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Serum Antidiuretic Hormone Level in Nocturnal Enuretic School Children in a Tertiary Care Hospital in Bangladesh: A Cross-Sectional Study

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ABSTRACT

Background and Aims: Primary nocturnal enuresis (PNE) is a common pediatric condition characterized by involuntary nighttime bed wetting. Primary monosymptomatic nocturnal enuresis (PMNE) is associated with altered antidiuretic hormone (ADH) secretion and lacks lower urinary tract symptoms. This study aimed to compare serum ADH levels between children with PMNE and a comparison group to explore its potential role in the pathophysiology of PMNE.

Methods: This cross-sectional study included 40 children aged 6–15 years with PMNE and 40 age-matched children without enuresis (comparison group) attending the Pediatric Nephrology Outpatient Department at the National Institute of Kidney Diseases and Urology (NIKDU) from January 2022 to July 2023. Blood samples and other clinical information along with laboratory investigation are done to ensure inclusion and exclusion criteria. Fasting serum ADH level, a competitive immunoassay was done with the Arg- Vasopressin ELISA kit. Relevant clinical and demographic data were analyzed using Student's *t*-test for continuous variables and Chi-square/Fisher's exact tests for categorical variables.

Results: The mean age of participants was 8.82 ± 2.71 years in the PMNE group and 9.01 ± 2.54 years in the comparison group ($p = 0.760$). There was no significant association between sex and PMNE ($p = 0.370$). Children with PMNE exhibited significantly lower serum ADH levels compared to the comparison group ($p < 0.05$). Additionally, children with more frequent enuretic episodes demonstrated a trend of lower ADH levels ($p < 0.05$).

Conclusion: This study provides evidence of a significant association between decreased diurnal serum ADH levels and PNE in children. These findings contribute to a better understanding of the pathophysiology of PNE and suggest potential avenues for novel treatment strategies, emphasizing the importance of evaluating ADH levels in PNE management.

1 | Introduction

Enuresis is defined as normal, nearly complete, evacuation of the bladder at the wrong place and time after the fifth year of life. Nocturnal enuresis [1] is defined by the International Children's Continence Society as urinary incontinence at night while sleeping in children aged 5 years or more with a frequency of at least one incidence per month [1]. It may also be

defined as repeated spontaneous voiding of urine during sleep in a child that persists beyond the normative age of maturation of urinary control [2]. Nocturnal enuresis or simply enuresis is both a symptom and a condition of intermittent nocturnal incontinence, that is incontinence in discrete episodes while asleep [1]. It is about 10% at the age of 7 years, 3.1% at 11–12 years and 0.5%–1.7% at 16–17 years and occurs more frequently in boys [3]. It is approximately 1%–2% in adults [4]. Nocturnal enuresis is subdivided into primary nocturnal enuresis (PNE), that is the child has never been dry and Secondary Nocturnal Enuresis, that is the child has experienced a symptom-free period of at least 6 months. NE is also classified as monosymptomatic nocturnal enuresis (MNE) and non-monosymptomatic nocturnal enuresis (NMNE) based on symptoms of lower urinary tract symptoms (LUTS), which is associated with the later one. Enuresis without LUT symptoms is defined as MNE where voided volumes are usually within the normal range [5]. Children with LUT symptoms (urinary incontinence, urgency, frequency, hesitancy, straining, weak stream, intermittency, holding maneuvers, incomplete emptying, post micturition dribbling) are classified as NMNE [6]. Based on frequency NE is divided into frequent NE that is ≥ 4/week and infrequent NE < 4/week [5]. Severe nocturnal enuresis means 2 or more episodes weekly [7]. Children with frequent nocturnal enuresis have more severe enuresis [8].

