

Clinical-Pathological Characteristics Analysis of Low-Grade Serous Ovarian Carcinoma (LGSOC) at Tertiary Hospital in Indonesia

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KEYWORDS

Clinical-pathological characteristics, Low-grade serous ovarian carcinoma (LGSOC), Ovarian cancer.

ABSTRACT

Objectives: Ovarian cancer, particularly Low-Grade Serous Ovarian Carcinoma (LGSOC), as rare cancer exhibits clinical-pathological characteristics that attract attention.

Methods: This study adopted an analytic observational study approach with a cross-sectional design, and used a total sampling method with medical records data from Dr. Soetomo Regional General Hospital patients from 2016 to 2022.

Results: In a study involving 51 LGSOC patients, the majority were diagnosed at Stage III. Common clinical symptoms involved abdominal distension, with some patients experiencing abdominal pain, while ascites occurred in 39.2% of patients, reflecting the impact of metastasis on the patient's physical condition. Elevated CA-125 levels (>35 U/ml) were detected in 92.2% of patients, with only 7.8% of patients showing CA-125 levels within the normal range (≤ 35 U/ml). There was a significant age difference between the two age groups compared, but no significant differences in clinical symptoms, tumor size, tumor bilaterality, or cancer stage between the two age groups. The research results indicate a significant difference in the presence of ascites between the two age groups, suggesting a potential relationship between ascites and patient age. Statistical analysis shows a connection between CA-125 levels and overall disease progression, although not significant in the younger age group. However, there is no significant correlation between CA-125 levels and tumor bilaterality, presence of residual tumor, or tumor size across all age groups. Although there is a trend that patients with high CA-125 levels tend to experience ascites, this difference does not reach statistical significance.

Conclusions: In this study, Low-Grade Serous Ovarian Carcinoma (LGSOC) majority of patients were diagnosed at Stage III. Despite a significant age difference, the results suggest a potential relationship between ascites and patient age, while high CA-125 levels were detected in most patients, though not always reflecting a significant level of disease progression.

1. Background

Globally, ovarian cancer stands as a prominent cause of female mortality. In Indonesia, ovarian cancer accounts for 7% of cancers in women, totaling 14,896 cases. Within East Java, the One-Stop Oncology Clinic (POSA) at Dr. Soetomo Regional General Hospital's Obstetrics and Gynecology Department documented 907 ovarian cancer patients over the past 7 years, ranking it second in prevalence after cervical cancer. The occurrence of ovarian cancer exhibits age-related variability, with the highest incidence observed in women over 40 years old (80%-90%), and 40% of cases are identified after the age of 65 (1-3).

Ovarian cancer is divided into several types based on the cell of origin, one of which is epithelial ovarian carcinoma. The histology of epithelial ovarian carcinoma includes High-grade serous cancer (HGSOC), Low-grade serous ovarian cancer (LGSOC), Endometrioid ovarian

cancer (ENOC), Mucinous ovarian cancer (MOC), and Clear cell ovarian cancer (CCOC) (4). HGSOC is commonly the predominant histotype, often diagnosed in advanced stages due to its rapid growth rate, origination in the fallopian tube, tendency to spread locally to the peritoneal cavity, and the delayed appearance of symptoms (5).

Research at Dr. Soetomo Regional General Hospital found 170 and 122 ovarian cancer patients in 2014 and 2015, with the most common histopathological type being epithelial (6). Another study from 2016-2020 identified 358 ovarian cancer patients, with some experiencing recurrence (7).

Symptoms, tumor size, bilaterality, CA 125 levels, stage, and residual tumor are significant clinicopathological variabilities in ovarian cancer. Mortality and recurrence depend on the stage, grading, type of surgery, and the presence of ascites (7).

One of the ovarian cancer types that attracts attention is LGSOC, which has lower malignant potential, younger age at diagnosis, and a slow clinical course. Although less aggressive compared to other types, advanced stage and comorbidities in elderly patients can impact treatment and overall outcomes (8).

2. Objectives

This study aims to better understand the clinicopathological characteristics of LGSOC, with the hope of providing guidance for more effective treatment.

