ADDIS ABABA UNIVERSITY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF GRADUATE STUDIES
DEPARTMENT OF MEDICAL BIOCHEMISTRY

ASSESSMENT OF MALNUTRITION AND INFLAMMATORY STATUS IN CERVICAL CANCER PATIENTS ATTENDING TIKUR ANBESSA SPECIALIZED HOSPITAL.

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Thesis submitted to Department of Medical Biochemistry, School of Graduate Studies, College of Health Sciences, and Addis Ababa University in partial fulfillment of the requirements for the degree of Master of Science (M.Sc) in Medical Biochemistry.

June, 2021
Addis Ababa, Ethiopia

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Declaration Sheet This is to clarify that thesis prepared by Etsegenet Assefa entitled "Assessment of Malnutrition and Inflammatory status in cervical cancer patients attending Tikur Anbessa specialized hospital**.**" is submitted in partial fulfillment of the requirement for the Degree of Master of Sciences in Medical Biochemistry complies with the regulations of the university and meets the accepted standards with respect to the originality and quality.

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Chair of the department or graduate program coordinator

Table of Contents

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List of table

List of figures

List of Abbreviation and Acronyms

ADA3……. Alteration/deficiency in activation-3

ALC …….. Absolute lymphocyte count

AMC …….. Absolute Monocyte count

BMI ……Body Mass Index

CBC ……Complete blood count

CRP……. C-reactive protein

EDTA……. Ethylenediaminetetraacetic acid

FGF……. Fibroblast growth factor

HGB……..Hemoglobin

HrHPV…… High risk types of Human Papilloma Virus.

HPV…… Human papilloma virus

IARC…… International Agency for Research on Cancer

IL-2 …….. Interleukin-2

INFγ……. Interferon gamma

LMR……. Lymphocyte to Mnocyte ratio

NLR…….. Neutrophil-to-lymphocyte ratio

PDGF……. Platelet-derived growth factor

PLR…….. Platelet to-lymphocyte ratio

PNI…….. Prognostic nutritional index

RDW……. Red cell distribution width

ROS…….. Reactive Oxygen Species

SIR…… Systemic inflammatory response

TASH……. Tikur Anbessa specialized hospital

TGF-β……. Transforming growth factor-β

TLR2…….. Toll-like receptor 2

TNF-α…….. Tumor Necrosis factor alpha

VEGF……Vascular endothelial growth factor

WBC …… White Blood Cells

WHO……. World Health Organization

Abstract

Background: Globally cervical Cancer is the fourth common cancer accounting for 6.6% of all female cancers. Oncogenic human papillomavirus (HPV) specifically types 16 and 18 is the most important risk factor associated with cervical cancer. Studies have indicated that approximately 88.33% of gynecological cancer patients experience malnutrition; and Inflammation that play a pivotal role in the progression of cervical cancer. Various nutritional and inflammatory parameters such as serum Total Protein, Albumin, Ferritin and Hematological parameters; Hemoglobin, LMR NLR, RDW and PLR used as Prognostic Biomarker of cancer associated with inflammation and malnutrition in cervical cancer patient.

Objective: The aim of the present study was Assessment of Malnutrition and Inflammatory Status in Cervical Cancer Patients attending Tikur Anbessa Specialized Hospital.

Methodology: Hospital based comparative cross-sectional study was conducted on 50 cervical cancer patients and 50 healthy individuals. Socio demographic data were collected by using standardized questionnaire. Anthropometric data and Blood collection was done through standardized techniques and Automated COBAS 6000 and Sysmex KX-21N hematology analyzers were used to analyze the samples. Statistical data analysis was held by SPSS version 25. Student's t-test was used to compare the mean value of continuous variables of two groups, one way analysis of variance (ANOVA) was used to compare the relationship of categorical variables between deferent stages of the cancer. 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.

Result: The mean age of cervical cancer patient and control group was 52.4 years. The cervical cancer Patients had significantly decreased Albumin and increased Total Protein and significantly increased Ferritin levels than controls group. Among hematological parameters there was a significantly increases in Red blood distribution width (RDW), Neutrophiles to Lymphocytes ratio (NLR) and Platelet to Lymphocytes ratio (PLR). There was also decrease in Hemoglobin and Lymphocyte to Monocyte ratio (LMR) in the cervical cancer Patients and also those parameters expresses their effect 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.

Conclusions: Malnutrition and inflammation are common experience in patients with cervical cancer. The result of this study showed low level of serum Albumin, Hemoglobin and LMR; and high level of serum Total Protein, Ferritin and other Hematological Parameters such as NLR, RDW and PLR. This may serve as markers for assessment of malnutrition and inflammation and may also use as a prognostic factor in cervical cancer patients. Therefore, further study is recommended on the assessment of malnutrition and inflammation in cervical cancer patients with a large group of participants.

Key words: Cervical cancer; Malnutrition; inflammation; Biochemical markers; Hematological parameters.

1 Introduction

1.1 Background

Cancer is a disease in which cells in the body grow out of control. 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 (WHO, 2006).

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. The mutations tell the cells to grow and multiply out of control, and they don't die. The accumulated abnormal cells form a mass (tumor). Cancer cells invade nearby tissues and can break off from a tumor to spread (metastasize) elsewhere in the body (Martin *et al*., 2013).

Cervical cancer is caused by the sexually transmitted HPV, which is the most common viral infection of the reproductive tract. Almost all sexually active individuals will be infected with HPV at some point in their lives and some may be repeatedly infected. The peak time for infection is shortly after becoming sexual active. 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. If untreated, these lesions may progress to cervical cancer (WHO, 2020).

Cancer occurs when cells in an area of the body grow abnormally. If abnormal cells on the surface of the cervix spread deeper into the cervix, or to other tissues or organs, the disease is then called cervical cancer, or invasive cervical cancer. Most cervical cancers are squamous cell carcinomas (This type of cervical cancer begins in the thin, flat cells lining the outer part of the cervix) and adenocarcinomas (This type of cervical cancer begins in the column-shaped glandular cells that line the cervical canal) (Prat, 2015).

Malnutrition in cancer patients has a negative consequence on their quality of life, response to treatment and overall survival. Malnutrition frequently a coincident in patient with chronic diseases and it is associated with adverse outcomes. It has been suggested that up to 20% of patients with cancer die because of the effects of malnutrition rather than the malignancy itself (Santarpia *et al*., 2011).

Almost all cases of cervical cancer come after infection of the cervical epithelium with oncogenic (HPV) types. It is clear that inflammation plays a significant role in regulating pathology of cervix, susceptibility to infection by the virus and has been interconnected with cervical inflammation and increased risk of cervical cancer (Sales, 2014).

Although most infections with HPV resolve spontaneously and cause no symptoms, persistent infection can cause cervical cancer in women. Successful primary (HPV vaccination) and secondary prevention approaches (screening for, and treating precancerous lesions) will prevent most cervical cancer cases. When we early diagnosed cervical cancer it is one of the most well curable forms of cancer, as long as it is detected early and managed; it can be prevented (https://www.who.int/health-topics/cervical-cancer). Cancer diagnosed in late stage can be controlled with appropriate treatment and palliative care. With a comprehensive approach to prevent, screen and treat, cervical cancer can be eliminated as a public health problem with in a generation (Njuguna, 2020).

1.2 Cervical cancer worldwide and in Ethiopia

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 (Arbyn *et al*., 2020). 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 (Fentie *et al*., 2020).

Annually more than half a million women are diagnosed with cervical cancer and its result over 300,000 deaths worldwide, globally it is the fourth common cancer accounting for 6.6% of all female cancers. About 85% of the global plague and 87% of deaths secondary to cervical cancer occur in the less developed country. East African region was

the highest in cervical cancer with age-standardized prevalence of 42.7 per 100,000 populations and mortality rate of 27.6 per 100,000 deaths. According to Federal Ministry of Health Ethiopia prevalence of cancer of the cervix is 13.4% which is the most common female cancer next to breast cancer 30.2% (Sibhat *et al*., 2019).

According to the 2009 WHO report, the age-adjusted incidence rate of cervical cancer in Ethiopia is 35.9 per 100,000 patients with 7619 annual number of new cases and 6081 deaths every year (Jemal *et al*, 2012). 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 (WHO, 2009).

Cervical cancer is the main cause of death throughout the world, especially in less developed countries. Reports of trends in cervical cancer mortality from less developed countries have been limited by poor data quality and inaccurate population estimates. It is also a leading cause of mortality worldwide with 270000 women every year. But, 85% of these deaths occur in the developing world (Ferlay *et al*, 2010). Cervical cancer is the leading cause of death (50,300) in African women. Rates vary substantially across regions, with the incidence and death rates in East Africa and West Africa is as high as the rates in North Africa (Abate, 2015).

