LncRNA MEG3 in Promoting Antiphospholipid Syndrome Nephropathy in Patients with Systemic Lupus Erythematosus

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Abstract: Antiphospholipid syndrome (APS) is an autoimmune disease characterized by recurrent thrombotic events and/or pregnancy morbidity associated with the presence of antiphospholipid antibodies (aPL). The role of long non-coding RNAs (lncRNAs) has been of particular interest in the pathophysiology of APS.
Objective: We aimed to investigate lncRNA Maternally Expressed Gene 3 (MEG3) in patients with SLE and to assess its association with susceptibility and clinicopathologic features of antiphospholipid syndrome nephropathy.
Patients and methods: A Controlled cross-sectional study was conducted at Faculty of Medicine, Zagazig University Hospitals, with 211 females. After the exclusion of 16 patients according to exclusion criteria, 95 patients had SLE and 100 healthy controls. **Results:** There were significantly higher values of LncRNA MEG3 relative expression level in the SLE group (5.29±2.8) compared to the control group (2.34±0.74), p< 0.001, Among patients with SLE, there were significantly higher values in APS groups (6.65±3.58) compared to non-APS group (4.5±1.97) p< 0.001. There were significant positive correlations between lncRNA MEG3 relative expression level and ESR, serum creatinine, LA, ACL -IgG, ACL -IgM, leukocyturia, and erythrocyturia. However, there were significant negative correlations between lncRNA MEG3 relative expression level and e GFR, C3, and hemoglobin. Interestingly, we further evaluated our results by linear regression test our results showed that serum creatinine, LA, ACL -IgM, C3, hemoglobin, and ACL -IgG were independently correlated with lncRNA MEG3 relative expression level among APL patients.
Conclusions: LncRNA MEG3 relative expression level was significantly higher in SLE in particular APS group compared to control group and significantly positively correlated with ESR, serum creatinine, LA, ACL -IgG, ACL -IgM, leukocyturia, and erythrocyturia.
Keywords: systemic lupus erythematosus, SLEDAI, lncRNA MEG3, APS nephropathy.

INTRODUCTION:

Antiphospholipid Syndrome (APS) is an autoimmune disorder, clinically characterized by pregnancy morbidity and/or a hypercoagulable state involving the venous or arterial vasculature. It may be assumed that APS is linked to antiphospholipid antibodies (APIs), including anti-cardiolipin antibodies (ACL), anti-beta2-glycoprotein I (anti-ß2GPI), and Lupus anticoagulant (LA). A growing body of evidence has documented that APS arises either as primary APS (PAPS) or secondary APS to other diseases for example systemic lupus erythematosus (SLE/APS) [1].

There is a lot of evidence that raised the fact that renal pathology could be due to thrombosis of the renal artery or the intra parenchymatous arteries, glomerular capillaries, or renal veins [2]. Diagnosis of APS nephropathy requires the presence of one or more acute or chronic typical intrarenal lesions on histology after ruling out other causes of renal microangiopathy[3].

Substantial evidence implicates molecular, genetic, and epigenetic mechanisms are considered as a critical mediator in the pathophysiology of APS as it has been suggested that APS induce genomic and epigenetic alterations that support a pro-thrombotic state. A preponderance of evidence suggests that 98% of the products are non-coding RNAs and those with a size length greater than 200 nucleotides (NT) are defined as long non-coding RNAs (lncRNAs) [4]. There are intriguing reports investigating the role of lncRNAs in the pathogenesis of autoimmune diseases and they observed that ncRNAs could participate in inflammatory pathways in autoimmune diseases and promote the release of inflammatory to aggravate or alleviate diseases [5]. It has been assumed that lncRNAs are widely found in many bodily fluids and are highly stable in the plasma, potentially serving as biomarkers for multiple diseases [6].

