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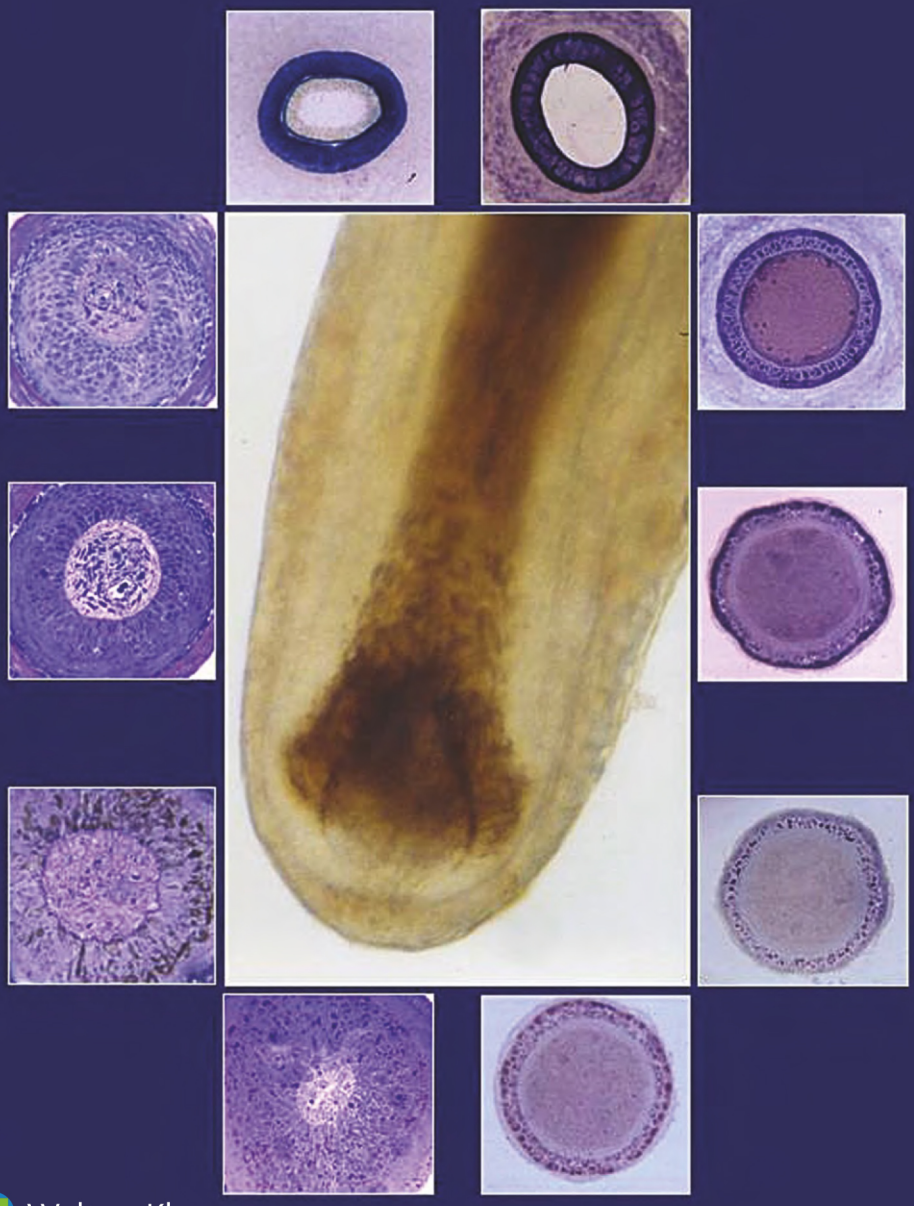

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YKL-40 A Sensitive Biomarker for Early Androgenetic Alopecia and Early Hidden Metabolic Syndrome

