ORIGINAL ARTICLE

Estimation of Transferrin Receptor (CD71) Representation on T CELLS tending from Patients with Rheumatoid Arthritis

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Abstract

Background: ***Damage to joints and non-articular organs such as the heart, kidneys, lungs, digestive system, eyes, skin, and nervous system can occur in rheumatoid arthritis(RA), a systemic autoimmune disease characterized by a persistent inflammatory process.***

Aim and objectives: ***To estimate transferrin receptor(CD71) representation on T cells in patients with RA.***

Subjects and methods: ***In this study, twenty patients were examined between March 2024 and October 2024 at Al-Hussien Hospital, Al-Azhar University, after being referred to the clinical pathology department from the rheumatology department.***

Results: ***CD71 and CD3 were increased in all RA patients in relation to the control group. CD71 has a role in the activity of RA. CD71 was low in controlled patients and increased in increased activity of RA. CD3 has been shown to be related to the reactivity of the disease, which ensures it is a T-lymphocyte-related autoimmune disease.***

Conclusion: ***CD71 has a role in activity and is low in controlled patients and increases in patients with increased activity of RA.CD3 has been shown to be related to the reactivity of the disease, which ensures it is a T-lymphocyte-related autoimmune disease. So, assessment of CD71 and CD3 is very helpful in the assessment of activity in rheumatoid patients.***

Keywords: Rheumatoid arthritis; Transferrin receptor(CD71); T CELLS

1. Introduction

Among the many immune-mediated illnesses, rheumatoid arthritis (RA) ranks high. The main sign of this condition is an inflammatory arthritis that causes swelling and discomfort in several joints, usually in the smaller joints of the body, such as the fingers and toes.[1]

The exact cause of RA remains a mystery, despite several postulated biomolecular pathways; one such possibility is that ACPAs are produced as a result of dysregulated citrullination.[2]

The causes of RA can be traced back to inflammatory cytokines like tumor necrosis factor(TNF)-α and interleukin-6(IL-6), as well as activated B cells and invading macrophages. The development of autoantibodies, including rheumatoid factor and ACPAs, is a key component of both innate and adaptive immunity, which contribute to the progression of disease.[3]

Cellular iron uptake is facilitated by transferrin receptors(CD71), which are glycoproteins linked to the cell membrane. Except for adult erythrocytes, all cells produce transferrin receptors because iron is essential for all cells. Because of their high iron need, highly proliferative cells also express a high level of the transferrin receptor.[4]

One protein that binds iron is transferrin. In its ligand state, it can bind to transferrin receptors, allowing for the targeted delivery of ions, medicines, genes, and proteins. By capturing, binding, transferring, storing, and using iron, transferrin regulates iron homeostasis. Transferrin plays an essential role in cytoprotection, differentiation, and development because of its iron-binding capabilities.[4]

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The researchers in this study set out to determine how many RA patients' T cells displayed the transferrin receptor(CD71).

2. Patients and methods

In this study, 20 patients were examined between March 2024 and October 2024 at Al-Hussien Hospital, Al-Azhar University, after being referred to the clinical pathology department from the rheumatology department. The study includes 2 equal groups:Group-1:20-patients diagnosed as RA(9-males, 11-females) and group-2:Control group 20-healthy age matched individuals(10-males, 10-females).

Inclusion criteria:

Age>20 years and<60, both sexes, and Patients who fulfil ACR/EULAR 2010 criteria for RA.[5]

Exclusion criteria:

Individuals with other autoimmune diseases, Renal diseases, Active infections, Associated co-morbidities, e.g., DM and hypertension, and Malignant tumours.

Ethical considerations:

All subjects were given a thorough description of the technique and its consequences before the study began, and the research followed all protocols approved by the Ethics Committee at Al-Hussein Hospital, Al-Azhar University.

Patients were subjected to laboratory investigations, general medical evaluation, complete history taking, clinical examination for the detection of joint deformity, joint pain, joint tenderness, and systemic affection.

Methods:

Sample collection:

EDTA vacutainer tube with five millilitres of peripheral blood. Within six hours after collection, the samples were left at room temperature to undergo processing for FCM immunophenotyping. The samples were tested for immunophenotyping using a flow cytometer. The FACS Calibur from Becton Dickinson(BD), and The FACS Canto.

