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Relationship between serum levels of T Cell Immunoglobulin and Mucin-Domain Containing Molecule-3 and Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease characterized by autoantibody production, immune complex deposition, and cytokine activation. T-cell immunoglobulin and mucin domain-containing molecule-3 (Tim-3) has a role in many chronic autoimmune diseases by regulating T cell immune responses and Th17/ Treg balance. Tim-3 was found to be elevated in the sera of patients with autoimmune diseases such as SLE. We aimed to quantify the serum levels of Tim-3 in patients with SLE and healthy controls and to investigate the relationship between their serum levels and the disease activity. This case-control study was conducted on 85 subjects: 25 participants age and sex-matched apparently healthy controls (group 1), 30 patients with SLE with disease activity (group 2), and 30 patients with SLE without disease activity (group 3). Group 2 was further subdivided into mild, moderate, and severe flare groups according to disease severity. Serum levels of Tim-3 in all groups were measured by ELISA. 2019 EULAR/ACR Classification Criteria for SLE was used to diagnose patients with SLE and SELENA SLEDAI was used to assess the disease activity. There was a highly significant increase in serum levels of Tim-3 in patient group as compared with controls ($p<0.001$). Also, there was a highly significant increase in serum levels of Tim-3 in group 2 when compared with group 3 and group 1 ($p<0.001$). There was a negative correlation between serum levels of Tim-3 and WBCs count ($r=-0.473$, $p=0.000$), platelets count ($r=-0.437$, $p= 0.000$), serum C3 levels ($r=-0.503$, $p=0.000$) and serum C4 levels ($r=-0.342$, $p=0.000$). Also, there was a positive correlation between serum levels of Tim-3 and 24-hour urine protein ($r=0.557$, $p=0.000$), presence of RBCs in urine (0.477, $p=0.000$), presence of pus in urine ($r=0.410$, $p=0.001$), ESR ($r=0.394$, $p=0.002$) and SELENA SLEDAI score ($r=0.643$, $p=0.000$). The area under the ROC curve (AUC) values indicated that the serum levels of Tim-3 was significantly discriminative of SLE patients from healthy controls, AUC

for serum Tim-3 was 0.768 (at a cut-off value >1.28 ng/mL, sensitivity was 80.00%, and specificity was 76.00%). Serum levels of Tim-3 were elevated in patients with SLE and was associated with the disease activity. These results suggested that serum Tim3 may represent prospective biomarkers for the diagnosis of SLE and its activity. This highlights the need for future research to identify how this association contributes to the development of SLE.

Keywords: Systemic lupus erythematosus; T cell immunoglobulin and mucin-domain-containing molecule 3.

1. Introduction

Systemic lupus erythematosus (SLE) is a worldwide chronic autoimmune disease that may affect every organ and tissue [1]. It is characterized by antibody production to nuclear and cytoplasmic antigens, multi-system inflammation, multiple clinical manifestations, and a relapsing and remitting course [2]. SLE has variable presentation, course, and prognosis [3]. SLE is one of the most overrepresented diseases in women, with a female to male ratio of 9-10:1 [4]. SLE is an inadequately defined syndrome. Etiology and pathogenesis remain largely unknown. SLE is on the other hand a syndrome that has challenged immunologists, biologists, genetics, and clinicians to solve its nature [5].

Both innate and adaptive immune responses appear to be involved in the development and perpetuation of SLE. [6]. Abnormalities in both cellular and humoral immune responses have been extensively studied in SLE. Dysfunctions in T cells and B cells contribute to loss of self-tolerance and production of autoantibodies, which is the characterization of SLE. The imbalance between regulatory T cells and Th17 cells is also involved in inducing inflammation and autoimmune tissue injury of SLE [7]. Breakdown of immune tolerance is critical in the development of SLE and T cells play an important role in this process. In addition it showing abnormal cytokine secretion and cell signal transduction, it can also lead to inappropriate recruitment and activation of B cells and dendritic cells in inflammatory sites [8].