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ABSTRACT

Background: Androgenetic alopecia (AGA) is a common dermatological problem, Does the onset of the AGA matters in the general health? YKL 40 may have role in the pathogenesis of early AGA and associated metabolic syndrome (MS). YKL 40, released by many inflammatory cells and its biological role is not well known. **Aim of the Work:** The estimation of serum level of YKL-40 in patients with AGA to detect its role in AGA and MS pathogenesis, onset and severity. **Materials and Methods:** This case–control study, 100 individuals were enrolled in our study; 70 AGA patients and 30 healthy controls. We obtained an informed written consent from each individual prior the participation. AGA was diagnosed clinically, and onset was evaluated as early onset alopecia (by the age of 30 years or earlier), YKL-40 level was measured by ELISA technique. **Results:** Patients showed highly significant higher serum YKL-40 level more than that of the healthy subjects ($P < 0.001$). There was highly significant increase in YKL-40 level among early onset male and female cases compared to late onset cases ($P < 0.001$ each). There was significant increase in MS elements in AGA cases than controls ($P < 0.05$), and highly significant increase in MS associations and severity among early onset male and female cases compared to late onset cases ($P < 0.001$ each). AGA patients with MS showed highly significant higher serum YKL-40 level more than that without ($P < 0.001$). There was highly significant increase in YKL-40 level among early onset AGA with MS compared to late onset cases with MS ($P < 0.001$ each).

Conclusions: High serum YKL-40 considered not only a biomarker of early onset AGA but also considered a potential sensitive predictor for early onset MS development and severity in patients with early onset AGA.

Key words: Androgenetic alopecia, Insulin resistance and YKL40, metabolic syndrome

INTRODUCTION

Hair is a marvelous structure with cosmetic function. Androgenetic alopecia (AGA) is the most common hair loss condition affects both sexes; AGA is thinning of scalp hairs that initiated by androgens in susceptible patients.[1] The onset of AGA mostly in late adolescence, gradual and slowly develops over years. The frequency and the grade of severity of AGA increases with age.[2] Up to 30% of males will have AGA by 30 years, 50% by 50 years, and 80% by 70 years.[3]

Chitinase-3-like protein1 YKL-40 is a 40 kDa heparin and chitin-binding glycoprotein that has three N terminal amino acids: tyrosine (Y), lysine (K), and leucine (L).[4] It is produced by inflammatory cells as neutrophils, endothelial cells, macrophages, fibroblasts, chondrocytes and cells of smooth muscle.[5] Although YKL-40 biological function is unknown, YKL-40 participation has been also evidenced during extracellular matrix remodeling, migration and proliferation of (malignant) cells, angiogenesis, macrophage-induced inflammation, and T-cell activity.[6] Elevated YKL-40 are seen in diseases that characterized by active inflammation and remodeling as ischemic

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cardiovascular diseases (CVDs), atherosclerosis, diabetes mellitus (DM), metabolic syndrome (MS), inflammatory bowel disease, pneumonia, and cancer.[7]

YKL-40 would be a better biomarker for significant activity rather than perception of symptoms.[8] Several studies have investigated the role of YKL-40 in relation to cancer. YKL-40 levels are particularly high in recurrent cancer and highly differentiated cancers, which are characterized by high vascularization and a high turnover of extracellular matrix.[9]

The link between early AGA and associated of MS had been suggested.[10] AGA might be the indicator for arterial stiffness.[11] The link between YKL-40, MS, obesity, morbid obesity, and CVD is very complex; YKL-40 is strongly associated with 34% increase in serum level of triglycerides (TG) and twice increased of ischemic stroke attacks risk.[12] Serum YKL-40 level was significantly associated with the presence of MS. Serum YKL-40 may be a novel and useful indicator for MS.[13]

The serum level of YKL-40 and AGA may be linked by direct mechanism or through MS. Therefore, we aimed to evaluate the serum YKL-40 levels in patients with early and late onset AGA and as a sensitive biomarker for early AGA and for the detection of early hidden MS.

MATERIALS AND METHODS

Study population

This case–control study with total number of 100 individuals were enrolled; 70 AGA patients (equal number of males and females) and 30 apparently healthy controls. This study was approved by faculty of medicine related local ethics committee on research of humans and we obtained an informed consent from each subject prior the participation. This protocol of research work was in accordance with Helsinki declaration of the human rights.

Individuals with known history of CVDs, infections, cancer or any chronic inflammatory conditions hepatic, renal disorders, connective tissue disorders, or thyroid disorders that influence YKL-40 metabolism were excluded from the study.

