ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 08, Issue, 01, pp.18644-18650, January, 2018

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

DIAGNOSTIC VALUE OF SERUM CANCER ANTIGEN 125 IN OVARIAN CANCER PATIENTS

[1,*]Rimaz Alhag Gurashi [2]Moawia E. Hummeida and [3]F. G. Abdelaziz

[1]Clinical Chemistry Department, Faculty of Medical Laboratory Sciences, Al- Neelain University, Sudan
[2]Department of OBGYN, Faculty of Medicine, Al Neelain University
[3]Gynological oncologist, Military Hospital, Omdurman, Sudan

ARTICLE INFO

Article History:
Received 05th October, 2017
Received in revised form
26th November, 2017
Accepted 20th December, 2017
Published online 31st January, 2018

Key Words:
Ovarian Cancer,
Biomarker,
CA125, Epithelial OV.

ABSTRACT

Amongst all gynecological cancers, ovarian cancer is the most lethal malignancy worldwide, aggressive local invasion and the lack of sensitive early screening methods, poses the most difficult in early diagnosis, furthermore, its high mortality rate has made it one of the most investigated fields in gynecological oncology during this year in USA. The aim of the study is to assess the level of serum biomarker cancer antigen (CA-125), among ovarian cancer women at Khartoum State - Sudan. and compare the findings of the cancer antigen (CA-125)serum concentration with the control group, and correlate with study variables. Then estimate the predictive values of this marker. (CA-125) testing were performed to all serum samples to determine the concentrations of cancer antigen CA-125automated immunoassay system (TOSOH BIOCIENCE).for quantitative determination of Cancer Antigen 125 (OVCA125).By the end of this study, concludes that epithelial ovarian cancer is the most common followed by germ cell tumors. Serum level of cancer antigen (CA-125) biomarker within the reference range in the control group. In contrast, increasing serum level in the ovarian cancer patients, A general agreement that a combination of multiple biomarkers may increase diagnostic sensitivity and specificity over use of individual markers (CA125).

Copyright © 2018, Rimaz Alhag Gurashi et al. *This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.*

Citation: Rimaz Alhag Gurashi, Moawia E. Hummeida and F. G. Abdelaziz, 2018. "Diagnostic Value of Serum Cancer Antigen 125 in Ovarian Cancer Patients", *International Journal of Development Research*, 8, (01), 18644-18650.

INTRODUCTION

Ovarian cancer has been called the "silent killer" because symptoms often become apparent only when the cancer has spread and is harder to treat. It's the fifth leading cause of cancer-related death in women in the United States and is the leading cause of gynecologic cancer deaths. Despite being one-tenth as common as breast cancer, it is three times more lethal, and carries a 1:70 lifetime risk. This year, approximately 20,180 women will be diagnosed with ovarian cancer, and 15,310 will die in USA from the disease (Jaime Prat, 2014). The high mortality rate of ovarian cancer is due to the lack of a screening strategy to detect early-stage disease. Ovarian cancer presents with very few, if any, specific symptoms. Twenty percent of patients are diagnosed at stage I and II when the disease is still confined to the ovary.

Corresponding author: **Rimaz Alhag Gurashi**
Clinical Chemistry Department, Faculty of medical Laboratory Sciences, Al- Neelain University, Sudan.

In patients diagnosed with advanced disease, the 5-year survival rate ranges from 20% to 25%, depending on the stage and grade of tumor differentiation (Schwartz, 2002). Of these patients, 80% to 90% will initially respond to chemotherapy, but less than 10% to 15% will remain in permanent remission (Schwartz, 2002). Over the past quarter of a century, several scientific developments have challenged traditional concepts in ovarian cancer. First, it was recognized that ovarian cancer is not a homogeneous disease, but rather a group of diseases-each with different morphology and biological behavior. Approximately 90% of ovarian cancers are carcinomas and, based on histopathology, immune his to chemistry, and molecular genetic analysis, at least five main types are currently distinguished: high-grade serous carcinoma (HGSC,70%); endometrioid carcinoma (EC,10%); clear-cell carcinoma (CCC,10%); mucinous carcinoma (MC, 3%); and low-grade serous carcinoma (LGSC, <5%) (Kurman *et al.*, 2014; Prat, 2012). These tumor types (which account for 98% of ovarian carcinomas) can be reproducibly diagnosed by light microscopy and are inherently different diseases, as indicated by differences in epidemiologic and genetic risk factors;

precursor lesions; patterns of spread; and molecular events during oncogenesis, response to chemotherapy, and prognosis (Kurman *et al*., 2014; Prat, 2012). Much less common are malignant germ cell tumors and potentially malignant sex cord-stromal tumors. The biomarker expression profile within a given histotype is consistent across stages. Ovarian cancers differ primarily based on histologic type (Jaime Prat, 2015; Shahrazad Ehdaivand, 2016). The International Federation of Gynecology and Obstetrics in US (FIGO) stages ovarian tumors on a scale of I to IV according to how well- or poorly-organized the tumors are and whether the cancer is metastasized. Stage I is cancer that is localized and contained in the ovary or ovaries. Stage II is cancer that has spread to other pelvic organs such as the uterus, bladder, or rectum, but is confined to the pelvis (Shahrazad Ehdaivand, 2016). Stage III is cancer that has spread to the lymph nodes and/or abdominal lining and organs, with possible superficial liver metastases. Stage IV is cancer that has spread to distant organs, such as the brain, bone, lungs, or liver parenchyma (Shahrazad Ehdaivand, 2016; Yao Chen *et al*., 2016).

