DOI: 10.1111/tmi.13675

RESEARCH ARTICLE

Assessing the performance of clinical diagnostic models for dehydration among patients with cholera and undernutrition in Bangladesh

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Abstract

Objective: Accurately assessing dehydration severity is a critical step in reducing mortality from diarrhoea, but is complicated by cholera and undernutrition. This study seeks to assess the accuracy of two clinical diagnostic models for dehydration among patients over five years with cholera and undernutrition and compare their respective performance to the World Health Organization (WHO) algorithm.

Methods: In this secondary analysis of data collected from the NIRUDAK study, accuracy of the full and simplified NIRUDAK models for predicting severe and any dehydration was measured using the area under the Receiver Operator Characteristic curve (AUC) among patients over five with/without cholera and with/without wasting. Bootstrap with 1000 iterations was used to compare the m-index for each NIRUDAK model to that of the WHO algorithm.

Results: A total of 2,139 and 2,108 patients were included in the nutrition and cholera subgroups respectively with an overall median age of 35 years (IQR = 42) and 49.6% female. All subgroups had acceptable discrimination in diagnosing severe or any dehydration (AUC > 0.60); though the full NIRUDAK model performed best among patients without cholera, with an AUC of 0.82 (95%CI:0.79, 0.85) and among patients without wasting, with an AUC of 0.79 (95%CI:0.76, 0.81). Compared with the WHO's algorithm, both the full and simplified NIRUDAK models performed significantly better in terms of their m-index ($p < 0.001$) for all comparisons, except for the simplified NIRUDAK model in the wasting group.

Conclusions: Both the full and simplified NIRUDAK models performed less well in patients over five years with cholera and/or wasting; however, both performed better than the WHO algorithm.

KEYWORDS
cholera, dehydration, diarrhoea, global health, undernutrition

Sustainable Development Goals: Good Health and Well-Being, Clean Water and Sanitation.

INTRODUCTION

Accounting for over 1.4 million reported deaths in 2019, diarrhoeal disease is the 8th leading cause of death globally among children and adults [1]. In 2019, there were over 6.5 billion cases of diarrhoeal disease globally with the highest burden of disease in Africa and southeast Asia [1]. While most cases of diarrhoea are self-resolving, up to 5% of cases in adults and older children lead to moderate or severe morbidity requiring medical intervention [2]. Bacterial pathogens account for some of the most severe and prevalent forms of acute diarrhoea in adults and older children with *Vibrio cholerae* (*V. cholerae*) being one of the most prevalent pathogens. *V. cholerae*, the pathogen responsible for cholera, produces an exotoxin that causes intestinal cells to secrete an enormous amount of water, leading to diarrhoea, decreased absorptive function and rapid loss of fluids and salts. It contributes to at least 1.2 million cases every year in endemic countries [3–6].

Undernutrition is one of the most important predictors of mortality with acute diarrhoea, especially among children in whom childhood wasting was responsible for 80.4% of diarrhoea deaths in 2016 [7]. Globally, in 2019 nutritional deficiencies accounted for over 49 million disability-adjusted life-years (DALYs) across all ages [1]. As is the case with diarrhoeal diseases, low-income countries are also more likely to be affected by undernutrition, ranking 6th in prevalent cases in 2019 among all ages [3]. Several studies have found that undernutrition exacerbates intestinal infections by increasing the duration and severity of illness. Conversely, enteric infections can impair absorptive function, decrease dietary intake and increase nutrient requirement, thereby increasing the risk of developing undernutrition [8–11]. This synergistic cycle can lead to worsening illness and long-term sequelae, which are especially problematic in younger children with underdeveloped immune systems and the elderly who may have other chronic co-morbidities [8–10].

Since mortality in patients with acute diarrhoea is caused by dehydration, accurately assessing dehydration severity remains a critical step in reducing morbidity and mortality from diarrhoeal diseases [13–18]. Though prior research has evaluated the relationship between undernutrition and dehydration in children, literature on the relationship between undernutrition and dehydration assessment specifically in adults [19,20] is scarce. Dehydration by as little as 2% of body weight, which corresponds to ~3–5% reduction in total body water, can lead to cognitive and physical impairment [21–23]. This is especially concerning among elderly populations, where co-morbidities can exacerbate the risk of dehydration [21–23]. A prospective cohort study in the United Kingdom found that elderly participants dehydrated at admission were six times more likely to die in hospital than those euhydrated [21]. Furthermore, determining the dehydration status in patients with acute diarrhoea has profound consequences for their treatment course as it can reduce the morbidity and mortality that results from inappropriate hydration of patients [24].

WHO's Integrated Management of Adolescent and Adult Illness (IMAI) guidelines recommend a simple four-symptom algorithm for determining the severity of dehydration in adults with acute diarrhoea [25]. Although recommended by WHO for use worldwide as the current standard for assessing dehydration and incorporated into Ministry of Health guidelines in most countries, the WHO IMAI algorithm has not yet been validated in a prospective observational study. It was originally adapted from a similar algorithm for children under five years, whose physiology and diarrhoea aetiology differ from older children and adults [4, 26–29,]. To fill this gap, two clinical diagnostic models, the full and simplified NIRUDAK models, were recently empirically derived and internally validated to assess dehydration severity in patients over five years with acute diarrhoea [30]. Despite the potential for reducing the morbidity and mortality of diarrhoeal diseases, the accuracy of these scoring systems has yet to be evaluated among two distinct subgroups of adolescents and adults with acute diarrhoea and undernutrition or those with diarrhoea specifically due to cholera. This secondary analysis of the NIRUDAK study seeks to assess the accuracy of the full and simplified NIRUDAK models among patients over five years of age with undernutrition and those with cholera and compare their respective performance to the WHO IMAI algorithm in these subgroups.

MATERIALS AND METHODS

Study setting and population

This study is a secondary analysis of data collected from the Novel Innovative Research for Understanding Dehydration in Adults and Kids (NIRUDAK) Study. The NIRUDAK Study was a prospective cohort study of patients over five years presenting with acute diarrhoea between March 2019 and March 2020 to the rehydration unit at the International Centre for Diarrhoeal Disease Research, Bangladesh's (icddr,b) Dhaka Hospital, which provides free clinical services to the surrounding urban and rural areas [31].

Study design

All patients over the age of five years old presenting with acute diarrhoea to icddrb's Short Stay Unit were eligible for enrolment. Study staff randomly selected patients for screening on arrival 24 h per day, seven days per week by blindly drawing a marble from a black pouch filled with white and coloured marbles each time a new patient arrived at the hospital. When a coloured marble was drawn from the pouch, the patient was selected for screening and enrolment. Acute diarrhoea was defined using the WHO definition of three or more loose or watery stools per day but not longer than 14 days [12]. Selected patients were excluded if they met the following criteria: diarrhoea lasting more than seven days, having fewer than three loose stools in the past 24 h

and having a definitive alternative diagnosis to gastroenteritis. All patients previously enrolled in the study were also excluded from the study. Patients and/or their guardians who did not meet an exclusion criterion were informed by study staff about the study's goals, risks and benefits. Verbal/written consent was obtained in the local language, Bangla. Ethical approval was obtained from icddr,b's and the Rhode Island Hospital's Institutional Review Board.

