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Clinicopathological spectrum of ovarian neoplasms with a special emphasis on risk of malignancy index – a single institutional study

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ABSTRACT

Background: Ovarian carcinoma remains one of the leading causes of cancer-related deaths in women, often diagnosed at advanced stages due to non-specific symptoms. Early differentiation between benign and malignant ovarian neoplasms is crucial for optimal management. **Aims and Objectives:** To evaluate the clinical and sociodemographic profiles, histopathological spectrum, ultrasonographic features, serum CA125 levels, and the diagnostic performance of the risk of malignancy index (RMI) in ovarian tumors at a rural tertiary care center. **Materials and Methods:** A retrospective cross-sectional study was conducted on 119 ovarian neoplasm cases from July 2022 to June 2023. Demographic, clinical, histopathological, and CA125 data were analyzed. RMI-2 was calculated, and its performance was compared with ultrasound (USG) scoring and CA125 levels. **Results:** Of 119 cases, 62.18% were benign, 5.04% borderline, and 32.77% malignant. The mean age was 39.8±14.9 years. Benign tumors predominated in pre-menopausal women, whereas malignancies were more frequent post-menopausally (P<0.0001). Elevated CA125 levels (>35 U/mL) were seen in 97.78% of malignant/borderline tumors. CA125 alone showed high sensitivity (97.78%) but lower specificity (67.57%). RMI demonstrated better diagnostic accuracy (84.87%) than CA125 or USG alone. However, RMI was less effective in differentiating mucinous tumors from benign lesions. **Conclusion:** Ovarian tumors exhibit diverse morphological patterns and demographic associations. RMI, combining clinical, biochemical, and radiological parameters, offers improved accuracy for pre-operative discrimination between benign and malignant ovarian tumors, guiding surgical management, particularly in resource-limited settings. Nonetheless, caution is warranted in interpreting RMI for mucinous neoplasms.

Key words: Ovarian tumors; Risk of malignancy index; CA125; Ultrasound scoring

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INTRODUCTION

Ovarian carcinoma (OC) is the eighth most common cause of cancer and cancer-related deaths in women. It exhibits varied histomorphology, leading to a complex and extensive classification system.[1] There were 324,603 new cases of OC globally in 2022. China had the largest number of new cases (61,060), followed by India (47,333) and the United States of America (USA) (21,179). Deaths were the highest in India (32,978), followed by China (32,646) and the USA (13,273).[2]

The American Cancer Society estimates that in 2025, in the USA, about 20,890 women will receive a new diagnosis of OC, and about 12,730 women will die from it.[3] Its lethality is due to its delayed clinical presentation, lending a 5-year survival rate of 17%.[4]

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Tobacco use, obesity, higher socioeconomic status, hormone replacement therapy, early menarche, late menopause, and endometriosis contribute to increasing rates, particularly among younger women.[1] Hereditary breast and OC syndrome is linked to high-grade serous carcinoma, and Lynch syndrome to endometrioid and clear cell types. Higher parity and oral contraceptive pill (OCP) use are protective, especially against non-mucinous subtypes such as clear cell and endometrioid carcinomas. Bilateral salpingo-oophorectomy, hysterectomy, and tubal ligation reduce the risk by preventing retrograde menstruation, lowering the likelihood of endometriosis and serous tubal intraepithelial carcinoma (STIC), both of which are implicated in ovarian carcinogenesis. The incidence of mucinous neoplasms, frequently metastatic, has increased due to stricter diagnostic criteria.[1,5-7]

Accurate distinction between primary ovarian tumors and metastases requires detailed clinico-radiological correlation, thorough gross examination (including surface, hilar, and extraovarian assessment), peritoneal fluid cytology, precise staging, and extensive sampling, supported by knowledge of diverse microscopic patterns.[1,7]

Despite the wide variation in histomorphology, the recent classification of OC into benign, borderline, low-grade, and high-grade tumors allows for more accurate detection of ovarian tumor morphology. Inclusion of borderline tumors and reclassification of certain site-specific neoplasms have changed OC incidence.[8]

