"DETERMINATION OF MOLECULAR TUMOR MARKER LEVELS HE4 (HUMAN EPIDIDYMIS PROTEIN 4) AND CA125 IN OVARIAN CANCERS": A CROSS SECTIONAL STUDY

BY

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DISSERTATION SUBMITTED TO THE
SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, TAMAKA, KOLAR, KARNATAKA,
IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF

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File size:	1.13M
Page count:	90
Word count:	17,017
Character count:	98,636
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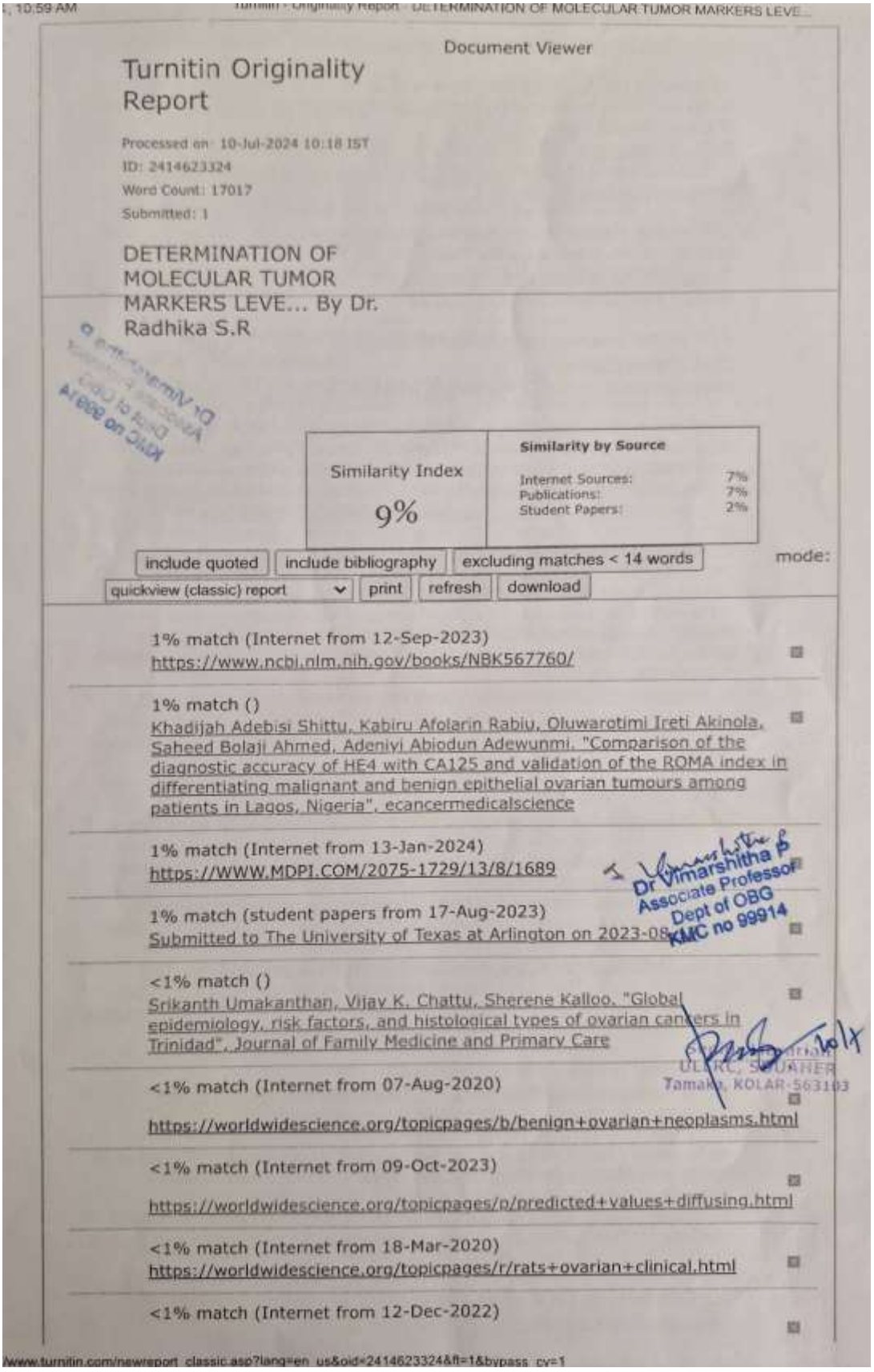

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ACKNOWLEDGEMENT

Dearest Almighty, thank you!

I am grateful for the path you've paved for me, which allowed me to follow and fulfill my dreams.

My sincere appreciation to my respected guide and co-guide, **Dr. Vimarshitha P, and Kalyani R** for their unwavering Guidance. Their valuable suggestions and kind encouragement throughout this study were immeasurable and empowered me to cultivate a profound comprehension of the subject.

I extend my heartfelt gratitude to **Dr. Vasantha Kumar.** His steadfast guidance, Keen scientific insight, practicality, a knack for solving the impossible, and ability to break complex ideas into simple terms taught me to think beyond the box. I wish to imprint his teachings throughout my career.

My genuine appreciation to **Dr. Munikrishna M, Dr. Sheela S R and Dr. Rathnamma. P** for their timely assistance and support. Their suggestions, intellectual stimulation, genuine interest, affection and comfort have been a constant source of inspiration. Besides, their insightful advice and dedication have been instrumental in completing this post-graduate program.

I am sincerely thankful to the esteemed faculty members–**Dr. Soumya, Dr. Megadeepa, Dr. Divya J Patil, Dr. Harshitha, Dr. Nandini, Dr. Aashritha, Dr. Kavya, Dr. Sukhini** for their insightful discussions during seminars and valuable suggestions. I appreciate their rigorous standards which challenged my thoughts and inspired me to improvise.

My heartfelt thanks to senior residents and my seniors for their practical tips, advice and constant encouragement.

I am also indebted to my girls**, Dr. Sankiya. M** and **Dr. Shruthi S.P** for always supporting me and providing encouragement and unconditional love and constantly motivating throughout my course.

I express my sincere thanks to my colleagues and dearest ones **Dr Ashwini, Dr Madhurya, Dr Meghana, Dr Shreya, Dr Lakshmi, Dr Anjali, Dr Ajitha** for their co-operation and help in carrying out this study. I also thank my beloved **juniors** for providing useful tips and clues in completing this vast work.

My acknowledgement would be incomplete without my dearest and beloved family, especially my parents**, Mr.Rajashekar S H** and **Mrs. Prabha Rajshekar,** and my grand parents.I am immensely indebted to themfor instilling the importance of deligence in me. You both have led by example to help me understand the harsh realities of life.Your resolute patience, encouragement also countless hours of listening to my rambles have enabled me to reach this height. Thank you Appa and Amma!

My heartfelt appreciation to my sister **Ms. Deepika R Shekar** for being with me through the ups and downs of life. You have always found the bright side during dark times, besides adding laughter to my boring life. I am amazed by the things that you would sacrifice just to be there for me.

Lastly, I would like to extend my gratitude to the nursing staff and hospital workers for their assistance in conducting the study. My humble acknowledgement to the patients and their next of kin for their cooperation during this research.

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LIST OF ABBREVIATIONS

Glossary	Abbreviation
HE4	Human Epididymis Protein 4
CA125	Cancer antigen 125
PARP	Poly (ADP-ribose) polymerase
p53	p53 mutations
HGSC	high-grade carcinoma
LGSC	Low-grade carcinoma
MOC	Ovarian mucinous carcinoma
GI	Gastrointestinal tract
CK7	Cytokeratin-7
TVUS	Transvaginal ultrasonography
CT scan	Computed Tomography Scan
ROMA	Risk of Ovarian Malignancy Algorithm
RMI	Risk of Malignancy Index
FIGO	Federation of Gynecology and Obstetrics
BSO	Bilateral salpingo-oophorectomy
SGO	Society of Gynecologic Oncology
ASGO	American Society of Clinical Oncology
EORTC	European Organization for Research and Treatment of Cancer
IV	Intravenous
IP	Intraperitoneally
MUC16	Mucin 16
GCIG	Gynecologic Cancer Intergroup
OC	Ovarian cancer
EOC	Epithelial ovarian cancer
ANN	Artificial Neural Network
ROC	Receiver operating characteristic
Hcg	Human chorionic gonadotropin
IFMA	Inhibin immunofluorometric assay
AMH	Anti-Müllerian hormone
GCT	Granulosa cell tumors
AFP	Alpha-fetoprotein
OGCT	Ovarian germ cell tumors
LDH	Lactate dehydrogenase

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ABSTRACT

BACKGROUND: The determination of molecular tumor markers HE4 (Human Epididymis Protein 4) and CA125 has become increasingly important for managing ovarian cancer. Ovarian cancer is asymptomatic, because it is often discovered at an advanced stage, and the death rate is increased. CA125 has been a traditional biomarker for ovarian cancer, but its limitations include false positives and poor sensitivity in early-stage disease.HE4, a newer biomarker, offers enhanced sensitivity and specificity, particularly when distinguishing benign gynecological disorders from ovarian cancer. Combining HE4 and CA125 biomarkers along with calculating the 'Risk of ovarian malignancy algorithm',' Risk malignancy index'enhances accuracy for diagnosis, facilitating better differentiation, whether the condition ismalignant and non-malignant. This dual-marker approach also improves the monitoring of treatment response and early detection of recurrence, contributing to more effective clinical management and improved patient outcomes.

AIMS: The overall aim of conducting the study is the evaluation of the molecular tumor markers level for those patients that have been diagnosed with ovarian tumors, notably CA125 and HE4

MATERIALS & METHODS: Women diagnosed with ovarian cancer, who had given consent for study underwent routine physical examination. Preoperative evaluations such as CA 125, and HE4 were done, and ROMA and the Risk malignancy index were calculated. "Elecsys CA 125 II and Elecsys HE4 test reagents" were used together with Cobas E 602 immunoassay analyzer to conduct the HE4 and CA 125 tests.Surgical intervention was done for patients with suspected ovarian malignancy, and sample was sent for histopathological examination.

RESULTS:54 females were part of the study population.HE 4 achieves a slightly higher diagnostic accuracy (69.45%) compared to CA 125 (65.56%). Overall, these metrics suggest HE 4 may be slightly more effective as a diagnostic biomarker than CA 125.But,combining HE4 and CA125 for diagnosis and assessing treatment response demonstrates notable efficacy.

This study reported that the sensitivity of this combination is 90.12%,specificity is 82.64%, and positive predictive value is 96.12% independently. The overall precision of diagnosis of the HE4 and CA125 combination stands at 69.25%.

CONCLUSION: The determination ofHE4 and CA125 levels is vitalin early diagnosis, treatment, and prevention of ovarian cancer. By overcoming current limitations through strategic recommendations. It is possible to maximize these biomarkers' clinical utility, leading to better patient care and outcomes.

KEY WORDS: Ovarian cancer, CA125, Human epididymis (HE4), Risk of ovarian malignancy algorithm (ROMA)

INTRODUCTION

INTRODUCTION

Ovarian cancer annually affects around 204,000 individuals, resulting in approximately 125,000 fatalities. In developed nations, ovarian cancer continues to pose the highest death rate among gynecologic malignancies. Ovarian cancer is in seventh rank both in terms of its prevalence among cancers and as a cause of death from cancer among women worldwide. It stands out as the most frequently diagnosed form of gynecological malignancy.[1]

According to the Globocan 2018 Fact Sheet, ovarian cancer cases are 3.44% (36,170 cases) of all cancer cases and is the third most prevalent disease among Indian women and ranks eighth overall.[2]One of the main causes of cancer-related fatalities among Indian women is ovarian cancer, responsible for 3.34% (24,015 deaths) of all cancer fatalities in 2018.Although 94% of cases have a hopeful 5-year survival probabilitywhen diagnosed at Stage I, only 15% of cases are detected at this early stage. Stages III and IV had the highest diagnosis rate (62%) and the lowest 5-year survival rate (28%)[3].Advanced-stage ovarian cancer has an unfavorable prognosis and has the highestcase-fatality ratio of any gynecological malignancy globally.

The stage at which ovarian cancer is detected significantly impacts survival rates.Hence, early identification offers the greatest potential for reducing mortality and managing the disease over the long term. Although initial findings suggest that screening may enhance survival, It's unclear how precisely screening affects the death rate from ovarian cancer.[4]

The primary goal for diagnosing adnexal masses is to differentiate if the condition is benign or malignant. Approximately 5–10% of females are expected to undergo surgical procedures for ovarian neoplasm's; 13-21% of these instances result in the discovery of malignancies. It's critical to accurately distinguish benign from malignant adnexal tumors prior to surgery for optimizing surgical approaches to pelvic tumors in women. The choice of the first surgical operation has a substantial effect on patients' prognosis. This is because the first laparotomy offers the best chance for maximum debunking and also aids in precisely determining the extent of the disease.[5]

World Health Organisation (WHO) has identified eight histological subtypes of epithelial ovarian cancer, namely mucinous, serous, transitional cell, squamous cell,

mixed epithelial, endometrioid, clear cell, and undifferentiated. These subtypes include tumors that are classed as borderline, malignant, or benign; depending on the subtype, further distinctions such as low or high grade may apply. A relatively indolent nature and/or limited propensity for malignancy are characteristics of borderline tumors.[6]Of these subtypes, serous tumors account for 30-70% of diagnosis. These are the most prevalent forms of ovarian cancer and are linked to the worst prognosis.

Tumor markers, Doppler ultrasonography, and grey-scale ultrasonography are a few of the non-invasive techniques available for differentiating whether the pelvic tumor is benign or malignant. The ability of serum tumor markers to differentiate between these masses has been thoroughly investigated. In around 80% of ovarian epithelial cancers, Serum CA-125 is elevated.It is one of the most often used indicators.However, blood CA-125 levels have low specificity and must be evaluated in addition to clinical and ultrasonographic (USG) results. Although CA-125 has less specificity as well as sensitivity screening in women who have not attained menopause, it has demonstrated more value in post-menopausal patients. Depending on the tumor stage, CA-125's diagnostic sensitivity for ovarian cancer varies. According to Li et al. (2009) andNustad et al. (1996),About 50% of individuals with stage 1cancerand 80–90% of women with 3rd , 4th stage cancer have abnormal blood results for CA-125.The FDA guidelines back up the importance of CA125 as a protein biomarker for tracking patients suffering from ovarian cancer and evaluating their response to treatment. The relationship between CA125 levels and survival outcomes and clinical stage provides important information for clinical decision-making. However, because CA125 may be secreted by non-tumor cells in an inflammatory milieu, relying only on it may not provide an accurate picture of tumor burden.[7]

Using CA125 levels alone for the diagnosis of EOC has limits because it can provide false positive results in patients with benign diseases as well as healthy persons. Less than 20% of EOC patients had lower-than-normal CA125 levels, which are associated with early stages and better prognosis.

According to recent studies, ovarian cancer patients had elevated levels of HE4, encoded by the WFDC2 gene.[8,9] According to earlier research, CA-125 and HE4 have similar specificity and sensitivity when it comes to ovarian cancer diagnosis.

The University Hospital of Quebec City recently evaluated the predictive power of, HE4 and CA125, for cancer death due to EOC.In both training and validation groups, the study discovered a strong correlation between HE4 levels and important prognostic markers. In the training cohort, HE4 performed similarly to CA125 in predicting death; however, a significant correlation was seen in the validation group. Nevertheless, this connection vanished from significance when preoperative prognostic variables were taken into account. Notably, HE4 showed a greater connection with death in womenwith serous ovarian cancer diagnoses. Therefore, in addition to other prognostic indicators, when assessing mortality in EOC, HE4 could prove to be helpful, particularly in cases with serous ovarian cancer.[8]

Most of the tumors have elevated levels of HE4 than CA125 levels.[9]In response to this discovery, dual marker algorithm known as ROMA was deduced, comprising HE4 and CA125 levels as well as the patients' pre- and postmenopausal statuses.[10] Severalstudies have demonstrated that with excellent specificity and sensitivity, ROMA beats other markers in identifying the existence of a malignant ovarian tumor.[11]

There is an urgent need to look for new cancer biomarkers to supplement or replace CA125, and efforts are now being done in this direction. This study is done to evaluate molecular tumor marker levels 'HE4 and CA125 in ovarian cancer'. Specifically, we seek to examine the potential utility of these markers in monitoring and diagnosing ovarian cancer, as well as their correlation with disease progression and prognosis. By evaluating the CA125 and HE4 expression levels, we aim to determine their individual and combined efficacy as biomarkers for detecting ovarian cancer, distinguishing between benign and malignant tumors, and predicting patient outcomes. The scope of this study encompasses both laboratory analysis of marker levels and clinical correlation with patient characteristics and disease parameters. The findings from this research endeavor are expected to contribute valuable insights into the prognosis and diagnosis through the utility of HE4 and CA125

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES

The study aims to look into levels of molecular tumor markers found in women whohave been diagnosed with ovarian tumors, notably HE4 and CA125

OBJECTIVES:

1. To assess CA125 tumor marker levels in epithelial ovarian tumors.

2. To assess HE4 tumor marker levels in epithelial ovarian tumors.

3.To compare sensitivity and specificity between HE4 and CA125 tumor markers in epithelial ovarian tumors.

NEED FOR THE STUDY

The determination of molecular tumor markers HE4 and CA125 is crucial due to several reasons. Ovarian cancer is often discovered in the patient at an advanced stage due to its asymptomatic nature in the early phases, leading to a poor prognosis. HE4 and CA125 are valuable biomarkers that increase the precision of the disease's early detection and surveillance. Traditionally, CA125 has been utilized for the detection and tracking of ovarian cancer. but it has limitations, such as false positives and lack of specificity. HE4, a more recently identified marker, has shown elevated specificity and sensitivity, particularly in differentiating ovarian cancer from benign gynecological conditions. The combined use of HE4 and CA125 improves diagnostic accuracy, enabling better differentiation between malignant and non-malignant conditions, which is essential for timely and appropriate treatment. Additionally, these markers are significant in monitoring treatment response and detecting recurrences, ultimately contributing to improved patient outcomes. Thus, assessing the CA125 and HE4level is vital for clinical management, aiding in early diagnosis, effective monitoring, and personalized treatment strategies.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

The primary cause of mortality among women who are detected with gynecological cancers is ovarian cancer. It ranks as the fifth most frequent reason of mortality of women globally.[12] Diagnosis usually occurs at advanced stages, leading to poor outcomes. Current screening tests offer limited predictive value, exacerbating the challenges of managing this disease. Comprehensive gynecological evaluation, including transvaginal ultrasound and the CA-125 assay, symbolizes important early detection techniques but has not significantly impacted morbidity or mortality.[13] Standard treatment involves platinum-based chemotherapy and surgery; however, in recent years, Poly (ADP-ribose) polymerase (PARP) inhibitors and anti- angiogenic Bevacizumab have been developed as potential therapies for dealing with this gynecological malignancy.[14]

There has been evidence of a significant recurrence rate following the first therapy, with many of these relapsed cases showing worse responses to treatment and being more likely to experience treatment failures. Consequently, there is an urgent requirement for improved prevention and detection strategies, as well as novel treatment approaches, based on an improved knowledge of the molecular characteristics of ovarian cancer.

ETIOLOGY:

Ovarian cancer is associated with various risk factors. It predominantly affects postmenopausal women, with advancing age linked to higher incidence rates, advanced disease stages, and lower survival rates. Parity has been identified as a protective factor in some case-control studies, with later age at childbirth correlating with reduced risk of ovarian cancer.[15]A primary risk factor is the history of breast or ovarian cancer in the family, and an additional increased risk is posed by a personal experience of breast cancer.[16] Research has also shown that smokers are at a higher risk, particularly for mucinous epithelial tumors.

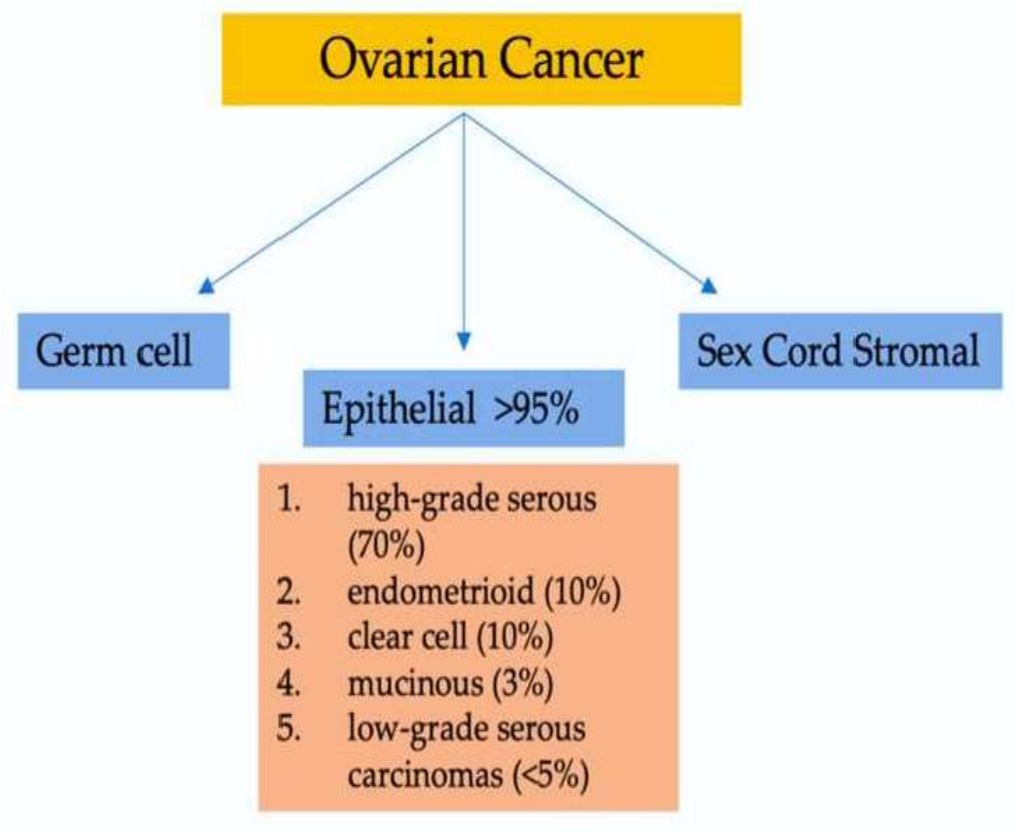


FIGURE 1: CLASSIFICATION OF OVARIAN MALIGNANCIES.