T cell immunoglobulin and mucin domain-containing molecule 3 (Tim-3), first discovered in 2002, is a member of the TIM family of immunoregulatory proteins. Tim-3 was originally identified as a receptor expressed on interferon-γ-producing $CD4^+$ and $CD8^+$ T cells [9]. Tim-3 is a transmembrane glycoprotein mainly expressed in Th1 and Th17 cells [10]. Tim-3 is detected in different types of immune cells, including T cells, regulatory T cells, dendritic cells, natural killer cells, B cells, mast cells, and macrophages [11]. Tim-3 has been implicated in both activation and inhibition of immune responses. Tim-3 is a negative regulatory molecule that is important for T-cell tolerance; it has a crucial role in autoimmunity and T-cell exhaustion [12]. These data suggested that the role of Tim-3 in SLE is complex and deserves further exploration. In the light of these data, we aimed to quantify serum levels of circulating Tim-3 in both patients with SLE and healthy control subjects and to investigate the relationship between their serum levels and SLE disease activity.

2. Subjects and Methods

2.1 Study design:

This case-control study was conducted on 25 participants age and sex matched apparently healthy control (group1), 30 patients with SLE with disease activity (group 2) and 30 patients with SLE without disease activity (group 3) during the period from April 2021 to December 2021. They were recruited from inpatient and outpatient clinics of the Internal Medicine department of Al-Zahraa university hospital, Faculty of Medicine (for Girls), Al-Azhar University. All patients enrolled

in this study were diagnosed with SLE according to 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) Classification Criteria for SLE [13]. Disease activity of SLE was assessed according to the Safety of Estrogen in Lupus Erythematosus National Assessment and SLE Disease Activity Index (SELENA SLEDAI) [14]. Patients with a history of atopy-related disease, such as asthma or allergic rhinitis and other allergic diseases, patients with diabetes mellitus, liver dysfunction, dys-lipoproteinemia, and other autoimmune diseases such as rheumatoid arthritis were excluded. Patients with disease activity (group 2) were further subdivided into mild, moderate, and severe flare groups as regards disease activity. All patients and control groups were (58 female and 2 male) and (22 female and 3 male) respectively and their ages ranged from (18-47 years) and (25-42 years) respectively. Before enrollment in this study, an informed written consent was obtained from each patient and controls after explaining the purpose of the study, which was approved by the Local Ethical Committee, Faculty of Medicine for Girls, Al–Azhar University, study ID approval number was (569), the data was kept confidential. All subjects had the right to withdraw from the study without affecting their management.

2.2 Blood sampling and measurements:

Under complete aseptic condition 5 ml of venous whole blood was withdrawn from each subject and divided into 3 portions; the first one was evacuated into an EDTA tube as an anticoagulant for CBC (performed by fully automated cell counter Sysmex XP300 Kobe, Japan), and ESR measurement (by Westergren method), the second portion on gel tube was centrifuged and the serum was separated for CRP (latex agglutination test), antinuclear antibody (ANA) and anti-double-stranded DNA (anti-dsDNA) done by indirect immunofluorescent technique, serum complement C3 and C4 levels (done by radial immunoassay (RIA), LDH and kidney function tests (performed by fully automated chemistry analyzer COBAS INTEGRA 400 plus (Roche Diagnostics GmbH, Mannheim, Germany), 24-hour urine was collected for measurement of protein (done on semi-automated chem 100 from Gesan). The third portion was centrifuged, separated, and frozen at −20°C for further measurement of Tim-3 by ELISA immunoassay Kits from Bioassay Technology Laboratory Company (Human Tim-3 ELISA kit Cat. No. E7351Hu, lot no. 202101018). ELISA Kit is a solid phase Enzyme-linked immunosorbent assay based on the sandwich principle. The plate has been pre-coated with a Human Tim-3 antibody. Tim-3 present in the sample is added and binds to antibodies coated on the wells. And then biotinylated Human Tim-3 antibody is added and binds to Tim-3 in the sample. Then streptavidin-HRP is added and binds to the biotinylated Tim-3 antibody. After incubation, unbound streptavidin-HRP is washed away during a washing step. The substrate solution is then added, and color develops in proportion to the amount of Human Tim-3. The reaction is then terminated by the addition of an acidic stop solution and absorbance is measured at 450 nm. Tim-3 is an ELISA kit with a sensitivity: of 0.017 ng/ml, Intra-Assay precision: CV< 8%, and Inter-Assay precision: CV<10%. Serum levels Tim-3 from patients with SLE and healthy controls were measured on the ELISA system which included a plate shaker-incubator (Thermo-Shaker from EU for Grant Instruments Ltd, Cambs, England) an ELISA washer (ELx50 from Biokit, Italy) and a plate reader (AS 1851 from DAS, Italy) according to the manufacturer’s instructions.

