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Research Article

Assessment of Malnutrition and Inflammatory Status in Cervical Cancer Patients attending Tikur Anbessa Specialized Hospital

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ABSTRACT

Gynecological cancer patients experience malnutrition and Inflammation that play a pivotal role in the progression of cervical cancer. The aim of the present study was to assess malnutrition and inflammatory status in cervical cancer patients through measurement of biochemical markers. Hospital based comparative cross-sectional study was conducted on 50 cervical cancer patients and 50 healthy individuals. Blood was collected and analyzed to gather biochemical and hematological data. Demographic and anthropometric data were also collected and data were statistically analyzed. The mean age was participants 52.4 years. Patients had decreased Albumin, Hemoglobin and Lymphocyte to Monocyte ratio and increased Total Protein, Ferritin, Red cell Distribution Width (RDW), Neutrophils to Lymphocytes ratio and Platelet to Lymphocytes ratio levels than controls group and also those parameters showed in cervical cancer from stage II to stage IV. Albumin negatively correlated with serum ferritin (r=-0.120*, p=0.002) and RDW (r= -0.018*, p=0.001) in cervical cancer patient and negatively correlated with serum total protein (r=0.943*, P<0.001) in control group. NLR positively correlated with PLR (r=0.764**, p=0.000) and LMR (R=1.000**, P=0.000) in cervical cancer patients. Albumin, Total Protein and Ferritin also Hemoglobin, NLR, RDW LMR and PLR may serve as markers for assessment of malnutrition and inflammation and may also use as a prognostic factor in cervical cancer patients.

Keywords: Cervical cancer; Malnutrition; Inflammation; Biochemical markers; Hematological parameters

INTRODUCTION

Gynecologic cancer is any cancer that starts in a woman's reproductive organs. Cancer is always named for the part of the body where it starts. When cancer starts in the cervix, it is called cervical cancer. The cervix connects the vagina (birth canal) to the upper part of the uterus [1]. Cervical cancer is the fourth most common cancer in women; in 2018, approximately 570 000 women were diagnosed with cervical cancer globally and about 311 000 women died from the disease [2]. Cervical cancer is a global significant public health problem and it is the second most well diagnosed cancer and third leading cause of cancer-related deaths in women [3]. Ethiopia is 35.9 per 100,000 patients with 7619 annual number of new cases and 6081 deaths every year [4]. Most of these Ethiopians often diagnosed at an advanced stage by the time they seek screening services. Records showed that nearly 22 million Ethiopian women over the age of 15, approximately 7,600 are diagnosed with cervical cancer and roughly 6,000 women die of the disease each year [5].

Cervical cancer begins when healthy cells in the cervix develop changes (mutations) in their DNA. Healthy cells grow and multiply at a set rate, eventually dying at a set time. Almost all cervical cancer cases (99%) are associated to infection with high-risk Human Papilloma Viruses (HPV), an extremely common virus transmitted through sexual contact [5]. The majorities of HPV infections resolve spontaneously and do not cause symptoms or disease. However, persistent infection with specific types of HPV (most frequently, types 16 and 18) may lead to precancerous lesions [6]. If untreated, these lesions may progress to cervical cancer [5]. Most cervical cancers are Squamous cell carcinomas (This type of cervical cancer begins in the thin, flat cells lining the outer part

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of the cervix) and Adenocarcinomas (This type of cervical cancer begins in the column-shaped glandular cells that line the cervical canal) [7].

Worldwide studies showed that the prevalence of malnutrition in cancer patients ranges from about 20% to more than 70%. However, 10%-20% of cancer patients' deaths are related to malnutrition, not the malignancy itself [8]. In fact, studies have indicated that approximately 88.33% of gynecological cancer patients will experience malnutrition. The various nutrition assessment methods may be arbitrarily divided into subjective (dietetic history), objective (serum albumin, hemoglobin, Body Mass Index (BMI), or comprehensive nutrition assessment tools [9].

There is increasing evidence that explained host inflammatory responses play a significant role in the development and progression of cancers; also cancer is related not only with inflammation at the site of the lesion, but also with deregulations of the host overall systemic immune response. In the case of cervical cancer, inflammation is an important factor related with the development, progression, and potential metastasis of the disease [10]. Ferritin and the role of hematological parameters such as the Platelet-to-Lymphocyte Ratio (PLR), Neutrophil-to-Lymphocyte Ratio (NLR), lymphocyte to monocyte ratio and RDW has been examined in gynecologic malignancies, such as cervical, ovarian, and endometrial cancer [11-13].

