Frequency and Characteristic of Concomitant Fibromyalgia in Patients with Rheumatoid Arthritis

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Research Article

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Abstract

Fibromyalgia (FM) is a confounding factor for diagnosing and assessing rheumatic disease activity. This study sought to assess the extent of this syndrome in rheumatoid arthritis (RA) patients at our rheumatology department. The RA patients were divided into 2 groups (RA with FM and RA without FM) according to the score of the FiRST questionnaire and modified 2016 criteria for FM. We compared the clinical data and disease activities of RA patients with and without FM. As a result, RA patients with FM showed higher levels of CRP, ESR, DAS28-ESR compared with RA patients without FM in both FiRST questionnaires and questionnaires developed to diagnose FM(2016 criteria).Furthermore, RA patients with FM showed higher levels of IgA compared to without FM. For the blood cells count, RA patients with FM showed higher levels of white blood cells, platelets and lower levels of hemoglobin compared with RA patients without FM. Only by FiRST Questionnaires, RA patients with FM showed higher levels of RF compared to without FM. However, all groups showed a similar pattern in anti-CCP and IgG, IgM. RA patients with FM showed lower levels of vitamin D (VD) and higher levels of interleukin (IL)-6 compared with RA patients without FM.In conclusion,FM is a common feature in RA, more associated with high values of disease activity such as ESR, CRP and DAS28-ESR.

Introduction

Rheumatoid arthritis (RA) is a kind of autoimmune disease with the characteristic of systemic swelling and pain of joints. Joint deformation and disability may occur if the RA patients were not under proper therapy.RA affects about 0.5 to 1% of the adult population. Pain of the joints is a central feature in RA, with may influence on the patients health and physical function. However, pain is also a common problem in the general population and could also be a disease in itself.

Fibromyalgia (FM) is a subgroup of chronic pain, which is considered to be the central pain syndrome. The clinical character of FM is the widespread pain and tenderness of the whole body. Many FM patients may suffer from the disturbed sleep, fatigue and emotional distress[1,2].Many autoimmune diseases may co-morbid FM, including RA. Other studies showed the rate of co-morbid of FM in RA is between 12% and 17%[3,4].On the contrast, the prevalence of FM in the general population is much lower, (1–4%) was reported[5,6].In RA patients, the prevalence of FM was reported to be 10-fold higher[3].FM are also reported to be more common in women[6].

For the RA patients, the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and 28-joint Disease Activity Score (DAS28)-ESR are commonly used to modified disease activity and may effect on treatment decisions.Other studies showed that concomitant FM among RA patients may increase the disease activity calculated by DAS28, mainly due to the patients' global assessment. DAS28 score may be influenced by pain, RA patients with concomitant FM are at risk of further intensive treatment of RA due to the high disease activity, such as the overuse of biology.

Other studies evaluating DAS28 and Health Assessment Questionnaire (HAQ) in RA patients with and without FM. These studies showed an elevated DAS28 and a decreased HAQ score in patients with FM compared to RA patients without FM[3].

Concomitant FM in RA is associated with the more frequent use of biological therapy[7].This raises the question of whether the over use of biologics in RA patients is duo to the inflammation, or is instead due to the pain and other centrally mediated symptoms caused by FM.

The first aim of our present study was to study the prevalence of FM in patients with RA. The second aim was to study the differences between RA with FM and RA without FM.

Patients And Methods

Patients. Our study included 279 RA patients from the clinic of the Department of Rheumatology, 1st Hospital of China Medical University, answered a FiRST questionnaire. Patients have been consecutively included after being diagnosed with RA according to the American College of Rheumatology (ACR) 1987 criteria[8]. Patients with an established diagnose of RA according to the 1987 or 2010 ACR classification criteria[8,9]were screened for concomitant FM by self-administered questionnaires.

Ethical approval

was obtained from the Regional Ethical Review Board at 1st Hospital of China Medical University. Our study followed the guidelines from the Helsinki Declaration. Written conformed consent from the participants was obtained. The patients were divided into 2 groups according to the score of FiRST questionnaire. Those with score ≥5and score<5.