EPIDEMIOLOGY:

In 2020, it was expected that there were 21,750 new cases recorded, accounting for 1.2% of cancer cases overall. It is projected that around 13,940 deaths will be attributed to ovarian cancer. It is expected that the survival rate, relative to 5 years, will be 48.6%. The 5-year survival rate lowers down significantly from 92.6% to 30.2% when found at an early local stage, with just 15.7% of occurrences recognized at the local stage, approximately 58% diagnosed at the metastasized stage. The average age-adjusted incidence rate per 100,000 individuals was 11.1 during the period of 2012-2016.The highest incidence rates are found among non-Hispanic whites (11.6 per 100,000), followed by non-Hispanic blacks, Asian and Pacific Islanders, American Indians and Alaska Natives (10.3 per 100,000), and Hispanics (10.1 per 100,000).Ninety percent of tumors that affect the ovaries are epithelial cancers with the most common kind being serous. The age-adjusted rates of new cases are trending decreasing, according to statistical research.[17]

The estimated age-adjusted occurrence of ovarian cancer in various population-based cancer registries in India ranges from 0.9 to 8.4 per 100,000 women. Incidence rates increase with age, peaking between 55 and 64 years. While most registries have observed a gradual rise in ovarian cancer incidence over time, the overall population prevalence remains low. Therefore, any screening strategy must exhibit high specificity, considering how intrusive follow-up testing for screen-positive results is, in order to obtain a respectable positive predictive value.

In many Western countries, there has been a trend towards reduced incidence and mortality of ovarian cancer, possibly due to preventive measures like increased oral contraceptive use, decreased utilization of postmenopausal hormone replacement therapy, and the adoption of risk-reduction surgeries.

Some studies classify primary peritoneal, fallopian tube and ovarian as one, while others distinguish independent sub-groups. The latter two types comprise 15-20% of cases approximately.

HISTOPATHOLOGY:

Epithelial ovarian cancer encompasses four primary histological types:serous, mucinous endometrioid, and clear cell tumors. These types exhibit various subtypes based on their distinct biology and responses to treatment. Less common subtypes include Brenner and seromucinous tumors.

Further classification of ovarian cancer categorizes it into subtypes: Type 1 and Type 2 tumors.More lethal type II tumors arise from ongoing ovarian cycles that cause endometriosis and inflammation. 'Endometrioid, serous tumors of low grade, clear cell, and mucinous' carcinomas are included in type I tumors, along with rare subtypes like Brenner tumors and seromucinous. They typically originate from atypical proliferative (borderline) tumors and tend to present at an early stage, displaying low proliferative activity and carrying a favorable prognosis, excludingclear cell carcinoma, it is oftenhigh-grade. Conversely, Type II tumors, like from serous tubal, type II tumors arise such as high-grade undifferentiated carcinoma, serous carcinoma, and carcinosarcoma. These are typically high-grade tumors, diagnosed at advanced stages, and exhibit aggressive progression with high proliferative activity and chromosomal instability, often characterized by p53 mutations.[18]

The most prevalent subtype of ovarian carcinoma is Ovarian serous carcinoma. It manifests as either low-grade (LGSC) or high-grade carcinoma (HGSC), with LGSC accounting for 10% and HGSC for 90% of all serous subtype tumors.Cytogenetic examination often reveals low nuclear atypia and infrequent mitosis with fewer molecular abnormalities in LGSC, but HGSC demonstrates considerable nuclear atypia, higher mitotic activity (>12 per 10 high-power fields), and more striking molecular anomalies.[19] HGSCs are typically diagnosed at an older age. The 10- year mortality rate is 70%.Compared to HGSCs, LGSCs are discovered during younger years and have more efficient prognosis.[20]

In ovarian endometrioid carcinomas, the postulation is that they originate from endometriosis. From a morphological perspective, sections that have been sliced exhibit both typical solid portions with significant bleeding and necrosis and cystic areas with soft masses and bloody fluid. Within this subtype, the most common genetic abnormality is a mutation in the beta-catenin gene. despite the fact that significant molecular markers are less well investigated in this group.The distinction between ovarian and uterine-derived endometrioid carcinomas can be made through molecular studies despite their morphological similarities.Compared to uterine cancers, ovarian endometrioid tumors are less likely to have microsatellite instability and PTEN alterations. Single ovarian carcinomas had a lower probability of beta-catenin mutation than synchronous tumors.[21]Women with ovarian endometrioid malignancies are detected in earlier stages.So they typically have a better prognosis

Ovarian mucinous carcinoma often exhibits heterogeneity, with benign and malignant elements coexisting within a single specimen.It is common to find KRAS mutations in certain malignancies. The intestinal subtype may not have stromal invasion, but it does show glandular formations with clinical features of adenocarcinoma. It is often associated with gastrointestinal tract (GI) metastases. Because of their close relationship, it might be difficult to differentiate metastatic mucinous appendix tumors from primary ovarian mucinous carcinomas. As a result, many gynecologic oncologists perform routine appendectomy MOC patients.[22]In borderline tumors of the intestinal subtype, microinvasion is less frequently detected. Invasive mucinous carcinoma is rare, with a favorable prognosis compared to the serous subtype, often diagnosed at stage I in

approximately 80% of cases. However, the molecular alterations responsible for benign mucinous tumor malignant conversion remain elusive.

Among all ovarian carcinomas, less than 5% are clear cell carcinomas that can be distinguished through histopathological analysis by cystic growth patterns, cellular clearing, and a distinctive hobnail growth pattern. Immunohistochemistry reveals that while stage I and II cancers mostly exhibit overexpression of BAX,Higher expression of BCL-2 which is an anti-apoptotic protein, is seen in metastatic lesions. Early-stage ovarian clear cell carcinoma tumors have a similar good prognosis to endometrioid cancers because they have a BCL-2/BAX ratio lesser relative to metastatic lesions.

In all serious malignancies, there is diffuse and strong cytokeratin-7 (CK7) staining; positive rates for mucinous ovarian tumors and other ovarian epithelial cancers range from 80% to 100%. Approximately 25% of metastatic colorectal tumors have CK7 positivity, compared to approximately 96% of ovarian adenocarcinomas.

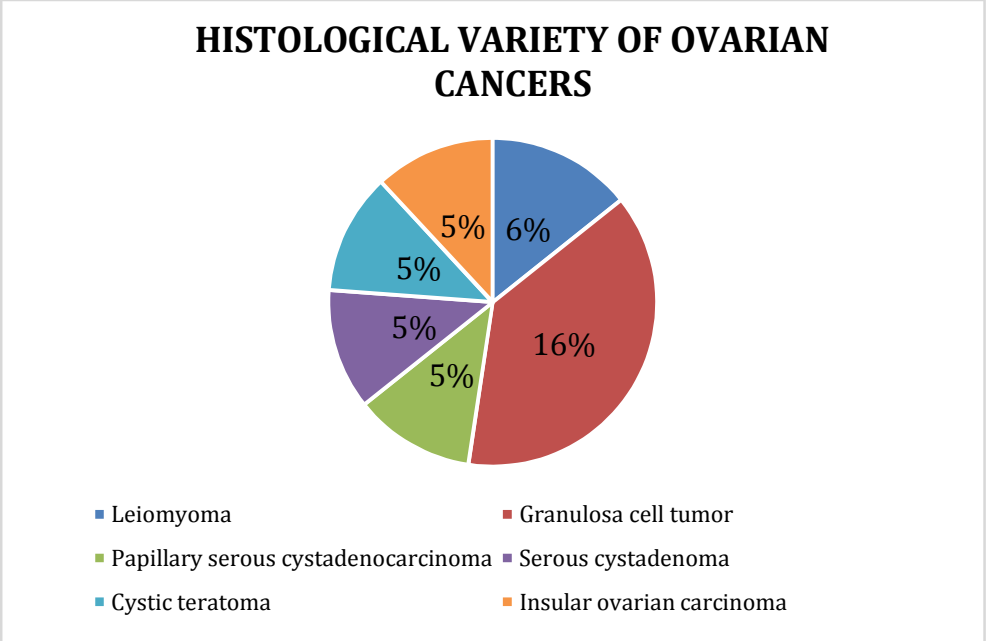


FIGURE 2: DISTRIBUTION OF DIFFERENT HISTOLOGICAL VARIETIES OF OVARIAN CANCER

CLINICAL FEATURES:

Ovarian cancer has non-specific symptoms, making early detection challenging as it can be mistaken for other conditions. Usually, these signs and symptoms appear when cancer is in its later stages (stage III or IV). Bloating, abdominal fullness, nausea, distention, bowel habit changes, early satiety, exhaustion, inadvertent weight loss, back pain, urinary symptoms, and dyspareunia are among the common presenting symptoms. These symptoms may manifest vaguely and manifest months prior to detection.[23]

In cases where suspicion of ovarian cancer is high, a thorough medical assessment must be conducted, comprising a rectovaginal assessment by keeping the bladder empty for the detection of abdominal and pelvic malignancies.In severe occurrences of disease, there may be ascites, reduced breath sounds, or palpable pelvic masses as a result of pleural effusions. In rare instances, 'Sister Mary Joseph nodule' may develop from metastases to the umbilicus.Additionally, the Lesar-Trélat sign, characterized by a sudden increase in seborrheic keratosis findings, may provide a clinical clue suggestive of occult cancer.[24]
Ovarian cancer can rarely present with paraneoplastic syndromes. Subacute cerebellar degeneration, caused by autoimmune reactions against cerebellar antigens induced by the tumor, may lead to symptoms such as diplopia, nystagmus, vertigo, ataxia, and dysarthria. These symptoms frequently appear months or even years before the main ovarian tumor is discovered.Trousseau's syndrome, characterized by high circulating parathyroid hormone-releasing protein levelsand hypercalcemia, is another symptom linked to ovarian cancer. Hypercalcemia can manifest as symptoms including altered mood, nausea, constipation, increased thirst, fatigue, and frequent urination.The quick diagnosis and treatment of ovarian cancer before it advances to an advanced stage is critical for early recognition of these paraneoplastic syndromes, as it guarantees the patient's eligibility for curative therapy.[25]

EVALUATION:

In patients suspected of having ovarian cancer, radiological imaging such as transvaginal ultrasonography (TVUS), which is highly sensitive, or ultrasonography of the pelvis and abdomenis usually used to evaluate how big and complex the tumor isand where it is present. Additional imaging modalities such as abdomen-pelvis and

chest CT scan, pelvic MRI,or PET scan can be utilized for detect tumor extension. Measurement of CA-125 levels is often conducted alongside imaging. Although the CA-125 level is increased in many cases of EOC, its sensitivity for early-stage cancers is limited; in postmenopausal women, higher specificity and positive predictive value were noted.[26]

Elevated CA-125 levels can also be seen in various benign conditions, necessitating the exploration of additional biomarkers to improve specificity diagnosis. One such biomarker under evaluation is HE4, which has demonstrated higher sensitivity for ovarian cancer, particularly in serous and endometrioid subtypes. Combining CA-125 and HE4 levels may offer improved diagnostic accuracy for malignant ovarian tumors in the future.[27]For determination of the possibility of malignancy, ROMA uses formulawhich includes the 'HE-4 and CA-125 levels' modified for pre- and post-menopausal status.[28]

- **RISK MALIGNANCY INDEX (RMI) :** A scoring system used to evaluate the likelihood of cancer in women with ovarian masses. Clinical information, ultrasonography results,and CA-125 levels—a tumor marker—are used to create the RMI score.The following elements are usually included in the RMI calculation:

1. **Ultrasound Score:** This is determined by the ovarian mass's ultrasound results. The precise standards employed may differ, but commonly evaluated characteristics encompass the mass's dimensions, the existence of solid elements, the irregularity of the edges, and the existence of ascites.

2. **Menopausal Status**: The patient's menopausal status is taken into account because it influences the computation of the RMI score overall.

3. **CA-125 Level:** This test gauges the amount of a tumor marker called CA-125, which can be raised in cases of ovarian cancer. It is a blood test.

- The formula for RMI ;**RMI=Ultrasound score× Menopausal status×CA-125 level**
- Steps to Calculate RMI:

1. Based on the ultrasound results of the ovarian mass, assign a number score. - The mass's size (e.g., >10 cm = 3 points, 5-10 cm = 2 points, <5 cm = 1 point), for example.

- Solid component presence (yes = 3 points, no = 0 points, etc.).
- Additional standards unique to the employed scoring scheme.

2. Based on whether the patient is premenopausal or postmenopausal, provide a numerical value. As an illustration:

Prior to menopause: 1 point Postmenopausal : 3 point

3. Based on the CA-125 level in IU/mL, assign a number. Higher levels usually correspond to higher scores.

4. To calculate the RMI score, multiply the values derived from the CA-125 level, status of menopause, andresults of ultrasound.

RMI scores typically range from 0 to around 200 in low-risk scenarios. Scores from around 200 to 450 are often considered intermediate risk, and scores above 450 are often considered high risk.

- **RISK OF OVARIAN MALIGNANCY ALGORITHM(ROMA) :**A tool used for the assessment of the likelihood of ovarian cancer in females with adnexal masses, particularly with combination of biomarkers CA-125 and HE4ROMA. It provides a numerical score that helps categorize cancer patients into high and low-risk categories

- ROMA is determinedusing the following formula: **ROMA = exp(logit score)×100**
- Where the logit score is calculated as:

Logit score=$-12.0+2.38\times\log_{10}(HE4)+0.0626\times HE4-8.09\times\log_{10}(CA\text{-}125)+0.718\times\log_{10}(CA\text{-}125)\times$(menopausal status)

- HE4 is the serum level of the protein
- CA-125 is the serum level of CA-125.
- Menopausal status\text{Menopausal status}Menopausal status is a binary variable where:

  Pre-menopausal = 0 ;Post-menopausal = 1

- Steps to Calculate ROMA:

  1. Measure the biomarkers’serum levels using appropriate laboratory assays.
  2. Take the logarithm (base 10) of HE4 and CA-125 levels.

3.Calculate Logit Score.Substitute the values into the formula for the logit score. Calculate each term separately.

4. Add up the values obtained from the above calculations to get the total logit score.

5. Plug the total logit score into the ROMA formula

The ROMA score provides a percentage that reflects the likelihood of ovarian cancer. A ROMA score < 11.4% suggests low risk. A ROMA score ≥ 11.4% suggests high risk.

For the best staging, an exploratory laparotomy is performed to extensively assess the abdominal and pelvic regions forcancer. This evaluation includes peritoneal surface inspection accompanied by biopsyand/or pelvic washings. The International Federation of Gynecology and Obstetrics has developed staging using which this procedure establishes the stage of ovarian cancer. The next steps usually involve dissection of the pelvic and para-aortic lymph nodes, omentectomy, bilateral salpingo-oophorectomy (BSO), and total abdominal hysterectomy.A pathologist analyzing tissue biopsies makes the concluding diagnosis about the histological type, grade, and stage.Moreover, CA-125 values may be utilizedto calculate RMI, which accounts for menopausal status and TVUS results. A high likelihood of malignancy is indicated by an RMI > 200, which has a specificity higher than 96%.

TUMOR MARKERS

Biomarkers are vital resources for the study and therapy of cancer since they offer quantifiable details about different cell types. As objective medical indicators, these molecular fingerprints consist of genes, proteins, and other molecular characteristics. Biomarkers help determine two things: first, the likelihood that a disease will progress or that pathological processes will occur, and second, they help evaluate the effectiveness of treatment therapies. Biomarkers are compounds that can be tested in body fluids and blood and are created by neoplasm cells or adjacent cells. They are useful for cancer screening, diagnosis, and therapy monitoring. Oncogenes and their derivatives, antigens, cytoplasmic proteins, enzymes, hormones, and receptors are a few examples of biomarkers.[29,30]

High specificity and sensitivity to a particular type of tumor, clinical validation, acceptance of pateints through prospective studies, and predicted values, both positive and negative for prognostic and predictive advantages are some of the essential attributes of the ideal cancer biomarker. Yet none of the biomarkers available today meet all of these perfect requirements. Biomarkers are classified according to the uses they have, such as screening, prognostication, determination of tumor's presence or absence, and molecular target identification for new treatments.[31,32]

Analyzing bodily fluids like blood/serum/plasma saliva, and urine utilizing noninvasive and minimally invasive techniques improves the search for tumor biomarkers. Urine is highlighted as an important waste product because it is more readily available, has a higher volume, and has a simpler proteome than blood.[33,34,35,36]With the potential to detect and track ovarian cancer, urine-based biomarkers are a promising avenue for not just better diagnosis but more efficient treatment of the condition.

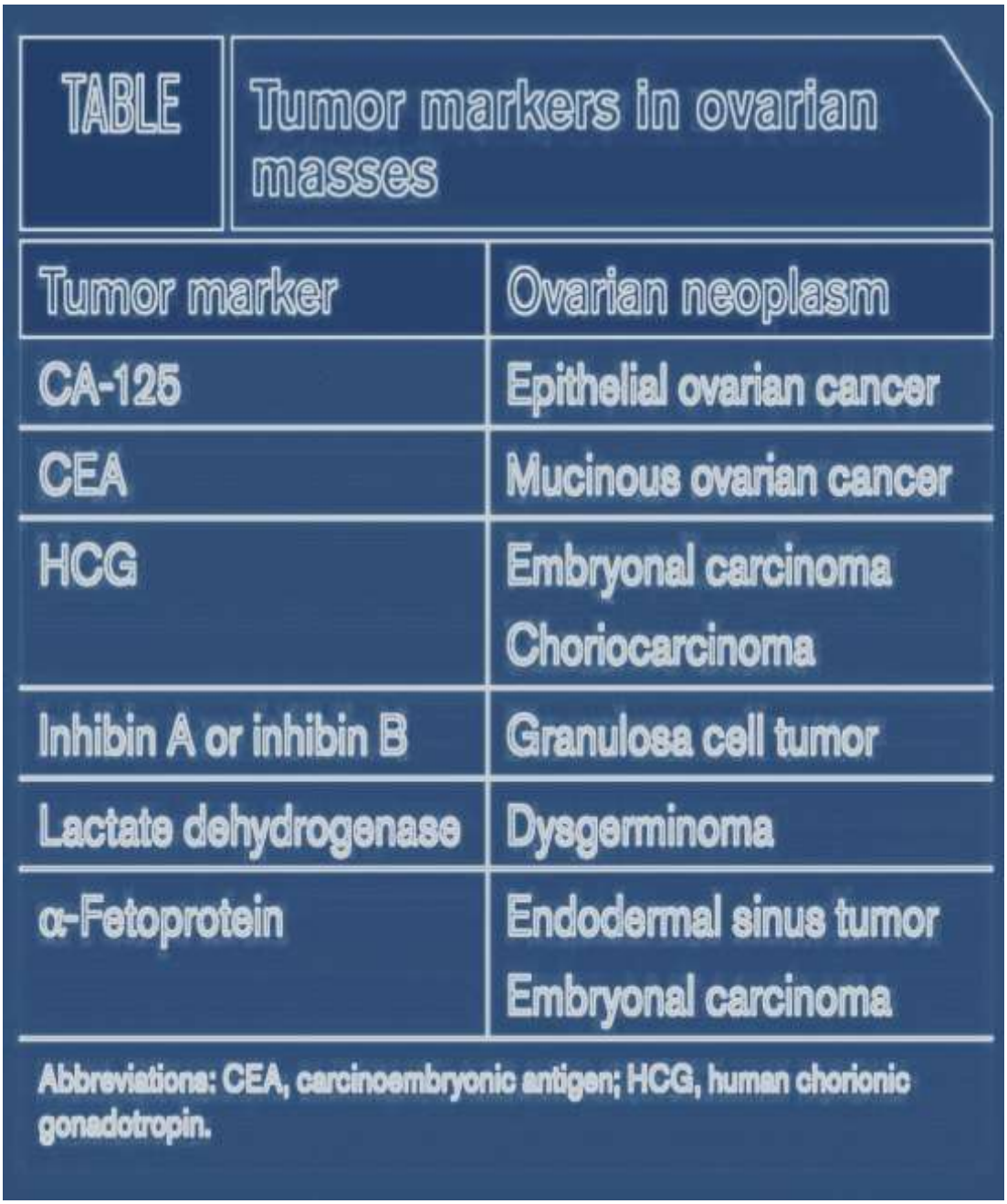


TABLE Tumor markers in ovarian masses

Tumor marker	Ovarian neoplasm
CA-125	Epithelial ovarian cancer
CEA	Mucinous ovarian cancer
HCG	Embryonal carcinoma Choriocarcinoma
Inhibin A or inhibin B	Granulosa cell tumor
Lactate dehydrogenase	Dysgerminoma
α-Fetoprotein	Endodermal sinus tumor Embryonal carcinoma

Abbreviations: CEA, carcinoembryonic antigen; HCG, human chorionic gonadotropin.