Maternally Expressed Gene 3 (MEG3), an embossed lncRNA within DLK1-MEG3 locus located at human chromosome 14q32 and on mouse chromosome 12 [7]. There is growing evidence that MEG3 expression levels are associated with many diseases; cancer [8-18], autoimmune disease [11], as well as metabolic diseases for example diabetic nephropathy [12]. The present study was designed to analyze the potential clinical usefulness of investigating lncRNA MEG3 relative expression level in patients with SLE and to assess its association with susceptibility and clinicopathologic features of antiphospholipid syndrome nephropathy.

PATIENTS AND METHODS

A Controlled cross-sectional study was conducted with 211 females. After the exclusion of 16 patients according to exclusion criteria, 95 patients had SLE and 100 healthy controls. All participants underwent complete history taking, thorough clinical examination. The flowchart of the study is shown in figure 1. Among 95 patients with SLE (the diagnosis of SLE were according to **Petri**[13]), 15 patients had APS (the diagnosis of APS, were according to **Miyakis *et al.*** [1]) the diagnosis of renal involvement was confirmed by renal biopsy. A history of proteinuria was defined as 500 mg or more per 24 hr. Disease activity was

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measured using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [14].

Ethical consent:

Approval of the study was obtained from Zagazig University academic and ethical committee. Every patient signed informed written consent for the acceptance of the operation. This work has been carried out following The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Laboratory assessments:

Laboratory assessments included high-sensitivity C-reactive protein (hsCRP) by Cobas 8000 (Roche, Germany) and complement C3, C4, and 24 hr urine protein by Cobas 6000 (Roche, Germany). Antinuclear antibodies (ANA), the ANA, and anti-dsDNA were estimated according to the manufacturer's instructions and Zagazig university hospital protocol. Anticardiolipin was performed by ELISA anticardiolipin IgG/IgM ORG515 (ORGENTEC Diagnostika Gmbh, Mainz, Germany). Renal biopsy samples were obtained from 12 patients among 15 patients with APS and investigated and classified by an experienced renal pathologist, using the 2004 International Society of Nephrology/Renal Pathological Society

Measurement of LncRNA MEG3 gene expression:

The expression of serum LncRNA MEG3 was measured via quantitative real-time-polymerase chain reaction (qRT-PCR). RNA isolation was done according to the manufacturer's instructions by using the miRNeasy Mini Kit (QIAGEN GmbH, Hilden, Germany) The primers sequence was: MEG3: 5′-GGCAGGATCTGGCATAGAGG-3′ (forward); 5′-CGAGTCAGGAAGCAGTGGGTT-3′ (reverse); GAPDH: 5′-GGAGCGAGATCCCTCCAAAAT-3′ (forward); 5′-GGCTGTTGTCATACTTCTCATGG-3′ (reverse).; was used for lncRNA normalization.

Statistical analysis

The collected data were coded, processed, and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi-square test ($\chi 2$) to calculate the difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data). P-value < 0.05 was considered significant.

RESULTS

The current study enrolled 211 subjects (100 healthy groups and 111 patients with SLE. We excluded 16 patients as shown in the flowchart (**Figure 1**). The sex, age, and ethnicity were matched between both groups. Among the apparent healthy control group, 80 subjects were Egyptian females their mean age was 32.0 ± 10.1 years in addition to 11 Egyptian males their mean age was 44.5 ± 8.8 years In the SLE group 84 patients were Egyptian females their mean age was 34.0 ± 9.4 years and 11 Egyptian males their mean age was 43.5 ± 11.34 years and duration of SLE were 5.6± 3.8 years.

