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Literature Review

A Retrospective Comparative Study of Clinicopathological Features in High-Grade and Low-Grade Serous Ovarian Carcinoma

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ABSTRACT

Backgroud: Ovarian carcinoma is the third most common malignancy in Indonesian women after breast and cervical cancer. Serous ovarian carcinoma is the most frequent subtype, divided into low-grade and high-grade types, each with distinct genetic and biological characteristics. **Objective:** This study aims to compare the clinicopathological features of high-grade and low-grade serous ovarian carcinoma. **Methods:** A retrospective cross-sectional study was conducted using 77 paraffin-embedded samples of serous ovarian carcinoma. Clinical and pathological data including age, body mass index (BMI), age at menarche, and parity were collected and analyzed using the chi-square test. **Results:** Patients aged >50 years accounted for most cases, with 64.3% presenting high-grade serous carcinoma (HGSC). Overweight/obesity was observed in 40.3% of cases. Early menarche (<13 years) was reported in 78%, and 42.7% were multiparous. No significant differences were found in clinical variables between HGSC and low-grade serous carcinoma (LGSC). Histopathologically, HGSC showed more pronounced cytologic atypia, necrosis, and metastasis. **Conclusion:** High-grade serous carcinoma demonstrates greater aggressiveness compared to its low-grade counterpart. Histopathological assessment plays a critical role in diagnosis, treatment decisions, and prognosis evaluation.

Introduction

Serous-type ovarian carcinoma is one of the most commonly found histopathological subtypes of ovarian cancer[1]. Serous ovarian carcinoma is a malignant epithelial-origin tumor with a high mortality rate[2]. The still-high mortality rate of serous-type ovarian cancer is caused by several factors, including: first, the tendency of ovarian cancer to metastasize far from its origin, making it sometimes difficult to identify that the primary cancer actually originated from the ovaries or fallopian tubes; this leads to ovarian cancer deaths appearing like the tip of an iceberg phenomenon. Second, the majority of women with ovarian cancer are diagnosed at an advanced stage of the disease. Third, early detection efforts for ovarian cancer still lag behind other gynecological cancers such as cervical and breast cancer. Fourth, preventive efforts such as BRCA mutation screening are still relatively expensive and only available at a few centers in Indonesia[3,4].

According to data from the American Cancer Society, the number of new ovarian cancer cases in the United States in 2022 was approximately 19,880, with an estimated 12,810 deaths[5]. This data places ovarian cancer as the fifth leading cause of cancer-related deaths among women[6]. Epidemiological data on the incidence of ovarian cancer in Indonesia in 2018, sourced

from the Center for Data and Information of the Indonesian Ministry of Health in 2019, ranked ovarian cancer third (3.8% of total gynecological malignancy cases) and eighth in terms of the proportion of cancer cases across genders[7]. Meanwhile, the mortality rate of ovarian cancer cases in Indonesia in 2018 was relatively high, accounting for 3.8% of the total incidence in that year[8].

Although the management of ovarian cancer has progressed significantly, patient survival remains poor. Understanding the contributing risk factors and the ability to clinically and histopathologically recognize this malignancy are crucial points in optimizing treatment.

Serous ovarian carcinoma is a unique type of ovarian cancer, as it is classified into two distinct entities: high-grade serous carcinoma (HGSC) and low-grade serous carcinoma (LGSC). High-grade serous carcinoma (HGSC) primarily originates from malignancies in the fallopian tubes, whereas low-grade serous carcinoma (LGSC) arises from the ovarian surface epithelium (OSE). Moreover, this classification reflects differences in carcinogenic pathways, mutation patterns, and prognoses between the two types of serous ovarian cancer[9].

This retrospective study aims to investigate the clinicopathological data of HGSC and LGSC. By comparing these two groups, we aim to identify and highlight differences in clinical characteristics, biological behavior, and potential prognoses between the patient groups. The findings of this study may contribute to a better understanding and recognition of these types of ovarian cancer.

