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# Comparison of Tumor CD8 in High- and Low-Grade Ovarian Carcinoma at Indonesia in 2021-2023

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**ABSTRACT**

**Background & Objective:** To conduct a study comparing tumor-infiltrating CD8+ T cells in high- and low-grade ovarian carcinoma in Indonesia Population. CD8+ T cells play a critical role in antitumor immunity, and their presence may reflect tumor aggressiveness and prognosis. Understanding their distribution helps in identifying potential therapeutic and prognostic markers for ovarian cancer.

**Materials & Methods:** This observational analytic study with a cross-sectional design was performed on patients diagnosed with primary high- and low-grade ovarian carcinoma based on histopathological examination at Dr. Soetomo Hospital from 2021 to 2023. Immunohistochemical examination was performed to assess CD8 expression in tumor tissue. Data was analyzed using Mann-Whitney and Chi-Square tests. P<0.05 was considered statistically significant.

**Results:** Out of 55 samples, 52.7% were high-grade ovarian carcinoma and 47.3% were low-grade. High CD8 expression was found in 72.4% of high-grade cases and 61.5% of low-grade cases. There was no significant difference between high-grade and low-grade ovarian carcinoma in CD8 expression (P=0.121). No significant relationship was found between age, age at menarche, CA-125 levels, and CEA levels with the histopathological type of ovarian tumor.

**Conclusion:** Although nulliparity is a known risk factor for ovarian carcinoma, this study found no significant difference in CD8+ T cell expression between high-grade and low-grade cases. CD8+ expression did not appear to influence the clinical characteristics in either group. Further studies with larger sample sizes are warranted to better understand the relationship between CD8+ T cell infiltration and the histopathological subtypes of ovarian carcinoma.

**Keywords:** Ovarian carcinoma, High grade, Low grade, CD8, Tumor Infiltrating Lymphocytes (TILs), Immunohistochemistry, CD8+ T cell

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## 1. Introduction

Epithelial ovarian carcinoma is a gynecological malignancy with the highest mortality rate. Global statistics from 2020 show 313,959 new cases of ovarian carcinoma with 207,252 deaths. Ovarian carcinoma ranks fifth as the most common cancer and fourth as the leading cause of cancer-related death among women. In Indonesia, ovarian cancer is the third most common cancer among women, with 13 50 cases and 5296 deaths in 2021 **(1)**.

Ovarian carcinoma is classified into several histological types. High-grade serous carcinoma accounts for 70% of cases and is characterized by TP53 mutations, chromosomal instability, and homologous recombination pathway deficiency. Low-grade serous carcinoma is rarer (2-5% of cases) and is associated with activation of the MAPK pathway through KRAS and BRAF mutations. These two types differ in molecular characteristics, prognosis, and therapeutic response **(2,3)**.

Most ovarian carcinoma cases are diagnosed at advanced stages (III/IV), associated with a poor prognosis. The tumor microenvironment plays a crucial role in the development and progression of ovarian carcinoma. The immune system acts as a

significant barrier against tumor formation and progression. Animal studies have shown that tumors grow more rapidly under immunodeficient conditions, particularly with deficiencies in cytotoxic CD8+ T lymphocytes, CD4+ helper T cells, or Natural Killer (NK) cells. CD8+ T cells are critical for anti-tumor immune responses by recognizing tumor antigens presented by MHC class I molecules and directly killing tumor cells through the release of cytotoxic granules and cytokines. However, the prognostic relationship of CD8+ Tumor-Infiltrating Lymphocytes (TILs) in ovarian carcinoma remains controversial **(4)**.

Tumor cells can develop mechanisms to evade recognition and elimination by the immune system, such as tryptophan and/or arginine catabolism by tumor or stromal cells, which suppresses CD8+ effector T cells and stabilizes regulatory T cells. Additionally, tumor cells can express inhibitory ligands that suppress CD8+ T cell activity. There remains a knowledge gap regarding differences in CD8 expression between high- and low-grade ovarian carcinoma. Previous studies have shown higher CD8+ lymphocyte infiltration in high-grade ovarian carcinoma compared to low-grade cases **(5,6)**. Therefore, the present study was conducted with aim to compare CD8 expression in high- and low-grade ovarian carcinoma at Dr. Soetomo Hospital, Surabaya, from 2021 to 2023.