FIGURE 3: TUMOR MARKERS IN OVARIAN CANCERS

CA-125:

The glycoprotein CA125 was discovered in 1981. It is produced by‘ mucin 16 (MUC16) genes and OC 125 monoclonal antibodies’ can be used to identify it in ovarian cancer tissues. In patients who are pre-menopausal or who are postmenopausal, the maximum level of CA125 is 35.0 U/mL.[37]

Significant importance is played by CA125 in diagnosis and prognosis. According to FDA guidelines, CA125 is a useful protein biomarker for tracking patients with ovarian cancer and assessing how well their treatment is working. Clinical decision-making can be aided by the correlation between CA125 levels and survival outcomes as well as the clinical stage. However, because non-tumor cells may secrete in an inflammatory milieu, CA125 alone might not be an accurate indicator of tumor burden.[38]

An increased CA125 level (>35 U/mL) following surgery indicates a higher likelihoodof tumor malignancy, decreased chemotherapy sensitivity, and residual illness. Based on CA125 values, the Gynecologic Cancer Intergroup (GCIG) has proposed standards for distinguishing between tumor remission and recurrence. Patients are classified as responders if they show a least 50% drop during a four-week period, and patients who show complete response have CA125 levels that are in the optimal range (<35 U/mL). A doubling of CA125 readings within a week indicates the progression or recurrence of ovarian cancer. It's important to keep in mind that persistent CA125 values less than 35 U/mL do not rule out the chance of lingering disease or recurrence.[39,40]

CA125 has become an important prognostic factor.It's crucial for prognosis that CA125 levels normalize less than35 U/mL by the third cycle of chemotherapy following the initial measurement.An extended progression-free survival and a positive response to treatment are indicated by lower levels of CA125 and faster normalization. A decrease in CA125 levels following neoadjuvant chemotherapy indicates that the debulking operation will go well. During first-line chemotherapy, routine CA125 monitoring aids in the identification of individuals with decreased drug sensitivity, allowing for prompt treatment modifications. Although CA125 is a reliable indicator of how the disease will proceed after chemotherapy, it has little bearing on post-chemotherapy survival. There's potential for insulin signaling-induced CA125 oversecretion to predict chemoresistance.

According to a recent study,women withCA125 levels below 10 U/mL had prolonged progression-free survival, underscoring the significance of lowering these levels. Nevertheless, it is still unclear how a maximal surgical effort may affect the reduction of CA125 readings.[41,42]

HE4

The glycoprotein HE4, which has a serine proteinase inhibitory function, is produced by the WFDC2 gene. Enzyme immunoassays can be found in patients' blood and urine and may be biomarkers for ovarian cancer. Certain subtypes of ovarian cancer exhibit over expression of HE4, with endometroid tumors showing 100% incidence and serousovarian cancers showing 93%. Due to this feature, it can help with differential diagnosis by helping to differentiate between different types of tumors. To deeply understand the molecular mechanisms behind HE4's involvement in the initiation and progression of ovarian cancer, more research is required.HE4's serine proteins inhibitory activity and its involvement in cancer biology suggest potential therapeutic targets that could be explored in future studies. The FDA issued a warning against using HE4 to screen for asymptomatic early-stage ovarian malignancies in 2008, but it did approve its use for monitoring patients who had already received an ovarian cancer diagnosis.[43]

A new study at the University Hospital of Quebec City examined diagnostic value HE4,as well as CA125, in predicting death rate among patients with epithelial ovarian cancer.In training and validation cohorts both, significant correlations between HE4 levels and critical prognostic variables were discovered. In the training cohort, HE4 outperformed CA125 in terms of mortality prediction, and a strong correlation was also seen in the validation cohort. Nevertheless, this association lost significance when preoperative prognostic variables were taken into account. Notably, HE4 showed a greater correlation with death in females with serous ovarian cancer. while HE4 enhances prognostic assessments, its clinical application must be integrated with comprehensive evaluation and other prognostic indicators to maximize its utility. Current guidelines advocate for the combinational use of HE4 with CA-125 and imaging techniques to optimize diagnostic accuracy and therapeutic decision-making in ovarian cancer management. Future research aimed at elucidating HE4's molecularmechanisms and refining its clinical implementation promises to further enhance its rolein improving outcomes for patients with serous ovarian cancer. Therefore, HE4 can

provide useful insight for predicting mortality in EOC when combined with other prognostic variables, especially in cases with serous ovarian cancer.

CA 15-3

In a 1988 study, 41% of patients especially those with advanced stages of the disease and ovarian cancer had higher levels of CA 15-3 (>30 U/mL). These increased levels were correlated with the presence of residual tumor, responsiveness to treatment, and development of the disease during chemotherapy. Additionally, notable distinctionswere seen between the cancer cohort and groups of benign as well as healthy controls, showing that cancer patients had higher than normal levels of tumor markers. When tumor markers like CA125 CA72-4, and CA15-3 are combined, the sensitivity is higher than when the individual markers are used alone. This suggests that the combinationmay be useful for diagnosing ovarian cancer.

In a different study, several serum indicators were used to assess an Artificial Neural Network model for initial identification. When it came to differentiating between cancer patients in their early stages and healthy persons, this model performed better. The composite index that was obtained from the artificial neural network (ANN) had greater diagnostic potential than CA125 by itself. The combinational use of many serum indicators via the ANN model, which increased both sensitivity as well as specificity in discovering Stage Iof the disease, demonstrated the promise of this strategy to improve ovarian cancer early detection and diagnosis.[44]

CA 19-9

Recent studies have explored the possible utility of a marker for gastric, hepatobiliary, and pancreatic cancers known as CA 19-9 for ovarian cancer (OC) screening. Studying six biomarkers, including CA19-9, Fah my et al. found encouraging results with high sensitivity and specificity, indicating that the biomarker may be useful for either diagnosing or ruling out the illness. In a study with 30 healthy controls and 120 patients with ovarian cancer and tumors, the ‘miRNA-204, CA125, hepcidin, ferroportin, CA19-9, micro fibril-associated glycoprotein 2,levels’other proteins evaluated. Patients with ovarian cancer had greater levels of ‘microRNA-204, CA125,CA19-9’ but lower levels of ‘hepcidin, micro fibril-associated glycoprotein2, and ferroportin’. Receiver operating characteristic (ROC) research revealed that CA125 and CA19-9 alone

showcased more efficiency in diagnosis. Combining them with microRNA-204 demonstrated the strongest diagnostic performance.[45]

Another retrospective investigation measured serum levels of CA19-9, CEA, and CA-125, before surgery in 314 individuals with mutinous ovarian tumors. The study looked into correlations between biomarker levels and clinic pathological variables and assessed their diagnostic effectiveness using ROC curves. Tumor pathology was impacted by raised levels of CEA CA19-9, and CA-125, as well as tumor size; larger mutinous tumors and elevated levels of these biomarkers revealed a favorable correlation with elevated risk. Out of the markers, CA-125 demonstrated most exceptional ability in distinguishing whether mutinous ovarian tumors were benign, borderline, or malignant. Tumor size and preoperative elevations of CA19-9, CA-125, and CEA can be helpful indicators in differentiating between different types of tumors.

HCG

Since ovarian cancer (OC) and other tumor types express human chorionic gonadotropin (hCG), it may be a useful prognostic and therapeutic target. Several isoforms of human chorionic gonadotropin (hCG) with distinct biological activity are found in bodily fluids. These include intact hCG, nicked free β-subunit (hCGβn), free β subunits (hCGβ), cleaved hCGn, and inactive hCGα, β-core fragment.

The predictive usefulness of hCG in epithelial ovarian cancer was examined in twotrials. According to one study, hCG mRNA and its expression were higher in EOC patients, and the expression was higher in samples with advanced disease. It was found that tumor spread and elevated hCG expression were independent adverse prognostic variables for survival over all. A further study that looked at the serum levels of hCG in women with ovarian tumors discovered that hCG was detected in 68% of the ovarian cancer tissues, with differences in the histological subtypes. The stage and grade of the tumor had a major impact on hCG expression. Higher 5-year survival rates were seen in women with hCG-positive tumors and LH-R-positive/FSH-R-negative malignancies.

Additionally, the LH/hCG receptor expression was examined in a variety of ovarian tumors, and the results showed that a significant percentage of ovarian malignancies, benign cystadenomas,and borderline tumorshad positive expression. A better prognosis

was linked to tumors that expressed the LH/hCG receptor, especially in cases of well-differentiated cancer morphologies. These results point to the possibility of using the LH/hCG and Hcg receptors as targets for novel therapies that maximize benefits and minimize side effects.[46]

INHIBIN

Growth factors known as inhibins, which are mostly produced by ovarian follicles and are involved in the regulation of fertility, are composed of the α and β subunits. Because different subtypes of ovarian cancer create varied quantities of inhibin species, measuring total inhibin is crucial to the investigation of this disease. Total inhibin is higher in postmenopausal patients with granulosa cell tumors and mucinous epithelial cancers. Inhibin enhances the identification of ovarian cancer, especially for certain subtypes when paired with CA125. But there is a limit to how well inhibin may be used as a marker in women who have not undergone menopause.

An investigation was conducted by utilizing the αC inhibin immune of luorometric assay and CA125, on the serum inhibin concentrations in ovarian cancer women whohad undergone menopause, results showed superior specificity and equivalent or better sensitivity than earlier techniques. While the combination of anti-Müllerian hormone (AMH) and inhibin B has the potential to be used for detection, monitoring of granulose cell tumors, postmenopausal women without ovarian cancer typically have undetectable levels of inhibin A and B. For some mucinous and serous epithelial cancers, total inhibin, which contains the free alpha subunit and inhibin A and B, may be beneficial upon combination with CA-125. The usefulness of the determination of inhibin for early tumor identification and premenopausal women is still unknown, though. Women with granulosa cell tumors have higher serum levels of inhibin, which makes it a useful tumor marker. Inhibin RIA and inhibin ELISA are two examples of assays that have been created and have the potential to be widely used. Although total inhibin levels in healthy postmenopausal women are generally low, they can identify cases of ovarian cancer. When inhibin and CA125 are combined, the detection of ovarian tumors is enhanced, leading to excellent sensitivity and specificity. The underlying molecular and pharmacological processes driving elevated inhibin levels in ovarian cancer are believed to be mediated by enhanced gonadotropins. Early-stage mucinous carcinomas are found to exhibit detectable amounts of inhibitor, indicating possible sensitivity at

this stage of the disease. Normal postmenopausal women frequently have undetectable inhibitor levels; nonetheless, when detected, the levels show a dose-response relationship with inhibin A. Monitoring inhibin B, a tumor burden biomarker, can be useful in assessing therapy response and predicting disease recurrence because GCTs can spread and occur again. Inhibin, specifically inhibin B, is a useful circulating tumor marker for GCTs. Therefore, more investigation is required for the comprehension of molecular path physiology and the developmental function of inhibin.[47]

AFP

A fetal serum protein called alpha-fetoprotein (AFP) can be developed as a marker to find malignant growths. However, high AFP levels are unusual in epithelial ovarian cancer, excessive AFP levels in EOC can result in misdiagnosis, especially in young women. This complicates the process of making an accurate diagnosis and emphasizes the value of thorough assessment. A study found a connection between aggressiveconduct and a poor prognosis and AFP-producing EOC. All cases had confirmed AFP expression, indicating that the EOC differentiated into components of the yolk sac. Older women's serum AFP levels are rarely checked, which could result in missed diagnosis.An additional investigation assessed various tumor markers, such as AFP, anddiscovered that they were useful in differentiating between benign cases of ovarian cancer and healthy persons. Ovarian cancers that produce AFP are uncommon and might be challenging to diagnose. Better management approaches are required because AFP-producing tumors are uncommon and have a poor prognosis. AFP has limits in early-stage screening, even though it is frequently utilized for ovarian germ cell tumors together with other blood indicators.Monitoring levels of βhCG and AFP is essential for prognosis,inhibin B is a useful tool for tracking granulosa-theca cell malignancies.According to a study, ovarian cancer may be correctly diagnosed with a combination of color Doppler, tumor marker testing, and transvaginal sonograph.[48]

LDH

One of the enzymes involved in glycolysis, lactate dehydrogenase (LDH), transforms pyruvate into lactic acid. Higher LDH blood levels were seen in ovarian cancer patients, according to studies, which suggests that neoplastic cells are releasing LDH into the surrounding medium. A Prospective study, Increased serum LDH values were observed in ovarian cancer patients. Sensitivity, specificity, positive predictive value, and negative

predictive value were found to be 60%, 86%, 70%, and 75%, respectively,when using a threshold level of 450 IU/mL for serum LDH. According to scientists, serum LDH levels may be a useful biochemical indicator for differentiating between benign and cancerous tumors.

In a 2017 study, Bastani et al. assessed serum marker diagnostic values such as prostasin, AFP, hCG + β, CA125,and LDHin EOC and their capability to distinguish benign tumors and EOCas well as healthy persons. Serum levels of CA125, LDH, and prostasin were significantly higher in EOC patients compared to benign tumor and healthy control groups. It has been established that higher EOC stages are associated with greater LDH levels. Prostasin, LDH, and CA125 together enhanced theprognostication of EOC status. In EOC patients, the multi-marker method has shown potential for more accurate distinct diagnosis.[49]

Emerging Tumor Markers

1. **Micro RNAs**
2. **Patterns of DNA Methylation**
3. **Circulating Tumor Cells**

The determination of molecular tumor marker levels HE4 and CA125 is a critical diagnostic and prognostic tool. HE4 and CA125 are established biomarkers for detection and monitoring. By analyzing their levels, clinicians can enhance early detection, differentiate if tumors are benign or malignant, and assess treatment response. This approach enables more precise patient management, facilitating timely interventions and improving outcomes. Additionally, the combination of HE4 and CA125 offers greater sensitivity and specificity than either marker alone, underscoring the importance of this dual-marker approach in comprehensive management.

IMPORTANCE OF EARLY DIAGNOSIS

The term "ovarian cancer" refers to a broad as well as intricate group of disorders that differ in their appearance and biological characteristics. Despite its lower prevalence compared to breast cancer, OC has a disproportionately high impact due to its significant contribution to mortality rates. Advanced stage III ovarian tumors often prove lethal for the majority of patients, with recurrence after surgical procedures and

chemotherapy observed in approximately 75% of cases. On a global scale, ovarian cancer is acknowledged as the deadliest type of gynecological malignancy and being fifth main reason for carcinoma-related mortality in Western females. Improving the effectiveness of screening techniques, including testing for particular biomarkers, may make it more likely that OC will be discovered early on.[50]

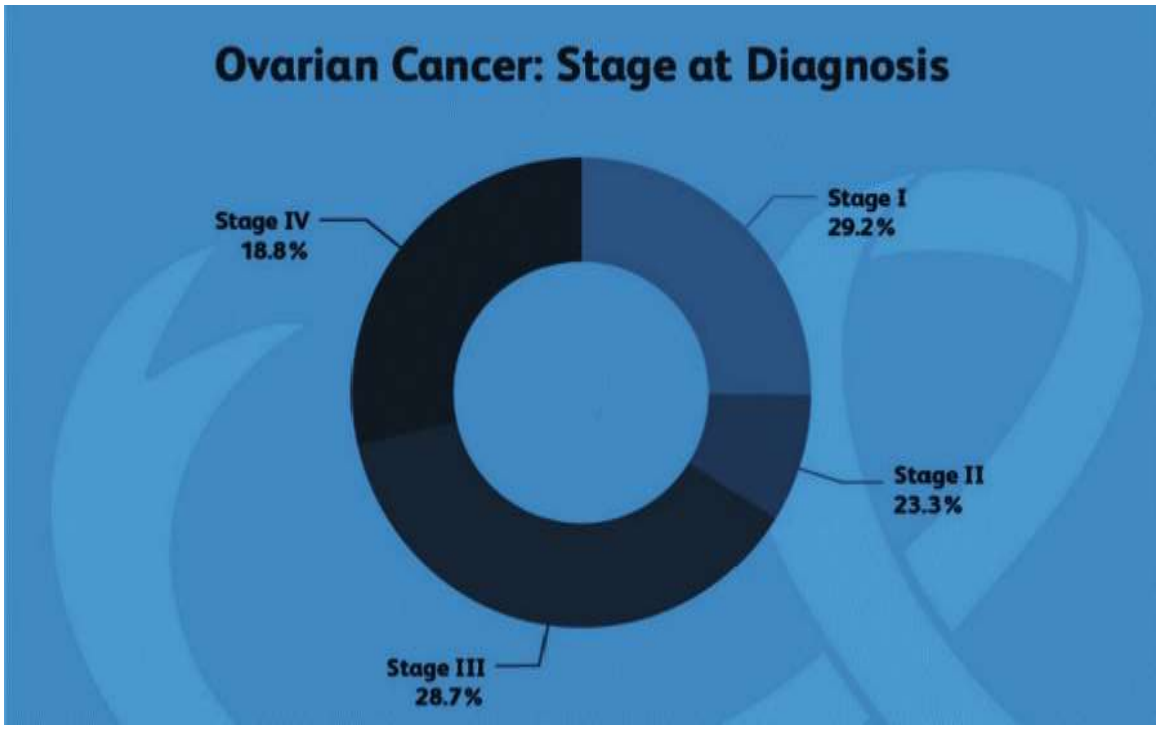


FIGURE 4: STAGE OF DIAGNOSIS

DIFFERENTIAL DIAGNOSIS:

The differential diagnosis comprises of:

1.Colon cancer

2. Metastatic gastrointestinal carcinoma

3.Gastric adenocarcinoma

4. Papillary adenocarcinoma

5. Undifferentiated adenocarcinoma

6. Small-cell adenocarcinoma

7.Serous adenocarcinoma

8.Uterine fibroids

9.Ovarian torsion

10.Endometriosis

11.Retroperitoneal mass

12.Embryologic remnants

13.Peritoneal cyst

14.Brenner tumors

COMPLICATIONS:

In their final six months, women who lost their lives to ovarian cancer have a number of difficulties. They are:

Constipation (49%)

Pedal edema (44%)

Weakness or fatigue (75%)

Anemia (34%)

Nausea or vomiting (71%)

In addition to nutritional problems, women who were not able to receive therapy are often discovered to have major consequences like ascites, intestinal blockage, pleural effusion, and bladder obstruction.[51]

MANAGEMENT:

Debulking Surgery

Chemotherapy and surgical procedures are commonly used in ovarian cancer treatment. The usual treatment for early-stage invasive epithelial ovarian carcinoma is complete surgical staging for lesions with minimal chance of developing into malignancy and a unilateral salpingo-ophorecto my while sparing the contra lateral ovary and uterus. Debunking surgery, however, has been demonstrated to have superior results in cases of advanced-stage ovarian cancer. This procedure may comprise a hysterectomy or a bilateral salpingo-oophorectomy (BSO). Exploratory laparoscopic surgery is frequently the first step in determining whether debunking surgery is beneficial for a patient. This process aids in determining whether a significant or persistent tumor load exists, which may impair blood flow to the afflicted location, resulting in tissue damage and possibly escalating resistance to multidrug treatment. Laparoscopic surgeries are preferred in some cases due to their less invasive nature and shorter recovery times compared to debulking surgeries. Additionally, it's recommended for ovarian cancer patients to undergo genetic risk evaluation and testing for germline and somatic mutations, such as BRCA1/2, if not previously done, as this information can guide maintenance therapy.

Primary Debulking Surgery Versus Neoadjuvant Chemotherapy

Women suspected with advanced stage IIIC or IV cancer are usually evaluated to see if surgery is needeed. Neoadjuvant chemotherapy is recommended for individuals considered not fit for undergoing surgery with a low possibility of achieving the desired results of cytoreduction in order to reduce the tumor burden. Clinical practice recommendations from the Society of Gynecologic Oncology and the American Society of Clinical Oncology state that patients who have a good surgical profile may consider primary cytoreductive surgery or neoadjuvant chemotherapy. Primary cytoreductive surgery is recommended but in case of a good chance of achieving cytoreduction to less than 1 cm with manageable morbidity. Patients must have a biopsy confirming the histological diagnosis of invasive ovarian cancer prior to beginning neoadjuvant chemotherapy, preferably using specimens from paracentesis or fine-needle aspiratio.[52] Numerous clinical trials comparing interval cytoreductive surgery with neoadjuvant chemotherapy to upfront main cytoreductive surgery have shown comparable overall median survival results.Notably, two phase III trials have demonstrated that neoadjuvant chemotherapy is not less effective than cytoreductive surgery, which is then followed by chemotherapy in patients with stage 4 cancer. From this, we can understand how important neoadjuvant chemotherapy is for womenwith advanced-stage invasive cancer who have a high tumor burden and are poor candidates for surgical intervention.The CHORUS trial, which enrolled women with stage IIIC–IV epithelial ovarian cancer, and the European Organization for Research and Treatment of Cancer (EORTC) phase III trial EORTC 55971 showed that neoadjuvant chemotherapy had a non-inferior median overall survival ascompared to primary cytoreductive surgery. Also,examination of patient's data from the trials revealed that femaleswith stage IV cancer had betterresults of survival with neoadjuvant chemotherapy followed by cytoreductivesurgical procedure. Patients who received primary cytoreductive surgery had better survival outcomes when their metastatic tumors were less invasive and in stage IIIC (<4.5 cm), according to an exploratory analysis of the EORTC 55971 research. Neoadjuvant treatment, however, improved survival rates for individuals with more invasive metastatic tumors and stage IV cancer (>4.5 cm).[53,54]

Maximal Cytoreductive Surgery

Whether surgery is done before or after neoadjuvant chemotherapy, achieving maximal cytoreduction is a critical component in enhancing median survival among women with stage III or IV disease. The best result is to have no remaining disease. 10% more maximal cytoreduction was linked to a 5.5% elevation in overall median survival,according to a meta-analysis that included 6885 patients with stage III and IV ovarian cancer. The mean weighted median survival time rose by 50% when cohorts with equal to or less than 25% maximal cytoreduction were compared to those with more than 75% maximal cytoreduction.[55]

Nevertheless, no statistically significant relationship was discovered in this investigation between the intensity of the platinum dose and the log median survival time.Interval cytoreductive surgery is typically performed in four cycles or less following neoadjuvant chemotherapy to ensure early surgical procedures during cancer. However, because there's a chance of less postoperative healing, the patient should rest for at least 20 days before surgery if bevacizumab was given as part of their original neoadjuvant chemotherapy regimen.[56]

Primary Chemotherapy and Neoadjuvant Therapy

Adjuvant chemotherapy increases overall and progression-free survival in the initial - stage, particularly in high-risk patients with suboptimal staging. However, because surgical treatment alone has an excellent survival probability, it is advised for grade 1 endometrioid carcinomas and epithelial ovarian cancers in stages IA or IB. Patients who are not properly staged but have residual illness benefit from adjuvant chemotherapy. In high-risk early-stage cancer with characteristics such as stage IC and stage II illness, adjuvant chemotherapy appears to be beneficial overall, especially in cases with clear cell or high-grade histology. The preferred treatment plan is frequently paclitaxel plus carboplatin, which is comparable to advanced ovarian cancer treatment.Advanced-stage ovarian cancer: Depending on the degree of tumor debulking, intravenous (IV) or intraperitoneal (IP) administration of platinum-based chemotherapy in combination with a taxane is the usual treatment for advanced ovarian cancer. Research such as the phase III trial GOG111 has shown that the combination of paclitaxel and cisplatin results in enhanced overall survival when compared to other regimens. In these regimens, carboplatin has proven to be a more effective and well-tolerated substitute for

cisplatin.However, because of increased toxicity, such as neutropenia, thrombocytopenia, neurotoxicity, and gastrointestinal problems, clinical usage of intraperitoneal chemotherapy has been uneven despite the efficacy of the treatment being proven in landmark trials such as GOG 104, GOG 114, and GOG 172, and GOG 252. Further confounding treatment considerations, the inclusion of bevacizumab in GOG 252 did not demonstrate any advantage of IV/IP chemotherapy over IV chemotherapy with bevacizumab.

