International Journal of Psychosocial Rehabilitation, Vol. 24, Issue 10, 2020
ISSN: 1475-7192

The Clinical Value of Serum Progranulin level as a biomarker for retinopathy in type 2 diabetic patients

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ABSTRACT

Background: *The increasing prevalence of type 2 diabetes mellitus (T2DM) calls for evolving a concomitant screening strategies for early disease detection and prediction of the complications. Progranulin (PRGN) was recently introduced as a biomarker of inflammation in T2DM. The Aim of this study was to assessment the Serum progranulin level as a biomarker for the presence and severity of retinopathy in type 2 diabetic patients.* ***Patients and Methods:*** *The current cross-sectional study was carried out conducted on (48 type 2 diabetic patients) at the Internal Medicine and ophthalmology out-patient clinic of Zagazig University Hospitals, during the period from May 2019 to October 2019. All patient referred to ophthalmic out-patient clinic for fundal examination by ophthalmologist ,in which diabetic retinopathy was diagnosed, a complete physical examination including the measurement of height, weight, body mass index, and blood pressure (BP) was performed for all patients.* ***Results:*** *The current study showed that there was a high statistical significant increase in serum Progranulin (PGRN) level in diabetic patients with retinopathy, there was a statistical significant positive correlation between serum PGRN level with disease duration, urea, creatinine level and urinary Albumin creatinine Ratio (ACR) of studied retinopathy patients and also there was a high statistical significant increase in serum PGRN level in diabetic patients with proliferative retinopathy.* ***Conclusions:*** *According to our results serum PGRN level could be used as a biomarker for the presence of microvascular retinal complication and to anticipate the severity of diabetic retinopathy in T2DM patients.*

Keywords: *Progranulin, Retinopathy, Nephropathy, Type 2 Diabetic, biomarker*

I. INTRODUCTION

Diabetic microangiopathy is a typical diabetic complication with the main characters of basement membrane thickening. Diabetic microvascular complications mainly occurred in the retina, nephridium, myocardium, nervous tissue, and toe. Clinically, it was usually reflected by diabetic nephropathy (DN), diabetic

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retinopathy (DR), and diabetic peripheral neuropathy (DPN). Its pathogenesis and prevention research have drawn considerable attention in recent years, but it remains controversial [1].

Progranulin is an evolving molecule which has both pro and anti-inflammatory properties. It plays varied functions in different tissues, cells and metabolic conditions. Firstly, it was identified as a growth factor and was considered as a potential biomarker in cancer. Also, it was considered as an adipokine associated with obesity, glucose intolerance, insulin resistance [2].

Furthermore, serum PGRN level is usually low, being up regulated in the inflammatory state suggesting its involvement in chronic subclinical inflammation associated with the pathogenesis of diabetic micro angiopathy, and also, it correlated with changes in disease metrics over time which point to its potential use as a biomarker for disease occurrence and progression in several pathologies [3].

The widespread expression of PGRN can be found in adipose tissue, epithelial tissue, gastrointestinal tract, reproductive organs, and so forth, which is involved in cell growth and survival and inflammatory response. Full-length PGRN promotes cell growth and survival and has anti-inflammatory activity. However, proteolytic cleavage of PGRN generates granulin peptides (GRNs), some of which promote inflammation. PGRN is rapidly cleaved into GRNs in tissues by elastase and PR3 to enhance inflammation. In addition, it was also found that circulating PGRN levels are elevated in patients with type 2 diabetes. Moreover, increased serum PGRN levels are associated with impaired glucose tolerance rather than impaired fasting glucose [4].

PGRN could stimulate the adipocytes to release more IL-6 as the increased secretion of IL-6 (by TNF-α) was completely blocked by ablation of PGRN gene in 3T3-L1 adipose cells. Taking these results into consideration, PRGR is closely related to the proinflammatory state frequently seen in diabetic microangiopathy and may be considered as a biomarker for the chronic inflammatory response in diabetic microangiopathy [5].

Progranulin was recently introduced as a biomarker of inflammation in T2DM. However, little data have been published as regarding progranulin in relation to diabetic micro angiopathy among T2DM patients [6].

The Aim of this study was to assessment the Serum progranulin level as a biomarker for the presence and severity of retinopathy in type 2 diabetic patients.

