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Original article

Association of nutritional status with clinical outcomes of critically ill pediatric patients with complex chronic conditions

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SUMMARY

Background & aims: There is a high prevalence of children with complex chronic conditions (CCCs) in pediatric intensive care units (PICUs). However, information on the nutritional status (NS) of this specific population is limited. This study aimed to evaluate the NS of critically ill pediatric patients with CCCs and to relate it to clinical outcomes.

Methods: A retrospective cohort study of children admitted to a PICU over a 4-year period. We classified NS according to body mass index-for-age (BMI/A) and height-for-age (H/A) z-scores, using the World Health Organization (WHO) growth curves as a reference. We recorded the presence of CCC according to the definition proposed by Feudtner et al. Severity on admission was measured using the Pediatric Index of Mortality 2 (PIM2). We assessed the following outcomes: mortality, multiple organ dysfunction syndrome during PICU stay, and PICU length of stay (LOS).

Results: We included 1753 children in the study. Presence of CCC accounted for 49.8% (873) of the sample. Among children with CCCs, 61.7% (539) had appropriate weight, 19.8% (173) were underweight, and 18.4% (161) were overweight. H/A was considered inadequate in 32.2% (281) of patients with CCCs, a higher rate than in those without CCCs (25.3%; 132) ($p < 0.001$). Regarding outcomes, underweight children had more organ dysfunctions and prolonged LOS. The association only remained for prolonged LOS when adjusting for confounders. Although underweight children had a higher PIM2-predicted risk of mortality, there was no significant difference in actual mortality between the three NS groups ($p = 0.200$).

Conclusions: The rates of nutritional inadequacies in patients with CCCs were high. Underweight was independently associated with prolonged LOS in children with CCC.

1. Introduction

Children with complex chronic conditions (CCCs), defined as the presence of any medical condition that can be expected to last at least 12 months and to severely involve either several different organ systems or one organ system, have lifelong health conditions associated with mortality, morbidity, functional limitations, and substantial health care needs [1,2]. With technological advances in medicine, reduction in mortality rates and improvements in social and health indicators, hospitalization rates for children with CCCs have increased in recent years, accounting for an increasing proportion of hospital resource utilization [3–5].

Abbreviations: BMI, body mass index; BMI/A, body mass index-for-age; CCC, complex chronic condition; GA, gestational age; H/A, height-for-age; LOS, length of stay; MODS, multiple organ dysfunction syndrome; MV, mechanical ventilation; NS, nutritional status; PICU, pediatric intensive care unit; PIM2, Pediatric Index of Mortality 2; SMR, standardized mortality ratio; WHO, World Health Organization.

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Studies indicate that the presence of chronic diseases may be associated with important nutritional disorders, which can increase hospital length of stay (LOS) and result in growth retardation and inadequate weight at the highest and lowest z-scores [6,7]. Many children with a CCC are admitted to the pediatric intensive care unit (PICU) for elective procedures, or for acute illnesses directly related or not to the underlying disease [8]. Nutritional status (NS) is an important factor in this context, since critically ill children have peculiar conditions that can compromise their NS [9]. However, there is limited information on the prevalence of nutritional inadequacies in children with CCCs in this setting, and studies often refer to the general population of the PICU or to a specific medical condition [10–13].

The association between NS and clinical outcomes in critically ill children has been increasingly recognized. In a study published by the Society of Critical Care Medicine (SCCM) and the American Society for Parenteral and Enteral Nutrition (ASPEN), malnutrition is associated with longer periods of mechanical ventilation (MV), higher risk of nosocomial infection, longer PICU LOS, and increased mortality [9]. Likewise, overweight has often been associated with unfavorable clinical outcomes [14–16]. In addition to the presence of a CCC and of factors related to the critical illness itself, inadequate NS may have implications for outcomes among critically ill children. [10,17].

Therefore, this study aimed to evaluate the NS of critically ill children with CCCs and, secondarily, to examine the relationship between NS and clinical outcomes.

2. Methods

2.1. Study design and population

We conducted a retrospective cohort study of children aged one month to 18 years admitted to the PICU of a university hospital in southern Brazil from June 2013 to December 2017. We collected data from the PICU's database and patients' electronic medical records. A patient readmitted to the PICU more than once was considered a new patient for each readmission. We excluded patients with PICU LOS <8 h, without anthropometric data records, and those who could not be assessed by the body mass index (BMI) curve (preterm infants who did not reach 40 weeks' corrected age). The study was approved by the institution's research ethics committee (protocol number 98363518.4.0000.5336). All investigators signed a data use agreement.

