Journal of Positive School Psychology http://journalppw.com
2022, Vol. 6, No. 6, 9358-9364

Clinical And Diagnostic Significance Of Anti - Cd74 In Patients With Ankylosing Spondylitis Of Uzbek Population

Nargiza Abdurakhmanova , Khalmurad Akhmedov , Ozimbay Jabbarov , Matluba Rakhimova , Mavjuda Tagaeva , Feruza Khalmetova , Laylo Tursunova

Tashkent Medical Academy.

ANNOTATION

The article presents data from our own studies on the importance of antibodies to CD74 in patients with ankylosing spondylitis with regard to the clinical and diagnostic aspects. The Anti- CD74 levels were compared with the length, clinical symptoms, activity and radiographic stages of the disease.

The results of the studies showed that there was no correlation between the length of the disease and the levels of Anti - CD74. However, the concentration level of antibodies was found to be high among patients at the first radiological stage of the disease. The marker also strongly correlated with the activity and severity of clinical symptoms in patients with ankylosing spondylitis.

Keywords: Anti - CD 74, ankylosing spondylitis, autoantibodies, cytokines, biomarker, cytokines, BASDAI, ASDAS, HLA - B 27

Introduction

Ankylosing spondylitis (AS) is a chronic autoimmune inflammatory rheumatic disease that mainly affects the axial skeleton and is characterized by inflammatory back pain, peripheral joint involvement leading to disability of patients [2, 7, 18, 21].

During the first years of morbidity with AS, patients are usually treated by neuropathologists with erroneous diagnoses of osteochondrosis, disc herniation, radiculopathy with a low therapeutic effect, and only after 5-8 years, patients visit the rheumatologists [1]. The diagnosis is usually carried out in compliance with the modified New York criteria and ASAS criteria, which are mainly based on the presence of sacroiliitis, but in the early pre-radiological stages, the diagnosis of AS is a difficult task for the rheumatologist due to the absence of specific markers [3, 27] . One of the very important laboratory markers of AS is the carriage of the HLA-B27 gene, which is determined immunologically [3]. However, approximately 1.3–6% of individuals tested positive for HLA-B27 develop AS, the method sensitivity is 60–95%, and its prevalence varies greatly in different populations and cohorts around the world [7, 20]. Unfortunately, the specificity of HLA-B27 is insufficient for diagnosing AS [20]. Increasingly, in the scientific world there is evidence about the role of autoantibodies for early diagnosis as well as detection of the activity of autoimmune diseases, such as ankylosing spondylitis [10, 12, 15, 17].

Human CD74, also known as human lymphocyte antigen, is an invariant gamma chain of the HLA class [8, 14, 27]. CD74 antigen takes part in the intracellular assembly of class II major histocompatibility complex (MHC) and hampers premature attachment of peptides to this complex [5, 12, 22]. CD74 affects the differentiation of B cells of the immune system [14, 24, 26]. The attachment of antibodies to CD74 antigen can initiate proinflammatory cytokine production, including tumor necrosis factor alpha (TNF-a), which has a significant role to play in the pathogenesis of AS [23, 24].

The rapid search of world scientists led to the identification of autoantibodies to antigen CD74, for the first time identified in 2013 N.B Baerlecken [5], in the present time being considered as a candidate biomarker for the diagnosis of AS, especially in its pre-radiological period [13, 14, 18]. Since then, the anti -CD74 biomarker has been one of the hotly

discussed markers [5, 11, 15, 17], a number of scientists claim its high diagnostic value [4, 5, 9, 14,19,25], but there are scientists who claim about the lack of its significance in the diagnosis of AS [6, 10, 13]. The presence of conflicting data concerning the role of Anti-CD74 in the diagnosis of AS, its distribution in various ethnic groups, as well as the study of its prevalence among Uzbeks, aroused some interest.

Aim of the study: to investigate the frequency of presence, the diagnostic role of Anti- CD74 and to identify its relationship with the duration, clinical symptoms, radiological stage, the disease activity in patients with ankylosing spondylitis amidst Uzbek population.