Risk Factors for Ovarian Cancer

According to American Joint Committee on Cancer 2012 and American Cancer Society2016, there are several specific factors that change a woman's likelihood of developing ovarian cancer include: Age, the risk of developing ovarian cancer gets higher with age and, rare in women younger than 40. Most ovarian cancers develop after menopause. Half of all ovarian cancers are found in women 63 years of age or older (American Joint Committee on Cancer, 2010). Obesity, Melinda M and coauthors (Melinda, 2012) have looked at the relationship of obesity and ovarian cancer. Overall (American Joint Committee on Cancer, 2010; American Cancer Society, 2016), it seems that obese women have a higher risk of developing ovarian cancer and obesity is associated with a weak adverse effect on the survival of women with ovarian cancer (Melinda M. Protani, 2012).

Reproductive history, several studies have suggested that the ovarian cancer risk reductions associated with parity and oral contraceptive use are weaker in postmenopausal than premenopausal women; yet little is known about the persistence of these reductions as women age. This question gains importance with the increasing numbers of older ovarian cancer women. parity women have a lower risk of ovarian cancer than nulliparity. The risk goes down with each full-term pregnancy and, women who have their first full-term pregnancy after age 35 or nulliparity have a higher risk of ovarian cancer (Valerie McGuire, 2016). Breastfeeding, the evidence that breastfeeding protects against ovarian cancer is well established epidemiologically, recent evidence finds a 37% reduction for ovarian cancer for women who have breastfed for a year or more (Chowdhury *et al*., 2015). Reduced risk of ovarian cancers related to prolong periods of time during which women do not ovulate or have their menstrual cycles. Later onset of puberty and first menstrual cycles, and an earlier menopause, both of which mean fewer lifetime ovulatory cycles, are associated with decreased risk of ovarian cancer. Contraceptive, women who have used oral and an injectable contraceptive have a lower risk of ovarian cancer. and the risk is lower the longer the contraceptives are used (Alison Volpe Holmes *et al*., 2017). Gynecologic surgery, tubal ligation may reduce the chance of developing ovarian cancer by up to two-thirds and, hysterectomy also seems to reduce the risk of getting ovarian cancer by about one-third (Valerie McGuire, 2016). Fertility drugs, researchers have found that using the fertility drug for longer than one year may increase the risk for developing ovarian tumors, the risk seemed to be increase the risk of low malignant potential ovarian tumor (Melinda M. Protani, 2012). Estrogen therapy and hormone therapy, recent studies done by Muhammad Zahid *et al*., (2014), suggest women using estrogens after menopause have an increased risk of developing ovarian cancer for at least 5 years, the increased risk is less certain for women taking both estrogen and progesterone (Zahid *et al*., 2014). About 5 to 10% of ovarian cancers are a part of family cancer syndromes resulting from inherited mutations in certain genes like what happened in hereditary breast and ovarian cancer syndrome, this syndrome is caused by inherited mutations in the genes BRCA1 and BRCA2, these genes are tumor suppressor genes involved in the regulation of cellular proliferation, chromosomal stability, and DNA repair which linked to a high risk of breast cancer as well as ovarian, fallopian tube, primary peritoneal cancers, pancreatic cancer and prostate cancer, are also increased (Sami Azrak, 2017). According to American collage of Obstetrician and Gynecologist in 2017 (American collage of Obstetrician and Gynecologist, 2017) the lifetime ovarian cancer risk for women with a BRCA1 mutation is estimated to be between 35% and 70%. For women with BRCA2 mutations the risk has been estimated to be between 10% and 30% by age 70. These mutations also increase the risks for primary peritoneal carcinoma and fallopian tube carcinoma. In comparison, the ovarian cancer lifetime risk for the women in the general population is less than 2% in USA (American collage of Obstetrician and Gynecologist, 2017).

PTEN tumor hamartoma syndrome (Cowden disease) people are primarily affected with thyroid problems, thyroid cancer, and breast cancer. Women also have an increased risk of ovarian cancer. It is caused by inherited mutations in the PTEN gene. Women with Hereditary nonpolyposis colon cancer (Lynch syndrome) have a very high risk of colon cancer and also have an increased risk of developing of ovarian and endometrial cancer and many different genes include MLH1, MLH3, MSH2, MSH6, TGFBR2, PMS1, and PMS2 which reduces ability to repair damage to its DNA. The lifetime risk of ovarian cancer in women with hereditary nonpolyposis colon cancer (HNPCC) is about 10%. Up to 1% of all ovarian epithelial cancers occur in women with this syndrome (American collage of Obstetrician and Gynecologist, 2017).