CD71 (APC) in Rheumatoid Arthritis:

First, to determine CD71 receptor presence on T-Cells and classify lymphocytes into B-lymphocytes and T-lymphocytes using(CD20 for B-lymphocytes and CD3 for T-lymphocytes).

Principle of the technique:

Flow cytometry is a technique for studying materials, typically individual cells, by exposing them to coherent light amplification by stimulated emission of radiation(LASER) and then measuring the amount of light scattered from the laser at both forward and side (90-degree) angles to the light source. The amount of light scattered at the forward angle is a fairly good indicator of the cell size. In order to do both quantitative and qualitative analyses of many features(multiparameters) of cell populations in bodily fluids, light scattering to the sides provides an approximate indicator of the level of cellular granularity.

A flow cell is encased in a narrow stream of fluid and used to aspirate a cell or particle suspension into it. They are guided through a concentrated laser beam one at a time. Any surface or interior cell structure that has a fluorescent material or several antibodies labelled with fluorochromes can re-emit light of the correct wavelength.[6]

Sample preparation:

Surface staining(Stain-Lyse-Wash method) of CDs (CD3, CD20, CD71):

The 5ml sterile test tubes(BD Falcon 5ml polystyrene) were correctly labelled and arranged in a specific order. Then, 20-100µl of the whole peripheral blood specimen was added to each tube. Then, 5µl of the matching labelled monoclonal antibody was added to each tube. After 30 minutes of dark incubation at 18-25°C, the tubes were removed.

A dilution of 1:10 was used to create FACS Lyse in distilled water. After adding 2 millilitres of the prepared FACS Lyse solution to each test tube, they were left to incubate in a dark place at room temperature for 10 minutes. After incubating the contents of the tube for five minutes at 2000 RPM at room temperature, the supernatant is centrifuged to remove the pellet. The remaining fluid is mixed thoroughly to resuspend the cells. After that, 2milliliters of isotonic PBS was added to each tube, and the tubes were centrifuged for 5 minutes at 2000RPM. Once again, the supernatant was thrown away.

After two rounds of washing with PBS, the samples were centrifuged for five minutes at 2000RPM. Once again, the supernatant was thrown away. In preparation for the last flow cytometric measurement, the cells were resuspended in a solution of sheath fluid containing 200-400µl.

Flow cytometric analysis:

The flow cytometer(BD FACS Calibre/BD FACS Canto) was used to evaluate the expression of CD 71 of T-lymphocytes, which were analyzed using BD Cell Quest Pro and FACS DIVA software, respectively. A trio of fluorescent parameter detectors and a 15-mW argon-ion laser are components of the BD FACS Calibre system. The wavelength of the laser is 488 nm. A focal lens concentrates the beam of light from the laser onto the flow cell. Fluorescently tagged particles in a flow cell can be studied for size, shape, granularity, and fluorescence intensity by analyzing scattered and fluorescent light. The FSC diode is used to gather the forward scatter(FSC) signal. A fluorescence collecting lens gathers side scatter(SSC) and fluorescent signals, which are then spectrally separated by a set of dichroic

mirrors(DMs) and filters.

The FACS Canto flow cytometer is a 3-laser 10-colour configuration. The blue solid-state laser is a 488nm wavelength, 20-mW laser that excites fluorochromes to be detected on 4-photomultiplier tubes(PMTs) with 530/30, 575/25, 695/40,780/60nm detector bands, respectively. These wavelengths correspond to detecting FITC, PE, PE-Cy5 and PE-Cy7 dyes. The other 2-solid solid-state lasers are red 640-nm solid-state, 40-mW and violet 405-nm solid-state, 30-mW lasers, respectively.

Every day, before starting work, the BD FACS Calibur flow cytometer was calibrated with BD Calibrite beads. This allowed the software to set detector voltages to target channel values and conduct a sensitivity test to compare the signal separation for each parameter to an expected minimum value, ensuring that the flow cytometer consistently produced accurate results.

