

Polymorphism of XRCC1 Arg³⁹⁹Gln may predict for development of end-stage renal disease. A PCR confirmed case-control study

Dalia M. Abd EL-Hassib^a, Magda A. Zidan^a, Medhat M. El Amawy^b, Hind A. Hegazy^a, Seham Gouda Ameen^{a,*}

^a Clinical and Chemical Pathology Department Faculty of Medicine, Benha University, Egypt

^b Internal Medicine Department Faculty of Medicine, Benha University, Egypt

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ABSTRACT

Objectives: Evaluation of the frequency of X-ray Cross Complementing group 1 (XRCC1) Arg³⁹⁹Gln polymorphism among patients with end-stage renal disease (ESRD) patients and to determine if a possible association was present.

Subjects & methods: Blood samples were obtained from 70 ESRD patients and 30 healthy volunteers as control group for routine laboratory investigations and genomic DNA was extracted using GeneJET Whole Blood DNA Purification Kit to detect XRCC1 codon 399 genotype Arg/Gln in exon 10. BCNL digestion resulted in two fragments of 389 and 121 bp for wild-type homozygous (Arg/Arg); one fragment of 510 bp for variant homozygous (Gln/Gln); and three fragments of 510, 389 and 121 bp for variant heterozygous (Arg/Gln).

Results: Compared to control subjects, ESRD patients showed significantly higher frequency of Arg/Gln genotype, but had significantly lower frequency of Arg/Arg genotype. Moreover, patients had significantly lower frequency of Arg allele in comparison to controls (57.1% vs. 83.3%, respectively). Furthermore, the frequency of recessive models; Gln/Gln + Arg/Gln was significantly higher, while the frequency of dominant models; Arg/Arg + Arg/Gln was non-significantly lower among patients than controls. Development of ESRD was positively correlated with the presence of XRCC1 Arg/Gln genotype, while was negatively correlated with the presence of XRCC1 Arg/Arg genotype. ROC curve analysis showed that presence of XRCC1 Arg/Arg genotype is a negative sensitive predictor, while XRCC1 Arg/Gln genotype is a positive significant predictor for development of ESRD and Regression analysis defined presence of XRCC1 Arg/Arg genotype as significant negative predictor for development of ESRD.

Conclusion: The results of the current study indicated an intimate relation between XRCC1 gene polymorphism and development of ESRD and the predictive value of its presence for the possibility of progression of chronic kidney disease to ESRD stage.

1. Introduction

Chronic kidney disease (CKD) is a serious worldwide public health problem and in Egypt, CKD and related traits is responsible for about 3.98% of all deaths (Ghazaly et al., 2020). CKD is defined as kidney damage causing an estimated glomerular filtration rate (eGFR) of <60 ml/min/1.73 m² persisting for at least 3 months, irrespective of the cause (Vaidya and Aeddula, 2020).

Increased production of reactive oxygen species can negatively affect the structure and function of the kidney through induction of

endothelial cell dysfunction, deposition of extracellular matrix, mesangial cell injury, dysfunction of the podocytes with increased transforming growth factor β and cellular apoptosis (Yanowsky-Escatell et al., 2020). Patients had CKD were found to have elevated levels of genomic damage which is inversely related to kidney function (Corredor et al., 2017).

Genetic factors and oxidative stress could play critical role in the progression of CKD to and the development of end-stage renal disease (ESRD) (Nomani et al., 2018). These effects of genetic factors showed widespread distributions and ethnicity relation, but no sex or age is

* Corresponding author.

E-mail addresses: dalia.ahmed@fmed.bu.edu.eg (D.M. Abd EL-Hassib), magda.mustafa@fmed.bu.edu.eg (M.A. Zidan), m.elamawy@fmed.bu.edu.eg (M.M. El Amawy), reem170186@fmed.bu.edu.eg (H.A. Hegazy), SEHAM.AMEEN@fmed.bu.edu.eg (S.G. Ameen).

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exempted (Gandhi et al., 2018). In African ethnicity, variants in the APO11, apoE, eNOS, XPD, XRCC1, renalase, ADIPOQ, and CCR2 genes were associated with CKD or other related traits (George et al., 2018). In Iranian population, G allele of chemerin rs17173608 decreased the risk of ESRD than T allele (Nomani et al., 2018). In children, there is significantly high frequency of the A allele of the G³⁹⁵A Klotho gene especially among children with CKD and those with CVD and LVH, and could be used as a risk marker for ESRD development (Elghoroury et al., 2018). In the Korean population, single nucleotide polymorphisms in genes of epidermal growth factor and its receptor was associated with ESRD risk (Kim et al., 2020).

