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# Interleukin 6 Examination as a Marker of Pre-Surgical Epithelial Type of Ovarian Malignancy: A Cross-Sectional Study

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**ABSTRACT**

**Background & Objective:** Ovarian cancer affects women worldwide. Immunoregulatory cytokines, particularly interleukin (IL)-6, can enhance tumorigenicity and are persistently secreted by ovarian cancer cells. This study aims to examine IL-6 as a marker of preoperative epithelial ovarian malignancy.

**Materials & Methods:** This study used a cross-sectional design on 81 eligible patients with ovarian neoplasms who were undergoing surgery at the Dr. Wahidin Sudirohusodo Hospital and its networking hospital from October 2021 to June 2022. The ELISA technique was used to measure serum IL-6 from the peripheral vein. In addition, the CA-125 levels, risk of malignancy (RMI) index, and proportion of blood cells were analyzed. Chi-square analysis of the data had been used.

**Results:** Most of the subjects were presented as malignant ovarian neoplasms (66.7%), followed by benign ovarian neoplasms (33.3%). IL-6 level ≥ 3.75 pg/mL was found in 72.8% of patients. In individuals with epithelial ovarian neoplasms, IL-6 levels did not significantly differ between malignant and benign types ($p > 0.05$). CA-125 levels, RMI, ascites, and tumor size differed significantly in patients with ovarian epithelial neoplasms between malignant and benign types ($p < 0.05$). Leukocyte levels, hemoglobin levels, platelet levels, age, parity, and age of menarche were not significantly different in epithelial ovarian neoplasm patients between malignant and benign types ($p > 0.05$).

**Conclusion:** The preoperative serum IL-6 level cannot be used as a marker of ovarian malignancy. However, this study confirms the relationship between the CA-125 level, RMI, ascites, and tumor size with the malignancy of ovarian tumors.

**Keywords:** Epithelial, Interleukin 6, Malignancy, Ovarian Neoplasm

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## 1. Introduction

Ovaries play a role in female fertility (1). Moreover, ovarian cancer is the eighth most prevalent type of cancer in women and the 18th most common type of cancer overall, making it a global issue. The incidence of ovarian cancer was around 300,000 new cases in 2018 and tended to increase in the young population (2, 3). Deaths caused by ovarian cancer are 9.7 out of 100,000 cases (4).

Various factors can increase the risk of ovarian cancer, including the demographics characteristics, age at menarche and menopause, parity, age at delivery, history of gynecological conditions, history of contraception, history of hormone therapy, family history, lifestyle habits, obesity, and physical activity, and socioeconomic status (5). For a more accurate prognosis and more tailored treatment, early diagnosis of ovarian cancer progression is crucial. These advantages can be done by examining biomarkers, such as interleukin-6 (IL-6). Prior studies revealed the prognostic potential of IL-6 and vascular endothelial growth factor (VEGF)-A to characterize ovarian cancer with ascites. The findings demonstrated that ovarian cancer patients had IL-6 levels that were comparatively greater than those of controls. The notion that peritoneal inflammation rises with the development of ovarian cancer is supported by the finding that patients with advanced ovarian cancer also have greater IL-6 levels than those with stage I/II disease (6).

Immunoregulatory cytokines include the pro-inflammatory cytokine IL-6. Continual autocrine and paracrine secretion of cytokines that promote tumorigenicity by ovarian cancer cells occurs in response to cues from the tumor microenvironment (TME). Leukocytes and fibroblasts are among the many cells found in TME. These cells respond to pro-inflammatory cytokines and secrete cytokines that have

a variety of effects. It was discovered that IL-6 promoted the cell cycle, enhanced resistance to chemotherapy, and produced TME in addition to directly stimulating greater invasion of cancer cells through basement membrane deterioration brought on by matrix metalloproteinase overexpression **(7)**. This study aims to determine the diagnostic significance of IL-6 in identifying benign and malignant ovarian neoplasms at the preoperative stage, as IL-6 has the potential to serve as an ovarian cancer biomarker.

## 2. Materials and Methods

Observational study design with the cross-sectional design was conducted on patients with ovarian neoplasms undergoing surgery at the Dr. Wahidin Sudirohusodo hospital, Hasanuddin University Hospital, Faisal Islamic Hospital, Siti Khadijah I Mother and Child Hospital, Ibnu Sina Hospital in Makassar from October 2021 to June 2022. All samples in the study had received adequate explanations and signed informed consent before being involved in the research. The Health Research Ethics Committee, Faculty of Medicine, Hasanuddin University (No: 104/UN4.6.4.5.31/PP36/2022) had examined and approved all research designs.

