The Prospective Assessment of Nutrition in Children with Cystic Fibrosis

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Abstract: *Aims*: Patients with Cystic Fibrosis (CF) have increased risk of malnutrition. Early detection of nutritional deterioration enables prompt intervention and correction. The aims of this project were to define the nutritional status of CF patients in Iran and New Zealand, compare and contrast the McDonald Nutritional Risk Screening (NRS) tool with the Australasian Guidelines for Nutrition in Cystic Fibrosis, and validate these results with each patient's evaluation by their CF clinical team.

Methods: Children with CF (2 - 18 years) were assessed during routine outpatient visits over one year. Anthropometric measurements were obtained. Both tools were applied and the results compared to their clinical evaluation (as gold standard) with calculation of specificity and sensitivity.

Results: Under-nutrition was seen more frequent in the 33 Iranian children than in the 36 New Zealand (NZ) patients (39% versus 0%, p=0.0001), whereas over-nutrition was more prevalent in NZ children (9% versus 17%, p=0.05). At the first visit, both guidelines were able to recognize 77% and 61% of under-nourished Iranian patients, respectively. The mean sensitivity and specificity for all visits for the McDonald tool were 83% & 73% (Iran) and 65% & 86% (NZ). Sensitivity and specificity for the Australasian guidelines were 79% & 79% (Iran) and 70% & 90% (NZ).

Conclusions: Both tools successfully recognised patients at risk of malnutrition. The McDonald tool had comparable sensitivity and specificity to that described previously, especially in Iranian patients. This tool may be helpful in recognizing at risk CF patients, particularly in developing countries with fewer resources.

Keywords: Cystic Fibrosis, Malnutrition, Nutritional Risk Screening (NRS), NRS tools, over-nutrition.

INTRODUCTION

Cystic Fibrosis (CF) is an autosomal recessive disease caused by a mutation in the CF trans membrane conductor (CFTR) gene [1]. CF is the most common genetic disease in Caucasian populations [1]. Over 400 people are diagnosed with CF in New Zealand (NZ) [2]. In Australia and New Zealand there are approximately 3000 patients diagnosed with CF, with 80-100 new diagnoses each year [3]. Although existing evidence indicates that the prevalence of CF is rare in Asia, it is felt to be underdiagnosed in that region [4].

It is well established that individuals with CF who have normal growth indices (i.e. weight for age (WFA), height for age (HFA) and weight for height (WFH)) have better pulmonary function, assessed by forced expired volume in one second (FEV1) [5]. A recent study in Spain has also shown a direct relationship between stunting and the risk of mortality in individuals with CF [6]. Consequently it is recommended that CF patients should be seen on a routine basis, with regular anthropometric measurements to monitor growth [3, 5, 7]. One goal for managing CF patients is to keep their body mass index (BMI) at or greater than the 50th percentile for their age and gender [8]. The identification of suboptimal growth will allow the CF team to intervene earlier and prevent further deterioration.

The United States (US) Cystic Fibrosis Foundation (CFF) consensus report introduced a nutritional risk screening (NRS) tool especially designed for CF in 2002 [7]. This tool classified patients with CF into three groups: acceptable, at risk and nutritional failure based on the patient's height and weight, percentage of ideal body weight, and weight for length (for zero to two years) or BMI percentile (for two to twenty years). More recently, in 2006, the Dietitians Association of Australia (DAA) prepared guidelines for the nutritional management of CF patients (Australasian Clinical Practice Guidelines for Nutrition in Cystic Fibrosis) as a reference for physicians and dietitians in Australia and New Zealand [3]. This will be referred to as the Australasian guidelines, which has also been used as a NRS tool.

A further tool for nutritional risk screening in patients with CF (referred to in the current paper as the McDonald NRS tool) was developed and validated by

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seven pediatric dietitians in 2008 [9]. This assessment showed substantial inter-observer agreement (k=0.75). In addition, the sensitivity and specificity of the tool when compared to an in-depth nutritional assessment by dietitians (considered as the gold standard) were 86% and 78%, respectively.

The specific aims of the current project were to define the current nutritional status of children with CF attending two outpatient CF clinics in Iran and New Zealand, and to compare and contrast the findings of the McDonald NRS tool with the Australasian Guidelines. A further objective was to validate these results by comparing with each patient's full evaluation by their respective CF clinical team.

