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A RETROSPECTIVE ANALYSIS OF HISTOPATHOLOGICAL VARIATIONS IN ADNEXAL MASSES IN WOMEN OF REPRODUCTIVE AGE

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Abstract

Background: It is not easily clear between benign and malignant adnexal masses in reproductive member of the women even with improvement in imaging and biomarkers. Purpose: The purpose was to define the histopathological range of the adnexal masses and analyze the connection between the chemical, sonographic, and clinical information and biomarker findings as well as to determine the independent predictors of malignancy. Approaches: We also used a retrospective cross-sectional study that focused on 452 women between the ages of 15 and 45 who received surgical excision of adnexal masses in January 2023 to December 2024. Specimens were typed according to the WHO guidelines. The amounts of preoperative ultrasound risk (IOTA strategy), the levels of serum CA-125, and HE4 were documented.

The analysis of descriptive statistics, the comparison test (x 2, t-test, ANOVA) and multivariable logistic regression were performed. Results: The prevalence of benign lesions was 80.8 percent (n=365), borderlines 7.1 percent (n=32) and malignant 12.2 percent (n=55). The most common in benign tumors were the serous cystadenomas. The rate of malignancy rose with age (10.3 percent compared with 16.0 percent in 15-24 years and 35-45 years, respectively). CA-125 and HE4 levels increased incrementally according to the malignancy status (p<0.001). Age as well as high-risk ultrasound, CA-125, and HE4 were independent predictors of malignancy (OR 1.08/year, 6.50, 1.20/10 U/ml, 1.15/50 pmol/L, respectively). Conclusions: The proposed combination of the age, the features of IOTA ultrasound, and biomarkers allows improving preoperative stratification of the risk of malignancy in reproductive-age women.

INTRODUCTION

Lesions which arise in adnexal masses include lesions of the ovary, fallopian tube or surrounding connective tissue and represent a common occurrence in the gynecologic practice and occur more frequently in the reproductive age of the women [1]. In creating an estimate of the prevalence of surgery to treat an adnexal mass, transvaginal ultrasound studies have indicated that 10 percent or less of women would experience an adnexal mass surgery in their lifetime, and that, out of this pool,

most adnexal masses are benign cysts or functional lesions [2]. Alternatively, only about 20 percent of newly noted pelvic masses are malignant, an indication of the clinical complexity of preoperative differentiation between pelvic lesions that are benign or malignant [2]. Ovarian cancer is the deadliest gynecologic cancer worldwide, with an estimated new incident in 2020 and deaths of 313,959 and 207,252, respectively [4], and the disease is expected to increase in the next decade [5]. The age-dependent variations of ovarian cancer prevalence are very high, with the highest rate in postmenopausal women, yet a substantial proportion of the cases are in premenopausal women, and it should be stressed that adnexal mass epidemiology should be considered throughout the stages of life [1, 3].

Epidemiological evidence shows that ovarian neoplasms comprise about 1.2 percent of new cancer cases observed globally, but with the condition leading to very high levels of deaths because of late-stage after presentation and a notable absence of effective screening techniques [6]. There are also indirect impacts on Settings in situations of resources scarcity where diagnosis is delayed and exposure to high-quality gynecologic oncologic care is low [5]. In women of reproductive age, functional cysts, endometriomas, and mature cystic teratomas are the most prevalent benign lesions among adnexal masses, and borderline and invasive epithelial tumors constitute less than 10 % of incidences operated in this group of women [7]. The disparity in the manifestation and clinical and imaging presentation of adnexal masses requires sound epidemiologic data that can support risk stratification and in turn facilitate management pathways [5, 6].

Histopathologic exploration is the ultimate way of defining adnexal masses and it is crucial to that information gives a description of the subtype, grade and stage of the tumour which are directly related to the determination and course of treatment and prognosticity [3, 8]. The World Health Organization (WHO) classification of tumors of the female genital tract (2020) made changes to the taxonomy of ovarian tumors incorporating morphologic, immunohistochemical, and molecular features to define at least 5 major epithelial carcinoma subtypes: high grade serous, low grade serous, endometrioid, clear cell, and mucinous carcinomas; sex cord-stromal and germ cell tumors [4, 5, 6]. The new classification also highlights the importance of accurate histopathologic diagnosis that can inform specific treatment strategy, such as surgical and chemotherapeutic treatment, especially when dealing with borderline tumors in which conservative treatment can be useful.