Despite this fact, very few women receive screening services in Ethiopia. Although there is no national cancer registry, reports from retrospective review of biopsy results have shown that cervical cancer is the most prevalent cancer among women in the country followed by breast cancer. Low level of awareness, lack of effective screening programs, overshadowed by other health priorities (such as AIDS, TB, malaria) and insufficient attention to women's health are the possible factors for the observed higher incidence rate of cervical cancer in the country (Hailu *et al*., 2020). This makes cervical cancer the second-most common cancer in the country, and the second-most deadly cancer among Ethiopian women (Begoihn *et al*., 2019).

One major determinant for the prognosis of cervical cancer is the stage at which the patient presents. Most patients in developing countries including Ethiopia present late with advanced stage disease, in which treatment may often involve multiple modalities including surgery, radiotherapy, chemotherapy, and has a markedly diminished chance of success. Several factors such as educational status, financial capability, location, presence of health care facilities determine the stage at which patients with cancer present to the health facility (Getahun *et al*., 2013).

1.3 Cervical cancer and HPV

There are many factors affecting the development of this life-threatening disease, such as the socio-economic status, the moment of sexual intercourse, alcohol consumption and/or smoking, as well as genetic factors, Immunosuppression and a large number of pregnancies and births (especially for young women) (Dijkstra *et al*., 2014). However, the most important factor that has a huge impact on the development of cervical cancer is primarily persistent infection with hrHPV (mainly types 16 and 18), which can lead to uncontrolled course of infection (Figure 1). In the data analysis of a multicentre comparative case study of the International Agency for Research on Cancer (IARC), the odds ratio (OR) for squamous cell carcinoma due to HPV infection was 158.2, with the analysis limited to studies using approved HPV detection techniques (Munoz *et al*., 2003).

Oncogenic human papillomavirus (HPV) is the most important risk factor associated with cervical cancer. HPV have been divided into high- and low-risk on the basis of their oncogenic potential. High risk HPV is considered to be the leading etiological cause for cervical cancer (Ahmed *et al*., 2015). About a dozen HPV types (including types 16, 18, 31, and 45) are called "high-risk" types because persistent infection has been linked to cancer of the oropharynx, larynx, vulva, vagina, cervix, penis, and anus. These cancers all involve sexually transmitted infection of HPV to the stratified epithelial tissue. Individuals infected with HPV increased risk of developing cervical cancer mostly HPV type 16 is the strain most likely to cause cancer and is present in about 47% of all cervical cancers (Boscolo, 2013).

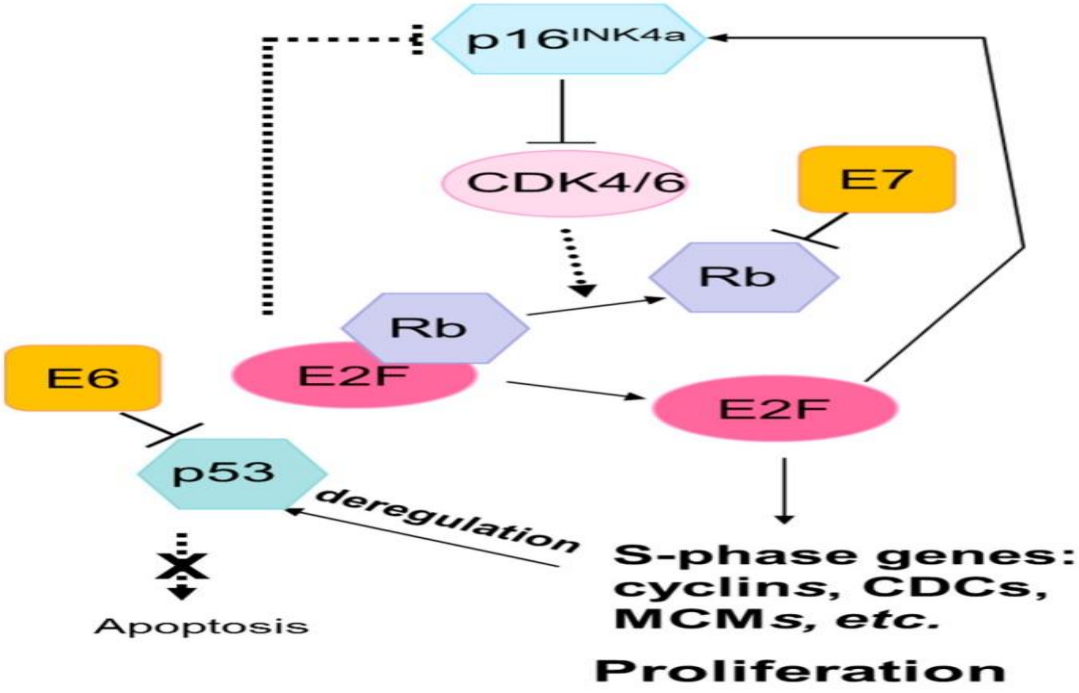

Figure 1: Schematic outline of critical steps of high-risk HPV induced carcinogenesis. Inactivation of the pRB and p53 tumor suppressor pathways and expression of the catalytic telomerase subunit hTERT constitute a subset of the steps that have been shown to be necessary for the generation of fully transformed human epithelial cells in vitro (Yugawa, 2009).

High-risk HPV E6 proteins eliminate the trophic sentinel response triggered by E7 expression through inactivation of p53. This process is essential for the life cycle of high-risk HPVs. High-risk HPV proteins E6 do not directly associate with p53 but form a complex with the cellular E6-AP protein the ubiquitin ligase E6-AP (E6-associated protein),which is essential for p53 interaction. E6-AP is the founding member of the homology to E6 carboxy terminus (HECT) family of E3 ubiquitin ligases (Park, 2002). E6-AP does not interact with p53 in the absence of E6, and its normal substrates are unknown. High-risk E6 proteins retarget E6-AP to induce ubiquitination and rapid proteasomal degradation of p53. HPV-16 E6 proteins may also interact with additional cellular factors that are important for the transcriptional activity of p53, including p300 and the transcriptional co-activator ADA3 (Alteration/deficiency in activation-3) (Yugawa, 2009).

1.4 Malnutrition and inflammation in cervical cancer

Malnutrition, used to describe a deficiency or imbalance of a wide range of nutrients, resulting in a measurable adverse effect on body composition, function and clinical outcome (Saunders and Trevor, 2010). Inflammation influences both, requirements and intake of food. All cancer patients should be screened properly for the risk or the presence of malnutrition. In all patients with the exception of end of life care energy and substrate requirements should be met by offering in a step-wise manner nutritional interventions from counseling to parenteral nutrition (Arends *et al*., 2017). Various nutritional parameters such as Prognostic Nutritional Indices like serum total protein and serum albumin (Laky *et al*., 2007) and serum ferritin and hematological parameters are a Prognostic Biomarker for cancer associated inflammation (Song *et al*., 2018).

1.5 Malnutrition and cervical cancer

1.5.1 Serum Albumin and Total protein

Worldwide studies show 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 (Beirer, 2021)**.** 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 (Das, 2014). The nutritional status of patients with gynecologic cancer has been evaluated basically by using, either alone or in combination, with several objective anthropometric and biochemical (eg, serum albumin, prealbumin, total protein, hemoglobin, transferin and vitamins) measurements (Laky *et al.*, 2008).

Serum proteins (albumin, transferrin, prealbumin, retinol-binding protein) are perhaps the most widely used laboratory measures of nutritional status (Feldman, 2009). A high total protein level could indicate dehydration or a certain type of cancer, such as multiple myeloma, that causes protein to accumulate abnormally. The normal range of serum total protein defined as 6.0-7.8 g/dL and in most cancer type the level is higher from normal

range. Serum total protein has also been described as an independent prognostic factor of survival in various cancers. The advantage of serum total protein level as a pretreatment prognostic factor in cancer patients is that it is inexpensive, reproducible and powerful (Gupta, 2010).

Albumin is the most abundant protein in human serum. It has been used for as an indicator of malnutrition in patients in clinically stable conditions (Keller, 2019) and (Cabrerizo *et al*., 2015). Serum albumin is closely correlated with degree of malnutrition and is regularly used as simple marker of nutritional status. Normal range of serum albumin is defined as 3.5-5.4 g/ dL and levels <3.5 g/dL is called hypoalbuminemia. There is slight or no hypoalbuminemia in early stages of cancer but as the disease progresses albumin levels drop significantly and serve as good indicators of prognosis of cancer. Hypoalbuminemia is a predictor of poor prognosis in cervical cancer patients. Hypoalbminemia before treatment can lead to poor tolerance to treatment in terms of treatment interruptions and can lead to poor treatment outcome as partial response or disease progression (Bhola, 2020).

Malnutrition and inflammation suppresses the synthesis of serum albumin, which can shows the nutritional status of patients, as well as the severity, progression, and prognosis of a disease. Serum albumin has been shown as an independent predictor of clinical outcomes in different cancers, such as lung cancer, breast cancer, colorectal cancer, ovarian, and cervical cancer (Zhang *et al.*, 2018). There is a clear relationship between serum albumin concentrations and all cause of mortality in elderly subjects. Inflammatory states and in particular, high concentrations of the cytokines IL-6 and TNF-alpha, were the main factors causing low levels of serum albumin. Systemic inflammation not only reduces albumin synthesis but increases its degradation and promotes its transcapillary leakage (Zhang, 2017).

