

## RESEARCH ARTICLE

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# Effect of XPD and TP53 Gene Polymorphisms on the Risk of Platinum-Based Chemotherapy Induced Toxicity in Bangladeshi Lung Cancer Patients

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## Abstract

**Background:** Platinum-based drugs, including cisplatin and carboplatin, are the most active and extensively used agents for treating lung cancer. Genetic polymorphisms of DNA repair gene XPD and tumor suppressor gene TP53 are connected with alterations in enzyme activity. They may help explain interindividual differences in toxicity outcomes after platinum-based chemotherapy for lung cancer. Therefore, this study aimed to investigate XPD Lys751Gln and TP53 Arg72Pro polymorphisms on the risk of platinum-based chemotherapy-induced toxicity in lung cancer patients in the Bangladeshi population. **Patients and Methods:** Study subjects comprised of 180 platinum-based chemotherapy treated histologically confirmed lung cancer patients. Genetic polymorphisms of XPD were ascertained by Polymerase Chain Reaction-based Restriction Fragment Length Polymorphism (PCR-RFLP), while TP53 genotypes were analyzed using the multiplex PCR-based method. Toxicity was assessed based on the Common Terminology Criteria for Adverse Events (CTCAE v5.0). **Results:** From the results, there was no significant association observed between grade 1-2 or grade 3-4 platinum-based chemotherapy induced toxicities like anemia and XPD codon 751 (Lys/Gln: OR=1.40, 95% CI=0.75-2.64,  $p>0.05$ ; Gln/Gln: OR=1.07, 95% CI=0.45-2.52,  $p>0.05$  and Lys/Gln+Gln/Gln: OR=1.31, 95% CI=0.73-2.38,  $p>0.05$ ) or TP53 codon 72 genetic polymorphisms (Arg/Pro: OR=0.64, 95% CI=0.34-1.17,  $p>0.05$ ; Pro/Pro: OR=0.46, 95% CI=0.15-1.42,  $p>0.05$  and Arg/Pro+Pro/Pro: OR=0.62, 95% CI=0.34-1.15,  $p>0.05$ ). Similar results were found between neutropenia, leukopenia, thrombocytopenia and gastrointestinal toxicities and XPD Lys751Gln or TP53 Arg72Pro genetic polymorphisms. **Conclusion:** These findings indicated that no significant association was found between either XPD codon 751 or TP53 codon 72 genetic polymorphisms and platinum-based chemotherapy-related toxicities in Bangladeshi lung cancer patients.

**Keywords:** Lung cancer- XPD- TP53- genetic polymorphism- platinum-based chemotherapy

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## Introduction

Lung cancer has become one of the cancers with high morbidity and mortality, and its global incidence is rising year by year. A relatively high incidence of lung cancer is observed in the Bangladeshi population, where it is the most prevalent cancer in males considering an incidence rate of 14.2% (Sung et al., 2021). In Bangladesh, the estimated lung cancer patients were found to be 196,000, and among them, 85% are aged 30 years or above (Hussain and Sullivan, 2013). Following the data published by the World Health Organization in 2017, lung cancer deaths in Bangladesh rise to 12,075 or 1.53% of total deaths (WHO, 2017). According to the GLOBOCON 2020 report, there were 12,999 (8.3%) new lung cancer cases in Bangladesh in 2020, considering both sexes and all ages (Sung et al., 2021).

Lung cancer treatment relies on cancer's specific cell type, the extent of spread, and the person's performance status. Platinum-based chemotherapy is widely accepted as a first-line treatment for patients with locally advanced non-small-cell lung cancer (NSCLC), where radiotherapy cannot be used for treatment and in those with non-small-cell lung cancer at the metastatic stage with good performance status. The platinum compounds mostly applied in NSCLC are cisplatin and carboplatin. Numerous randomized clinical trials along with meta-analyses have proved the supremacy of platinum-based over non-platinum-based therapy (Pujol et al., 2006; D'Addario et al., 2005). Some agents, paclitaxel, docetaxel, gemcitabine, and vinorelbine, have been included in platinum-based therapy doublets and have been confirmed to be equally important efficient. Unfortunately, after treatment, survival rates for patients are still low at

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only 29% (NSCLC Meta-Analyses Collaborative Group, 2008). However, the prime obstacle to effective treatment with cisplatin, carboplatin, and other platinum agents is the occurrence of chemoresistance and various associated toxicities that restrict these agents from gaining their full potential (Hildebrandt et al., 2009).

