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Cachexia in oral squamous cell carcinoma Sudanese patients: an exploratory study

Safaa Merghani Awadallah^{1*}, Hind Ahmed Osman Elhag² and Yousif Eltohami³

Abstract

Background Cachexia status is a drastic issue in cancer patients. The main goal of this study; which is considered the first of its kind in Sudan, was to enhance our understanding of the clinical implications of oral cancer cachexia. Newly diagnosed Sudanese patients with oral squamous cell carcinoma (OSCC) were evaluated for the incidence and impact of cachexia.

Methods This is a longitudinal descriptive study conducted at Khartoum Teaching Dental Hospital before April 2023. A number of 40 OSCC participants above 18 years old were analyzed for Cachexia based on weight loss, low hemoglobin levels, albumin levels, elevated C-reactive protein, decreased mid-upper arm circumference, loss of appetite, and anorexia. Data were collected over three visits, and analyzed using descriptive and bivariate statistics.

Results The study included 40 newly diagnosed patients with OSCC, with a mean of age 56.8 years. The incidence of cachexia was 33.2% before surgery, 55% one month postoperatively, and 65% six months later. Cachexia was significantly correlated ($p < 0.05$) with delayed wound healing ($p = 0.008$), prolonged nasogastric feeding tube usage ($p = 0.023$), interrupted adjuvant therapy ($p = 0.003$), and mortality ($p = 0.007$). Low BMI, loss of appetite, food intake, low hemoglobin, and elevated CRP were significant diagnostic criteria as well ($p < 0.05$).

Conclusions In this study, Cachexia was found to be a critical prognostic factor for OSCC patients. Larger-scale clinical research in Sudan is needed to provide definitive findings and strategies to support nutritional status during therapy.

Keywords Cachexia, Oral squamous cell carcinoma, Wound healing, Adjuvant therapy, Nasogastric tube, Death

Background

Oral squamous cell carcinoma (OSCC) is the cause of more than 90% of oral cancers worldwide. Incidence has been found to be influenced by age [1], socioeconomic level, and access to medical services [2]. The primary site of OSCC is primarily responsible for deaths as a result of dysphagia, aspiration pneumonia, carotid artery erosion, severe hemorrhage, cachexia, and malnutrition [3].

The word cachexia is of Greek origin, derived from the words “kakos” and “hexis,” which indicate a “bad condition” associated with chronic illnesses such as cancer. The Society for Cachexia and Wasting Disorders stated that cachexia is a complex metabolic syndrome

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associated with underlying illness and characterized by the loss of muscle with or without the loss of fat mass [4]. Cachexia should be suspected if there is an involuntary weight loss of greater than 5% of premorbid weight within six months, especially in the presence of muscle wasting or $>2\%$ in depleted patients or BMI less than 20% [5]. Cachexia is thought to be the primary cause of death in 20–40% of cancer patients [6], and it can reach up to 93% in head and neck SCC patients before death [7]. Additional studies have concluded that the criteria for cachexia diagnosis include reduced muscle strength, fatigue, anorexia, low fat-free mass index, abnormal biochemistry (C-reactive protein >5.0 mg/dl, IL-6 >4.0 pg/ml, anemia <12 g/dl, and low serum albumin <3.2 g/dl), and weight loss of at least 5% in 12 months or less in the presence of an underlying illness. This study aims to understand and address the pressing issue of cancer cachexia, a challenging condition to diagnose and treat in underdeveloped nations, in this case Sudan.

Methods

The study enrolled 40 Sudanese OSCC patients aged above 18, newly diagnosed, and surgically operable, with exclusions for neo-adjuvant therapy, recurrent OSCC, other malignancies, weight-affecting medical conditions, missing data, or lost to follow-up.

Study design

The study is a longitudinal descriptive study conducted in a hospital setting, by analyzing patients' medical records, diagnosis, and treatment plans based on inclusion/exclusion criteria (Fig. 1). Patients were assessed for cachexia over 3 visits: preoperatively, one month after, and six months later. Cachexia diagnosis was made based on, significant weight loss (more than 5% or 2% in depleted patients or BMI <20) plus three or more of the following criteria: Hb below 11 mg/dL (anemia),

hypoalbuminemia, S. albumin <3.2 g/dL, elevated C-reactive protein (CRP) >5 mg/dL, mid-upper arm circumference (MUMC) <25 cm for males and <23 cm for females, anorexia, and appetite loss.