Serum albumin is a surrogate marker of the nutritional sufficiency in an individual. In the Indian cancer patients, socio-economic factors impact both access to cancer care and feasibility of therapy, as patients with insufficient nutrition may have increased treatment related adverse effects and decreased rate of survival (Bharthuar *et al*., 2018*).* Pretreatment serum albumin can be used as a prognostic factor in cervical cancer patients.

Low levels of serum albumin are associated with poor outcome in cancer patients; perhaps serum albumin can be used as an independent indicator of the need for aggressive nutrition intervention *(*Bhola *et al*., 2020*).* Hypoalbuminemia is often observed in patients with advanced cancer and is usually considered to be a marker of malnutrition and cachexia. It has also been reported that albumin is involved in SIR and survival in various types of cancer (Haraga *et al*., 2016).

1.6 Inflammation and cervical cancer

1.6.1 Serum Ferritin

There is increasing documentation that host inflammatory responses play a significant role in the development and progression of cancers. There are some data that cancer is associated 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 (Vitkauskaite *et al*., 2020).

Ferritin is an acute phase protein and is also released from; thus levels are elevated in inflammatory disorders, liver disease, excess alcohol or malignancy (Koperdanova and Cullis, 2015). Serum ferritin mirrors the degree of acute and chronic inflammation in infectious, rheumatologic, hematologic and malignant disease (Kernan *et al.,* 2018). 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 ferritin levels can be high in people who have liver disease or different types of cancer (Debra *et al*., 2020).

Ferritin gene transcription is unregulated in conditions of inflammation where inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukin-2 (IL-2) signal to increase binding of NF-κB to the transcription enhancer FER2 upstream of the IRE and coding region. It has been shown that the NF-κB pathway is extremely responsive to inflammation. Evidence for this pathway stems from activation of toll like receptor 2 (TLR2) in macrophages consequential in IRP-independent up regulation of H-ferritin, as well as direct pharmacological activation of the NF-κB pathway. Similarly, it has been shown that H-ferritin expression is also responsive to tumor necrosis factor alpha (TNF-α), interleukin-2 (IL-2), and IL-10. The elevated existence of ferritin in

serum has long been considered in clinical settings to be an acute phase inflammatory marker, as elevated serum ferritin levels have been associated with increased levels of pro-inflammatory cytokines. Potential sources of serum ferritin during inflammation include secretion by macrophages and/or release from cells due to tissue damage, both indicators of inflammation or infection (Chiou and Connor, 2018).

Several lines of documentation have demonstrated that ferritin is a multi-functional protein with possible roles in proliferation, angiogenesis, immunosuppressant, and iron delivery. In the context of cancer, ferritin is detected at higher levels in the sera (serum) of many cancer patients, and the higher levels correlate with aggressive disease and poor clinical outcome. Furthermore, ferritin is highly expressed in tumor-associated macrophages which have been latterly recognized as having crucial roles in tumor progression and therapy resistance (Alkhateeb and Connor, 2013).

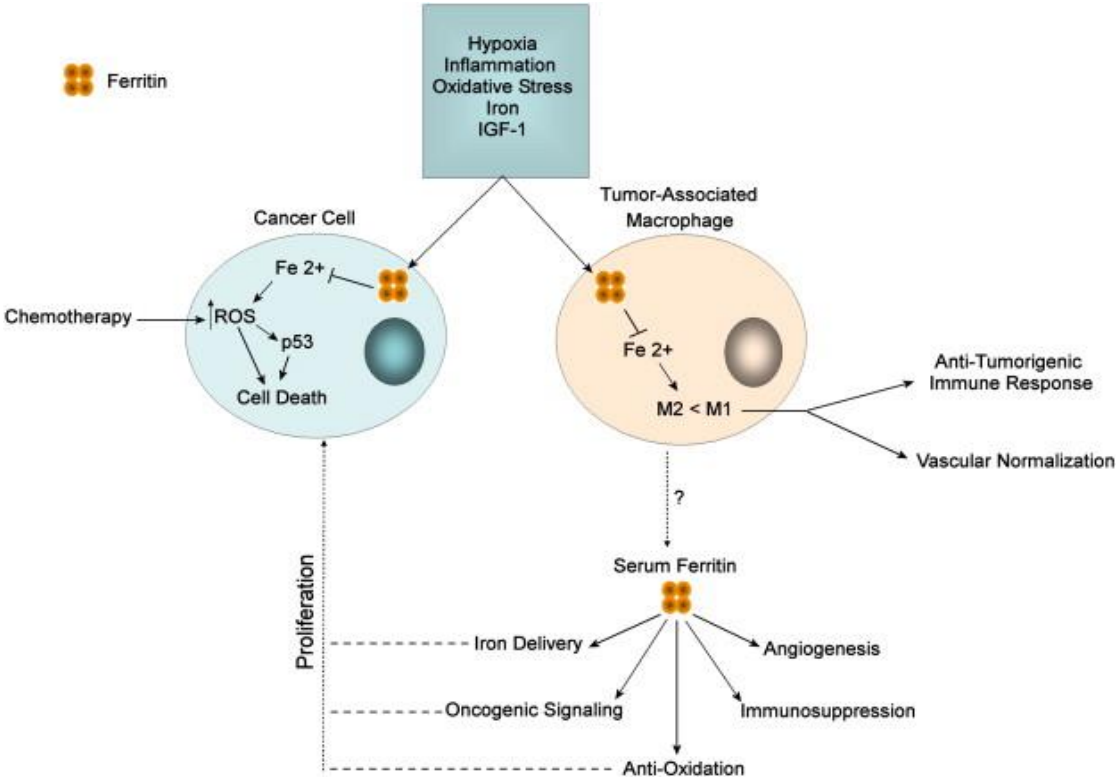

Figure 2: The function and regulation of ferritin in tumors. Ferritin protects cancer cells from the iron-induced generation of reactive oxygen species (ROS) thus increasing their resistance to chemotherapy. In tumor-associated macrophages, ferritin plays a role in maintaining a pro-tumorigenic (M2) program. Aside from its intracellular roles, serum (extracellular ferritin) can stimulate angiogenesis, immunosuppression, and proliferation through various mechanisms (Alkhateeb and Connor, 2013).

1.6.2 Hematological profile

Complete blood count parameters have been present to be diagnostic biomarkers for many cancer related diseases correlated with inflammatory process; complete blood picture is a routine test which is used frequently by clinicians to support the working diagnosis of several diseases. The role of hematological parameters in clinical outcomes has been examined in gynecologic malignancies, such as cervical, ovarian, and endometrial cancer (Gasparyan *et al*. 2011).

Complete blood count such as the platelet- to- lymphocyte ratio (PLR), neutrophil- to-lymphocyte ratio (NLR), lymphocyte to monocyte ratio and RDW has been demonstrated

as significant predictors in cervical cancer as well as other cancers (Yayla *et al.*, 2018). Systemic inflammatory response (SIR) is significantly important prognostic factor for survival in different types of cancer (Absenger *et al*., 2013). Inflammation and cancer show a strong association, and pretreatment levels of inflammatory cells, including neutrophils, lymphocytes and monocytes and platelets are reported as prognostic factors in various cancers (Gong *et al*., 2019).

1.6.2.1 platelet- to- lymphocyte ratio (PLR)

Platelets, as critical sources of cytokines, bind vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and transforming growth factor-β (TGF-β) family of proteins, which enables platelets to act as reservoirs for secreted growth factors that regulate tumor angiogenesis, cell proliferation, migration, and metastasis (Gay *et al.*, 2011). Lymphocytes play critical roles in the host immune response. They can inhibit the proliferative and metastatic ability of cancer cells via inducing cytotoxic cell death and cytokine production (Terzic *et al.*, 2010). Low lymphocyte counts may lead to inadequate immune responses, resulting in poor survival of many cancers. Thus, PLR may represent a balance between the tumor promotion reaction and antitumor immune function (Gay *et al.*, 2011).

1.6.2.2 Neutrophil to lymphocyte ratio (NLR)

Neutrophil is hallmark of acute inflammation and play a pivotal role in chronic inflammatory diseases including cancer. There are some pro-inflammatory factors in the tumor microenvironment reported to extend neutrophil survival time such as the interferon gamma (INFγ), and activate tumor-associated neutrophils in different conditions, which results in anti-tumor and pro-tumor functions of neutrophils (Wu *et al.*, 2019).Tumor-associated neutrophils (TAN) play a major role in cancer biology (Absenger *et al.,* 2013). High concentrations of blood neutrophils are seen in patients with advanced cancer and are associated with poor survival Similarly, there is abundant evidence for an adverse prognostic value of neutrophil to lymphocyte ratio (NLR) on breast cancer (Gago *et al*., 2020).