Those biomarkers detected at higher levels in the sera (serum) of many cancer patients, correlate with aggressive disease and poor clinical outcome. This research is the first of its kind in Ethiopia that try to address cervical cancer with malnutrition and inflammation efficacy on assessments of markers and prognostic factor by measuring biomarkers.

MATERIALS AND METHODS

Study area and period

The study was done at cancer Center of Tikur Anbessa Specialized Hospital (TASH) and Department of Medical Biochemistry, Addis Ababa University from November 2020-June 2021.

Study design

Hospital based Comparative cross sectional study was used to determine serum level of Albumin, Total Protein and Ferritin also Hemoglobin, NLR, RDW LMR and PLR among cervical cancer patients who were attending at cancer center of TASH within the study period. The study population consisted of 50 cervical cancer patients attending at cancer center of TASH in the time interval of the study period with age matched 50 healthy individuals as controls. Convenient sampling method was used to recruit patients; Blood analysis was conducted at Ethiopian Public Health Institute (EPHI) and TASH diagnostic laboratory.

Data collection

Experiments involving human subjects (Blood sample) and approved with reference No SOM/DRERC/BCHM01/2021 by Department Research and Ethics Review Committee, Department of Biochemistry, College of Health Sciences, Addis Ababa University

All participate informed that the purpose of this study and understood; participation in this study is entirely voluntarily.

Anthropometric measurement

Body mass index is a useful clinical data to diagnose obesity because it is correlated with total body fat. Values of BMI can be classified as follows. BMI ≤ 18.5 Underweight, BMI=18.5-24 normal weight, BMI=25-29.9 overweight and BMI ≥ 30 obese. BMI has been calculated as weight (kg) divided by height in square meters (m^2).

Blood sample collection and biochemical analysis

A total of (5 mL) of venous blood sample was collected; the process of blood sample collection was through aseptic/sterile technique. About 2 mL of the blood was collected in EDTA coated tubes for Complete Blood Count (CBC) analysis. The other 3 mL of Blood was collected into standardize Serum Separator Tube (SST) without anticoagulant from each participant by trained nurse and allowed to stand for 30 min at room temperature to allow complete clotting and clot retraction. The sample was then centrifuged at 4000 rpm for 10 min by using HuMax 14 k centrifuge to extract the serum. Then the serum was transferred from SST tube into Nunc tube and stored at -20°C in the refrigerator till biochemical analysis was carried out. The serum extracted was then used to determine the levels of serum Ferritin level, Albumin and Total protein using an automated COBAS 6000 analyzer (Roche, Germany).

Data analysis

The data were collected using a questionnaires were checked for completeness. Collected quantitative data was coded, entered into a computer, processed, edited, and analyzed using SPSS software version 25 package. Continuous variables were presented as mean ± standard error and compared using the student t tests and one way Analysis of Variance (ANOVA). Other associations were performed with Pearson's correlation coefficient. A P-value of <0.05 at 95% confidence level was considered to be statistically significant in all the analyses.

Ethical consideration

Before starting data collection and preliminary study, ethical approval with reference No SOM/DRERC/BCHM01/2021 was obtained from the Department Research and Ethics Review Committee, Department of Biochemistry, College of Health Sciences, Addis Ababa University.

All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from all participants or, if participants are under 16, from a parent and/or legal guardian.

RESULTS

In this study a total of 100 study participants enrolled among these 50 of them were cervical cancer patients and 50 healthy individuals as control groups. The average age of the cervical cancer patients and control groups were 52.4 ranging from 32 to 72 years. From 50 cervical cancer patient attending at TASH, 41 (82%) came from rural residence and 9 (18%) from urban residence, 46 (92%) of the study participant were married, 2 (4%) single and 2 (4%) divorced. When we see their educational status 31 (62%) of them were illiterate, 18 (36%) up to high school and 1 (2%) diploma. Most of the control groups were came from urban residence 34 (68%), 16 (32%) from rural residence. 47 (94%) of the control participant were married and 3 (6%) single. The educational status; 27 (54%)

were up to high school, 17 (34%) illiterate and 6 (12%) diploma and above. Most of the cervical cancer patients in the study were of low economic status 45 (90%), and also the control groups 31 (62%) (Table 1).