The related personal data, demographic and tumor-related factors were collected. The main diagnostic variables were recorded over 3 visits, tools that have been used for the diagnostic variables are as follows: For anorexia and appetite loss, a short nutritional assessment questionnaire (SNAQ) was used. Body weight measurements (BMI) were obtained using a calibrated scale when patients were dressed in light indoor wear with bare feet to ascertain the patient's weight. The adjustment factor for clothing was determined by deducting weight differentials of 1.6 kg and 2.0 kg for males and 1.3 kg for females, respectively. The calculation of the body mass index involved dividing the body weight, measured in kilograms, by the height, measured in meters. Weight loss $>5\%$ or 2% in patients with BMI less than 20 was considered. Muscle wasting was quantified using MUMC and triceps skinfold thickness (TSF). Since CT scans, electromyography, muscle, or nerve biopsy were unavailable in Sudan. The investigator measured the mid-arm circumference twice per visit using a tape measure attached to the midpoint of the non-dominant upper arm. Repeated measures of TSF were taken at the same point using the skinfold caliper. Formula of MUMC (cm) = MAC - $[3.14 * TSF]$.

Laboratory tests for inflammatory and metabolic alterations include hemoglobin, CRP, and serum albumin. CRP and S. albumin levels were measured in a non-fasting status, blood was analyzed using the Mindray system.

Cachexia is diagnosed in patients with hemoglobin levels below 11 mg/dl (anemia), C-reactive protein levels above 5 mg/dl, and serum albumin levels below 3.2 g/dl (hypoalbuminemia).

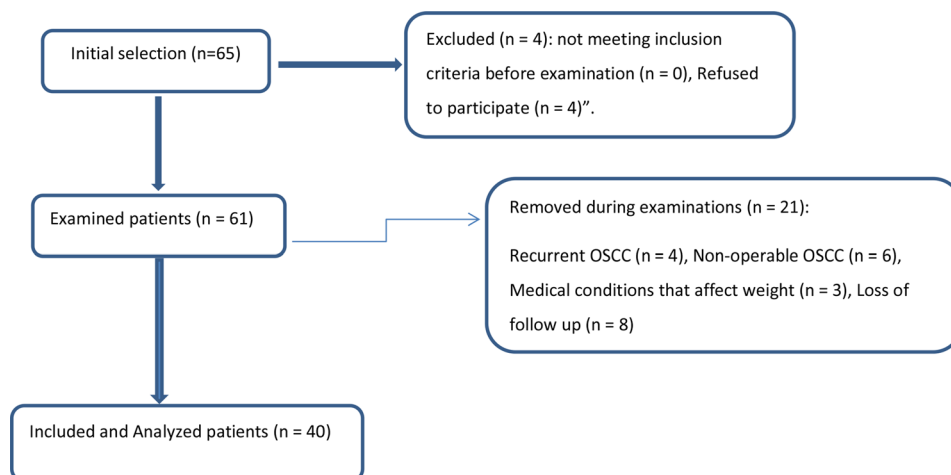


Fig. 1 Flow chart of the study design

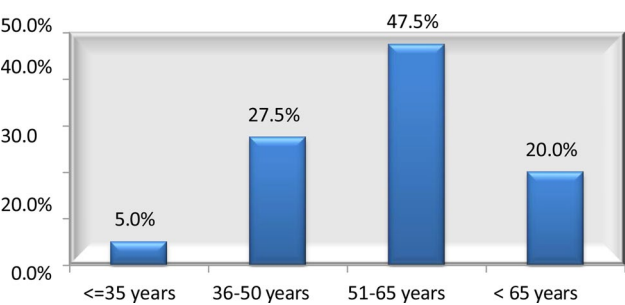


Fig. 2 Sample distribution by age

Table 1 Sample distribution by habits

Habit	Frequency	Percentage
None	19	47.5%
Smoking + Snuff dipping	9	22.5%
Smoking only	5	12.5%
Snuff dipping only	5	12.5%
Both + Alcohol	2	5%