Statistical analysis:

Data were collected, revised, coded, and entered into the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations, and ranges when parametric and median, and inter-quartile range (IQR) when data were found non-parametric. Also, qualitative variables were presented as numbers and percentages. The comparison between groups regarding qualitative data was done by using the Chi-square test and/or Fisher exact test when the expected count in any cell was found less than 5. The comparison between two independent groups with quantitative data and parametric distribution was done by using the independent t-test while non-parametric distribution was done by using the Mann-Whitney test. The comparison between more than two groups regarding quantitative data and parametric distribution was done by using the One-Way ANOVA test followed by post hoc analysis using the LSD test while non-parametric distribution was done by using the Kruskal-Wallis test followed by post hoc analysis using the Mann-Whitney test. Spearman correlation coefficients were used to assess the correlation between two quantitative parameters in the same group. The best cut-off point with sensitivity, specificity, positive and negative predictive value, and area under the curve (AUC) for the prediction of SLE patients was done by using ROC curve. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following: P-value > 0.05: Nonsignificant (NS); P-value < 0.05: Significant (S); P-value < 0.01: Highly significant (HS).

3. Results

Concerning the results of this study; there was a highly significant increase in serum levels of Tim-3 in patient group when compared with controls (P<0.001) (Table 1). Also, there was a highly significant increase in serum levels of Tim-3 in active group when compared with inactive group and controls (p<0.001) (Table 2).

There was a significant decrease between active and inactive groups as regard WBCs count (p=0.002), platelets count (p= 0.001), serum C3 (normal cases 19 (63.3%) decreased 11 (36.7%) in active group while normal 27 (90%) and decreased 3 (10%) in inactive group, p=0.015) and serum C4 (normal cases 20 (66.7%) decreased 10 (33.3%) in active group while normal 27 (90%) and decreased 3 (10%) in inactive group, p= 0.028). Also, we found significant increase between active and inactive group as regard 24-hour urine protein (p= 0.001), ESR (p=0.005), CRP normal 24 (80%) and high 6 (20%) in active group while normal 29 (96.7%) and high 1 (3.3%) in inactive group, p=0.044), anti-dsDNA negative cases 10 (33.3%). positive cases 20 (66.7%) in active group while negative cases 20 (66.7%) and positive cases 10 (33.3%) in inactive group, p=0.01) (Table 3).

Also, there was significant increase in serum Tim-3 levels between mild, moderate and severe flare groups (p= 0.004) (Table 4)

There was significant difference between mild, moderate and severe flare group as regard WBCs count (p=0.019), platelets count (p=0.007), 24-hour urine protein (p= 0.003), ESR (p= 0.001), CRP normal (10) (100%) and high (0) 0.0% in mild flare group, normal (9) 90%, high (1) 10% in moderate flare group and normal (5) 50%, high (5) 50% in severe flare group, p=0.013), anti-ds DNA positive (4) 40% in mild flare group, positive (6) 60% in moderate flare group and positive (10) 100% in severe flare group, (p=0.015) and presence of lupus nephritis positive (5) 50% in mild flare group, (6) 60% in moderate flare group and (10) 100% in severe flare group), (p= 0.036) (Table 5).

There was a negative correlation between serum levels of Tim-3 and WBCs count

(r=-0.473, p=0.000), platelets count (r=-0.437, p= 0.000), serum C3 levels (r=-0.503, p=0.000) and serum C4 levels (r=-0.342, p=0.000). On the other hand, there was a positive correlation between serum levels of Tim-3 and 24-hour urine protein (r=0.557, p=0.000), presence of RBCs in urine (0.477, p=0.000), presence of pus in urine (r=0.410, p=0.001), ESR (r=0.394, p=0.002) and SLENA-SLEDAI score (r=0.643, p=0.000) (Table 6) (Figure 1, 2, 3, 4).

Also, there was a positive relationship between serum levels of Tim-3 and the presence of cast in urine (p=0.018), CRP (p=0.007), anti-dsDNA (p=0.013), and presence of lupus nephritis (p=0.000) (Table 7)

We plotted the area under the Receiver operating characteristics (ROC) curve (AUC) values to validate the potential utility of serum Tim-3 as a diagnostic biomarker of SLE. When distinguishing SLE patients from healthy controls, AUC for serum Tim-3 was 0.768 (at a cut-off point >1.28 ng/mL, sensitivity was 80.00%, and specificity was 76.00%) (Table 8) (Figure 5).

Table (1). Comparison between patient and control groups regarding serum levels of Tim-3.