3. Methods

This study employed an analytical observational study approach with a cross-sectional design and applied the total sampling method. The data used were retrospective data from the medical records of patients diagnosed with low-grade serous ovarian carcinoma (LGSOC) epithelial ovarian cancer at Dr. Soetomo Regional General Hospital within the timeframe from 2016 to 2022. The research was conducted at the Obstetrics Oncology Clinic, Diagnostic Center Building, Dr. Soetomo Regional General Hospital, Surabaya, during the period from August 2023 to December 2023. The study population included all patients diagnosed with LGSOC epithelial ovarian cancer at Dr. Soetomo Regional General Hospital during that period. Inclusion criteria involved patients with histopathological confirmation of LGSOC and complete medical records regarding clinicopathological characteristics, while exclusion criteria included unreadable medical records, missing medical records, and patients with types of epithelial ovarian cancer other than LGSOC. Data sources were derived from the registration book of the Obstetrics Oncology Clinic at Dr. Soetomo Regional General Hospital, medical records, and the SPSS program for data processing. Data analysis was conducted using the Chi-Square statistical test to evaluate the relationship between categorical variables such as symptoms, bilaterality, stage, and residual tumor with age groups. The level of statistical significance was set at $p < 0.05$. This study has obtained approval from the Ethics Commission for basic/clinical research at Dr. Soetomo Regional General Hospital/Faculty of Medicine, Airlangga University Surabaya, and the confidentiality of subject data is maintained by not identifying names and using data solely for research purposes.

4. Results

This study involved 51 patients with Low-Grade Serous Ovarian Carcinoma (LGSOC) epithelial ovarian cancer, with an average age of 44.35 years and significant age variation ($SD=46$). From the research findings, 39.2% of patients were asymptomatic, 51% experienced abdominal distension, and 9.8% had abdominal pain. The majority of patients (80.4%) had tumors larger than 10 cm. Regarding tumor bilaterality, 64.7% were unilateral cystic masses, and 35.3% were bilateral cystic masses. Most patients (39.2%) were diagnosed at Stage III, while ascites occurred in 39.2% of patients, reflecting the impact of metastasis on the patient's physical condition. In the context of treatment, positive outcomes were observed with 78.4% of patients having no residual tumor after treatment.

Table 1. Characteristics of research subjects

Characteristics	Category	Total (N=51)
Age (Mean ± SD) (Years)		44.35 ± 46
Symptoms, n (%)	Asymptomatic Enlarged abdomen (<i>abdominal distension</i>) <i>Abdominal pain</i>	20 (39.2) 26 (51) 5 (9.8)
Tumor Size, n (%)	≤10 cm >10 cm	10 (19.6) 41 (80.4)
Bilaterality, n (%)	Unilateral Cyst Mass Bilateral Cyst Mass	33 (64.7) 18 (35.3)
Stage, n (%)	I II III IV	18 (35.3) 10 (19.6) 20 (39.2) 3 (5.9)
Ascites, n (%)	There is None	20 (39.2) 31 (60.8)
Residue, n (%)	Any (any) None	11 (21.6) 40 (78.4)
CA-125 Level, n (%)	Normal (≤ 35 U/ml) Abnormal (>35 U/ml)	4 (7.8) 47 (92.2)

Table 2. Characteristics of subjects in both groups

Characteristics	Category	Group (%)		p-value
		≤ 40 years (n=19)	> 40 years (n=32)	
Age, n (%)		31.63 ± 7.174	51.91 ± 7.647	0.005*
Symptoms, n (%)	Asimptomatic Enlarged abdomen (<i>abdominal distension</i>) <i>Abdominal pain</i>	7 (36.8) 10 (52.6) 2 (10.5)	13 (40.6) 16 (50) 3 (9.4)	0.963

Table 3. Tumor Characteristics in both groups

Characteristics	Category	Group (%)		p-value
		≤ 40 year (n=19)	>40 year (n=32)	
Tumor Size, n (%)	≤10 cm	4 (21.1)	6 (18.8)	0.036
	>10 cm	15 (78.9)	26 (81.3)	
Bilaterality, n (%)	Unilateral Cyst	13 (68.4)	20 (62.5)	0.669
	Bilateral Mass Cyst	6 (31.6)	12 (37.5)	
Stage, n (%)	I	7 (36.8)	11 (34.4)	0.756
	II	5 (26.3)	5 (15.6)	
	III	6 (31.6)	14 (43.8)	
	IV	1 (5.3)	2 (6.7)	
Ascites	There is	11 (57.9)	9 (28.1)	0.035*
	None	8 (42.1)	23 (71.9)	
Residue, n (%)	Any (any)	5 (26.3)	6 (18.8)	0.525
	None	14 (73.7)	26 (81.3)	
CA-125 Level, (Mean ± SD)		468.895 ± 604.5504	579.901 ± 916.1741	0.597