While OC primarily affects post-menopausal women, pre-menopausal and perimenopausal women are also at risk, particularly for type II tumors (as classified by clinical, genetic, and embryological models of carcinogenesis). Notably, stages 1 and 2 are often asymptomatic in these cases. If diagnostic delays can be minimized, especially at stage 3A, early detection and intervention through various screening methods could significantly improve survival rates. Some epithelial tumors occur in younger age groups and often have a better prognosis (type I-endomtrioid, clear cell, etc.), regardless of their stage, contributing to the lower death rates observed in stages 1 and 2, as opposed to aggressive type II tumors (high-grade serous, carcinosarcoma, etc.). The clinical patterns vary according to the different types and subtypes of ovarian tumors. Screening methods (measuring serum CA125 levels) show different expression levels, with the highest levels found in the epithelial tumor group. The subtypes within the epithelial group also exhibit distinct serum CA125 expression patterns.[8]

OCs, particularly borderline tumors, tend to produce peritoneal deposits without significant invasion into the ovarian stroma. They are defined by strict histopathological criteria and generally have a more favorable prognosis than their malignant counterparts.[1,7]

Ovarian cancer is called a silent killer as it does not produce any obvious symptoms in early stages, and according to the National Cancer Registry Programme report (ICMR), 2020, age standardized ratio (ASR) varies among states, highest being in Papum Pare (13.7%) followed by Kamrup (9.8%) and Delhi (9.5%).[9,10]

Epithelial tumors are the most common, serous adenocarcinoma being the most common malignant subtype (cases presented mostly in advanced stage). Patient age and tumor laterality provide important clues regarding the tumor type.[1,11]

CA125, a tumor marker, is a glycoprotein produced by neoplastic cells exhibiting epithelial differentiation. Its serum levels are closely linked to the biological behavior and tumor burden in OCs. Elevated CA125 levels are observed in about 80% of OC cases; levels below 35 U/mL are considered within the normal range.[8,12]

It is raised in only about 50% early cases. No single diagnostic modality (pelvic examination, ultrasonography, or serum CA125 measurement) can reliably determine the specific type or nature of an ovarian neoplasm. However, when combined into the risk of malignancy index (RMI), these parameters can help predict whether an adnexal mass is benign or malignant, thereby aiding in clinical decision-making. The RMI, first introduced in 1990 as RMI 1, is calculated as the product of the menopausal status score (M), ultrasound (USG) findings score (U), and the absolute serum CA125 level. At a cutoff value of 200, this has demonstrated a sensitivity of 87.5% and a specificity of 97.7%.[9]

Aims and objectives

In this context, we plan to study the clinical and sociodemographic profiles of patients with ovarian tumors, characterize the histopathological spectrum of these tumors, analyze ultrasonographic features based on scoring systems, and evaluate serum CA125 levels. We aim to correlate these findings with the calculated RMI, with the objective of assessing the frequency distribution of benign and malignant neoplasms and determining the diagnostic and prognostic performance of various investigation modalities. No such attempt has been made from our region.

MATERIALS AND METHODS

This is a single institutional retrospective cross-sectional study conducted at the Department of Pathology of a rural tertiary care center after IEC approval (Memo No.:

IEC/NBMC/M-06/001/2023, Dated: May 2nd, 2023). All cases of ovarian neoplasms attending our institution and whose biopsy specimens were sent to the Department of Pathology from July 2022 to June 2023 were considered. There were a total of 119 cases (consecutive sampling). The sample size was calculated using the prevalence data of studies as mentioned below.