Staff training and oversight

Local general practice nurses with at least two years of clinical experience were hired to collect data for this study. Prior to the start of the study, research staff received one week of practical training on all study procedures, including the assessment of clinical signs of dehydration.

Study procedures

Upon consent, clinical assessments for signs of dehydration were completed independently by two research nurses blinded to each other's assessment. Symptoms/signs of dehydration were chosen *a priori* based on a review of the literature and consultation with expert clinicians at icddr,b (Appendix 1) [30]. Patients were weighed on arrival and again every 4 h to the nearest tenth of a kilogram using an electronic scale to determine their post-hydration stable weight. Patients who did not achieve a stable weight before discharge were asked to return for a post-illness weight check once their diarrhoea had resolved completely. Mid-upper arm circumference (MUAC) was measured in millimetres using standardised measuring tapes. After completion of the initial assessment, all patients were managed according to standard icddr,b's protocols, which follow WHO's IMAI and Integrated Management of Childhood Illness (IMCI) guidelines [25,29]. Socio-environmental, historical and demographic information were obtained from either the patient or guardian. Two stool specimens were collected from each patient – one for analysis to the clinical microbiology laboratory and one for storage in 70% ethanol. Each specimen was screened for common enteric pathogens using stool culture. Study procedures were not allowed to delay any emergent care, such as placing an intravenous line.

Assessment of dehydration status

Per cent weight change with rehydration was used as the criterion standard for per cent dehydration, which correlates almost perfectly with per cent volume loss and has been recommended as the most practical method for assessing per cent dehydration in patients over 5 years old by several studies [32–36]. As a litre of water weighs one kilogram, each litre of water lost in sweat, urine or diarrhoea results in one kilogram of body weight loss, and each litre gained through rehydration results in one kilogram of weight gain. Generally, patients with dehydration rapidly gain weight as they are rehydrated until they achieve their pre-illness stable weight at which point, they will stop gaining weight as their kidneys diuresis excess fluid [32]. For each patient enrolled, the two highest consecutive weight measurements that differed by less than 2% were averaged to determine their stable weight, which was used as their post-illness weight [37]. For patients who did not reach a stable weight prior to discharge, their return weight was used as their post-illness weight. Per cent dehydration was calculated using the following formula [37]:

Per cent Dehydration = 100%*[(Post-Illness Weight–Admission Weight)/Post-Illness Weight].

Based on review of literature and international guidelines developed by WHO and the United States Center for Disease Control, we categorise severe dehydration as >9%, some dehydration as 3–9% and no dehydration as <3% [30,38–40].

Assessment of nutritional status

Several studies support the use of MUAC as an efficient screening tool for evaluating nutritional status among patients over five years old, especially adults [41–45]. Compared with body mass index (BMI), MUAC is not only a less resource-intensive measure but is also more strongly and consistently associated with an increased mortality risk in older individuals with a low initial MUAC than low BMI [41,45–48]. For this study, nutritional status was determined using the MUAC measurement collected during initial clinical assessment. Patients between the ages of 5 and 9 years were categorised as wasted if the MUAC measurement was <145 mm and as non-wasted if it was ≥145 mm. Patients between the ages of 10 and 14 years were categorised as wasted if MUAC measurement was <185 mm and as non-wasted if it was ≥185 mm. For patients 15 years of age and older, wasting was defined as a MUAC measurement <210 mm and non-wasting if it was ≥210 mm (Table 1) [49–51].

Assessment of cholera status

Patients were classified as having *V. cholerae* via laboratory confirmation. Isolation, identification, serogrouping and

TABLE 1 MUAC cut-off measurements and classification

Age (years)	MUAC Measurement (mm)	Classification
5 – 9	<145	Wasting
5 – 9	≥145	Non-Wasting
10 – 14	<185	Wasting
10 – 14	≥185	Non-Wasting
≥ 15	<210	Wasting
≥ 15	≥210	Non-Wasting

biotyping of stool samples were performed using standard procedures [52]. *V. cholerae* was cultured and isolated by growth on tellurite taurocholate gelatin agar (TTGA) media with enrichment in bile peptone broth. Only samples which were negative in direct culture were subcultured. TTGA plates were checked for distinct *V. cholerae* colonies – smooth, transparent, black-centred colonies with gelatin liquefaction. Microbial identification was completed according to Vibrio spp. Identification Flow Sheet. Kirby-Bauer standard disc diffusion method on Muller–Hinton agar with commercial discs was used to determine antimicrobial susceptibility [53]. For the purpose of this study, patients who did not have culture growth or were negative for *V. cholera* were categorised as non-cholera, while those who had a laboratory confirmed positive result were categorised in the cholera group.

Data analysis

Demographic and clinical characteristics were analysed using descriptive statistics, including number/proportions for categorical variables and medians with corresponding interquartile ranges (IQR) for continuous variables. The methods used for the derivation and internal validation of the full and simplified NIRUDAK models have been published previously [30].

Model assessment and comparison

The performance of three clinical diagnostic models of dehydration in patients over five years of age (the simplified NIRUDAK model, the full NIRUDAK model and the WHO algorithm) was compared in two distinct subgroups: by nutritional status (wasting versus no wasting) and diarrhoea type (cholera versus non-cholera). Both NIRUDAK models were derived using forward stepwise regression techniques on the entire study population and internally validated using a bootstrap, while the WHO IMAI algorithm, which utilises four predictors, has not been validated for the assessment of dehydration in patients over five years old (Appendix 2) [30]. Each model's accuracy in predicting severe dehydration or any dehydration was assessed for discrimination using the area under the receiver-operating characteristic (ROC) curve (AUC) within both the nutrition and cholera subgroups. Using these ordinal models, two submodels were compared within each subgroup: one for severe dehydration (severe versus not severe) and one for any dehydration (severe/some versus none). The m-index was computed using the weighted average of the six pairwise AUC values (i.e. none versus some, some versus none, some versus severe, severe versus some, none versus severe and severe versus none) to create a single measure of accuracy for each model [54,55]. The average m-index is a measure of accuracy for ordinal prediction models similar to the AUC, where a values of 0.5 is no better than chance and 1 represents a perfect model. Internal validation of the three models was also performed in each subgroup using bootstrapping with 1000 iterations to correct for over-optimism by estimating the m-index and then comparing the m-index of each NIRUDAK model to the WHO IMAI algorithm. The m-index computed on each bootstrap data set *b* and its complement (the observations left out of the bootstrap dataset) was denoted by $C^{WHO}_{train,b}$ and $C^{WHO}_{test,b}$, respectively, for the WHO model, and by $C^{NIRUDAK}_{train,b}$ and $C^{NIRUDAK}_{test,b}$, respectively, for the NIRUDAK models. P-values for the comparison were calculated as the proportion where $C^{WHO}_{train,b} < C^{NIRUDAK}_{train,b,}$ and as the proportion where $C^{WHO}_{test,b} < C^{NIRUDAK}_{test,b}$. Statistical significance was established at an alpha level of 0.001. All statistical analyses were performed using R Version 3.6.3.