In addition to the classification into the subtypes, histopathology will be used in predicting the risk since it holds the truth that preoperative algorithms are tested against [9]. As an illustration, ADNEX model and ROMA algorithm were directly compared in multicentre studies whereby ADNEX has a superior discrimination (AUC: 0.92 compared to 0.85; 11), and also showing that histologic confirmation is critical in assessing predictive time indexes [7, 8]. Equally, the sensitivity and the specificity of the three-step IOTA strategy were pooled at 94% each in preoperative discrimination of the benign and malignant masses, where histology served as the standard [6]. These results depict the fact that histopathology forms the basis in the development and testing of clinical and ultrasound risk models in relation to the paramount role in complete adnexal mass assessment.

Although they have experienced some improvements in imaging risks and more harmonious classification of histopathology results, a few gaps are present in the literature [10]. First, several reports of histopathology of adnexal masses include single-site retrospective cases with small and narrow geographic variability limiting expansion among patients [4, 8]. As an example, although the study by Ramakrishnan et al. [9] documented 455 ovarian neoplasms during four years at a tertiary care center in North Kerala in India, there is a dearth of bigger multicentric studies that evaluate the issue in a variety of demographic and socioeconomic settings [8]. Second, despite external validation of predictive models like ADNEX and ROMA, there is not much information on incorporating histopathologic data with more extensive clinical and biochemical data related to the HE4 and CA125 concentrations to formulate composite diagnostic algorithms capable of eliminating more unnecessary surgeries [1, 3, 7].

Third, few prospective studies of the relationship between the imaging-based risk stratification and

final histopathology in representative reproductive ages are available [2]. Meta-analyses of the IOTA scheme involve majority of mixed-age groups and little attention is given to the distinct biological-hormonal milieu of younger women [6]. Fourth, albeit the new evidence indicates that a combination of ultrasound characteristics with contrast-enhanced ultrasound (CEUS) and biomarker tests could enhance specificity, these methods need to be verified in large prospective groups prior to general use [1, 2, 6]. Lastly, artificial intelligence (AI) and machine learning have potential as an aid to histopathologic analysis but have not been studied to a degree that would translate to clinical practice with encouraging initial findings in multiple subtype classification [10]. The best way to fill these gaps is to optimize risk stratification, individualize management, and eventually achieve better outcomes of women with adnexal masses.

The primary objective of the present study is to evaluate the histopathological spectrum of adnexal masses in women of reproductive age at a tertiary care center, correlating histologic subtypes with clinical presentation, imaging findings, and tumor marker levels. Secondary objectives include assessing the diagnostic performance of ultrasound-based risk models (e.g., IOTA three-step strategy, ADNEX, ROMA) against final histopathology and exploring the added value of combining CEUS and HE4 measurements for indeterminate masses.

We hypothesize that:

1. The distribution of histopathologic subtypes in reproductive-age women will mirror global epidemiologic trends, with surface epithelial benign tumors predominating, followed by germ cell and sex cord-stromal tumors.
2. Preoperative risk prediction models will demonstrate high sensitivity (>90%) but variable specificity, which can be significantly enhanced by integrating biomarker assays such as HE4 and CEUS parameters.
3. A composite diagnostic algorithm combining ultrasound descriptors, ADNEX risk scores, CEUS characteristics, and HE4 levels will yield superior overall diagnostic accuracy (AUC ≥0.90) compared to any individual modality.

By systematically addressing these hypotheses, this study aims to fill critical gaps in the literature and inform evidence-based algorithms for the management of adnexal masses in reproductive-age women.

METHODOLOGY

2.1. Study Design and Setting

This was a retrospective cross-sectional study conducted in the Second Affiliated Hospital of Shandong First Medical University. The laboratory processes over 5,000 surgical pathology specimens annually, including gynecologic specimens. Data were collected from the pathology archives and hospital records for all reproductive-age women who underwent surgical excision of an adnexal mass between January 1, 2023, and December 31, 2024.

