

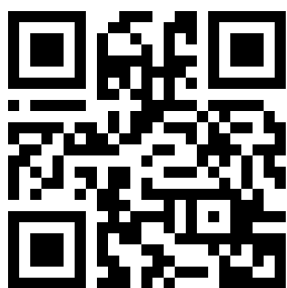
Assessment of T helper 17-associated cytokines in thromboangiitis obliterans

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Background: The management of thromboangiitis obliterans (TAO) remains a medical challenge because of its unknown etiology. It is also not known whether it is a systemic or localized disease or a type of autoimmune vasculitis.

Methods: In this study, we evaluated the serum level of IL-17 and IL-23 which increase in both systemic inflammation and autoimmunity, in 60 TAO patients and 30 age- and smoking habit-matched controls. Also, IL-22, which has reported high level during infection but not in autoimmunity, was evaluated.

Results: The serum levels of IL-17, IL-22 and IL-23 were significantly higher in the TAO patients in comparison with the controls ($P < 0.001$). Notably, the serum levels of IL-17, IL-22 and IL-23 were highest in the patients with the chief complaint of chronic ulcer and lowest in the patients with gangrene ($P < 0.05$). Also, the serum level of IL-22 was significantly higher in the anemic patients in comparison with the non-anemic patients ($P = 0.03$).

Conclusion: Owing to our findings, TAO appears more likely to be a systemic disorder rather than a localized vasculopathy. Therefore, treatment protocols based on systemic treatment of TAO patients may be more helpful than localized treatment, such as bypass surgery and endovascular procedures. Also, according to our findings regarding the high level of IL-22, the trigger of TAO development may be an infectious pathogen. However, additional research is highly recommended to investigate whether TAO is an infectious disease or an infectious-induced autoimmunity.

Keywords: thromboangiitis obliterans, Buerger's disease, autoimmunity, interleukin-17, interleukin-22, interleukin-23

Introduction

Thromboangiitis obliterans (TAO), or Buerger's disease, is an episodic, non-atherosclerotic peripheral vascular disease, which is usually seen in young male smokers and is especially common in the Middle East, Southeast Asia, the Far East and Eastern Europe. Its highly inflammatory thrombosis formation could lead to occlusions of small- and medium-sized vessels and, consequently, can lead to tissue gangrene and limb loss.¹

The etiology of TAO remains unknown. It is also not known whether it is a systemic or localized disease.² Therefore, management of TAO remains a medical challenge. Although there is a close relationship between TAO outcomes and smoking, smoking on its own cannot explain the low prevalence, male gender-based and geographical distribution of the disease.³ It has been suggested that TAO might be a type of autoimmune vasculitis. However, unlike in other types of vasculitis, TAO patients usually do not demonstrate a favorable response to immunosuppressants.^{4,5}

In addition, there is evidence that the trigger of TAO development might be an infectious pathogen, such as *Porphyromonas gingivalis* or *Rickettsiales*. However, this hypothesis has neither been confirmed nor ruled out.^{6,7}

Owing to the fact that consideration of TAO as a systemic inflammatory disease influences treatment policies, more investigation regarding this issue is needed.

Notably, the presence of pro-inflammatory cytokines and inflammatory mediators in plasma is known as systemic inflammation.⁸

Until recently, the serum levels of several cytokines and inflammatory mediators in TAO have been measured, and the results of measurement indicate evidence for systemic inflammation.^{7,9–13} However, TAO is not yet considered a systemic disease, and some treatment protocols, such as endovascular or bypass surgery, are pursued based on the assumption that TAO is a localized vasculopathy.¹⁴

In this study, we evaluated the serum level of IL-17 and its inducer, the so-called IL-23 in TAO patients and controls. It has been demonstrated that these cytokines increase in both systemic inflammation and autoimmunity.^{9,15,16} Also, a high serum level of IL-22 has been reported during infection but not in autoimmunity.¹⁷ If all of these cytokines were significantly higher in TAO patients than in controls, it could indicate that TAO is more likely a systemic inflammatory disease.^{9,18} To differentiate the trigger of systemic inflammation, it was hoped that IL-22 would provide a clue regarding whether the TAO trigger is more likely an infection or an auto-antigen.¹⁹