Peutz-Jeghers syndrome is a rare genetic syndrome caused by STK11 gene mutations this syndrome develops polyps in the stomach and intestine in teenagers. Women with this syndrome have an increased risk of both epithelial ovarian cancer and sex cord tumor with annular tubules (SCTAT). Personal history of breast cancer has an increased risk of developing ovarian cancer, because one subtype of breast cancer shares many genetic features with high-grade serous ovarian cancer, a cancer that is very difficult to treat, according to researchers supported by the National Institutes of Health (Francis, 2012). The findings suggest that the two cancers are of similar molecular origin, which may facilitate the comparison of therapeutic data for subtypes of breast and ovarian cancers (Francis, 2012). There are many lowering ovarian cancer risk factors including, history of pregnancy has a 50% lower risk of ovarian cancer than women who were never pregnant (nulliparous), and a protective effect is shown in women with

multiple pregnancies, oral contraceptive, tubal ligation and hysterectomy also have been associated with a reduced risk of ovarian cancer (Jacobs, 2004).

Causes Ovarian Cancer

There are many theories about the causes of ovarian cancer, can be classified to exogenous and endogenous factors. The exogenous factors including, Estrogen therapy and hormone therapy, smoking and alcohol induced, exposure to carcinoids materials and radiation, diet with heavy fatty and proceeding meat (Melinda M. Protani, 2012). Endogenous factors, the hormonal imbalance is important causes of ovarian cancer because it's hormonal dependent cancer, also researchers find a relationship between ovulation and the risk of developing ovarian cancer (Sami Azrak, 2017; American collage of Obstetrician and Gynecologist, 2017). Genetic mutations either inherited mutations in the BRCA1 and BRCA2 genes, as well as the genes related to other family cancer syndromes linked to an increased risk of ovarian cancer, such as PTEN tumor hamartomasyndrome, Peutz-Jeghers syndrome, MUTYH-associated polyposis, and the many genes that can cause hereditary nonpolyposis colon cancer (MLH1, MLH3, MSH2, MSH6, TGFBR2, PMS1, and PMS2). or acquired like the TP53 tumor suppressor gene or the HER2 oncogene mutation,

Incidence and Prevalence

According to American cancer society an estimated 22,400 new cases of ovarian cancer in 2017 and about 14,080 deaths will occur in 2017, accounts for 5% of all cancers in women, and A total of 7,378 new cases were reported in the UK in 2014 and it has the highest mortality of all gynecological cancers, accounting for 6% of all cancer deaths in women (Hristina Fotopoulou *et al*., 2014) Although ovarian cancer occurs most commonly after menopause (average age is 63), it may develop at any age. A woman's risk of developing ovarian cancer in her lifetime is 1 in 71, and her risk of dying from the disease 1 in 95. The 5 years survival rate for ovarian cancer is relatively low (46%) because most patients are diagnosed with distance stage disease, for which survival is 29%. Survival also varies subsequently by age, with women younger than 45 much more likely to survive 5 years than women 75 and older (77% versus 20%) (http//s: www. American cancer society.com).

Diagnosis of ovarian cancer

History, is nonspecific in that symptoms in early-stage disease are either absent or vague and may resemble menopausal symptoms and intestinal illnesses. Individuals in later stages may report indigestion, gas, nausea, vomiting, loss of appetite, a feeling of fullness after small meals, pelvic or abdominal pain, swelling, increased frequency or urgency of urination, unexplained change in bowel habits, unexplained weight gain or loss, pain during intercourse, ongoing fatigue, lower back pain, shortness of breath, and, in rare cases, postmenopausal vaginal bleeding. These symptoms usually do not become apparent until the later stages of the disease when the cancer mass is large enough to interfere with pelvic organs such as the bladder or rectum, or after the cancer has metastasized to the abdominal cavity. Obtaining a personal obstetric and gynecologic history and a family history of gynecologic disease may be important in diagnosis (National Comprehensive Cancer Network, 2013).