RESULTS

Enrolment and study population characteristics

From March 2019 to March 2020, a total of 4,440 patients over five years presenting to icddr,b with diarrhoea were randomly selected for screening, of whom 2,172 were enrolled in the NIRUDAK study [30]. A total of 2039 patients achieved a stable weight prior to discharge with a median time of 18 h. Of the 133 patients who did not achieve a stable weight prior to discharge, 107 returned to Dhaka Hospital to obtain a final weight within a median time of 3 days [30]. After excluding 33 (1.5%) patients missing data on either their final post-illness weight ($n = 26$) or one or more predictors ($n = 7$), 2,139 were included in the nutritional subgroup (Figure 1). For the cholera subgroup, after excluding an additional 31 patients who did not have a stool culture completed, 2,108 were included in this subgroup analysis (Figure 1).

The overall median age for enrolled patients was 35 years (25^{th} and 75^{th} percentile 18 and 60 years). Females comprised 49.6% of the study participants (Table 2).

Model performance

Cholera subgroups

Discrimination, measured using the AUC, for predicting severe dehydration was 0.70 for the full NIRUDAK model and 0.64 for the simplified NIRUDAK model among those with cholera. By contrast in the non-cholera subgroup, the full and simplified NIRUDAK models showed stronger performance (AUC 0.82 and 0.76, respectively). For predicting any dehydration, the full NIRUDAK model had an AUC of 0.72 and the simplified NIRUDAK model had an AUC of 0.70 among patients with cholera. Similarly to the severe dehydration category, the AUC for the full (0.76) and simplified (0.73) NIRUDAK models in the non-cholera subgroup performed better for those categorised in the non-cholera subgroup (Table 3) (Figure 2).

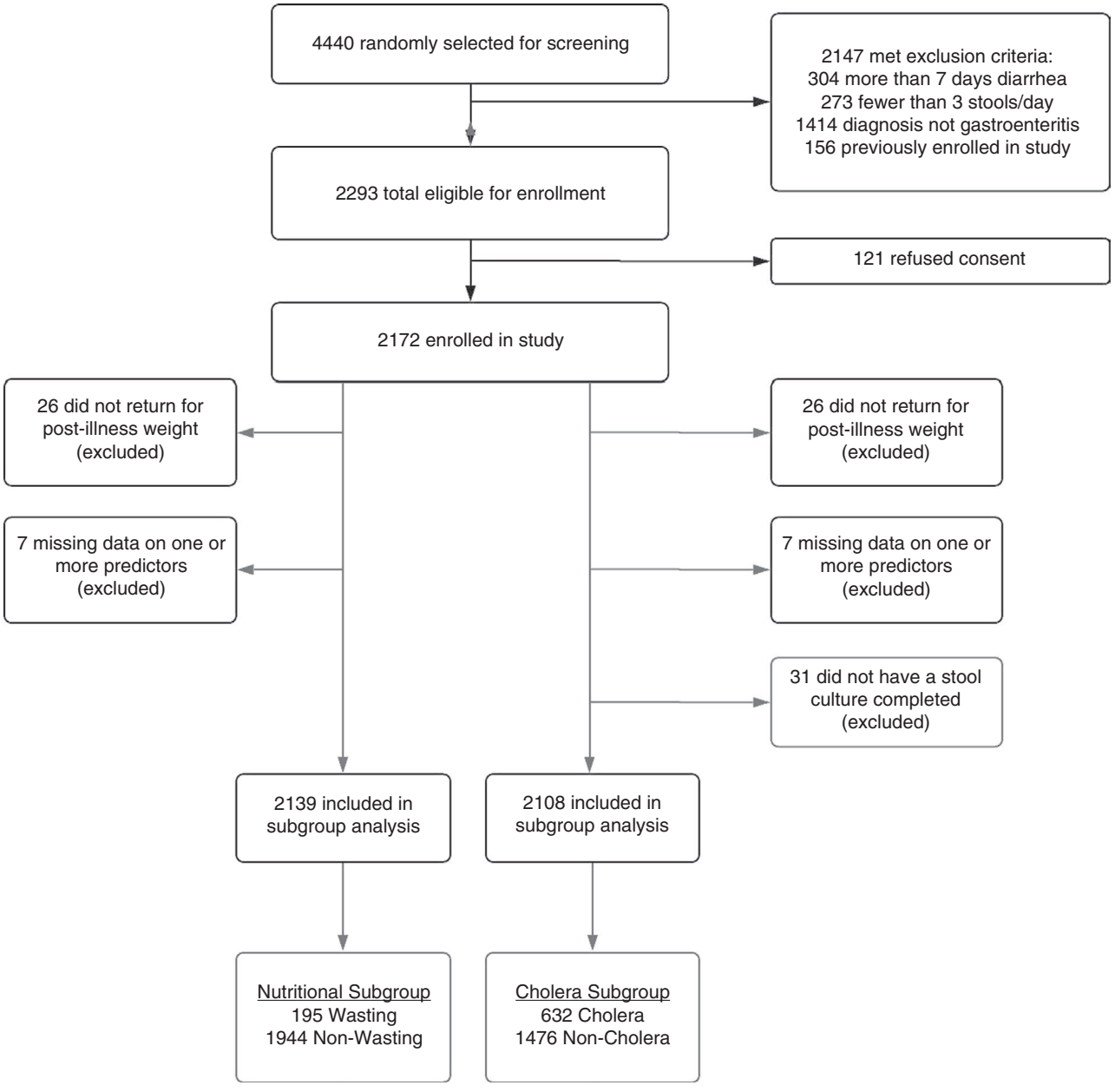

FIGURE 1 Study flow diagram for patient enrolment

Nutrition subgroups

For patients with wasting, the full NIRUDAK model had an AUC of 0.69, and the simplified NIRUDAK model had an AUC of 0.67 in predicting severe dehydration. Conversely, the AUC performed better among the non-wasting subgroup for both the full and simplified NIRUDAK models (0.79 and 0.73 respectively). For predicting any dehydration, the full NIRUDAK model had an AUC of 0.69 and the simplified NIRUDAK model had an AUC of 0.65 for patients categorised with wasting. As was the case in the severe dehydration category, the AUC had a stronger performance for the full (0.77) and simplified (0.73) NIRUDAK models in the non-wasting subgroup (Table 4) (Figure 3).