AGA diagnosis was established by detailed medical history, clinical examination, and trichoscopic features using Dermlite® 3 with 20× magnification power to assess hair density (hair/cm^2) where number of hairs were assessed manually (more than 20% variability in hair diameter between affected and uninvolved areas). Especially females to exclude diffuse alopecia areata and frontal fibrosing alopecia, and onset was evaluated as early onset alopecia (by the age of 30 years or earlier)[14] and the various grades of AGA severity according to the Hamilton–Norwood classification in males and according to Ludwig classification in females. The diagnosis of MS was in accordance to criteria declared by National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII, 2001).[15] This was modified to add the World Health Organization's waist circumference cutoff points, by the presence of 3 of the following: Abdominal circumference >102 cm in men and 88 cm in women. Hypertriglyceridemia >150 mg/dl. High-density lipoprotein cholesterol (HDL-C) <40 mg/dl in men and <50 mg/dl in women. Blood pressure (BP) >130/85 mmHg. Glycemia >100 mg/dl. BMI ≥25 was taken as overweight and ≥30 as obesity, per the WHO definition.[16]

Laboratory tests

A 5-mL of venous blood was obtained from each subject. Samples were centrifugated at 1262 g for about 10–15 min, aliquot and rapidly refrigerated at −20°C till the test. The serum level of YKL-40 was measured by a double antibody ELISA Kit from Sun Red Biotechnology Company, made in Shanghai, China, catalogue NO (201-12-2064).

Statistical analysis

Obtained data were statistically analyzed by SPSS (Statistical Package for Social Science) version 18 software (SPSS Inc., Chicago, IL, USA). The collected data were arranged as number (percentage) and were analyzed using Chi-square test. Mann–Whitney test for normally and non-normally distributed numerical variables, respectively. Pearson correlation coefficient also calculated the correlation between quantitative data.

Receiver operating characteristic (ROC) curve analysis was used to identify optimal cutoff values of different parameters with maximum sensitivity and specificity for prediction of the outcome. Accuracy is measured by the area under the ROC curve. An area of 1 represents a perfect test; an area of 0.5 represents a worthless test. A rough guide for classifying the accuracy of a diagnostic test is the traditional academic point system: 0.90–1 = excellent (A); 0.80–0.90 = good (B); 0.70–0.80 = fair (C); 0.60–0.70 = poor (D); and 0.50–0.60 = fail (F). The level of statistical significance in this work was $P \leq 0.05$.

RESULTS

A total of 70 AGA patients, the range of duration was from 1 to 22 years and mean about 7.17 years, the mean age of patients was 38.5 ± 8.67 (ranging 18–50) years. Among enrolled patients; 51.4% had early onset AGA (by age 30 years or earlier) and 48.6% had late onset. The most common grades among male were II and VI (22.9% and 20%, respectively) and among female II and III (40% and 40%, respectively).

The mean serum levels of YKL-40 in AGA cases and control were (58.1 ± 72) ng/ml versus (11.8 ± 2.47) ng/ml. Patients showed highly significant higher serum YKL-40 level more than that of the healthy controls ($P < 0.001$) [Table 1]. There was highly significant increase in YKL-40 level among early onset male and female cases compared to late onset cases (99.06 ± 80.58), (97.13 ± 86.67) versus (16.02 ± 6.66), (15.49B ± 4.90) ng/ml, respectively ($P < 0.001$ each) [Table 2 and Figures 1, 2].

There was significant increase in MS association in AGA cases than controls ($P < 0.05$), and highly significant increase in MS associations and severity among early onset male and female cases compared to late onset cases ($P < 0.001$ each) [Table 3].

The mean serum levels of YKL-40 in AGA cases with MS were highly significantly higher (103.80 ± 86.31) ng/ml versus (19.62 ± 10.10) ng/ml those cases without ($P < 0.001$) [Table 4]. There was highly significant increase in YKL-40 level among early onset AGA with MS compared to late onset AGA with MS ($P < 0.001$ each)

There were significantly increased BP, total cholesterol (TC), TG, and fasting blood sugar (FBS) in all

Table 1: Comparison between cases and control groups in YKL-40 level

Variable YKL-40	AGA		MW test	*P*
	Cases (*n*=70)	Control (*n*=30)		
X±SD	58.1±72	11.8±2.47	4.78	<0.001** (HS)
Median	23.05	11.9		
Range	1.4-290.7	7.1-15.5		