Screening for concomitant FM was performed by patient-administered questionnaires based on the FiRST or on the modified 2016 ACR diagnostic survey criteria for FM.

Clinical disease assessments. Disease activity was measured by the composite index DAS28. ESR and CRP were analyzed by routine methods at each clinic. Rheumatoid factor(RF) and anti-cyclic citrullinated peptide antibody (anti-CCP)were measured by routine methods.

Statistical methods. Statistical analyses were performed by SPSS 18 software. Unpaired T test was used to test differences between groups and $p<0.05$ was considered statistically significant. Correlations were performed by the Spearman's test.

Results

Demographic and clinical characteristics. For the clinical data of RA patients, see Tab1. Two hundred and seventy-nine RA patients were included in our study. The mean disease duration of RA patients was

4.25±4.53 years and the mean age was 50.11±13.52 years.Two hundred and forty-nine patients were women (89.2%). The DAS28 was 5.01±1.37.

Tab 1. The Demographic and clinical characteristics of RA patients

Clinical characters	value
Sex (female/male)	249/30
Age (years)	50.11±13.52
Disease duration (years)	4.25±4.53
ESR(mm/h)	28.92±23.74
CRP(mg/L)	14.11±25.78
Anti-CCP (U/mL)	264.04±214.03
RF (IU/mL)	74.39±103.23
DAS28	5.01±1.37

Prevalence of FM.22.6% (63/279) of the RA patients were diagnosed as FM according to the FiRST questionnaire. The modified 2016 diagnostic criteria for FM were applied to 248 RA patients. Among them,32 (12.9%) fulfilled the modified 2016 diagnostic criteria for FM.

For the RA patients diagnosed as FM by FiRST questionnaire, mostly were women (p=0.027) (See Tab 2). No significant difference between RA patients with and without FM was observed regarding gender by modified 2016 diagnostic criteria for FM.Furthermore, mostly were older patients with FM compared with without FM (p=0.005 by FiRST questionnaire) (Fig. 1A), (p=0.002 by modified 2016 diagnostic criteria for FM) (Fig. 1B). No significant difference between RA patients with and without FM was observed regarding disease duration (p=0.35) whether by FiRST questionnaire or by modified 2016 diagnostic criteria for FM.

Tab.2 The Demographic of RA patients with FM by FiRST questionnaire

	Female	Male	Total
RA with FM	61/ 96.8%	2/ 3.2%	63
RA without FM	188/ 87.0%	28/ 13.0%	216
Total	249/89.2%	30/ 10.8%	279

Of the RA patients with FM whether diagnosed by FiRST questionnaire or by modified 2016 diagnostic criteria for FM, 53% were treated with biological therapy vs 22% of RA patients without FM (p = 0.001).There were no significant differences between the groups in disease-modifying antirheumatic drug(DMARD) treatment.

Comparation of disease activity between RA patients with FM and without FM. For the FiRST Questionnaires, the mean CRP and ESR were much higher in RA patients with FM (22.89±29.46 mg/L and 38.77±24.17 mm/h, respectively) compared to without FM (11.55±24.08 mg/L and 26.09±22.89 mm/h, respectively)(p=0.006, p=0.000, respectively) (Fig. 2A).DAS28 in the FM group was 5.07 compared to 4.48 in the non-FM group (p =0.0009) (Fig. 2A).

For the modified 2016 diagnostic criteria for FM, the mean CRP and ESR were much higher in RA patients with FM (27.29±33.08 mg/Land 39.76±22.18 mm/h, respectively) compared to without FM (11.95±21.09 mg/L and 25.79±21.99 mm/h, respectively)(p=0.014, p=0.003, respectively) (Fig. 2B). DAS28 in the FM group was 5.62 compared to 4.49 in the non-FM group (p<0.0001) (Fig. 2B).

