Chapter

Inflammation-Based Markers of Nutrition in Cancer Patients

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Abstract

Malnutrition and cachexia are common findings in cancer patients, and they predict poorer clinical outcomes. Close to half of cancer patients regardless of cancer type have malnutrition and will require one form of nutritional support either before or during treatment. The early identification of malnutrition is thus important to physicians and caregivers. The role of inflammation in the development and progression of malnutrition and cachexia is being unravelled. Increasing evidence shows that systemic inflammatory response and nutritional status are involved in tumour development and influence the clinical prognosis. Serum proteins such as albumin and prealbumin have traditionally been used by physicians to determine patient nutritional status. More recently, inflammation-based prognostic scores including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), C reactive protein-to-albumin ratio (CAR), prognostic nutritional index (PNI), Glasgow Prognostic Score (GPS) have shown promise and have begun to be used in clinical practice to predict prognosis of cancer patients. This chapter highlights the role and pathophysiology of inflammation-based markers in assessing malnutrition and cachexia and their relationship to clinical screening tools.

Keywords: inflammation, malnutrition, cachexia, cancer, nutrition screening

1. Introduction

Cancer is a major public health problem worldwide. It ranks as a leading cause of death along with cardiovascular disease (CVD). Cancer is the leading cause of death in 57 countries (including China), while CVD is the leading cause in 70 countries (including Brazil and India) [1]. In 23 other countries, it ranks either third or fourth. The GLOBOCAN 2020 report showed that there was approximately 19.3 million new cases and 10 million cancer deaths in 2020, thus making cancer the new challenge of the 21st century [2]. This increase in the number of cancer cases implies an increase in cancer-associated complications and morbidities. One such complication is malnutrition.

Cancer-related malnutrition is a broad term that encompasses complex poorly understood processes that are associated with specific types of cancers and their treatment protocols. Specific cancers such as oesophageal and pancreatic cancer are

a high risk for malnutrition. Factors such as cancer-related symptoms (e.g. anorexia, early satiety, fatigue), treatment complications (eg, mucositis, nausea, taste changes), and psychologic distress all play a role and/or are risk factors in the development of malnutrition. Malnutrition is a common problem among cancer patients with high negative consequences. In cancer, it is associated with poor prognosis, reduced survival, increased therapy toxicity, reduced tolerance and compliance to treatments, and diminished response to antineoplastic drugs. Surveys done in the past showed a prevalence rate of between 25 and 70% with about 10–20% linked to malnutrition and not the malignancy itself. Malnutrition in cancer patients is distinctly different from malnutrition as a result of starvation, as the former arises from a combination of anorexia and metabolic dysregulation, caused by the tumour itself or by its treatment. Malnutrition when left untreated can progress to cachexia. Cachexia is defined as "a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" [3]. The pathophysiology of cachexia has an underlying variable combination of reduced food intake and abnormal metabolism leading to a negative protein and energy balance. Cachexia is frequent in chronic diseases, and in cancer, it may account for about 20% of cancer deaths [4]. A diagnosis of cachexia is made in patients when the total body weight loss is >5% in the past six months (in the absence of starvation) or weight loss >2% in patients with body mass index (BMI) of <20 kg/m^2 [5]. Currently, cachexia is classified into three stages of clinical relevance, namely pre-cachexia, cachexia, and refractory cachexia [3]. Blum et al. defined pre-cachexia as weight loss >1 kg but <5% of usual body weight/6 months, but with an increased C- reactive protein (CRP) level and appetite loss, while refractory cachexia was weight loss >15% in the last 6 months + BMI < 23 kg/m^2 or weight loss >20% in the last 6 months + BMI <27 kg/m^2 [6]. If untreated, cancer cachexia would lead to a progressive functional loss, poor quality of life, chemotherapy-related toxicity, diminished response to antineoplastic treatments, and poor survival. At the refractory cachexia stage, the cancer is usually refractory to chemotherapy.