**HS – Highly significant; AGA – Androgenetic alopecia; SD – Standard deviation; MW – Mann-Whitney test

Table 2: Comparison between early and late onset male and female androgenetic alopecia cases in YKL-40 level

Variable	Early AGA	Late AGA	MW test	*P*
Male cases (YKL-40)	*n*=18	*n*=17		
X±SD	99.06±80.58	16.02±6.66	4.85	<0.001** (HS)
Median	41.75	16.8		
Range	20-256	1.4-29.2		
Female cases (YKL-40)	*n*=18	*n*=17		
X±SD	97.13±86.67	15.49±4.90	4.72	<0.001**
Median	39.7	13.2		
Range	20.40-290.70	8.6-26.6		

**HS (*P*<0.01). SD – Standard deviation; MW – Mann-Whitney test; HS – Highly significant; AGA – Androgenetic alopecia

Table 3: Comparison between early and late onset male and female androgenetic alopecia cases as regards metabolic syndrome

Variable	Early AGA	Late AGA	χ^2	*P*
Male cases	*n*=18	*n*=17		
No MS	5 (27.8)	15 (88.2)	13.05	<0.001**
Yes	13 (72.2)	2 (11.8)		
Female cases	*n*=18	*n*=17		
No MS	2 (11.1)	16 (94.1)	24.12	<0.001**
Yes	16 (88.9)	1 (5.9)		

**HS – Highly significant; MS – Metabolic syndrome; AGA – Androgenetic alopecia

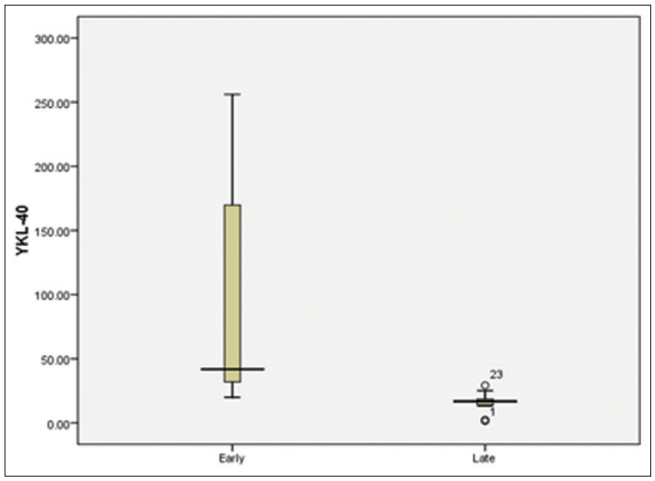

Figure 1: Comparison between early and late cases in male group in YKL-40

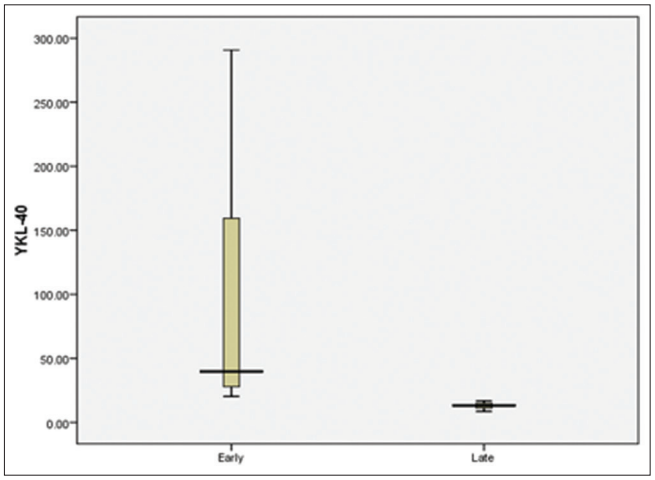

Figure 2: Comparison between early and late cases in female group in YKL-40

cases ($P < 0.05$ each) except TG in early onset male cases was highly significantly increased ($P < 0.001$) and significant decrease in HDL among early onset male and female cases ($P < 0.05$).

Receiver operating curve analysis showed the sensitivity of serum YKL-40 in diagnosis of AGA at cutoff 14.25 was 81.4%, specificity was 93.3% and the accuracy was 83.5% ($P < 0.001$) and in diagnosis of early onset AGA at cutoff 20.35 was 97.2%, specificity was 85.3% and the accuracy was 91.4% ($P < 0.001$) [Figures 3 and 4].