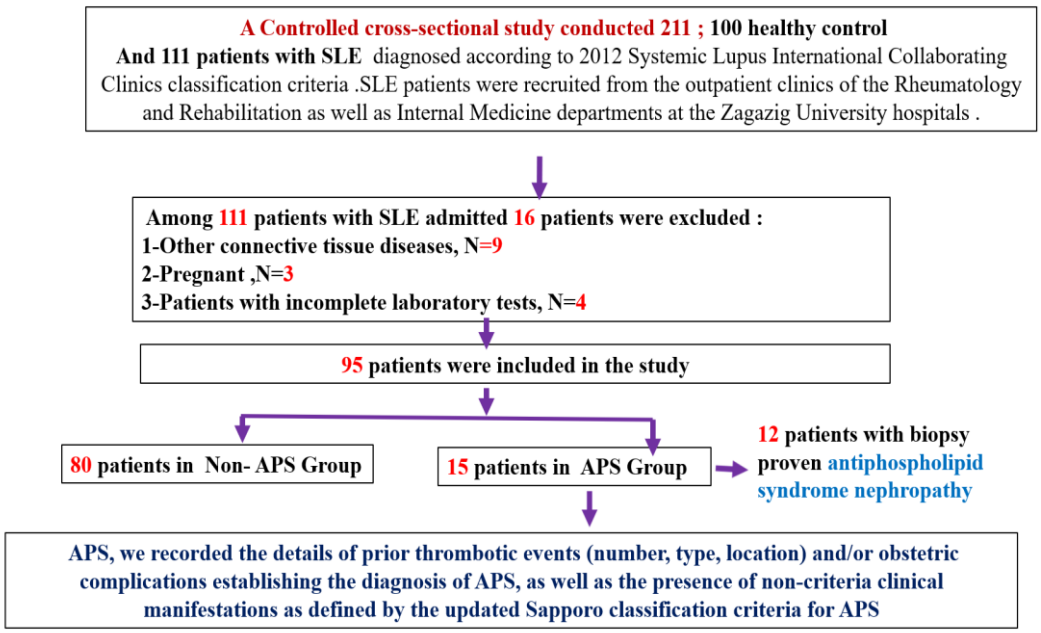

Figure (1): Flowchart of the study.

Clinical characteristics and laboratory parameters of all enrolled patients with SLE (n=95): The prevalence of clinical characteristics and laboratory parameters of patients with SLE are shown in **Table 1**.

Table (1): Clinical characteristics, and laboratory parameters of all enrolled patients with SLE.

Variable	SLE

	Group (n=95)
Fever	29
Hypertension	33
Discoid rash	42
Photosensitivity	38
Oral ulcers	39
Alopecia	38
Pleurisy	42
Pericarditis	37
Arthritis	42
Vasculitis	16
Myositis	2
Cataract	3
Retinal change/optic atrophy	1
Seizures	5
Psychosis	2
Headache	7
SLEDAI	16.8±3.1
Leukocyturia (cells/hpf)	6.2±1.86
Erythrocyturia (cells/hpf)	5.2±1.86
UACR (mg/g)	244.3±30.6
Serum creatinine (mg/dL)	1.83±0.15
Serum urea (mg/dL)	37.09± 2.67
eGFR CKD-EPI, ml/min/1.73m^2	63.7±2.17
Hemoglobin (g/dL)	9.5±0.913
White blood cells (109/L)	5.31±1.02
Neutrophils (109/L)	3.4±0.5
Platelets (109/L)	193.8± 19.6
CRP (mg/dL)	9.18±2.26
ESR (mm/h)	30.7±2.76
LA	33.7±6.8
aCL -IgG	18.7±3.8
aCL -IgM	19.1±1.8
C3 (mg/dl)	42.87± 4.02
C4 (mg/dl)	11.2±2.95

SLE; systemic lupus erythematosus, SLEDAI; systemic lupus erythematosus disease activity; eGFR; estimated glomerular filtration, ESR; erythrocyte sedimentation rate, ANA; antinuclear antibodies; CRP; C-reactive protein, aCL -IgG; Anticardiolipin IgG, aCL-IgM; Anticardiolipin IgM, LA; lupus anticoagulant C3; complement 3, C4: complement 4. P<0.05.

Clinical characteristics and laboratory parameters of patients with APS and non- APS Group as summarized in Table 2:

The current results detected that there are non-significant differences between patients with APS and non- APS regards clinical characteristics. Clinical characteristics and obstetric parameters of patients with APS are summarized in **Table 3.**

The APSN histologic lesions:

According to the current study, 12 renal biopsy samples were obtained from patients with APSN, the most prevalent APS nephropathy histologic lesions are diffuse proliferative GN (25%) and thrombotic microangiopathy (25%) as presented in table 3.