In addition 42 (82%) of the cervical cancer patients don't drink alcohol, 8 (16%) were non habitual drinker. Out of the 50 cervical cancer patient 17 (34%) had meal 2 times a day, 30 (60%) 3 times a day and 3 (6%) 4 times a day. About 44 (88%) of cervical cancer group prefer to eat teff and 6 (12%) prefer to eat wheat. When it comes to the BMI, 13 (26%) of them were less than 18.5 (underweight), and 37 (74%) between 18.5 and 25 (ideal weight).

Among the control group 41 (82%) were not alcohol drinker, 9 (18%) non habitual drinker, and their appetite status (22(44%), 27(54%) and 1(2%) were healthy, moderate and poor appetite respectively. 3 (6%) of control group eat 2 times a day, 43 (86%) eat 3 times a day and 4 (8%) eat 4 times a day. 45 (90%) prefer to eat teff and 5 (10%) prefer to eat wheat. In the case of BMI of control group 5 (6%) were less than 18.5 (underweight), 45 (90%) between18.5 and 25 (ideal weight) (Table 2). None of the study participants (both the cervical cancer patient and control group) were not smokers and never used any supplements (vitamin and minerals) before.

With regards to cancer stage, stage II cervical cancer patients were the highest in proportion (48%), stage III and stage IV were (22%) and (8%) respectively (Figure 1). Duration of time with cervical cancer, less than 1 year (42%), 1-2 years (44%) and more than 2 years (14%) (Figure 2).

Assessment of malnutrition among the cervical cancer patients and control groups was assessed using anthropometric measurement and biochemical tests using standard kits.

The cervical cancer patient had lower mean albumin level (3.40 ± 0.55 g/dl) than the control group (6.47 ±5.48 g/dl) with P=0.002, and they had higher mean value of Total protein level (7.45 ± 0.57 g/dl) than the control (7.16 ± 0.31 g/dl) with a P=0.011. There is statistically significant difference between the two groups in the case of albumin and total protein. The mean value of body mass index was 1.74 ± 0.44 kg/m^2 for cervical cancer patient and 1.90 ± 0.30 kg/m^2 for control group with (p=0.003). There was significant difference in mean value of ferritin level (215.11 ± 129.43) for cervical cancer patient and (50.19 ± 25.31) for control group with (p=0.000). There is statistically significant difference between the two groups in the case of ferritin and BMI (Table 3).

Table 1: Socio-demographic characteristics of the study groups.

Variable		Patients N (%)	Control N (%)
Residence	Urban	9 (18)	34 (68)
	Rural	41 (82)	16 (32)
Marital status	Single	2 (4)	3 (6)
	Married	46 (92)	47 (94)
	Divorced	2 (4)	0 (0)
Education	Illiterate	31 (62)	17 (34)
	Up to high school	18 (36)	27 (54)
	Diploma and above	1 (2)	6 (12)
Socioeconomic status	Low	45 (90)	31 (62)
	Middle	5 (10)	19 (38)
	High	0 (0)	0 (0)

Table 2: Socio- demographic and anthropometric characteristics of the study groups.

Variable	Patients N (%)	Control N (%)	High
Alcohol consumption	Non-drinker	42 (82)	41 (82)
	Non-habitual	8 (16)	9 (18)
Meals per day	2 times	17 (34)	3 (6)
	3 times	30 (60)	43 (86)
	4 times	3 (6)	4 (8)
Kind of food prefer to eat daily	Teff	44 (88)	45 (10)
	Wheat	6 (12)	5 (10)
Body mass index Kg/m^2	Less than 18.5 (underweight)	13 (26)	5 (6)
	18.5-25 (ideal weight)	37 (74)	45 (90)
	25-30 (overweight)	0 (0)	0 (0)

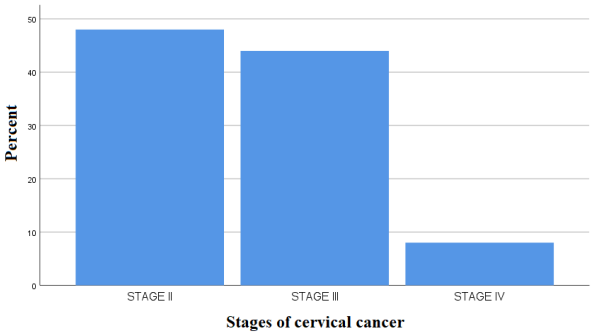

Figure 1: Proportion of cervical cancer patients' by stages.