1.6.2.3 Lymphocytes and Monocytes

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 (Gong *et al*., 2019).

Lymphocytes play critical roles in the host immune response. They can inhibit the proliferative and metastatic ability of cancer cells via inducing cytotoxic cell death and cytokine production. Tumor-infiltrating lymphocytes are involved in several stages of tumor progression. Conversely, low lymphocyte counts may lead to inadequate immune responses, resulting in poor survival of many cancers. Also LMR may represent the balance between antitumor immune reaction and tumor promotion function (MA *et al.,* 2018).

1.6.2.4 Red cell distribution width (RDW)

Red cell distribution width (RDW) is a measure of erythrocyte volume variability, and has also recently has been considered as an indicator of inflammation. Elevated RDW was shown to contribute to cancer progression and prognosis in relation to breast, lung, esophageal, and gastrointestinal tract cancers. In addition to being a routine marker of erythrocyte heterogeneity, RDW is also used for the differential diagnosis of anemia (Huang *et al*., 2016).

Inflammation is a key regulator of cancer initiation and progression. Recently, RDW, which plays a critical role in inflammatory response, has attracted attention because of the connection between inflammation and cancer and RDW increases in malignant tumors Furthermore, higher RDW levels are also significantly associated with advanced stages of cancer and metastasis (Yang *et al*., 2018).

1.6.2.5 Hemoglobin

Nutritional deficiencies can lead to a low red blood cell count, low levels of hemoglobin in these cells, or red blood cells that do not function as they should; Anemia is a term for these issues. Iron-deficiency anemia is the most common type, but low levels of folate or vitamin B-12 can also cause the condition, and a low vitamin C intake can contribute to

it. The role of hemoglobin levels in clinical outcomes has been extensively examined in gynecologic malignancies, such as cervical, ovarian, and endometrial cancer (Gasparyan *et al*. 2011).

Acute and chronic inflammation affect hemoglobin synthesis, Cancer cells that infiltrate the bone marrow can directly suppress hematopoiesis and cause anemia. 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. Cancer patients tend to lose their appetite, leading to nutritional deficiencies. Almost half of the patients diagnosed with gynecologic cancer, have anemia at diagnosis. This interaction leads to the up-regulation of specific inflammatory cytokines such as IL-1, gamma interferon, and tumor necrosis factor alpha (TNF-α), which decrease differentiation of erythroid precursors in the bone marrow, interfere with normal iron utilization, and inhibit normal hypoxia-driven erythropoietin production (Das *et al*., 2014).

1.7 Statement of the problem

Cervical cancer is a public health problem; it is the fourth common cancer accounting for 6.6% of all female cancers. In Ethiopia, cervical cancer is the second most common female cancer with an age-standardized prevalence rate estimated in 2018 of 18.9/100,000 and about 6294 new cases and 4884 deaths estimated annually (Fentie *et al*., 2020).

The prevalence of cervical cancer has dramatically increased worldwide; significant differences in the incidence of cervical cancer among different countries including Ethiopia can be attributed to the following main factors: the existence, Duration and quality of screening programs, and changes in cervical cancer risk factors, particularly those related to sexual behaviors that cause changes in exposure to HPV (Momenimovahed and Salehiniya, 2017). Low level of awareness, lack of effective screening programs, overshadowed by other health priorities (such as AIDS, TB, malaria), low economic status and insufficient attention to women's health are the possible factors for the observed higher incidence rate of cervical cancer in the country (Abate, 2015).

Research indicated that, malnutrition and inflammation is correlated to most cancer types including cervical cancer. Experts agree that the best way forward for cervical cancer is to focus not on treatment but rather on prevention, specifically on nutrition. The numerous beneficial health effects of regulation of Albumin, Total protein and Ferritin and hematological parameters; Hemoglobin, NLR, LMR, RDW and PLR have received significant scientific attention. So, the aim of this study was assessment of malnutrition and inflammatory status in cervical cancer patients.

1.8 Significance of the study

Cervical cancer is second most commonly diagnosed cancer and third leading cause of cancer-related deaths in women worldwide and a great majority of cervical cancer is associated with malnutrition and inflammatory status. As a result, cervical cancers patients are able to consider and advised to start manage nutritional status. Early screening for cervical cancer is a key intervention in reduction of maternal deaths. Hence, this study aimed to assess malnutrition and inflammation status of cervical cancer in patients.

Ferritin, Albumin, Total protein and Hematological parameters; Hemoglobin, NLR, LMR, RDW and PLR may be used as prognostic parameters in patients with cervical cancer. Evaluating and examining serum Ferritin, Total protein and Albumin parameters and hematological profiles like Hemoglobin, NLR, LMR, RDW and PLR, and other associated risk factors in patients with cervical cancer in our setup will significantly be important to help shape clinical as well as public health care of patients and the population. In addition, the result obtained from this study was expected to pave the way for further related studies to be broadly and extensively done.

1.9 Hypothesis of the study

HO: Means of serum Albumin, Total protein and Hematological profile among cervical cancer and control groups are not significantly different.

HA: Means of serum Albumin, Total protein and Hematological profile among cervical cancer and control groups are significantly different.

2 Objectives

2.1 General Objective

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

2.2 Specific objectives

- To determine and compare the serum level of Ferritin, Albumin, Total Protein and Hematological parameters (Hemoglobin, Red cell distribution width (RDW), lymphocyte to Monocyte ratio (LMR), Neutrophil to Lymphocyte (NLR) and Platelet to Lymphocyte (PLR)) among Cervical Cancer and healthy control groups.
- To assess the prognostic significance of Albumin, Ferritin and Hematological (Hemoglobin, RDW, LMR, NLR and PLR) parameter in Cervical Cancer.
- To assess serum Albumin, Total protein and Hemoglobin as nutritional status and ferritin, RDW, LMR, NLR and PLR as an inflammatory status of Cervical Cancer.
- To correlate the level of serum Albumin, Ferritin, Total Protein, Hemoglobin, RDW, LMR, NLR and PLR with the stage of the cancer.

3 Methods and materials

3.1 Study Area

The study was conducted at cancer Center of Tikur Anbessa Specialized Hospital (TASH). TASH is a large referral teaching hospital, under the administration of Addis Ababa University, located in Lideta Sub City in Addis Ababa, Ethiopia. This referral hospital is the main teaching hospital for both clinical and preclinical training of health and health related disciplines. In TASH there are different clinics that provide specialized service for patients. Among these cancer center is the one which provide specialized service for patients with different type of cancer.

3.2 Study design and period

Hospital based Comparative cross sectional study was conducted from November 2020 – June 2021.

3.3 Source population

The source population for this study was cervical cancer patients attending at Tikur Anbessa Specialized Hospital and healthy control group attending Nefas Silk lafto sub-city health center.

3.4 Study population

The study population consisted of 50 cervical cancer patients attending at cancer center of Tikur Anbessa Specialized Hospital in the time interval of the study period with age matched 50 healthy individuals as controls. Hence a total 100 study populations was participated in the study.

3.5 Sample Size determination and Sampling Technique

A consecutive sampling technique was used until the required sample size was achieved. The sample size was determined by using the G* Power software statistical power analyses for Windows (version 3.1.2.9) with the following assumption: power (1-β error probability) is 95%, 80% of effect size, two tail, 1:1 ratio, and the critical value ($Z\ \alpha/2$) at 95% ($\alpha = 0.05$). The minimum sample size computed based on the above assumption was

84. However, to increase the validity of our data we deliberately increased 16 cervical cancer patient and control group (19 % from the original sample size) and the total sample size became 100. Therefore, in this study total of 100 study group were enrolled (50 cervical cancer patents and 50 control group).

3.5 Study variables

3.5.1 Dependent Variable

- Serum Ferritin
- Serum Albumin
- Serum Total protein
- Hematological profile (Hemoglobin, LMR, PLR, RDW and NLR)

3.5.2 Independent variables

- Socio-demographic characteristics
- Duration of the disease
- Stages of cervical cancer
- Anthropometric indicators
- Appetites
- Patients before and after Surgery

3.6 Inclusion and exclusion criteria

3.6.1. Inclusion criteria

All cervical cancer patients attending at cancer center of Tikur Anbessa Specialized Hospital during data Collection period were included in the study.

3.6.2 Exclusion criteria

- Patients with mental health problems, hearing impairments and those patients who will not able to provide the appropriate information were excluded.
- Pregnant women
- HIV and Tuberculosis patients
- Patient on treatments (chemo-therapy, radiation etc.)

3.7 Data Collection and Measurement

3.7.1 Data collection procedures

Each cervical cancer patients who visited Tikur Anbessa Specialized Hospital of cancer center during the study period with age and sex matched with healthy individuals as controls are selected from Nefas Silk lafto sub-city health center was evaluated for eligibility criteria to be included in the study. The selections of patients were continuing until the required number of patients was fulfilled. The data was collected mainly by questionnaire, anthropometric and blood collection.