Nocturnal Enuresis is a heterogenous disorder. Several pathophysiology mechanisms have been proposed for many years [9]. A valid summary of the current proposal is that enuresis is a result of a mismatch between nocturnal urine production, nocturnal bladder storage capacity and the ability to arouse from sleep [5]. These mechanisms are possibly due to disorder of central nervous system, CNS signal processing and the default mode network [1, 2, 5]. About 30% of patients with nocturnal enuresis are MNE which is nocturnal enuresis without LUT symptoms [8]. MNE is a result of mismatch between nocturnal urine output and bladder capacity and the large nocturnal urine production in patients with NE seems to be caused at least partly by an altered circadian rhythm of serum ADH [10, 11]. Genetic influence and maturational delay may also have a role in the pathophysiology of PNE [12]. A diurnal rhythm of ADH with constant levels during the daytime (8 am–10 pm) and a highly significant rise at night (10 pm–8 am) was found in normal subjects. While in NE a significantly less pronounced rise in ADH level compared to normal subjects is noted at night. Abnormal diurnal rhythm of ADH with lack of the normal nocturnal rise has been reported in nocturnal polyurea as well as good response to ADH analog, Desmopressin. It is also stated that this circadian defect in ADH secretion may be a fluctuating phenomenon. Nocturnal urine production measured at home in higher on wet nights than on dry nights [11]. Hereditary factor is found to be associated with NE, especially in severe nocturnal enuresis [7]. The incidence of NE is 44% if one parent has suffered from NE around 77% if both parents have a history of NE and it is around 15% if none of the parents and their blood-related relatives have positive history. Genetic influences are also proved in NE by cytogenetic analysis [13]. Besides this sleep disturbance associated with periodic limb movements also has an association with the pathophysiology of nocturnal enuresis [14].

This study was conducted to investigate the hypothesis that primary monosymptomatic nocturnal enuresis (PMNE) could be related to a disturbance in ADH secretion at night compared to a comparison group. If we can establish the hypothesis of alteration of serum ADH level from normal circadian rhythm and its association in this enuretic group it will be beneficial in future management plan of this condition. The objective of this article is to compare the serum ADH level between enuretic and comparison group children.

2 | Methods and Materials

This was a prospective, analytical, cross-sectional study with a comparison group conducted in the outpatient department of pediatric nephrology, NIKDU from January 2022 to July 2023. Children with PNE aged between 6 and 15 years and also a comparison group of the same age group seeking treatment for any other disease in the outpatient department were included in this study during this period. Diagnosed patients with PNE were enrolled by maintaining inclusion and exclusion criteria. In inclusion criteria were designed to select only children with MNE, and we systematically excluded those with NMNE, who exhibited daytime LUT symptoms. By focusing exclusively on children with MNE, we ensured that our study group was as homogenous as possible, allowing us to specifically assess the role of ADH in nocturnal enuresis without the confounding effects of daytime LUT symptoms. As all the participants were aged between 6 to 16; minor's informed written consent was obtained from parents and also assent from children aged 11 or more was taken. Ethical clearance was obtained from the institutional ethical committee of NIKDU (NIKDU/ERC/2022/85). Quality assurance measurements were recorded with a semi-structured questionnaire. Detailed history, thorough clinical examination & relevant investigations were done. Blood pressure was measured with a (ALPK2) aneroid sphygmomanometer after 5–10 min rest in a supine position. Polyuria and polydipsia were excluded by questionnaires and also by voiding a diary consisting of fluid intake and output chart. For laboratory investigations other than ADH 2.5 mL of blood was taken for RBS, S. creatinine, S. electrolytes. Both groups had normal routine laboratory tests showing normal urine R/E, especially normal specific gravity (done by urinometer) to exclude central diabetes insipidus, normal serum electrolytes (done by electrodes technique) specially serum sodium to exclude nephrogenic diabetes insipidus, normal serum RBS (done by Trinder's method) to exclude diabetes mallitus and normal serum creatinine (done by modified Jaffe method). USG of KUB (done by Chison USG machine) was done to exclude significant post-voidal residue or any other anomalies.

Following 8 h overnight fasting 2.5 mL venous blood sample was drawn in a Vacutainer from each participant with all aseptic measures. Samples were collected between 7 and 7:30 am while resting for 10 min keeping in mind that the time will still be on the peak diurnal elevated level. Then blood sample was allowed for clotting and the serum was separated after centrifugation at 3000 rpm/min for 5 min. Supernatant clear serum was taken in cryotubes and immediately within 1 h of collection transported to the BIRDEM lab by me for ELISA testing in a sample carrier box with an ice pack. Fasting Serum ADH level, a competitive immunoassay was done by Thermo Scientific Multiskan GO analyzer made in Finland using the Arg- Vasopressin ELISA kit in the Department of Laboratory Science Division, BIRDEM, Dhaka.