According to the National Cancer Registry Programme report (ICMR), the ASR varies among states, the highest being in Papum Pare (13.7%), followed by Kamrup (9.8%) and Delhi (9.5%). The World Cancer Research Fund documented worldwide ASR as 6.7% – India having 6.6% ASR, whereas the USA with 7.3%, Japan with 9.8%, the UK with 9.2%, Russia and the Philippines with >11%. China and Brazil have an ASR of 5.7% and 5.1%, respectively. When we calculated sample size with worldwide ASR 6.7% using the formula of prevalence/proportions (Z^2 P [1-P]/d^2 – where Z stands for confidence level at 95% and the value being 1.96; d stands for precision at 5% and the value being 0.05), it came out to approximately 96. We calculated with ASR 9.8% in Kamrup/Philippines, and it came to around 135. As many North-East people get treated at our center, we also calculated the highest ASR of Papum Pare District (13.7%), and it resulted in a size of approximately 183. Due to variations in ASR, we decided that our sample size should not be <96 (considering the world ASI as 6.7%), and we would include all patients reported within our study period of 1 year, as the maximum possible number of patients would be accommodated in our study, considering high ASR% in many districts in India. Recurrent neoplasms were excluded.[2,10]

Demographic, clinicoradiological, histopathological, and CA125 data were collected and tabulated. Serum CA125 levels were correlated with histopathology and other clinical parameters. CA125 estimation was performed using a sandwich-type chemiluminescent immunoenzymatic assay (Type 3) employing biotinylated monoclonal and enzyme-labeled antibodies targeting distinct epitopes. A cutoff of 35 U/mL was considered normal.[9]

RMI 2 was calculated by multiplying the menopausal score (1 for pre-menopausal, 4 for post-menopausal), the USG score, and the absolute CA125 value. The USG score was based on five features: multiloculation, solid areas, bilaterality, ascites, and metastasis. A score of 1 was assigned if none or one feature was present, and 4 if more than one was identified. An RMI cutoff of 200 was used to distinguish benign from malignant tumors.[9]

Tumor frequency distributions were determined, and correlations between tumor type and all collected variables were analyzed.

Statistics

Results were tabulated using Microsoft Excel and analyzed using Graphpad Prism (Version 10.4.1, 2024, Boston). Continuous variables were planned to be analyzed using Student's unpaired t-test, and categorical variables using the Chi-square test/Fisher's exact test. A P=0.05 was considered statistically significant.

Inclusion criteria

All cases of ovarian neoplasms attending our institution and whose biopsy specimens were sent to the Department of Pathology from July 2022 to June 2023 were included in our study.

Exclusion criteria

Non-neoplastic ovarian lesions and recurrent ovarian neoplasms were not included in this study.

RESULTS

Epidemiology

Among 119 patients, 74 (62.18%) were benign, 6 (5.04%) were borderline, and 39 (32.77%) were malignant. The mean age was 39.8±14.9 years (range: 13–80). The youngest case (13 years) had dysgerminoma; the oldest (80 years) had high-grade serous adenocarcinoma.

Benign tumors were most common in the 21–45 age group (70%), whereas malignancies peaked in the 66–75 age group (51.28%). Borderline tumors predominated in the 46–55 age group (66.67%).

Nulliparous women made up 49% of cases; endometrioid and clear cell tumors occurred only in this group. Early menarche and late menopause were seen in 56% and 54% of malignant cases, respectively. OCP use was reported in 36% of malignant patients.

Post-hysterectomy and tubal ligation were associated with lower malignancy rates (26% and 36%, respectively).

Common symptoms included menstrual irregularities (56.25%), abdominal pain (30.75%), including torsion and abdominal swelling (6.2%). Only 3.3% had the classic triad of symptoms; 3.5% presented with non-specific complaints.

Histomorphology

Of 74 benign ovarian tumors, 56 (75.67%) were cystic, 10 were solid, and 08 were mixed. All six borderline tumors were of mixed type. Among 39 malignant tumors, 35 (90%) were heterogeneous or mixed, whereas two each were solid and cystic.

