

Comparison of Continuous and Intermittent Bolus Enteral Nutrition in Patients with Severe Traumatic Brain Injury: a Randomized Controlled Trial

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Abstract

Introduction: Severe traumatic brain injury (TBI) is associated with impaired gastric motility and dysregulated glucose homeostasis, making optimal enteral nutrition challenging. This study compared continuous and intermittent bolus enteral nutrition in terms of gastric residual volume (GRV), glycemic variability, and gastrointestinal tolerance in patients with severe TBI.

Patients and Methods: An assessor-blinded, randomized controlled trial was conducted in 60 adult patients with severe TBI admitted to the intensive care unit. Participants were randomly assigned to continuous (n = 30) or intermittent bolus enteral nutrition (n = 30) during the first 24 hours after ICU admission. GRV was measured every 4 hours using gastric ultrasonography. Glycemic variability was assessed using the coefficient of variation (CV), and diarrhea was recorded as a marker of gastrointestinal tolerance. GRV was analyzed using repeated-measures analysis of variance (ANOVA), while glycemic fluctuation and diarrhea incidence were analyzed using Fisher's exact and chi-square tests.

Results: Sixty patients were analyzed, with comparable baseline characteristics between groups. Repeated-measures ANOVA demonstrated a significant overall effect of feeding method on GRV ($F(1,58) = 158.235$, $p < 0.001$) and a significant time $\times$ group interaction (Greenhouse-Geisser corrected $F(3.980,230.814) = 3.437$, $p = 0.010$). During the 24-hour observation period, continuous feeding resulted in a lower overall GRV than intermittent bolus feeding (mean difference 18.9 mL; 95% CI 15.9–21.9). Glycemic fluctuation was similar between groups ($p = 0.500$), whereas diarrhea occurred less frequently with continuous feeding (20.0% vs 50.0%, $p = 0.008$).

Conclusion: During the first 24 hours of ICU admission, continuous enteral nutrition was associated with lower overall GRV and a lower incidence of diarrhea than intermittent bolus feeding, while glycemic fluctuation was comparable between groups. Further studies are warranted to evaluate long-term clinical outcomes.

Keywords: Enteral nutrition; Brain injuries; Intensive care units; Blood glucose; Gastric emptying

Introduction

Severe traumatic brain injury (TBI) continues to be a leading cause of morbidity and mortality globally, especially in critically ill patients in need of intensive care. These patients frequently develop a hypermetabolic and hypercatabolic state, accompanied by impaired gastric motility and metabolic dysregulation, which contribute to poor clinical outcomes.

Early nutritional support plays a pivotal role in mitigating catabolism and promoting recovery. However, nutritional management remains challenging due to feeding intolerance and glycemic instability.^{1,2}

Approximately 68% of patients with severe TBI develop malnutrition as a result of the systemic stress response, while stress-induced insulin resistance contributes to hyperglycemia.¹ In Indonesia, traumatic brain injury accounts for 11.9% of trauma cases, highlighting its clinical burden.³

Enteral nutrition is recommended as the preferred route of nutritional support in critically ill patients with preserved gastrointestinal function, as it maintains gut integrity and reduces infectious

complications compared with parenteral nutrition.⁴ Nevertheless, the optimal method for delivering enteral nutrition remains controversial. Intermittent bolus feeding is generally considered more physiological and practical, whereas continuous feeding has been hypothesized to improve gastrointestinal tolerance and metabolic stability. Previous studies and meta-analyses have demonstrated inconsistent results, with no clear superiority of either method in general critically ill populations. Importantly, evidence specifically evaluating patients with severe TBI remains limited.^{5,6}

Given the high risk of gastric intolerance, glycemic fluctuation, and diarrhea in severe TBI, determining the optimal enteral