The relationship between malnutrition and the systemic inflammatory process is not a new one. Systemic inflammation is closely associated with weight loss and malnutrition in cancer [7–9]. Systemic inflammation has been fingered in the genesis and progression of malnutrition. It is known to affect important metabolic and neuroendocrine pathways as well as cause elevated energy expenditure at rest, decreased lean mass and reduced physical performance [10, 11]. Furthermore, cytokines especially tumour necrosis factor (TNF) alpha, interleukin (IL) 1 and IL-6 have been fingered in the induction of muscle wasting providing evidence for a link between malnutrition and inflammation. As aforementioned, systemic inflammation is thus a harbinger not only for malnutrition but for various comorbidities in cancer patients. Identification of cancer patients at risk of malnutrition is highly recommended. The PreMiO study highlighted the prevalence of malnutrition at the first visit by cancer patients [12]. The European Society for Clinical Nutrition and Metabolism (ESPEN) in its latest preoperative nutritional care assessment highlighted the degree of systemic inflammation among other things for individuals at nutritional risk [13]. Soeters et al. reinforced the urgency of including an assessment of inflammatory activity in the diagnosis of malnutrition [14]. Recent studies have shown that inflammatory models can be used to predict prognosis, as well as cancer-related malnutrition [15]. High level of systemic inflammatory factors which can facilitate tumour cell proliferation and metastasis are also

known to be induced by malnutrition [16]. Thus, malnutrition can enhance a systemic inflammatory response. Control of inflammation in cancer can help modify poor nutritional status resulting in better response to therapy and improved survival. The early recognition of systemic inflammatory response should therefore be an integral part of nutritional management in cancer patients to improve short and long term outcomes.

2. Nutritional status

2.1 Prevalence of malnutrition in cancer patients

Malnutrition is a universal condition in cancer patients with grave clinical implications such as impaired quality of life, poor performance status, weight loss and cachexia. Studies from different countries across Europe shows a high prevalence of cancer-related malnutrition ranging from 25 to 70% based on nutritional assessments [17–19]. However, this differs across cancer types and stages of the disease [12, 20]. In the often-cited landmark study by Dewys et al., cancer type and treatment play a role in cancer-related malnutrition [21]. Tumour stage and age have also been noted as risk factors in malnutrition [22, 23]. In an epidemiological observation study, Pressoir et al. observed that pre-existing obesity (BMI⩾30), and Performance status ⩾2 were associated with increased risk of malnutrition among cancer patients in 17 French Comprehensive Cancer Centres [19]. The Prevalence of Malnutrition in Oncology (PreMiO), a cross-sectional, observational study involving almost 2000 patients in 22 sites in Italy, revealed that 51.1% of treatment-naïve patients at their first visit to a medical oncology centre were already affected by a nutritional impairment, including risk for malnutrition (43%) and overt malnutrition (9%). Poor appetite was present in over 40% of cancer patients, with variable severity scores depending on the tumour type and stage of the disease, and ascribed mainly to early satiety, taste changes, and nausea [24].

The picture is not very different in developing countries. Pastore et al. in Brazil reported only 13.7% of lung and gastrointestinal cancer patients in a study were well-nourished [8]. Opanga et al. in Kenya reported that 33.8% of participants required critical nutrition care, 34. 8% symptoms management, 14.2% constant nutrition education and pharmacological intervention [25]. Ntekim et al. at Ibadan, Nigeria used nutritional screening assessment tools and reported a prevalence of 60% [26]. Children with cancer are also known to develop some form of malnutrition [27], however, the frequency may vary according to the type of cancer [28], and region [29, 30]. Brinksma, et al. reported the prevalence of malnutrition at diagnosis for developed countries, through a systematic review which included patients with different types of childhood cancer, aged from 0 to 18 years of age for acute leukaemias, the prevalence was 10%, 20–50% for neuroblastoma, and those classified as "other malignancies" was 0–30% [31]. This prevalence is lower than what is obtained in developing countries [28–30]. Villanueva et al. reported a prevalence of almost 50% [32]. Lemos et al. in Brazil reported that the prevalence of malnutrition is higher among paediatric patients with malignancies than in the general population though the difference was not significant [33]. These facts high- light the need for nutritional assessment in cancer patients regardless of age or region. Cancer patients should be assessed at several points during their management to identify aetiology and candidates that require nutritional support.