Chemotherapy for the Elderly population

A randomized controlled trial investigated elderly patients 70 years of age or older with comorbidities who had stage III-IV cancer. It found that carboplatin monotherapy led to worse survival outcomes compared to carboplatin-paclitaxel given either three weekly or weekly. However, when combinatorial therapy was given, a modified dose-dense regimen of weekly carboplatin plus paclitaxel showed better tolerability with reduced toxicity compared to conventional three-week scheduling. However, the MIT07 phaseIII trial showed that it did not increase progression-free survival, and because of the reduction in high-grade neutropenia, febrile neutropenia, thrombocytopenia, and neuropathy, it could still be prescribed for older patients who are weak. To improve the prediction of chemotherapy tolerance, a prospective trial with a focus on older women (70 years and above) and a variety of chemotherapy regimen combinations is now underway. According to preliminary data, patients who scored better on the instrumentalactivities of daily living at baseline had a higher chance of finishing all four chemotherapy cycles and a lower risk of experiencing high-grade toxicity.

Maintenance Therapy

Maintenance therapy aims in the prevention of the growth of residual cancer cells by slowing down their division, thus preventing disease recurrence. Numerous randomized trials have compared maintenance therapy to observation to assess its efficacy.

1. Platinum-based agent
2. Anti-angiogenic inhibitor
3. Poly (ADP)-ribose polymerase (PARP) inhibitors
4. Immunotherapy
5. Vaccines

MATERIALS AND METHODS

MATERIALS AND METHODS

Source of data: The study was conducted on women who were diagnosed with epithelial ovarian tumors by clinical examination and confirmed by ultrasonography and tumor markers at the department of OBG, RL Jalappa Hospital, Kolar, during the study period from September 2022 to December 2023.

Study design: Cross-sectional study

Study Duration: September 2022 to December 2023.

Method of collection of data: A cross-sectional study is conducted in epithelial ovarian tumor patients who will be coming to obstetrics and gynecology OPD at RL JALAPPA hospital, Tamaka, Kolar attached to SRI DEVRAJ URS MEDICAL COLLEGE under SRI DEVRAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH CENTRE.

All patients who were diagnosed with ovarian cancer and who had given consent for the study underwent routine physical examinations. Preoperative evaluation such as CA 125 and HE4 was done, and the Risk malignancy index and risk of ovarian malignancy algorithm were calculated.CA 125 and HE4 tests were performed with a Cobas E 602 immunoassay analyzer using Elecsys CA 125 II and Elecsys HE4 test reagents.Surgical intervention was done for patients with suspected ovarian malignancy, and the specimen was sent for histopathological examination.

Sample size : 54

As per ICMR 2019 [10] fact sheets regarding ovarian cancer

P=3.44% q=3.44%,q=(100-p)=96.6%, alpha=0.05% and power of test=95%, l=5%

n= 4Pq/l2 n =4x3.44x96.6/52 n=54

FORMULA:

n = 2sp2 [z1-ά/2+z1-ß] 2 / µd2 sp2 = s12 + s22 / 2

Where, s12= Standard deviation in the first group s22= Standard deviation in the second group μd2= Mean difference between the samples ά = Significance level

1-ß = Power of test

Inclusion Criteria:

1. Women aged above 18 years who gave written informed consent for study participation
2. All Peri and post-menopausal women who had been diagnosed with ovarian tumors.

Exclusion Criteria:

1. Less than 18 years of age
2. Women diagnosed with non-epithelial ovarian tumors
3. Ectopic pregnancy or normal pregnancy.

Methodology:

- A study was conducted in patients coming to obstetrics and gynecology OPD at RLJALAPPA hospital, Tamaka, Kolar attached to SRI DEVRAJ URS MEDICAL COLLEGE under SRI DEVRAJ URS ACADEMY OF HIGHEREDUCATION AND RESEARCH CENTRE.
- Detail history of the patient like age, menstrual status, obstetric history, relevant medical and family history, and presenting symptoms was noted. General examination, systemic and pelvic examination was done.
- Ultrasonography was done in all the patients, Risk malignancy index is calculated and CT scan and MRI was done if required.
- Informed consent was taken from all patients, before the collection of biological samples and surgery,
- CA-125 and HE4 levels were evaluated in all patients suspected of ovarian tumors.
- All patients diagnosed with a pelvic mass of suspected ovarian origin were scheduled for surgery
- Histopathological examination of the surgically removed tissue was processed in the Department of Pathology of our institute.

Statistical analysis:

It was conducted using SPSS version 21.0 for Windows. Data will be entered in MS Excel office. Data analysis will be done by using SPSS Software version 24.

Categorical variables were expressed as exact numbers and percentages, and continuous variables were shown as mean ± SD.

Two methods were used to analyze categorical variables: “Fisher's exact test and the Chi-square test.”

Serum HE4 and CA-125 diagnostic performance were calculated and compared, including sensitivity, specificity, and predictive values. The sensitivity and specificity of both tests will be analyzed by using ROC curve analysis. A p-value<0.05 indicated statistical significance.

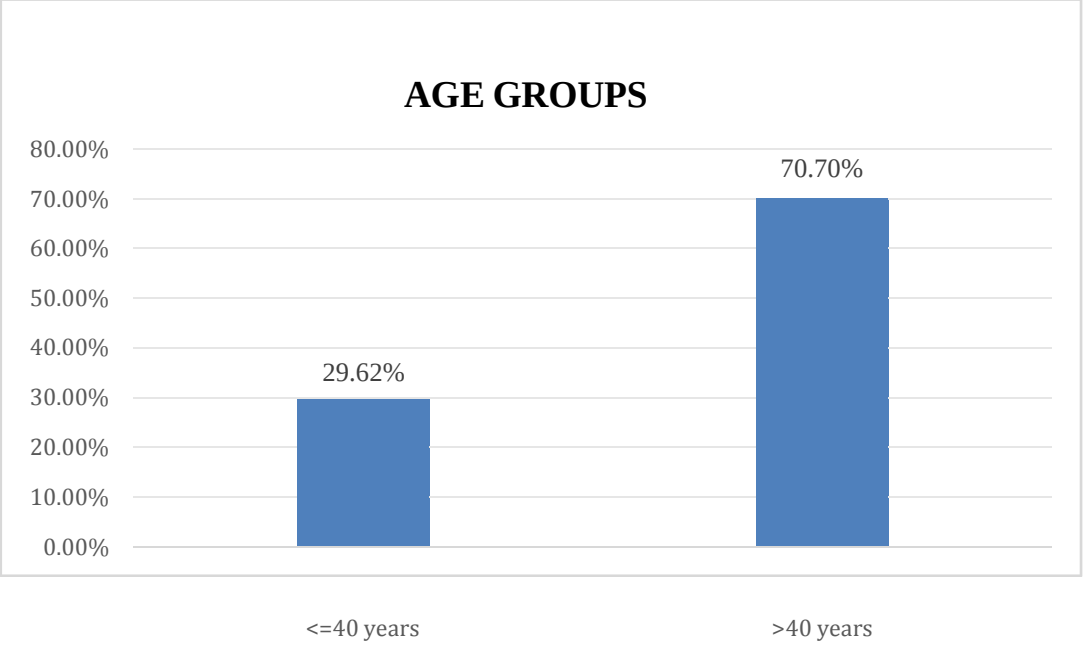
OBSERVATION AND RESULTS

OBSERVATION AND RESULTS

TABLE-1: DESCRIPTIVE ANALYSIS OF AGE GROUPS IN THE STUDY POPULATION

Age groups	Cases (n=54)	Percentage
</= 40 years	16	29.62%
>40 years	38	70.70%

GRAPH- 1: DESCRIPTIVE ANALYSIS OF AGE GROUPS IN THE STUDY POPULATION.

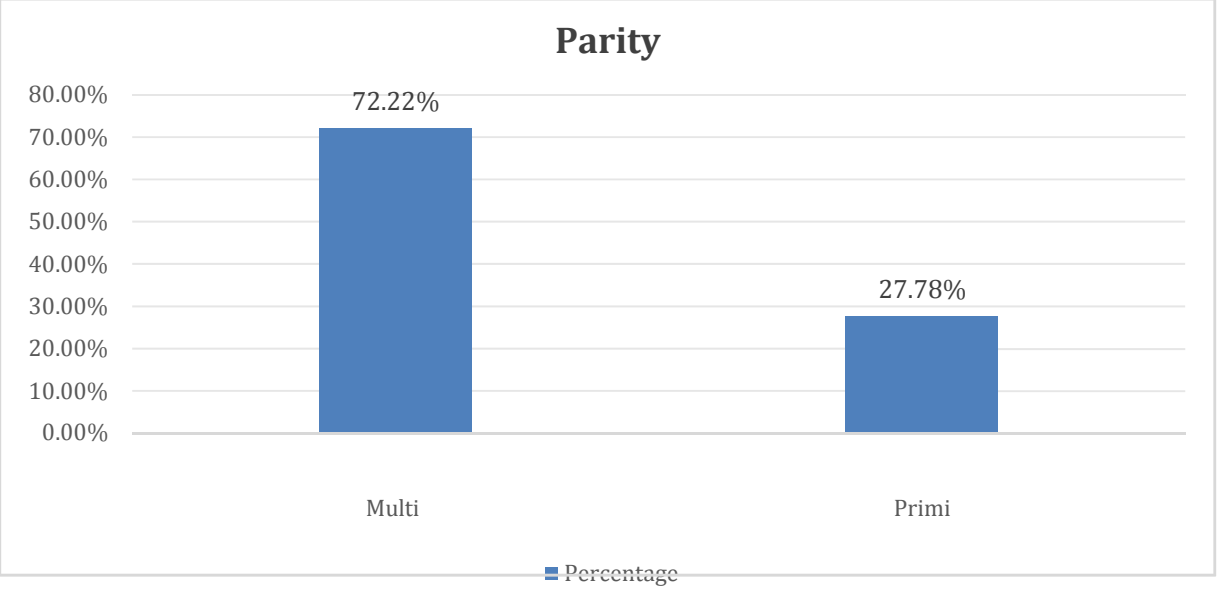


The data reveals that out of the total population under study, 16 individuals fall into the age group of 40 or below, constituting approximately 29.62% of the sample. Conversely, a larger portion of the population, comprising 38 individuals, belongs to theage group exceeding 40 years, representing about 70.70% of the total.

TABLE-2: DESCRIPTIVE ANALYSIS OF PARITY IN THE STUDY POPULATION.

Parity	Cases (n=54)	Percentage
Multi	39	72.22%
Primi	15	27.78%
Total	54	100.00%

GRAPH -2: DESCRIPTIVE ANALYSIS OF PARITY IN THE STUDY POPULATION

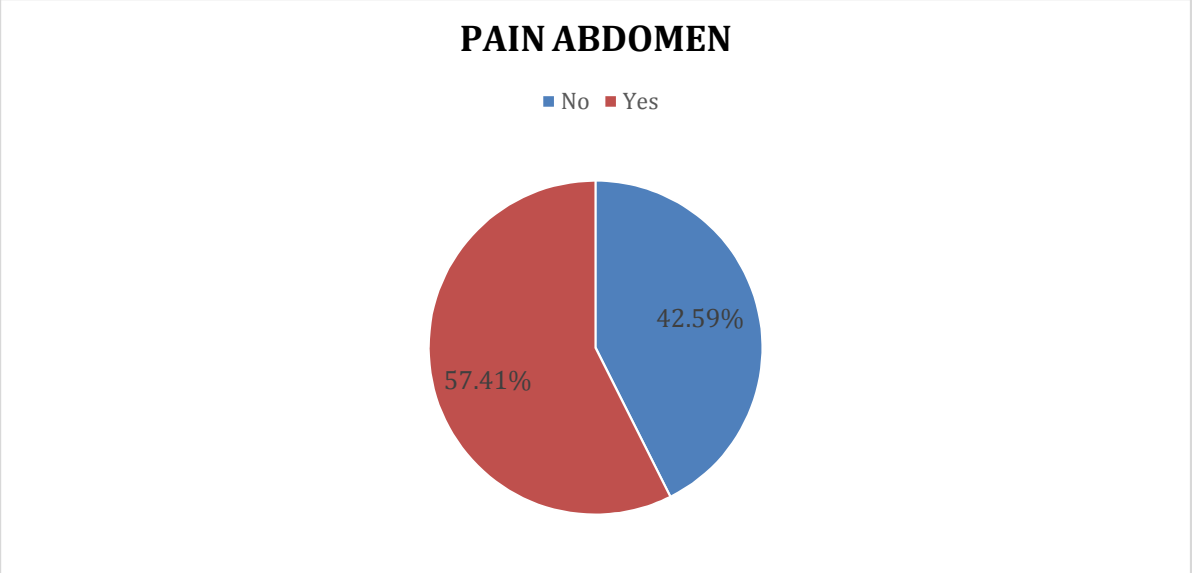


The term "multi" refers to individuals who have had multiple pregnancies, while "primi" denotes those experiencing their first pregnancy. Among the total population under study, 39 cases fall into the multi-parity category, constituting approximately 72.22% of the sample. Conversely, a smaller proportion of the population, comprising 15 cases, belongs to the primi-parity group, representing about 27.78% of the total.

TABLE-3: DESCRIPTIVE ANALYSIS OF PAIN ABDOMEN IN THE STUDY POPULATION.

Pain abdomen	**Cases (n=54)**	**Percentage**
No	23	42.59%
Yes	31	57.41%
Total	**54**	100.00%

GRAPH -3: DESCRIPTIVE ANALYSIS OF PAIN ABDOMEN IN THE STUDY POPULATION

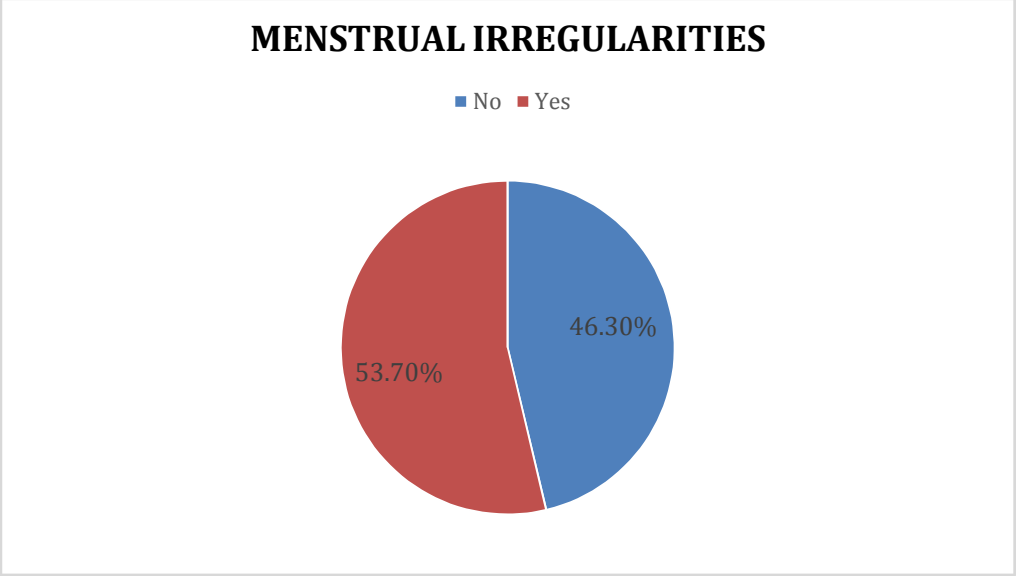


Among the total population under study, 31 cases are categorized as experiencing pain abdomen, constituting approximately 57.41% of the sample. Conversely, 23 cases represent individuals not experiencing pain abdomen, accounting for about 42.59% of the total.

TABLE-4: DESCRIPTIVE ANALYSIS OF MENSTRUAL IRREGULARITIES IN THE STUDY POPULATION.

Menstrual irregularities	Cases (n=54)	Percentage
No	25	46.30%
Yes	29	53.70%
Total	54	100.00%

GRAPH-4: DESCRIPTIVE ANALYSIS OF MENSTRUAL IRREGULARITIES IN THE STUDY POPULATION.

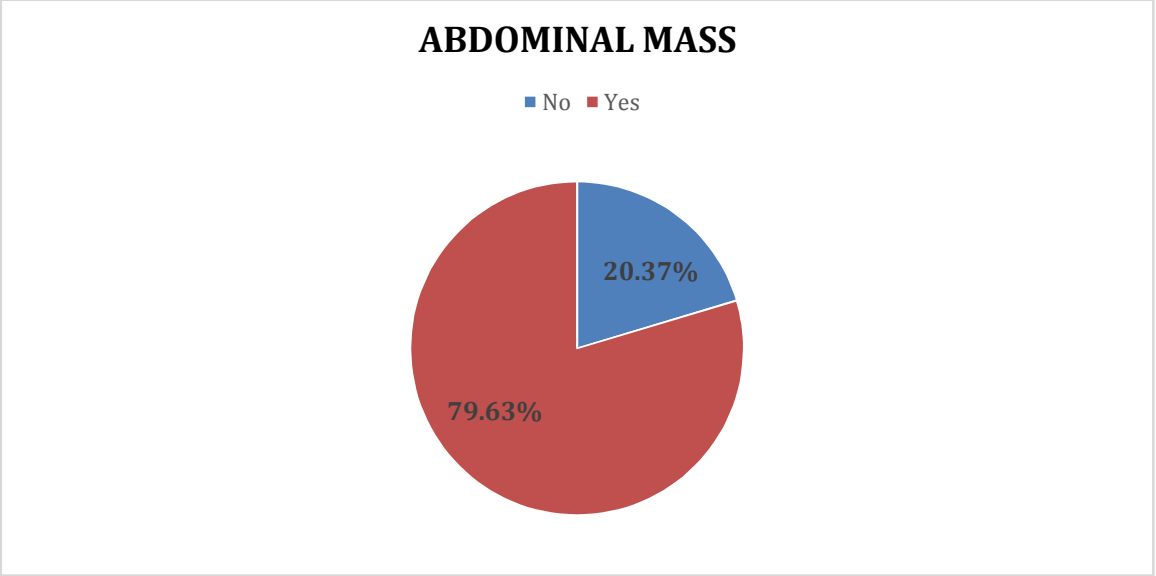


Out of the total population under study, 29 cases are classified as experiencing menstrual irregularities, constituting approximately 53.70% of the sample. Conversely, 25 cases represent individuals without menstrual irregularities, accounting for about 46.30% of the total.

TABLE-5: DESCRIPTIVE ANALYSIS OF ABDOMINAL MASS IN THE STUDY POPULATION

Abdominal mass	Cases (n=54)	Percentage
No	11	20.37%
Yes	43	79.63%
Total	54	100.00%

GRAPH-5: DESCRIPTIVE ANALYSIS OF ABDOMINAL MASS IN THE STUDY POPULATION

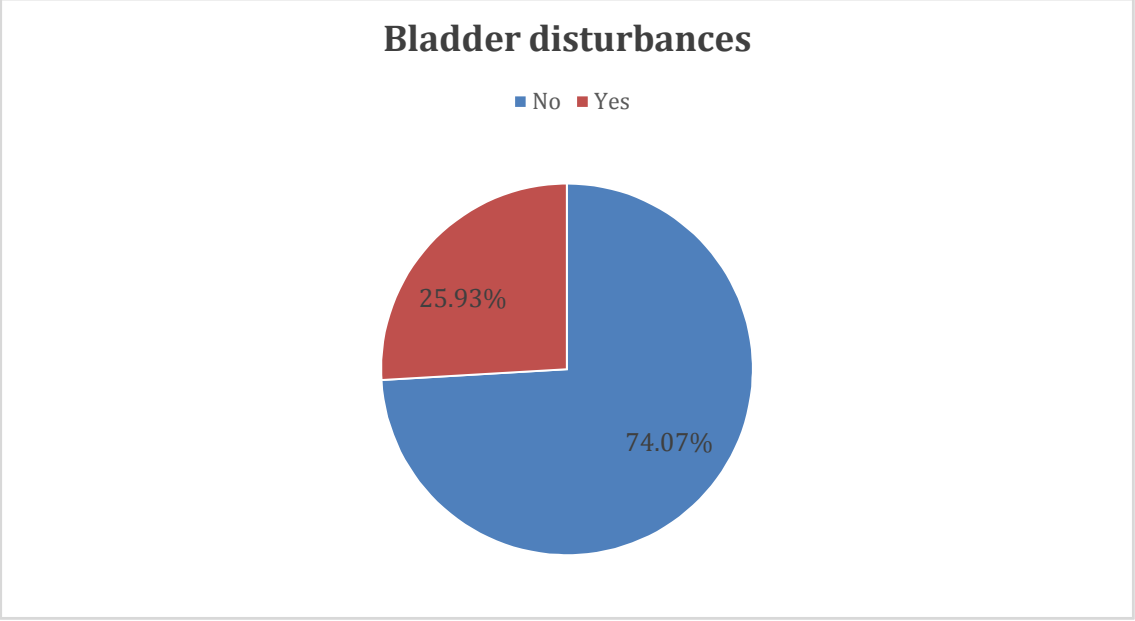


Out of the total population under study, 43 cases are categorized as having abdominal mass, constituting approximately 79.63% of the sample. Conversely, 11 cases represent individuals without abdominal mass, accounting for about 20.37% of the total.