Platinum-based therapies are related to significant increases in several toxicities and nausea and vomiting. Platinum-induced anemia can be occurred due to various factors, such as early reduction in hemoglobin level after treatment, old age, cumulative platinum dose, inability to respond to chemotherapy, and following administration accumulation of the high amount of residual platinum in the bloodstream (Clarke and Pallister, 2005; Pivot et al., 2000). Cisplatin-associated toxicities vary from mild to severe, with nephrotoxicity and peripheral neurotoxicity considered the most severe. For carboplatin, hematological toxicity is dose-limiting, with thrombocytopenia being a more prominent problem than leucopenia. Even though carboplatin is non-toxic to the kidney, renal function considerably alters the carboplatin-induced thrombocytopenia severity (Glezerman and Jaimes, 2016).

Several polymorphisms have been reported as crucial for the function and metabolism of platinum drugs; most of them frequently occur in DNA repair genes. Genetic polymorphisms in these pathways are associated with multiple toxicity effects and are considered predictive tools for the pretreatment assessment of platinum-containing chemotherapy toxicities. Xeroderma pigmentosum complementary group D (XPD/ERCC2) has an ATP-dependent DNA helicase activity involved in NER (Nucleotide Excision Repair) as well as in basal transcription being a part of the transcription factor IIIH. Polymorphisms in XPD alter DNA repair and are associated with chemotherapy resistance, survival, and cancer appearance (Benhamou and Sarasin, 2002; Giovannetti et al., 2011). XPD Lys751Gln polymorphism can modify the total DNA repair efficacy and participate in removing platinum–DNA adducts, which can underpin the antitumor potential of platinum drugs if persist (Jung and Lippard, 2007).

The p53 protein, in comparison to the DNA repair proteins, does not appear to influence cisplatin transformation or metabolism directly. Nevertheless, it plays a significant task in mediating the cellular responses to DNA damage (Jung and Lippard, 2007). The Arg72Pro polymorphism is being located in the proline-rich region of p53, where the replacement of Arg with Pro may directly modulate the presumed SH3-binding domain structure. In addition, the Arg72 protein is more effective in apoptosis function, while the Pro72 form initiates more G1 arrest and is much superior at mediating p53-dependent DNA restore (Bojesen and Nordestgaard, 2008).

Nevertheless, the application of genotypic analysis of XPD and TP53 genes as a predictor of clinical outcome to platinum-based treatments remains controversial, and additional studies are needed. Therefore, the present study was carried out to evaluate the possible correlations of XPD Lys751Gln and TP53 Arg72Pro polymorphisms with the toxicity of platinum-based chemotherapy in Bangladeshi patients with lung cancer.

## Materials and Methods

### *Patients Selection Criteria*

The study was carried out following the provisions of the recent version of the Helsinki Declaration (WMA, 2013) and after approval by the Ethical Review Committees of the Department of Biochemistry and Molecular Biology, University of Dhaka. A total of 180 lung cancer patients with histologically diagnosed lung cancer as per the International Association of Lung Cancer (Travis, 2011) reported to Ahsania Mission Cancer and General Hospital, Dhaka Medical College Hospital, and Bangabandhu Sheikh Mujib Medical University formed the study group. Before enrollment, all the patients were explained about the investigational nature of this protocol, and informed consent was received from each patient. Patients with a previous history or record of other severe diseases such as kidney disease, cardiovascular disease, and other metastasized cancer were excluded from the study. Patients' details were collected using a structured questionnaire regarding age, gender, chemotherapy-related toxicities, and family history of chronic diseases.

### *Toxicity Evaluation Criteria*

Toxicities of platinum-based chemotherapy like anemia, neutropenia, leukopenia, thrombocytopenia, and gastrointestinal toxicity in lung cancer patients were evaluated according to the National Cancer Institute for Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0) (2017).

### *Sample Collection and DNA Extraction*

About three milliliters (3.0 mL) of venous blood samples were obtained from patients in sterile tubes (EDTA-Na<sub>2</sub>-containing) for genotyping study and stored at –20°C until DNA extraction. Genomic DNA was extracted using the organic extraction procedure described by Bailes et al., (2007).