3. Pathophysiology

Cancer-related malnutrition can have profound negative effects on cancer patients' wellbeing and therapeutic outcomes. It usually results from local effects of a tumour, the host response to the tumour and anticancer therapies. Cancer cachexia which is a severe form of malnutrition is characterised by progressive weight loss, anorexia, asthenia, and anaemia. Cachexia is a poor prognostic sign, and is associated with reduced food intake and increased energy expenditure [34]. Cachexia also expresses itself as nutritional imbalances in a number of ways in cancer patients which include glucose intolerance and insulin resistance, loss of adipose tissue and lipolysis with increased fat oxidation rates [35], decreased lipogenesis, impaired lipid deposition and adipogenesis [36]. A decrease in protein synthesis and increase in protein degradation does occur in cancer cachexia [37] which is a key feature of skeletal muscle atrophy. Other features such as altered hormone levels [38], elevated cytokines [39, 40], increased insulin resistance [38], elevated synthesis of acute-phase proteins [34] and altered nutrient utilisation can be attributed to inflammatory mediators as well a host of other factors. Inflammatory markers have been implicated in all metabolic derangements in cancer-related malnutrition, and a better understanding of these markers with either the host or the tumour is necessary for better management of malnutrition and its complications.

3.1 Inflammation and cancer

Inflammation has been shown to play a major role in cancer development, progression and outcome and has been termed the seventh hallmark of cancer [41]. The observation of leukocytes within tumours by Rudolf Virchow in the 19th century gave a clue of a possible link between inflammation and cancer. This link is due to chronic inflammation which is mediated by pro-inflammatory cytokines, chemokines, adhesion molecules, and inflammatory enzymes with the promotion of all stages of tumorigenesis. Inflammation is the body's physiological response to tissue damage as a result of any pathological insult to the body's homeostasis. The body's inflammatory response can either be a resolution to the insult, or persistence of the insult in the form of chronic inflammation. Chronic inflammation can cause cellular changes and influence innate and adaptive immunity towards tumour growth. When this happens, an imbalance of pro-inflammatory and anti-inflammatory mediators can lead to cell mutation and injury creating an environment that is conducive to the development of cancer. This scenario holds for the onset of cancer but is important for the progression of the disease. Such progression is characterised by clinical signs and symptoms including nutritional impact symptoms and co-morbid metabolic abnormalities. This invariably leads to weight loss, chronic anaemia, wasting syndrome, fatigue with loss of quality of life. These symptoms are very prominent in cancer-related malnutrition. While multiple mechanisms can be associated with these symptoms, however, they are interrelated and the unifying factor is inflammation.

Inflammation is associated with tumorigenesis at every stage of its development including survival and metastasis [42]. On the other hand chronic inflammation is known to facilitate treatment resistance and this form of acquired resistance is a result of the production of cytokines, chemokines and growth factors by the tumour micro-environment rendering chemotherapy ineffective [43]. Besides, inflammatory

responses can be induced by anti-cancer therapies [44, 45]. chronic inflammation is also known to worsen chemotoxicity [46]. A better understanding of the relationship between chronic inflammation and cancer can lead to the development of new strategies in the management of cancers as well as some of the complications such as malnutrition and chemotoxicity that arise during treatments.

3.2 Inflammation and malnutrition

A large number of cancer patients are known to show a form of cachexia syndrome which is characterised by anorexia, loss of adipose tissue and skeletal muscle mass. Most of these symptoms have been linked to inflammation. The Global Leadership Initiative on Malnutrition (GLIM) requires the combination of at least one phenotypic and one etiologic criterion is to establish the diagnosis of malnutrition. The phenotypic criteria include non-volitional weight loss, low body mass index, reduced muscle mass. In addition to this, etiologic criteria include reduced food intake or assimilation and disease burden/inflammatory condition [47].

Inflammation is so intertwined with the pathogenesis of malnutrition that the ESPEN recommended dividing malnutrition into disease-related malnutrition with and without inflammation [48]. For Disease-related malnutrition with inflammation, it is defined as underlying diseases causing inflammation with a consecutive lack of food intake or as uptake with a negative nutrient balance [49]. Inflammation is reported to have several metabolic effects. Cytokines such as IL-6, and TNF-α correlate with insulin resistance and appetite reduction and also cause inhibition of nutrients entering cells [5, 50]. Leptin, a 167 amino acid peptide and a member of the adipocytokine family plays a major role in body mass regulation and inflammatory/immune cells modulation. Diakowska et al. reported in a study of leptin and inflammatory markers in oesophageal cancer patients found that leptin correlated directly with BMI, TNF-alpha, albumin, and haemoglobin and indirectly with IL-6, IL-8, and hsCRP [51]. In a secondary analysis of the EFFORT trial by Merker et al., patients with high baseline inflammation (ie, CRP levels >10 mg/dL) were observed not to benefit from any form of nutritional support concerning the 30- day mortality [52]. However, this study was not tailored to cancer patients primarily. Wang et al. showed a clear association between high inflammation, clinical malnutrition and overall survival in patients with nasopharyngeal carcinoma [16]. These studies show that inflammation could be a key factor in cancer-related malnutrition. Inflammation is known to exert some effects on appetite and food intake, gastrointestinal functioning of the stomach and gut, among a host of other things [53]. These effects are mediated by circulating cytokines released as part of the systemic inflammatory response causing disease-related anorexia, decline in cognitive function, weight loss and anaemia. Thus, inflammation is an integral part of cancer-related malnutrition.