Research methods and materials:

During 2020-2022, in the Tashkent City Clinical Hospital №3 and the Multidisciplinary Clinic of the Tashkent Medical Academy, 176 AS diagnosed patients were examined, out of which 148 were men and 28 women. The control group consisted of 50 middle-aged volunteers with no health disorders. The AS was pinpointed pursuant to the modified New York criteria adopted for diagnosing AS. The mean age of the patients was 36.2±5.1 years, the mean duration of the disease was 7.8 ±1.46 years. The axial form occurred in 59.4%, the peripheral form of AS in 40.6% of patients. The activity of the disease was studied using the BASDAI and ASDAS scales, the visual analogue scale (VAS) was used to assess the pain syndrome. The radiological stage of sacroiliitis was determined in conformity with Kellgren (1979). All patients underwent in-depth clinical and laboratory, immuno-biochemical studies with the detection of anti - CD74.

To measure the content of autoantibodies to the CD74 antigen in the obtained samples of patient sera, an ELISA method was used using Cloud - Clone reagents. corp. (USA) according to the instructions supplied with the kit.

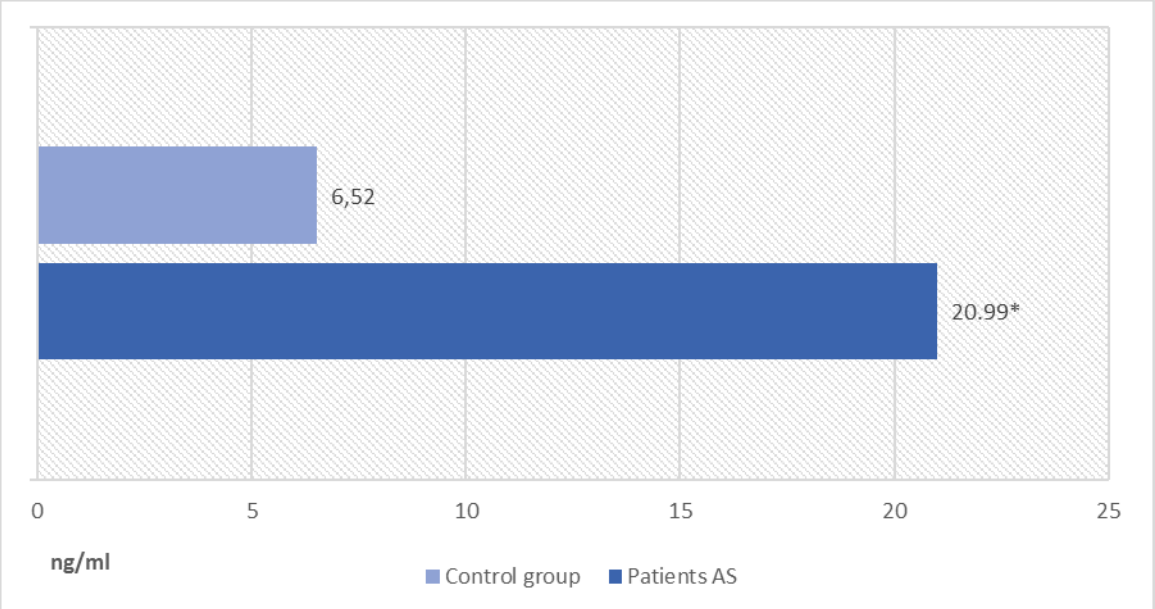
Statistical analysis of the study findings was conducted by means of Microsoft Office Excel 2019, "Statistics" applications on a PC. Correlation analysis was conducted with the use of Spearman's rank correlation test.

Research results:

Results of our study showed that the axial form occurred in 59.4%, the peripheral form of AS in 40.6% of patients. Carriage of HLA- B 27 was positive in 78.6% of patients.