		Patients group	**Control group**	**Test value**	**P-value**	**Sig.**
		No. = 60	**No. = 25**			
Tim-3 (ng/ml)	Median (IQR)	2.13 (1.37 – 4.15)	1.11 (0.90 – 1.28)	-4.347	<0.001	HS
	Range	0.35 – 34.3	0.23 – 15.49			

Table (2). Comparison between control, inactive and active groups regarding serum levels of Tim-3.

Tim-3 (ng/ml)	**Activity**			**Test value**	**P-value**	**Sig.**
	Control group (Group 1)	**Inactive (Group 3)**	**Active (Group 2)**			
	No. = 25	**No. = 30**	**No. = 30**			
Median (IQR)	1.11 (0.90 – 1.28)	1.67 (1.02 – 2.17)	3.85 (2.04 – 6.38)	31.575	<0.001	HS
Range	0.23 – 15.49	0.35 – 7.98	1.3 – 34.3			

Table (3). Comparison between inactive and active groups regarding the laboratory parameters

		Activity				Test value	P-value	Sig.
		Inactive (Group 3)		Active (Group 2)				
		No. = 30		No. = 30				
WBCs (10^3/mm^3)	Mean ± SD	8.63 ± 2.72		6.30 ± 2.78		3.286	0.002	HS
	Range	5.4 – 17.4		3.2 – 13.8				
Platelets (10^3/mm^3)	Mean ± SD	319.83 ± 89.32		243.40 ± 85.00		3.395	0.001	HS
	Range	180 – 562		27 – 431				
24-hour urine protein (g)	Median (IQR)	0.2 (0.15 – 0.3)		1.15 (0.54 – 2.0)		-4.340	0.001	HS
	Range	0.02 – 2.5		0.07 – 5.0				
ESR (mm/hr)	Median (IQR)	30 (20 – 45)		48 (30 – 65)		-2.794	0.005	HS
	Range	5 – 120		11 – 144				
Urea (mg/dl)	Median (IQR)	33.5 (28 – 37)		34 (26 – 46)		-0.834	0.404	NS
	Range	10 – 94		8.6 – 120				
Creatinine (mg/dl)	Median (IQR)	0.7 (0.6 – 0.9)		1.0 (0.7 – 1.35)		-2.98	0.003	HS
	Range	0.6 – 2.0		0.5 – 3.14				
CRP	Normal	29 (96.7%)		24 (80.0%)		4.043	0.044	S
	High	1 (3.3%)		6 (20.0%)				
C3 (mg/dl)	Normal	27	90.0%	19	63.3%	5.963	0.015	S
	Decreased	3	10.0%	11	36.7%			
C4 (mg/dl)	Normal	27	90.0%	20	66.7%	4.812	0.028	S
	Decreased	3	10.0%	10	33.3%			
Anti- dsDNA	Negative	20	66.7%	10	33.3%	6.667	0.010	S
	Positive	10	33.3%	20	66.7%			

Table (4). Comparison between mild, moderate and severe flare groups regarding serum levels of Tim-3.

Tim-3 (ng/ml)	SELENA-SLEDAI score			Test value	P-value	Sig.
	Mild flare	Moderate flare	Severe flare			
	No. = 10	No. = 10	No. = 10			
Median (IQR)	2.14 (1.74 – 3.12)	3.57 (2.36 – 6.92)	5.61 (4.02 – 12.62)	10.974	0.004	HS
Range	1.30 – 3.96	1.94 – 9.09	2.0 – 34.3			

Table (5). Comparison between mild, moderate and severe flare groups regarding the laboratory parameters.