Tumors were classified as per the 2022 WHO classification for tumors of the Female Genital Tract. Into surface epithelial tumors (82 cases), germ cell tumors (26), sex cord-stromal tumors (9), and secondary tumors (2). Overall, benign tumors constituted 62.18% of cases, malignant tumors 32.77%, and borderline tumors 5.04%.[1]

Surface epithelial tumors comprised the largest category (68.90%), followed by germ cell tumors (21.85%), sex cord-stromal tumors (7.56%), and secondary tumors (1.68%). Among surface epithelial tumors, benign subtypes were most common (52.44%), followed by malignant (40.24%) and borderline tumors (7.32%).

Serous tumors were the predominant surface epithelial subtype, accounting for 48 out of 82 cases (58.5%). Within germ cell tumors, mature teratomas comprised 88.46% of cases, whereas dysgerminomas accounted for 11.54%. Among sex cord-stromal tumors, fibromas constituted 88.89% and adult granulosa cell tumors 11.11%. Only two cases (1.68%) of metastatic OC were observed (Table 1 and Figure 1a-e).

Among 119 cases, 50 tumors (42.02%) were right-sided, 57 (47.90%) left-sided, and 12 (10.09%) bilateral.

A total of 66 patients (55.46%) were pre-menopausal, comprising 56 benign, four borderline, and six malignant cases. Fifty-three patients (44.54%) were post-menopausal, with 18 benign, two borderline, and 33 malignant tumors. Benign tumors were significantly more frequent in pre-menopausal women, whereas malignancies were more common in post-menopausal women (Chi-square=37.90, P<0.0001) (Table 2).

Serum CA125 was measured in all cases using a 35 U/mL cutoff. Among benign tumors, 67.57% (50/74) had CA125 ≤35 U/mL, whereas 32.43% were elevated. Nearly all borderline/malignant tumors (97.78%; 44/45) had levels >35 U/mL, except one borderline tumor (34.8 U/mL).

Mean CA125 levels were 51.98±164.58 U/mL (benign), 61.6±14.66 U/mL (borderline), and 718.17±346.48 U/mL (malignant), with a significant difference between benign and malignant groups (Chi-square=48.79, P<0.00001). Elevated serum CA125 level was found in both epithelial and non-epithelial tumors, including metastasis.

CA125 showed sensitivity (Sn) of 97.78%, specificity (Sp) of 67.57%, positive predictive value (PPV) of 64.71%, negative predictive value (NPV) of 98.04%, and accuracy of 78.99% (Table 3).

RMI and USG score analysis

The RMI-2, calculated as the product of USG score (U), menopausal status (M – pre-menopausal with score 1 and post-menopausal with score 4), and CA125 level, was used to differentiate benign from malignant tumors, with a cutoff of 200.

U (multiloculations, solid areas, bilaterality, ascites, and metastasis) was scored 1 for ≤1 suspicious feature and 4 for ≥2 features. Among benign tumors, 46 had U=1 and 28 had U=4. In malignant/borderline cases (n=45), 28 had U=4 and 17 had U=1 (Chi-square=6.68, P=0.0098) (Figure 2a and b).

Both U and RMI (Chi-square=54.0341, df=1, P<0.00001) showed statistically significant results in differentiating

Table 1: Distribution of ovarian tumors (n=119)

Type of tumor (%)	Sub-types (n)-%	Benign (n) (62.18%)	Borderline (n) (5.04%)	Malignant (n) (32.77%)
Surface epithelial tumors (68.90) Benign – 52.44	Serous tumors (48)-58.5	Serous cystadenoma (31) Serous adenofibroma (2)	Serous borderline tumor (2)	Low-grade serous carcinoma (5) High-grade serous carcinoma (8)
Borderline – 7.32 Malignant – 40.24	Mucinous tumors (21)-25.6	Mucinous cystadenoma (6)	Mucinous borderline tumor (4)	Mucinous carcinoma (11)
	Seromucinous tumor (2)-2.44	Seromucinous cystadenoma (2)	-	-
	Brenner tumor (2)-2.44	Benign Brenner tumor (2)	-	-
	Endometrioid tumors (8)-9.76	-	-	Endometrioid carcinoma (8)
	Clear cell tumors (1)-1.22	-	-	Clear cell carcinoma (1)
Germ cell tumors (21.85)	Mature teratoma (23)-88.46	(23)	-	-
	Dysgerminoma (3)-11.54	-	-	(3)
Sex cord-stromal tumor (7.56)	Fibroma (8)-88.89	(8)	-	-
	Adult granulosa cell tumor (1)-11.11	-	-	(1)
Secondary tumor (1.68)	Metastatic OC	-	-	(2)

