Research Square

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Refeeding Syndrome in Head and Neck Cancer: Diagnostic and Indigenous Diet-Based Protocols for Survival and Nutritional Assessment in a Single-Centre Prospective Study in Assam, India

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Research Article

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Abstract

Introduction: Refeeding Syndrome (RFS) is a potentially fatal metabolic disorder that can occur after prolonged periods of starvation in severely malnourished patients. In head and neck cancer (HNC) patients undergoing radio(chemo)therapy, RFS can be a hidden cause of mortality. Methods: In a single-centre study, the prevalence of HNC patients at high risk of developing RFS was detected as per the National Institute for Health and Care Excellence (NICE) criteria. Further, the effect of an omega-3 fatty-acid-enriched diet plan was assessed amongst patients in two groups: control (n = 43 participants; 58.8 ± 11.6 years, 70% male) and diet treatment (n = 47 participants; 57.7

± 12.02 years, 66% male). Results: The incidence of high RFS risk in HNC patients was 41.5%. All diagnosed patients were supplemented with electrolytes for two weeks, leading to a 100% survival rate until one month. The omega-3 fatty-acid-enriched diet plan was found to stabilize the net body weight and body mass index in a week and showed a minimal net positive increase in a month, compared to the iso-calorific and iso-nitrogenous diet of the control group. Conclusions: This pilot study highlights the importance of developing diagnostic and indigenous diet-based protocols for HNC patients at risk of RFS. To the best of our knowledge, this is the first study on RFS in HNC patients in India and South Asia.

1. Introduction

Refeeding Syndrome (RFS) can be defined as a severe anabolic reaction upon the ingestion of food, orally, enterally, or parenterally, after prolonged periods of starvation or malnourishment [1]. RFS was first described in starved prisoners of early post-World War II as deaths along with cardiac and neurological abnormalities were observed after

the commencement of feeding [2]. Its pathophysiology is characterized by hypophos-phatemia, biochemical and intracellular abnormalities, such as sodium and fluid balance disturbances, changes in glucose, protein, fat metabolism, thiamine deficiency, hypoka-laemia, and hypomagnesaemia [3, 4]. A more recent understanding of RFS characterizes the term as a spectrum of biochemical abnormalities and clinical consequences character-ized by electrolytic and fluid shifts, but RFS has lacked a universally accepted clinical def-inition until date [5]. It is key to note that RFS is not an abnormal metabolic reaction but a normal physiological reaction to the initial stage of feeding malnourished subjects [6]. De-spite considerable impactful research on RFS, its global incidence remain unknown, and further standardization is required for optimal prevention and treatment strategies [4, 7–9].

RFS is associated with comorbidities, such as increased infection risk, delayed wound healing, anorexia, depression, and reduced response to chemotherapy and radiotherapy in cancer patients. Among patient populations, head and neck cancer (HNC) patients are particularly susceptible to RFS [9]. HNC or upper digestive tract cancer patients are par-ticularly at risk for RFS owing to prolonged periods of poor nutritional intake, arising from their difficulty in swallowing (dysphagia), odynophagia, oral lesions, food aversion, suboptimal compliance with respect to feeding, and it is compounded by the side effects of chemotherapy, radiotherapy, high metabolic demands due to cancer cachexia, cancer-related hypermetabolism, and infection [10, 11]. Furthermore, HNC patients are especially at risk of chronic alcohol abuse, tobacco abuse

(smoking, oral), and poor nutrition, which are often systemic in economically disadvantaged backgrounds [12]. Therefore, formulat-ing a suitable plan for electrolytic, mineral, and vitamin supplementation is essential.

Ravasco et al. were the first to report the advantages of nutritional counselling on nutritional status, quality of life, and outcomes in HNC patients during radiotherapy [13]. Nutrition therapy for cancer patients is advised as a life-long intervention as it helps main-tain a healthy body weight, muscle mass, corrects malnutrition, and counteracts the side effects of radio-chemotherapy [14]. A randomized controlled trial studying oral supple-ments for lung cancer patients determined that, to counteract the suboptimal compliance issue while achieving the benefits of omega-3 fatty acid supplementation, patients pre-ferred to consume palatable oral food over oral nutritional supplements, and more feasi-ble methods of supplementation were required [15]. For orally feeding HNC patients with dysphagia, developing the right consistency for ease of feeding and palatability is espe-cially key. To prevent cancer-related weight loss and maintain the nutritional status of patients, a personalized diet, such as patients' nutritive and energy-restrictive require-ments, locally available food items palatable to the indigenous populations, initial body weight, metabolic alterations, cachexia, appetite loss, and swallowing ability, should be considered [16, 17].