		SELENA-SLEDAI score			Test value	P-value	Sig.
		Mild flare	Moderate flare	Severe flare			
		No. = 10	No. = 10	No. = 10			
WBCs ($10^3/mm^3$)	Mean ± SD Range	8.18 ± 3.34 4 – 13.8	5.81 ± 2.40 3.5 – 11.7	4.91 ± 1.27 3.2 – 7.2	4.611	0.019	S
Platelets ($10^3/mm^3$)	Mean ± SD Range	290.00 ± 97.27 152 – 431	260.30 ± 26.60 235 – 318	179.90 ± 76.80 27 – 324	6.058	0.007	HS
Urea (mg/dl)	Median (IQR) Range	30.5 (26 – 60) 19 – 120	34 (29 – 44) 8.6 – 46	37 (33 – 63) 21 – 112	1.216	0.544	NS
Creatinine (mg/dl)	Median (IQR) Range	1.11 (0.8 – 1.5) 0.67 – 3.14	0.84 (0.6 – 1.0) 0.5 – 1.7	1.04 (0.73– 1.4) 0.69 – 2.3	3.155	0.207	NS
24-hour urine protein (g)	Median (IQR) Range	0.57 (0.2 – 0.88) 0.07 – 1.6	1.24 (0.50 – 2.0) 0.1 – 4.4	2.07 (1.35 – 3.8) 1.14 – 5.0	11.613	0.003	HS
CRP	Normal High	10 (100.0%) 0 (0.0%)	9 (90.0%) 1 (10.0%)	5 (50.0%) 5 (50.0%)	8.750	0.013	S
ESR (mm/hr)	Median (IQR) Range	30.0 (20.0 – 45.0) 11 – 52	51.0 (40 – 55) 19 – 65	100 (60 – 120) 35 – 144	15.029	0.001	HS
Anti- dsDNA	Negative Positive	6 (60.0%) 4 (40.0%)	4 (40.0%) 6 (60.0%)	0 (0.0%) 10 (100.0%)	8.400	0.015	S
Lupus nephritis	Negative Positive	5 (50.0%) 5 (50.0%)	4 (40.0%) 6 (60.0%)	0 (0.0%) 10 (100.0%)	6.667	0.036	S

Table (6). Correlation between serum levels of Tim-3 and other parameters in patient groups.

	Tim-3 (ng/ml)	
	R	p-value
WBCs ($10^3/mm^3$)	**-0.473**	**0.000**
Platelets ($10^3/mm^3$)	**-0.437**	**0.000**
24-hour urine protein (g)	**0.557**	**0.000**
RBCs in urine	**0.477**	**0.000**
Pus in urine	**0.410**	**0.001**
ESR (mm/hr)	**0.394**	**0.002**
C3 (mg/dl)	**-0.503**	**0.000**
C4 (mg/dl)	**-0.342**	**0.000**
SELENA-SLEDAI score	**0.643**	**0.000**

Table (7). Relationship between serum levels of Tim-3 and other laboratory parameters in patient groups.

		Tim-3		Test value	P-value	Sig.
		Median (IQR)	Range			
Cast in urine	Negative	2.03 (1.36 – 3.85)	0.35 – 9.09	2.360	0.018	S
	Positive	6.33 (2.42 – 14.24)	1.08 – 34.30			
CRP	Normal	2.02 (1.36 – 3.12)	0.35 – 15.86	2.695	0.007	HS
	High	6.92 (4.84 – 12.62)	0.89 – 34.30			
Anti- dsDNA	Negative	1.91 (1.15 – 2.63)	0.35 – 9.09	2.484	0.013	S
	Positive	3.12 (1.94 – 5.00)	0.89 – 34.30			
Lupus nephritis	Negative	1.85 (1.08 – 2.36)	0.35 – 6.66	3.593	0.000	HS
	Positive	3.45 (2.0– 6.92)	0.89 – 34.30			

Table (8). ROC curve analysis for Tim-3 as a predictor of SLE patients

	Cut off point	AUC	Sensitivity	Specificity	+PV	-PV
Tim-3 (ng/ml)	>1.28	0.768	80.00	76.00	88.9	61.3