The BD FACSDivaTM CS&T research beads, developed for use with BD™ flow cytometers running BD FACSDivaTM software, are utilized to verify the Cytometer quality control(QC) parameters for BD FACS Canto. With the use of the beads, the program can detect, catalogue, and report data from BD digital flow cytometers that are compatible. The lasers of the cytometer are used to excite the fluorochromes that have been dyed onto the CS&T beads.

Polystyrene beads with light, medium, and dark dye concentrations make up CS&T research beads. When combined with the BD FACSDiva software, these three beads, which have modest intrinsic coefficients of variation, allow for a wide range of measures, including laser stability and alignment, linearity, automatic performance tracking, and daily data consistency.

For multicolour flow cytometric analysis, colour compensation is carried out using BD™ CompBead particles, which are microparticles made of polystyrene. These particles are utilised to adjust the settings for fluorescence compensation. To adjust compensation levels manually or using the automated compensation setup in BD FACSDivaTM software, mix BD CompBead particles with a fluorochrome-coupled antibody. The resulting populations will be distinguishable as positive and negative (background fluorescence-stained).

Each fluorescence channel, as well as the forward and side scatter signals, was plotted on a logarithmic scale. We evaluated data in the following way: for every specimen, we looked at around 10,000 cells.

Interpretation of the results:

Using isotype control via quadrant application, we evaluated the expression or absence of several CD markers after counting 10,000 cells. The mean fluorescence intensity(MFI) was acquired as determined by the FACSDIVA program.

Statistical analysis:

Statistical Program for the Social Sciences(SPSS) version 24 was used for data analysis. The mean±SD was used to express the quantitative data. The qualitative data were presented using percentages and frequencies. The middle value of a discrete set of integers, calculated by dividing the sum of values by the number of values, is called the mean or average. The dispersion of a group of values can be measured by looking at their standard deviation(SD). If the standard deviation is small, then the values cluster around the set mean, and if it's large, then the values are more dispersed.

The following tests were done:

When comparing means that are not regularly distributed, a one-way analysis of variance(ANOVA) is used. For data with an atypical distribution, the Kruskal-Wallis test(KW) is used when comparing more than two means. If the data were not parametric, the chi-square test was employed for the comparison. The probability, denoted as P-value, was deemed significant when it was less than 0.05, highly significant when it was less than 0.001, and insignificant when it was greater than 0.05.

3. Results

Table 1. Demographic data of studied groups.

DEMOGRAPHIC DATA		PATIENTS (N=20)	CONTROL (N=20)	STAT. TEST	P-VALUE
SEX	Males	9 45%	10 50%	X2=0.1	0.75 NS
	Females	11 55%	10 50%		
AGE	Mean±SD	39.3±7.6	37.3±7.3	0.85	0.4 NS
	Min-Max	26-50	26-47		

T:independent sample t-test. NS:P>0.05 is considered non-significant.X2:chi-square test.

There was no sex-related statistically significant difference(P=0.75) between the patient and control groups under study. There were nine men (45%) and eleven women(55%), in the patient group. In contrast, there were 10-males(50%) and 10 - emales in the control group(50%).

There was no age-related statistically significant distinction(P=0.4) between the patient and control groups under study. The mean age of the patients was 39.3±7.6 years, with a range of 26 to 50 years. In contrast, the control group's mean age was 37.3±7.3 years, with a range of 26–47 years.

Table 2. Comparison of studied groups(patients and control) as regard laboratory data.

LABORATORY DATA		PATIENTS (N=20)	CONTROL (N=20)	T	P-VALUE
CREATININE	Mean±SD	1.6±0.7	0.8±0.3	4.644	<0.001
	Min-Max	0.4-3.1	0.3-1.2		HS
UREA	Mean±SD	53.4±19.8	23.5±9.3	6.099	<0.001
	Min-Max	22-100	7-38		HS
AST	Mean±SD	31.6±12.2	23±10.1	2.427	0.02 S
	Min-Max	18-65	4-38		
ALT	Mean±SD	30.5±14.3	24.9±8.9	1.504	0.141
	Min-Max	15-70	11-39		NS
CRP	Mean±SD	40.4±10.9	2.2±1.1	15.610	<0.001
	Min-Max	15-54.1	1-4		HS