Materials and Methods

Research Design

This study is an analytical observational study with a cross-sectional design, conducted at the Anatomical Pathology Laboratory of the Faculty of Medicine, Hasanuddin University, from January to June 2023. The aim of this study is to evaluate and compare the clinicopathological data of high-grade and low-grade serous ovarian carcinoma cases.

Sample

The study population comprised all ovarian tumor resection specimens submitted to the Anatomical Pathology Laboratory of Dr. Wahidin Sudirohusodo General Hospital (RSWS) Makassar from 2020 to 2022, specifically those diagnosed as high-grade serous carcinoma (HGSC) or low-grade serous carcinoma (LGSC). Diagnosis was confirmed through histopathological examination using hematoxylin-eosin (H&E) staining. The inclusion criteria consisted of ovarian epithelial tumor tissues with confirmed HGSC or LGSC diagnosis by certified anatomical pathologists. Only samples with adequate preservation and complete clinical data relevant to the variables under investigation were considered. Exclusion criteria applied to specimens that were damaged or compromised during the re-cutting process, rendering them unsuitable for analysis. Additionally, samples with incomplete clinical data, such as missing patient age, tumor size, or staging information, were excluded from the final analysis. This careful selection process aimed to ensure data reliability and consistency in the evaluation of histopathological and clinical characteristics associated with HGSC and LGSC cases. The final sample set was determined based on the availability and integrity of the specimens and their supporting documentation, allowing for accurate comparison and interpretation of pathological features between the two carcinoma subtypes.

Data Collection Techniques

The research workflow included the collection and classification of all histopathology slides previously diagnosed as HGSC and LGSC,

followed by a re-evaluation of the diagnosis by two anatomical pathology experts based on WHO diagnostic criteria. Clinicopathological data collected from each sample included patient age, body mass index (BMI), age at menarche, parity history, and histological characteristics such as lymphovascular invasion, metastasis, and tumor necrosis. BMI values were calculated by dividing body weight in kilograms by the square of height in meters. BMI categories followed the Asia-Pacific classification, in which overweight is defined as a BMI of 23–24.9 kg/m², and obesity as a BMI ≥25 kg/m².

Histopathological diagnosis of HGSC is characterized by a predominant solid growth pattern, with other variations such as papillary, glandular, cribriform, or slit-like spaces. The nuclei exhibit marked atypia, extreme pleomorphism (more than 3-fold variation), high atypical mitotic activity (>5 mitoses/mm² or >12 mitoses/10 HPF), and frequently the presence of multinucleated cells and necrosis. In contrast, LGSC shows a more variable architectural pattern, ranging from micropapillary and macropapillary structures to small nests and glandular formations. The nuclei typically show mild to moderate atypia, minimal pleomorphism (<3-fold variation), low mitotic activity (1–2 mitoses/mm² or 3–5 mitoses/10 HPF), frequent presence of psammoma bodies, and rarely show necrosis.

Data Analysis Techniques

The obtained data were analyzed using IBM SPSS Statistics software version 22.0. Comparative analysis between the HGSC and LGSC groups was performed to assess the significance of differences in clinical and histopathological characteristics.

Ethical Consideration

This study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Hasanuddin University. All data used were retrospective and did not contain patient identifiers, ensuring that confidentiality and ethical standards were maintained in accordance with the principles of the Declaration of Helsinki.

Result

This study successfully collected a total of 77 samples, comprising 56 cases of high-grade serous carcinoma (HGSC) and 21 cases of low-grade serous carcinoma (LGSC). Overall, the youngest patient with serous carcinoma was 25 years old, the oldest was 70 years old, the median age was 51, and the mean age was 50.43 years. There was no significant association between age and tumor differentiation; however, there was a tendency for LGSC to occur more frequently in patients under the age of 50 (64.3%) (Table 1).