Increased oxidative stress induces DNA damage that is repaired by excision repair pathways principally through base excision repair (BER) mechanisms (Ma et al., 2020). BER is a central DNA repair mechanism responsible for the maintenance of genome integrity and tight adaptation of BER capacity is essential for DNA stability (Clementi et al., 2020). Prolonged cellular exposure to DNA-damaging agents induces BER deficiency by down-regulating the central scaffold protein; X-ray repair cross-complementing gene 1 (XRCC1) (Chauhan and Michalak, 2020).

The XRCC1 is a DNA repair enzyme that plays a crucial role in BER pathway by generating a single nucleotide repair patch (Zeng et al., 2013). The XRCC1 is a 31.9 kb length gene which is located on chromosome 19q13.2–3 (Yin et al., 2012) and encodes for a protein works as scaffold by interacting with key enzymes of BER because it has no catalytic activity in itself (Zeng et al., 2013). This XRCC1 protein acts through upregulating the expression of the BER gene apurinic/apyrimidinic endonuclease 1 and functions in a complex with DNA polymerase- β , DNA ligase III and poly ADP-ribose polymerase to facilitate the repair of damaged bases (Batar et al., 2016). The XRCC1 has five non-synonymous and synonymous variants of XRCC1 (Singh et al., 2016). The XRCC1 genotype Arg³⁹⁹Gln has been shown to change neoconservative amino acid and thus result in alternation of DNA repair capacity (Bu et al., 2014), while XRCC1 Gln⁶³²Gln showed positive association with lung cancer (Singh et al., 2016).

1.1. Objectives

This study targets to evaluate the frequency of XRCC1 Arg³⁹⁹Gln polymorphism among a sample of Egyptian ESRD patients and to determine if a possible association was present.

1.2. Setting

Departments of Clinical & Chemical Pathology and Internal Medicine [Nephrology Unit], Faculty of Medicine, Benha University.

1.3. Design

Prospective Case-control comparative study.

2. Subjects & methods

The current study was conducted after approval of the Local Ethical Committee of the study protocol since May 2019 till Feb 2020. The study targeted to collect blood samples from 70 ESRD patients who were maintained on regular hemodialysis at Internal Medicine Department [Nephrology Unit], Benha University for at least 6 months (Vaidya and Aeddula, 2020). For comparative purpose, blood samples were obtained from 30 healthy volunteers of cross-matched age and sex with enrolled patients and were chosen from subjects attending Blood Bank at Benha University Hospital for blood donation after passing pre-donation clinical and laboratory investigations.

The sample size was calculated using Gpower software, with minor allele frequency in the first group was 0.429 and in the second group was 0.167, at alpha of 0.05, sample size of one group was 30 and the second group was 70, the achieved power will be 75%, that could be accepted,

and was applicable to our financial aids.

2.1. Data collection

Patients and controls' data were collected; demographic data included age, sex and body mass index (BMI) that was defined as weight in kilograms divided by the square of the height in meters (Bray, 1992). Patients were graded according to the international classification of BMI (WHO, 1995) into: underweight (BMI < 18.5 kg/m²); normal weight range (BMI = 18.5–24.99 kg/m²); overweight (BMI = 25–29.99 kg/m²); Obese (BMI > 30 kg/m²). Medical history was obtained with special regard to family history of CKD and/or ESRD. Socioeconomic status was graduated according to the principle of 5-class as lower, working, middle, upper-middle and upper classes. Education categories included no formal schooling, primary school, high school incomplete or graduate, vocational school, university graduate and post-graduate (Quon and McGrath, 2015). Occupational status was graded as not working, domestic service, manual work, self-employed farmer, technical or managerial.