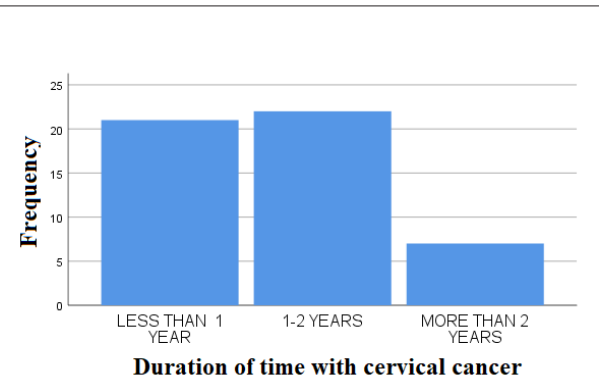

Figure 2: Duration of time with cervical cancer of patients.

Table 3: Comparison of mean value of anthropometric, biochemical measurements of the cervical cancer patients and control groups.

Variable	Patients (n=50) Mean ± SD	Control (n=50) Mean ± SD	P-value
Age	52.62 ± 10.00	52.18 ± 9.03	0.081
BMI kg/m^2	1.74 ± 0.44	1.90 ± 0.30	0.003*
Albumin g/dl	3.40 ±0.55	6.47±1.48	0.002*
Total protein g/dl	7.45 ± 0.57	7.16± 0.31	0.101
Ferritin Ng/ml	215.11 ± 129.43	50.19 ± 25.31	0.000*

Note: *P value<0.05 is statistically significant.

Hematological indices among cervical cancer patient and control group show that: There was difference in mean value of hemoglobin (13.24 ± 3.24) in cervical cancer and (14.95 ± 4.95) in control group with (p=0.158) and there was significant difference in mean value of RDW (15.71 ± 3.43) in cervical cancer patient and (11.25 ± 1.73) in control group with (p=0.000). In addition, the NLR for the cancer patients (2.33 ± 0.64) and for control group (1.47 ± 0.60) with (p=0.000) and PLR for cervical cancer patients (60.53 ± 13.95) and (45.01 ± 6.09) for control group with (p=0.001). There is significant difference between cervical cancer patient and control in the case of Hemoglobin, NLR and PLR and none significant difference in mean value of LMR (3.00 ± 0.32) in cervical cancer patients and (3.43 ± 0.42) in control group with (p=0.006) (Table 4).

The effect of the stages of cancer on the different inflammatory and nutritional biomarkers was assessed through one way ANOVA. There was significant difference in mean value of serum Albumin (P=0.010) and serum Feritin (P=0.004) and total protein (p=0.012), and also RDW, NLR and PLR with (p=0.030), (p=0.021) and (p=0.004) respectively with clinical stage of cervical cancer but there is none statistical significant difference in Hemoglobin (P=0.401) and LMR (0.816) (Table 5).

As shown in Table 6, Albumin negatively correlated with serum ferritin (r=-0.120*, p=0.002) and RDW (r=-0.018*, p=0.001) in cervical cancer group and also negatively correlated with serum total protein (r=0.943*, P=0.001) in control group. Neutrophiles to lymphocytes Ratio (NLR) positively correlated with platelet to lymphocytes ratio (PLR) (r=0.764**, p=0.000) and Red cell Distribution Width (RDW) (r=1.000**, p=0.000) in the cervical cancer patients.

Table 4: Comparison of mean value of H, NLR, RDW%, LMR and PLR among cervical cancer patients and control group.

Variable	Patients (n=50) Mean ± SD	Control (n=50) Mean ± SD	P-value
Hemoglobin 10/µ	13.24 ± 3.24	14.95 ± 4.95	0.158
RDW %	15.71 ± 3.43	11.25 ± 1.73	0.000*
NLR	2.33 ± 0.64	1.47 ± 0.60	0.000*
PLR	60.53 ± 13.95	45.01 ± 6.09	0.001*
LMR	3.001 ± 0.32	3.435 ± 0.42	0.006

Note: *P value<0.05 is statistically significant.

Table 5: One-way ANOVA test showing the effect of cancer stages on biochemical and hematological parameters in cervical cancer patients.