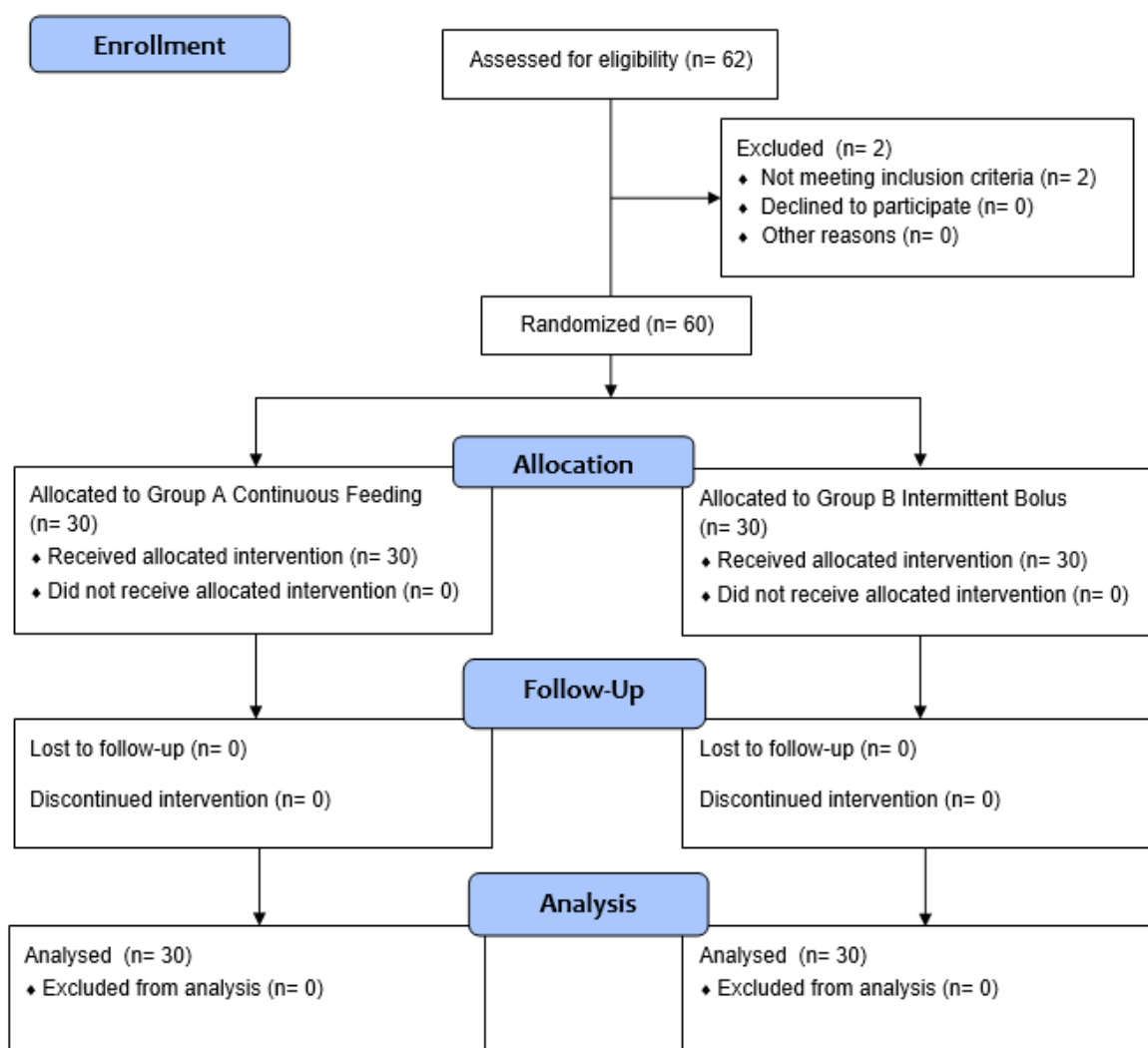


Figure 1. CONSORT Flow Diagram

feeding strategy is clinically relevant. This study aimed to compare continuous and intermittent bolus enteral feeding in terms of gastric residual volume, glycemic variability, and diarrhea in patients with severe TBI.

Patients and Methods

Trial Design

This study was a prospective, assessor-blinded, randomized controlled trial conducted in the intensive care unit of a tertiary referral hospital between November and December 2025. Patient recruitment commenced only after approval had been obtained from the Institutional Ethics Committee on 14 November 2025 (2767/UN14.2.2.VII.14/LT/2025). Informed written consent was obtained from all participants or their legally authorized representatives before enrolment.

Participants

Eligible participants were adult patients (≥ 18 years) with severe TBI, defined as a Glasgow Coma Scale (GCS) score ≤ 8 confirmed by clinical and radiological assessment. Eligible patients were required to have an indication for enteral nutrition via nasogastric tube and to initiate feeding within 24 hours of admission. Predicted body weight was restricted to 50–70 kg to ensure homogeneity in nutritional requirements.