There were no significant differences between the two ovarian carcinoma groups in terms of age at menarche ($p > 0.05$), parity history ($p > 0.05$), or body mass index (BMI) ($p > 0.05$). A total of 46 samples showed metastasis, while 31 samples did not. Among the metastatic cases, 40 were from the HGSC group ($p < 0.05$). Twenty-seven samples showed lymphovascular invasion, while 50 samples did not. Lymphovascular space invasion (LVSI) refers to the presence of tumor cells within the lumen of lymphatic and/or vascular vessels (see Figure 1.C). LVSI is associated with poor prognosis. In this study, there was no significant association between lymphovascular invasion and tumor differentiation. Necrotic areas were found in 44 samples, while 33 samples did not show necrosis. Of the necrotic cases, 40 were from the HGSC group ($p < 0.05$) (Table 1).

This pattern of findings reinforces the biological differences between HGSC and LGSC, particularly in terms of tumor aggressiveness and metastatic potential. The predominance of metastasis and necrosis in the HGSC group aligns with its known

aggressive clinical behavior and poorer prognosis. These results highlight the importance of early detection and accurate histopathological assessment, including evaluation of metastatic spread and necrotic features, to guide appropriate therapeutic strategies and improve patient outcomes.

Table 1. Sample Characteristics of Serous Type Ovarian Carcinoma

Variable	n (%)	HGSC (N=56)	LGSC (N=21)	P-value*
Age (years)				
<50 years	32 (41.6)	20 (35.7)	12 (64.3)	0.150
>50 years	45 (58.4)	36 (64.3)	9 (35.7)	
BMI (kg/m²)				
Underweight	12 (15.6)	9 (16.1)	3 (14.3)	0.961
Normal	31 (40.3)	22 (39.3)	9 (42.8)	
Overweight/Obese	31 (40.3)	22 (39.3)	9 (42.8)	
Missing	3 (3.9)	3 (5.4)	0	
Age at Menarche				
<13 years	58 (78.4)	42 (79.2)	16 (76.2)	0.499
≥13 years	16 (21.6)	11 (20.8)	5 (23.8)	
Parity				
Nulliparous	18 (24.0)	11 (20.4)	7 (33.3)	0.437
Primiparous	25 (33.3)	18 (33.3)	7 (33.3)	
Multiparous	32 (42.7)	25 (46.3)	7 (33.3)	
Lymphovascular Invasion				
Yes	27 (35.1)	20 (35.7)	7 (33.3)	1.000
No	50 (64.9)	36 (64.3)	14 (66.7)	
Metastasis				
Yes	46 (60.0)	40 (71.4)	6 (28.6)	0.002
No	31 (40.0)	16 (28.6)	15 (71.4)	
Tumor Necrosis				
Yes	44 (57.1)	40 (71.4)	4 (19.0)	0.000
No	33 (42.9)	16 (28.6)	17 (81.0)	

Source: *Medical Records Data, RSWS*
*******Chi-square test*

Discussion

Ovarian cancer is a heterogeneous group of tumors, with malignant cells originating from epithelial cells, germ cells, or stromal/sex cord cells. Among these three origins, approximately 90% of ovarian cancers arise from the ovarian surface epithelium.

Based on the differentiation patterns of the epithelial neoplasms, the World Health Organization (WHO) classifies epithelial ovarian neoplasms into eight groups: serous type, mucinous type, endometrioid type, clear cell type, transitional/Brenner tumor, carcinosarcoma, mixed epithelial tumor, and undifferentiated carcinoma. Among these, the serous type is the most common form of ovarian cancer.