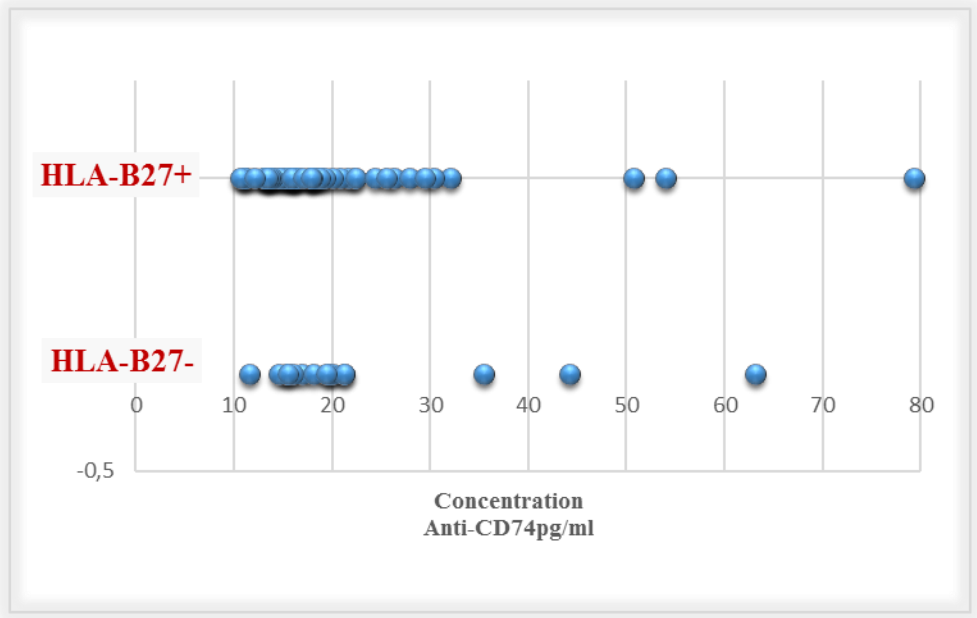
And following the intensity of the pain syndrome according to VAS was 7.2 ± 2.3 , C-reactive protein was 38.6 ± 9.3 mg / l. Based on the BASDAI the AS activity was found to be at an average of 4.7 ± 1.8 points. Whereas the AS activity research along the ASDAS scale resulted in the high 4.1±0.8 points.

When studying the level of Anti - CD 74, the following results were revealed: in patients with AS, the indicator was significantly increased ($p<0.001$) and the average figure was 20.6±1.46 ng / ml (n =70), and in the control group 6, 52±0.59 ng / ml (n =30) (Pic. 1), in 6.6% of healthy people (n =2) an elevated level of Anti - CD 74 was detected and in 7.1 % of patients (n =5) the titer was low.



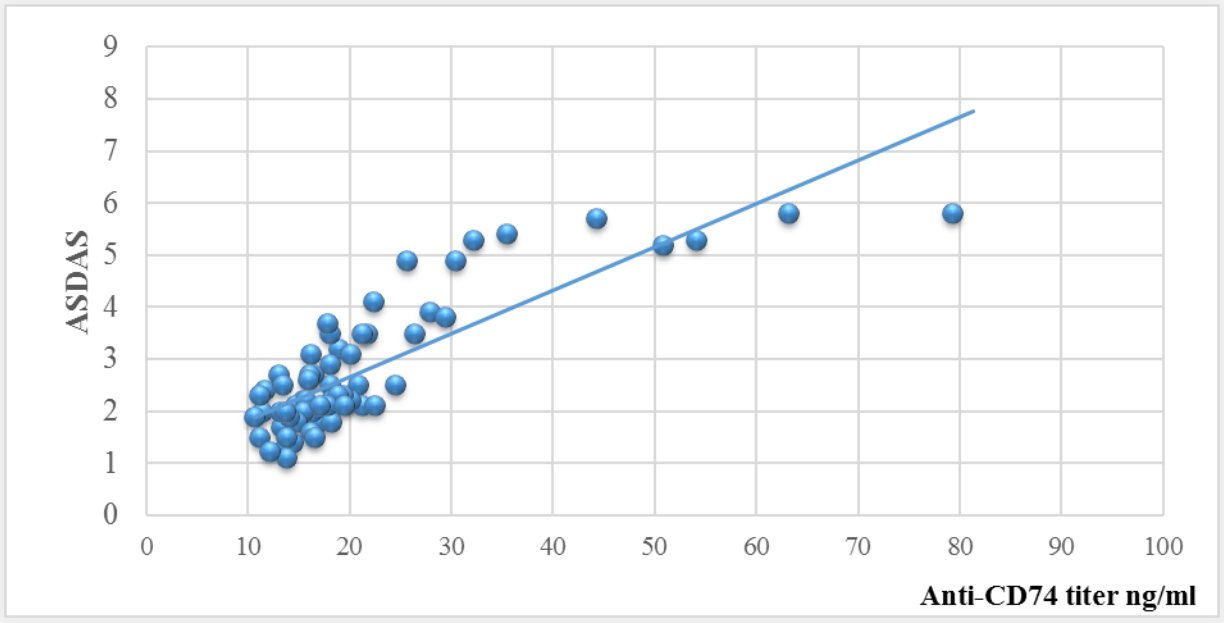
Pic.1 The level of Anti - CD 74 in the studied groups

