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Original Research Article

Role of pre-operative serum IL-6 and CA-125 in the prediction of malignant ovarian tumor

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ABSTRACT

Background: Ovarian cancer is the most lethal gynecological malignancy. The present study was therefore designed to determine the accuracy of IL-6 and CA-125 in the early diagnosis of malignant ovarian tumors. The aim of the study was to evaluate the predictive value of pre-operative serum IL-6 and CA-125 levels in identifying malignant ovarian tumors.
Methods: This cross-sectional study took place at BSMMU and NICRH in Dhaka, Bangladesh, from February 2022 to January 2023. It involved 94 women undergoing surgery for suspected ovarian tumors. The Mann-Whitney test was used to compare IL-6 and CA-125 levels between groups. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated to correlate serum markers with histopathological diagnoses. Statistical analysis used SPSS version 23.0 with significance set at $p<0.05$.
Results: The study involved 94 patients with ovarian tumors, where the mean age was higher in those with malignant tumors. The most common malignant histopathological finding was serous carcinoma (34%), while benign tumors often included endometriotic cysts (12.8%) and mucinous cystadenomas (10.6%). Elevated levels of IL-6 and CA-125 were significantly associated with malignant tumors ($p<0.05$). Both IL-6 and CA-125 showed high diagnostic accuracy in identifying malignant ovarian tumors when used alone or in combination, as indicated by receiver-operator characteristic curves.
Conclusions: Serum IL-6 shows higher sensitivity and specificity for detecting malignant ovarian tumors, both epithelial and non-epithelial, making it a valuable diagnostic tool alongside CA-125 in assessing suspicious ovarian masses.

Keywords: Malignant ovarian tumor, Serum IL-6, CA-125, Biomarkers, Pre-operative assessment

INTRODUCTION

Ovarian cancer is the most lethal gynecological malignancy.[1] It is also a growing problem in our country. The annual mortality rate per 100,000 people from ovarian cancer in Bangladesh has increased by 40.3% since 1990, an average of 1.8% per year. The incidence of ovarian cancer was predicted to be 3,132 in Bangladesh in 2015.[2] Ovarian cancer represents the fifth most commonly diagnosed cancer among women worldwide, with a 46% survival rate 5 years after diagnosis.[3]

Ovarian cancer has a relatively asymptomatic nature in its early stages. Due to its subtle symptomatology and lack of specialized screening methods, around 70% of patients present with advanced disease (FIGO stage III and IV) at the time of diagnosis.[4]

The novel targeted molecular therapies against this disease continue to be challenging due to high mortality and the lack of early screening, resulting in delayed diagnosis. Standard investigation tools for adnexal masses currently in place include clinical examination, assays of tumor markers, and ultrasound assessment. None of these techniques is very sensitive or specific for predicting malignancy when considered separately.[5]

Thus, there is a need for the development of reliable serum biomarkers for early detection of ovarian cancer, which are both optimally sensitive and specific, remaining a long-awaited priority. Currently, there is no recommended effective early detection test for ovarian cancer in the general population. Most ovarian cancers develop from three categories of cells: epithelial cells, germ cells, and sex cord stromal cells. Among these, epithelial ovarian cancer accounts for 90% of cases. A commonly accepted and frequently used tumor marker is CA-125.[6]

However, CA-125 is not exclusively expressed in ovarian tumor cells but also by other cell types including the pleura, peritoneum, and Mullerian epithelia. Several factors undermine the significance of CA-125 as a biomarker because it is absent in about 20% of ovarian cancers and elevated in some benign and physiological conditions (such as liver cirrhosis, endometriosis, peritonitis, menstruation, and pregnancy).[6]

Inflammation has been shown to play many roles in ovarian cancer tumor growth, with the proinflammatory cytokine interleukin-6 (IL-6) established as a key immune regulatory cytokine.[7] The serum level of IL-6 is frequently elevated in women with ovarian carcinoma and predictive of poor clinical outcomes.[8] Therefore, interleukin-6 in combination with conventional tests like CA-125 may be a useful clinical biomarker for triaging patients with suspected malignant ovarian masses.

IL-6 and its proinflammatory family members, including oncostatin M, have been found to directly stimulate enhanced invasion of cancer cells through the basement membrane, facilitated by the overexpression of matrix metalloproteinases. Thus, understanding the important role of IL-6 and its family members in the pathogenesis of ovarian cancer tumor growth and metastasis may lead to novel treatments, improved detection methods, and overall clinical outcomes.