MATERIAL AND METHODS

Population and CF Team

Children aged between two and eighteen years, with confirmed CF were assessed during their routine outpatient visits for twelve months (three to four consecutive visits) in Mashhad, Iran and Christchurch, New Zealand. In New Zealand, the clinical team was composed of a pediatrician, CF nurse, dietitian and physiotherapist who assessed each patient and determined a nutritional risk score for each patient. In Iran the clinical team included a pediatric gastroenterologist and a CF nurse. Background patient details (age, gender, ethnicity and comorbidities) were obtained from patient charts. The clinical teams were not aware of the results of NRS tools' assessments.

Anthropometry

Anthropometric measurements (weight and height) were undertaken at each visit. BMI percentile, WFH and HFA z-scores were calculated at each visit to assess each patient's current nutritional status. Mid-Upper Arm Circumference (MUAC) measurements were also obtained in all children younger than five years. All measurements were obtained in standard fashion using standard equipment (Weighing Scale: Buerer pso7, Ulm, Germany; Stadiometer: Seca 213, Germany; Measuring mat: Wyeth (NZ) Ltd). BMI was calculated utilizing the standard formula (weight/height^2, kg/m^2). WHO normal values were utilized to derive z-scores for all measurements [8].

Application of McDonald NRS Tool

At each visit, the McDonald NRS tool was applied to all patients [9]. The patient's mean daily weight gain was calculated by comparing their current weight with their previous record (measured at or more than ninety days prior).

The minimally acceptable rate of height and weight gain (as detailed in the initial report [9]) was derived from The Fels Longitudinal Study of healthy children [10, 11]. After summing up the patient's points, they would be categorized as: Zero point: no risk, 1 point: Low risk, 2-3 points: Moderate risk, and 4 points: High risk.

Application of Australasian Guidelines

These guidelines were also applied to each patient for all visits. According to these guidelines, patients with acceptable/normal nutritional status were considered as low risk for malnutrition [3]. Those with BMI percentile at 10-25th centile or with weight loss over one to three months or with plateau in weight gain over two to four months were considered to be at moderate risk. Finally, the patients with BMI percentile less than 10th centile or those with weight falling two or more percentile bands or those with no weight gain for six months were considered to be at high risk for malnutrition [3].

Comparison between the Two NRS Tools and the CF Team Assessments

Subsequently, the results of the McDonald NRS tool and the Australasian guidelines were compared to the assessment of independent nutritional risk factors as determined by the in-depth assessment of the CF team. With consideration of the clinical team score as the gold standard, the validity of the two NRS scores were assessed in each visit and specificity and sensitivity values were calculated.

In addition, an assessment was made to observe the ability of the two tools and the clinical team to identify patients with a subsequent decline in their BMI centile of ten percent or more between two consecutive visits.

The study in New Zealand was approved by the University of Otago Human Ethics Committee. For Iranian patients, the study was approved by the Institutional Board of the Dr. Sheikh Hospital. At the time of enrolment, the protocol and the nature of study was explained in detail to parents or caregivers and the children. Consent was obtained from caregivers or parents and children aged over 16 years of age, whilst assent was also obtained from children between 10 and 16 years of age. All study participants were provided with anopportunity to withdraw from the study if they wished.

Statistical Analysis

SPSS software 19-x for windows (IBM Corporation, New York, USA) was used for statistical analysis. Kappa agreement was obtained between the tools and the clinical score. Chi-square tests were used for comparison of data between groups. Epi Info (version 3.5.3.) was used to determine BMI, WFA, HFA, WFH and MUAC z-scores.

RESULTS

Patient Characteristics

Thirty three children in Iran and thirty six children in New Zealand with confirmed CF were assessed (Table **1**). One NZ family did not consent to participation in the study: all other NZ subjects were included. All children in Iran agreed to participate in the study. One of the Iranian children died after their initial visit, and was not included subsequently.

All Iranian patients were of Iranian ethnicity, while 34/36 (95%) of NZ patients were NZ European and just 2(5%) patients were of Maori ethnicity. The mean number of hospital admissions per year for NZ and Iranian patients were 0.55 ± 1.2 and 0.62 ± 0.69, respectively (p=0.72). Type 1 diabetes mellitus was observed in 5% and coeliac disease was reported in 2.5% of the NZ patients. None of the Iranian children were known to have a concurrent disease.

The prevalence of under-nutrition in Iranian patients was much higher than NZ patients (39% and 0%, respectively; p=0.0001). On the other hand, over-nutrition (including overweight and obesity) was more prevalent in NZ patients (9% in Iran versus 17% in NZ; p=0.05).