Table (2): Clinical characteristics, and laboratory parameters of patients with APS and non- APS Group.

Variable	Non- APS Group (n=80)	APS Group (n=15)	P-value
Hypertension	33	4	0.123
Discoid rash	42	6	0.336
Photosensitivity	38	8	0.211
Oral ulcers	39	6	0.311
Alopecia	38	9	0.345
Pleurisy	42	8	0.135
Pericarditis	37	6	0.312
Arthritis	42	7	0.122
Vasculitis	16	3	0.327
Myositis	2	1	0.321
Cataract	3	2	0.344
Retinal change/ optic atrophy	9	1	0.338
Seizures	11	2	0.228
Psychosis	12	1	0.123
Headache	8	2	0.358
SLEDAI	14.1±2.96	18.29±7.1	<0.001*
Leukocyturia (cells/hpf)	5.500±1.978	7.6571±1.588	<0.001*
Erythrocyturia (cells/hpf)	4.500±1.978	6.657±1.588	<0.001*
UACR (mg/g)	168.1±4.1	374.6±27.1	<0.001*
Serum creatinine (mg/dL)	1.69±0.15	2.09±0.17	<0.001*
Serum urea (mg/dL)	32.19± 4.1	45.5±3.615	<0.001*
eGFR CKD-EPI, ml/min/1.73m^2	71.5±6.574	50.3±6.4	<0.001*
Hemoglobin (g/dL)	9.59±0.813	9.5±0.713	0.636
White blood cells (109/L)	5.21±0.9	5.51±0.1	0.150
Neutrophils (109/L)	3.3±0.6	3.5±0.7	0.346
Platelets (109/L)	193.6±19.6	194.8±19.6	0.923
CRP (mg/dL)	8.4±1.8	10.45± 2.5	<0.001*
ESR (mm/h)	22.7±1.0	44.3±3.2	<0.001*
LA	16.1±3.8	45.1±4.8	<0.001*
aCL -IgG	11.7±2.8	32.7±5.3	<0.001*
aCL -IgM	10.1±1.8	34.1±2.7	<0.001*
C3 (mg/dl)	55.87± 9.2	35.06± 2.34	<0.001*
C4 (mg/dl)	10.2±2.95	7.93±1.09	<0.001*

SLE; systemic lupus erythematosus, SLEDAI; systemic lupus erythematosus disease activity; eGFR; estimated glomerular filtration, ESR; erythrocyte sedimentation rate, ANA; antinuclear antibodies; CRP; C-reactive protein, aCL -IgG; Anticardiolipin IgG, aCL-IgM; Anticardiolipin IgM, LA; lupus anticoagulant C3; complement 3, C4: complement 4. P<0.05.

Table (3): Clinical characteristics, obstetric and laboratory parameters of patients with APS Group

Variable	APS Group (n=15)
Deep vein thrombosis	5
Livedo reticularis	1
Stroke	1
Pulmonary embolism	3
Autoimmune hemolytic anemia	3
Skin ulcers	4
Myocardial infarction	3
Early pregnancy loss (10> weeks)	5
Pre-eclampsia/eclampsia	2
APS nephropathy histologic lesions	
Focal proliferative glomerulonephritis	1
Diffuse proliferative glomerulonephritis	3
Membranous nephropathy	2
Thrombotic microangiopathy	3
Organized thrombi with or without recanalization in arteries and arterioles	1
Fibrous arterial and arteriolar occlusions	1
Focal cortical atrophy	1

lncRNA MEG3 relative expression level in studied groups:

There were significantly higher values of LncRNA MEG3 relative expression level in the SLE group (5.29±2.8) compared to the control group (2.34±0.74), p< 0.001, **Figure 2a** Regarding LncRNA MEG3 relative expression level in Non- APS and APS groups, there were significantly higher values in APS groups (6.65±3.58) compared to non-APS group (4.5±1.97) p< 0.001, **Figure 2b**.