The diagnostic criteria and management of RFS with nutritional support were deter-mined by the National Institute for Health and Care Excellence (NICE) guidelines, and the British Association of Parenteral And Enteral Nutrition (BAPEN) recommendations were followed for supplementing the crucial nutrients. The NICE criteria (2006), which were used in this study, have since been revised based on recent clinical trials and meta-analyses [12, 18]. Some of the most recent guidelines comprising a consensus-supported algorithm for RFS detection were updated by Friedli (2018), the American Society for Par-enteral and Enteral Nutrition (2020), and Cook et al. (2022) [6, 7, 19].

In this single-centre pilot study, we aimed to diagnose RFS in HNC patients as per the NICE criteria and report the prevalence of patients at high risk for RFS. Thereon, the effectiveness of a weekly feeding protocol that was developed by a medical team (based on optimal nutritional intake, omega-3 fatty acid content, calorie restriction, and consid-ering the individual patients' body weight and severity of RFS) was checked in a prospec-tive cohort-based study. The diet was administered by the patients' caretakers at home

and was based on indigenously available food products to ensure palatability and com-pliance. A prospective cohort study was conducted to check the effect of the diet on body weight (BW) and body mass index (BMI) in a week and in a month.

2. Materials and Methods

2.1. RFS Diagnosis and Prevalence

In June 2015, 376 patients were diagnosed with head and neck malignancies at the Department of Otorhinolaryngology and Head and Neck Surgery, Assam Medical Col-lege and Hospital, Dibrugarh, Assam, India. All patients at high risk of developing RFS were assessed as per the major and minor criteria of the

2006 NICE guidelines [18], which included the need for meeting at least one major criterion or two minor criteria, as shown in Table 1.

Table 1
Refeeding Syndrome (RFS) diagnosis using NICE guidelines (derived from [12]).

Major Characteristics	Minor Criteria
BMI less than 16 kg/m2	BMI less than 18.5 kg/m2
Unintentional weight loss greater than 15% in the past 3–6 months	Unintentional weight loss greater than 10% in the last 3–6 months
Little or no nutritional intake, < 10 days	Little or no nutritional intake, > 5 days
Low levels of blood serum K+, $PO_4$2− or Mg2 + levels prior to feeding.	History of chemotherapy, alcohol abuse, or chronic use of insulin, diuretics, antacids.

2.2. Clinical Characteristics for RFS Assessment

The RFS-diagnosed patients were supplemented with electrolytes and vitamins as per the BAPEN guidelines for two weeks. Upon clinical presentation, routine blood ex-amination was conducted to determine the platelet count, blood sugar, urea, creatinine levels, AST:ALT ratio, serum Na+, K+, Mg2+, $PO_4$2−, and Ca2 + levels, along with the serum total protein and fraction levels. Furthermore, the patient characteristics of electrocardio-gram reading, the Eastern Co-operative Oncology Group (ECOG) physiological score, and the weight and height (for BMI calculation) were determined.

2.3. Study Design

The study was approved and funded by the Indian Council of Medical Research. Verbal informed consent was obtained from the patients, following which 104 HNC pa-tients with RFS were continuously allocated into two groups. In the control group, fifty patients followed a conventional diet, standard in the clinic. For the 54 patients in the diet treatment group, a medical team including a dietician developed an optimized diet chart to ensure the optimal calorie and nutrient intake. The weekly diet chart for the diet treat-ment group is shown in Table 2. The electrolyte supplementation of all the RFS-diagnosed patients removed the confounding independent variable of electrolytic differences be-tween the groups, and the formulated diet's effect on the BW and BMI could, hence, be suitably compared to the control.

2.3.1. Inclusion Criteria

The inclusion criteria to assess the effectiveness of an indigenous-based diet for feed-ing HNC patients involved, first, the diagnosis of RFS, and second, obtaining consent from the patients or caretakers to participate in the study. During the data analysis stage, seven patients, respectively, each from the control and diet treatment groups, were excluded due to data entry errors. The patient selection process is presented in Fig. 1 in the form of a CONSORT flowchart. The net differences in BMI and BW for each patient

were cal-culated to check the effect of the formulated diet with respect to our standard clinical practice, as further described in Section 2.5.