II. SUBJECTS AND METHODS

The current cross-sectional study was conducted on (48 type 2 diabetic patients) admitted to the Internal Medicine and ophthalmology out-patient clinic of Zagazig University Hospitals, during the period from May 2019 to October 2019. Patients were defined according to American Diabetes Association (ADA) criteria [7] or if they were on anti-diabetic drugs.

The number of patients (48) represents the total number of patients fulfilled the criteria available in the department during the study period

Diabetic patients were further subdivided into 24 diabetic patients with Diabetic retinopathy (cases group), in addition to 24 diabetic patients without Diabetic retinopathy (control group)

inclusion criteria: (Age 40y-70y**,** DM type 2, Duration of DM more than four years and HbA1c 7%-11%)**.**

Exclusion criteria: Those with history of malignancy, diabetic macro vascular complications, other endocrine disease which affect glucose metabolism, liver disease, other causes of renal disease, inflammatory disease, infection, urinary tract infection, pregnancy, history of drug abuse and those with T1DM were excluded from that study.

All patients were subjected to

full history taking (history for the present and past illness, medication, age, sex, and diabetes duration were obtained, family history).

Physical examination [A complete physical examination including the measurement of height, weight, body mass index, and blood pressure was performed on each subject]

All patients were referred to ophthalmic out-patient clinic for fundal examination by ophthalmologist, in which diabetic retinopathy was diagnosed according to Classification of diabetic retinopathy and diabetic macular edema [8].

They were divided into two groups (after meeting inclusion criteria): Group (I): including 24 patients with diabetic retinopathy. Group (II): including 24 patients with no diabetic retinopathy as a control.

Laboratory investigations including : [fasting blood sugar (FBS) and 2 h post prandial blood sugar (PPG), Glycated hemoglobin **(**HbA1c), Kidney functions, including blood urea nitrogen (BUN) and creatinine, Urinary albumin creatinine, and serum progranulin, complete urine analysis.

Diabetic retinopathy was assessed by ophthalmologist and classified based on severity into three subgroups normal, non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) using fundus examination. NPDR was diagnosed based on one or more of the following features: micro aneurysms, intra retinal hemorrhages, hard and soft exudates, venous beading and intra retinal micro vascular abnormalities while, those without these abnormalities in the retina were categorized as normal diabetic retinopathy (NDR). On the other hand, PDR is considered if there was neovascularization, pre-retinal hemorrhages, vitreous hemorrhage, or pan retinal laser photo coagulation scars. The severity of DR in the worse affected eye was used for retinopathy grading. Some confusing cases were diagnosed through fundus fluorescein angiography (FFA) [9].

PGRN

The determination of serum PRGN was carried by enzyme linked immunosorbent assays (ELISA) according to the manufacturers' instructions (Human Progranulin ELISA Kit, KONO Biotech Co., Ltd.,China). Five milliliter of blood samples were collected from each participant in the study after an overnight fast and then centrifuged at 3000 g for 10 min and the separated serum was stored at −80 °C until they were analyzed. Sensitivity was 7.8 ng/mL for PGRN and the specificity of the immunosorbent assay was estimated to be 100%. Whereas the inter and intra assay coefficient of variation was less than 10% for serum samples and was done under internal quality control [10].

Procedure [11]

1. Prepare all reagents, standard solutions and samples as instructed. Bring all reagents to room temperature before use. The assay is performed at room temperature.

2. Determine the number of strips required for the assay. Insert the strips in the frames for use. The unused strips should be stored at 2-8°C.

3. Add 50µl standard to standard well.

1. Add 40µl sample to sample wells and then add 10µl anti-PGRN antibody to sample wells, then add 50µl streptavidin-HRP to sample wells and standard wells (Not blank control well）. Mix well. Cover the plate with a sealer. Incubate 60 minutes at 37°C.

2. Remove the sealer and wash the plate 5 times with wash buffer. Soak wells with at least 0.35 ml wash buffer for 30 seconds to 1 minute for each wash. For automated washing, aspirate all wells and wash 5 times with wash buffer, overfilling wells with wash buffer. Blot the plate onto paper towels or other absorbent material.

