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Comparing the Accuracy, Sensitivity, Specificity, and Predictive Values of Two Biomarkers in Detecting Malignant Ovarian Tumors

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Abstract

Introduction: Ovarian cancer presents a significant challenge in oncology due to its high mortality rates primarily stemming from late-stage diagnoses. Early detection through reliable biomarkers such as CA-125 and IL-6 is crucial for improving patient outcomes. ***Aim of the study:*** This study aimed to compare the accuracy, sensitivity, specificity, and predictive values of CA-125 and IL-6 in detecting malignant ovarian tumors. ***Methods:*** A cross-sectional analytical study was conducted at the Department of Gynecological Oncology, BSMMU, and NICRH, Dhaka, Bangladesh. A total of 94 women with suspected ovarian tumors underwent preoperative assessment of CA-125 and IL-6 levels. Receiver-operator characteristic (ROC) curves were utilized to determine optimal cut-off values. ***Result:*** In this study of 94 women with ovarian tumors, we evaluated the diagnostic performance of CA-125 and IL-6 biomarkers. CA-125 showed a sensitivity of 83.0% and specificity of 51.2% at a cut-off of ≥89.0 u/ml, while IL-6 exhibited 84.9% sensitivity and 80.5% specificity at ≥9.5 pg/ml. Combining CA-125 and IL-6 improved specificity to 95.1%, maintaining a sensitivity of 77.4%. These findings underscore the potential of biomarker combinations in enhancing diagnostic accuracy for detecting malignant ovarian tumors. ***Conclusion:*** IL-6 exhibited higher sensitivity and specificity compared to CA-125 in detecting malignant ovarian tumors. The combined use of both biomarkers improved specificity while maintaining reasonable sensitivity, suggesting their potential utility in clinical practice for early detection and management of ovarian malignancies.

Keywords: Malignant ovarian tumor, Serum IL-6, CA-125, Biomarkers, Ovarian cancer.

INTRODUCTION

Ovarian cancer remains a significant challenge in oncology due to its high mortality rates and often late-stage diagnosis [1]. Among ovarian cancers, distinguishing between malignant and benign tumors is critical for timely and appropriate clinical management [2]. Biomarkers play a pivotal role in this regard, offering potential tools for early detection, monitoring treatment response, and predicting prognosis [3]. Two of the most studied biomarkers in ovarian cancer diagnostics are CA-125 and IL-6 [4]. This introduction explores their roles, comparing their accuracy, sensitivity, specificity, and predictive values in detecting malignant ovarian tumors [5].

Ovarian cancer is the fifth leading cause of cancer-related deaths in women worldwide, primarily due to its insidious onset and late diagnosis [1,6]. It

encompasses a diverse group of malignancies originating from different cell types within the ovary, each with distinct biological behaviors and clinical outcomes [7]. The majority of ovarian tumors are epithelial in origin, with serous carcinomas being the most common subtype [3]. Non-epithelial tumors, such as germ cell and stromal tumors, are less frequent but also contribute to the overall disease burden. Despite advances in treatment modalities, the prognosis for ovarian cancer remains poor, particularly when diagnosed at advanced stages. This emphasizes the critical need for effective screening and diagnostic tools that can detect ovarian malignancies earlier in their natural history, when treatment options are more likely to be effective [8].

Biomarkers are measurable indicators of biological processes, disease states, or responses to therapy. In the context of ovarian cancer, biomarkers serve several crucial purposes, including screening high-risk populations, aiding in diagnosis, monitoring disease progression, and predicting treatment outcomes [5]. CA-125, a glycoprotein antigen, has been the cornerstone biomarker in ovarian cancer for decades. Elevated serum levels of CA-125 are associated with ovarian malignancies, particularly epithelial ovarian carcinomas, and are routinely used in clinical practice for monitoring disease response and recurrence [6]. IL-6, a pro-inflammatory cytokine, has garnered increasing interest for its potential role in ovarian cancer. It is involved in various biological processes, including inflammation, immune regulation, and tumorigenesis [7]. Studies have shown that IL-6 levels are elevated in patients with ovarian cancer compared to those with benign ovarian conditions, suggesting its utility as a diagnostic biomarker [8].

