Complement Levels and Risk of Organ Involvement in Patients with Systemic Lupus Erythematosus

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Abstract:

Objectives: to estimate the effect of complement level changes on clinical manifestations, visceral damage and mortality in our patients with SLE.

Patients and method(s): A cross sectional study including 50 patients attending to South Valley University Hospitals have been included in the study for assessment of complement levels in patients with SLE and correlating complement levels with renal, neuropsychiatric, cardiac and hematological manifestations of SLE.

Result(s): The most common organ system involved was the musculoskeletal system, with arthritis in 76% of the cases. This was followed by cutaneous manifestations (72%), then lupus nephritis (62%), CNS lupus (44%), hematological (30%) and lastly CVS (12%). Non of our cases showed liver impairment. Around two thirds of patients with renal involvement had consumed complement, compared to only 26% among those with no renal involvement; with a significant difference. It also shows that there is no significant difference between hypertension and complement level. Over 72% of patients with CNS involvement had consumed complement, compared to only 32% among those with no CNS involvement; with a significant difference. There is no significant relation between blood disorders, arthritis, mucocutaneous in lupus patients and complement consumption.

Conclusion: Our study suggested that complement consumption was strongly associated with lupus nephritis and to a lesser extent; CNS lupus, but not with other organ involvement in SLE patients.

Keywords: SLE, Complement, Organ involvement.

Introduction:

SLE is a chronic autoimmune disease characterizes by different types of autoantibodies and variable disease activity that results in multi-organ tissue damage and potentially life-threatening complications. The incidence of SLE is variable according to many ethnic, socio-economic and other factors, but generally is around 1–10 per 100.000 person-years with a prevalence of 20–70 per 100 000 according. It is about 6-10 times more frequent in females(**Ahmadpoor et al., 2014;Scolnik et al., 2014**).

The complement system is an important pathway of innate immunity and plays a major role in SLE.5 Complement participation may occur in at least two ways. First, deficiency of some complement components may be involved in the pathogenesis of disease development. In particular, complete deficiency of the complement component C1 has been associated with an elevated risk of SLE in up to 90% of persons with this hereditary condition. Other complement components such as C2 and C4 have also been blamed. Second, the strong activation of complement is proved to be associated with disease activity and injury to certain organs(**Holers, 1999;Manderson et al., 2004**).

Many complement products have been assigned different degrees of clinical value in evaluating disease activity, such as serum CH50, levels of C3, C4, C3d, C4d, C3a, C4a, C5b–9, Ba, Bb and urine C3d.6 9 10.

Our objective was to estimate the effect of complement level changes on clinical manifestations, visceral damage and mortality in our patients with SLE.

Patient and methods:

Study Setting and Design: This study is a cross-sectional study of 50 patients attending to South Valley University Hospitals have been included in the study for assessment of complement levels

in patients with SLE and correlating complement levels with renal, neuropsychiatric, cardiac and hematological manifestations of SLE.

Study Population: Study population included patients attending to South Valley University Hospitals. The sample included patients of both sex and of different age.

Data Collection

All of the participants were subjected to the following:

Full history: included demographic data and personal history, detailed history of general health condition.

History of chronic medical conditions (DM, hypertension, etc).History of SLE as regards onset of the symptoms, disease duration, therapeutic history, history of major organ involvement of SLE and disease activity.

Examination: included general examination and vital signs. Systematic examinations with concentration on those suggesting renal, cardiopulmonary, neuropsychiatric or hematological complications of SLE.

Investigation :included Routine investigations (CBC with differential WBCs count),Liver functions (ALT, AST, albumin and bilirubin) , Renal functions (serum creatinine, blood urea, urine analysis, urine 24 hour protein or P/C ratio),Abdominal ultrasound, Chest X ray or CT for suspected cases of cardiopulmonary complications, Brain CT or MRI for suspected cases of neuropsychiatric cases , Immunological investigations of SLE(ANA by immunofluorescence. AntidsDNA by ELISA) and Measurement of complement level (C3/C4).

Statistical Analysis

Statistical package for social sciences (IBM-SPSS) version 23 was used for statistical data analysis. Frequencies, descriptive statistics, Chi square test were done. The probability of less than 0.05 was used as cut off point for all significant tests.