Parameters	Stage II (n=24)	Stage III (n=22)	Stage IV (n=4)	P- Value
Ferritin ng/ml	163.15 ± 39.849	186.40 ± 75.803	250.09 ± 61.044	0.004*
Albumin g/dl	3.406 ± 0.594	3.384 ± 0.551	3.340 ± 0.444	0.1
Total protein g/dl	7.447 ± 0.609	7.481 ± 0.557	7.545 ± 0.343	0.102
Hemoglobin 106/µ	11.74 ± 2.024	11.39 ± 2.021	10.400 ± 3.980	0.401
RDW %	15.009 ± 1.974	16.357 ± 4.645	16.825 ± 1.436	0.030*
NLR	2.127 ± 0.593	2.522 ± 0.657	2.585 ± 0.563	0.021*
PLR	56.238 ± 11.878	64.013 ± 14.664	67.225 ± 17.256	0.004*
LMR	3.465 ± 0.2805	3.326 ± 0.4022	3.306 ± 0.4787	0.816

Note: *P value<0.05 is statistically significant RDW: Red cell Distribution width; NLR: Netrophil to Lymphocyte ratio; PLR: Platelet to Lymphocyte; LMP: Lymphocyte to Monocyte ratio.

Table 6: Pearson correlation co-efficient between anthropometric and biochemical indices for cervical cancer patient and control groups.

			Age	Ferritin ng/ml	Rdw (%)	TP g/dl	Hgb(%)
Al g/dl	Patient n=50	R	0.167	-0.120*	-0.018*	0.119	0.078
		P	0.098	0.002	0.001	0.41	0.593
	Control n=50	R	0.267	0.009	0.049	0.943*	0.034
		P	0.061	0.951	0.737	0.001	0.814
	PLR	LMR	Rdw (%)	Hgb (%)	0.816	0.816	0.816
NLR	Patient n=50	R	0.764**	-0.105	1.000**	-0.166	0.816
		P	0	0.467	0	0.25	0.816
	Control n=50	R	0.211	0.026	0.068	0.045	0.816
		P	0.14	0.852	0.64	0.755	0.816

Note: *Correlation is significant at the 0.005 level (2-tailed); TP: Total Protein; Al: Albumin; Hgb: Hemoglobin; RDW: Red cell Distribution Width; Hgb: Hemoglobin; RDW: Red cell Distribution Width; NLR: Neutrophil to Lymphocyte Ratio; PLR: Platelet to Lymphocyte Ratio; LMR: Lymphocyte to Monocyte Ratio.

DISCUSSION

Cervical cancer is the commonest malignancy of females all over the world. Annually more than half a million women are diagnosed with cervical cancer and result in over 300,000 deaths worldwide [14]. According to Ethiopian Federal Ministry of Health prevalence of cancer of the cervix is 13.4% which is the most common female cancer next to breast cancer 30.2% [15].

Studies have indicated that approximately 88.33% of gynecological cancer patients experience malnutrition [9]. Different factors including, Total protein, Albumin and Hemoglobin are used to evaluate the nutritional status in patients with gynecological cancer [16]. There is increasing evidence that showed the host inflammatory responses play a significant role in the development and progression of cancers. There are some data that showed cancer is associated not only with inflammation at the site of the lesion, but also with deregulations of the host overall systemic immune response by influencing the host immune response to tumors [10].

The results of the present study indicated that there was no statistically significant difference between the mean ages of cervical cancer patient and the control groups. Most of the cervical cancer patients came from rural residence and have low income and were illiterate. Lack of adequate information is one of the major problems for the design of cancer control strategies in Ethiopia [17]. Women

with low educational level and income are more likely to have less awareness of cervical cancer and preventive mechanisms which consequently may lead to inadequate screening and gynecological follow up [18]. Pervious study showed that alcohol drinker and smoker are well malnourished and increased risk for inflammation and cancer [19]. In our study the cervical cancer patients were non habitual drinker and not smokers. Cervical cancer patient appetites were described as moderate and poor compared to control group who had moderate and healthy. Anthropometric indicator; BMI was also lower in cervical cancer patients compared to the control group, BMI have been used to evaluate nutritional status [20].