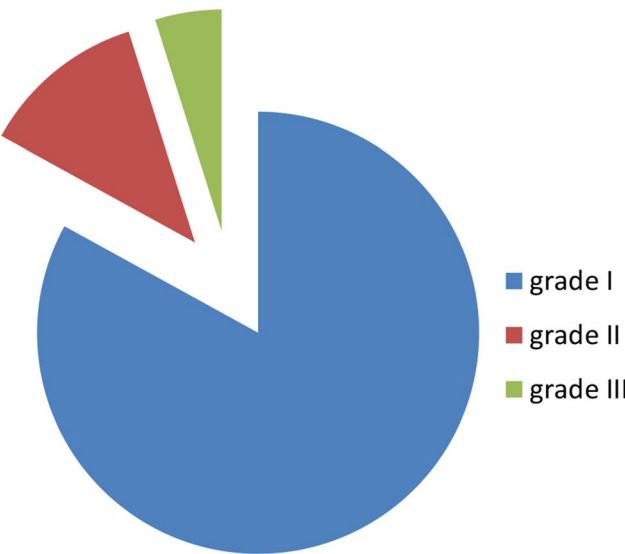


Fig. 3 Histological grading

All statistical analysis was set at 95% confidence level. Descriptive statistics were conducted for variables (such as age, site, etc.), bivariate and multivariate analysis were done. Association study ($p\text{-value} < 0, 05$) was done between cachexia and all variables.

Results

The study included 40 patients with mean age 56.8 years old, male were 57.5%, and 42.5% were female (Fig. 2). Those who revealed positive history of habits were 52.5% as shown in (Table 1). The anterior gingiva-labial area had the highest incidence of OSCC at 40%, followed by the lower posterior are 30%. No cases of isolated tongue cancer were encountered in this study. Furthermore, the majority of the patients (82.5%) had well differentiated

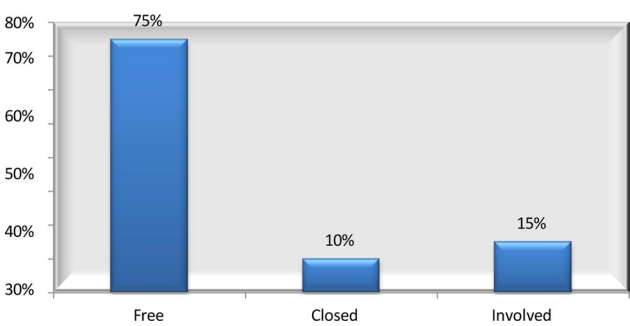


Fig. 4 Surgical margins

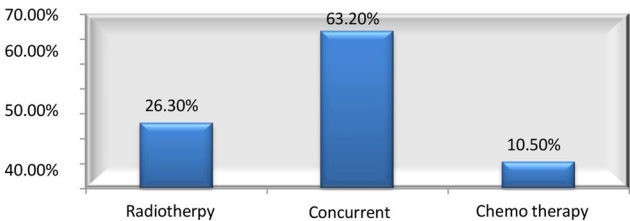


Fig. 5 Type of adjuvant

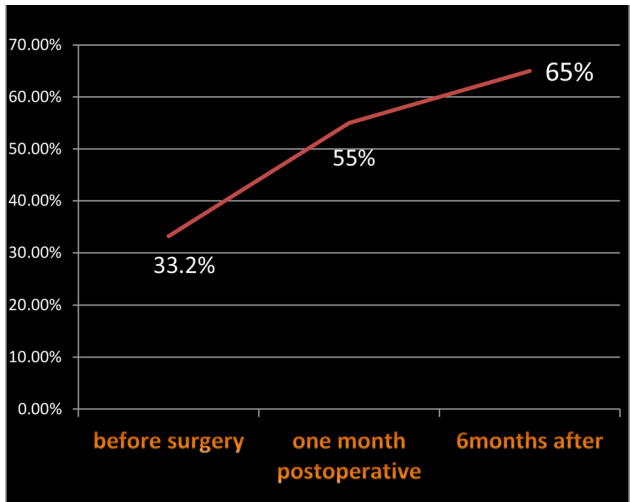


Fig. 6 The incidence of cachexia

OSCC (Fig. 3). Late stages (stage III and IV) were 2.5% and 97.5% respectively. 75% of the cases had free margins (Fig. 4).

Postoperative wound healing was delayed in 50% of the patients. Recurrence appeared in 37.5%, while two patients had residual cancers. Nineteen out of forty patients (47.5%) had postoperative adjuvant therapy, with the majority (63.2%) receiving concurrent chemo-radiation (Fig. 5). According to the study, 63.2% of overall patients had the adjuvant therapy duration of more than 11 week.

The incidence of cachexia was 33.2% at the time of diagnosis, 55% one month after surgery, and 26 out of 40 patients (65%) were cachectic six months later (Fig. 6).