Materials and methods

We analyzed plasma samples from 60 male Caucasian patients from February 2016 through February 2019. TAO diagnosis was clinically confirmed according to Shionoya's criteria with angiography confirmation.²⁰ To prevent bias regarding the influence of smoking on Th17-associated cytokines, 30 age- and smoking habit-matched male Caucasian controls were enrolled in this study. The clinical manifestations of the patients, along with complete blood count (CBC) data, were documented for each patient. IL-22, IL-23 and IL-17 were evaluated using the ELISA method (ZellBio GmbH, Ulm, Germany). This study has been approved by the ethical committee of Mashhad University of Medical Sciences and all patients and controls signed a written consent form before participating in this study (ethical code: MUMS-961500). The data were analyzed using Statistical Package for the Social Sciences (SPSS) version 11.5 (SPSS Inc., Chicago, IL, USA).

Results

Demographic features

In total, 60 TAO patient plasma samples and 30 plasma samples from age-, gender- and smoking habit-matched controls were enrolled in the current study. All of the TAO patients were Caucasian men with a previous TAO diagnosis according to Shionoya's criteria and angiography confirmation who reported due to paraesthesia (35%), pain (35%), chronic ulcer (14%) or gangrene (16%). The mean age of the patients was 42 ± 7 years. The mean daily cigarette smoking was 18 ± 13 cigarettes per day (maximum 60 and minimum 2 cigarettes/day), and the mean duration of smoking was 21 ± 8 years (maximum 37 and minimum 2 years). The duration of disease diagnosis was 7.7 ± 5.3 years (maximum 16 and minimum 1 year).

Complete blood count results

According to the most recent definition of anemia by the WHO,²¹ 25% of the patients had anemia (hemoglobin < 13 g/dL), with a mean of 12 ± 0.9 g/dL. Approximately, 18% had hemoglobin (Hgb) > 13 g/dL (14.4 ± 1 g/dL), but with abnormal mean corpuscular volume, mean corpuscular hemoglobin (MCH) and MCH concentration (MCHC) indices. Approximately, 36% of the patients had Hgb > 14 g/dL, with a mean of 16 ± 1.2 g/dL.

According to the definition of neutrophilia (i.e., absolute neutrophil count > 7700 cells/ μ L),²² approximately 11% of the patients had neutrophilia, with a mean of 8510 ± 89 cells/ μ L.

A total of 45% of the patients had platelet aggregation in the CBC analysis. Notably, 45% of the patients also had low mean platelet volume (MPV), with a mean of 8.7 ± 0.4 fL, and the rest of the patients had normal MPV, with a mean of 10.2 ± 0.2 fL.

Th17-associated cytokines

The mean levels of IL-17, IL-22 and IL-23 in the TAO patients and the control group are summarized in Table 1. The serum levels of IL-17, IL-22 and IL-23 were significantly higher in the TAO patients in comparison with the controls ($P < 0.001$).

Among the TAO patients, the serum levels of IL-17, IL-22 and IL-23 were highest in the patients with the chief complaint of chronic ulcer and lowest in the patients with gangrene (Figure 1).

Also, the serum level of IL-22, but not IL-17 or IL-23, was significantly higher in the anemic patients, with a Hgb

Table 1 The independent-samples *t*-test was used to compare the serum levels of IL-17, IL-22 and IL-23 between the thromboangiitis obliterans (TAO) patients and the control group. The data are presented as mean \pm SD. The level of statistical significance is $P < 0.05$

| | TAO | Controls | t |
|---------------|------------------|------------------|-----------------------|
| IL-17 (ng/L) | 11.4 \pm 4.37 | 5.74 \pm 2.5 | 6.528 ($P < 0.001$) |
| IL-23 (ng/L) | 25.44 \pm 11.7 | 11.82 \pm 5.39 | 6.03 ($P < 0.001$) |
| IL-22 (pg/mL) | 11.81 \pm 7.83 | 5.59 \pm 2.7 | 4.208 ($P < 0.001$) |

level of less than 13 g/dL in comparison with the non-anemic patients, with a Hgb level of >14 g/dL ($P = 0.03$) (Figure 2).

Similarly, the serum levels of IL-17 and IL-22 were significantly higher in the patients with neutrophilia (Figure 3).

The serum levels of IL-17, IL-22 and IL-23 showed no significant differences between the patients with or without platelet aggregation. However, the serum level of IL-22 was significantly lower in the patients with low MPV ($P = 0.001$) (Figure 4).