The present study was therefore designed to determine the accuracy of IL-6 and CA-125 in the early diagnosis of malignant ovarian tumors. The study also aimed to find the cutoff values of these two biomarkers at which they were most sensitive and specific for distinguishing ovarian malignancies from benign conditions.

Objective

The objective of the study was to evaluate the predictive value of pre-operative serum IL-6 and CA-125 levels in identifying malignant ovarian tumors.

METHODS

This cross-sectional analytical study was conducted at the Departments of Gynecological Oncology, Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University (BSMMU), and the Department of Gynecological Oncology, National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh, from February 2022 to January 2023. The study population included women admitted with diagnosed cases of suspected ovarian tumors who underwent surgery. The sample size was determined based on expected mean serum IL-6 concentrations from a previous study, resulting in a minimum required sample size of 94 patients.

Inclusion criteria

Women diagnosed with ovarian tumors by clinical examination and ultrasonography were included in the study.

Exclusion criteria

Women with ovarian tumors already on treatment or who had received treatment; metastatic or recurrent malignant ovarian tumors; pregnant women with ovarian tumors; patients with active inflammation, significant trauma, or open wounds; and patients with significant known concomitant heart, liver, or vascular disease were excluded.

Institutional approval was obtained from the IRBs of BSMMU, NICRH, and BCPS. Ethical guidelines were followed, and informed consent was obtained from all participants. Data collection involved structured interviews, clinical examinations, and laboratory investigations. A structured pre-tested questionnaire was used for data collection. Blood samples were collected 24 to 48 hours preoperatively, centrifuged, and the serum was frozen until measurement. Serum IL-6 was measured using a sandwich chemiluminescence immunoassay with the MAGLUMI 2000 plus analyser. Statistical analysis was performed using SPSS version 23. Continuous variables were summarized by mean and standard deviation or median, and categorical variables by frequencies and percentages. The Mann-Whitney test was used to compare IL-6 and CA-125 levels between groups. ROC curve analysis was conducted to determine optimal cut-off values for IL-6 and CA-125. Sensitivity, specificity, PPV, NPV, and accuracy were calculated to correlate serum

markers with histopathological diagnoses. A p value ≤0.05 was considered statistically significant.

RESULTS

Table 1 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%) patients 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.

Table 2 shows according to histopathological findings, majority malignant tumor about 32 (34%) in serous carcinoma; 8 (8.5%) in dysgerminoma; 4 (4.3%) in mucinous cyst adenocarcinoma; 3 (3.2%) in endometrioid adenocarcinoma; 2 (2.1%) in yolk sac tumors and other such as granulosa cell tumor, malignant Brenner tumor, mixed germ cell tumor, spindle cell sarcoma/GIST 1 (1.1%). Benign tumor was about 12 (12.8%) in endometriotic cyst; 10 (10.6%) in mucinous cystadenoma; 8 (8.5%) in mature cystic teratoma and others

Table 1: Demographic characteristics of study population (n=94).

Variables	Malignant ovarian tumor (n=53)		Benign ovarian tumor (n=41)		P value
	N	%	N	%	
Age (in years)					
≤20	11	20.8	9	22.0	[a]0.067[ns]
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	
>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	[b]0.644[ns]
Primary	22	41.5	14	34.1	
Secondary	15	28.3	15	36.6	
Higher secondary	4	7.5	6	14.6	
Graduate	1	1.9	1	2.4	
Post graduate	1	1.9	0	0.0	
Marital status					
Married	40	75.5	26	63.4	[b]0.532[ns]
Unmarried	10	18.9	13	31.7	
Divorced	2	3.8	1	2.4	
Widow	1	1.9	1	2.4	

a: fisher's exact test; b: Chi-square test; s: significant ns: not significant.

Table 2: Distribution of the patients according to histopathological findings (n=94).

Histopathological findings	Number of patients	Percentage
Malignant (n=53)		
Serous carcinoma	19	20.2
Serous adenocarcinoma	8	8.5
Serous papillary adenocarcinoma	3	3.2
Serous papillary carcinoma	2	2.1
Dysgerminoman	8	8.5
Mucinous cyst adenocarcinoma	4	4.3
Endometrioid adenocarcinoma	3	3.2
Yolk sac tumors	2	2.1
Granulosa cell tumor	1	1.1
Malignant brenner tumor	1	1.1
Mixed germ cell tumor	1	1.1
Spindle cell sarcoma/GIST	1	1.1
Benign (n=41)		

Continued.