A number of case–control studies investigating symptoms in women with ovarian cancer and comparing them to symptoms in women without ovarian cancer demonstrate that patients with ovarian cancer are symptomatic for a variable period before diagnosis and challenge the perception of ovarian cancer as the "silent killer" (Network SIG, 2013). Pelvic examination, many conditions that can affect women's health are often evaluated through pelvic examination. These conditions include malignant diseases, such as ovarian, uterine, vaginal, andcervical cancer; infectious diseases, such as bacterial vaginosis, candidiasis, genitalwarts, genital herpes, trichomoniasis, and pelvic inflammatory disease; and other benign conditions, such as cervical polyps, endometriosis, ovarian cysts, dysfunction of the pelvic wall and floor, and uterine fibroids. Pelvic examination is a common part of the physical examination; 44.2 millionpelvic examinations were performed in the United States in 2012. Although it is a common part of the physical examination, it is unclear whether performing screening pelvic examinations in asymptomatic women has a significant effect on disease morbidity and mortality (https:// www.hrsa.gov/womensguidelines2 016/index.html. Accessed January 17, 2017; www.aafp.org/afp.). Routine imaging tests, are noninvasive diagnostic imaging such as ultrasound performed with a transvaginal probe, computed tomography (CT), and magnetic resonance imaging (MRI), may help distinguish between benign and cancerous tumors. X-ray procedures are used if involvement of the colon or urinary tract is suspected.

In women who have gastrointestinal symptoms, examination of the GI tract with upper and lower endoscopy is indicated to help rule out GI conditions and evaluate for bowel obstruction, and Positron Emission Tomography (PET) by radioactoring sugars to detect small group of cancer cells (National Comprehensive Cancer Network, 2013). Laboratory investigations, included complete blood count (CBC), chemistry profile with a liver function tests (LFT) combined with alpha-fetoprotein (AFP), total serum proteins, and cancer antigen 125. Histopathological examination of ovarian tumors one of the most important method to differentiate between ovarian cancer types, used in staging and also in predicting the prognosis (Jyothi Kancherla *et al*., 2017). Tumor markers and Malignancy Indices, prospectively acquired evidence from the United Kingdom Collaborative Trial of Ovarian Cancer Screening Cancer (UKCTOCS) - with 46,237 women triaged using MMS in whom serial CA-125 measurements were interpreted via the risk of ovarian cancer algorithm (ROCA) - has shown that screening by using ROCA doubles the number of screen-detected EOC compared with a fixed cut off of 35 IU/ml (https://www. rcog.org.uk/en/ guidelines-research services / guidelines / clinical -governance-advice-1a/). A Risk of Malignancy Index (RMI) was developed to estimate the probability of malignancy and the need to refer the patient to a tertiary hospital for optimal treatment. RMI is calculated by multiplying the menopausal status by the CA125 value and by certain sonographic features. Risk of Malignancy Index (RMI) = M x CA125 x U. RMI > 200 = Suspicious for malignancy.

Cancer Antigen 125 (CA125)

Discovered initially by Bast and colleagues in 1983. CA 125, also known as mucin 16 (muc 16), is a transmembrane glycoprotein derived from epithelium of coelomic and müllerian origin. The extracellular membrane domains of CA 125 bind to antibodies to render quantitation of levels for clinical use.

In the original study on CA 125, bast *et al* (27), reported that only 1% of healthy donors had a CA125 level greater than 35 U/mL, and only 0.2% of healthy donors had a CA 125 level greater than 65 U/mL. Thus, 35 U/mL was accepted as a cutoff for the upper limit of normal (ULN) for CA 125 levels in the first-generation CA 125 assays. Clinical labs typically use an immunoassay using monoclonal antibodies with specificities against CA 125's two major antigenic domains. For women with ovarian cancer, CA 125 levels were found to correlate with tumor burden in 93% of cases (Drescher, 2011). However, elevations in CA125 were not exclusive in ovarian cancers; patients with malignancies of other origins, including breast, lung, and gastrointestinal, had an elevation in CA 125. According to review of published literature on CA 125 in the past 5 years and cited in the National Library of medicine (Pub Med). Screening of CA 125 cannot adequately be characterized as a screening test because of the overall low incidence of ovarian cancer in the general population and the risk of a false-positive result. When the data were re-analyzed based on a categorization of women as high- and low-risk based on CA 125 and ultrasound findings, the detection rate of ovarian cancer was improved for those at high risk, although false- positive results were still reported (q. As a screening test, the positive predictive value of CA 125 is less than 4% based on the literature review of published on CA 125 in the past 5 years and cited in the National Library of medicine (Pub Med)is unacceptably low for a screening test. This is especially true when follow-up diagnostic procedures are invasive and carry a significant risk to the patient. In light of these and other data, the US Preventive Services Task Force gives screening for ovarian cancer with CA 125 its lowest ranking, a graded recommendation, indicating that there are no benefits from the use of CA125 as a screening test (Cancer Treatment Centers of America, 2012).

Although the role of CA 125 as a screening test is not supported, other research suggests that following serial changes of CA 125 may be more effective than seeing whether CA 125 is raised. The data on serial CA 125 measurements is supported by the work of Skates, (Wisal Adam, 2017) who hypothesized that each woman has her own baseline CA 125 and will have variation around that baseline, and that further evaluation may be indicated when there is a rise outside of this normal variation. Using these principles, the risk of Ovarian Cancer Algorithm (ROCA) was developed using serial CA 125 levels, age, and statistical risk of having a change point (rapid rise in CA 125 above baseline) (Wisal Adam, 2017).