3. Add 50µl substrate solution A to each well and then add 50µl substrate solution B to each well. Incubate plate covered with a new sealer for 10 minutes at 37°C in the dark.

4. Add 50µl Stop Solution to each well, the blue color will change into yellow immediately.

5. Determine the optical density (OD value) of each well immediately using a microplate reader set to 450 nm within 30 min after adding the stop solution.

Test principle

- This kit was a Enzyme-Linked Immunosorbent Assay (ELISA).
- PGRN was added to the wells pre-coated with PGRN monoclonal antibody.
- After cubation a biotin-conjugated anti-human PGRN antibody was added and binds to human PGRN.
- After incubation unbound biotin-conjugated anti-human PGRN antibody was washed away during a washing step. Streptavidin-HRP was added and binds to the biotin-conjugated anti-human PGRN antibody.
- After incubation unbound Streptavidin-HRP was washed away during a washing step. Substrate solution was then added and color develops in proportion to the amount of human PGRN.
- The reaction was terminated by addition of acidic stop solution and absorbance is measured at 450 nm.

Reagent Provided

Standard Solution (800ng/ml)	0.5ml x1
Pre-coated ELISA Plate	12 * 8 well strips x1
Standard Diluent	3ml x1
Streptavidin-HRP	6ml x1
Stop Solution	6ml x1

Substrate Solution A	6ml x1
Substrate Solution B	6ml x1
Wash Buffer Concentrate (30x)	20ml x1
Biotin-Conjugate Anti-human PGRN Antibody	1ml x1
User Instruction	1
Plate Sealer	2 pics
Zipper bag	1

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

All clinical and demographic data was recorded on investigative report form. These data analyzed using SPSS version 20. Description of quantitative variables was given as mean, and Standard deviation (SD). Chi square test (χ^2 –test) was used to compare qualitative variables between groups. The t-test was used to compare quantitative variables in parametric data. We used Kolmogorov-Smirnov and Levene tests to determine the distribution characteristics of variables and variance homogeneity. Differences between quantitative independent groups by t test or Mann Whitney. P-value (level of significance): $p<0.05$= significant ; $P<0.001$= highly significant.

III. RESULTS

Table 1: baseline characteristics among the studied population

Variables	**Frequency**				**X^2**	**P-value**
	Cases=24 (with Retinopathy)		**Controls=24 (Without Retinopathy)**			
	N	**%**	**N**	**%**		
Sex						
Male	12	50	13	54.2	0.09	0.773
Female	12	50	11	45.8		NS
	Studied groups				t-test	**P-value**

	Cases=24 (with Retinopathy)	**Controls=24 (Without Retinopathy)**		
Age **(years)** Mean ±SD Range	**59.3 ± 5.9 (47-68)**	**51.2 ± 6.1 (40-62)**	**4.62**	<0.001 HS
Duration of diabetes (years) Mean ±SD Range	12.2 ± 4.29 7-20	7.4 ± 2.45 4-12	4.75	**<0.001 HS**
Weight (Kg) Mean ±SD Range	79.6 ± 10.99 (62-110)	82.3 ± 14.1 (64-130)	0.754	0.455 NS
Height (m) Mean ±SD Range	1.69 ± 0.1 1.59-1.78	1.68 ± 0.1 1.54-1.86	0.00	1.0 NS
BMI(Kg/m^2) Mean ±SD Range	28.2 3.8 23.7-40.4	29.1 ± 3.8 24.4-41.1	0.842	0.404 NS
SBP(mmHg) Mean ±SD Range	145.4 ± 14.4 120-170	132.7 ± 19.3 110-160	2.59	**0.01 S**
DBP(mmHg) Mean ±SD Range	88.3 ± 8.3 70-100	83.5 ± 10.2 70-100	1.79	**0.08 NS**
Drugs used				
Variables	**Frequency**		**X^2**	**P-value**

	Cases=24 (with Retinopathy)		**Controls=24 (Without Retinopathy)**			
	N	%	N	%		
Drugs used					**0.03***	**6.99**
OHD	**8**	**33.3**	**17**	**70.8**		
Insulin	**13**	**54.2**	**5**	**20.8**		
OHD + insulin	**3**	**12.5**	**2**	**8.4**		