Model validation and comparison to WHO IMAI algorithm

Cholera subgroups

Overall, the three models among those without cholera performed better than among those in the cholera subgroup. Among those with and without cholera, all three models had the same performance on the training data as their respective validation data except for the NIRUDAK simplified model which performed slightly better on the validation data for those with cholera (0.67 versus 0.68) (Table 5). The best performing model with the highest average m-index across 1000 bootstrap iterations was the full NIRUDAK model within the non-cholera subgroup (0.76, 95% CI: 0.74, 0.79),

TABLE 2 Population characteristics of patients enrolled in the study

	Diarrhoea Status		Nutritional Status	
	Cholera (*N* = 632)	**Non-Cholera (*N* = 1476)**	**Wasting (*N* = 195)**	**Non-Wasting (*N* = 1944)**
Sociodemographic Variables[a]				
Age (years)	26.5 (15, 60)	35 (18, 60)	16 (11, 60)	35 (19, 60)
Sex				
Female	284 (44.9)	761 (51.6)	109 (55.9)	954 (49.1)
Male	348 (55.1)	715 (48.4)	86 (44.1)	990 (50.9)
Home location				
Urban	526 (83.2)	1079 (73.1)	148 (75.9)	1480 (76.1)
Rural/Suburban	106 (16.8)	397 (26.9)	47 (24.1)	464 (23.9)
Years of Education[b]	4 (0, 8)	4 (0, 8)	3 (0, 6)	4 (0, 8)
Monthly household income (USD)	153 (118, 212)	165 (118, 236)	142 (118, 189)	165 (118, 236)
Clinical Variables[a]				
Days of diarrhoea prior to arrival	0 (0, 1)	0 (0, 1)	1 (0, 2)	0 (0, 1)
Diarrhoeal episodes in past 24 h	15 (10, 20)	15 (10, 20)	15 (10, 20)	15 (10, 20)
Dehydration Category				
Severe dehydration	101 (16.0)	175 (11.9)	58 (29.7)	219 (11.3)
Some dehydration	447 (70.7)	971 (65.8)	109 (55.9)	1322 (68.0)
No dehydration	84 (13.3)	330 (23.4)	28 (14.4)	403 (20.7)

[a]Categorical variables were summarised as number (per cent), continuous variables summarised as median (25th, 75th percentiles).
[b]For patients under 16 years old, years of mother's education was used.

TABLE 3 ROC AUC by cholera status among patients over five years old

	ROC AUC (95% Confidence Interval)	
	Severe Dehydration	**Any Dehydration**
Full NIRUDAK Model		
Cholera	0.70 (0.65, 0.75)	0.72 (0.66, 0.78)
Non-Cholera	0.82 (0.79, 0.85)	0.76 (0.73, 0.79)
Simplified NIRUDAK Model		
Cholera	0.64 (0.59, 0.69)	0.70 (0.64, 0.76)
Non-Cholera	0.76 (0.72, 0.80)	0.73 (0.70, 0.76)

while the lowest m-index was demonstrated by the WHO model within the cholera subgroup (0.58, 95% CI=0.54, 0.61). As illustrated in Figure 4, both NIRUDAK models performed significantly better than the WHO IMAI algorithm in terms of their m-index for both those with and without cholera ($p < 0.001$ for all comparisons).

Nutrition subgroups

All three models in both the wasting and non-wasting categories either had the same or better performance on the training data compared with their respective validation data. The best performance was observed among those with non-wasting by the NIRUDAK full model (0.75, 95% CI = 0.73, 0.77), while the WHO model among those with wasting had the lowest performance (0.55, 95% CI = 0.49, 0.60). Overall, all models had better performance in the non-wasting group compared to the wasting group (Table 6). In patients with wasting, the full NIRUDAK model was significantly better than the WHO IMAI algorithm in terms of its average m-index ($p < 0.001$), as illustrated in Figure 5. For the simplified NIRUDAK model, the average m-index was slightly better than the WHO IMAI algorithm though this did not reach statistical significance ($p = 0.003$). For the non-wasting group, both NIRUDAK models were significantly better than the WHO IMAI algorithm in terms of their average m-index ($p < 0.001$ for all comparisons) (Figure 5).

DISCUSSION

The WHO IMAI algorithm is generally considered the standard of care for managing dehydration related to diarrhoea in resource-limited settings in patients over five years of age [25,29]. This algorithm was adapted from the WHO IMCI algorithm, specifically created for children under five years of age even though adult physiology and diarrhoea aetiology differ from young children. Conversely, the full and simplified NIRUDAK models were derived specifically for patients over five years of age. When compared to the NIRUDAK models, two clinical signs of the WHO IMAI algorithm, mental status and thirst, were not chosen for inclusion in either of the NIRUDAK models (Appendix 2) [30]. This suggests that these two clinical signs may not function well as predictors of dehydration in older patients.