DISCUSSION

AGA is a genetically determined disease with progressive course through its gradual conversion of hairs from terminal into vellus like hairs.[17] Pathophysiology that links AGA and MS has not been fully established; excess androgens underpin both mechanisms.[18]

As regards relation between AGA and YKL 40, we found that AGA patients had significant higher serum YKL-40 level more than control group ($P < 0.001$). Furthermore, there was a highly significant increase in YKL-40 among early onset male and female cases compared to late onset cases ($P < 0.001$ each) suggesting the possible role of YKL in AGA pathogenesis even in early stages, which can be explained by many mechanisms;

Cytokines, such as Transforming Growth Factor beta 1 (TGF-β1), interleukin (IL)-1α, and Tumor Necrosis Factor alpha (TNF-α), have inhibitory and pro-apoptotic effects that induce catagen.[19-21] YKL-40 is stimulated by locally pro-inflammatory cytokines such as TNF-α and IL-1β.[4] YKL-40 levels correlated with pro-inflammatory TNFα and IL-1β levels.[22]

Hair follicle micro-inflammation and AGA is a multistep process that could be involved in the generation of the inflammatory response.[23] Langerhans cells or alternatively keratinocytes could present antigen to infiltrating T lymphocytes and induce T-cell proliferation. The antigens are selectively destroyed by infiltrating macrophages, or natural killer cells.[24] On sustained inflammation, together with connective tissue remodeling, where collagenases play an active role. Collagenases are contributed to perifollicular fibrosis by preparing tissue matrix and basal membranes for macrophages and T-cell adhesion.[19] Dermal papillae cells proliferation and differentiation were studied for their role in the pathogenesis of AGA as DPCs from balding scalp contain more androgen receptors than nonbalding scalp,[25] and oxidative stress role in AGA pathogenesis by significant alteration of DPCs morphology, migration, proliferation, senescence, and TGF-β signaling.[26] Whereas YKL-40 play a major role in epithelial-mesenchymal (transition, migration and proliferation), tissue differentiation, angiogenesis, remodeling and inflammation.[27] YKL-40 produced by activated macrophages can promote Th1 immunity.[28]

Table 4: Relation between cases with and without metabolic syndrome in YKL-40 level

Variable YKL-40	Cases with MS (*n*=32)	Without MS (*n*=38)	MW test	*P*
X±SD	103.80±86.31	19.62±10.10	4.95	<0.001** (HS)
Median	90.2	15		
Range	12.9-290.7	1.4-50.2		

**HS – Highly significant; MS – Metabolic syndrome; SD – Standard deviation; MW – Mann-Whitney test

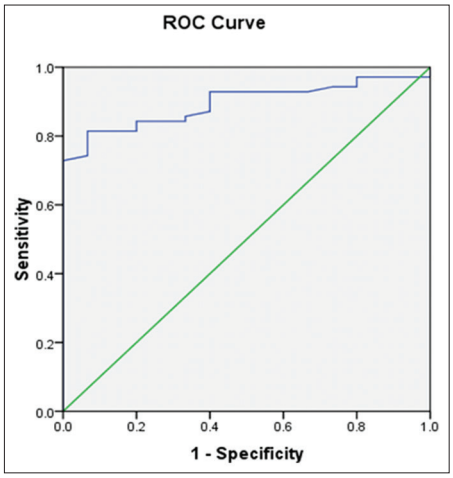

Figure 3: Validity of YKL-40 in diagnosis of AGA

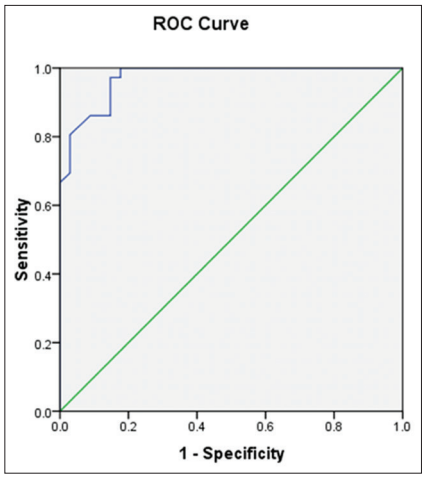

Figure 4: Validity of YKL-40 in diagnosis of early onset AGA among the studied group