NS: P-value>0.05 is not significant S: P-value<0.05 is significant

HS: P-value<0.001 is high significant

Table (1) showed that there was a high statistical significant difference among both studied diabetic cases with retinopathy and those without retinopathy regarding age (p-value<0.001), as retinopathy group were older than the other group with mean of 59.3 ± 5.9 years versus 51.2±6.1 years respectively. While both groups were matched as regard sex. Also, the duration of diabetes was statistically significant longer among cases with retinopathy than those without retinopathy with mean of 12.2 ± 4.29 versus 7.4 ± 2.45, also systolic blood pressure was significantly higher among cases with retinopathy. Also, there was 54.2% of retinopathy patients received insulin only as treatment and 33.3% received OHD, while 70.8% of patients without retinopathy medicated by OHD and only 20.8% on insulin, and the difference between both groups was statistically significant.

Table 2: laboratory data among the studied groups

Variables	**Studied groups**		**t-test**	**P-value**
	Cases=24 (with Retinopathy)	**Controls=24 (Without Retinopathy)**		
FBS (mg\dl)				
Mean ±SD	205.5 ± 38.6	169.2 ± 29.8	3.65	0.001
Range	150-280	128-240		HS
Hb A1C%				
Mean ±SD	8.99 ± 1.17	7.95 ± 0.87	3.54	0.001

Range	(7.2-11)	(7-10)		HS
Variables	**Studied groups**		**t-test\ MW***	**P-value**
	Cases=24 (with Retinopathy)	**Controls=24 (Without Retinopathy)**		
Urea (mg/dl)				
Mean ±SD	34.6 ± 8.55	24.8 ± 4.41	**5.03**	**<0.001**
Range	20-49	18-30		**HS**
Creatinine (mg/dl)				
Mean ±SD	0.96 ± 0.16	0.75 ± 0.19	**4.7**	**<0.001**
Range	(0.6-1.3)	(0.4-1.1)		**HS**
Urinary ACR(mg/gm)				
Mean ±SD	**308.4 ± 575.6**	**21.5 ± 17.2**	**2.7***	**0.007**
Range	**6.42-2159.8**	**6.22-81.97**		**S**
Variables	**Studied groups**		**MW**	**P-value**
	Cases=24 (with Retinopathy)	**Controls=24 (Without Retinopathy)**		
PGRN (µg/ml)				
Mean ±SD	95.3 ± 108.8	16.2 ± 5.9	2.69	0.007
Range	11.4-350.9	11.4-35		S

S: P-value<0.05 is significant **HS:** P-value<0.001 is high significant

Table (2) showed that both fasting blood sugar and glycated hemoglobin HbA1C was significantly higher among diabetic cases with retinopathy than those without retinopathy. All kidney function (urea, creatinine, ACR) measures were significantly higher among diabetic cases with retinopathy than those without retinopathy. Also, there was a high statistical significant increase in serum PGRN level among diabetic patients with retinopathy (ranged from 11.4 up to 350.9 µg/ml) than those without retinopathy, that presented with serum range of 11.4 up to 35 µg/ml only of PGRN.

Table 3: Relation between type of retinopathy with disease duration and physical examination of the studied cases

Variables	Studied cases (n=24)		t-test\ MW*	P-value
	PDR=10	NPDR=14		
Duration of diabetes				
Mean ±SD	14.2 ± 5.2	10.7 ± 2.9	1.71*	0.124
Range	8-20	7-16		NS
Weight (Kg)				
Mean ±SD	79.9 ± 13.8	79.4 ± 9.03	0.109	0.915
Range	62-110	70-100		NS
Height (m)				
Mean ±SD	1.7 ± 0.05	1.7 ± 0.1	0.106	0.917
Range	1.54-1.78	1.59-1.76		NS
BMI(kg/m²)				
Mean ±SD	28.3 4.8	28.1 ± 3.02	0.162	0.871
Range	24.6-40.4	23.7-31.7		NS
SBP(mmHg)				
Mean ±SD	146 ± 18.4	145 ± 11.6	0.164	0.871
Range	120-170	130-160		NS
DBP(mmHg)				
Mean ±SD	91 ± 7.7	86.4 ± 8.4	1.39	0.184
Range	80-100	70-100		NS
Variables	**Studied cases (n=24)**		**t-test**	**P-value**
	PDR=10	**NPDR=14**		
FBS(mg/dl)				
Mean ±SD	214.3 ± 43.5	199.2 ± 34.98	0.905	0.377

