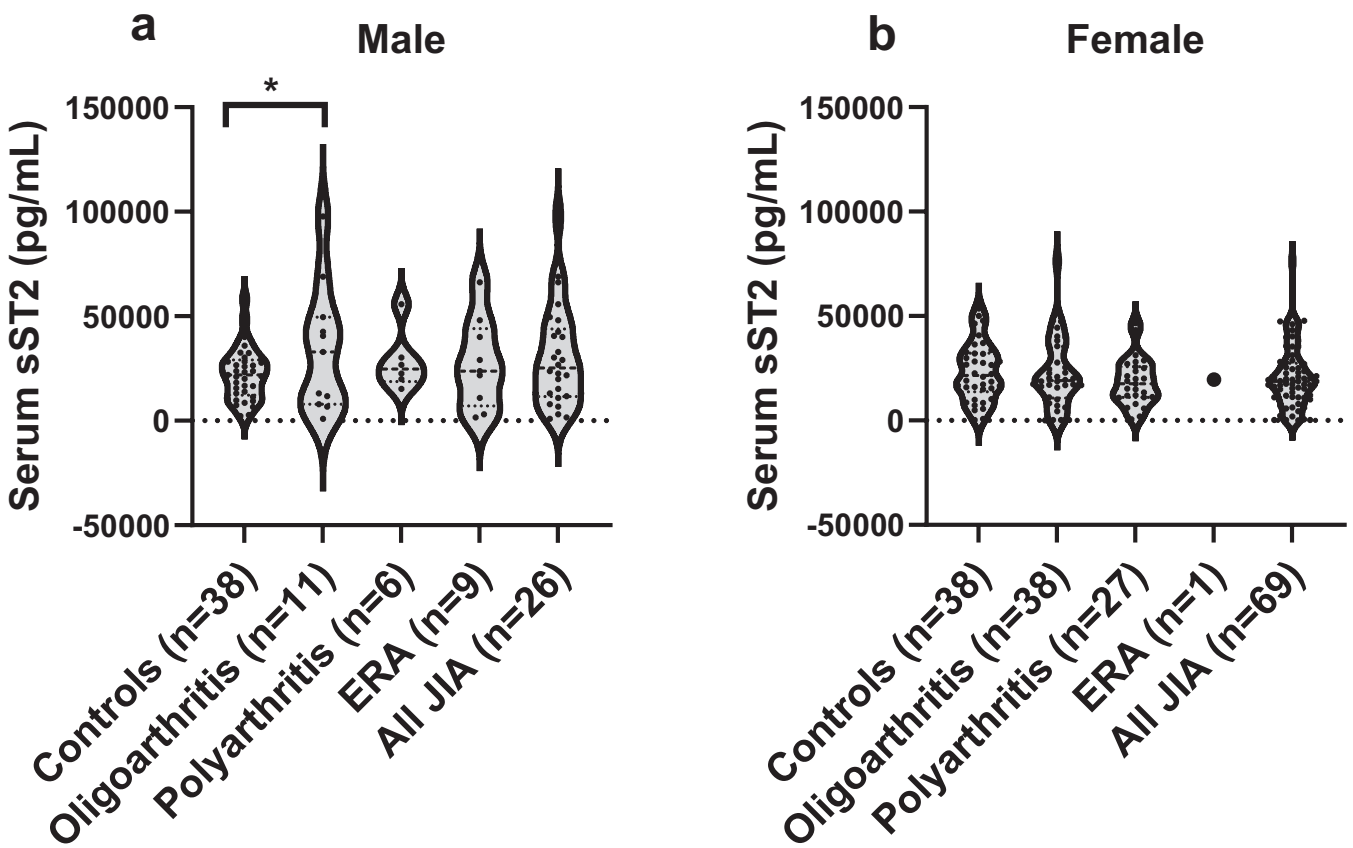

FIGURE 2 | Serum sST2 levels in males and females with different subtypes of JIA compared to controls.

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lower in CID (19,400 pg/mL; IQR: 15.3), LDA (18,700 pg/mL; IQR: 13.0), and MDA (15,400 pg/mL; IQR: 39.8) groups than in the HDA group (27,700 pg/mL; IQR: 23.1) (Figure 3a), but the differences were not statistically significant. Higher levels of IL–33 were found in patients with CID than those with active disease. (Figure 3b).

At the time of sampling, eight subjects (8, 8%) were not under active treatment, 34 (37.4%) were on disease-modifying antirheumatic drugs (DMARDs) only, 18 (19.8%) were receiving biologics only, and 31 (34.1%) were receiving both treatments. The treatments did not demonstrate a statistically significant impact on serum sST2 or IL–33 levels.