3.7.2 Questionnaire

Standardized semi-structured questionnaire which is assumed in such a way that it can meet the objectives of this study was used during face-to-face interview and review of documented medical records for duration and stages with cervical cancer. Socio demographic variables (age, residence…etc), appetite, kind of food they eat …etc were collected using face to face interview questions. Variables including duration of time and stages of cervical cancer were collected from patients' medical records.

3.7.3 Anthropometric measurement

Physical measurements like weight and height taken using standardized methods and adjusted equipment. Weight was measured in kilogram and height was measured in centimeter with Stadiometer to determine the Body Mass Index (BMI) was calculated from the body weight (kg) and height (meter) as follows:- BMI = Weight (in kg) / (Height in m) ^{2}.

Based on the National Institutes of Health Guidelines on overweight and obesity (Janssen and Ross, 2002), Subjects with BMI below 18.5 kg/m2 are classified as underweight, BMIs from 18.5 kg/m2 to 25 kg/m2 are classified as normal, BMIs from 25.0 to 30 kg/m2 are classified as overweight, and BMIs at or above 30.0 kg/m2 are considered obese (Ali and Lindström, 2005).

3.8 Biochemical/ Laboratory tests

Five milliliter (5mL) of blood sample was collected; the process of blood sample collection was through aseptic/sterile technique. About 2mL of the blood was collected in EDTA coated tubes for CBC analysis. Other 3mL 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 HuMax14k centrifuge to extract the serum. Then the serum was transferred from SST tube into Nunc tube and stored at -20^{o}c in the refrigerator. The serum extracted was then used to determine the levels of serum Ferritin level, Albumin and Total protein.

3.8.1 Test Principles of the Laboratory Analysis

3.8.1.1Determination of Serum ferritin Level

Test Principle:

When an antigen – antibody reaction occurs between ferritin in a sample and an anti-ferritin antibody which has been sensitized to latex particle agglutination occurs. This agglutination is measured spectrophotometrically at wavelength of 450 nm and detected as an absorbance with the magnitude of the change being proportional to the quantity of ferritin in the sample. The actual concentration is then determined by Extrapolation from a calibration ferritin curve at 170mM.

3.8.1.2. Determination of Serum albumin Level

Test Principle:

The method is based on the specific binding of bromocresol green (BCG) an anionic dye and the protein at acidic pH with resulting shift in the absorption wavelength of the complex. The intensity of the color formed is proportional to the concentration of albumin in the sample and the absorbance of the samples was measured at 630 nm

$$\text{BCG} + \text{Albumin} \longrightarrow \text{BCG} - \text{albumin complex}$$

3.8.1.3 Determination of total protein

Test principle

Total protein was determined by using an Automated COBAS 6000 Measurement was performed by a Biuret reaction using a total protein reagent kit. A protein in the sample was combined with the reagent producing alkaline copper-protein chelate. The rate of change in absorbance is monitored by a detector at 545 nm. The observed rate of chelate formation is directly proportional to the total protein concentration in the sample.

Table 1: Reference Values for serum ferritin, albumin and total protein (Ethiopian public health institute).

Parameters	Reference range	Units
Serum ferritin	30-200	ng/ml
Serum albumin	3.5-5.4	g/dl
Serum total protein	6.0-7.8	g/dl

3.8.1.4 Determination of hematological Parameters (CBC)

The analysis was performed by using automated hematology analyzer (Sysmex KX-21N, USA) using EDTA anti coagulated fresh venous blood sample (Sysmex, 2000). Principally sysmex analyzer is based on the electronic resistance (impedance) detection method for counting and sizing recognition of the leukocytes, erythrocyte, and platelet using three hydraulic systems and displays the results on the liquid crystal displayer (LCD) and will be printed out the results in thermal paper.

Table 2: Reference Values for hematological profile (TASH diagnostic laboratory)

Parameters	Reference range	Units
HGB	12.5-16.3 $x10^6$	µl
RDW	12.1-14.2	%

3.9 Data quality control and management

The data quality assessment was started with socio-demographic data collection and has gone through blood sample collection, laboratory test and final data entry and statistical analysis. The blood sample was taken under aseptic techniques with standard operational procedure. In order to maintain the quality of laboratory result every laboratory procedure

following standard operating procedure (SOP) and quality control (QC) were performed to check the performance of chemistry and hematological analyzer by running quality control materials daily before analysis of the samples and analysis of specimen has been carried out in Ethiopian public health institute (EPHI) and TASH diagnostic laboratory. Great attention in data insertion to software on computer was sought. The complete result was rechecked repeatedly to maintain the overall quality of data.

3.10 Data processing and analysis

After checking for completeness and cleaning, processing and analysis of the data obtained from laboratory analyses of the blood samples and questionnaires was performed by coding and entering the data into SPSS software version 25 package and the different variables were tested and analyzed. Simple descriptive statistics was used to present the socio demographic and clinical characteristics of the study subjects. 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.

3.11 Ethical Consideration

The study was conducted after the proposal was evaluated and approved by Department of Biochemistry Research and Ethical Review Committee of the Department of Biochemistry, School of Medicine, and College of Health Sciences and formal written institutional ethical authorization letter with protocol number: M.Sc. 01/21 was issued. Data was collected after obtaining informed consent and agreement from the patients under study.

4 Results

4.1 Sociodemographic characteristics

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 and above. Most of the control groups were came from urban residence 34 (68%), 16 (32%) from rural residence. 47 (94%) of the control-participle were married and 3 (6%) single. 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 3)

Table: 3 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)

In addition 42 (82%) of the cervical cancer patients don't drink alcohol, 8 (16%) of them were non habitual drinker. Out of the 50 cervical cancer patient 17 (34%) of them had meal 2 times a day, 30 (60%) 3 times a day and 3 (6%) 4 times a day. Also 44 (88%) 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%) between18.5 and 25 (ideal weight).

Among the control group 41 (82%) of them 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%) eat 2 times a day,43 (86%) eat 3 times a day and 4 (8%) eat 4 times a day. 45 (90%) of them prefer to eat teff and 5 (10%) prefer to eat wheat. In the case of BMI of control group 5 (6%) of them were less than 18.5 (underweight), 45 (90%) between18.5 and 25 (ideal weight) (Table 4). 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.

Table 4: Socio- demographic and anthropometric characteristics of the study groups

Variable		Patients N (%)	Control N (%)
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)
What kind of food you 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)

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 3). Duration of time with cervical cancer, less than 1 year (42%), 1-2 years (44%) and more than 2 years (14%) (Figure 4).