Histopathological findings	Number of patients	Percentage
Endometriotic cyst	12	12.8
Mucinous cystadenoma	10	10.6
Mature cystic teratoma	8	8.5
Chronic salpingo oophoritis	3	3.2
Hemorrhagic cyst	2	2.1
Serous cystadenofibroma	2	2.1
Serous cystadenoma	2	2.1
Angiomyolipoma with chronic cervicitis with squamous metaplasia with leiomyoma	1	1.1
Granulomatous inflammation (TB)	1	1.1

Table 3: Distribution of the study population by preoperative estimation of serum IL-6 levels and serum CA-125 levels of benign and malignant ovarian tumors according to histopathological findings (n=94).

Variables	Malignant ovarian tumor (n=53)	Benign ovarian tumor (n=41)	P value
	Median	Median	
IL-6 (pg/ml)	18	5.5	0.001[s]
CA-125 (u/ml)	215	87.7	0.001[s]

s: significant; ns: not significant.

Table 4: 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

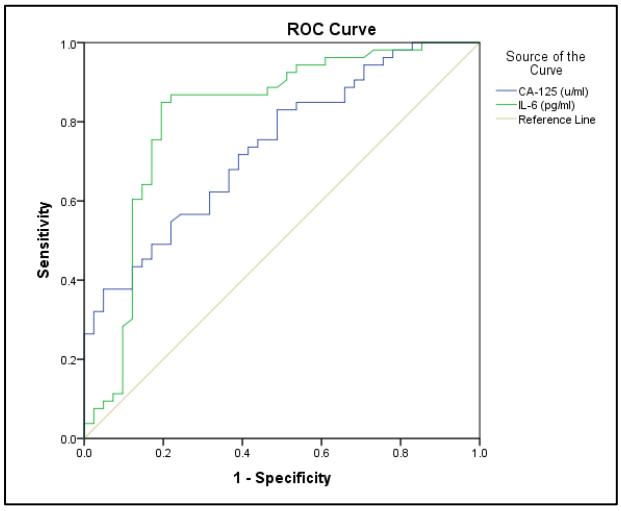

Figure 1: Receiver-operator characteristic curves of IL-6 and CA-125.

Table 3 shows that the level of serum IL-6 was elevated in malignant ovarian tumor. The difference was statistically significant ($p<0.05$) between two groups. The level of serum CA-125 was elevated in malignant ovarian tumors. The difference was statistically significant ($p<0.05$) between two groups.

Table 4 shows the accuracy or validity of serum IL-6, CA-125 and combined (CA-125+ IL-6) in malignant ovarian tumor patients.

DISCUSSION

Ovarian malignant tumors are the most lethal gynecological malignancies. Due to their subtle symptomatology and lack of specific screening methods, most patients present with advanced disease at the time of diagnosis. Thus, there is a need for the development of reliable serum biomarkers for early detection of ovarian malignancy that are optimally sensitive and specific, which remains a long-awaited priority.

In this study, it was observed that the mean age was 34.5±14.4 years in the benign ovarian tumor group and 40.7±17.4 years in the malignant ovarian tumor group. A similar observation was found in different studies; Jammal et al reported a mean age of 49.9±14.1 years for malignant neoplasms, while Kampan et al reported mean ages of 60.1±1.59 years in malignant ovarian tumors and 54.8±3.07 years in benign ovarian tumors.[9,10] The

relationship between age and the outcome of ovarian cancer remains uncertain, although many researchers have pointed out that younger age at diagnosis is associated with improved outcomes.

In this study, there were 53 cases of malignant ovarian tumors and 41 cases of benign ovarian tumors. These findings are consistent with the study conducted by Baru et al. However, Ibrahimkhil et al showed in their study that benign tumors were 81.8% more common than malignant tumors, which differed from my study.[11]

In this study, among the histological subtypes of malignant ovarian tumors, serous carcinoma was found in 20.2% of patients, serous cyst adenocarcinomas in 8.5%, papillary serous adenocarcinomas in 3.2%, dysgerminoma in 8.5%, mucinous cyst adenocarcinoma in 4.3%, endometrioid adenocarcinoma in 3.2%, yolk sac tumor in 2.1%, serous papillary carcinoma also in 2.1%, and granulosa cell tumor in 1.1% of patients. Among the histological subtypes of benign tumors, endometriotic cysts were found in 12.8% of patients, mucinous cystadenomas in 10.6%, mature cystic teratomas in 8.5%, and serous cystadenomas in 2.1% of patients. The pattern and distribution of histological subtypes in this study did not correlate with those of Jammal et al and Kampan et al possibly due to ethnic differences and variations in registry procedures and classifications used.[9,10]