Results:

Table 1. Age and duration of the study group

	Mean	Median	Std. Deviation	Min.	Max.
Age	28.82	26.5	9.258	16	52
Disease duration	3.356	2.5	2.84	0.3	9

This table shows that the mean age of the study group ranged from 16-52 years, with a mean of 28.8 years and the mean disease duration was around 3.4 years, with a wide range from only 4 months to over 9 years, reflected in the high standard deviation of 2.8 years.

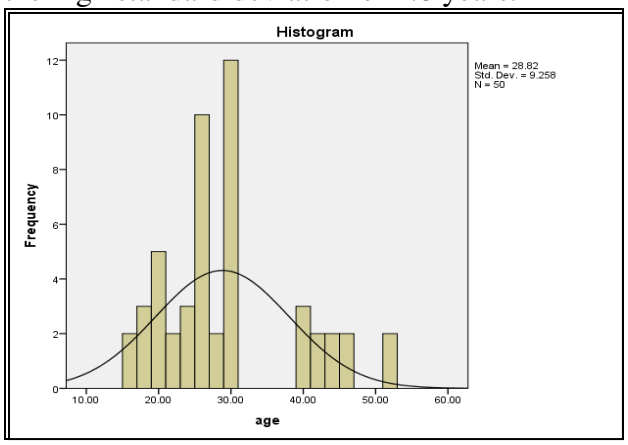

Figure 1. Age of the study group

Table 2. Sex of the study group

		No	Percent
Sex	Male	4	8.0
	Female	46	92.0
	Total	50	100.0

This table shows that 92% of the cases were females, with only 4 cases (8%) were males.

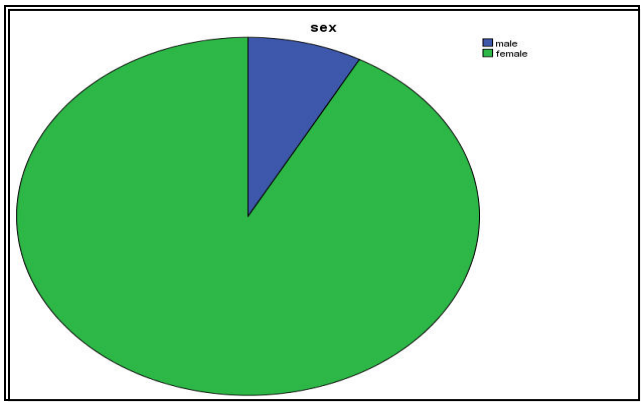

Figure 2. Sex of the study group

Table 3. Organ involvement of the study population

		No	Percent
Cardiovascular	Hypertension	6	12%
	Pericarditis	0	0
Hematologic	Thrombocytopenia	4	8%

lupus	Leucopenia	11	22%
	Hemolytic anemia	0	0
	Allover	15	30%
Renal	Lupus nephritis	31	62%
CNS	Neuropsychiatric lupus	22	44%
MSK	Arthritis	38	76%
Mucocutaneous	Cutaneous lupus	36	72%
Liver	Abnormal liver functions	0	0

This table shows that the most common organ system involved was the musculoskeletal system, with arthritis in 76% of the cases. This was followed by cutaneous manifestations (72%), then lupus nephritis (62%), CNS lupus (44%), hematological (30%) and lastly CVS (12%). Non of our cases showed liver impairment.

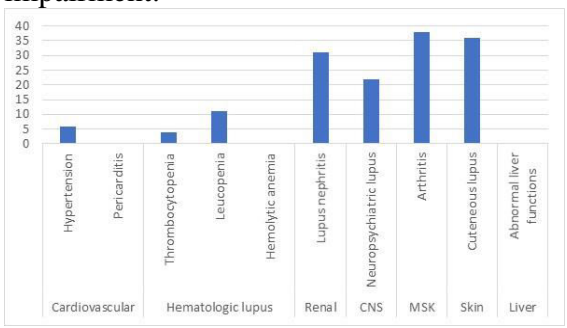

Figure 3. Organ involvement of the study population

Table 4. ANA and anti dsDNA

		No	Percent
ANA	Positive	47	94%
	Negative	3	6%
Anti dsDNA	Positive	39	78%
	Negative	11	22%

This table shows that ANA was positive in nealr all of the cases, except 3 cases (6%), and anti dsDNA was positive in 78% of the cases.