The diagnostic performance of biomarkers is typically evaluated based on parameters such as sensitivity, specificity, accuracy, positive predictive value (PPV), and negative predictive value (NPV). Sensitivity refers to the proportion of true positive results among all individuals with the disease, while specificity indicates the proportion of true negative results among all individuals without the disease [9]. CA-125 has demonstrated reasonable sensitivity for detecting ovarian cancer, particularly in epithelial tumors, but its specificity is limited due to elevations in benign conditions such as endometriosis and pelvic inflammatory disease [10]. This challenges its utility as a standalone diagnostic tool, necessitating complementary biomarkers or imaging modalities for improved accuracy. In contrast, IL-6 shows promise as a complementary biomarker to CA-125. Its elevation in ovarian cancer reflects the underlying inflammatory processes associated with tumor growth and metastasis [11]. Studies have highlighted IL-6's potential to discriminate between malignant and benign ovarian tumors with higher specificity than CA-125 alone [12].

Integrating biomarkers into clinical practice involves addressing several challenges. One major hurdle is the variability in biomarker levels across different ovarian cancer subtypes and stages, complicating their interpretation and clinical utility [13]. Furthermore, factors such as patient age, menopausal status, and concurrent medical conditions can influence biomarker levels, necessitating personalized diagnostic algorithms [14]. Another critical consideration is the cost-effectiveness of biomarker testing, especially in resource-limited settings. While CA-125 assays are widely available, IL-6 testing may require specialized laboratory techniques and validation studies to establish standardized cutoff values and performance characteristics [15].

The future of biomarker research in ovarian cancer lies in identifying novel biomarkers or panels that enhance diagnostic accuracy, predict treatment responses, and guide personalized therapeutic strategies. Integrating multiomics approaches, including genomics, transcriptomics, and proteomics, holds promise for uncovering molecular signatures that can refine ovarian cancer diagnosis and management [16]. Moreover, advancements in imaging technologies, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), coupled with biomarker assays, offer a multimodal approach to enhance diagnostic precision and therapeutic monitoring [17].

Objective

The objective of this study is to compare the diagnostic accuracy, sensitivity, specificity, and predictive values of CA-125 and IL-6 as biomarkers for detecting malignant ovarian tumors.

METHODOLOGY & MATERIALS

This cross-sectional analytical study was conducted at the Department of Gynecological Oncology and Department of Microbiology & Immunology, Bangabandhu Sheikh Mujib Medical University (BSMMU), and Department of Gynecological Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh, over a one-year period from February 2022 to January 2023. The study enrolled 94 consecutive women with diagnosed cases of suspected ovarian tumors who underwent surgery. Purposive sampling was employed to include eligible patients meeting the inclusion criteria of clinical and ultrasound-diagnosed ovarian tumors, while excluding those already undergoing treatment, with metastatic or recurrent malignant ovarian tumors, pregnant women, or significant concomitant heart, liver, or vascular diseases. Preoperatively, 3 ml of venous blood was collected from each patient 24 to 48 hours before surgery. Serum samples were immediately centrifuged and stored at -20°C until analysis. Serum IL-6 levels were quantified using the MAGLUMI series Fully-auto chemiluminescence immunoassay analyzer (Maglumi 2000 plus) at the Department of Microbiology and

Immunology, BSMMU. Data analysis was performed using SPSS 23.0 (SPSS, Chicago, IL). Descriptive statistics such as mean ± standard deviation or median (interquartile range) were used for continuous variables, depending on their distribution, while categorical variables were summarized as frequencies and percentages. Nonparametric methods, including the Mann-Whitney U test, were employed to compare IL-6 and CA-125 levels between benign and malignant tumor groups. Receiver operating characteristic (ROC) curves was constructed to determine optimal cut-off values for IL-6 and CA-125, with areas under the curve calculated to assess diagnostic accuracy. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were computed to evaluate the diagnostic performance of IL-6 and CA-125 in detecting malignant ovarian tumors. Ethical approval was obtained from the Institutional Review Boards of BSMMU and NICRH, and informed consent was obtained from all participants, ensuring confidentiality and adherence to ethical guidelines throughout the study.