We also compared Anti - CD 74 with the number of patients with HLA - B 27 carriage. In our sample, 78.6% of patients were found to be carriers of the HLA - B 27 allele and 4.3% of patients served as carriers of " HLA - B 27+" and 2.8% of patients with " HLA - B 27-" had negative Anti - CD 74 values (Pic. 2).



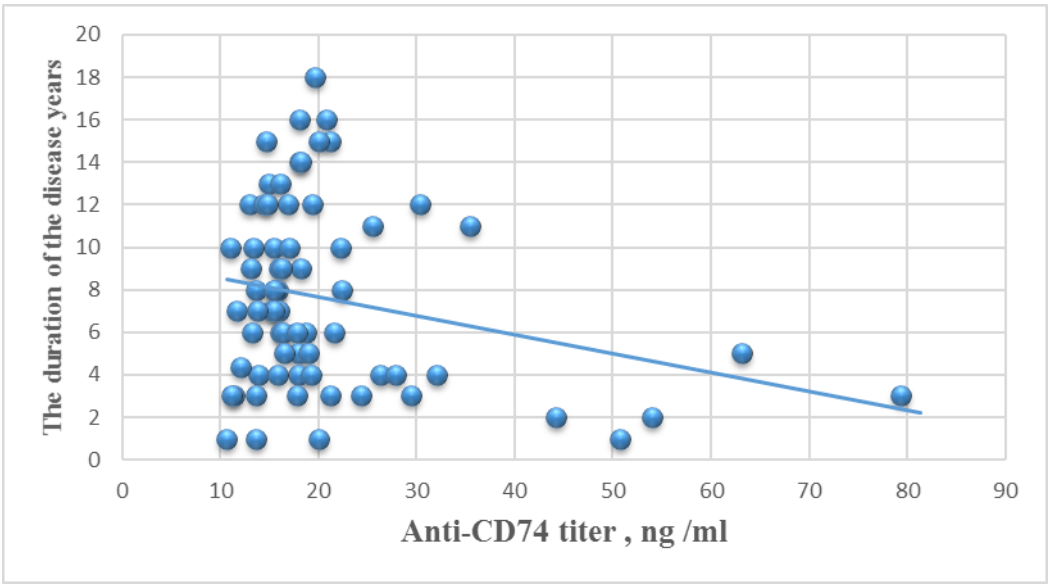
Pic. 2. The level of Anti - CD 74 depending on the presence of carriage of HLA - B 27 genotype.

The average AS activity according to the ASDAS scale was 2.74±0.14, indicating high activity. When comparing the Anti - CD 74 titer with the ASDAS -ESR level, we found a high positive correlation (r = 0.82). This suggests that the higher the activity of the disease, the higher the titer of Anti - CD 74 (Pic. 3).