### *Genotyping Assay*

A genotyping assay of XPD was performed by PCR-Restriction Fragment Length Polymorphism (RFLP) method. On the other hand, TP53 genotype was assessed by allele-specific multiplex PCR method where PCR assay performed individually for identifying the presence of either Arg or Pro p53 polymorphic allele. The primer sequences and PCR conditions were derived from the previously published papers (Mitra et al., 2009; Papadakis et al., 2002). For RFLP, the PCR product (413 bp) of XPD Lys751Gln SNP was digested with the restriction enzyme PstI (37°C for 16 hours in a water bath). Enzyme digestion product was electrophoresed through a 3% agarose gel following ethidium bromide staining to visualize the targeted XPD fragments of 413 bp, 322 bp, and 91 bp. For TP53, the β-globin gene serves as an internal control to avoid false-negative readings. The co-amplified PCR products of TP53 were analyzed on a 2% agarose gel following staining with ethidium bromide. The Arg allele and Pro allele presence were confirmed by 199 bp and 177 bp PCR amplified products.

### Statistical Analysis

According to toxicity grades, the Fisher's exact tests were performed through GraphPad Prism, version-8, to assess the association between genotype and platinum-based chemotherapy-induced toxicity. The relative association between them was determined by calculating the odds ratio (OR) with 95 % confidence intervals (CIs) and level of significance (p). A  $p < 0.05$  was regarded as the level of significance.

## Results

### Patient characteristics

In this study, a total of 180 lung cancer patients were recruited and analyzed. The included patients were aged between 40 and 85 years with a mean age of  $55.83 \pm 0.66$  years. Most lung cancer patients were above 50 years ( $n=137$ , 76.11%) and administered with platinum-based chemotherapeutic agents. Among 180 patients with lung carcinoma, 109 patients were males, and 71 patients were females. Moreover, 128 lung cancer patients (71.11%) were smokers, whereas only 52 patients (28.89%) were nonsmokers. Among the cases, stage IIIB represented the highest frequency at 65% (117 patients) compared with stage IIIA at 35% (63 patients). The details of different combination of chemotherapy received by lung cancer patients were recorded as carboplatin + paclitaxel, 31.67% (57 patients); carboplatin + gemcitabine, 23.33% (42 patients); cisplatin + etoposide, 18.89 (34 patients); cisplatin + paclitaxel, 7.22% (13 patients); cisplatin + docetaxel, 6.67 (12 patients); carboplatin + etoposide, 5% (9 patients); carboplatin + docetaxel, 3.89% (7 patients); and carboplatin + doxorubicin, 3.33% (6 patients) (Table 1).

### Toxicity to chemotherapy

Toxicity outcomes presented in Table 1 were recorded in platinum-based chemotherapy-treated lung cancer patients. These toxicities were grouped into (a) under grade 1-2 toxicity (b) under grade 3-4 toxicity shown in two columns. Here, grade refers to the severity of different platinum-based chemotherapy-induced toxicities. The most frequent toxicities observed included anemia, neutropenia, leukopenia, thrombocytopenia, and GI toxicity. Both 1-2 and 3-4 grades anemia were observed in 90 (50%) patients. On the other hand, grade 1-2 neutropenia was observed in 97 (53.89%) patients, whereas grade 3-4 neutropenia was observed in 83 (46.11%) patients. Moreover, 115 (63%) patients were found with grade 1-2 leukopenia, while 65 (36.11%) patients were identified with grade 3-4 leukopenia. Among the hematological toxicities, the highest percentage (81.67%) of patients was found with grade 1-2 thrombocytopenia, whereas the number of patients with grade 3-4 thrombocytopenia was minimal (33 patients). The only non-hematological toxicity included in this study was GI toxicity, where 1-2 grade GI toxicity occurred in 141 (78.33%) patients, and 3-4 grade GI toxicity occurred in 39 (21.67%) patients. However, during the study, no serious adverse events were reported.

### XPD Lys751Gln genotype analysis and effects on platinum-based chemotherapy-induced toxicities

Among 180 lung cancer patients, the frequencies of XPD genotypes, homozygous wild type (Lys/Lys), heterozygous mutant variant (Lys/Gln), homozygous mutant variant (Gln/Gln), and combined mutant variant (Lys/Gln+Gln/Gln) were 44.44% (80 patients), 41.67% (75 patients), 13.89% (25 patients) and 55.56% (100 patients) respectively.