RESULT

Table I: Demographic characteristics of study population (n=94)

Variables	Malignant ovarian Tumor (n=53)		Benign ovarian Tumor (n=41)		P value
	n	%	n	%	
Age (years)					
≤20	11	20.8	9	22.0	
21-30	5	9.4	10	24.4	
31-40	7	13.2	10	24.4	
41-50	15	28.3	8	19.5	
51-60	8	15.1	2	4.9	[a]0.067[ns]
>60	7	13.2	2	4.9	
Mean±SD	40.7	±17.4	34.5	±14.4	
Range (min-max)	14.0	-70.0	15.0	-70.0	
Educational status					
Illiterate	10	18.9	5	12.2	
Primary	22	41.5	14	34.1	
Secondary	15	28.3	15	36.6	
Higher secondary	4	7.5	6	14.6	[b]0.644[ns]
Graduate	1	1.9	1	2.4	
Post graduate	1	1.9	0	0.0	
Marital status					
Married	40	75.5	26	63.4	
Unmarried	10	18.9	13	31.7	[b]0.532[ns]
Divorced	2	3.8	1	2.4	
Widow	1	1.9	1	2.4	

ns= not significant
[a]p value reached from unpaired t-test
[b]p value reached from chi square test

Table I shows the demographic characteristics of study population 94 was observed that more than half of the patients 29 (70.8%) belong to ≤ 40 years in benign ovarian tumors and 30(56.6%) patient of malignant ovarian tumors belong to age ≥40 years. The mean age was 34.5±14.4 years in benign ovarian tumors group and 40.7±17.4 years in malignant ovarian tumors. The difference in mean age approaches significance (P=0.067), it is not statistically significant. A higher percentage of patients with malignant tumors were illiterate (18.9%) compared to those with benign tumors (12.2%). Secondary education was also prevalent in both groups, with slightly more benign tumor patients (36.6%) compared to malignant tumor patients (28.3%). The differences in educational status between the two groups were not statistically significant (P=0.644), indicating that educational status does not have a significant impact on the differentiation of ovarian tumors in this sample. A larger proportion of malignant tumor patients were married (75.5%) compared to benign tumor patients (63.4%). The P value of 0.532 indicates that marital status differences between the two groups are not statistically significant.

Table II: Receiver-operator characteristic (ROC) curve of IL-6 and CA-125 for prediction of malignant ovarian tumor

Biomarker	Cut of value	Sensitivity	Specificity	Area under the ROC curve	95% Confidence interval (CI)	
					Lower bound	Upper bound
CA-125 (u/ml)	≥89.0	83.0	51.2	0.737	0.639	0.836
IL-6 (pg/ml)	≥9.5	84.9	80.5	0.815	0.718	0.911
Combined (CA-125+IL-6)	CA-125 (≥89.0 u/ml) + IL-6 (≥9.5 pg/ml)	77.4	95.1	0.749	0.652	0.846

Table II illustrates the performance of CA-125, IL-6, and their combination in predicting malignant ovarian tumors using ROC curve analysis. IL-6 has a higher area under the ROC curve (0.815) compared to CA-125 (0.737), indicating better overall performance. The combination of both biomarkers provides a sensitivity of 77.4% and a specificity of 95.1%, highlighting a strong ability to correctly identify non-malignant cases while maintaining substantial sensitivity.

Table III: Evaluation of sensitivity, Specificity, accuracy, positive and negative predictive values of the CA-125, IL-6 and combined (CA-125+ IL-6) for prediction of malignant ovarian tumor

Validity test	IL-6	CA-125	Combined (CA-125+ IL-6)
Sensitivity	84.9	83.0	77.4
Specificity	80.5	51.2	95.1
Accuracy	83.0	69.1	85.1
Positive predictive value	84.9	68.8	95.3
Negative predictive value	80.5	70.0	76.5

Table III evaluates the diagnostic performance of IL-6, CA-125, and their combination. IL-6 shows a sensitivity of 84.9% and specificity of 80.5%, making it a reliable marker for detecting malignant ovarian tumors. CA-125 has lower specificity (51.2%) and overall accuracy (69.1%). However, the combined use of CA-125 and IL-6 enhances specificity to 95.1% and accuracy to 85.1%, with an impressive positive predictive value of 95.3%. This indicates that combining these biomarkers provides a robust method for accurately identifying malignant cases while minimizing false positives.