After each new CA 125 level is drawn, it can be incorporated into the algorithm, and the patient's risk recalculated. CA 125 for Diagnostic Purposes, the positive predictive value of CA 125 in women with an adnexal mass is 35% to 91%, and the negative predictive value ranges between 67% and 90% (Matz, 2017). The sensitivity of CA 125 in distinguishing between benign and malignant masses ranges between 61% and 90%, while specificity ranges between 35% and 91% (Matz, 2017). The wide variation in these values is due to different inclusion criteria for premenopausal women across studies. Although few studies have looked at the role of CA 125 in the diagnosis of an adnexal mass in pre- versus postmenopausal women, it is generallyaccepted to be a better marker in postmenopausal women, probably because ovarian cancer is a more common diagnosis in these patients, postmenopausal women with malignant masses compared with premenopausal women with malignant disease, which may be partially explained by differences in tumor histology (http://www. Uspreventive services taskforce.org/uspstf/ uspso var.ht m.). The aim of the study is to assess the level of serum biomarker cancer antigen (CA-125), Human among ovarian cancer women at Khartoum State - Sudan. and compare the findings of the cancer antigen (CA-125) serum concentration with the control group, and correlate with study variables. Then estimate the predictive values of this marker.

MATERIALS AND METHODS

MaterialsA total of 90 Sudanese ladies age range (16-80) years old attending Gynological Oncology clinics in Omdurman Military hospitals - Khartoum state from May 2015 to December 2016 was included in the study. The study was analytical comparative cross-sectional study. The sample population was divided into two main groups; study group including 53 (58.8%) Ovarian cancer patient with an age of 16 to 80 years, and control group including 37 (31.2%) aged match apparently healthy individuals according to the study Inclusion criteria including of Sudanese women diagnosed with primary ovarian cancer and excluded any women diagnosed with other cancer types rather than ovarian cancer.

History and background data were collected from participants using verbal interviews and pre-designed questionnaire. Clinical presentation includes an enlarged ovary on a pelvic exam, ascites, and histopathological examinations to regulate the tumor type, ovarian cancer type, and staging of the disease, then followed by metastatic status of cancer. Five ml blood samples were collected from each participant; sera were separated, and then stored at -20oC for subsequent testing. Biomarker testing were performed to all serum samples to determine the concentrations of cancer antigen (CA-125), AIA-600 II Automated Immunoassay System (TOSOH BIOCIENCE).Informed and written consents were obtained from all participants prior to involvement in the study.

METHODS

AIA-600II Automated Immunoassay System (TOSOH BIOCIENCE) Instrument includes analyzer, power conditioner, and accessory kits. Common reagents include AIA-PACK substrate set, and lyophilized. For quantitative determination of Cancer Antigen 125 (OVCA125) Principle, the ST AIA-PACK OVCA125 was a two –site immune enzymometric assay which is perform entirely in the ST AIA-PACK OVCA125, test cups. CA 125 present in the tested sample was pound with the monoclonal antibodies immobilized on magnetic solid phase and enzyme- labeled monoclonal antibodies in test cups. The magnetic beads were washed to remove unbound enzyme - labeled monoclonal antibodies then incubated with a fluorogenic substrate, 4-methylelumbelliferyl phosphate (4MUP). The amount of enzyme- labeled monoclonal antibodies that bound to the beads was directly proportional to the OVCA125concentration in the test sample. Preparation of Reagents and sample, allowed all reagents to reach room temperature (18-25°C) prior to use, reagents preparation done in three steps firstly, the ST AIA- PACK substrate constituent (100ml) to the lyophilized ST AIA- PACK substrate reagent and mixed to dissolved solid materials. Then wash solution was prepared by wash concentrate (100 ml) to 2 litters CAP Class D.W mixed well and adjusted to 2.5 litters finally, diluent concentrate(100ml) to 4 L D.W mixed well and completed to 5L.

Assayed Procedure, after insuring sufficient quantity of ST AIA-PACK test cups for the numbers of samples to be run. Serum samples were loaded as instructed in operator's manual. Calculations of Results, the calibrator of the OVCA125were prepared gravimetrically and compared to internal reference standard and stability of the curve up to 90 days, which monitored by quality control performance and dependent on proper reagent handling and TOSHO AIA system maintenance according to manufacturer's instructions.

Detection range OVCA125 8 U/ml – 1.100 U/ml

Quality control the controls were running with calibration curve for the OVCA125, a statistically significant number of controls were assayed to establish mean values and acceptable ranges to assure proper performance. Using control sera at both normal and pathological levels. The checking of the following technical areas: Pipetting and timing devices; photometer, expiration dates of reagents, storage and incubation conditions, aspiration and washing methods were done.