Table 1. Basic Characteristics, Treatment, and Toxicity of the Study Patients

Characteristics	Cases (n=180) n (%)
Age (Year) <sup>a</sup>	55.83±0.66
Age distribution	
<50 years	43 (23.88) <sup>b</sup>
>50 years	137 (76.11)
Gender	
Male	109 (60.56)
Female	71 (39.44)
Smoking status	
Non smokers	52 (28.89)
Smokers	128 (71.11)
Staging	
Stage IIIA	63 (35.00)
Stage IIIB	117 (65.00)
Chemotherapy Regimens	
Carboplatin + Paclitaxel	57 (31.67)
Carboplatin + Gemcitabine	42 (23.33)
Cisplatin + Etoposide	34 (18.89)
Cisplatin + Pacitaxel	13 (7.22)
Cisplatin + Docetaxel	12 (6.67)
Carboplatin + Etoposide	9 (5.00)
Carboplatin + Docetaxel	7 (3.89)
Carboplatin + Doxorubicin	6 (3.33)
Toxicity	
Anemia	
Grade 1-2	90 (50.00)
Grade 3-4	90 (50.00)
Neutropenia	
Grade 1-2	97 (53.89)
Grade 3-4	83 (46.11)
Leukopenia	
Grade 1-2	115 (63.89)
Grade 3-4	65 (36.11)
Thrombocytopenia	
Grade 1-2	147 (81.67)
Grade 3-4	33 (18.33)
GI toxicity	
Grade 1-2	141 (78.33)
Grade 3-4	39 (21.67)

<sup>a</sup>Mean±SEM; <sup>b</sup>Numbers in parentheses show percentages.

Table 2. XPD (Codon 751) Genotypes Effect on Platinum-Based Chemotherapy-Induced Toxicities According to Toxicity Grades

Toxicities	Genotypes	Grade 1-2	Grade 3-4	OR (95 % CI)	p value
Anemia	Lys/Lys	43	37	1.0 (Ref.)	-
	Lys/Gln	34	41	1.40 (0.75-2.64)	0.34
	Gln/Gln	13	12	1.07 (0.45-2.52)	0.99
	Lys/Gln+Gln/Gln	47	53	1.31 (0.73-2.38)	0.45
Neutropenia	Lys/Lys	46	34	1.0 (Ref.)	-
	Lys/Gln	38	37	1.32 (0.71-2.49)	0.42
	Gln/Gln	13	12	1.25 (0.52-2.94)	0.65
	Lys/Gln+Gln/Gln	51	49	1.30 (0.72-2.37)	0.45
Leukopenia	Lys/Lys	51	29	1.0 (Ref.)	-
	Lys/Gln	45	30	1.17 (0.61-2.28)	0.74
	Gln/Gln	19	6	0.56 (0.20-1.46)	0.34
	Lys/Gln+Gln/Gln	64	36	0.98 (0.53-1.79)	0.99
Thrombocytopenia	Lys/Lys	66	14	1.0 (Ref.)	-
	Lys/Gln	60	15	1.18 (0.54-2.61)	0.84
	Gln/Gln	21	4	0.89 (0.29-2.79)	0.99
	Lys/Gln+Gln/Gln	81	19	1.11 (0.52-2.28)	0.85
GI toxicity	Lys/Lys	64	16	1.0 (Ref.)	-
	Lys/Gln	58	17	1.17 (0.53-2.61)	0.70
	Gln/Gln	19	6	1.26 (0.42-3.72)	0.78
	Lys/Gln+Gln/Gln	77	23	1.20 (0.58-2.44)	0.72

Odds ratios (OR) and 95% confidence interval (95%CI); \*p<0.05 considered as level of significance.