2.2. Data collection and variables

We collected clinical and demographic data from all patients, including age in months, sex, weight and height, gestational age (GA) at birth (for children up to 24 months of age), severity, type of patient (medical or surgical), and need for MV during PICU stay. Early readmission (return to the PICU within 72 h of discharge), each readmission was considered as a new patient in the study.

Severity on PICU admission was measured using the Pediatric Index of Mortality 2 (PIM2) [18]. We used the PIM2 score, calculated by the medical team within the first hour of admission, as a categorical variable for analysis. Patients with a PIM2 score above the 75th percentile of the sample were classified as having the "worst prognosis".

We analyzed the following clinical outcomes: PICU LOS, analyzed in days and classified as prolonged LOS in patients with LOS above the 75th percentile of the sample; and presence of multiple organ dysfunction syndrome (MODS), defined as the presence of at least two organ dysfunctions during PICU stay; and mortality [19].

2.3. Complex chronic condition classification

We recorded the presence of CCC at each admission according to the definition proposed by Feudtner et al., [20] based on the evaluation of the patient's medical history taken by the medical team upon admission. We recorded the information using a CCC classification system divided into 10 categories that include neurological/neuromuscular, respiratory, renal/urological, hematological/immunological, gastrointestinal, metabolic, and cardiovascular diseases, genetic or congenital defects, neoplasms, and disorders related to prematurity or neonatology. Patients who were classified into two or more categories were considered to have "associated CCC". This stratification was performed in order to identify whether patients with two or more CCC could have different outcomes.

2.4. Nutritional status

We obtained anthropometric parameters (weight and height) from the patients' medical records. These measurements were performed within 24 h of admission to the PICU. In cases in which these measurements could not be performed, we considered the most recent measurements recorded in hospital records or in the patient's vaccination card.

We assessed NS based on BMI-for-age (BMI/A) and height-for-age (H/A) z-scores calculated in the World Health Organization (WHO) Anthro software, version 3.2.2, for children under 5 years of age and AnthroPlus software, version 1.0.4, for children and adolescents aged 5–19 years [21,22]. We used the cutoffs established by the WHO growth curves as a reference. Both parameters cover all age groups included in the present study. For patients with GA at birth <37 weeks, defined as prematurity, we corrected their age before assessing NS. For the assessment of BMI/A, we classified the patients as follows: underweight (z-score < -2), appropriate weight (z-score ≥ -2 and $< +2$), and overweight (z-score $\geq +2$). We used H/A as a complementary analysis to characterize the sample by identifying patients with short stature, defined as z-score < -2 [23,24].

2.5. Statistical analysis

For descriptive analysis, we presented the data as median and interquartile range (IQR) for variables with skewed distribution, and as numbers and percentages for categorical variables. To compare the NS groups, we used the chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables with skewed distribution, both followed by post hoc Bonferroni's correction. A multivariable logistic regression adjusted for potential confounders (age, sex, type of hospitalization and PIM2) was conducted to investigate the independent association between study outcomes and NS groups. We analyzed the data in SPSS, version 20 (IBM SPSS Statistics 20), and set the level of significance at 5% ($p < 0.05$) for all analyses.

3. Results

3.1. Patient profiles and overall mortality

A total of 1841 admissions occurred during the study period. We excluded 88 (4.8%) patients because they did not meet the eligibility criteria, for a total of 1753 admissions analyzed in the study. Among the admissions, 211 patients were readmitted to the unit. The patient selection flowchart is shown in Fig. 1.