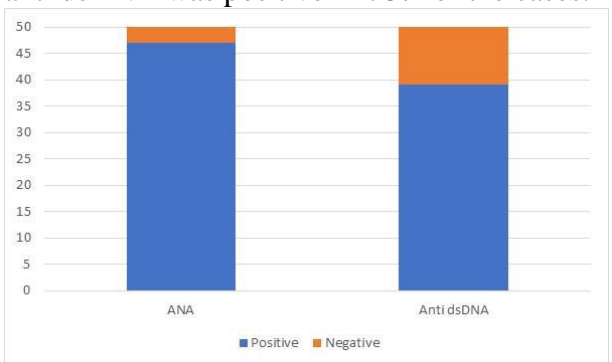

Figure 4. ANA and anti dsDNA

Table5.C3 and C4in our study population

	Mean	Median	Std. Deviation	Min.	Max.
C3	85.79	97.50	43.901	10	158
C4	23.02	17	17.078	3	60

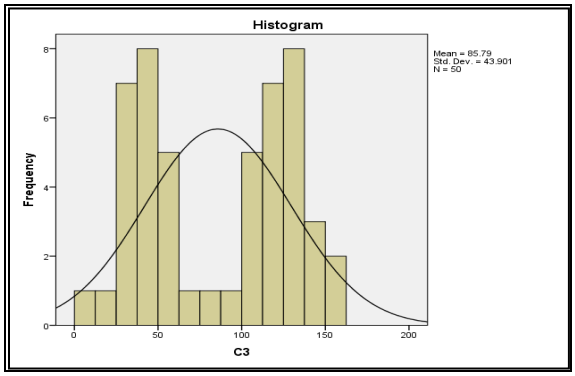

Figure 5. C3

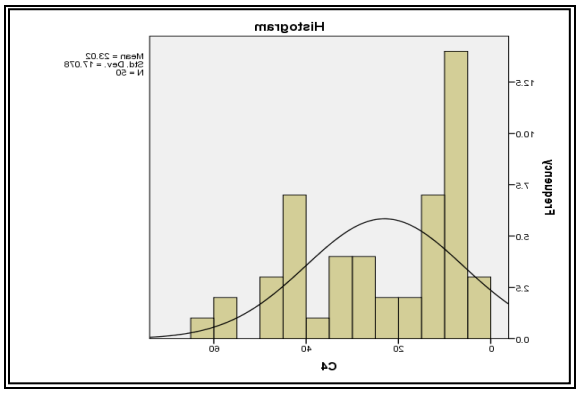

Figure 6. C4

Table 6. Complement consumption in our study population

		No	Percent
C3	Normal	24	48%
	Consumed	26	52%
C4	Normal	25	50%
	Consumed	25	50%
Complement	Normal	25	50%
	Consumed	25	50%

This table shows that half of our cases had complement consumption, and the other half had normal levels of both C3 and C4.

Table 7. Complement and renal involvement and blood pressure

		Complement				p-value
		Normal		Consumed		
		No	%	No	%	
Renal involvement	Yes	11	35.5%	20	64.5%	.009*
	No	14	73.7%	5	26.3%	
Blood pressure	Normal	20	45.5%	24	54.5%	0.189
	Hypertension	5	83.3%	1	16.7%	
Blood disorders	Normal	19	54.3%	16	45.7%	0.355
	Impaired	6	40%	9	60%	
CNS lupus	Yes	6	27.3%	16	72.7%	0.004*
	No	19	67.9%	9	32.1%	
Arthritis	Yes	20	52.6%	18	47.4%	0.508
	No	5	41.7%	7	58.3%	
Mucocutaneous	Yes	17	47.2%	19	52.8%	0.529
	No	8	57.1%	6	42.9%	

This table shows that around two thirds of patients with renal involvement had consumed complement, compared to only 26% among those with no renal involvement; with a significant difference. It also shows that there is no significant difference between hypertension and complement level. Over 72% of patients with CNS involvement had consumed complement, compared to only 32% among those with no CNS involvement; with a significant difference. There is no significant relation between blood disorders, arthritis, mucocutaneous in lupus patients and complement consumption.