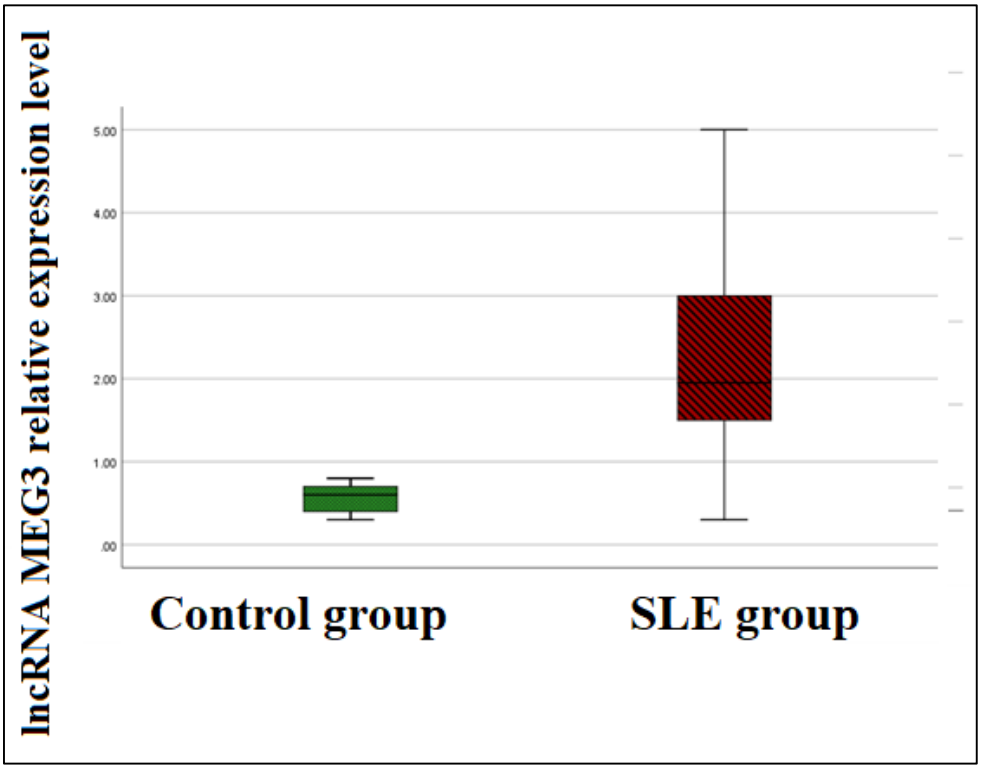

Figure (2a): LncRNA MEG3 relative expression level in studied groups.