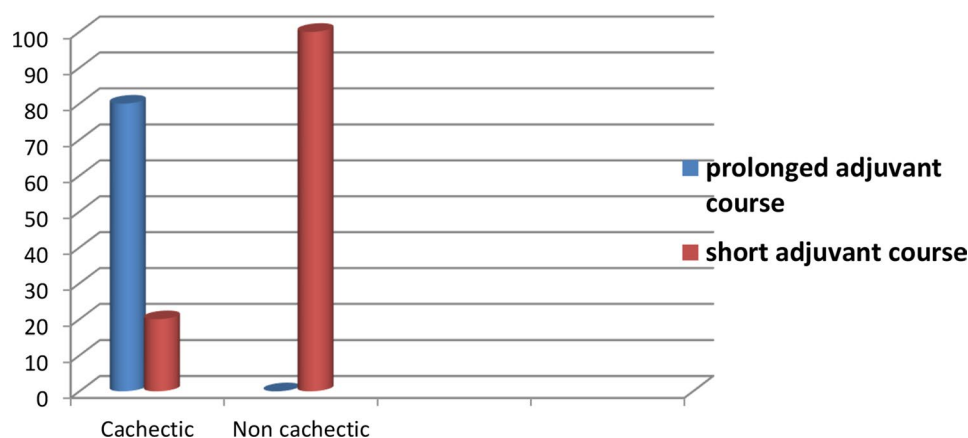


Fig. 7 Adjuvant course duration in cachectic & non cachectic patients

Table 2 Nasogastric tube duration

NG tube duration	Frequency	Percentage
None	2	5%
3weeks or less	23	57.5%
More than 3weeks	15	37.5%

There was no link between cachexia and the presence or type of adjuvant therapy, however prolonged adjuvant duration was significantly associated with cachexia (Fig. 7). The duration of nasogastric tubes was also observed; 57.5% used it for three weeks or less (Table 2).

Cachexia was observed in patients with delayed wound healing and prolonged nasogastric feeding tube duration (Fig. 8). The findings from the three visits' diagnostic variables (BMI, MUMC, Hb, CRP, Albumin) are projected in the table (Table 3).

Table 3 The means of the diagnostic variables over the 3 visits

Diagnostic variables	Before surgery	After one month	After 6months
BMI	22.4	21.2	19.6
MUMC (female) cm	19.6	19.4	18.5
MUMC (Male) cm	20	19.3	18.5
HB (mg/dl)	12.9	11.7	11.9
CRP(mg/dl)	31.3	26.2	21.2
S. Albumin (mg/dl)	4.4	3.8	4

The mortality rate was 25% from the overall patients, with an average period of 6.8 months following surgery. A significant association between cachexia and death was found (p-value=0.001). The majority of the deceased patients were cachectic. Low BMI, loss of appetite, amount of food intake, low Hb, and elevated CRP were significant diagnostic criteria in cachectic patients (Table 4), while S.albumin wasn't (p-value 0.051). Only 23.1% of cachectic patients showed hypoalbuminemia, (p-value < 0.05 was considered statistically significant)

Discussion

Cachexia is a set of metabolic and inflammatory changes linked with a variety of chronic illnesses, including cancer, that are characterized by weight loss, muscle wasting, decreased appetite, and reduced nutritional intake