## 2. Materials and Methods

This observational analytic research with a cross-sectional design was conducted in the Department of Obstetrics and Gynecology and the Anatomical Pathology Laboratory of Dr. Soetomo Hospital, Surabaya. The study sample consisted of 55 patients diagnosed with ovarian carcinoma treated at this Hospital between 2021 and 2023 who met the inclusion criteria. Inclusion criteria were patients diagnosed with primary high- or low-grade ovarian carcinoma based on histopathological examination of tumor tissue obtained through surgical procedures. Exclusion criteria were patients diagnosed with secondary ovarian carcinoma, primary non-epithelial ovarian tumors, and cases with damaged histopathological tissue specimens.

Ovarian carcinoma was classified as high- or low-grade based on histopathology results. Age was categorized as ≤40 years, 41-50 years, 51-60 years, and ≥61 years based on medical records. Parity was categorized as 0, nulliparous, or ≥1. Menopause status was divided into menopausal and non-menopausal. Malignancy risk index was categorized as high or low risk based on anamnesis, medical records, and Ultrasonography (US).

Immunohistochemical examination was performed using paraffin blocks rich in tumor tissue. The Ventana Benchmark XTTM fully automated staining device was used, with 3-5-micron sections taken on lysine-coated slides from selected paraffin blocks. CD8 antibodies (Dako, prediluted-auto-ready antibody; Mouse Monoclonal Primary Antibody, clone CD8/144B) were used for immunohistochemical staining. The Ultraview Universal DAB detection kit was employed for staining. For negative control, the primary antibody was omitted and tonsil tissue served as the positive control for CD8. Slides were examined by pathologists to assess CD8+ Tumor-Infiltrating Lymphocytes (TILs). Only CD8+ TILs in the epithelial tumor component (tumor islets) were evaluated. CD8+ TIL expression was classified as high if there were≥20 positive-stained cells per high-power field (HPF). This cutoff is in accordance with previous study by Pizarro et al., (2023) that stated intraepithelial CD8 is an independent prognostic factor for overall survival, as high intraepithelial CD8 found in 60.8% of early stage high grade serous ovarian carcinoma.

Categorical data were analyzed as frequencies and percentages. Continuous data were presented as mean±standard deviation or median based on the normality of data distribution (Shapiro-Wilk test). For continuous data, the Mann-Whitney U test was used, while the Chi-Square or Fisher's Exact test was applied for categorical data. Statistical significance was defined as $P<0.05$.

## 3. Results

A total of 55 patients diagnosed with ovarian carcinoma were treated at Dr. Soetomo Hospital, Surabaya, between 2021 and 2023. The mean age of the subjects was 49.80 years, and the mean age at menarche was 12.55 years. Regarding parity, 10 individuals (36.4%) were nulliparous and 26(52.7%) were postmenopausal (Table 1).

Based on tumor staging, 16 patients (29.1%) were in stage I, 10 (18.2%) in stage II, 27 (49.1%) in stage III, and 2 (3.6%) in stage IV. Histopathological examination showed that 29 patients (52.7%) had high-grade tumors. Also, high CD8 expression was observed in 37 patients (67.3%) (Table 2).

The mean CA125 level was 1054.01 U/mL (minimum of 1.73 U/mL and maximum of 14.445.73 U/mL). Meanwhile, the mean CEA level was 3.38 ng/mL, ranging from 0.07 ng/mL to 47.23 ng/mL.

Among 29 patients with high-grade histopathology, 21 (72.4%) exhibited high CD8 expression. In contrast, of 26 patients with low-grade histopathology, 16 (61.5%) had low CD8 expression. The Mann-Whitney test showed no significant differences in CD8 expression based on ovarian tumor histopathology (P=0.122) (Figure 1).