The role of XPD gene polymorphisms both individually and combined on the platinum-based chemotherapy-induced toxicities according to toxicity grades was shown

in Table 2. In the present study, no statistical significant association was obtained for variant genotypes of XPD with platinum-based chemotherapy induced toxicities like

Table 3. TP53 (Codon 72) Genotypes Effect on Platinum-Based Chemotherapy-Induced Toxicities According to Toxicity Grades

Toxicities	Genotypes	Grade 1-2	Grade 3-4	OR (95 % CI)	p value
Anemia	Arg/Arg	28	38	1.0 (Ref.)	-
	Arg/Pro	54	47	0.64 (0.34-1.17)	0.21
	Pro/Pro	8	5	0.46 (0.15-1.42)	0.23
	Arg/Pro+Pro/Pro	62	52	0.62 (0.34-1.15)	0.16
Neutropenia	Arg/Arg	32	34	1.0 (Ref.)	-
	Arg/Pro	57	44	0.73 (0.39-1.33)	0.34
	Pro/Pro	8	5	0.59 (0.19-1.80)	0.55
	Arg/Pro+Pro/Pro	65	49	0.71 (0.39-1.33)	0.28
Leukopenia	Arg/Arg	39	27	1.0 (Ref.)	-
	Arg/Pro	66	35	0.77 (0.41-1.46)	0.42
	Pro/Pro	10	3	0.43 (0.12-1.58)	0.35
	Arg/Pro+Pro/Pro	76	38	0.72 (0.39-1.35)	0.34
Thrombocytopenia	Arg/Arg	55	11	1.0 (Ref.)	-
	Arg/Pro	80	21	1.31 (0.59-2.82)	0.55
	Pro/Pro	12	1	0.42 (0.04-3.11)	0.68
	Arg/Pro+Pro/Pro	92	22	1.20 (0.55-2.58)	0.69
GI toxicity	Arg/Arg	53	13	1.0 (Ref.)	-
	Arg/Pro	78	23	1.20 (0.58-2.54)	0.7
	Pro/Pro	10	3	1.22 (0.32-4.68)	0.72
	Arg/Pro+Pro/Pro	88	26	1.21 (0.57-2.48)	0.71

Odds ratios (OR) and 95% confidence interval (95%CI); \*p<0.05 considered as level of significance.

anemia (OR=1.40, 95% CI=0.75-2.64,  $p>0.05$ ; OR=1.07, 95% CI=0.45-2.52,  $p>0.05$  and OR=1.31, 95% CI=0.73-2.38,  $p>0.05$ ); neutropenia (OR=1.32, 95% CI=0.71-2.49,  $p>0.05$ ; OR=1.25, 95% CI=0.52-2.94,  $p>0.05$  and OR=1.30, 95% CI=0.72-2.37,  $p>0.05$ ); leukopenia (OR=1.17, 95% CI=0.61-2.28,  $p>0.05$ ; OR=0.56, 95% CI=0.20-1.46,  $p>0.05$  and OR=0.98, 95% CI=0.53-1.79,  $p>0.05$ ); thrombocytopenia (OR=1.18, 95% CI=0.54-2.61,  $p>0.05$ ; OR=0.89, 95% CI=0.29-2.79,  $p>0.05$  and OR=1.11, 95% CI=0.52-2.28,  $p>0.05$ ) and gastrointestinal toxicity (OR=1.17, 95% CI=0.53-2.61,  $p>0.05$ ; OR=1.26, 95% CI=0.42-3.72,  $p>0.05$  and OR=1.20, 95% CI=0.58-2.44,  $p>0.05$ ) in lung cancer patients.

#### *TP53 Arg72Pro genotype analysis and effects on platinum-based chemotherapy-induced toxicities*

In the studied lung cancer patients, the frequency of arginine homozygous (Arg/Arg) was 36.67% (66 patients), proline homozygous (Pro/Pro) was 7.22 % (13 patients), arginine/proline heterozygous (Arg/Pro) was 56.11% (101 patients), whereas combined mutant variant (Arg/Pro+Pro/Pro) was 63.33% (114 patients).