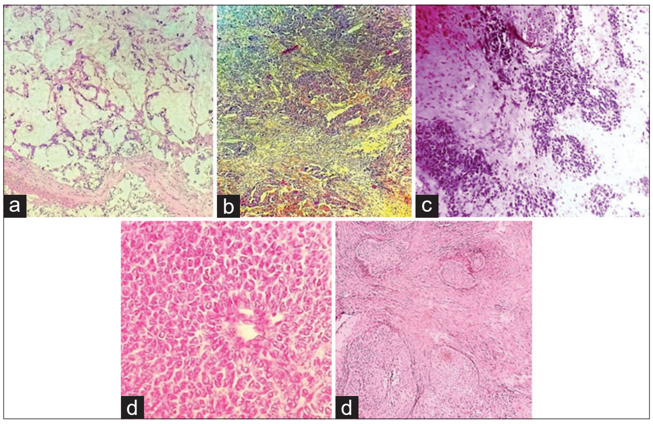

Figure 1: Histomorphology; (a) mucinous adenocarcinoma (×40), (b) endometrioid carcinoma (×40), (c) immature neuroepithelium (×40), (d) call-exner body (×100), (e) Brenner's tumor (×40)

Table 2: Ovarian tumor and menopausal status showing Chi-square=37.90, df=2, P<0.0001

Tumor type	Pre-menopausal	Post-menopausal	Total
Benign	56	18	74
Borderline	4	2	6
Malignant	6	33	39
Total	66	53	119

Table 3: CA125 level in ovarian tumors

Serum CA125 level	Malignant (including BT)-45	Benign-74
>35 units/mL	44 TP	24 FP
<35 units/mL	1 FN	50 TN

Chi-square 48.7912, df=1, P<0.00001. Sn: 97.78%, Sp: 67.57%, PPV: 64.71%, NPV: 98.04%, accuracy: 78.99%. NPV: Negative predictive value, PPV: Positive predictive value, Sn: Sensitivity, Sp: Specificity

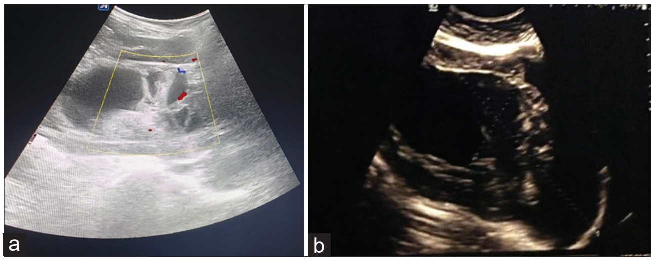

Figure 2: (a and b) score with ultrasound of ovary; (a) multiloculated solid-cystic ovarian mass with U score 4 – patient had ascites too, (b) large cystic space-occupying lesion with U score 1

Table 4a: U score in ovarian tumors

U score	Malignant (including 6 BT)	Benign
4	28	28
1	17	46

Chi-square6.6786, df=1, P<0.009758. Sn: 62.22%, Sp: 62.16.%, PPV: 50%, NPV: 73.02%, accuracy: 62.15%. NPV: Negative predictive value, PPV: Positive predictive value, Sn: Sensitivity, Sp: Specificity