ESR	Mean±SD	66.2±21.8	9.7±3.6	11.410	<0.001
	Min-Max	22-95	1-15		HS
ANA	Mean±SD	58.4±19.8	5.4±2.9	11.833	<0.001
	Min-Max	28-95	1-10		HS
ACCP	Mean±SD	116.6±69.4	9.1±4.5	6.917	<0.001
	Min-Max	25-271	1-15		HS
RF	Mean±SD	54.8±19.6	7.7±3.4	10.577	<0.001
	Min-Max	22-85	1-12		HS
HB	Mean±SD	9.6±1.3	12.3±1.9	-5.328	<0.001
	Min-Max	7.4-11.8	9.2-15		HS
TLC	Mean±SD	8.4±2.9	8±2.7	0.396	0.694
	Min-Max	4.5-14.1	3.8-12		NS
PLTS	Mean±SD	280.2±90.9	265.5±70.6	0.573	0.570
	Min-Max	80-415	169-367		NS
CD3	Mean±SD	78±2.5	72.2±0.9	9.591	<0.001
	Min-Max	73.8-82.1	70.7-73.6		HS
CD71	Mean±SD	20.4±10.7	2.3±1.2	7.496	<0.001
	Min-Max	5-37.8	0.5-4.1		HS

T: t-test for independent samples. It is deemed very significant when HS:P<0.001.

It is deemed non-significant if NS:P>0.05. Statistical significance is defined as S:P<0.05.

High statistically significant(P<0.001) increased creatinine in patients' group(mean=1.6±0.7) with range of(0.4-3.1) when compared with that of control group(mean=0.8±0.3) with range of(0.3-1.2) in all studied patients.

High statistically significant(P<0.001) increased urea in patients' group(mean=3.4±19.8) with range of(22-100) when compared with that of control group(mean=23.5±9.3) with range of(7-38) in all studied patients.

A statistically significant(P=0.02) increased AST in patients' group(mean=31.6±12.2) with range of(15-70) when compared with that of control group(mean=23±10.1) with range of(4-38) in all studied patients.

No statistically significant(P=0.141) difference between studied groups(Patients and Control) as regard ALT.

High statistically significant(P<0.001) increased CRP in patients' group(mean=40.4±10.9) with range of(15-54.1) when compared with that of control group(mean=2.2±1.1) with range of(1-4) in all studied patients.

High statistically significant(P<0.001) increased ESR in patients' group(mean=66.2±21.8) with range of(22-95) when compared with that of control group(mean=9.7±3.6) with range of(1-15) in all studied patients.

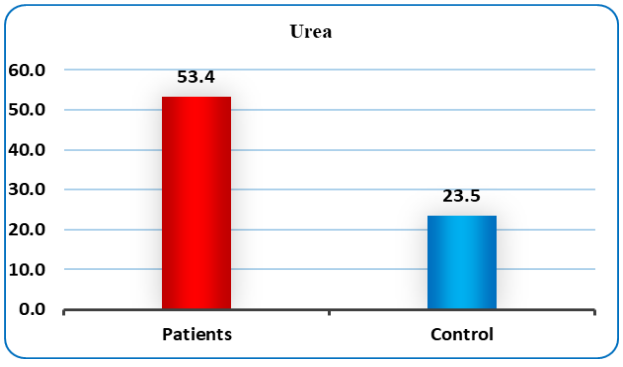

Figure 1. Comparison of studied groups (patients and control) as regard urea.

Table 3. Description of disease activity in patients' group.

		PATIENTS (N=20)	
ACTIVITY	Active	15	75%
	Not Active	5	25%

As regard disease activity, it was active in 15-patients(75%) and not active in 5-patients(25%) of patients group.

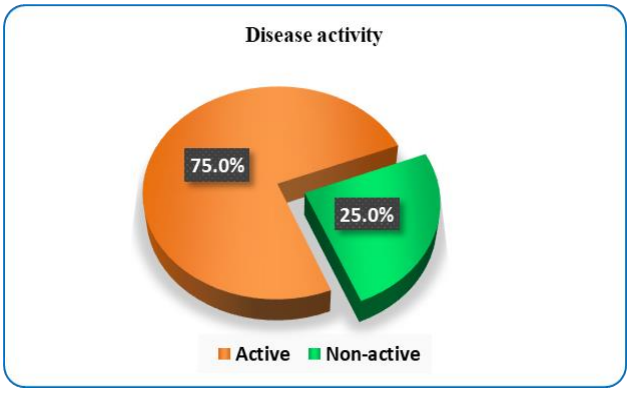

Figure 1. Description of disease activity in patients' group.