Statistical analysis

Raw data were entered into a spread sheet of SPSS statistical package program, data were rearranged as appropriate. Descriptive analysis was performed to all study variables. Data was analyzed using SPSS version 21. The results expressed as mean, standard deviation, median, frequency and percentage. Descriptive statistic was done to obtained the frequencies and percentages of the study variables and clinical data. Independent–sample T-test was demonstrated to compare the mean concentration of OVC biomarker parameter CA125in OVC cancer versus healthy individual (control groups). One-way ANOVA was used to mean concentration of OVC biomarker parameters CA125across the OVC stages. Graphs were done using Microsoft excel and Graph Pad Prism version 6. P-value ≤ 0.05 was considering as significantly difference. All statistics tests were done in confidence interval 95%.

RESULTS

Clinical Results Ninety (100%) Sudanese ladies were enrolled in this study. They were distributed into two groups; Study group including 53 (58.8%) newly diagnosed ovarian cancer patients age ranged (16-80) years old, and Control group including 37 (31.2%) age match apparently healthy individuals. Study group include 32% in the reproductive age and about 68% elderly female. The frequency and percentage of signs and symptoms shown that 79.0 % from the study group suffering from abdominal bloating, 62% loss of appetite,68% urinate more frequent, 57% irregular bowel movement, 70% presented with increased abdominal size, about 85% with abdominal pain, all study group deny history of ovarian cancer in their families, only 13% of ovarian cancer patient using pills as contraceptive as well as 4%hormonal therapy consumption, 8%Caesarean as gynecological surgery. As well as about 51% of the study group were para and multi-parity compared with 49% were nulliparous, and 45% of this study group suffering from asities when clinical examination done and confirmed by ultrasonography also signify percentage of the left (Lt), right (Rt), and Bilateral ovarian mass as 19%, 34%, and 47% respectively. Histopathological results, the present study showed 97% of the ovarian cancer were epithelial cell origin and only 3 % were germ cell origin. Staging of ovarian cancer among study group grading from stage 1,2,3 and,4 were 11%, 13%,19% and 57% respectively. Serum biomarker results, the present study showed differences of serum biomarker cancer antigen (CA-125levels among ovarian cancer and control individuals. CA125 mean concentration was 225.96 U/ml in the study group, and 13.52 U/ml in the control group shown significant difference with p-value 0.0001 along with mean concentration of Para/ multi parity and Nulliparous sub groups of ovarian cancer patients were 215.21 U/ml, 237.13 U/ml respectively shown insignificant difference with (P-value = 0.290). Mean concentrations of this marker among cancer stages 1,2,3, and 4 shown 277.6U/ml, 296.9U/ml, 121.4U/ml and, 233.9U/ml respectively, which shown insignificant difference with p-values (0.671). The sensitivity 91%, Specificity 89%, Positive predictive value 85%, and Negative predictive value 63% .

DISCUSSION

Amongst all gynecological cancers, ovarian cancer is the most lethal malignancy worldwide, aggressive local invasion and the lack of sensitive early screening methods, poses the most difficult in early diagnosis, furthermore, its high mortality rate has made it one of the most investigated fields in gynecological oncology during this year in USA ovarian cancer ranks fifth in cancer deaths among women (National Comprehensive Cancer Network (NCCN), 2016), a woman's risk of getting ovarian cancer during her lifetime is about 1 in 75, her lifetime chance of dying from ovarian cancer is about 1 in 100 according to Ovarian Cancer Treatment Statistics and Results of Cancer Treatment Centers of America 2012 (Cancer Treatment Centers of America, 2012). Even though OVC mainly develops in older women there is younger age range were reported in review study done by Wisal etal 2017 (Wisal Adam *et al*., 2017), among Sudanese ovarian cancer patient which agree with our study because there were thirty tow percent within reproductive age. The results of the present work affirm that, around fifty seven percent of all ovarian cancers included in this study were diagnosed at an advanced stage and only eleven percent in early stage. Then the five-year survival rate for patients with clinically advanced ovarian cancer is only fifteen to twenty percent, in striking contrast to a five-year survival rate of over ninety percent for patients with stage I disease (Matz, 2017). In this study, we found the common symptoms among OVC patients involved in the clinical presentation are abdominal bloating, pelvic pain, abdominal pain, increase abdominal size vaginal discharge with the highest frequent, and vaginal bleeding with low frequency, these findings similar to cancer facts and figures published in 2017 by American cancer society (http//s: www. American cancer society.com). Ultrasonography as noninvasive diagnostic test in women with pelvic, bilateral, and ascites are helpful in predicting the likelihood that mass is malignant (American Family Physician, 2017). Ovarian tumors were unilateral in 53% of cases and bilateral in 47% with right side predominance This also chimes with the findings of Jyothi Kancherla et al (Jyothi Kancherla *et al*., 2017).