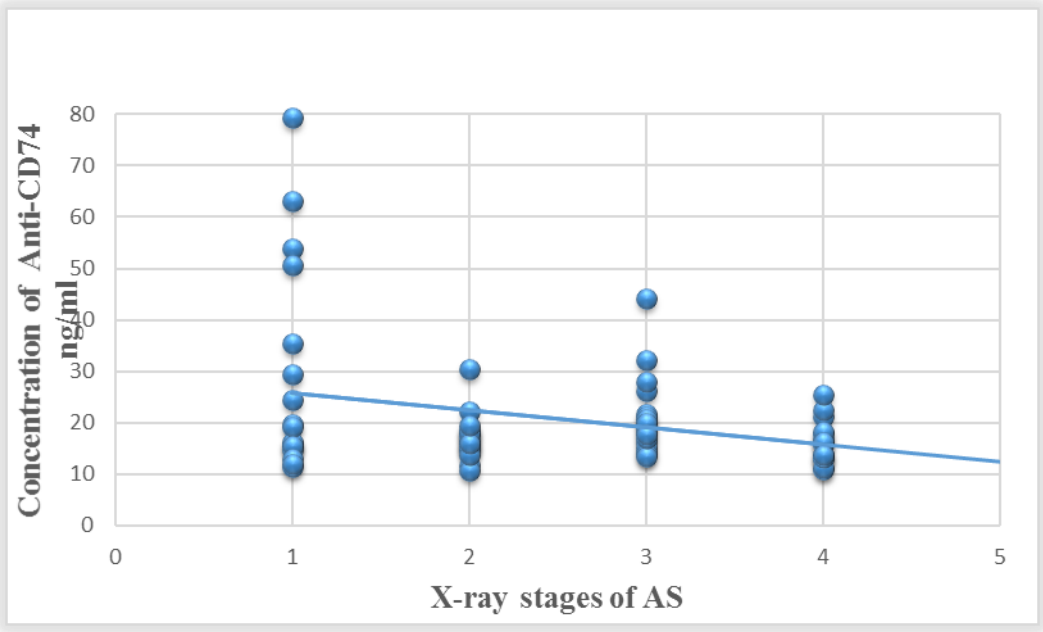
Pic.3. Association of anti-CD74 titer and ASDAS-ESR in patients with AS (r = 0.82).

When comparing the duration of the AS disease and the Anti - CD74 concentration, we did not reveal an association between the two parameters and the correlation coefficient was r = -0.26, which indicates a weak negative relationship between the two signs (pic.4).



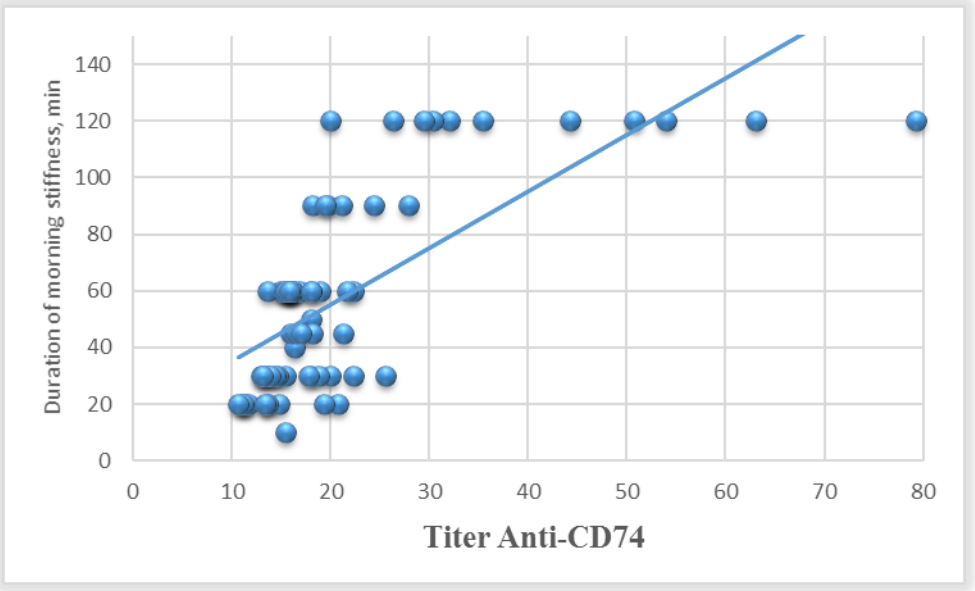
Pic.4. Association of titer against CD74 to disease duration amid AS - patients (r = -0.26).

In our investigation, we have completed a comparative analysis between the Anti - CD 74 titer and the radiographic stages of the disease in the study group. As can be seen from Pic. 5, higher concentration of Anti - CD74 was noted in patients with stage I of X-ray disease, and lower numbers were in patients with stage IV disease.