The prevalence of children with CCCs in our sample was 49.8% (873). The median age in these patients was 27.6 months (IQR, 7.7–92.1), higher than that of patients without CCCs (median, 12.6

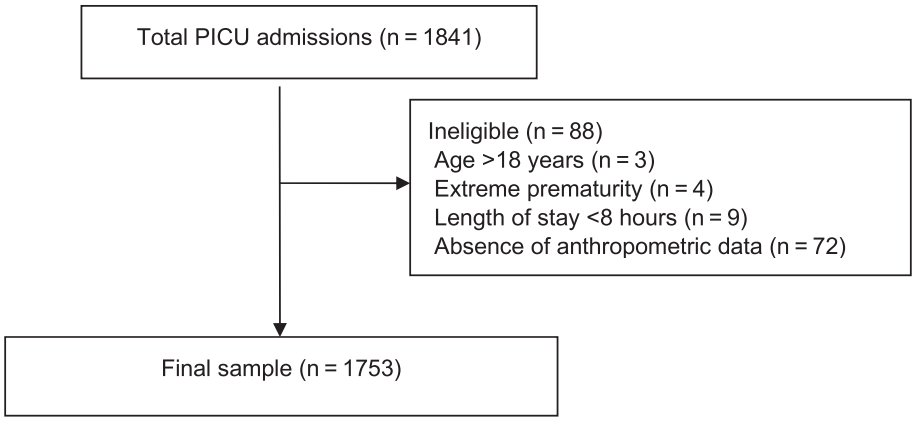

Fig. 1. Flowchart of inclusion of patients in the study. n, number of admissions; PICU, pediatric intensive care unit.

months; IQR, 3.3–61.1; $p \leq 0.001$); 54.1% of the total sample was younger than 24 months. Patients with CCC had a higher rate of early readmission (3,8% vs 1,7%; $p = 0.008$). Mortality was higher in patients with CCCs (5.8%) than without CCCs (1.9%; $p < 0.001$). Underweight was more prevalent in patients with CCCs (19.8%) than without CCCs (11.0%; $p \leq 0.001$), as was overweight (18.4% vs 14.4%; $p = 0.023$) (Table 1).

3.2. Nutritional status and outcomes of patients with CCC

Overall, children with underweight were younger than those overweight or appropriate weight. Among the CCC, patients classified as having neurological conditions had the biggest prevalence of overweight ($p < 0.001$), while in patients with respiratory disorders underweight was more frequent ($p = 0.002$). Regarding outcomes, MODS and prolonged LOS were more frequent in underweight children ($p = 0.026$; $p < 0.001$). Expected mortality (measured by the PIM2 score) was different between the three NS groups ($p \leq 0.001$), with a higher score for underweight children. Likewise, a higher rate of patients classified as having "worse prognosis" was observed in the low weight group ($p = 0.015$). In the mortality outcome, there was no significant difference between the three NS groups ($p = 0.2$) (Table 2).

Table 3 shows the model of logistic regression that demonstrates significant association of the under and overweight groups in children with CCC admitted into the PICU. In the multivariable analysis, children with CCC were more likely to be underweight and overweight than those without CCC. There was no association between NS and MODS. After adjusting for confounders, compared to children with appropriate weight, those from the underweight group had a chance 56% higher of prolonged LOS (OR = 1.56; 95% CI 1.03–2.37).

4. Discussion

We found a high prevalence of weight and height inadequacies in critically ill pediatric patients with CCCs compared with those without CCCs. In this cohort of patients with CCC, we identified that the underweight group is independently associated with prolonged LOS. The results add to the scant literature on the impact of nutritional status on clinical outcomes in critically ill children with CCC.

Table 1
Demographic and clinical characteristics, nutritional status and outcomes of patients with and without CCCs.

Characteristic	Total sample (1753)	Without CCC (880)	With CCC (873)	p-value
Age in months, md (IQR)	19.5 (5.1–79.3)	12.6 (3.3–61.1)	27.6 (7.7–92.1)	*<0.001
Age ≤ 24 months, n (%)	948 (54.1)	535 (60.8)	413 (47.3)	*<0.001
Male, n (%)	953 (54.4)	484 (55.0)	469 (53.7)	0.591
Medical patient, n (%)	1140 (65)	695 (79.0)	445 (51.0)	*<0.001
Early readmission (<72 h), n (%)	48 (2.7)	15 (1.7)	33 (3.8)	*0.008
PIM2 (%), md (IQR)	1.2 (0.35–3.1)	1.1 (0.3–23.7)	1.35 (3.7–45)	*<0.001
Need for MV, n (%)	764 (43.6)	382 (43.4)	382 (43.8)	0.883
Weight in kg, md (IQR)	10.5 (6.0–21.9)	9.5 (5.5–19.0)	12.0 (6.8–23.0)	*<0.001
Height in cm, md (IQR)	81 (62–116)	74 (59–110)	86 (65–120)	*<0.001
BMI/A, n (%)				
Underweight	269 (15.3)	96 (11.0)	173 (19.8)	*<0.001
Appropriate weight	1196 (68.2)	657 (74.7)	539 (61.7)	*<0.001
Overweight	288 (16.4)	127 (14.4)	161 (18.4)	*0.023
H/A, n (%)				
Appropriate stature	1340 (76.4)	748 (85.0)	592 (67.8)	*<0.001
Short stature	413 (23.6)	132 (15)	281 (32.2)	*<0.001
Outcomes				
Mortality, n (%)	68 (3.9)	17 (1.9)	51 (5.8)	*<0.001
PICU LOS in days, md (IQR)	3 (2–9)	4.0 (2–9)	3.0 (2–8)	*0.042
MODS	732 (41.8)	312 (35.5)	420 (48.1)	*<0.001