Patients were excluded if they had pre-existing severe gastrointestinal disorders (including paralytic ileus or intestinal obstruction), required high-dose vasopressor support (norepinephrine >0.3 $\mu\text{g/kg/min}$), had treatment-limitation decisions, or declined participation.

Participants were withdrawn if they developed hemodynamic instability

requiring escalation of vasopressors, aspiration events, endocrine complications, were discharged from the intensive care unit within 24 hours, or died during the study period.

Interventions

All participants received enteral nutrition via a nasogastric tube using a standardized enteral formula to ensure consistency of nutritional composition across groups. The formula used in this study was a commercially available peptide-based enteral formula (Peptibren®, PT Kalbe Farma, Tbk), specifically formulated to support patients with neurological injury and high metabolic stress. This formula provides an energy density of approximately 1 kcal/mL, allowing adequate caloric delivery while minimizing fluid overload, which is particularly relevant in patients with severe TBI.

The use of a single standardized enteral formula in both intervention groups was intended to eliminate potential confounding effects related to differences in nutrient composition, thereby ensuring that the observed outcomes were attributable solely to the feeding method.

Participants assigned to the continuous group received enteral nutrition via infusion using a nutritional bag system. Feeding was initiated at 50 mL/h for the first 3 hours, followed by a 1-hour rest period, and continued cyclically over 24 hours. Water flushes of 50 mL were administered prior to each rest period. Gastric residual volume was monitored every 4 hours during feeding.

Participants assigned to the intermittent bolus group received enteral nutrition divided into six equal portions over 24 hours. Each bolus (approximately 150 mL) was administered every 4 hours by gravity

over 5–10 minutes. Water flushes of 50 mL were administered after each feeding.

In both groups, enteral feeding was initiated within the first 24 hours following ICU admission and monitoring of outcomes was conducted during this period.

Outcomes

The primary outcome was GRV, measured every 4 hours using bedside gastric ultrasonography. All ultrasound examinations were performed by a single senior anesthesiology resident who had received formal training in gastric ultrasonography, thereby minimizing inter-operator variability. Patients were positioned in the right lateral decubitus position, and a low-frequency curved-array probe was placed over the epigastric paramedian region to identify the gastric antrum. The antero-posterior and craniocaudal diameters of the antrum were measured, and the antral cross-sectional area was calculated using the validated Perlas formula to estimate GRV. Measurements were obtained using a standardized scanning protocol without averaging multiple acquisitions. Formal intra- or inter-observer reliability testing was not performed.

Secondary outcomes included glycemic variability and incidence of diarrhea. Blood glucose levels were measured at baseline, 2 hours after feeding initiation, and subsequently every 4 hours using a portable glucometer. Glycemic variability was assessed using the coefficient of variation (CV), calculated by dividing the standard deviation by the mean glucose level and multiplying by 100%. A CV $\leq 36\%$ was considered indicative of stable glycemic control.

Diarrhea was established as the passage of loose or watery stools occurring more than

three times within a 24-hour period or stool volume exceeding 200 g/day, as documented by ICU nursing staff.

Sample Size

Sample size was calculated based on the primary outcome (gastric residual volume), using the formula for comparison of two independent means:

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$$

In this formula, n represents the required sample size per group. The term $Z_{\alpha/2}$ corresponds to the standard normal deviate for a significance level (α) of 5%, while Z_{β} corresponds to a statistical power of 80%. The parameters σ_1 and σ_2 denote the standard deviations of the outcome in each group, and $(\mu_1 - \mu_2)$ represents the expected difference in mean GRV between the two groups.

The calculation was based on data reported by Banaei et al. (2022), which reported a mean GRV of 39.78 mL in the continuous group and 43.98 mL in the intermittent bolus group, with standard deviations of 4.94 and 7.18, respectively.⁵ Using these parameters ($Z_{\alpha/2} = 1.96$ and $Z_{\beta} = 0.84$), the minimum required sample size was 27 participants in each group.

To account for potential dropout, an additional 10% was added, resulting in a final sample size of 30 participants per group. Therefore, a total of 60 participants were included in this study.