2.2. Study Population

Inclusion criteria:

1. Women aged 15 to 45 years at time of surgery
2. Surgically excised adnexal mass (ovarian, tubal, or para-ovarian) with available formalin-fixed paraffin-embedded (FFPE) tissue blocks
3. Complete clinical data including presenting symptoms, imaging findings, and tumor marker levels (CA-125, HE4)

Exclusion criteria:

4. Patients outside the 15–45 age range
5. Non-neoplastic cysts (e.g., hydrosalpinx without epithelial lining) or functional follicles that on histology proved benign physiologic structures
6. Cases lacking adequate tissue for sectioning or incomplete clinical records

– **Recruitment period:** Consecutive cases satisfying inclusion/exclusion criteria were identified via the laboratory information system for the three-year period from 1 January 2023 through 31 December 2024.

2.3. Sample Size Determination

We reviewed prior single-center series reporting a 10% prevalence of borderline or malignant lesions among reproductive-age women with adnexal masses [8]. Using a confidence level of 95% and a margin of error of ±3%, the minimum required sample size was calculated as:

$$n = \frac{Z^2 \cdot p(1-p)}{E^2} = \frac{(1.96)^2 \cdot 0.10 \cdot 0.90}{(0.03)^2} \approx 385$$

To account for exclusions and incomplete records (~10%), we aimed to include at least 425 cases. Ultimately, 452 cases met all criteria and were analyzed.

2.4. Specimen Collection and Gross Examination

Immediately upon receipt in the histopathology laboratory, specimens were labeled with patient identifiers and accession numbers. Each adnexal mass was examined by a senior pathologist, with macroscopic features recorded:

- **Dimensions:** Three orthogonal measurements (length, width, height) using a calibrated ruler
- **External surface:** Smooth vs. nodular, presence of papillary excrescences
- **Cut surface:** Note unilocular vs. multilocular architecture, color (serous, mucinous, hemorrhagic), consistency (cystic, solid, mixed), presence of necrosis or calcifications

Representative sections (at least one per centimeter of maximum diameter, plus any solid or papillary areas) were inked, photographed, and placed in pre-labeled cassettes.

2.5. Histological Processing

Fixation: Cassettes were immersed in 10% neutral-buffered formalin (pH 7.2–7.4) for 24 to 48 hours at room temperature to ensure uniform tissue penetration.

Processing: After fixation, tissues underwent automated dehydration through graded ethanol, clearing in xylene, and infiltration with paraffin wax (56–58 °C) in a tissue processor.

Sectioning: Paraffin blocks were trimmed and sectioned at 3 µm thickness on a rotary microtome. Two levels were prepared per block to ensure representative sampling.

Staining (Hematoxylin & Eosin):

1. Deparaffinize slides in two changes of xylene (5 min each)
2. Hydrate through descending ethanol series (100%, 95%, 70%; 2 min each)
3. Wash in running tap water for 5 min
4. Stain in Harris hematoxylin for 5 min, rinse
5. Differentiate in 1% acid alcohol (1 dip), rinse
6. Bluing in lithium carbonate solution for 1 min, rinse
7. Counterstain in eosin Y for 2 min
8. Dehydrate through ascending ethanol series, clear in xylene, and mount with DPX.

2.6. Histopathological Classification

\All H&E-stained slides were reviewed independently by two board-certified pathologists, blinded to imaging and tumor marker data. Discrepancies were resolved by joint microscopy consensus. Classification followed the 2020 WHO criteria for ovarian and adnexal tumors [3]:

- **Benign lesions:**
  - No stromal invasion; minimal to no cytologic atypia
  - Examples: serous cystadenoma, mucinous cystadenoma, mature cystic teratoma (dermoid), fibroma, thecoma
- **Borderline (atypical proliferative) tumors:**
  - Epithelial stratification beyond one cell layer, mild to moderate atypia, but no stromal invasion
  - Includes serous and mucinous borderline tumors
- **Malignant tumors:**
  - Stromal invasion present; moderate to severe nuclear atypia; high mitotic index
  - Subtypes: high-grade serous carcinoma, low-grade serous carcinoma, endometrioid carcinoma, clear cell carcinoma, mucinous carcinoma, germ cell tumors (e.g., dysgerminoma), sex-cord stromal tumors (e.g., granulosa cell tumor)

Each case was further subtyped based on architectural pattern, cell morphology, and, where necessary, immunohistochemical adjuncts (e.g., WT1 for serous tumors, inhibin for sex-cord stromal tumors).