TABLE-6: DESCRIPTIVE ANALYSIS OF BLADDER DISTURBANCES IN THE STUDY POPULATION.

Bladder disturbances	Cases (n=54)	Percentage
No	40	74.07%
Yes	14	25.93%
Total	54	100.00%

GRAPH -6 : DESCRIPTIVE ANALYSIS OF BLADDER DISTURBANCES IN THE STUDY POPULATION.

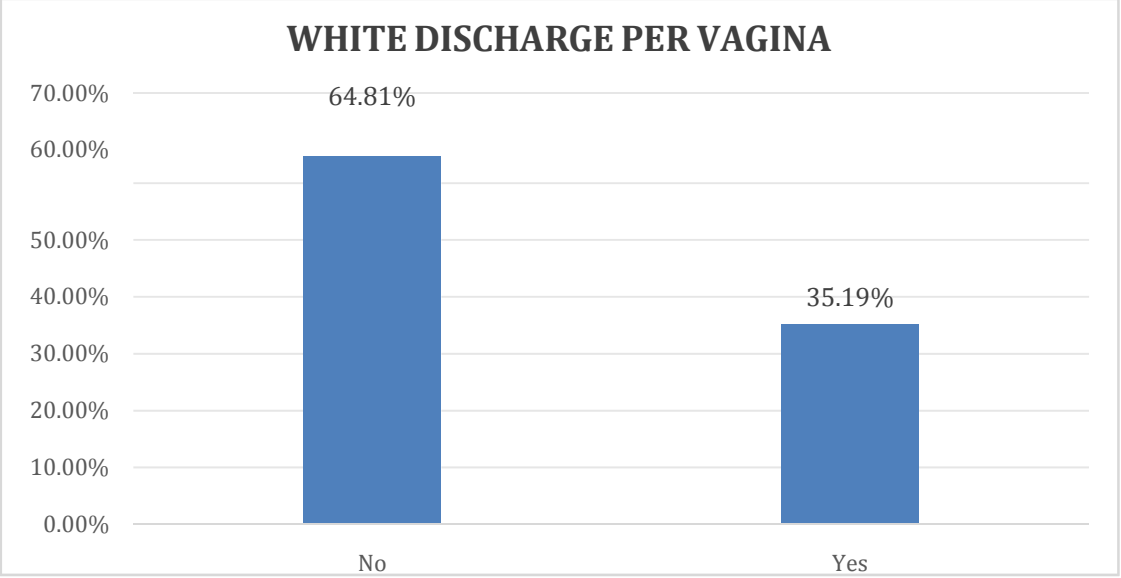


Among the total population under study, 40 cases are classified as not having bladder disturbances, constituting approximately 74.07% of the sample. Conversely, 14 cases represent individuals with bladder disturbances, accounting for about 25.93% of the total. The inclusion of the "Total" row ensures a comprehensive overview of all cases surveyed, summing up to 54 individuals.

TABLE-7: DESCRIPTIVE ANALYSIS OF WHITE DISCHARGE PER VAGINA IN THE STUDY POPULATION

White discharge	Cases (n=54)	Percentage
No	35	64.81%
Yes	19	35.19%
Total	54	100.00%

GRAPH -7: DESCRIPTIVE ANALYSIS OF WHITE DISCHARGE IN THE STUDY POPULATION



Among the total population under study, 35 cases are categorized as not having white discharge, constituting approximately 64.81% of the sample. Conversely, 19 cases represent individuals with white discharge, accounting for about 35.19% of the total. The inclusion of the "Total" row ensures a comprehensive overview of all cases surveyed, summing up to 54 individuals.

TABLE-8: DESCRIPTIVE ANALYSIS OF GROSS EXAMINATION IN THE STUDY POPULATION

Gross Examination		
Solid	**Cases (n=54)**	**Percentage**
No	31	57.41%
Yes	23	42.59%
Total	54	100.00%
Cystic	**Cases (n=54)**	**Percentage**
No	33	61.11%
Yes	21	38.89%
Total	54	100.00%
Both Solid and Cystic	**Cases (n=54)**	**Percentage**
No	44	81.48%
Yes	10	18.52%
Total	54	100.00%
Gross appearance	**Cases (n=54)**	**Percentage**
COMPLEX	10	18.52%
CYSTIC	21	38.89%
SOLID	23	42.59%
Total	54	100.00%

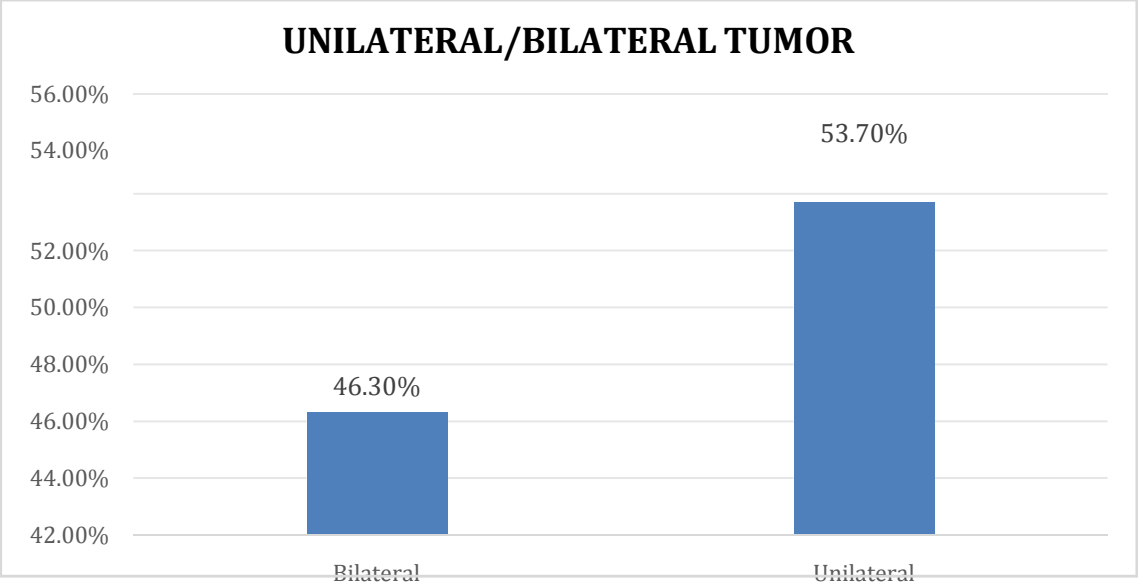
The table offers a comprehensive descriptive analysis of gross examination findings within the study population, detailing various aspects of the examination. Firstly, it categorizes cases based on whether a solid gross appearance was observed or not. Out of the total sample of 54 individuals, 31 cases (57.41%) exhibited no solid gross appearance, while 23 cases (42.59%) presented a solid gross appearance.Secondly, the table addresses cystic gross examination findings, indicating whether cystic features

were observed or not. It reveals that 33 cases (61.11%) showed no cystic gross appearance, whereas 21 cases (38.89%) displayed cystic features. Furthermore, the table examines cases where both solid and cystic gross appearances were observed. It indicates that in 44 cases (81.48%), neither solid nor cystic gross features were identified, while in 10 cases (18.52%), both solid and cystic characteristics were present.Lastly, the table provides an overview of the overall gross appearance classification. It delineates three categories: complex, cystic, and solid. Among the total sample, 10 cases (18.52%) were classified as complex, 21 cases (38.89%) as cystic, and 23 cases (42.59%) as solid

TABLE-9: DESCRIPTIVE ANALYSIS OF UNILATERAL/BILATERAL TUMOR IN THE STUDY POPULATION

Unilateral / Bilateral tumor	Cases (n=54)	Percentage
Bilateral	25	46.30%
Unilateral	29	53.70%
Total	54	100.00%

GRAPH- 8: DESCRIPTIVE ANALYSIS OF UNILATERAL/BILATERAL TUMOR IN THE STUDY POPULATION

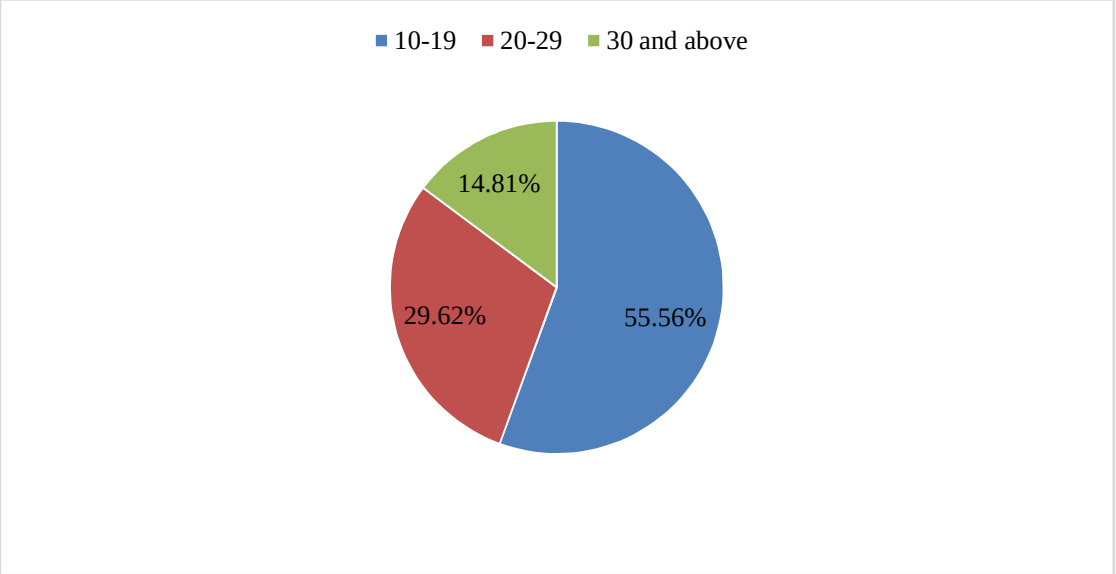


Among the total sample of 54 individuals, 29 cases (53.70%) were identified as unilateral, indicating that the condition manifested on one side. Conversely, 25 cases (46.30%) were classified as bilateral, denoting that the condition affected both sides.The inclusion of the "Total" row ensures a comprehensive overview of all cases surveyed.

TABLE-10: DESCRIPTIVE ANALYSIS OF SIZE OF TUMOR GROUPS IN THE STUDY POPULATION

Size of tumor groups (cm)	Cases (n=54)	Percentage
11-19cm	30	55.56%
20-29cm	16	29.62%
30 and above	8	14.81%

GRAPH -9 : DESCRIPTIVE ANALYSIS OF SIZE OF TUMOR GROUPS IN THE STUDY POPULATION

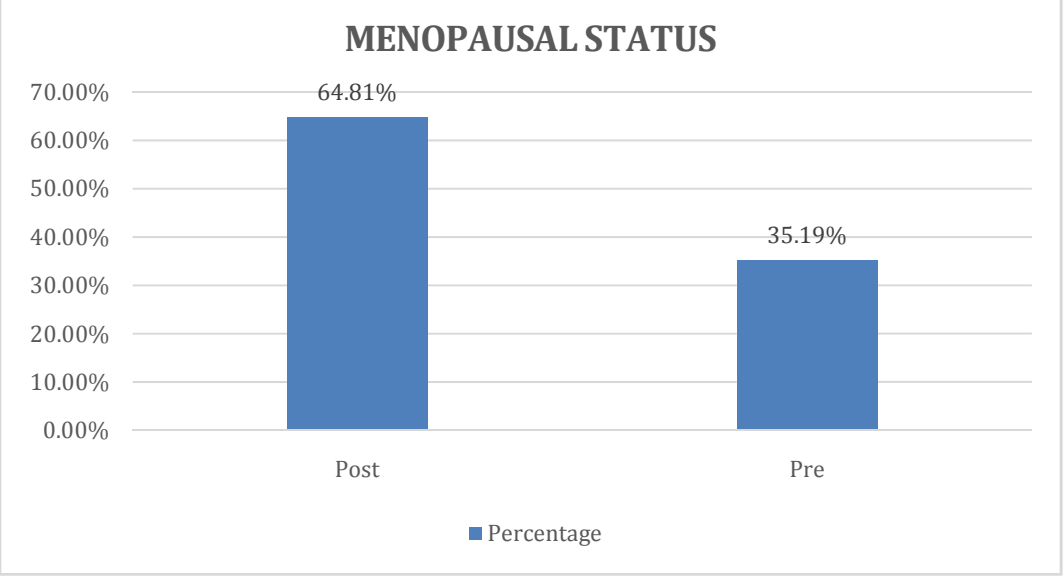


The table offers a descriptive analysis of the size of tumor groups (in centimeters) within the study population, categorizing cases based on the range of tumor sizes. It delineates three size groups: 11-19 cm, 20-29 cm, and 30 cm and above. Among thetotal sample of individuals under study, 30 cases (55.56%) fall within the size range of 11-19 cm, indicating a predominant occurrence within this category. Additionally, 16 cases (29.62%) are observed in the size range of 20-29 cm, while 8 cases (14.81%) are recorded in the 30 cm and above category.

TABLE-11: DESCRIPTIVE ANALYSIS OF MENOPAUSAL STATUS IN THE STUDY POPULATION

Menstrual History	Cases (n=54)	Percentage
Post-Menopausal	35	64.81%
Pre- Menopausal	19	35.19%
Total	**54**	**100.00%**

GRAPH-11: DESCRIPTIVE ANALYSIS OF MENOPAUSAL STATUS IN THE STUDY POPULATION



Among the total sample of 54 individuals under study, 35 cases (64.81%) are classified as post-menopausal, indicating that the individuals have ceased menstruation for at least 12 consecutive months, marking the transition from reproductive to non-reproductive status. Conversely, 19 cases (35.19%) are identified as pre-menopausal, suggesting that menstruation is still occurring in these individuals.

TABLE-12:DESCRIPTIVE ANALYSIS OF USG FEATURES IN THE STUDY POPULATION

CYSTIC	**Cases (n=54)**	**Percentage**
No	20	37.04%
Yes	34	62.96%
Total	54	100.00%
SOLID	**Cases (n=54)**	**Percentage**
No	43	79.63%
Yes	11	20.37%
Total	54	100.00%
BOTH SOLID AND CYSTIC	**Cases (n=54)**	**Percentage**
No	38	70.37%
Yes	16	29.63%
Total	54	100.00%
MULTI CYST	**Cases (n=54)**	**Percentage**
No	34	62.96%
Yes	20	37.04%
Total	54	100.00%
UNICYST	**Cases (n=54)**	**Percentage**
No	39	72.22%
Yes	15	27.78%
Total	54	100.00%
THIN SEPTATIONS	**Cases (n=54)**	**Percentage**
No	34	62.96%
Yes	20	37.04%

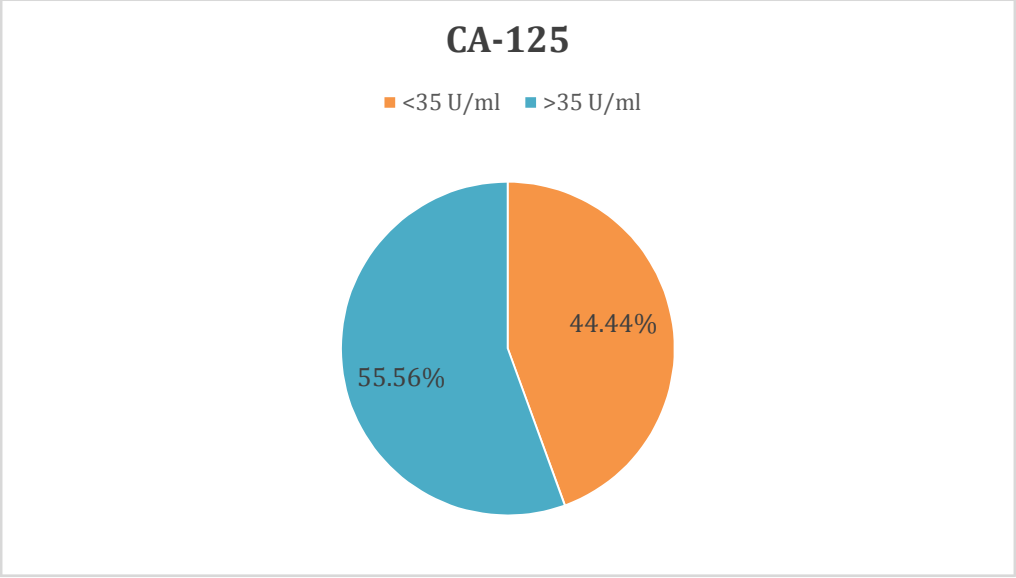
Total	54	100.00%
THICK SEPTATIONS	**Cases (n=54)**	**Percentage**
No	42	77.78%
Yes	12	22.22%
Total	54	100.00%

The table presents a detailed descriptive analysis of ultrasound (USG) features within the study population, categorizing cases based on various characteristics observed in the imaging data. Among the 54 individuals examined, the majority, comprising 62.96% of the sample, exhibited cystic features in their USG scans, indicating the presence of fluid-filled sacs. Conversely, solid features were less prevalent, with only 20.37% of cases displaying such characteristics. Furthermore, a subset of individuals, representing 29.63% of the population, showed both cystic and solid features concurrently. Additionally, the presence of multiple cysts was observed in 37.04% of cases, while unilateral cysts were found in 27.78% of individuals. Regarding septation, 37.04% of cases exhibited thin septation, while 22.22% displayed thick septation. The inclusion of the "Total" row ensures a comprehensive overview of all cases surveyed.

TABLE-13: DETERMINATION OF CA-125

CA-125(U/ml)	**Cases (n=54)**	**Percentage**
<35 U/ml	24	44.44%
>35 U/ml	30	55.56%
Total	54	100.00%

GRAPH -12 : DETERMINATION OF CA-125

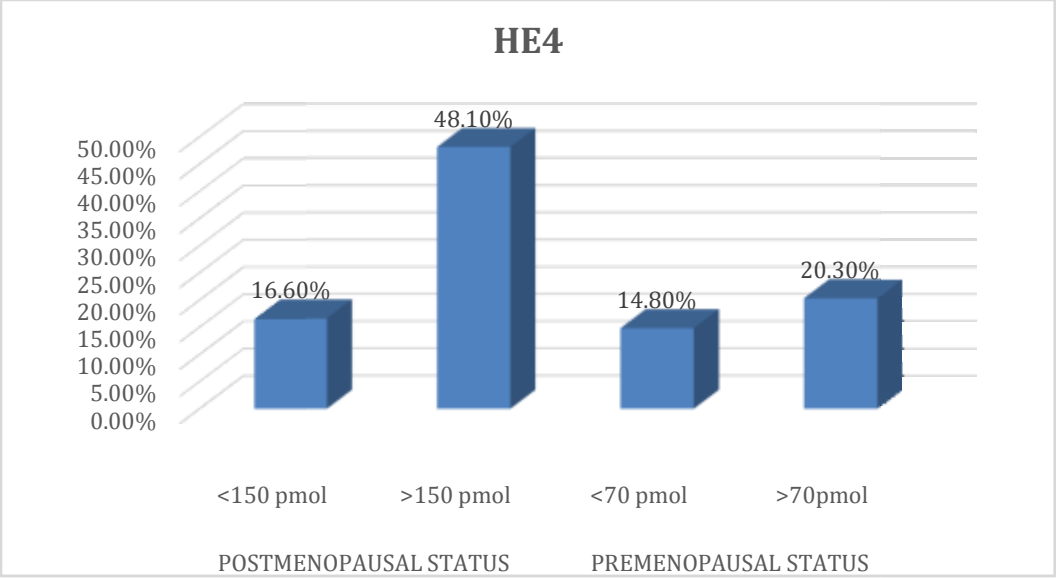


The table categorizes the cases on the basis their CA-125 levels, with two distinct groups: those with CA-125 levels less than 35 U/ml and those with levels morethan 35 U/ml. According to the data, 24 cases (44.44%) have CA-125 levels below 35 U/ml, while 30 cases (55.56%) have levels above 35 U/ml.

Table-14: DETERMINATION OF HE-4.

HE-4(pmol)	Cases (n=54)	Percentage
POSTMENOPAUSAL WOMEN		
<150 pmol	9	16.6%
>150 pmol	26	48.1%
PREMENOPAUSAL WOMEN		
<70 pmol	8	14.8%
>70pmol	11	20.3%
Total	54	100.00%

GRAPH-13: DETERMINATION OF HE-4.