Randomisation

Participants were enrolled through consecutive sampling and randomly assigned in a 1:1 ratio using a computer-generated randomization sequence. Allocation concealment was maintained with sealed opaque envelopes that were

opened immediately before the intervention.

Blinding

Due to the nature of the intervention, personnel administering enteral nutrition could not be blinded. However, outcome assessments, including gastric residual volume, blood glucose measurements, and gastrointestinal outcomes, were performed by an independent investigator blinded to group allocation. The treating clinical team was also blinded to treatment allocation, except for the personnel responsible for administering the assigned feeding protocol.

Statistical Methods

Statistical analyses were performed using IBM SPSS Statistics (IBM Corp., Armonk, NY, USA). All analyses followed the intention-to-treat principle. Continuous variables were summarized as mean $\pm$ standard deviation or median (interquartile range), according to data distribution, while categorical variables were expressed as frequencies and percentages. Data normality was assessed using the Kolmogorov–Smirnov test.

The primary outcome, gastric residual volume (GRV), was analyzed using repeated-measures analysis of variance (ANOVA), with feeding method as the between-subject factor and time as the within-subject factor. Mauchly's test was used to assess sphericity, and the Greenhouse–Geisser correction was applied when the assumption of sphericity was violated. Continuous baseline variables were compared using the independent *t*-test or Mann–Whitney *U* test, as appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test. A two-tailed *P* < 0.05 was considered statistically significant.

Results

A total of 60 patients with severe TBI were enrolled and included in the final analysis, with 30 patients allocated to the continuous enteral nutrition group and 30 to the intermittent bolus feeding group. The mean age was 38.67 ± 12.88 years in the continuous group and 38.37 ± 11.48 years in the intermittent bolus group. Male patients predominated in both groups, accounting for 63.3% vs 60.0% of participants in the continuous and intermittent bolus groups, respectively. Body mass index and other baseline characteristics were comparable between the groups, with no statistically significant differences observed (Table 1).

Group A: continuous feeding group; Group B: intermittent bolus group; BMI: Body Mass Index, ^T= Independent T-test, ^C: Chi-square test.

Table 1. Baseline characteristics of the study participants

Variables	Group A (n=30)	Group B (n=30)	<i>p</i> -value
Age (years), mean $\pm$ SD	38.67 ± 12.88	38.37 ± 11.48	0.462 ^T
Sex, n(%)			
Male	19 (63.3)	18 (60)	0.791 ^C
Female	11 (36.7)	12 (40)	
Body weight (kg), mean $\pm$ SD	55.57 ± 7.76	58.60 ± 9.89	0.096 ^T
Height (cm), mean $\pm$ SD	162.50 ± 8.10	162.20 ± 7.30	0.359 ^T
BMI (kg/m ²), mean $\pm$ SD	21.21 ± 3.46	22.20 ± 4.30	0.165 ^T

Repeated-measures ANOVA demonstrated that GRV changed significantly over time (Greenhouse–Geisser corrected $F(3.980, 230.814) = 18.360$, $p < 0.001$, partial $\eta^2 = 0.240$). A significant interaction between time and feeding method was observed

($F(3.980, 230.814) = 3.437, p = 0.010$, partial $\eta^2 = 0.056$), indicating that the pattern of GRV over time differed between the continuous and intermittent bolus feeding groups. Moreover, the continuous enteral nutrition group had a significantly lower overall GRV than the intermittent bolus feeding group throughout the 24-hour observation period ($F(1, 58) = 158.235, p < 0.001$, partial $\eta^2 = 0.732$) (Tables 2 and 3).

Table 2. Comparison of gastric residual volume at 4, 8, 12, 16, 20, and 24 hours

Variables, GRV (mL), mean $\pm$ SD	Group A (n=30)	Group B (n=30)
GRV at 4 hours	69.67 $\pm$ 16.07	93.32 $\pm$ 9.93
GRV at 8 hours	67.73 $\pm$ 11.31	94.39 $\pm$ 9.93
GRV at 12 hours	74.54 $\pm$ 10.67	93.43 $\pm$ 10.51
GRV at 16 hours	85.73 $\pm$ 9.53	98.18 $\pm$ 12.90
GRV at 20 hours	83.79 $\pm$ 10.53	101.33 $\pm$ 13.47
GRV at 24 hours	88.60 $\pm$ 11.18	102.61 $\pm$ 15.31

Group A: continuous feeding group; Group B: intermittent bolus group, GRV: Gastric Residual Volume

Glycemic variability did not differ significantly between groups. Stable glycemic control was observed in 29 patients (96.7%) in the continuous group and 28 patients (93.3%) in the intermittent bolus group, with no statistically significant difference ($p = 0.500$) (Table 4).