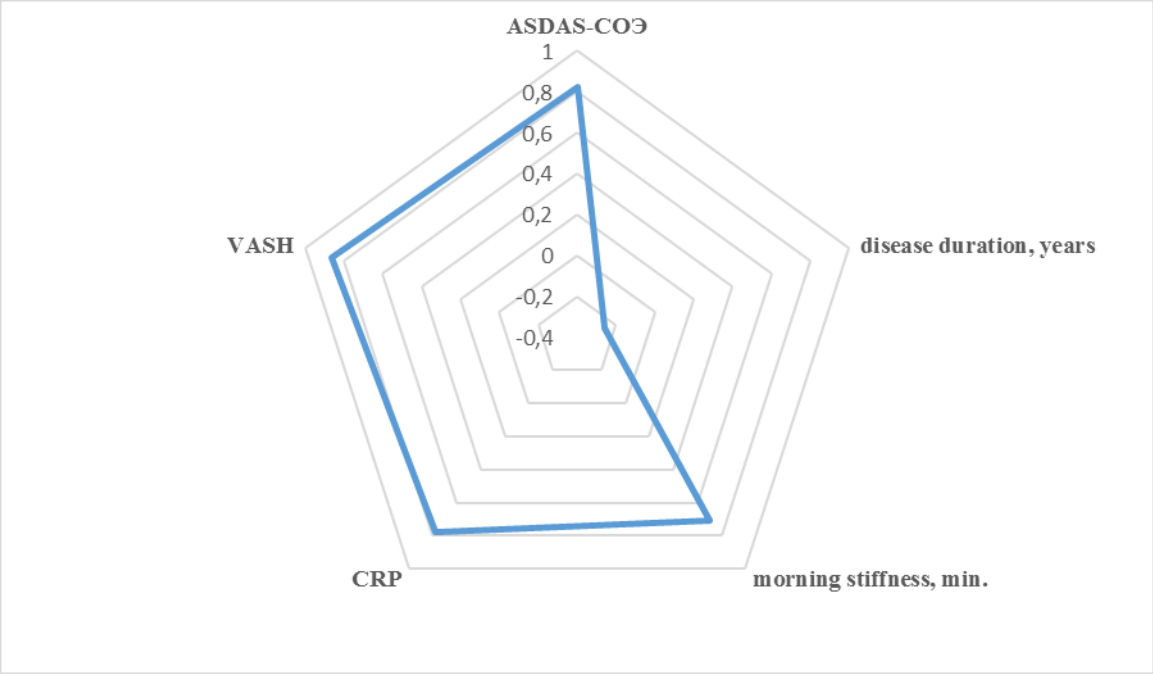
Pic.5. Comparative analysis of anti-CD74 titer at various radiological stages of AS.

The next step in our work was the associative analysis of the anti-CD74 titer with the duration of morning stiffness. Correlation analysis illustrated a strong positive correlation (r = 0.708) between the two features (Pic. 6). A high titer of anti-CD74 was accompanied by prolonged morning stiffness in the study sample.



Pic.6. Comparative analysis of anti-CD74 titer and duration of morning stiffness among AS suffering group (r = 0.708) .

Multivariate mathematical analysis revealed a strong positive correlation of Anti - CD74 between disease activity according to ASDAS – ESR, C - reactive protein (CRP), duration of morning stiffness, VAS, negative weak correlation with the duration of AS disease (Pic. 7.).



Pic.7. Correlation analysis of Anti - CD74 with clinical and laboratory signs of AS.

Discussion

The first works related to Anti -CD 74 appeared in 2013 by a group of scientists from Germany who studied this marker in 216 patients with spondylitis and presented the first data that anti-CD74 can be a biomarker for the early detection of AS [5]. However, the examination results of anti -CD74 antibodies in spondylitis had been conflicting [14, 17]. Further studies by some scientists did not reveal a difference in anti-CD74 with healthy individuals [6,10,13]. For example, Chao - Jun Hu investigated anti-CD74 in AS patients in the Han population of China [10]. The author did not reveal the diagnostic

value of anti -CD74. In 2018, a large SPACE cohort was investigated, led by Janneke J. de Winter , in which 54.7% of patients had antibodies against CD74 IgG and 63.1% of antibodies against CD74 IgA [6]. But the researchers did not reveal the relationship of the marker with the duration of the disease and concluded that this marker cannot be recommended for diagnosing the early pre-radiological stage of AS [6]. On the contrary, in 2020 Marwa et al. revealed a relationship with the duration and activity of AS [13]. The inconsistency of the available data caused us some interest, so we conducted this investigation to evaluate the rate of IgG antibodies to CD74 within AS- patients in comparison with the control group of healthy people and to identify the diagnostic value of this marker in patients with spondylitis.