To investigate the PMNE along with the level of ADH, we conducted a comparative analysis between children diagnosed with PMNE and a control group without enuresis. Socio-demographic and clinical features for both groups of participants have been measured with mean and standard deviation (SD) for continuous variables, and frequencies and percentages for categorical variables. To compare the continuous variables between these two groups we have used the student *t*-test, and for the categorical variables Chi-square test and Fisher's exact test for sparse data have been used. And also, the ADH levels among the participants with different number of enuretic nights per week have been compared with one-way ANOVA test. All the tests were two-tailed, where p-value < 0.05 is considered statistically significant. All statistical calculations were done using Microsoft Excel 2003 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc. Chicago, IL, USA) version 25 for Microsoft Windows.

TABLE 1 | Association between socio-demography and clinical history of the participants (N = 80).

Association between socio-demography and clinical history of the participants	Enuretic group (case, $n = 40$)	Non-enuretic group (control, $n = 40$)	p-value
Age in years			
6–8	26 (65%)	21 (52.5%)	
9–11	5 (12.5%)	11 (27.5%)	0.242*
12–15	9 (22.5%)	8 (20.0%)	
Mean ± SD	8.82 ± 2.71	9.01 ± 2.54	0.760**
Education of the household head			0.265***
No education	6 (15.0%)	1(2.5%)	
Primary	15 (37.5%)	19 (47.5%)	
High school	15 (37.5%)	15 (37.5%)	
College & University	4 (10.0%)	5(12.5%)	
Occupation of the household head			0.165***
Business	12 (30%)	21 (52.5%)	
Service	25 (62.5%)	16 (40.0%)	
Day laborer	2 (5%)	2 (5%)	
Others	1 (2.5%)	3 (7.5%)	
Occupation of the Mother			> 0.99***
Housewife	34 (85%)	35 (87.5%)	
Service	5 (12.5%0	4 (10.0%)	
Business	1 (2.5%)	1 (2.5%0	
Monthly income of the family (in taka)			0.367
< 10,000	1 (2.5%)	0 (0%)	
10,000–25,000	20 (50.0%)	25 (62.5%)	
> 25,000	19 (47.5%)	15 (37.5%)	
Blood relative parents	2 (5.0%)	1 (2.5%)	> 0.99*
Any other family members with NE	10 (25%)	3 (7.5%)	0.066
Parents had same problem			
One parent	13 (32.5%)	0 (0%)	
Both parent	1 (2.5%)	0 (2.5%)	0.001
Absent	26 (65.0%)	40 (100%)	
Number of enuretic nights per week			
< 4times/week (Infrequent NE)	5 (12.5%)	0 (0%)	
≥ 4times/week (Frequent NE)	35 (87.5%)	0 (0%)	< 0.001
Never	0 (0%)	40 (100%)	

*Chi-square test.
**Student t test.
***Fisher's exact test.

3 | Results

The majority of the participants were between 6 and 8 years of age in both groups (65% vs. 52.5%). Mean ages were seen 8.82 ± 2.71 years and 9.01 ± 2.54 years in the case group and comparison group respectively with no significant differences ($p = 0.760$) (Table 1). There was no significant association between the nocturnal enuresis and sex ($p = 0.370$), although majority of patients were female in the case group (57.5%) where the comparison group was male predominant (52.5%) (Figure 1). The majority of household heads in both groups had completed primary or high school education, were employed in service or business sectors, and had an income ranging from 10,000 to 25,000 BDT. Most mothers were homemakers, with a minority engaged in service or business. No significant differences were observed in these variables between the groups ($p = 0.367$; Table 1). In this study, majority of the participants were from Dhaka city (67%) and the rest 33% patients were from various other cities of the country. In this study, 35% of the comparison group participants were from Dhaka city whereas majority of the comparison group patients were from various other cities of the country (Figure 2).

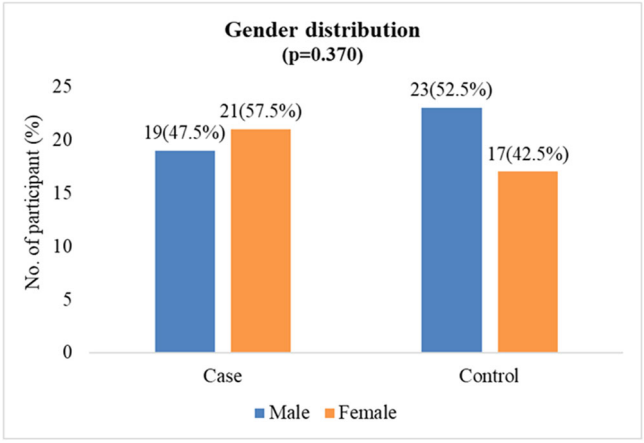

FIGURE 1 | Gender distribution for case and control group; females are pre-dominant in the case group and males are in the control group.