2.2. Blood sampling & investigations

An 8-ml peripheral venous blood sample was obtained by venipuncture under complete aseptic conditions. Blood samples were collected and numbered by a lab assistant and were divided as follows:

1. 2-ml of whole blood was put in a tube containing sodium fluoride (2 mg sodium fluoride/ ml blood) to prevent glycolysis for estimation of blood glucose levels using glucose oxidase method (Tinder, 1969).
2. 2-ml of whole blood was put in EDTA tube (about 1.8 mg triK EDTA/ 1 ml blood) for hemoglobin estimation (Dacie and Lewis, 1984).
3. 2-ml of whole blood was put in a plain tube and serum was separated for colorimetric estimation of serum levels of serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (Huang et al., 2006), urea (Weatherbum, 1967) and creatinine (Jaffe, 1886) and eGFR was calculated according to serum creatinine levels.
4. 2-ml of whole blood was stored, as whole blood, immediately after collection at 20 °C until use. Genomic DNA was extracted using GeneJET Whole Blood DNA Purification Kit (Thermo Fisher scientific) according to the manufacturer's instructions. XRCC1 codon 399 genotype was detected using a PCR-RFLP method. An Arg/Gln in exon 10 (codon 399) were amplified to form an undigested fragment of 510 bp, using the following primers 5'-ACCTTGCTTTTCTGTGTC-3' (forward) and 5'-TAGTCTGCTGGCTCTGGGCT-3' (reverse) as described by Radwan et al. (Radwan et al., 2015). PCR cycles included heating up to 94 °C for 3 min, followed by 30 cycles of heating to 94 °C for 30 s, 56 °C for 60 s min, 72 °C for 45 s and a final extension step at 72 °C for 10 min. Then, the 510 bp PCR products were digested with FastDigest BcnI enzyme (Thermo Scientific) at 37 °C for 5 min and analyzed on 1% agarose gel. BcnI digestion resulted in two fragments of 389 and 121 bp for wild-type homozygous (Arg/Arg); one fragment of 510 bp for variant homozygous (Gln/Gln); and three fragments of 510, 389 and 121 bp for variant heterozygous (Arg/Gln) as shown in Fig. 1.

2.3. Study outcomes

1. The primary outcome is the presence of XRCC1 gene polymorphism in study subjects
2. The secondary outcomes include:
 - a. The frequency of Arg/Arg, Arg/Gln and Gln/Gln genotypes in study subjects
 - b. The results of statistical analyses for possible relationships and predictivity of these genotypes with ESRD

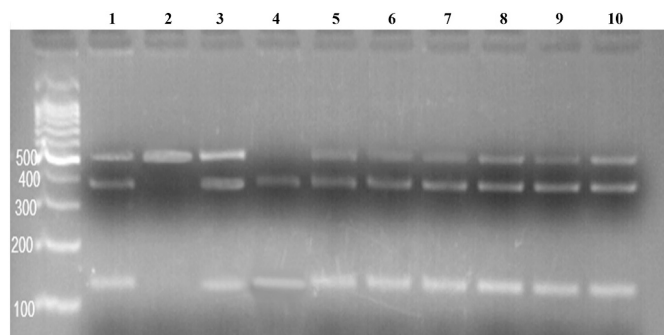


Fig. 1. Gel electrophoresis of XRCC1(Arg399Gln) gene polymorphism shows homozygous wild Arg/Arg genotype as two bands at 389 and 121 bp [lane 4], homozygous variant Gln/Gln genotype as one band at 510 bp [lane 2] and heterozygous variant Arg/Gln genotype as three bands at 510, 389 & 121 bp [lane 1, 3, 5, 6, 7, 8, 9, 10].

2.4. Statistical analysis

Obtained data were presented as mean \pm SD, numbers and percentages. Results were analyzed using paired *t*-test, One-way ANOVA Test and Chi-square test (X^2 test). Possible relationships were investigated using Pearson's correlation analysis. Regression analysis (Stepwise method) was used for stratification of studied parameters as specific predictors. Sensitivity & specificity of studied parameters as predictors for patients' outcome were evaluated using the receiver operating characteristic (ROC) curve analysis judged by the area under the curve (AUC) that was compared versus null hypothesis that AUC = 0.5. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015; IBM, South Wacker Drive, Chicago, USA) for Windows statistical package. *P* value <0.05 was considered statistically significant.

3. Results

Seventy ESRD patients were included as study group and 30 cross-matched volunteers were enrolled as control group. The frequency of patients had family history of CKD or ESRD was significantly ($p = 0.0225$) higher in comparison to the control group. Demographic and socioeconomic data of patients and controls showed non-significant differences as shown in Table 1.

