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**Research article** 

# Quality of Life (QoL) of cancer patients and its association with nutritional and performance status: A pilot study



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# ABSTRACT

*Background:* Quality of Life (QoL), for long, has been a multifactorial concerning issue in oncology. The aim of this study was to determine QoL of cancer patients and its association with nutrition, and performance status. *Methodology:* This was a hospital based cross-sectional study carried out at 2 cancer centers and one tertiary level hospital in Dhaka city during the months of July to December, 2019. Data was collected through structured interviews and analyzed by SPSS-25 statistical package software. *Results:* Among 279 participants, 14(5.02%) had high QoL, 35(12.54%) had average QoL, 150(53.76%) had low

Results: Among 279 participants, 14(5.02%) had high QoL, 35(12,54%) had average QoL, 150(53.76%) had low QoL, and remaining 80(28.67%) had very low QoL. The prevalence of severe malnutrition was 12.5% and 43.7% of patients had poor performance status. A statistically significant association between QoL and, nutritional and performance status was identified (p < 0.05). The ANOVA also indicated a statistically significant variation in QoL score among nutritional categories (P < 0.01) and performance status (P = 0.013).

*Conclusion:* A relatively higher prevalence of poor QoL was identified in this study which varies among nutritional categories and performance statuses. The proper management of predictors of QoL is imperative during treatment procedures.

### 1. Introduction

Cancer is a crucial economic and public health concern and its burden is expected to spiral. According to recent observations, the burden of cancer deaths has reached 9.6 million [1,2]. An increasing trend in mortality from cancer is observed which supposedly can be influenced by the demographic and epidemiological transitions that are taking place [3]. In Bangladesh, cancer is the second most leading cause of mortality [4].

The QoL is one of the most concerning health issues for oncology patients. It is a specific and multidimensional type of patient-reported outcomes (PROs) which is perceived by patients as something that encompasses the patients' social, financial, psychosocial, and physical activities [5,6]. Due to the improvement in medical science and continuing advancement in early detection and treatment, the expected survival time of cancer patients has become longer. This has resulted in an increased interest in exploring the health-related quality of life (HRQoL)

of cancer survivors. So, there is a consequent need to satisfy cancer patients' requirements which would enable them to live a healthy life [7]. In many cases, cancer patients experience sleep disturbance, depression and poor quality of life after being diagnosed and treated for cancer. So, the assessment of QoL among cancer patients is essential in order to design interventions for improving patients' outcomes [7,8]. Likewise, QoL assessment assists people realize how treatment, disease, and health impact quality of life. Furthermore, it helps to understand potential beneficial and risky aspects of a treatment thus help in weighing the impact of a decision.

Cancer and various types of treatments of cancer affect nutritional status of patients through various types of alterations such as alterations in physiological and psychological functions. And along with that reduction in food intake may have an impact on a patient's QoL by negatively influencing the nutritional status [7,9]. Social factors may have a very different impact on different cancer types and on different steps along the cancer continuum, from the time of an individual's

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exposure to a carcinogenic agent to early diagnosis, treatment, and survival [10]. Social determinants affect all steps of the cancer continuum, like treatment, end-of-life care, diagnosis, and prevention. The selection of a hospital for cancer patients has an effect on the quality of life too [11]. It is important to study how all these socio-environmental variables impact QoL, and how QoL is associated with other measures namely nutrition and performance status.

Though there are several studies in the Western population that reported a relationship between nutritional status and QoL [12,13], to the best of our knowledge, there are very few robust and reliable studies concerning the quality of life, and nutritional status of cancer patients in Bangladesh where nutritional status was measured by anthropometric measures, laboratory tests, or dietary assessment [14,15]. It is imperative to fill up this research gap in an area as important and as sensitive as QoL of cancer patients. Moreover, studies focusing its association to nutritional, and performance status is very rare throughout the world. Therefore, the present study aims to explore the association of QoL of cancer patients with nutritional and performance status.