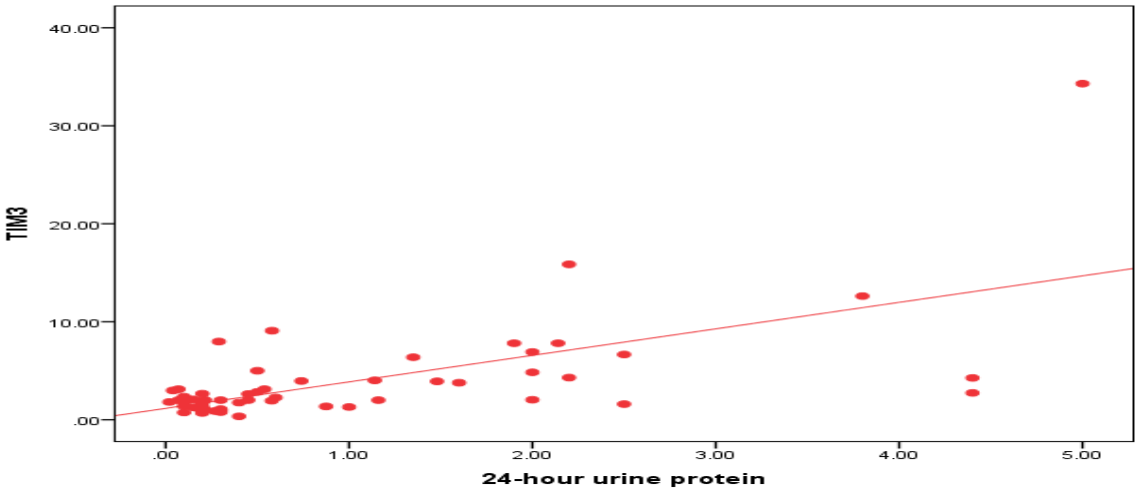

Figure 1. Correlation between serum levels of Tim-3 and 24-hour protein.