There was significant decrease in mean value of Albumin in cervical cancer patients compared to control groups; but it is within the range value (3.5 g/dL to 5.4 g/dL). Similar to other findings, the reduction in serum albumin concentration could be because of the host body experience inflammation based cancer and a state of high physiological stress, with tumor hypoxia/necrosis and local tissue damage [21,22]. In an attempt to counteract these changes, the body responds with a systemic release of pro-inflammatory cytokines and growth factors. When faced with these stimuli, human hepatocytes increase their production of acute-phase proteins, such as CReactive Protein (CRP), and decrease the production of albumin. This response is often accompanied by a nutritional and functional decline of patients, especially among those with advanced cancer. Similar to several other reports this reduced albumin level in serum of cervical cancer patients may be due to the role of albumin as extracellular antioxidant scavenger, a disproportionate increase in albumin degradation without a corresponding increase in synthesis can contribute to hypoalbuminemia [23]. It is known that the serum albumin concentration may change under oxidative stress, such as the stress associated with cancer. According to it has also been shown that, in patients with cancer, there is an increase in vascular permeability and hence increase in the albumin-flux across the capillary wall towards the extra-vascular compartment [15]. This is due to the release of tumor necrosis factor, which may increase micro-vascular permeability, leading to hypoalbuminemia.

Albumin negatively correlated with serum ferritin in cervical cancer patient group. The low albumin level in patients may increase susceptibility to infection and inflammation, reduce quality of life and increase mortality. Increased degradation and decreased synthesis of albumin with increasing cancer stages and inflammation leads to elevated level of serum ferritin. Serum albumin also positively correlated with Total protein in control group and negatively correlated with RDW in cervical cancer patients; according to malnutrition is another hallmark of cancer because of reduction in appetite and weight which consequently contribute to the increase in RDW [12]. The low albumin level is associated with increased RDW level in cancer patients which also indicated the relationship between high RDW level and poor nutritional status in patients with cancer [24].

The mean value of total proteins is elevated among cervical cancer patients compared to the control groups; but it is within the range value (6.0 d/gL to 7.8 d/gL) and this result is supported by as the plasma circulates through the tissues, it collects proteins that are released from their original locations due to certain physiological events, including tissue remodeling, trauma and cell death, which lead to an increase in total serum protein [25]. It could be also due to chronic (long-term) inflammation or inflammatory disorders [26]. The Increase in serum total protein level is because cancer patients synthesize different kinds of proteins such as globulins, immunoglobulin, enzymes and positive acute phase proteins. Our result was in line with studies done by lymphocytes produce globulins to the levels that are high enough to compensate for the lowered albumin levels in the serum [13,27].

Ferritin is what's known as an acute phase reactant. This means that when the body experiences inflammation, ferritin levels will go up. That's why the ferritin levels in our study were high in people who have cancer and this is supported by [28]. The result of this study shows there was significant higher mean value of Serum Ferritin, which significantly increases in cervical cancer than the control groups. It might be the result of the recognition that serum ferritin levels mainly represent a consequence of cell stress and damage and this supported by serum ferritin levels can be raised significantly in response to inflammation [29]. Serum ferritin actually originates from damaged cells (and thus reflects cellular damage), that it contains some iron but has lost or liberated and the protein part of ferritin is assumed to be benign and is causative of disease. Elevated ferritin levels are usually due to causes such as acute or chronic inflammation, smoking and alcohol consumption; in our study the cervical cancer patients are non-habitual drinker and not smokers and also Ferritin concentrations increase drastically in the presence of an infection or cancer [30]. The cancer-associated elevation in serum ferritin is most likely induced by an inflammatory state and according to the cancer-associated elevation of serum ferritin is most likely caused by an inflammatory state, and a study demonstrated that ferritin is secreted from tumor associated macrophage, ferritin which is secreted by macrophages and responds to systemic inflammation could be a host based prognostic factor to reflect the status of patients [31]. Hepatocytes, Kupffer cells, proximal tubular renal cells and macrophages have all been shown to secrete ferritin in various *in vivo* and *in vitro* conditions. Cultured cells release ferritin into surrounding media when grown in the presence of IL-1β and TNF-α [11].

The hematological markers of inflammation in Complete Blood Count (CBC) panel are potentially useful in determining the prognosis of the disease. The systemic inflammatory response was characterized with the infiltration of leukocytes, such as neutrophil, which were attracted by the cytokines and chemokines secreted from the tumor cells [32].