In contrast, the incidence of diarrhea was significantly lower in the continuous enteral nutrition group than in the intermittent bolus group. Diarrhea was observed in 6 patients (20.0%) in the continuous group compared with 15 patients (50.0%) in the intermittent bolus group, representing a statistically significant difference (Table 5).

Discussion

Patients with severe TBI in the intensive care unit experience a hypermetabolic and hypercatabolic state, which predisposes them to malnutrition, impaired gastric emptying, and metabolic instability. This condition is driven by neuroendocrine stress responses, including increased catecholamines, cortisol, and insulin resistance, which contribute to hyperglycemia and secondary brain injury.^{1,2,7} Enteral nutrition remains the preferred route of nutritional support as it preserves gut barrier integrity, reduces infectious complications, and is more physiologically appropriate than parenteral nutrition.⁴ However, impaired gastric motility in this population makes the choice of feeding method an important determinant of gastrointestinal tolerance and clinical outcomes.

The primary finding of this study was that continuous enteral nutrition was associated with significantly lower gastric residual volume than intermittent bolus feeding throughout the 24-hour observation period. Repeated-measures ANOVA demonstrated both a significant overall effect of feeding method and a significant interaction between feeding method and time. This finding is consistent with the physiological mechanism of gastric emptying, where gradual nutrient delivery reduces intragastric pressure, improves antral motility, and prevents vagally mediated inhibition of gastric emptying. In contrast, bolus feeding introduces a large volume within a short period, leading to gastric distension, increased intragastric pressure, and delayed gastric emptying.⁸

Table 3. Results of repeated-measures ANOVA for gastric residual volume during the 24-hour observation period

Repeated-measures ANOVA			
(Greenhouse–Geisser correction)	F (df)	<i>p</i>-value	partial η^2
Time effect	18.360 (3.980, 230.814)	<0.001	0.240
Group effect	158.235 (1, 58)	<0.001	0.732
Time × Group interaction	3.437 (3.980, 230.814)	0.010	0.056

GRV = gastric residual volume; η^2 = partial eta squared. Data were analyzed using repeated-measures ANOVA. Because Mauchly's test indicated violation of the sphericity assumption ($W = 0.584$, $p = 0.007$), Greenhouse–Geisser correction was applied to the within-subject (time) and time × group effects

Table 4. Comparison of glycemic variability between groups

Glycemic Variability, n (%)	Group A (n=30)	Group B (n=30)	<i>p</i>-value
Stable	29 (96.7)	28 (93.3)	0.500 ^f
Unstable	1 (3.3)	2 (6.7)	

Group A: continuous feeding group; Group B: intermittent bolus group, ^f: Fisher's exact test (two cells had expected counts < 5)

Table 5. Comparison of gastrointestinal tolerance based on diarrhea incidence

Diarrhea Incidence, n (%)	Group A (n=30)	Group B (n=30)	<i>p</i>-value
Yes	6 (20)	15 (50)	0.008 ^c
No	24 (80)	15 (50)	

Group A: continuous feeding group; Group B: intermittent bolus group, ^c: *Chi-square test*.

These findings are consistent with previous randomized trials and recent meta-analyses demonstrating improved gastrointestinal tolerance and reduced feeding intolerance with continuous feeding.^{6,9} Current clinical guidelines also support this approach, recommending continuous enteral nutrition in patients with severe neurological injury due to better tolerance profiles.⁴

From a clinical perspective, lower gastric residual volume may indicate better enteral feeding tolerance and fewer interruptions in nutritional delivery. However, this study

did not evaluate aspiration-related complications or other longer-term clinical outcomes; therefore, these potential benefits should be interpreted cautiously. These factors are particularly important in patients with severe TBI, where maintaining adequate nutritional support plays a critical role in recovery and prevention of complications.^{10,11}

Although the reduction was modest, even small improvements in feeding tolerance may reduce interruptions in nutritional delivery during the early phase of neurocritical care. Therefore, its clinical

significance should be interpreted cautiously, particularly because routine GRV monitoring alone is no longer recommended to assess feeding intolerance or aspiration risk. Nevertheless, the lower GRV observed in the continuous feeding group was accompanied by a significantly lower incidence of diarrhea, suggesting improved gastrointestinal tolerance. Whether this reduction translates into clinically important outcomes such as fewer aspiration events, reduced pneumonia, shorter ICU stay, or improved survival remains to be determined in future studies.