Comparation of antibodies and immunoglobulin between RA patients with FM and without FM. For the FiRST Questionnaires, the RF levels were higher in RA patients with FM compared to without FM (p=0.048) (Fig. 3A). For the modified 2016 diagnostic criteria for FM, the mean RF levels in RA patients with FM was slightly elevated, but not statistically significance compared to without FM (p=0.065) (Fig. 3B).There were no significantly differences in anti-CCP levels between with and without FM whether by FiRST Questionnaires or by modified 2016 diagnostic criteria for FM (p=0.102, p=0.430, respectively) (Fig. 3A, B).

Furthermore, we showed the significant difference in IgA levels between with and without FM by two criteria (p=0.018, p=0.015, respectively) (Fig. 3A, B). There was no significant difference of other immunoglobin (IgG, IgM) between with and without FM patients.

Comparation of blood analysis between RA patients with FM and without FM. By the FiRST Questionnaires, the RA patients with FM showed higher levels of white blood cells, platelets and lower levels of hemoglobin compared with RA patients without FM (p=0.001, p=0.025, p=0.005, respectively)

(Fig. 4A). The same differences were showed between RA patients with and without FM classified by modified 2016 diagnostic criteria for FM (p=0.005, p=0.024, p=0.002, respectively) (Fig. 4B).

Comparation of sera vitamin D3 levels between RA patients with FM and without FM. For the FiRST Questionnaires, the VD levels were lower in RA patients with FM compared to without FM (14.60 vs 16.84, p=0.0293) (Fig. 5A). For the modified 2016 diagnostic criteria for FM, the mean VD levels in RA patients with FM were lower than RA patients without FM (13.71 vs 16.68, p=0.0283) (Fig. 5B).

Comparation of sera IL-6 levels between RA patients with FM and without FM. For the FiRST Questionnaires, the IL-6 levels were higher in RA patients with FM compared to without FM (126.6 VS 84.07, p=0.0327) (Fig. 6A). For the modified 2016 diagnostic criteria for FM, the mean IL-6 levels in RA patients with FM was also higher than RA patients without FM (159.4 vs 85.16, p=0.0043) (Fig. 6B).

Discussion

Our study showed the prevalence of FM in RA patients and its relation to disease activity and function in RA.Of the patients with RA, 22.6% reported FM according to FiRST questionnaire and 12.9% according to 2016 diagnosis criteria of FM.Our data was the similar with other studies data[3,4].The prevalence of FM in RA patients was much higher than that of the general population (1–3% reported)[10,11].Most of RA patients with FM were older population and women. These results suggest us to pay more attention to the concomitant of FM in RA patients. To classified whether the pain of RA patients is caused by RA itself or by FM, as the treatment is totally different.

FM in RA patients may cause persistent widespread chronic pain despite adequate control of the inflammation. The mechanism of FM is not fully understood, one explanation could be central sensitization of the central nervous system[12,13].

Our study also showed RA patients with FM has higher levels of disease activity compared to RA patients without FM, including ESR, CRP and DAS28.

Study showed that prevalence of FM in sero-positive RA patients were 1.8 times higher than seronegative RA patients. No relationship with age was found[14]. In contrast, in our study, variables related to antibodies production such as RF and CCP were less distinctly associated with FM. Nevertheless, by the blood analysis, the RA with FM group showed higher levels of white blood cells and platelets number compared with RA patients without FM. The anemia in RA with FM group was severe than RA without FM patients. Other study showed more antirheumatic treatment (especially biologic drugs), because of overe stimation of the disease activity. Coexistence of FM inpatients with RA should be identified so that the patients may get adequate treatment not only of the rheumatic disease but also of the noninflammatory pain disorder.

RA patients with FM showed a lower level of VD compared with RA patients without FM. Prescribe of VD may relieve the symptom of FM in RA patients. IL-6 play an important role in the pathogenesis of RA and

anti-IL-6 biologic therapy make RA patients improve a lot. Our study showed RA patients with FM had higher levels of IL-6 compared with RA patients without FM.