Age analysis showed a significant difference between the ≤ 40 years group (n=19) and > 40 years group (n=32), with average ages of 31.63 years and 51.91 years, respectively (p-value = 0.005*). Although there were no significant differences in clinical symptoms, tumor size, tumor bilaterality, or cancer stage between the two age groups, there was a significant difference in the presence of ascites (p-value = 0.035*). A significant relationship was detected between CA-125 levels and disease progression across all age groups (p-value = 0.047), although in the analysis of the younger age group, this relationship was not statistically significant. Although there was a trend that patients with high CA-125 levels were more likely to experience ascites, this difference did not reach a statistically significant level. There was no significant difference in the distribution of CA-125 levels between patients with tumors ≤ 10 cm and > 10 cm in the entire age group. No significant correlation was observed between CA-125 levels and tumor bilaterality in all age groups, and there was no significant relationship between CA-125 levels and the presence of residual tumors in the entire age group.

Table 4. Relationship between CA-125 and tumor characteristics across age groups

	Characteristics	Category	CA-125 Level,n (%)		p-value
			Normal (≤ 35 U/ml)	Abnormal (>35 U/ml)	
All age groups	Tumor size, n (%)	≤10 cm	1 (25)	9 (19.1)	0.777
		>10 cm	3 (75)	38 (80.9)	
≤40 years	Tumor size, n (%)	≤10 cm	0 (0)	4 (22.2)	0.596
		>10 cm	1 (100)	14 (77.8)	
>40 years	Tumor size, n (%)	≤10 cm	1 (33.3)	5 (17.2)	0.497
		>10 cm	2 (66.7)	24 (82.8)	
All age groups	Bilaterality, n (%)	Unilateral Cyst Mass	3 (75)	30 (63.8)	0.654
		Bilateral Cyst Mass	1 (25)	17 (36.2)	
≤40 years	Bilaterality, n (%)	Unilateral Cyst Mass	1 (100)	12 (66.7)	0.485
		Bilateral Cyst Mass			
>40 years	Bilaterality, n (%)	Unilateral Cyst Mass	2 (66.7)	18 (62.1)	0.876
		Bilateral Cyst Mass	1 (33.3)	11 (37.9)	
All age groups	Stage, n (%)	I	4 (100)	14 (29.8)	0.047

		II	0 (0)	10 (21.3)	
		III	0 (0)	20 (42.6)	
		IV	0 (0)	3 (6.4)	
≤40 years	Stage, n (%)	I	1 (100)	6 (33.3)	0.613
		II	0 (0)	5 (27.8)	
		III	0 (0)	6 (33.3)	
		IV	0 (0)	1 (5.6)	
>40 years	Stage, n (%)	I	3 (0)	8 (27.6)	0.097
		II	0 (0)	5 (17.2)	
		III	0 (0)	14 (48.3)	
		IV	0 (0)	2 (6.9)	
All age groups	Ascites, n (%)	There is	0 (0)	20 (42.6)	0.094
		None	4 (100)	27 (57.4)	
≤40 years	Ascites, n (%)	There is	0 (0)	11 (61,1)	0.228
		None	1 (100)	7 (38,9)	
>40 years	Ascites, n (%)	There is	0 (0)	9 (31)	0.255
		None	3 (100)	20 (69)	
All age groups	Residue, n (%)	Any (any)	0 (0)	11 (23.4)	0.275
		None	4 (100)	36 (76.6)	
≤40 years	Residue, n (%)	Any (any)	0 (0)	5 (27.8)	0.539
		None	1 (100)	13 (72.2)	
>40 years	Residue, n (%)	Any (any)	0 (0)	6 (20.7)	0.382

		None	3 (100)	23 (79.3)	
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5. Discussion

This study extensively analyzes the clinical characteristics of patients with Low-Grade Serous Ovarian Carcinoma (LGSOC) based on age groups, namely those below 40 years and those above 40 years. Despite the significant age difference, this study did not show striking differences in clinical symptoms in LGSOC patients based on age groups.

Our findings align with previous literature highlighting that the survival of LGSOC patients is influenced by various factors, including histology, cancer stage, and the extent of remaining cancer after surgery. These factors underscore the importance of prognostic determinants in the management of LGSOC patients (9–11).