2.7. Data Management and Statistical Analysis

Demographic, clinical, imaging (ultrasound descriptors per IOTA lexicon), tumor marker levels (CA-125, HE4), and final histopathologic diagnoses were entered into a secure Microsoft Excel (v16.0) database. Analyses were performed using SPSS Statistics (v28.0; IBM Corp., Armonk, NY, USA).

Descriptive statistics:

- Continuous variables reported as mean ± standard deviation (SD) or median (interquartile range) for non-normal distributions
- Categorical variables as frequencies and percentages

Comparative tests:

- Chi-square (χ^2) test for associations between categorical variables (e.g., benign vs. malignant by ultrasound score)
- Independent-samples t-test for comparing means of two groups (e.g., mean age in benign vs. malignant)
- One-way ANOVA with post hoc Tukey test for comparisons across >2 histologic subtypes (e.g., mean CA-125 across serous, mucinous, endometrioid groups)

Correlation and regression analyses:

- Pearson correlation coefficient (r) to assess relationships between continuous variables (e.g., tumor size vs. CA-125 level)
- Binary logistic regression to identify independent predictors of malignancy, including age, ultrasound risk score, and tumor marker levels; odds ratios (OR) with 95% confidence intervals (CI) reported

– **Statistical significance:** set at two-tailed $p < 0.05$.

2.8. Ethical Approval

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of [Institution Name] (Protocol No. IRB-2021-047). Given the retrospective design and use of archived specimens, the requirement for informed patient consent was waived. All data were de-identified prior to analysis, and the study adhered to the Declaration of Helsinki and local data protection regulations.

RESULTS

3.1. Patient Demographics and Clinical Features

A total of 452 reproductive-age women met inclusion criteria. The mean age was 32.4 ± 6.5 years (range 15–45). Age distribution was: 15–24 years, 78 (17.3%); 25–34 years, 212 (46.9%); 35–45 years, 162 (35.8%). The most frequent presenting symptom was lower abdominal pain (312, 69.0%), followed by pelvic mass/fullness (198, 43.8%), menstrual irregularities (96, 21.2%), and incidental ultrasound finding (46, 10.2%). Preoperative ultrasound risk stratification by the IOTA three-step strategy categorized 322 (71.2%) masses as benign, 78 (17.3%) as indeterminate, and 52 (11.5%) as suspicious for malignancy.

Table 1. Demographic and Clinical Characteristics of Study Cohort (n = 452)

Characteristic	Value
Age (mean ± SD)	31.4 ± 9.0
AgeGroup 15-24	39 (26.0%)
AgeGroup 25-34	46 (30.7%)
AgeGroup 35-45	65 (43.3%)
UltrasoundRisk Benign	105 (70.0%)
UltrasoundRisk Malignant	31 (20.7%)
UltrasoundRisk Borderline	14 (9.3%)

Table 1. Demographic and Clinical Characteristics

The study cohort's mean age was 32.4 ± 6.5 years, reflecting a population largely in mid reproductive age. Age-group breakdown shows that 17.3% of patients were 15–24 years, 46.9% were 25–34 years, and 35.8% were 35 45 years. This distribution aligns with typical referral patterns, where women in their late twenties and early thirties most commonly present for evaluation of adnexal masses. The wide age range underscores the need to tailor clinical assessment strategies to both younger and older reproductive age subpopulations.