Hemoglobin level is affected by many factors including malnutrition, Cancer patients experience nutrition impact symptoms such as decreased appetite, pain, nausea, constipation, vomiting, and diarrhea which are adequately addressed, and then it is likely that improvements will be made in the patients' nutritional status [9]. The result of this study showed that there is decrease in the mean value of serum hemoglobin in cervical cancer patients compared to the control group and this is supported by [33]. Furthermore, the cancer cells release cytokines that can lead to iron sequestration, reducing the production of Red Blood Cells (RBCs). Tumors may result in chronic blood loss from the tumor site, leading to progressive anemia from the cancer and organ damage [34]. This problem is compounded by blood losses, nutritional deficiencies, or the presence of inflammatory cytokines associated with cancers and chronic disease. Cancer patients tend to lose their appetite, leading to nutritional deficiencies. Almost half of the patients diagnosed with gynecologic cancer have anemia at diagnosis [35]. The mean value of RDW significantly increases in cervical cancer compared to the control groups similar to other finding [36]. RDW, which plays a critical role in inflammatory response, has attracted attention because of the connection of inflammation

and cancer results in increases RDW in malignant tumors. RDW is well-known inflammatory marker of systemic inflammatory response; this study is in line with that identified RDW was as an inflammatory marker in patients with cancer due to its positive association with widely used plasma inflammatory biomarkers such as C-reactive Protein (CRP) and interleukin (IL)-6 levels [36,37]. Elevated RDW level may reflect the presence of immature red blood cell. This is also supported by that the various cytokines affect erythropoiesis *via* erythropoietin (EPO) production, inhibition of erythroid progenitors, and reduction in iron release [38]. Previous *in vitro* and *in vivo* studies have demonstrated that EPO production was inhibited by inflammatory cytokines such as IL-6, interferon-gamma (IFN-γ), IL-1β, and tumor necrosis factor-alpha (TNF-α). In addition, IL-1α and IL-1β play important roles in suppression of erythroid progenitors. Poor nutritional status in patients with cancer may contribute to the elevation of RDW, according to the deficiency of various minerals and vitamins such as iron, folate and vitamin B12; also low albumin level is associated with increased RDW [24].

Neutrophil-Lymphocyte Ratio (NLR) is calculated by dividing the absolute Neutrophil count by the absolute lymphocyte, Lmphocyte to Monocyte ratio also calculated by dividing the absolute lymphocyte count by absolute Monocyte count and the Platelet-Lymphocyte Ratio (PLR) is calculated as the ratio of the Platelet to lymphocyte count (obtained from the same blood sample) [39].

The mean value of NLR and PLR significantly increased in cervical cancer compared to the control groups, the present study was in line with that indicated both increased NLR and PLR are predictive biomarker for the presence of cervical cancer [40]. A strong relationship between NLR and inflammation has been reported in previous studies the issue of inflammation has received considerable critical attention not only in initiation and promotion but also in the progression, invasion, and metastasis of a tumor [41]. NLR may be recognized as the marker of the balance between precancerous inflammatory state and cancerous state, and higher NLR might be indicative for tumor development and this study supported by [13]. NLR is strongly associated with overall survival in patients with various types of cancer including cervical cancer. A high NLR is correlated with the poor prognosis of cervical carcinoma patients [41,13]. NLR positively correlated with PLR and RDW in the cervical cancer patients. Variety of inflammation factor are generate during the onset of cancer, also with respect to malnutrition, patients with malignant tumors often have malnutrition, gastrointestinal dysfunction and impaired immune function [42].

Lymphocyte to Monocyte Ratio (LMR) is a useful predictive factor in various cancers, the result of this study shows that there is decrease in the mean value of LMR in cervical cancer patients compare to the control group and this study is supported by decreased lymphocyte numbers are therefore considered to be responsible for an insufficient immunologic reaction to the tumor, thus promoting tumor progression and metastasis [40]. Monocytes are known to infiltrate tumors and differentiate into tumor-associated macrophages, which are involved in tumor proliferation, invasion, metastasis, neovascularization, and recurrence. Increased levels of monocytes thus reflect a high tumor burden in patients with cancer [43]. In such a mechanism, LMR is believed to reflect the host immune status and the degree of tumor progression. The decreased level of LMR associated with inflammation and cancer; according to showed solid tumors are generally infiltrated with leukocyte subsets, among which monocytes and lymphocytes play major roles in the inflammatory response [44]. Either each of these two leukocyte subsets or combination of peripheral LMR, has been demonstrated independently associated with the prognosis of various cancers. A lower lymphocyte count and high monocyte count were both significantly related to mortality in ovarian cancer this has been showed by low lymphocyte count and high monocyte count reflect insufficient anti-tumor immunity and an elevated tumor burden, a low LMR is therefore associated with a poorer prognosis [45].