The assessment revealed that in the case group, two patients had parents who were blood-related relatives. Ten patients in the case group had a family history of similar issues among blood-related relatives. Furthermore, around 13 patients in the case group had at least one parent who also experienced NE. Notably, none of the parents in the comparison group had any history of nocturnal enuresis, and this difference was statistically significant ($p < 0.001$) (Table 1).

This study found that there were almost the same measurements in anthropometric factors of height and weight, as well as in pulse rate, systolic blood pressure, and diastolic blood pressure. Notably, these differences were not statistically significant. According to the findings, majority of the patients from case group had more than four enuretic nights per week whereas 12.5% patient had less than 4 enuretic nights per week. On the other hand, the comparison group showed 100% non-enuresis as expected and this difference were statistically significant ($p < 0.001$) (Table 1).

Based on the results, participants who did not have a history of nighttime bedwetting had higher levels of the ADH hormone in their serum. Conversely, individuals who urinated more than four times a week had lower ADH hormone levels and this association was found statistically significant ($p = 0.001$) (Table 2). Assessment of random blood sugar and s. creatinine was found 6.07 versus 6.17 mmol/L and 0.53 versus 0.56 mg/mL respectively. Urinary specific gravity was found almost similar between both groups. Protein and pus cells were not found among the participants. Similar findings of serum electrolytes (Na, K, Cl) were seen in both groups. None of the laboratory findings showed any significant differences between these groups (Table 3). Among the case and comparison groups, the ADH level in the given time period was lower than the comparison group and the differences were found statistically significant ($p < 0.001$) (Table 3).

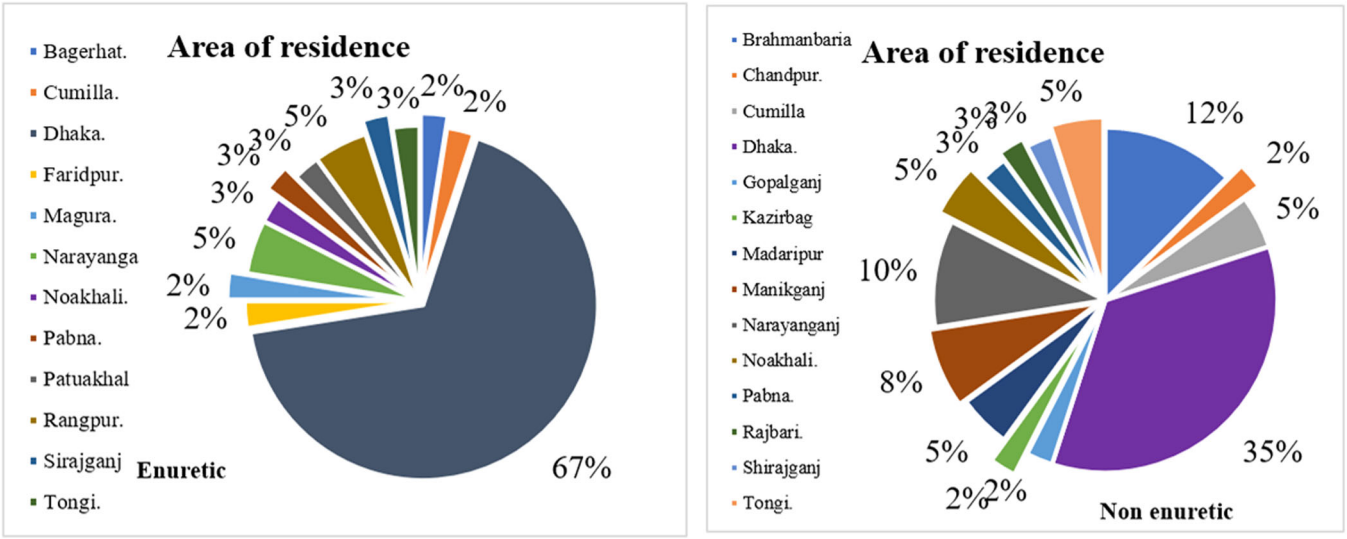

FIGURE 2 | Demographic distribution of the patients (Enuretic and non-enurectic); a large number of patients are from Dhaka for both the groups.