Examining the relationship between CA-125 levels and tumor size in LGSOC patients across different age groups reveals variations in size associated with CA-125 levels, particularly among younger individuals. Despite occasional lack of statistical significance, these findings emphasize the intricate interplay between CA-125 and tumor characteristics in LGSOC. Additionally, the absence of a significant correlation between CA-125 and tumor size in patients over 40 suggests age-related distinctions in this relationship. It's crucial to note that elevated CA-125 levels often coincide with higher overall disease stages, though this is not universally applicable to specific age groups. These results align with prior research suggesting that CA-125 may not consistently serve as a reliable marker for LGSOC progression. While in line with certain studies, it's important to highlight variations in LGSOC patient characteristics across different research, underscoring the disease's complexity and the potential impact of demographic factors and disease stage on research outcomes (12–14).

This study explores the connection between CA-125 levels and ascites presence in LGSOC patients. Prognosis is determined by elevated CA-125 levels (>35 U/ml), associated with a reduction in progression-free survival. However, the efficacy of CA-125 could be improved by combining it with other markers. Referring to prior research by Waluyo et al., the older age group displayed a higher average CA-125 level (257.918 ± 643.504) compared to the younger age group ($74,417 \pm 63,022$), consistent with earlier observations of elevated CA-125 in ovarian cancer cases. Notably, patients aged 12-18 exhibited a 54% increase in CA-125 levels (12,13).

In general, there is no notable correlation between CA-125 and the presence of ascites, a result consistent across all age groups, encompassing both young and older patients. Relevant studies also underscore divergent outcomes. For instance, Ming et al.'s (2014) research emphasizes chemotherapy resistance in low-grade serous ovarian cancer, a subtype of LGSOC. Their findings reveal chemotherapy resistance in patients with low-grade serous carcinoma, where positive ascites is linked to a more unfavorable disease progression. On the other hand, Quan et al.'s (2021) study suggests that ascites volume doesn't significantly correlate with age at diagnosis or tumor differentiation (12).

This study also investigates the correlation between CA-125 levels and the presence of residual tumor after treatment, irrespective of the patient's age. There is no significant distinction between patient groups with normal and high CA-125 concerning the presence of tumor residue. This discovery implies that factors other than CA-125 may exert more influence on the development of tumor residue in LGSOC patients. However, these findings offer preliminary indications, and further research with a larger sample and consideration of other relevant variables may be necessary to gain a more profound understanding of this relationship, particularly within the young and elderly LGSOC patient cohorts. Some previous studies underscore the potential limitations of CA-125 in predicting the presence of tumor residue in LGSOC patients (11). Additionally, surgical decisions and the extent of cytoreduction do not solely depend on CA-125

levels but also on other factors such as the patient's age and clinical characteristics (15)(16). A study also suggests that biomarker response and radiological response may vary in LGSOC patients undergoing neoadjuvant chemotherapy, indicating the complexity of assessing treatment effectiveness (10).

The majority of Low-Grade Serous Ovarian Carcinoma (LGSOC) patients were mostly diagnosis at Stage III. Common clinical symptoms involve abdominal enlargement, abdominal pain, and the occurrence of ascites. Elevated CA-125 levels (>35 U/ml) are detected in most patients. Despite significant age differences, there are no observable significant differences in clinical symptoms, tumor size, tumor bilaterality, or cancer stage between age groups. However, there is a significant difference in the presence of ascites between the two age groups. Overall, there is no significant difference in CA-125 levels associated with disease progression, tumor bilaterality, residual tumor presence, ascites, or tumor size across all age groups.

This study has limitation that it was retrospective. The ideal study would be a long-term prospective study. However, feasibility is a consideration, given that cases are relatively rare. In this study, despite collecting data for six years from one center, only 51 cases were obtained. This study's strength is that it is the first largest single center study from Indonesia and seeks to reveal the role of age in the clinicopathological profile of LGSOC in Indonesia. This study is a preliminary study to explore LGSOC in this country. The suggestion is that further prospective study is needed with a larger sample and multicenter studies to represent Indonesia's population.

Footnotes

Authors Contribution: **Ach. Fahrur Rozi Mukti**: Conceptualization, Data curation, Formal analysis, Writing – original draft. **Brahmana Askandar Tjokropawiro**: Conceptualization, Supervision, Writing – review & editing. **Pungky Mulawardhana**: Supervision, Formal analysis, Writing – review & editing

Conflict of Interest: The authors declare no conflict of interest

Ethical Approval: This study has obtained approval from the Ethics Commission for basic/clinical research at Dr. Soetomo Regional General Hospital/Faculty of Medicine, Airlangga University Surabaya, and the confidentiality of subject data is maintained by not identifying names and using data solely for research purposes.

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