Histopathological distribution in our study group is similar to many published works (US Preventive Services Task Force, 2014; Skates, 2012), ovarian epithelial cell being the most common and followed by Germ cell, which present in different age ranges included in this study, Germ cell neoplasm present among younger age in the study group, present study findings are broadly similar to Kancherla etal (Jyothi Kancherla *et al*.,

2017) who reported that surface epithelial tumors were most common (80%) followed by germ cell tumors (16%). Laboratory analysis displayed that there were elevated levels of CA 125 in the study group when comparing with control group which agree with a study done by Randa et al. 2016 (Randa, 2016), and disagree with the same study in the proportional of CA125 serum level with the stage of cancer (Randa, 2016). Also in this study, we found that the sensitivity of CA125 were 91%, Specificity 89%, Positive predictive value 85%, and Negative predictive value 63% these finding agree with a study by Moore et al. (Moore RG etal2012). However, other malignant and benign diseases also express CA-125, thereby limiting its reliability as a tumor marker. In particular, CA-125 has a high false-positive rate among women with benign gynecological conditions such as endometriosis, and a low sensitivity in identifying patients with early-stage ovarian cancer, the limitations for clinical use of the tumor marker CA125 have long been recognized and have prompted numerous studies for novel markers.

Sensitivity 98% and specificity98% than CA125 as well as PPV 92% and NPV86% This suggests similar to NCCN Guidelines Version 2013 (https://www.rcog.org .uk/en/guid elines-research services /guidelines / clinical -governance-advice-1a/). Hellstrom and colleagues showed that secreted HE4 was detected in high levels in the serum of ovarian this group found that measurement of HE4 showed sensitivity and specificity comparable to that of CA125 for differentiating women with ovarian cancer from normal controls (Jyothi Kancherla *et al*., 2017). Høgdall, Estrid and colleagues for the first time in Denmark presented a single marker, with a higher diagnostic prediction than the golden standard CA 125 (Høgdall, 2011). Drescher, at Hutchinson Cancer Research Center, USA found that HE4 performance better than CA125 serum levels which get same results with our study (Drescher, 2011)

Conclusion

By the end of this study, concludes that epithelial ovarian cancer is the most common followed by germ cell tumors. Serum level of cancer antigen (CA-125) biomarkerwithin the reference range in the control group. In contrast, increasing serum level in the ovarian cancer patients, A general agreement that a combination of multiple biomarkers may increase diagnostic sensitivity and specificity over use of individual markers (CA125).

Recommendations

Further studies for stablishing new novel markersfor ovarian cancer with a golden standard CA125, and pointing to a rationale for further research assessing potential clinical usefulness.

REFERENCES

Alison Volpe Holmes, Heather G. Jones, Brock C. Christensen, Breastfeeding and Cancer Prevention, April, 2017. NH Comprehensive Cancer Collaboration in partnership with Dartmouth-Hitchcock Norris Cotton Cancer Center and its NCI National Outreach Network Community Health Educator Site.

American cancer society, cancer facts and figures 2017.special section: Rare cancers in adults. Atlanta 2017. http//s: www. American cancer society.com

American Cancer Society. Cancer Facts and Figures 2016. Atlanta, GA: American Cancer Society; 2016.

American collage of Obstetrician and Gynecologist, fact sheet in BRCA1 and BRCA2 mutations. Oct2017.

American college of Obstetricians and Gynecologists. Practice bulletin no. 83: management of Adnexal masses. Washington, dc: American college of Obstetricians and Gynecologists; 2007. http://www.usp reventivese rvicestask for ce.org /uspstf/uspsovar.htm.

American Family Physician. screening for Gynecologic Conditions with Pelvic Examination: Recommendation Statement, August 15, 2017. Volume 96, Number 4 www.aafp.org/afp.

American Joint Committee on Cancer. Ovary and Primary Peritoneal Carcinoma. In: AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010: 419-428.

Cancer Treatment Centers of America (CTCA) 2012. Ovarian Cancer Treatment Statistics and Results.

Chowdhury R, Sinha B, Sankar MJ, *et al*. 2015. Breastfeeding and maternal health outcomes: a systematic review and metaanalysis. Acta Paediatr.104(467):96-113

Drescher, Urban N. Hartge. Potential role of HE4 in multimodal screening for epithelial ovarian cancer 2011, USA.

Francis S. 2012. Collins. Study reveals genomic similarities between breast cancer and ovarian cancers. National Cancer Institute (NCI) and the National Human Genome Research Institute (NHGRI), both part of NIH. Sept. 23,.

Health Resources & Services Administration. Women's preventive services guidelines. https:// www.hrsa.gov/ womensguidelines2016/index.html. Accessed January 17, 2017.

Høgdall, Estrid, Nedergaard, Karlsen. Diagnostic value of HE4, CA125 and the roma index in ovarian cancer. 2011, Denmark.