In this study, the median serum IL-6 level was found to be 18.0 pg/ml in the malignant ovarian tumor group and 5.5 pg/ml in the benign ovarian tumor group. Similar findings were observed in Micheli et al who reported a median serum IL-6 level of 7.8 pg/ml in the benign neoplasia group and 20.3 pg/ml in the malignant neoplasia group.[12] Previous studies have reported that IL-6 concentrations correlate with tumor stage in ovarian carcinoma and are associated with patient survival.[13] Several studies have also shown higher IL-6 and IL-10 levels in the serum or peritoneal fluid of ovarian cancer patients compared to those with benign ovarian tumors.[14,15] Kampan et al reported that IL-6 concentrations were higher in the serum of ovarian cancer patients compared to those with benign ovarian masses or normal ovaries (median IL-6: 28.3 vs. 6.4 vs. 1.2 pg/ml, $p<0.0001$).[10]

In this study, the median serum CA-125 level was found to be 215.0 U/ml in the malignant group and 87.7 U/ml in the benign group, with a statistically significant difference ($p<0.05$). This finding correlated with the results of Kampan et al where patients with ovarian malignancy had higher serum CA-125 levels (median 372 U/ml) compared to those with benign masses (median 26 U/ml), and the difference was statistically significant ($p=0.0002$).[5] They also observed higher mean serum CA-125 levels in patients with ovarian cancer (1125±2270, median 372, range: 29-10430 IU/ml) compared to those with benign masses (47.8±55.1, median: 26, range: 5-177 IU/ml), with statistical significance ($p=0.0002$).

In this current study, based on receiver-operator characteristic (ROC) curves, IL-6 had the best area under the curve. ROC curves were constructed using IL-6 and CA-125 for patients with malignant ovarian tumors, revealing an IL-6 cutoff value of ≥9.5 pg/ml as the optimal combination of sensitivity and specificity for detecting malignant ovarian tumors. At this cutoff value, the sensitivity and specificity of IL-6 in diagnosing malignant ovarian tumors were found to be 84.9% and 80.5%, respectively. ROC curves were also constructed using IL-6 in combination with CA-125 for malignant ovarian tumors, with a sensitivity of 77.4% and specificity of 95.1%. Based on the ROC curve, the combined IL-6 and CA-125 area under the curve was 0.749, indicating an acceptable test for identifying malignant ovarian tumors. Micheli et al observed significant differences in serum cytokine levels between patients with malignant and benign neoplasia, specifically for IL-6 ($p=0.007$), with a cutoff value of 11.3 pg/ml, which was consistent with my study.[12] In this study, women with high CA-125 values (cut-off ≥89.0 U/ml) had a sensitivity and specificity of 83.0% and 51.2%, respectively, for diagnosing malignant ovarian tumors. Kampan et al reported AUC values of 0.986 for CA-125 and 0.976 for IL-6, with a combined AUC of 0.99.[5] Serum IL-6 in combination with CA-125 for distinguishing patients with high-grade serous ovarian cancer from those with benign ovarian masses is consistent with my current study.

In the present study, the accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of the combined biomarker (IL-6+CA-125) for differentiating between malignant and benign tumors were found to be 85.1%, 77.4%, 95.1%, 95.3%, and 76.5%, respectively. Kampan et al reported a sensitivity of 100%, specificity of 91.7%, accuracy of 95.4%, positive predictive value of 90.9%, and negative predictive value of 100.0% for (CA 125+IL-6), which aligned with the findings of the present study.[5] Therefore, comparing the validity tests of the single biomarker (IL-6) with the combined biomarker (IL-6+CA-125) showed that the combined serum biomarker levels were more accurate and specific in differentiating between benign and malignant ovarian tumors.

The results of this study indicated that preoperative measurement of serum IL-6 levels in combination with serum CA-125 levels may serve as predictive biomarkers due to their superior specificity and accuracy. Thus, these two markers may reinforce the detection of malignant ovarian tumors, potentially improving the life expectancy of ovarian cancer patients.

Limitations

The study had some limitations. The study was conducted over a short period of time with a relatively small sample size. Due to time constraints, it was not possible to collect large-scale data, which may limit the generalizability of the findings. The reference values for serum IL-6 and CA-

125 can vary between different laboratories, making it challenging to standardize and compare positive and negative results across studies. This variability might affect the consistency and reproducibility of the results.