DISCUSSION

Ovarian cancer continues to be a significant concern in oncology due to its high mortality rate and the tendency for late-stage diagnosis. Early and accurate differentiation between malignant and benign ovarian tumors is crucial for improving patient outcomes. This study evaluates the diagnostic performance of two biomarkers, CA-125 and IL-6, and their combination, offering a detailed comparison with findings from other studies.

In our study, the mean age was 34.5±14.4 years in the benign ovarian tumors group and 40.7±17.4 years in the malignant ovarian tumor group. Similar findings were observed in other studies. For instance, Jammal *et al.*, reported a mean age of 49.9±14.1 years for malignant neoplasms, while Kampan *et al.*, found a mean age of 60.1±1.59 years for malignant ovarian tumors and 54.8±3.07 years for benign ovarian tumors [18,19]. The relationship between age and ovarian cancer outcomes remains uncertain, though many researchers suggest that younger age at diagnosis is associated with better outcomes.

In our study, CA-125 alone demonstrated a sensitivity of 83.0% and a specificity of 51.2%, with an accuracy of 69.1%. IL-6 showed a higher sensitivity of 84.9% and a specificity of 80.5%, with an accuracy of 83.0%. These findings indicate that IL-6 is more accurate and reliable than CA-125 when used independently. The combined use of CA-125 and IL-6 resulted in an accuracy of 85.1%, significantly improving the specificity to 95.1% and providing a balanced diagnostic tool with enhanced predictive value. Similar studies have reported varying degrees of sensitivity and specificity for CA-125 and IL-6. For instance, Meys *et al.*, reported a CA-125 sensitivity of 79% and specificity of 78% [20]. Another study by Kaijser *et al.*, found a sensitivity of 80% and specificity of 75% for CA-125 in detecting malignant ovarian tumors [21]. These differences can be attributed to variations in study design, population characteristics, and diagnostic criteria. IL-6, being a pro-inflammatory cytokine, has been investigated less extensively than CA-125 but shows promising results. Tempfer *et al.*, reported an IL-6 sensitivity of 67% and specificity of 80% [22]. Our findings of higher sensitivity and specificity for IL-6 may reflect advancements in assay techniques and the inclusion criteria of our study population.

The combination of CA-125 and IL-6 in our study significantly improved diagnostic performance, with a sensitivity of 77.4%, specificity of 95.1%, and accuracy of 85.1%. This combined approach maximizes the strengths of each biomarker while compensating for

their individual limitations. The high specificity of 95.1% is particularly noteworthy, suggesting that the combined biomarkers are highly effective in correctly identifying non-malignant cases and reducing false-positive rates. Comparative studies have shown similar benefits of using combined biomarkers. Moore *et al.*, demonstrated that combining CA-125 with HE4 improved diagnostic accuracy, reporting a sensitivity of 76.4% and specificity of 95% [23]. Although HE4 is different from IL-6, the principle of combining biomarkers to enhance diagnostic precision is supported by these findings. The improved specificity observed in our study aligns with the goal of minimizing unnecessary interventions and focusing treatment on truly malignant cases.

The positive predictive value (PPV) and negative predictive value (NPV) are critical for understanding the clinical utility of biomarkers. In our study, IL-6 had a PPV of 84.9% and an NPV of 80.5%, whereas CA-125 had a PPV of 68.8% and an NPV of 70.0%. The combination of CA-125 and IL-6 significantly improved these values, with a PPV of 95.3% and an NPV of 76.5%. High PPV indicates that a positive test result is highly likely to reflect true malignancy, which is essential for making informed clinical decisions. High NPV means that a negative test result reliably indicates the absence of malignancy, allowing clinicians to confidently rule out cancer in patients. The combination of CA-125 and IL-6 provides a robust diagnostic tool with high PPV, which is crucial in reducing the psychological and physical burden on patients by avoiding overdiagnosis and overtreatment. A study by van Gorp *et al.*, emphasized the importance of combining multiple biomarkers to enhance diagnostic accuracy. They reported a PPV of 94% and an NPV of 78% when combining CA-125 with other markers like HE4 and CEA [24]. Our study's findings are consistent with these results, reinforcing the value of using a multimarker approach in ovarian cancer diagnostics.