4 | Discussion

JIA is a heterogeneous autoimmune disorder in children, characterized by joint and systemic inflammation [1]. Although immune cell imbalances and cytokine signaling are known to contribute to its pathogenesis [3], the role of IL–33 and its receptor sST2 in nonsystemic JIA subtypes remains poorly understood. This study provides new insight into the role of serum sST2 and IL–33 in nonsystemic JIA, disease activity, with particular attention to gender-related differences. In this study, male o-JIA patients had significantly higher sST2 levels than controls, whereas no difference was observed in females. There was a trend toward higher sST2 levels in active disease, whereas IL–33 levels were highest in patients with inactive disease.

Previous studies have reported conflicting results regarding the effects of sex on serum sST2 levels [18, 19]. Dieplinger et al. reported higher sST2 levels in healthy males (24.9 ng/mL; 95% nonparametric reference interval 8.6–49.3 ng/mL) than in females (16.9 ng/mL; 95% nonparametric reference interval 7.2–33.5 ng/mL) [18], while Ye et al. did not find sex to affect sST2 levels [19]. Here we did not find significant differences between male and female controls. However, male JIA patients, particularly those with o-JIA, had higher serum sST2 levels compared to both female patients and controls.

Next, we studied whether serum sST2 and IL–33 levels were correlated with age. In the control group, participants ranged in age from 7 to 15 years [17], and no correlation was observed between age and serum sST2 levels within this age range. In contrast, the patient group exhibited a broader age range, from under 2 years to 16 years, and within this group, serum sST2 levels showed a positive correlation with age. Previously, Lu et al. found no correlation between sST2 and age in healthy individuals [12], which is in line with our observation among the controls. However, Ye et al. have reported opposite findings [19]. In their study, sST2 levels increased with age, particularly in males, a result that aligns with our findings among JIA patients [19]. These gender- and age-specific differences in sST2 levels may reflect underlying immunological or hormonal influences and warrant further investigation. In our study, levels of IL–33 were not influenced by gender or age.

Elevated concentrations of sST2 and IL–33 have been shown to correlate with disease activity in previous studies [13, 14]. Ishikawa et al. reported that sST2 levels were elevated in patients with so-JIA and correlated with disease activity [13]. In another study, they found higher IL–33 in patients with RF+ *p*-JIA, also correlating with disease activity [20] Additionally, Noor-eldeen et al. found that serum IL–33 correlated with RF+, while SF IL–33 correlated with disease activity [15]. We found