Table 4b: RMI in ovarian tumors

RMI	Malignant (including 6 BT)	Benign
>200	33 (3 BT)	06
<200	12 (3BT)	68

Chi-square=54.0341, df=1, P<0.00001. Sn: 73.33%, Sp: 91.89%, PPV: 84.62%, NPV: 85%, accuracy: 84.87%. NPV: Negative predictive value, PPV: Positive predictive value, RMI: Risk of malignancy index, Sn: Sensitivity, Sp: Specificity

Table 4c: RMI in serous versus mucinous ovarian malignancy

RMI	Serous malignant tumor (malignant-13+BT-2)	Mucinous malignant tumor 15 (Malignant-11+BT-4)
<200	0	11 (8+3)
>200	15 (13+2)	4 (3+1)

Fisher's exact test revealed P<0.0001. There is a significant association between tumor type and RMI level, with serous tumors significantly more likely to have RMI>200. P<0.0001. RMI: Risk of Malignancy Index

benign, borderline, and malignant tumors, but RMI showed better Sn, Sp, PPV, NPV, and accuracy than the U score and better Sp, PPV, as well as accuracy than serum CA125 value. Interestingly, it was found in our study that mucinous BT and malignant tumors had an RMI score <200 in 11 cases out of 15 cases, and 4 cases of BT and malignant tumors had an RMI >200. RMI is not that efficient in differentiating mucinous neoplasm in relation to serous ones. Here, we compared serous and mucinous BT and malignant tumors together, and statistical significance was there, thus affirming the fact that RMI >200 value did not surface in many mucinous malignancies (Table 4a-c).

DISCUSSION

The age range in our study was 13–80 years, with the youngest case (dysgerminoma) at 13 and the oldest (high-grade serous adenocarcinoma) at 80, similar to findings by Pallikkara et al., Most benign tumors occurred in the 21–45 age group, consistent with the study mentioned but slightly differing from Yar Elmastas et al.[11,12]

In our study, most malignant tumors occurred in the 66–75 age group, which is similar to Yar Elmastas et al. Early menarche (56%) and late menopause (21–54%) were frequent in malignant cases. OCP use was reported in 36%. Only 26% of malignancies were seen post-hysterectomy, and 36% in patients with tubal ligation, supporting their protective role as documented in WHO and Mills and Sternberg's diagnostic surgical pathology, among many.[1,7,12]

Menstrual irregularities (56.25%) were the most common symptom, followed by abdominal pain (30.75%), swelling (6.2%), and other complaints, different from Mehra et al., as abdominal pain was the most common presenting symptom in their study.[13] Nulliparity was observed in 49% of cases, including all endometrioid and clear cell tumors and it supports the facts documented by WHO.[1] Benign tumors were mainly cystic, whereas malignant and borderline tumors were predominantly mixed or solid, partially discordant with study done by Mahajan et al., which documented that all the malignant neoplasms had prominent solid component (100%) but most common radiologic finding was solid-cystic (67.58%).[14]

In our study, benign tumors were most common (62.18%), followed by malignant (32.77%) and borderline tumors (5.04%), similar to findings by Mahajan et al., in which they found that among the neoplastic tumors, 63.3% were benign, followed by 32.6% malignant, and rest 4.1% were borderline tumors.[14] Yar Elmastas et al. reported post-operative histopathological results as benign neoplasm in 82% of patients, borderline in 3%, and malignant in 15% of patients, a little bit higher in the benign percentage, lowering the malignant percentage.[12] However, our malignant and borderline tumor rates differed from Pallikkara et al., who reported 78.36% benign,[11] 11% malignant, and 6.53% borderline tumors (P=0.0005). Most tumors were unilateral (89.91%), consistent with studies by Pallikkara et al.[11]

We found that serous neoplasm was the most common in both benign and malignant groups, but Yar Elmastas et al. reported that mucinous adenocarcinoma was more than its serous counterpart.[12]