CONCLUSION

This study revealed that serum IL-6 has better sensitivity and specificity for detecting malignant ovarian tumors, both epithelial and non-epithelial. Serum CA-125 has overall predictive value for detecting only epithelial ovarian tumors. Therefore, the measurement of serum IL-6 may be a useful diagnostic tool in conjunction with CA-125 for the preoperative assessment of suspicious ovarian tumors, both malignant and benign. Comparison of the validity tests between the single biomarker (IL-6) and the combined biomarker (IL-6+CA-125) showed that serum CA-125 alone, along with IL-6 levels, is more specific and accurate in differentiating benign from malignant ovarian tumors.

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REFERENCES

1. Kim SI, Lee M, Kim HS, Chung HH, Kim JW, Park NH, et ak. Effect of BRCA mutational status on survival outcome in advanced-stage high-grade serous ovarian cancer. J Ova Res. 2019;12(1):40.
2. Hoque ME, Karim S, Siddiqui MMR, Ahmed T. Report on Three cases of advance ovarian cancer upon Bangladeshi population: successful management with bevacizumab based chemotherapy. Anwer Khan Mod Med Coll J. 2017;8(2):157-61.
3. Doherty JA, Peres LC, Wang C, Way GP, Greene CS, Schildkraut JM. Challenges and opportunities in studying the epidemiology of ovarian cancer subtypes. Curr Epidemiol Rep. 2017;4(3):211-20.
4. Ozols RF, Rubin SC, Thomas G, Robboy S. Epithelial ovarian cancer. In: Hoskins WJ, Perez CA, Young RC, eds. Principle and Practice of gynaecologic oncology. Philadelphia: Lippincott Williams and Wilkins; 2005: 919-22.
5. Kampan NC, Madondo MT, Reynolds J, Hallo J, McNally OM, Jobling TW, et al. Pre-operative sera interleukin-6 in the diagnosis of high-grade serous ovarian cancer. Scientif Rep. 2020;10(1):2213.
6. Rastogi M, Gupta S, Sachan M. Biomarkers towards ovarian cancer diagnostics: present and future prospects. Braz Arch Biol Technol. 2016:59.
7. Browning L, Patel MR, Horvath EB, Tawara K, Jorcyk CL. IL-6 and ovarian cancer: Inflammatory cytokines in promotion of metastasis. Cancer Manag Res. 2018;10:6685.
8. Mustea A, Konsgen D, Braicu EI, Pirvulescu C, Sun P, Sofroni D, et al. Expression of IL-10 in patients with ovarian carcinoma. Anticancer Res. 2006;26(2):1715-8.
9. Jammal MP, Martins-Filho A, Silveira TP, Murta EFC, Nomelini RS. Cytokines and prognostic factors in epithelial ovarian cancer. Oncology. 2016;10:38333.
10. Kampan NC, Kartikasari AER, Deceneux C, Madondo MT, McNally OM, Flanagan KL, et al. Combining TNFR2-expressing tregs and il-6 as superior diagnostic biomarkers for high-grade serous ovarian cancer masses. Cancer. 2023;15(3):667.
11. Ibrahimkhil AS, Malakzai HA, Haidary AM, Hussaini N, Abdul-Ghafar J. Pathological features of ovarian tumors, diagnosed at a tertiary care hospital in Afghanistan: a cross-sectional study. Cancer Manag Res. 2022:3325-33.
12. Micheli DC, Jammal MP, Martins-Filho A, Cortes JR, Souza CN, Nomelini RS, et al. Serum cytokines and CXCR2: potential tumour markers in ovarian neoplasms. Biomarkers. 2020;25(6):474-82.
13. Guo Y, Xu F, Lu T, Duan Z, Zhang Z. Interleukin-6 signaling pathway in targeted therapy for cancer. Cancer Treat Rev. 2012;38(7):904-10.
14. Mustea A, Konsgen D, Braicu EI, Pirvulescu C, Sun P, Sofroni D, et al. Expression of IL-10 in patients with ovarian carcinoma. Anticancer Res. 2006;26(2):1715-8.
15. Van Der Zee AG, De Bruijn HW, Krans M, De Cuyper EM, Hollema H, Limburg PC, et al. Higher levels of interleukin-6 in cystic fluids from patients with malignant versus benign ovarian tumors correlate with decreased hemoglobin levels and increased platelet counts. Cancer. 1995;75(4):1004-9.

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