In general, our study showed high prevalence of FM in RA patients and concomitant FM is likely to influence clinical measures of disease activity, such as ESR, CRP and DAS28 values, as well as subjective responses to therapy. This finding is in accordance with several other studies[15–17].

Identification of RA patients with FM contributions to their symptoms which is not under the inflammatory influences seems to be very important as it can help to balance physician and patient expectations and advance the development of more targeted treatment strategies.

Declarations

Acknowledgments

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Author contribution

JL and XL designed the study and revised the manuscript.ZYG and ZHC performed the experiments. ZYG drafted the manuscript.TS and DFL analyzed the data.

Conflicts of interest

The authors confirm that there are no conflicts of interest.

Data availability statement

The data performed to support the findings of this study are available from the corresponding author upon request.

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Figures

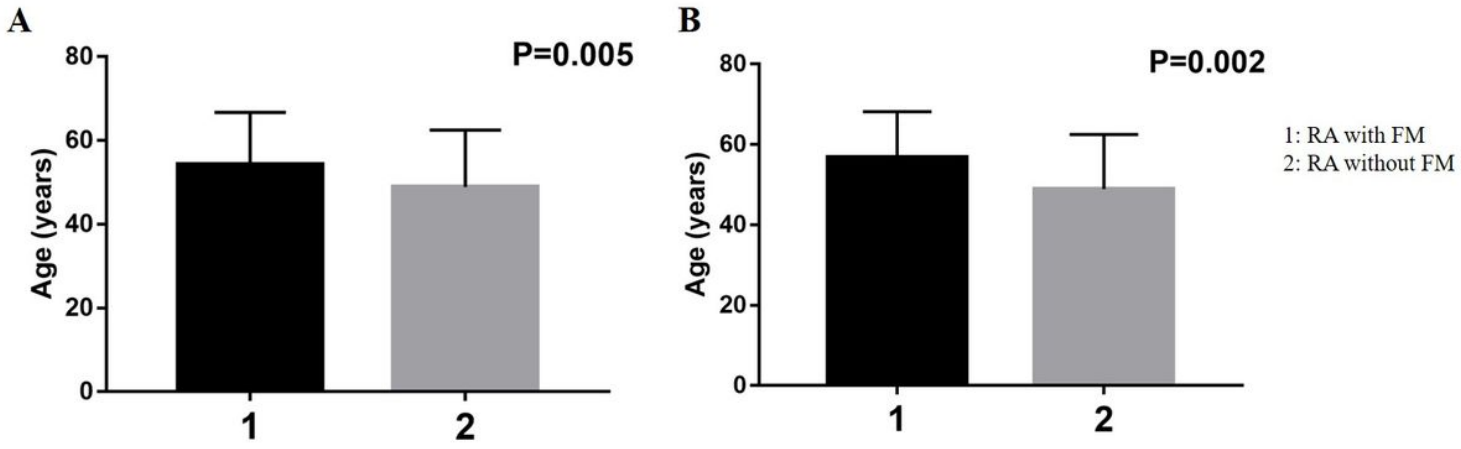

Figure 1

Comparison of age and course of disease in RA patients with and without FM. A No difference in age between RA patients with and without FM. p=0.005 B No difference in duration between RA patients with and without FM. (p=0.35)