Benign tumors were significantly more common in pre-menopausal women and malignancies in post-menopausal women (Chi-square=37.9047, P<0.0001) in our study. A study by Huwidi et al. stated that menopausal status was not associated with disease status (P=0.237).[9] However, Hada et al. found that post-menopausal malignancy constituted 70.4%, whereas in pre-menopausal patients, only 29.6% had malignant ovarian neoplasm. Mustafin et al. also documented that ovarian neoplasms' worldwide incidence had been shown to peak in the early post-menopausal period around the ages of 55–64, with a median age at diagnosis of 63.[15,16]

In our study, mean serum CA125 levels were 51.98±164.58 U/mL in benign tumors, 61.6±14.66 U/mL in borderline tumors, and 718.17±346.48 U/mL in malignant tumors. Serum CA125 levels are significantly increased in malignant tumors (P<0.00001). Diagnostic performance showed Sn 97.78% (95% confidence interval [CI]: 88.23–99.94%), Sp 67.57% (CI: 55.68–78%), PPV 64.71% (CI: 56.82–71.87%), NPV 98.04% (CI: 87.73–99.71%), and accuracy 78.99% (CI: 70.57–85.92%).

Huwidi et al. reported lower Sn (87.5%), Sp (58.1%), PPV (28%), and NPV (96.2%). Garg and Kaur showed Sn 78%, Sp 60%, PPV 29%, and NPV 93%, with only Sp and NPV concordant with our results, possibly due to more malignant cases in our cohort. Huwidi et al. also noted lower mean CA125 in benign (41 U/mL) and malignant tumors (635 U/mL), though with similar statistical significance (P<0.00001).[9,17]

CA125 is often elevated in serous epithelial cancers and correlates with prognosis, but it is also raised in sex cord-stromal tumors. Chowdhury et al. documented that the CA125 serum level was increased in adult granulosa cell tumors and fibromas, along with some microcystic and Sertoli–Leydig Cell tumors, while using it as a baseline and advanced stage treatment evaluation.[18] Nasioudis et al. stated that patients with early-stage sex cord-stromal tumors with pre-operative elevated serum CA125 levels are associated with worse survival.[19] In our study, 4 benign fibromas and 1 granulosa cell tumor showed raised CA125 levels.

In our study, we measured only CA125 in germ cell tumors even. Other markers, such as human chorionic gonadotropin, Alpha-fetoprotein, and lactate dehydrogenase, were not assessed in our study.[20] The relationship between CA125 and germ cell tumors has not been explored enough, and a few studies exist. Yuan-qui Wang showed that mature cystic teratomas with torsion had elevated serum CA125 along with CA 19-9 and a neutrophil-lymphocyte ratio. Moreover, when compared to the control, statistically significant results were found (P<0.001). Another study showed that elevated pre-operative serum CA125 over 249.5 U/mL in malignant germ cell tumors was significantly associated with poorer survival. We also found elevated serum CA125 in mature cystic teratoma (17.39%) and dysgerminoma (100% with high CA125) in our study.[21,22]

Interestingly, 10 benign surface epithelial tumors had raised CA125 in our series. Coexisting endometriosis was explained in some cases, e.g., serous, mucinous, and endometrioid cystadenomas. Different textbooks and studies stated and reported CA125 elevation in benign conditions such as endometriosis, fibroids, PID, and various non-ovarian malignancies. Three large benign epithelial tumors required close follow-up due to possible undetected STIC, warranting radiological or positron emission tomography-computed tomography surveillance.[1,7,15,20,23]

In our study, the U score had Sn 62.22%, Sp 62.16%, PPV 50%, NPV 73.02%, and accuracy 62.15% (Chi-square=6.6786, P<0.009758), lower than CA125, especially in Sn and NPV, similar to Garg's and Kaur findings at U score 3; However, at U score 1 Sn is more than CA125 level prediction. Huwidi et al. reported better U-score performance (Sn 100%, Sp 69.8% PPV 38.1 %) than CA125, except for Sp, and these findings differed from our results.[9,17]