Approximately 70% of serous ovarian cancers are high-grade serous carcinoma (HGSC), with an average age of onset around 65 years. Meanwhile, the proportion of cases LGSC accounts for approximately 3.4–5% of total ovarian cancers, with an average age of onset around 43 years. This study also found a relatively high proportion of HGSC cases compared to LGSC cases (56 vs. 21). Although not statistically significant, this finding aligns with the literature, which shows that the age of onset for HGSC patients tends to be above 50 years, while only 35.7% of LGSC cases have an onset age over 50 years. This study found that menarche age under 13 years was similarly dominant in both groups of serous ovarian cancer. This result

corresponds with previous findings that early menarche can be a risk factor for ovarian cancer. Early menarche and late menopause are associated with earlier and prolonged stimulation/damage to the ovarian surface epithelium (OSE). Meanwhile, no significant relationship was found regarding body mass index (BMI) and parity history, both in terms of case proportions and comparisons between the two ovarian cancer groups. This may be due to the limited sample size, which is a limitation of this study. Several other factors have been associated with increased ovarian cancer risk, including: nulliparity (women who have never been pregnant); never breastfeeding; white race, especially European Jewish, Icelandic, and Hungarian descent; ovarian cancer incidence increases up to the 70s age group and then slightly decreases in the 80s; dietary patterns and obesity; family history such as HBOCS (Hereditary Breast and Ovarian Cancer Syndrome), Lynch syndrome, and family history of ovarian and/or breast cancer, especially in first-degree relatives such as mother or sisters, which can increase ovarian cancer risk up to threefold; use of postmenopausal hormone therapy; and history of pelvic inflammatory disease (PID)[10,11].

Berdasarkan klasifikasi klinikopatologi dan molekular, karsinoma ovarium terbagi secara dualistik menjadi karsinoma ovarium tipe I dan tipe II. Tipe I adalah *low-grade serous carcinoma* bersama dengan karsinoma endometrioid, clear cell carcinoma, karsinoma musinosum, tumor *brenner/ transitional cell carcinoma.* Tipe II adalah *high gradeserous carcinoma,* bersama dengan undifferentiated carcinoma dan carcinosarcoma, ditandai dengan mutasi p53[3,10,12,13].

Low-grade serous carcinoma is known to develop slowly and progressively from precursor lesions such as serous cystadenoma, which then progresses to serous borderline tumor (SBT), and eventually becomes low-grade serous carcinoma. Although less common than HGSC, low-grade serous carcinoma can metastasize because it is a genetically stable cancer type with a low number of mutations (mutations in BRAF and KRAS even occur before the appearance of the precursor SBT lesion). Low-grade serous