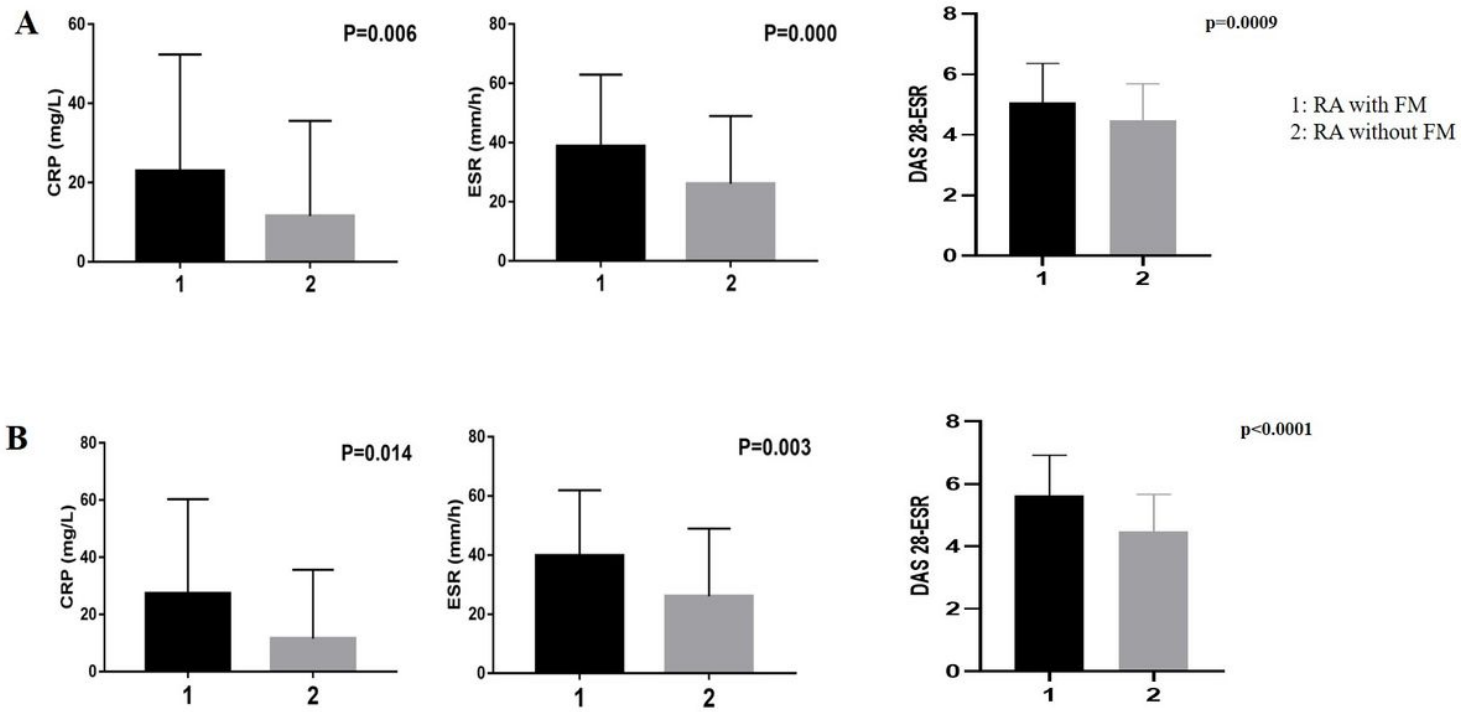

Figure 2

Comparison of disease activity between RA patients with FM and without FM. A: Comparison of disease activity between RA patients with FM and without FM in the FiRST Questionnaires.B: Comparison of disease activity between RA patients with FM and without FM in the modified 2016 diagnostic criteria for FM.