2.3.2. Electrolytic Supplementation Protocol

Based on the NICE and BAPEN guidelines, patients diagnosed to be at risk for RFS were supplemented orally with 200–300 mg of thiamine daily, along with 1–2 tablets of vitamin B complex, which was supplemented thrice daily (or intravenously); multi-vita-min/trace elements were administered once daily for at least two weeks. Electrolyte im-balance was corrected by the daily supplementation of 2–4 mmol/kg/day of K+, 0.3–0.6 mmol/kg/day of PO42−, and 0.2 mmol/kg/day of intravenous or 0.4 mmol/kg/day of oral administration of Mg2+ [12, 20]. The electrolytic supplementation as per the BAPEN guide-lines (and nutritional rehabilitation considerations) was directly derived from Mehanna et al. (2009), which is an update on the original NICE guidelines specifically for HNC pa-tients with RFS [12, 18].

2.3.3. Nutritional Supplementation Protocol

The weekly diet chart for the diet treatment group is shown in Table 2. The electrolyte supplementation of all the RFS-diagnosed patients removed the confounding independ-ent variable of electrolytic differences between the groups, and the formulated diet's effect on the BW and BMI could, hence, be suitably compared to the control. The timepoints for BW and BMI assessment at the clinic were one week and a month (4 weeks). However, the patients were fed by their caretakers at home and the administration could not be closely monitored.

Table 2
Weekly feeding protocol formulated for head and neck patients with Refeeding syn-drome.

Time/ Day	7 am	9 am	11 am	1 pm	3 pm	5 pm	7 pm	9 pm
1	Banana shake	Banana shake	Banana shake	Rice, dal, soybean	Banana shake	Rice, dal, soy-bean	Rice, dal, soybean	Rice, dal, soy-bean
2	Rice flakes, milk	Rice flakes, milk	Rice flakes, milk	Rice, dal, carrot, soy-bean	Rice, dal, car-rot, soybean	Rice flakes, milk	Rice, dal, carrot, soy-bean	Rice, dal, car-rot, soybean
3	Banana smoothie	Banana smoothie	Banana smoothie	Fish soup	Banana smoothie	Fish soup	Fish soup	Fish soup
4	Rice flakes, milk	Rice flakes in milk	Rice flakes in milk	Soybean soup	Soybean soup	Rice flakes, milk	Soybean soup	Soybean soup
5	Rice powder cooked in milk, banana	Rice powder, milk, banana	Rice powder, milk, banana	Rice, dal, soybean	Rice, dal, soy-bean	Rice powder milk, banana	Rice, dal, soybean	Rice, dal, soy-bean
6	Moong dal khi-chdi	Moong dal khichdi	Fish soup	Fish soup	Moong dal khichdi	Moong dal khichdi	Fish soup	Fish soup
7	Banana shake	Banana shake	Banana shake	Rice, dal, carrot, soy-bean	Banana shake	Rice, dal, car-rot, soybean	Rice, dal, carrot, soy-bean	Rice, dal, car-rot, soybean

2.4. Feeding Protocol

As per the NICE guidelines, the diet chart was prepared to feed 10 Kcals/kg/day (of their body weight), and the feeding was gradually increased after 4–7 days since the com-mencement of the course. For severely malnourished subjects with a BMI of less than 14 kg/m2 with negligible food intake for over two weeks, the feeding was commenced at a maximum of 5 kcal/kg/day, such that a 35 kg patient would be fed 1225 Kcal/week The control group followed a conventional iso-caloric and iso-nitrogenous diet along with the prescription of three scoops of conventional protein powder, twice a day, amounting to a diurnal protein intake of 27–30 g, which was our existing clinical recommendation for HNC patients. The 2006 NICE guidelines mentioned electrolytic supplementation to be sufficient for RFS treatment, while feeding

continued [12]. We were, therefore, convinced that the patients in the control group (as well as the RFS risk-diagnosed patients not en-rolled in the study) would not be at risk of RFS if feeding was commenced alongside, as per our standard diet recommendation. However, all patients were cautioned to start feeding slowly in the initial week.