Maximum number of severe malnutrition cases had advanced stages of cancer (stage III/IV), which of course is expected [46]. When we combined the effects of cancer site and stage on nutrition the result implied that there is severe malnutrition towards the later stages, Cases are at risk even in stage I [9].

Approximately 88.33% of all cancer patients will experience malnutrition at some stage during the clinical course of their disease [9]. In our study there was significant decrease in serum albumin level and increase in serum ferritin level in cervical cancer patients in relation to pathological stages, which is in line with other studies this may be due to increased degradation and decreased synthesis of albumin with increasing cancer stages and inflammation increase as cancer stages increase and lead to elevated level of serum ferritin [15].

Serum Hemoglobin showed significant decreases among stages of the cervical cancer patients. There is significant decrease in serum hemoglobin from cervical cancer stage II to stage IV. It may due to the production of cytokines such as interleukin (IL)-6 are increased as inflammation increase by certain cancer type [37]. In our study there is a Decrease in the LMR among stages of the cervical cancer patients from stage II to stage IV. The Absolute Monocyte Count (AMC) and Absolute Lymphocyte Count (ALC) were significantly correlated with the clinical outcome of stage of cervical cancer patients. Decreased lymphocytes and the increased Monocyte with the stage of cancer in the blood and in the tumor stroma are significantly related to tumor growth and lymph node metastasis in cervical cancer [47].

Increased RDW, NLR and PLR have been shown to be associated with stage, invasiveness, prognosis of characteristics of different cancer type [40]. In the present study there is significant increase in NLR, RDW and PLR from cervical cancer stage II to stage IV. This is in line with Zhu and his colleagues who demonstrated that increased RDW, NLR and PLR have been shown to be associated with stage, invasiveness, prognosis of characteristics of different cancer type including cervical cancer as inflammatory response continuously progresses in patients as disease advances. In addition, NLR and PLR were found to be independent predictors of cervical cancer. Higher RDW levels are also significantly associated with advanced stages of cancer and metastasis. According to the deficiency of various minerals and vitamins such as Iron, folate and vitamin B12, also low albumin level is associated with increases RDW among different stages too [24].

CONCLUSION

The nutritional status of patients with gynecologic cancer has been evaluated by various nutritional parameters such as Prognostic Nutritional Indices including serum albumin, total protein, and hemoglobin. Inflammation is an important factor related with the development, progression, and potential metastasis of the cancer.

Ferritin and complete blood count and their ratios such as the PLR, NLR, RDW and LMR have been demonstrated as significant predictors in cancer. Cervical cancer patients present with different stages of malnutrition. The consequences of malnutrition include impairment of immune functions and poor quality of life.

The significant decrease in serum Albumin and Hemoglobin of the cervical cancer patients are indicator of the malnutrition because of the deficiency of various minerals and vitamins. Their concentration may change under high oxidative stress and physiological stress; the production of cytokines such as interleukin (IL)-6 is increased as inflammation increase that lowers serum albumin. The high serum Total protein also indicates cancer patients synthesize different kinds of proteins like CRP to compensate for the lowered albumin levels in the serum. The significant increase in ferritin, PLR, RDW and NLR and decrease in LMR of cervical cancer has shown the inflammation status and they may promote the immune-stimulatory activities.

From this study we conclude that malnutrition and inflammation might have a prognostic factor of cervical cancer. The low Serum Albumin, Hemoglobin and the high Total protein are indicators of the malnutrition status and the high serum Ferritin, RDW, LMR, NLR and PLR are indicator of the inflammation status of cervical cancer. Hence, it can be taken as a base line study and might require further study on large group of participants to just improve the lives of cervical cancer patient and also to address other effect of malnutrition and inflammation.

LIMITATION OF THE STUDY

Due to limitation of money and time small sample size was taken. We couldn't exclude some factor that might affect nutritional and inflammation status, infection and other hematological disorder (Biochemical markers have their own limitations and their level is affected by different disease).

DATA AVAILABILITY

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

AUTHORS' CONTRIBUTIONS

Etsegenet Assefa drafts the paper and writes the literature review. Maria Degef, Wondemagegnhu Tigeneh, Ñatesan Gnanasekaran, Mezegebu Legesse and Tadesse Lejisa assisted in guidance, critical assessment also data collection and analysis.

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