# 2. Methods

# 2.1. Study design and tools

This hospital based cross-sectional study was conducted in two cancer centers and one tertiary level hospital of Dhaka city during July 2019 to December 2019. We used the QoL questionnaire version II-Indian scenario (Bengali version), designed and validated by Vidhubala, et al. (2011) to assess the quality of life of our study participants [16]. The tool has 41 items with a maximum score of 176 (Supplementary file 1). Among the 41 structured items, 39 were in 4-point scales ranging from "not at all" [1] to "very much" [4]. For item number 40 (physical condition of patient in overall view) and 41 (the overall Quality of Life), the response option ranged from "very poor" [1] to "excellent" [10] in the previous 15 days. QoL was categorized into five according to scoring pattern: Above 165 (very high QoL), 147–165 (high QoL), 118–146 (average QoL), 99–117 (low QoL), and below 99 (very low QoL).

Since QOL tool was a standardized tool, it was translated into local (Bengali) language. Reliability of the tool was established using Cronbach's alpha coefficient formula by administering into twenty-five samples. The reliability coefficient of the tool was r = 0.88. Which was close to the reliability coefficient conducted in Kannada language (r = 0.84) [17].

Nutritional diagnosis was performed by the Patient-Generated Subjective Global Assessment (PGSGA) tool [18]. The tool allows classifying the nutritional assessment into three categories: A = well nourished; B = suspected or moderate malnutrition and; C = severe malnutrition. The use of previous nutrition parameters (anthropometric, biochemical and immunological) to assess nutritional status has been questioned in view of the many non-nutritional factors affecting the results [18,19]. Since the introduction of the PG-SGA, it has been validated and utilized in both cancer and non-cancer patient populations internationally. Numerous studies have shown the association between PG-SGA scores and specific nutritional parameters, for example weight loss, BMI, skinfold measures and hand grip strength. PGSGA relies majorly on weight history, changes in dietary intake of the patients, presence of gastrointestinal symptoms, functionality, and physical examination. Both earlier and recent data have demonstrated the PG-SGA's ability to predict clinical outcomes, for example survival, postoperative complications, length of stay, quality of life and hospitalization costs [20,21]. Despite being identified as an ideal method of assessing nutrition status of cancer patients, the tool has not been utilized for the nutrition assessment of cancer patients in Bangladesh.

The performance status (PS) was obtained from the scale developed by the Eastern Cooperative Oncology Group (ECOG). The ECOG categorizes performance scales into five categories ("Zero"-fully active; "One'- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; "Two- Ambulatory and capable of all selfcare but unable to carry out any work activities; "Three- Capable of only limited selfcare; "Four- Completely disabled; "Five- "Dead". We have considered 'the limited functional capacity leads to difficulties in preparing and food intake' as the cutoff point. Thus, this variable was stratified in PS < 2 and PS  $\geq$  2, because PS = 2 indicates inability to perform any work activity [22].

Body mass index (BMI) was measured as weight in kg/height in meter<sup>2</sup>. We have used age- and sex-specific chart by the US Centers for Disease Control and Prevention to classify BMI. A Bengali version of the questionnaire was used to collect information from respondents regarding socio-demographic, cancer and treatment related variables which was pretested among 5% of the sample population prior to data collection. Back translation was done to assess the accuracy of translation (Supplementary file 1).

### 2.2. Sample size

We have estimated the sample size based on single population proportion formula [23]. A study conducted in 2017 found more than 80% cancer patients had poor QoL using the same tool [17]. Considering it as reference, the required sample size was, n = 246 when the allowable error was 5%. During the study period we were able to take 279 complete interviews.

# 2.3. Sampling and data collection

This was a hospital based cross sectional study where convenient sampling technique was used. Participants were recruited from both inpatient's department (IPD) and out-patients department (OPD). Participants aged less than 19 years and more than 75 years and not able to follow simple instruction or respond were excluded from the study. Sections on weight history, changes in dietary intake, presence of nutrition impacting symptoms, and physical examination was carried out by experienced medical doctors in facilities. Information on dietary intake and nutrition symptoms was reported by participants while information on weight history, type of cancer stage and any other illness was retrieved from participants medical records.

# 2.4. Statistical analysis

Data were entered in Microsoft XL (2013) and checked for consistency and completeness. For data analysis, IBM SPSS (version 25) statistical package software was used. We have performed descriptive statistics, chi-square test, ANOVA and eta-square test for specific purposes. Results with p-values of <0.05 were considered to be statistically significant.