The diurnal intake of calories, protein, fat, and polyunsaturated fatty acid (PUFA) levels for each week is shown in Table 3. The PUFA intake was higher on the third and sixth days. Each meal was prepared to be 50 mL in volume, and the patients were to be fed every 2 h to ensure small frequent meals, amounting to a total of 400 mL/day for each day of the week. The ingredients/recipe and total calorific value of each food item are shown in Supplementary Table S1, while Supplementary Table S2 depicts the calories, protein, fat, and PUFA levels (in grams) of the food preparations. Some of the most com-monly available food items in the region include rice, pulses, fish, banana, beans, soy-abeans, and other vegetables and fruits.

Table 3
Diurnal intake of carbohydrate, protein, fat, polyunsaturated fatty acids (PUFAs) for the diet treatment group.

Day	Carbohydrates (g)	Protein (g)	Fat (g)	PUFA (g)
1	98.2	26.06	14.17	14.50
2	89.5	27.2	14.62	14.62
3	81.4	31.62	16.62	44.35
4	86.77	31.92	9.28	18.81
5	93.9	27.4	14.27	14.62
6	91.7	35.97	14.20	45.71
7	103.5	16.5	14.27	14.50

All nutritive value of foods in grams per 100 g of edible portion.

2.5. Data Analysis

For comparing the changes in BW and BMI of the patients in the two groups, the measurements from the succeeding timepoints were subtracted from the preceding one, yielding absolute values of BW and BMI changes for each patient. The calculated net BW and BMI changes were irrespective of individual characteristics and co-morbidities, and the net changes (such as 0.5 kg decrease, 1 kg increase) were comparable between the groups. We reasoned that, as an indicator of health for generally malnourished subjects, an increase in the weight and BMI in the diet treatment group would reflect the diet plan's effectiveness. Student's t-test was conducted to check the significance of the absolute changes in BW and BMI between the two groups, from week 0 to week 1 and until month 1.

A sample size of about fifty patients was initially allocated for each group, but fol-lowing exclusion, it was reduced. The sample size between the groups did not have to be adjusted as their sizes were comparable (n = 43 and n = 47 for the control and treatment groups, respectively), which, being more than 40, was more than the minimum recom-mended sample size for fitting the central limit theorem of 30 subjects [21]. During

the data analysis stage, a statistical model for stratifying the age groups (35–55 and 56–80 years) and cancer stages was initially tabulated to suitably compare the BW and BMI changes between the two groups, but this was deemed unnecessary as the absolute BW and BMI changes reflected the net increase or decrease, irrespective of individual charac-teristics. The analyses were conducted in MS Excel Office 365, and a p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Prevalence and Clinical Characteristics of HNC Patients at Risk of RFS

Among the 376 patients presenting with head and neck malignancies, as per the NICE criteria, RFS was detected in 156 patients in April 2015. As the definition of RFS remains unclear to date, the prevalence of 41.48% reflects that the patients with HNC were at high risk for RFS. The characteristics of the patients in the control and diet intervention groups (after the exclusion) are shown in Table 4. The tumour locations of all 104 patients who were followed-up for one month were also presented. All followed-up patients sur-vived until the end of the month, and the survival rate after electrolytic supplementation was, therefore, 100%.

The age and cancer stages of the patients in both groups were closely comparable. The control group (n = 43 patients) was made up of 70% men, and the average age was

58.8 ± 11.6 years, while the 47 patients in the diet intervention group were 66% men, and the average age was 57.7 ± 12.02 years. In the control and diet intervention groups, respec-tively, 31% and 30% patients were in the fourth stage of cancer. As for the second and third stages of cancer, the control group had 17% and 50% patients, respectively, while the intervention group had 32% and 36% patients, respectively. The baseline weight, BMI,

initial levels of potassium, sodium, phosphate, magnesium, calcium ions, haemoglobin, albumin, globulin, and total blood protein were similar, as well.

Table 4
Patient characteristics.