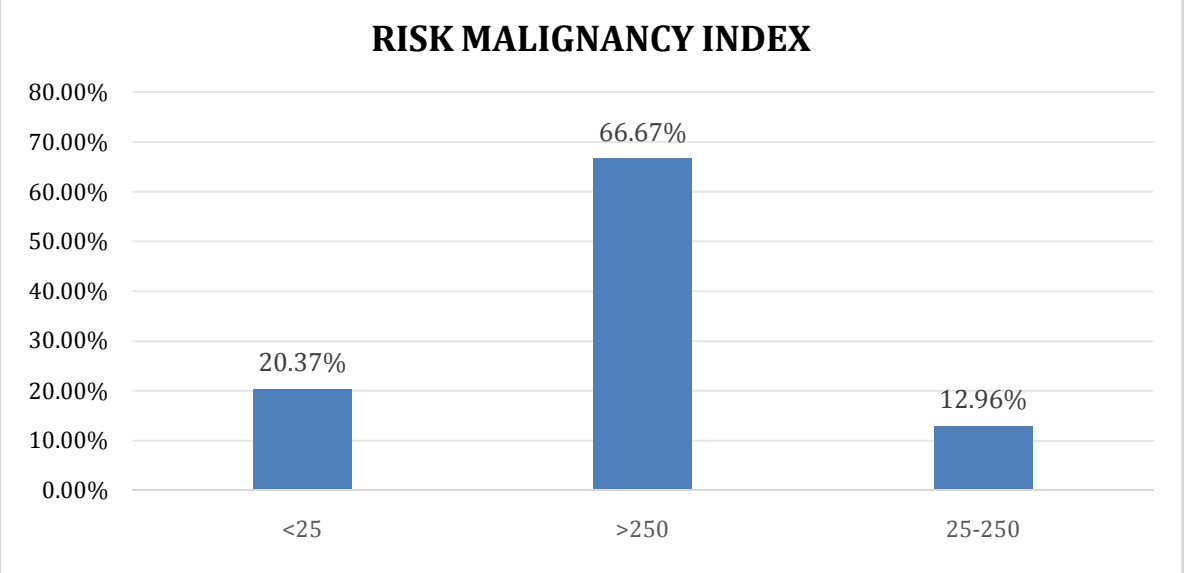
The table indicates that out of a total of 54 cases, 9 cases had HE-4 levels below 150 pmol (picomoles per liter), while the remaining 26 cases (61.11%) had HE-4 levels exceeding 150 pmol in postmenopause women.In premenopause wo en, 8 cases had less than 70pmol HE-4 level.Elevated levels of HE-4 can be associated with certain

medical conditions, and this data provides insight into the distribution of HE-4 levels within the study population.

TABLE-15: DESCRIPTIVE ANALYSIS OF RISK MALIGNANCY INDEX IN THE STUDY POPULATION.

RMI (Risk of malignancy index) IU/ml	Cases (n=54)	Percentage
<25	11	20.37%
25-250	7	12.96%
>250	36	66.67%
Total	54	100.00%

GRAPH- 14: DESCRIPTIVE ANALYSIS OF RISK MALIGNANCY INDEX IN THE STUDY POPULATION.

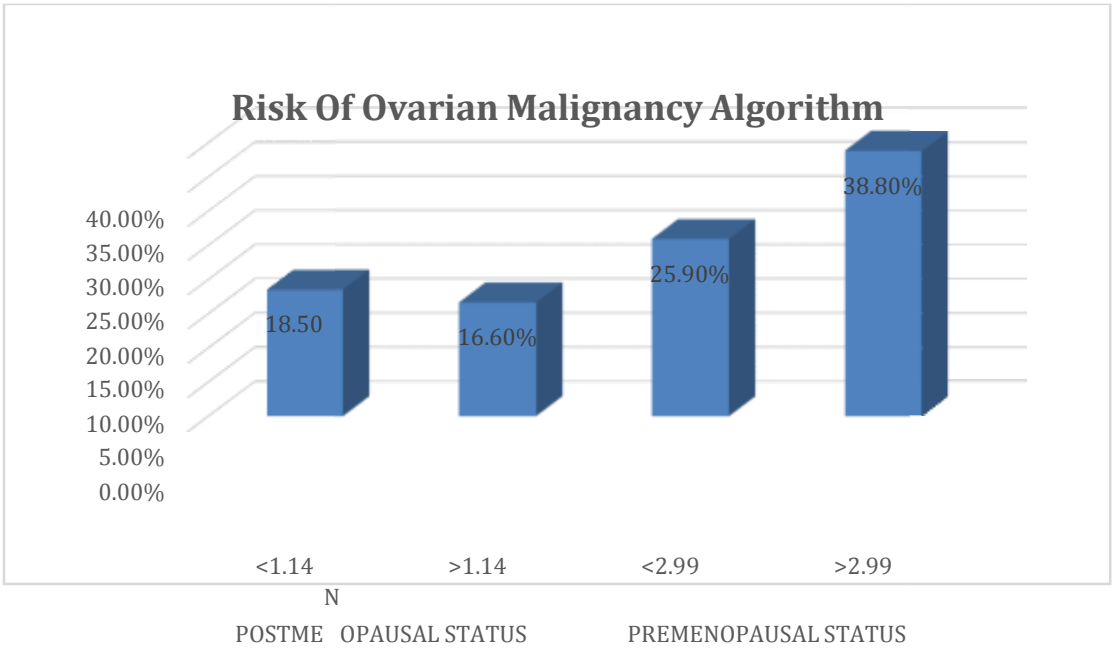


The table offers a descriptive analysis of the Risk of Malignancy Index (RMI) within the study population, categorizing cases based on different RMI ranges. Among the 54 individuals examined, the majority, comprising 66.67% of the sample, were classified with an RMI greater than 250, suggesting a high risk of malignancy. Conversely, a smaller proportion of cases, accounting for 20.37%, had an RMI of less than 25,indicating a lower risk of malignancy. Additionally, 12.96% of cases fell within theRMI range of 25 to 250.

TABLE-16: DISTRIBUTION OF ROMA (RISK OF OVARIAN MALIGNANCY ALGORITHM)

ROMA (Risk of Ovarian Malignancy Algorithm)	Cases(n =54)	Percentage
POSTMENOPAUSAL STATUS		
<1.14	10	18.5%
>1.14	9	16.6%
PREMENOPAUSAL STATUS		
<2.99	14	25.9%
>2.99	21	38.8%
Total	54	100.00%

GRAPH-15: DISTRIBUTION OF ROMA (RISK OF OVARIAN MALIGNANCY ALGORITHM).

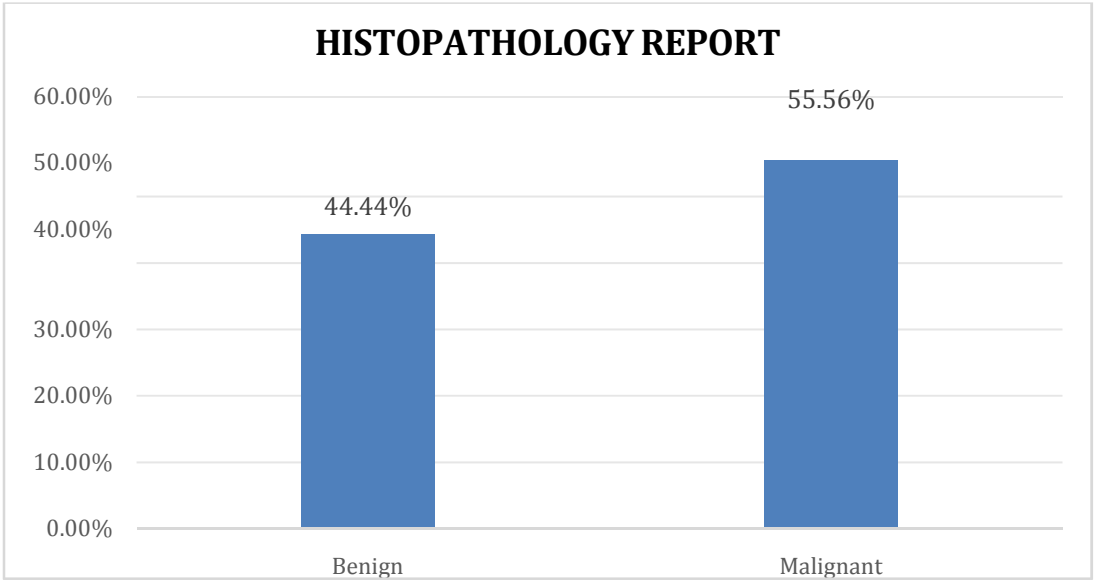


The table presents the distribution of the ROMA (Ovarian Malignancy Risk Algorithm) among a total of 54 case .19 cases belonged to postmenopausal status,among which 10cases had ROMA less than 1.14 score, indicating a low risk of malignancy, and 9 cases had ROMA more than 1.14, indicating a high risk of malignancy.While 35cases belonged to premenopausal status,among which 14 cases had ROMA less than 2.99 scores indicating a low risk of malignancy, and 21 cases had more than 2.99 ROMA scores indicating a low risk of malignancy.

TABLE- 17: DISTRIBUTION OF HISTOPATHOLOGY REPORT.

Histopathology report	Cases(n =54)	Percentage
Benign	24	44.44%
Malignant	30	55.56%
Total	54	100.00%

GRAPH-16: DISTRIBUTION OF HISTOPATHOLOGY REPORT.

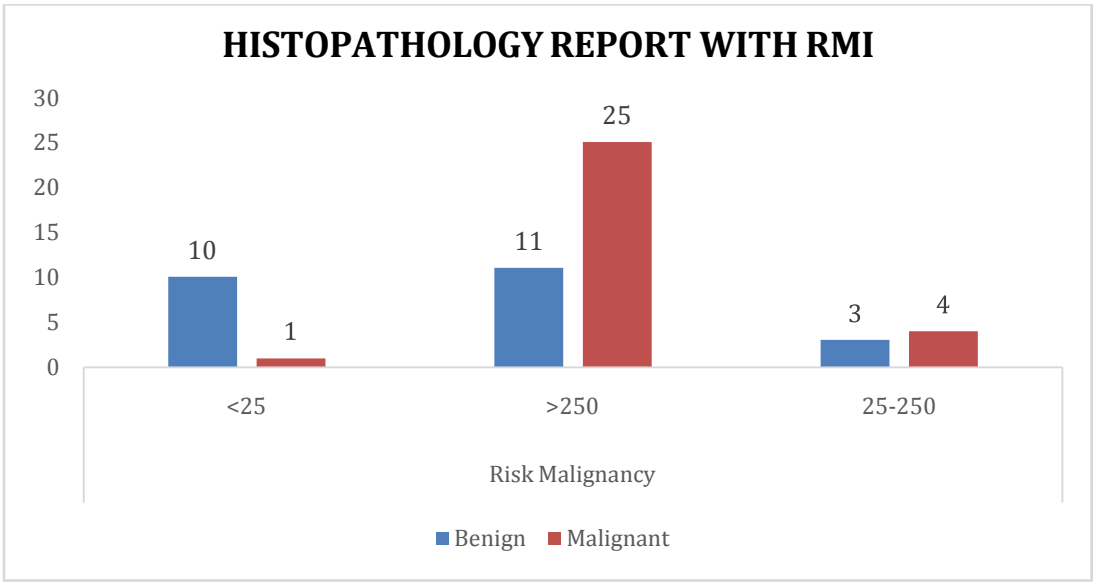


The table presents the distribution of cases based on histopathology reports within the study population, categorizing individuals into benign and malignant outcomes. Among the total of 54 individuals examined, 55.56% of cases were diagnosed as malignant based on histopathological examination, indicating the presence of cancerous tissue. Conversely, 44.44% of cases were categorized as benign, suggesting the absence of cancerous growth.

TABLE- 18: COMPARISION OF HISTOPATHOLOGY REPORT WITH RISK MALIGNANCY INDEX IN THE STUDY POPULATION.

Histopathology report	Risk Malignancy index (IU/ml)			Chi square	p value
	<25	25-250	>250		
Benign	10	3	11	12.43	0.001
Malignant	1	4	25		
Total	**11**	**7**	**36**		

GRAPH-17: COMPARISION OF HISTOPATHOLOGY REPORT WITH RISK MALIGNANCY INDEX IN THE STUDY POPULATION.



Among the cases classified as benign based on histopathology reports, 10 were associated with an RMI of less than 25, 11 with an RMI greater than 250, and 3 with an RMI falling between 25 and 250. Conversely, among the malignant cases, 1 was linked to an RMI of less than 25, 25 were associated with an RMI greater than 250, and 4 were categorized with an RMI between 25 and 250. The chi-square value calculated for this comparison is 12.43, with a corresponding p-value of 0.001, indicating a statistically significant association between histopathological reports and RMI categories.

TABLE-19: COMPARISION OF HISTOPATHOLOGY WITH CA125.

Histopathology report	CA-125 (U/mL)	
	Mean ± SD	P value
Benign	20.5 ± 7.28	<0.001
Malignant	77.27 ± 29.14	

Histopathology reports are categorized into benign and malignant outcomes, while CA-125 levels are represented as mean values with their corresponding standard deviations. Among cases classified as benign based on histopathology reports, the mean CA-125 level was 20.5 units/ml, with a standard deviation of 7.28. In contrast, among malignant cases, the mean CA-125 level was notably higher at 77.27 units/ml, with a standard deviation of 29.14. The p-value associated with this comparison is less than 0.001, indicating a statistically significant difference in CA-125 levels between benign and malignant histopathology reports

TABLE-20: COMPARISION OF HISTOPATHOLOGY WITH HE 4.

Histopathology report	**HE 4 (pmol/l)**	
	Mean ± SD	**P value**
Benign	196.56 ± 220.04	<0.001
Malignant	525.283 ± 462.04	

Histopathology reports are categorized into benign and malignant outcomes, while HE4 levels are represented as mean values with their corresponding standard deviations. Among cases classified as benign based on histopathology reports, the mean HE4 level was 196.56 pmol/L, with a standard deviation of 220.04. In contrast, among malignant cases, the mean HE4 level was notably higher at 525.283 pmol/L, with a standard deviation of 462.04. The p-value associated with this comparison is less than 0.001, showinga statistically significant difference in HE4 levels between benign and malignant histopathology reports.

TABLE-21: COMPARISION OF SENSITIVITY AND SPECIFICITYOF CA125 AND HE4 IN EPITHELIAL OVARIAN TUMORS.

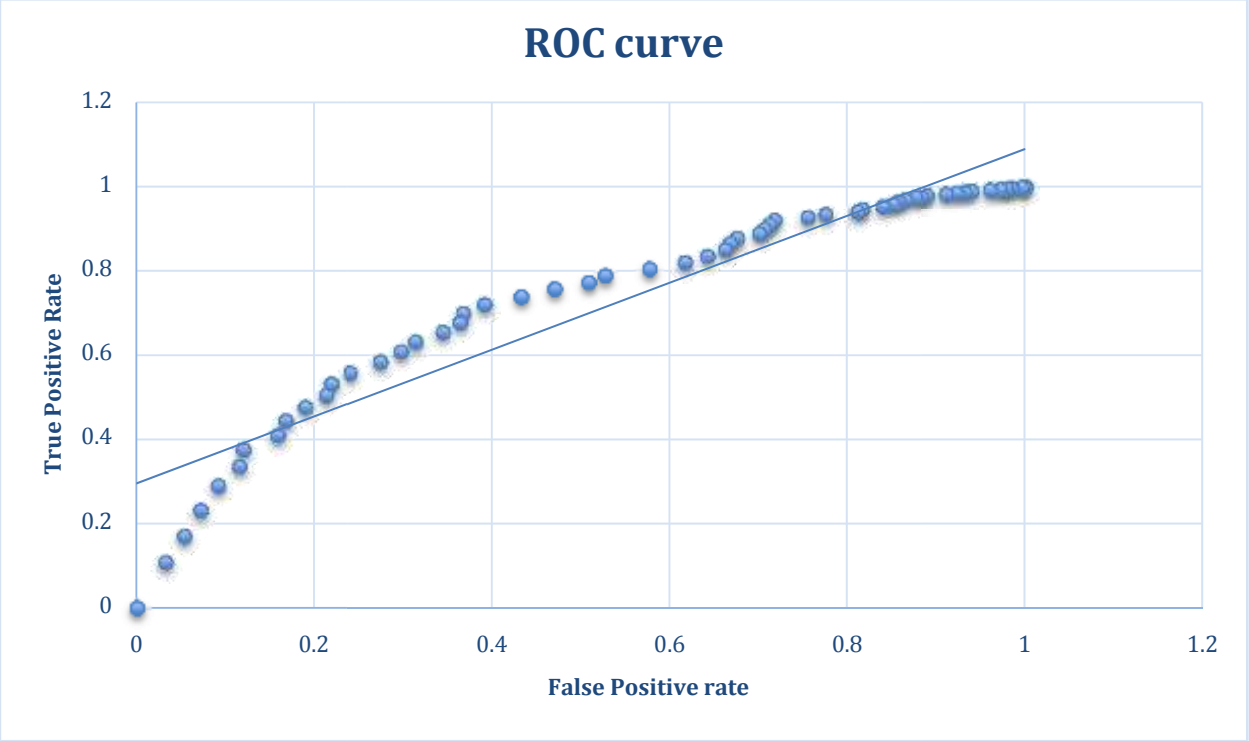
Parameter	**CA125(U/mL)**	**HE 4(pmol/l)**
Sensitivity	86.16%	84.16%
Specificity	88.45%	90.43%
False positive rate	51.69%	47.56%
False negative rate	33.64%	35.47%
95% Confidence interval	0.786-0.981	0.914-0.992
Positive predictive value	94.21%	98.15%
Negative predictive value	81.45%	75.45%
Diagnostic accuracy	65.56%	69.45%

The data compares the diagnostic performance of two biomarkers, CA 125 and HE 4, for a certain condition. CA 125 demonstrates slightly higher sensitivity (86.16%) but lower specificity (88.45%) compared to HE 4 (84.16% sensitivity, 90.43% specificity). HE 4 also shows lower false positive and false negative rates. However, HE 4 boasts a higher positive predictive value (98.15%) while CA 125 has a better negative predictive value (81.45%). HE 4 achieves a slightly higher diagnostic accuracy (69.45%) compared to CA 125 (65.56%). Overall, these metrics suggest HE 4 may be slightly more effective as a diagnostic biomarker for the condition than CA 125.

TABLE -22 : COMPARISION OF HE4 AND CA125 IN DIAGNOSING OVARIAN CANCER AND EVALUATING TREATMENT RESPONSE

Parameter	**HE4 + CA 125**
Sensitivity	90.12%
Specificity	82.64%
False positive rate	65.25%
False negative rate	36.15%
95% Confidence interval	0.845-0.975
Positive predictive value	96.12%
Negative predictive value	80.36%
Diagnostic accuracy	69.25%

The combined use of HE4 and CA125 in diagnosis and treatment response demonstrates notable efficacy. The sensitivity of this combination is 90.12%, indicating a high ability to correctly identify those with the disease. Its specificity is 82.64%, reflecting a strong capability to correctly identify those without the disease. However, false positive rate is 65.25%, false negative rate is 36.15%.95% confidence interval for these measuresranges from 0.845 to 0.975. The positive predictive value is 96.12%, suggesting that most positive test results are true positives, while the negative predictive value is80.36%, indicating that a significant proportion of negative results are true negatives. The overall diagnostic accuracy of the HE4 and CA125 combination stands at 69.25%.



The table compares the specificity and sensitivity of CA125 and HE4 in detecting epithelial ovarian tumors, along with other diagnostic parameters and their corresponding confidence intervals (CI). Specificity measures a test's capacity to accurately identify people without the ailment, whereas sensitivity measures a test's ability to correctly identify people with the condition. According to the data presented, the sensitivity of CA125 in detecting epithelial ovarian tumors is 83.16%, with a 95% CI ranging from 62.66% to 97.52%. In contrast, the sensitivity of HE4 is not provided in this table. However, CA125 demonstrates a higher sensitivity compared to HE4. Specificity, on the other hand, represents the proportion of true negative results among individuals without the condition. The specificity of CA125 is 39.43%, with a 95% CI ranging from 22.69% to 69.52%. This suggests that CA125 has a lower specificity in correctly identifying individuals without epithelial ovarian tumors. Additionally, the table provides other diagnostic parameters such as the false positive rate, false negative rate, positive predictive value, negative predictive value, and diagnostic accuracy. These parameters offer further insights into the performance of CA125 and HE4 in diagnosing epithelial ovarian tumors. The percentage of people without the illness who test positive is known as the false positive rate, and the percentage of people who test negative is known as the false negative rate.

DISCUSSION

DISCUSSION

Despite advancements in treatments aimed at improving the survival rate relative to five years, ovarian cancer is the most lethal form of cancer of the reproductive tract infemales. The survival rate over five years is high at 90% when cancer is localized to theovaries; 25% of cases are detected at a preliminary stage. Unfortunately, most of the cases are diagnosed at later stages, resulting in a significant drop in the five-yearsurvival rate to less than 20%, with many patients presenting with metastatic disease. This lack of precise early warning signs contributes to the challenge of identifying ovarian tumors at stage I.[57]

CA125 continues to be the major tumor marker. suggested for prognostic, diagnostic, and post-treatment monitoring purposes. However, a significant limitation of CA125 is its absence of specificity, as elevated levels may be observed in a considerable number of women with both benign and malignant conditions.[58,59,60,61]

Numerous efforts have been made to enhance the diagnostic accuracy of CA125. Of these, significant attention has been directed towards HE4. This is becoming one of the most promising indicators for improving specificity and sensitivity.[62]
The purpose of the study is to determine levels of molecular tumor markers HE4 and CA125in ovarian cancer.