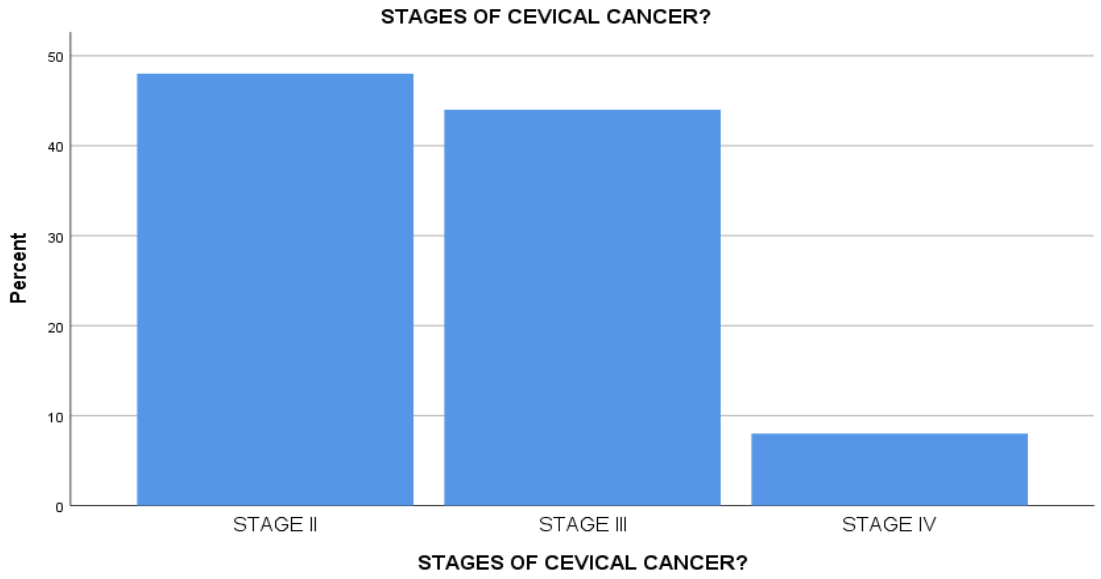

Figure 3: Proportion of cervical cancer patients' by stages

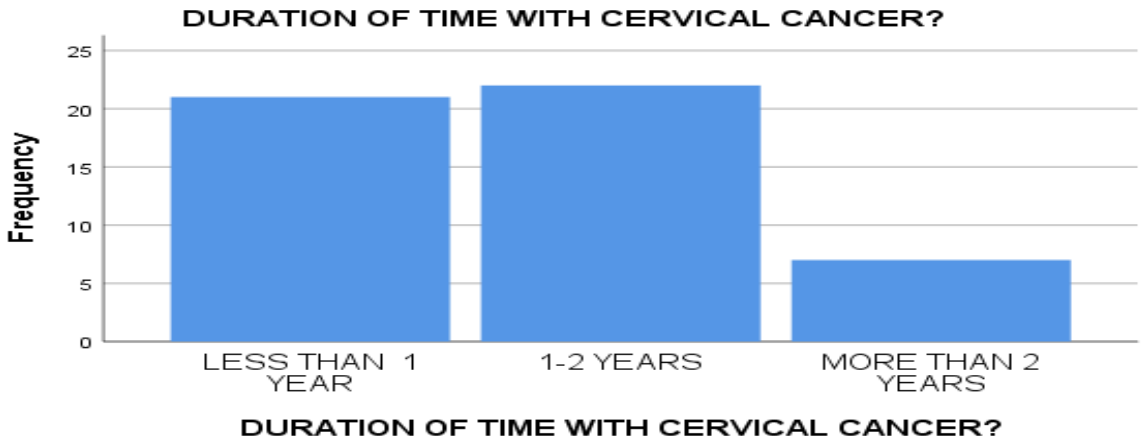

Figure 4: Duration of time with cervical cancer of patients.

4.2 Biochemical tests

Assessment of malnutrition among the cervical cancer patients and control groups was assessed using anthropometric measurement and biochemical tests using standard kits. The age group ranged between 32 and 72 years. There was a good matching with regards to age between the cervical cancer patients and control group. There was no statistically significant difference between the mean ages of patient and the control groups.

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 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 5).

Table 5 : 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*
*P value < 0.05 is statistically significant			

4.3 Hematological parameters

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 also 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 6).

Table 6 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 106 /µ	13.24 ± 3.24	14.95± 4.95	0.158
RDW %	15.71 ± 3.43	11.25 ±1.73	0.000*
NLR	2.338 ± 0.642	1.476 ± 0.605	0.000*
PLR	60.538±13.955	45.018±6.095	0.001*
LMR	3.001±0.326	3.435±0.428	0.006
*P value < 0.05 is statistically significant			

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 7).

Table 7: 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	0.100
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

*P value < 0.05 is statistically significant

As shown in Table 8 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 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: 8 Pearson correlation co-efficient between anthropometric and biochemical indices for cervical cancer patient and control groups.

			Age	BMI kg/m^2	Ferritin ng/ml	NLR	PLR	LMR	RDW %	TP g/dl	Hgb %
Alb g/dl	Cervical cancer (n=50)	R	0.167	0.66	-0.120*	-0.109	-0.116	0.103	-0.018*	0.119	0.078
		P	0.098	0.648	0.002	0.449	0.421	0.475	0.001	0.410	0.593
	Control group (n=50)	R	0.267	0.051	0.009	0.102	0.086	0.006	0.049	0.943*	0.034
		P	0.061	0.725	0.951	0.483	0.551	0.965	0.737	0.001	0.814

* Correlation is significant at the 0.005 level (2-tailed).TP; total protein, Alb; Albumin, BMI; body mass index, Hgb; hemoglobin, NLR; Neutrophil to lymphocyte Ratio, PLR; Platelet to lymphocyte ratio, LMR; lymphocyte to monocyte ratio.

			Age	Alb g/dl	BMI	Ferritin ng/ml	TOL G/dl	PLR	LMR	RDW %	Hgb %
NLR	Cervical cancer (n=50)	R	0.208	-0.109	0.141	-0126	0.030	0.764**	-0.105	1.000**	-0.166
		P	0.129	0.449	0.329	0.382	0.834	0.000	0.467	0.000	0.250
	Control group (n=50)	R	0.096	0.102	-1.62	-0.178	0.036	0.211	0.026	0.068	0.045
		P	0.508	0.483	0.260	0.217	0.805	0.140	0.852	0.640	0.755

** Correlation is significant at the 0.001 level (2-tailed),*.TP; Total protein; ALB; Albumin, BMI; body mass index, Hgb; hemoglobin, NLR; Neutrophil to lymphocyte ratio, PLR; Platelet to lymphocyte ratio. LMR; lymphocyte to monocyte ratio.

5 Discussions

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 (Ahmed *et al*., 2015). 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% (Sibhat *et al*., 2019).

Studies have indicated that approximately 88.33% of gynecological cancer patients experience malnutrition (Das, 2014). Different factors including, Total protein, Albumin and Hemoglobin are used to evaluate the nutritional status in patients with gynecological cancer (Zhang *et a*l., 2018). There is increasing documentation 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 influences the host immune response to tumors (Vitkauskaite *et al*., 2020).

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 (Hailu *et al*., 2020). 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 (Islam *et al*., 2018). Pervious study showed that alcohol drinker and smoker are well malnourished and increased risk for inflammation and cancer (Meadows and Zhang, 2015); 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 (Ali and Lindström, 2005).

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 to 5.4 g/dL) similar to other findings (Haraga *et al.,* 2016; Bhola *et al*., 2020) the reduction in serum albumin concentration could be because of the host body experience inflammation based cancer there is state of high physiological stress, with tumor hypoxia/necrosis and local tissue damage. 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 C- reactive protein (CRP), and decrease the production of albumin. Our study also supported by Nazha *et al*. (2015) this response is often accompanied by a nutritional and functional decline of patients, especially among those with advanced cancer. Similar to several other reports Kowalski *et al*. (2012) and Roche *et al*. (2008), 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. It is known that the serum albumin concentration may change under oxidative stress, such as the stress associated with cancer. According to, Nazha *et al*. (2015) 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. 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 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 Perlstein, (2009) malnutrition is another hallmark of cancer because of reduction in appetite and weight which consequently contribute to the increase in RDW. 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 (Wang *et al*., 2019).

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 to 7.8 d/gL) and this result is supported by Dhakar et *al.,* (2002), Gao *et al*. (2005) and Sabine *et al*., (2002), 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. It could be also due to chronic (long-term) inflammation or inflammatory disorders (Kuraishy *et al*. 2011)**;** 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 Jain *et al*. (2011) and Kibrom *et al*. (2020). Lymphocytes produce globulins to the levels that are high enough to compensate for the lowered albumin levels in the serum.

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 was high in people who have cancer, such as cervical cancer this study supported by (Alkhateeb and Connor, 2013). 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 Kell *et al*. (2014) serum ferritin levels can be raised significantly in response to inflammation serum ferritin actually originates from damaged cells (and thus reflects cellular damage), that it contains some iron but has lost or liberated most of its normal content, and that since 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 (Wang *et al*., 2010). The cancer-associated elevation in serum ferritin is most likely induced by an inflammatory state and according

to Song *et al*., (2018) 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. 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 (Kernan *et al*., 2019).

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 (Sherwood and Toliver-Kinsky, 2004).

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 (Das *et al.*, 2014). 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 (Rodgers *et al*., 2014 and Panesar, 2013). 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 (Panesar, 2013). 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 (Rodgers *et al*., 2014).

The mean value of RDW significantly increases in cervical cancer compared to the control groups similar to other finding Yang *et al*., (2018). 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 Zheng and Guo, 2019 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. Elevated RDW level may reflect the presence of immature red blood cell. This is also supported by (Pietrangelo and Trautwein, 2004) that say various cytokines affect erythropoiesis via erythropoietin (EPO) production, inhibition of erythroid progenitors, and reduction in iron release. 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 Wang et al., (2019); the deficiency of various minerals and vitamins such as iron, folate and vitamin B12, also low albumin level is associated with increases RDW.

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) (Bazzi *et al*., 2016).

The mean value of NLR and PLR significantly increase in cervical cancer compared to the control groups, the present study was in line with Zhu *et al*. (2018) and Proctor *et al*. (2012) that indicated both increased NLR and PLR are predictive biomarker for the presence of cervical cancer. A strong relationship between NLR and inflammation has been reported in previous studies (zhu *et al*. (2018) the issue of inflammation has received considerable critical attention in not only initiation and promotion but also in the progression, invasion, and metastasis of a tumor. 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 also this study supported by Proctor *et al*. (2012), 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 (Tas *et al*., 2019). NLR positively correlated with PLR and RDW in the cervical cancer patients. Variety of inflammation factor during the onset of cancer, also with respect to malnutrition, patients with malignant tumors often have malnutrition, gastrointestinal dysfunction and impaired immune function (Qin *et al*., 2017).

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 Stotz *et al*., 2019; Zheng *et al*., 2014) decreased lymphocyte numbers are therefore considered to be responsible for an insufficient immunologic reaction to the tumor, thus promoting tumor progression and metastasis. 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. In such a mechanism, LMR is believed to reflect the host immune status and the degree of tumor progression. The decrease level of LMR associated with inflammation and cancer; study by Hu *et al*., (2014) shows Solid tumors are generally infiltrated with leukocyte subsets, among which monocytes and lymphocytes play major roles in the inflammatory response. 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 showed that Bishara *et al.,* (2008) 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.