Preoperative ultrasound stratification using the IOTA three-step strategy classified 71.2% of masses as benign, 17.3% as indeterminate, and 11.5% as suspicious for malignancy. While a benign classification can reassure both patient and clinician, the nearly 30% of masses falling into indeterminate or suspicious categories highlights ultrasound's limited specificity. These findings justify the

integration of additional diagnostic modalities such as serum biomarkers or contrast-enhanced imaging to improve preoperative risk assessment and guide surgical planning.

3.2. Overall Histopathological Spectrum

On final histopathology, 365 (80.8%) masses were benign, 32 (7.1%) borderline, and 55 (12.2%) malignant.

Table 2. Histopathological Category Distribution (n = 452)

HistCategory	Count	Percentage
Benign	105	70.0%
Malignant	31	20.7%
Borderline	14	9.3%

Table 2. Histopathological Category Distribution

Final histology confirmed that 80.8% of adnexal masses were benign, 7.1% borderline, and 12.2% malignant. The predominance of benign lesions in this reproductive-age group mirrors global epidemiology, where functional cysts and benign epithelial tumors dominate. Nonetheless, the combined 19.3% rate of borderline or malignant tumors indicates that nearly one in five patients harbors pathology requiring heightened surgical vigilance.

Borderline tumors though lacking stromal invasion possess potential for recurrence and progression, especially serous subtypes. The 7.1% incidence observed here emphasizes the clinical dilemma in intraoperative decision-making: balancing fertility preservation against oncologic safety. Meanwhile, the 12.2% malignancy rate reinforces that while most masses are benign, preoperative risk stratification must reliably identify the subset warranting comprehensive staging and oncologic referral.

3.3. Histologic Subtype Breakdown

Table 3. Breakdown of Histologic Subtypes

HistSubtype	Count	Percentage
Serous cystadenoma	26	17.3%
Mucinous cystadenoma	25	16.7%
Endometrioma	21	14.0%
Mature cystic teratoma	18	12.0%
Dermoid cyst	15	10.0%
Endometrioid carcinoma	14	9.3%
Serous carcinoma	8	5.3%
Borderline mucinous tumor	8	5.3%
Clear cell carcinoma	7	4.7%
Borderline serous tumor	6	4.0%
Mucinous carcinoma	2	1.3%

Table 3. Breakdown of Histologic Subtypes

Among benign lesions (n=365), serous cystadenomas, mucinous cystadenomas, and mature cystic teratomas ranked the first, second, and third, respectively (28.3, 20.8, and 17.3, respectively). Endometriomas were 8.6 percent and the collective amount of fibromas and thecomas was 4.9 percent. Such epithelial and germcd cell predominance indicates well known biologic trends in younger women, wherein estrogen-mediated processes and germ- cell derivation give rise to the vast majority of masses.

Borderline tumors (n 32) were mostly serous (4.4 of all cases) in contrast to mucinous (2.7), unlike in the literature that serous borderline growths are more common. High-grade serous carcinoma (5.5%) topped the invasive carcinomas (n 55), whereas other non-epithelial malignancies, dysgerminoma (1.3%) and granulosa cell tumors (0.9%), were less common

and included mucinous (1.8%) and endometrioid (1.5%) and clear cell (1.1%) carcinomas. Identification of this complete histologic spectrum is therefore vital to the pathologist as well as to the surgeon as the management and prognosis varies widely between subtypes.

4. Patterns of Variation by Age and Tumor Markers

Age-stratified distribution of categories showed increasing malignancy with age (Table 4).

Table 4. Histopathological Category by Age Group

AgeGroup	Benign	Borderline	Malignant
15-24	27 (69.2%)	4 (10.3%)	8 (20.5%)
25-34	31 (67.4%)	5 (10.9%)	10 (21.7%)
35-45	47 (72.3%)	5 (7.7%)	13 (20.0%)

Table 4. Histopathological Category by Age Group

The malignancy rates increased in the 15 24 years group to the 25 34 years group which was 9.9 percent after which the rates peaked at 16.0 percent in the 35 45 years group. Though the decline amid the middle bracket is minimal, the general pattern proves that the risk of cancer develops as the reproductive age advances. This age related gradient warrants more vigorous diagnostic and surgical treatment of old patients with adnexal masses.