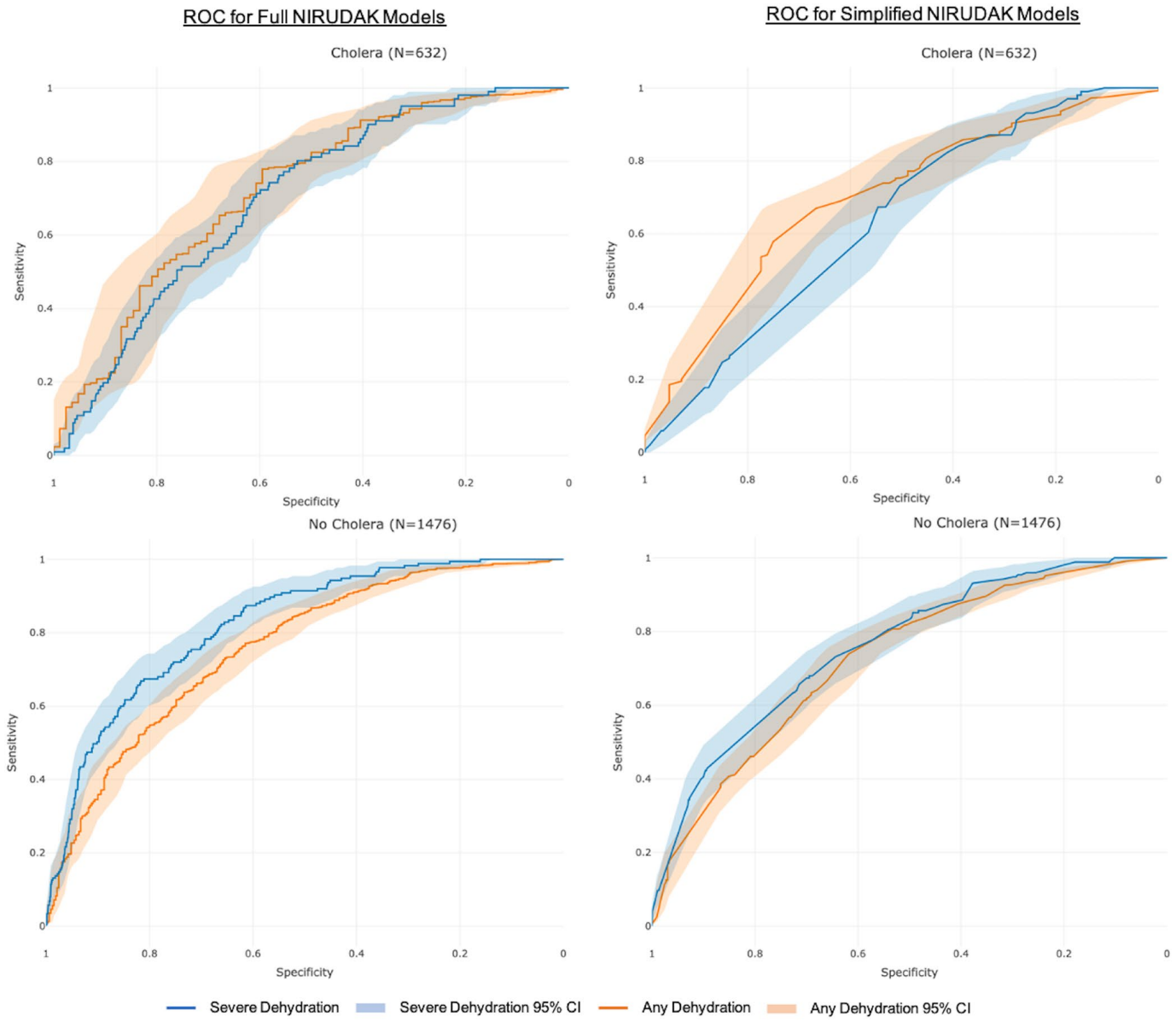

FIGURE 2 ROC Curves of the full and simplified NIRUDAK models for severe and any dehydration in the diarrhoea subgroup analysis

TABLE 4 ROC AUC by nutritional status among patients over five years old

	ROC AUC (95% Confidence Interval)	
	Severe Dehydration	**Any Dehydration**
Full NIRUDAK Model		
Wasting	0.69 (0.61, 0.76)	0.69 (0.58, 0.80)
Non-Wasting	0.79 (0.76, 0.81)	0.77 (0.74, 0.79)
Simplified NIRUDAK Model		
Wasting	0.67 (0.59, 0.75)	0.65 (0.55, 0.76)
Non-Wasting	0.73 (0.70, 0.77)	0.73 (0.71, 0.76)

When compared to the WHO IMAI algorithm, the full and simplified NIRUDAK models performed significantly better in both cholera and non-cholera subgroups as well as in the non-wasting subgroup. The full NIRUDAK model also performed significantly better than the WHO IMAI algorithm among patients with wasting, though the simplified NIRUDAK model did not (Appendix 2).

Several studies have suggested that overall appearance and abnormal physiological responses during clinical assessment are distorted in children and adults with wasting [56,57]. As such, many of the clinical signs that are normally used to assess dehydration, such as skin pinch or general appearance, are often unreliable in these patients, making it difficult to accurately determine dehydration severity. This study supports such findings as both the full and simplified NIRUDAK models were less accurate in patients with wasting for the detection of severe dehydration as well as any dehydration. Overall, both NIRUDAK models have acceptable discrimination in all subgroups for assessing whether patients had severe or any dehydration based on standards in the literature [58].

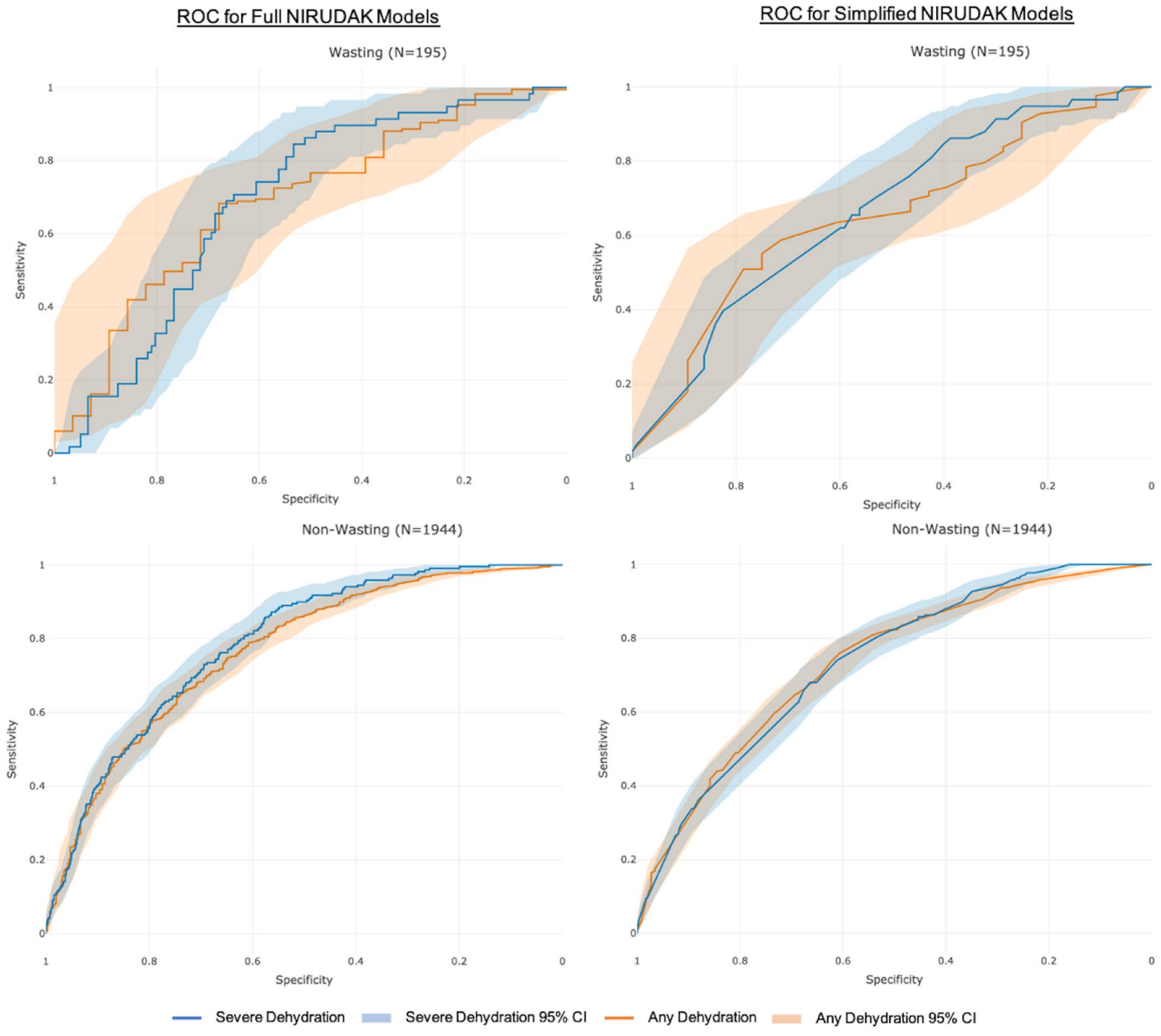

FIGURE 3 ROC Curves of the full and simplified NIRUDAK models for severe and any dehydration in the nutritional subgroup analysis

TABLE 5 Summary of model performances via bootstrap measured using m-index within the cholera subgroups

	Training Set M-Index	Validated M-Index (95% Confidence Interval)
NIRUDAK Full Model		
Cholera	0.70	0.70 (0.65, 0.74)
Non-Cholera	0.76	0.76 (0.74, 0.79)
NIRUDAK Simplified Model		
Cholera	0.67	0.68 (0.65, 0.73)
Non-Cholera	0.72	0.72 (0.70, 0.74)
WHO Model		
Cholera	0.58	0.58 (0.54, 0.61)
Non-Cholera	0.61	0.61 (0.58, 0.63)

In all cases, the lower bounds of the 95% confidence intervals for the AUCs of both of these models were greater than 0.5, the level at which discrimination is not better than chance.