No statistically significant difference was identified between the two feeding methods for glycemic fluctuation. This finding suggests that glycemic control in critically ill patients is influenced predominantly by the systemic stress response rather than by the method of enteral nutrient delivery. Severe TBI triggers a neuroendocrine cascade characterized by increased catecholamines, cortisol, glucagon, and insulin resistance, leading to stress-induced hyperglycemia.^{1,7} Elevated glucose levels can exacerbate cerebral edema, oxidative stress, and ischemic injury, contributing to worse neurological outcomes.² However, previous studies and meta-analyses have shown that the method of enteral nutrition does not significantly affect glycemic fluctuation in critically ill populations. Therefore, glycemic management should primarily rely on standardized insulin protocols and close glucose monitoring rather than modification of feeding strategy alone.^{12,13}

The incidence of diarrhea was significantly lower in the continuous feeding group, indicating better gastrointestinal tolerance compared with intermittent bolus feeding. This finding may be explained by differences in intestinal physiology.

Continuous feeding provides a steady nutrient flow that maintains stable intestinal osmolality and promotes efficient absorption, whereas bolus feeding increases osmotic load and stimulates rapid intestinal transit, leading to diarrhea.⁸ Additionally, rapid nutrient delivery may reduce mucosal contact time, impairing absorption and increasing luminal fluid secretion. Similar findings have been reported in critically ill populations, where intermittent feeding is associated with higher rates of diarrhea and gastrointestinal intolerance.^{6,9,11,14}

Clinically, reduced diarrhea may improve fluid balance, electrolyte homeostasis, and continuity of enteral nutrition. However, whether these benefits translate into improved patient recovery or other long-term clinical outcomes was not evaluated in the present study.⁷

This study provides additional evidence supporting continuous enteral nutrition may improve short-term gastrointestinal tolerance in patients with severe TBI without adversely affecting glycemic fluctuation during the first 24 hours of ICU care.

This study has several limitations should be acknowledged. First, clinically important outcomes such as aspiration, ventilator-associated pneumonia, adequacy of nutritional delivery, ICU length of stay, and mortality were not evaluated. Second, this study did not assess gastrointestinal hormonal biomarkers such as motilin or gastrin, which could provide further insight into the mechanisms underlying gastric motility and feeding tolerance. Future studies with longer observation periods and inclusion of mechanistic biomarkers are needed to better understand the long-

term impact of enteral feeding strategies in this population.

A further limitation is that detailed data on concomitant ICU therapies that may influence gastric emptying and glycemic control, such as sedatives, opioids, neuromuscular blocking agents, prokinetics, antiemetics, and stress-ulcer prophylaxis, were not systematically collected. Although all patients received routine ICU care according to institutional practice, the potential influence of these co-interventions cannot be excluded. Finally, the relatively small sample size may have limited the statistical power to detect differences in secondary outcomes.

Conclusion

Continuous enteral nutrition was associated with lower gastric residual volumes and a lower incidence of diarrhea than intermittent bolus feeding during the first 24 hours of ICU admission in patients with severe traumatic brain injury, while glycemic fluctuation did not differ significantly between groups. These findings are limited to the 24-hour observation period, and further studies are needed to determine whether they translate into improved long-term clinical outcomes.

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Conflict of Interest

The author(s) report no conflict of interest.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Author's Contributions

Conceptualization: AFC, SS. Methodology: AFC. Investigation: AFC, IWA, SS. Data curation: AFC, IWA, SS. Formal analysis: AFC, IBK. Writing – original draft: AFC. Writing – review & editing: AFC, IWA, SS. Supervision: IBK, IWA. All authors approved the final manuscript.

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