No significant associations were found between age (P=0.278), age at menarche (P=0.289), CA125 levels (P=0.133), or CEA levels (P=0.742) and ovarian tumor histopathological types (Table 3).

The mean CA125 level in patients with high CD8 expression was 1321.12 U/mL, while the mean CA125 level in those with low CD8 expression was 504.95 U/mL. There was no significant relationship between CD8 expression and CA125 levels in ovarian tumor patients (P=0.229). This result may suggest that CD8 expression might not be usefull in understanding the basic immune micro envirointment in ovarian cancer.

**Table 1. Demographic characteristics of ovarian tumor patients**

| Demographic characteristics | n= 55 |
|---|---|
| **Age, years** | |
| **Mean (SD)** | 49.80(12.27) |
| **Median (Min – Max)** | 51(19-77) |
| **Menarche, years** | |
| **Mean (SD)** | 12.55(1.03) |
| **Median (Min – Max)** | 12(10-15) |
| **Parity, n (%)** | |
| **Nulliparous** | 20(36.4) |
| **Primiparous** | 11(20) |
| **Secondiparous** | 14(25.5) |
| **Multipara** | 8(14.5) |
| **Grandemultiparous** | 2(3.6) |
| **Menopause, n (%)** | |
| **Yes** | 29(52.7) |
| **Not yet** | 26(47.3) |

**Table 2. Frequency distribution of stage, tumor histopathology, and CD8 expression results in ovarian tumor patients.**

| Clinical features | n = 55 |
|---|---|
| **Stages** | |
| **IA** | 2(3.6) |
| **IB** | 3(5.5) |
| **IC** | 11(20) |
| **IIA** | 7(12.7) |
| **IIB** | 3(5.5) |
| **IIIA** | 4(7.3) |
| **IIIB** | 4(7.3) |
| **IIIC** | 19(34.5) |
| **IVB** | 2(3.6) |
| **Histopathology, n (%)** | |
| **High Grade** | 29(52.7) |
| **Low Grade** | 26(47.3) |
| **CD8 expression, n (%)** | |
| **High** | 37(67.3) |
| **Low** | 18(32.7) |

**Table 3. Relationship between age, age at menarche, tumor markers Ca125, CEA, and ovarian tumor histopathology**

| | Histopathology of Ovarian Tumor | | P |
|---|---|---|---|
| | High Grade | Low Grade | |
| **Age, years** | | | |
| **Mean (SD)** | 51.55(9.91) | 47.85(14.42) | 0.278[a] |
| **Median (Min-Max)** | 51(25-77) | 51(19-70) | |
| **Menarche, years** | | | |
| **Mean (SD)** | 12.66(1.14) | 12.42(0.90) | 0.289[b] |
| **Median (Min-Max)** | 13(10-15) | 12(10-15) | |
| **Ca 125, U/mL** | | | |
| **Mean (SD)** | 980.64(1756.35) | 1135.85(2823.02) | 0.133[b] |
| **Median (Min-Max)** | 183.71(6.3-6035.9) | 507.75(1.73-14445.73) | |
| **CEA, ng/mL** | | | |
| **Mean (SD)** | 2.23(2.25) | 4.67(9.43) | 0.742[b] |
| **Median (Min-Max)** | 1.73(0.07-12.31) | 1.73(23.0-47.23) | |

[a]T Independent, [b]Mann Whitney

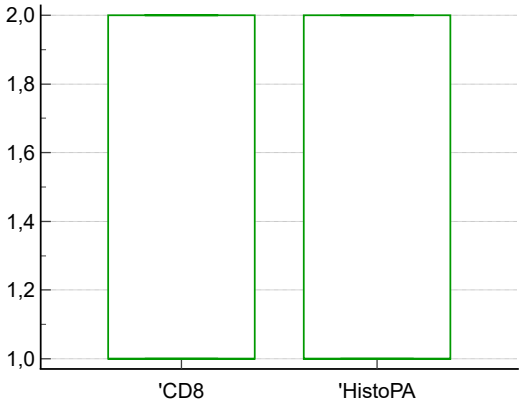



**Figure 1. CD8 expression based on ovarian tumor histopathology**

## 4. Discussion

Ovarian cancer occurs more frequently in older women compared to younger women and is rare in those under 40 years of age **(7)**. In this study, the mean age of the subjects in the present study was 49.80 years (19-77 years). The prevalence of ovarian carcinoma increases rapidly after age of 45 years8 The risk of ovarian cancer rises with age, with two-thirds of cases diagnosed in women aged 50 years and above **(9)**.