The results of our study showed the presence of an increased titer of Anti - CD 74 compared with healthy ones, as well as the presence of a relationship between antibody titer and disease activity. When comparing Anti - CD 74 to the carriage of the HLA - B 27 allele , an increase in antibody titer was found in patients with both positive and negative numbers of this marker, which indicates the possibility of using Anti - CD 74 in patients with AS, especially in the absence of carriage polymorphism HLA - B 27, which is comparable to the work of Ziade et al. [28]. In addition, we compared the Anti - CD 74 titer with ASDAS disease activity and found a strong positive correlation. The antibody titer increased with disease activity, patients with very high Anti - CD 74 titer had high disease activity and patients with low disease activity had lower titer, 5 patients who had low titer had very low ASDAS activity.

In our sample, we did not find a correlation between Anti - CD 74 and the duration of the disease, which may be associated with a different rate of progression of the disease, but at the same time we found a connection with the radiological stages of the disease, in patients with the first stage, the antibody titer was higher compared to IV X-ray stage of the disease, which indicates its diagnostic value on the initial stages of the illness.

When constructing associative relationship between the duration of morning stiffness and the titer of Anti - CD 74, a strong positive relationship was revealed; high marker titers were associated with longer, and low numbers with shorter morning stiffness.

Our results are comparable with the data of foreign researchers who have shown the clinical, pathogenetic and diagnostic role of Anti - CD 74 in AS. In conclusion, we can say that Anti - CD 74 can be used to diagnose and assess the activity of the inflammatory process in AS, but since there were no patients with pre-radiological stage of AS in our sample, further studies with this group of patients are needed.

Conclusion:

1. With negative values of HLA - B 27 carriage, high levels of anti - CD 74 indicate a systemic inflammatory process, which allows it to be used as an additional marker for diagnosing AS.
2. Titer Anti - CD 74 has a strong correlation with the activity of ankylosing spondylitis, which makes it possible to use this marker to assess the severity of the inflammatory process in AS.

Reference:

1. Rakhimbaeva G.S., Yusupova D.Yu. Discogenic radiculopathy in the practice of a neurologist// J. _ NEVROLOGYA. Uzbekistan. 3(87), 2021.-p.36-38
2. Abdurakhmanova NM High concentration of tumor necrosis factor in ankylosing spondylitis patients after COVID-19. british medical journal. Volume 1, No.1.1, January 2022
3. Akhmedov Kh.S., NM Abdurakhmanova. Clinical features of ankylosing spondilitis in the post-covid period. American Journal of Medicine and Medical Sciences 2021, 11(11): 788-790 DOI: 10.5923/j.ajmms.20211111.09
4. Baraliakos X, Baerlecken N, Witte T, et al. High prevalence of anti-CD74 antibodies specific for the HLA class II-associated invariant chain peptide (CLIP) in patients with axial spondyloarthritis. Ann Rheum Dis 2014; 73:1079-82.
5. Baerlecken NT, Nothdorft S, Stummvoll GH, et al. Autoantibodies against CD74 in spondyloarthritis. Ann Rheum Dis 2014; 73:1211-4.
6. De Winter JJ, van de Sande MG, Baerlecken N, et al. Anti-CD74 antibodies have no diagnostic value in early axial spondyloarthritis: data from the