Discussion

TAO is regarded as an inflammatory, occlusive, peripheral vascular disease. The etiology of TAO remains unknown.^{2,3} However, the close relationship between TAO and smoking was noted soon after the definition of the disease by Leo Buerger. Currently, smoking cessation is a mandatory feature of TAO treatment. However, smoking on its own cannot explain the low prevalence and geographical distribution of TAO.^{1,2} Even TAO classification is challenging: it is usually viewed as a peripheral arterial disease rather than a type of vasculitis, and TAO patients are typically referred to angiologists or vascular surgeons as opposed to rheumatologists.²³ Although several studies found significantly higher serum levels of tumor necrosis factor- α (TNF- α), IL-1 and IL-6 as the negative feedback of TNF and IL-1 in TAO patients in comparison to smoker controls,^{9,10,12} TAO is not yet considered a systemic disease.

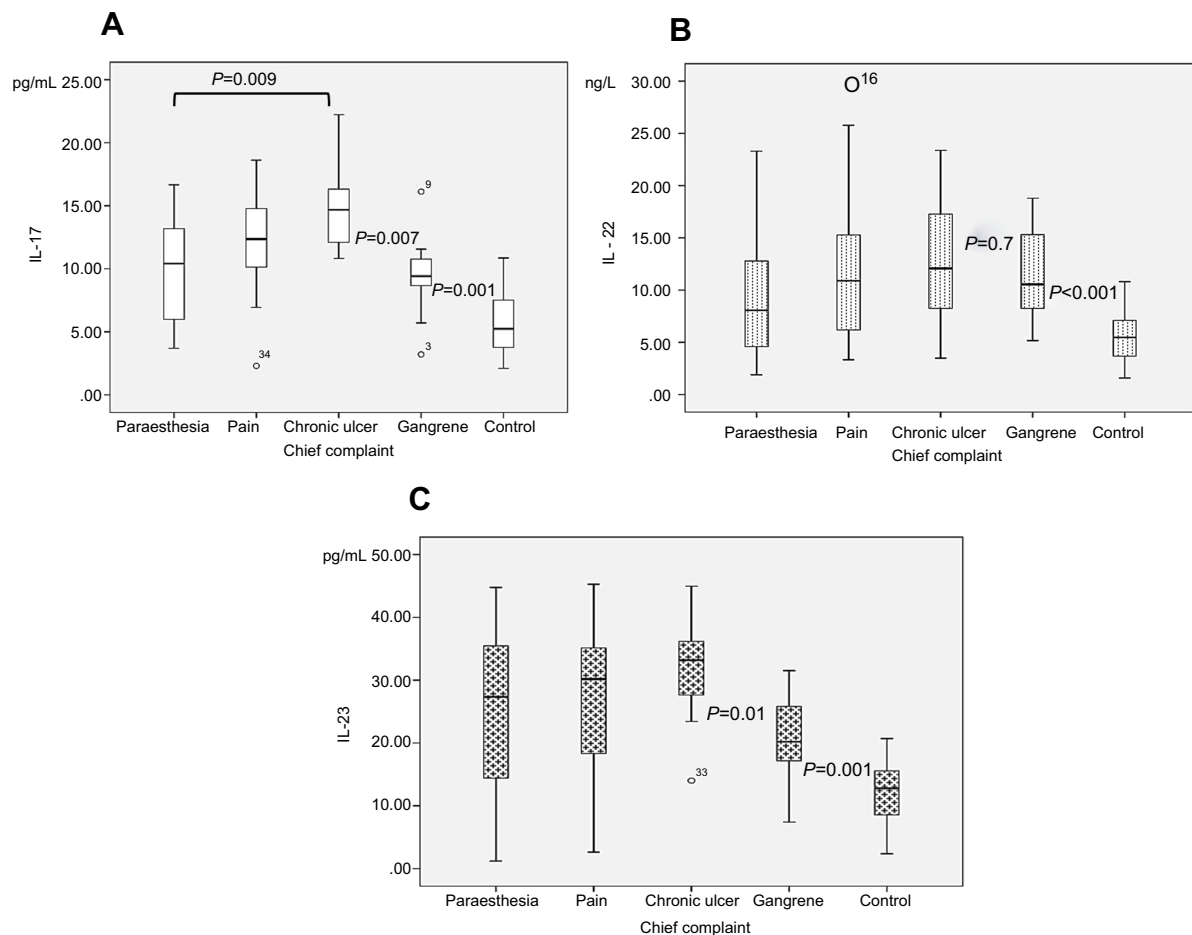


Figure 1 Serum levels of (A) IL-17, (B) IL-22 and (C) IL-23 in different clinical manifestations of thromboangiitis obliterans, including paraesthesia, pain, chronic ulcer and gangrene. The lowest levels of IL-17, IL-22 and IL-23 were seen in the patients with chief complaints of paraesthesia and gangrene. Also, the highest serum levels of IL-17, IL-22 and IL-23 were found in the patients suffering from chronic, non-healing ulcer.

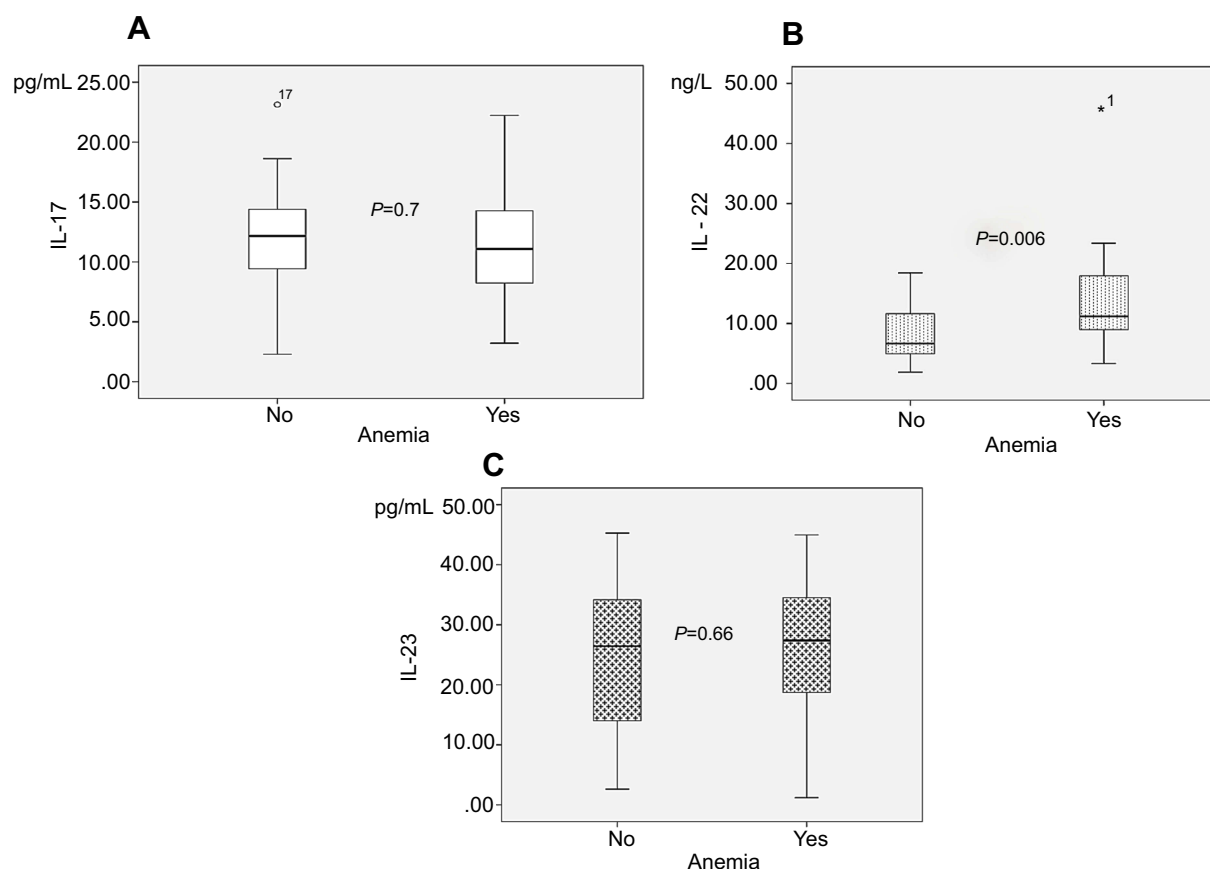


Figure 2 The mean serum levels of (A) IL-17, (B) IL-22 and (C) IL-23 in the anemic and non-anemic thromboangiitis obliterans patients.