Likewise, XPD genotypes, no significant association of Arg/Pro, Pro/Pro, and Arg/Pro+Pro/Pro genotypes of TP53 with platinum-based chemotherapy-induced toxicities were found when Arg/Arg genotype was considered as the reference group (Table 3)

## Discussion

According to patients' genetic characteristics, a pharmacogenetic approach to individualize the chemotherapy regimens represents an innovative and intriguing challenge as it could deliver the most active agent to each patient. To date, platinum-based chemotherapy keeps on being the mainstay for the treatment of advanced lung cancer. However, since the cytotoxic impacts of platinum are not explicit, multiple systems appear to be involved in the mechanism of toxicity during chemotherapy. Therefore, researchers had an enormous interest in identifying the effect of genetic factors on platinum-based chemotherapy-induced toxicities taking into account interindividual differences. Hence, the detection of SNPs that assists in predicting either sensitivity or toxicity to chemotherapy is of great value in choosing patients who will be improved from a chemotherapy regimen. In the current study, we included 180 lung cancer patients treated with platinum-based regimens and explored the effect of XPD Lys751Gln and TP53 Arg72Pro genetic polymorphisms on platinum-induced grade 1–2 and 3–4 toxicities.

In most studies, the identification of genetic polymorphisms that influence platinum-related toxicities was indecisive. Polymorphisms in genes that encode nucleotide excision repair (NER) pathway are significantly the most critical genetic determinants with susceptibility to platinum-based chemotherapy-induced toxicities (Perez-Ramirez et al., 2017). The NER pathway repairs DNA intrastrand crosslink's caused by platinum-based chemotherapy, and XPD is among the most common candidate genes related to platinum-based toxicities

(Zhang et al., 2018). However, no significant association between the genotypes in XPD codon 751 and platinum-induced severe toxicities was observed in our analysis. Although several studies have addressed the correlation between SNPs in codon 751 of XPD and platinum-based chemotherapy response in NSCLC patients, only a few studies have focused on chemotherapy toxicity (Giachino et al., 2007; Tibaldi et al., 2008; Booton et al., 2006). Nevertheless, one study anticipated that the grade of neutropenia manifested a significant association with the XPD haplotype, where the XPD751 lysine allele was related to greater Grade 4 neutropenia in contrast to the XPD751 glutamine allele. However, no significant relation was found between XPD haplotype and anemia, thrombocytopenia, and/or nonhematologic toxicity (Booton et al., 2006).

Moreover, no significant trend was observed in our study toward the association between TP53 gene polymorphisms and the risk of platinum-based chemotherapy-induced toxicities with anemia, neutropenia, leukopenia, thrombocytopenia, and gastrointestinal toxicity in lung cancer patients similar to XPD genotypes. These findings align with a previous meta-analysis conducted with four studies consisting of 1,033 patients to identify the correlation between TP53 Arg72Pro polymorphism and grade 3–4 hematological toxicity. However, no significant association of Arg72Pro polymorphism with grade 3–4 hematological toxicity was found (OR = 0.82, 95% CI: 0.59–1.15,  $p= 0.25$ ) (Liu et al., 2020). In this study, the lack of such association can be ascribed to the small sample size, resulting in a low power to identify significant differences in the distribution of genotypes between grade 1–2 and grade 3–4. Moreover, though all patients of this study were treated with platinum-based agents, the use of non-platinum drugs, such as paclitaxel, gemcitabine, etoposide, docetaxel, and doxorubicin, may influence toxicity profiles as a part of the chemotherapy regimens. In addition, the cumulative dosage aggravates platinum-induced toxicities; hence, several cycles of chemotherapy can also affect the results. Furthermore, other factors may affect platinum-induced toxicities, such as tumor molecular features, demographic characteristics, comorbidity, and intestinal bacteria.

In conclusion, the results of our study suggested no significant association of XPD Lys751Gln and TP53 Arg72Pro polymorphisms with the platinum-based chemotherapy-related toxicities in Bangladeshi lung cancer patients. Therefore, further prospective, high-quality pharmacogenomics research with a large sample size is required to evaluate the proper role of genetic polymorphisms on platinum-related toxicities in lung cancer patients. Eventually, by conducting additional studies in this field, we might be able to foster a much more precise comprehension of genetic variations among individuals and their association in determining treatment outcomes along with treatment-related toxicities. As a result, in the future, it may be possible to select chemotherapies and treatments according to individual genetic profiles, considering their probability of having treatment-related severe toxicities.

## Author Contribution Statement

Tahsin Nairuz conceptualized, designed, performed experiments, data analysis and interpretation and drafted the manuscript. Most Umme Bushra follows up patients' enrollment, helps in sample collection and data management. Yearul Kabir provided overall concept, guidance and support to the study and critically reviewed the manuscript. All authors have read and approved the final manuscript.

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