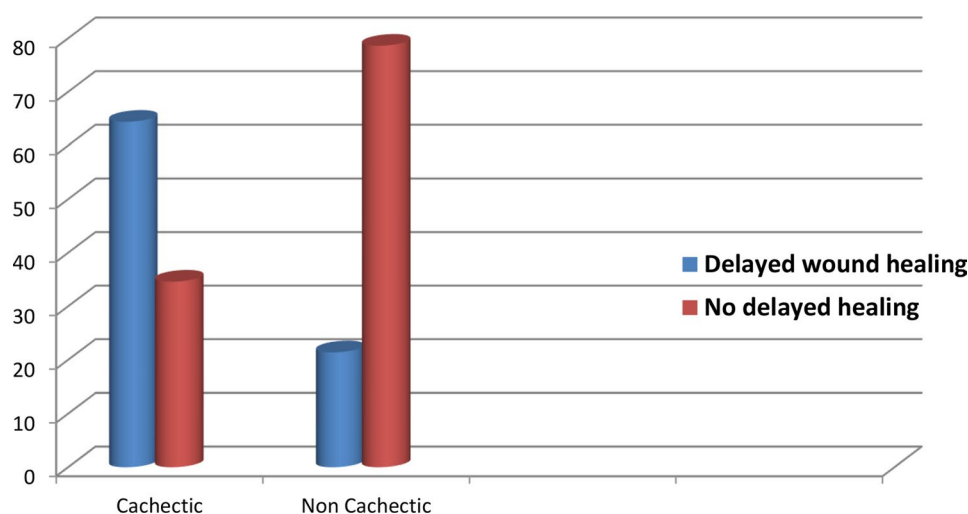


Fig. 8 Cachexia and delayed wound healing

Table 4 Summary of the variables significantly associated with cachexia

p-value < 0.05	Variable
0.041	Gender
0.025	type of resection
0.000	Appetite after Six months of surgery
0.000	Amount of food intake after Six months of surgery
0.004	BMI after Six months of surgery
0.004	Hemoglobin after Six months of surgery
0.026	C-reactive protein after One month of surgery
0.000	C-reactive protein after six months of surgery
0.023	Nasogastric tube duration
0.008	Postoperative delayed wound healing
0.003	Package time of adjuvant
0.007	Death

[8]. Not all malnourished individuals are cachectic, although all cachectic patients exhibit malnutrition [9, 10]. Cachexia and malnutrition are linked to compromised immunity [11], poor physical performance [12], higher radiotherapy-induced toxicities [13], longer adjuvant courses [14], hospital readmission [15], and death [16, 17]. In this longitudinal descriptive study, the incidence of cancer cachexia among OSCC patients was 33.2%, 55.5%, and 65% prior to treatment, one month and six months after surgery respectively. A correlation was found between cachexia and delayed wound healing, a longer period spent on a nasogastric feeding tube, disrupted adjuvant course, and death ($p < 0.05$). With a mean time of death of 6.8 months following surgery, nearly all the deceased patients were cachectic, accounting for 25% of the total patient population. This highlights how crucial it is to treat cancer patients by considering cachexia implications while constructing a treatment plan.

The incidence of cachexia in HNC, particularly oral cancer, has been the subject of controversies in scientific literature published over the last 20 years. Our preoperative incidence record 33.2% is nearly close to the 31% (20 out of 65) preoperative incidence by Orell-Kotikangas et al., while Jager-Wittenaar et al. (2017) reported the record to be 46% (12 out of 26 cases). Moreover, Kown et al. (2017) reported 6.1% (22 out of 361), Jones et al. (2022) reported a prevalence of 53.6% (135 out of 252), and Solís-Martínez et al. (2022) found a prevalence of approximately 72% (57 out of 79 patients). These differences relate to the location and stage of the tumor at diagnosis.

It has been consistently shown that advanced stage HNSCC at diagnosis is correlated with low socioeconomic level [18]; the results in this study revealed that (60%) of the patients were illiterate, had low incomes (70%), and were using smoking and Toombak, the two main causes of OSCC in Sudan. Early detection and treatment of HNSCC in Sudan, as well as cachexia per se,

are compromised by a number of factors, including poverty, educational attainment, and inadequate treatment.

The type of surgery and its effects on cachexia were not clearly documented. Fresh frozen section biopsies help with immediate reconstruction in developed countries, and free vascularized flaps provide great rehabilitation for patients, these procedures are not available in Sudan. After surgery the patients' ability to swallow and form an oral seal is compromised, in addition to adjuvant problems including dysphagia and xerostomia. According to our research, patients who had segmental mandibulectomy demonstrated a strong correlation with cachexia (p-value 0.025), particularly for the anterior mandible when there was no functioning prosthetic reconstruction.

Nutritional counseling and intervention are essential in supporting cancer patients. Cachexia frequently coexists with anorexia due to the synthesis of pro-inflammatory cytokines (IL-1 α , IL-1 β , IL-6, and TNF- α), which end with more anorexigenic signals. Furthermore crucial alterations in the metabolism of carbohydrates include insulin resistance, glucose intolerance, and increased gluconeogenesis from amino acids and lactate. All of the aforementioned issues worsen cancer patients' nutritional condition, make them less responsive to dietary therapy, and require further specialized care. For this reason, a dietician plays an important role in a multidisciplinary team along with other specialists. Nutritional therapy for cachexia include pharmacological, enteral, and parenteral approaches. Enteral nutrition is often advised in cases of malnutrition or impaired oral feeding lasting more than seven days [19]. NG tubes are used for the first three weeks following head and neck procedures to boost proper healing and reduce intraoral wound infection. The study found that 50% of cachectic patients had been using NG tubes for longer than three week. The study's analysis revealed a correlation ($P = 0.023$) between cachexia and the duration of NG tube use. In Sudan, Dietary counseling and cachexia management are not popular practices, and the surgical team's expertise is essential in requesting and adhering to this aspect of treatment.