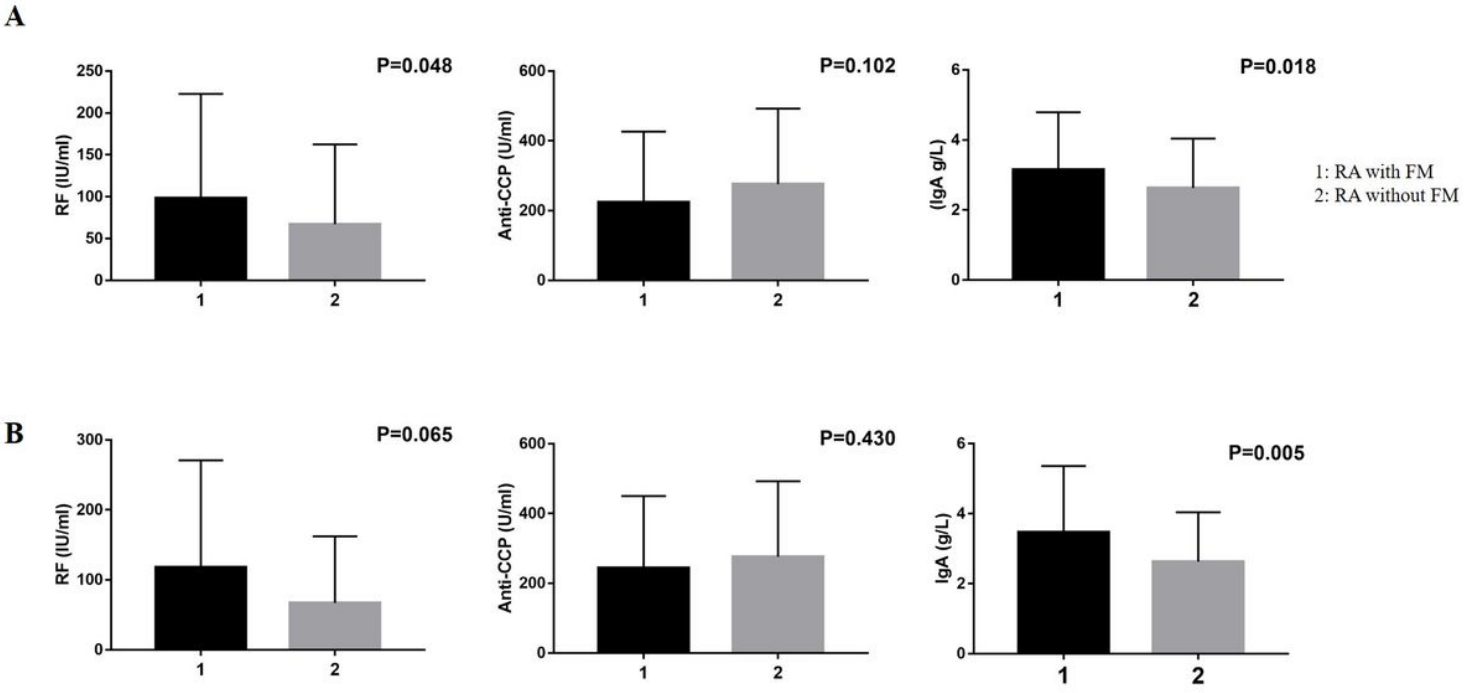

Figure 3

Comparation of IgA levels between RA patients with FM and without FM. A:Comparison of IgA levels between RA patients with FM and without FM in the FiRST Questionnaires.B: Comparison of IgA levels between RA patients with FM and without FM in the modified 2016 diagnostic criteria for FM.