Maximum number of severe malnutrition cases had advanced stages of cancer (stage III/IV), which of course is expected (Laky *et al*., 2007). 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 (Ono, 2020).

Approximately 88.33% of all cancer patients will practice malnutrition at some stage during the clinical course of their disease (Das, 2014). 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 Irungu *et al*. (2015), 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.

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 (Busti *et al*., 2018). 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 in stage cervical cancer patients. Decreased lymphocytes and the increased Monocyte stage of cancer in the blood and in the tumor stroma are significantly related to tumor growth and lymph node metastasis in cervical cancer (Shen e*t al.*, 2015).

Increased RDW, NLR and PLR have been shown to be associated with stage, invasiveness, prognosis of characteristics of different cancer type Kose *et al*. (2015) and Zhu *et al*; (2018). In the present study there is significant increase in NLR, RDW and PLR from cervical cancer stage II to stage IV. Similarly 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 Wang *et al*., (2019) 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.

6 Conclusions

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 has 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 indicate of the malnutrition because of the deficiency of various minerals and vitamins also the 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 indicating 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 show 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 indicate the malnutrition status and the high serum Ferritin, RDW, LMR, NLR and PLR are indicant 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.

7 Strength and limitations of the study

7.1 Strength of the present study

- It will give strength to focus on the assessment of malnutrition and inflammation status among cervical cancer patients to be manageable by determine the level of serum albumin, total protein, ferritin and hematological parameters at early stage.
- As strength, the data collection period was overlapped with the outbreak of COVID-19 pandemic; the data were collected through questionnaires filed by face-to-face interview. And analyzed by SPSS version 25 model to gather biochemical and hematological data.

7.2 The limitations in the present 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).

8 Recommendations

Health institutions and researcher should plan further study with large sample size to investigate on malnutrition and inflammation on cervical cancer. It will be appropriate to asses' ferritin, total protein albumin and hematological indices. A proper awareness and health education needs to be given to cervical cancer patients about malnutrition and inflammation status and cancer patients should be screened for malnutrition at frequent intervals and managed accordingly.

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9 References

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10 Annex One: Information sheet

10.1 Subject Information sheet (English version):

Principal Investigator**: _____Name_____**

Addis Ababa University

College of health Science

Department of Medical Biochemistry

Dear participant! Here, I the undersigned, at Addis Ababa University College of Health Science, Department of medical biochemistry. Currently I will be undertaking research on a topic entitled as ASSESSMENT OF MALNUTRITION AND INFLAMMATORY STATUS OF DIFFERENT STAGES OF CERVICAL CANCER patients who are attending cancer center of TikurAnbesa Specialized Hospital. For this study, you will be selected as a participant and before getting your consent, you need to know all necessary information related to the study which will be detailed as follows.

Introduction

Privacy is the state of being free from intrusion, and in the context of health care it concerns the responsibility of a care provider to protect a clients from any disclosure (i.e., discovery by others), even unintentional, of personal health data, by providing security to the patient and the patient's records. Confidentiality, in contrast, is the limiting of information to only those for whom it is appropriate. Therefore this information sheet briefly provides the necessary guide to be considered during the study.

Objective the main aim of this study is to assess serum level of ferritin, albumin and hematological Parameters at different period of cervical cancer patients who are attending cancer center of TikurAnbesa Specialized Hospital during the study period.

Participants to be included: all cervical cancer patients who are cervical cancer patients who are not starting therapy.

Risks and discomfort: Participant in this project will not cause more discomfort and no need of extra sample other than sample taken for diagnostic purpose. The amount of blood taken from each volunteer throughout the study period is 5ml which will not affect your health. There is no major risk in participating in this research, as the whole procedure is carried out by physician and /or health professionals following the standard good clinical practice.

Benefits:-There is no immediate benefit in participating in this study. However you will have the chance to know your serum level of ferritin, albumin and hematological parameter from the laboratory result. And if your result reveals any incidental health problems that need immediate treatment, you will be referred to an appropriate health facility. In addition your participation will contribute in improving the health delivery system for cervical cancer patients.

Incentive:-There is no financial or material incentive in participating in this study.

Confidentiality: The information that we will collect from this research project will be kept confidential. Information about you that will be collected from the study will be stored in a file, which will not have your name on it, but a code number assigned to it. Which number belongs to which name will be kept under lock and key, and it will not be revealed to anyone except the principal investigator**.**

Participant Rights

Your participation is entirely voluntary and up to you to decide. Also you have the right not to answer any questions you do not want to. If in the middle you decide to stop filling questions and no longer participate, you can stop without worry.

Persons to contact:

If you have any question, you can ask at any time. If you have additional questions about the study, you can contact the:

Principal investigator: Thank you for your cooperation.

If you are voluntary to participate in the study we kindly request you to provide your response for the questionnaire in the next page.

10.2 Subject Information sheet (Amharic version):

የተሳታፊዎች የፈቃደኝነትና መተማመኛ መረጃ መስጫ ቅፅ

የተሳታፊ ስም _____

በአዲስ አበባ ዩኒቨርሲቲ

የጤና ሳይንስ ኮሌጅ የሕክምና

ባዮኬሚስትሪ ትምሕርት ክፍል፡

እኔ እፀገነትአሰፋ አዲስ አበባ ዩኒቨርሲቲ ጤና ሳይንስ ኮሌጅ የህክምና ባዮኬሚስትሪ የድህረ ምረቃ ተማሪ ስሆን የመመረቂ ያጽሁፌን በጥቁር አንበሳ ስፔሻላይዝድ ሆስፒታል የማኅጸን ጫፍ ካንሰር ህሙማን ክትትል ክፍል ውስጥ ASSESSMENT OF MALNUTRITION AND INFLAMMATORY STATUS OF DIFFERENT STAGES OF CERVICAL CANCER በሚል ርእስ በመስራት ላይ ነኝ፡፡ለዚህ ጥናት ደግሞ እርስዎ የተመረጡ ስለሆነ ክዚህ ቀጥሎ የሚገኝዉነ መረጃ አንብበዉ በጥናቱ ላይ መስማማትዎን ወይም አለመስማማትዎን እንዲያረጋግጡ በትህትና እጠይቃለሁ፡፡

<u>መግቢያ</u>፡- ጥናቱ ከእርሶ የሚወስዳቸዉ ማንኛዉም መረጃወች ሚስጥራዊነት ሙሉበሙሉ የተጠበቀ ሲሆን እርሶ በጥናቱ አለመሳተፍም ሆነ በማንኛዉም ሰአት ተሳትፎዎን ማቋረጥ ይችላሉ፡፡

<u>የጥናቱአላማ</u>፡-የትናቱ ዋና አላማ በጥቁር አንብሳ ስፔሻላይዝድ ሆስፒታል በማኅጸን ጫፍ ካንሰር ህሙማን የ ferritin, albumin and hematological Parameters በደም ወይም ሴረም ውስጥ ያለውን መጠን መለካት እና ማወዳደር ነዉ፡፡የጥናቱ ዉጤት ለማኅጸን ጫፍ ካንሰር ህሙማን ጤና እንክብካቤ የሚጠቅም ሲሆን ከዚህም በተጨማሪ እርስዎም ከላይ የተጠቀሱት ንነገሮች እንዲያውቁ ይረዳዎታል፡፡በጥናቱ ላይ የሚያደርጉት ተሳትፎ ሙሉበሙሉ በእርሶ በጎ ፈቃደኝነት ላይ የተመሰረተ ነዉ፡፡

የጥናቱ ተሳፍ:- በማኅጸን ጫፍ ካንሰር ህሙማን እና ህክምና ያልጀመሩ

አደጋ እና አለመመቸት፡- ፕሮጀክቱ ለምርመራ ዓላማ ከተወሰደ ናሙና በስተቀር የበለጠ እና ተጨማሪ ናሙና አያስፈልገውም ።በጥናቱ ወቅት ከእያንዳንዱ ፈቃደኛ ሰው የሚወሰደው የደም መጠን 5 ሚሊ ነው ይህም በጤንነትዎ ላይ ተጽዕኖ አያሳድርም አጠቃላይ ሂደቱ የሚከናወነው መደበኛ የጥሩ ክሊኒኩን በመከተል በሐኪም ወይም በጤና ባለሙያ ስለሆነ በዚህ ጥናት ውስጥ ለመሳተፍ ትልቅ አደጋ የለውም ።

ጥቅማጥቅም፡- በጥናቱ ውስጥ ለመሳተፍ አስገደጀ ሁኔታ የለም ፣ ሆኖም የላቦራቶሪ ውጤቱን የፌሪቲን አልበሚን እና የደም ህመም መለኪያዎን የማወቅ እድል ይኖርዎታል ። እናም ውጤቱ አስቸኳይ ህክምና የሚያስፈልገው ድንገተኛ የጤና ችግር ካለ ወደ እርስዎ ይላካል

ማበርታቻ:- በጥናቱ ውስጥ ለመሳተፍ የገንዘብ ወይም ቁሳዊ ማበረታቻ የለም

ሚስጥራዊነት:- ከዚህ የምርምር ፕሮጀክት የምንሰበስበው መረጃ በሚስጥር ይቀመጣል ከእርሶው የሚሰበሰበው መረጃ በስምህ ላይ በማይገኝበት ፋይል ውስጥ በተመደበው ፋይል ውስጥ ይቀመጣል ።

የተሳፍዎች መበት፡- ማንኛውም ጥያቄ ካለ በማንኛውም ጊዜ መጠየቅ ይችላሉ ። ስለ ጥናቱ ተጨማሪ ጥያቄዎች ካሉዎት ማነጋገር ይችላሉ ።

በጥናቱ ለመሳተፍ ፈቃደኛ ከሆኑ እባክዎ ከዚህ ቀጥሎ ባለዉ የስምምነት ቅጽ ላይ በመፈረም ይተባበሩ።።

በጥናቱ ለመሳተፍ ፈቃደኛ ከሆኑ በሚቀጥለው ገጽ ላይ ለጥያቄው መልስዎን እንዲሰጡ በትህትና እንጠይቃለን ።

እናመሰግናለን!!!