This study involved patients with ovarian neoplasms who had an established diagnosis based on clinical and histopathological examination results, had never received chemotherapy or immunosuppressant therapy, had no history of other malignancies, were not infertile due to endometriosis or other infectious diseases, and were not in a state of fever with body temperature. >37.5$^0$C, and the leukocyte count is not > 10,000/mcl. Damaged sample blood specimens or other conditions that made them unfit for testing were excluded from the study. Samples were then taken by consecutive random sampling using the Lemeshow formula. The assigned alpha and beta values are 95% and 80%, respectively. The P1 value was determined from the proportion of ovarian malignancy at IL-6 levels ≥ 3.75 pg/mL namely 0.65. The P2 value is determined from the proportion of ovarian malignancy at IL-6 levels < 3.75 pg/mL, which is 0.15 **(8)**. Based on the calculation results, a minimum sample of 36 patients was obtained. Researchers anticipate dropping out of 10% for 3.6 samples. The minimum total sample required for the entire sample is 36 + 3.6 samples = 39.6 samples (approximately 40 samples).

The main variable in this study was the IL-6 level, measured from 3 CCs of patient serum samples taken from the peripheral vein. This blood sample was then measured with a human IL-6 ELISA assay kit using a standard procedure that had been used previously. Based on the results of this examination, patients were then grouped into high IL-6 levels (≥ 3.75 pg/mL) and low IL-6 levels (< 3.75 pg/mL).

Other data analyzed were age, parity, and age at menarche obtained from medical records. In addition, clinical parameters such as ascites and tumor size are also examined through physical examination. Ascites are characterized by distention of the abdominal wall with bulging of the flanks. Meanwhile, tumor size was measured based on the diameter of the mass in cm and was divided into two categories, namely <10 cm and > 10 cm.

Data from other investigations that were measured and analyzed were CA-125 levels, RMI index, and proportion of blood cells. Preoperative serum CA125 levels were examined from the patient's blood sample using an ELISA kit in units of U/mL. Patients will be divided into two groups based on the findings of this measurement, those with 35 U/mL and those without 35 U/mL. The RMI index scores patients based on a number of clinical characteristics, including menopausal status, ultrasound results, and CA 125 blood levels. The formula RMI = U x M x CA-125 is used to determine RMI as a function of the ultrasound score (U), menopausal status (M), and CA-125 readings. A cut-off value of 200 will categorize patients with high and low-index RMA. The proportion of the patient's blood cells was obtained from a complete blood count of preoperative peripheral venous blood samples, which included leukocytes, hemoglobin, and platelets. The normal levels determined in this study were leukocytes ≤ 10 x 103/µL, hemoglobin ≥ 12 g/dL, and platelets ≤ 400 x 103/µL.

The collected data were organized into groups according to their purpose and type, and then SPSS for Windows version 23 was used to analyze them. To measure the frequency distribution, univariate analysis was used. The Chi-Square test was used to compare the levels of IL-6 and the aggressiveness of ovarian epithelial neoplasms. Fisher's test is an alternative if the conditions for the Chi-Square test cannot be fulfilled. For interpreting the results, a P-value of 0.05 or lower is regarded as significant.

## 3. Results

In this study, 81 samples were obtained as subjects of ovarian neoplasm patients who were treated and planned to undergo surgery. The characteristics of the study sample can be seen in Table 1. Most of the study subjects were aged <60 years (88.9%), primipara/multipara/grand multipara (59.3%), and the age of menarche was more than or equal to 12 years (87, 7%). Based on the physical examination results, most of the study subjects did not have ascites (55.6%), and the tumor size was greater than or equal to 10 cm (59.3%). Laboratory examination results showed that most of the study subjects had normal leukocyte levels (67.9%), anemia (65.4%), thrombocytosis (56.8%), IL-6 levels ≥ 3.75 pg/mL (72.8%), CA-125 levels ≥ 35 (U/mL) (72.8%), and RMI ≥ 200 (72.8%).