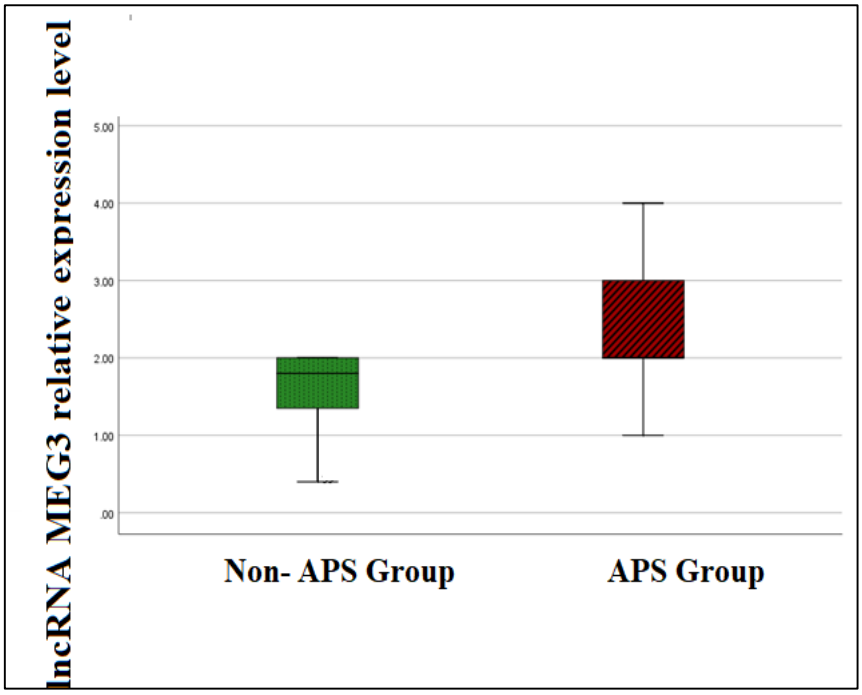

Figure (2b): LncRNA MEG3 relative expression level in Non- APS and APS groups.

Pearson correlation between lncRNA MEG3 relative expression level and laboratory variables in APL group:

There were significant positive correlations between lncRNA MEG3 relative expression level and ESR, serum creatinine, LA, ACL -IgG, ACL -IgM, leukocyturia, and erythrocyturia. However, there were significant negative correlations between lncRNA MEG3 relative expression level and e GFR, C3, and hemoglobin ($p< 0.001$) (**Table 4**).

Table (4): Pearson correlation between lncRNA MEG3 relative expression level and laboratory variables in the APL group.

	lncRNA MEG3	
	r	p
ESR	0.511	<0.001*
e GFR	-0.326	<0.001*
Serum creatinine	0.474	<0.001*
LA	0.496	<0.001*
aCL -IgG	0.412	<0.001*
aCL -IgM	0.566	<0.001*
C3	-0.394	<0.001*
Hemoglobin	-0.474	<0.001*
White blood cells	0.014	0.0871
Leukocyturia	0.457	<0.001*
Erythrocyturia	0.592	<0.001*

Linear regression analyses:

To evaluate the main effectors of lncRNA MEG3 relative expression level among the APL group, a linear regression analysis test was done. Our results showed that serum creatinine, LA, ACL -IgM, C3, hemoglobin, and ACL -IgG were independently correlated with lncRNA MEG3 relative expression level among APL patients ($p< 0.001$) (**Table 5**).

Table (5): Linear regression analyses to test the influence of the main independent variables against lncRNA MEG3 relative expression level (dependent variable) in the APL group.

Model	Unstandardized Coefficients		Standardized Coefficients	t	P-value	95% CI	
	B	SE	Beta			Lower Bound	Upper Bound
(Constant)	0.144	0.085		0.29-	0.768	1.109	0.821
ESR (mm/h)	0.099	0.014	0.113	1.542	0.127	0.029	0.227
e GFR	0.005	0.001	0.425	1.785	0.078	0.012	0.001
Serum creatinine	0.430	0.13	1.286	2.804	<0.001*	0.734	0.125
LA	0.047	0.016	0.541	2.959	<0.001*	0.015	0.078
White blood cells	0.002	0.001	0.171	0.572	0.569	0.008	0.004
aCL -IgM	0.018	0.008	0.241	2.318	<0.001*	0.003	0.034
C3 (mg/dl)	0.305	0.068	0.384	4.460	<0.001*	0.170	0.440
Hemoglobin	6.757	1.132	0.267	2.157	<0.001*	12.957	0.557
aCL -IgG	31.228	4.909	0.576	6.362	<0.001*	21.512	40.945
Leukocyturia	0.286	0.092	0.341	0.730	0.467	0.494	1.066
Erythrocyturia	0.404	00.099	0.502	1.349	0.181	0.999	0.192

* significant P-value (P<0.05)

The accuracy of LncRNA MEG3 relative expression level as a discriminator between SLE and control groups by ROC analysis.

We investigated the diagnostic value of LncRNA MEG3 relative expression level by ROC curve test as presented in **Figure 3a**. The cutoff value was 0.91 and the AUC were 0.958 (95% CI = 0.92-0.992). Additionally, the sensitivities and the specificities were (96.8% and 97%).