Age (years)	**Control** (***n*** **= 43)**	**Diet Treatment** (***n*** **= 47)**
	58.8 ± 11.6	**57.7 ± 12.02**
Sex		
Male	30 (70)	31 (66)
Female	13 (30)	16 (34)
Cancer stage		
I	1 (2)	1 (2)
II	7 (17)	15 (32)
III	21 (50)	17 (36)
IV	13 (31)	14 (30)
ECOG Score		
I	2 (5)	4 (9)
II	15 (35)	17 (37)
III	15 (35)	23 (50)
IV	11 (25)	2 (4)
Weight (kg)	44.74 ± 7.7	45.74 ± 7.5
BMI (kg/m2)	17.66 ± 2.3	18.28 ± 2.6
K+ (mmol/kg/day)	3.6 ± 0.8	3.36 ± 0.6
Na+ (“ “)	135.64 ± 6.2	134.1 ± 7.2
PO4− (“ “)	2.9 ± 0.6	2.8 ± 0.8
Mg2+ (“ “)	2 ± 0.5	1.8 ± 0.5
Ca2+ (“ “)	8.3 ± 2.2	8.2 ± 0.7
Hemoglobin (g/dL)	9.6 ± 2.2	10.5 ± 1.9
Globulin (“)	3.35 ± 0.6	3.4 ± 0.7
Albumin (“)	3.06 ± 0.6	3.2 ± 0.6
Total protein (“)	6.4 ± 0.6	6.6 ± 0.9
Tumor location	*(n* = 50*)*	*(n* = 54*)*
Oral cavity	6 (12)	10 (18.6)

Age (years)	Control (*n* = 43)	Diet Treatment (*n* = 47)
	58.8 ± 11.6	**57.7 ± 12.02**
Salivary gland	-	2 (3.7)
Oropharynx	6 (12)	7 (13)
Hypopharynx	6 (12)	6 (11)
Larynx	-	14 (26)
Esophagus	23 (46)	13 (24)
Unknown primary	9 (18)	2 (3.7)

Data are presented as mean ± SD and number (percentage, %). Rounded to first decimal.

3.2. Nutritional Therapy Stabilized Patient BW and BMI Compared to the Control

The net BW and BMI differences between the groups at the timepoints of 1 week and a month from the pre-treatment stage are shown in Table 5. From the pre-treatment stage to week 1, the absolute BW and BMI changes in the control group were − 0.45 ± 0.6 kg and

0.22 ± 0.3 kg/m2, respectively, while in the diet treatment group, the BW and BMI changes were 0.09 ± 0.6 kg and 0.046 ± 0.2 kg/m2, indicating no loss of BW and BMI, compared to the control, which indicated a trend towards further loss. The differences were significant (p = 0.00008 and p = 0.0002, for BW and BMI changes, respectively). Thereon, from week 1 to month 1, the BW and BMI changes were − 1.3 ± 1.5 kg and − 0.6 ± 0.6 kg/m2, respectively, in the control group, which in the diet treatment group were 1.3 ± 0.9 kg and 0.5 ± 0.4

kg/m2, respectively, (p = 9.7 × 10 − 14 and p = 1.2 × 10 − 14 for BW and BMI changes, respec-tively). The total BW and BMI changes from the pre-treatment stage to the first month were − 1.78 ± 1.7 kg and − 0.8 ± 0.7 kg/m2 in the control group and 1.4 ± 1.1 kg and 0.57 ±

0.47 kg/m2 in the diet treatment group, respectively (p = 1.2 × 10 − 14 and p = 4.4 × 10 − 16 for BW and BMI changes, respectively). The median weight gain in a month was 1.45 kg, in contrast to the control, where the median weight loss was 2 kg. Among individual pa-tients, the exceptions were as follows: in the diet treatment group, after feeding continued for a week and one month, a slight reduction in BW and BMI was found in six and three patients, respectively. In contrast, in the control group, BW gain in the one-week period was nil, while six patients had a slight increase in BW and BMI at the one-month period.

Table 5
Weight and Body mass index (BMI) changes in the control and diet treatment groups until a month.

Week 0:	**Control (*n* = 43)**	**Diet treatment (n = 47)**	***p*-Value**
*Initial Weight (*kg*)*	44.74 ± 7.7	45.74 ± 7.5	-
*Initial BMI (*kg/m2*)*	17.66 ± 2.3	18.28 ± 2.7	-
Week 0 to Week 1:			
*Weight (*kg*)*	43.38 ± 8.9	45.83 ± 7.5	-
*BMI (*kg/m2*)*	16.96 ± 2.7	18.33 ± 2.6	-
*Weight (*kg*) change*	−0.45 ± 0.6	0.09 ± 0.6	****
*BMI (*kg/m2*) change*	−0.22 ± 0.3	0.046 ± 0.2	****
Week 1 to Month 1:			
*Final Weight (*kg*)*	42.18 ± 8.9	47.14 ± 7.2	-
*Final BMI (*kg/m2*)*	16.48 ± 2.6	18.86 ± 2.6	-
*Net Weight (*kg*) change*	−1.3 ± 1.5	1.3 ± 0.9	****
*Net BMI (*kg/m2*) change*	−0.6 ± 0.6	0.5 ± 0.4	****
Total weight change	−1.78 ± 1.8	1.4 ± 1.1	****
Total BMI change	−0.8 ± 0.7	0.57 ± 0.47	****