Abbreviations: n, number of patients; IQR, interquartile range; md, median; CCC, complex chronic condition; kg, kilogram; cm, centimeter; BMI/A, body mass index-for-age; H/A, height-for-age; PICU, pediatric intensive care unit; LOS, length of stay; MODS, multiple organ dysfunction syndrome; MV, mechanical ventilation; PIM2, Pediatric Index of Mortality 2.
* Significance ($P < 0.05$). Pearson's chi-square test or Kruskal-Wallis test, depending on the distribution of variables.

Table 2
Demographic and clinical characteristics and outcomes by nutritional status group in patients with CCCs.

Characteristic	Underweight n = 173	Appropriate weight n = 539	Overweight n = 161	*p-value*
Age in months, md (IQR)	9.20 (4.2–38.1)	24.5 (7.7–82.0)	88.1 (32.7–128.7)	**<0.001*
Age≤24 months, n (%)	118 (68.2)	264 (49.0)	31 (19.3)	**<0.001*
Male, n (%)	95 (54.9)	294 (54.5)	80 (49.7)	*0.522*
Medical patient, n (%)	111 (64.2)	268 (49.7)	66 (41.0)	**<0.001*
Associated CCC, n (%)	61 (35.3)	136 (25.2)	41 (25.5)	**0.031*
Early readmission (< 72 h), n (%)	9 (5.2)	18 (3.3)	6 (3.7)	*0.535*
PIM2 (%), md (IQR)	1.98 (0.64–6.17)	1.3 (0.36–4.53)	1.04 (0.25–2.63)	**<0.001*
Worse prognosis (PIM2 ≥ p75), n (%)	60 (34.7)	155 (28.8)	33 (20.5)	**0.015*
Need for MV, n (%)	91 (52.6)	241 (44.7)	50 (31.1)	**<0.001*
LOS in days, md (IQR)	4.0 (2.0–13)	3.0 (2.0–7.0)	2.0 (2.0–6.5)	**<0.001*
CCC types				
Cardiovascular	26 (15,0)	73 (13,5)	17 (10,6)	*0,466*
Neurological	61 (35,3)	245 (45,5)	101 (62,7)	**<0,001*
Respiratory	55 (31,8)	119 (22,1)	25 (15,5)	**0,002*
Neoplasms	8 (4,6)	39 (7,2)	15 (9,3)	*0,244*
Genetic or Congenital defects	25 (14,5)	66 (12,2)	17 (10,6)	*0,553*
Metabolic	5 (2,9)	7,0 (1,3)	4 (2,5)	*0,315*
Renal/Urological	8 (4,6)	28 (5,2)	8 (5,0)	*0,955*
Gastrointestinal	47 (27,2)	132 (24,5)	33 (20,5)	*I,359*
Hematological/Immunological	–	7,0 (1,3)	–	*0,112*
Prematurity	24 (13,9)	48 (8,9)	3 (1,9)	**<0,001*
Outcomes				
Mortality, n (%)	15 (8.7)	27 (5.0)	9 (5.6)	*0.2*
Prolonged LOS (≥ 9 days), n (%)	65 (37.6)	123 (22.8)	28 (17.4)	**<0.001*
MODS, n (%)	99 (57.2)	245 (45.5)	76 (47.2)	**0.026*

Abbreviations: n, number of patients; IQR, interquartile range; CCC, complex chronic condition; PIM2, Pediatric Index of Mortality 2; MV, mechanical ventilation; MODS, multiple organ dysfunction syndrome; LOS, length of stay.
* Significance (P < 0.05). Pearson's chi-square test or Kruskal–Wallis test, depending on the distribution of variables.