Application of NRS Tools in Iranian Children

The two tools were applied to all patients at baseline, and then reapplied during subsequent outpatient visits. As one of the under-nourished patients died after her first visit, subsequent scores were not able to be obtained for this individual.

On the first visit, the McDonald tool recognized 77% (10/13) of the currently under-nourished Iranian patients in its moderate to high risk group, while the Australian guidelines recognized 61% (8/13) of the

Table 1: Demographic and Nutritional Characteristics of Sixty Nine Children with CF

	Iran	NZ	P- Value
Number of patients	33	36	NA
Male	20	20	0.63
Median age (range (years))	5.4 (2- 12.92)	9.41 (2- 17)	0.008
Ethnicity	Iranian	NZ European (34) Maori (2)	NA
Median weight (range (kg))	16.9 (7.6- 34)	33.5 (11.3- 79.3)	0.0001
Median height (range (cm))	106 (77- 149.5)	138.3 (86.8 – 179.2)	0.001
Median MUAC[a] (range (cm))	15.7 (11.5- 19.5)	16.3 (15.4 – 17.4)	0.001
WFH[b] z-score (mean± SD)	-0.73 (±1.57)	0.08 (±0.52)	0.09
BMI[c] z-score (mean± SD)	-0.57 (±1.54)	0.23 (±0.76)	0.05
MUAC z-score (mean ± SD)	-1.08 (± 1.61)	-0.35 (± -0.46)	0.18

[a]MUAC: Mid Upper Arm Circumference.
[b]WFH: Weight For Height.
[c]BMI: Body Mass Index.

Table 2: Performance of the Two NRS Tools in Thirty Three Iranian Patients with CF over Consecutive Outpatient Visits

VISIT		SENSITIVITY	SPECIFICITY
1	McDonald tool	77	70
	Australasian guidelines	77	92
2	McDonald tool	83	80
	Australasian guidelines	61	64
3	McDonald tool	86	82
	Australasian guidelines	64	64
4	McDonald tool	87	78
	Australasian guidelines	67	54
Mean of all	McDonald tool	83	78
	Australasian guidelines	67	69

The sensitivity and specificity for each tool on each visit and mean of all visits is shown, with the CF Team assessment considered as the gold standard.

under-nourished children in its at risk groups (p=0.02). Fifteen percent (2/13) of the under-nourished patients were considered to be at low risk by the clinician. The sensitivity and specificity values of the two tools on each visit were calculated (Table **2**).

In this cohort, sixteen patients had a decrease in BMI centile of 10% or greater between two of their visits. Eight of these occasions were identified as being at risk by the clinical team (50%), while the McDonald tool and the Australasian guidelines recognized nine (56%) and eight (50%) of these occasions, respectively. The three assessments together were able to recognize twelve of the sixteen events (75%).

Eleven patients had a 20% or greater decrease in BMI centile on their subsequent visit. Of these, seven were identified by the McDonald tool, six by the Australasian guidelines and four by the clinical team. Altogether, the three assessments were able to identify a decrease in BMI in ten of these eleven patients (91%).

The sensitivity of both tools, especially the McDonald tool, increased on each visit in the Iranian patients (Table **2**). The mean sensitivity for the McDonald tool for all visits over the year was 83%, while the mean specificity was 66%. In contrast, the sensitivity and specificity values for the Australasian guidelines were 79% and 69%, respectively. The two tools had fair to moderate agreements with the clinical team (kappa value ranged from 0.29 to 0.43 in different visits).

Table 3: Performance of the Two NRS Tools in Thirty Six New Zealand Patients with CF over Consecutive Outpatient Visits

VISIT		SENSITIVITY	SPECIFICITY
1	McDonald tool	64	77
	Australasian guidelines	54	95
2	McDonald tool	73	92
	Australasian guidelines	73	96
3	McDonald tool	62	89
	Australasian guidelines	71	89
4	McDonald tool	100	83
	Australasian guidelines	100	83
Mean of all	McDonald tool	75	85
	Australasian guidelines	75	91

The sensitivity and specificity for each tool on each visit and mean of all visits is calculated. The CF Team assessment was considered to be the gold standard at each time point.

Application of NRS Tools in NZ Children

Both tools were also applied to New Zealand CF patients during their three-monthly visits for a period of twelve months. The sensitivity of both tools increased from 64% and 54% respectively in the first visit to 100% for both at the last visit (Table **3**). The mean overall sensitivity for both tools was the same (75%), while the Australasian guidelines had slightly higher mean specificity (91% versus 85%).