### 2.5. Ethics approval and consent to participate

Prior to data collection an ethical approval was obtained from the Ethics Review Committee of North South University. Informed written consent was taken from each study participants and the purpose of the study was fully clarified.

# 3. Results

During the data collection period, 279 cancer patients were interviewed following the inclusion and exclusion criteria. The participants were aged between 19 to 74 years old and the mean age was 49.24  $\pm$  15.7(SD) and the median age was 54 year. Among males the mean age was around 51 years and for females it was 47 years. The mean height of study participants was 159.97  $\pm$  8.09(SD) cm (male:163.5; female: 154.6) with maximum 183cm and minimum 146cm. The maximum weight measured was 92 kg with mean 56.51  $\pm$  10.03(SD) kg (male: 56.6; female: 56.4) and the highest BMI was 35.5 with average of 22.09  $\pm$ 

## Table 1. Descriptive statistics of Anthropometric measurements of cancer patients, 2019.

Sex	Minimum	Maximum	Median	$Mean \pm SD$	Percentiles			
					05	25	75	95
Male	19	74	55	$50.7 \pm 15.7$	24	36	64	71
Female	22	71	51.5	$47.1 \pm 15.5$	22	32	58.5	68
Male	148	183	163	$163.5\pm7.0$	153	158	168	175
Female	146	178	153.5	$154.6\pm 6.5$	147	151	158	267
Male	44	84	55	$56.6 \pm 8.7$	45	50	61	71
Female	40	92	55	$56.4 \pm 12.4$	40	49	60	85
Male	15.21	28.76	20.44	$21.16\pm2.8$	17.6	19.5	22.9	26.6
Female	16.98	35.49	24.12	$23.48 \pm 4.2$	17.3	19.7	25.0	33.6
	Sex Male Female Female Male Female Male Female	SexMinimumMale19Female22Male148Female146Male44Female40Male15.21Female16.98	SexMinimumMaximumMale1974Female2271Male148183Female146178Male4484Female4092Male15.2128.76Female16.9835.49	SexMinimumMaximumMedianMale197455Female227151.5Male148183163Female146178153.5Male448455Female409255Male15.2128.7620.44Female16.9835.4924.12	SexMinimumMaximumMedianMean $\pm$ SDMale197455 $50.7 \pm 15.7$ Female2271 $51.5$ $47.1 \pm 15.5$ Male148183163 $163.5 \pm 7.0$ Female146178 $153.5$ $154.6 \pm 6.5$ Male4484 $55$ $56.6 \pm 8.7$ Female4092 $55$ $56.4 \pm 12.4$ Male15.2128.76 $20.44$ $21.16 \pm 2.8$ Female16.98 $35.49$ $24.12$ $23.48 \pm 4.2$	Sex         Minimum         Maximum         Median         Mean $\pm$ SD         Percentiles 05           Male         19         74         55         50.7 $\pm$ 15.7         24           Female         22         71         51.5         47.1 $\pm$ 15.5         22           Male         148         183         163         163.5 $\pm$ 7.0         153           Female         146         178         153.5         154.6 $\pm$ 6.5         147           Male         44         84         55         56.6 $\pm$ 8.7         45           Female         40         92         55         56.4 $\pm$ 12.4         40           Male         15.21         28.76         20.44         21.16 $\pm$ 2.8         17.6           Female         16.98         35.49         24.12         23.48 $\pm$ 4.2         17.3	Sex         Minimum         Maximum         Median         Mean $\pm$ SD         Percentiles           Male         19         74         55         50.7 $\pm$ 15.7         24         36           Female         22         71         51.5         47.1 $\pm$ 15.5         22         32           Male         148         183         163         163.5 $\pm$ 7.0         153         158           Female         146         178         153.5         154.6 $\pm$ 6.5         147         151           Male         44         84         55         56.6 $\pm$ 8.7         45         50           Female         40         92         55         56.4 $\pm$ 12.4         40         49           Male         15.21         28.76         20.44         21.16 $\pm$ 2.8         17.6         19.5           Female         16.98         35.49         24.12         23.48 $\pm$ 4.2         17.3         19.7	SexMinimumMaximumMedianMean $\pm$ SDPercentilesMale19745550.7 $\pm$ 15.7243664Male227151.547.1 $\pm$ 15.5223258.5Male148183163163.5 $\pm$ 7.0153158168Female14617855.556.6 $\pm$ 8.745.050.061Male44845556.6 $\pm$ 8.745.05061Female40925556.4 $\pm$ 12.4404960Male15.2128.7620.4421.16 $\pm$ 2.817.619.522.9Female16.9835.4924.1223.48 $\pm$ 4.217.319.725.0

3.06(SD) (male: 21.1; female: 23.4) with median of 21.99 (male: 20.44; female: 24.12) (Table 1).