**Table 1. Frequency distribution of the characteristics of the study participant**

| Characteristics | Frequencies | Percentage (%) |
|---|---|---|
| **Age** | | |
| **< 60 years** | 72 | 88.9 |
| **≥ 60 years** | 9 | 11.1 |
| **Parity Status** | | |
| **Nullipara** | 33 | 40.7 |
| **Primi/multi/grandmultipara** | 48 | 59.3 |
| **Age at Menarche** | | |
| **< 12 years** | 10 | 12.3 |
| **≥ 12 years** | 71 | 87.7 |
| **Ascites** | | |
| **Yes** | 36 | 44.4 |
| **No** | 45 | 55.6 |
| **Tumor size (cm)** | | |
| **< 10** | 33 | 40.7 |
| **≥ 10** | 48 | 59.3 |
| **Leukocyte Count** | | |
| **Leukocytosis** | 26 | 32.1 |
| **Normal** | 55 | 67.9 |
| **Hemoglobin** | | |
| **Anemia** | 53 | 65.4 |
| **Normal** | 28 | 34.6 |
| **Thrombocyte Count** | | |
| **Thrombocytosis** | 46 | 56.8 |
| **Normal** | 35 | 43.2 |
| **IL-6 (pg/mL)** | | |
| **< 3.75** | 22 | 27.2 |
| **≥ 3.75** | 59 | 72.8 |
| **CA-125 (U/mL)** | | |
| **< 35** | 22 | 27.2 |
| **≥ 35** | 59 | 72.8 |
| **RMI** | | |
| **< 200** | 22 | 27.2 |
| **≥ 200** | 59 | 72.8 |

**RMI: Risk of Malignancy Index**

The histopathological examination results after surgery in the samples are shown in Table 2. Most of the subjects in this study were patients with malignant ovarian neoplasms (66.7%), and 33.3% were patients with benign ovarian neoplasms. Most of the subjects of this study were early-stage ovarian cancer (54.3%), and 45.7% were patients with advanced ovarian cancer. Most of the patients had mucinous histopathology results (39.5%).

**Table 2. Frequency distribution of postoperative histopathological examination results**

| Characteristics | Frequencies | Percentage (%) |
|---|---|---|
| **Neoplasm** | | |
| **Malignant** | 54 | 66.7 |
| **Benign** | 27 | 33.3 |
| **Stage** | | |
| **Early** | 44 | 54.3 |
| **Advanced** | 37 | 45.7 |
| **Histopathology type** | | |
| **Mucinous** | 32 | 39.5 |
| **Serosa** | 23 | 28.4 |
| **Endometrioid tumor** | 15 | 18.5 |
| **Squamous** | 5 | 6.2 |
| **Dermoid cyst** | 5 | 6.2 |
| **Clear cell tumor** | 1 | 1.2 |

Table 3 compares the demographic characteristics, menarche, and parity status of patients with malignant and benign ovarian neoplasms. Between benign and malignant ovarian tumors, there were no significant differences in the proportion of age, parity status, or age of menarche category (all had a P-value > 0.05). Most patients aged <60 years were in the category of malignant and benign ovarian neoplasms (both had a proportion of 88.9%). In addition, most patients had primi/multi/grand multipara status in malignant and benign ovarian neoplasms (61.1% and 55.6%, respectively). In terms of menarche, most patients with malignant and benign ovarian neoplasms experienced it before the age of 12 (90.7% and 81.5%, respectively).

**Table 3. Comparison of demographic characteristics, parity status, and menarche in patients with malignant and benign ovarian neoplasms**

| Characteristic | Malignant | | Benign | | Total | | p-value* |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| **Age** | | | | | | | |
| **< 60 years** | 48 | 88.9 | 24 | 88.9 | 72 | 88.9 | 1.000 |
| **≥ 60 years** | 6 | 11.1 | 3 | 11.1 | 9 | 11.1 | |
| **Parity** | | | | | | | |
| **Nullipara** | 21 | 38.9 | 12 | 44.4 | 33 | 40.7 | 0.631 |
| **Primi/multi/grandmultipara** | 33 | 61.1 | 15 | 55.6 | 48 | 59.3 | |
| **Age at Menarche** | | | | | | | |
| **< 12 years** | 5 | 9.3 | 5 | 18.5 | 10 | 12.3 | 0.288 |
| **≥ 12 years** | 49 | 90.7 | 22 | 81.5 | 71 | 87.7 | |

***Chi-square test**

Table 4 compares the clinical status, IL-6, CA-125, RMI, and the proportion of complete blood counts in individuals with benign and malignant ovarian neoplasms. Between benign and malignant ovarian neoplasms, there were significant variations in the proportion of ascites types and tumor size (all with a P-value > 0.05). Most patients with malignant ovarian neoplasms had ascites (57.4%). In patients with benign ovarian neoplasms, most did not have ascites (81.5%). As for the tumor size category, most (92.6%) had tumor sizes ≥ 10 cm for malignant ovarian neoplasms and 70.4% for benign ovarian neoplasms.