spondyloarthritis caught early (SPACE) cohort. Arthritis Res Ther 2018;20:38.
7. Ebrahimiadib N, Berijani S, Ghahari M, Pahlaviani FG. Ankylosing Spondylitis. J Ophthalmic Vis Res. 2021 Jul 29;16(3):462-469. doi: 10.18502/jovr.v16i3.9440. eCollection 2021 Jun-Sep.
8. Farr Laura et al. CD74 Signaling Links Inflammation to Intestinal Epithelial Cell. Regeneration and Promotes Mucosal Healing. Cell Mol Gastroenterol Hepatol. 2020;10(1):101-112. doi: 10.1016/j.jcmgh.2020.01.009. Epub 2020 Jan 28.
9. Gaydukova I, Rebrov A, Maslyanskiy , A, et al. Diagnostic value of anti-CD74 autoantibodies in axial spondyloarthritis and axial psoriatic arthritis. Results of open-label, cross-sectional, controlled, multicenter progress study. Ann Rheum Dis. 2018;77:348.
10. Hu Chao Jun et al. CD74 auto-antibodies display little clinical value in Chinese Han population with axial spondyloarthritis. Medicine (Baltimore). 2020 Dec 11; 99(50): e23433. doi:10.1097/MD.0000000000023433
11. Larida B. Autoantibodies against CD74 is a new diagnostic marker for spondyloarthritis (SpA). 2015 ACR/ ARHP annual meeting September 29, 2015.
12. Liu Y, Liao X, Shi G. Autoantibodies in spondyloarthritis, focusing on anti-CD74 antibodies. Front Immunol 2019;10:5.
13. Lan Do et al. Anti-CD74 IgA autoantibodies in radiographic axial spondyloarthritis: a longitudinal Swedish study. Rheumatology (Oxford). 2021 Oct; 60(9): 4085–4093.
14. Marva et al. Diagnostic value of anti-CD74 antibodies in early and late axial spondyloarthritis and its relationship to disease activity. Rheumatology 2020;00:1–6. doi:10.1093/rheumatology/keaa292
15. Maksymowych W.P. Biomarkers for diagnosis of axial spondyloarthritis, disease activity, prognosis, and prediction of response to therapy. Front Immunol 2019; 10:305.
16. Mauro D. Ankylosing spondylitis: an autoimmune or autoinflammatory disease? Nat Rev Rheumatol. 2021 Jul;17(7):387-404. doi: 10.1038/s41584-021-00625-y.
17. Prajzlerova K et al. . An update on biomarkers in axial spondylarthritis. Autoimmunity Reviews. 2016.
18. Rakhimova MB, Kh.S. Akhmedov The impact of sequelae of COVID-19 on the course of ankylosing spondylitis. Central Asian journal of medicine. Vol. 2021. Issue 4., p.11
19. Riechers E, Baerlecken N, Baraliakos X, et al. Sensitivity and specificity of autoantibodies against CD74 in nonradiographic axial spondyloarthritis. Arthritis Rheumatol 2019; 71:729-35.
20. Rosenbaum JT, Weisman MH et. al. HLA-B27 is associated with reduced disease activity in axial spondyloarthritis. sci rep. 2021 Jun 10;11(1):12331. doi: 10.1038/s41598-021-91829-5.
21. Rosine, N. et al. FRI0361 Innate versus adaptive. IL-17A producing cells in axial spondyloarthritis. Ann. Rheum. Dis. 78 (Suppl. 2), 862–863 (2019).
22. Seda Colak et al. The association of anti-CD74 antibody with spondyloarthropathies. Eur J Rheumatol. 2021 Oct;8(4):207-210. doi: 10.5152/eurjrheum.2021.20090.
23. Sogkas G, Klose K, Baerlecken N, et al. CD74 is a T cell antigen in spondyloarthritis. Clin Exp Rheumatol 2020; 38:195-202.
24. Stein et al. CD74: A New Candidate Target for the Immunotherapy of B-Cell Neoplasms. Clin Cancer Res 2007; 13:5556s-5563s.
25. VaKempen TS et al. Impaired proteolysis by SPPL2a causes CD74 fragment accumulations that can be recognized by anti-CD74 autoantibodies in human ankylosing spondylitis. Eur. J. Immunol. 2020.0:1–11
26. Witte T, Köhler M, Georgi J, et al. IgA antibodies against CD74 are associated with structural damage in the axial skeleton in patients with axial spondyloarthritis. Clin Exp Rheumatol 2020;Mar 28. Epub ahead of print.
27. Xu Shanshan et al. Anti-CD74 antibodies in spondylarthritis: A systematic review and meta-analysis. Seminars in Arthritis and Rheumatism. Volume 51, Issue 1, February 2021, Pages 7-14
28. Ziade NR, Mallak I, Merheb G, et al. Added value of anti-CD74 autoantibodies in axial spondyloarthritis in a population with low HLA-B27 prevalence. Front Immunol 2019; 10:574.