Modifiable risk factors for ovarian cancer include nulliparity, hormone replacement therapy, smoking, and high-fat diets. Non-modifiable risk factors include advanced age, genetic predisposition, family history, personal cancer history, early menarche, and late menopause. In this study, 36.4% of the subjects were nulliparous. Nulliparous women are at a 24% higher risk of developing ovarian cancer compared to women with at least one child, likely due to endocrine and metabolic factors **(7,10)**.

In the current study, the mean age at menarche among subjects was 12.55 years (10-15 years), and 52.7% of the subjects were postmenopausal. Approximately 75% of ovarian cancer cases are diagnosed after menopause. A woman's total lifetime ovulatory cycles are significantly associated with the risk of ovarian cancer **(7)**.

The staging system used for ovarian cancer is the FIGO staging system, which consists of four stages. In stage I, the cancer is confined to the ovaries or fallopian tubes. In stage II, the cancer spreads to other pelvic organs. In stage III, the cancer spreads more extensively within the peritoneal cavity or to retroperitoneal lymph nodes. In stage IV, the cancer spreads to distant organs **(11)**. In this study, 16 (29.1%), 10 (18.2%), 27 (49.1%), and 2 (3.6%) subjects were diagnosed with stage I, II, III, and IV, respectively. Ovarian cancer is typically asymptomatic, which leads to most cases being identified at advanced stages. More than 70% of ovarian cancer patients are initially diagnosed at advanced stages (stage III/IV) due to the lack of a single reliable and specific early detection procedure for ovarian cancer **(7,12)**.

In serous ovarian carcinoma, FIGO grade 1 is considered low-grade, while FIGO grades 2 and 3 are considered high-grade **(13)**. In the present study, 29 (52.7%) subjects had high-grade histopathology, while 26 (47.3%) had low-grade histopathology. Another study reported that approximately 68% of all ovarian cancer cases are high-grade serous carcinoma. In some cases, high-grade serous carcinoma develops from precursor lesions in the fallopian tubes. TP53 gene mutations are considered a hallmark of high-grade serous carcinoma **(11)**. Point mutations in oncogenes or tumor suppressor genes are uncommon in high-grade serous carcinoma. Low-grade serous ovarian carcinoma is a rare subtype of epithelial ovarian carcinoma (accounting for 2-5% of all ovarian carcinomas and approximately 5-10% of serous ovarian carcinomas) and occurs in younger populations **(14)**. Another study found that 3% of all ovarian cancer cases are low-grade serous carcinoma **(7)**.

T lymphocytes navigate and scan the body for foreign substances. Effector and naive T cells migrate to form adaptive immunity to combat infections and cancer. CD8 T cells are the primary killers of pathogens and neoplastic cells, with CD4 T cells playing an important role in maintaining CD8 responses and preventing exhaustion. CD8 T cells are part of lymphocytes that detect peptide antigens presented by Major Histocompatibility Complex (MHC) class I molecules. Active CD8 T cells form an immunological synapse between supramolecular activation complexes and adhesion molecules on the surface of target cells **(15)**. Cancer cells act as targets for CD8 cell activation by processing and presenting tumor antigen peptides via MHC class I. CD4+ cells interact with CD8 cells to modulate their activation and facilitate optimal proliferation and activation of CD8 cells. Once activated, CD8 Cytotoxic T Lymphocytes (CTLs) destroy cancer cells through the exocytosis of granules (perforin and granzyme) and receptor-ligand-mediated apoptosis (Fas ligand and TRAIL). Activated CD8 cells release interferon-gamma and tumor necrosis factor-alpha to induce cytotoxicity in target cells and stimulate macrophage M1-mediated anti-tumor responses **(16)**.