Routine laboratory investigations detected significantly lower hemoglobin concentration and serum albumin with significantly higher fasting blood glucose, and serum urea and creatinine in patients' samples in comparison to control samples. However, serum AST and ALT levels were non-significantly higher in patients than in controls. Estimated GFR was significantly lower in patients than controls.

The frequency of detected Arg/Gln genotype was significantly ($p = 0.000086$) higher, while the frequency of detected Arg/Arg was significantly ($p = 0.000014$) lower among patients in comparison to controls. On contrary, the frequency of detected Gln/Gln genotype was non-significantly ($p = 0.372$) higher among patients than controls. There was significantly ($p = 0.00045$) lower Arg allele frequency among patients in comparison to controls (57.1% vs. 83.3%, respectively). However, the frequency of recessive models; Gln/Gln + Arg/Gln was significantly ($p = 0.00001$) higher, while the frequency of dominant models; Arg/Arg + Arg/Gln was non-significantly ($p = 0.0552$) lower among patients than controls (Table 2, Fig. 2).

Spearman's correlation analysis showed that the development of ESRD was positively correlated with the presence of family history of CKD and the presence of XRCC1 Arg/Gln genotype, while was negatively correlated with the SES and type of work and with the presence of XRCC1 Arg/Arg genotype. ROC curve analysis of the significantly correlated variables excluded type of work as predictor for ESRD development, while showed that presence of XRCC1 Arg/Arg genotype

Table 1

Demographic and socioeconomic data of study subjects.

Variables		Control group (n = 30)	Patients group (n = 70)	P value
Age (years)	<40	3 (10%)	4 (5.7%)	0.743
	40–60	23 (76.7%)	56 (80%)	
	>60	4 (13.3%)	10 (14.3%)	
	Mean	51.5 \pm 7.6	54.1 \pm 6.2	
Weight (kg)		83.4 \pm 7.4	81.3 \pm 6.6	0.165
Height (cm)		170.2 \pm 3.5	169.1 \pm 2.9	0.107
BMI (kg/m ²)	Grade			0.772
	Average	2 (6.7%)	4 (5.7%)	
	Overweight	25 (83.3%)	61 (87.2%)	
Mean	Obese	3 (10%)	5 (7.1%)	0.523
		28.7 \pm 1.9	28.4 \pm 1.8	
Educational status	No formal	3 (10%)	10 (14.3%)	0.648
	1ry school	2 (6.7%)	12 (17.1%)	
	Incomplete high school	4 (13.3%)	12 (17.1%)	
	High school graduate	7 (23.3%)	10 (14.3%)	
	Vocational school	6 (20%)	11 (15.7%)	
	University graduate	7 (23.3%)	13 (18.6%)	
	Post graduate	1 (3.3%)	3 (2.9%)	
Socioeconomic status	Lower	5 (16.7%)	24 (34.3%)	0.341
	Working	7 (23.3%)	16 (22.9%)	
	Middle	7 (23.3%)	14 (20%)	
	Upper-middle	9 (30%)	11 (15.7%)	
Occupational status	Upper	2 (6.7%)	5 (7.1%)	0.235
	Not working	2 (6.7%)	13 (18.6%)	
	Domestic service	4 (13.3%)	18 (25.7%)	
	Manual work	11 (36.7%)	17 (24.3%)	
	Farmer	7 (23.3%)	13 (18.6%)	
	Technical	3 (10%)	5 (7.1%)	
Family history of CKD	Managerial	3 (10%)	4 (5.7%)	0.0225
	Yes	2 (6.6%)	21 (30%)	
	No	28 (93.4%)	49 (70%)	

Data are shown as number, percentages, mean, standard deviation; BMI: Body mass index; CKD: Chronic kidney disease; P indicates significance of differences between both groups; $P < 0.05$ indicates significant difference; $P > 0.05$ indicates non-significant difference.

Table 2

Genotype and frequency of each allele of XRCC1 Arg399Gln gene polymorphism of study subjects.

Group variables		Control (n = 30)		Study (n = 70)	
		N	%	N	%
Allele frequency	Gln	10	16.7	60	42.9
	Arg	50	83.3	80	57.1
Hardy Weinberg p value		0.125		0.018	

is a negative sensitive predictor, while low SES and presence of family history of ESRD and/or XRCC1 Arg/Gln genotype as positive significant predictors for development of ESRD (Fig. 3). Regression analysis of these significant predictors defined presence of family history of ESRD as significant positive and presence of XRCC1 Arg/Arg genotype as significant negative predictors for development of ESRD (Table 3).