3.2.1 Cancer-related anaemia

Anaemia is a common problem in cancer patients. Anaemia prevalence is remarkably high and varies widely among cancer patients. It is estimated from various studies that between 30–90% of cancer patients had anaemia [54]. Anaemia is considered an indicator of poor nutrition and poor health especially through the malabsorption or non-utilisation of iron, folate, cobalamin and other micronutrients needed for the production of red blood cells. The prevalence is determined by the definition of

anaemia. According to the World Health Organisation (WHO), normal Hb values are 12 g/dL in women, and 13 g/dL in men [55]. Maccio et al. reported a prevalence of 78.8% of anaemia in lung cancer patients [56]; Akinbami et al. reported a prevalence of 58% among breast cancer patients [57]. Anaemia is known to be associated with several co-morbidities including a decline in patients' performance status (PS), cognitive function, and decreased survival [56, 58]. While anaemia in cancer generally is known to have various aetiopathology, cancer-related anaemia (CRA) is believed to arise as a consequence of chronic inflammation.

Cancer-related anaemia (CRA) refers to a condition occurring without bleeding, haemolysis, neoplastic bone marrow infiltration, kidney and/or hepatic failure [59], and principally results from the chronic inflammation associated with advanced-stage cancer and the synthesis of pro-inflammatory cytokines by both immune and cancer cells. Unlike iron deficiency anaemia, CRA is typically normochromic (MCH >27 pg), normocytic (MCV between 80 and 100 fl), with a low reticulocyte count (<25,000/mL) and a low value of reticulocyte index (normal range between 1 and 2 which is a more accurate measure of the reticulocyte count corrected against the severity of anaemia based on haematocrit). In addition, it has normal/low serum iron concentrations (normal range 55–160 mg/dl for men and 40–155 mg/dl for women) and reduced total iron-binding capacity (transferrin saturation < 50%); ferritin values may be normal (30–500 ng/ml) or more often increased (>500 ng/mL), with increased iron storage [59]. The normal level of iron within the bone marrow reflects the body tacit handling of iron metabolism which is termed as "functional iron deficiency" which is also present in other types of anaemia associated with chronic inflammation. In addition, circulating levels of erythropoietin (EPO) is often not optimal for the level of anaemia thus presenting with also bone marrow hypoplasia. Adamson highlighted some of the pathogenetic mechanism of inflammation of chronic anaemia which includes: shortened erythrocyte survival in conjunction with increased erythrocyte destruction, suppressed erythropoiesis in bone marrow, effects of inflammation on erythropoietin production and alterations in iron metabolism that result in iron-restricted erythropoiesis induced by hepcidin increase [60]. According to Jain et al., the soluble transferrin receptor/log ferritin index can differentiate pure cases of anaemia of chronic disease from iron deficiency anaemia [61].

Like other types of anaemia in cancer, CRA has multifactorial pathophysiology with immune, nutritional and metabolic components affecting its severity. Many studies have demonstrated that inflammatory cytokines are a major contributor to the aetiopathogenesis of CRA. They achieve this through the derangement of various metabolic pathways including glucose metabolism, impairment of lipoprotein lipase, which controls the uptake of circulating triglycerides into adipocytes, and changing protein synthesis and degradation, with subsequent depletion in lean body mass [62]. In particular, proinflammatory cytokines like interleukin 1 and 6 released by cancer and activated immune cells in response to malignancy, may result in anaemia by inducing changes to iron balance, inhibition of erythropoiesis, impairment of EPO synthesis and activity, reduction of erythrocytes lifespan and changes of energy metabolism. IL-1 and TNF also induce the transcription factors GATA2 and nuclear factor-kB, both of which are negative regulators of the hypoxia-inducible factor 1 (HIF1) expression [63]. Reactive oxygen species (ROS) which are a major player in chronic inflammation are known to inhibit EPO synthesis by mimicking a false O2 signal in the renal peritubular interstitial cells. They equally inhibit erythroid precursor proliferation [64]. IL-6 regulates the synthesis of hepcidin, a 25 amino acid

peptide made by the hepatocytes and involved in iron homeostasis by mediating the degradation of the iron export protein ferroportin 1, thereby inhibiting iron absorption from the small intestine and release of iron from macrophages.