In this study, high CD8 expression was observed in 67.3% of subjects. Cancer cells interact with the tumor microenvironment to induce tumorigenic inflammation and suppress T cell activation. CD4+ Th1 cells secrete cytokines such as TNF and IFN-γ, which may efficiently suppress angiogenesis and promote the proliferation and activation of CD8 Tumor-Infiltrating Lymphocytes (TILs). Neoadjuvant chemotherapy plays a role in inducing various local changes in the tumor microenvironment, including the activation of CD8 and CD4 T cells. This may be due to degraded protein antigens being presented by MHC class I

molecules, stimulating CD8 T lymphocytes to produce pro-inflammatory cytokines that kill tumor cells **(18)**.

The mean CA-125 level in the subjects of the current research was 1054.01 U/mL. CA-125 is elevated in 85% of serous ovarian carcinomas but can also rise in other conditions **(19)**. Approximately 75% of ovarian cancer cases exhibit elevated CA-125 levels. CA-125 levels tend to increase in older women. Elevated CA-125 levels are associated with tumor invasion, tissue destruction, and inflammation caused by malignancy. A CA-125 level >30 U/mL has a sensitivity of approximately 81% and a specificity of about 75% in predicting malignancy **(20)**.

Carcinoembryonic Antigen (CEA) belongs to the immunoglobulin family and is associated with various endothelial cell functions, such as adhesion, proliferation, and cell migration, both in vivo and in vitro. CEA inhibits apoptosis and plays a role in tumor pathogenesis. It is a non-specific serum marker which increases in various malignancies, including ovarian cancer **(21)**. The mean CEA level in the subjects of the present study was 3.38 ng/mL. Badge et al. did not find elevated CEA levels in women with ovarian cancer **(20)**. Sagi-Dain et al. suggested that high CEA levels might help distinguish between primary ovarian cancer and metastatic tumors **(22)**.

According to the findings of the present study, no significant relationship was found between CD8 expression and the histopathological type of ovarian tumors. Farrag et al., reported that CD8 was not associated with tumor stage, lymph node metastasis, distant metastasis, or FIGO staging. Additionally, no correlation was observed between ascites, peritoneal deposits, residual disease, or recurrence and CD8 expression. CD8 expression was negatively associated with PD-L1 expression. Overall survival in patients with CD8 expression ≥10% was significantly higher compared to those with CD8 expression <10%. It is suggested that ovarian cancer is inherently an immunogenic tumor. A significant negative correlation exists between high CD8 levels and PD-L1 tumor expression. PD-L1 is expressed on tumor cells and plays a crucial role in immune evasion and development of tumor microenvironment. It inhibits reactive T-cell activity by binding to the PD-1 receptor, rendering tumor cells resistant to CD8-mediated and Fas-ligand-mediated lysis. Additionally, PD-L1 promotes T-cell tolerance by reversing signals through CD80 expressed on T cells **(23)**.

Intraepithelial CD8 levels are an independent prognostic factor for overall survival **(24)**. A study by Oktari et al. found that the higher the density of intratumoral CD8 TILs (tumor-infiltrating lymphocytes), the higher the density of stromal CD8 TILs **(8)**. Moreover, Goode et al., reported that 83% of high-grade serous ovarian carcinomas exhibited higher levels of CD8 TILs compared to other subtypes, possibly due to increased antigen expression enhancing the immune response to recognize tumor cells as antigens **(25)**. Similarly, Pizarro et al., found high intraepithelial CD8 levels in 60.8% of early-stage high-grade serous ovarian carcinomas **(24)**. Yang et al. also noted that high-grade serous ovarian carcinomas had higher CD8 infiltration compared to endometrioid carcinomas **(26)**. Khashaba et al., demonstrated elevated CD8 expression in all cases of high-grade serous ovarian carcinomas, with the highest levels in the immunoreactive subtype and the lowest in the proliferative subtype **(18)**. The presence of CD8 T cells is a strong positive prognostic marker in high-grade serous ovarian carcinoma **(27)**.