Underweight on admission to the PICU is a condition that still affects many hospitalized patients and has often been associated with worse outcomes, with poor short-term outcomes, such as mortality and LOS [12,25] When it occurs concomitantly with a CCC, complications in this population may lead to even more severe events.

Underweight was more commonly associated with unfavorable clinical outcomes than appropriate weight and overweight. Similar rates have been reported in previous studies conducted in PICUs [12,14]. In the present study, the underweight group was associated with prolonged LOS. This finding is consistent with that of a study of hospitalized children conducted in Europe, where disease-related malnutrition was common and associated with prolonged LOS [9]. In addition to underweight, this finding may be influenced by other factors such as the presence of CCCs, infections, gastrointestinal complications, and organ dysfunctions, which may contribute to longer PICU and hospital LOS [9,25].

It is important to consider the double burden on children with CCCs, that is, the critical state of the disease and the severity of the CCC. Studies show that inadequate NS, especially underweight, is associated with higher mortality rates in critically ill patients [12,26]. Our findings demonstrated that the overall mortality rate in our sample did not support the hypothesis that inadequate NS in patients with CCCs is associated with this outcome. This result may be due to an insufficient sample size when stratifying the NS into weight group categories. The same was reported by Sharma et al., who found no association between weight and mortality groups [27]. In contrast, predicted mortality from PIM2 was higher for children with CCC with low birth weight. PICU mortality prediction scores are important tools for evaluating unit performance. Neither

Table 3
Odds ratio for PICU admission by Complex Chronic Condition and outcomes MODS and Prolonged LOS by nutritional status.

			Unadjusted model		Fully-adjusted model[a]	
			OR (CI95%)	p	OR (CI95%)	p
	All n = 1780 (100%)	CCC n = 873 (100%)				
Underweight	296 (16.9)	173 (19.8)	2.20 (1.67–2.89)	0.000	2.49 (1.86–3.35)	0.000
Appropriate weight	1196 (68.2)	539 (61.7)	1.00		1.00	
Overweight	288 (16.4)	161 (18.4)	1.54 (1.19–2.00)	0.001	1.38 (1.04–1.84)	0.026
MODS	n = 873	n = 420				
Underweight	173 (19.8)	99 (57.2)	1.60 (1.14–2.27)	0.007	1.29 (0.89–1.87)	0.184
Appropriate weight	539 (61.7)	245 (45.4)	1.00		1.00	
Overweight	161 (18.4)	76 (47.2)	1.07 (0.75–1.53)	0.696	1.38 (0.94–2.04)	0.104
Prolonged LOS[b]	n = 873	n = 216				
Underweight	173 (19.8)	65 (37.5)	2.04 (1.41–2.94)	0.000	1.56 (1.03–2.37)	0.037
Appropriate weight	539 (61.7)	123 (22.8)	1.00		1.00	
Overweight	161 (18.4)	28 (17.4)	0.71 (0.45–1.12)	0.143	1.02 (0.60–1.72)	0.946

Abbreviations: n, number; OR, odds ratio; CI, confidence interval; CCC, complex chronic condition.
[a] Adjusted for age, sex, type of hospitalization (medical or surgical), and Pediatric Index of Mortality (PIM2).
[b] Prolonged LOS: > 9 daysv.

of the two most commonly used predictive scores in pediatrics, the PIM-2 and the Pediatric Risk of Mortality (PRISM III), includes NS as a variable [18,28]. The inclusion of this variable is being speculated. Studies have shown a high risk of mortality in children who were severely malnourished and who were admitted to the PICU, and it can be concluded that, as in our study, the predictive score may have overestimated this risk [26,27].

Among the CCC categories, children with respiratory diseases had a higher prevalence of underweight in our study. Previous studies describing different diagnostic groups also found high rates of underweight children with respiratory diseases [14,29]. In view of these findings, it should be noted that critically ill underweight children are more susceptible to the catabolic effects of the disease, including increased energy needs, and to malabsorption and insufficient nutrient supply due to feeding difficulties and treatment side effects [6,9,12].