Table 4. Correlation between disease activity and laboratory data in patients' group.

LABORATORY DATA		ACTIVE (N=15)	NOT ACTIVE (N=5)	T	P-VALUE
CREATININE	Mean±SD	1.7±0.7	1.5±0.9	0.473	0.64 NS
	Min-Max	0.6-3.1	0.4-2.5		
UREA	Mean±SD	55.5±20	46.8±19.9	0.847	0.41 NS
	Min-Max	30-100	22-77		
AST	Mean±SD	33.4±13.1	26.2±8.1	1.149	0.266
	Min-Max	18-65	19-40		NS
ALT	Mean±SD	33.3±15.5	22.2±3.1	1.559	0.136
	Min-Max	15-70	19-26		NS
CRP	Mean±SD	44±6.7	29.6±14.6	3.073	0.007 S
	Min-Max	30-54.1	1-51.4		
ESR	Mean±SD	76.6±11.5	34.8±12.8	6.862	<0.001
	Min-Max	58-95	22-56		HS
ANA	Mean±SD	63.1±20.7	44±4.1	2.014	0.059
	Min-Max	28-95	39-50		NS
ACCP	Mean±SD	141.7±60.9	41±19.4	3.583	0.002 S
	Min-Max	75-271	25-73		
RF	Mean±SD	59.9±15.4	39.2±24.3	2.259	0.036 S
	Min-Max	24-85	22-80		
HB	Mean±SD	9.4±1.3	10.2±1.1	-	0.257
	Min-Max	7.4-11.5	9.1-11.8	1.170	NS
TLC	Mean±SD	8.5±2.7	8±3.7	0.351	0.730
	Min-Max	4.5-13	4.7-14.1		NS
PLTS	Mean±SD	278.3±95.9	286±84	-	0.874
	Min-Max	80-415	198-389	0.160	NS
CD3	Mean±SD	79.2±1.3	74.2±0.4	8.378	<0.001
	Min-Max	77.2-82.1	73.8-74.9		HS
CD71	Mean±SD	25.5±6.7	5.1±0.1	6.690	<0.001
	Min-Max	11.4-37.8	5-5.2		HS

T: test for independent samples. It is deemed very significant when HS:P<0.001.

It is deemed non-significant if NS:P>0.05. Statistical significance is defined as S:P<0.05.

A statistically significant(P=0.007) increased CRP in patients with active disease(mean=44±6.7) with range of(30-54.1) when compared with that of patients with non-active disease(mean=29.6±14.6) with range of(15-51.4) in patients' group.

High statistically significant(P<0.001) increased ESR in patients with active disease(mean=76.6±11.5) with range of(58-95)

when compared with that of patients with non-active disease(mean=34.8±12.8) with range of(22-56) in patients' group.

No significant(P=0.059) correlation between disease activity and ANA in patients' group.

A statistically significant(P=0.002) increased ACCP in patients with active disease(mean=141.7±60.9) with range of(75-271) when compared with that of patients with non-active disease(mean=41±19.4) with range of(25-73) in patients' group.

A statistically significant(P=0.036) increased RF in patients with active disease(mean=59.9±15.4) with range of(24-85) when compared with that of patients with non-active disease(mean=39.2±24.3) with range of(22-80) in patients' group.

High statistically significant(P<0.001) increased CD3 in patients with active disease(mean=79.2±1.3) with range of(77.2-82.1) when compared with that of patients with non-active disease(mean=5.1±0.1) with range of(5-5.2) in patients' group.

High statistically significant(P<0.001) increased CD71 in patients with active disease(mean=25.5±6.7) with range of(11.4-37.8) when compared with that of patients with non-active disease(mean=5.1±0.1) with range of(5-5.2) in patients' group.