****, $p < 0.0001$.

4. Discussion

The incidence of RFS in HNC patients in a month in a single-centre university hospi-tal in Assam, India, was firstly determined, using the NICE criteria for the diagnosis. Thereon, the replenishment of the electrolytic imbalance was found to be effective, as the survival rate was 100% in both groups of the study. The recommendation of a refeeding diet treatment plan was found to be statistically effective in maintaining BW and BMI, in contrast to the control group.

While previous guidelines stressed the importance of adequate replenishment of electrolytes, vitamins, and minerals prior to the commencement of feeding, either enter-ally or parenterally, the update in the 2006 NICE guidelines specifically for HNC patients by Mehanna et al. (2009) suggested the feeding to be sufficient as long as the replenish-ment occurred in parallel, although it potentially risks prolonging the period of malnutri-tion [12]. The incidence of mortality in both groups was zero in one month, compared to previous reports of

occurrences of mortality of HNC patients in the clinic due to unknown reasons, owing to RFS, as per our investigations, based on which this study was concep-tualized. It could, therefore, be said that the electrolytic replenishment along with either an iso-calorific diet or formulated diet from the initial days would be an effective minimal clinical protocol for malnourished patients at risk of RFS, and to further improve the over-all health status of the patient, nutritional interventions are key.

Upon the recommendation of a diet chart for the nutritional rehabilitation of HNC patients with RFS, in the control group, a slight mean net reduction in BW in one month was observed (− 5% net BW change), while that of the diet treatment group (3% net BW change) stabilized and tended towards an increase, as did the BMI. A distinguishing fea-ture of our feeding plan was the frequency of feeding throughout the day, which was personalized to be calorie-restricted for severely malnourished patients, based on the di-etician's supervision. Although the changes in BW and BMI in both groups were minimal, given the tumour-derived catabolism, disease-related malnutrition, and nullifying of pos-itive effects of an increase in energy or nutrient intake [4], the increase in the average BW and BMI could be seen as a positive effect. However, it is key to note that the diet treat-ment plan involved small frequent feeding, in contrast to the control. Future studies in-vestigating the feeding and diagnosis of HNC patients with RFS can be designed based on the most recent data, which include an evidence-based and consensus-supported algo-rithm, instead of the 2009 guidelines followed in this study, especially considering that RFS can occur at various stages of the treatment procedure in HNC patients [6].

There is need for awareness of the crucial subject of RFS in HNC patients, especially as this is the first study on RFS in HNC from India or South Asia (at large), to the best of our knowledge. To date, RFS remains largely underreported in clinical practice, and pre-vious studies have determined an independent association of malnutrition incidence in HNC patients at a 45.6% prevalence [5]. Based on collective analysis of case reports and broader definitions of RFS (such as electrolyte disturbances, specifically hypophos-phatemia, or an outcome of malnutrition), various incidence rates of RFS across patient populations have been reported: 48% in severely malnourished patients, 34% in the inten-sive care unit, 33% in anorexia nervosa, and 9.5% in hospitalization from gastrointestinal fistulae [22]. To spread awareness of RFS, recent high-impact publications, meta-analyses, and systemic reviews mention the need for systematic education on the topic [4–9]. Fur-thermore, studies have also expressed the importance of accounting for RFS when devel-oping a nutrition protocol for COVID-19 hospitalized patients [23].

One of the aims of the study was to develop a diet treatment plan that was palatable and would, thereby, tackle the issue of suboptimal compliance. Furthermore, the diet table in this study can be a reference for formulating nutritional protocols, based on commonly available food items regionally across India to boost the body's defensive mechanisms. The feeding schedule was formulated to ensure the daily intake of fish, as it has omega-3 PUFAs, which modulates catabolism and appetite, thereby reducing muscle degradation and weight loss in cancer patients. The dietary plan for rehabilitating patients with RFS should be adapted based on the metabolic patterns of individual patients, and previous studies have stressed the need for early RFS diagnosis, interdisciplinary medical teams, and oncology specialist training on nutritional subjects in this regard [5]. The immune-modulating effects and positive effects of BW preservation of omega-3 fatty acids are well-documented; to improve weight gain in starved anorexia nervosa patients without the risk of RFS, high-energy liquid nutrition, omega-3 fatty acids, and dietary supplements have been recommended [15].