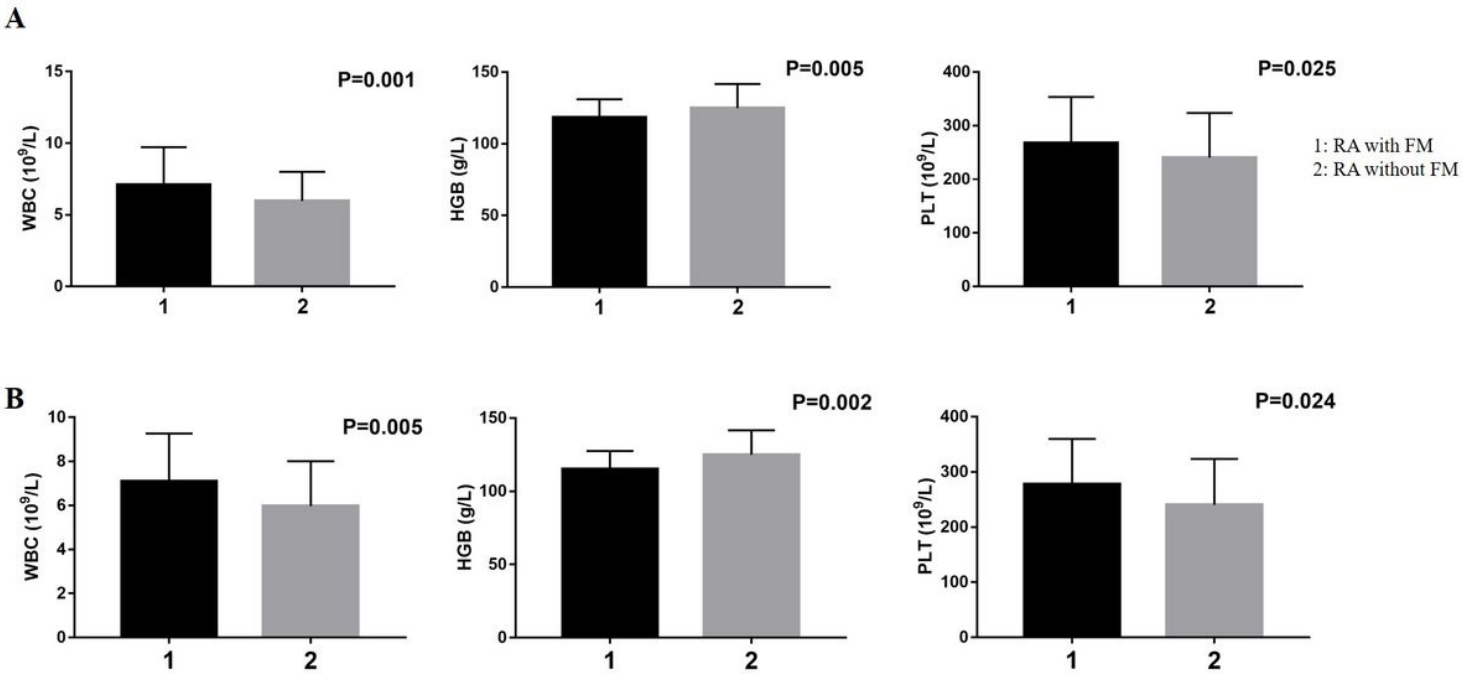

Figure 4

Comparation of blood analysis between RA patients with FM and without FM. A:Comparison of blood analysis between RA patients with FM and without FM in the FiRST Questionnaires.B: Comparison of

blood analysis between RA patients with FM and without FM in the modified 2016 diagnostic criteria for FM.