This may be because of the unfavorable response of TAO to immunosuppressant medication and its favorable response to smoking cessation.^{5,23}

In this study, the serum levels of IL-17, IL-22 and IL-23 were significantly higher in the TAO patients in comparison to the controls. Even in the patients without manifestation of critical limb ischemia and those in the silent phase of the disease with only toe paraesthesia, the Th17-related cytokines were significantly higher than in the controls. This finding may indicate that Th17-related cytokines play a role in the development and pathology of TAO.

Notably, the increased number of circulating Th17 cells and increased serum levels of IL-17 and IL-23 have been demonstrated in systemic vasculitis.²⁴ Also, a study in 2012 on 20 TAO patients demonstrated a significantly higher level of Th17 in comparison to the controls, and the authors concluded that TAO could be an autoimmune disorder.⁹ However, high levels of IL-17 and IL-23 have also been demonstrated in infectious diseases.^{25–29} In this study, we evaluated not only the serum levels of IL-17 and IL-23 but also IL-22 in a larger sample size of TAO

patients (n=60) in different phases of the disease along with a smoking habit-matched control group to control for the bias of influence of smoking on Th17.

Th17 cells are a subset of T helper cells that play a key role in inflammation by activating neutrophils and enhancing the production of inducible nitric oxide synthase by neutrophils.³⁰ As such, Th17 cells play a role in immune defense against extracellular bacteria, the released outer membrane vesicles of intracellular bacteria, and also fungal species. It has been demonstrated that Th17 cells can play a role in autoimmune diseases, possibly by indirectly influencing anti-neutrophil cytoplasmic antibodies (ANCA) production.^{31,32}

IL-17 is the main cytokine of Th17.³³ Notably, co-secretion of IL-17 and IL-22 indicates that the source of both cytokines is Th17.^{19,34} However, it has been demonstrated that there is an array of cell types, the so-called Th22, that can produce IL-22 independent of IL-17.³⁵ IL-22 induces antimicrobial peptides from epithelial cells and also recruits the neutrophils to sites of bacterial invasion.^{36,37} In addition, it has been demonstrated that IL-22 can regulate wound healing and angiogenesis.³⁸ IL-23 is the key