Approximately 29.62% of the study population, totaling 16 individuals, are aged 40 or younger. In contrast, about 70.70% of the sample, consisting of 38 individuals, are over 40 years old. Early menarche and late menopause may lead to more ovulatory cycles, which in turn may increase the possibility of the occurrence of ovarian cancer, according to the idea of incessant ovulation. On the other hand, the gonadotropin theory suggests that a later menopausal onset could potentially lower risk by delaying the riseof post-menopausal gonadotropin hormones. Studies looking into menarche age, however, produce contradictory findings. Some people find a minor increase in risk with late menarche (beyond age 18), while others report a reduced risk. Aging during natural menopause and the risk of ovarian cancer also have conflicting results.While some research found no correlation, others suggest that a later age at menopause is linked to a higher risk.These contradictory results could be the result of heterogeneity in tumor

subtypes, disparities in classifications, or recollection bias. The information at hand indicates that, in spite of these complications, any effect magnitude is probably going to be modest.[62]

Among the total study population, 31 cases were categorized as experiencing abdominal pain, constituting approximately 57.41% of the sample. In contrast, 23 cases represented individuals without abdominal pain, accounting for about 42.59% of the total.
The main risk factors for ovarian cancer are family history, age, and germline mutations in genes, including BRCA1, BRCA2, and others with different disease penetrance. After a thorough examination of all ovarian cancer patients, it was discovered that 24% of them had a germline loss-of-function mutation, meaning that just over one-fifth of cases had heritable ovarian cancer.65 It seems that the remaining cases are intermittent. Other risk variables, which are of less importance, have been discovered with differing degrees of consistency. These include pregnancy, parity, infertility, and different reproductive features.

Research on hormonal and reproductive variables has been a key area of interest.Though the results are not always consistent, nulliparity, early menarche, late menopause, and infertility have all been associated with an increased risk of ovarian cancer.[63]Three known protective factors are high parity, oral contraceptive usage, and bilateral prophylactic salpingo-oophorectomy.[64]

Out of the total study population, 43 cases were categorized as having abdominalmasses, constituting approximately 79.63% of the sample. Conversely, 11 cases represented individuals without abdominal masses, accounting for about 20.37% of the total.

Among the total study population, 40 cases were classified as not having bladder disturbances, comprising approximately 74.07% of the sample. Conversely, 14 cases represented individuals with bladder disturbances, accounting for about 25.93% of the total. Including the "Total" row provides a comprehensive overview of all cases surveyed, summing up to 54 individuals.

The issue of urinary system dysfunction in oncology patients is often underestimated, given its secondary importance compared to the primary health concerns associated with malignant tumors.[65,66] However, this issue must not be overlooked, as highlighted by analysis conducted by from Strauchon et al.[67] and Ramaseshan et al. [68] Conversely, an analysis by Bretschneider et al. found no correlation between the type of cancer and the frequency of urination disruptions.However, it was shown that while the urge to urinate was more common in women over 50, bladder pain was statistically substantially more common in women with gynecological tumors under 50. .[68] Additionally, White et al. found that Compared to women in good health, individuals with endometrial cancer had higher rates of urine incontinence. (odds ratio [OR]: 1.31; $p < 0.05$).[69]

Among the study population, 35 cases (64.81%) did not have white discharge, while 19 cases (35.19%) did. Including the "Total" row provides a comprehensive overview, totaling 54 individuals.

In the sample of 54 individuals, 31 cases (57.41%) had no solid gross appearance, while 23 cases (42.59%) did. For cystic features, 33 cases (61.11%) showed none, whereas 21 cases (38.89%) did. Both solid and cystic appearances were absent in 44 cases (81.48%), but present in 10 cases (18.52%). Overall, 10 cases (18.52%) were classified as complex, 21 cases (38.89%) as cystic, and 23 cases (42.59%) as solid.

A simple cyst is the most often found ovarian tumor. Even though numerous studies have determined that simple cysts are most likely benign and do not signal the onset of cancer, experts and professional guidelines continue to advise continued monitoring of these lesions.Despite the widespread belief that these masses are benign, this prescription still stands because of the dismal prognosis of malignant ovarian cancer andthe fear that even benign masses carry a tiny, yet unknown, risk of cancer.

In the total sample of 54 individuals, 29 cases (53.70%) were identified as unilateral, meaning the condition affected one side. Conversely, 25 cases (46.30%) were classified as bilateral, indicating the condition affected both sides. Including the "Total" row provides a comprehensive overview of all cases surveyed.

The findings were largely consistent with studies by Kanpurwala et al. [70] and Modepalli[71] and Venugopal. However, in the study by Garg et al.[72], there were significantly fewer bilateral cases. (4.7%), which could be attributed to their smaller sample size (n = 85). Among the total sample, 30 cases (55.56%) fall within the 11-19 cm size range, indicating this is the most common category. Additionally, 16 cases (29.62%) are in the 20-29 cm range, and 8 cases (14.81%) are 30 cm and above.

In our study conducted by Neha Gupta et al.[73],most of the cases (41.8%) were found to be in the size range of 5–10 cm, which is consistent with the findings of Manoja et al. [74] Among the 54 individuals examined, the majority (66.67%) had an RMI greater than 250, indicating a high risk of malignancy. In contrast, 20.37% had an RMI of less than 25, suggesting a lower risk of malignancy. Additionally, 12.96% of cases fell within the RMI range of 25 to 250.

Almost identical observations were made by Manoja et al.[74] and Kuladeepa et al.However malignant tumors were more likely to be bilateral; they accounted for 53.8% ofbilateral cases. Among the 14 bilateral cases, serous carcinoma was the most prevalent (9 cases, 64.3%), followed by mucinous carcinoma (2 cases, 14.3%), mixed germ cell tumors (2 cases, 14.3%), and endometrioid carcinoma (1 case, 7.1%).

Histopathology reports are categorized into benign and malignant outcomes, with CA-125 levels represented as mean values and corresponding standard deviations. Forbenign cases, the mean CA-125 level was 20.5 units/ml with a standard deviation of 7.28. In contrast, malignant cases had a higher mean CA-125 level of 77.27 units/ml with a standard deviation of 29.14. When it comes to benign and malignant cases, CA-125 values range significantly. as indicated by the comparison's p-value of less than 0.001.

The data compares the performance of two biomarkers, CA 125 and HE 4, for a specific condition. CA 125 shows slightly higher sensitivity (86.16%) but lower specificity (88.45%) than HE 4, which has 84.16% sensitivity and 90.43% specificity. HE 4 also has lower false positive and false negative rates. Additionally, HE 4 has a higherpositive predictive value (98.15%), while CA 125 has a better negative predictive value (81.45%). HE 4 achieves slightly higher diagnostic accuracy (69.45%) compared to CA

125 (65.56%). Overall, these metrics suggest that HE 4 may be slightly more effective as a diagnostic biomarker for the condition than CA 125.While ovarian cancer has been diagnosed with the ROMA index CA 125 andHE4areprimarily studied in the white population. The precision of CA 125 with HE4 and the ROMA score was evaluated in a prospective cross-sectional study that took into consideration the possibility that normal findings in white people would differ from those in the black community. Prior tosurgical intervention, the aim was to distinguish whether tumors were benign or malignant epithelial ovarian tumors in order to facilitate proper referrals.[75]

Compared to the group with benign disease, the group with epithelial ovarian cancer had higher serum HE4 levels. as seen in this investigation by Shittu KA et al[75]. This conclusion is similar with a prior study by Montagnana et al.[76] in Verona, Italy. They found that, when compared to the group with benign ovarian tumors, the mean serum level of HE4 was considerably higher in their prospective observational analysis. Similarresults have also been observed in a number of other research.

The capability of a test to correctly recognize people with a condition is known as sensitivity, whereas the capability to correctly recognize people without the ailment is referred to as specificity. According to the presented data, CA125 has a sensitivity of 83.16% (95% CI: 62.66% - 97.52%) for detecting epithelial ovarian tumors, although the sensitivity of HE4 is not provided in the table. Nevertheless, CA125 exhibits higher sensitivity compared to HE4.

Specificity reflects the proportion of true negative results among individuals without the condition. CA125 shows a specificity of 39.43% (95% CI: 22.69%—69.52%), indicating lower specificity in correctly identifying individuals without epithelial ovarian tumors.

Moreover, the table includes additional diagnostic parameters such as positive predictive value, negative predictive value, false positive rate, false negative rate, and diagnostic accuracy. These metrics provide further insights into the performance of CA125 and HE4 in diagnosing epithelial ovarian tumors. The false positive rate denotes the proportion of individuals without the condition who test positive, while the false

negative rate represents the proportion of individuals with the condition who test negative.

In the study conducted by Shittu KA et al. 75, In comparison to CA 125, HE4 showed more sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). This finding is consistent with Hamed et al.[77]'s research in Egypt,higher specificity (95% versus 85%),sensitivity (90% versus 83.3%), PPV (93.1%versus 80.7%), and NPV (92.7% versus 87.2%) of HE4 in comparison to CA 125.However, Zhang et al.[78] in China and Pitta et al.[79] in Brazil reported that compared to HE4, CA 125 exhibits greater sensitivity, specificity, and positive and negativepredictive values.

To improve diagnostic accuracy, the clinical practice of ovarian cancer has shifted toward a multi-marker strategy, as the limitations of using a single tumor marker for diagnosis have been acknowledged in a number of clinical contexts. Positive predictive value (PPV) and specificity are increased when both tumor markers are included in the ROMA prediction probability. In their investigation, Anastasi et al. also reported 100% PPV and specificity for ROMA. Better prediction of the absence of ovarian cancer is implied by higher specificity as opposed to employing just one tumor marker. The decrease in PPV results in fewer unwarranted referrals, related expenses, and lost time. Furthermore, it reduces the need for midline laparotomies, which are still considered the gold standard of care, allowing patients to have more aesthetically acceptable incisions. The precision of the diagnosis of HE4, the ROMA index, and CA 125 in separating benignfrom malignant tumors was evaluated using ROC analysis. The ensuing area under the curve values demonstrates that, for this purpose, HE4 is a good test, whereas ROMA is an outstanding test, and CA 125 is a decent test. As such, ROMA performs better than either tumor marker by itself. As a tumor marker, HE4 outperformed CA 125 on the basis of diagnostic accuracy for determining if cancer is benign or malignant.It showed improved specificity, sensitivity positive predictive value (PPV), and negative predictive value (NPV). The addition of HE4 to CA 125 improves its usefulness, and the ROMA index's combination of these two biomarkers improves diagnostic precision even further. When combined, the ability to differentiate whether a tumor is benign or malignant ovarian tumor may be improved over the use of each tumor marker alone. This could lead to more suitable referrals for definitive care.

SUMMARY

SUMMARY

- The study was undertaken to determine the tumor marker levels CA125 and HE4 in the women diagnosed with ovarian cancers.
- Total 54 subjects were taken into consideration in the study. Preoperative evaluation such as CA 125 and HE4 was done, and RMI and ROMA were calculated for all the subjects included in the study population. Surgical intervention was done for patients with suspected ovarian malignancy and specimen was sent for histopathological examination.
- According to the data,44.44% have CA-125 levels below 35 U/ml,55.56% have levels above 35 U/ml.In postmenopausal women, 16.60% had HE-4 levels below 150 pmol (picomoles per liter), and 48.10% had HE-4 levels exceeding 150 pmol.In premenopausal women,14.80% had less than 70pmol HE-4 level and 20.30% had more than 70pmol HE-4 level.
- Among the 54 individuals examined,66.67% of the sample were classified with an RMI greater than 250, suggesting a high risk of malignancy, and 20.37% had an RMI of less than 25, indicating a lower risk of malignancy.12.96% of cases fell within the RMI range of 25 to 250.
- Among the 54 individuals examined ,18.5% had ROMA less than 1.14 score indicating low risk of malignancy and 16.60% had ROMA more than 1.14 score indicating high risk of malignancy among postmenopausal women. While 25.90%. had ROMA less than 2.99 score indicating low risk of malignancy and 38.80% had more than 2.99 ROMA scores indicating low risk of malignancy.
- The sensitivity of this combination tumor markers CA125 and HE4 is90.12%,specificity is 82.64%,false positive rate is 65.25%, and the false negative rate is 36.15%,positive predictive value is 96.12%, negative predictive value is 80.36% respectively. overall diagnostic accuracy of the HE4 and CA125 combination stands at 69.25%.
- The resulting area under the curve (AUC) values indicate that CA 125 is a fair test, HE4 is a good test, while ROMA is an excellent test for this purpose.
- HE4 has emerged as a promising biomarker, demonstrating superior specificity and sensitivity in differentiating ovarian cancer from benign conditions compared to CA125.

- The study shows that a combination of CA125 and HE4 tumor markers along with ROMA calculation gives better results in differentiating between benign or malignant ovarian tumors, early detection diagnosis, and management

CONCLUSION

CONCLUSION

The determination of molecular tumor marker levels, specifically HE4 and CA125, is critical. These biomarkers are instrumental in improving the early detection and diagnostic accuracy of the disease. While CA125 has been the traditional marker used, its limitations necessitate the use of additional markers like HE4, which offers greater specificity and sensitivity. HE4 has emerged as a promising biomarker, demonstrating superior sensitivity and specificity in distinguishing ovarian cancer from benign conditions compared to CA125.

However, combination of HE4 and CA125 in ROMA has shown enhanced accuracy in predicting ovarian cancer risk, and also differentiate between malignant and benign ovarian conditions. Combined use of HE4 and CA125 offers significant advancements in ovarian cancer management, facilitating early diagnosis, improved treatment monitoring, and timely recurrence detection, ultimately leading to better patient outcomes.

LIMITATIONS

LIMITATIONS

- False positive results may result from high CA125 in benign diseases such as endometriosis, menstruation, and pelvic inflammatory disease.CA125 sensitivity can vary on the basis of the stage of ovarian cancer, being less effective in early-stage detection.
- While HE4 offers better specificity, but may not be effective in determining certain subtypes of ovarian cancer, such as mucinous tumors.
- The usage of combination testing of HE4 and CA125 is limited due to its potential cost and unavailability in some clinical contexts. There is no universally accepted cutoff value for HE4, which can lead to variability in test results and interpretation.

RECOMMENDATIONS

RECOMMENDATIONS

- Utilize a combination of CA125 and HE4 for better diagnostic accuracy and early detection of ovarian cancer.
- Implement regular monitoring protocols using these markers to track treatment response and detect recurrence early.
- Establish standardized cutoff values and testing protocols to reduce variability in test results and improve clinical reliability.
- Invest in research to identify and validate additional biomarkers that can improve the detection of all ovarian cancer subtypes, including those less effectively detected by HE4.
- Develop cost-effective testing strategies to ensure broader accessibility and implementation in various healthcare settings.
- Combine biomarker testing with imaging and other diagnostic techniques to enhance overall diagnostic accuracy and patient management.

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ANNEXURES

ANNEXURES

PROFORMA

"DETERMINATION OF MOLECULAR TUMOR MARKER LEVELS HE4 (HUMAN EPIDIDYMIS PROTEIN 4) AND CA125 IN OVARIAN CANCERS: A CROSS SECTIONAL STUDY".

Investigator: Dr. Radhika S R

Name: IP No of patient: Age/Sex:

- **Present complaints:**

- Mass per abdomen
- Abdominal pain
- Any menstrual irregularities
- Urinary symptoms
- GIT symptoms
- Edema of lower limbs
- Any discharge per vagina

- **Menstrual history**

- Age of menarche
- Past menstrual cycle :
- Regular/irregular, Amount of flow- scanty/ moderate/ excessive; Dysmenorrhoea: yes/no; Associated clots - yes/no

- **Obstetric history**

- Married life
- Consnguinous/ non consnguinous
- Parity
- Last delivery
- Tubectomised/not

- **Past history**

TB/DM/HTN/Bronchial asthma/any surgeries/ thyroid/ cardiac diseases.

H/O use of oral contraceptives in the past

- **Family history**

TB/DM/HTN/Bronchial asthma/any surgeries, Any similar complaints inthe family

- **Personal history**

- Diet – Veg/mixed
- Appetite – Normal/ decreased
- Sleep – Normal/ disturbed
- Bowel – regular / irregular
- Bladder – Normal/ increased/ decreased

- **General physical examination**

- Built / Nourishment
- Icterus/clubbing/cyanosis/pallor/pedal/ edema/Lympadenopathy
- Temperature – Febrile / afebrile
- Pulse - BP - RR- SPO2-

- **Systemic examination**

- Cardiovascular system
- Respiratory system
- Abdominal examination

a. Inspection :

Shape

Movement of quadrants with respiration

Mass / swelling

Size

Shape

Extent

Any engorged vein

b. Palpation :

Local raise of temperature

Tenderness

Mass :Size Extent Surface Consistency Borders

Movements with respiration Any organomegaly

c. Percussion – Ascities – present / absent

d. Auscultation – Any bruit- present/absent

- **Per speculum examination**:

- **Per-vaginal examination**:

- Cervix- consistency/ position/ mobility/tenderness
- Uterus – size/position/ mobility/tenderness
- Mass felt bimanually separate from uterus/ not
- Abdominal mass movement transmitted to cervix/not
- Forniceal examination – full/ free, tender/non tender

- **Per rectal examination:**

- **Investigations**

a. Complete blood count: Blood group:
b. LFT: RFT: HIV, HBsAg :
c. Urine – albumin, sugar, microscopy
d. Chest xay:
e. USG abdomen and pelvis :
f. CT scan of abdomen and pelvis :
g. Tumourmarkers**:**

- **CA125 –**
- **HE4 –**

h. Risk malignancy index(RMI):
i. ROMA(RISK OF OVARIAN MALIGNANCY ALGORITHM):

- **Treatment**

- Surgery :Per operative findings –
- Anesthesia – GA/spinal

- **Histopathological examinationreport:**

- **Diagnosis:**

PATIENT INFORMATION SHEET

Study title**: DETERMINATION OF MOLECULAR TUMOR MARKER LEVELS HE4 (HUMAN EPIDIDYMIS PROTEIN 4) AND CA125 IN OVARIAN CANCER: A CROSS SECTIONAL STUDY".**

Study location: R L Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar. Patients who are of clinically indicated for induction admitted to OBG department of R L Jalappa hospital attached to Sri Devaraj Ursmedical college are recruited in the study after obtaining patient information consent.

Details-

Please read the following information and discuss with your family members. You can ask any question regarding the study. If you agree to participate in the study we will collect information (as per proforma) from you or from a person responsible for you or both. Relevant history will be taken. This information collected will be used only for dissertation and publication. The relevant investigations which are required such as CA125 and HE4 will be funded by me.

All information collected from you will be kept confidential and will not be disclosed to any outsider. Your identity will not be revealed. This study has been reviewed by the Institutional Ethics Committee and you are free to contact the member of the Institutional Ethics Committee. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study. For further information contact

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R L Jalappa hospital,
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ರೋಗಿಯ ಮಾಹಿತಿ ಹಾಳೆ

ಅಧ್ಯಯನ ದಶೀಕರಿಕೆ: ಆಣ್ವಿಕಟಟ್ಟುಮ ಮಾರ್ಕರ್‌ರಾಗಳ ಮಟ್ಟಗಳ ನಿರ್ಣಯ HE4 (ಹ್ಯೂಮನ್ ಎಪಿಡಿಡಿ ಮಿಸ್ಟ್ರೋಸೀನ್ 4) ಮತ್ತು ಅಂಡಾಶಯದ ಕ್ಯಾನ್ಸರ್‌ನಲ್ಲಿ CA125.