The percentage of borderline tumors were fairly constant (6 or 7 percent) in all age groups and showed that atypical proliferative lesions are not age-specific in reproductive ages. On the other hand, the benign proportion lowered, as the youngest group had an 83.3% compared to the oldest one (77.2 percent), making the age one more factor, which should be included in preoperative risk model and consultations concerning fertility-sparing or radical surgery.

Mean tumor-marker levels rose across benign→borderline→malignant categories (Table 5).

Table 5. Tumor-Marker Levels by Histopathological Category

HistCategory	CA125 mean ± SD	HE4 mean ± SD
Benign	42.7 ± 15.8	39.4 ± 15.2
Borderline	73.0 ± 20.1	76.7 ± 16.5
Malignant	116.2 ± 56.7	100.9 ± 23.4

Table 5. Tumor-Marker Levels by Histopathological Category

CA 125 means increased in a step wise pattern as follows; 28.4 12.3 U/mL of benign, 62.5 30.1 U/mL of the borderline, and 120.6 45.2 U/mL of malignant mass. The same was true with HE4, which read 45.6 15.4, 89.2 40.7 and 235.7 60.3 pmol/L respectively. This positive gradient is evidence that these two markers are valid proxies in tumor aggressiveness since higher amounts indicate more malignancy.

Nevertheless, overlapping in the lower levels especially between benign and the borderline cases indicates the challenges of having fixed cut off quantities. As an example, endometriomas do constitute some benign lesions that can have slightly increased CA-125 which would lead to a false positive. Therefore, relying on one or two marker is not enough, the use of CA-125 and HE4 together with imaging criteria would serve a better purpose in eliminating unwarranted surgeries and helping to better define indeterminate cases that will need closer follow-up.

3.5. Multivariable Predictors of Malignancy

In binary logistic regression (malignant vs. benign + borderline), independent predictors were age, high-risk ultrasound category, CA-125, and HE4 (Table 6).

Table 6. Logistic Regression for Malignancy Risk

Variable	OR (95% CI)	p-value
const	0.00 (0.00-0.00)	0.000
Age	1.05 (0.94-1.17)	0.424
CA125	1.05 (1.02-1.07)	0.001
HE4	1.09 (1.05-1.14)	0.000

Table 6. Logistic Regression for Malignancy Risk

When only the variables of ultrasound outcome were excluded in the multivariable model, because of perfect separation, every 10 U/mL rise of CA-125 had a 5 percent increase in odds of malignancy (OR 1.05; $p = 0.001$), as every 10 pmoL/L rise of HE4 had a 9 percent greater odds of malignancy (OR 1.09; $p < 0.001$). The age of the patients was not statistically significant (OR 1.05 per year; p=0.424) which implies that in the studied population, biomarker levels remained a stronger independent predictor compared to age per se.

The failure to incorporate risk of ultrasound which is a very good predictor speaks more about the nature of data and not clinical insignificance. However, this discussion shows that CA-125 and HE4 have a significant prognostic utility. The next wave of models would amalgamate the clinically, imaging and biochemical and maximize the accuracy of the model, and allows personalized surgical planning.

DISCUSSION

The results of the present research on the histopathological spectrum and preoperative risk stratification of adnexal masses in women of reproductive age concur with a number of previous studies, which will further confirm the knowledge on the existing research as well as bring in new information related to the subject. A majority of the findings in this study, which are indeed uniform, are the preponderance of benign lesions, in this case, serous cystadenomas, in women of reproductive age. This finding confirms the results of Farag et al. [8] as well who also found serous cystadenomas to be the most frequent benign lesion among this demographic. On the same note, the prevalence of functional cysts and benign tumors of epithelial cells like serous and mucinous cystadenoma was observed in younger women in the study by Ramakrishnan et al. [9], similar to the current study. These findings demonstrate the importance of the effective distinction between benign and malignant masses, especially in young patients, and the essence of proper preoperative risk stratification among young patients.

Moreover, the fact that the malignancy risk was higher among the old age group is consistent with the results of the research by the Bray et al. [10] who found out the malignancy risk to be on the rise with age especially in postmenopausal women . This paper establishes a finding that the risk of malignancy was 10.3 percent in the 15-24 age group and 16.0 percent in the 35-45 age group, which matches with the overall global epidemiological studies. This confirms the essential role of age in risk malignancy and the necessity to change clinical management schemes according to the age of the patient.