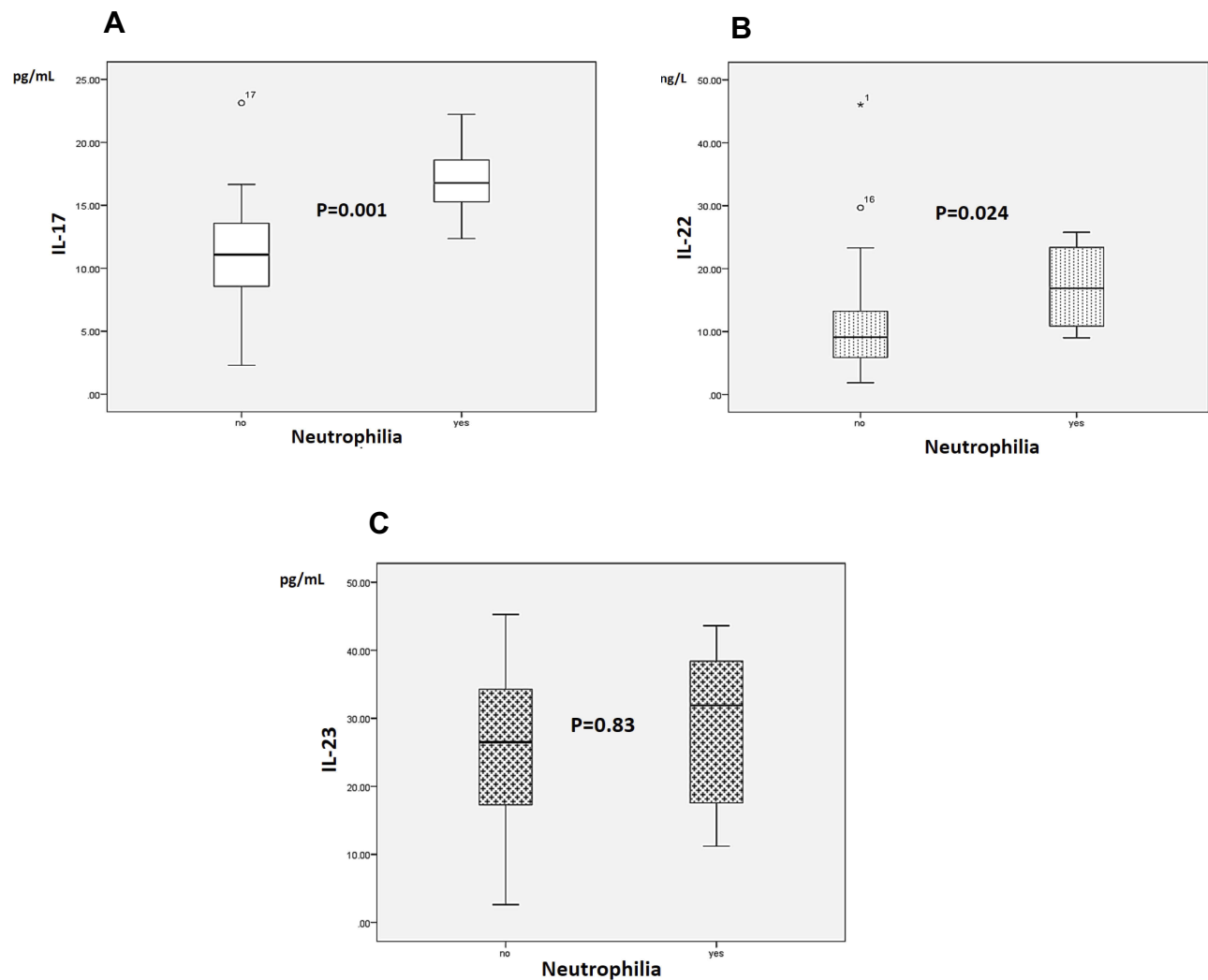


Figure 3 The mean serum levels of (A) IL-17, (B) IL-22 and (C) IL-23 in thromboangiitis obliterans patients with and without neutrophilia.

cytokine required for IL-17 and IL-22 secretion from Th17, and its main source is monocyte and dendritic cells.³⁹

In this study, the serum levels of both IL-17 and IL-23 significantly decreased in the patients with a chief complaint of gangrene, which might have been due to the omission of Th17 in the gangrenous tissue. However, owing to the fact that the serum levels of the studied cytokines in the patients with gangrenous tissue were also significantly higher than in the controls, there must be another source of Th17 in TAO, such as the lymph nodes. On the other hand, high levels of the studied cytokines, regardless of the clinical manifestations of the TAO patients, may indicate that TAO is more likely a systemic disease rather than a localized vasculopathy.

Moreover, according to a significantly higher serum level of IL-22 in the TAO patients in comparison with the controls, evidence of a high serum level of IL-22 during active

infection, and no evidence supporting the role of IL-22 in developing ANCA antibodies, TAO appears to be a systemic disease that is triggered by an infectious pathogen.^{6,7}

However, our findings cannot offer a conclusion regarding whether TAO is an infectious-induced autoimmunity or entirely an infectious disease.^{2,3}

Notably, 32.5% of the TAO patients had anemia (Hgb <13 g/dL), and IL-22 was significantly higher in the anemic patients as compared to the non-anemic patients. In this vein, it has been demonstrated that IL-22 plays a role in inducing hepcidin production. Hepcidin is a systemic iron hormonal regulator that generally increases with inflammation and infection and acts as a host defense mechanism to decrease iron availability for pathogens. Therefore, IL-22 may play a role in the induction of anemia by increasing hepcidin and, consequently, reducing the access of erythroblasts to iron for the production of hemoglobin.^{40,41}