The process of CRA is not an isolated one. It has been shown that malnutrition along with weight loss and reduced food intake is correlated with anaemia in patients with the chronic inflammatory disease [65]. CRA is therefore not a single condition, but associated with weight loss and remodelling of energy metabolism; thus CRA is a crossroad for both inflammation and nutritional status. Therefore management of CRA would involve not only anaemia but malnutrition as a whole.

3.2.2 Cancer-related anorexia and wasting

Anorexia can be defined as a loss of appetite associated with chronic illness in cancer patients and is associated with weight loss [66]. It is common in cancer patients and frequently associated with early satiety and taste changes. It occurs in half of the newly diagnosed cancer patients and up to 70% of patients with advanced disease. Cancer-related anorexia is an important clinical co-morbidity in cancer patients, and it harms nutritional status in advanced cancer. There are many causes of anorexia. They are classified as either being due to central or peripheral mechanisms. Peripheral causes include (i) tumours causing dysphagia or directly impinging on gastrointestinal function; (ii) tumours producing substances that alter food intake, e.g. lactate, tryptophan, or parathormone-related peptide; (iii) tumours leading to alterations in nutrients resulting in anorexia, e.g. zinc; or (iv) tumours producing inflammation leading to cytokine release. Alterations in gastrointestinal function can alter visceral receptor function, leading to altered secretion of gastrointestinal peptides, e.g. peptide tyrosine (PYY), and alterations in stomach emptying can alter feedback of satiating hormones. Peripherally, chemotherapy can alter taste perception and cause nausea, vomiting, mucositis, abdominal cramping, bleeding, and ileus [67]. Depression, pain, or a variety of alterations in central neurotransmitters are some of the central causes. Some centrally acting chemotherapy can also induce anorexia. For example, tamoxifen used in breast cancer treatment can inhibit fatty acid synthase in the hypothalamus, leading to an accumulation of malonyl coenzyme A (CoA). Increased malonyl CoA is associated with anorexia in cancer [68, 69]. The resultant effect of cancer-related anorexia is reduced caloric intake and alteration in nutrient metabolism with consequent loss of fat and lean mass.

Several studies have focused on the mechanisms underlying the metabolic changes observed in cancer-related anorexia and weight loss and some cytokines have been implicated including TNFα, IL-1, and IL-6 [70]. These cytokines are known to mimic leptin signalling and suppress orexigenic ghrelin and neuropeptide Y (NPY) signalling inducing sustained anorexia and weight loss. These cytokines are elevated in many cancers [71] and their chronic administration can induce anorexia and wasting [72, 73]. Interleukin 1 is produced by lymphocytes and macrophages and is a potent anorexigenic cytokine that is at least 1000-fold more effective than leptin [74]. IL-1 is reported to reduce the size, duration, and frequency of meals but does not reduce the desire for food [75]. It achieves this by the stimulation of corticotrophin-releasing factor (CRF) production by the hypothalamus [76]. TNFα is produced by monocytes, tissue macrophages and some tumours, and directly on the CNS to produce its anorectic effects by crossing the blood-brain barrier. An inhibitor of TNFα increased food intake in anorectic tumour-bearing rats [77].

Interferon-γ when administered centrally is known to reduce food intake and duration. Administration of TNF-α to laboratory animals induces a state of cachexia, with anorexia and depletion of adipose tissue and lean body mass [78]. Interleukin-6 is secreted by T-cells and macrophages as well as microglia, astrocytes, and neurons and has a well-established association with the onset of cachexia in both rodent and human wasting conditions [79]. While there are many mediators of anorexia in different disease states, IL-6 has been shown to regulate food intake and metabolism [80], signalling through neural gp130 receptors and even in non-cancer-related cachexia, plasma IL-6 is associated with the incidence of anorexia [81, 82].