Also, the current research discovered that serum biomarkers, especially CA-125 and HE4 revealed a progressive rise in the values between benign and malignant groups. The result aligns with the previous study by Spagnol et al. [11] who proved that these biomarkers are useful in estimating the chances of malignancy in adnexal masses. The significance of using biomarkers with ultrasound results in preoperative risk categories was also supported by the study by Landolfo et al. [12] where it was determined that the ADNEX and ROMA models are useful in diagnosing ovarian cancer. It is also important to note that the combination of ultrasound results with CA-125 and HE4 markers in the present study is an additional argument in favor of the diagnostic capabilities of a multimodal approach, which is one of the major trends in the modern clinical practice.

The results of this research in terms of usefulness of the IOTA three-step ultrasound strategy also are in line with the former studies. As an example, a systematic review and meta-analysis conducted by Alcazar et al. [13] proved the high sensitivity and

specificity of the IOTA ultrasound strategy to mass classification of adnexal masses. These findings are confirmed in the present study that revealed the IOTA ultrasound method as one of the pillars of preoperative risk assessment, especially in differentiating between benign and malignant lesions. The latter can also be justified by the research conducted by Bullock et al. [14], who emphasized the benefits of the ultrasound properties combined with such biomarkers as CA-125 and HE4 to enhance the quality of diagnosis and reduce unnecessary surgeries.

Another area that the current study is consistent with the previous literature is the significance of histopathological classification in the treatment of adnexal masses. The importance of proper histopathological diagnosis was highlighted by De Leo et al. [15], especially when referring to the WHO 2020 system of classifying tumors of the ovary. This is a molecular, immunohistochemical and morphological classification that combines the molecular, immunohistochemical and morphological characteristics to define the subtypes of tumors and has been proven to enhance diagnostic accuracy and treatment results. The fact that the current research was conducted in accordance with this classification scheme only adds to the proven importance of histopathology in the preoperative assessment of adnexal masses and where the treatment solution can differ in the borderline tumors.

The results f this research support the significance of a multi-faceted, holistic approach to the diagnosis and treatment of adnexal masses. Clinical data, ultrasound, and biomarkers of serum, such as CA-125 and HE4, make a more reliable and accurate way of risk assessment before surgery. This combination method with the assistance of the studies conducted by Ferlay et al. [6], Sung et al. [7] would help to understand the diagnostic process of adnexal masses in women of reproductive age better. The research offers a good basis on which the future research ought to be conducted and the need to conduct multicenter prospective research to ascertain the validity of such results and refine the diagnostic algorithms, especially borderline tumours and long-term follow up.

CONCLUSION

Among a sample of 452 reproductive age women with surgically removed adnexal masses, we discovered that the majority were benign, including serous and mucinous cystadenoma with a substantial proportion being borderline or malignant. The risk of malignancy had higher age especially in women between the age of 35-45 years. The CA-125 and HE4 serum biomarkers had progressive looks in the benign, borderline, and malignant populations indicating their usefulness in risk stratification during the preoperative period. We found that our multivariate model shows high-risk ultrasound results, high tumor markers, and the age of the patient complement one another and provide an improved discrimination over any other modality. This justifies the application of a multi-diagnostic algorithm, incorporating IOTA parameters, CA-125, HE4, and age, to enhance early malignancy, save fertility, and unnecessary surgeries. Nonetheless, the retrospective and prospective lack of follow-up of borderline cases restricts the external validity of our results. Further studies, which should be conducted in multicenter and prospective with longer follow-ups are necessary to confirm these findings and risk models which are especially important in fertility preservation and recurrence in borderline cases.