We have analyzed several common socio-demographic variables of interviewed cancer patients. Out of 279 cancer patients, 101 (36.2%) were between 40-60 years old and 75 (26.9%) were more than 60 years old. The prevalence of underweight (19.0%) was higher among the cancer patients and 65.6% patients were in the normal BMI range. More than 54% cancer patients had more than six members in their family and 53.8% didn't do any kinds of beneficial activity or were unemployed. Our study found more male cancer patients (59.9%) following the global trend. Majority of the participants were Muslim (91.4%) following the national trend of Bangladesh (Table 2).

Largest group of cancer patients had completed higher secondary education or was highly educated (30.8%), plausibly due to the fact that educated people are more conscious regarding their health which more often results in early diagnosis and treatment. More than 66.0% of participants were married and have existing partners and more than 51.0% participants didn't have a history of smoking. Patients who came for treatment in hospital were relatively from high or middle-income groups, as 66.3% of the participant's monthly family income were between 40,000 to 80,000 Bangladeshi Taka and 15.4% had more than 80,000 Bangladeshi Taka (Table 2).

We had categorized all cancer patients into 6 categories according to the cancer localization. The largest portion was lung cancer (28.3%), followed by upper gastrointestinal tract (22.9%) and reproductive system (15.4%) and also categorized according to the cancer stages where metastasis was present in 19.4% patients (Table 3).

Out of 279 cancer patients, only 140 (50.2%) accurately followed the dietary instructions from nutritionist/oncologist given as a part of treatment protocols. We have also categorized the patients according to the treatment duration where 38.4% patients were undergoing treatment process for less than 6 months. Around 44.0% patients were taking chemotherapy, 40.5% went through the surgical treatment process, and around half of the participants were taking palliative care. Most of the

Variables	Category	Frequency	Percentag
Age	Less than 40 years	103	36.9
	Forty to sixty years	101	36.2
	Over sixty years	75	26.9
BMI category	Underweight	53	19.0
	Overweight	43	15.4
	Normal	183	65.6
Household Members	$\leq 6$	128	45.9
	>6	151	54.1
Occupation	Paid work	26	9.3
	Retired/get benefit	44	15.8
	Unemployed	150	53.8
	Business/Others	59	21.1
Sex	Male	167	59.9
	Female	112	40.1
Religion	Muslim	255	91.4
	Others	24	8.6
Education	Uneducated	70	25.1
	Informal/Primary	38	13.6
	Over sixty years75Underweight53Overweight43Normal183 $\leq 6$ 128>6151Paid work26Retired/get benefit44Unemployed150Business/Others59Male167Female112Muslim255Others24Uneducated70Informal/Primary38Secondary85Higher secondary or more86Married and partner existing185Unmarried or partner not existing94Smoker/Ex-smoker135Never smoke144<40,000 Taka	30.5	
	Higher secondary or more	86	30.8
Marital status	Married and partner existing	185	66.3
	Unmarried or partner not existing	94	33.7
Smoking history	Smoker/Ex-smoker	135	48.4
	Never smoke	144	51.6
Monthly family income	<40,000 Taka	51	18.3
	40,000–80,000 Taka	185	66.3
	>80 000 Taka	43	15.4

Table 2. Frequency distribution of sociodemographic characteristic of cancer patients, 2019.