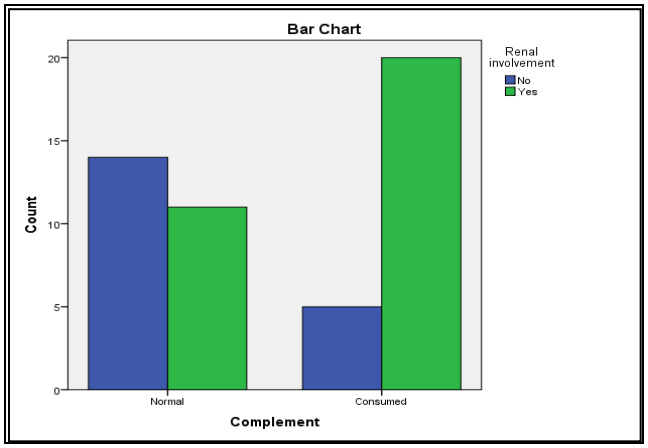

Figure 7. Complement and renal involvement

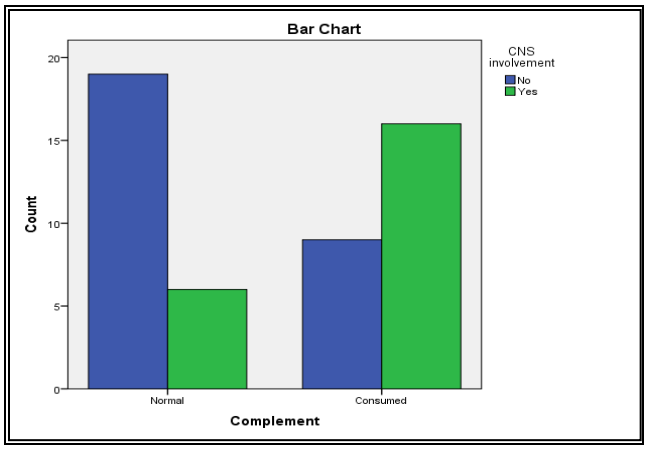

Figure 8. Complement and CNS lupus

Discussion:

SLE is a chronic autoimmune disease characterized by fluctuating disease activity, with multiorgan affection which may lead to life-threatening outcomes(**Ahmadpoor et al., 2014;Scolnik et al., 2014**).

Many complement products have been assigned different degrees of clinical value in assessing disease activity, such as serum CH50, levels of C3, C4, C3d, C4d, C3a, C4a, C5b–9, Ba, Bb and urine C3d (**Holers, 1999**).

Our objective was to estimate the impact of complement level changes on clinical manifestations, visceral injury and mortality in our patients with SLE.

The mean age of our study group ranged from 16-52 years, with a mean of 28.8 years. 92% of the cases were females, with only 4 cases (8%) were males. The mean disease duration was around 3.4 years, with a wide range from only 4 months to over 9 years, reflected in the high standard deviation of 2.8 years.

In study of**(Gandino et al., 2017)** the mean age at diagnosis was 34.2 years with SD 15.8 which older than our patients, their study included 89.6% females which was similar to ours.

The mean duration of SLE at the start of study of **(Ho et al., 2001)** was 11.4 years, with a range of 2–35 years which was longer than disease duration in our study.

The most common organ system involved in our study was the musculoskeletal system, with arthritis in 76% of the cases. This was followed by cutaneous manifestations (72%), then lupus nephritis (62%), CNS lupus (44%), hematological (30%) and lastly CVS (12%). Non of our cases showed liver impairment.

In current study, ANA was positive in near all of the cases, except 3 cases (6%), and anti dsDNA was positive in 78% of the cases, half of our cases had complement consumption, and the other half had normal levels of both C3 and C4.

Around two thirds of our patients with renal involvement had consumed complement, compared to only 26% among those with no renal involvement; with a significant difference.