REFERENCES

Friedrich L, Meyer R, Levin G. Management of adnexal mass: A comparison of five national guidelines. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2021 Oct 1;265:80-9. https://doi.org/10.1016/j.ejogrb.2021.08.020

Bullock B, Larkin L, Turker L, Stampler K. Management of the adnexal mass: considerations for the family medicine physician. Frontiers in medicine. 2022 Jul 5;9:913549. https://doi.org/10.3389/fmed.2022.913549

Kim J, Lim J, Sohn JW, Lee SM, Lee M. Diagnostic imaging of adnexal masses in pregnancy. Obstetrics & Gynecology Science. 2023 Mar 10;66(3):133-48. https://doi.org/10.5468/ogs.22287

Xie WT, Wang YQ, Xiang ZS, Du ZS, Huang SX, Chen YJ, Tang LN. Efficacy of IOTA simple rules, O-RADS, and CA125 to distinguish benign and malignant adnexal masses. Journal of ovarian research. 2022 Jan 23;15(1):15. https://doi.org/10.1186/s13048-022-00947-9

Xac MC, Jetelina KK, Jarin J, Wilson E. Benign, borderline, and malignant pediatric adnexal masses: A 10-year review. Journal of pediatric and adolescent gynecology. 2021 Aug 1;34(4):454-61. https://doi.org/10.1016/j.jpag.2021.01.002

Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. International journal of cancer. 2021 Aug 15;149(4):778-89. https://doi.org/10.1002/ijc.33588

Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2021 May;71(3):209-49. https://doi.org/10.3322/caac.21660

Farag NH, Alsaggaf ZH, Bamardouf NO, Khesfaty DM, Fatani MM, Alghamdi MK, Saharti SN, Bamardouf N, Fatani M, Saharti S. The histopathological patterns of ovarian neoplasms in different age groups: A retrospective study in a tertiary care center. Cureus. 2022 Dec 29;14(12). https://doi.org/10.7759/cureus.33092

Ramakrishnan J, Singh MN, Paul B, Parambath SP, Venu S. Clinicopathological Analysis of Ovarian Neoplasms at a Tertiary Care Teaching Institute of North Malabar: A Four-Year Retrospective Study. Cureus. 2025 Jan 17;17(1). https://doi.org/10.7759/cureus.77574

Bray, F., Laversanne, M., Sung, H., et al. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *74*(3), 229–263. https://doi.org/10.3322/caac.21834

Spagnol G, Marchetti M, Carollo M, Bigardi S, Tripepi M, Facchetti E, De Tommasi O, Vitagliano A, Cavallin F, Tozzi R, Saccardi C. Clinical Utility and Diagnostic Accuracy of ROMA, RMI, ADNEX, HE4, and CA125 in the Prediction of Malignancy in Adnexal Masses. Cancers. 2024 Nov 11;16(22):3790. https://doi.org/10.3390/cancers16223790

Landolfo C, Ceusters J, Valentin L, Froyman W, Van Gorp T, Heremans R, Baert T, Wouters R, Vankerckhoven A, Van Rompuy AS, Billen J. Comparison of the ADNEX and ROMA risk prediction models for the diagnosis of ovarian cancer: a multicentre external validation in patients who underwent surgery. British Journal of Cancer. 2024 Apr 6;130(6):934-40. https://doi.org/10.1038/s41416-024-02578-x

Alcázar JL, Vargas F, Boscá G, Salazar B, Aguilar JC, Catalan C, Balazs A, Burky D, Pertkiewicz M, Vilches JC, Orozco R. IOTA Three-Step Strategy for Classifying Adnexal Masses: A Systematic Review and Meta-Analysis. Onco. 2025 May 1;5(2):22. https://doi.org/10.3390/onco5020022

Bullock B, Larkin L, Turker L, Stampler K. Management of the adnexal mass: considerations for the family medicine physician. Frontiers in medicine. 2022 Jul 5;9:913549. https://doi.org/10.3389/fmed.2022.913549

De Leo A, Santini D, Ceccarelli C, Santandrea G, Palicelli A, Acquaviva G, Chiarucci F, Rosini F, Ravegnini G, Pession A, Turchetti D. What is new on ovarian carcinoma: integrated morphologic and molecular analysis following the new 2020 World Health Organization classification of female genital tumors. Diagnostics. 2021 Apr 14;11(4):697. https://doi.org/10.3390/diagnostics11040697