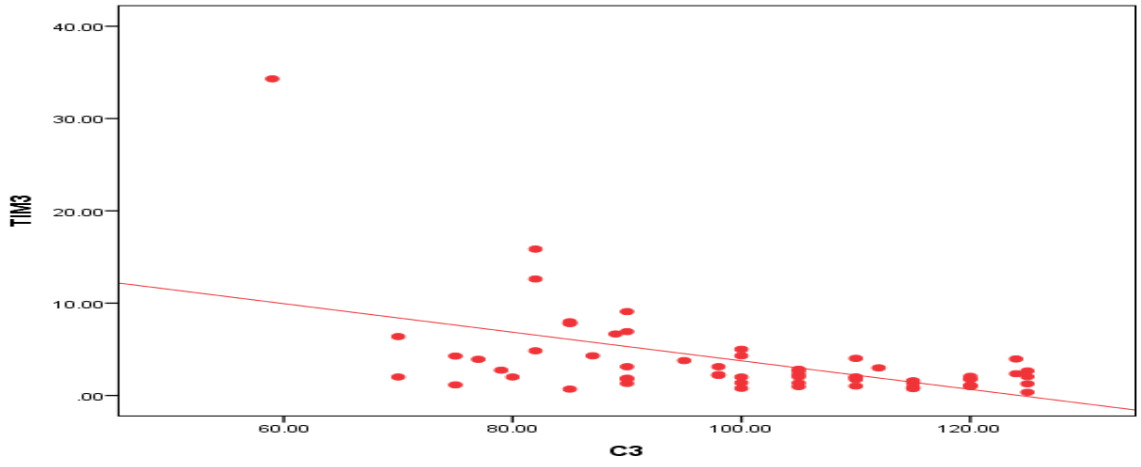

Figure 2. Correlation between serum levels of Tim-3 and C3

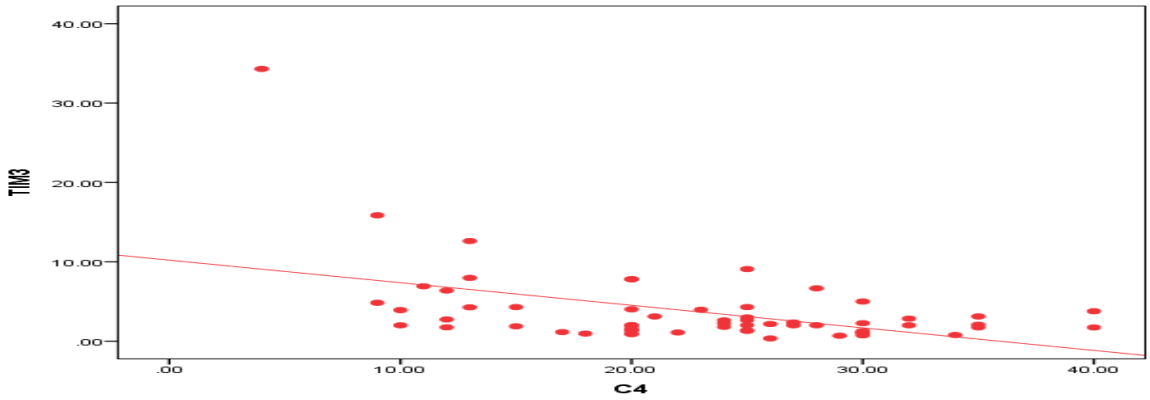

Figure 3. Correlation between serum levels of Tim-3 and C4

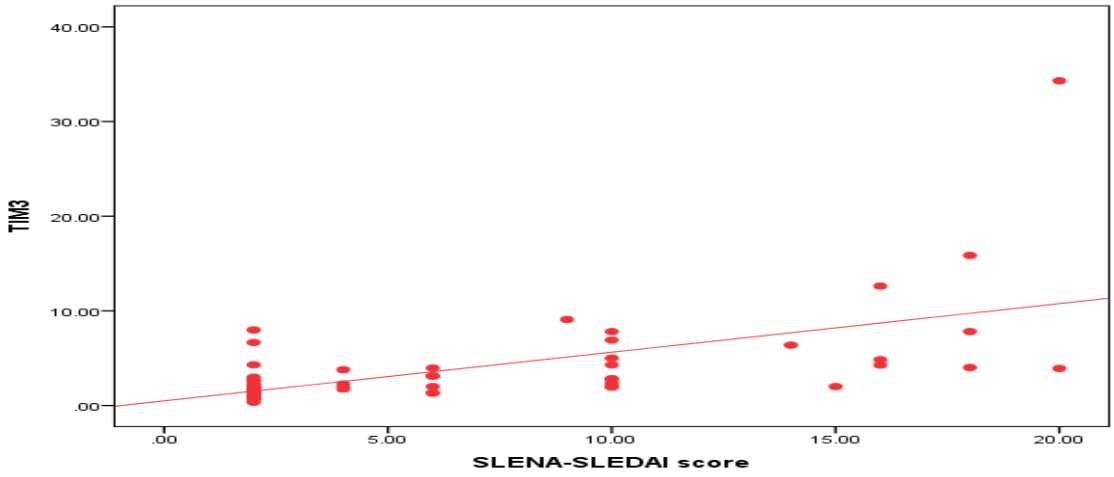

Figure 4. Correlation between serum levels of Tim-3 and SELENA-SLEDAI score

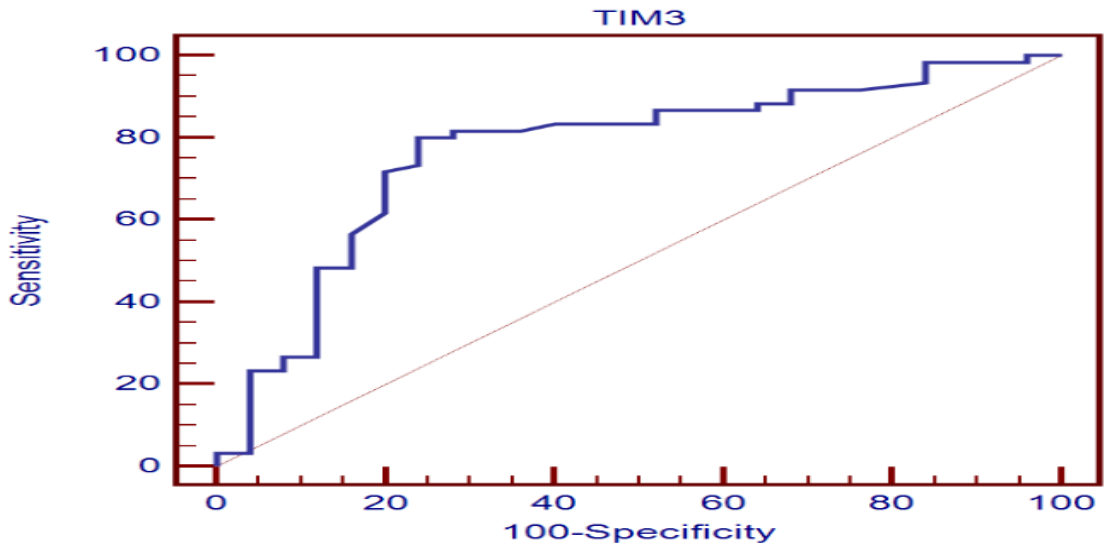

Figure 5. ROC curve plot of serum Tim-3 in SLE patients.

4. Discussion

Human SLE is a chronic systemic autoimmune disease of largely unclear etiology that can affect many organs [15]. SLE is a multifactorial disease with unknown exact etiology, however, several genetic, immunological, endocrine, and environmental factors play a role in the etiopathogenesis of SLE [16]. SLE is characterized by the loss of immunological tolerance against nuclear antigens. The clinical and paraclinical tools to assess disease activity and predict the disease course are inadequate, and identification of easily accessible biomarkers are required for SLE [17]. SLE, despite treatment advances, continues to be associated with premature mortality. However, recent therapeutic advances have not improved mortality or the development of end-stage renal disease.[18]

T cell immunoglobulin and mucin domain-containing molecule-3 (Tim-3) is a relatively newly discovered group of molecules with a conserved structure and important immunological functions [19]. They participate in the regulation of T helper-1 (Th-1) and Th-2 responses and so have some roles in organ-specific inflammatory and autoimmune diseases like asthma, allergy, and rheumatoid arthritis [20]. Tim-3 has been found to play an important role in SLE.[21]

In our study, we found a highly significant increase in serum levels of Tim-3 in patient group when compared with controls, this was in agreement with Asano et al. [10], who found that serum levels of Tim-3 were significantly higher in SLE patients than controls. They demonstrated that a possible link between Tim-3 and SLE and, circulating Tim-3 works in SLE patients as an anti-immune mediator.