Ten patients had a decrease in BMI centile of 10% or greater between two of their visits. Five (50%) of these children had been recognized as being at risk by the CF team. Four (40%) of these patients were also identified by the two tools. The McDonald tool or Australasian guidelines did not identify any children in addition to those recognized by the Clinical Team.

DISCUSSION

Chronic diseases such as CF are associated with an increased risk of developing malnutrition. Furthermore, better nutrition in patients with CF is associated closely with survival [12]. In 2010, Salvatore *et al*. [13] reviewed 114 studies evaluating outcomes in individuals with CF. Fourteen of the included reports focused on growth and nutrition outcomes in subjects with CF, with overall agreement that good nutritional status relates closely to enhance respiratory function and prognosis. Although scheduled visits are essential for following these patients to avoid missing any signs of malnutrition, certain clinical guidelines have been developed to assist in these assessments [1, 3]. NRS tools specifically designed for individuals with CF could be helpful for early recognition of malnutrition. These tools might be particularly important in developing countries, such as Iran, where resources and well-trained personnel may not be available. These tools could be administered by either a dietitian or another trained staff member.

In this study, one recently developed NRS tool (McDonald) was applied to CF patients along with the Australasian guidelines for nutritional assessment of CF patients in two separate countries (one developing and one developed country). The sensitivity and specificity of the McDonald tool in the original description of the tool was 86% and 78%, respectively, when compared with an in-depth nutritional assessment [9]. Even though the rates of under-nutrition and over-nutrition in Iranian and NZ patients were markedly different, the sensitivity and specificity of the McDonald tool in both groups was similar and comparable to the results of the original description of this tool (Tables **2** and **3**). The consistency of these results across three different countries supports the utility and validity of this tool.

The specificity of the Australasian guidelines was slightly higher than that seen with the McDonald tool, especially in NZ patients. This difference may be due to the Australasian guidelines being the current reference in this population. Hence this guideline may influence the decision making of members of the CF team regarding patients' nutritional status and their future care plans.

The screening tools were also assessed for their ability to identify patients who had declining BMI centile between two separate visits. The McDonald tool was able to identify more patients with declining BMI (≥ 10%) than the clinical team in the Iranian cohort (while Australasian guideline was able to identify the same number of patients). Both tools were able to identify more patients than the clinical team when a 20% decline was considered (65% and 54%, respectively, in comparison to 36% by the clinical team). Thus, application of these tools, especially the McDonald tool could prevent the under-recognition of at risk CF patients. Although decreasing BMI is not the only predictor of nutritional deterioration in individuals with CF, this finding emphasizes the potential of these tools, especially in a setting with fewer resources.

However, this benefit of the two tools was not seen in the NZ cohort. Neither tool was able to add additional utility to the assessment provided by the clinical team. This likely reflects the benefits of a broader clinical team in NZ.

It is appropriate to mention that although these tools are helpful for early identification of children at nutritional risk, they do not replace an in-depth nutritional assessment. A full nutritional assessment, conducted at least annually, remains important for each patient with CF [14]. In Australia and NZ, nutritional assessment by a dietitian is a key part of routine three-monthly visits for all pancreatic insufficient (PI) CF patients. However, regular application of these tools would be beneficial in other countries, such as Iran, where there is less access to dietetic expertise.

Nutritional assessment is also important for pancreatic sufficient (PS) CF patients. These patients have less nutritional compromise, and consequently have longer expected life span than PI patients. Nonetheless, PS patients still have increased nutritional demands compared to their peers without CF. Furthermore, some of these children will develop pancreatic insufficiency over time with progressive decline in exocrine pancreatic function [15, 16]. Currently in Christchurch, children with PS do not have regular dietetic review. Application of a reliable NRS tool may permit the early detection of nutritional deterioration in this sub-group of children with CF who may not currently have regular assessment.

Overall, this study included a total of 69 children in two separate centers, with all but one of the available children included. The study protocol was maintained consistently in both centers, with multiple repeated assessments over time. These data are likely representative of the respective countries: however replication of the study in additional settings would provide confirmation of the data.

In conclusion, both tools successfully recognized patients at risk of malnutrition. The McDonald tool had comparable sensitivity and specificity to that described previously, especially in Iranian patients. This tool may be helpful in recognizing at risk CF patients, particularly in developing countries with fewer resources.

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