Accurately assessing dehydration severity remains a critical step in reducing morbidity and mortality from diarrhoeal diseases. Inappropriate triaging of patients due to the misclassification of their hydration status can lead to undertreating or unnecessarily providing invasive interventions, potentially causing immediate complications, long-term sequelae and depletion of healthcare resources, which is especially burdensome in low-resource settings. Assessing dehydration in patients with cholera or undernutrition presents further challenges in providing targeted treatment for those with acute diarrhoea. Though 80% of patients present with mild to moderate symptoms and can be treated using

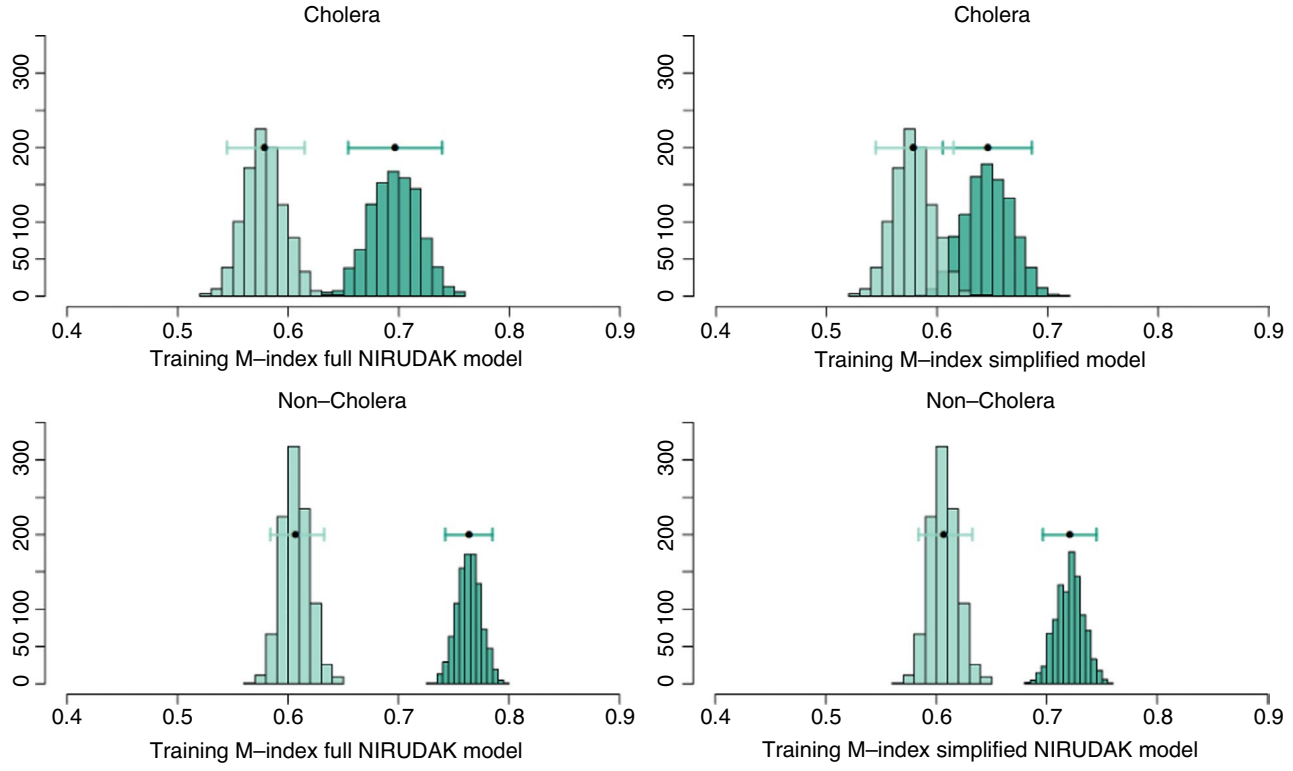

FIGURE 4 Comparison of m-indices of NIRUDAK full, NIRUDAK simplified models and WHO IMAI algorithm within the cholera subgroup. Each histogram shows the distribution of m-indices derived from the bootstrap samples. The full NIRUDAK models (on the left) and simplified NIRUDAK models (on the right) are represented in dark green, and the WHO IMAI algorithm is light green. The bar at the top of each histogram gives the mean m-index and 95% confidence interval bands derived from the bootstraps

TABLE 6 Summary of model performances via bootstrap measured using m-index within the nutritional subgroup

	Training Set M-Index	Validated M-Index (95% Confidence Interval)
NIRUDAK Full Model		
Wasting	0.68	0.69 (0.63, 0.76)
Non-Wasting	0.75	0.75 (0.73, 0.77)
NIRUDAK Simplified Model		
Wasting	0.63	0.65 (0.58, 0.72)
Non-Wasting	0.72	0.72 (0.70, 0.74)
WHO Model		
Wasting	0.54	0.55 (0.49, 0.60)
Non-Wasting	0.60	0.61 (0.58, 0.63)

oral rehydration solution alone, if diarrhoea from cholera is left untreated this highly virulent disease can lead to severe dehydration and kill children and adults within hours [59,60]. Undernutrition worsens intestinal infections by increasing the duration and severity of illness, while enteric infections, like cholera, are particularly deleterious as they increase the risk for further morbidity, such as undernutrition [61]. This cycle of enteric infections both exacerbating and being exacerbated by undernutrition further complicates accurate assessment of dehydration. The synergistic effect of undernutrition on diarrhoea severity is supported by this study, as a larger portion of patients with wasting had severe dehydration compared to those without wasting. This study also found cholera and undernutrition are more common in younger, poorer and more dehydrated individuals. Males are more likely to have cholera, while females are more likely to be undernourished. Such findings should be considered when clinically assessing dehydration in patients with acute diarrhoea or developing targeted health interventions.