4. Discussion

ESRD patients had significantly higher frequency of Arg/Gln genotype, but significantly lower frequency of Arg/Arg in comparison to control subjects. Moreover, the frequency of Arg allele was significantly lower with non-significantly lower frequency of dominant models; Arg/Arg + Arg/Gln, while the frequency of recessive models; Gln/Gln + Arg/Gln was significantly higher among patients than control subjects. These findings indicated a possible causal/effect relationship between

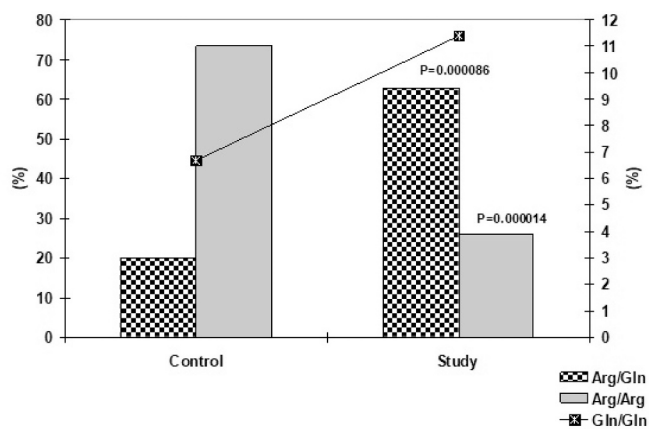


Fig. 2. Distribution of study population according to the detected XRCC1 genotype.

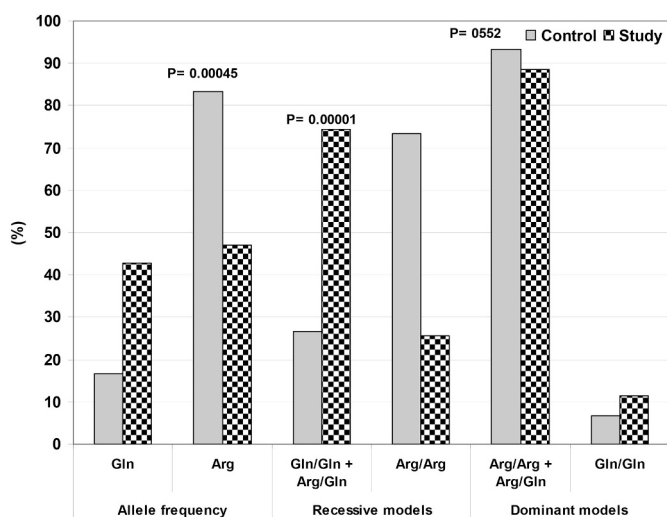


Fig. 3. Frequency of alleles and models among patients and controls.

genotype of X-ray Cross Complementing group 1 (XRCC1) gene and development of ESRD and a possible protective role Arg/Arg genotype of XRCC1 gene against development or progression of CKD to ESRD stage.

These results supported that previously reported by Trabulus et al. (Trabulus et al., 2012) who detected significantly higher frequency of the XRCC1 399-Gln allele in patients with ESRD than in controls and found patients had XRCC1 399-Arg/Gln or 399-Gln/Gln genotype had significantly higher risk of ESRD than those with 399-Arg/Arg genotype.

Table 3

Statistical analysis of demographic and socioeconomic variables, and XRCC1 genotypes as predictors for development of ESRD.

Statistical method variable	Spearman's correlation		ROC curve analysis			Regression analysis	
	Rho	p	AUC (SE)	P	95% CI	β	P
Age	0.166	0.098	Excluded				
BMI	0.140	0.163	Excluded				
Family history of CKD	0.230	0.021	0.369 (0.060)	0.039	0.251–0.487	0.231	0.010
Education level	-0.137	0.175	Excluded				
Socioeconomic status	-0.214	0.033	0.375 (0.059)	0.049	0.261–0.490	Excluded	
Type of work	-0.202	0.044	0.602 (0.058)	0.106	0.488–0.717	Excluded	
Gln/Gln genotype	0.073	0.472	Excluded				
Arg/Arg genotype	-0.445	<0.001	0.262 (0.056)	<0.001	0.153–0.371	-0.456	<0.001
Arg/Gln genotype	0.393	<0.001	0.714 (0.055)	0.001	0.606–0.822	Excluded	

Rho: Spearman's correlation coefficient; ROC curve analysis: Receiver operating characteristic curve analysis; AUC: Area under curve; SE: Standard error; CI: Confidence interval; β: Standardized coefficient; BMI: Body mass index; CDK: Chronic kidney disease; P indicates significance of result; $P < 0.05$ indicates significant value; $P > 0.05$ indicates non-significant value.