Range	160-280	150-279		NS
Hb A1C%				
Mean ±SD	9.2 ± 1.27	8.9 ± 1.12	0.666	0.514
Range	(7.4-11)	(7.2-11)		NS
Variables	**Studied cases (n=24)**		**MW**	**P-value**
	PDR=10	**NPDR=14**		
PGRN (µg/ml)				
Mean ±SD	188.7 ± 113.1	28.7 ± 23.9	4.69	0.001
Range	45.3-350.9	11.4-75.4		HS

NS: P-value>0.05 is not significant

Table (3) showed that there was no statistical significant relation between type of retinopathy and physical examinations of the studied cases, although the duration of diabetes was longer among cases with proliferative retinopathy (PDR) but without statistically significant difference between both groups. Also, showed that fasting blood sugar or glycated hemoglobin A1C, were higher among diabetic cases with proliferative retinopathy (PDR) than in (NPDR) but it had no statistically significant value. Also, their was a high statistical significant increase in serum PGRN level among diabetic patients with proliferative retinopathy ranged from 45.3 up to 350.9 µg/ml than those with non-proliferative retinopathy, that presented with serum range of 11.4 up to 75.4 µg/ml only of PGRN.

IV. DISCUSSION

Micro vascular complications of T2DM are associated with severe morbidity, mortality and a huge economic burden. So, there is an important need to identify new biomarker able to identify disease onset and progression and can be used as a therapeutic target for management of these complications. [10].

Progranulin is an evolving molecule which has both pro and anti-inflammatory properties. It plays varied functions in different tissues, cells and metabolic conditions. Firstly, it was identified as a growth factor and was considered as a potential biomarker in cancer. Also, it was considered as an adipokine associated with obesity, glucose intolerance, insulin resistance [2].

In the present study, there was a high statistically significant difference between both studied groups regarding age (p-value<0.001), which is nearly to the study of **Zaky et al. [5]** who found that there was a statistical significant difference among diabetic cases with retinopathy and those without retinopathy regarding age (p-value=0.032) while there was no significant difference regarding sex. But in contrast to our results the study of **Lin et al., [4],** who found that there was no statistical difference between the groups with regard to age

their studied groups. Also, **Albeltagy et al., [10]** concluded that there was no significant difference between both groups as regards age.

The current studies showed that there was a high statistical significant difference between studied groups regarding duration of diabetes (p value<0.001). This came in agreement with **Nicoletto et al. [12]** who found that the was a high statistical significant difference between their studied groups (p value <0.001). But our results were in contrast to the study of **Gouliopoulos et al., [13]** who concluded there was no statistical significant difference between both studied groups (diabetic cases with retinopathy and those without retinopathy) regarding duration of diabetes.

The present study, showed that there was no statistical significant difference between studied groups regarding BMI. This was in disagreement with study of **Mamdouh [14]** who found that there was a statistical significant difference regarding BMI index between studied groups. This difference could be contributed to the small sample size of our study.

The present study, showed that a statistical significant difference between studied groups regarding the systolic blood pressure (p value = 0.01). This came in agreement with **Paushter et al. [15]** who found a statistical significant difference between studied groups regarding systolic blood pressure (p value <0.03). But our results were in contrast to the study of **Nicoletto and Canani [12]** who concluded there was no statistical significant difference between studied groups regarding systolic blood pressure.

In the present study, there was a high statistical significant difference between studied groups regarding fasting blood sugar and glycated hemoglobin A1C (p value = 0.001). This came in agreement with **Jian et al. [16]** who found a similar results (p value <0.001).

In the current study, there was a high statistical significant difference between studied groups regarding urea and creatinine (P**<0.001)**, while there was a statistical significant difference between studied groups regarding urinary ACR (P= **0.007**).

But the study of **Zaky et al. [5]** showed that there was a high statistical significant difference between studied groups regarding urinary ACR (p value <0.001).