Hristina Fotopoulou, Marcia Hall, Derek Cruickshank, Hani Gabra, Raji Ganesan, Cathy Hughes, Sean Kehoe, Jonathan Ledermann, Jo Morrison, Raj Naik, Phil Rolland, Sudha Sundar. British Gynaecological Cancer Society (BGCS) Epithelial Ovarian /Fallopian Tube / Primary Peritoneal Cancer.2014;1-48.Guidelines: https://www.rcog.org.uk/en/guidelines-research services /guidelines / clinical -governance-advice-1a/

Jacobs IJ, Menon U. 2004. Progress and challenges in screening for early detection of ovarian cancer. MolCell Proteomics; 3:355^66.

Jaime Prat. 2014. Staging classification for cancer of the ovary, fallopian tube, and peritoneum. Int J Gynecol Obstet;124(1):1-5.JGynecol Oncol Vol. 26, No. 2:87-89 http:// dx.doi.org /10.3802 /jgo.2015.26.2.87

Jyothi Kancherla, Raghu Kalahasti, K P A Chandra Sekhar, Srikanth Babu Yarlagadda, S Parimala Devi 2017. Histomorphological Study of Ovarian Tumors: An Institutional Experience of 2 Years. International Journal of Scientific Study | June 2017 | Vol 5 | Issue 3.

Kurman RJ, Carcangiu ML, Herrington CS, Young RH. 2014. WHO classification of tumors of female reproductive organs. 4th ed.Lyon: International Agency for Research on Cancer.

Matz M. 2017.Factors influencing ovarian cancer survival worldwide. London School of Hygiene & Tropical Medicine . DOI:

Melinda M. Protani, Christina M. Nagle, and Penelope M. 2012. Webb. Obesity and Ovarian Cancer Survival: A Systematic Review and Meta-analysis, www.aacrjournals.org, DOI: 10.1158/1940-6207.CAPR-12-0048

Muhammad Zahid, Cheryl L. Beseler, James B. Hall, Tricia LeVan, Ercole L. Cavalieri and Eleanor G. 2014. Rogan. Unbalanced estrogen metabolism in ovarian cancer, International Journal of Cancer . 25 January.DOI: 10.1002/ijc.28565

National Comprehensive Cancer Network (NCCN). Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Available from: http://www.nccn.org/ professionals /physician_gls/pdf/ovarian.pdf. 2016. USA

National Comprehensive Cancer Network. NCCN Guidelines Version 4. Hereditary Breast and/or Ovarian Cancer Syndrome. 2013. USA.

Network SIG. 2013. Management of epithelial ovarian cancer. SIGN Publication No 135. Edinburg:SIGN.

Prat J. 2012. Ovarian carcinomas: five distinct diseases with different origins, genetic alterations, and clinicopathological features. Virchows Arch; 460:237-49.

Randa E. Mohammed, Rania M. SidAhmed, Ahmed M. Alhaj. Application of CA 125 in the Diagnosis and Follow up of Ovarian Cancer International Institute of Cancer- Wad Medani,2016; Vol 3 (4) pp.13-18, Sudan.

Sami Azrak. 2017. Hereditary Ovarian Cancer and Germline Mutations: Review Article. *Journal of Genetics and Genetic Engineering* Volume 1, Issue 1, PP 31-42.

Schwartz PE. 2002. Current diagnosis and treatment modalities for ovarian cancer. *Cancer Treat Res.,* 107:99 - 118.

Shahrazad Ehdaivand, *et al*. 2016. WHO classification of Ovarian Neoplasms, Pathology Outlines.com, Inc.

Skates S. OcS: 2012. Development of the risk of ovarian cancer algorithm (ROCA) and ROCA screening trials. Int J Gynecol Cancer. 22(suppl 1):S24-S26.

Terry, K. L., H. Schock, R. T. Fortner, etal 2016. "A prospective evaluation of early detection biomarkers for ovarian cancer in the European EPIC cohort." Clin Cancer Res. 22(18):4664-75.

US Preventive Services Task Force. Screening for Ovarian cancer. Accessed November 10, 2014

Valerie McGuire, Patricia Hartge, Linda M. Liao , Rashmi Sinha , Leslie Bernstein, Alison J. Canchola , Garnet L. Anderson , Marcia L. Stefanick, Alice S. Whittemore . Parity and Oral Contraceptive Use in Relation to Ovarian Cancer Risk in Older Women. 2016; DOI: 10.1158/1055-9965.EPI-16-0011.

Wisal Adam, Rimaz A. Gurashi, Moawia Alsadig Humida and F.G. Abdelaziz. Ovarian Cancer in Sudan. Journal of Medical and Biological Science Research 2017;Vol. 3 (4), pp. 37-41.

Yao Chen, Suihai Wang, Tiancai Liu, Yingsong Wu, Ji-Liang Li, and Ming Li, 2016. WAP four-disulfide core domain protein 2 gene (WFDC2) is a target of estrogen in ovarian cancer cells. Journal of Ovarian Research 2016; 9:10.

****