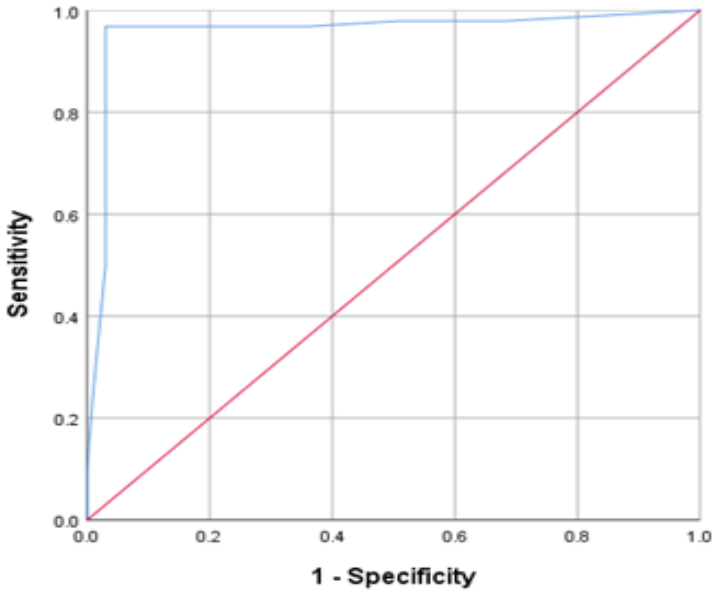

Figure (3a): Receiver operator characteristic (ROC) curve for lncRNA MEG3 relative expression level as a discriminator between SLE and control groups.

The accuracy of LncRNA MEG3 relative expression level l as a differentiator between APS Group and Non-APS groups s by ROC analysis.

We further investigated the diagnostic value of lncRNA MEG3 relative expression level by ROC curve test as presented in **Figure 3b**. The cutoff value was 1.95 and the AUC was 0.771 (95% CI = 0.666–0.876). Additionally, the sensitivities and the specificities were (90.9% and 82.1%).

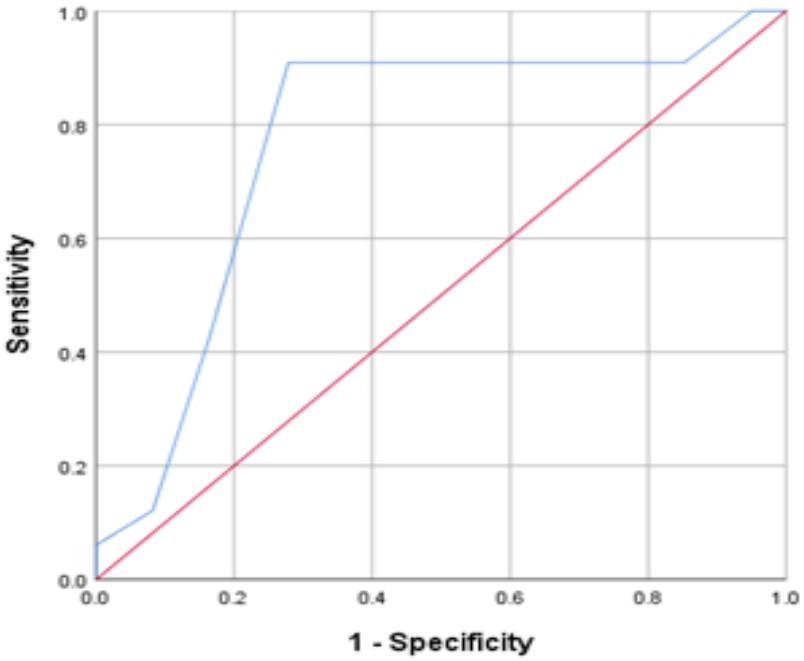

Figure (3b): Receiver operator characteristic (ROC) curve for lncRNA MEG3 relative expression level as a differentiator between APS Group and Non- APS Group groups.