TABLE 2 | Association between number of enuretic nights per week with serum ADH levels of the participants ($n = 80$).

Variables	Serum ADH level	*p*-value*
Number of enuretic nights per week		**0.001**
≥ 4 times/week (Frequent NE)	21.30 ± 16.39	
< 4times/week (Infrequent NE)	31.97 ± 19.97	
Never	39.22 ± 22.09	

*One-way ANOVA test was done.

TABLE 3 | Association between clinical sign-symptoms and investigations with the participants (N = 80).

Factor	Labels	Case, $n = 40$	Control, $n = 40$	*P** value
Sign and symptoms				
How many times passes urine at night in a month	< 4/week	3 (8%)	1 (2%)	0.329
	≥ 4/week	3 (8%)	1 (2%)	
	Never	34 (84%)	38 (96%)	
Constipation	Absent	24 (60%)	33 (82%)	**0.048**
	Present	16 (40%)	7 (18%)	
Sleep Pattern	Frequent nighttime awakening	4 (10%)	1 (2%)	**< 0.001**
	Unable to awake with stimulation	30 (75%)	1 (2%)	
	Uninterrupted sleep	6 (15%)	38 (96%)	
Systolic Blood pressure	Mean (±sd)	96 (±10.14)	96.38 (±9.61)	0.866
Diastolic Blood pressure	Mean (±sd)	61.25 (±8.3)	62.75 (±19.08)	0.650
Pulse	Mean (±sd)	83.4 (±5.31)	82.7 (±6.56)	0.601
Investigation				
Serum ADH level (ng/mL)	Mean (±sd)	22.64 (±16.97)	39.22 (±22.1)	< 0.001
Specific gravity	Mean (±sd)	1.02 (±0)	1.02 (±0)	0.123
Presence of pus cell	Absent	4 (10%)	11 (28%)	0.086
	Present	36 (90%)	29 (72%)	
RBSM (mol/L)	Mean (±sd)	6.07 (±0.47)	6.17 (±0.48)	0.328
Serum. Creatinine (mg/dL)	Mean (±sd)	0.54 (±0.11)	0.57 (±0.13)	0.303
Serum. Sodium (Na)	Mean (±sd)	139.22 (±1.64)	139.57 (±2.09)	0.407
Serum. Potassium (K)	Mean (±sd)	3.96 (±0.27)	4.02 (±0.23)	0.238
Serum. Chloride (Cl)	Mean (±sd)	100.67 (±2.39)	100.65 (±1.72)	0.957

*Chi-square test for categorical variables for association; *t*-test for numerical variable for mean difference.

We have found significant association of nocturnal enuretic disease with constipation and sleep patterns. Among the NE (Case) participants about 40% has constipation whereas it is only 18% among the non-NE (Control). Most of the NE (Case) patients were unable to awake with stimulation (75%) whereas almost all Non-NE can have uninterrupted sleep (96%). The mean Serum ADH level is significantly low in NE (case) participants compared to the non-NE (control) group (Table 3).

4 | Discussion

Nocturnal enuresis [1] is involuntary bedwetting during sleep in patients with no congenital or acquired defects of the central nervous system. Global and ethnic variation is unclear, perhaps because access to medical attention varies widely and so cases often go unreported [15]. In this cross-sectional study, 80 school-going children were included in the age group of 6 to 15 years where majority of the children were among 6 to 8 years age group and the mean age was found among nocturnal children was 8.82 ± 2.71 years. Other study also showed similar results with maximum prevalence found in the age group of 8–9 years (22.96%) [16]. The study has also reported that with advancing age, the prevalence decreased.

This study showed nocturnal enuresis was slightly high among the female group. Similar results were seen in other studies [16] where other studies showed boys were more predominant [17, 18]. The present study had also reported that there were no statistically significant associations of education of the

household head, occupation of the father and mother and monthly income of the families among both groups. Other studies found that there was statistically significant association of nocturnal enuresis with lower socioeconomic status [19]. The study has also revealed different prevalence rates from different localities of our country. The majority of patients were from Dhaka city followed by other cities outside of Dhaka. Other studies also showed different prevalence among different regions of the world. The differences in the age groups and different socio-demographic characteristics were the main reasons in these different prevalence rates [16, 18].