In the present study, there was a statistical significant difference between studied groups regarding serum PGRN level (p = 0.007). This is in agreement with **Ezz and Abd El A zeem [2]** study which reported that serum PRGN concentrations were elevated in type 2 diabetic patients compared to those of healthy control group and that increase was augmented in patients with nephropathy. Similar to other study of **Shafaei et al., [3],** serum progranulin levels showed no statistically significant difference between different genders among diabetic group which indicate that, there was no impact of sexon serum PRGN levels.

in agreement with our study, **Albeltagy et al.[10]** found statistically significant increase in the mean serum progranulin levels in diabetic patients compared to healthy controls. Moreover, serum PRGN levels were significantly elevated in type 2 diabetic patients with micro vascular complications and in those without complications than in control subjects, with the highest levels among diabetic patients with microvascular complications

In contrary to our results, **Mamdouh, [14],** found that there was no statistical significant difference between studied groups regarding serum PGRN level ($P > 0.5$).

In the present study, there was positive correlation between serum PGRN level with FBS and HbA1c but not significant. While **Lin et al. [4]** reported that there was no remarkable correlation was found between PGRN and FBS, HbA1c.

On the other hand, this came in disagreement with **Li et al. [17] and Qu et al. [18]** whom found that there was a significant positive correlation between PGRN and parameter of glucose metabolism namely Hb A1C, fasting plasma glucose in DM patients.

In the present study, there was statistically significant positive correlation between serum PGRN level with duration of diabetes. This came in agreement with **Colhoun and Marcovecchio [19]** who reported significant positive correlation of PGRN with duration of DM.

Albeltagy et al. [10] and **Lin et al. [4]** both found that there was a highly significant positive correlation between serum PGRN and disease duration,.

In the current study, there was highly significant positive correlation between serum PGRN level with kidney function tests(s.Cr, urea and ACR) (p value = 0.003) between studied groups. This agree with **Shafaei et al. [3]** who found there was positive correlation between progranulin and other renal parameters (sCr, urea and ACR).

Also, this was in consistency with **Lin et al. [4]** study that showed that there was a significant positive correlation between serum PGRN and sCr.

In the current study, there was a statistical significant difference between studied groups regarding urea. Which in agreement with the study of **Lin et al. [4] who** found that there was **a** statistical significant difference between both groups regarding urea.

In the present study, there was no statistical significant difference between studied groups regarding creatinine. Which in disagreement with the study of **Shafaei et al. [3]** wh**o** found that there was **a** statistical significant difference between both groups regarding creatinine.

V. Conclusion:

According to our results serum PGRN level could be used as a biomarker for the presence of microvascular retinal complication and to anticipate the severity of diabetic retinopathy in T2DM patients.

Recommendations: Further studies are needed to understand the exact mechanisms underlying the increase of progranulin in patients with diabetic micro angiopathy and further studies using larger populations and longer duration will be needed to confirm our observations and to validate the current findings .

Abbreviations:

T2DM: Type 2 diabetes mellitus; BP : blood pressure; PGRN: Progranulin; ACR : Albumin creatinine Ratio; DN : diabetic nephropathy; DR : Diabetic retinopathy; DPN: diabetic peripheral neuropathy; GRNs:

granulin peptides; FBS : fasting blood sugar; PPG: post prandial blood sugar; HbA1c : Glycated hemoglobin; BUN: blood urea nitrogen; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; NDR: normal Diabetic retinopathy; FFA: fundus fluorescein angiography; ELISA : enzyme linked immunosorbent assays; BMI: body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; OHD: Oral hypoglycemic drugs.

Declarations

-Ethics approval and consent to participate

A written informed consent was taken from all participants after explaining details and benefits as well as risks to them. The ethical committee of Faculty of Medicine, Zagazig University, approved this study. The ethics committee's reference number is ZU-IRB# 4995-18-11-2018

-Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests.

-Funding

No financial disclosure

-Authors' contributions

YSS, NRA; IMW and IAH collected patients' samples and clinical data. IAH prepared sample for laboratory investigations and wrote the paper. Statistical analysis, interpretation of data, and preparation the paper for submitting international was done by YSS. Critical revision of the manuscript was performed by all of the authors. All authors have read and approved the final manuscript.

-Acknowledgements

Not applicable

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