As RFS is primarily a catabolic starvation-induced pathway, a recent study investi-gated the autophagy pathway in an RFS-induced myocardial injury mice model [24]. Fu-ture biomedical and translational research on such topics is likely to have a considerable impact. For instance, monitoring phosphorus levels would be essential for diagnosing RFS and investigating RFS at a molecular and cellular level. Phosphorus being essential for global cellular processes, such as the structural integrity of the cell membrane, energy storage, and pH regulation (by acid–base buffering), means that even small drops in se-rum phosphorus can lead to widespread dysfunction in all cellular processes. In RFS, pro-longed depletion of phosphorus in the body occurs because of much greater use of phos-phate in cells caused by the insulin spike.

Among the limitations of the study, as the feeding of the diet treatment and control groups could not be closely monitored in the hospital, the results of this nutritional inter-vention study would solely reflect the effect of the recommendation of a detailed feeding protocol for HNC patients with RFS to be enforced at home. Furthermore, although BMI is an anthropometric indicator of nutritional status in adult populations and useful for identifying malnutrition, it is not considered a reliable measure of nutritional status or body composition [25]. As mentioned by Mehler et al. (2010), “weight gain greater than two to three pounds per week are usually not nutritionally sound and may represent edematous fluid retention or retained bowel contents from constipation” [26]. An assess-ment of malnutrition using the GLIM criteria or of nutritional risk would be a way for-ward in the assessment of patient populations susceptible to RFS, especially in developing countries where malnourishment is a systemic issue. As per past literature, a more effi-cient clinical indicator for the assessment of health is handgrip strength, as conducted in a randomized control trial on RFS patients by Olsen et al. [27]. Furthermore, checking the patients’ BW and BMI beyond one month would have provided further meaningful in-sight. Another limitation was that the feeding plan involved small frequent meals, which was not the same in the control group; researchers might consider studying the independ-ent effect of small frequent meals in feeding malnourished HNC patients, given the eating difficulty due to cancer. A recent study from Thailand highlighted the importance of nu-trition counselling, oral nutritional supplementation, immunonutrients, enteral nutrition, and parenteral nutrition, for treating RFS in HNC patients [28]. The high-impact studies published in European and American journals on risk factors and incidence rates provide much-needed insights to continue the research on RFS.

5. Conclusions

To the best of our knowledge, this is the first study reporting the incidence of RFS risk in HNC patients from India or South Asia, and prior studies on RFS from India seem to be mainly on malnutrition and tuberculosis. This pilot study urges discussions on the necessity for RFS awareness, clinical protocols for diagnosis, electrolytic monitoring and supplementation, and nutritional rehabilitation of HNC patients in India. Furthermore, the challenges in diagnosing patients at high risk of RFS remain unresolved, and subopti-mal compliance of feeding during radio(chemo)therapy remains a major challenge for pa-tients with HNCs. The formulation of an indigenously sourced diet highlights the im-portance of developing multidisciplinary clinical teams for oncological care, improving feeding compliance. There is an urgent need for clinical and public health research-based efforts, especially in semi-urban and economically disadvantaged areas. Through our re-sults, we wish to create fundamental awareness of this condition and provide our feeding protocol as a resource for future research to model similar diet plans for feeding patients with RFS across

geographical regions. The need of the hour is to routinely check for RFS in HNC patients based on available diagnostic criteria and emphasize the need for further high-quality research.

Declarations

Institutional Review Board Statement

Ethical review and approval were waived for this study owing to the minimum intervention nature of the study. As per the 2006 NICE guidelines, the treat-ment for refeeding syndrome is the replenishment of electrolytes and minerals, while commencing feeding to reduce the duration of starvation. All RFS-diagnosed patients were advised to commence the safe standard iso-calorific and iso-nitrogenous diet (as usually prescribed), except for the pa-tients allocated in the experiment group, who were provided with the specific diet of the study. The patients were continuously allocated to either groups. The diet was not enforced in the clinic and were implemented by the patients' caretakers at home, as discussed as a limitation of the study.