The family history was also found to be a risk factor for nocturnal enuresis. It was shown that a family history of nocturnal enuresis with only one parent had a significantly higher percentage in case groups where no comparison group patient had this family history. Family history has been found to have a significant association including a family history of bedwetting, and consanguineous marriage. Family history of bedwetting in parents is predictive of bedwetting as was found in this study also. Other studies were also consistent with this finding [19, 20]. It has been shown that the majority of the children from the case group had frequent nocturnal enuresis where as a small number of children had infrequent nocturnal enuresis.

Our study discussed the Clinical and laboratory findings of the participants, and the parameters were non-significant among groups as we expected. Serum antidiuretic hormone was found significantly lower in case group than in comparison in our study with statistical significance. Normally, the production of more concentrated urine during nocturnal sleep occurs due to increased nocturnal plasma ADH levels. Decreased nocturnal ADH excretion leads to increased nocturnal urine production, which may lead to polyuria and NE. This is similar to several study findings [10, 11, 13]. The high percentage of reversed ADH secretion in NE patients supports this notion. Few other studies also found an association between ADH with nocturnal enuresis [21, 22]. In a study done in Egypt, low levels of diurnal antidiuretic hormone levels were found compared to a comparison group and a genetic study was done to find an association; and the results indicated positive associations [13].

It was shown that children with more enuretic night per week have lower diurnal ADH level in comparison to less enuretic night weekly with statistical significance which is similar to another study [13]. This study being a cross-sectional study, cannot comment on the longitudinal nature of spontaneous resolution with increasing age. The study was based only on the questionnaire and responses from the parents. Besides, all samples were collected from a single center and no generic association was not evaluated. ADH is a particularly unstable hormone, which can make it difficult to obtain measurements that perfectly reflect the in vivo situation. This is a known limitation in studies that involve ADH measurement. Again, both daytime and nighttime ADH samples were not taken to establish reversed rhythm of ADH among enuretic and comparison group. To accurately assess circadian variations, multiple samples collected at different times throughout the day and night would be required. Future research should address this gap by including a more comprehensive sampling schedule to better understand ADH's circadian rhythm in relation to nocturnal enuresis.

5 | Conclusion

This study evaluated the intriguing relationship between PNE in children and serum Antidiuretic Hormone [20] levels. We observed significantly lower ADH levels in children with PNE, suggesting a potential role of ADH in the pathophysiology of this condition. Additionally, a strong association was found between a family history of PNE and the presence of the condition in the child. This finding guides us for need of further genetic evaluation. The study was found to be consistent with the underlying mechanisms of nocturnal enuresis in children and the potential utility of ADH assessment in PNE management. The distinctive ADH pattern highlights its importance in understanding and potentially treating PNE in a perfectly designed way. This study contributes valuable insights into a common pediatric condition and offers a promising path for future investigations and therapeutic strategies.

Author Contributions

Jannatul Fardous: conceptualization, investigation, writing–original draft, methodology, validation; visualization, writing–review and editing, software, formal analysis, project administration, data curation. **Anjuman Ara:** visualization, data curation, methodology, investigation; writing–review and editing. **Md Iqbal Hossain:** visualization, methodology, formal analysis, data curation, writing–review and editing. **Asma Labony:** visualization, methodology, investigation, project administration, writing–review and editing. **Tanjila Afrin:** visualization, methodology, data curation, resources. **Rezwana Ashraf:** writing–review and editing, visualization, resources, supervision. **Reaz Uddin:** visualization, writing–review and editing, methodology. **Habiba Jesmin:** methodology, formal analysis, resources. **Md Kabir Alam:** supervision, writing–original draft, writing–review and editing. **Mohammad Ashraful Amin:** writing–review and editing, visualization, supervision, writing–original draft. **Anwar Hossain Khan:** supervision, project administration, writing–original draft. **Zahid Hasan Khan:** writing–original draft, writing–review and editing, visualization, supervision.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Transparency Statement

The lead author Zahid Hasan Khan affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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