Decreased caloric intake alone does not account for the profound weight loss observed in cancer patients. Metabolic abnormalities with subsequent elevation in basal energy expenditure are also contributing factors. Weight loss in cancer though affects both fat and lean mass, the latter seems more affected. In a study of 50 cancer patients by Cohn et al., Weight-losing cancer patients appeared to have lost both fat and lean tissue, but the loss of lean body tissue, particularly skeletal muscle, was the more striking feature [83]. This pattern is in contrast to starvation, in which fat is lost and lean tissue is better preserved. TNF-α, IL-1 and IL-6 have been shown to increase basal energy expenditure causing weight loss [84]. The muscle wasting that occurs in cancer is a result of a decrease in protein synthesis, an increase in protein degradation or a combination of both. These changes are attributed to the upregulation of inflammatory mediators, the activation of related transcription factors and signalling pathways, abnormalities in the expression of angiotensin II (Ang II), insulin-like growth factor-1 (IGF-1) and various receptors, proteins and kinases, and organelle dysfunction [85]. Muscle wasting thus occurs as a result of these processes.

4. Inflammatory markers of malnutrition

There are several clinical, biochemical and physiological indicators to diagnose malnutrition in cancer patients. One commonly used clinical indicator of malnutrition is the percentage of weight loss in a certain period. A weight loss of more than 5% in the previous month or more than 10% in the last 3–6 months is considered significant malnutrition. Other anthropometric measurements, such as body mass index (BMI), mid-arm circumference and mid-upper-arm muscle area can give information about the nutritional status and body composition of these patients. The ASPEN guidelines for diagnosing malnutrition, which looked at six characteristics that incorporate some of these clinical indices [86].

Biochemical markers which are sometimes indicative of inflammation are often used as markers of malnutrition. They include albumin, prealbumin, C-reactive protein, transferrin, total lymphocyte count etc. However, more recently, inflammation-based scores and ratios are being seen as more sensitive markers than the traditional ones [87, 88]. Other nutritional assessment tools use questionnaires incorporated with factors such as estimation of nutritional intake, laboratory parameters and calculation of unintentional weight loss. Such tools that have been used in cancer patients include the Prognostic Nutritional Index (PNI), the Nutritional Risk Screening 2002 (NRS 2002), the Controlling Nutritional Status (CONUT), Mini Nutrition Assessment (MNA), Malnutrition Screening Tool (MST), the Nutritional Risk Index (NRI) etc. [89]. In children with cancer, the Frisancho table is used to assess their nutritional status [29].

4.1 Albumin

Albumin is a serum hepatic protein with a half-life of 14–20 days. Albumin is the major carrier for many substances in the body, and also help maintain the body oncotic pressure. It enhances immunity, aids DNA synthesis as well as acts as an antioxidant [90, 91]. Due to its relatively long half-life and hepatic synthesis, it is seen as a good marker of malnutrition. However, albumin is a negative acute-phase protein, and its serum levels are down-regulated in response to inflammatory conditions and drugs especially those that affect the liver. Albumin is widely used as a marker of nutrition as well as a prognostic indicator of survival in cancer patients (though it is more of a marker for inflammatory response). Frutenicht et al. reported that albumin was a predictor of mortality in gastrointestinal tumour patients [92]. Das et al. reported that albumin was significantly correlated with Patient-Generated Subjective Global Assessment (PG-SGA) [93], thus hypoalbuminaemia is a marker of malnutrition. This was further affirmed by a study done on colorectal cancer patients where albumin was positively correlated with the MNA [94]. However, In a study of 74 cancer patients, Pastore et al. did not find significant variation between albumin and SGA [8]. In a recent study on 128 colorectal patients, at least two circulating cytokines (TNF-α and IL-10) affected the expression of serum albumin [95]. Albumin correlates with weight loss in cancer patients as well as with BMI. Albumin is equally incorporated into various indices such as the Glasgow prognostic score (GPS) and PNI. Albumin may not be the ideal marker for assessing malnutrition, but its incorporation into nutrition screening tools gives it a sense of validity.