ಅಧ್ಯಯನಸ್ಥಳ: ಆ ಎರ್‌ಲ್ಲಾಲಪ್ಪ ಆಸ್ಪತ್ರೆ ಮತ್ತು ಸಂಶೋಧನಾ ಕೇಂದ್ರವು ಶ್ರೀ ದೇವರಾಜ್ ಅರ್ಸ್ ಮೆಡಿಕಲ್ ಕಾಲೇಜುಗೆ ಲಗತ್ತಿಸಲಾಗಿದೆ, ಟಿಮಕ, ಕೋಲಾರ. ಇಂಡಕ್ಷನ್‌ಗಾಗಿ ಪ್ರಾಯೋಗಿಕವಾಗಿ ಸೂಚಿಸಲಾದ ರೋಗಿಗಳು OBG ಗೆ ದಾಖಲಾಗಿದ್ದಾರೆ ಶ್ರೀ ದೇವರಾಜ್ ಅರಸ್ ವೈದ್ಯಕೀಯ ಕಾಲೇಜಿಗೆ ಹೊಂದಿ ಕೊಂಡಿರುವ ಆರ್‌ಎಲ್ಲಾಲಪ್ಪ ಆಸ್ಪತ್ರೆಯ ವಿಭಾಗವನ್ನು ನೇಮಕ ಮಾಡಿಕೊಳ್ಳಲಾಗಿದೆ ರೋಗಿಯ ಮಾಹಿತಿಯ ಒಪ್ಪಿಗೆಯನ್ನು ಪಡೆದ ನಂತರ ಅಧ್ಯಯನ. ವಿವರಗಳು ದಯವಿಟ್ಟು ಕೆಳಗಿನ ಮಾಹಿತಿಯನ್ನು ಓದಿ ಮತ್ತು ನಿಮ್ಮ ಕುಟುಂಬದ ಸದಸ್ಯರೊಂದಿಗೆ ಚರ್ಚಿಸಿ ನೀವು ಯಾವುದೇ ಪ್ರಶ್ನೆಯನ್ನು ಕೇಳಬಹುದು ಅಧ್ಯಯನದ ಬಗ್ಗೆ. ನೀವು ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ಒಪ್ಪಿದರೆ ನಾವು ಮಾಹಿತಿಯನ್ನು ಸಂಗ್ರಹಿಸುತ್ತೇವೆ (ಪ್ರೊಫಾರ್ಮಾ ಪ್ರಕಾರ) ನಿಮ್ಮಿಂದ ಅಥವಾ ನಿಮಗೆ ಅಥವಾ ಇಬ್ಬರಿಗೂ ಜವಾಬ್ದಾರರಾಗಿರುವ ವ್ಯಕ್ತಿಯಿಂದ. ಸಂಬಂಧಿತ ಇತಿಹಾಸವನ್ನು ತೆಗೆದುಕೊಳ್ಳಲಾಗುವುದು. ಈ ಮಾಹಿತಿ ಸಂಗ್ರಹಿಸಿದ ಪ್ರಬಂಧ ಮತ್ತು ಪ್ರಕಟಣೆಗೆ ಮಾತ್ರ ಬಳಸಲಾಗುತ್ತದೆ. ಸಂಬಂಧಿತ ತನಿಖೆಗಳು CA125 ಮತ್ತು HE4 ನಂತಹ ಅಗತ್ಯವಿರುವುಗಳಿಗೆ ನಮ್ಮಿಂದ ಹಣ ನೀಡಲಾಗುತ್ತದೆ. ನಿಮ್ಮಿಂದ ಸಂಗ್ರಹಿಸಲಾದ ಎಲ್ಲಾ ಮಾಹಿತಿಯನ್ನು ಗೌಪ್ಯವಾಗಿ ಇರಿಸಲಾಗುತ್ತದೆ ಮತ್ತು ಯಾವುದೇ ಹೊರಗಿನವರಿಗೆ ಬಹಿರಂಗ ಪಡಿಸಲಾಗುವುದಿಲ್ಲ. ನಿಮ್ಮ ಗುರುತನ್ನು ಬಹಿರಂಗ ಪಡಿಸಲಾಗುವುದಿಲ್ಲ. ಈ ಅಧ್ಯಯನವನ್ನು ಸಾಂಸ್ಥಿಕ ನೀತಿ ಶಾಸ್ತ್ರ ಸಮಿತಿಯು ಪರಿಶೀಲಿಸಿದೆ ಮತ್ತು ನೀವು ಸಾಂಸ್ಥಿಕನೈತಿಕ ಸಮಿತಿಯ ಸದಸ್ಯರನ್ನು ಸಂಪರ್ಕಿಸಲು ಮುಕ್ತರಾಗಿದ್ದೀರಿ. ಬಲವಂತ ಇಲ್ಲ ಈ ಅಧ್ಯಯನವನ್ನು ಒಪ್ಪಿಕೊಳ್ಳಲು. ನೀವು ಭಾಗವಹಿಸಲು ಬಯಸದಿದ್ದರೆ ನೀವು ಪಡೆಯುವ ಕಾಳಜಿಯು ಬದಲಾಗುವುದಿಲ್ಲ. ನೀವು ಈ ಅಧ್ಯಯನದಲ್ಲಿ ಭಾಗವಹಿಸಲು ನೀವು ಸ್ವಯಂ ಪ್ರೇರಣೆ ಯಿಂದ ಒಪ್ಪಿಕೊಂಡರೆ ಮಾತ್ರ ಹೆಚ್ಚಿರಳಿನ ಗುರುತನ್ನು ಸಹಿ ಮಾಡುವ ಅಗತ್ಯ ಎದೆ.

ಹೆಚ್ಚಿನ ಮಾಹಿತಿಗಾಗಿ ಸಂಪರ್ಕಿಸಿ

ಡಾ. ರಾಧಿಕಾ ಎಸ್ ಆರ್

ದೂರವಾಣಿಸಂಖ್ಯೆ- 9591819146

ಸ್ನಾತಕೋತ್ತರ ಪದವಿ, ಪ್ರಸೂತಿ ಮತ್ತು ಸ್ತ್ರೀ ರೋಗ ವಿಭಾಗ ಆರ್‌ಎಲ್ಲಾಲಪ್ಪಆಸ್ಪತ್ರೆ, ಕೋಲಾರ.

INFORMED CONSENT FORM

I Mrs.__have been explained in my own understandable language, that I willbe included in a study which is "**DETERMINATION OF MOLECULAR TUMOR MARKER LEVELS HE4(HUMAN EPIDIDYMIS PROTEIN 4)AND CA125 IN OVARIAN CANCER: A CROSS SECTIONAL STUDY".**

I have been explained that my clinical findings, investigations, postoperative findings will be assessed and documented for study purpose.

I have been explained my participation in this study is entirely voluntary, and I can withdraw from the study any time and this will not affect my relation with my doctor or the treatment for my ailment.

I have understood that all my details found during the study are kept confidential and while publishing or sharing of the findings, my details will be masked.

I have principal investigator mobile number for enquiries.

I in my sound mind give full consent to be added in the part of this study.

Signature of the patient:
Name:

Investigator signature :
Name:

Place:
Date:

ಮಾಹಿತಿನೀಡಿದಒಪ್ಪಿಗೆನಮೂನೆ

ನಾನು ಶ್ರೀಮತಿ _____ ಅನ್ನು ನನ್ನ ಸ್ವಂತ ಆರ್ಥವಾಗುವ ಭಾಷೆಯಲ್ಲಿ ವಿವರಿಸಿದ್ದೇನೆ, ಅದು "ಮಾಲೆಕ್ಯುಲರ್ ಟ್ಯೂಮರ್ ಮಾರ್ಕರ್ಸ್ ಮಟ್ಟಿಗಳು HE4 (ಹ್ಯೂಮನ್ ಎಪಿಡಿಡಿಮಿಸ್ ಪ್ರೊಟೀನ್ 4) ಮತ್ತು ಅಂಡಾಶಯದ ಕ್ಯಾನ್ಸರ್‌ನಲ್ಲಿ CA125 ಅನ್ನು ನಿರ್ಧರಿಸುವುದು" ಎಂಬ ಅಧ್ಯಯನದಲ್ಲಿ ನನ್ನನ್ನು ಸೇರಿಸಲಾಗುವುದು.

ನನ್ನ ಕ್ಲಿನಿಕ ಲ್ಯಾಬೋರೇಟರಿಗಳು, ತನಿಖೆಗಳು, ಶಸ್ತ್ರ ಚಿಕಿತ್ಸೆಯ ನಂತರದ ಸಂಶೋಧನೆಗಳು ಎಂದು ನನಗೆ ವಿವರಿಸಲಾಗಿದೆ ಅಧ್ಯಯನ ಉದ್ದೇಶಕ್ಕಾಗಿ ಮೌಲ್ಯ ಮಾಪನ ದಾಖಲಿಸಲಾಗಿದೆ. ಈ ಅಧ್ಯಯನದಲ್ಲಿ ನನ್ನ ಭಾಗವಹಿಸುವಿಕೆಯು ಸಂಪೂರ್ಣವಾಗಿ ಸ್ವಯಂ ಪ್ರೇರಿತವಾಗಿದೆ ಎಂದು ನನಗೆ ವಿವರಿಸಲಾಗಿದೆ ಮತ್ತು ನಾನು ಹಿಂತಪಡೆಯಬಹುದು

ಯಾವುದೇ ಸಮಯದಲ್ಲಿ ಅಧ್ಯಯನ ಮತ್ತು ಇದು ನನ್ನ ವೈದ್ಯರೊಂದಿಗಿನ ನನ್ನ ಸಂಬಂಧ ಅಥವಾ ನನ್ನ ಚಿಕಿತ್ಸೆಯ ಮೇಲೆ ಪರಿಣಾಮ ಬೀರುವುದಿಲ್ಲ

ಅಧ್ಯಯನದ ಸಮಯದಲ್ಲಿ ಪತ್ತೆಯಾದ ನನ್ನ ಎಲ್ಲಾ ವಿವರಗಳನ್ನು ಗೌಪ್ಯವಾಗಿ ಮತ್ತು ಸಮಯದಲ್ಲಿ ಇರಿಸಲಾಗಿದೆ ಎಂದು ನಾನು ಅರ್ಥ ಮಾಡಿಕೊಂಡಿದ್ದೇನೆ

ಸಂಶೋಧನೆಗಳನ್ನು ಪ್ರಕಟಿಸುವುದು ಅಥವಾ ಹಂಚಿಕೊಳ್ಳುವುದು, ನನ್ನ ವಿವರಗಳನ್ನು ಮರೆಮಾಚಲಾಗುತ್ತದೆ.

ವಿಚಾರಣೆಗಾಗಿ ನಾನು ಪ್ರಧಾನ ತನಿಖಾಧಿಕಾರಿಯ ಮೊಬೈಲ್ನಂಬರ್ಯನ್ನು ಹೊಂದಿದ್ದೇನೆ.

ಈ ಅಧ್ಯಯನದ ಭಾಗದಲ್ಲಿ ಸೇರಿಸಲು ನನ್ನ ಉತ್ತಮ ಮನಸ್ಸಿನಲ್ಲಿ ನಾನು ಸಂಪೂರ್ಣ ಒಪ್ಪಿಗೆಯನ್ನು ನೀಡುತ್ತೇನೆ.

ರೋಗಿಯಸಹಿ:
ಹೆಸರು:

ತನಿಖಾಧಿಕಾರಿಸಹಿ:
ಹೆಸರು:
ದಿನಾಂಕ:

MASTER CHART

Sr. No.	Age	Parity	Mode of presentation							Gross Examination				Size	Unilateral/ Bilateral	Menopausal Status	USG features								USG Score	Ca 125	HE4	RMI	ROMA	Histo-patho report
			PA	MI	MASS	DISTEN	WD	BLADDER	BOWEL	Solid	Cystic	Both	Gross				CYSTIC	SOLID	BOTH	ASCITIS	MULTI CYST	UNI CYST	THIN SEP	THICK SEP						
										gross(1)	gross(2)	gross(3)	appreance																	
1	42	PRIMI	Yes	No	Yes	No	No	Yes	No	No	No	Yes	COMPLEX	38	Unilateral	Pre	No	No	Yes	No	No	Yes	Yes	No	1	<35	36.7	>250	<1.14	Benign
2	47	MULTI	No	No	Yes	No	No	No	No	No	No	Yes	COMPLEX	17	Unilateral	Post	No	No	Yes	No	Yes	No	No	Yes	2	>35	1245.6	<25	>2.99	Malignant
3	52	MULTI	No	No	No	Yes	No	No	No	No	Yes	No	CYSTIC	22	Unilateral	Post	Yes	No	No	Yes	No	No	No	No	2	<35	46.7	<25	<2.99	Benign
4	43	MULTI	No	No	Yes	No	No	No	No	No	Yes	No	CYSTIC	30	Bilateral	Post	Yes	No	No	No	No	No	Yes	No	1	<35	125.9	>250	<2.99	Benign
5	38	PRIMI	No	No	Yes	No	No	No	No	No	Yes	No	CYSTIC	16	Bilateral	Post	Yes	No	No	No	Yes	No	No	No	1	<35	42.7	>250	<2.99	Benign
6	41	MULTI	Yes	No	Yes	No	No	No	No	Yes	No	No	SOLID	19	Unilateral	Post	Yes	No	No	No	No	No	No	Yes	3	>35	1180.9	25-250	>2.99	Malignant
7	30	MULTI	Yes	Yes	Yes	No	No	No	No	No	No	Yes	COMPLEX	12	Bilateral	Pre	Yes	No	No	No	No	Yes	Yes	No	3	>35	654.3	>250	> 1.44	Malignant
8	42	MULTI	Yes	Yes	Yes	No	No	No	No	Yes	No	No	SOLID	24	Unilateral	Post	No	Yes	No	No	No	No	No	No	2	<35	110.3	<25	<2.99	Benign
9	39	PRIMI	No	No	Yes	No	No	No	No	No	Yes	No	CYSTIC	19	Bilateral	Post	No	No	Yes	No	Yes	No	Yes	No	3	>35	2256.3	>250	>2.99	Malignant
10	42	MULTI	Yes	No	Yes	No	No	No	No	Yes	No	No	SOLID	27	Unilateral	Pre	Yes	No	No	No	Yes	No	No	Yes	3	>35	714.9	>250	> 1.44	Malignant
11	30	MULTI	Yes	Yes	Yes	No	No	No	No	No	No	Yes	COMPLEX	13	Bilateral	Pre	No	No	Yes	No	Yes	No	No	No	2	<35	29.1	>250	<1.14	Benign
12	44	MULTI	Yes	Yes	Yes	No	No	No	No	Yes	No	No	SOLID	38	Unilateral	Post	Yes	Yes	No	No	No	Yes	Yes	No	1	<35	441.9	25-250	<2.99	Benign
13	56	PRIMI	Yes	Yes	Yes	No	Yes	No	No	No	Yes	No	CYSTIC	17	Bilateral	Post	Yes	Yes	No	No	No	No	No	No	2	>35	314.6	>250	>2.99	Malignant
14	60	MULTI	Yes	Yes	No	No	Yes	No	No	Yes	No	No	SOLID	22	Bilateral	Post	No	No	Yes	Yes	No	Yes	No	No	1	<35	31.7	<25	<2.99	Benign
15	72	MULTI	No	No	Yes	Yes	Yes	No	No	Yes	No	No	SOLID	30	Unilateral	Post	Yes	No	No	No	No	Yes	Yes	No	3	>35	415.2	>250	>2.99	Malignant
16	45	MULTI	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	CYSTIC	16	Bilateral	Pre	No	No	Yes	No	Yes	No	No	Yes	3	>35	541.3	>250	> 1.44	Malignant
17	33	MULTI	No	No	No	Yes	Yes	No	No	No	Yes	No	CYSTIC	19	Unilateral	Post	Yes	No	No	Yes	No	No	No	No	1	<35	804.5	>250	<2.99	Benign
18	48	PRIMI	No	Yes	No	Yes	No	Yes	No	No	Yes	No	CYSTIC	12	Unilateral	Post	Yes	No	No	No	No	No	Yes	No	2	<35	216.4	<25	<2.99	Benign
19	63	NULLI	No	Yes	Yes	Yes	No	Yes	No	Yes	No	No	SOLID	24	Unilateral	Post	Yes	No	No	No	Yes	No	No	No	3	>35	1256.9	>250	>2.99	Malignant
20	42	NULLI	No	Yes	Yes	No	No	Yes	No	Yes	No	No	SOLID	11	Unilateral	Pre	Yes	No	No	No	No	No	No	Yes	2	>35	461.5	>250	> 1.44	Malignant
21	44	MULTI	Yes	Yes	Yes	No	Yes	Yes	No	Yes	No	No	SOLID	24	Bilateral	Post	Yes	No	No	No	No	Yes	Yes	No	3	>35	476.9	>250	>2.99	Malignant
22	54	MULTI	Yes	No	Yes	No	No	Yes	No	No	No	Yes	COMPLEX	16	Unilateral	Post	No	Yes	No	No	No	No	No	No	3	<35	111.9	25-250	<2.99	Benign
23	33	MULTI	Yes	No	Yes	No	Yes	Yes	No	No	No	Yes	COMPLEX	18	Unilateral	Pre	No	No	Yes	No	Yes	No	Yes	No	3	<35	30.6	>250	<1.14	Benign

24	60	PRIMI	Yes	No	Yes	No	No	Yes	No	Yes	No	No	SOLID	28	Unilateral	Post	Yes	No	No	No	Yes	No	No	Yes	3	>35	125.6	>250	>2.99	Malignant
25	38	PRIMI	No	No	Yes	No	No	No	No	No	Yes	No	CYSTIC	10	Bilateral	Post	No	No	Yes	No	Yes	No	No	No	2	>35	314.5	>250	>2.99	Malignant
26	41	MULTI	Yes	No	Yes	No	No	No	No	Yes	No	No	SOLID	18	Unilateral	Post	Yes	Yes	No	No	No	Yes	Yes	No	3	>35	216.7	>250	>2.99	Malignant
27	30	MULTI	Yes	Yes	Yes	No	No	No	No	No	No	Yes	COMPLEX	12	Bilateral	Pre	Yes	Yes	No	No	No	No	No	No	3	<35	55.7	>250	<1.14	Benign
28	42	MULTI	Yes	Yes	Yes	No	No	No	No	Yes	No	No	SOLID	24	Unilateral	Post	No	No	Yes	Yes	No	Yes	No	No	3	>35	326.5	25-250	>2.99	Malignant
29	39	PRIMI	No	No	Yes	No	No	No	No	No	Yes	No	CYSTIC	19	Bilateral	Post	Yes	No	No	No	No	Yes	Yes	No	1	<35	99.2	<25	<2.99	Benign
30	42	MULTI	Yes	No	Yes	No	No	No	No	Yes	No	No	SOLID	27	Unilateral	Pre	No	No	Yes	No	Yes	No	No	Yes	2	>35	58.9	>250	> 1.44	Malignant
31	28	MULTI	Yes	Yes	Yes	No	No	No	No	No	No	Yes	COMPLEX	13	Bilateral	Pre	Yes	No	No	Yes	No	No	No	No	3	<35	713.6	>250	<1.14	Benign
32	44	MULTI	Yes	Yes	Yes	No	No	No	No	Yes	No	No	SOLID	38	Unilateral	Post	Yes	No	No	No	No	No	Yes	No	3	<35	245.1	<25	<2.99	Benign
33	56	PRIMI	Yes	Yes	Yes	No	Yes	No	No	No	Yes	No	CYSTIC	17	Bilateral	Post	Yes	No	No	No	Yes	No	No	No	3	<35	106.7	<25	<2.99	Benign
34	60	MULTI	Yes	Yes	No	No	Yes	No	No	Yes	No	No	SOLID	22	Bilateral	Post	Yes	No	No	No	No	No	No	Yes	3	>35	418.6	>250	>2.99	Malignant
35	72	MULTI	No	No	Yes	Yes	Yes	No	No	Yes	No	No	SOLID	30	Unilateral	Post	Yes	No	No	No	No	Yes	Yes	No	2	>35	563.1	>250	>2.99	Malignant
36	45	MULTI	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	CYSTIC	16	Bilateral	Pre	No	Yes	No	No	No	No	No	No	3	<35	31.7	25-250	<1.14	Benign
37	33	MULTI	No	No	No	Yes	Yes	No	No	No	Yes	No	CYSTIC	19	Unilateral	pre	No	No	Yes	No	Yes	No	Yes	No	3	>35	36.7	>250	> 1.44	Malignant
38	48	PRIMI	No	Yes	No	Yes	No	Yes	No	No	Yes	No	CYSTIC	12	Unilateral	Post	Yes	No	No	No	Yes	No	No	Yes	3	>35	946.1	>250	>2.99	Malignant
39	38	PRIMI	No	No	Yes	No	No	No	No	No	Yes	No	CYSTIC	24	Bilateral	Post	No	No	Yes	No	Yes	No	No	No	2	>35	487.2	>250	>2.99	Malignant
40	41	MULTI	Yes	No	Yes	No	No	No	No	Yes	No	No	SOLID	11	Unilateral	Pre	Yes	Yes	No	No	No	Yes	Yes	No	3	<35	78.4	<25	<1.14	Benign
41	30	MULTI	Yes	Yes	Yes	No	No	No	No	No	No	Yes	COMPLEX	24	Bilateral	Pre	Yes	Yes	No	No	No	No	No	No	3	<35	65.9	>250	<1.14	Benign
42	42	MULTI	Yes	Yes	Yes	No	No	No	No	Yes	No	No	SOLID	16	Unilateral	Post	No	No	Yes	Yes	No	Yes	No	No	3	>35	461.2	25-250	>2.99	Malignant
43	39	PRIMI	No	No	Yes	No	No	No	No	No	Yes	No	CYSTIC	18	Bilateral	Post	Yes	No	No	No	No	Yes	Yes	No	3	>35	547.2	>250	>2.99	Malignant
44	42	MULTI	Yes	No	Yes	No	No	No	No	Yes	No	No	SOLID	28	Unilateral	Pre	No	No	Yes	No	Yes	No	No	Yes	2	>35	128.6	>250	> 1.44	Malignant
45	30	MULTI	Yes	Yes	Yes	No	No	No	No	No	No	Yes	COMPLEX	10	Bilateral	Pre	Yes	No	No	Yes	No	No	No	No	3	>35	136.7	>250	> 1.44	Malignant
46	44	MULTI	Yes	Yes	Yes	No	No	No	No	Yes	No	No	SOLID	18	Unilateral	Post	Yes	No	No	No	No	No	Yes	No	3	<35	561.3	>250	<2.99	Benign
47	56	PRIMI	Yes	Yes	Yes	No	Yes	No	No	No	Yes	No	CYSTIC	12	Bilateral	Pre	Yes	No	No	No	Yes	No	No	No	3	<35	298.1	<25	<1.14	Benign
48	60	MULTI	Yes	Yes	No	No	Yes	No	No	Yes	No	No	SOLID	22	Bilateral	Pre	Yes	No	No	No	No	No	No	Yes	2	>35	146.5	>250	> 1.44	Malignant
49	72	MULTI	No	No	Yes	Yes	Yes	No	No	Yes	No	No	SOLID	37	Unilateral	Post	Yes	No	No	No	No	Yes	Yes	No	3	>35	314.5	>250	>2.99	Malignant
50	45	MULTI	No	Yes	Yes	Yes	Yes	No	No	No	Yes	No	CYSTIC	14	Bilateral	Pre	No	Yes	No	No	No	No	No	No	3	<35	216.7	>250	<1.14	Benign

51	33	MULTI	No	No	No	Yes	Yes	No	No	No	Yes	No	CYSTIC	15	Unilateral	Post	No	No	Yes	No	Yes	No	Yes	No	3	>35	326.5	25-250	>2.99	Malignant
52	48	PRIMI	No	Yes	No	Yes	No	Yes	No	No	Yes	No	CYSTIC	21	Unilateral	Post	Yes	No	No	No	Yes	No	No	Yes	3	>35	318.5	>250	>2.99	Malignant
53	56	PRIMI	Yes	Yes	Yes	No	Yes	No	No	No	Yes	No	CYSTIC	30	Bilateral	Post	No	No	Yes	No	Yes	No	No	No	2	<35	216.7	<25	<2.99	Benign
54	60	MULTI	Yes	Yes	No	No	Yes	No	No	Yes	No	No	SOLID	28	Bilateral	Post	Yes	Yes	No	No	No	Yes	Yes	No	3	>35	366.5	>250	>2.99	Malignant