Patients undergoing radiotherapy (RT) or chemo-radiation therapy (CRT) may lose up to 10% of their pre-therapy body weight. If this loss exceeds 20% of the total body weight, the patient may experience toxicities related to the treatment, and have a worse prognosis [20, 21]. Our findings demonstrated a strong correlation ($p = 0.003$) between cachexia and interrupted course of postoperative adjuvant therapy. The main early processes in cancer cachexia that result in hypercatabolism include the systemic inflammatory response, which includes a rise in pro-inflammatory cytokines (interleukins, interferon- γ , TNF α , and NF $\kappa\beta$), reactive oxygen species, and catabolic mediators generated by host and tumor cells [22].

The metabolism of proteins, fats, and carbohydrates is changed as a result of this. HNC patients experience increased susceptibility to infection, fatigue, dyspnea as well as compromised oral function. HNC and cachexia have a negative impact on survival [23], and treatment-related adverse effects [24]. Cachexia and muscle wasting influence the wound healing through multiple overlapping mechanisms. Reduction in physical activity and insufficient nutrition exacerbate neuromuscular junction insufficiency and disturb the equilibrium between the breakdown and production of muscle proteins [25]. Evidence suggests that inflammatory cytokines suppress collagen production and keratinocyte [26], resulting in compromised wound healing. Recurrence and cachexia are also linked in the literature. Kown M's study discovered a significant association between cachexia at 6 and 12 months and mortality or recurrence. Our results revealed that 13 out of 15 patients with recurrence were cachectic, representing 50% of all cachectic patients. However, in this study there was no statistically significant association between cachexia at 6 months and recurrence (p-value 0.084). In agreement with Kown's study, there was a significant association between cachexia at 6 months and death (p-value 0.007). Almost all deceased patients (25% of the total sample) were cachectic at the time of death.

Low BMI, loss of appetite, anemia and elevated C-reactive protein were significant diagnostic criteria in cachectic patients while serum albumin wasn't significant (P-value 0.051). Only (23.1%) of cachectic patients had decreased S. albumin. The sample size and short follow-up period is a limitation to strongly suggest of albumin inaccuracy in the diagnosis of cachexia. It is noteworthy to emphasize that since the study was conducted in a single hospital, the original sample size of 65 patients was dropped to 40 (Fig. 1); yet, this is a considerably acceptable size when compared to the OSCC patients who visited Sudan's primary OMFS referral hospital [27].

Conclusion

According to the current study, the incidence of cachexia was 33.2% pre-treatment, 55% one month after surgery, and 65% at six months. Cachexia is a crucial predictor of treatment outcome and prognosis in head and neck cancer. Dietary counseling and pharmacological therapy for cachexia shouldn't be neglected in HNC management protocols. Cachexia in Sudan must have more studies.

Abbreviations

KTDH	Khartoum Teaching Dental Hospital
OSCC	Oral Squamous Cell Carcinoma
HNSCC	Head and Neck Squamous Cell Carcinoma
RT	Radio-Therapy
CRT	Chemo Radiation Therapy
BMI	Body Mass Index
MAMC	Mid Arm Muscle Circumference

Hb	Hemoglobin
CRP	C-Reactive Protein
NG tube	Nasogastric feeding Tube

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Author contributions

S.A and Yo.El designed and developed the study. S.A collected the data, analyzed, interpreted the data, prepared the figures and wrote the article. Yo.El, main supervisor reviewed and finalized the study. H.El was a contributor in writing the manuscript. All authors have read and approved the final version of the article.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding authors on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the research and ethics committee of the federal Ministry of Health, Khartoum State and KTDH. Informed consent was obtained from all patients before commencing the study. This study adhered to the Declaration of Helsinki. Serial numbers were assigned to patients, to keep names unidentified. In cases where patients needed consultation and/or intervention based on the findings of their investigations, the researcher notified the patients and contacted the physician immediately.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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