LIMITATIONS & FUTURE DIRECTIONS

These data were collected from at a single study site, icddr,b, a non-profit urban diarrhoeal hospital that serves a catchment area of nearly 17 million people, including many people living in suburban/rural regions surrounding Dhaka city [31]. However, the results of this study may not be generalisable to other populations. Any clinical diagnostic tool will be limited by the skills of the provider applying it in practice. To improve generalisability of this study to the most common clinical providers in low-resource settings worldwide, non-specialised clinical nurses were hired to collect data for the NIRUDAK study from outside of icddr,b [30]. Because only 195 of 2,139 patients enrolled in the NIRUDAK study had wasted, inferences are less precise in this group, as reflected in the wide AUC confidence bands for estimating severe and any dehydration. Wasting is less prevalent in patients over five years than in younger populations, as discussed in

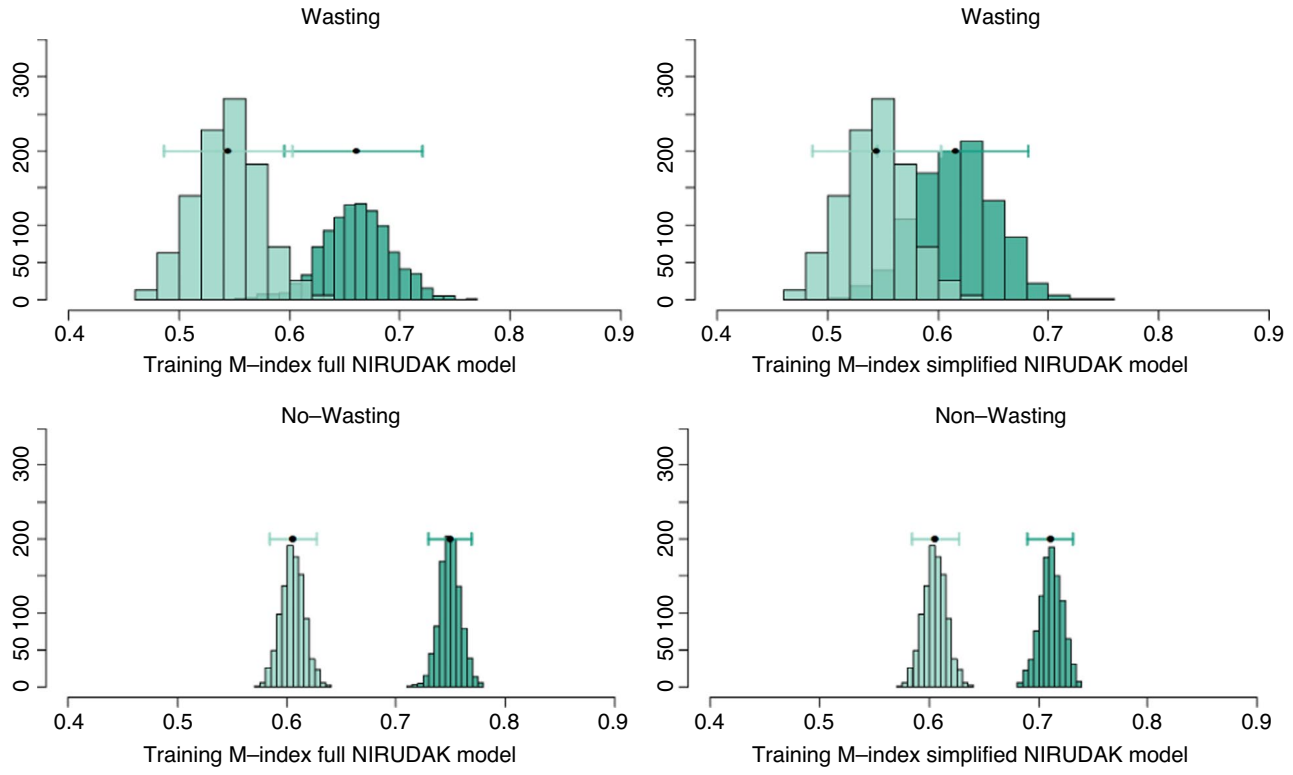

FIGURE 5 Comparison of m-indices of NIRUDAK full, NIRUDAK simplified models and WHO IMAI algorithm within the nutritional subgroup. Each histogram shows the distribution of m-indices derived from the bootstrap samples. The full NIRUDAK models (on the left) and simplified NIRUDAK models (on the right) are represented in dark green, and the WHO IMAI algorithm is in light green. The bar at the top of each histogram gives the mean m-index and 95% confidence interval derived from the bootstraps

several studies [3,62,63]. So, while the NIRUDAK models may not perform as well in this subgroup as in others, it is unlikely to be an issue for many adults and elderly patients, even in low-resource settings.

While both NIRUDAK models have been internally validated, external validation in a new study population is also recommended for further generalisability. Incorporation of the models into a mobile phone application is also underway, which will simplify their use in practice.

CONCLUSION

Assessing dehydration severity remains a critical step in reducing morbidity and mortality from diarrhoeal diseases. However, accurate determination of dehydration severity is further complicated by both cholera and undernutrition, in which many clinical signs normally used to assess dehydration are less reliable. This subgroup analysis of data from the NIRUDAK study is the first to compare the accuracy of two clinical diagnostic models of dehydration (the full and simplified NIRUDAK models) in patients over five years by diarrhoea aetiology and nutritional status. While all subgroups had acceptable discrimination in determining whether patients had severe or any dehydration, the results of this study demonstrate that both the full and simplified NIRUDAK models performed less well in patients with cholera and wasting, illustrating the difficulties of assessing dehydration accurately in these groups. Nonetheless, compared with the WHO IMAI algorithm, the current standard of care for managing acute diarrhoea in low-resource settings, both NIRUDAK models performed significantly better in nearly all subgroups. Such findings should provide healthcare workers with confidence in using both the full and simplified NIRUDAK models to assess dehydration severity in patients with cholera and undernutrition in contexts with limited resources. Further research should be conducted to explore potential differences in the accuracy of clinical signs of dehydration and clinical diagnostic models of dehydration in new patient populations.

DECLARATIONS

The authors would like to thank all study participants and study staff at icddr,b's Dhaka Hospital for their help and support. Funding was provided through grants from the National Institute for Health (NIH) National Institute for Diabetes and Diarrheal and Kidney Diseases (NIDDK). The funders had no role in the study design, data collection or reporting processes. The de-identified NIRUDAK Study dataset used for this secondary analysis is available on Open Science Framework. Link: https://osf.io/pncms/.

ACKNOWLEDGEMENTS

The authors would like to thank all study participants and study staff at icddr,b's Dhaka Hospital for their help and support.

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APPENDIX 1

PRE-DEFINED PROTOCOLS FOR MEASUREMENT OF ALL CLINICAL VARIABLES [30].

Mental Status

Mental status was assessed by observing and interacting with the patient. If the patient was awake and able to respond appropriately to questions and commands, the mental status was classified as 'Normal'. If the patient's eyes were closed, or the patient was staring into space, or the patient was slow to respond to questions or commands, the patient's mental status was classified as 'Confused/Lethargic'.

Thirst

Thirst was evaluated by pouring a small amount of water into a cup and offering it to the patient. The patient's thirst was classified as 'Normal' if the patient sipped the water slowly or 'Drinks Eagerly' if they drank it quickly. The patient's thirst was classified as 'Refuses/Unable to Drink' if they refused or were unable to drink water.

Skin Pinch

A skin pinch test was performed on the patient by grasping a fold of skin on the side of their abdomen between the thumb and index finger and rapidly releasing the skin while counting how many seconds it took for the skin to flatten again. 'Rapid' was defined by the skin flattening immediately (in the blink of an eye). 'Slow' was defined by the skin flattening in about one second. 'Very Slow' was defined by the skin flattening in two or more seconds.