**Table 4. Comparison of preoperative clinical status, laboratory findings, and RMI levels between malignant and benign ovarian neoplasms**

| Biomarker | Malignant | | Benign | | Total | | p-value* |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| **Ascites** | | | | | | | |
| **Yes** | 31 | 57.4 | 5 | 18.5 | 36 | 44.4 | 0.001 |
| **No** | 23 | 42.6 | 22 | 81.5 | 45 | 55.6 | |
| **Tumor size (cm)** | | | | | | | |
| **< 10** | 4 | 7.4 | 8 | 29.6 | 12 | 14.8 | 0.017 |
| **≥ 10** | 50 | 92.6 | 19 | 70.4 | 69 | 85.2 | |
| **IL-6 Level (pg/mL)** | | | | | | | |
| **< 3.75** | 13 | 24.1 | 9 | 33.3 | 22 | 27.2 | 0.377 |
| **≥ 3.75** | 41 | 75.9 | 18 | 66.7 | 59 | 72.8 | |
| **CA-125 Level (U/mL)** | | | | | | | |
| **< 35** | 5 | 9.3 | 17 | 63.0 | 22 | 27.2 | 0.001 |
| **≥ 35** | 49 | 90.7 | 10 | 37.0 | 59 | 72.8 | |
| **RMI** | | | | | | | |
| **< 200** | 2 | 3.7 | 20 | 74.1 | 22 | 27.2 | 0.001 |
| **≥ 200** | 52 | 96.3 | 7 | 25.9 | 59 | 72.8 | |
| **Leukocyte count** | | | | | | | |
| **Leukocytosis** | 18 | 33.3 | 8 | 29.6 | 26 | 32.1 | 0.736 |
| **Normal** | 36 | 66.7 | 19 | 70.4 | 55 | 67.9 | |
| **Hemoglobin** | | | | | | | |
| **Anemia** | 36 | 66.7 | 17 | 63.0 | 53 | 65.4 | 0.741 |
| **Normal** | 18 | 33.3 | 10 | 37.0 | 28 | 34.6 | |
| **Thrombocyte count** | | | | | | | |
| **Thrombocytosis** | 33 | 61.1 | 13 | 48.1 | 46 | 56.8 | 0.267 |
| **Normal** | 21 | 38.9 | 14 | 51.9 | 35 | 43.2 | |

***Chi-square test**
**RMI: Risk of Malignancy Index**

Between benign and malignant ovarian tumors, there was no significant variation in the proportion of IL-6 level categories (P = 0.377). Preoperative IL-6 levels in the majority of patients with malignant and benign ovarian neoplasms were greater than or equivalent to 3.75 pg/mL, or 75.9% for malignant ovarian neoplasms and 66.7% for benign ovarian neoplasms, respectively. The proportion of benign and malignant ovarian tumors in the CA-125 and RMI categories, however, was significantly different (both had P=0.001). In this investigation, there were no significant differences in the percentages of leukocytosis, anemia, and thrombocytosis between the groups of benign and malignant ovarian tumors (all had p>0.05).

Table 5 compares the levels of IL-6, CA-125, and RM in patients with ovarian neoplasms based on early and advanced stages. The proportion of IL-6 level categories between the early and advanced phases of ovarian cancer did not change significantly (p=0.126). Preoperative IL-6 levels in most patients with early and advanced ovarian cancer, 81.8% for advanced and 65.9% for early stages, were greater than or equivalent to 3.75 pg/mL. The proportions of CA-125 and RMI categories between early and advanced stages of ovarian cancer in this investigation did, however, differ significantly (both had p-value < 0.005).

**Table 5. Comparison of preoperative IL-6, CA-125 and RMI levels based on ovarian malignancy stage**

| Biomarker | Early | | Advanced | | Total | | p-value* |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| **IL-6 Level** | | | | | | | |
| **< 3.75 pg/mL** | 15 | 34.1 | 7 | 18.9 | 22 | 27.2 | 0.126 |
| **≥ 3.75 pg/mL** | 29 | 65.9 | 30 | 81.8 | 59 | 72.8 | |
| **CA-125 Level** | | | | | | | |
| **< 35 U/mL** | 18 | 40.9 | 4 | 10.8 | 22 | 27.2 | 0.002 |
| **≥ 35 U/mL** | 26 | 59.1 | 33 | 89.2 | 59 | 72.8 | |
| **RMI** | | | | | | | |
| **< 200** | 19 | 43.2 | 3 | 8.1 | 22 | 27.2 | 0.000 |
| **≥ 200** | 25 | 56.8 | 34 | 91.9 | 59 | 72.8 | |