Conversely, overweight was not associated with worse clinical outcomes in the present study. Despite this result, the physiological risk associated with this nutritional diagnosis should not be neglected. Overweight can influence the inflammatory immune response, prolong hospital LOS, and increase the risk of hospital mortality in children [15,30]. It is also worth noting that, in our study, children with neurological diseases were more frequently overweight and underweight than children with other CCC types. In this population, such nutritional profiles may be explained by complications resulting from the underlying diseases, which can affect the physical and cognitive functions necessary for adequate nutrition or lead to decreased energy expenditure due to physical limitations, low muscle tone, metabolic disorders, and inadequate nutritional therapy [31–33].

Short stature was observed in almost one-third of patients with CCCs in our sample. Growth failure is a multifactorial finding that may be related to long disease duration, physical inactivity, and therapies (such as glucocorticoids) [6]. In a multicenter study, the prevalence of short stature was higher in children with endocrine, nutritional, or metabolic diseases [7]. Anthropometric criteria must be strictly applied to these patients, as they can be erroneously classified as appropriate weight or even overweight [6].

Clinical status at admission is an important aspect to be discussed in the present study, as we found a high prevalence of patients with CCCs with higher rates of neurological, respiratory, and gastrointestinal diseases. In addition, these patients had longer LOS and higher early readmission and mortality rates than otherwise healthy patients with acute illnesses. Similar findings have been reported in hospitalized pediatric patients with CCCs [4,34,35]. The high proportion of children with CCCs observed in this study and in the recent literature may be related to technological advances in neonatal and pediatric critical care as well as in nutritional care, which have resulted in improved survival for these patients [36].

Great variability in definitions and difficulties in identifying these patients hindered a proper comparison of our results with those reported in the literature [1,37–39]. Most studies conducted in PICUs assess the NS of the general population of the unit. Studies address NS in patients with chronic diseases, but these etiologies can be elusive. PICU studies often use CCCs to characterize a sample and to adjust severity in the general population [12,15]. A strength of our study is that we offer a specific focus on the NS and outcomes of critically ill pediatric patients with CCCs, according to the criteria established by Feudtner et al. [20].

This study has some limitations that need to be addressed. Because this is a single-center study, caution should be exercised when extrapolating the data to other PICUs with different characteristics. We consider each hospitalization as a new patient, because we believe that they could have different outcomes. However, these outcomes may be related. NS assessment based on BMI alone has limitations, as body composition, which was not considered in this study, is an important factor in identifying body fat percentage and loss of lean body mass, which can lead to greater risks associated with overweight and underweight. Another important aspect is that changes in fluid balance, which can lead to changes in the anthropometric measurements of critically ill children, were not considered [9]. Therefore, the fact that anthropometric measurements may be compromised in PICU patients, together with the retrospective nature of the study and NS assessment only by BMI rather than by specific growth curves, may have underestimated or overestimated NS assessment. There were few patients who needed evaluation by specific growth curves to justify the analysis. For the same reason, we chose to use only WHO child growth charts to standardize the statistical analysis. Nutritional assessment should not only be based on anthropometry but also consider clinical criteria. In this context, comparable reassessments that take into account the two criteria should be performed at regular intervals to allow for the identification of children at high nutritional risk. Finally, we analyzed a mixed (medical/surgical) PICU that included groups of patients with different admission profiles and severity within a comprehensive age range, thus hindering the comparisons of patients with CCCs. Despite these limitations, we highlight the importance of better understanding the nutritional behavior of these patients, since they are increasingly present in PICUs [5,34].

5. Conclusion

In summary, patients with CCC admitted to the PICU had higher rates of nutritional inadequacies and unfavorable clinical outcomes when compared to patients without CCC. Underweight was independently associated with prolonged LOS in this population.

Authorship - credit author statement

GRHA: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing, Visualization, Validation. **CADC:** Conceptualization, Methodology, Validation, Resources, Writing - Review & Editing, Supervision. **FC:** Conceptualization, Software, Validation, Formal analysis, Investigation, Resources, Writing - Review & Editing. **CTT**: Conceptualization, Validation, Software, Formal analysis, Data Curation, Writing - Review & Editing, Project administration. **HF**: Conceptualization, Validation, Data Curation, Writing - Review & Editing, Project administration. **ISS:** Conceptualization, Validation, Software, Formal analysis, Data Curation, Writing - Review & Editing, Project administration. **PCRG**: Conceptualization, Formal analysis, Writing - Review & Editing, Validation, Data Curation, Supervision.

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Declaration of competing interest

None to be declared.

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