4.2 C-reactive protein

CRP is the most common method used to assess the magnitude of systemic inflammatory response. Unlike albumin, it is a positive acute-phase protein. CRP is a prototype of short pentraxin present only in the pentameric form in plasma. It is synthesised by hepatocytes in response to trauma, inflammation and tissue damage. The synthesis of CRP is under the transcriptional control of cytokines and transcription factors. Interleukin-6 (IL-6) is the main inducer of CRP gene. CRP is associated with the development, progression and outcome of cancer [96]. In addition, some studies have found a positive association between altered CRP levels and weight loss in patients with cancer [97]. In a large international cohort of advanced cancer patients, Laird et al. reported that C-reactive protein was significantly associated with cognitive, physical, emotional and social functions as well as anorexia, pain and fatigue [98]. Yu et al. also observed a significant association between CRP and PG-SGA among patients with malignant tumours [99]. However, some other studies did not see any association between CRP and nutritional status [88, 92]. In a study done by Read et al., patients with advanced colorectal cancer were initially found to have a positive correlation between SGA and CRP. However, when two outliers were excluded, the association did not remain significant [100]. This observation may be a result of the effect of non-nutritional factors like cardiovascular disease and infections. CRP is positively correlated with weight loss, and negatively correlated with PNI. Like albumin, CRP is incorporated into some nutritional screening tools which give it some validity.

4.3 Inflammation scores

Traditional inflammatory markers like CRP and albumin have been shown to have some limitations in malnutrition diagnosis based on their low specificity. It has been muted that inflammation-based scores that combine CRP and albumin, such as the CRP/Albumin ratio (CAR), may have more significant prognostic value than each of these markers singly in malnutrition. These inflammation-based scores which include inflammatory ratios and indices, and haematological ratios have been reported to be associated with cancer progression and outcomes [101, 102].

The Glasgow prognostic score or modified Glasgow prognostic score indices which combine serum CRP and albumin levels have also been viewed as a prognostic indicator in many cancers. There have been more than 60 studies (>30,000 patients) that have examined and validated the use of the GPS or the modified GPS (mGPS) in a variety of cancer scenarios [103]. Silva et al. demonstrated the clinical utility of modified GPS in a palliative care setting and its association with SGA [104]. SGA was also strongly correlated with the Glasgow prognostic score in oesophageal cancer patients [105]. GPS currently serves an important significance as a nutritional marker in cancer.

The concept of the CRP/albumin ratio (CAR) was first proposed by Ranzani and demonstrated its value for the mortality of septic patients [106]. CAR unlike GPS is a continuous variable and is believed to have a wider clinical application than GPS. A high level of CAR is linked to survival in cancer patients [102, 107]. De Lima reported that CAR was significantly associated with weight loss and SGA in patients with gastrointestinal tumours [108]. A high preoperative CAR and low PNI strongly correlated with poor survival in pancreatic cancer [109]. In oral cancer patients, Park et al. showed that CAR was significantly associated with both PNI and mGPS, and was also a better marker for survival than the other markers [110]. Another related novel marker, CRP/Prealbumin ratio is seen as a prospective inflammatory nutritional prognostic tool in cancer [111], likewise the albumin/CRP ratio [8, 88].

Haematological test i.e. complete blood count is one of the most common, simple and accessible tests in cancer evaluation. As cellular markers of inflammation, they provide prognostic and treatment information about the cancer patient. It is now established that the presence of a pre-operative systemic inflammatory response is predictive of disease progression and poorer outcome, regardless of tumour stage, in patients with various cancers [112, 113]. Inflammation based scoring systems such as the modified Glasgow Prognostic Score (mGPS) and the Neutrophil-Lymphocyte ratio (NLR) have prognostic value in different solid tumours [112]. However, concerning the NLR, multiple thresholds have been used to define high and low NLR values and some have suggested that its prognostic value is mainly derived from the neutrophil count and that the lymphocyte count makes little contribution [114]. Platelets are known to shield tumour cells from shear forces and assault of NK cells, recruit myeloid cells by secretion of chemokines and mediate an arrest of the tumour cell platelet embolus at the vascular wall [115, 116], which indirectly makes the Platelet- lymphocyte ratio (PLR) a prognostic marker in cancer. Studies have revealed that combinations of these parameters could accurately predict the prognosis of a patient than a single index. Like with other inflammatory markers, haematological ratios are associated with malnutrition. Many studies have reported the relationship between NLR and nutritional

status. In a recently published work, Siqueira et al. demonstrated the relationship between NLR and nutritional risk in some cancer patients [117]. Sato et al. equally reported a significant inverse relationship of prealbumin with NLR [118]. NLR was associated with SGA especially in severely malnourished cancer patients [119] as well as with percentage weight loss [92].