***Chi-square test**
**RMI: Risk of Malignancy Index**

## 4. Discussion

Most ovarian neoplasm patients exhibited IL-6 levels greater than or equivalent to 3.75pg/mL. According to a prior study, women with a suspected ovarian tumor and an elevated IL-6 level were given primary triage and standard testing (CA125 or RMI score) **(9)**. According to research by Kampan et al **(8)** patients with advanced ovarian cancer had a mean IL-6 level 24 times greater than that of healthy ovaries. IL-6 levels with a cut-off of 3.75 pg/mL can be utilized as a biomarker with 100% sensitivity, 76.8% specificity, 69.7% positive predictive value, and 100% negative predictive value for the diagnosis of malignancy of ovarian neoplasms **(8)**.

The immunoregulatory cytokine IL-6 is pro-inflammatory. Consistent autocrine and paracrine secretion of cytokines that promote tumorigenicity by ovarian cancer cells occurs in response to stimuli from the tumor microenvironment (TME). Numerous cells, such as leukocytes and fibroblasts, are found in TME. These cells respond to pro-inflammatory cytokines and secrete cytokines that have a variety of effects, such as chemoresistance, resistance to apoptosis, invasion, angiogenesis using vascular endothelial growth factor overexpression, and accelerated growth of distant metastases. Through basement membrane degradation carried on by matrix metalloproteinase overexpression, IL-6 directly promotes greater invasion of cancer cells. It also drives the cell cycle, increases chemotherapeutic resistance, and results in TME **(7, 10)**.

The recent study revealed no substantial difference in the IL-6 levels between malignant and benign neoplasms. This finding differs from earlier research, which indicated that the three groups malignant and benign, benign and normal, and malignant and normal ovaries had preoperative IL-6 concentration differences that were larger than twofold **(8)**. Women with and without endometriosis had serum IL-6 levels that were comparable. This study supports those findings **(11)**. Contrarily, women with endometriomas have lower serum IL-6 levels than women with ovarian cancer **(12)**. Moreover, IL-6 expression levels were higher in T3 tumors compared to T2 and T1 tumor samples. IL-6 expression increased in line with tumor grade, but there was no statistically significant difference. This variation in results may be due to differences in sample size and the small number of samples **(13)**.

Human ovarian epithelial cells can generate IL-6 during follicular development, albeit amounts might not be detectable. In contrast, advanced ovarian cancer is found to have high levels of circulating IL-6. The primary producers of IL-6 in the tumor microenvironment are peritoneal mesothelial cells or tumor cells. When used as a marker to distinguish between cancerous and non-cancerous ovarian tumors, IL-6 has a sensitivity of 100%, a specificity of 76.8%, a positive predictive value of 69.7%, and a negative predictive value of 100% at a threshold of >3.75 pg/ml. When used alone, CA125 serum or RMI has a higher probability of false positives. Hence, ovarian endometrioma with artificially elevated CA125 should be distinguished from malignant illness using IL-6 and CA125 together **(8)**.

The present study revealed a substantial difference between malignant and benign neoplasms in CA-125 levels. In 2011, the National Institute for Health and Care Excellence (NICE) advised primary care physicians to test women with symptoms of suspected ovarian cancer for CA-125. If the CA-125 result is below 35 U/mL, additional research is advised. The usual upper limit for CA-125, which was determined by a study in which 1% of healthy women and 82% of patients with ovarian cancer had CA-125 levels >35 U/mL, was chosen as the cut-off value of 35 U/ml **(14)**. Moreover, elevated CA-125 levels were found in the majority of advanced malignancies, and they were

significantly related to ovarian cancer. This finding is consistent with other studies showing that individuals with ovarian cancer had considerably elevated CA-125 levels. These levels were closely correlated with the histological type and stage of the disease. The sensitivity, specificity, and accuracy of CA-125 for malignant ovarian cancer were 75.97%, 79.59%, and 78.15%, respectively **(15)**. This finding is probably because CA125 is involved in metastatic formation by adhesion to the peritoneal mesothelium **(16)**.