DISCUSSION

A preponderance of evidence suggests that APS can affect any part of the kidney such as renal arteries and veins, intrarenal arteries and arterioles, and glomerular capillaries and characteristic microvascular nephropathy lesions are included in the non-criteria manifestations of APS. Additionally, APSN is defined as a renal small vessel vasculopathy characterized by acute thrombosis and/or chronic arterial and arteriolar lesions [15].

Given the possible association between genetic and epigenetic signatures as well as pro-atherosclerotic, pro-thrombotic, and inflammatory states in autoimmune diseases in particular SLE and APS, recent studies have been conducted [16]. However, till now there are still gaps in our understanding of the development and progression of these co-morbidities in APS and SLE [17]. Thus, the current study aimed to assess the lncRNA MEG3 relative expression level in patients with SLE and to assess its association with susceptibility and clinicopathologic features of antiphospholipid syndrome nephropathy.

The diagnosis of APS nephropathy should include at least one of the following lesions: thrombotic microangiopathy (acute lesion), interlobular fibrous intimal hyperplasia, arterial and arteriolar recanalizing thrombi, fibrous arterial occlusion, and focal cortical atrophy [18].

Our findings revealed that the prevalence of APS among SLE patients was 15.8% and the most prevalent APS nephropathy histologic lesions are diffuse proliferative GN (25%) and thrombotic microangiopathy (25%). According to Tektonidou and his colleagues, APS nephropathy existed in 39.5% of patients with aPL, compared with only 4.3% of patients without aPL[19]. In a study conducted by **Mok *et al.*** [20] about 40% of patients with SLE have aPL, but less than 40% of them will eventually have thrombotic events. Though some reports are controversial, only a few patients with primary APS progress to SLE [21].

The interesting result of our study was that there were significantly higher values of LncRNA MEG3 relative expression level in the SLE group compared to the control group. Interestingly there were significantly higher values of LncRNA MEG3 relative expression level in APS groups compared to the non-APS group.

lncRNAs have been confirmed to perform a vital role in many diseases, including cancers and metabolic disorders [22].

According to **Li *et al.*** [12] study about the role of MEG3 expression level in diabetic nephropathy, they observed that the MEG3 expression level was increased significantly in serum and kidney tissue of untreated db/db mice compared to the control group they proposed that MEG3 may aggravate this disease by promoting ECM proteins.

Cons, similarly, reports of Song et al showed that the levels of LncRNA MEG3 relative expression were higher in serial exosomes of patients with RA compared to controls [23].

The results presented here are innovative as this study performs a robust evaluation of LncRNA MEG3 relative expression level as an epigenetic marker of inflammation. Even more importantly, the correlation of LncRNA MEG3 with clinical as well as laboratory parameters of the APL group. the current study findings observed that there were significant positive

correlations between lncRNA MEG3 relative expression level and ESR, serum creatinine, LA, aCL -IgG, aCL -IgM, leukocyturia, and erythrocyturia. However, there were significant negative correlations between lncRNA MEG3 relative expression level and e GFR, C3, and hemoglobin. Interestingly, we further evaluated our results by linear regression test our results showed that serum creatinine, LA, aCL -IgM, C3, hemoglobin, and aCL -IgG were independently correlated with lncRNA MEG3 relative expression level among APL patients.

For further assessment of the diagnostic power LncRNA MEG3 relative expression level in differentiating SLE from the control group. We found that the sensitivities and the specificities were (96.8% and 97%). regarding differentiating non- APS from APS groups the sensitivities and the specificities were (90.9% and 82.1%).

CONCLUSION

The current results detected that LncRNA MEG3 relative expression level was significantly higher in SLE in particular APS group compared to control group. In addition, there were significant positive correlations between lncRNA MEG3 relative expression level and ESR, serum creatinine, LA, aCL -IgG, aCL -IgM, leukocyturia as well as erythrocyturia.

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