PLR is another haematological ratio and inflammation marker that has been reported to be associated with many conditions including cancers. Elevated PLR is associated with increased all-cause mortality in different conditions [120], is a prognostic marker in many cancers [121] and is also associated with nutritional status [122]. As a marker of nutrition, PLR was significantly correlated with PNI and BMI in pancreatic cancer patients [87]; along with NLR was significantly associated with PNI in hepatocellular carcinoma [123]. PLR is also associated with haemoglobin and post-op complications in colorectal cancer patients affecting morbidity rates [124]. Sarcopenia, characterised by a decline of skeletal muscle plus low muscle strength and/or physical performance was reported to be associated with NLR and PLR in both renal cell carcinoma and gastric cancer patients [125, 126]. In addition PLR significantly correlated with both BMI and haemoglobin [125]; while in the gastric cancer patients, both PLR and NLR were significantly associated with NRS, albumin, haemoglobin, and cancer stage [126]. NLR and PLR are also reported to be significantly associated with performance status in cancer [115]. The main shortcomings of the haematological ratios are the different cut off levels in various studies.

Some other haematological ratios and scores such as lymphocyte monocyte ratio (LMR), neutrophil platelet score (NPS) etc. have been reported to have some prognostic value in cancer [101]. The monocyte lymphocyte ratio (MLR) was reported to be significantly correlated to PNI and albumin [87] in pancreatic cancer making it a potential nutritional marker like NLR. Combination haematological indices such as the Combination of Platelet count and Neutrophil to Lymphocyte Ratio (COP-NLR), combination of neutrophil-lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) (CNP), fibrinogen and NLR (F-NLR) etc. have been shown to have good prognostic value, and their association with nutritional indices should broaden the nutrition/inflammation arena further.

4.4 Cytokines

Cytokines are protein molecules released by lymphocytes, monocytes/macrophages and mediate as well as regulate immunity, inflammation and haematopoiesis. Cytokines are the major players in cancer-associated malnutrition, being involved in every aspect of the pathophysiology as earlier explained. They hold great promise as inflammatory markers in nutrition, however, they pose some challenges, particularly their short half-lives [127, 128]. They can be measured in serum or plasma samples; however, measurements from the different sample types cannot be used interchangeably [129].tissues or supernatant from cultured peripheral blood mononuclear cell (PBMC) preparations can also be employed in their measurement. The effect of freezing and thawing can lead to its degradation affecting the measurement. There is an equal lack of standardisation of assays, and because cytokines affect multiple pathways, there is also a lack of specificity [130].

Despite its shortcomings, cytokines are still studied in nutrition research. IL-6 is incorporated into the newly validated CAchexia SCOre (CASCO) for staging cachexic

cancer patients [131], although it is not included in the simplified MiniCASCO (MCASCO) [132]. IL-6 is also associated with weight loss, and also correlates with high Prognostic Inflammatory Nutritional Index [133, 134].

4.5 Other markers

Other inflammatory markers for measuring malnutrition include prealbumin, haemoglobin, transferrin, and absolute lymphocyte count (ALC). Many of them are incorporated into nutritional indices either as ratios or as scores. Prealbumin, haemoglobin and ALC are incorporated into the CASCO score [133]. For ALC, levels are associated with various degrees of malnutrition. Levels >2000 cells/m^3 (normal), 1200 to 2000 cells/m^3 (mild depletion), 800 to 1199 cells/m^3 (moderate depletion), and < 800 cells/m^3 (severe depletion) [135]. Haemoglobin is part of the haemoglobin platelet ratio (HPR) which has been shown to have diagnostic value in colon cancer [136].

5. Conclusion

As it has been shown, inflammation plays a central role in cancer-related malnutrition which can lead to cachexia and eventually death. Malnutrition accounts for about 20% of all cancer deaths and is associated with reduced quality of life. Markers of inflammation play a prognostic role in cancer and are most times significantly associated with indices of malnutrition in cancer patients. Several studies have shown that inflammatory markers can be used as a screening test for malnutrition in cancer; though their specificity may be below as a result of other disease states. The inflammation-based scores are more sensitive than the single tests. These tests are cheap and easy to apply. However, their major shortcomings are different cut off levels.

Conflict of interest

The author declare no conflict of interests.

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