This study showed significant differences in RMI between malignant-benign neoplasms and early-advanced stages. A grading system called RMI combines a number of different clinical criteria. RMI was created to increase the accuracy of ovarian cancer diagnosis **(17)**. Compared to other criteria, RMI is more reliable at identifying malignant from benign tumors **(18)**. RMI can distinguish benign ovarian tumors from malignant ones. RMI offers a sensitivity of 70.6%, a specificity of 83.9%, a PPV of 75%, and an NPV of 80.6% using a cut-off level of 200 to indicate malignancy **(17)**.

Leukocytosis, anemia, and thrombocytosis had comparable proportion between malignant and benign ovarian cancer. There was no noticeable variation in leukocyte levels between individuals with benign and malignant ovarian neoplasms **(19)**. Leukocyte and hemoglobin levels between benign and malignant ovarian neoplasms did not differ significantly **(20)**. Leukocytes assist the immune system to defend against disease and infections. The leukocyte count will rise if an immunological response occurs, as in the case of malignancy **(21)**. However, this was not observed in this study. In addition, 61.1% of thrombocytosis patients had stage 3 ovarian cancer, and 61.1% had grade 3 tumors **(22)**. IL-6 is released by cancer cells, which increases thrombopoietin produced by the liver and cancer cells and contributes as a factor in paraneoplastic thrombocytosis. Plasma thrombopoietin levels and thrombocytosis were both substantially correlated with ovarian tumor and plasma IL-6 expression in human samples. An underlying thrombocytosis in ovarian cancer is an indicator of a bad prognosis **(23)**. The IL-6 levels in this study were not significantly associated with the aggressiveness of ovarian neoplasms, platelet levels were also not significantly associated with this.

Most individuals with ovarian neoplasms do not have ascites. Moreover, ascites between malignant and benign neoplasms differed significantly. A palpable pelvic mass, ascites, or reduced breath sounds due to pleural effusion may also be noticed in situations of advanced malignancy. One of the typical signs of ovarian cancer found at the time of initial diagnosis, ascites can be present at an early stage but is more frequently observed in late illness. Amount of 7–10% of ascites patients experience subsequent cancer **(24)**. Ascites develops as a result of the implantation of ovarian cancer cells, which causes inflammation and injury. This stimulation of immune and stromal cells causes the release of cytokines like IL-1, IL-6, and IL-8, which further promotes tumor angiogenesis and ascites formation by increasing VEGF secretion by cancer cells **(25)**.

Most patients with ovarian neoplasms have substantial tumor size. Moreover, there were substantial differences between benign and malignant tumor sizes. McDonald et al **(26)** evaluated a number of tumor characteristics that are related to malignancy. According to statistics, tumor size with a diameter threshold of 10 cm is associated with a higher chance of malignancy **(26)**. There were benign lesions in 47 of the 58 patients (81%) and malignant lesions in 9 of the patients (15.6%) with tumor diameters ranging from 11 to 42 cm, with a median value of 22.75 cm and a mean diameter of 24.66 8.50 cm. However, the outcomes were not significantly different **(27)**. The pathological diagnosis of ovarian tumor malignancy is correlated with tumor size. The median tumor size for malignant tumors was 18 cm (range 3-40 cm), whereas the median tumor size for benign mucinous tumors was 10 cm (range 2-60 cm) **(28)**.

This research has several limitations. The comparative test was not comprehensive, considering there was no comparison between epithelial and non-epithelial ovarian cancer in this study. In addition, the observational research design with a relatively small number of samples tests the relationship between variables with relatively low external validity. A multicenter study with relatively larger samples is suggested to truly describe the relationship between IL-6 levels and malignant ovarian neoplasms.

## 5. Conclusion

The proportion of patients with the malignant type of ovarian epithelial neoplasm is greater than the benign type. More patients with the malignant type of ovarian epithelial neoplasm than the benign type had preoperative IL-6 levels below 3.75 pg/mL. IL-6 levels did not significantly differ between patients with malignant and benign ovarian epithelial neoplasms, nevertheless.

## 6. Declarations

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## Ethical Considerations

This article is not an extract from a research project or thesis and does not have a code of ethics.

## Authors' Contributions

A.U. conceived and designed the analysis, collected the data, contributed data or analysis tools, and wrote the paper. S.R. and T.I. conceived and designed the analysis, contributed data or analysis tools, and wrote the paper. F.H. contributed data or analysis tools and performed the analysis. J.R. and A.R. conceived and designed the analysis.

## Conflict of Interest

The authors declare no conflict of interest.

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## Consent to participate

Informed consent was obtained from all individual participants included in the study.

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