# Table 3. Frequency distribution of cancer and treatment related variables, 2019.

Variable	Category	Frequency	Percentage
Cancer localization	Breast	44	15.8
	Lower gastrointestinal tract	32	11.5
	Lung	79	28.3
	Upper gastrointestinal tract	64	22.9
	Reproductive system	43	15.4
	Others	17	6.1
Stage	Stage 0	37	13.3
	Stage I	69	24.7
	Stage II	63	22.6
	Stage III	61	21.9
	Stage IV	49	17.6
Metastasis	No	225	80.6
	Yes	54	19.4
Follow dietician	No	139	49.8
	Yes	140	50.2
Treatment duration	Less than 6 months	107	38.4
	6–12 months	83	29.7
	More than 12 months	89	31.9
Chemotherapy	No	155	55.6
	Yes	124	44.4
Surgical treatment	No	166	59.5
	Yes	113	40.5
Palliative	No	144	51.6
	Yes	135	48.4
Hospital stay	No (OPD)	73	26.2
	Up to 15 days	142	50.9
	>15 days	64	22.9

patients interviewed were hospitalized, where 22.9% were hospitalized for more than 15 days (Table 3).

According to scoring, quality of life was categorized in five categories (very high, high, average, low and very low). No participants got enough scores to attain a very high QoL category. However, 14 (5.02%) respondents had high QoL, 35 (12.54%) had average QoL, 150 (53.76%) participants had low QoL, and remaining 80 (28.67%) had very low QoL (Figure 1).

Nutritional status was classified into three categories (A = well nourished, B = suspected or moderate malnutrition and C = severe malnutrition). Only 35 (12.50%) of our study participants had severe malnutrition and 152 (54.50%) had moderate malnutrition (Figure 2).

Performance status (PS) was obtained from the scale developed by the Eastern Cooperative Oncology Group (ECOG) where 19.7% of the patients were fully active, 36.9% were restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. On the other hand, 29% of patients were ambulatory and capable of all selfcare but unable to carry out any work activities, 11.8% were capable of only limited selfcare, and the remaining 2.5% were completely disabled. After using the cut-off point, more than 43% of patients found having poor performance status (PS  $\geq$  2) (Figure 3).

We have conducted Chi-square test/Fisher's Exact Test to identify the association between dependent and independent variables. Both nutritional status ( $\chi 2 = 15.52$ ; p = 0.001) and performance status ( $\chi 2 = 21.54$ ; p = 0.002) had statistically significant association with QoL. Eta-square ( $\eta 2$ ) were calculated to see the effect of nutritional status and performance status (PS) on quality of life. From our analysis,  $\eta 2 = 0.077$ 



Figure 1. Quality of Life of Cancer patients, 2019.



Figure 2. Nutritional status of Cancer patients, 2019.



Figure 3. Performance status of the cancer patients, 2019.

indicates medium effect thus, nutrition status has 7.7% effect on quality of life score of cancer patients (0.01 ~ small, 0.06 ~ medium, and >0.014 ~ large effect). The analysis variance also indicates a statistically significant variation in QoL score among nutritional categories (F = 10.99; p < 0.01) and performance statuses (p = 0.013) (Table 4).

#### 4. Discussion

Our study aimed at exploring cancer patients' quality of life (QoL) status– and sought their association with nutritional and performance status. In this attempt, we obtained ranges of data pertaining to various important aspects of cancer patients' life.

Cancer patients generally have a worse quality of life compared to the general population [24]. We have observed that only 17.56% participants have good or average QoL which corroborated with a recently conducted study findings (17.7%) using the same QoL tool [17].

Our study has also identified the nutritional status of cancer patients using PGSGA tool. Where, 12.5% had severe malnutrition and 54.5% had moderate malnutrition. A study conducted in Brazil in similar study settings observed the prevalence of malnutrition was 71.1%, with similar frequencies between moderate (35.4%) and severe malnutrition (35.7%) [22]. A previous study, although having small sample size (n = 57) using the same assessment tool reported 15.5% were well-nourished, 31.6% were moderately malnourished, and 52.6% were severely malnourished [25]. In contrast to our result, a study from Iceland reported 40% of the cancer patient were malnourished [26]. The difference can be attributed to several factors: difference in assessment tool, difference in study populations' ethnicity, and sample size.

We also observed a statistically significant association between QoL and nutritional status of the patients (p < 0.05). We further calculated Eta-square and found that nutrition status has a 7.7% effect on the quality of life scores of cancer patients. Among nutritional categories, the analysis variance indicates a statistically significant variation. The previously conducted studies have also observed a statistically significant association of QoL with nutritional status [6,27].