Karakaya et al., associated CD8 T lymphocytes with poor prognosis, showing shorter disease-free and overall survival rates. Also, among chemotherapy patients, the presence of CD8 T lymphocytes was linked to shorter disease-free and overall survival, and more frequently observed in advanced stages **(28)**. Other studies indicated that CD8 T lymphocyte infiltration correlated with advanced stages, higher tumor grades, and metastases in epithelial ovarian tumors. These findings suggest that CD8 may negatively influence the antitumor immune response **(29,30)**. Murakami et al., also found a significant correlation between CD8 lymphocytes and immunoreactive subtype of high-grade serous ovarian carcinoma **(31)**.

Low-grade serous ovarian carcinoma exhibits fewer mutations and appears to have fewer Tumor-Infiltrating Lymphocytes (TILs). MEK and BRAF inhibition promote an immune microenvironment in melanoma by suppressing immunosuppressive signals, leading to increased intratumoral CD8 T cells. Animal studies suggest improved survival with MEK/BRAF inhibitors when combined with anti-PD1 therapy **(2)**.

In the present research, mean age of the subjects with high- and low-grade histopathology types was 51.55 and 47.85 years, respectively. No significant correlation was found between age and histopathology type. Similarly, Cappuccio et al. reported a mean age of 57 years for high-grade ovarian cancer and 54 years for low-grade with no significant association. Low-grade ovarian cancer tends to be diagnosed at a younger age, potentially due to the accumulation of somatic mutations with age **(8,32)**.

According to the results of the present study, mean menarche age for subjects with high- and low-grade types was 12.66 and 12.42 years, respectively, with no significant correlation. Additionally, there was no significant association between menopausal status and histopathology type. A greater number of ovulatory cycles, characterized by earlier menarche and later menopause, increases the risk of ovarian cancer by promoting cell division and predisposing to malignant neoplasms **(33)**.

The findings of the current research showed that the mean CA-125 levels in subjects with high- and low-grade histopathology were 980.64 U/mL and 1135.85

U/mL, respectively, with no significant association. CA-125 levels rise due to tumor invasion, tissue destruction, and malignancy-related inflammation. However, CA-125 has a lower predictive value for low-grade ovarian cancer compared to high-grade ovarian cancer **(20,34)**. A research showed that the mean CEA levels for high- and low-grade histopathology were 2.23 ng/mL and 4.67 ng/mL, respectively. No significant relationship was found between CEA levels and histopathology type. CEA is a non-specific serum marker elevated in various malignancies, making it an unreliable indicator of cancer origin **(21)**.

This study had some limitations including the total sample may proper but our subgroup analyses (e.g., stage IV: n=2) lack statistical power that it has to be considered in taking further action. Moreover, this study didn't have inter-rater reliability data for CD8 scoring, due to limited number of samples. Survival outcomes were not analyzed in this cohort, as no statistically significant differences were observed between the groups.

## 5. Conclusion

As evidenced by the results of the present study, nulliparity is a known risk factor for ovarian cancer. Significant associations were observed between age and ovarian tumor stage and between histopathology type and tumor stage. However, no significant correlation was found between age, menarche age, CA-125, or CEA levels and ovarian tumor histopathology type. Additionally, no significant association was found between CD8 expression, CA-125 levels, and histopathology in ovarian tumor patients. Further prospective cohort studies are needed to assess the relationship between CD8 expression and the prognosis and survival of high- and low-grade ovarian carcinoma patients, providing a more comprehensive understanding of CD8's role in the progression of ovarian carcinoma, as well as the possible relation with stromal interactions that might explain the lack of CD8 difference.

## 6. Declarations


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### Ethical Considerations

Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Airlangga University/Dr. Soetomo General Hospital, Surabaya.

### Authors' Contributions

ZT and BAT performed conceptualization. WS supervised the research process. ZT wrote the original draft of the article. BAT, WS, PH and PM contributed to the writing-review and editing of the article. Formal analysis was done by BU, and data curation was performed by GA.

### Conflict of Interest

The authors declared no conflict of interest.


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