Also, Radwan et al. (Radwan et al., 2015) detected significantly higher frequency of the XRCC1 399Gln allele and found the association of Gln allele of XRCC1 Arg399Gln polymorphism with the Asn allele of XPDAsp312Asn polymorphism or with the Gln allele of XPD Lys751Gln polymorphism was highly significantly associated with ESRD development.

Thereafter, Yesil-Devecioglu et al. (Yesil-Devecioglu et al., 2019) found polymorphic Gln allele of XRCC1 gene was significantly related with type-2 diabetes mellitus (T2DM) and diabetic nephropathy especially XRCC1 399Gln polymorphism that was found to related with an increased susceptibility to T2DM and diabetic nephropathy.

Recently, Corredor et al. (Corredor et al., 2020a) showed significant associations between genomic damage and genes XRCC1, and ERCC2, which are directly involved in DNA repair pathways. Moreover, Corredor et al. (Corredor et al., 2020b) through another works found that different genes were association with biochemical parameters characteristic for CKD, such as C-reactive protein level that was associated with XRCC1 gene polymorphism.

Statistical analyses of the obtained results showed that development of ESRD was positively correlated with the presence of XRCC1 Arg/Gln genotype, while was negatively correlated with the presence of XRCC1 Arg/Arg genotype, ROC curve analysis showed that presence of XRCC1 Arg/Arg genotype is a negative sensitive predictor, while XRCC1 Arg/Gln genotype is a positive significant predictor for development of ESRD and Regression analysis defined presence of XRCC1 Arg/Arg genotype as significant negative predictor for development of ESRD. These results indicated the intimate relation between XRCC1 gene polymorphism and development of ESRD and the predictive value of its presence for the possibility of progression of CKD to ESRD stage. In line with these data, George et al. (George et al., 2018) investigated the association between CKD, ESRD or related traits and 30 polymorphisms in 11 genes and found variants in the XRCC1 genes were associated with CKD or other related traits. Also, Corredor et al. (Corredor et al., 2020a) concluded that genomic instability can be considered as biomarker of the CKD status.

The reported association between XRCC1 gene polymorphism and progression of CKD to ESRD could be attributed to the effect of oxidative stress as evidenced by the reciprocal relationship between oxidative stress and kidney disease where oxidative stress was shown to be enhanced in patients with ESRD with increased production of ROS that induces DNA damage and affects DNA damage repair pathways (Zouridakis et al., 2016; Tanaka et al., 2016) and on the other side, oxidative stress with increased production of reactive oxygen species (ROS) were found to be the main cause of the progression of CKD into ESRD (Wei et al., 2020). Meanwhile, protein product of XRCC1 gene has distinct roles for genome integrity in oxidative stress through ATR-Chk1 DNA damage response pathway (Cupello et al., 2019), so impaired XRCC1 activity secondary to gene polymorphism allows unantagonized effects of oxidative stress on the vulnerable chronically diseased kidney leading

to rapid progression into ESRD stage.

5. Conclusion

The results of the current study suggested a strong relation between XRCC1 gene polymorphism and development of ESRD and the predictive value of its presence for the possibility of progression of chronic kidney disease to ESRD stage.

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Ethics approval and consent to participate

All patients gave their written informed consent. Proteomic analyses were approved by the local ethical committee of Benha Faculty of Medical.

Availability of data and materials

Not applicable

Authors' contributions

MZ designed the study and analyzed the data. DN contributed to the design and implementation of the research, to the analysis of the results. ME contributed to sample preparation and worked on the manuscript. HH aided in interpreting the results. SA aided in interpreting the results, contributed to the final version of the manuscript, and wrote the manuscript. All authors discussed the results and commented on the manuscript.

Declaration of Competing Interest

The authors declare that they have no competing interests.

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