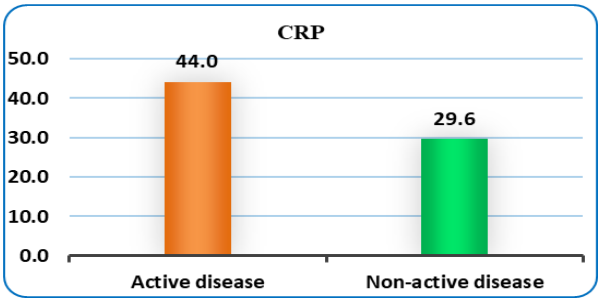

Figure 2.Correlation between disease activity and CRP in patients' group.

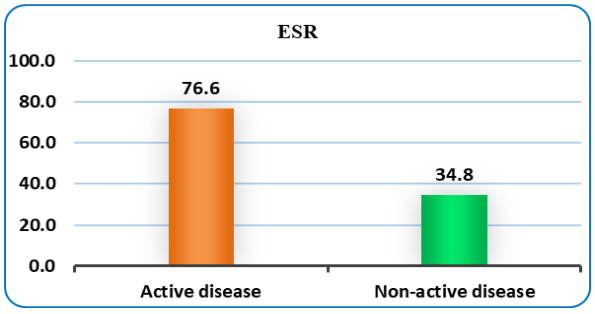

Figure 3. Correlation between disease activity and ESR
in patients' group.

Table 5. Diagnostic performance of CD3& CD71 in discrimination between patients' group and control group:

	CUT OFF	AUC	SENSITIVITY	SPECIFICITY	PPV	NPV	P-VALUE
CD3	>73.56	1	100%	100%	100%	100%	<0.001
CD71	>4.1	1	100%	100%	100%	100%	<0.001

PPV:positive predictive value.AUC:Area under curve NPV:negative predictive value.

At a cutoff level of>73.56, CD3 exhibits excellent patient-control discrimination with 100% sensitivity, 100% specificity, 100% PPV, and 100% NPV(AUC=1 & P-value<0.001).

At a threshold level of>4.1, CD71 exhibits excellent patient-control discrimination with 100% sensitivity, 100% specificity, 100% PPV, and 100% NPV(AUC=1 & P-value<0.001).

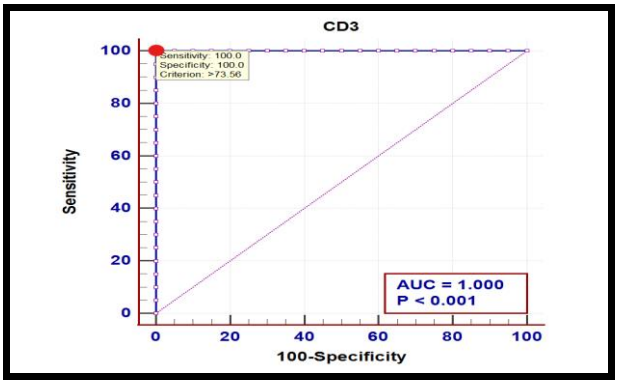

Figure 5. ROC curve of CD3 in discrimination between patients
group and control group.

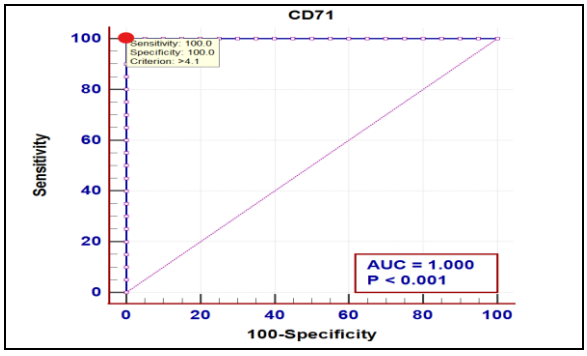

Figure 6.ROC curve of CD71 in discrimination between patients group and control group

4. Discussion

Estimation of transferrin receptor(CD71) representation on T CELLS tending from patients with RA.[7]

Highly statistically significant(P<0.001) increased CD3 in patients with active disease(mean=79.2±1.3) with a range of(77.2-82.1) when compared with that of patients with non-active disease(mean=5.1±0.1) with a range of(5-5.2) in the patient group.