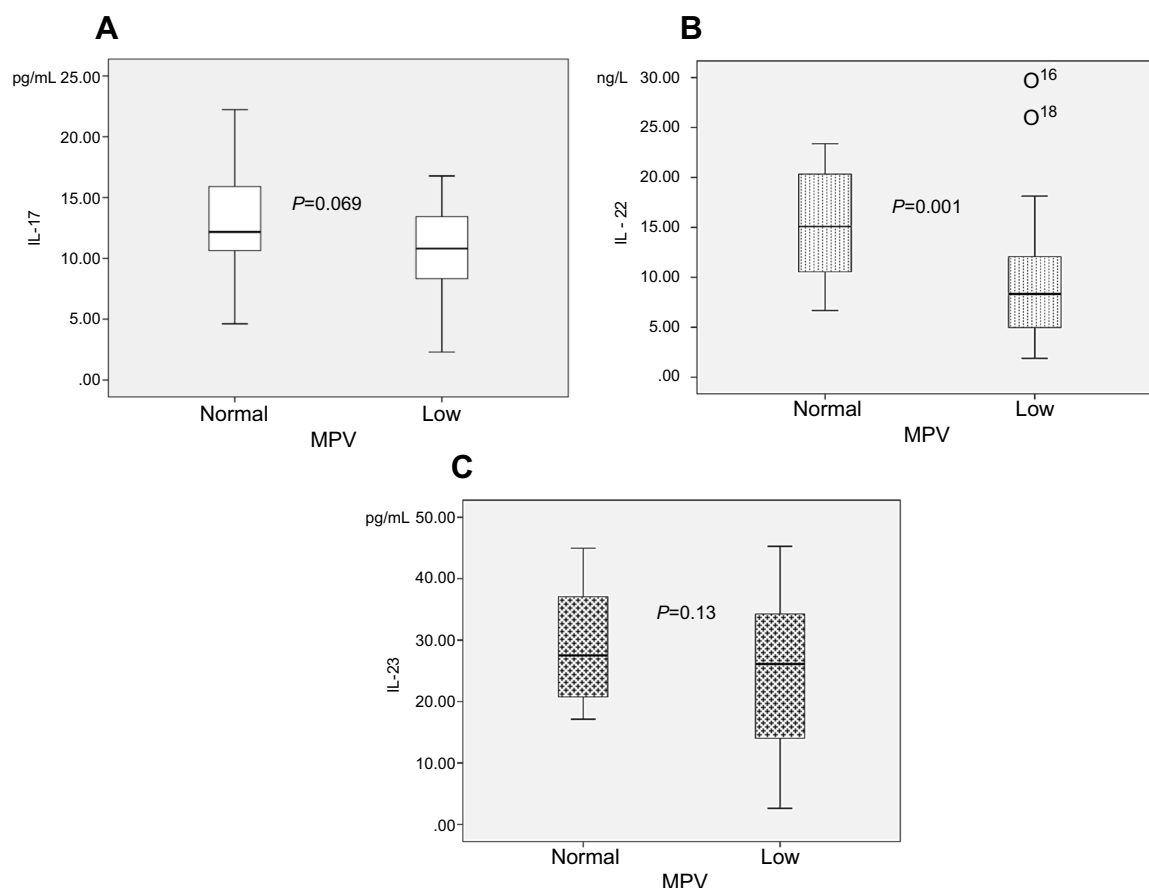


Figure 4 The mean serum levels of (A) IL-17, (B) IL-22 and (C) IL-23 in thromboangiitis obliterans patients with low and normal mean platelet volume.

Owing to the fact that neutrophils are the source of IL-17 and IL-22 production during infection by promoting the synthesis of antimicrobial peptides,^{42–44} significantly higher levels of IL-17 and IL-22 in the patients with neutrophilia are a reasonable outcome and may suggest support for the role of an infectious pathogen in the pathogenesis of TAO.

Several research reports have been published on the association between IL-17, IL-22 and IL-23 and platelet aggregation.^{45,46} However, according to our findings, no significant differences in the serum levels of these cytokines in the patients with or without platelet aggregation were observed. This finding may indicate that another, as yet unknown cause must be identified for platelet aggregation in TAO patients. Also, given the significant correlation between IL-22 and MPV, we did not find adequate research to justify this relationship.

Conclusion

Given the significantly higher serum levels of IL-17, IL-22 and IL-23 even in the TAO patients in the quiescent phase of the disease in comparison to the controls, TAO

appears more likely a systemic disorder rather than a localized vasculopathy, and Th17-related cytokines could play a role in the pathology of TAO. Therefore, treatment policies based on systemic treatment of TAO patients may be more helpful than localized treatment, such as bypass surgery and endovascular procedures. Also, our findings relative to the high level of IL-22, particularly in the patients with neutrophilia and a low level of MPV, suggest that the trigger of TAO development may be an infectious pathogen. However, additional research is highly recommended to investigate whether TAO is an infectious disease or an infectious-induced autoimmunity.

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Disclosure

The authors report no conflicts of interest for this work.

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