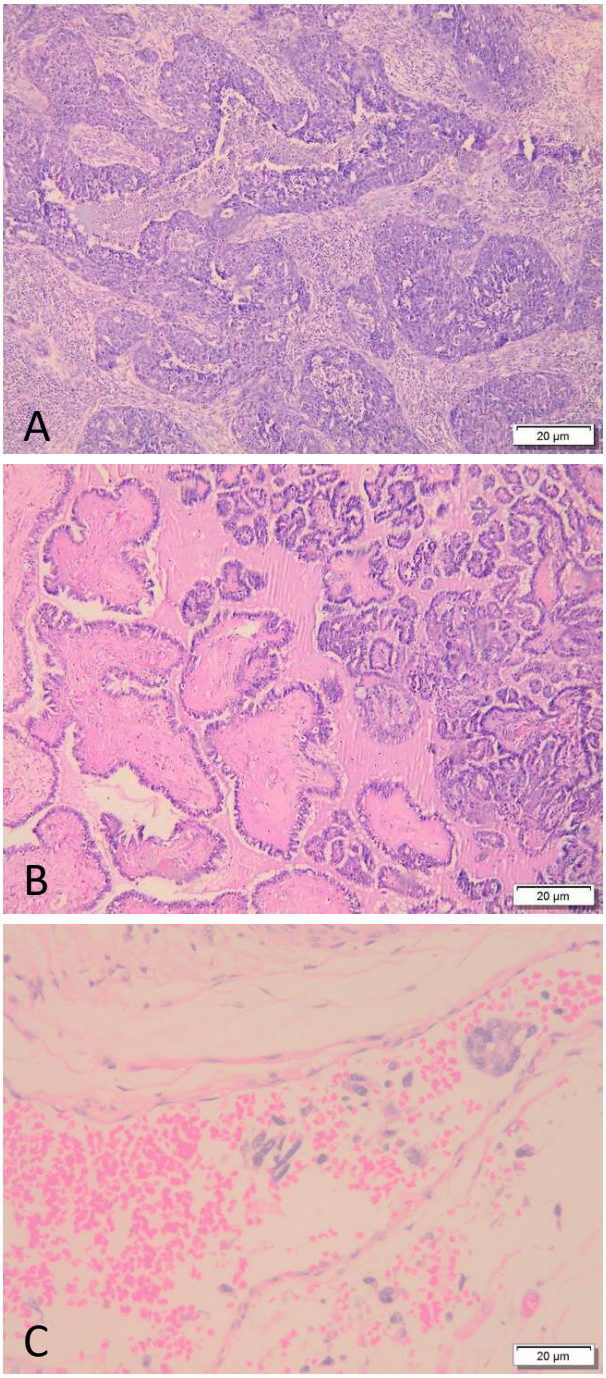

Figure 1. A. High-grade serous carcinoma; B. Low-grade serous carcinoma; C. Invasi limfovaskular positif

carcinoma has DNA copy numbers more similar to SBT compared to high-grade serous carcinoma[12,14].

Meanwhile, high-grade serous carcinoma exhibits rapid malignant progression even at early stages, is genetically unstable leading to frequent chromosomal rearrangements, and has a poor prognosis due to often being diagnosed at advanced stages[3,12]. At the molecular level, the characteristics of low-grade carcinoma include TP53 mutation in 80% of cases, high Ki67 proliferation index of 50–75%, HER2/neu overexpression in 20–67%, p16 inactivation in 15%, HLA-G overexpression in 61%, apoE overexpression in 66%, and in hereditary/familial ovarian carcinoma cases, BRCA1 and BRCA2 mutations occur in up to 90%[4,10,12,15].

Our findings indicate that HGSC has a significantly higher metastatic potential compared to LGSC (p-value 0.002), marked by a significantly higher incidence of peritoneal metastasis and malignant ascites. The high metastatic potential is associated with poorer prognosis and increased patient mortality. Peritoneal metastasis (peritoneal carcinomatosis) in HGSC is suspected to occur through a mechanism of peritoneal seeding, where tumor cells detach from the primary tumor and spread to the peritoneal surface[16,17]. Although lymphovascular space invasion (LVSI) is often linked to metastasis in various cancers, our findings suggest that the metastatic mechanism in HGSC may be more complex and not solely dependent on LVSI. Differences in molecular profiles between HGSC and LGSC, such as TP53 mutations and MYC amplification in HGSC, may play a key role in enhancing metastatic potential.

These findings have significant clinical implications. Patients with HGSC require closer monitoring and may need more aggressive therapy to prevent and treat metastasis. Further research is necessary to identify biomarkers that can predict early metastasis in HGSC, as well as to develop more effective therapies to prevent and treat peritoneal metastasis.

Conclusion

This study successfully demonstrated a significant difference in the incidence of metastasis and necrosis between high-grade serous ovarian carcinoma (HGSC) and low-grade serous ovarian carcinoma (LGSC). These results confirm the higher aggressiveness of HGSC compared to LGSC. Peritoneal metastasis was the most common finding in HGSC, indicating the importance of histopathological examination of the omentum and cytology of ascitic fluid in staging, prognosis determination, and disease management.

Further research is needed to identify specific biomarkers for HGSC that can be used for early diagnosis and prognosis prediction. In addition, more in-depth studies on the mechanisms of peritoneal metastasis would be highly beneficial for the development of more targeted therapies.

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