The performance status of the participants was also observed to have statistically significant association with QoL (p < 0.05) and ANOVA also indicates a significant variation. This is also supported by a recently conducted study in similar settings [22].

We interviewed 279 patients with cancer and found a mean age of  $49.24 \pm 15.7$  (SD) years, which is around 51 years for male and 47 years for female. A prior study conducted 2015 in Bangladesh found a mean age of 59.8 for male and 49.3 for female [28]. According to Cancer Research-UK, since 1990 the cancer rate has increased by 21% among the 25-49 years age group and 12% among the 50-74 years age group [29]. This indicates that the incidence of cancer has been increasing in the middle-aged group. A study conducted in Kenya observed the mean age of cancer patients was 51.6 years which is close to our findings [21]. The prevalence of underweight group was high (19.0%) among the interviewed patients. The mean BMI obtained in our study was 22.09 (male:21.16; female:23.48). This is particularly important as a meta-analysis of 22 clinical trials suggested sex-related factors may interact with patients BMI and, in turn, affect cancer survival. It further suggested a higher BMI at the time of the diagnosis of cancer may play a protective role for men [30]. Regarding age distribution, we found 36.2% (n = 101) cancer patients belonged to the 40-60 age group. A previous study reported that maximum frequency was observed in the 51-60 years' age group for male and 41-60 years for female [28]. Our finding is in congruence with this result, although this study was based on data collected from the 2003-2012 period. This study also found that 53.8% of cancer patients are not involved in any income-generating activity. This may hint at patients' physical and/or mental inability to get involved in work/get employment due to the disease condition. Previous studies have reported that cancer survivors have a 1.4 times higher risk of unemployment when compared to healthy controls [31]. Furthermore, it has been observed across studies that between 26.0% and 53.0% of cancer survivors either lose their job or quit their occupation during or after the treatment [32].

Our study observed a high percentage of educated people (74.98%). One probable reason could be that educated people are more concerned regarding their health. Therefore, they are more likely to seek earlier diagnosis and treatment of the disease [33]. We categorized cancer patients based on cancer localization and found lung cancer patients to bag the largest portion (28.3%) followed by upper gastrointestinal tract cancer. A previous report supports our finding as they have reported esophageal cancer and lung cancer as the top two most prevalent cancers in the context of Bangladesh [2].

Our study has limitations with low sample size, non-homogeneous data, convenience approach and possibility of response related biases. The findings of this study would pave ways for future research focusing on the need for interventional studies which would work to decrease the adverse impact of different factors on the QoL in patients with cancers. Longitudinal research needs to be carried out to assess the effect of other factors (life-style, behavioral factors, psychological factors, etc.) on QoL. Another rationale to strongly recommend further longitudinal study would be to identify the underlying mechanisms that link various factors to QoL in cancer patients. Furthermore, it is also imperative to establish the direction of causality.

Table 4. ANOVA and Eta-squ	are test of nutritional status and perf	ormance status with QoL.			
Variables	Category	QoL (Mean $\pm$ SD)	F value	Significance	$\eta 2$
Nutrition category	Well nourished	$114.88\pm16.79$	11.546	<0.01	0.077
	Moderate malnutrition	$108.95\pm14.95$			
	Severe malnutrition	$100.29\pm15.45$			
Performance status (PS)	<2 (good)	$111.95\pm14.89$	6.294	0.013	0.022
	$\geq 2$ (poor)	$107.08 \pm 17.48$			

#### 5. Conclusions

The result revealed in the study showed high prevalence of low-very low QoL and malnutrition among cancer patients in Dhaka city. The QoL score was statistically different across nutritional status groups, and performance status. These outcomes can alert health professionals about the urgency to have increased attention to nutrition during treatment procedures. Many of our findings may also open avenues of new research to be explored in future.

# Availability of data and materials

The datasets arose and used in the current study is available from the corresponding author on reasonable request.

#### **Declarations**

#### Author contribution statement

M. Alam: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

T. Rahman and Z. Afroz: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

P. Chakrobarty and A. Wahab: Contributed reagents, materials, analysis tools or data; Wrote the paper.

S. Zaman: Conceived and designed the experiments; Wrote the paper.

M. Hawlader: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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#### Competing interest statement

The authors declare no conflict of interest.

#### Additional information

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