Informed Consent

Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest:

The authors declare no conflict of interest.

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Author Contributions:

The study was conducted at Assam Medical College (AMC) under the guid-ance of N.S. (responsible for validation, investigation, project administration, funding acquisition) by N.S., M.G., R.R.V. and I.G. The dietician consulted for designing the feeding protocol and writing was A.K. The formal analysis, data presentation, and writing—reviewing, editing, was by R.B. The study was conceptualized by M.G. (AMC alumni) who wrote the original draft. All authors have read and agreed to the published version of the manuscript.

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Data availability statement:

The dataset used during the current study is available from the corre-sponding author on reasonable request.

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Figures

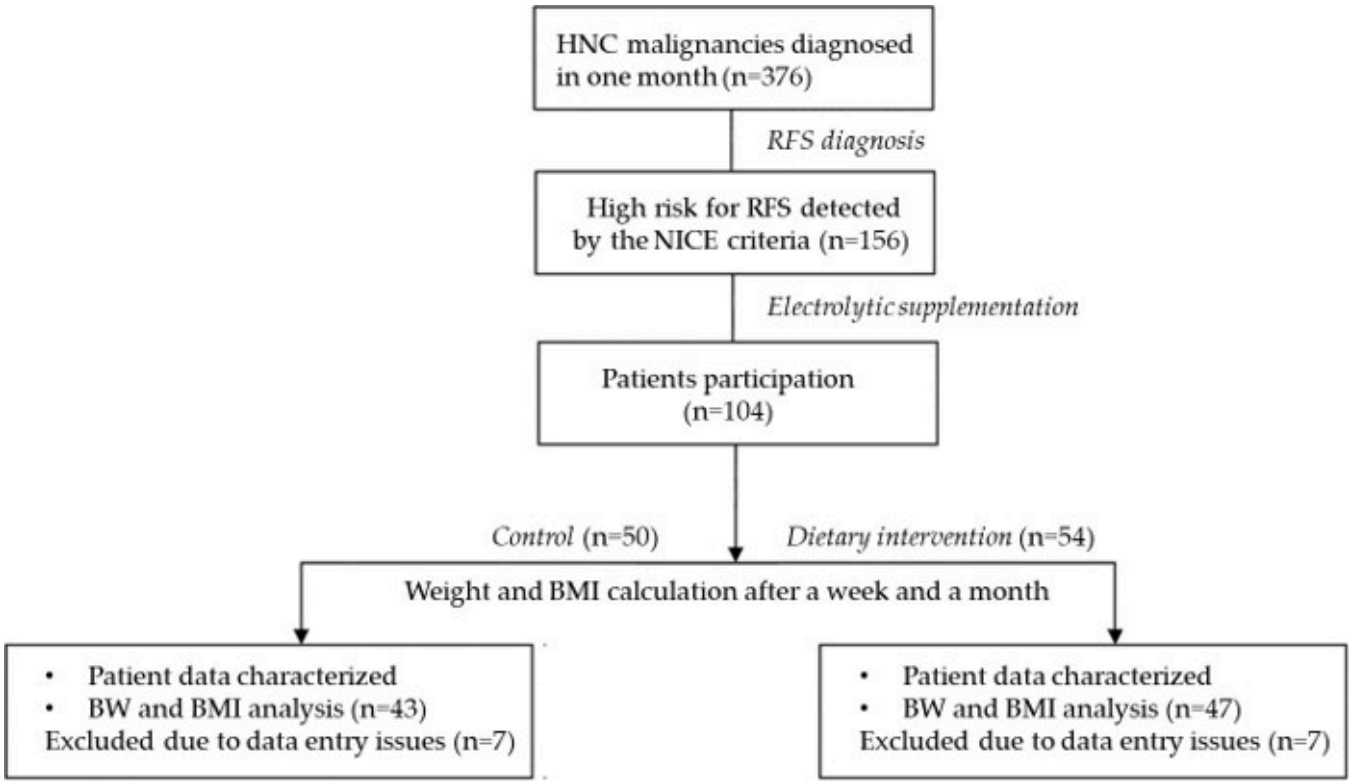


Figure 1

Figure 1. CONSORT diagram of the study. BMI, Body mass index; BW, Body weight; HNC, head and neck cancer; NICE, National Institute for Health and Care Excellence; RFS, Refeeding syn-drome.

Supplementary Files

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