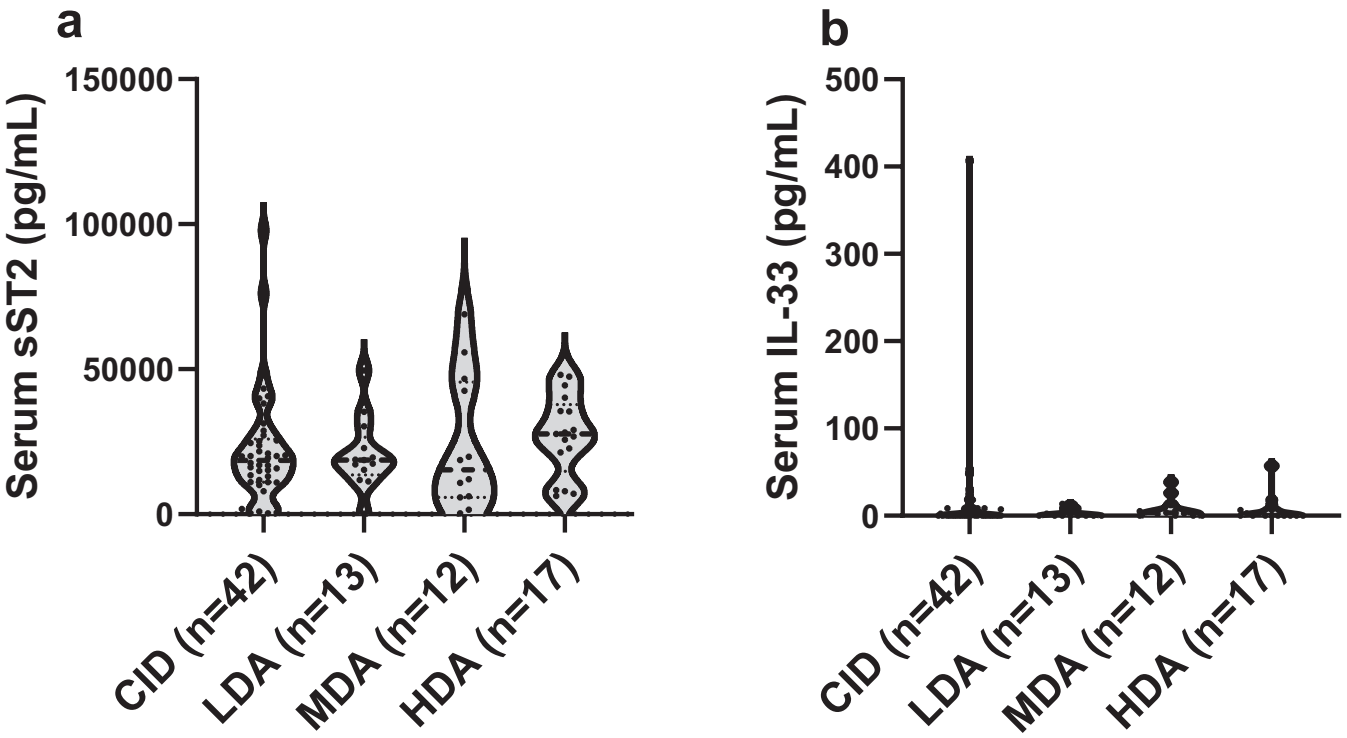

FIGURE 3 | Serum sST2 and IL–33 levels across different activity states of JIA (CID, inactive; HDA, high disease activity; LDA, low disease activity and MDA, moderate disease activity).

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no significant correlation between serum sST2 or IL–33 levels and disease activity in o-JIA, p-JIA or ERA. This suggests that serum sST2 or IL–33 are less reliable inflammatory markers than CRP or ESR in patients with these JIA subtypes. Notably, our study revealed a trend toward higher levels in patients with inactive disease, in contrast with previous studies that reported elevated IL–33 concentrations in active disease states [15]. In our study, the number of patients in each disease activity group was relatively small, which may affect the results and contributed to variability in IL–33 levels. In addition, Noor-eldeen et al. have reported significantly higher concentrations of IL–33 in the sera of patients with JIA compared to our findings [15]. In their cohort only 15% of patients were receiving a biologic (tocilizumab) [15], whereas in our cohort 43.9% of patients were on biologics, most of whom were receiving a TNF-inhibitor, which may partially explain the differences in the results.

Additionally, there are a few considerations to keep in mind when evaluating sST2 and IL–33 as biomarkers of disease activity in JIA. Both sST2 and IL–33 showed greater individual variability than CRP or ESR, and a single measurement, without baseline or follow-up samples limits assessment of temporal changes and its potential as a dynamic marker of disease activity and treatment response. When evaluating disease activity biomarkers, potential influences such as seasonality, fasting status, and time of day should be considered, as they may affect biomarker levels. Soluble ST2 concentrations appear to be independent of fasting status, unaffected by freeze–thaw cycles, and with minimal effects from hemolysis, lipemia, icterus, or rheumatoid factor in the Presage assay [21]. However, IL–33 may be influenced by fasting [22, 23]. In our study, patients and controls were not required to fast before the blood test. However, this was not monitored and therefore we cannot completely rule out the potential influence of fasting on serum IL–33 levels.

There are certain limitations in this study. Firstly, the small sample size limits the statistical power and generalizability of the findings. Secondly, many of the IL–33 measurements in our study fell below the limit of detection (LOD). To address this, values below the LOD were imputed as half of the lowest detectable concentration, following the approach used in our previous publications. This method facilitates comparison with earlier studies and ensures consistency across datasets. However, it is important to acknowledge that this imputation strategy may influence the distribution of the data and potentially reduce statistical power.

Furthermore, this study is exploratory in nature and focuses on clinically relevant variables. The relatively small number of patients in certain subgroups limits the robustness of statistical analyses. Consequently, formal corrections for multiple comparisons, such as the Bonferroni method, were not applied. While this approach allows for the identification of potentially meaningful associations, it also increases the risk of type I errors. Therefore, the findings should be interpreted with caution and considered hypothesis-generating. Future studies with larger sample sizes and appropriate statistical correction methods are warranted to validate these results.

In conclusion, despite the certain limitations, our findings provide novel insight into the role of sST2 and IL–33 in nonsystemic JIA patients. Notably, we observed a gender-related difference in sST2 levels of JIA patients. This finding warrants further exploration, as it may provide a deeper understanding of the pathophysiology of JIA and potential implications for monitoring disease progression and treatment response.

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Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of The Hospital District of Southwest Finland (ETMK 31/1801/2020, 16.6.2020).

Consent

Before enrolment in the study the patients and their guardians were informed about the procedures and the aim of the study and their informed written consent was obtained.

Conflicts of Interest

M.M. has attended congresses funded by pharmaceutical companies, including Pfizer, Novartis, Roche, and Sobi. H.R. has attended congresses funded by Novartis. The funders had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results. J.T., S.K., J.M., and Q.H. declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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