While CA-125 remains a widely used biomarker for ovarian cancer, other markers have been explored to improve diagnostic accuracy. HE4 (Human Epididymis Protein 4) has shown promise in various studies. Karlsen *et al.*, reported that HE4 had a sensitivity of 73% and specificity of 92% [25]. Combining HE4 with CA-125 improved overall diagnostic performance, similar to our findings with IL-6. The choice of biomarkers can depend on factors such as assay availability, cost, and specific clinical contexts. IL-6, being an inflammatory marker, may also provide insights into the tumor microenvironment and potential therapeutic targets.

Limitations of the study

Our study has several limitations, including a relatively small sample size, which may limit the generalizability of the findings. Larger multicenter studies are needed to validate these results and explore the potential of IL-6 and other biomarkers in diverse populations. Additionally, while our study focused on preoperative biomarker levels, serial measurements over time could provide valuable information on tumor dynamics and treatment response. Longitudinal studies assessing the prognostic value of CA-125 and IL-6 in monitoring disease progression and recurrence are warranted.

CONCLUSION

In conclusion, our study demonstrates that IL-6 outperforms CA-125 in terms of sensitivity, specificity, and overall accuracy for detecting malignant ovarian tumors. The combination of CA-125 and IL-6 significantly enhances diagnostic performance, providing a powerful tool for distinguishing between malignant and benign ovarian tumors. These findings underscore the importance of using multiple biomarkers to improve diagnostic precision and clinical decision-making in ovarian cancer management. Future research should continue to explore and validate these findings in larger and more diverse cohorts, aiming to integrate multimarker approaches into standard clinical practice for ovarian cancer diagnostics.

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Ethical approval

The study was approved by the Institutional Ethics Committee.

REFERENCES

1. Ferlay, J., Colombet, M., Soerjomataram, I., Mathers, C., Parkin, D. M., Piñeros, M., ... & Bray, F. (2019). Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *International journal of cancer*, *144*(8), 1941-1953.
2. Kurman, R. J., & Shih, I. M. (2010). The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. *The American journal of surgical pathology*, *34*(3), 433-443.
3. Prat, J., & FIGO Committee on Gynecologic Oncology. (2014). Staging classification for cancer of the ovary, fallopian tube, and peritoneum. *International Journal of Gynecology & Obstetrics*, *124*(1), 1-5.
4. Cannistra SA. Cancer of the ovary. N Engl J Med. 2004;351(24):2519-2529.
5. DUFFY, M. J., BONFRER, J. M., Kulpa, J., Rustin, G. J. S., Soletormos, G., Torre, G. C., ... & Zwirner,

M. (2005). CA125 in ovarian cancer: European Group on Tumor Markers guidelines for clinical use. *International Journal of Gynecologic Cancer*, *15*(5).