Insulin resistance (IR) means at normal insulin level, target tissues are unable to mount normal glucose-lowering response by suppression of endogenous glucose production, suppression of lipolysis, cellular uptake of available plasma glucose, and net glycogen synthesis. This IR necessitates increased insulin secretion to compensate, so fasting plasma insulin levels increase.[29] IR has a pathogenetic role in the miniaturization of hair follicles. Vasoactive substances with endothelial dysfunction in IR lead to microcirculatory disturbance, perifollicular vasoconstriction, and vascular wall proliferation of smooth muscle. This leads to microvascular insufficiency, local-tissue hypoxia, and progressive miniaturization of hair follicles.[30] High scores of IR showed in males with early onset AGA.[31] YKL-40 was positively correlated with IR.[4] YKL-40 was inversely correlated with insulin-like growth factor 1.[32]

In this work, there was significant increase in MS in AGA cases than controls ($P < 0.05$), there was highly significant increase in MS associations among early onset male and female cases compared to late onset cases ($P < 0.001$ each).

The relationship between AGA and MS is still matter of controversy. Studies have reported link between AGA and many chronic diseases separately but making elements of MS including hypertension,[33] abnormal serum lipid profiles,[34,35] obesity,[34] IR,[34,36] and CVD.[37] However, other studies not supported these associations.[38,39]

There was a significant association between AGA and MS as HDL-C was found to be of particular importance in patients with moderate or severe AGA.[40] This was in line with Dharam Kumar study[41] study who found a significant link between MS and AGA after adjusting other factors. In between components of MS, HDL is a specifically significant factor associated with AGA. Patients with moderate or severe AGA may have higher risk for developing MS and early detection of this in patients with moderate or severe AGA may be essential in early intervention to reduce the risk of dangerous complications. Similar results were seen in studies conducted by.[10,42,43] In contrast to our study results reported by Mumcuoglu *et al.*'s study,[31] there were no significant difference between AGA patients and controls. As regards the onset, hypertension was highly prevalent in early-onset females with AGA that gives a clue for early-onset AGA to be a strong suggesting factor for early-onset severe coronary heart disease.[44] Hormonal and metabolic abnormalities have been reported in men with early-onset AGA.[45]

In this work, AGA patients with MS showed highly significant higher serum YKL-40 level more than that without ($P < 0.001$). There was highly significant increase in YKL-40 level among early onset AGA with MS compared to late onset cases with MS ($P < 0.001$ each).

As regards higher YKL-40 level in AGA with MS than without can be explained as MS defined as a collection of many clinical signs mainly cardiovascular and diabetes[41] and YKL-40 is strongly linked to same elements as MS,[13] morbid obesity,[46] DM type 2[47] and type 1 also.[48]

There were significantly increased SBP, DBP, TC, TG, and FBS in all cases ($P < 0.05$ each) Except TG in early onset male cases was highly significantly increased ($P < 0.001$) and significant decrease in HDL among early onset male and female cases ($P < 0.05$).

In males, the value of high-density lipoprotein in cases (48.43%) was lower and statistically very highly significant when compared to the controls. There was statistical significance increase in frequency of DM, HPT, and dyslipidemia among early onset AGA male cases.[49,50]

CONCLUSIONS

This work had found that YKL-40 may have a role in the pathogenesis of AGA by direct mechanisms and indirectly through associated MS. We have also demonstrated that not only serum level of YKL 40 is increased in AGA patients but also that its level may reflects the early onset, long duration, and association with MS components and their severity. YKL-40 is a promising sensitive biomarker for understanding the pathogenesis of AGA and detection of early cases. AGA may be seen in older ages due to many factors in pathogenesis, however in our study, we found increased YKL 40 and MS components and severity in younger AGA persons with short-time disease duration, these data may increase awareness of doctors about susceptible patients as minimal lifestyle alterations in young early AGA patients can decrease the risk of MS.

These results were based on a relatively small number of patients that was a major limitation of this study and we recommend doing the work in larger scale of patient.

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This were an authors' own work. Laboratory investigations were done in clinical pathology laboratory.

Conflicts of interest

There are no conflicts of interest.

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