Also, our results were matched with Jin et al [22] who found that serum levels of Tim-3 in SLE patients were significantly elevated than controls. They showed that the expression of Tim-3 in SLE is increased and plays an immunosuppressive role, and these changes mediate the chronic inflammatory response observed in many patients, and targeted therapy influencing the Tim-3 is thus attractive for use in SLE patients.

On the contrary, Yuan et al [23] found that serum Tim-3 levels were significantly decreased in SLE patients as compared with controls. The discrepancies between the two studies may be explained by the different patient characteristics (age, disease duration), the disease activity, and presumably, by the treatment they received.

Also, we found a highly significant increase in serum level of Tim-3 in SLE patients with disease activity when compared with those without activity and healthy controls, this was in accordance with Zhao et al. [7], who found that plasma level of Tim-3 in active SLE patients was more frequently detected than those in stable SLE patients and healthy controls. They showed that plasma Tim-3 was fluctuating during remission and exacerbations, which implicated its potential roles in establishing this molecule as a possible clinical marker for disease activity.

In our study, we found a negative correlation between serum levels of Tim-3 and WBCs, platelets count, serum C3 and C4 levels. Also, we found a positive correlation between serum levels of Tim-3 and 24-hour urine protein, presence of RBCs, cast and pus in the urine, anti-dsDNA, ESR, and CRP. Our results are partially in accordance with Zhao et al. [7] who found that serum Tim-3 levels were negatively correlated with C3 and C4 and positively correlated with anti-dsDNA and ESR. They demonstrated that serum Tim-3 could potentially be used as a novel biomarker of SLE disease progression. However, they found no significant association between serum Tim-3 levels and WBCs, or platelets counts. This discrepancy from our study could be explained by the variations in the sample size of SLE patients studied.

Also, our results are in agreement with Asano et al. [10] who found that serum

level of Tim-3 was negatively correlated with C3 and C4 levels. They showed that a further longitudinal study with a large number of SLE patients with different disease phenotypes is required to determine the role of serum Tim-3 in SLE pathophysiology. Contrary to our results, they found no correlation between serum Tim-3 and anti-double stranded-DNA antibody titer. This could be explained by differences in patient sample sizes.

On the contrary, Jin et al [22] found no significant correlations between serum Tim-3 levels and other SLE clinical parameters. This discrepancy could be explained by the method he used and the differences in patient sample sizes.

In this study, we found a positive correlation between serum levels of Tim-3 and SELENA SLEDAI score and the presence of lupus nephritis. These data are in agreement with Asano et al. [10] who found that serum levels of Tim-3 were positively correlated with the disease activity. They concluded that there was a relationship between serum Tim-3 and SLE disease activity and SLE-related organ involvement. This indicates that serum Tim-3 can reflect the SLE disease activity and higher disease activity in SLE patients can increase the risk of subsequent organ damage. Furthermore, serum Tim-3 levels can be used to discriminate between SLE patients with and those without organ damage. Their results indicated that serum levels of Tim-3 is a clinically useful biomarker and can be a predictor of SLE disease activity.

Also, we found that the AUC values indicated that the serum Tim-3 levels were significantly discriminative of SLE patients from controls with high sensitivity (80.0 %) and specificity (76.0 %). These results were going with Zhao et al. [7] who found that the AUC for plasma Tim-3 was 0.849 (at a cut-off value of 0.120 ng/ml, sensitivity was 76.52% and specificity was 83.72 %), and these results suggested that plasma Tim-3 may represent prospective biomarkers for the diagnosis of SLE.

5. Conclusion

Serum levels of Tim-3 were elevated in patients with SLE and were associated with the disease activity. These results suggested that serum Tim-3 may represent prospective biomarkers for the diagnosis of SLE and its activity. This highlights the need for future research to identify how this association contributes to the development of SLE.

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