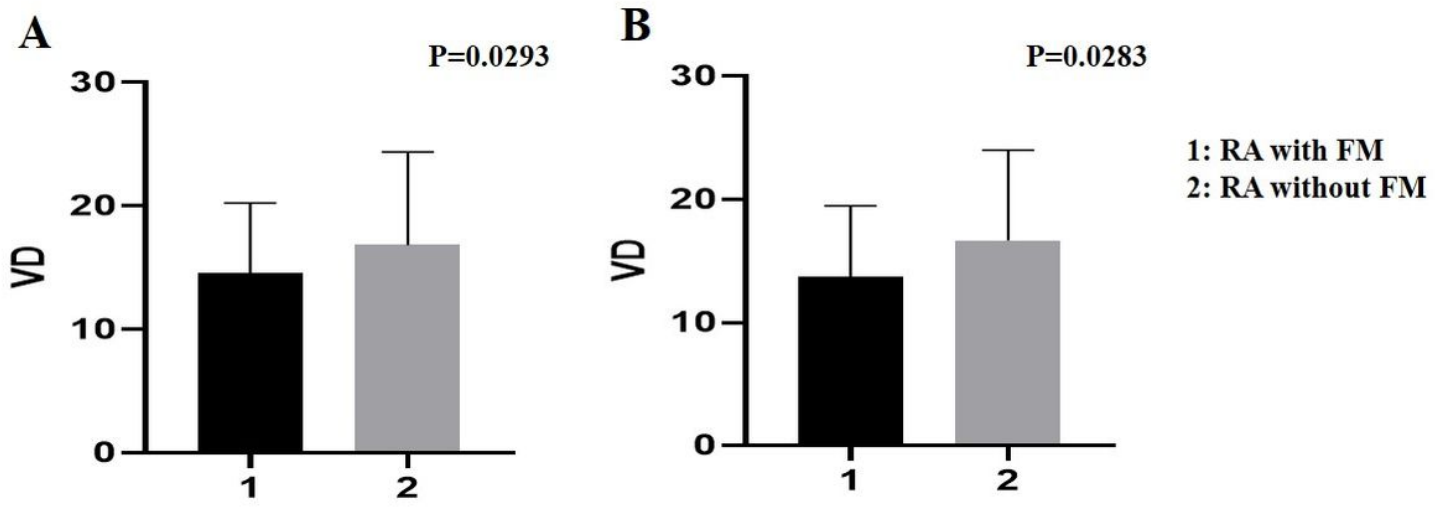

Figure 5

Comparation of sera vitamin D3 levels between RA patients with FM and without FM. A:Comparison of sera vitamin D3 levels between RA patients with FM and without FM in the FiRST Questionnaires.B: Comparison of sera vitamin D3 levels between RA patients with FM and without FM in the modified 2016 diagnostic criteria for FM.

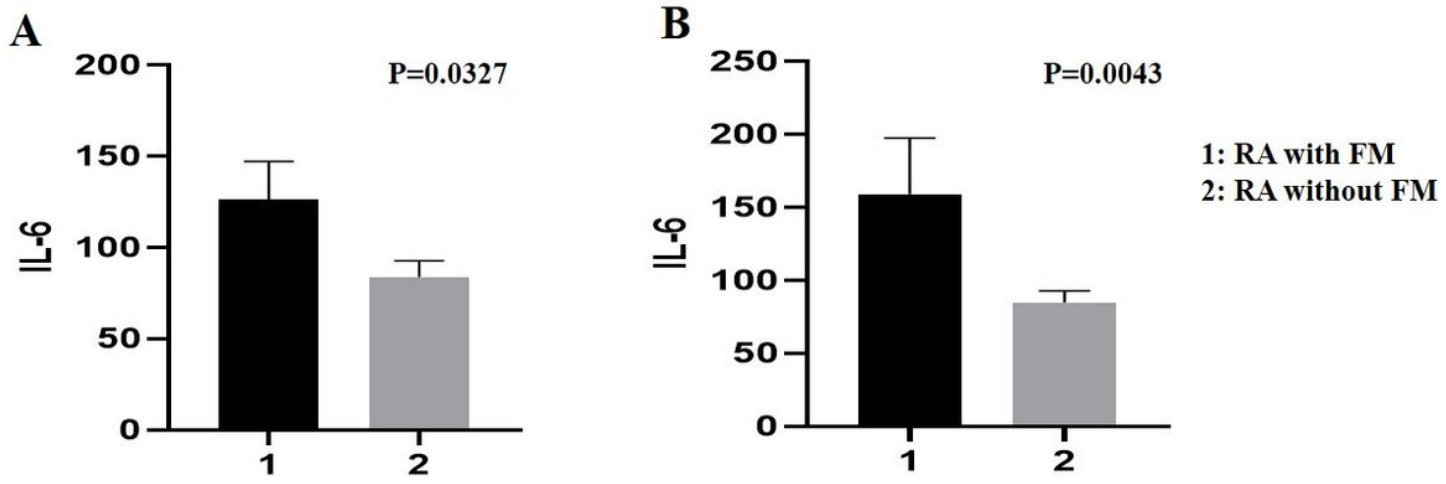

Figure 6

Comparation of sera IL-6 levels between RA patients with FM and without FM. A:Comparison of sera IL-6 levels between RA patients with FM and without FM in the FiRST Questionnaires.B: Comparison of sera IL-6 levels between RA patients with FM and without FM in the modified 2016 diagnostic criteria for FM.