Eye Level

The patient's eye level was evaluated by viewing the patient's face from the side of the stretcher at the level of the patient and identifying whether the patient's eyelid was below their orbital rim with their eyes closed. If so, their eye level was classified as 'Sunken', otherwise it was classified as 'Normal'. If it was unclear based on visualisation, nurses were instructed to place the lateral aspect of one finger across the patient's orbital rim, with their finger touching both the superior and inferior portions of their orbital rim while the patient's eyes were closed. The eye level was classified as 'Normal' when the nurse could feel the eyelid touching their finger and 'Sunken' when

the eyelid was below the level of the orbital rim and not touching their finger.

Mucous Membranes

The patient's mucous membranes were evaluated by asking the patient to open their mouth and observing the oral cavity. When the patient's lips appeared normal and saliva was clearly visible on or around the tongue, the patient's mucous membranes were classified as 'Normal'. When their lips appeared dry or there was little or no moisture on or around the tongue, their mucous membranes were classified as 'Dry'.

Respiration Depth

Respiration depth was evaluated by observing the patient's abdomen while lying flat. If their skin did not sink below the level of their lower ribs at any point during the respiratory cycle, their respiration depth was classified as 'Normal'. If their skin did sink below the level of the lower ribs at any point during the respiratory cycle, their respiration depth was classified as 'Deep'.

Radial Pulse

Radial pulse was evaluated by placing two fingers just proximal to the patient's wrist crease on the radial side of the forearm and comparing the patient's radial pulse to one's own. If they were similar, the patient's radial pulse was classified as 'Strong'. If the patient's radial pulse felt weaker, it was classified as 'Decreased'. When the patient's radial pulse could not be felt at all, it was classified as 'Absent'.

Capillary Refill

Capillary refill was evaluated by pressing on the edge of the nailbed of the patient's thumb, making note of the time for the colour to return once pressure was released. If the patient had nail polish, the pad of their thumb was used instead. If the colour returned in 2 seconds or less, the capillary refill was classified as 'Normal'. If it took longer than 2 seconds to return, the capillary refill was classified as 'Prolonged'.

Urine Output

Urine output was evaluated by asking the patient or their family about their urination in the last 8 h. If the patient felt their urine output was normal for them over this time period, it was classified as 'Normal'. If the patient felt their urination was less frequent or darker (more concentrated) than normal over this time period, their urine output was classified as 'Decreased/Dark'. If the patient had not urinated at all in the past 8 h or only a few drops, their urine output was classified as 'Minimal/None'.

Vomiting Episodes in 24 h

Vomiting episodes in 24 h were assessed by asking the patient or their family member how many discrete episodes of vomiting the patient had in the past 24 h.

Diarrhoeal Episodes in 24 h

Diarrhoeal episodes in 24 h were assessed by asking the patient or their family member how many discrete episodes of diarrhoea the patient had in the past 24 h.

Duration of Diarrhoea

Duration of diarrhoea was assessed by asking the patient or their family member how long ago the patient began experiencing diarrhoea.

Heart Rate

Heart rate was assessed by placing a pulse oximeter on the patient's finger to measure their heart rate while lying flat. If the pulse oximeter was unable to measure heart rate, then the nurse listened to the heart beat with a stethoscope and counted the number of beats over 60 seconds using a stopwatch. A second heart rate measurement was taken while the patient was sitting up by elevating the head of the stretcher to 90 degrees (with a 30-second delay between obtaining the flat and seated measurements to allow time for the heart rate to adjust). The heart rate difference was calculated as the seated heart rate minus the flat heart rate. Standing heart rate was not assessed as many patients were unable to stand due to the severity of illness.

Systolic/Diastolic Blood Pressure

The patient's blood pressure was obtained while the patient was lying flat using an automated blood pressure cuff. If the patient was receiving IV fluids, the arm opposite of the IV line was used so as to not interfere with treatment. If the automatic blood pressure cuff was not able to obtain a measurement on the first try, a manual cuff was used instead. For children, a manual, child-sized blood pressure cuff was used to measure blood pressure. A second blood pressure measurement was taken while the patient was sitting up by elevating the head of the stretcher to 90 degrees (with a 30-second delay between obtaining the flat and seated measurements to allow time for the heart rate to adjust). The blood pressure difference was calculated as the seated blood pressure minus the flat blood pressure. Standing blood pressure was not assessed as many patients were unable to stand due to the severity of illness.

MUAC

The mid-upper arm circumference (MUAC) was assessed by bending the patient's left elbow to 90 degrees

while their left arm was hanging loosely at their side (not stretched out) and measuring the midpoint between the tip of the shoulder and the tip of the elbow. A standard MUAC tape was wrapped around the arm at the measured midpoint, and the observed number was recorded in millimetres.

APPENDIX 2

TABLE A1 Predictors included in the full and simplified NIRUDAK models and their regression coefficients [30].

	Full NIRUDAK Model	Simplified NIRUDAK Model
	Regression Coefficients (95% CI)	**Regression Coefficients (95% CI)**
Age (per 1 year increase)	−0.01 (−0.01, −0.00)	-
Skin Pinch		
Rapid (Reference Level)	1	1
Slow	0.71 (0.47,0.95)	0.68 (0.46,0.91)
Very Slow	1.53 (1.15,1.91)	1.34 (1.00,1.69)
Eye Level		
Normal (Reference Level)	1	1
Sunken	0.70 (0.48,0.93)	0.60 (0.38,0.83)
Respiration Depth		
Normal (Reference Level)	1	1
Deep	0.37 (0.16,0.58)	0.58 (0.37,0.79)
Vomiting Episodes in 24 h		
<1 (Reference Level)	1	-
1–5	0.39 (0.06,0.73)	-
6–10	0.69 (0.35,1.03)	-
>10	0.91 (0.54,1.28)	-
Systolic BP Flat (per 1 mmHg increase)	−0.01 (−0.02,−0.01)	-
MUAC (per 1 mm increase)	−0.01 (−0.01,−0.01)	-
Sex		
Female (Reference Level)	1	
Male	0.36 (0.17,0.55)	
Radial Pulse	-	
Strong (Reference Level)	-	1
Decreased	-	0.44 (0.22,0.66)
Absent	-	1.07 (0.42,1.70)
Urine Output		
Normal (Reference Level)	-	1
Decreased/Dark	-	0.29 (−0.03,0.60)
Minimal/None	-	0.58 (0.16,0.99)
Intercept		
Any Dehydration	–3.38	0.29
Severe Dehydration	0.66	4.08

Full NIRUDAK Model Equation	Simplified NIRUDAK Model Equation
Probability of severe dehydration $=\frac{1}{1+\exp(-\sum x*\beta+\beta_0)}$	Probability of severe dehydration $=\frac{1}{1+\exp(-\sum x*\beta+\beta_0)}$
probability of severe dehydration $=\frac{1}{1+\exp(-\sum x*\beta+\beta_0)}$	probability of severe dehydration $=\frac{1}{1+\exp(-\sum x*\beta+\beta_0)}$