6. Bast Jr, R. C., Klug, T. L., John, E. S., Jenison, E., Niloff, J. M., Lazarus, H., ... & Knapp, R. C. (1983). A radioimmunoassay using a monoclonal antibody to monitor the course of epithelial ovarian cancer. *New England journal of medicine*, *309*(15), 883-887.
7. Rose-John, S. (2012). IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. *International journal of biological sciences*, *8*(9), 1237.
8. Duan, Z., Foster, R., Bell, D. A., Mahoney, J., Wolak, K., Vaidya, A., ... & Seiden, M. V. (2006). Signal transducers and activators of transcription 3 pathway activation in drug-resistant ovarian cancer. *Clinical Cancer Research*, *12*(17), 5055-5063.
9. Schisterman, E. F., Perkins, N. J., Liu, A., & Bondell, H. (2005). Optimal cut-point and its corresponding Youden Index to discriminate individuals using pooled blood samples. *Epidemiology*, *16*(1), 73-81.
10. Molina, R., Escudero, J. M., Augé, J. M., Filella, X., Foj, L., Torné, A., ... & Pahisa, J. (2011). HE4 a novel tumour marker for ovarian cancer: comparison with CA 125 and ROMA algorithm in patients with gynaecological diseases. *Tumor Biology*, *32*, 1087-1095.
11. Bromberg, J., & Wang, T. C. (2009). Inflammation and cancer: IL-6 and STAT3 complete the link. *Cancer cell*, *15*(2), 79-80.
12. Scambia, G., Testa, U., Benedetti Panici, P., Foti, E., Martucci, R., Gadducci, A., ... & Mancuso, S. (1995). Prognostic significance of interleukin 6 serum levels in patients with ovarian cancer. *British journal of cancer*, *71*(2), 354-356.
13. Cargnin, S., Canonico, P. L., Genazzani, A. A., & Terrazzino, S. (2017). Quantitative analysis of circulating cell-free DNA for correlation with lung cancer survival: a systematic review and meta-analysis. *Journal of Thoracic Oncology*, *12*(1), 43-53.
14. Barak, V., Meirovitz, A., Leibovici, V., Rachmut, J., Peretz, T., Eliashar, R., & Gross, M. (2015). The diagnostic and prognostic value of tumor markers (CEA, SCC, CYFRA 21-1, TPS) in head and neck cancer patients. *Anticancer research*, *35*(10), 5519-5524.
15. Deligeoroglou, E., Eleftheriades, M. & Athanasopoulos, N., (2005). Inhibin-A, activin-A, human chorionic gonadotropin, and alpha-fetoprotein as serum markers in the diagnosis of ectopic pregnancy. *Fertil Steril*. 83(2):367-371.
16. Slamon, D. J., Godolphin, W., Jones, L. A., Holt, J. A., Wong, S. G., Keith, D. E., ... & Press, M. F. (1989). Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. *Science*, *244*(4905), 707-712.
17. Tomao, F., Boccia, S. M., Sassu, C. M., Chirra, M., Palaia, I., Petrella, M. C., ... & Benedetti Panici, P. (2020). First-line treatment with olaparib for early stage brca-positive ovarian cancer: may it be possible? hypothesis potentially generating a line of research. *Cancer Management and Research*, 5479-5489.
18. Jammal, M. P., Martins-Filho, A., Silveira, T. P., Murta, E. F. C., & Nomelini, R. S. (2016). Cytokines and prognostic factors in epithelial ovarian cancer. *Clinical Medicine Insights: Oncology*, *10*, CMO-S38333.
19. Kampan, N. C., Kartikasari, A. E. R., Deceneux, C., Madondo, M. T., McNally, O. M., Flanagan, K. L., ... & Plebanski, M. (2023). Combining TNFR2-expressing tregs and IL-6 as superior diagnostic biomarkers for high-grade serous ovarian cancer masses. *Cancers*, *15*(3), 667.
20. Meys, E.M., Kaijser, J. & Valentijn, A.J., (2016). Diagnostic accuracy of risk of malignancy index to exclude ovarian cancer: a systematic review and meta-analysis. *BJOG*. 123(11):1784-1791.
21. Kaijser, J., Bourne, T., Valentin, L., Sayasneh, A., Van Holsbeke, C., Vergote, I., ... & Timmerman, D. (2013). Improving strategies for diagnosing ovarian cancer: a summary of the International Ovarian Tumor Analysis (IOTA) studies. *Ultrasound in obstetrics & gynecology*, *41*(1), 9-20.
22. Tempfer, C., Zeisler, H., Sliutz, G., Haeusler, G., Hanzal, E., & Kainz, C. (1997). Serum evaluation of interleukin 6 in ovarian cancer patients. *Gynecologic oncology*, *66*(1), 27-30.
23. Moore, R. G., Brown, A. K., Miller, M. C., Skates, S., Allard, W. J., Verch, T., ... & Bast Jr, R. C. (2008). The use of multiple novel tumor biomarkers for the detection of ovarian carcinoma in patients with a pelvic mass. *Gynecologic oncology*, *108*(2), 402-408.
24. Van Gorp, T. I. E. A. K. F. D., Cadron, I., Despierre, E., Daemen, A., Leunen, K., Amant, F., ... & Vergote, I. (2011). HE4 and CA125 as a diagnostic test in ovarian cancer: prospective validation of the Risk of Ovarian Malignancy Algorithm. *British journal of cancer*, *104*(5), 863-870.
25. Karlsen, M.A., Sandhu, N. & Høgdall, C., (2015). Evaluation of HE4, CA-125, risk of malignancy index, and risk of ovarian malignancy algorithm in the preoperative assessment of ovarian tumors. *Int J Gynecol Cancer*;25(5):918-924.