Why RMI

Type I and type II OC differ morphologically, genetically, and prognostically, including variations in CA125 expression, which is higher in type II tumors with serous histology than in mucinous and other types.[8]

CA125 can be elevated in benign conditions, and levels vary with factors such as age, race, reproductive history, endometriosis, and surgeries such as hysterectomy etc. Therefore, HE4, imaging alternatives, and CA125 with high cutoff values are used for low-volume type II tumors.[8,19] USG in pre-menopausal women has a high false-positive rate, limiting its screening utility, and the biggest drawback to its usage in ovarian cancer screening is that it is dependent on the expertise of the examiner.[17]

RMI translates adnexal mass morphology into objective scores, reducing examiner bias and outperforming single parameters such as CA125, menopausal status, or USG alone. Gynecologic oncologists performing cytoreductions require accurate pre-operative staging, and RMI is better at avoiding unnecessary surgery.[17,24]

Modified versions RMI 2, 3, 4, and RMI 5 have emerged since its inception in 1990. Some studies favor RMI 3 and 4; others report similar performance across RMI 1, 2, 3, and 4, documenting an insignificant difference between RMI 2 and 4 in malignant cases. Accordingly, RMI 2 was selected in our low-resource setting for its high sensitivity and NPV, reducing false negatives as Hada et al. showed.[15,24-26]

In our study, RMI showed Chi-square=54.0341, P<0.00001, with Sn 73.33%, Sp 91.89%, PPV 84.62%, NPV 85%, and accuracy 84.87%. Garg and Kaur found that at an RMI of 200 cutoff , Sn was 56%, Sp was 93%, PPV was 63% and NPV was 91%. Sp and NPV were at par with our study, but Sn and PPV were lower. Priyanka et al. reported slightly higher Sn (80.6%) and NPV (96%).[17,24]

We found that RMI had higher Sp and PPV than CA125 alone, similar to the study by Huwidi et al., but lower Sn and NPV, not concordant with the same study, as they showed the same Sn and slightly higher NPV. Garg and Kaur reported RMI results (Sn 70.59%, Sp 87.8%, PPV 70.5%, and NPV 87.8%) comparable to ours, with significant P-values; their lower Sn aligns with our findings. Across studies, RMI outperformed U and M scores individually, except for slightly higher Sn for U in the Huwidi et al. study.[9,17]

RMI 4 and 5 were developed to improve sensitivity, incorporating tumor size (RMI 4) and refined scoring for menopausal status and CA125 levels (RMI 5), along with other tumor markers, such as HE4, and other modalities like the Risk of Malignancy Algorithm, etc. CA125 cutoff and RMI cutoff levels were set at different levels to increase prediction probability.[12,15,24,25]

RMI was less effective in distinguishing mucinous tumors compared to serous types in our study, and Garg and Kaur also stated that RMI would not be considered a reliable modality in predicting mucinous malignancy. Serum CA 125 level is increased in metastatic tumors in our study, similar to Charkhchi et al.[8,17]

Limitations of the study

It was a single institutional study within a limited time frame. Being a rural center with logistical constraints RMI3,4,5 could not be studied .and newer tumor markers were not included.

CONCLUSION

Ovarian tumors are one of the most common tumors, having diverse presentations and morphological patterns. Ovarian malignancy is still one of the leading causes of mortality. Despite many diagnostic modalities, no definitive, cost-effective screening test is prevalent, especially in a rural tertiary care center like ours. Hence, if we consider RMI by combining clinical, radiological, and biochemical parameters followed by scoring, then it will guide the gynecologists and oncologists to decide the proper mode of intervention, thus reducing the revision surgery load and mortality.

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JBS- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article; **MB-** Concept, design, clinical protocol, data collection and interpretation; **RDP-** Design of study, data collection, data interpretation; **SM-** Clinical data collection and management; **DS-** Reviewing manuscript, editing, statistical designing and analysis; **BKG-** Literature survey.

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