With an AUC of 1 and a p-value less than

0.001, CD3 is highly effective in differentiating between patients and controls at a cutoff level of>73.56, exhibiting 100% sensitivity, 100% specificity, 100% PPV, and 100% NPV.

Highly statistically significant(P<0.001) increased CD71 in patients with active disease(mean=25.5±6.7) with a range of(11.4-37.8) when compared with that of patients with non-active disease(mean=5.1±0.1) with a range of(5-5.2) in the patient group.

An AUC of 1 and a p-value less than 0.001 indicate that CD71 is highly effective in differentiating between patients and controls at a cutoff level greater than 4.1, with a sensitivity and specificity of 100%, PPV of 100%, and NPV of 100%.

Between CD3 and CRP in the patient group, there is a positive correlation(r=0.616) that is statistically significant(P=0.004).

There is a strong positive connection(r=0.71) between CD3 and ESR in the patients' group, which is statistically significant(P<0.001).

Among the patients surveyed, there was a positive correlation(r=0.586) between CD3 and ACCP that was statistically significant(P=0.007).

Within the patient population, there was a positive association(r=0.453) between CD3 and RF that was statistically significant (P=0.045).

The association between CD3 and CD71 in the patients' group was highly significant (P<0.001) and positive(r=0.808).

There was no statistically significant relationship between CD3 and any of the other biomarkers measured in this patient cohort.

There was a positive connection(r=0.532) between CD71 and CRP in the patients' group, which was statistically significant(P=0.016).

There was a positive connection (r=0.687) between CD71 and ESR in the patients' group, which was statistically significant(P=0.001).

Among the patients surveyed, there was a positive correlation(r=0.617) between CD71 and ACCP that was statistically significant(P=0.004).

There is a strong positive correlation (r=0.808) between CD71 and CD3 in the patients' group, which is statistically significant(P<0.001).

There was no statistically significant relationship between CD71 and any of the other laboratory variables examined in this class of individuals.

Such results are concordant with those of Semenzato et al.[8] They found that compared to controls, RA patients had a higher percentage of CD3+ and CD57+ cells. The T cell receptor α/β was expressed by these cells. A whopping 80% of cells showed CD8 accessory molecule expression and 20% CD4 accessory molecule expression. These CD3+, CD57+ cells expressed the leukocyte common antigen CD45RA isoform in the blood. Blood did not express the HLA-DR antigen, whereas synovial fluid did. Lastly, the length of RA was associated with the percentage of these cells in the blood.

Also, the results of the current study are concordant with those of Jadon et al.,[9] who revealed that for 21 patients (8-anakinra, 13-etanercept) and 23 patients (8-anakinra, 15-etanercept), paired synovial samples and magnetic resonance imaging (MRI) scans were available, correspondingly. Following therapy, there was a significant difference in the levels of CD3 (ΔCD3) and CD68 (ΔCD68sl) in the synovial sublining layer between disease responders and non-responders (P=0.005 and 0.013, respectively). ΔDAS28 (r=0.49, P=0.025) and ΔMRI (r=0.58, P=0.009) were found to be linked with ΔCD3, whereas ΔCD68 and ΔFVIII were not.

The results of the present study were concordant with those of Ghazi et al.[10]. The study encompassed 46 RA patients, comprising 42 females and 4 males. Their ages ranged from 25 to 66 years, and the mean duration of their disease was 6.5 years. The mean age of the patients was 47.67 years. The majority of our patients, 37 out of a total of 78.4%, had high disease activity, while the remaining nine patients, or 19.6%, had mild disease activity, according to the DAS28 classification system. In the RA group, 34 individuals (73.9%) tested positive for the antibody, whereas in the control group, just 3 people (21.4%) tested positive.

Our results are not concordant with those of Curtis et al.[11] which suggest that CD3+ T cells might not be the only immune cells driving inflammation.

4. Conclusion

CD71 has a role in activity and is low in controlled patients and increases in patients with increased activity of RA.CD3 has been shown to be related to the reactivity of the disease, which ensures it is a T-lymphocyte-related autoimmune disease. So, assessment of CD71 and CD3 is very helpful in the assessment of activity in rheumatoid patients.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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