Similar to our findings, **(Gandino et al., 2017)** found in their study that serum C3 and C4 were consumed in patients with renal manifestations.

Also,**(Ho et al., 2001)** found in their study that decrease in C3 or C4 levels was strongly associated only with concurrent renal SLE activity.

The decrease in complement at the time of renal affection maybe reflects consumption by immune complexes and deposition in tissues, particularly the kidneys **(Porcel et al., 1992)**.

In our study, there was no significant difference between hypertension and complement level, also there is no significant relation between blood disorders in lupus patients and complement consumption.

Contrary to our findings, **(Ho et al., 2001)**found that significant relation between blood disorders in lupus patients and complement consumption.

Also, **(Teke et al., 2017)** found a significant relation between cytopenias and C3 and/or C4 consumption. In their study, they found that complement consumption was detected in over 53% of cases with cytopenias; compared to only 30% among those without cytopenias. The difference from our study may be due to higher number of cases in their study (221 cases). Taking individual blood components, they found that C3 deficiency was an independent risk factor for anemia and lymphopenia, while C4 deficiency was an independent risj factor for leucopenia. Non of them was an independent risk factor for thrombocytopenia, but C4 deficiency was an independent risk factor for "cumulative cytopenia".

Over 72% of patients in our study with CNS involvement had consumed complement, compared to only 32% among those with no CNS involvement; with a significant difference.

Our results agree with **(Magro-Checa et al., 2016)** who found a significantly higher prevalence of C3 and C4 among cases with neuropsychiatric lupus compared to those without neuropsychiatric manifestations (46% versus 26%; respectively for C3 deficiency, and 33% versus 24%; respectively for C4 deficiency). Also, they found that diffuse neuropsychiatric manifestations were associated with more complement deficiency prevalence than focal neuropsychiatric manifestations (65% versus 38%; respectively for C3 deficiency, and 53% versus 22% for C4 deficiency).

We found also that there is no significant relation between arthritis, mucocutaneous manifestations lupus patients and complement consumption.

(Petri et al., 2012) did not find an association between complement consumption and organ damage. The strongest predictors of damage in their study appeared to be age and current corticosteroid dose.

In study of **(Gandino et al., 2017)**, the 10-year survival rate was about 90% which like other series **(Kasitanon et al., 2006)**, and according to their results, complement behavior did not seem to influence survival**(Gandino et al., 2017)**.

Some studies have suggested that the terminal attack complex is more sensitive than C3 or C4 in measuring SLE **(Porcel et al., 1995)**. However, results from other studies have shown that the terminal attack complex correlated poorly with SLE disease activity **(Manzi et al., 1996)**.

Other studies measuring complement activation products allow for a different, albeit, controversial, approach to monitoring lupus disease activity. Elevated levels suggest that SLE (or other diseases in question) is active, while low levels indicate that consumption is greater than synthesis **(Walport, 2002)**.

Unfortunately, direct measurement of complement activation products is not routinely accessible, is short-lived and may also be influenced by activation during the procurement and freeze thawing. Newer data, however, has identified serum cell-bound complement activation products (CB-CAPS) with half-lives as long as the hematopoietic cells with which C3d and C4d (erythrocytes EC4d, B-type lymphocytes BC4d) are bound **(Liu et al., 2010)**.

These CB-CAPS are identified in most patients with SLE and have demonstrated greater specificity and sensitivity compared to using low serum complements for the diagnosis of lupus**(Kalunian et al., 2012)**.

Similar studies have demonstrated that elevated levels of complement split products, particularly those of the alternative and terminal pathway activation, may more accurately reflect disease activity than conventional monitoring of complement C3 and C4 in predicting an impending SLE flare **(Buyon et al., 1992, Cavallo 1994)**.

More studies are indicated to clarify this concept and are ongoing with CB-CAPS demonstrated to be fairly specific (80-90%) for and present even in mild SLE **(Liu et al., 2010;Kalunian et al., 2012)**.

Conclusion:

Our study suggested that complement consumption was strongly associated with lupus nephritis and to a lesser extent; CNS lupus, but not with other organ involvement in SLE patients.

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