11 Annex Two. Informed Consent form

11.1 Informed Consent form (English Version)

Participant Code _____

In undersigning this document, I am giving my consent to participate in the study entitled as Assignment of ferritin, albumin and hematological parameters among women with cervical cancer at Tikur Anbessa Specialized Hospital. I have been informed that the purpose of this study is to assess serum level of ferritin, albumin and haematological parameter and associated risk factors at different period of cervical cancer patients who are attending cancer center of TikurAnbesa Specialized Hospital Addis Ababa, Ethiopia, I have understood that participation in this study is entirely voluntarily. I have been told that my answers to the questions will not be given to anyone else and no reports of this study ever identify me in any way. I have also been informed that my participation or

non-participation or my refusal to answer questions will have no effect on me. I understood that participation in this study does not involve risks. I understood that is the contact person if I have questions about the study or about my rights as a study participant.

Respondent‘s signature_____ Date _____

Investigator signature_____ Date _____

11.2 Informed consent form (Amharic Version)

የተሰታፍው መለያ ቀጥር :_____

የፈቃደኝነት ማረጋገጫ ቅጽ

የምርምር ጥናቱ ክፍል የሆኑ መረጃዎችና ሂደቶች ከተብራሩልኝ በኋላ ASSESSMENT OF MALNUTRITION AND INFLAMMATORY STATUS OF DIFFERENT STAGES OF CERVICAL CANCER በሚል ርዕስ የማኅጸን ጫፍ ካንሰር ህሙማን የተመጣጠነ ምግብ እጥረትን እና የቁስለት እብጠት ሁኔታን በሚያባቡሱ ንጥረነገሮች እና ተዛማጅነት ያላቸው ንጉዳዮች ለማጥናት በተዘጋጀው ጥናታዊ ፅሁፍ ለመሳተፍ ሙሉ ፈቃደኝነቴን አሳይቻለሁ።እኔም በተብራራልኝ መንገድ ተረድቻለሁ።ምርምሩ ምንም የተለየየ ገንዘብ ጥቅማጥቅም የሌለው፣አደጋ የማያስከትል መሆኑን እንዲሁም የሚደርገው ተሳትፎ እና መረጃ በሚስጢር

የሚያዝና ለማንም ተላልፎ የማይሰጥ መሆኑን ተረድቻለሁ።ስለዚህ በዚህ የምርምር ጥናት ላይ ለመሳተፍ ፈቃደኛ መሆኔን በፊርማዬ አረጋግጣለሁ።

የመረጃ ሰብሳቢው ስም----------

የተሳታፊው ስም----------

ፊርማ ----------

ቀን ----------

12 AnnexThree: Questionnaire

Dear respondents, given below are the items specifying necessary information expected from you. The questionnaire is a part of the study for the masters of degree at Addis Ababa university school of graduate studies. The objective of the research is to assess the level of serum ferritin, albumin and hematological parameter of cervical cancer patients. This study is purely academic and all your responses will be used in strict confidentiality

in accomplishing the requirements of the study. Your genuine answer for the questions in the questionnaire has an immense value to the completion of the study.

12.1 Part 1: questioner in English

Personal information: please make a circle" on the options that best describes you.

Name or Code; …….

1. Age in year: _____

2 .Height_____ weight _____ BMI_____

3. From which residence you came?

A. Urban B. Rural

4. What is your marital status?

A. Single B. Married C. Divorced D. Widowed

5. Educational Level: A) illiterate B) up to high school C) diploma and above

6. Occupation: _____

8. Alcohol consumption:

A. Non-drinker B .non-habitual C. habitual drinker

9. Smoking status:

A) Currently smoker, B) quitted smoking, C) never smoking D) missing information

Part 2 Health information: please make a circle" on the options that you choose

1. Duration of time with the disease (cervical cancer)?

A. Less than 1 year B. 1-2 years C. More than 2 years

2. Stage of cervical cancer?

A. stage I B. stage II C. stage III D. stages VI

3. Are you taking any vitamin or mineral supplements?

What and how often? _____

8 How many times a day does you eat?

A 2x b 3x c 4x

9

Weight_____ (kg) and

Height_____ (meter)

BMI = Weight (in kg) / (Height in m) ^{2}.

A Less than 18,5 (Underweight) B 18,5-25 (Ideal weight) C 25-30 (Overweight)

D 30-35 (Moderate obesity) E 35-40 (Obesity) F More than 40 (Morbidly obese)

Parameters
Hmoglobin 10^6 /µ
RDW %
LYMPHOCYTES %

MONOCYTES %
NEUTROPHILS %
PLATELET /µL
NLR
PLR
LMR

12.2 Part II: - Questionnaire in Amharic

ለክቡራን ተሳታፊዎች ከዚህ በታች የተዘረዘሩት ጥያቄዎች ከእናንተ የሚፈለጉ ናቸው።ጥያቄው በአዲስ አበባ ዩኒቨርስቲ ለድህረ ምረቃ ጥናት የሚያስፈልጉ ናቸው።የዚህ ጥናት አላማ የማኅጸን ጫፍ ካንሰር ህሙማ ሆነው የተመጣጠነ ምግብ እጥረትን እና የቁስለት እብጠት ሁኔታን

በሚያባቡሱ ንጥረነገሮች ሁኔታ ማጥናት ነው።የእናንተ መልስ መስጠት ለዚህ ጥናት አላማ ዕውን መሆን አስፈላጊ ነው።ለትብብርዎ እናመሰግናለን!!!

ክፍልአንድ

ግላዊመረጃ፡- ከዚህ በታች እርስዎን በትክክል የሚገልጽዎትን ክብ ያድር

ሚስጥራዊ ቁጥር፡- .....

ዕድሜ በዓመት _____

አድራሻ፡ ---

የትምህርት ደረጃ:

ሀ. የቀለምት/ትያልተማሩ ለ. እስከመሰናዶ የተማሩ ሐ. ዲፕሎምና ከዛበላይ የተማሩ

ጋብቻ ሁኔታ

ሀ ያላገባች ለ የተፋታች ሐ ያገባች

ቋሚ የመኖሪያ ቦታ

ሀ ክፍለሀገር ለ ከተማ

የመጠጥ ሁኔታ፡-

ሀ. እጠጣለሁለ. ለ. አልጠጣም ሐ. አልፎ አልፎ

የማጨስ ሁኔታ

ሀ. በጭራሽአላጨስም ለ. አሁን አቁሜያለሁ ሐ. አልፎ አልፎ

ክፍል ሁለት

የጤና መረጃ፡- ከዚህ በታች እርስዎን በትክክል በሚገልፅ ላይ ክብ ያድርጉ

በማጎጸን ጫፍ ካንሰር በሽታ ጋር የቆዩበት ግዜ

ሀ. ከ 1 አመት ላነሰ ግዜ ለ. 1-2 አመት ሐ. ከ 2 አመት በላይ

የማጎጸን ጫፍ ካንሰ ደረጃው

ሀ. ደረጃ 1 ለ. ደረጃ 2 ሐ. ደረጃ 3 መ.ደረጃ 4

ተጨማሪየ ቨይታሚንና ሚንራል ንጥረነገር ይወስዳ

ምን _____ ለምን ያህል ጊዜነው _____

ቁመት (በሜትር) ..... ክብደት በኪሎ ግራም..... የሰውነት ክብደት ልኬት (ኪ.ግ./ሜ2).....

በደም ወይም ሴረም ውስጥ ያለው መጠን

Parameters	
Hmoglobin 10^6 /µ	
RDW %	
LYMPHOCYTES %	
MONOCYTES %	
NEUTROPHILS %	
PLATELET /µL	

NLR
PLR
LMR